EBOOKS

SCIENTIFIC AMERICAN®

UNDERSTANDING Autism

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From the Editors of Scientific American

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Letters to the Editor

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UNDERSTANDING AUTISM

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Table of Contents

Islands of Genius
by Darold A. Treffert and Gregory L. Wallace

2.3
Inside the Mind of a Savant
by Darold A. Treffert and Daniel D. Christensen

2.4
Think Better: Tips from a Savant
by Jonah Lehrer and Daniel Tammet

SECTION 3
Who's at Risk?

3.1
Why Autism Strikes More Boys Than Girls
by Janelle Weaver

3.2
Maternal Age and Autism
by Katie Moisse

3.3
The Father Factor
by Paul Raeburn

SECTION 4
Genetic Causes

4.1
Genetics Research Challenges Ideas about Mental Illness
by Jamie Horder

4.2
Gene Sleuths: Looking for Patterns
by Katherine Harmon

SECTION 7
Treatments and Therapies

Introduction: Unraveling the Mystery

The term “autism” first appeared in the early 1900s and comes from the Greek word “autos,” meaning self, used to describe conditions of social withdrawal—or the isolated self. Around 1910, a Swiss psychiatrist used the term to refer to certain symptoms of schizophrenia. It wasn’t until the 1960s that the medical community began to see autism as a separate condition. While our understanding since then has grown exponentially, research has been fraught with controversy. Autism appears to be on the rise, depending on how you define it; and, with findings that suggest that its causes are more complex than imagined, parents and parents-to-be are rightfully concerned. Will there ever be a cure? Moreover, does autism necessarily “doom” kids to lives of social isolation, or can its limitations be at least partially overcome if it’s recognized and treated earlier?

In this eBook, we’ve gathered the most current information on autism—how it’s diagnosed, who’s at risk, genetic and environmental causes, treatments and therapies. Autism is just one of three diagnoses that the DSM (Diagnostic and Statistical Manual of Mental Disorders) includes in what it collectively calls autism spectrum disorder (or ASD). The other two are Asperger’s syndrome and pervasive developmental disorder, not otherwise specified (commonly abbreviated as PDD-NOS).

In Section 1, we take a look at the symptoms, or traits, of ASD, which include three main disabilities: lack of social skills, lack of communication skills, and repetitive behaviors. While the symptoms usually don’t show up before a child is two, recognizing them earlier might help alleviate some of the developmental problems that occur later in untreated kids. In “Early Intervention,” Marissa Fessenden writes about how toddlers who received speech therapy not only improved their verbal communication skills at the time, but continued to benefit years later. This section also discusses how having autism should not overly restrict children; in fact, many autistics have unusual and outstanding talents, and several stories point out the

benefits to recognizing these and encouraging autistic kids to develop those skills.

Section 2 features a handful of excellent pieces on the phenomenon of autistic savantism—a small percentage of autistics show extraordinary mental abilities—while Section 3 examines the contributing effects of maternal and paternal age. It seems that advanced age of both Mom and Dad are correlated with autism, and other studies indicate that autism is more prevalent in boys for a reason—increased testosterone levels during fetal development.

The complicated genetic causes of autism are analyzed in Section 4. More and more studies are showing that while autism can be caused by a single mutation, many cases are caused by numerous, small changes across the genome. Twin studies have shown that epigenetics must play a role, too, and most recently, scientists have implicated copy number variations—structural changes in the genome where large swaths of genes have been duplicated or deleted, and which are not inherited from Mom or Dad. In "Autism and the Technical Mind," Simon Baron-Cohen makes a case for why autism seems to crop up more often in children of "geeks," while a series of articles looks at another piece of the puzzle—mirror neurons, and how these specialized cells might be what's behind the "theory of mind," which is lacking in autistics.

Section 5 addresses possible environmental causes. Lately, numerous studies have pointed out that these have to play some role in triggering and/or causing the disease. Section 6 takes a look at the nature of the autism "epidemic", including two important stories by Ferris Jabr—"Redefining Autism" and "By the Numbers"—discussing changes to the diagnostic criteria in the DSM-5. Finally, Section 7 addresses the most current therapies. Two companion pieces by Nancy Shute take us on a journey through the minds of parents, many of whom are desperate to help their autistic kids lead easier, productive and more fulfilling lives. While science rushes to offer better options, this eBook gives a synopsis of the state of the union—what we know and what we don't know about this challenging condition.

-Jeanene Swanson
Book Editor

SECTION 1

Diagnosing Autism

Searching for the Onset of Autism

by Mariette DiChristina

Early behavioral intervention has shown some promise as a way to help children with autism. But it's difficult to see the hallmarks of autism before two years of age with today's diagnostic criteria. Could we find other methods?

Seeking to answer that question is Jed Elison at the California Institute of Technology, who is working with Ralph Adolphs at Caltech and Joe Piven at the University of North Carolina among other colleagues around the U.S. and Canada. Elison provided some preliminary findings at the Neuromagic 2012 conference held from May 7 to 10, 2012 on San Simón, the Island of Thought, near Vigo, Spain.

Today's criteria, from the psychiatric bible called the DSM-IV, include attributes of social impairments, communication deficits, and repetitive patterns of behavior and restricted interests (either in intensity or content). "There's a biological reality," said Elison, "that you can't capture perfectly with a classification system like this." Nevertheless, there's "no question that the classification system serves a very important role in identifying kids who require specialized clinical services." Recognizing the condition early can help. "There's some evidence that early intervention alleviates" some of the behavioral challenges for these children, he added.

Elison and collaborative partners of the Infant Brain Imaging Study Network are recruiting families who have a child with autism and an infant sibling under six months of age. Because autism has a genetic component, they employ what they call the "high-risk-sibling" strategy to prospectively characterize the earliest markers of autism. They conduct longitudinal studies with the younger siblings—making an assessment of these infants at

six months, 12 months and 24 months. Ideally, they will define the onset of symptoms and its developmental course.

In addition to assessing behavior, the researchers are also examining brain development, specifically the development of white matter microstructure, using diffusion tensor imaging. White matter includes part of the neuron called the axon that is responsible for transmitting electrical signals throughout the brain. “Cognitive and social-cognitive development requires efficient information processing, which consequently requires efficient signal transmission,” said Elison. White matter is not developing the same in infants who go to on develop autism, and a recent study suggests that these differences may appear as early as six months.

What about behavioral differences? The researchers are also very interested in subtle attentional and visual-orienting patterns that may be different very early in life. These behaviors are very important for subsequent social-cognitive development and might be amenable to targeted intervention.

Elison highlighted that many of the scientific themes relevant to magic or sleights of hand, including attentional orienting and joint attention, making eye contact, perceiving biological motion, and theory of mind (that is, making inferences about the mental or emotional state of another individual) are especially important themes for autism researchers. “Deficits in any of these areas could make individuals with autism less susceptible to magic,” said Elison.

Drawing a connection to the theme of the conference in his conclusion, Elison questioned whether susceptibility to magic or sleights of hand might also vary with development. Several of the attending magicians pointed out that performers must tailor their approach for different audiences and that very young children present unique challenges, because they may still engage in “magical thinking”—believing in unseen causes—and because their cultural knowledge and social-cognitive skills aren’t yet fully formed.

--Originally published: Scientific American online, May 15, 2012.

Mixed Signals: Social Intuition Goes Awry

by Bruce M. Hood

At the end of *Casablanca*, when Humphrey Bogart finally tells Ingrid Bergman to get on the plane back to her husband, the young mother watching the afternoon TV movie sheds a tear. Instinctively, her two-year-old tries to comfort her by offering his teddy bear to her. Both the mother and child are displaying intuitive awareness of others' mental states and emotions.

Social intuition comes naturally to most of us, but not all. Autism is a developmental disorder that affects around one in 500 individuals (although this figure appears to be on the rise and depends largely on how you define it). In general, autism can be thought of as a disorder with three major disabilities: a profound lack of social skills, poor communication and repetitive behaviors. It is regarded as a spectrum disorder because it covers a broad range and individuals vary in the extent to which they are affected. All those with the disorder share problems with social intuition, however.

Individuals with autism have a problem with socializing because they lack a repertoire of developmental social skills that enable humans to become expert mind readers. Not mind reading in the way Spock from *Star Trek* could do, but rather the capacity to infer what others are thinking in different circumstances. Over the course of early childhood typical youngsters increasingly become more sophisticated at understanding that other people have mental states that motivate their behavior. For example, if you leave your bag in the office, then I know that you believe it to be there even though the cleaner has handed it in to lost and found. I can understand you hold a false belief. This ability is called having a "theory of mind," and it is a natural ability in typical children. By the time the average child is around four years old, he or she interprets other people as being goal-directed and purposeful and as having preferences, desires, beliefs and even

misconceptions. Without this repertoire of social skills, a human is effectively mind blind—unable to understand what others are thinking and why they do the things they do.

Not only do typical children become intuitive mind readers, but they also become agony aunts as well. They begin to understand others' sadness, joy, disappointment and jealousy as emotional correlates of the behaviors that make humans do the things they do. Again, by four years of age, children have become expert at working the social arena. They will copy, imitate, mimic and generally empathize with others, thereby signaling that they, too, are part of the social circles that we all must join to become members of the tribe. They share the same socially contagious behaviors of crying, yawning, smiling, laughing and pulling disgusted faces that signal they share the same emotional experiences of those around them.

Baffled by Behavior

No wonder individuals with autism find direct social interaction frightening. If you cannot figure out other people, then such interaction must be intensely baffling and stressful. They often do not like direct eye contact, do not prefer to look at faces compared with other things, do not copy, do not mimic, do not yawn when others yawn or retch when others retch, or laugh or join in with the rich tapestry of social signals we share as a species. This inability may be why individuals with autism generally withdraw into activities that do not involve other people.

The incidence of autism is higher in identical twins, who share nearly 100 percent of their genes, compared with fraternal twins, who share only 50 percent, which indicates that there is a genetic component to the disorder. Also, the greater incidence in males compared with females strongly implicates a biological basis. To date, tantalizing evidence exists based on brain-imaging studies that regions in the prefrontal cortex—most notably the frontoinsular and the anterior cingulate cortex, which are activated by social interaction in normal individuals—are relatively inactive in individuals with autism. Autopsy data also indicate that the frontoinsular and the anterior cingulate cortex structures are abnormal in autism disorder.

John Allman of the California Institute of Technology thinks that much of this social deficit may come down to a lack of a special class of spindle

neurons, sometimes called Von Economo neurons after their discoverer, who made the observation in 1925. Spindle neurons consist of a very large bipolar neuron that is found only in the frontoinsular and anterior cingulate cortex and thought to provide the interconnection between brain regions that are activated by social learning. This location may explain why spindle neurons have been found solely in species that are particularly social, including all the great apes, elephants, and whales and dolphins.

Humans have the biggest population of spindle neurons located in the frontoinsular and anterior cingulate cortex areas—the same regions that may be disrupted in autism spectrum disorder. Spindle neurons are thought to work by keeping track of social experiences, leading to a rapid appreciation of similar situations in the future. They provide the basis of intuitive social learning when we watch and copy others. It may be no coincidence that the density of spindle neurons in these social regions increases from infancy to reach adult levels somewhere around the fourth birthday in typical children, the watershed when most child development experts agree that there is noticeable change in social intuition skills. This may also explain why individuals with autism, who have disrupted frontoinsular and anterior cingulate cortical areas, have difficulty working out what the rest of us just know without having to think very much.

--Originally published: Scientific American online, March 7, 2011.

Extraordinary Perception

by Wray Herbert

When Pulitzer Prize–winning music critic Tim Page was in second grade, he and his classmates went on a field trip to Boston. He later wrote about the experience as a class assignment, and what follows is an excerpt:

"Well, we went to Boston, Massachusetts, through the town of Warrenville, Connecticut, on Route 44A. It was very pretty, and there was a church that reminded me of pictures of Russia from our book that is published by Time-Life. We arrived in Boston at 9:17. At 11 we went on a big tour of Boston on Gray Line 43, made by the Superior Bus Company like School Bus Six, which goes down Hunting Lodge Road where Maria lives and then on to Separatist Road and then to South Eagleville before it comes to our school. We saw lots of good things like the Boston Massacre site. The tour ended at 1:05. Before I knew, it we were going home. We went through Warrenville again, but it was too dark to see much. A few days later it was Easter. We got a cuckoo clock."

Page received an unsatisfactory grade on his essay. What's more, his irate teacher scrawled in red across the top of the essay: "See me!" As he recalls in his memoir *Parallel Play* (Doubleday, 2009), such incidents were not uncommon in his childhood, and he knew why he was being scolded: "I had noticed the wrong things."

A Question of Focus

The subtitle of Page's memoir is *Growing Up with Undiagnosed Asperger's*, and indeed Page didn't learn until age 45 that he suffers from what is called autism spectrum disorder, or ASD. ASD is usually defined by impairments in social interaction and communication, but many people with autism and Asperger's syndrome (in which symptoms are milder) also tend

to fixate on and remember seemingly irrelevant information in their world. Their attention seems to be awry, or to use Page's words, they notice the wrong things.

But why? What's going on in the autistic mind that makes the details of bus routes infinitely fascinating? Why are people like Page so easily distracted from the main act? Psychologists at University College London think that it might be a mistake to consider such distractibility as simply a deficit. To the contrary, Anna Remington and John Swettenham and their colleagues speculate that people with ASD might have a *greater* than normal capacity for perception, so that what appears as irrelevant distraction is really a cognitive bonus. They decided to test the idea in the lab.

Selective Attention

Remington and Swettenham studied a group of people with autism spectrum disorder, most of whom had Asperger's, along with normal controls. They asked all the subjects to look at a computer screen, which displayed various combinations of letters and dots forming a ring. The subjects were instructed to very rapidly determine if the letters N or X were present in the ring and then hit the corresponding key on the keyboard. Some of the circles—those with more letters—were more difficult to process than others. There were also other letters floating outside the circle, but the subjects were specifically instructed to ignore those letters. Those floating letters were the laboratory equivalent of an irrelevant distraction in the real world.

The psychologists were measuring perceptual capacity—that is why they varied the complexity of the task. As expected, everyone was slower at the task when the ring contained more letters. The researchers were also measuring distractibility. When a letter outside the ring was one of the target letters (N or X), the subjects often took a longer time finding the N or X in the ring—indicating they were distracted by the presence of a target letter in the location that they were supposed to ignore.

The psychologists reasoned that as long as the subjects' total perceptual capacity was not exhausted, they would also process the irrelevant, distracting letters within their visual field. Once they had surpassed their

perceptual capacity—once the ring of letters was sufficiently complex—irrelevant processing would stop. So if ASD subjects in fact have greater processing capacity, then they should process more distracting information even as the main task becomes increasingly complex.

In an experiment, a ring of dots and letters appeared on a screen, and subjects had to indicate as quickly as possible whether the ring contained an N or an X, while ignoring the extra letter off to the side. People with autism spectrum disorder were equally as fast and accurate as the controls, and they continued to notice the extraneous letter as the task became more complex (with more letters appearing in the ring), suggesting that they have better than normal perceptual abilities.

Illustrated by Anna Remington

Seeing the Bigger Picture

And that is exactly what they found. As the researchers reported online in the journal *Psychological Science*, although there was no difference among subjects in either reaction time or accuracy on the main task, those with ASD processed the irrelevant letters while solving much more complex problems. Their reaction times indicated that they were still noticing when the extra letter was an N or X, while also finding the target letter in the ring with the same speed and accuracy as the normal controls. Put another way, they weren't ignoring the main task, nor were they distracted away from it. Instead they were completing their work and moving on, using their untapped capacity.

But here's the rub. Although this increased distractibility may be a talent rather than a deficit, the psychologists point out, it nonetheless can have detrimental consequences in real-life situations. Just ask Tim Page about his uncanny facility for bus routes.

--Originally published: Scientific American Mind 21, 68-69.
(March/April 2010)

Early Intervention: Speech Therapy

by Marissa Fessenden

Autistic children struggle with many obstacles, including learning to speak. And, experts have noted, if these children learn verbal skills by age five, they tend to become happier and higher-functioning adults than do their nonverbal peers. Thirty years ago, psychiatrists expected only half of all autistic children would gain speaking abilities. Recent studies, however, indicate that as many as 80 percent of children with autism can learn to talk. One such study in 2006 showed that toddlers who received intensive therapy aimed at developing foundational oral language skills made significant gains in their ability to communicate verbally. Now researchers have followed up with a number of those kids and found that most of them continued to reap the benefits of that therapy years after it had ended.

Several early behaviors build a foundation for language. These abilities have also been linked to whether a child can anticipate another person's mental state and use that understanding to explain and predict behavior. Developing this "theory of mind" may be a central difficulty for children with autism. Kasari's team targeted two of the early behaviors in their work: The first is the ability to engage in symbolic play, in which one object represents another—a child pretending a doll is his parent, for instance. The second is joint attention, wherein a child divides focus between an object and another person. This behavior can be thought of as "sharing looks." For example, when a child points to show a playmate a toy train, she looks at the moving train and checks to see if her playmate is engaged.

In the initial study, Connie Kasari of the University of California, Los Angeles, and her colleagues evaluated 58 children between three and four years old in a randomized controlled study. The children played with trained graduate students for 30 minutes each day over a period of five to six weeks. The time-intensive interventions focused on either symbolic play

or joint attention. A third group, serving as a control, participated in playtime but was not directed to complete tasks and goals.

Independent clinical testers assessed the children before and after the intervention. They measured language and cognitive skills with standard tests, evaluated play level and diversity, and interaction with a caregiver. The initial study, published in 2006, showed that the joint-attention group was better at showing and pointing behavior whereas the symbolic play group showed more symbolic behavior, both in terms of play level and diversity. Twelve months after the therapy period, Kasari's group assessed the kids' language skills. On a standard language test, the two intervention groups showed spoken language improvement that corresponded to 15 to 17 months of development; the control group had only made a nine-month gain during the same period. Younger children and children at the lowest language levels prior to the intervention made the largest improvements. Kasari was initially surprised the groups showed such progress. The most important aspect of both interventions, she says, was "engaging the child for periods of time with a social partner."

In the new study, Kasari's team revisited 40 of the children five years later. The researchers found that 80 percent of them, who were by then eight to nine years old, still had "useful, functional spoken language." A small number of children remained nonverbal, which Kasari says is typical for studies of children with autism. Some children do not seem to be able to learn useful language by age five, but studies suggest it is possible to acquire language later. The new studies show a method for teaching preschool-aged children basic skills that will help them develop language by five and continue to make improvements years later. The researchers detailed their findings in the May 2012 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*.

Previous studies have targeted skills important to language development, but many only looked at small groups of children or infrequent treatment sessions, Kasari notes. Understanding what makes a treatment successful or not is vital. "We need to distill down the active ingredients in early intervention," she says, "then take these elements and match them to programs."

This kind of long-term follow-up is rare. “The study is important in terms of raising expectations of what can be accomplished, and in raising awareness of how much work it takes,” says Sally J. Rogers, a psychiatry professor with the MIND Institute at the University of California, Davis. Rogers, who was not involved in the research, emphasized that because the subjects were very young, the study builds on evidence indicating that the earlier the intervention the better—and children even younger than the toddlers in the original study could benefit. This has important pubic policy implications, she says, because there is little funding for children younger than three.

Finding a one-size-fits-all approach to helping autistic kids talk may be tricky, however: Autism affects each child differently, Rogers observes, and even the best interventions will have varied outcomes.

--Originally published: Scientific American online, July 17, 2012.

The Hidden Potential of Autistic Kids

by Rose Eveleth

When I was in fifth grade, my brother Alex started correcting my homework. This would not have been weird, except that he was in kindergarten—and autistic. His disorder, characterized by repetitive behaviors and difficulty with social interactions and communication, made it hard for him to listen to his teachers. He was often kicked out of class for not being able to sit for more than a few seconds at a time. Even now, almost 15 years later, he can still barely scratch out his name. But he could look at my page of neatly written words or math problems and pick out which ones were wrong.

Many researchers are starting to rethink how much we really know about autistic people and their abilities. These researchers are coming to the conclusion that we might be underestimating what they are capable of contributing to society. Autism is a spectrum disease with two very different ends. At one extreme are “high functioning” people who often hold jobs and keep friends and can get along well in the world. At the other, “low functioning” side are people who cannot operate on their own. Many of them are diagnosed with mental retardation and have to be kept under constant care. But these diagnoses focus on what autistic people cannot do. Now a growing number of scientists are turning that around to look at what autistic people are good at.

Researchers have long considered the majority of those affected by autism to be mentally retarded. Although the numbers cited vary, they generally fall between 70 to 80 percent of the affected population. But when Meredyth Edelson, a researcher at Willamette University, went looking for the source of those statistics, she was surprised that she could not find anything conclusive. Many of the conclusions were based on intelligence

tests that tend to overestimate disability in autistic people. “Our knowledge is based on pretty bad data,” she says.

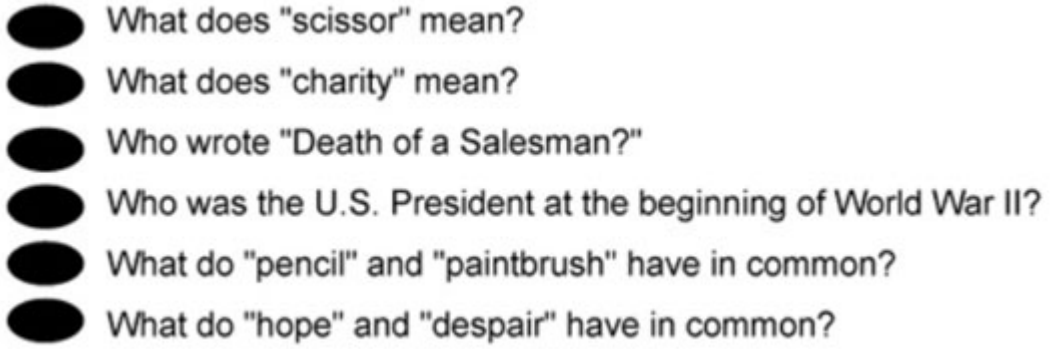
This hidden potential was recently acknowledged by Laurent Mottron, a psychiatrist at the University of Montreal. In an article in *Nature*, he recounts his own experience working with high-functioning autistic people in his lab, which showed him the power of the autistic brain rather than its limitations. Mottron concludes that perhaps autism is not really a disease at all—that it is perhaps just a different way of looking at the world that should be celebrated rather than viewed as pathology.

Having grown up with two autistic brothers—Alex, four years younger than I, and Decker, who is eight years younger—Mottron’s conclusion rings true. As I watched them move through the public schools, it became very clear that there was a big difference between what teachers expected of them and what they could do. Of course, their autism hindered them in some ways—which often made school difficult—yet it also seemed to give them fresh and useful ways of seeing the world—which often don’t show up in the standard intelligence tests.

That is because testing for intelligence in autistic people is hard. The average person can sit down and take a verbally administered, timed test without too many problems. But for an autistic person with limited language capability, who might be easily distracted by sensory information, this task is very hard. The most commonly administered intelligence test, the Wechsler Intelligence Scale for Children (WISC) almost seems designed to flunk an autistic person: it is a completely verbal, timed test that relies heavily on cultural and social knowledge. It asks questions like “What is the thing to do if you find an envelope in the street that is sealed, addressed and has a new stamp on it?” and “What is the thing to do when you cut your finger?”

These more open-ended questions are similar* to those in the Wechsler Intelligence Scale test.
These questions asked orally, are much harder for autistic children to answer.

*To preserve the integrity of the test, these images are not exact replicas of questions from the Wechsler exam.



This year Decker was kicked out of a test much like WISC. Every three years, as he moves through the public school system, his progress is re-evaluated as a part of his Individualized Education Plan—a set of guidelines designed to help people with disabilities reach their educational goal.

This year, as part of the test, the woman delivering the questions asked him, "You find out someone is getting married. What is an appropriate question to ask them?"

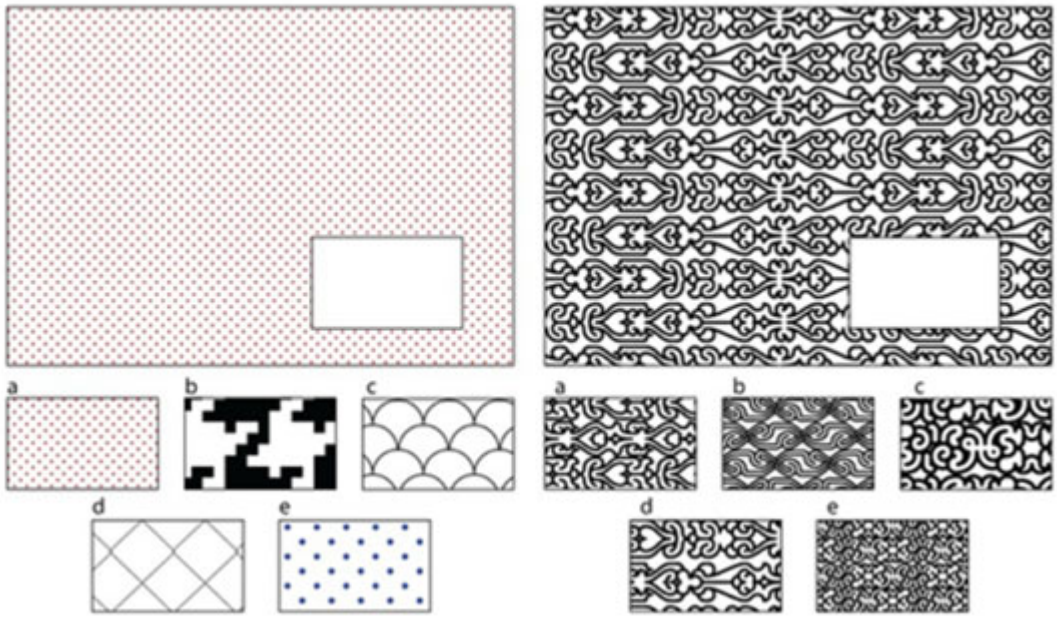
My brother's answer: "What kind of cake are you having?"

The proctor shook her head. No, she said, that's not a correct answer. Try again. He furrowed his brow in the way we have all learned to be wary of—it is the face that happens before he starts to shut down—and said, "I don't have another question. That's what I would ask." And that was that. He would not provide her another question, and she would not move on without one. He failed that question and never finished the test.

A test does not have to be like this. Other measures, like Raven's Progressive Matrices or the Test of Nonverbal Intelligence (TONI), avoid these behavioral and language difficulties. They ask children to complete designs and patterns, with mostly nonverbal instructions. And yet they often are not used.

These pattern recognition questions are similar* to those that someone taking the Raven Progressive Metrics Test would have to answer. Test takers have 40 minutes to complete 60 such questions. Can you arrive at the answer? (Left: a, Right: d).

*To preserve the integrity of the test, these images are not exact replicas of questions from the Raven exam.



The average child will score around the same percentile for all these tests, both verbal and nonverbal. But an autistic child will not. Isabelle Soulieres, a researcher at Harvard University, gave a group of autistics both WISC and the Raven test to measure the difference between the two groups. Although she expected a difference, she was surprised at just how big the gap was. On average, autistic students performed 30 percentile points better on the Raven test than on WISC. Some kids jumped 70 percentile points. "Depending on which test you use, you get a very different picture of the potential of the kids," she says. Other studies have confirmed this gap, although they found a smaller jump between tests.

The "high functioning" autistic children, with the least severe version of the disability, were not the only ones to score higher. Soulieres conducted a study at a school for autistic children considered intellectually disabled. Using the Raven test, she found that about half of them scored in the average range for the general population. "Many of those who are considered low-functioning—if you give them other intelligence tests, you will find hidden potential," she says. "They can solve really complex problems if you give them material that they can optimally process."

What this means, she says, is that schools are underestimating the abilities of autistic children all across the spectrum. The widespread use of the

WISC in schools has helped set expectations of autistic kids too low—assuming that they will not be able to learn the same things that the average child can. Based on the test results, people come to the conclusion that autistic children cannot learn, when perhaps they do not learn the same way other people do.

The hidden potential of autistic people seems to fall in common areas—tasks that involve pattern recognition, logical reasoning and picking out irregularities in data or arguments. Soulieres describes working with an autistic woman in her lab who can pick out the slightest flaws in logic. “At first, we argue with her,” Soulieres laughs, “but almost each time, she’s right, and we’re wrong.”

Recognizing these talents, rather than pushing them aside to focus on the drawbacks of autism, could benefit not just autistic people, but everyone else as well. Mottron chronicles how much better his science got by working with his autistic lab partner. I got far higher marks on my homework than I would have without Alex, even though his corrections were sometimes infuriating. And many think their potential extends beyond science to all professions, if given the right chances.

Just because a test says someone has potential, that does not mean it is easy to realize. My brother Decker’s teachers are convinced—and the tests confirm—that he has hidden potential. But in class, he often falls behind when trying to listen to instructions and gets frustrated when trying to catch up. “It doesn’t mean that it’s easy for them in everyday life, or that it’s easy for their parents or teachers,” Soulieres says. “But it shows that they have this reasoning potential, and maybe we have to start teaching them differently and stop making the assumption that they won’t learn.”

More and more people are starting to wonder what gems might lie hidden in the autistic brain. And if my brothers are any indication, if we keep looking, we will find them.

--Originally published: Scientific American online, November 30, 2011.

SECTION 2

Autistic Savants

A Transparent Enigma

by Madhusree Mukerjee

At 7 A.M. in a nondescript apartment in Hollywood, Calif., Tito Mukhopadhyay is hunched over his breakfast bowl, spooning milk and cereal into his mouth. His eyes flit around and his hand shakes. When he is finished, his mother, Soma Mukhopadhyay, pulls him off the chair and manhandles him into the shower, dashing in from time to time when he yells for assistance. Finally Tito emerges, dressed, to bend over Soma's tiny frame so she can comb his thick black hair. Abruptly he charges out the door and half-walks, half-runs down the hallways until he is outside. Golden sunshine on his face, he flaps and spins his hands with absorption.

Later I ask him: "Would you like to be normal?" In rough but legible script, he scrawls: "Why should I be Dick and not Tito?"

At 15, Tito displays all the signs of classic "low-functioning" autism. Years ago in India, a doctor told his parents that the boy could not understand what was happening around him. "'I understand very well,' said the spirit in the boy," he related in *The Mind Tree*, a book he penned between the ages of eight and 12. (Tito typically refers to himself in the third person.) Indeed, he wrote about having two distinct selves: a "thinking self—which was filled with learnings and feelings" and an "acting self" that was "weird and full of actions" occurring independently of his thoughts.

Autistic intelligence varies widely, from severe retardation to savant syndrome. Tito combines extreme neurological disability with an ability to write—and so can tell the world of a bizarre internal condition.

Wanting to talk, Tito once stood before a mirror pleading for his mouth to move. "All his image did was stare back," he wrote. Parents often take an autistic's unresponsiveness to be stubbornness; Tito's writings dispel that

notion. He has trouble moving his muscles at will, and now he speaks in barely intelligible grunts that his mother must often translate. He "saw himself as a hand or as a leg and would turn around to assemble his parts to the whole," Tito explains of another typical activity, rotation. Spinning his hands helps him to become more aware of bodily sensations.

Conflicting and overwhelming sensory input seems to beset autistics, who respond by shutting off one or another sense at a time, notes neurologist Yorram S. Bonneh of the Weizmann Institute of Science in Rehovot, Israel. Tito, for instance, routinely fails to hear and see someone at the same time and so avoids eye contact—a defining characteristic of autism. In 2001 Bonneh and others found that if Tito was presented with a bright red flash and a simultaneous voice saying "blue," he responded, "I saw blue" or "I am confused." He turned out to have a hierarchy of senses: hearing overrode vision, and both extinguished touch. Sometimes he could feel nothing at all with his fingers. Such startling effects as he displayed had hitherto remained hidden, for a low-functioning autistic does not normally cooperate with experimenters.

All the interfering signals lead to "a fragmented world perceived through isolated sense organs," Tito has written. He comprehends the world by reading or when his mother reads aloud to him—physics, biology, poetry. "It is because of my learning of books, that I could tell that the environment was made of trees and air, living and nonliving, this and that," he wrote.

