

TALES *from* SPECTRUM

2018

TALES

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They say if you've met a child with autism, you've met just one child with autism. The condition is an enduring scientific puzzle, and at *Spectrum*, we put much of our energy into covering the fast-breaking science in this field.

Each week, we publish a stream of new findings, expert opinion and emerging techniques for our core audience of scientists, as well as the autism community at large.

Separate from this news cycle, though, we also commission journalists to spend months at a time digging into bigger trends in autism. This reporting leads to our 'Deep Dives,' analyses that probe in depth how people experience and study autism.

In this collection of Deep Dives, we present a wide range of these stories — from how girls with autism are so often misdiagnosed and why children on the spectrum can be clumsy, to the condition's little-known connection with cancer and its overlap with addiction.

Through the spectrum of these stories, we hope to convince you that if you've read one story about autism, you've read just one story about autism.

— TEAM SPECTRUM

chapter

SEEING THE SPECTRUM

ORIGINALLY PUBLISHED 13 JANUARY 2016

EXTRA- ORDINARY MINDS

Some people with autism have an exceptional talent for music, math, art or language. What accounts for their extraordinary brains?

by
LINDA MARSA

photographs by
PATRICK FALLON

THE LINK BETWEEN SAVANTISM AND AUTISM



IT DON'T MEAN A THING IF IT AIN'T GOT that swing," Rex Lewis-Clack croons, his head joyfully bobbing in time with the Duke Ellington standard. The 20-year-old musician accompanies himself on a grand piano, deftly striking the keys with a dexterity reminiscent of the Duke himself. Then he segues into an exquisitely executed rendition of Chopin's *Fantaisie Impromptu*. Lewis-Clack has the sweet-faced, blond good looks of a teen heartthrob. But the haunting melody that seems to flow from his fingertips is masterful. It fills the high-ceilinged living room of the Los Angeles beachfront condo he shares with his mother, Cathleen Lewis. After the last strains echo through the apartment, he rocks back and forth on the piano bench and flaps his hands in excitement, seemingly elated, and flashes a wide, triumphant smile.

This cherubic young man was born blind, due to a congenital condition called septo-optic dysplasia. He had serious cognitive disabilities as a child, and severe symptoms of autism: Even the faintest noises would make him scream, and he

was so sensitive to touch that he kept his hands balled up in fists. "On his third Christmas, we had to go out of the room to open presents because he couldn't stand the ripping sound of the wrapping paper," recalls Lewis. "He wouldn't eat solid foods and pretty much lived off liquids for his first few years. It seemed like he was a prisoner in his own body." His doctors predicted he would never walk or talk.

When he was 2, Lewis-Clack's father gave him a piano keyboard. It became his gateway to the outside world. Lewis-Clack taught himself to play the piano, says Lewis, "and would play until he dropped from exhaustion." When he began formal lessons at age 5, his teacher noticed his remarkable gifts. Lewis-Clack has perfect pitch, a phenomenon that occurs in about 1 in 10,000 people: He can identify a musical note immediately, even when he hears it completely out of context. Although he cannot see and cannot read music, he only needs to hear most songs once to play them back perfectly. And he has whole libraries of music stored in his brain. "One day, Rex sat down

and played through all 21 of Chopin's nocturnes, and played them perfectly even though he had only studied or played six of them [before]," says Lewis. Unbeknownst to her, he had memorized the other 15.

Lewis-Clack doesn't talk much, responding to most questions with short sentences. "I crack the eggs," he amiably offers when asked how he'll help his mom prepare a pumpkin pie for the holidays. He communicates mostly through his music: He played in his first concert at age 7 and now travels around the world to perform in fundraisers to benefit people with disabilities. Because of his exceptional musical talent and his intellectual disability, he is considered a savant — one of those unusual people who struggles with tasks that most people find simple, yet has extraordinary abilities that few could hope to attain.

Savant syndrome is a loose term that refers to people who have a combination of significant cognitive difficulties, often stemming from autism, and profound skills — "islands of genius," in the words of Wisconsin-based psychiatrist Darold Treffert, an independent scholar who has studied savants for more than half a century. Once thought to be rare in people with autism, found in no more than 1 out of 10 individuals, research over the past few years suggests savantism may be more common: As many as one in three people with autism may possess exceptional abilities.

Exactly how and why savantism happens is unclear. But some evidence suggests that savants may have experienced an undetected injury to the left hemisphere of their brain *in utero* or in infancy, triggering compensatory recruitment in the right brain that unleashes unusual abilities.

Most savants have special abilities in musical, artistic, mathematical or mechanical domains, coupled with extraordinary memory. Stephen Wiltshire, for instance, a British savant and artist who was diagnosed with autism at age 3, has been

called a "human camera" because of his ability to draw landscapes from memory after seeing them only once. Other savants possess the uncanny skill of 'calendar calculating' — quickly computing the day of the week of any arbitrary date in the past or future — highlighted in the 1988 Oscar-winning movie "Rain Man." Still others may have a facility with foreign languages, the ability to measure distances or heights with precision without using instruments, or exceptional map-reading skills. But only a handful possess Lewis-Clack's extraordinary gift.

ORDINARY GENIUS

Savants were described in the medical literature as early as the late 18th century, but the past few decades have provided a better understanding of the phenomenon. An extensive survey in 1978 suggested the 1 in 10 estimate, and it became an article of faith.

But research in the past 10 years has generated some controversy about the actual incidence of savantism. Some researchers say these seemingly extraordinary abilities may just reflect the fact that many people with autism have a different skill set than their typical peers do. "People with autism are natural specialists — when they dig in, they quickly become expert," says Laurent Mottron, a psychiatrist at the University of Montreal.

People with autism tend to do poorly on standardized tests of intelligence that have time limits and rely on verbal instructions, cultural familiarity and social interactions. Evaluations such as the Raven's Standard Progressive Matrices, which measures reasoning and creative problem-solving, provide a better gauge of intelligence.

When researchers use these more appropriate methods of assessing intelligence, the peak

abilities thought to be a sign of savantism — the ‘islands of genius’ in people believed to be profoundly impaired — disappear. “There is a bell curve in savantism, just like the bell curve of intelligence,” says Mottron. The high-scoring end of the bell curve in autism includes a few people whose exceptional abilities in certain domains exceed those of most people without autism.

This interpretation is in line with that of a 2009 study conducted by psychologist Patricia Howlin of the Institute of Psychiatry at King’s College London. In that study of 93 individuals with autism, parent reports and test scores indicated that 39 — roughly 40 percent — had exceptional skills, both in comparison with their other abilities and with skill levels found in the general population. Those abilities include what are called ‘splinter skills,’ such as the capacity to perform complex mathematical calculations mentally without pen and paper.

Howlin’s study included two different measures: The participants either had a ‘savant skill,’ such as superior mathematical, musical or artistic abilities, or a memory for dates, places, routes or facts, or they had ‘exceptional cognitive skill,’ defined as an intelligence quotient (IQ) two standard deviations above the mean score of 130. A few individuals fit both categories.

Traditional studies of people with autism may be skewed, Howlin points out, because many of the participants are from a self-selected population: the people who are referred to psychologists because of their severe deficits. Meanwhile, those with autism who are functioning well may be under-studied simply because they’ve integrated well into society and aren’t brought to the attention of researchers. “The trouble is that we don’t know an awful lot about people with autism who manage well in the world because we study the individuals who haven’t managed too well,” says Howlin.

