

Explorations and revelations taking place at the medical school

Nancy Minshew reports that rapid and early brain growth and lack of neural connections bring about autism. LEFT: Katie and Joyce Douglas.



BEDEVILED NO MORE

AUTISM LINKED TO RAPID BRAIN GROWTH | BY DAVID R. ELTZ

All was right with beautiful blue-eyed baby Katie until the devil stole her soul one night. Her mom, Joyce Douglas, couldn't shake the bewildering, irrational feeling for years. How could she? Douglas had put Katie, then 16 months old, down for the night, and the next morning she plucked a different toddler from the crib. She was Katie in body, but *who* Katie had been, her spirit, seemed to have vanished.

Overnight Katie, who by then had mastered "mama" in her three-word vocabulary, refused her mother's attention. She no longer spoke. She was withdrawn. She seemed happy only sitting in a corner, turning the pages of a book, over and over and over; or lying in the tub, on her back, spinning in the enveloping water, tuning out everything and everyone.

After Katie finally was diagnosed with autism in mid-1996 at the age of 2-and-a-half, Douglas blamed herself. She did something wrong, she thought. And she had no idea how to help her daughter, who by then had lived in her own world as long as she'd shared her mother's. Douglas would lie awake at night, obsessing, *I must be the worst mother in the world. Please, God, make Katie well; kill me instead.* "There were so many fires. I couldn't put them out," she says.

"I couldn't fix this one."

At the time, Douglas didn't know that autism runs in families and is on the rise. (It's now diagnosed in one in 170 children worldwide. The rise is partly because high-functioning disorders like Asperger's syndrome are now classified under the broadening umbrella of autism.) And Douglas didn't know that as she was quitting her job and learning about life with an autistic child, Nancy Minshew was establishing one of the first centers of excellence in autism research, the University of Pittsburgh's Autism Research Program, funded by the National Institute of Child Health and Human Development. Nor did she know that because autism research had previously received little federal funding, Minshew, an associate professor of psychiatry and neurology, was just beginning to help change how doctors and other scientists approached the disease.

Minshew had a pretty good idea of what autism was about the first time she encountered it. Around 1985, then a young pediatric neurologist at the mental retardation center at Western Psychiatric Institute and Clinic, Minshew could hear the voices of children from the playground outside her office. Some just weren't right: flat, monotoned, seemingly emotionless. Their timbres were symptomatic of prosody disorders, such as the aphasia often experienced by stroke victims; but the voices were from children with autism. Minshew thought, *This has to be a neurological disorder of the cerebral cortex.*

Her way of thinking, however, was not in vogue. Back then, our understanding of autism, first described in 1943, had advanced little under decades of Freudian scrutiny. As recently as the 1970s, the disorder was characterized primarily as a problem of attention and sensory perception, possibly the result of amnesia. Some in the autism field adhered to the notion that bad parenting, particularly that of cold mothers, caused the disease.

Still, Minshew didn't go unnoticed. Thomas

Detre, former senior vice chancellor for health sciences, recruited the stellar scientist in 1984 from the University of Texas Southwestern Medical Center—Dallas for thinking beyond traditional psychiatric theory. Soon, Minshew was forming a concrete profile of the lack of neural function in autism. Beginning in 1988 in a variety of articles, Minshew reported that impairments associated with autism—in social skills, language, memory, and reasoning—were problems involving higher order information processing, distributed throughout the brain.

Minshew had observed that children like Katie could not learn words and colors, how to play with toys, how to tie their shoes and dress themselves, unless they were taught through strict, repetitive therapy. (And there was no guarantee of achieving the same results if the therapist or parent changed the circumstance or place in which the child was taught.) For instance, once Douglas discovered the therapy network in Pittsburgh, met Minshew and other experts, and began to understand the disease, she started to teach Katie the words "yes" and "no." Each day she set in front of Katie foods the child liked and disliked, asking again and again if she wanted them. Sometimes Katie said "yes" to the food she liked most, ice cream. Half the time she did not. It was frustrating, for both mother and daughter, but finally, after engaging in the exercise for months, Katie consistently began to answer correctly.

By 1997, Minshew described the first detailed study of neuropsychologic functioning in autism. She specifically identified a feature common to all the deficits associated with the disease: Autism, she proposed, was a disorder of the brain failing to process complex information.