Born in India, Tito learned to communicate through his mother's unrelenting efforts. Living alone with her son in Indian cities that boasted autism specialists (Tito's father worked in a distant town), Soma Mukhopadhyay, who is trained as a chemist and educator, tried every imaginable trick to get her strange child to respond. When one expert said Tito was retarded, she cried bitter tears and went to a different doctor. Her first success with Tito came after she found him staring at a calendar; she pointed at the numbers, saying them out loud. In one heady week before the age of four, Tito learned to add and subtract numbers and compose words by pointing to numbers and letters written on a board.

Because experts suspected Soma to be cueing Tito, she taught him to write. She tied a pencil to his hand and forced it to trace the alphabet until he could do it alone. Still, she observes him with profound intensity and

snaps her fingers the moment Tito's thoughts stray—which is all the time during my visit. He seems to be beset by random neural firings. If she didn't intervene, Soma explains, he would write words from a different sentence in the middle of one he had already started.

"The fidelity of the method will be very, very difficult to replicate," predicts Richard Mills of the National Autistic Society in London, who met Tito in Bangalore and introduced him to the Western world. Soma now works with several children in Los Angeles, using her so-called rapid prompting method, reportedly with spectacular success. She communicates using whichever sensory channel is open in a child, and he or she responds by pointing to letters or pictures. Often she enables the pointing by touching a hand or shoulder (according to Tito, touching allows a child to feel the body part and so control it), and she cuts off stray thoughts. Unfortunately, Mills points out, autism is bedeviled by claims of treatments that eventually evaporate, and Soma's method has yet to be scientifically validated.

Even if they can communicate, few autistics are likely to reveal personae anywhere as complex as Tito's. One day, he wrote, things become transparent: "A transparent room, then a transparent ceiling . . . and a transparent reflection of myself showing only the rainbow colours of my heart." Experts long believed that autistics lack imagination and introspection. Lorna Wing, also at the National Autistic Society, explains that these qualities are in fact present but impaired—autistics tend to be uninterested in and unempathetic with others.

A popular theory, championed by Uta Frith of the Medical Research Council in London, holds that autistics lack an intuitive "theory of mind"—that is, they cannot automatically perceive what someone else is thinking. Not "getting" deception or nuance, they are straitlaced and humorless. Temple Grandin of the University of Illinois, for instance, is a high-functioning autistic whose phenomenal ability to visualize and to empathize with cows allowed her to design more humane slaughterhouses. In her fascinating book *Thinking in Pictures*, Grandin notes that she can comprehend others and even deceive people. Nevertheless, her understanding comes with sustained intellectual effort: she studies people as primatologists study chimpanzees.

Grandin's book reads as if she were part robot—Tito's, on the other hand, reads as if he were an unusually creative and perceptive child, albeit one to whom very odd things happen. The "theory of mind" idea fails to apply to Tito, states Michael Merzenich of the University of California at San Francisco. Wing counters that those who use language with ease, as Tito does, indeed perform well on tests of the theory of mind. But even Tito, she argues, has trouble applying his theory of mind to behave appropriately in complex social situations.

During an evening drive to the beach, the conversation somehow turns to Darwin. "You should say autistics are the most evolved of humans," Tito opines. "It is a recent mutation." I protest, startled at such a claim. "Just making fun. Can't I make fun?" he replies abruptly—it was I who didn't get it. After a while he adds that in my story I should "put the fun part, because it tells [about] the theory of mind."

The beach is chilly, breezy and dark, but Tito strides ahead. After calling to him to stop, his mother rolls up his trouser legs. He enjoys "the water, the sound and the air" at the beach, he later explains. "I always like the air." Facing the vast black ocean, Tito stands alone, bare toes dipped into the sand and surf, hands spinning and flapping.

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Islands of Genius

by Darold A. Treffert and Gregory L. Wallace

Leslie Lemke is a musical virtuoso. At the age of 14 he played, flawlessly and without hesitation, Tchaikovsky's Piano Concerto No. 1 after hearing it for the first time while listening to a television movie several hours earlier. Lemke had never had a piano lesson—and he still has not had one. He is blind and developmentally disabled, and he has cerebral palsy. Lemke plays and sings thousands of pieces at concerts in the U.S. and abroad, and he improvises and composes as well.

Richard Wawro's artwork is internationally renowned, collected by Margaret Thatcher and Pope John Paul II, among others. A London art professor was "thunderstruck" by the oil crayon drawings that Wawro did as a child, describing them as an "incredible phenomenon rendered with the precision of a mechanic and the vision of a poet." Wawro, who lives in Scotland, is autistic.

Kim Peek is a walking encyclopedia. He has memorized more than 7,600 books. He can recite the highways that go to each American city, town or county, along with the area and zip codes, television stations and telephone networks that serve them. If you tell him your date of birth, he can tell you what day of the week it fell on and what day of the week it will be when you turn 65 "and can retire." Peek can identify most classical compositions and knows the date the music was published or first performed as well as the composer's birthplace and dates of birth and death. He is also developmentally disabled and depends on his father for many of his basic daily needs. His abilities provided the inspiration for the character Raymond Babbitt, whom Dustin Hoffman played in the 1988 movie *Rain Man*.

Lemke, Wawro and Peek all have savant syndrome, an uncommon but spectacular condition in which people with various developmental disabilities, including autism, possess astonishing islands of ability and brilliance that stand in jarring juxtaposition to their overall mental handicap. Savant syndrome is seen in about one in 10 people with autism and in approximately one in 2,000 people with brain damage or mental retardation. Of the known savants, at least half are autistic and the remainder have some other kind of developmental disorder.

Much remains mysterious about savant syndrome. Nevertheless, advances in brain imaging are permitting a more complete view of the condition, and a long-standing theory of left hemispheric damage has found support in these imaging studies. In addition, new reports of the sudden appearance of savant syndrome in people with certain forms of dementia have raised the intriguing possibility that some aspects of such genius lie dormant in all of us.

Down's Definition

Descriptions of savant syndrome appear in the scientific literature as early as 1789. Benjamin Rush, the "father of American psychiatry," described the lightning-quick calculating ability of Thomas Fuller, who understood little math more complex than counting. When Fuller was asked how many seconds a man had lived by the time he was 70 years, 17 days and 12 hours old, he gave the correct answer of 2,210,500,800 a minute and a half later—and he had taken into account 17 leap years.

It was not until 1887, however, that the remarkable coexistence of deficiency and superiority was more completely laid out. That year J. Langdon Down, who is best known for having identified Down syndrome, described 10 people with savant syndrome. He had met these fascinating individuals during his 30 years as superintendent of the Earlswood Asylum in London. He coined the now discarded term "idiot savant," using the then accepted classification of an idiot as someone with an IQ of less than 25, combined with a derivative of the French word savoir, which means "to know."

More than a century has passed since Down's original description. Today we know a great deal more about this perplexing set of abilities from the

100 or so cases described in the scientific literature. It is now clear that savant syndrome generally occurs in people with IQs between 40 and 70—although it can occur in some with IQs as high as 114. It disproportionately affects males, with four to six male savants for every one female. And it can be congenital or acquired later in life following disease (such as encephalitis) or brain injury.

Narrow Repertoire

The skills that savant syndrome gives rise to are limited for the most part, and they tend to be based in the right hemisphere. That is, they are predominantly nonsymbolic, artistic, visual and motor. They include music, art, mathematics, forms of calculating and an assortment of other abilities, such as mechanical aptitude or spatial skills. In contrast, left hemisphere skills are more sequential, logical and symbolic; they include language and speech specialization.

Most musical savants have perfect pitch and perform with amazing ease, most often on the piano. Some are able to create complex compositions. And for some reason, musical genius often seems to accompany blindness and mental retardation, as it does for Lemke. One of the most famous savants was “Blind Tom” Bethune, who lived from 1849 to 1908. In his time, he was referred to as “the eighth wonder of the world.” Although he could speak fewer than 100 words, he could play beautifully more than 7,000 pieces on the piano, including many of his own works. (Some of his compositions were recorded by musician John Davis and released on CD.)

For their part, savant visual artists use a variety of media, although they most frequently express themselves through drawing and sculpture. Artistic savant Alonzo Clemons, for example, can see a fleeting image of an animal on a television screen and in less than 20 minutes sculpt a perfect replica of that animal. His wax model will be correct in every detail, every fiber and muscle and proportion.

Mathematical savants calculate incredibly rapidly and often have a particular facility with prime numbers. Curiously, the obscure skill of calendar calculating that Peek demonstrates is not confined to mathematical savants; it seems to coexist with many different skills.

Several other abilities appear less frequently. A rare savant may have extensive language ability—that is, the capacity to memorize many languages but not to understand them. Other unusual traits include heightened olfactory, tactile and visual sensitivity; outstanding knowledge in fields such as history, neurophysiology, statistics or navigation; and spatial ability. For instance, a musical and blind savant named Ellen can navigate in thick forests or other unfamiliar spaces without running into objects. Ellen also has a perfect appreciation of passing time despite the fact that she doesn't have access to a watch or clock, even in Braille. This ability was discovered one day when her mother let her listen to the "time lady" on the telephone. After listening for a short while to the recorded voice intone the hour and seconds, Ellen apparently set her own internal clock. Since then, she has been able to tell what time it is to the second, no matter the season.

Savant skills are always linked to a remarkable memory. This memory is deep, focused and based on habitual recitation. But it entails little understanding of what is being described. Some early observers aptly called this "memory without reckoning." Down himself used the phrase "verbal adhesion" to characterize it. One of his patients was a boy who had read the six-volume *History of the Decline and Fall of the Roman Empire*, by Edward Gibbon, and could recite it back word for word, although he did so without any comprehension.

Although they share many talents, including memory, savants vary enormously in their levels of ability. So-called splinter-skill savants have a preoccupation and mild expertise with, say, the memorization of sports trivia and license plate numbers. Talented savants have musical or artistic gifts that are conspicuously above what would be expected of someone with their handicaps. And prodigious savants are those very uncommon people whose abilities are so advanced that they would be distinctive even if they were to occur in a normal person. Probably fewer than 50 prodigious savants are alive at the moment.

Whatever their talents, savants usually maintain them over the course of their life. With continued use, the abilities are sustained and sometimes even improve. And in almost all cases, there is no dreaded trade-off of these wonderful abilities with the acquisition of language, socialization or daily

living skills. Instead the talents often help savants to establish some kind of normal routine or way of life.

Looking to the Left Hemisphere

Although specialists today are better able to characterize the talents of savants, no overarching theory can describe exactly how or why savants do what they do. The most powerful explanation suggests that some injury to the left brain causes the right brain to compensate for the loss. The evidence for this idea has been building for several decades. A 1975 pneumoencephalogram study found left hemispheric damage in 15 of 17 autistic patients; four of them had savant skills. (A pneumoencephalogram was an early and painful imaging technique during which a physician would inject air into a patient's spinal fluid and then x-ray the brain to determine where the air traveled. It is no longer used.)

A dramatic study published by T. L. Brink in 1980 lent further credence to the possibility that changes to the left hemisphere were important to savant syndrome. Brink, a psychologist at Crafton Hills College in California, described a normal nine-year-old boy who had become mute, deaf and paralyzed on the right side when a bullet damaged his left hemisphere. After the accident, unusual savant mechanical skills emerged. He was able to repair multigeared bicycles and to design contraptions, such as a punching bag that would weave and bob like a real opponent.

The findings of Bernard Rimland of the Autism Research Institute in San Diego support this idea as well. Rimland maintains the largest database in the world on people with autism; he has information on more than 34,000 individuals. He has observed that the savant skills most often present in autistic people are those associated with right hemisphere functions and the most deficient abilities are associated with left hemisphere functions.

In the late 1980s Norman Geschwind and Albert M. Galaburda of Harvard University offered an explanation for some causes of left hemispheric damage—and for the higher number of male savants. In their book *Cerebral Lateralization*, the two neurologists point out that the left hemisphere of the brain normally completes its development later than the right and is therefore subject to prenatal influences—some of them detrimental—for a longer period. In the male fetus, circulating testosterone

can act as one of these detrimental influences by slowing growth and impairing neuronal function in the more vulnerable left hemisphere. As a result, the right brain often compensates, becoming larger and more dominant in males. The greater male-to-female ratio is seen not just in savant syndrome but in other forms of central nervous system dysfunction, such as dyslexia, delayed speech, stuttering, hyperactivity and autism.

Newly Savant

In recent years, more data have emerged to support the left hemisphere hypothesis. In 1998 Bruce L. Miller of the University of California at San Francisco examined five elderly patients with frontotemporal dementia (FTD), one form of presenile dementia. These patients had developed artistic skills with the onset and progression of their dementia. They were able to make meticulous copies of artworks and to paint beautifully. Consistent with that in savants, the creativity in these five individuals was visual, not verbal. Single-photon-emission computed tomography (SPECT) showed that injury was predominantly on the left side of the brain. Miller examined seven other patients who had developed musical or artistic ability after the appearance of FTD. He found damage on the left as well.

Miller, Craig Hou of Washington University and others then compared these images with those of a nine-year-old artistic autistic savant named DB. SPECT scans of DB revealed a higher-than-normal blood flow in part of his neocortex but decreased flow in his left temporal lobe. (The neocortex is involved with high-level cognitive function; the temporal lobe is responsible for some aspects of memory and emotion.) Miller is hoping to study other artistic savants to see if the findings hold true for them as well. But the fact that DB and older FTD patients with newfound savant skills have the same pathology is quite striking and suggests that researchers will soon be able to identify precisely the neurological features associated with savant syndrome.

The seemingly limitless memory of savants will mostly likely be harder to pinpoint physiologically. Mortimer Mishkin of the National Institute of Mental Health has proposed different neural circuits for memory, including a higher-level corticolimbic circuit for what is generally referred to as semantic or cognitive memory, and a lower-level corticostriatal circuit for

the more primitive habit memory that is most often referred to as procedural memory. The memory of savants seems to be the noncognitive habit form.

The same factors that produce left hemispheric damage may be instrumental in producing damage to higher-level memory circuits. As a result, savants may be forced to rely on more primitive, but spared, habit memory circuits. Perhaps brain injuries—whether they result from hormones, disease, or prenatal or subsequent injury—produce in some instances certain right brain skills linked with habit memory function. In those situations, savant syndrome may appear.

Rain Man in Us All?

The emergence of savantlike skills in people with dementia raises profound questions about the buried potential in all of us. Accordingly, several researchers are seeking to unlock what has been called the "little Rain Man in each of us." One group has used a technique called repetitive transcranial magnetic stimulation (rTMS) in 17 normal individuals, eight male and nine female. Tracy Morrell of the University of South Australia, Robyn L. Young of Flinders University in Adelaide and Michael C. Ridding of Adelaide University applied magnetic stimulation to the area in the left temporal lobe that Miller identified as damaged in his FTD patients.

In their study, the team reports that only two participants experienced a series of short-lived skills, such as calendar calculating, artistic ability and enhanced habit memory. Others discovered a new skill here and there, also lasting just a few hours. The researchers suggest that savant skills may be limited to a small percentage of the normal population in the same way that they are limited to a small percentage of the disabled population.

Nevertheless, many experts believe that real potential exists to tap into islands of savant intelligence. Allan Snyder and John Mitchell of the Centre for the Mind in Canberra, Australia, argue that savant brain processes occur in each of us but are overwhelmed by more sophisticated conceptual cognition. Autistic savants, they conclude, "have privileged access to lower levels of information not normally available through introspection."

Our view is also that all of us have some of the same circuitry and pathways intrinsic to savant functioning but that these are less accessible—in part because we tend to be a left-brain society. Sometimes, though, we

can find elements of the savant in ourselves. At certain moments, we just "get" something or discover a new ability. And some procedures—including hypnosis; interviews of subjects under the influence of the barbiturate sodium amytal, which induces relaxation; and brain stimulation during neurosurgery—provide evidence that a huge reservoir of memories lies dormant in every individual. Dreams can also revive those memories or trigger new abilities.

A Window into the Brain

No model of brain function will be complete until it can explain this rare condition. Now that we have the tools to examine brain structure and function, such studies can be correlated with detailed neuropsychological testing of savants. We hope the anecdotal case reports that have characterized the literature on this topic for the past century will soon be replaced by data comparing and contrasting groups of normal and disabled people, including prodigies, geniuses and savants.

Savant syndrome provides a unique window into the brain with regard to questions of general intelligence versus multiple forms of intelligence. It may also shed light on brain plasticity and central nervous system compensation, recruitment and repair—areas of research that are vital in understanding and treating such diverse conditions as stroke, paralysis and Alzheimer's disease.

But savant syndrome has relevance outside the scientific realm. Many lessons can be learned from these remarkable people and their equally remarkable families, caretakers, therapists and teachers. One of the greatest lessons is that they have been shaped by far more than neural circuitry. The savants thrive because of the reinforcement provided by the unconditional love, belief and determination of those who care for them. Savant syndrome promises to take us further than we have ever been toward understanding both the brain and human potential.

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Inside the Mind of a Savant

by Darold A. Treffert and Daniel D. Christensen

When J. Langdon Down first described savant syndrome in 1887, coining its name and noting its association with astounding powers of memory, he cited a patient who could recite Edward Gibbon's *The Decline and Fall of the Roman Empire* verbatim. Since then, in almost all cases, savant memory has been linked to a specific domain, such as music, art or mathematics. But phenomenal memory is itself the skill in a man named Kim Peek. His friends call him "Kim-puter."

He can, indeed, pull a fact from his mental library as fast as a search engine can mine the Internet. He read Tom Clancy's *The Hunt for Red October* in one hour and 25 minutes. Four months later, when asked, he gave the name of the Russian radio operator in the book, referring to the page describing the character and quoting several passages verbatim. Kim began memorizing books at the age of 18 months, as they were read to him. At the time of writing, he has learned 9,000 books by heart. He reads a page in eight to 10 seconds and places the memorized book upside down on the shelf to signify that it is now on his mental "hard drive."

Kim's memory extends to at least 15 interests—among them, world and American history, sports, movies, geography, space programs, actors and actresses, the Bible, church history, literature, Shakespeare and classical music. He knows all the area codes and zip codes in the U.S., together with the television stations serving those locales. He learns the maps in the front of phone books and can provide Yahoo-like travel directions within any major U.S. city or between any pair of them. He can identify hundreds of classical compositions, tell when and where each was composed and first performed, give the name of the composer and many biographical details, and even discuss the formal and tonal components of the music. Most intriguing of all, he appears to be developing a new skill in middle life.

Whereas before he could merely talk about music, for the past two years he has been learning to play it.

It is an amazing feat in light of his severe developmental problems—characteristics shared, in varying extents, by all savants. He walks with a sidelong gait, cannot button his clothes, cannot manage the chores of daily life and has great difficulties with abstraction. Against these disabilities, his talents—which would be extraordinary in any person—shine all the brighter. An explanation of how Kim does what he does would provide better insight into why certain skills, including the ordinarily obscure skill of calendar calculating (always associated with massive memory), occur with such regularity among savants. When an interviewer offered that he had been born on March 31, 1956, Kim noted, in less than a second, that it was a Saturday on Easter weekend.

Imaging studies of Kim's brain thus far show considerable structural abnormality. These findings cannot yet be linked directly to any of his skills; that quest is just beginning. Newer imaging techniques that plot the brain's functions—rather than just its structure—should provide more insight, though. In the meantime, we believe it is worthwhile to document the remarkable things that Kim can do. People like him are not easily found, and it is useful to record their characteristics for future research. Savantism offers a unique window into the mind. If we cannot explain it, we cannot claim full understanding of how the brain functions.

An Unusual Brain

Kim was born on November 11, 1951 (a Sunday, he will tell you). He had an enlarged head, on the back of which was an encephalocele, or baseball-size "blister," which spontaneously resolved. But there were also other brain abnormalities, including a malformed cerebellum. One of us (Christensen) did the initial MRI brain scans on Kim in 1988 and has followed his progress ever since.

The cerebellar findings may account for Kim's problems with coordination and mobility. But more striking still is the absence of a corpus callosum, the sizable stalk of nerve tissue that normally connects the left and right halves of the brain. We do not know what to make of this defect, because although it is rare, it is not always accompanied by functional

disorders. Some people have been found to lack the structure without suffering any detectable problems at all. Yet in people whose corpus callosum has been severed in adulthood, generally in an effort to prevent epileptic seizures from spreading from one hemisphere to the other, a characteristic "split-brain" syndrome arises in which the estranged hemispheres begin to work almost independently of each other.

It would seem that those born without a corpus callosum somehow develop back channels of communication between the hemispheres. Perhaps the resulting structures allow the two hemispheres to function, in certain respects, as one giant hemisphere, putting functions normally rather separate under the same roof, as it were. If so, then Kim may owe some of his talents to this particular abnormality. In any case, the fact that some people lacking a corpus callosum suffer no disabilities, whereas others have savant abilities, makes its purpose less clear than formerly thought. Neurologists joke that its only two certain functions are to propagate seizures and hold the brain together.

Theory guides us in one respect. Kim's brain shows abnormalities in the left hemisphere, a pattern found in many savants. What is more, left hemisphere damage has been invoked as an explanation of why males are much more likely than females to display not only savantism but also dyslexia, stuttering, delayed speech, and autism. The proposed mechanism has two parts: male fetuses have a higher level of circulating testosterone, which can be toxic to developing brain tissue; and the left hemisphere develops more slowly than the right and therefore remains vulnerable for a longer period. Also supporting the role of left hemisphere damage are the many reported cases of "acquired savant syndrome," in which older children and adults suddenly develop savant skills after damage to the left hemisphere.

What does all this evidence imply? One possibility is that when the left hemisphere cannot function properly, the right hemisphere compensates by developing new skills, perhaps by recruiting brain tissue normally earmarked for other purposes. Another possibility is that injury to the left hemisphere merely unveils skills that had been latent in the right hemisphere all along, a phenomenon some have called a release from the "tyranny" of the dominant left hemisphere.

Kim underwent psychological testing in 1988. His overall IQ score was 87, but the verbal and performance subtests varied greatly, with some scores falling in the superior range of intelligence and others in the mentally retarded range. The psychological report concluded, therefore, that "Kim's IQ classification is not a valid description of his intellectual ability." The "general intelligence" versus "multiple intelligences" debate rages on in psychology. We believe that Kim's case argues for the latter point of view.

Kim's overall diagnosis was "developmental disorder not otherwise specified," with no diagnosis of autistic disorder. Indeed, although autism is more commonly linked with savantism than is any other single disorder, only about half of all savants are autistic. In contrast with autistic people, Kim is outgoing and quite personable. One thing that does seem necessary for the full development of savant skills is a strong interest in the subject matter in question.

Memory and Music

In Kim's case, all the interests began in rote memorization but later progressed to something more. Although Kim generally has a limited capacity for abstract or conceptual thinking—he cannot, for example, explain many commonplace proverbs—he does comprehend much of the material he has committed to memory. This degree of comprehension is unusual among savants. Down himself coined the interesting phrase "verbal adhesion" to describe the savant's ability to remember huge quantities of words without comprehension. Sarah Parker, a graduate student in psychology at the University of Pennsylvania, in a description of a savant named Gordon stated it more colorfully when she noted that "owning a kiln of bricks does not make one a mason." Kim not only owns a large kiln of bricks, he has also become a strikingly creative and versatile word mason within his chosen areas of expertise.

Sometimes his answers to questions or directions are quite concrete and literal. Once when asked by his father in a restaurant to "lower his voice," Kim merely slid lower into his chair, thus lowering his voice box. In other cases, his answers can seem quite ingenious. In one of his talks he answered a question about Abraham Lincoln's Gettysburg Address by responding, "Will's house, 227 North West Front Street. But he stayed there only one night—he gave the speech the next day." Kim intended no joke, but when

his questioner laughed, he saw the point; since then, he has purposely recycled the story with humorous intent and effect.

Yet Kim does have an undeniable power to make clever connections. He once attended a Shakespeare festival sponsored by a philanthropist known by the initials O.C., whose laryngitis threatened to keep him from acknowledging a testimonial. Kim—a fan of Shakespeare, and like him, an incorrigible punster—quipped, "O.C., can you say?"

Such creative use of material that had originally been memorized by rote can be seen as the verbal equivalent of a musician's improvisation. Like the musician, Kim thinks quickly, so quickly that it can be difficult to keep up with his intricate associations. Often he seems two or three steps ahead of his audiences in his responses.

A rather startling new dimension to Kim's savant skills has recently surfaced. In 2002 he met April Greenan, director of the McKay Music Library and professor of music at the University of Utah. With her help, he soon began to play the piano and to enhance his discussion of compositions by playing passages from them, demonstrating on the keyboard many of the pieces he recalled from his massive mental library. Kim also has remarkable long-term memory of pitch, remembering the original pitch level of each composition.

He possesses complete knowledge of the instruments in the traditional symphony orchestra and readily identifies the timbre of any instrumental passage. For example, he presented the opening of Bedrich Smetana's orchestral tone poem *The Moldau*, by reducing the flute and clarinet parts to an arpeggiated figure in his left hand and explaining that the oboes and bassoons enter with the primary theme, which he then reduced to pitches played singly and then in thirds by his right hand (the left-hand figure continuing as it does in the score). His comprehension of musical styles is demonstrated in his ability to identify composers of pieces he had not previously heard by assessing the piece's musical style and deducing who that composer might be.

Though Kim is still physically awkward, his manual dexterity is increasing. When seated at the piano, he may play the piece he wishes to discuss, sing the passage of interest or describe the music verbally, shifting

seamlessly from one mode to another. Kim pays attention to rhythm as well, lightly tapping the beat on his chest with his right hand or, when playing, tapping his right foot.

Greenan, a Mozart scholar, makes these observations: “Kim’s knowledge of music is considerable. His ability to recall every detail of a composition he has heard—in many cases only once and more than 40 years ago—is astonishing. The connections he draws between and weaves through compositions, composer’s lives, historical events, movie soundtracks and thousands of facts stored in his database reveal enormous intellectual capacity.” She even compares him to Mozart, who also had an enlarged head, a fascination with numbers and uneven social skills. She wonders whether Kim might even learn to compose.

Life after *Rain Man*

It is not surprising that Kim’s prodigious memory caught the attention of writer Barry Morrow at a chance meeting in 1984 and inspired him to write the screenplay for *Rain Man*, whose main character, Raymond Babbitt, is a savant played by Dustin Hoffman. The movie is purely fictional and does not tell Kim’s life story, even in outline. But in one remarkably prescient scene, Raymond instantly computes square roots in his head, and his brother, Charlie, remarks, “He ought to work for NASA or something.” For Kim, such a collaboration might well happen.

NASA has proposed to make a high-resolution 3-D anatomical model of Kim’s brain architecture. Richard Boyle, director of the NASA BioVIS Technology Center, describes the project as part of a larger effort to overlay and fuse image data from as wide a range of brains as possible—and that is why Kim’s unusual brain is of particular value. The data, both static and functional, should enable investigators to locate and identify changes in the brain that accompany thought and behavior. NASA hopes that this detailed model will enable physicians to improve their ability to interpret output from far less capable ultrasound imaging systems, which are the only kind that can now be carried into space and used to monitor astronauts.

The filming of *Rain Man* and the movie’s subsequent success proved to be a turning point in Kim’s life. Before then, he had been reclusive, retreating to his room when company came; afterward, the confidence he

gained from his contacts with the filmmakers, together with the celebrity provided by the movie's success, inspired him and his father, Fran Peek, to share Kim's talents with many audiences. They became enthusiastic emissaries for people with disabilities, and over the years they have shared their story with more than 2.6 million people.

We believe that Kim's transformation has general applicability. Much of what scientists know about health comes out of the study of pathologies, and certainly much of what will be learned about normal memory will come from the study of unique or unusual memory. In the meantime, we draw some practical conclusions for the care of other persons with special needs who have some savant skill. We recommend that family and other caregivers "train the talent," rather than dismissing such skills as frivolous, as a means for the savant to connect with other people and mitigate the effects of the disability. It is not an easy path, because disability and limitations still require a great deal of dedication, patience and hard work—as Kim's father, by his example, so convincingly demonstrates.

Further exploration of savant syndrome will provide both scientific insights and stories of immense human interest. Kim Peek provides ample evidence of both.

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Think Better: Tips from a Savant

by Jonah Lehrer and Daniel Tammet

Daniel Tammet is author of two books, Born on a Blue Day *and* Embracing the Wide Sky. *He is also a linguist and holds the European record for reciting the first 22,514 digits of the mathematical constant pi. Former* Scientific American Mind *contributing editor Jonah Lehrer chats with Tammet about the way his memory works, why the IQ test is overrated, and a possible explanation for extraordinary feats of creativity.*

Scientific American Mind: Your memoir, *Born on a Blue Day*, documented your life as an autistic savant. You describe, for example, how you are able to quickly learn new languages and remember scenes from years earlier in cinematic detail. Are you ever surprised by your own abilities?

Daniel Tamet: I have always thought of abstract information—numbers, for example—in visual, dynamic form. Numbers assume complex, multidimensional shapes in my head that I manipulate to form the solution to sums or compare when determining whether they are prime or not.

For languages, I do something similar in terms of thinking of words as belonging to clusters of meaning so that each piece of vocabulary makes sense according to its place in my mental architecture for that language. In this way, I can easily discern relations between words, which helps me to remember them.

In my mind, numbers and words are far more than squiggles of ink on a page. They have form, color, texture, and so on. They come alive to me, which is why as a young child I thought of them as my "friends." I think this is why my memory is very deep, because the information is not static. I

say in my book that I do not crunch numbers (like a computer). Rather I dance with them.

None of this is particularly surprising for me. I have always thought in this way so it seems entirely natural. What I do find surprising is that other people do not think in the same way. I find it hard to imagine a world where numbers and words are not how I experience them!

Mind: In *Embracing the Wide Sky*, you criticize the IQ test as a vast oversimplification of intelligence. You write: "There is no such thing as proofs of intelligence, only intelligence." Could you explain what you mean by that?

Tammet: When I was a child, my behavior was far from being what most people would label "intelligent." It was often limited, repetitive and antisocial. I could not do many of the things that most people take for granted, such as looking someone in the eye or deciphering a person's body language, and only acquired these skills with much effort over time. I also struggled to learn many of the techniques for spelling or doing sums taught in class because they did not match my own style of thinking.

I know from my own experience that there is much more to intelligence than an IQ number. In fact, I hesitate to believe that any system could really reflect the complexity and uniqueness of one person's mind or meaningfully describe the nature of his or her potential.

The bell curve distribution for IQ scores tells us that two thirds of the world's population has an IQ somewhere between 85 and 115. This means that some four and a half billion people around the globe share just 31 numerical values ("he's a 94," "you're a 110," "I'm a 103"), equivalent to 150 million people worldwide sharing the same IQ score. This sounds a lot to me like astrology, which lumps everyone into one of 12 signs of the zodiac.

Even if we cannot measure and assign precise values to it in any "scientific" way, I do very much think that intelligence exists and that it varies in the actions of each person. The concept is a useful and important one for scientists and educators alike. My objection is to thinking that any "test" of a person's intelligence is up to the task. Rather we should focus on

ensuring that the fundamentals (literacy, etcetera) are well taught and that each child's diverse talents are encouraged and nourished.

Mind: You also describe some scientific studies on what happens inside the brain when we learn a second language. Do you think this research should change the way we teach languages?

Tammet: Thanks to the advances in modern scanning technology, we know more today than ever before just what's happening inside the brain when we're learning a language. That we can speak at all is nothing less than an astonishing cognitive achievement.

Learning a second language, particularly when that language is not one that the person has to use on a regular basis, is an extremely difficult task. I think it is a mistake to underestimate the challenges of it. Students should be aware that the difficulties they will face are inherent in what they are doing and not any failing on their part.