LEFT VS. RIGHT

Where the exceptional talents of people with autism stem from is an enduring mystery, but some of the puzzle pieces are starting to fall into place.

More than 30 years ago, pioneering San Diego psychologist Bernard Rimland developed the world’s largest database of people with autism, with more than 34,000 individuals. Rimland noticed that their savant skills, such as artistic expression or the ability to mentally manipulate three-dimensional (3D) objects, were most frequently right-hemisphere faculties. Their difficulties, such as trouble communicating, often appeared in functions controlled by the left hemisphere.

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**People with
autism are natural
specialists.**

”
LAURENT MOTTRON

In many types of brain injury or in dysfunction caused by stroke or neurodegenerative diseases, doctors have noticed that a defect in the left hemisphere may lead to a compensatory improvement in typically right-hemisphere functions. It’s as if the injury is “releasing the brain from the tyranny of the left hemisphere,” in Treffert’s words. No longer held in check, right-hemisphere abilities appear to suddenly blossom.

Brain imaging provides glimpses into the mechanism underlying the emergence of these



Different drummer: When Lewis-Clack was a baby, doctors predicted he would never speak.

exceptional talents. Some early clues came from imaging studies of acquired savantism: ordinary people of average intelligence and ability who suffered a severe brain injury and suddenly developed new skills, such as musical talents, the ability to speak foreign languages, or superior skills in mathematics or art.

Bruce Miller, a neuroscientist at the University of California, San Francisco, witnessed this phenomenon firsthand when some of his elderly patients who suffered from frontotemporal dementia (FTD), a degenerative brain disorder that primarily affects the front left-side portion of the brain, spontaneously developed an interest in art. As the dementia progressed, these individuals became gripped by the urge to create, and their paintings improved.

Miller and his colleagues used single-photon emission computed tomography, a technique

that captures blood flow changes in the brain and reflects neuronal activity, on a dozen people with FTD who had developed new artistic talents. The scans revealed damage to the anterior temporal lobe of their left hemisphere and the orbitofrontal cortex, regions associated with logic, verbal communication and comprehension. Miller and his team theorized that the selective brain degeneration essentially ‘released’ dormant abilities in the right brain, which is dominant for some key features of artistic expression, including visual construction — the ability to copy drawings or put puzzles together — and some forms of creative thinking.

When they compared these scans with those from a young artist with autism who had had a compulsive urge to draw since early childhood, the researchers found “remarkable parallels.” Like the people with FTD, the 9-year-old savant

showed loss of function in the left temporal lobe, paired with heightened activity in regions of the right brain that process sensory inputs and visual information.

Imaging studies by Mottron’s team and others shed more light on savantism’s possible neurological underpinnings. Mottron’s group has found that people with autism who have average IQ scores are nonetheless up to 40 percent faster than their peers without autism at solving complex logical problems. Their analytical skills may account for this superiority in manipulating numbers. The team has also found that people with autism possess enhanced perceptual abilities: They excel at discerning patterns against the backdrop of complex environments, spotting embedded details that others miss, and often have exceptional ability in mentally manipulating 3D shapes.

In a 2012 meta-analysis of functional imaging studies, Mottron’s group found enhanced activity in people with autism in brain regions associated with visual processing, object recognition, visual imagery and visual expertise, the ability to differentiate between similar objects — for example, different types of birds. “These results suggest that enhanced reliance on visual perception has a central role in autistic cognition,” says Mottron.

Famously, the well-known animal behavioral scientist Temple Grandin, who was diagnosed with autism as a child, has said that she “thinks in pictures.” She says her acute vision enables her to notice details that most people gloss over but animals detect and may be frightened of, such as shiny objects that reflect the sun’s rays. This heightened visual processing helps her in her work designing low-stress environments for livestock.

Mottron says enhanced perception may contribute to logical ability, which might explain the superior skill of some people with autism in solving complex logical puzzles. Heightened perception could also aid in the acquisition of three abilities

associated with savants: perfect pitch, hyperlexia — precocious reading ability in a very young child — and synesthesia, a condition in which sensory stimuli is jumbled so that hearing a sound might produce a visualization of a color. Mottron’s team summed up all these changes as the “functional re-dedication of perceptual brain regions to higher-order cognitive functions” — in other words, the brain seems to redeploy its resources, so that regions normally engaged in one purpose are recruited to take on more advanced tasks.

Essentially, what this means is that the brains of people with autism are more flexible than those of their peers. (This ‘plasticity’ doesn’t help them overcome their social deficits, however, because the intricacies of social interactions cannot usually be processed perceptually or logically, Mottron says.) In general, people with autism recruit different neural pathways than controls do to accomplish a particular task. They also may have more activity in regions associated with perception. In the same way that losing one sensory faculty, such as eyesight, may prompt the brain to compensate by reallocating more neural resources to produce exceptional hearing ability, the brains of people with autism may be better able to reorganize. That leads to enhanced perception; if that faculty is combined with knowledge and other forms of expertise, the result is savant skills. This, Mottron says, may be our best hint as to how savant abilities are acquired.

CHANCE ENCOUNTER

In 1998, Joanne Ruthsatz, then a graduate student in psychology, stumbled upon a possible explanation of the roots of savantism during a chance meeting in a fast food joint in southern Louisiana. She had traveled to the bayou country

to interview a 6-year-old musical prodigy who was playing guitar at music festivals across the South. After undergoing a battery of IQ and aptitude tests, all the guitar phenom wanted to do was go to McDonald's. So the trio — the boy, his mother and the scientist — trooped out to the local hamburger emporium. "Just by chance, the child's aunt and his teenage cousin came in," Ruthsatz recalls. "While the two sisters talked, the cousin grunted and flapped his hands. Later, the mother told me her nephew had severe autism. And I thought: What are the chances of them being first cousins like that?"

“
**Autism and
savantism may
have a common
genetic root.**
”

JOANNE RUTHSATZ

As it turned out, the odds are quite significant. In a 2007 study, Ruthsatz distributed the Autism Spectrum Quotient, a test devised by British researchers to measure traits associated with autism, to three sets of people, each including 10 individuals: One group included prodigies and their first-degree family members (parents or siblings), another included individuals with autism and their family members, and the third included individuals without any diagnoses and their family members. The prodigy families and the families of those with autism both scored higher on traits associated with autism, including difficulty with

social skills, difficulty switching attention (the ability to multitask), and enhanced attention to detail. Because individuals with autism are often keenly attuned to seemingly extraneous details, Ruthsatz found it especially interesting that the prodigies outscored them on this characteristic.

Since that fateful meeting, Ruthsatz, now a psychologist at Ohio State University in Mansfield, has collected extensive profiles on 30 children who were deemed prodigies (she identified them through the Internet, via press attention and by referral). By the end of 2011, she had discovered that three of the first nine prodigies she investigated had been diagnosed with autism early in life but no longer met the criteria. "They no longer qualified for a spectrum diagnosis," says Ruthsatz. What's more, five of the nine had at least one close family member with autism. One prodigy had two siblings, a father, grandmother and an aunt on the autism spectrum. "It means that the two conditions may have a common genetic root," says Ruthsatz, coauthor of the upcoming "The Prodigy's Cousin: The Family Link Between Autism and Extraordinary Talent."

