RESOLVING THE MYSTERIES OF AUTISM

by Steve Kohler

In Mallinckrodt Institute of Radiology's East Building, what was a technologically sophisticated but otherwise plain magnetic resonance imaging (MRI) suite has been converted into a cozy nursery with rocking chairs, a crib, and blankets. Customized to accommodate an uncommon group of study participants, it's the site of seminal research into autism, and the pioneering subjects are just six months old.

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The infants arrive in the evening to be rocked and cuddled by their parents, then put comfortably to bed—in the bore of the scanner. For as long as 10 days before their imaging appointment, the infants have become accustomed to the subdued knock, buzz, and beep of the high-tech imager as their parents have played them a tape of the noises they'll hear during the scanning process. The babies wear little earplugs, under noise-shielding headphones. And after they're deeply asleep and perfectly still, late-night scans record exquisitely detailed images of their heads and brains. They are exposed to no radiation and need no anesthesia or injection of contrast agents.

The research is so noninvasive and unobtrusive that the babies often sleep right through it. If they fuss a little, the scanning pauses; if they wake, the session ends. Their parents agree to participate even though they probably have their hands full with both an autistic child and a new baby. That's one measure of how deeply committed they are to resolving the mysteries of autism.

DIAGNOSTIC IMAGING AND EARLY INTERVENTION

The infants offer invaluable insights to the research team because, first, they are siblings of children diagnosed with autism and, due to autism's genetic component, are far more likely to develop the disorder than are the population at large. The tender age of the subjects is also crucial because autism is "clearly a problem of early brain development," says Kelly Botteron, MD, associate professor of psychiatry and of radiology. "Early intervention is where the future of autism treatment lies."

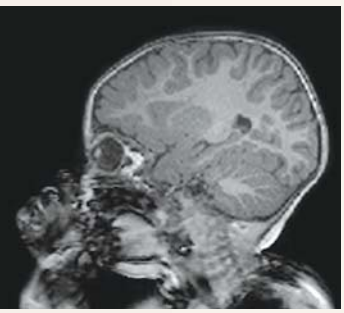
Today, by the time a diagnosis of autism is stable, the effectiveness of intervention may already have been limited. To help change that, the youngsters are participating in a five-year national study funded by the National Institutes of Health-sponsored Autism Centers of Excellence (ACE) Network.

Summarizing the goal of the research, Botteron, the principal investigator of its St. Louis arm, says it will "relate images of the infants' developing brains to the diagnosis of autism," helping to understand the underlying neurophysiology and provide a target for further research. "A study connecting imaging to diagnosis has never been done in infants before," she says.

Kelly Botteron, MD: "MRI offers the unique opportunity to noninvasively study structural and functional neural development in vivo in young children."

The children—who will be scanned at six months, 12 months, and 24 months of age—will be joined by a control group of identically aged, healthy youngsters with no predisposition to autism. All of the youngsters will likewise be carefully tested to either make a diagnosis of autism or rule it out. Any abnormalities revealed by the scans can then be associated with developing autism and perhaps to the wider range of related disorders

known as autism spectrum disorders (ASD), providing new insights into those conditions as well. Because the brain is developing so rapidly during these early days of life, the researchers face the challenge of making sure all subjects are scanned and cognitively tested within a week of the designated birth anniversaries. In fact, the researchers say that the rate limiting factor in what they will be able to learn is their ability to recruit participants, and they ask for help in spreading the word about their need for families that have infants or babies on the way and an autistic older child.



While this MRI scan was being done, the sleeping infant quite naturally was sucking his thumb.

Previous studies of head circumference have demonstrated a relationship between general brain overgrowth and autism, Botteron says, but despite increasing interest in understanding autism, sophisticated imaging studies have been surprisingly few. In fact, until recently, many researchers believed it was not possible to get accurate and reliable images of such tiny and sometimes uncooperative subjects, she says.