One of the most interesting scientific discoveries about how language works (and how it could be taught) is "phonaesthesia"—that certain sounds have a meaningful relation to the things they describe. For example, in many languages the vowel sound "i" is associated with smallness—little, tiny, petite, *niño*, and so on—whereas the sound "a" or "o" is associated with largeness—grand, gross, *gordo*, etcetera. Such links have been found in many of the world's languages. These findings strongly imply that learners would benefit from learning to draw on their own natural intuitions to help them understand and remember many of the foreign words that they come across.

Another finding, by cognitive psychologists Lera Boroditsky, Lauren A. Schmidt and Webb Phillips, might also offer a useful insight into an important part of learning a second language. The researchers asked German and Spanish native speakers to think of adjectives to describe a range of objects, such as a key. The German speakers, for whom the word "key" is masculine, gave adjectives such as "hard," "heavy," "jagged" and "metal," whereas the Spanish speakers, for whom "key" is feminine, gave responses such as "golden," "little," "lovely" and "shiny." This result suggests that native speakers of languages that have gendered nouns remember the different categorization for each by attending to differing

characteristics, depending on whether the noun is “male” or “female.” It is plausible that second-language learners could learn to perceive various nouns in a similar way to help them remember the correct gender.

Regardless of how exactly a person learns a second language, we do know for sure that it is very good for your brain. There is good evidence that language learning helps individuals to abstract information, focus attention, and may even help ward off age-related declines in mental performance.

Mind: You advocate a theory of creativity defined by a cognitive property you call “hyperconnectivity.” Could you explain?

Tammet: I am unusually creative—from visualizing numerical landscapes composed of random strings of digits to the invention of my own words and concepts in numerous languages. Where does this creativity come from?

My brain has developed a little differently from most other people’s. Aside from my high-functioning autism, I also suffered from epileptic seizures as a young child. In my book, I propose a link between my brain’s functioning and my creative abilities based on the property of hyperconnectivity.

In most people, the brain’s major functions are performed separately and not allowed to interfere with one another. Scientists have found that in some brain disorders, however, including autism and epilepsy, cross-communication can occur between normally distinct brain regions. My theory is that rare forms of creative imagination are the result of an extraordinary convergence of normally disconnected thoughts, memories, feelings and ideas. Indeed, such hyperconnectivity within the brain may well lie at the heart of all forms of exceptional creativity.

Mind: How were you able to recite from memory the first 22,514 numbers of pi? And do you have advice for people looking to improve their own memory?

Tammet: As I have already mentioned, numbers to me have their own shapes, colors and textures. Various studies have long demonstrated that being able to visualize information makes it easier to remember. In addition, my number shapes are semantically meaningful, which is to say that I am

able to visualize their relation to other numbers. A simple example would be the number 37, which is lumpy like oatmeal, and 111, which is similarly lumpy but also round like the number three (being 37 × 3). Where you might see an endless string of random digits when looking at the decimals of pi, my mind is able to "chunk" groups of these numbers spontaneously into meaningful visual images that constitute their own hierarchy of associations.

Using your imagination is one very good way to improve your own memory. For example, actors who have to remember hundreds or even thousands of lines of a script do so by actively analyzing them and imagining the motivations and goals of their characters. Many also imagine having to explain the meaning of their lines to another person, which has been shown to significantly improve their subsequent recall.

Here is another tip from my book. Researchers have found that you are more likely to remember something if the place or situation in which you are trying to recall the information bears some resemblance—color or smell, for example—to where you originally learned it. A greater awareness therefore of the context in which we acquire a particular piece of information can help improve our ability to remember it later on.

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SECTION 3

Who's at Risk?

Why Autism Strikes More Boys Than Girls

by Janelle Weaver

Autism, a developmental disorder that causes deficits in social behavior and communication, affects four times as many boys as girls. Because of this extreme gender imbalance, some scientists posit that sex hormones may contribute to the disease. Now researchers have identified for the first time a gene that may help explain the gender discrepancy and underlie some common autism symptoms.

In 2010 biologist Valerie Hu of the George Washington University Medical Center and her colleagues found that brains of people with autism have low levels of a protein produced by a gene called retinoic acid–related orphan receptor-alpha (RORA). Now they report in a study published in *PLoS ONE* that this gene interacts with certain types of estrogen and testosterone found in the brain.

Hu and her team examined neural cells in their lab. They found that RORA controls the production of an enzyme called aromatase, which converts testosterone to estrogen. But in their tests, the presence of testosterone made RORA less active, leading to a decline in aromatase and a buildup of even more testosterone. Estrogen had the opposite effect. In a typical brain the balance of sex hormones regulates RORA activity and keeps hormone levels steady, but any imbalance can be exacerbated by this loop.

Next, the researchers confirmed that brain tissue from donors who had autism indeed contains low amounts of the RORA protein and aromatase. The authors suggest that a deficiency in these molecules causes the chemical loop to spiral out of control, resulting in an accumulation of testosterone that may cause autism. In most females, higher levels of estrogen could be protecting them from the disorder.

In addition to the gender bias, RORA might be implicated in the abnormal routines that characterize autism. For instance, mice that lack this gene fixate on objects and show limited exploratory behavior, similar to individuals with autism. “I don’t think any single gene is going to explain all of the pathology associated with autism, but RORA does explain quite a few of them,” Hu says.

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Maternal Age and Autism

by Katie Moisse

It is common knowledge: As women get older, pregnancy becomes a riskier enterprise. Advanced maternal age is linked to a number of developmental disorders in children, such as Down's syndrome. Now, a study has confirmed that older mothers are more likely to give birth to a child with autism, too.

The authors of the epidemiological study, published in *Autism Research*, examined the parental age of more than 12,000 children with autism and nearly five million "control" children between 1990 and 1999, all living in California. The researchers found that mothers over 40 had a 51 percent higher risk of having a child with autism than mothers 25 to 29, and a 77 percent higher risk than mothers under 25.

Autism—a developmental disorder characterized by impaired social interaction and communication—appears to be on the rise. The U.S. Centers for Disease Control and Prevention now estimates that as many as one in 110 children in the U.S. has an autistic spectrum disorder—a group of developmental disorders including autism, Asperger's syndrome and pervasive developmental disorder. The prevalence of autistic spectrum disorders in California in 2007 was 12 times that from 1987, representing an average annual growth of 13 percent, according to a report from the California Department of Developmental Services. Only a fraction of these extra cases can be explained by changes to diagnostic criteria and earlier diagnoses.

Maternal age is also increasing in the U.S. A California-based study reported a three-fold increase in the number of births to women aged 40 to 44 between 1982 and 2004. But this trend toward delayed childbearing accounted for less than 5 percent of the total increase in autism diagnoses in

California over the decade, according to the study—a finding that surprised Janie Shelton, a doctoral student in University of California, Davis's Department of Public Health Sciences and the study's lead author. "I would have expected to see more of a contribution, because age is a risk factor and women are having kids later," she says.

Earlier work had suggested that both maternal and paternal ages are independently associated with autism risk. But the current study found that paternal age is only a risk factor when the mother is under 30. It follows similar results obtained from the same California sample, published in September 2009 in the *American Journal of Public Health*, which showed that pooling data artificially inflates the risk of paternal age, and that advanced maternal age likely poses the greater risk. "It's nice to see replication of prior work," says Peter Bearman, co-author of the 2009 paper. Neither research team investigated whether increasing maternal age worsened autistic symptoms, although a 2007 study published in the *Journal of Autism and Development Disorders* that measured autistic children's cognitive and social function failed to make that link.

Mothers over 35 are at a higher risk for prolonged labor, premature or breeched deliveries, and birth to babies with low Apgar scores (a rating index used to evaluate the condition of a newborn infant)—all factors that have been associated with autism. But they might also be more likely to seek diagnoses to explain their child's abnormal behavior. "That's definitely an important thought, and I think that there is some evidence to suggest that people with higher education and higher socioeconomic status in general are more adept at navigating the diagnostic process here in California," Shelton says. "[Parents] need to be motivated to get the diagnostic and treatment services that are granted to them by the state. There are certain cases we're missing because the parents don't know about the services that are available or they haven't worked out how to navigate the system yet." The proportion of parents of autistic children with fewer than 24 years of combined education in the study was smaller than that of "control" birth parents, (19 percent and 36 percent, respectively).

Other contributors to the increasing incidence of autism remain unclear. "We're doing a lot of research into environmental risk factors," Shelton says, describing ongoing research into possible nutritional factors and toxic

chemical exposure during labor and development. It is possible that the increased risk associated with maternal age might reflect the mother's longer cumulative exposure to unknown environmental factors, the authors report.

The research team published an earlier report in the same journal describing high-incidence geographic clusters in California, another finding in line with Bearman's work that suggests environmental processes and social influences (why someone would live in a particular neighborhood) might be contributing factors. Maternal autoimmunity is another theory proposed by the researchers, who previously reported that some mothers of autistic children had antibodies to fetal brain proteins in their plasma. These antibodies (which might increase in number with age) could transfer into the fetus and interfere with early brain development, the researchers report.

Whereas biomedical studies are required to uncover the mechanisms underlying the disorder, Shelton says the present epidemiological study was important in clarifying the nuanced relationship between maternal age and autism, and defining its contribution to the rise in cases. It might have even provided biological clues. "It really is a maternally mediated biological process that's going on," Shelton says.

Although it is rising, the risk of autism is still very low and shouldn't affect the decision to have children at any age, Shelton says. "People should pursue their families whenever it's right for them," she says, adding that soon-to-be parents should "just stay as healthy as possible," and steer clear of dangerous exposures. She also encourages parents with autistic children to get involved in research. "I think parents are anxious because science hasn't figured it out yet. If they have the opportunity to be involved in supporting science and autism research, that's a great thing."

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The Father Factor

by Paul Raeburn

When my wife, Elizabeth, was pregnant, she had a routine ultrasound exam, and I was astonished by the images. The baby's ears, his tiny lips, the lenses of his eyes and even the feathery, fluttering valves in his heart were as crisp and clear as the muscles and tendons in a Leonardo da Vinci drawing. Months before he was born, we were already squabbling about whom he looked like. Mostly, though, we were relieved; everything seemed to be fine.

Elizabeth was 40, and we knew about all the things that can go wrong in the children of older mothers. We worried about Down syndrome, which is more common in the offspring of older women. Elizabeth had the tests to rule out Down syndrome and a few other genetic abnormalities. That was no guarantee the baby would be okay, but the results were reassuring to us.

The day after Henry was born, while we were still bleary-eyed from a late-night cesarean delivery, we caught part of a report on the hospital television about an increased risk of autism in the children of older fathers. Until then, all we'd thought about was Elizabeth's age—not mine. We'd had no idea that my age could be an important factor in our baby's health.

When we got home, I looked up the study. Researchers had analyzed medical records in Israel, where all young men and most women must report to the draft board for mandatory medical, intelligence and psychiatric screening. They found that children born to fathers 40 or older had nearly a sixfold increase in the risk of autism as compared with kids whose fathers were younger than 30. Children of fathers older than 50—that includes me—had a ninefold risk of autism.

The researchers said that advanced paternal age, as they call it, has also been linked to an increased risk of birth defects, cleft lip and palate, water on the brain, dwarfism, miscarriage and "decreased intellectual capacity."

What was most frightening to me, as someone with mental illness in the family, is that older fatherhood was also associated with an increased risk of schizophrenia. The risk rises for fathers with each passing year. The child of a 40-year-old father has a 2 percent chance of having schizophrenia—double the risk of a child whose father is younger than 30. A 40-year-old man's risk of having a child with schizophrenia is the same as a 40-year-old woman's risk of having a child with Down syndrome.

We wouldn't know for two years or so whether Henry had autism. And because schizophrenia does not usually appear until the early 20s, we had decades to wait before we would know if Henry was affected.

Advancing Years

Data collected by the National Center for Health Statistics, part of the Centers for Disease Control and Prevention, show that in the U.S. the number of births to men aged 40 to 49 nearly tripled between 1980 and 2004, rising from 120,702 to 328,465. Much of that jump is the result of an increase in the overall population. But there has been a shift over the past generation toward more older fathers beyond what can be accounted for by the growth in population. Birth *rates* for men in their 40s (a number that takes population growth into account) have risen by up to 40 percent since 1980—whereas birth rates for men younger than 30 have fallen by as much as 21 percent.

The idea that a father's age could affect the health of his children was first hinted at a century ago by an unusually perceptive and industrious doctor in private practice in Stuttgart, Germany. Wilhelm Weinberg was a loner who devoted much of his time to caring for the poor, including delivering 3,500 babies during a 40-year career. He also managed to publish 160 scientific papers without the benefit of colleagues, students or grants. His papers, written in German, did not attract much attention initially; most geneticists spoke English. It was not until years later that some of Weinberg's papers were recognized as landmarks.

One of these was a 1912 study noting that a form of dwarfism called achondroplasia was more common among the last-born children in families than among the first-born. Weinberg didn't know why that was so, but he speculated that it might be related to the age of the parents, who were obviously older when their last children were born. Weinberg's prescient observation was confirmed decades later when research showed that he was half right: the risk of dwarfism rose with the father's age but not the mother's.

Since then, about 20 inherited ailments have been linked to paternal age, including progeria, the disorder of rapid aging, and Marfan syndrome, a disorder marked by very long arms, legs, fingers and toes, as well as life-threatening heart defects. More recent studies have linked fathers' age to prostate and other cancers in their children. And in September 2008 researchers linked older fathers to an increased risk of bipolar disorder in their children.

Eggs vs. Sperm

Dolores Malaspina, a professor of psychiatry at the New York University Langone Medical Center, was in college when her sister, Eileen, who was two years younger, began behaving in ways the family couldn't explain. At first, Malaspina recalls, Eileen seemed like she was going through the usual problems of adolescence. Eileen's behavior became harder to overlook, however, and she was soon diagnosed with schizophrenia.

It was the early 1970s, when many psychiatrists believed schizophrenia was caused by a dominant, overpowering mother who rejected her child. Further, Eileen's doctors said, there was no treatment. The damage done by a schizophrenia-inducing mother was irreparable.

At the same time Eileen was deteriorating, Malaspina earned a master's in zoology and took a job at a drug company, where she drifted into research on substances that could alter brain chemistry. She was in the job for a while before she made the connection with her sister. "I was looking at molecules in the lab that might be related to psychosis," she says. "My sister had very bad psychosis." Researchers were then beginning to establish a biological basis for schizophrenia that would ultimately demolish the so-called schizophrenogenic-mother theory. Malaspina quit

her job, went to medical school, became a psychiatrist and focused her research on schizophrenia.

While schizophrenia was being recast as a biological illness, most researchers still looked to mothers as the cause of the illness. A woman's eggs age as she does, and it seemed reasonable to conclude that they deteriorate over the years, giving rise to increased problems in her offspring. Sperm are freshly manufactured all the time.

That's not quite the way biology works, however. Because sperm are being continuously manufactured, genetic copying is going on constantly. Geneticists think it is that incessant copying and recopying that gives rise to the genetic errors that cause dwarfism, Marfan syndrome and the other inherited ailments. Malaspina decided to explore whether genetic errors in sperm might be at least partly responsible for schizophrenia. It was an unfashionable line of research. Nobody worried about fathers because everybody assumed mothers were the source of most problems in children. But Malaspina and others were beginning to think about it differently.

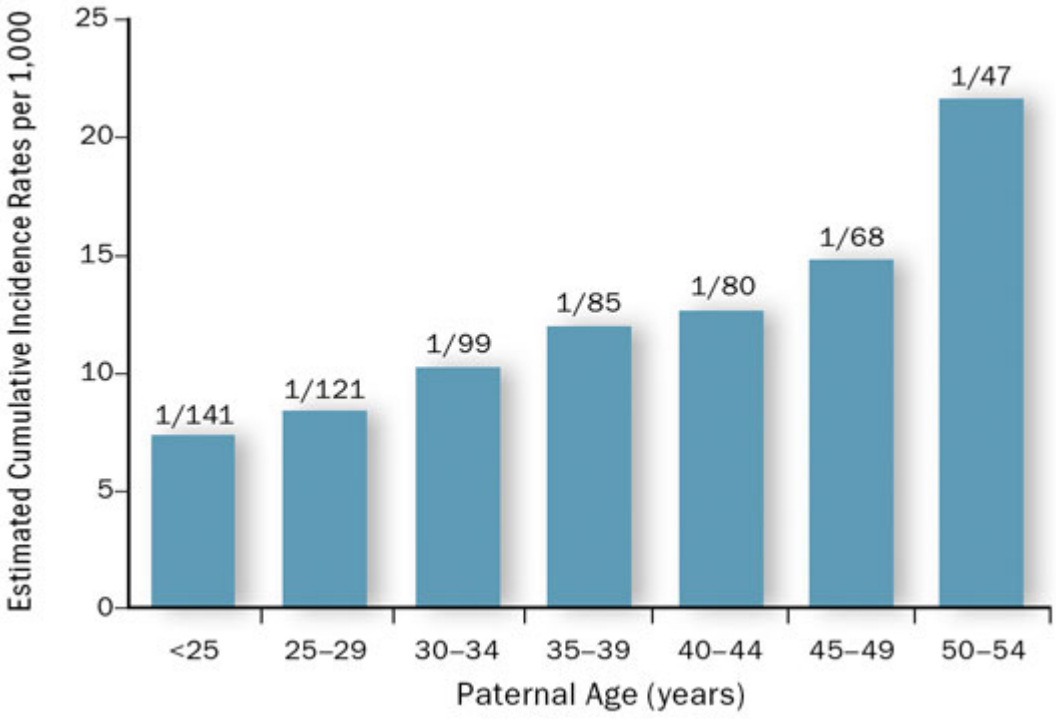
Schizophrenia and Autism

Later, while doing her residency at Columbia University, Malaspina learned about a unique research opportunity in Israel. During the 1960s and 1970s, all births in and around Jerusalem were recorded in conjunction with information on the infants' families, including the ages of the parents. And all those children received a battery of medical tests as young adults, a requirement of Israel's military draft. Because the records cover an entire population, the data are free from the biases that might creep in if researchers looked at, say, only people who graduated from college or only those who went to see a doctor.

Malaspina used the Israeli group to look first at the risk of schizophrenia in children of older fathers—and then at the risk of autism. Then she correlated birth and family information on some 90,000 children with information on which of them had developed schizophrenia as recorded on their military physicals. In 2001 Malaspina and her colleagues reported that paternal age was strongly linked to the risk of schizophrenia, as she had suspected.

A Rising Risk

The rate of offspring estimated to have an onset of schizophrenia by age 34 grows with paternal age.



Illustrated by Dolores Malaspina et al.

It was the first large-scale study to link sporadic cases of schizophrenia to fathers' age, and few researchers believed it. "We were absolutely convinced it was real, but other people didn't think it was," Malaspina says. "Everybody thought men who waited to have children must be different." That is, maybe these older fathers had some of the makings of schizophrenia themselves—not enough for the disease to be recognized but enough that it took them a little longer to get settled, married and have children.

Other groups tried to repeat the study using different populations. In all these studies, researchers took a close look at whether there was something about the older fathers—unrelated to age—that increased the risk of schizophrenia in their children. When they did, the link with age became even clearer. "That result has been replicated at least seven times," says Robert K. Heinssen, chief of the schizophrenia research program at the National Institute of Mental Health (which has funded some of Malaspina's work). "We're talking about samples from Scandinavia, cohorts in the

United States, Japan. This is not just a finding that pertains to Israeli citizens or people of Jewish background."

Malaspina knew that the draft-induction tests identified young men and women with autism, and she realized that, too, could be looked at to see whether it was linked to paternal age. "There are similarities between autism and schizophrenia—they both have very severe social deficits," says one of her collaborators, Abraham Reichenberg, a neuropsychologist at the Mount Sinai School of Medicine and the Institute of Psychiatry at King's College London. "There was some reason to think similar risk factors might be involved." In 2006 they and their colleagues published a report showing that the children of men who were 40 or older were nearly six times as likely as the kids of men who were younger than 30 to develop autism or a related disorder.

Autism and related disorders—referred to as autism spectrum disorders—occurred at a rate of six in 10,000 among the children of the younger fathers and 32 in 10,000 among the children of the older fathers. (That is closer to five times the risk, but statistical adjustments showed the risk was actually about six times higher in the offspring of the older dads.) In the children of fathers older than 50, the risk was 52 in 10,000.

That was the study I heard about the day after my son Henry was born.

Reichenberg interprets these results as very solid findings: "In epidemiology, you look for an odds ratio of two. Anything above that, you're happy. When you have an odds ratio more than five, you're excited." The study could not absolutely rule out some effect of older mothers, but "we're pretty confident that the paternal age risk holds no matter what the maternal age," he says.

As these studies were being done, Malaspina asked Jay Gingrich, a psychiatrist and neuroscientist at Columbia who works with mice, whether he could look for the same effect in the offspring of older mouse fathers.

Gingrich can't ask his mice whether they are suffering delusions or hearing voices. But he can give them tests that people with schizophrenia have difficulty passing. In one such test he looked at how mice reacted when startled by a loud sound. Mice are like people—when they hear a loud noise, they jump. And there is more similarity than that: when mice or

people hear a soft sound before being startled, they don't jump as much. It is called prepulse inhibition; the soft pulse inhibits the reaction to the louder one. "It's abnormal in a number of neuropsychiatric disorders, including schizophrenia, autism, obsessive-compulsive disorders and some of the others," Gingrich says. And he found that the response was abnormal in mice with older fathers.

The results were so striking that Gingrich thought they were too good to be true. He and a postdoctoral researcher, Maria Milekic, collected data on 100 offspring of younger dads and another 100 offspring of older dads before they decided the results were correct.

Missing a Mechanism?

Not everyone agrees on what Malaspina's results mean. Daniel R. Weinberger, a psychiatrist and schizophrenia expert at the National Institute of Mental Health, for instance, accepts the findings—that the incidence of schizophrenia is higher in the children of older fathers. But he does not agree with Malaspina that this could be one of the most important causes of schizophrenia. The reason, he says, is researchers know too little about which genes conspire to cause schizophrenia: "It's a seminal observation, but like many seminal observations, it doesn't identify a mechanism." Weinberger wants to know exactly how this happens before he can say what it means.

Malaspina has thought a lot about the mechanism. What happens to the sperm of men as they age that could give rise to these increased risks in their offspring? The first thought was a classic kind of genetic mutation—a typo in the DNA, a stutter or some other scramble of the code.

There is, however, another possibility. The genetic code we are familiar with is expressed in the DNA itself. But there is a second genetic code, separate from what is embedded in the DNA. To distinguish it from the genetic code, it is referred to as "epigenetic" information. It is like a bar code imprinted on the outside of a gene. The information in that bar code can turn the gene on or off—sometimes inappropriately. If it turns the wrong genes on or off, it can affect health and disease just as surely as can changes in the DNA itself.

Malaspina has not yet proved it, but she suspects that as men grow older they develop defects in the machinery that stamps this code on the genes. These imprinting defects may give rise to the increased risk of schizophrenia, autism and perhaps some of the other ailments related to paternal age.

It is not possible to poke around in people's brains to see whether those who have schizophrenia show errors in this imprinting. But that can be done in Gingrich's mice. He is just now beginning to examine the imprinting in the brain tissue of his mice, and he is betting he will find errors there. That is precisely the kind of research that could address Weinberger's concerns about the mechanism responsible for increasing the incidence of schizophrenia in the children of older dads.

This research could represent an important advance in understanding schizophrenia and autism. "This is work that we will pursue and fund, because we're so eager to get the genetics worked out," says Thomas R. Insel, a psychiatrist and director of the National Institute of Mental Health. "It's a very interesting observation." With persistence—and some luck—the research could lead to better treatments or even, one day, a cure for schizophrenia and autism.

Some researchers worry that these new findings are just among the first of the problems that might ultimately be associated with older dads. "If there is one common disease that we know is associated with older biological fathers, we can safely assume there are more remaining to be discovered," says University of Chicago psychiatrist Elliot S. Gershon.

Gershon's prediction has already come true. In September 2008 researchers in Sweden, in collaboration with Reichenberg, reported that the children of older fathers had an increased risk of acquiring bipolar disorder. And the risk increased as the fathers' age rose, encouraging confidence in the results.

For now, prospective parents might want to rethink their plans about when to have children, says Herbert Meltzer, a psychiatrist and widely recognized schizophrenia expert at Vanderbilt University. He believes the risks for children of older fathers will eventually be seen to be as noteworthy as the risks facing older mothers. "It's going to be more and

more of an issue to society," he notes. "Schizophrenia is a terrible disease, and anything that can be done to reduce it is terribly important."

Meltzer thinks women should take a man's age into consideration when choosing a partner to have children with. And men might want to think about having sperm stored when they are young. Because despite the advances in understanding autism and schizophrenia, treatment is limited and difficult, and a cure remains elusive.

As for Henry, that decision has been made. The question, for me, is whether I would make the same choice, knowing what I know now. Despite the increase in risks, the absolute risks "to any individual child of a man at any age are quite small," Malaspina says.

My answer: I don't know.

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SECTION 4

Genetic Causes

Genetics Research Challenges Ideas about Mental Illness

by Jamie Horder

The search for the genetic roots of psychiatric illnesses and behavioral disorders such as schizophrenia, autism and ADHD has a long history, but until recently, it was one marked by frustration and skepticism. In the past few years, new techniques have begun to reveal strong evidence for the role of specific genes in some cases of these conditions but in a way few people expected.

To understand what makes the new discoveries so novel, it's necessary to appreciate how our genes can go wrong. The human genetic code can be thought of as an encyclopedia in multiple volumes. Our normal genome contains 46 chromosomes, so that's 46 volumes. Each chromosome is a long string of the chemical DNA and the information is "written" in the form of a molecular alphabet with just four letters: A, T, C and G.

There are three ways in which something can go wrong here. First, a whole chromosome can be either missing or duplicated. This drastic change is almost always fatal. (The exceptions include Down Syndrome.)

Second, single-nucleotide polymorphisms (SNPs, or "snips" as everyone calls them) are when a single base-pair is different, corresponding to a misprinted character.

Finally, copy-number variants (CNVs) are when a stretch of DNA is either missing (deleted), or repeated (duplicated), a bit like a page that's either fallen out or been printed twice. As you can imagine, CNVs tend to be more serious than SNPs, because they affect more of the DNA. This is only a general rule, however. There are plenty of serious SNPs, and plenty

of harmless CNVs. It all depends on where they happen, and whether they interfere with important genes.

For a long time, it was widely assumed that SNPs were responsible for psychiatric disorders, in what's called the "common-variant model" of disease. The idea was that any given risk variant might be quite common, but it would only increase your risk of suffering a disease by a small amount. Those who carried a large number of risk variants would develop the disease. Those with a moderate number might get mild symptoms, and so on.

Yet this just didn't work out. Before the writing of this article, it became feasible to scan huge numbers of SNPs quickly and cheaply. These "genome-wide association studies" (GWAS) tested hundreds of thousands of variants. Moving quickly to exploit the new technology, psychiatrists conducted GWAS after GWAS comparing people with diseases to those without—but very little came out. There are a few common SNPs which seem to be associated with some disorders, like autism and schizophrenia, but only a handful, and they have very small effects.

The same is true of other areas of genetics as well. Known SNPs only account for a small percentage of the risk of many common medical disorders or traits that are thought to be genetic, like heart disease, height, and obesity. Psychiatry, however, is especially barren.

It's always possible that even bigger studies, looking at even more SNPs, might be able to find more associations. Some recent research has suggested that there are many variants of extremely small effect still to be found for schizophrenia and bipolar disorder. So there's still life in SNPs, but it's fair to say that compared to 5 years ago people regard them with rather more skepticism.

CNVs, however, have just taken off—in the nick of time, some say. What's emerging from these studies, however, may be, in its own way, revolutionary as well.

Psychiatric interest in CNVs was sparked by a landmark paper that appeared in *Nature* in September 2008. It was authored by an international consortium of schizophrenia researchers, led by employees at an Icelandic

company, deCODE Genetics. They found a number of CNVs which seemed to be associated with schizophrenia.

Since then, CNV studies have taken off in the same way as GWAS did 5 years before. There's now good evidence for the involvement of deletions and duplications in autism, attention-deficit hyperactivity disorder (ADHD), schizophrenia, and intellectual disability (aka mental retardation). By contrast, however, studies in bipolar disorder have been negative.

A typical finding is that, comparing a group of patients to some healthy controls, the rate of CNVs in the patients is higher, and these CNVs are especially likely to disrupt genes involved in brain development and function. For instance, in one recent ADHD study from a group led by Cardiff University's Nigel Williams and colleagues, published in *The Lancet*, the authors found large, rare deletions or duplications in 15 percent of the children with the disorder compared to 7 percent of the controls.

When this study appeared, many media sources reported it as evidence that scientists had found "the ADHD gene". There are two problems with this interpretation. Firstly, only a small proportion of patients carried "large rare" CNV. 85% did not carry any, although more detailed future studies, able to detect smaller CNVs, might have found more (the smaller they are, the harder they are to detect.)

The deeper problem is that there wasn't just one CNV. In fact, there were dozens of different large deletions or duplications in the ADHD group. This is similar to the results of other CNV studies.

Furthermore, even when the same CNV turns up repeatedly in many independent patients, these patients very often have *different diseases*. Many of the leading risk CNVs for autism, say, have also been found in ADHD and schizophrenia, epilepsy, or intellectual disability—and vice versa.

To take just one example, the "15q13.3" deletion, so called because it affects a particular part of Chromosome 15, has been found in people with schizophrenia, epilepsy, autism, and possibly even antisocial behaviors.

So although scientists set out trying to discover the genetic causes of named psychiatric disorders like "autism" and "schizophrenia," they're

increasingly finding that these diagnoses don't correspond to particular genes at all.

Instead, it may be that these diagnostic categories are just describing particular symptoms of certain genetic disorders. So, rather than saying that 15q13.3 deletion causes schizophrenia, for example, in the future we might say that some of the features of schizophrenia are amongst the effects of the 15q13.3-deletion-syndrome.

It's only early days yet, but as this research advances further, and as technology allows ever-smaller CNVs to be picked up, these kinds of genetic findings may present a serious challenge for existing psychiatric diagnostic systems.

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Gene Sleuths: Looking for Patterns

by Katherine Harmon

The underpinnings of autism are turning out to be even more varied than the disease's diverse manifestations. In four studies and an analysis published in June 2011 researchers have added some major landmarks in the complex landscape of the disease, uncovering clues as to why the disease is so much more prevalent in male children and how such varied genetic mutations can lead to similar symptoms.

Large genetic studies have ruled out the idea that the malfunction of a universal gene or set of genes causes autism. And the papers, which assessed the genomes of about 1,000 families that had only one autistic child, revealed that the genetic mutations that are likely responsible for the disorder are exceedingly rare—sometimes almost unique to an individual patient. Even some of the most common point of mutations were found in only about 1 percent of autistic children.

This finding means that the number of genes lurking behind autism spectrum disorder (ASD) is at least "in the hundreds," says Matthew State of Yale University's Program on Neurogenetics and co-author of one of the studies. "That's a significant change from the '90s when it was [thought to be] five to 15." And getting a handle on such rare genetic mutations—even in the growing autistic population—is challenging.

Despite the rarity of these genetic code errors, researchers could detect some important patterns in the disparate data. One aberrant gene has already been linked to other social disorders. And by analyzing the role of these genes in neural development, one team of researchers suggests different genetic mutations might often disturb an entire common network.

Down the road, these developments might benefit treatment, too. “It sets the stage to think about it in a new way,” says State, whose group’s work appeared in *Neuron*.

These large studies are “a good step forward,” says Simon Gregory, an associate professor of molecular genetics and microbiology at Duke University, who was not involved in any of the research. They “enable us to confirm what we’d thought about genetic rearrangements” and are “very important” in having pinpointed new relevant pathways, he notes.

Family Patterns

Although autism has been established as a genetically based disease, it does not seem to be passed along in families in the same way that Huntington’s disease is. Because those with ASD rarely end up having children of their own, mutations are unlikely to become widespread in populations.

Studies of twins and other families in which more than one child has ASD have shown that autism does have strong genetic roots, but the new studies sought to get past the commonalities and search instead families in which only one child has the disease.