Further research added detail to the earlier findings. In a 2012 study of eight prominent child prodigies, Ruthsatz documented many characteristics that are often found in children with autism, such as difficulties in social settings and obsessive attention to detail. The prodigies also had remarkable skills in working memory — the ability to manipulate information stored in short-term memory banks — scoring two standard deviations above the mean. Six out of eight of the prodigies scored in the 99.9th percentile.

In 2015, Ruthsatz's team identified a potential genetic link between prodigies and people with autism. In genetic samples from 11 prodigies and from the family members of people on the autism spectrum, they discovered a common mutation on chromosome 1, in a region known as 1p31-q21.



Listen up: Lewis-Clack has perfect pitch and an exceptional memory for songs.

The research team has yet to pinpoint the exact location of the genetic variant, and as yet has no theories about how the variant may contribute to some of the characteristics shared by prodigies and savants. The team is searching for a genetic modifier in the prodigies that might be protective against autism, which might explain why they no longer have the diagnosis.

In the meantime, scientists and the public alike continue to be fascinated and inspired by people such as Rex Lewis-Clack, who straddles the world of the prodigy and the savant.

In 2013, Lewis-Clack and his mother launched a foundation for after-school programs for blind children with autism in southern California. His mother talks about all the things he has done, such as performing at fundraisers for Best Buddies International, serenading Vice President Joseph Biden and his family at their Washington, D.C., residence for a reception honoring Eunice

Kennedy Shriver, and being greeted like a rock star at a music festival in Freiburg, Germany, where the whole town turned out to hear him play. “That made me feel great,” Lewis-Clack says, beaming. The affable young man spends most of his days immersed in music, taking voice and piano lessons and learning improvisation techniques.

Lewis-Clack’s gifts transformed him from a timid toddler into a celebrated performer who plays to packed houses at concert halls throughout the world. After the Chopin, I ask him if he would play another tune. “No,” he responds, firmly but not in an unfriendly way. I ask his mother if it would be okay to ask if I can give him a hug as a way of expressing my appreciation for the mini-concert, and she smiles and nods vigorously. Lewis-Clack rises from the piano bench, arms open wide, and gently envelops me, as if it’s the most natural thing in the world.

Misdiagnosed,
misunderstood or
missed altogether,
many women with
autism struggle to get
the help they need.

THE LOST GIRLS

by

**APOORVA
MANDAVILLI**

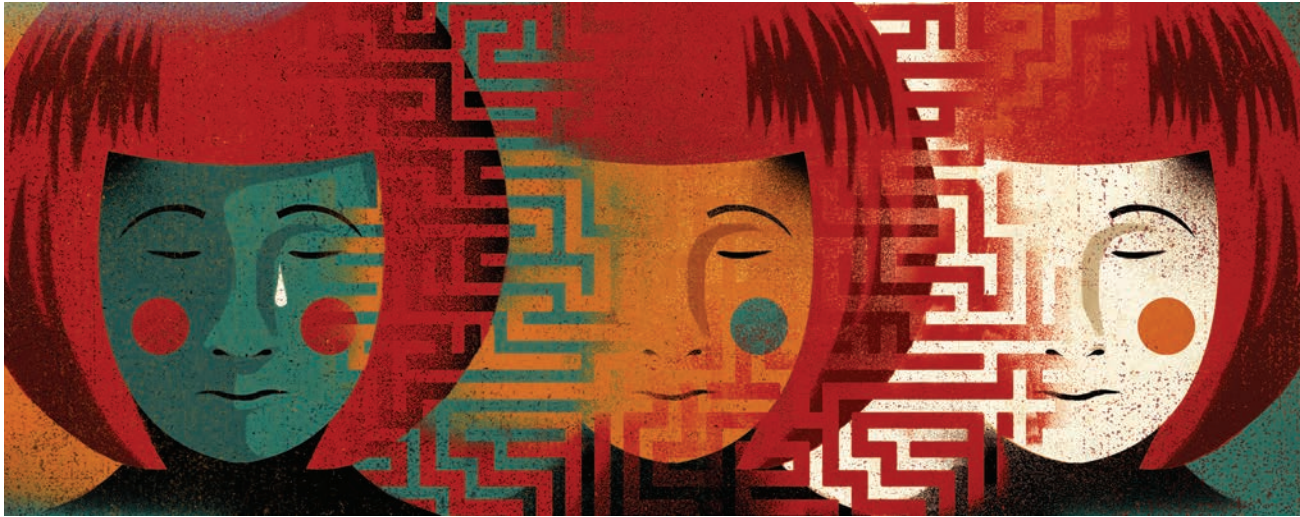
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IT TOOK 10 YEARS, 14 PSYCHIATRISTS, 17 medications and 9 diagnoses before someone finally realized that what Maya has is autism. Maya loves numbers, and with her impeccable memory, she can rattle off these stats: that the very first psychiatrist she saw later lost his right to practice because he slept with his patients. That psychiatrist No. 12 met with her for all of seven minutes and sent her out with no answers. That during her second year at Cambridge University in the U.K., industrial doses of the antipsychotic quetiapine led her to pack on more than 40 pounds and sleep 17 hours a day. (Maya requested that her last name not be used.)

But those numbers don't do justice to her story. It's the long list of diagnoses Maya collected before she was 21, from borderline personality disorder to agoraphobia to obsessive-compulsive disorder, that begin to hint at how little we understand autism in women.

Her conversation with psychiatrist No. 14 went something like this:

Do you hear things that others don't? Yes. (Maya's hearing is excellent.)

Do you think others are talking about you behind

your back? Yes. (Maya's extended family is particularly gossipy.)

The psychiatrist didn't explain exactly what he was trying to assess. Literal to a fault, Maya didn't explain what she meant by her answers. She left his office with her eighth diagnosis: paranoid personality disorder.

Maya does have some of the conditions she's been diagnosed with over the years — she's been depressed since the age of 11, has crippling social anxiety, and in her teens, wrestled with anorexia. But these were just expressions of the autism that was there for anyone to see had they looked closer. "It's all secondary to the Asperger's," says Maya, now 24. "I get depressed and anxious because life is difficult; it's not the other way around."

It's not uncommon for young women like Maya to be repeatedly misdiagnosed. Because autism is at least three times as common in boys as in girls, scientists routinely include only boys in their research. The result is that we know shockingly little about whether and how autism might be different in girls and boys. What we do know is grim: On average, girls who have mild symptoms of autism are diagnosed two years later than boys. There's some debate about why this might be so.

From the start, girls' restricted interests seem more socially acceptable — dolls or books, perhaps, rather than train schedules — and may go unnoticed. But the fact that diagnostic tests are based on observations of boys with autism almost certainly contributes to errors and delays.

As they enter their teens, girls struggle to keep up with the elaborate rules of social relationships. Cribbing style notes on what to say and how to say it, many try to blend in, but at great cost to their inner selves. Starting in adolescence, they have high rates of depression and anxiety — 34 and 36 percent, respectively. A few studies have also found an intriguing overlap between autism and eating disorders such as anorexia, although the studies are too small to estimate how many women have both.