ADVANCED TECHNOLOGY

The techniques the investigators will use to safely and effectively image the young subjects have been developed over years of experience at Washington University and Mallinckrodt Institute. Robert McKinstry, MD, PhD, associate professor of radiology and of pediatrics, participated in devising the

ABOUT AUTISM

Autism is a neurobiological developmental disorder usually diagnosed by three years of age. It interferes with a person's ability to communicate, the capacity to relate to others and cognitive function. Those with autism often display repetitive motions and follow rigid routines. Autism carries a strong genetic component, but the genetics of the disorder are complex and not well-understood.

It lasts throughout a lifetime but does not shorten life expectancy, although people with autism often suffer from a number of physical ailments including recurring infections, asthma, and digestive disorders. There is no cure, but early intervention can reduce the severity of symptoms, and behavioral or cognitive intervention can help children gain self-care, social, and communication skills.

Autism is one of a group of disorders known as ASD, for autism spectrum disorders, with a wide range of symptoms and severities. Together, autism spectrum disorders affect an estimated 1.5 million Americans, according to the Autism Society of America (ASA).

Controversy exists over just how rapidly the incidence of autism is increasing. Improved diagnostic procedures contribute to larger numbers, but there also appears to be an actual rise in the number of cases. According to the group Autism Speaks, prevalence has risen until one in every 150 children is diagnosed with autism, making it more prevalent than pediatric cancer, diabetes, and AIDS combined. It affects boys disproportionately.

A diagnosis of autism can be life changing for a family; frequently, one parent must devote full time to providing care. The lifetime cost of that care has been estimated at between $3.5 million and $5 million. In the United States, all autism-related expenses may be as high as $90 billion annually, according to the ASA.

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sedative-free scanning of infants during a 1999 to 2007 national MRI study of normal brain development. So far in the autism study, the protocol has been used to scan the first five young subjects, with unqualified success.

McKinstry, who is chief of Mallinckrodt Institute's Pediatric Radiology section, also designed the imaging protocol and scanning implementation for the autism study. High-speed MRI is capable of structural neuroimaging—the capacity to visualize parts of the brain such as the amygdala and the frontal centers where facial processing occurs, both areas of concern to autism researchers. The technology reveals the volume and shape of the brain's gray matter, made up of nerve cell bodies.

But the latest evolution of sophisticated MRI technology, called diffusion tensor imaging (DTI), goes a big step further. DTI reveals the secrets of white matter, the long tentacles of nerve cells (or axons) that compose the wiring connecting the various parts of the brain. "DTI images the microstructure that carries signals, showing whether the wires are properly organized, aligned, and insulated," McKinstry says. "We can follow them from one point in the brain to another and test whether the connections play a role in autism."

DTI uses radio waves and magnetic pulses to nudge water molecules in the brain. Water in the axons is constrained by the myelin sheaths that protect them, much like a wire's insulation, so it tends to move along the wire rather than dispersing in every direction like water molecules elsewhere. By making images of the water's organized movement, investigators can map the wires and locate their terminals.

A COLLABORATIVE EFFORT

The researchers will make scans of the 100 infants with autistic older siblings whom they hope to enroll in St. Louis, plus the control group. Similar efforts at the University of North Carolina, the University of Washington at Seattle, and the University of Pennsylvania will bring the total number of infants scanned to 400, along with 160 healthy, contrast subjects. The large majority will not go on to develop autism, but perhaps 60 of the youngsters are expected to be diagnosed with the disorder, given established statistics. Data from the four centers then will be collected and analyzed at two additional coordinating centers at the Montreal Neurologic Institute and the University of Utah. To recruit qualified participants who can visit at precise times requires a region-wide effort, Botteron says, and support groups such as Autism Speaks are helping by alerting their highly motivated members.