Then Minshew collaborated on work showing *why* such disorders were likely to occur. In one study (*Neurology*, December 1999), Minshew and colleagues conducted MRI tests of nonmentally retarded people with autism, focusing on the amygdala (the emotional center of the brain) and the hippocampus (an area central to memory). Comparing

brain scans of people with autism and people without the disorder, the study showed that the volumes of these areas were smaller in people with autism compared with those of control subjects.

The smaller size of these brain regions indicated that the normal foundation of neural connections with the neocortex that develop in children to support memory for certain complex behaviors was not present in those with autism. Minshew and her collaborators have since made functional MRI images using saccadic paradigms that reveal, for the first time, that the neural wiring simply isn't present in the autistic people they've studied. "To be able to look at the wiring and say, 'It's not there,' I just think is phenomenal," Minshew says.

The missing neural wiring further explains a biological basis for the cognitive disabilities associated with autism. Because of the developing connections, when a 15-month-old learns the word "tree," he can point to any tree or even a hanging plant and comprehend what he means when he says it. But Minshew had seen all along that this development was

BOUND BY RULES

During a scene in *Rain Man*, Charlie Babbit (Tom Cruise) and his autistic brother, Raymond (Dustin Hoffman), drive down a highway. Charlie is driving. Raymond suddenly says, "I'm a good driver," and reaches over, taking the wheel. The car swerves. Charlie regains control of the vehicle, then screams at his brother. Raymond, agitated, starts rocking, and explains that he buys his underwear only at a certain Kmart on a certain street in Cincinnati.

He has no concept of the danger he just put them in. In his head, Raymond knows how to drive, so he tries to. When Charlie yells, Raymond rocks and talks about underwear because that's what he always does when he's upset. This is his "comfort rule." According to a recent study by Nancy Minshew, an associate professor of psychiatry and neurology at Pitt, such behavior is the result of a fundamental disconnect in Raymond's abstract reasoning abilities (*Neuropsychology*, July 2002).

People with autism can only identify concepts; they can't understand them, Minshew says. Because they can't form prototypes, they don't react well to novel situations, like being yelled at or shopping at a new store. Instead, they revert to a "rule"—such as rocking their bodies—which their brains use to comfort them. According to Minshew, Raymond doesn't have the neural wiring to solve problems; his brain selects a rule that identifies specific problems, or concepts. And if he doesn't find one for a given problem, his brain chooses his comfort rule—the Kmart rock. —DRE

not happening in autistic people. And those with autism couldn't seem to understand concepts, be they tree, God, or woman.

"They just don't get it," Minshew says.

She once heard a boy say, "I don't like Christmas. I don't like presents. I don't like surprises. I'll make a deal with you; I'll come down and open one present on Christmas morning, provided I know what's inside beforehand." He had simplified the concept of Christmas as a ritual of surprise, missing the symbolic connection to the story of the three kings who brought gifts and goodwill to a child deemed the messiah.

Minshew's latest imaging study, published jointly with researchers at the University of Washington in Seattle, shows that from birth to about age 3, the neocortical areas and the gray and white matter in the brains of autistic children grow faster than in other developing children (*Neurology*, July 2002). The abnormal growth correlates to the time when symptoms like Katie's turning inward begin to occur, usually around the age of 15 months. So when a child's brain wiring is supposed to be forging refined circuitry that allows her over a period of months to start crawling, walking, pointing, talking, and reasoning, instead there's a premature acceleration of growth that fouls up the entire network of development. The effect of the early overdevelopment is abundantly clear: It halts the maturation of neural wiring.