Even after a girl gets the right diagnosis, she may be offered behavioral therapy and specialized lesson plans, but they're essentially the same services offered to a boy in the same situation. Scientists and service providers rarely acknowledge the additional challenges being female may bring, whether physical, psychological or societal. There are no guidebooks for these girls or their families about how to deal with puberty and menstruation, how to navigate the dizzying array of rules in female friendships, how to talk about romance and sexuality or even just stay safe from sexual predators. Advocates and scientists in other disciplines have run up against and resolved many of these same problems, but in autism, the fact that boys and girls are different is sometimes treated as if it's a startling new discovery.

In the past two to three years, there has been an uptick in the attention paid to the issues that affect women with autism. More money is now available for scientists to study whether and how autism differs in boys and girls. This past year, the journal *Molecular Autism* dedicated two special issues to research specifically exploring the

influence of sex and gender on autism. "Almost overnight, we went from a couple of people talking about sex differences to everyone studying this as a major factor in the field," says Kevin Pelphrey, Harris Professor at the Yale Child Study Center.

Unpublished results from Pelphrey's lab confirm what common sense suggests: Women with autism are fundamentally different from men with autism. Autism's core deficits may be the same for both, but when the symptoms intersect with gender, the lived experience of a woman with autism can be dramatically different from that of a man with the same condition.

GIRL POWER

From its first clear description in 1943 by Leo Kanner, autism has been known to crop up in more boys than girls. But why this is so remains a mystery.

At first, scientists looked for the simplest explanation: that a boy who carries a faulty stretch of DNA on his single X chromosome develops autism, whereas a girl who inherits the same mutation would be unaffected because she has a second X chromosome to compensate.

But the search for this X-factor went nowhere. "I think the thinking is now moving more to the idea that women are protected, which I know sounds like two sides of the same coin, but it plays out in a different way," says Stephan J. Sanders, assistant professor of psychiatry at the University of California, San Francisco. The idea is that, for as-yet unknown reasons, women can tolerate more mutations than men can, and so need a bigger genetic hit to develop autism.

A 2012 paper that laid out this 'female protective effect' in autism marked a turning point in the field, bringing the topic of girls with autism

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**You can see by
meeting with me
that I’m quite chatty
and that people
wouldn’t guess that
I have Asperger’s.**
”

into the spotlight. “Once the genetics community became interested in it, it just absolutely took off,” says Pelphrey.

Around the same time, Pelphrey and his collaborators won a five-year, \$13 million grant to probe the differences between girls and boys with autism, as well as their unaffected siblings. They are recruiting 250 girls with autism between 6 and 17 years old at six sites across the U.S. They plan to characterize the behavior, genetics, and brain structure and function of these girls and compare these findings with data from 125 boys who have autism, as well as from 50 children in each of the following groups: typically developing boys, typically developing girls, unaffected male siblings and unaffected female siblings of children with autism. “We’re trying to address the question: Are girls different? And how are they different?” says Pelphrey.

A few studies have explored this question. There seems to be an overall consensus among scientists that at the more severe end of the spectrum — characterized by low intelligence quotient (IQ) and repetitive behaviors — there is little outward difference between girls and boys

with autism. It’s at the other end of the spectrum that the science is fuzzier. Given the small numbers of women with autism in the studies, there are few definitive answers.

“Clinically, my general impression is that young girls with autism are different [from boys], but it has been very hard to show that in any kind of a scientific way,” says Catherine Lord, director of the Center for Autism and the Developing Brain at Weill Cornell Medical College in New York City. On average, girls are more chatty, less disruptive and less likely to be entranced by trains or moving vehicles than boys are, she says. However, she adds, this is also true of typical girls and boys, so it becomes difficult to separate gender differences in autism from gender differences in general.

Early studies estimated that at the high-IQ end, the male-to-female ratio is as high as 10-to-1. The picture emerging from studies looking at girls with autism over the past few years suggests this ratio is artificially inflated, either because girls at this end of the spectrum hide their symptoms better, or because the male-biased diagnostic tests aren’t asking the questions that might pick up on autism in these girls — or both.

“For some males, you can make the diagnosis at least provisionally in your mind within 10 minutes of them coming into your office,” says Simon Baron-Cohen, director of the Autism Research Center at Cambridge University in the U.K. “Whereas for some of the women, it might take half an hour or not till halfway through a three-hour diagnostic interview before they’re revealing what’s behind the mask.”

HIDDEN HURT

It takes hours to see glimpses of the pain Maya has endured over the years. She makes eye contact,

pokes fun at herself and takes turns in conversation — things people with autism are generally known to have trouble doing. On a warm June day in London, dressed casually in a T-shirt and shorts, she looks like any other British 20-something. “You can see by meeting with me that I’m quite chatty and that people wouldn’t guess that I have Asperger’s,” she says.

Maya is proud of her accomplishments — and rightfully so. She excelled at school: She could read fluently by age 5 and began reading four or five books a week. She was lead violinist at her school, performing at the Barbican Centre in London, and can also play piano and viola. She taught herself to play the clarinet, and after 9 months of lessons, performed a Mozart concerto at her school.

But as the conversation turns more intimate, she and her mother reveal the agony that has formed the backdrop to her achievements. At 4, Maya had severe separation anxiety and screamed every time strangers entered her nursery school. Later, at her all-girls school, she sat by herself at playtime, and read everywhere, even on stage at a cousin’s raucous wedding. She struggled with small talk, regularly made social faux pas — blurted out the denouement of a mystery, or reciting divorce statistics at an engagement party — and rambled on about her interests so long that her mother devised a secret gesture, a tap on the watch, to signal her to stop.

Any small disruption in her routine — dinner on the table 10 minutes later than promised, a late appointment, her little brother sitting in her favorite chair — could ruin her week. (“It’s not something I like about myself,” Maya says. “I can’t help having this need for wanting everything to be the same — but I do.”) She rarely got a good night’s sleep and had debilitating nightmares. She turned down invitations to ‘aimless’ social activities such as shopping, and called other girls out when

they flouted the school’s rules, turning would-be friends into enemies.

By the time she was 8, she was bullied so much at school that she became sick with anxiety every Sunday night. At 11, her parents finally switched schools, but she was bullied here as well — even on the 45-minute bus ride each way.

Looking for the common factor, Maya’s logical mind pinned the blame on herself rather than on the cruel social games of girlhood. “I thought: ‘Everything’s different — the school’s different, the people are different, yet the bullying is the same,’” she recalls. “Therefore, the only thing it can be is that something’s wrong with me.”

The bullying got violent and more vicious as she got older. She recalls one set of girls telling her that the world would be a better place if she weren’t in it, and that they felt really sorry for her parents. Ever honest herself, Maya believed them: “I won’t say things unless they’re true, so I thought, why would they?”

When she was about 12, Maya began secretly cutting herself. Like many girls with autism at this age, Maya was keenly aware of all the ways in which she was being excluded by her peers. She became intensely depressed, launching her long and dysfunctional relationship with the psychiatric establishment.

At 15, to keep herself occupied during the unstructured summer holidays, Maya began volunteering with boys who have autism — at first only because the organization was around the corner. She never made the connection that she might have something in common with them. She brought one of the young boys home to visit once, and still neither her father, a physician, nor her mother, a clinical virologist, picked up on any similarities.

“My picture of autistic was what this little boy was like — and that’s not what Maya’s like. He was



nonverbal, disruptive,” her mother, Jennifer, says. “I would not have made the connection with all the unhappiness she experiences.”