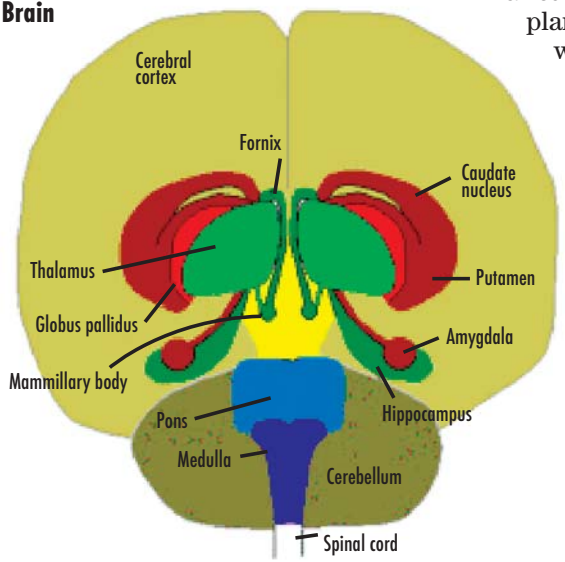
CHALLENGES AND POSSIBLE SOLUTIONS

Another challenge faced by the researchers is making accurate autism diagnoses at very young ages. John Constantino, MD, who brings a large autism research portfolio to the study, says that many in the field believe that the symptoms of autism must be appreciable at even six months, but "we're just not sure." For those youngest children, he will observe and archive video recordings that can be revisited for even the most subtle clues. And he will use the still-face paradigm, in which a caregiver who has been interacting with a child quickly disengages; the sudden

Left: In this autism study, Dr. Robert McKinstry combines his clinical interest in pediatric neuroradiology with his expertise in MRI.

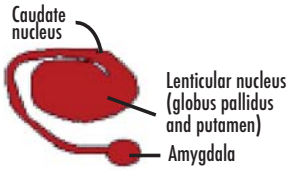
indifference upsets most normal babies, but autistic infants often are not bothered, he says. Constantino, associate professor of psychiatry and of pediatrics, says the researchers also may be able to employ eye-tracking technology to measure precisely where babies focus their attention for a "finer-grained evaluation." A broader range of established tests will be used to evaluate the subjects as they reach 12 months and 24 months of age. Finally, Constantino will make a firm diagnosis when the subjects reach three years, the age at which diagnoses are widely regarded as stable.

The Brain



The brain as viewed from the underside and front. The thalamus and Corpus Striatum (Putamen, caudate and amygdala) have been splayed out to show detail.

Corpus Striatum



The researchers' hope for the work is that it will produce observable differences in the brains of autistic children that can serve as a basis for discerning the mechanisms by which the disorder develops. McKinstry says that, ideally, the study could lead to a diagnostic tool to be used as a means to assess children who may be at risk and even become the basis for developing strategies to limit disability.

More likely, Botteron says, is that the research may eventually help to sort out the effectiveness of the wide range of treatments and interventions that are available. Families have several broad varieties and dozens of individual plans from which to choose when considering treatment. "Many of the approaches are untested, and it would be helpful to know which ones work," she says. Any treatment shown to be symptomatically effective could be evaluated using the study's results to see if underlying physiological changes are affected by a given treatment. For example, the well-regarded approach called applied behavioral analysis (ABA) that is generally regarded as a successful treatment approach could be tested to reveal if and how the underlying physiology is normalized as the treatment progresses.

Botteron warns that the size of the sample of children who eventually develop autism—perhaps 60—is small and that autism is aggravatingly complicated, most likely attributable to several or even many causes, and with a wide range of symptoms and severities. For one study to unravel all of its complexities is not possible. Nonetheless, "families are desperate for something to help," Botteron says, and the young volunteers who go to sleep in Mallinckrodt Institute's scanner are providing a first look at the condition as it develops—a big step in a promising new direction before they can even walk. MIR

John Constantino, MD, has more than 10 years experience in autism research.

Editor's Note: For more information about participating in this important study, go online at http://infantsibs-stlouis.org. Or call Study Coordinator Lisa Flake, MSW, toll free at 1-888-845-6786.