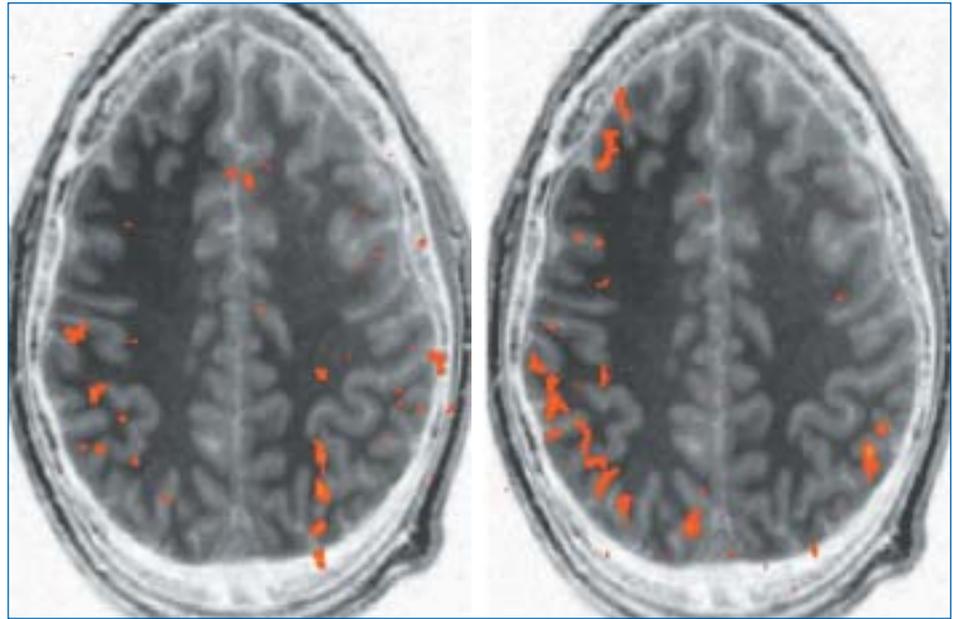
"It's like, instead of planes coming into O'Hare Airport in a very controlled, coordinated way, they all come in at once, too fast, heading for the same place . . . *Kablam!*" says Minshew. "You don't see that in any other disorder. And that's why you have autism."

Now Minshew wants to know how the brain forms prototypes. "If you don't think that's another major piece of the puzzle—" she says, trailing off.

Douglas, now an executive with the Advisory Board on Autism and Related Disorders, for which Minshew is an adviser, is working so that other mothers don't have to face devils in the night. She also plans to enroll Katie, now 8 and entering second grade, in some of Minshew's studies.

The change in their lives has settled on them, accepted if not embraced. Katie, even more beautiful now, with platinum blond hair and China-doll features, takes dance lessons without special adaptations. She's a nice kid; she doesn't complain. She'll get along okay in life, Douglas says. "I wouldn't change Katie for the world.

"I just worry a lot." ■



COURTESY SWEENEY, LUNA, MINSHEW

Pitt's Nancy Minshew recently collaborated with Beatriz Luna and the University of Illinois' John Sweeney on a functional magnetic resonance imaging (fMRI) study that offers the first visual evidence that the neural wiring of people with autism is incomplete. In the scan on the right, the areas illuminated in red in the brain of a person without the disorder indicate pronounced neural activity as the subject performs a high-level executive function. The neural activity differs in the image on the left in a scan of the brain of an autistic subject asked to perform the same task.

NO BIT PARTS

It was just another third-year rotation. Roger Jou (Class of '03) was working with Antoine Douaihy, assistant professor of psychiatry and medical director of the dual diagnosis unit at Western Psychiatric Institute and Clinic. It was just another rotation, but there was something about Douaihy. His patients had substance abuse problems and psychiatric disorders, but Douaihy never just gave them medication. He tried to change their thought processes. Maybe explain a different view to them. And he sort of did that for Jou, too. Douaihy didn't just introduce him to psychiatry, he invited him to *Don Giovanni*, Jou's first opera.

After this rotation, Jou wanted to pursue neuropsychiatry. A colleague told him that Antonio Hardan, assistant professor of psychiatry, was doing research on autism with Nancy Minshew (see p. 8), and the lab often worked with students. Jou thought it would be a good opportunity to get his feet wet.

Instead he was immersed. Jou got involved with three research projects. In two, he examined MRIs to determine how brains of autistic people appear to differ from others. He also examined the effect of an anticonvulsant on 15 adolescents and children with autism. Researchers reported that valproic acid, another anticonvulsant, reduces some autistic traits, like aggression, but it can damage the liver. Since the anticonvulsant Jou and Hardan are studying works similarly, they thought it might hold promise as a therapy. As the results of their limited trial come in, it looks as if the drug reduces hyperactivity and enhances attention. The researchers have also seen minor reductions in anxiety. Not only is Jou playing a part in potential new therapies, he'll be a coauthor on a paper the lab is submitting for publication and was chosen to present the group's work at the National Medical Students Conference on Psychiatry and Neuroscience at Columbia University.