The bullying stopped at 16 when Maya was moved into a new class at the school. But soon after, she became obsessed with controlling her

weight. Like many other adolescent girls with autism, she developed an eating disorder. The way she sees it now, that preoccupation was an outgrowth of another aspect of her autism — her love of numbers. “I was obsessed with decreasing the number of calories I ingested, and the numbers on the scale going down,” she says. Anorexia also resonated with her perfectionistic streak. “It’s fine if it’s something like learning musical instruments,” she says. “It’s not so fine if you decide to starve yourself, because I wanted to do that to perfection as well.”

Over the next two years, Maya became “a master of disguise,” hiding her food and exercising in secret, even on a family safari in Kenya in July 2009. “You know what I remember about that trip? I remember that I gained 400 grams in two weeks; that’s what I remember,” Maya says.

Each accomplished target led to the next until at one point Maya, who is 5 feet 6.5 inches, weighed just under 44 kilos (about 97 pounds). “The anorexia has been, from my perspective, possibly the most difficult thing to cope with, out of all the things we have gone through,” says her mother Jennifer.

In August 2009, relenting to her parents’ pleas, Maya went back to her first psychiatrist. She emerged with six diagnoses, including anorexia, generalized anxiety, bipolar disorder and agoraphobia.

In October of that year, despite the ongoing anorexia, Maya’s parents drove her to Cambridge University, her life’s dream until that point, crying all the way home because they were so worried about her. At first, Maya seemed to thrive — she enjoyed her classes, and made friends who were “quirky” like her, her mother says. But soon, she stopped talking about her new friends, and when her friends would knock on her door, she simply wouldn’t answer. The depression that had come

and gone since she was 11 resurfaced. “I didn’t want to socialize, I didn’t want to see anyone, it was too difficult,” Maya says. She also began taking overdoses of her meds, enough to get her on the radar of the local mental health team.

Maya’s second year was the same. She continued to struggle with anorexia: “It clocked that my goal was to weigh nothing.” Then one day, her counselor at Cambridge pointed out that even if she had no fat or muscle, she would still carry the weight of her bones. “Therefore, I could never weigh nothing, even if I was dead,” Maya recalls thinking. As is the case for many people with autism, facts hold great power for Maya. The logic of the counselor’s statement got through to her like no amount of pleading from her parents had. “I realized that what I was doing was completely pointless. I was never going to get where I wanted to.”

The relief from the decision to stop controlling her weight carried Maya through her second year. The family once again went on an exotic holiday, this time to the Galapagos, and Maya seemed at peace. She swam with the dolphins — and she ate.

But back at Cambridge for her final year, she again sank into a deep depression. Her mother, who had rented an apartment in town and slept on Maya’s floor one or two nights a week, urged her to leave university so she could focus on feeling better. Quitting went completely against the grain for Maya. “I don’t give up on things,” she says. “I hate it when plans change. My plan was to finish school, go to university, graduate. My plan was not to get so depressed that I had to leave university.” But four weeks into the term, after getting no help from a university psychiatrist (the one who allotted her seven minutes), she made the difficult decision to leave.

Far from making her feel better, however, leaving Cambridge made her feel as if she had no future. Overweight and sluggish, she slept through her days at her parents’ house. On the 29th of

December, after going out to lunch (which Maya finds stressful), cooking her family dinner (which she loves to do), and a pleasant and unremarkable night of watching television with them, Maya took more than 30 tablets of paracetamol (acetaminophen), about 15 codeine pills and all the quetiapine she could lay her hands on.

“Nothing was getting better,” she says. “I just gave up; I’d had enough of life.”

A short while after taking the pills, Maya panicked that she was still awake, and that she might begin to vomit, something she dreads. She woke her parents and, within a half hour of arriving at the emergency room, fell into a coma.

SOCIAL NETWORKS

Social isolation, bullying and depression are not exclusive to girls with autism — boys experience them too. But for older girls with autism, the intricacies of their social world add layers of complexity.

In early childhood, boys and girls with autism are about the same. If anything, girls appear to be more social — whether because they actually are or are just perceived to be. As they edge closer to adolescence, however, girls with autism lose this early social advantage, becoming less and less likely to have friends, and more likely to be isolated. “It can be very, very tough for them,” says Pelphrey.

For some girls, that may be a result of having mostly been in classes with boys who have autism. But even for girls who are placed in mainstream schools, the rituals of female adolescence can be boring or bewildering.

Adolescent boys tend to socialize in loosely organized groups focused on sports or video games, allowing a boy with minimal social skills to slide by, says Kathy Koenig, associate research

scientist at the Yale Child Study Center. “For girls, socialization is all about communication, all about social-emotional relationships — discussions about friendship, who likes who and who doesn’t like who and who is feuding with who,” Koenig says. “Girls on the spectrum don’t get it.”

Adolescence can be a confusing time for any young girl, but for a girl with autism, “trying to make friends and not understanding why the friendships aren’t lasting, or why you’re not being included when people are making plans” can be incredibly isolating, says Baron-Cohen. “You’re aware enough to know that you’re failing, basically.”

Ostracized and aware of it, adolescent girls with autism become highly anxious and depressed, and many develop eating disorders. This trend remains constant until late middle age, when clinicians suspect that, as they are known to do in the general population, the differences in mood disorders between men and women with autism may even out.

There are any number of programs for people with autism that teach specific behavioral skills — improving eye contact or turning your body toward the person you’re speaking to, for example. But there is almost nothing to give adolescent girls the kind of emotional support that only comes from true companionship.

In the U.S., there seem to be just three such programs — one at Yale, one at the University of Kansas, and a new center in New York City.

The Yale program, which Koenig launched more than three years ago, brings girls with autism together for yoga, or to make jewelry or to watch the blockbuster movie “Frozen” — the same kinds of activities typical girls might do. There are different groups for young girls, teenagers and young women, with about 102 families registered in total. Some groups are purely social, but others offer training for interviews, or provide support for women in college.

The Kansas program, called Girls’ Night Out, goes one step further by pairing typical girls and girls with autism. Groups of girls might visit a hair or nail salon, a coffee shop or gym, or learn how to buy clothes appropriate for their age and the weather.

“I was worried at the beginning that people would think I was trying to change them, that I was focusing on appearance,” says program director Rene Jamison, clinical associate professor at the University of Kansas in Kansas City. But hearing from parents and from the girls themselves what a difference it has made to their confidence levels has been reinforcement enough, Jamison says.

Learning to brush their own hair or teeth and to use deodorant can make all the difference to teenage girls in social situations, Jamison says. “These are skills that other girls are picking up on naturally, and getting better at,” she says. “That’s not happening naturally for some of the girls we work with, and so, just like social skills, it has to be an explicitly taught thing sometimes.”

GROWING UP

Even with early diagnosis, with social skill and behavioral training and numerous other avenues of help, girls with autism and their families have little help coping with a key milestone: puberty.

Isabel Haldane, or ‘Lula,’ as everyone calls her, is 11, and for most of her life has had multiple experts dedicated to helping her navigate the world, beginning with her anthropologist parents. Until she was about 15 months old, Lula seemed precocious, walking early and rapidly picking up words. Sometime between 15 and 18 months, she lost her words and began humming — the closest approximation of the sound, her mother says, is



in the movie “Finding Nemo” when the character Dory is trying to imitate a humpback whale — during the day, and wailing in frustration all night. She also didn’t make eye contact or respond to her name, so by age 2, she was diagnosed with autism and recruited into an early intervention program.