“You see clearly that if you compare the autistic kids with their [unaffected] siblings, they have more of these mutations,” says Dennis Vitkup of the Department of Biomedical Informatics at Columbia University and co-author of one of the studies published in *Neuron*.

In assessing such a large and diverse data set several of the studies all alighted on a genetic explanation for one of the most striking patterns in ADS: why at least four times as many boys than girls are diagnosed with the disease.

Girls, it seems, might better resist the development of autistic signs: Bigger genetic disruptions are necessary to cause ASD to manifest in girls than in boys, according to the new analyses. Girls might be better protected against autism-causing genetic anomalies, Vitkup suggests, because they tend to have stronger social inclinations than boys.

Although the ability of girls to withstand genetic mayhem might seem to predispose them to become silent carriers of autism, the new analysis shows

that mothers were no more likely than fathers to pass on harmful mutations.

Social Genes

To decipher the code of autism, researchers are also looking outside of the ASD patient community to other developmental and social disorders.

One of the few rare mutations that cropped up in some autistic children in the studies were extra copies of 7q11.23 (shorthand for denoting the positions, or loci, of the genes on the chromosome—in this case on the long arm, or "q," of chromosome 7). As several of the research teams pointed out, deletion of this region has been implicated in Williams-Beuren syndrome (WBS), a disease that tends to make people especially gregarious, empathetic and social.

"There's clearly something in that small region—of 25 or so genes—that's having a significant impact of social interactions," State says. "Within that relatively very small region in the genome there are going to be keys to studying neurology and social development."

Mutations at other regions of the genome did crop up more than once in the study group. And a copy error at 7q11.23 or other loci did not necessarily translate into similar levels of IQ or developmental disability in different patients. Hence, factors other than errors at these loci must also be playing a role in the manifestation of ASD.

Rather than wait for additional genome scans to turn up more potential mutations, however, many research teams are already creating models of how these mutations might impact neurological development.

Although such model building might seem premature given the ever-changing genetic terrain of the disease, "having a way to begin to interrelate them might actually help to study them," says Huda Zoghbi, of the Department of Molecular and Human Genetics of Baylor College of Medicine, who co-authored an analysis of the three *Neuron* studies. So rather than get mired in finding each possible gene, she says, it makes sense to "go back and forth between the genetics and the functional studies."

Finding the Function—and Dysfunction

Vitkup and his team conducted just such a functional, model-based approach. Their paper, published online in the same issue of *Neuron*, looked closely at the location and likely effects of the mutations among families that have only one ASD child. By figuring out which genes communicate with each other, he says, you can "see if mutations try to disrupt genes that are next to each other," and thus what common pathway different mutations might be messing up. He likens it to a hunt for a criminal that might be committing robberies in different states but with the same modus operandi, perhaps choosing similar targets each time.

With a little computer-assisted detective work he and his team found one cluster of pathways that many of the errant genes seemed to be interrupting. And it turned out to be a crucial cluster, involved in synaptic development and the movement of neurons in the young, developing brain. As neurons branch out to form connections, if some pathways are disrupted, the connections can become abnormal.

In a sample of about a dozen cases, Vitkup says, most of the patients had disruptions that would encourage an overabundance of particular neuronal connections. Such a pattern provides evidence for the excess of connections in autistic children producing the opposite behavior pattern from WBS, whose patients have fewer than normal connections. But, he says, the jump from genetic mutations to social skills is difficult.

Nevertheless, that mutations implicated in ASD would be linked to this sort of neuronal network "is logical by the phenotype," Vitkup says. And for future studies and diagnoses, he says, it "can help because we can now look to see if there is a new mutation somewhere in the genome and we can see how close—or how related—the new mutation is to our cluster."

He and his team currently have several dozen genes mapped into their network, but he expects the list to grow to as many as 500 in the next few years as more individuals with ASD are included in these studies and as sequencing technology improves. And there might well turn out to be other key clusters of pathways that are discovered, which will have an entirely different list of implicated genetic mutations, Vitkup says.

Zoghbi and her team, whose work was published in *Science Translational Medicine*, have gone through much of the same data to find patterns in the

types of proteins that these rare mutations might be affecting. A new genetic mutation can change the way proteins are made—they might be made incorrectly, too often or not at all. “This can have a domino effect on many other proteins that could affect how a neuron talks to another neuron,” Zoghbi explains. She likens it to a self-contained neighborhood in which each person has a particular skill set. If everyone is present and working well together, the garbage will get collected and the streetlights will stay on. But if one or two people are missing or unable to do their work properly, major systems will start to falter, “because the other ones don’t have those skills,” she says. Likewise, “a group of proteins is needed for a cell to function well.”

With just a couple dozen proteins flagged a few years ago, Zoghbi and her team now have hundreds that they have added to the growing list of autism instigators.

“The more we understand the function of the proteins involved in autism —and by what pathways they might impart that change—we might begin to ask, ‘Where can we intervene, and would one intervention help just one patient or a group?’”

Screening and Treatment

By better understanding the numerous routes autism can take to perturbing common pathways, new avenues of treatment might open up sooner. Currently, treatment is based on behavior or serendipity, State says, adding, “we’re very far behind other areas of medicine in that respect.” But, he says, if a genetic screen can find even a rare mutation in a child before symptoms appear—or even in utero—behavioral therapy could start earlier, improving that child’s level of functioning.

And for pharmaceutical development, if treatments can be pinpointed to improving a common pathway, rather than fixing a particular genetic error, they might be able to treat a wider range of ASD patients instead of each individual type of mutation. But interventions like these are “easier said than done,” Zoghbi notes. “There are lots of proteins involved and lots of genes involved.”

Genetics are, of course, just part of the increasingly complex autism puzzle. “Two people can have exactly the same mutation” and not have the

same degree of developmental disorder, State says. “The question of why is the multimillion-dollar question.”

To help sort out this increasingly urgent answer, Gregory advocates for a broad-spectrum approach. “It’s not going to be one thing, it’s going to be a collection,” he says. “Between genetic, genomic and epigenetic, we’ll identify what causes the spectrum.” (Epigenetics refers to the environmental modification of genetic activity; such changes can be heritable.) And within these, the environment is often another complicating factor, as a person’s genetic makeup can render them more or less sensitive to environmental influences—whether that is from social bonding or purported chemical influences.

But one thing is well established in autism research: as scientists look deeper into the disease the complexities multiply almost exponentially. Gregory suggests that one of the next steps will be to assess the mechanisms behind epigenetic influences in autism. But “that becomes a harder thing to answer,” he says, speaking from experience in that field. DNA methylation and its effect on genes varies in different types of tissue, adding another layer of challenge to parsing the interdependent effects.

The other research teams are also hard at work on the next batch of studies. State’s group is expanding their study to include some 1,600 more families as well as homing in on gene regions that they have already found.

The rush of studies in the past couple years has been thanks in large part to technological advances as well as a push to study the disease more closely. “The down payment in the early part of this century is really paying off,” State says. But Gregory is eagerly anticipating “the next big leap forward” in higher-resolution sequencing, which will allow is group and others to “identify these very small changes” that researchers are now only just getting a taste of.

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Runaway Neurons: Excessive Brain Growth in Autism

by Ferris Jabr

As a baby grows inside the womb, its brain does not simply expand like a dehydrated sponge dropped in water. Early brain development is an elaborate procession. Every minute some 250,000 neurons bloom, squirming past one another like so many schoolchildren rushing to their seats at the sound of the bell. Each neuron grows a long root at one end and a crown of branches at the other, linking itself to fellow cells near and far. By the end of the second trimester, neurons in the baby's brain have formed trillions of connections, many of which will not survive into adulthood—the least traveled paths will eventually wither.

Sometimes, the developing brain blunders, resulting in "neuro-developmental disorders," such as autism. But exactly why or how early cellular mistakes cause autism has eluded medical science. Now, Eric Courchesne of the University of California, San Diego, thinks he has linked atypical gene activity to excessive growth in the autistic brain. With the new data, he has started to trace a cascade of genetic and cellular changes that he thinks define autism. Although intrigued by Courchesne's work, other researchers caution that explosive neural growth is not necessarily a defining feature of all autistic brains.

Since 1998 Courchesne has been searching autistic brains for unusual structural features. His studies suggest that while in the womb, the autistic brain sprouts an excess of neurons and continues to balloon during the first five years of life, as all those extra neurons grow larger and form connections. Sometime after age four or five, Courchesne has also found, autistic brains actually start to lose neural connections, faster than typical brains.

In a study published November 2011 in JAMA, *The Journal of the American Medical Association*, Courchesne reported that children with autism have 67 percent more neurons in their prefrontal cortex (PFC) than typical children. Located in the area of the brain just behind the eyes, the PFC is responsible for what psychologists call "executive functions"—high-level thinking, such as planning ahead, inhibiting impulses and directing attention. In his 2011 study Courchesne sliced up brain tissue from six autistic children and seven typical children who had passed away and counted the number of cell bodies in the sections to estimate the total number of neurons in their PFCs.

Now, Courchesne and his colleagues have analyzed DNA and RNA in 33 cubes of brain tissue from people who passed away, 15 of whom were autistic (nine children and six adults) and 18 who had typical brains (seven children and 11 adults). Looking at the order of DNA's building blocks reveals whether individual genes have mutations; measuring levels of RNA indicates how often those genes were translated into proteins. Such gene expression, Courchesne and his colleagues found, varied between autistic and typical brains. In brain tissue from both autistic children and autistic adults, genes coding for proteins that identify and repair mistakes in DNA were expressed at unusually low levels. Additionally, all autistic brains demonstrated unusual activity levels for genes that determine when neurons grow and die and how newborn neurons migrate during early development. Some genes involved in immune responses, cell-to-cell communication and tissue repair, however, were expressed at unusual levels in adult autistic brains, but not in autistic children's brains. The results appeared in *PLoS Genetics* in March 2012.

By combining these findings with his earlier discoveries, Courchesne has started to construct a kind of timeline of autism in the brain. Perhaps, as the brain of a future autistic child develops in the womb, something—an inherited mutation or an environmental factor like a virus, toxin or hormone—muffles the expression of genes coding for proteins that usually fix mistakes in sequences of DNA. Errors accumulate. The genetic systems controlling the growth of new neurons go haywire, and brain cells divide much more frequently than usual, accounting for the excess neurons found in the PFC of autistic children. Between birth and age five, the extra neurons in the autistic brain grow physically larger and form more

connections than in a typical child's brain. Unused connections are not pruned away as they should be. Later, in adolescence and adulthood, the immune system reacts against the brain's overzealous growth, which might explain the unusual levels of immune genes Courchesne found in his later study and why, in earlier work, he had discovered that when autistic children become teenagers, some brain regions actually start shrinking compared with typical brains.

Not all researchers, however, accept that the patterns of brain growth Courchesne has discovered are relevant to everyone with autism. Nicholas Lange, a biostatistician in the psychiatry department at Harvard Medical School, says that Courchesne analyzed too few samples in his new study to generalize the results to the larger autistic community. Some researchers have surfaced evidence that around 15 percent of autistic children have smaller than usual heads, a condition known as microcephaly, which indicates an abnormally small brain. David Amaral of the University of California, Davis, has previously told reporters that in an unpublished neuroimaging study, he found that only about 11 of 114 autistic children had unusually large brains. Other researchers point out that, in his research with tissue samples from brain banks, Courchesne fails to compare the number of neurons in the cerebral cortex with other parts of the brain—it remains unclear why only the PFC would explode in growth.

But acquiring enough preserved tissue from brain banks to conduct meaningful studies is no easy task—they are incredibly coveted resources, and Courchesne's study relies on a respectable sample. Looking at gene expression in postmortem brain tissue offers insights into the biology of autism that neuroimaging studies and analysis of DNA and RNA in blood cannot provide because different cell types express different sets of genes. Courchesne's findings at least partially echo earlier research by Daniel Geschwind of the University of California, Los Angeles, who also linked autism to unusual activity of genes that control immune responses and how neurons organize themselves in the developing brain. Although Courchesne's concept of autistic brain development is far from flawless or complete, it remains one of the most cohesive theories offered so far—one that suggests the possibility of treatment as well. If scientists definitively link autism to a characteristic sequence of changes in gene expression and

unusual neural growth, then it becomes possible to target and reverse any one of the thousands of steps in that sequence.

"Each individual autistic person likely has their own specific profile of dysregulated [sic] genes," Courchesne says, "which means that autism is a very complicated problem. But it's now knowable. We are getting at core knowledge. If we confirm that the starting point is gene activity, we can do something about it, because gene activity can be modified."

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Autism and the Technical Mind

by Simon Baron-Cohen

In 1997 my colleague Sally Wheelwright and I conducted a study involving nearly 2,000 families in the U.K. We included about half these families because they had at least one child with autism, a developmental condition in which individuals have difficulty communicating and interacting with others and display obsessive behaviors. The other families had children with a diagnosis of Tourette's syndrome, Down syndrome or language delays but not autism. We asked parents in each family a simple question: What was their job? Many mothers had not worked outside the home, so we could not use their data, but the results from fathers were intriguing: 12.5 percent of fathers of children with autism were engineers, compared with only 5 percent of fathers of children without autism.

Likewise, 21.2 percent of grandfathers of children with autism had been engineers, compared with only 2.5 percent of grandfathers of children without autism. The pattern appeared on both sides of the family. Women who had a child with autism were more likely to have a father who had been an engineer—and they were more likely to have married someone whose father had been an engineer.

Coincidence? I think not.

A possible explanation involves a phenomenon known as assortative mating, which usually means "like pairs with like." I first encountered the concept in an undergraduate statistics tutorial at the University of Oxford in 1978, when my tutor told me (perhaps to make statistics a little more lively) that whom you have sex with is not random. When I asked her to elaborate, she gave me the example of height: tall people tend to mate with tall people, and short people tend to mate with short people. Height is not the only characteristic that consciously and subconsciously influences partner

selection—age is another example, as are personality types. Now, more than 30 years later, my colleagues and I are testing whether assortative mating explains why autism persists in the general population. When people with technical minds—such as engineers, scientists, computer programmers and mathematicians— marry other technical-minded individuals, or their sons and daughters do, do they pass down linked groups of genes that not only endow their progeny with useful cognitive talents but also increase their children's chances of developing autism?

System Check

I began studying autism in the 1980s. By then, the psychogenic theory of autism—which argued that emotionally disinterested mothers caused their children's autism—had been soundly refuted. Michael Rutter, now at King's College London, and others had begun to study autism in twins and had shown that autism was highly heritable. Genetics, not parenting, was at work.

Today researchers know that an identical twin of someone with autism is around 70 times more likely to develop autism, too, compared with an unrelated individual. Although researchers have uncovered associations between specific genes and autism, no one has identified a group of genes that reliably predicts who will develop the condition. The genetics of autism are far more complex than that. What I have been interested in understanding, however, is how genes for autism survive in the first place. After all, autism limits one's abilities to read others' emotions and to form relationships, which in turn may reduce one's chances of having children and passing on one's genes.

One possibility is that the genes responsible for autism persist, generation after generation, because they are co-inherited with genes underlying certain cognitive talents common to both people with autism and technical-minded people whom some might call geeks. In essence, some geeks may be carriers of genes for autism: in their own life, they do not demonstrate any signs of severe autism, but when they pair up and have kids, their children may get a double dose of autism genes and traits. In this way, assortative mating between technical-minded people might spread autism genes.

Because “geek” is not the most scientific term, and for some may be pejorative, I needed to formulate a more precise definition of the cognitive talents shared by technical-minded people and people with autism. In the early 2000s Wheelwright and I surveyed nearly 100 families with at least one child with autism and asked another basic question: What was their child’s obsession? We received a diverse array of answers that included memorizing train timetables, learning the names of every member of a category (for instance, dinosaurs, cars, mushrooms), putting electrical switches around the house into particular positions, and running the water in the sink and rushing outside to see it flowing out of the drainpipe.

On the surface, these very different behaviors seem to share little, but they are all examples of systemizing. I define systemizing as the drive to analyze or construct a system—a mechanical system (such as a car or computer), a natural system (nutrition) or an abstract system (mathematics). Systemizing is not restricted to technology, engineering and math. Some systems are even social, such as a business, and some involve artistic pursuits, such as classical dance or piano. All systems follow rules. When you systemize, you identify the rules that govern the system so you can predict how that system works. This fundamental drive to systemize might explain why people with autism love repetition and resist unexpected changes.

Collaborating once again with Wheelwright, who is now at the University of Southampton in England, I put the link between systemizing and autism to the test. We found that children with Asperger’s syndrome—a form of autism with no language or intelligence impairments—outperformed older, typically developing children on a test of understanding mechanics. We also found that on average, adults and children with Asperger’s scored higher on self-report and parent-report measures of systemizing. Finally, we found that people with Asperger’s scored higher on a test of attention to detail. Attention to detail is a prerequisite for good systemizing. It makes a world of difference when trying to understand a system if you spot the small details or if you mistake one tiny variable in the system. (Imagine getting one digit wrong in a math calculation.) When we gave the test of attention to detail to parents, both the mothers and fathers of children with autism were also faster and more accurate than those of typically developing children.

Engineers aren't the only technical-minded people who might harbor autism genes. In 1998 Wheelwright and I found that math students at the University of Cambridge were nine times more likely than humanities students to report having a formal diagnosis of autism, including Asperger's, which will be folded into the broader "autism spectrum disorder" in the newest edition of psychiatry's guidebook, the *DSM-5*. Whereas only 0.2 percent of students in the humanities had autism, a figure not so different from the rate of autism reported in the wider population at the time, 1.8 percent of the math students had it. We also found that the siblings of mathematicians were five times more likely to have autism, compared with the siblings of those in the humanities.

In another test of the link between autism and math, Wheelwright and I developed a metric for measuring traits associated with autism in the general population, called the Autism Spectrum Quotient (AQ). It has 50 items, each representing one such trait. No one scores zero on the test. On average, typically developing men score 17 out of 50, and typically developing women score 15 out of 50. People with autism usually score above 32. We gave the AQ to winners of the British Mathematical Olympiad. They averaged 21 out of 50. This pattern suggested that—regardless of official diagnoses—mathematical talent was also linked to a higher number of traits associated with autism.

The Silicon Valley Phenomenon

One way to test the assortative mating theory is to compare couples in which both individuals are strong systemizers with couples who include only one strong systemizer—or none. Two-systemizer couples may be more likely to have a child with autism. My colleagues and I created a Web site where parents can report what they studied in college, their occupations, and whether or not their children have autism (www.cambridgepsychology.com/graduateparents).

Meanwhile we are exploring the theory from other angles. If genes for technical aptitude are linked to genes for autism, then autism should be more common in places around the world where many systemizers live, work and marry—places such as Silicon Valley in California, which some people claim has autism rates 10 times higher than the average for the general population.

In Bangalore, the Silicon Valley of India, local clinicians have made similar observations. Alumni of the Massachusetts Institute of Technology have also reported rates of autism 10 times higher than average among their children. Unfortunately, no one has yet conducted detailed and systematic studies in Silicon Valley, Bangalore or M.I.T., so these accounts remain anecdotal.

My colleagues and I, however, have investigated the rates of autism in Eindhoven, the Silicon Valley of the Netherlands. Royal Philips Electronics has been a major employer in Eindhoven since 1891, and IBM has a branch in the city. Indeed, some 30 percent of jobs in Eindhoven are in the IT sector. Eindhoven is also home to Eindhoven University of Technology and High Tech Campus Eindhoven, the Dutch equivalent of M.I.T. We compared rates of autism in Eindhoven with rates of autism in two similarly sized cities in the Netherlands: Utrecht and Haarlem.

In 2010 we asked every school in all three cities to count how many children among their pupils had a formal diagnosis of autism. A total of 369 schools took part, providing information on about 62,505 children. We found that the rate of autism in Eindhoven was almost three times higher (229 per 10,000) than in Haarlem (84 per 10,000) or Utrecht (57 per 10,000).

Male Minds

In parallel with testing the link between autism and systemizing, we have been examining why autism appears to be so much more common among boys than among girls. In classic autism, the sex ratio is about four boys to every girl. In Asperger's, the sex ratio may be as high as nine boys for every girl.

Likewise, strong systemizing is much more common in men than in women. In childhood, boys on average show a stronger interest in mechanical systems (such as toy vehicles) and constructional systems (such as Lego). In adulthood, men are overrepresented in STEM subjects (*s*cience, *t*echnology, *e*ngineering and *m*ath) but not in people-centered sciences such as clinical psychology or medicine. We have been investigating whether high levels of the hormone testosterone in the fetus, long known to play a role in "masculinizing" the developing brain in

animals, correlate with strong systemizing and more traits associated with autism. A human male fetus produces at least twice as much testosterone as a female fetus does.

To test these ideas, my colleague Bonnie Auyeung of the Cambridge Autism Research Center and I studied 235 pregnant women undergoing amniocentesis—a procedure in which a long needle samples the amniotic fluid surrounding a fetus. We found that the more testosterone surrounding a fetus in the womb, the stronger the children's later interest in systems, the better their attention to detail and the higher their number of traits associated with autism. Researchers in Cambridge, England, and Denmark are now collaborating to test whether children who eventually develop autism were exposed to elevated levels of testosterone in the womb.

If fetal testosterone plays an important role in autism, women with autism should be especially masculinized in certain ways. Some evidence suggests that this is true. Girls with autism show "tomboyism" in their toy-choice preferences. On average, women with autism and their mothers also have an elevated rate of polycystic ovary syndrome, which is caused by excess testosterone and involves irregular menstrual cycles, delayed onset of puberty and hirsutism (excessive body hair).

Prenatal testosterone, if it is involved in autism, is not acting alone. It behaves epigenetically, changing gene expression, and interacts with other important molecules. Similarly, the link between autism and systemizing, if confirmed through further studies, is unlikely to account for the full complexity of autism genetics. And we should not draw the simplistic conclusion that all technical-minded people carry genes for autism.

Investigating why certain communities have higher rates of autism, and whether genes that contribute to the condition are linked to genes for technical aptitude, may help us understand why the human brain sometimes develops differently than usual. People with autism, whose minds differ from what we consider typical, frequently display both disability and exceptional aptitude. Genes that contribute to autism may overlap with genes for the uniquely human ability to understand how the world works in extraordinary detail—to see beauty in patterns inherent in nature, technology, music and math.

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The Early Origins of Autism

by Patricia Rodier

Autism has been mystifying scientists for more than half a century. The complex behavioral disorder encompasses a wide variety of symptoms, most of which usually appear before a child turns three. Children with autism are unable to interpret the emotional states of others, failing to recognize anger, sorrow or manipulative intent. Their language skills are often limited, and they find it difficult to initiate or sustain conversations. They also frequently exhibit an intense preoccupation with a single subject, activity or gesture.

These behaviors can be incredibly debilitating. How can you be included in a typical classroom if you can't be dissuaded from banging your head on your desk? How can you make friends if your overriding interest is in calendars? When children with autism also suffer from mental retardation—as most of them do—the prognosis is even worse. Intensive behavioral therapy improves the outcome for many patients, but their symptoms can make it impossible for them to live independently, even if they have normal IQs.

I became involved in the search for autism's causes relatively recently—and almost by accident. As an embryologist, I previously focused on various birth defects of the brain. In 1994 I attended a remarkable presentation at a scientific conference on research into birth defects. Two pediatric ophthalmologists, Marilyn T. Miller of the University of Illinois at Chicago and Kerstin Strömland of Göteborg University in Sweden, described a surprising outcome from a study investigating eye motility problems in victims of thalidomide, the morning-sickness drug that caused an epidemic of birth defects in the 1960s. The study's subjects were adults who had been exposed to the drug while still in the womb. After examining these people, Miller and Strömland made an observation that had somehow

eluded previous researchers: about 5 percent of the thalidomide victims had autism, which is about 30 times higher than the rate among the general population.

When I heard these results, I felt a shock of recognition, a feeling so powerful that I actually became dizzy and began to hyperventilate. In the effort to identify autism's causes, researchers had long sought to pinpoint exactly when the disorder begins. Previous speculation had focused on late gestation or early postnatal life as the time of origin, but there was no evidence to back up either hypothesis. The connection with thalidomide suddenly threw a brilliant new light on the subject. It suggested that autism originates in the early weeks of pregnancy, when the embryo's brain and the rest of its nervous system are just beginning to develop. Indeed, Miller and Strömland's work convinced me that the mystery of autism could soon be solved.

Genetic Factors

At least 16 of every 10,000 babies is born with autism or one of its related disorders. Since autism was first identified in 1943, scientists have made great strides in describing its symptoms. The biological basis for autism, however, has been elusive—an unfortunate circumstance, because such an understanding could enable researchers to identify the leading risk factors for autism and possibly to design new treatments for the condition.

The Spectrum of Autism Disorders

A diagnosis of autism requires that the patient exhibit abnormal behaviors in three categories [see list] and have especially notable deficits in the category of social interaction. In addition, clinicians have identified several related disorders that share some of the behavioral features of autism but have different emphases or additional symptoms. For example, Pervasive Development Disorder, Not Otherwise Specified (PDD-NOS) denotes patients who miss fulfilling the autism criteria in one of the three categories. As is true of autism, PDD-NOS includes patients with the whole range of IQs. Asperger syndrome is used to describe patients with normal IQs and no evidence of language delay. Two much rarer diagnoses are Childhood Disintegrative Disorder, in which normal early development is followed by regression to severe disability, and Rett syndrome, a progressive neurological disorder that occurs only in females.

Although many scientists have long known that autism is an inherited disease, recent family studies by Peter Szatmari's group at McMaster University in Ontario suggest that it is the spectrum of symptoms that runs in families rather than a single diagnosis. For example, a child with autism may have a brother with Asperger syndrome, or a woman with autism may have a nephew with PDD-NOS. These family studies strongly suggest

that at least three of the diagnoses—autism, PDD-NOS and Asperger syndrome—arise from some of the same inherited factors.

Diagnostic Categories

Impairment of Social Interaction: Failure to use eye contact, facial expression or gestures to regulate social interaction; failure to seek comfort; failure to develop relationships with peers.

Impairment of Communication: Failure to use spoken language, without compensating by gesture; deficit in initiating or sustaining a conversation, despite adequate speech; aberrant language (for example, repeating a question instead of replying).

Restricted and Repetitive Interests and Behaviors: Abnormally intense preoccupation with one subject or activity; distress over change; insistence on routines or rituals with no purpose; repetitive movements, such as hand flapping.

By examining the inheritance of the disorder, researchers have shown that autism runs in families, though not in a clear-cut way. Siblings of people with autism have a 3 to 8 percent chance of being diagnosed with the same disorder. This is much greater than the 0.16 percent risk in the general population but much less than the 50 percent chance that would characterize a genetic disease caused by a single dominant mutation (in which one faulty gene inherited from one parent is sufficient to cause the disorder) or the 25 percent chance that would characterize a single recessive mutation (in which a copy of the faulty gene must be inherited from each parent). The results fit best with models in which variants of several genes contribute to the outcome. To complicate matters further, relatives of people with autism may fail to meet all the criteria for the disorder but still have some of its symptoms. Although these relatives may have some of the gene variants linked to autism—whatever they may be—for some reason the genetic factors are not fully expressed in these individuals.

Studies of twins in the U.K. confirm that autism has a heritable component but suggest that environmental influences play a role as well. For example, if genetic factors alone were involved, monozygotic (identical) twins, who share the same genes, should have a 100 percent chance of sharing the same diagnosis. Instead, when one twin has autism, the second twin has only a 60 percent chance of being diagnosed with the same disorder. That twin also has an 86 percent chance of having some of

autism's symptoms. These figures indicate that other factors must modify the genetic predisposition to the disorder.

The Embryology of Autism

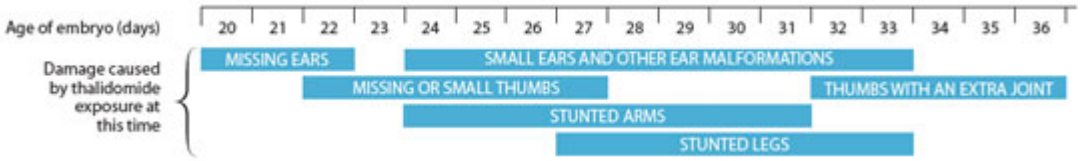
Several environmental risk factors are already known. In utero exposure to rubella (German measles) or to birth defect–causing substances such as ethanol and valproic acid increases the chances that autism will develop. People with certain genetic diseases, such as phenylketonuria and tuberous sclerosis, also have a greater chance of developing autism. None of these factors, however, is present frequently enough to be responsible for many cases. Furthermore, most exposures to diseases or hazardous substances would be likely to affect both members of a pair of twins rather than just one. Some of the environmental influences must be more subtle than those identified so far. Researchers do not know how the multiple factors combine to make some people display symptoms while allowing others to escape them. This variation makes the search for autism's causes especially difficult.

In their 1994 study Miller and Strömland added another environmental contributor to autism: thalidomide exposure in utero. All their subjects—Swedish adults born in the late 1950s and early 1960s—exhibited some of the malformations for which thalidomide is infamous: stunted arms and legs, misshapen or missing ears and thumbs, and neurological dysfunctions of the eye and facial muscles. Because scientists know which organs of the embryo are developing at each stage of pregnancy, they can pinpoint the exact days when a malformation can be induced: the thumb is affected as early as day 22 after conception, the ears from days 20 to 33, and the arms and legs from days 25 to 35. What made the new study so exciting for me was Miller and Strömland's discovery that most of the thalidomide victims with autism had anomalies in the external part of their ears but no malformations of the arms or legs. This pattern indicated that the subjects had been injured very early in gestation—20 to 24 days after conception—before many women even know they are pregnant.

Thalidomide Timeline

Birth defects caused by thalidomide vary depending on when the mother was exposed to the drug. A 1994 study showed that thalidomide victims with autism had ear anomalies and

normal limbs, suggesting that the drug triggered the disorder 20 to 24 days after conception, when the embryo's nervous system is starting to form.



Credit: Johnny Johnson

For embryologists, nothing tells us so much about *what* happened to an embryo as knowing *when* it happened. In the case of thalidomide-induced autism, the critical period is much earlier than many investigators would have guessed. Very few neurons form as early as the fourth week of gestation, and most are motor neurons of the cranial nerves, the ones that operate the muscles of the eyes, ears, face, jaw, throat and tongue. The cell bodies of these neurons are located in the brain stem, the region between the spinal cord and the rest of the brain. Because these motor neurons develop at the same time as the external ears, one might predict that the thalidomide victims with autism would also suffer from dysfunctions of the cranial nerves. Miller and Strömland confirmed this prediction—they found that all the subjects with autism had abnormalities of eye movement or facial expression, or both.

The next logical question was, "Are the cases of autism after thalidomide exposure similar to cases of unknown cause, or are they different?" Aside from their behavioral symptoms, people with autism have often been described not only as normal in appearance but as unusually attractive. They are certainly normal in stature, with normal-to-large heads. The few studies that have tested nonbehavioral features of people with autism, however, have concluded that there are indeed minor physical and neurological anomalies in many cases, and they are the same ones noted in thalidomide-induced autism. For example, minor malformations of the external ears—notably posterior rotation, in which the top of the ear is tilted backward more than 15 degrees—are more common in children with autism than in typically developing children, children with mental retardation or siblings of children with autism. Dysfunctions of eye movement had been associated with autism before the thalidomide study, and lack of facial expression is one of the behaviors used to diagnose the condition.

The Neurobiology of Autism

Is it possible that all the symptoms of autism arise from changes in the function of the cranial nerves? Probably not. It is more likely that the nerve dysfunctions in people with autism reflect an early brain injury that not only affects the cranial nerves but also has secondary effects on later brain development. That is, the injury to the brain stem might somehow interfere with the proper development or wiring of other brain regions, including those involved in higher-level functions such as speech, resulting in the behavioral symptoms of autism. Or perhaps the ear malformations and cranial nerve dysfunctions are only side effects of an injury that we don't understand. Whatever the true situation may be, the anomalies in patients with autism of unknown cause were much the same as the anomalies in the thalidomide victims with autism. The conclusion was clear: many cases of autism, if not all, are initiated very early in gestation.