After working with Douaihy and Hardan, Jou's thinking he'd like to pursue a clinical research career. He loves the investigative nature of the bench and still craves the human interaction of the clinic. Jou came into the lab summer nights and weekends, whenever necessary, but made it a point to patronize the arts as well. He enjoyed City Theatre's recent production of *Blackbird*, which is about a drug-addicted couple. He couldn't resist, however, diagnosing the characters' personality disorders while watching the play. —MH

LANGUAGE STUDIES

DOES DNA COME IN DIFFERENT LANGUAGES?

BY ROBIN KRIEGER MEJIA

Proteins are workhorse molecules, helping us do everything from building muscle to keeping our hormone levels in check. And when our bodies create malformed proteins, the problems can be as serious as the benefits bestowed by the regular molecule. A modified hemoglobin protein causes sickle cell anemia. Transmissible spongiform encephalopathies, of which mad cow disease is an example, are also caused by misshapen proteins.

How a protein contorts itself into a given shape is critical to good health, and yet we don't really understand why a protein forms the exact three-dimensional shape it does.

If DNA is the book of life, as is sometimes said, the truth is we are still learning to read. Even when scientists know the genetic code and resulting amino acid sequence of a protein, it's still impossible to predict exactly what its final shape will be. Now, a small group of scientists is challenging one of biology's most basic assumptions. The University of Pittsburgh's Judith Klein-Seetharaman and collaborators suggest that DNA may not be a universal code for life, in the sense that the relationship between amino acid sequence and protein shape may not be uniform across species. They speculate that the DNA of different organisms could actually be written in different languages.

Klein-Seetharaman, who joined the Department of Pharmacology in March, notes identical strings of amino acids can create custom folds, depending on the organism; alternatively, proteins with different sequences can fold into similar shapes. In fact, many very different types of organisms contain similarly shaped proteins, and these proteins sometimes have noticeable variations in their amino acid sequence. So perhaps the DNA sequences that code for specific shapes or functions are species-specific. Much the way French and English use the same alphabet to create different sentences, a bacterium and a person may use the same nucleotides to code for different things. The idea makes sense: Each species' cells provide a unique environment for the folding process.

With Raj Reddy at Carnegie Mellon University

(CMU) and others at Pitt, CMU, the Massachusetts Institute of Technology, the Canadian Research Council, and Boston University, Klein-Seetharaman hopes to learn to read various species' protein languages. The collaborators are applying statistical models used in linguistics to problems of protein folding, and they're turning heads. The group recently received \$9 million from the National Science Foundation to support the project.

The availability of large amounts of text enabled linguists to develop computer programs that analyze the structure of language, extract meaning, and make predictions. Klein-Seetharaman and collaborators hope they'll be able to use the huge amount of genetic code that has been sequenced in recent years in the same way. The goal, says Klein-Seetharaman, is to see, "Can we derive some set of rules of what constitutes the 'words' of protein sequences?"

Already the researchers have clues. Rare sequences of DNA code tend to be more important to the final shape of a protein than common ones. A similar rule applies in texts—rare words tend to define the meaning of a passage.

And what qualifies as a rare sequence varies between species, supporting the notion that we may need to learn to read a different language for each species we study.

Or perhaps scientists will just need to become accustomed to different dialects. Klein-Seetharaman wonders if interpreting genetic codes from species to species may more closely parallel making sense of, say, British versus American English, rather than translating between English and French.

Klein-Seetharaman, a native of Germany, is willing to learn whatever organic language is needed to pursue her lab work. The PhD biochemist worked with Nobel laureate H. Gobind Khorana at the Massachusetts Institute of Technology. She studies G-protein-



DAVID POHL

At the most basic level, do humans share an organic alphabet with, yet speak a language different from, other life forms?

coupled receptors, which are important to many biological pathways and may hold promise for new drug designs. Getting enough of these receptors, which come from human cells, for her studies can be difficult. "That's often the limiting step in doing the experiment that gets you the exciting results," she says. But understanding the language of various species' proteins could allow her to enhance current recombinant technology. By manipulating human gene sequences according to the language rules of bacteria, she hopes to one day employ the bacteria to manufacture experimental receptors that "fold right" for her purposes.

If Klein-Seetharaman and her colleagues are on the right track, becoming fluent in DNA languages, or dialects, could have huge medical implications. ■