Since then, Lula has had combinations of speech therapy, playtime therapy, pivotal response therapy — a form of applied behavioral analysis, the most common autism treatment — occupational therapy and social skills training. Starting at age 3, she placed into her local public school in suburban Connecticut, where she spends 11 months of the year, but she still has therapists

who work with her for about five hours a week at school, and another hour a week at home.

Thanks to all this help, by age 5, Lula was mostly toilet trained and began to talk. By 9, she began sleeping through the night, and her parents could finally stop taking turns staying up with her all night. She scores below average on traditional IQ tests, but like many children with autism, she is adept at some things and stumped by others. She can shower, dress herself, pack her bag and wait for the school bus at the bottom of her parents’ driveway, but she might do it all at 5 a.m., hours before she’s supposed to. She can decode any word — ‘catastrophe,’ for example, or ‘encyclopedia’

—but ask her what the word means and she might respond with “I love Scott Walker” (a classmate, not his real name).

Many of the school’s students have known Lula since she was 5. But while the other girls have moved on to dance and gymnastics and music recitals, Lula is still mostly fixated on Hello Kitty. As kind as the girls are to Lula, they see themselves more as her protectors than as her friend.

Lula feels any social rejection acutely. She has memorized the birthdays of all of her friends but knows she is only invited to two parties a year. On a recent afternoon, as she arranged and rearranged her Hello Kitty-themed room, she perseverated about not seeing her friends at camp and about not wanting to get older.

Lula’s periods began just before she was 10, and she is fully developed physically, a beautiful brown-haired girl who looks older than her years. Puberty has brought enormous unforeseen challenges. Although Lula has learned how to use sanitary pads and sometimes remembers to change them, she doesn’t always think to dispose of them properly. “I didn’t even realize how much instruction it took to deal with a monthly occurrence. I didn’t know where to go on the Internet or who to ask,” says Hillary Haldane, Lula’s mother. “Where is the tutorial on this?”

Lula also shows a preteen’s healthy curiosity in sex, but none of the embarrassment or hesitation that might typically accompany it. A boy at school Lula has taken a shine to comes up in conversation often. She might announce that she wants to touch his penis, or smell his crotch. When she has blurted out these comments in school, her teachers’ reaction has been to isolate her. Knowing it goads the adults around her, Lula has taken to doing it even more.

“As we go into middle school, this is the biggest fear I have: her saying these things and then being ridiculed or bullied for it,” says Haldane.

Even more worrying for her parents is the sort of attention she might attract outside school: “It’s so terrifying with the sexual predatory behavior that she might face, especially because her body is quite developed, and her sexual curiosity, and how much more I have to consider what her behavior signals to others as opposed to if she was a boy on the spectrum.”

DEEPER WORRIES

Safety is an enormous concern for women who cannot advocate for themselves, and it weighs heavily on families’ minds. For Karleen, whose daughter Leigh, 28, is a nonverbal woman with autism, fighting for her daughter’s dignity has become nearly a full-time occupation. (Karleen asked that her and Leigh’s last names not be included, to protect Leigh’s privacy.)

Leigh uses a few words but, for the most part, cannot follow commands or speak. The youngest of three siblings, Leigh, like Lula, lost speech at 15 months and was diagnosed at 2. But she is unable to care for herself at all, and because of her tendency to hurt herself and others, needs around-the-clock care. “When she’s anxious, Leigh can strip right down. She can be trapped that way buck naked, until she can get the anxiety under control,” says Karleen. When she has her period, Leigh’s anxiety can skyrocket so much that she might shred pads into tiny pieces.

After years of searching, Leigh’s family, based in Belmont, Ontario, found her a residential program that created the kind of calm and routine that Leigh needs. But the agency must follow union guidelines on equal employment, meaning that it might pair Leigh up with a male attendant.

For the past two years, Karleen has been appealing to officials at every level of the agency

to allow only female attendants to work with her daughter — to no avail. In fact, she says, the agency may have to refer Leigh elsewhere because it cannot afford the legal fees to explore whether the law would allow it to only hire female attendants.

A former public health nurse who worked in women's shelters, Karleen is only too aware of the potential for abuse, particularly with male attendants. "I think this could be a huge issue in the future," Karleen says. The equal employment opportunity law was meant to protect people's rights, Karleen says, but is paradoxically harming women like Leigh who need support and cannot advocate for themselves. "If you are able-bodied and you can speak or you can gather support, then you can challenge that or work that legislation on your own behalf, but if you're someone like Leigh, then how can you be protected?"

DIFFERENT WORLDS

Whether it is Leigh's thorny legal situation, Lula adjusting to her budding sexuality or Maya's run-ins with psychiatrists who misunderstood her pain, the issues that dog women with autism have everything to do with their gender. For the first time, scientists are beginning to incorporate what they know about typical girls and their social world to understand girls with autism.

For example, it's been known for decades that boys' and girls' social worlds are starkly divergent and that they learn the rules to function in these worlds in disparate ways. "There's really good data to show that in typical girls and boys, the socialization trajectory is different," says Koenig. "People never took that into account when they're studying autism."

The multisite project that Pelphrey leads is making headway into learning how girls with

autism are different — both by recording their behavior and by scanning their brains. For example, one of the cardinal observations about autism is that people with the condition seem uninterested in, or at least disengaged from, social interactions. Intriguing brain imaging evidence from Pelphrey's lab suggests that this is true only for boys with autism.

"The most surprising thing — it might not be surprising to the clinicians out there, but to the scientists — is that we're seeing strong social brain activation or function in girls with autism, which is, strictly speaking, counter to everything we've reported ourselves and other groups have reported," says Pelphrey. "Their social brains seem to be intact."

The social brain is an interconnected set of brain regions, including the face processing fusiform gyrus; the amygdala, an emotion hub; and the superior temporal sulcus, which tracks other people's attention and movements. Imaging studies have reported that the social brain is underactive in people with autism, but Pelphrey's lab has found that if typical girls have the most active social brains and boys with autism the least active, typical boys would tie with girls who have autism somewhere in the middle. "That kind of blew us away," he says.

Particularly interesting is the unpublished observation that in girls with autism, the social brain seems to communicate with the prefrontal cortex, a brain region that normally engages in reason and planning, and is known to burn through energy. It may be that women with autism keep their social brain engaged, but mediate it through the prefrontal cortex — in a sense, intellectualizing social interactions that would be intuitive for other women.

"That suggests compensation," Pelphrey says. It also jibes with women like Maya saying they have learned the rules of social interactions,



Rainbow chart: A color-coded guide can help girls with autism know whom they can hug and who just gets a wave.

but find it draining to act on them all day. “It’s exhausting because it’s like you’re doing math all day,” Pelphrey says.

Pelphrey is right that this finding isn’t entirely a surprise to clinicians. Some scientists who regularly see women with autism have picked up on their remarkable ability to learn the rules enough to camouflage their symptoms — the way Maya has learned to. (“I don’t like making eye contact,” Maya says. “I do it because I have to and I know it’s appropriate.”)

This means clinicians have to be more creative when diagnosing women on the spectrum, rather than simply looking for, say, repetitive behavior, as they might with men. “Without their self-report

telling you how stressful it is to maintain appearances, you wouldn’t really know,” says Francesca Happé, director of the MRC Centre at King’s College London. “They have good imitation, good intonation in their language, body language — surface behavior isn’t very useful for a diagnosis, at least for a certain set of women on the spectrum.”