The region of the brain implicated by the thalidomide study—the brain stem—is one that has rarely been considered in studies of autism or in studies of other kinds of congenital brain damage, for that matter. On a simplistic level, neurobiologists associate the brain stem with the most basic functions: breathing, eating, balance, motor coordination and so forth. Many of the behaviors disturbed in autism, such as language, planning and interpretation of social cues, are believed to be controlled by higher-level regions of the brain, such as the cerebral cortex and the hippocampus in the forebrain.

Yet some symptoms common in autism—lack of facial expression, hypersensitivity to touch and sound, and sleep disturbances—do sound like ones more likely to originate in the brain regions associated with basic functions. Furthermore, the most consistently observed abnormality in the brains of people with autism is not a change in the forebrain but a reduction in the number of neurons in the cerebellum, a large processing center of the hindbrain that has long been known to have critical functions in the control of muscle movement.

One reason for scientists' confusion about the brain regions involved in autism may be that our assumptions about where functions are controlled are shaky. For example, the laboratory group led by Eric Courchesne of the University of California at San Diego has shown that parts of the cerebellum are activated during certain tasks requiring high-level cognitive

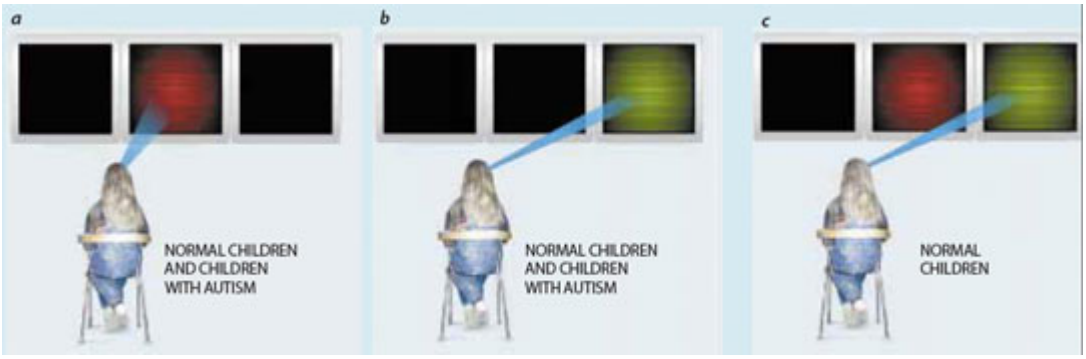
processing. Another difficulty is that the symptoms of autism are so complex. If simpler behavioral abnormalities could be shown to be diagnostic of the disorder, researchers might have a better chance of identifying their source in the nervous system.

A Simpler System of Autism

Scientists at York University and the Hospital for Sick Children in Toronto have identified an autism-related behavior that is much simpler than the array of behaviors that have traditionally been used to diagnose the condition. Susan Bryson and her doctoral student Reginald Landry have found that children with autism respond abnormally to a task involving their reactions to visual stimuli. Because this mental activity is probably mediated by a primitive part of the brain—most likely the brain stem or the cerebellum, or both—the discovery has important implications for the neurobiology of autism. Bryson and Landry's work could also help clinicians develop a simpler way to test children for the disorder.

In their study Bryson and Landry observed the reactions of two groups of children, those with autism and those without it, as they watched lights flashing on video screens. The children ranged in age from four to seven. In the first test, each child was placed in front of a three-screen panel, and a flashing light appeared on the middle screen. This stimulus prompted all the children to focus their eyes on the flashes (*a*). Then the middle screen went blank, and a flashing light appeared on the far-right or far-left screen of the panel. Both groups of children shifted their eyes to that screen (*b*). In the second test, however, the lights on the middle screen kept flashing while the lights appeared on the other screen. The children without autism shifted their eyes to focus on the new stimulus (*c*), but the children with autism remained "stuck" on the first stimulus and failed to turn their eyes to the new one (*d*). The two tests were repeated many times for each child.

Bryson and Landry found that children with other kinds of brain damage are perfectly normal in their ability to disengage from one stimulus and focus on another. Children with autism, however, repeatedly fail to disengage from the first stimulus, even if they are highly intelligent. Researchers suspect that this ability is a low-level brain function because it typically appears in infants—as early as three to four months after birth—and in children with low IQs. Animals also orient themselves toward new stimuli, so scientists could conceivably use a similar test in animal studies to verify whether genetic manipulations or toxicologic exposures have produced this symptom of autism.



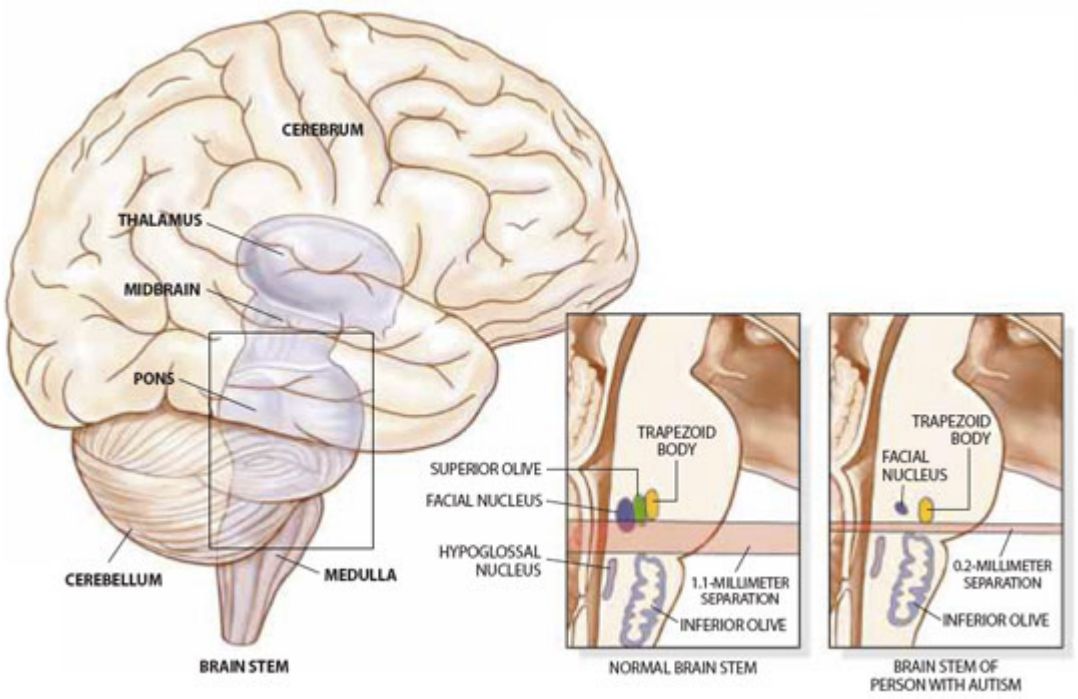
Credit: Daniels & Daniels

In 1995 our research team had the opportunity to follow up on the thalidomide study by examining the brain stem of a person with autism. The tissue samples came from the autopsy of a young woman who had suffered from autism of unknown cause; she had died in the 1970s, but fortunately the samples of her brain tissue had been preserved. When we examined the woman's brain stem, we were struck by the near absence of two structures: the facial nucleus, which controls the muscles of facial expression, and the superior olive, which is a relay station for auditory information. Both structures arise from the same segment of the embryo's neural tube, the organ that develops into the central nervous system. Counts of the facial neurons in the woman's brain showed only about 400 cells, whereas counts of facial neurons in a control brain showed 9,000.

Overall, the woman's brain was normal in size; in fact, it was slightly heavier than the average brain. I hypothesized that the brain stem was lacking only the specific neurons already identified—those in the facial nucleus and the superior olive—and to test that idea I decided to measure the distances between a number of neuroanatomical landmarks. I was surprised to discover that my hypothesis was absolutely wrong. Although the side-to-side measures were indeed normal, the front-to-back measures were astonishingly reduced in the brain stem of the woman with autism. It was as though a band of tissue had been cut out of the brain stem, and the two remaining pieces had been knit back together with no seam where the tissue was missing.

For the second time in my life, I felt a powerful shock of recognition. I heard a roaring in my ears, my vision dimmed, and I felt as though my head might explode. The shock was not generated by the unexpected result but by the realization that I had seen this pattern of shortening before, in a paper that showed pictures of abnormal mouse brains. When I retrieved the article from the stacks of papers on my office floor, I found that the correspondence between the brain I had been studying and the mouse brains described in the article was even more striking than I had remembered. Both cases exhibited shortening of the brain stem, a smaller-than-normal facial nucleus and the absence of a superior olive. Additional features of the mice were clearly related to other anomalies associated with autism: they had ear malformations and lacked one of the brain structures controlling eye movement.

AUTISM'S EFFECTS include changes to the brain stem, the region just above the spinal cord. The brain stem of a person with autism is shorter than a normal brain stem: the structures at the junction of the pons and the medulla (such as the facial nucleus and the trapezoid body) are closer to the structures of the lower medulla (the hypoglossal nucleus and the inferior olive). It is as though a band of tissue were missing. The brain stem of a person with autism also lacks the superior olive and has a smaller-than-normal facial nucleus. Such changes could occur only in early gestation.



Credit: Terese Winslow

What had altered the brains of these mice? It was not exposure to thalidomide or any of the other environmental factors associated with autism but the elimination of the function of a gene. These were transgenic "knockout" mice, engineered to lack the expression of the gene known as *Hoxa1* so that researchers could study the gene's role in early development. The obvious question was, "Could this be one of the genes involved in autism?"

The literature supported the idea that *Hoxa1* was an excellent candidate for autism research. The studies of knockout mice showed that *Hoxa1* plays a central role in development of the brain stem. Groups in Salt Lake City and London had studied different knockout strains with similar results. They found that the gene is active in the brain stem when the first neurons are forming—the same period that Miller and Strömland had identified as

the time when thalidomide caused autism. *Hoxa1* produces a type of protein called a transcription factor, which modulates the activity of other genes. What is more, *Hoxa1* is not active in any tissue after early embryogenesis. If a gene is active throughout life, as many are, altered function of that gene usually leads to problems that increase with age. A gene active only during development is a better candidate to explain a congenital disability like autism, which seems to be stable after childhood.

Hoxa1 is what geneticists call a "highly conserved" gene, meaning that the sequence of nucleotides that make up its DNA has changed little over the course of evolution. We assume that this is a characteristic of genes that are critical to survival: they suffer mutations as other genes do, but most changes are likely to be fatal, so they are rarely passed on to subsequent generations. Although many other genes appear in several forms—for example, the genes that encode eye color or blood type—highly conserved genes are not commonly found in multiple versions (also known as polymorphic alleles, or allelic variants). The fact that no one had ever discovered a variant of *Hoxa1* in any mammalian species suggested that my colleagues and I might have trouble finding one in cases of autism. On the other hand, it seemed likely that if a variant allele could be found, it might well be one of the triggers for the development of the disorder.

Zeroing in on *HOXA1*

The human version of the gene, labeled as *HOXA1*, resides on chromosome 7 and is relatively small. It contains just two protein-coding regions, or exons, along with regions that regulate the level of protein production or do nothing at all. Deviations from the normal sequence in any part of a gene can affect its performance, but the vast majority of disease-causing variations are in the protein-coding regions. Thus, we began the search for variant alleles by focusing on the exons of *HOXA1*. Using blood samples from people with autism and from subjects in a control group, we extracted the DNA and looked for deviations from the normal sequence of nucleotides.

The good news is that we have identified two variant alleles of *HOXA1*. One has a minor deviation in the sequence of one of the gene's exons, meaning that the protein encoded by the variant gene is slightly different from the protein encoded by the normal gene. We have studied this newly

discovered allele in detail, measuring its prevalence among various groups of people to determine if it plays a role in causing autism. (The other variant allele is more difficult to investigate because it involves a change in the physical structure of the gene's DNA.) We found that the rate of the variant allele among people with autism was significantly higher than the rate among their family members who do not have the disorder and the rate among unrelated individuals without the disorder. The differences were much greater than would be expected by chance.

The bad news is that, just as the family studies had predicted, *HOXA1* is only one of many genes involved in the spectrum of autism disorders. Furthermore, the allele that we have studied in detail is variably expressed —its presence does not guarantee that autism will arise. Preliminary data indicate that the variant allele occurs in about 20 percent of the people who do not have autism and in about 40 percent of those who do. The allele approximately doubles the risk of developing the condition. But in about 60 percent of people with autism, the allele is not present, meaning that other genetic factors must be contributing to the disorder.

To pin down those factors, we must continue searching for other variants in *HOXA1*, because most genetic disorders result from many different deviant alleles of the same gene. Variations in other genes involved in early development may also predispose their carriers to autism. We have already discovered a variant allele of *HOXB1*, a gene on chromosome 17 that is derived from the same ancestral source as *HOXA1* and has similar functions in the development of the brain stem, but its effect in autism appears to be minor. Other investigators are scrutinizing candidate regions on chromosome 15 and on another part of chromosome 7. Although researchers are focusing on alleles that increase the risk of autism, other alleles may decrease the risk. These could help explain the variable expression of the spectrum of autism-related disorders.

Even a minimal understanding of the genetic basis of autism would be of great value. For example, researchers could transfer the alleles associated with autism from humans to mice, engineering them to be genetically susceptible to the disorder. By exposing these mice to substances suspected of increasing the risk of autism, we would be able to study the interaction of environmental factors with genetic background and perhaps compile an

expanded list of substances that women need to avoid during early pregnancy. What is more, by examining the development of these genetically engineered mice, we could learn more about the brain damage that underlies autism. If researchers can determine exactly what is wrong with the brains of people with autism, they may be able to suggest drug therapies or other treatments that could ameliorate the effects of the damage.

Devising a genetic test for autism—similar to the current tests for cystic fibrosis, sickle cell anemia and other diseases—would be a much more difficult task. Because so many genes appear to be involved in the disorder, one cannot accurately predict the odds of having a child with autism by simply testing for one or two variant alleles in the parents. Tests might be developed, however, for the siblings of people with autism, who often fear that their own children will inherit the disorder. Clinicians could look for a set of well-established genetic risk factors in both the family member with autism and the unaffected sibling. If the person with autism has several high-risk alleles, whereas the sibling does not, the sibling would at least be reassured that his or her offspring would not be subject to the known risks within his or her family.

Nothing will make the search for autism's causes simple. But every risk factor that we are able to identify takes away some of the mystery. More important, new data spawn new hypotheses. Just as the thalidomide results drew attention to the brain stem and to the *HOXA1* gene, new data from developmental genetics, behavioral studies, brain imaging and many other sources can be expected to produce more welcome shocks of recognition for investigators of autism. In time, their work may help alleviate the terrible suffering caused by the disorder.

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Broken Mirrors: A Theory of Autism

by Vilayanur S. Ramachandran and Lindsay M. Oberman

At first glance you might not notice anything odd on meeting a young boy with autism. But if you try to talk to him, it will quickly become obvious that something is seriously wrong. He may not make eye contact with you; instead he may avoid your gaze and fidget, rock his body to and fro, or bang his head against the wall. More disconcerting, he may not be able to conduct anything remotely resembling a normal conversation. Even though he can experience emotions such as fear, rage and pleasure, he may lack genuine empathy for other people and be oblivious to subtle social cues that most children would pick up effortlessly.

In the 1940s two physicians—American psychiatrist Leo Kanner and Austrian pediatrician Hans Asperger—independently discovered this developmental disorder, which afflicts about 0.5 percent of American children. Neither researcher had any knowledge of the other's work, and yet by an uncanny coincidence each gave the syndrome the same name: autism, which derives from the Greek word *autos*, meaning "self." The name is apt, because the most conspicuous feature of the disorder is a withdrawal from social interaction. More recently, doctors have adopted the term "autism spectrum disorder" to make it clear that the illness has many related variants that range widely in severity but share some characteristic symptoms.

Ever since autism was identified, researchers have struggled to determine what causes it. Scientists know that susceptibility to autism is inherited, although environmental risk factors also seem to play a role. Starting in the late 1990s, investigators in our laboratory at the University of California, San Diego, set out to explore whether there was a connection between autism and a newly discovered class of nerve cells in the brain called mirror neurons. Because these neurons appeared to be involved in abilities such as

empathy and the perception of another individual's intentions, it seemed logical to hypothesize that a dysfunction of the mirror neuron system could result in some of the symptoms of autism. Over the past decade, several studies have provided evidence for this theory. Further investigations of mirror neurons may explain how autism arises, and in the process physicians may develop better ways to diagnose and successfully treat the disorder.

Explaining the Symptoms

Although the chief diagnostic signs of autism are social isolation, lack of eye contact, poor language capacity and absence of empathy, other less well known symptoms are commonly evident. Many people with autism have problems understanding metaphors, sometimes interpreting them literally. They also have difficulty miming other people's actions. Often they display an eccentric preoccupation with trifles yet ignore important aspects of their environment, especially their social surroundings. Equally puzzling is the fact that they frequently show an extreme aversion to certain sounds that, for no obvious reason, set off alarm bells in their minds.

The theories that have been proposed to explain autism can be divided into two groups: anatomical and psychological. (Researchers have rejected a third group of theories—such as the "refrigerator mother" hypothesis—that blame the disorder on poor upbringing.) Eric Courchesne of U.C.S.D. and other anatomists have shown elegantly that children with autism have characteristic abnormalities in the cerebellum, the brain structure responsible for coordinating complex voluntary muscle movements. Although these observations must be taken into account in any final explanation of autism, it would be premature to conclude that damage to the cerebellum is the sole cause of the disorder. Cerebellar damage inflicted by a stroke in a child usually produces tremors, swaying gait and abnormal eye movements—symptoms rarely seen in autism. Conversely, one does not see any of the symptoms typical of autism in patients with cerebellar disease. It is possible that the cerebellar changes observed in children with autism may be unrelated side effects of abnormal genes whose *other* effects are the true causes of the disorder.

Perhaps the most ingenious of the psychological theories is that of Uta Frith of University College London and Simon Baron-Cohen of the

University of Cambridge, who posit that the main abnormality in autism is a deficit in the ability to construct a "theory of other minds." Frith and Baron-Cohen argue that specialized neural circuitry in the brain allows us to create sophisticated hypotheses about the inner workings of other people's minds. These hypotheses, in turn, enable us to make useful predictions about others' behavior. Frith and Baron-Cohen are obviously on the right track, but their theory does not provide a complete explanation for the constellation of seemingly unrelated symptoms of autism. Indeed, saying that people with autism cannot interact socially because they lack a "theory of other minds" does not go very far beyond restating the symptoms. What researchers need to identify are the brain mechanisms whose known functions match those that are disrupted in autism.

One clue comes from the work of Giacomo Rizzolatti and his colleagues at the University of Parma in Italy, who in the 1990s studied neural activity in the brains of macaque monkeys while the animals were performing goal-directed actions. Researchers have known for decades that certain neurons in the premotor cortex—part of the brain's frontal lobe—are involved in controlling voluntary movements. For instance, one neuron will fire when the monkey reaches for a peanut, another will fire when the animal pulls a lever, and so on. These brain cells are often referred to as motor command neurons. (Bear in mind that the neuron whose activity is recorded does not control the arm by itself; it is part of a circuit that can be monitored by observing the signals in the constituent neurons.)

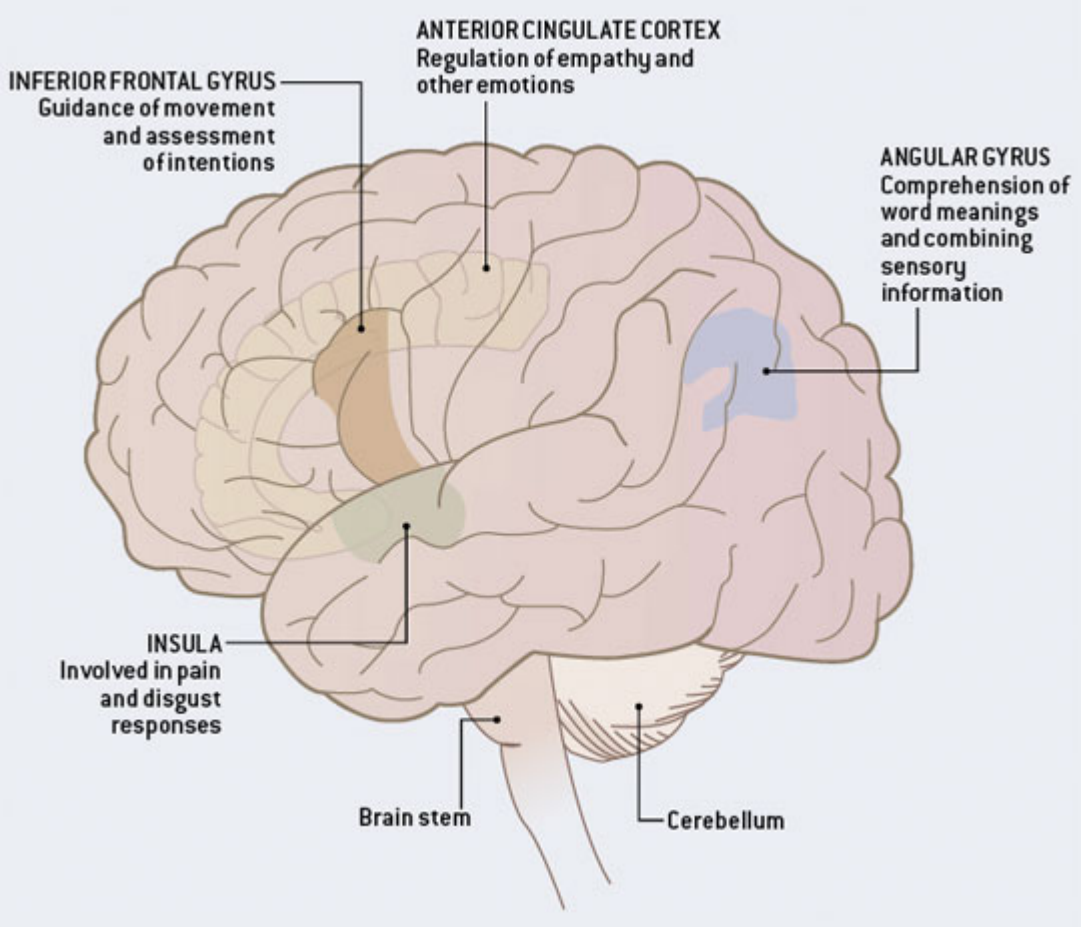
What surprised Rizzolatti and his co-workers was that a subset of the motor command neurons also fired when the monkey watched another monkey or a researcher perform the same action. For example, a neuron involved in controlling the reach-for-the-peanut action fired when the monkey saw one of his fellows making that movement. Brain-imaging techniques subsequently showed that these so-called mirror neurons also exist in the corresponding regions of the human cortex. These observations implied that mirror neurons—or, more accurately, the networks they are part of—not only send motor commands but also enable both monkeys and humans to determine the intentions of other individuals by mentally simulating their actions. In monkeys, the role of the neurons may be limited to predicting simple goal-directed actions, but in humans the mirror neuron system may have evolved the ability to interpret more complex intentions.

Later research showed that mirror neurons are located in other parts of the human brain, such as the cingulate and insular cortices, and that they may play a role in empathetic emotional responses. While studying the anterior cingulate cortex of awake human subjects, investigators found that certain neurons that typically fire in response to pain also fired when the person saw someone else in pain. Mirror neurons may also be involved in imitation, an ability that appears to exist in rudimentary form in the great apes but is most pronounced in humans. The propensity to imitate must be at least partly innate: Andrew Meltzoff of the University of Washington has shown that if you stick your tongue out at a newborn baby, the infant will do the same. Because the baby cannot see its own tongue, it cannot use visual feedback and error correction to learn the skill. Instead there must be a hardwired mechanism in the child's brain for mapping the mother's visual appearance—whether it be a tongue sticking out or a smile—onto the motor command neurons.

Language development in childhood also requires a remapping of sorts between brain areas. To imitate the mother's or father's words, the child's brain must transform auditory signals in the hearing centers of the brain's temporal lobes into verbal output from the motor cortex. Whether mirror neurons are directly involved in this skill is not known, but clearly some analogous process must be going on. Last, mirror neurons may enable humans to see them selves as others see them, which may be an essential ability for self-awareness and introspection.

THE ANATOMY OF AUTISM

People with autism show reduced mirror neuron activity in the inferior frontal gyrus, a part of the brain's premotor cortex, perhaps explaining their inability to assess the intentions of others. Dysfunctions of mirror neurons in the insula and anterior cingulate cortex may cause related symptoms, such as the absence of empathy, and deficits in the angular gyrus may result in language difficulties. People with autism also have structural changes in the cerebellum and brain stem.



Credit: Lucy Reading-Ikkanda

Suppressing Mu Waves

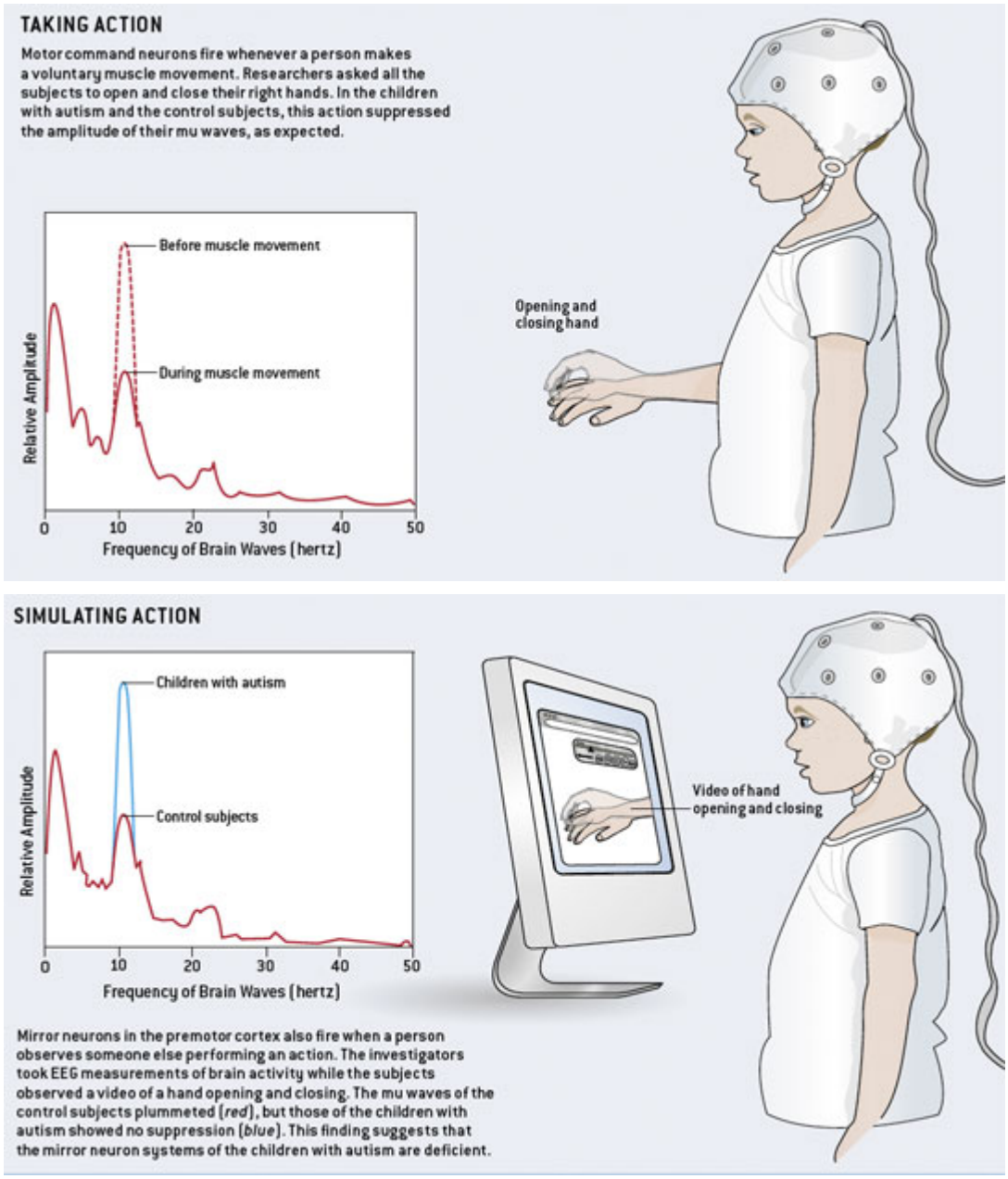
What has all this to do with autism? In the late 1990s our group at U.C.S.D. noted that mirror neurons appear to be performing precisely the same functions that seem to be disrupted in autism. If the mirror neuron system is indeed involved in the interpretation of complex intentions, then a breakdown of this neural circuitry could explain the most striking deficit in people with autism, their lack of social skills. The other cardinal signs of the disorder—absence of empathy, language deficits, poor imitation, and so on—are also the kinds of things you would expect to see if mirror neurons were dysfunctional. Andrew Whitten's group at the University of St. Andrews in Scotland made this proposal at about the same time we did, but the first experimental evidence for the hypothesis came from our lab, working in collaboration with Eric L. Altschuler and Jaime A. Pineda of U.C.S.D.

To demonstrate mirror neuron dysfunction in children with autism, we needed to find a way to monitor the activity of their nerve cells without putting electrodes in their brains (as Rizzolatti and his colleagues did with their monkeys). We realized that we could do so using an electroencephalogram (EEG) measurement of the children's brain waves. For more than half a century, scientists have known that an EEG component called the mu wave is blocked anytime a person makes a voluntary muscle movement, such as opening and closing one's hands. Interestingly, this component is also blocked when a person watches someone else perform the same action. One of us (Ramachandran) and Altschuler suggested that mu-wave suppression might provide a simple, noninvasive probe for monitoring mirror neuron activity.

We decided to focus our first experiments on a high-functioning child with autism—that is, a child without severe cognitive impairments. (Very young, low-functioning children did not participate in this study because we wanted to confirm that any differences we found were not a result of problems in attention, understanding instructions or the general effects of mental retardation.) The EEG showed that the child had an observable mu wave that was suppressed when he made a simple, voluntary movement, just as in normal children. But when the child watched someone else perform the action, the suppression did not occur. We concluded that the child's motor command system was intact but that his mirror neuron system was deficient. This observation, which we presented at the annual meeting of the Society for Neuroscience in 2000, provided a striking vindication of our hypothesis.

FOCUSING ON MU WAVES

To study the mirror neuron system in people with autism, researchers relied on the observation that the firing of neurons in the premotor cortex suppresses the mu wave, a component of the electroencephalogram (EEG) measurement of the brain's activity. (Mu waves range from eight to 13 hertz.) Investigators monitored the mu waves of children with autism and control subjects as they made voluntary muscle movements and then watched the same actions on video.



Credit: Lucy Reading-Ikkanda

One has to be careful, however, of generalizing from a single case, so our lab group later conducted a more systematic series of experiments in 10 high-functioning individuals with autism spectrum disorder and 10 age- and gender-matched control subjects. We saw the expected suppression of mu waves when the control subjects moved their hands and watched videos of a moving hand, but the EEGs of the subjects with autism showed mu suppression only when they moved their own hands.

Other researchers have confirmed our results using different techniques for monitoring neural activity. A group led by Riitta Hari of the Helsinki University of Technology found mirror neuron deficits in children with autism by employing magnetoencephalography, which measures the magnetic fields produced by electric currents in the brain. More recently, Mirella Dapretto of the University of California, Los Angeles, and her colleagues used functional magnetic resonance imaging to show a reduction in mirror neuron activity in the prefrontal cortices of individuals with autism. And Hugo Théoret of the University of Montreal and his co-workers used transcranial magnetic stimulation, a technique that induces electric currents in the motor cortex to generate muscle movements, to study mirror neuron activity in subjects with autism. In the control subjects, induced hand movements became more pronounced when the subjects watched videos of the same movements; this effect was much weaker in the subjects with autism.

Taken together, these findings provide compelling evidence that people with autism have dysfunctional mirror neuron systems. Scientists do not yet know which genetic and environmental risk factors can prevent the development of mirror neurons or alter their function, but many research groups are now actively pursuing the hypothesis because it predicts symptoms that are unique to autism. In addition to explaining the primary signs of autism, deficiencies in the mirror neuron system can also account for some of the less well known symptoms. For instance, researchers have long known that children with autism often have problems interpreting proverbs and metaphors. When we told one of our subjects to “get a grip on yourself,” he took the message literally and started grabbing his own body. Though seen in only a subset of children with autism, this difficulty with metaphors cries out for an explanation.

Understanding metaphors requires the ability to extract a common denominator from superficially dissimilar entities. Consider the bouba/kiki effect, which was discovered by German-American psychologist Wolfgang Köhler more than 60 years ago. In this test, a researcher displays two crudely drawn shapes, one jagged and one curvy, to an audience and asks, “Which of these shapes is bouba and which is kiki?” No matter what languages the respondents speak, 98 percent will pick the curvy shape as bouba and the jagged one as kiki. This result suggests that the human brain

is somehow able to extract abstract properties from the shapes and sounds —for example, the property of jaggedness embodied in both the pointy drawing and the harsh sound of kiki. We conjectured that this type of cross-domain mapping is analogous to metaphors and must surely involve neural circuits similar to those in the mirror neuron system. Consistent with this speculation, we discovered that children with autism perform poorly at the bouba/kiki test, pairing the shapes and sounds incorrectly.

But which part of the human brain is involved in this skill? The angular gyrus, which sits at the crossroads of the brain's vision, hearing and touch centers, seemed to be a likely candidate—not only because of its strategic location but because nerve cells with mirror neuron–like properties have been identified there. When we studied nonautistic subjects with damage to this area of the brain, we found that many of them fail the bouba/kiki test and have a disproportionate difficulty understanding metaphors, just like people with autism. These results suggest that cross-domain mapping may have originally developed to aid primates in complex motor tasks such as grasping tree branches (which requires the rapid assimilation of visual, auditory and touch information) but eventually evolved into an ability to create metaphors. Mirror neurons allowed humans to reach for the stars, instead of mere peanuts.

Can the Mirrors Be Repaired?

The discovery of mirror neuron deficiencies in people with autism opens up new approaches to diagnosing and treating the disorder. For example, physicians could use the lack of mu-wave suppression (or perhaps the failure to mimic a mother sticking out her tongue) as a diagnostic tool to identify children with autism in early infancy, so that the currently available behavioral therapies can be started as quickly as possible. Timely intervention is critical; the behavioral therapies are much less effective if begun after autism's main symptoms appear (typically between ages two and four).

An even more intriguing possibility would be to use biofeedback to treat autism or at least alleviate its symptoms. Doctors could monitor the mu waves of a child with autism and display them on a screen in front of the patient. If the child's mirror neuron functions are dormant rather than completely lost, it may be possible for him or her to revive this ability by

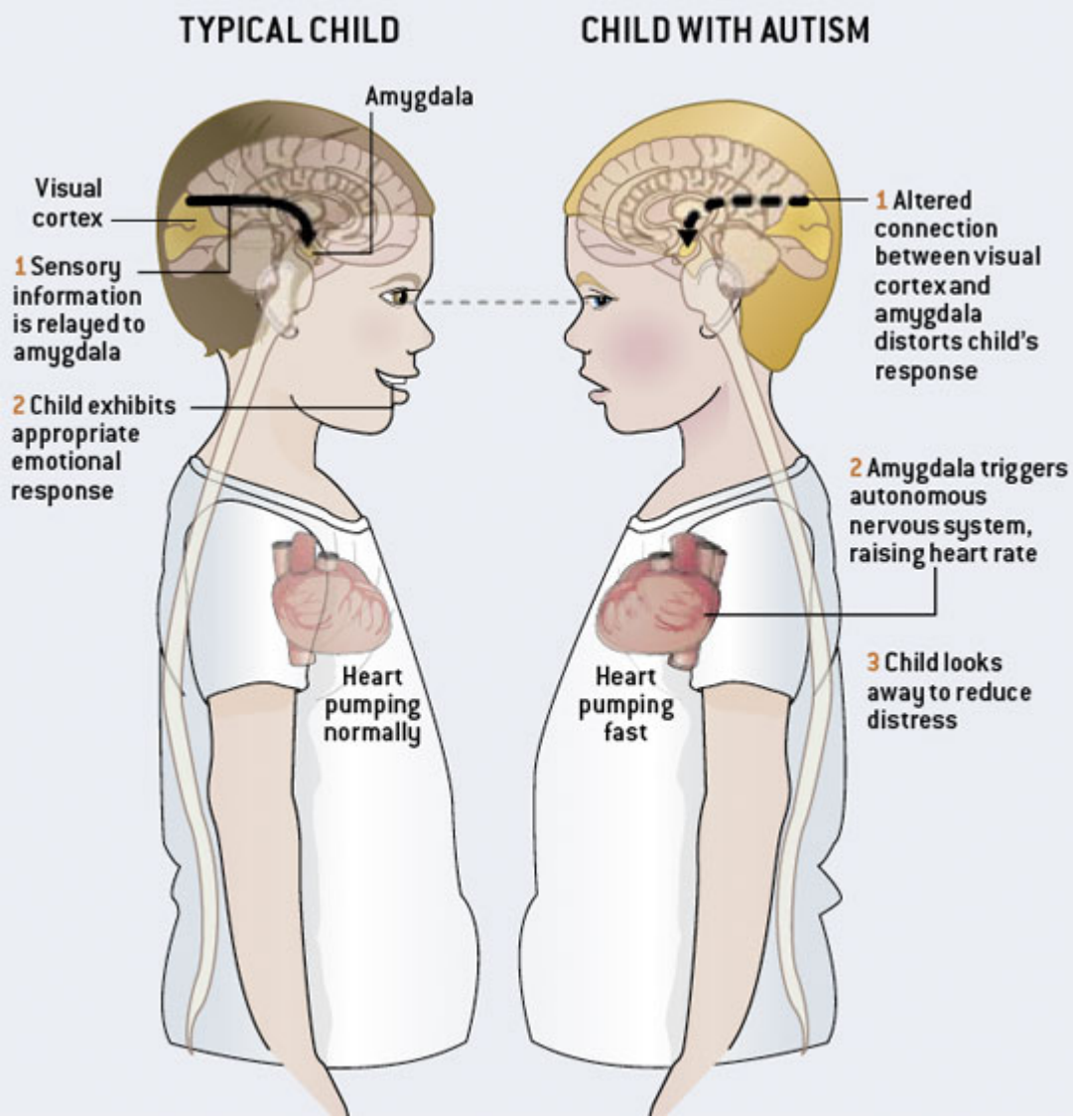
learning—through trial and error and visual feedback—how to suppress the mu waves on the screen. Our colleague Pineda is pursuing this approach, and his preliminary results look promising. Such therapies, though, should supplement rather than replace the traditional behavioral-training techniques.

Another novel therapeutic approach might rely on correcting chemical imbalances that disable the mirror neurons in individuals with autism. Our group (including students Mikhi Horvath and Mary Vertinsky) has suggested that specialized neuromodulators may enhance the activity of mirror neurons involved in emotional responses. According to this hypothesis, the partial depletion of such chemicals could explain the lack of emotional empathy seen in autism, and therefore researchers should look for compounds that stimulate the release of the neuromodulators or mimic their effects on mirror neurons. One candidate for investigation is MDMA, better known as ecstasy, which has been shown to foster emotional closeness and communication. It is possible that researchers may be able to modify the compound to develop a safe, effective treatment that could alleviate at least some of autism's symptoms.

Such treatments, however, may offer only partial relief, because other symptoms of autism cannot be explained by the mirror neuron hypothesis—for example, repetitive motions such as rocking to and fro, avoidance of eye contact, hypersensitivity, and aversion to certain sounds. In an attempt to determine how these secondary symptoms might arise, our lab group (in collaboration with William Hirstein of Elmhurst College and Portia Iversen of Cure Autism Now, a nonprofit foundation based in Los Angeles) has developed what we call the salience landscape theory.

THE SALIENCE LANDSCAPE THEORY

To account for some of the secondary symptoms of autism—hypersensitivity, avoidance of eye contact, aversion to certain sounds, and so on—researchers have developed the salience landscape theory. In a typical child, sensory information is relayed to the amygdala, the gateway to the emotion-regulating limbic system. Using input from stored knowledge, the amygdala determines how the child should respond emotionally to each stimulus, creating a salience landscape of the child's environment. In children with autism, though, the connections between the sensory areas and the amygdala may be altered, resulting in extreme emotional responses to trivial events and objects.



Credit: Lucy Reading-Ikkanda

When a person looks at the world, he or she is confronted with an overwhelming amount of sensory information—sights, sounds, smells, and so on. After being processed in the brain's sensory areas, the information is relayed to the amygdala, which acts as a portal to the emotion-regulating limbic system. Using input from the individual's stored knowledge, the amygdala determines how the person should respond emotionally—for example, with fear (at the sight of a burglar), lust (on seeing a lover) or indifference (when facing something trivial). Messages cascade from the amygdala to the rest of the limbic system and eventually reach the autonomic nervous system, which prepares the body for action. If the person is confronting a burglar, for example, his heart rate will rise and his

body will sweat to dissipate the heat from muscular exertion. The autonomic arousal, in turn, feeds back into the brain, amplifying the emotional response. Over time, the amygdala creates a salience landscape, a map that details the emotional significance of everything in the individual's environment.

Our group decided to explore the possibility that children with autism have a distorted salience landscape, perhaps because of altered connections between the cortical areas that process sensory input and the amygdala or between the limbic structures and the frontal lobes that regulate the resulting behavior. As a result of these abnormal connections, any trivial event or object could set off an extreme emotional response—an autonomic storm—in the child's mind. This hypothesis would explain why children with autism tend to avoid eye contact and any other novel sensation that might trigger an upheaval. The distorted perceptions of emotional significance might also explain why many children with autism become intensely preoccupied with trifles such as train schedules while expressing no interest at all in things that most children find fascinating.

We found some support for our hypothesis when we monitored autonomic responses in a group of 37 children with autism by measuring the increase in their skin conductance caused by sweating. In contrast with the control subjects, the children with autism had a higher overall level of autonomic arousal. Although they became agitated when exposed to trivial objects and events, they often ignored stimuli that triggered expected responses in the control group.

But how could a child's salience landscape become so distorted? Investigators have found that nearly one third of children with autism have had temporal lobe epilepsy in infancy, and the proportion may be much higher given that many epileptic seizures go undetected. Caused by repeated random volleys of nerve impulses traversing the limbic system, these seizures could eventually scramble the connections between the visual cortex and the amygdala, indiscriminately enhancing some links and diminishing others. In adults, temporal lobe epilepsy results in florid emotional disturbances but does not radically affect cognition; in infants, however, the seizures may lead to a more profound disability. And, like autism, the risk of temporal lobe epilepsy in infancy appears to be

influenced by both genetic and environmental factors. Some genes, for example, could make a child more susceptible to viral infections, which could in turn predispose the child to seizures.

Our findings on autonomic responses may help explain the old clinical observation that high fever sometimes temporarily alleviates the symptoms of autism. The autonomic nervous system is involved in controlling body temperature; because fever and the emotional upheavals of autism appear to be regulated by the same neural pathways, perhaps the former can mitigate the latter.

The salience landscape theory could also provide an explanation for the repetitive motions and head banging seen in children with autism: this behavior, called self-stimulation, may somehow damp the child's autonomic storms. Our studies found that self-stimulation not only had a calming effect but also led to a measurable reduction in skin conductance. This result suggests a possible symptomatic therapy for autism. Hirstein is now developing a portable device that could monitor an autistic child's skin conductance; when the device detects autonomic arousal, it could turn on another device, called a squeeze vest, that provides a comforting pressure by gently tightening around the child's body.

Our two candidate theories for explaining the symptoms of autism—mirror neuron dysfunction and distorted salience landscape—are not necessarily contradictory. It is possible that the same event that distorts a child's salience landscape—the scrambled connections between the limbic system and the rest of the brain—also damages the mirror neurons. Alternatively, the altered limbic connections could be a side effect of the same genes that trigger the dysfunctions in the mirror neuron system. Further experiments are needed to rigorously test these conjectures. The ultimate cause of autism remains to be discovered. In the meantime, our speculations may provide a useful framework for future research.

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What's So Special about Mirror Neurons?

by Ben Thomas

In the early 1990s, a team of neuroscientists at the University of Parma made a surprising discovery: Certain groups of neurons in the brains of macaque monkeys fired not only when a monkey performed an action—grabbing an apple out of a box, for instance—but also when the monkey watched someone else performing that action; and even when the monkey heard someone performing the action in another room.

In short, even though these "mirror neurons" were part of the brain's motor system, they seemed to be correlated not with specific movements, but with specific goals.

Over the next few decades, this "action understanding" theory of mirror neurons blossomed into a wide range of promising speculations. Since most of us think of goals as more abstract than movements, mirror neurons confront us with the distinct possibility that those everyday categories may be missing crucial pieces of the puzzle—thus, some scientists propose that mirror neurons might be involved in feelings of empathy, while others think these cells may play central roles in human abilities like speech.

Some doctors even say they've discovered new treatments for mental disorders by reexamining diseases through the mirror neuron lens. For instance, UCLA's Marco Iacoboni and others have put forth what Iacoboni called the "broken mirror hypothesis" of autism—the idea that malfunctioning mirror neurons are likely responsible for the lack of empathy and theory of mind found in severely autistic people.

Ever since these theories' earliest days, though, sharp criticism has descended on the claims they make. If it turns out that mirror neurons play only auxiliary roles—and not central ones—in action understanding, as

many opponents of these claims contend, we may be looking in entirely the wrong place for causes of autism and speech disorders. We could be ignoring potential cures by focusing on a hypothesis that's grown too popular for its own good.

And through it all, the mirror neuron field continues to attract new inquisitive minds. September 2012 marked the first-ever Mirror Neurons: New Frontiers Summit in Erice, Sicily, where researchers championing all sides of the debate gathered to share their findings and hash out their differences.

In the wake of the Summit, I caught up with some of the world's top mirror neuron experts, and asked them to bring me up to date on their latest findings, debates, and discussions. Their insights paint a more subtle, nuanced picture of mirror neurons' role than anyone originally suspected.

Can Mirror Neurons Understand?

There's something strange about the range of actions mirror neurons respond to. They don't respond to pantomimes, or to meaningless gestures, or to random animal sounds. They seem specially tuned to respond to actions with clear goals—whether those actions are perceived through sight, sound, or any other sensory pathway.

This realization led the discoverers of mirror neurons to put forth what they call the "action understanding" hypothesis—that mirror neurons are the neural basis for our ability to understand others' actions. On this hypothesis rests a kingdom: If it's true, Iacoboni may be right that we can treat autism and speech disorders by repairing the human mirror neuron system. But this kingdom's borders have fallen under relentless attack since its very earliest days.

One of the first scientists to question the "action understanding" hypothesis was UC Irvine's Greg Hickok. Though Hickok doesn't dispute the existence of mirror neurons, he's highly skeptical about their supposed central role in empathy, speech, autism and understanding—and he's spent the past 10 years publishing research regarding those doubts.

The question of whether mirror neurons allow us to understand movement gestures, Hickok explains, is only one of the "action understanding"

school's unsupported claims—researchers who argue for a mirror neuron-centric model of speech comprehension also bear the burden of proving their claim that the motor system is involved in representing the meaning of action-related language.

What the "action understanding" school originally claimed, Hickok says, was that mirror neurons provide the neural mechanism for *attaching* meanings to motor actions—but in recent years, many of those same researchers have been leaning away from that claim, and toward the contention that mirror neurons themselves actually encode the meanings of actions. And both of these claims, according to Hickok, remain unsupported by hard evidence.

"Iacoboni and the other 'action understanding' supporters are conflating two logically independent questions," Hickok explains. "Their original claim was that mirror neurons provide the mechanism for attaching meaning to actions like hand and speech gestures. But the second question —which they conflate with the first—is whether the meanings of actions are coded in motor systems." In other words, before we can say for sure whether mirror neurons are necessary for understanding others' actions, we first need to establish whether these neurons associate actions with their meanings, code the meanings themselves, or neither.

"It could be that mirror neurons facilitate your understanding a reaching movement," Hickok adds, "but don't themselves represent the semantics of the concept 'reach' generally." In short, even if mirror neurons do enable your brain to access the concept 'reach,' that doesn't mean they themselves are the neurons that encode that concept.

Over the years, Hickok has led several dozen studies that find dissociations between motor control and conceptual understanding. If he's right, and mirror neurons help code movements but not semantic concepts of them, researchers may be looking for the causes of autism and speech disorders in areas that merely reflect, rather than produce, the symptoms—like picking trash out of a creek while ignoring the garbage dump upstream.

Take patients with Broca's aphasia, for instance. These patients, who've suffered severe damage to the motor areas of their brain's left hemisphere, have major trouble joining words into coherent phrases. Ask a person with

Broca's aphasia about the last time he visited the hospital, and he'll say something like, "hospital... and ah... Wednesday... Wednesday, nine o'clock... and oh... Thursday... ten o'clock, ah doctors." Even so, a patient with Broca's aphasia can still understand sentences he hears others say. "If the neural system supporting speech production were critical to speech recognition," Hickok says, "Broca's aphasia should not exist."

To use a more familiar example, babies—and, arguably, even dogs—clearly understand the meanings of many words without having the motor ability to say them. By the same token, we can understand the meaning of a verb like "echolocate" without having any understanding of how to perform it.

Thus, Hickok says, "hearing the word 'kiss' activates motor lip systems not because you need lips to understand the action," but because your previous experiences with the word "kiss" are associated with movements involved in kissing. Mirror neurons, then, don't encode the meaning of the word "kiss" itself; they simply happen to fall downstream of that understanding in your brain's river of associations.

What all this implies, Hickok says, is that "action understanding is clearly not a function of the motor system." If we want to find the neural correlates of understanding itself, Hickok suggests, we should concentrate our search upstream from the motor cortex, in brain regions like the superior temporal sulcus (STS), which plays a central role in our ability to associate objects with goals—to decide, in other words, what an action or object is "for."

Not everyone's thrilled by this line of argument, though. "When one looks at the data," Iacoboni says, "true examples of dissociation between action understanding and action production are very rare." Action understanding doesn't always require motor-cortex activity, he agrees; but in many instances, mirror neurons do indeed appear to be crucial for it.

For example, patients with damaged motor cortices seem to have trouble placing photos of people's actions in chronological order—though they have no trouble ordering photos of, say, a falling ball. Cases like these, Iacoboni says, argue strongly for mirror neurons' importance in understanding the intentions of other people's actions. This means, he says,

that the concepts of "action" and "understanding" need to be integrated into a single model of mirror neuron function—not picked further apart.

But action execution and action understanding fall apart naturally, Hickok contends. "This is evident in the fact that the inability to produce speech following brain damage or in developmental speech disorders, for example, does not cause speech recognition deficits. It is also plainly evident in the fact that we can understand actions that we can't perform, such as fly, slither, or coil."

As you may have noticed by now, a specter that's even harder to pin down lurks throughout this whole debate: We have no empirical rubric for action understanding; no experiment that can tell us for sure whether it's happening—because there's no real agreement about what exactly "understanding" is. It's a weirdly recursive question: Understanding implies meaning; and so far, neither Hickok nor his opponents have been able to pin down what "meaning" means in neurological terms. "The fact is, we don't know exactly how semantic understanding is achieved neurally," Hickok says. "I certainly don't know."

Does Association Mean Understanding?

It doesn't always take a brand-new discovery to shake up an old debate—sometimes what's needed is a new way of seeing the data. In the mirror neuron debate, that fresh approach comes courtesy of Cecilia Heyes, a professor of psychology at Oxford's All Souls College. At the 2012 New Frontiers Summit, Heyes presented her case for an altogether different approach to studying mirror neuron function. The really important question, she says, isn't whether mirror neurons encode understanding, but whether they qualify as a special class of neuron at all.

Mirror neurons, in Heyes' view, aren't evolved specifically "for" understanding, imitation, or any other purpose—rather, they're simply ordinary motor-cortex neurons that happen to take on special roles as we learn to associate motor actions with sounds, feelings, goals and so on. "Special-purpose mechanisms can be forged by evolution or by learning," Heyes says—and if we can figure out what makes certain neurons, but not others, take on mirror properties in the first place, we'll be in a much better position to examine what they're up to.

As for the question of whether mirror neurons "do" meaning, association, or both, Heyes thinks it may boil down to how we choose to define "meaning" and "understanding." "I don't think it's right to contrast meaning and association," she says. "In principle, mirror neurons could be a product of associative learning *and* help us to understand the meaning of actions." But before we can find that out with a lab experiment, she adds, supporters and defenders of the "action understanding" hypothesis will need to explain what exactly it is that they're claiming or denying, so we know what we're looking for.

Hickok, for his part, says Heyes' hypothesis actually supports his argument that mirror neurons don't constitute the basis of action understanding—after all, he explains, if mirror neurons associate incoming stimuli with motor responses, why does the concept of "understanding" need to enter the picture at all? "The mirror neuron system links sensory stimuli to the motor system for the control of action," he says. "It's a system that acts reflexively and adaptively." So as far as describing mirror neurons' function in terms of sensory-motor association, Hickok says, Heyes is right on the money.

While Iacoboni also agrees that Heyes' hypothesis is reasonable, he cautions that mirror neurons are still a special kind of associative cell: One that's specialized for action-oriented associations. "Why should mirror neurons respond to specific actions," Iacobini asks, "if they're just learning visuomotor associations?" Why, in other words, do they respond not to just any action-related stimulus, but only to actions that have goals?

And it's on this question of goal-orientedness—and what it implies about the human mind—that the views of Hickok, Heyes, and the Parma school all diverge once again.

Does Empathy Depend on Mirror Neurons?

No matter whose side of the debate you're on, Vittorio Gallese cuts an imposing figure. One of the original discoverers of macaque mirror neurons —and a father of the "action understanding" theory—Gallese has spent the past three decades vigorously defending the centrality of mirror neurons in our ability to know what others' actions are "for."

“The data strongly suggest that mirror neurons map between an observer’s goals and the acting animal’s motor goals,” Gallese says. These neurons fire in relation to the goal of grasping, he explains, whether it’s performed by a hand, a pincer, or another tool; whether it’s performed by oneself or another individual; whether the other’s movement is seen or merely heard. The only common factor in all these events, Gallese says, is the goal they aim to achieve.

Gallese actually agrees with Hickok that understanding can take place without mirror neuron activation. However, he notes, “only through the activation of mirror neurons can we grasp the meaning of others’ behavior from within.” In other words, mirror neurons enable us to understand other people’s actions in terms of our own movements and goals—to empathize with them.

Hickok will have none of it. Gallese, he says, is trying to quietly slip out of his original hypothesis that mirror neurons associate meanings with actions, and into a more evasive “claim that they allow ‘understanding from the inside,’ whatever that means.”

Gallese has an answer at the ready: If not in mirror neurons, then where else should we look for action understanding? Surely not in the STS, as Hickok advocates. “Evidence demonstrates that only the motor system—not the STS—can generalize a motor goal independently from the effector accomplishing it,” Gallese says: When it comes to directly mapping others’ motor goals against our own, mirror neurons are still the only serious contenders in town. That kind of perceptual mapping, says Gallese, is what he means by “understanding from the inside.” More work is necessary, he acknowledges, to establish the exact nature of this kind of understanding—but nevertheless, its dependence on mirror neurons is clear.

Iacoboni is somewhat less sanguine. “Admittedly, it is very difficult to obtain empirical evidence that unequivocally proves this hypothesis,” he says—though he’s quick to add that “both imaging and neurological evidence are compellingly consistent with it.” The evidence is also consistent, he adds, with the idea that mirror neuron function is significantly altered in people on the autism spectrum of disorders (ASD)—implying a correlation between autism and “broken” mirror neurons.

That may be so, Heyes interjects—but ASD is too complex a range of disorders to lay at the feet of a single malfunctioning neuron system. "Iacoboni doesn't ask," she says, "whether atypical mirror mechanism activity generates—rather than merely accompanies—autism spectrum disorders." If, as Hickok contends, mirror neurons lie far downstream in the process of action understanding, this abnormal mirror-neuron activation may simply be another symptom of autism, rather than its cause.

Gallese agrees—partially. "It is very unlikely that autism can be simply equated to a mere malfunctioning of the mirror neuron mechanism," he says—but nevertheless, "many of the social cognitive impairments manifested by ASD individuals might be rooted in their incapacity to organize and directly grasp the intrinsic goal-related organization of motor behavior." Mirror neurons map others' motor goals to our own; autistic individuals have trouble grasping others' goals; therefore, Gallese argues, some kind of correlation clearly exists.

But there's an even more serious problem with this line of reasoning, says Morton Ann Gernsbacher, a prominent autism researcher at the The University of Wisconsin-Madison. "It has been repeatedly demonstrated," Gernsbacher says, "that autistic persons of all ages have no difficulty understanding the intention of other people's actions." Not only that—decades of research have also shown that autistic people can perform imitation tasks as well as or better than non-autistic participants, and that they can be highly responsive to imitation by others.

And so, once again, we come back to the question of what kind of understanding it is that we're talking about here: Can people with autism really be said to "understand" an action they can't readily imitate it? Gernsbacher says that, obviously, the answer's yes. Gallese would argue that this isn't "understanding from the inside," but a more abstract kind.

Iacoboni, as usual, takes a more integrative view: "Current theories of empathy suggest a multilayer functional structure, with a core layer of automatic responses to reproduce the affective states of others. Mirror neurons are likely cellular candidates for the core layer of empathy." And it's that core layer of empathy, Iacobini says, that likely lies at the root of true action understanding.

In the final analysis, the one conclusion that's emerged loud and clear from all these debates is that mirror neurons aren't the end-all of understanding, empathy, autism, or any other brain function. The closer we examine the parts these neurons play, the more we find ourselves peering between the cracks of these mental processes—watching them unravel into threads that run throughout the brain. It may very well turn out that "meaning" and "understanding" aren't single processes at all, but tangled webs of processes involving motor emulation, abstract cognition, and other emotional and instinctual components whose roles we're only beginning to guess.

After decades of research, these strange cells continue to astound and confound us—not only with their unique abilities, but with the hidden complexity to which they may provide a key. But, as so often happens in neuroscience, we may end up having to pick the lock before we understand exactly how the key fits into it.

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SECTION 5

Environmental Causes

Sunshine State: Vitamin D Deficiency

by Gabrielle Glaser

As evidence of widespread vitamin D deficiency grows, some scientists are wondering whether the sunshine vitamin—once only considered important in bone health—may actually play a role in one of neurology's most vexing conditions: autism.

The idea, although not yet tested or widely held, comes out of preliminary studies in Sweden and Minnesota. In the summer of 2008, Swedish researchers published a study in *Developmental Medicine and Child Neurology* that found the prevalence of autism and related disorders was three to four times higher among Somali immigrants than non-Somalis in Stockholm. The study reviewed the records of 2,437 children, born between 1988 and 1998 in Stockholm, in response to parents and teachers who had raised concerns about whether children with a Somali background were overrepresented in the total group of children with autism.

In Sweden, the 15,000-strong Somali community calls autism "the Swedish disease," says Elisabeth Fernell, a researcher at the Karolinska Institute in Stockholm and a co-author of the study.

In Minnesota, where there are an estimated 60,000 Somali immigrants, the situation was quite similar: There, health officials noted reports of autism among Somali refugees, who began arriving in 1993, comparable to those found in Sweden. Within several years of arrival, dozens of the Somali families whose children were born in the U.S. found themselves grappling with autism, says Huda Farah, a Somali-born molecular biologist who works on refugee resettlement issues with Minnesota health officials. The number of Somali children in the city's autism programs jumped from zero in 1999 to 43 in 2007, says Ann Fox, director of special education programs for Minneapolis schools. The number of Somali-speaking

children in the Minneapolis school district increased from 1,773 to 2,029 during the same period.

Few, if any, Somalis had ever seen anything like it. “It has shocked the community,” Farah says. “We never saw such a disease in Somalia. We do not even have a word for it.”

What seemed to link the two regions was the fact that Somalis were getting less sun than in their native country—and therefore less vitamin D. The vitamin is made by the skin during sun exposure, or ingested in a small number of foods. At northern latitudes in the summertime, light-skinned people produce about 1,000 international units (IUs) of vitamin D per minute, but those with darker skin synthesize it more slowly, says Adit Ginde, an assistant professor at the University of Colorado Denver School of Medicine. Ginde recommends between 1,000 to 2,000 IUs per day, calling current recommendations of 200 IUs per day outmoded.

It’s hard to definitively assess the extent to which Somali immigrant families in Sweden and Minnesota are experiencing increased rates of autism. Somalia doesn’t have great records of the condition, says Rebecca Berkowitz, who works for a United Nations–affiliated NGO called Global Education Motivators. “Children in Somalia may not even be getting diagnosed with autism due to the overall lack of awareness of the disorder,” Berkowitz says, in a nod to the fact that there is no Somalian word for it. And Swedish scientists have reported autism rates overall have risen since they began studying the epidemiology of the disorder in the mid-1980s—just as U.S. Centers for Disease Control officials have noted an increase.

Still, proponents of the vitamin D–autism link say there is biological plausibility to their theory. They cite a 2007 review by Allan Kalueff, a researcher now at Tulane University, in *Current Opinion in Clinical Nutrition and Metabolic Care*. That review—based on more than 20 studies of animals and humans—concluded that vitamin D during gestation and early infancy was essential for “normal brain functioning.”

At the same time, the theory needs a lot of data to back it before others will give it much credence, given how many other potential reasons there are for a climb in autism rates. Even Kalueff says he isn’t sure how vitamin D could be related to autism, even if it is an important player in the brain:

“Discussions around autism specifically may be a right step or a wrong step, but they should not distract us from a much bigger picture.”

Catherine Lord, the director of the University of Michigan at Ann Arbor’s Autism and Communication Disorders Center, says she finds the Swedish study intriguing. “But it is going to be really important to replicate these findings,” says Lord, who has studied the disorder for 40 years and has been instrumental in developing autism diagnostic instruments used in practice and research worldwide. “We are talking about a small group of children with a lot of social factors, including that these kids are very conspicuously different from your average Swedish child, and being assessed by people who are from very different culture.” There is also the issue of consanguinity, she says, as many Somalis marry cousins. “This doesn’t mean the study is wrong," she says. “But we need methodical testing.”

So Fernell and her colleagues are now measuring vitamin D blood levels in mothers and children with autism of both Somali and Swedish origin and comparing them with a control group of mothers and healthy children. She will not say how many subjects the study includes, describe any preliminary results nor say when it will be complete. Farah says Minneapolis researchers are now preparing to study the vitamin D levels of pregnant Somalis, other ethnic groups and Minnesotans of European stock. (That data is particularly hard to come by because Vitamin D levels are not typically screened in pregnancy in the U.S., says Stacy Brooks, a spokeswoman for the American College of Obstetricians and Gynecologists.)

The other potential reasons for a climb in autism rates: There is increased attention to the condition in the U.S., and Somalis are more likely to see a doctor after moving here. Also, genes, studies have found, may play a role; a number of papers, including a 1989 study of five Nordic countries and a 1995 British study, found that the concordance rate among identical twins was as high as 90 percent. (Then there is the much-ballyhooed but ultimately disproved link to vaccines.)

Somali refugees, in particular, faced multiple stressors as they adjusted to their new lives in Sweden and Minnesota: They had fled civil war, lost a supportive tribal culture, and replaced a diet of fruit, fresh meat and grains with processed food. Perhaps, most importantly, they had traded family

compounds and regular exposure to the equatorial sun for cloistered high-rise apartments.

But some of those potential cultural reasons could also point to vitamin D. Surrounded by strangers, the predominantly Muslim women covered themselves almost continuously when outdoors, says Gregory A. Plotnikoff, medical director of the Penny George Institute for Health and Healing in Minneapolis. Plotnikoff, an internist, speaks Somali and has many Somali patients. That meant less exposure to the sun for pregnant women, who would have worn less modest dress in private areas of their own family compounds.