Overall, the concept of compensation in women with autism hasn’t been well studied, Happé says. Compensation could be cognitive — learning the rules intellectually rather than instinctively, as Pelphrey describes it — or social, such as learning to mimic others. There are also societal factors at play. “Are we more tolerant, at least in some Western societies, of a girl who is

very, very quiet and socially aloof, compared to a boy? I don't know; I suppose you could say we have higher expectations of women," says Happé. "All of these are hypotheses and they're only interesting if they're testable."

A few teams, including those led by Happé and Baron-Cohen, are trying to find ways to get behind the masks. Baron-Cohen's group is developing what he calls a "faux pas test." If a woman is getting by learning social rules one rule at a time, as Maya has, she's bound to make a lot of mistakes, he says, because she's likely to encounter a situation for which she hasn't yet learned the rules. Happé is similarly creating tests based on real-life scenarios in which her team asks women not only why somebody said something, but also what they themselves would say next. "That really trips people up. It would require them to, on the spot, get it," she says.

Baron-Cohen, Happé and others caution, however, that in some cases, women may have learned to cope enough that they don't actually need a diagnosis.

"If they're coping, do they want to think of themselves or for others to think about them in that way?" asks Happé. "Then it becomes a big ethical issue, doesn't it?"

NEW UNDERSTANDING

In Maya's case, learning she is on the spectrum took some getting used to. But she says she's very glad to have an explanation now for all of the difficulties she thought were unrelated to one another.

After she came out of her coma, Maya spent a week in intensive care and nine weeks in a terrifying psychiatric unit with severely ill patients. One threw a boiling cup of tea at a nurse, and another head-butted a nurse so hard that her teeth went

through her lip. In the early days, Maya deliberately burned her arm with the hot water available for making tea, and threatened to try to kill herself again as soon as she got home.

But as the weeks passed, she started to feel better. She was given an antidepressant that seemed to work for her, and she lost the weight she had gained when taking quetiapine. She met a young woman who has since become her best friend. Then, several months after she left the hospital, she got the autism diagnosis.

“
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”

After her disastrous encounter with the psychiatrist who decided she has paranoid personality disorder, a doctor who had been kind to her while in the hospital offered to take Maya back as a patient. It was only when Maya began complaining about the ridiculousness of offices being closed on 'bank holiday' Mondays ("Weekdays are for work!") and how overwhelming it was for her to walk down a noisy street that the psychiatrist added up the signs to arrive at the correct diagnosis.

A full 18 months after Maya came home from the hospital, she went back to Cambridge for her

final year and switched her focus from genetics to psychology and cognitive neuroscience. She burst into Baron-Cohen's office at Cambridge one day while he was in a meeting, announced that she has Asperger syndrome and asked if he would supervise her dissertation on mirror neurons and autism. He agreed. She still had bouts of depression, but her stay in the hospital taught her how and when to ask for help. "When I came out of hospital, I basically lived along the lines of 'if it's stressful, don't bother doing it,'" she says. "Nothing is worth getting that depressed."

The university accommodated her diagnosis, allowing her to take her exams alone and with breaks in between, and in June 2014, despite some ongoing depression, Maya graduated from Cambridge. "If you can go in two-and-a-half years from being locked in a psych unit to graduating from Cambridge, you can do anything, really," Maya says.

After graduation, Maya worked for a year at a local primary school, supporting boys with autism in the class. She didn't tell the school she has autism, and successfully held down the job all year. She enjoyed it so much, in fact, that last month she began training to be a primary school teacher, specializing in mathematics, and plans to either teach mathematics or work with special needs children. And this time, Maya revealed on the application form that she has autism. "She agonized about it a lot; she didn't want people to prejudge her," says Jennifer.

Outside of her teacher training, Maya spends time with her best friend, even going on a holiday together "with massive success," and has dated men on the spectrum. Most of all, she is committed to learning how to take care of herself the way only she can. One day this summer, she went on a 'fun run' — "which as far as I'm concerned are two words that should not be put in the same sentence," she says — a loud and colorful obstacle

course that Maya researched thoroughly online and prepared for with ear plugs. When she has a bad day, she has learned to wind down with multiple episodes of "Grey's Anatomy," which she has watched enough times to be able to fake being a doctor. She and her brother now laugh about her need to sit in the same seat at the dinner table, and her parents have learned to respect her need for solitude, despite their fears about what she might do when alone.

She has also been talking about her autism — at town council meetings, to groups of teachers and trainee therapists — and helping to train the staff at doctors' offices to accommodate people with autism's need for order and quiet.

Maya still gets depressed, still rarely has a night free of nightmares, and may still go into a tailspin if her routines are disrupted. But she is better than she was at asking for support — and often gets it from a therapist who specializes in autism whom she sees every other week, or more often if necessary.

"The more I understand myself, the more I can explain to other people what I find difficult, and the more they can help me," she says. "Life isn't easy for me, but I understand myself so much better now."

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THE MOST TERRIFYING CHILDHOOD CONDITION YOU'VE NEVER HEARD OF

Childhood disintegrative disorder, a rare and severe condition, rapidly melts away a child's abilities. A new theory proposes that this little-known condition turns back the developmental clock.

by

DAVID DOBBS

photographs by

CRISTINA PYE



IT'S DIFFICULT TO TELL WHAT GINA PACE wants unless you already know what she wants. But sometimes that's easy, and this is one of those times: Gina wants pizza. "I-buh!" she says repeatedly — her version of "I want." We all do.

We are sitting at Abate's in New Haven, Connecticut, a town famous for — among other things — pizza and science. Gina and her father, Bernardo, who live on Staten Island in New York City, have made the two-hour drive here for both. The pizza is in the oven. The science is already at table, represented by Abha Gupta, a developmental pediatrician at Yale's renowned Child Study Center. Gupta is one of the few scientific experts on a condition that Bernardo and Gina know through hard experience. Gina, now 24, was diagnosed 20 years ago with childhood disintegrative disorder, or CDD.

CDD is the strangest and most unsettling developmental condition you have probably never

heard of. Also known as Heller's syndrome, for the Austrian special educator who first described it in 1908, it is a late-blooming, viciously regressive form of autism. It's rare, striking about 1 or 2 in every 100,000 children. After developing typically for two to ten years (the average is three or four), a child with CDD will suffer deep, sharp reversals along multiple lines of development, which may include language, social skills, play skills, motor skills, cognition and bladder or bowel control.

The speed and character of this reversal varies, but it often occurs in a horrifyingly short period — as short as a couple of months, says Gupta. In about 75 percent of cases, this loss of skills is preceded by days or weeks in which the child experiences intense anxiety and even terror: nightmares and waking nightmares and bouts of confused, jumpy disturbance that resemble psychosis. (In the 1970s and 1980s, the diagnostic term used for CDD in many countries was 'disintegrative psychosis.') During this anxiety-ridden

prologue, known as a ‘prodrome,’ a child will often seem keenly aware that something is wrong. He’ll say he’s scared. He’ll pace and hold his head and say it hurts. As the increasingly frightened parents watch, he loses speech, motor skills, and most means of social contact. It is as if something is erasing everything he has become.