And there is other evidence for a vitamin D link: Cornell University researchers published a study in *Archives of Pediatrics & Adolescent Medicine* showing that children in rainy (and therefore more overcast) counties of Oregon, Washington and California were two times more likely to be diagnosed with autism than their counterparts in drier parts of the state. “Our research is sufficiently suggestive of an environmental trigger for autism associated with precipitation, of which vitamin D deficiency is one possibility,” says study co-author Michael Waldman, a professor of management and economics at Cornell’s Johnson Graduate School of Management. “Further research focused on vitamin D deficiency is clearly warranted.” His research on environmental links to autism are ongoing; he plans to publish in the coming months but will not disclose any of his studies until they are accepted by a journal.

Gene Stubbs, an associate professor emeritus of psychiatry and pediatrics at Oregon Health & Science University, says the preliminary research is already intriguing. “We don’t have proof, but I am certainly leaning in the direction that this hypothesis could be correct for a proportion of kids,” says Stubbs, who has been studying autism for 30 years. He is launching a pilot study of 150 pregnant women who have at least one child diagnosed with the disorder. The women will receive 5,000 IUs of vitamin D3 during gestation and 7,000 IUs during lactation. “If we find that we are able to reduce the recurrence rate of autism within families substantially enough, others will want to study this in larger groups with larger controls.”

--Originally published: Scientific American online, May 20, 2008.

Risk Factors During Pregnancy

by Katherine Harmon

Mothers-to-be know they must be extra vigilant about what they put in their bodies—avoiding too much seafood, and making sure they get plenty of fruits and vegetables, for instance. But research has been piling up suggesting that the mother's overall weight and metabolic health before—and while—she is pregnant can also have a lasting impact on her children's physical and developmental health.

Now a study suggests that mothers who are obese or diabetic during pregnancy are more likely to have kids with developmental disorders and possibly autism. The findings were published in *Pediatrics*.

Women with type 2 or gestational diabetes were 2.3 times more likely to have a child that would have some form of developmental disorders other than autism. (Some 11.6 percent of children with developmental disorders had a mother who had had diabetes while pregnant, whereas 6.4 percent normally developing children had a mother with diabetes.) And women who were obese or had another metabolic condition were also less likely to have children with normal neuro-behavioral development, according to the study.

"Over a third of U.S. women in their childbearing years are obese, and nearly one-tenth have gestational or type 2 diabetes during pregnancy," Paula Krakowiak, a biostatician at the University of California, Davis Health System and co-author of the new study, said in a prepared statement. "Our finding that these maternal conditions may be linked with neurodevelopmental problems in children raises concerns and therefore may have serious public health implications."

For the report, Krakowiak and her colleagues studied 1,004 children aged two to five years–517 of whom had autism, 172 of whom had a different developmental disorder and 315 of whom were developing normally–and their mothers. The subjects were recruited as part of the Childhood Autism Risks from Genetics and the Environment study, which is run in California.

Autistic children whose mothers had a metabolic condition also tended to perform more poorly on language and social engagement tests than autistic children of women who did not have these conditions. And kids who had not been diagnosed with autism spectrum disorder performed worse on early learning and adaptive behavior tests if they had had a mother with one or more metabolic conditions.

The researchers are not yet sure why this link might exist. One theory is that abnormal glucose and insulin levels in a woman who is obese or has diabetes or metabolic syndrome during pregnancy might reduce the amount of oxygen and iron available to the fetal brain.

With the incidence of obesity, diabetes and autism all on the rise, Krakowiak and her colleagues noted that more study is needed into this association—and quickly.

--Originally published: Scientific American online, April 9, 2012.

Epigenetics and Our Understanding of Heredity

by Kara Rogers

In a study published in late 2011 in *Nature*, Stanford University geneticist Anne Brunet and colleagues described a series of experiments that caused nematodes raised under the same environmental conditions to experience dramatically different lifespans. Some individuals were exceptionally long-lived, and their descendants, through three generations, also enjoyed long lives. Clearly, the longevity advantage was inherited. And yet, the worms, both short- and long-lived, were genetically identical.

This type of finding—an inherited difference that cannot be explained by variations in genes themselves—has become increasingly common, in part because scientists now know that genes are not the only authors of inheritance. There are ghostwriters, too. At first glance, these scribes seem quite ordinary—methyl, acetyl, and phosphoryl groups, clinging to proteins associated with DNA, or sometimes even to DNA itself, looking like freeloaders at best. Their form is far from the elegant tendrils of DNA that make up genes, and they are fleeting, in a sense, erasable, very unlike genes, which have been passed down through generations for millions of years. But they do lurk, and silently, they exert their power, modifying DNA and controlling genes, influencing the chaos of nucleic and amino acids. And it is for this reason that many scientists consider the discovery of these entities in the late 20th century as a turning point in our understanding of heredity, as possibly one of the greatest revolutions in modern biology—the rise of epigenetics.

Epigenetics and the State of Chromatin

In Brunet's lab, epigenetic inheritance is a big deal. Their *Nature* paper was the first to describe the phenomenon as it applies to longevity across

generations, a breakthrough that emerged out of their quest to better understand the role of chromatin in inheritance.

Chromatin is a compact fiber of proteins and DNA that exists in either a condensed or a relaxed state. It assumes its condensed form during cell division in order to facilitate the splitting of chromosomes for distribution to daughter cells. Segments of the fiber, however, may retain this form when a cell is not dividing, with the result that genes occurring in these segments are fixed in an inactive state. Other stretches of the fiber, on the other hand, relax and open to allow regulatory proteins to access the DNA and activate genes.

Certain epigenetic modifications, such as the binding of methyl groups to histone proteins, the bobbins around which DNA is wound for chromatin packaging, are responsible for holding the fiber in an open state. But modifications are dynamic. During development, for example, chemical moieties attach to and detach from histones or DNA in an orchestrated fashion, their fluid dance aiding the execution of important functions, such as the establishment of patterns of gene expression for different types of tissues and the silencing of parental genes, a phenomenon known as parental, or genomic, imprinting.

Modifications can also accumulate during an organism's lifetime. Because some of these acquisitions may affect DNA passed through the germline (in eggs and sperm) and may not be beneficial, they are erased at the time of reproduction, and the chromatin is returned to its original state. The process is not faithful, however, so some modifications slip through. In this way, chromatin modifications in parent DNA that are not reprogrammed are transmitted to the next generation.

Epigenetic Inheritance of Longevity in Nematodes

There is increasing evidence that epigenetic modifications are transgenerational (inherited through multiple generations) in a variety of species. Examples include coat color in mammals, eye color in *Drosophila*, symmetry in flowers, and now longevity in *C. elegans*. These findings are exciting and raise intriguing questions about the seemingly limitless nature of epigenetics.

But the work of teasing out epigenetic modifications and their effects is arduous. To uncover the involvement of methylation in nematode longevity, Brunet and colleagues began by assessing the lifespans of *C. elegans* that were deficient in one of three genes, *ash-2, wdr-5*, or *set-2*; decreased or absent expression of these genes previously had been found to increase longevity in the species. They then crossed nematodes with genetic deficiencies with nematodes of normal genetic composition, pairings that in typical Mendelian fashion yielded wild-type (genetically normal) individuals, as well as individuals carrying the genetic alterations. Measurements of longevity were recorded for each of these populations and were compared with those of control populations (wild-type nematodes descended from wild-type parents). The findings revealed that the controls lived an average lifespan, whereas wild-type nematodes genetically identical to the control population but descended from mutant parents lived 20 to 30 percent longer.

Thus, the genetic deficiencies, though not inherited, had effected some type of change that endowed the genetically normal offspring of mutants with the same length lifespan that the mutants themselves experienced. The change, the Stanford team deduced, was methylation.

The proteins encoded by *ash-2, wdr-5* and *set-2* are part of a histone methylation complex known as H3K4me3, which is found across species ranging from yeast to humans. But the mechanisms underlying the inheritance of longevity are not clear. As Brunet explained, “We did not observe a global decrease in H3K4me3 levels in genetically wild-type descendants from mutants that are deficient in H3K4me3. We interpret that as saying there is not a global dearth of H3K4me3 that is inherited epigenetically.” Thus, the team’s current model is that when the proteins are scarce or absent, H3K4me3 methylation is lost at specific locations in the genome, and longevity-associated modifications in chromatin state, or possibly other types of modifications (e.g., non-coding RNAs), are passed to the next generation.

Transgenerational Inheritance of Acquired Characters in Humans

Epigenetics has given life to Lamarckism and the previously discarded idea that characteristics acquired during an individual’s life are heritable. In fact, many scientists already have warmed up to this idea. “There seems to

be a renewed acceptance for the Lamarckian concept (in limited cases)," Brunet said. "This could change our understanding of inheritance in that it would add another component, probably minor, but present, in addition to Mendelian genetics."

It also adds another layer of significance to our daily lives. A number of environmental factors, from nutrients to temperature to chemicals, are capable of altering gene expression, and those factors that manage to penetrate germline chromatin and escape reprogramming could, in theory, be passed on to our children and possibly our grandchildren.

But while several studies have suggested that transgenerational epigenetic inheritance can occur in humans, actual evidence for it is scant. Among the more convincing cases thus far involves the synthetic estrogen compound diethylstilbestrol (DES), which was used in the mid-20th century to prevent miscarriages in pregnant women. DES, however, dramatically increases the risk of birth defects. It is also associated with an increased risk for vaginal and breast cancers in daughters and an increased risk of ovarian cancer in maternal granddaughters of women exposed to DES during pregnancy. Studies in mice have suggested that neonatal DES exposure causes abnormalities in the methylation of genes involved in uterine development and uterine cancer; in mice these abnormalities were still present two generations down the line, suggesting a transgenerational effect.

Given the elusive nature of inherited epigenetic modifications, it seems that, despite decades of investigation, scientists remain on the brink of understanding. The possibilities, however, seem endless, even with the constraint that, to be inherited, epigenetic modifications must affect gene expression in the germline, a feat that even genetic mutations rarely accomplish. But with the skyrocketing prevalence of conditions such as obesity, diabetes, and autism, which have no clear genetic etiology in the majority of cases, as Brunet pointed out, "It seems that all complex processes are affected by epigenetics."

While scientists continue to search for definitive evidence of transgenerational epigenetic inheritance in humans, the implications so far suggest that are our lifestyles and what we eat, drink, and breathe may directly affect the genetic health of our progeny.

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SECTION 6

Understanding the Autism "Epidemic"

Is There Really an Epidemic?

by Scott O. Lilienfeld and Hal Arkowitz

If the statistic "one in 166" has a familiar ring, perhaps that's because you recently heard it on a television commercial or read it in a magazine. According to widely publicized estimates, one in 166 is now the proportion of children who suffer from autism. This proportion is astonishingly high compared with the figure of one in 2,500 that autism researchers had accepted for decades. Across a mere 10-year period—1993 to 2003—statistics from the U.S. Department of Education revealed a 657 percent increase in the nationwide rate of autism.

Not surprisingly, these bewildering increases have led many researchers and educators to refer to an "autism epidemic." Representative Dan Burton of Indiana also declared in 2001 that "we have an epidemic on our hands." But what's really going on?

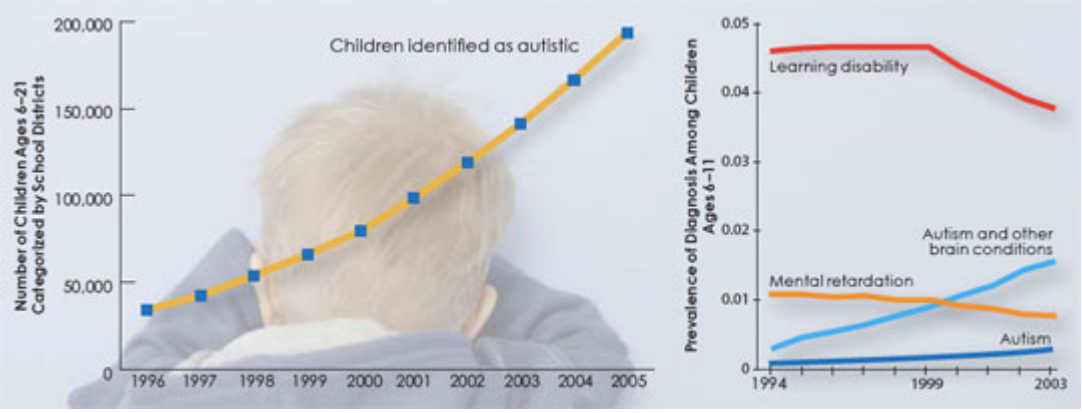
Before we explore this question, a bit of background is in order. Autism is a severe disorder that first appears in infancy. Individuals with autism are characterized by problems with language, social bonding and imagination. All suffer from serious communication deficits, and some are mute. They do not establish close relationships with others, preferring to remain in their own mental worlds. They engage in highly stereotyped and repetitive activities, exhibiting a marked aversion to change. About two thirds of autistic individuals are mentally retarded. For reasons that are unknown, most are male.

The causes of autism remain enigmatic, although studies of twins suggest that genetic factors play a prominent role. Still, genetic influences alone cannot account for such a rapid and astronomical rise in a disorder's prevalence over a matter of just a few years. As a consequence, investigators have turned to environmental factors for potential

explanations. The causal agents proposed include antibiotics, viruses, allergies, enhanced opportunities for parents with mild autistic traits to meet and mate, and, in one recent study conducted by Cornell University researchers, elevated rates of television viewing in infants. Few of these explanations have been investigated systematically, and all remain speculative.

More Autism … or Different Labeling?

Soaring numbers of children reported as autistic by school districts are often cited as proof that the incidence of the condition is rising (*left*). But changes in diagnostic criteria could also account for that pattern. One study found that as au tism seemingly increased, the prevalence of learning disabilities and mental retardation dropped—which suggests that in some cases, one diagnosis substituted for another (*right*).



Credit: Individuals with Disabilities Education Act Data Website (left graph), Paul T. Shattuck (right graph)

Are Vaccines the Problem?

Yet one environmental culprit has received the lion's share of attention: vaccines. At first blush, vaccines would seem to make a plausible candidate for the source of the epidemic. The debilitating symptoms of autism typically become apparent shortly after age two, not long after infants have received vaccinations for a host of diseases. Indeed, many parents claim that their children developed autism shortly after receiving inoculations, either following a vaccine series for mumps, measles and rubella (German measles)—the so-called MMR vaccine—or following vaccines containing thimerosal, a preservative that contains mercury.

Much of the hype surrounding a link between vaccines and autism was fueled by a widely covered investigation of 12 children published in 1998 by British gastroenterologist Andrew Wakefield and his colleagues. The study revealed that symptoms of autism emerged shortly after the children

received the MMR vaccine. The paper was fully retracted in 2010. Public interest in the vaccine-autism link was further stoked by the provocatively entitled book *Evidence of Harm* (St. Martin's Press, 2005), written by investigative journalist David Kirby, which was featured in an extended segment on NBC's *Meet the Press*.

Yet recently published research has not been kind to this much ballyhooed link. The results of several large American, European and Japanese studies demonstrate that although the rate of MMR vaccinations has remained constant or declined, the rate of autism diagnoses has soared. In addition, after the Danish government stopped administering thimerosal-bearing vaccines, the rates of autism continued to rise. These studies and others summarized by the Institute of Medicine suggest there is little evidence that vaccines cause autism. It is possible that vaccines trigger autism in a small subset of children, but if so that subset has yet to be identified.

Changing Criteria

Making matters more confusing, ample reason exists to question the very existence of the autism epidemic. Vaccines may be what scientists call an "explanation in search of a phenomenon." As University of Wisconsin–Madison psychologists Morton Ann Gernsbacher and H. Hill Goldsmith and University of Montreal researcher Michelle Dawson noted in a 2005 review, there is an often overlooked alternative explanation for the epidemic: changes in diagnostic practices. Over time the criteria for a diagnosis of autism have loosened, resulting in the labeling of substantially more mildly afflicted individuals as autistic.

Indeed, the 1980 version of the American Psychiatric Association's diagnostic manual (*DSM-III*) required individuals to meet six of six criteria for an autism diagnosis. In contrast, the 1994 version (*DSM-IV*), which is currently in use, requires individuals to meet any eight of 16 criteria. Moreover, whereas *DSM-III* contained only two diagnoses relevant to autism, *DSM-IV* contains five such diagnoses, including Asperger's syndrome, which most researchers regard as a high-functioning variant of autism.

Legal changes may also be playing a significant role. As Gernsbacher and her colleagues have noted, an amended version of the Individuals with

Disabilities Education Act (IDEA), passed by Congress in 1991, requires school districts to provide precise counts of children with disabilities. IDEA has resulted in sharp surges in the reported numbers of children with autism. Nevertheless, these numbers are not based on careful diagnoses of autism or on representative samples of the population. As a consequence, researchers who rely on "administrative-based estimates," which come from government data submitted by schools, will arrive at misleading conclusions about autism's prevalence.

They must instead rely on "population-based estimates," which are developed from statistically reliable and representative surveys of autism's occurrence in the general population. Further contributing to the reported increase may be the "Rain Man effect," the public's increased familiarity with autism following the 1988 Academy Award–winning film starring Dustin Hoffman and Tom Cruise.

Swapped Diagnoses

Two recent studies buttress assertions that the autism epidemic may be more illusory than real. First, in 2005 psychiatrist Suniti Chakrabarti of the Child Development Center in Stafford, England, and psychiatrist Eric Fombonne of McGill University conducted an investigation that used rigorous population-based estimates to track the prevalence of autism diagnoses from 1992 to 1998 in a sample of more than 10,000 children in the same area of England. They found no support for a change in prevalence, suggesting that when researchers maintain the same criteria for autism, the rates of diagnosis do not change over time.

Second, a 2006 article by University of Wisconsin–Madison psychologist Paul Shattuck cited "diagnostic substitution": as the rates of the autism diagnosis increased from 1994 to 2003, the rates of diagnoses of mental retardation and learning disabilities decreased. It is possible that the overall "pool" of children with autismlike features has remained constant but that the specific diagnoses within this pool have switched.

It is still too early to exclude the possibility that autism's prevalence is growing, but it is unlikely that it is growing as swiftly as many have suggested. As the late Eastern Michigan University sociologist Marcello Truzzi once said, extraordinary claims require extraordinary proof. The

claim of an enormous epidemic of autism diagnoses is indeed extraordinary. Yet the evidence for this claim leaves much to be desired.

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Redefining Autism: The New DSM Criteria

by Ferris Jabr

People have been arguing about autism for a long time—about what causes it, how to treat it and whether it qualifies as a mental disorder. The controversial idea that childhood vaccines trigger autism also persists, despite the fact that study after study has failed to find any evidence of such a link. Now, psychiatrists and members of the autistic community are embroiled in a more legitimate kerfuffle that centers on the definition of autism and how clinicians diagnose the disorder. The debate is not pointless semantics. In many cases, the type and number of symptoms clinicians look for when diagnosing autism determines how easy or difficult it is for autistic people to access medical, social and educational services.

The controversy remains front and center because the American Psychiatric Association (APA) has almost finished redefining autism, along with all other mental disorders, in an overhaul of a hefty tome dubbed the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*—the essential reference guide that clinicians use when evaluating their patients. The newest edition of the manual, the *DSM-5*, is slated for publication in May 2013. Psychiatrists and parents have voiced concerns that the new definition of autism in the *DSM-5* will exclude many people from both a diagnosis and state services that depend on a diagnosis.

The devilish confusion is in the details. When the APA publishes the *DSM-5*, people who have already met the criteria for autism in the current *DSM-IV* will not suddenly lose their current diagnosis as some parents have feared, nor will they lose state services. But several studies recently published in child psychiatry journals suggest that it will be more difficult for new generations of high-functioning autistic people to receive a diagnosis because the *DSM-5* criteria are too strict. Together, the studies conclude that the major changes to the definition of autism in the *DSM-5*

are well grounded in research and that the new criteria are more accurate than the current *DSM-IV* criteria. But in its efforts to make diagnosis more accurate, the APA may have raised the bar for autism a little too high, neglecting autistic people whose symptoms are not as severe as others. The studies also point out, however, that minor tweaks to the *DSM-5* criteria would make a big difference, bringing autistic people with milder symptoms or sets of symptoms that differ from classic autism back into the spectrum.

A New Chapter

Autism is a disorder in which a child's brain does not develop typically, and neurons form connections in unusual ways. The major features of autism are impaired social interaction and communication—such as delayed language development, avoiding eye-contact and difficulty making friends—as well as restricted and repetitive behavior, such as repeatedly making the same sound or intense fascination with a particular toy.

The *DSM-5* subsumes autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS)—which are all distinct disorders in *DSM-IV*—into one category called autism spectrum disorder (ASD). The idea is that these conditions have such similar symptoms that they do not belong in separate categories, but instead fall on the same continuum.

Essentially, to qualify for a diagnosis of autistic disorder in *DSM-IV*, a patient must show at least six of 12 symptoms, which are divided into three groups: deficits in social interaction; deficits in communication; and repetitive and restricted behaviors and interests. In contrast, the *DSM-5* divides seven symptoms of ASD into two main groups: deficits in social communication and social interaction; and restricted, repetitive behaviors and interests.

The APA collapsed the social interaction and communication groups from *DSM-IV* into one group in the new edition because research in the last decade has shown that the symptoms in these groups almost always appear together. Research and clinical experience has also established that heightened or dulled sensitivity to sensory experiences is a core feature of autism, which is why it appears in *DSM-5* but not in the preceding version.

The psychiatric community has generally applauded these changes to the criteria for ASD.

What is in question is how many of the *DSM-5* criteria a patient must meet to receive a diagnosis—too many and the manual excludes autistic people with fewer or milder symptoms; too few and it assigns autism to people who don't have it. Since the 1980s the prevalence of autism has dramatically increased worldwide, especially in the U.S. where the Centers for Disease Control and Prevention estimates that nine per 1,000 children have been diagnosed with ASD. Many psychiatrists agree that the increase is at least partially explained by loose criteria in *DSM-IV*.

"If the *DSM-IV* criteria are taken too literally, anybody in the world could qualify for Asperger's or PDD-NOS," says Catherine Lord, one of the members of the APA's *DSM-5* Development Neurodevelopmental Disorders Work Group. "The specificity is terrible. We need to make sure the criteria are not pulling in kids who do not have these disorders."

Relaxed Requirements

Three studies published recently conclude that the *DSM-5* criteria for ASD are too strict, but that a few small changes would make them appropriately inclusive. One might think that the APA would conduct such research themselves, but studies that explicitly compare *DSM-IV* and *DSM-5* criteria are not an official part of the revision process. Rather, researchers who are not helping revamp the *DSM*, but were interested in how the new edition will change psychiatric diagnosis, decided to find out for themselves.

Marja-Leena Mattila of the University of Oulu in Finland conducted the only epidemiological study published so far that explicitly compared the two editions' criteria for autism. (Mattila used *DSM-5* criteria posted to the *DSM-5* Development Web site in February 2010; the criteria have the same basic structure as the new specifications posted in January 2011, but they are far less detailed and descriptive.) In her study, Mattila surveyed a sample of more than 5,000 Finnish schoolchildren and identified 26 eight-year-olds with an IQ of 50 or higher who qualified for autistic disorder in the *DSM-IV*. Of those 26, only 12 qualified for ASD in the *DSM-5*. But when Mattila lowered the threshold for ASD by requiring only two of the

three symptoms in the social interaction and communication group, 25 of the 26 children qualified for ASD in the both the *DSM-5* and its predecessor. Her work appears in the June 2011 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*.

Similarly, Thomas Frazier of the Center for Autism at the Cleveland Clinic performed a series of statistical analyses on symptom reports from nearly 7,000 ASD children, looking for the symptoms that appeared together most frequently. When he programmed a computer to figure out what kind of diagnostic model best reflected the naturally occurring clusters of symptoms, Frazier found that a model with two groups of symptoms—just like the one in the *DSM-5*—captured how the symptoms clustered in the children better than the *DSM-IV* or any other model. He also found that the *DSM-5* model misdiagnosed autism in only 3 percent of the children, whereas the *DSM-IV* model misdiagnosed autism in 14 percent. When Frazier relaxed the *DSM-5* requirements from five out of seven criteria to four out of seven, he brought back about 12 percent of ASD children that the model originally neglected.

William Mandy of University College London also used statistical analyses to evaluate the *DSM-5* criteria and concluded that the two-group *DSM-5* model is overall more accurate than the three-group *DSM-IV* model, but a little too restrictive. Both Frazier's study and Mandy's study are published in the *Journal of the American Academy of Child and Adolescent Psychiatry*.

"They got the major changes right," Mandy says of the APA. "But recent evidence shows that borderline people might miss out on a diagnosis in *DSM-5* because they don't have clinical levels of some symptoms, such as repetitive behavior. The real issue is threshold." Not all psychiatrists agree that the stricter *DSM-5* criteria should be relaxed, because they think that many people currently diagnosed with Asperger's or PDD-NOS do not in fact have autism and that the new definition of ASD should not include these people. Some parents of children with severe autism are also in favor of stricter criteria, arguing that children who are most in need should receive state services over others with milder symptoms.

Darrel Regier, vice chair of the *DSM-5* Task Force, says that he is well aware of the recent studies and that the committee will consider whether

they need to revise the *DSM-5* criteria for ASD even further. The APA is supposed to finalize all changes to the *DSM* this year and publish the new edition in May 2013. When asked if he thinks the APA can adjust the revisions to criteria not only for ASD, but for all the other disorders in the *DSM-5* by the end of this year, Regier says "there is plenty of time."

--Originally published: Scientific American online, January 30, 2012.

By the Numbers: Autism Is Not a Math Problem

by Ferris Jabr

At a meeting of the Icelandic Medical Association in January 2012, Yale University child psychologist Fred Volkmar gave a presentation on how the American Psychiatric Association (APA) is changing the definition of autism. In his talk, Volkmar came to a startling conclusion: more than half of the people who meet the existing criteria for autism would not meet the APA's new definition of autism and, therefore, may not receive state educational and medical services.

The APA defines autism in a reference guide for clinicians called the *Diagnostic and Statistical Manual for Mental Disorders (DSM)*. The newest version of the manual, the *DSM-5*, is slated for publication in May 2013.

In Iceland, Volkmar presented data from an unpublished preliminary analysis of 372 high-functioning autistic children and adults with IQs above 70. On a key PowerPoint slide that Volkmar shared with *Scientific American*, he notes that there are 2,688 ways to get a diagnosis of autistic disorder in *DSM-IV*, but only six ways to get a diagnosis of autism spectrum disorder in *DSM-5*. Although intriguing at first glance, it turns out that both these numbers are slightly wrong—and that they are pretty much useless when comparing the *DSM-IV* and *DSM-5*. You cannot reduce autism to a math problem.

Scientific American wanted to explore this gaping discrepancy further, so we asked astronomer and Hubble Fellow Joshua Peek of Columbia University to code a computer program that would calculate the total possible ways to get a diagnosis of autistic disorder in *DSM-IV* and the total possible ways to get a diagnosis of autism spectrum disorder in *DSM-5*. You can do the math by hand, too, if you like: It all comes down to factorials. The *DSM-IV* criteria are a set of 12 items in three groups from which you

must choose 6, with at least two items from group one and at least one item each from groups two and three. The *DSM-5* criteria are a set of seven items in two groups from which you must choose five, including all three items in group one and at least two of the four items in group two. Peek's program crunched the numbers: there are 2027 different ways to be diagnosed with autism in *DSM-IV* and 11 ways to be diagnosed with autism in *DSM-5*.

One might think that those statistics make it absurdly easy to qualify for a diagnosis of autism in *DSM-IV* and incredibly difficult to meet the criteria for autism in *DSM-5*, but those numbers alone don't tell you anything unless you understand how common each symptom of autism is in the general population. Symptoms of autism are not randomly distributed throughout the population and the symptoms do not cluster together in random combinations. Research in the past decade has shown that some symptoms appear together much more often than others. In fact, that is one of the main reasons that the APA has consolidated the *DSM-IV* criteria for autism into fewer, denser and more accurate criteria in the *DSM-5*. The idea is that the *DSM-IV* criteria allowed for too many possible combinations, many of which rarely occur; the *DSM-5* criteria, in contrast, better reflect the most common combinations of symptoms.

Specifically, the APA has merged two distinct groups of symptoms from the *DSM-IV*—deficits in communication and deficits in social interaction—into one group in the *DSM-5* because someone with autism almost always has both kinds of symptoms.

Most psychiatrists applaud this consolidation because, as several recently published studies have shown, the new criteria are more precise: they rarely assign autism to people who do not have it. However, the *DSM-5* criteria may be a little too strict, ignoring some autistic people with milder symptoms. Two recently published studies suggest an easy fix: if the new criteria require that patients meet one fewer symptom—four out of seven instead of five out of seven—high-functioning autistic people will not be excluded.

--Originally published: Scientific American online, January 30, 2012.

SECTION 7

Treatments and Therapies

The Autism Diet

by Mark Alpert

If you can believe the many testimonials posted on the Web, a diet free of gluten and casein is a miracle treatment for autism. Parents of children suffering from the disorder, which is characterized by impaired social and communication skills, fervently describe astounding improvements that occurred as soon as they removed gluten (a mixture of plant proteins found in wheat, rye and barley) and casein (the main protein in dairy products) from their kids' meals. Surveys indicate that as many as 40 percent of children with autism have been placed on special diets at one time or another. This enthusiasm is grounded more in hope than in science; so far researchers have no good evidence that dietary interventions can alleviate the symptoms of autism. Recently, however, investigators have launched the first rigorous tests of the diets, and the results may be available within a year.

The assumption behind the diets is that people with autism often have gastrointestinal abnormalities that allow unusual amounts of digestive by-products into the body (the so-called leaky gut syndrome). The by-products of gluten and casein, according to one hypothesis, disrupt brain function by altering opioid activity, which is involved in pain regulation and social bonding. Another theory posits that the gut leakage triggers a harmful immune response. These hypotheses are far from rock-solid; in fact, scientists have not even confirmed that people with autism have a higher-than-normal incidence of gastrointestinal problems. But the causes of autism are so poorly understood and the disorder is so variable that some investigators are willing to consider the possibility that gluten and casein may somehow exacerbate symptoms in some children, perhaps just by producing intestinal discomfort.

Unfortunately, the initial studies of diets that eliminate gluten and casein were badly flawed. Although half a dozen research groups reported improvements in behavior and cognition in autistic children after several months on the elimination diets, nearly all the studies lacked control subjects, individuals who continued to digest the suspect proteins. Because the researchers did not compare the restricted-diet children with a control group, they could not specify whether the behavioral and cognitive gains actually resulted from the diets, from the children's maturation or from other therapies conducted at the same time.

The new studies, in contrast, involve control subjects and have a double-blind design: neither the researchers nor the parents will know whether the autistic children are consuming gluten or casein, so the evaluations of the children's behavior will not be tainted by wishful thinking. In a study led by Robin Hansen of the University of California, Davis, all participants go on a gluten-free diet for two months; then, for the next two months, half the subjects eat daily snacks containing gluten while the other half get indistinguishable gluten-free snacks. Susan Hyman of the University of Rochester is running a similar study testing the behavioral effects of both gluten and casein. An investigation at the University of Pittsburgh Medical Center will monitor the effects of combining the gluten-free, casein-free diet with supplements of omega-3 fatty acids, another popular but unproved therapy for autism.

The researchers have run into some trouble recruiting autistic subjects. Many parents who are committed to the gluten-free, casein-free diet do not want to participate because their children may be included in a control group and receive the offending substances. "It's a hard study to do, but it's worth doing," says Susan E. Levy, director of the Regional Autism Center at Children's Hospital of Philadelphia.

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The Autism Pill

by Alla Katsnelson

Until now, attempts at treating autism have been limited to drugs that target peripheral symptoms such as anxiety, aggression and repetitive behaviors. But researchers hope that data from a crop of new drugs in development will allow them, for the first time, to treat an underlying mechanism of the condition, potentially helping those with autism to communicate.

The majority of autism cases are idiopathic, meaning that researchers have yet to understand their cause. But some animal studies of autism have pointed to signaling problems in the brain. Targeting those signaling problems, some researchers think, may ameliorate autism symptoms once thought to be intractable.

Researchers have gleaned some of this information by studying a handful of diseases caused by single-gene glitches that can result in autism. Such disorders account for about 15 to 20 percent of autism cases, says Geraldine Dawson, scientific director of Autism Speaks. In fragile X, which causes autism in a significant number of cases, the points of contact between neurons contain too much glutamate, a chemical messenger that transmits excitatory signals. “There’s an optimal level of activation” in the brain, and this equilibrium is disrupted in fragile X, explains Randall L. Carpenter, co-founder and CEO of Cambridge, Mass.–based biotech firm Seaside Therapeutics. The company is developing drugs that aim to rebalance levels of excitatory and inhibitory messengers, known as neurotransmitters. Hitting that sweet spot may allow the brain to develop the necessary connections for weeding out background noise and focusing on important information, Carpenter says. That, in turn, might allow patients to feel less overwhelmed by sensory stimuli and to have an easier time interacting with others.

Yet do those with idiopathic autism suffer from that same glutamate imbalance? That is what Seaside is working to find out. The company's most advanced drug, arbaclofen, dampens glutamate activity and has reversed some symptoms in mouse models of fragile X. Data so far also suggest some benefits in humans. "The big question is whether these same drugs can address symptoms in people with idiopathic autism," Dawson says. Seaside's study exploring that question is due out later this year. If arbaclofen works in at least some of these individuals, that finding would offer the first evidence that certain cases of idiopathic autism share the same well-studied neurobiological flaws as single-gene permutations of autism. More important, it would show, for the first time, that autism is treatable with drugs. "That will be a watershed moment," Dawson says.

Still, big questions remain. Thus far, researchers have had little success designing drugs that target glutamate without side effects. And should the drugs work, researchers will still need to determine at what age they would be most beneficial, because autism begins early in development. But the results of Seaside's trials and those of similar drugs in the pipeline, Dawson says, "are going to be a huge step to understanding what the path to discovery is going to be."

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Detecting Autsim Early

by Ulrich Kraft

Anyone who has spent even a little time with an autistic boy or girl soon becomes familiar with the behaviors that set these children apart: lack of eye contact, trouble verbalizing, overreacting or underreacting to activities around them, difficulty in expressing their feelings and in understanding the emotions of others. But how do parents and doctors know if a baby, who is too immature to be gauged on any of these traits, has autism? Early diagnosis has proved difficult.

Inability to detect autism until a child is two or three years old is a terrific disadvantage. It "eliminates a valuable window of treatment opportunity, when the brain is undergoing tremendous development," says David G. Amaral, professor of neurobiology and psychiatry at the University of California, Davis.

Amaral and researchers at other institutions, however, are closing in on techniques that could detect autism in babies as young as six months and perhaps even at birth. The results of these new tests—some controversial—are expanding the understanding of autism and raising hopes for much earlier, specialized care that could improve a toddler's chances for a more normal life as a child, teenager and adult.

A Simple Blood Test?

Autism affects a wide variety of developmental traits. Some young autistic children speak; others do not. Some possess almost average intellectual abilities; others are severely limited. As they grow older, certain autistic individuals display incredible talents in very specific domains. Known as savants, they can memorize an entire book in hours or solve complex math problems faster than people using a calculator. The 1988

movie *Rain Man* dramatized these abilities in a character named Raymond Babbitt, played by Dustin Hoffman, who won an Oscar for the role. Babbitt was based on a real savant named Kim Peek, who continues to astonish today.

It is no wonder, then, that determining whether a young child is autistic is fraught with uncertainty. Diagnosis typically involves rating a child's behaviors against a set of standards. The exercise usually is not conclusive until at least the child's second birthday. That is why scientists are seeking an earlier and more accurate test, and they are getting closer. At the International Meeting for Autism Research in Boston in May 2005, Amaral presented the initial results of a landmark study. His team compared blood samples from 70 autistic children ages four to six with samples from 35 randomly selected subjects in the same age group. The autistic children had a higher proportion of two basic immune system cells known as B cells and T cells. Significant differences also became apparent in more than 100 proteins and small molecules commonly found in the bloodstream.

After further analysis, the team decided that the pilot study results were strong enough to launch a full-scale investigation. In March 2006, Amaral announced that U.C. Davis's Medical Investigation of Neurodevelopmental Disorders Institute, which he heads, was starting the Autism Phenome Project. It will enroll 900 children with autism plus 450 more who have developmental delays and 450 who are developing normally. Researchers will analyze the children's blood proteins, immune systems, brain structures and functions, genetics and environmental exposures. The participants will be two to four years old at the outset and will be followed for several years. Amaral thinks it is probable that telltale genetic markers will be found. But it will take several years before the project is finished and analyzed and longer still before a routine test could be administered at a doctor's office.

If the blood profiles prove to be reliable, the screening could occur just after a baby is born. But the validity of detection that early in life requires more scrutiny. Amaral says there is a growing view among experts that not all individuals who have autism are "doomed at birth," as has been commonly believed. "It may be that some children have a vulnerability, such as a genetic abnormality," he says, "and that something they encounter after being born, perhaps in their environment, triggers the disorder."

Environment is suspected in part because the incidence of autism is fairly high in American children. The disorder affects one in every 500 to one in every 166 children, according to the U.S. Centers for Disease Control and Prevention. The unexplained preponderance has frustrated scientists trying to find answers. Furthermore, tremendous variation exists among symptoms, "which leads us to believe that autism is a group of disorders rather than a single disorder—several autisms versus one," Amaral says. The blood work possibly could define distinct subtypes. Behavioral experts are reaching the same conclusion, many preferring the term "autism spectrum disorder" rather than simply "autism."

Earlier Treatment Is Key

An early diagnosis is so important because it would allow treatment to begin sooner, while the brain is still significantly strengthening and pruning neural networks. A paradigm shift is taking place on this issue, too. For a long time, scientists believed that functional deficits in certain brain regions caused autism—complications in brain structure that no change in wiring among neural networks would fix. Now they think symptoms arise because of communications problems between brain regions—problems that rewiring could solve if babies received specific therapy.

"The neuronal networks apparently do not coordinate very well," explains Fritz Poustka, director of child and adolescent psychiatry at Goethe University in Frankfurt, Germany. Poustka says regions that get too little input from other parts of the brain do not develop well. This effect is well known among children who were neglected when they were young, some isolated from almost all human contact. A child who develops this way shares some similar consequences, such as poor use of language and difficulty in making social connections. "A quick diagnosis of autism would enable us to stimulate the networks very early in life by deliberately providing the right inputs," Poustka says. He cannot say if such interventions would "cure" the disorder, but he believes that intensive behavioral training could make the symptoms milder.

Although Poustka doubts that markers in the blood would permit early diagnosis, he favors attempts to try to define telltale traits as young as possible to maximize the success of treatment. In speech development, for example, the best results are achieved when deliberate exercises are

instituted before the child's second birthday. By the time a boy or girl is three or four, deficits can still be reduced, but fundamental changes are no longer possible, because the critical period during which speech develops has passed by.

Behaviors Untangled

Whether or not Amaral's project leads to common blood tests, it could prove beneficial to behavioral approaches as well because it includes developmentally delayed children. The standardized checklists that doctors now use for diagnosis, such as the "autism diagnostic observation schedule," are adequate only for children who are at least one and a half to two and a half years old. And then, usually only for the so-called high functionals—autistic children with IQs over 80. The tests are inconclusive for many of the other suspected individuals because children who are delayed in their intellectual development often score similarly to children who truly have autism. It is difficult to determine whether cognitive problems are being misdiagnosed as symptoms of autism, Poustka says. Delay, or a completely different disorder, can prompt what appear to be autismlike patterns.

A Canadian research team is trying to clarify this overlap. Led by Lonnie Zwaigenbaum, a developmental pediatrician at McMaster University in Ontario, they devised a 16-point observational checklist called the Autism Observation Scale for Infants and used it to evaluate 65 one-year-old children, all of whom had older siblings with autism and therefore had an above-average chance of developing the disorder themselves. They also assessed another 23 babies with no familial ties to or signs of autism.

Zwaigenbaum's group reappraised the children when they were two, this time using traditional tests. They found that almost all the children who were diagnosed as autistic at age two had seven or more distinguishing traits when they were only one. "The predictive power of these markers is remarkable," Zwaigenbaum says.

Even among children just six months old, certain behavioral patterns forecast the onset of the disorder, notably a passive temperament and low physical activity levels. By their first birthdays, the children who later turned out to be autistic were easily irritated, had problems with visual

tracking, tended to focus on a very few objects, failed to look around for a speaker who said their name, and barely interacted with others. They also tended to have certain obsessive motions, such as stroking surfaces, yet made very few gestures toward other people. And they understood less spoken language than their age-mates who were later identified as nonautistic.

As Amaral acknowledged about his first blood-profile exploration, Zwaigenbaum notes that further studies must include children who are at risk for other developmental disorders to help distinguish which symptoms are specific to autism. He is also open to the possibility of environmental influences in triggering or at least exacerbating autism. He says it is hard to know if the traits his group identified are early manifestations of the disorder or if they contribute to a pattern of development that may lead to autism.

Either way, his investigation, Amaral's and those of others are all improving our understanding of when autism starts, providing hope for earlier diagnosis and more effective treatment. The goal, of course, is to offer toddlers a greater chance at a more fruitful childhood, which in turn raises their chances for more satisfying years as teenagers and adults. The many challenges that autistic individuals face as they mature—learning, communicating with others, making and keeping friends, building life skills, securing a job, finding love—will be less daunting if they can get off to an earlier, better start.

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Desperate for an Autism Cure

by Nancy Shute

When Jim Laidler's oldest son, Benjamin, was diagnosed with autism, he and his wife started looking for help. "The neurologists were saying, 'We don't know what causes autism, and we don't know what the outcome for your son will be,'" Laidler relates. "No one was saying, 'Here's what causes it; here's what treats it.'"

But when the Laidlers, who live in Portland, Ore., searched the Web, they found dozens of "biomedical" treatments that promised to improve or even cure Benjamin's inability to talk, interact socially or control his movements. So the parents tried them on their son. They began with vitamin B_6 and magnesium, the nutritional supplements dimethylglycine and trimethylglycine, vitamin A, gluten- and casein-free diets, the digestive hormone secretin, and chelation, a drug therapy designed to purge the body of lead and mercury. They applied the purported treatments to Benjamin's little brother, David, who also was diagnosed with autism. Chelation did not seem to help much. Any effect from secretin was hard to tell. The diets showed promise; the Laidlers hauled special food with them everywhere. And Mom and Dad continued to feed the boys dozens of supplements, calibrating doses up and down with every change in behavior.

The first sign that their experiments had failed came when Laidler's wife, who had become increasingly skeptical, quit giving Benjamin supplements. She waited two months before telling her husband. Her silence ended the day Benjamin grabbed a waffle off a buffet during a family trip to Disneyland and wolfed it down. The parents watched with horror, convinced that he would regress the instant he went off his restricted diet. He didn't.

Jim Laidler should have known better. He is an anesthesiologist. He was aware from the beginning that the treatments he was using on his children had not been tested in randomized clinical trials, the gold standard for medical therapies. “At first I tried to resist,” he says. But hope won out over skepticism.

Hundreds of thousands of parents every year succumb to the same desire to find something—anything—that might alleviate the symptoms of their struggling sons and daughters: lack of speech and communication, inept social interactions, repetitive or restrictive behaviors such as hand flapping or fixating on objects. As many as 75 percent of autistic children are receiving “alternative” treatments not developed by conventional medicine, according to some studies. And yet the therapies are often bogus. They have not been tested for safety or effectiveness, they can be expensive, and some of them may actually do harm. Fortunately, recent spikes in autism diagnoses and parent activism are pushing more federal and private funding toward research that could someday yield scientifically proved results.

No Cause, No Cure

The demand for autism treatments is rising largely because more children are being diagnosed under broader criteria. Back in the 1970s, when autism was called “infantile psychosis”—a mix of social deficits and mental retardation—the condition was considered rare. Pediatricians would tell parents who were worried that, say, their eight-month-old wasn’t making eye contact, to wait and see.

Studies indicated that about five children in 10,000 had autism, but the rate grew higher when doctors redefined the condition as autism spectrum disorder, which included milder symptoms. By the time an updated version of psychiatry’s bible, the *Diagnostic and Statistical Manual of Mental Disorders*, known as the *DSM*, was published in 1994, doctors had added Asperger’s syndrome—a high-functioning form popularized in the movie *Rain Man*—and a catchall group termed “pervasive developmental disorder, not otherwise specified.” Doctors also started realizing the benefits of early diagnosis and treatment. In 2007 the American Academy of Pediatrics recommended universal screening of all children for autism between 18 and 24 months. By then, the autism rate had shot up to one in 110 children.

Whether greater diagnoses reflect a true rise in cases is a matter of controversy, because little is known about what causes the condition. “For the large majority of people with autism, we don’t even know a clear-cut genetic factor,” says David Amaral, research director of the MIND Institute at the University of California, Davis, and president of the International Society for Autism Research. No biomarkers are available to tell which children are at risk or to gauge how well treatments work. The greatest body of research is on behavioral interventions designed to teach social interaction and communication, which appear to help some children to varying degrees.

The lack of empirically vetted therapies makes it far easier for sellers of untested treatments to market hope. “What you’ve got is a combination of pseudoscience and fraud,” says Stephen Barrett, a retired psychiatrist in Chapel Hill, N.C., who reports on dubious medical treatments at his Web site Quackwatch.com. “Parents are under a great deal of stress. They so want their kid to be better. They see improvement over time, and they give credit to the wrong thing.” Those gains are not because of the “treatment,” he says, but because children mature as they age.

Snake-oil salesmen litter the Web. One site tells parents they can “defeat the autism in your child” by buying a $299 book; another touts a video of “an autistic girl improving after receiving stem cell injections.” Many parents acknowledge that they get their information from the Internet, and “a lot of parents rely on anecdotal reports, friends or other parents,” says Brian Reichow, an associate research scientist at the Yale Child Study Center. “In autism, the research has not caught up with the treatments.”

Hope doesn’t come cheap, either. Alternative treatments such as lying in a pressurized, hyperbaric oxygen chamber (used to overcome compression sickness), which temporarily increases blood oxygen levels, cost $100 an hour or more, with one to two hourly sessions recommended daily. Sensory integration therapy, which can range from wrapping children in blankets or placing them in a hug machine to having them play with scented clay, can cost up to $200 an hour. Purveyors charge as much as $800 an hour for consultations and thousands more for vitamins, supplements and lab tests. Parents in an ongoing survey by the Interactive Autism Network at the Kennedy Krieger Institute in Baltimore report spending an average of $500

a month out-of-pocket. The one treatment for autism that has been proved to be somewhat effective—behavioral therapy—can also be the most expensive, at $33,000 or more a year. Although state early-intervention programs and public school districts often cover these costs, the wait for free evaluations and services can be long. All told, direct medical and nonmedical costs for autism add up to an average of $72,000 a year, according to the Harvard School of Public Health.

Dubious Therapies

Illustrated by Bryan Christie

Medical Snake Oil

Unproved therapies extend to medications. Some practitioners prescribe drugs approved for other illnesses. The compounds include Lupron, which blocks the body's production of testosterone in men and estrogen in women;

it is used to treat prostate cancer and to "chemically castrate" rapists. Doctors also have prescribed the diabetes drug Actos and intravenous immunoglobulin G, usually used for leukemia and pediatric AIDS. All three medications have serious side effects and have never been tested for safety or efficacy in autism.

Chelation, the primary treatment for lead poisoning, is another legitimate medical therapy turned autism "cure." The drug converts lead, mercury and other metals into chemically inert compounds that the body can excrete in urine. Some people think exposure to such metals, particularly the methylmercury used as a preservative in vaccines, can cause autism, even though no studies have demonstrated such a link. Indeed, autism diagnosis rates continued to climb after methylmercury was phased out of most vaccines in 2001. Chelation can cause kidney failure, particularly in the intravenous form favored for autism. In 2005 a five-year-old boy in Pennsylvania with autism died after being given intravenous chelation.

Concern led the National Institute of Mental Health to announce plans in 2006 for a randomized, controlled trial of chelation for autism. But the institute shelved the study in 2008 because officials could find "no clear evidence for direct benefit," and the treatment put the children at "more than a minimal risk." Their worry arose in part from lab studies that showed cognitive problems in rats that received chelation and did not have metal poisoning. "I don't think anybody had much faith that chelation would be the answer for a large number of children," says Thomas R. Insel, director of the NIMH. His researchers, he adds, are "more interested in testing medications that have a mechanistic basis."

Predictably, the abandoned study fueled charges that Big Science was ignoring alternative treatments. Money has always flowed more to discovering cures that work than to discrediting ones that don't. Until very recently, most autism research has been conducted in the social sciences and special education fields, where research budgets are modest and protocols are far different than medicine's. At times only a single child is involved in a study. "We would not even call it evidence," says Margaret Maglione, associate director of the Southern California Evidence-Based Practice Center at RAND.

Many Haystacks, Few Needles

State-of-the-art scientific research simply does not exist for many autism treatments, and where it does, the number of people studied is often small. In 2007 the Cochrane Collaboration, an independent evaluator of medical research, reviewed casein- and gluten-free diets, which are based on the premise that compounds in casein, a milk protein, and in gluten, a wheat protein, interfere with receptors in the brain. Cochrane identified two very small clinical trials, one with 20 participants and one with 15. The first study found some reduction in autism symptoms; the second found none. A randomized, controlled trial of 14 children, reported by Susan Hyman, an associate professor of pediatrics at the University of Rochester School of Medicine and Dentistry, found no changes in attention, sleep, stool patterns or characteristic autistic behavior. "Slowly the evidence is starting to accumulate that [diet] is not the panacea people are hoping for," says Susan E. Levy, a pediatrician at Children's Hospital of Philadelphia who has evaluated the evidence with Hyman.

Levy has firsthand experience with the level of effort needed to sway public opinion. Secretin became a hot commodity after a 1998 study reported that three children had better eye contact, alertness and use of expressive language after being given the hormone during a diagnostic procedure for gastrointestinal problems. Media outlets, including *Good Morning America* and *Ladies' Home Journal*, recounted parents' joyous tales of children transformed. The National Institute of Child Health and Human Development rushed to fund clinical trials. By May 2005 five randomized clinical trials had failed to reveal any benefit, and interest in secretin waned. It took years for that to play out, says Levy, who helped conduct several of the trials: "Research is very labor-intensive, and progress may be slow." Parents may feel helpless, she adds, and "they don't want to leave any stone unturned."

The good news is that rising demand for proved treatments is attracting money for research. When the first International Meeting for Autism Research was held in 2001, barely 250 people attended. In May 2010, 1,700 researchers, graduate students and parent advocates showed up for the meeting in Philadelphia. New technologies and increased public awareness have helped make autism a more appealing research focus. And in the mid-1990s parents began adopting the sophisticated lobbying and fund-raising

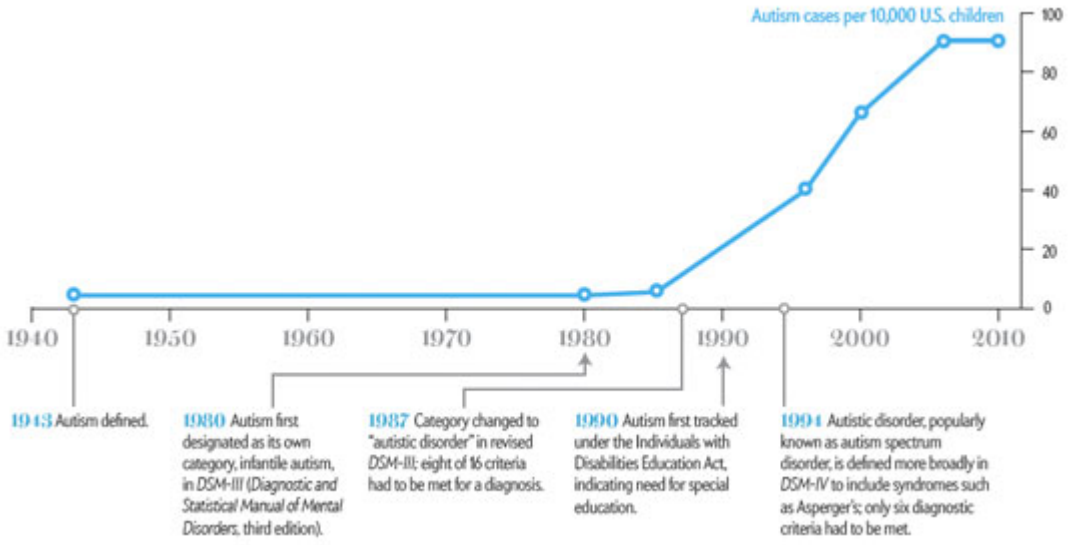
tactics used for AIDS and breast cancer, leaning on foundations and the federal government.

As a result, in the past decade U.S. research funding for autism has increased by 15 percent a year, with an emphasis on clinical applications. The National Institutes of Health allocated $132 million for autism work in 2009, with an additional $64 million from the American Recovery and Reinvestment Act, much of which is being earmarked to develop patient registries and other investigative tools. Private foundations, including the Simons Foundation and Autism Speaks, contributed $79 million in 2008. According to Autism Speaks, about 27 percent of all funding is being spent on investigating treatments, 29 percent on causes, 24 percent on basic biology and 9 percent on diagnosis.

These new pursuits encompass efforts to find out if early intervention with behavioral therapies that teach children social skills through repetition and reward can be used successfully with children when they are very young, when the brain is in the thick of learning language and social interaction. A study by several universities, released online in November 2009, found that children who were given two years of behavioral therapy for 31 hours a week, starting when they were between 18 and 30 months old, made substantial gains in IQ (17.6 points, compared with 7 points in the control group), and in skills of daily living and language. Seven of the 24 children in the treatment group improved enough that their diagnosis was upgraded from autism to the milder “not otherwise specified” form; only one child in the 24 who were given other interventions was given a milder diagnosis. The Autism Treatment Network has built a registry of more than 2,300 children for research on treatments for medical complications often suffered by autistic children, especially gastrointestinal issues and difficulty sleeping, and it plans to develop guidelines that could be used by pediatricians nationwide.

Broader Definition, More Cases

For decades autism was considered rare, perhaps a form of schizophrenia. Rigorous definition in psychiatric manuals began in 1980 but broadened to “autism spectrum disorder” by 1994. As a result, more and more U.S. children were diagnosed, prompting schools to offer special education, parents to call for better treatments and practitioners to offer an increasingly confusing array of unproved therapies.



Illustrated by Bryan Christie

Toward a True Science of Autism

Efforts to find medications, including those used in other neurological disorders, may have higher hurdles to clear. Medical interventions have been "a bit of a disappointment," Insel says. For example, antidepressants that boost the neurotransmitter serotonin in the brain are very effective in reducing the repetitive hand motions of obsessive-compulsive disorders, but a review by the Cochrane Collaboration reported that the drugs did nothing to alleviate the repetitive motions typical of autism. Among the new candidates are a medication that enhances REM sleep, which is lacking in children with autism, and oxytocin, a hormone that promotes childbirth and lactation and is thought to encourage mother-infant bonds. A study published by the National Center for Scientific Research in France found that 13 teenagers with Asperger's were better at identifying images of faces after inhaling oxytocin. A big leap would have to be made between that one study and the notion that oxytocin could mitigate autism's most devastating symptoms. Insel says: "We have a lot of work to do."

That work is starting to be done. In June 2010, a consortium of researchers who scanned the genes of 996 grade-schoolers found rare, novel genetic variations in children with autism. Some of the glitches affect genes that control communication across synapses—the contact points between neurons in the brain, a key focus of autism inquiries. "The actual mutations are different [among individuals], but there may be some commonalities in

the biological pathways," says Daniel Geschwind, a professor of neurology and psychiatry at the David Geffen School of Medicine at U.C.L.A., a study leader. Geschwind is also a founder of the Autism Genetic Resource Exchange database of DNA samples from more than 1,200 families with autism, which was used in the study. Tests to confirm a culprit, or treatments that might fix the glitch, are still years away.

For now, more parents may be choosing not to experiment, if only so they can sleep at night. Michael and Alison Giangregorio of Merrick, N.Y., decided when their son, Nicholas, was diagnosed at age two that they would use only evidence-based treatments such as applied behavioral analysis. "It's difficult enough and challenging enough to help my son," Michael says. "I was not willing to try experimental therapies. I need to do what clinicians and researchers have taken the time to prove works and to prove that it doesn't do any additional harm." Nicholas is now nine, and although he remains nonverbal, behavioral therapy has taught him to use physical signals when he needs to go to the bathroom. He can now wash his hands, sit through dinner in a restaurant and walk down an aisle in the drugstore without flapping his hands. "Obviously, the goal of my family, and most families, is to lead as normal a life as possible," says Michael, a 45-year-old Wall Street trader. "Normal is going out to dinner as a family."

Jim Laidler's path to the same place was far more crooked. Although he embraced alternative treatments for his sons, he also tried to persuade practitioners that they needed to apply the rigor of mainstream science in evaluating such options. "I kept harping on it. Did you do any controls?" he says. His oldest son, now 17, will probably never be able to live on his own, yet his younger son is in a regular middle school. Of the many treatments the family tried, Laidler, 51, says: "This is basically shamanism in a lab coat." Thousands of desperate parents are hoping that science will one day offer stronger medicine.

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Alternative Treatments: How Good Is the Evidence?

by Nancy Shute

Parents who research treatments for autism are confronted with a bewildering array of options, almost all of which have never been tested for safety and effectiveness. Organizations like The Cochrane Collaboration, which reviews the quality of evidence for medical treatments, are putting more effort into evaluating popular alternative treatments.

So far, the most comprehensive review of alternative autism treatments comes from two pediatricians: Susan Hyman of the University of Rochester School of Medicine Golisano Children's Hospital at Strong and Susan Levy, a clinical professor of pediatrics at the University of Pennsylvania School of Medicine and The Children's Hospital of Philadelphia. Their 2008 analysis gave each treatment a letter grade for the quality of the research conducted up to that point; the mark, however, is not a ranking of the treatment's safety or effectiveness.

The two pediatricians based the grades on the amount of testing done on the treatments, which in most cases was skimpy at best. Research that got an "A" grade included randomized control trials, the gold standard for medical research, and meta-analyses, which compare research from different labs. A "B" went to treatments that had been studied in "well-designed controlled and uncontrolled trials," according to Hyman. The "C" grades, the lowest category (there were no "D"s or "F"s), were based on case reports, theories and anecdotes, which are not considered acceptable for mainstream medical research.

Research on just one treatment, secretin, was good enough to earn an A. In short, there is a lot more work that needs to be done toward testing

popular alternative treatments and getting more potential treatments into development at research institutions and pharmaceutical companies.

Dietary supplements

B6/Mg++—Grade: B

Vitamin B6 and magnesium have been a popular treatment for autism over the past 20 years. The Cochrane Review identified three studies that compared outcomes of B6 and magnesium treatment with those for placebo or no treatment, but just 28 subjects were treated altogether. One study found no improvements; another reported improvement in IQ and social behaviors. But all the studies suffered methodological weaknesses aside from the small sample size.

DMG—Grade: B

Dimethylglycine (DMG), an antioxidant and derivative of the amino acid glycine, is marketed as an immune system booster. Two small double-blind studies of DMG found it had no effect on autism symptoms.

Melatonin—Grade: B

Melatonin is a hormone produced by the pineal gland that regulates sleep. Melatonin supplements are popular for self-treating insomnia or jet lag. Many people with autism-spectrum disorders report sleeping problems, and at least one study has found improvements in falling asleep and staying asleep.

Vitamin C—Grade: B

Vitamin C, an antioxidant, is often part of vitamin supplements given to children with autism. One study reported less repetitive behavior in a double-blind, placebo-controlled trial of vitamin C in 18 children with autism.

Amino Acids—Grade: C; L-Carnosine—Grade: B

Neurotransmitter abnormalities have long been a focus of autism research. Some amino acids act as neurotransmitters or prompt their production, so amino acids like tryptophan have been tried as alternative treatments. No trials have studied the benefits of supplementation with

tryptophan, taurine, lysine or GABA. L-carnosine, a molecule made of two amino acids that has antioxidant properties, is marketed as an anti-aging remedy. One double-blind, placebo-controlled trial of L-carnosine in 31 children with autism found improved expressive and receptive vocabulary.

Omega-3 fatty acids—Grade: B

Polyunsaturated fatty acids, in particular omega-3 fatty acids, are crucial for brain development and cannot be manufactured in the body. Essential fatty acid supplements such as fish oil have become popular for children with autism. A randomized, double-blind, placebo-controlled, six-week pilot study found behavior improvements in 13 children with severe behavior problems as a result of autism.

Folic acid—Grade: C

Oxidative stress is a theory that some people have advanced to account for the atypical brain development seen in autism, and abnormal levels of antioxidants have been reported in children with autism. But there are no randomized, controlled trials testing the notion that supplementation with folic acid, a water-soluble B vitamin that helps produce and maintain new cells, would have beneficial effects.

Secretin—Grade: A

Secretin, a gastrointestinal hormone, is one of the most extensively studied autism treatments. More than a dozen well-designed, well-executed studies have failed to find any benefit.

Pharmaceutical treatments

Antibiotics—Grade: C

Parent reports of frequent respiratory or gastrointestinal infections in children with autism are used to support the theory that the children have immune system problems, but those findings have not been confirmed. One study found short-term behavioral improvement in 11 children treated with oral vancomycin. But there are no other data supporting the use of antibiotics, and the researchers in that study said they would not recommend it for routine treatment.

Antifungal agents—Grade: C

Treatment with antifungal agents is based on the premise that imbalances in intestinal flora or other immune factors lead to an overgrowth of yeast. No controlled trials have tested antifungals as an autism treatment despite the popularity of medications such as nystatin (Mycostatin) and fluconazole (Diflucan).

Gastrointestinal medications—Grade: C

Children with autism frequently have symptoms such as reflux, constipation and diarrhea, and eat only a very limited number of foods. There are no evidence-based studies on the efficacy of digestive enzymes or probiotics for treating these symptoms.

Hyperbaric Oxygen Therapy—Grade: C

Hyperbaric oxygen therapy (HBOT) is used in conventional medicine to treat carbon monoxide poisoning and to speed wound healing, and it has become popular as an autism treatment based on theories that implicate gut or brain inflammation or lack of blood flow to the brain. There are no randomized clinical trials of HBOT for autism. One open trial of 18 children with autism found some decrease in C-reactive protein, a marker for inflammation, and parents reported improved behavior. But the subjective measures and the fact that many of the children were also taking antioxidant supplements "make this study difficult to interpret," Hyman and Levy report.

Immune therapies—Grade: C

Some alternative practitioners recommend treatment with intravenous immunoglobulin-G, on the premise that immune deficits cause symptoms of autism. One open trial reported subjective improvements, but two other trials with specific outcome measures found no benefit.

Other approaches

Chelation—Grade: C

One alternative theory holds that mercury is poorly eliminated by children with autism, and that the toxic metal alters immune function and development. Epidemiological studies have failed to find a link between the use of the ethyl mercury–based preservative thimerosal in vaccines and

autism. Despite this, chelation, the standard treatment for heavy metal poisoning, is marketed as an off-label treatment for autism. There are no controlled studies testing chelation's safety or effectiveness as an autism treatment, and at least one child has died after being treated with EDTA (ethylenediamine tetraacetic acid) chelation for autism.

Gluten-free/casein-free diet (GF/CF)—Grade: B

This diet is a popular alternative treatment for autism, based on the premise that the proteins gluten (found in wheat) and casein (in milk) aggravate autistic symptoms because they in some way mimic opiate neuropeptides. One small single-blind trial found some improvements; larger double-blinded trials have found none. Hyman and Levy speculate that improvements seen by parents may be from removing lactose from the diets of children who are lactose intolerant.

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