People with CDD, although quite impaired, may retain certain skills and abilities, some more than others. Gina (who was one of those spared an acutely anxious period before her onset), for example, walks well, skillfully rides a bike, listens to and generally minds directives, dresses herself, has no trouble eating, and suffers none of the bathroom issues that plague many people with the condition. With a little help, she sometimes reads books written for fifth-graders — a reading level far above what her general language and intelligence assessments would predict.

Yet she does not speak well, and whether communicating through speech or on her iPad — which she uses to type words from her large vocabulary — she generally sticks to simple two-word sentences. Every once in a while, though, she surprises Bernardo. Once, beholding a perfume ad in which a young man gazes longingly at a young woman, she said to Bernardo, “The boy is looking kisses at the girl.” She also plays a mean iPad solitaire, and she will almost surely stomp you in a word-finder game. “She spots the backwards and diagonal words as fast as she does the regular ones,” laments Bernardo, a recently retired literature professor at the City University of New York who speaks Italian as well as English. “She crushes me.”

Gina needs constant care and accommodation, and she always will. She has a hearty appetite and little sense of restraint with food. As a result, she is a bit heavy, and Bernardo worries about a heightened risk for type 2 diabetes. Gina generally respects others’ space, but sometimes, eager to get

your attention or to emphasize a point, she may grab your forearm with a strength and urgency that some people might mistake for aggression. There seems to be much she doesn’t understand and far more she can’t convey: Her inner life remains obscure even to Bernardo. At 24, she stands little chance of learning new skills or even recovering those she had when she was 3.

Bernardo knows this. He is not here hoping that Gupta and her colleagues can spark some breakthrough in Gina’s development. He knows that Gina’s condition is rare enough that she may reveal as much about the diagnosis as the diagnosis reveals about her. The two of them have come to New Haven to let Gina see a bit more of the world, to perhaps glean some small but useful insights from Gupta. By surrendering his daughter to a series of behavioral, cognitive, neurological and genetic evaluations — quizzes, puzzles, brain scans, blood draws — he hopes to give Gupta a chance to understand this confounding condition and its utterly mysterious biology.

CHASING A MYSTERY

The pizzas arrive, and as Bernardo doles out slices, we talk about Italy, wine, science, life — and Gina. Bernardo, 61, who retired a month ago, tells us he is thinking of building a wood-fired pizza oven in his backyard. He often interrupts himself to respond to Gina, who is alternately quietly absorbed in her food and vocally interested in others’. “Gina, there’s plenty of pizza,” Bernardo reassures her. He asks us not to offer Gina our slices, because if we do, Gina might start helping herself not just from our plates but also from those of diners at other tables. “It’s happened,” he says, smiling. ‘Pace’ is Italian for peace or tranquility, and Bernardo manages to retain his as he juggles all this. Perhaps

taking their cue from him, patrons at nearby tables seem to accept Gina's fidgety, sometimes loud presence with equanimity.

I ask Gupta how she came to study CDD. For its mysteries, she says. Primarily, she means the mystery of regression. CDD is not the only subset of autism in which children regress. The most thorough review on this topic found that about one-third of all people with autism appear to experience some regression before their diagnosis — a small but significant loss of attained skills or abilities, rather than just a slowing of progress. But estimates vary depending on how parents or clinicians define 'regression.' When measured by a more objective benchmark, such as documented loss of language, the regression rate drops to the mid-teens.

Regression in CDD is not just later than in classic autism, but uniquely severe. When it comes fast as well, it can be terrifying. In her talks, Gupta shows a video of an 8-year-old boy with sandy blond hair in a terror-filled prodrome. The boy moves in a hopelessly agitated state around his family's house, raising his hands to hold his head or his face, then lowering them, again and again, as he paces and says he is scared. He cannot stand still. Finally, he bolts out the front door.

The boy stayed in that acutely agitated state 20 hours a day, 7 days a week, for a full month. "No idea what was bothering him, he couldn't say," says Julie Wolf, a Yale psychologist who saw this boy several times over the years (and who will evaluate Gina during her Yale visit). A few weeks after the video was taken, the boy's language began to fade, as did the bright, funny, socially active, curious person he had been. In a video taken nearly three years later, he sits on a rug looking blankly at the camera.

Aside from its late and often intense onset, CDD presents much like other cases of autism that feature profound social and cognitive impairment.

But to Gupta and others at Yale and elsewhere who study it, the speed, intensity and depth of CDD's regression make it a good place to look for neurological or genetic dynamics that might tell us something about autism in general. How, biologically, is so much lost so quickly? Even though CDD is essentially "the first autism," described by Theodor Heller three decades before Leo Kanner defined autism, scientists know almost nothing of how it develops. Studying autism by looking at CDD, autism's sharpest, most dramatic form, say Gupta and her collaborators, is like studying running by observing Olympic sprinter Usain Bolt: The extreme can inform the norm.

Unfortunately, Gupta tells us, this research is endangered, because in 2013 the American Psychiatric Association dropped the CDD diagnosis from its statistical manual, the DSM-5, absorbing it into the manual's broadened definition of autism spectrum disorder. This muddies the path for people who have CDD or study it. CDD is a diagnosis of exclusion, often made only after parents have taken their child to multiple specialists who look for infections, brain inflammation, tumors, blown blood vessels and other physical causes. The loss of the specific diagnosis may lead clinicians to mistake the panicky prodrome as brain inflammation or psychosis — and leave parents in the dark that much longer.

Gupta says her grant proposals are being rejected, with notes asking why she's studying a condition that doesn't exist. "The funding was already hard to get," says Gupta. "This makes it even harder."

AWAY IN ROME

Just before Christmas of 1994, when Gina was 2, she got on a plane with her parents and her

6-year-old sister Sonia and flew to Rome, where Bernardo had snagged a one-year Fulbright fellowship teaching American literature and history. In this new city amid new people and a new language, Gina's regression, slower and more subtle than in many cases of CDD, didn't register with her parents at first. Gina had hit all of her milestones, and, like the rest of her loquacious family, talked fluidly and fluently.

"I didn't know any better," Bernardo recalls in the closely observed memoir he is now writing about his daughter. "Neither did anyone else: mother, aunts and uncles, grandparents, friends, pediatricians, friends, Romans, and countrymen."

The first sign, at least in retrospect, was a reticence, he recalls in the memoir, that Gina hadn't been displaying as she blossomed through her second and into her third year: "a little less eye contact ... a little less chatter, a little more pointing." In the stroller, rolling around Rome, she sometimes sat quietly upright, not relaxed, her eyes fixed forward.

For a time, these changes seemed explainable by their move to Italy. Her older sister was in school full-time, while Gina went to preschool just two or three days a week. It didn't seem odd that Gina had few friends over and tended to play quietly alongside them.

"*She just needs time* is the truce I offer the situation," writes Bernardo about that year, "as if it were mine to offer. *Piano, piano*, the Italians say: little by little."

Yet by October 1995, when Gina was 3, both her parents were shocked but not exactly surprised when a teacher said she thought Gina might have autism. Six months later, after the family moved back to the United States, a specialist in New York agreed — "she was emphatic about it," says Bernardo — and suggested they see Yale's Fred Volkmar, a leading expert, then and now, in obscure developmental disorders, including CDD.

Gina, now 4, was far behind where she'd been a year before. Volkmar told them she had CDD.

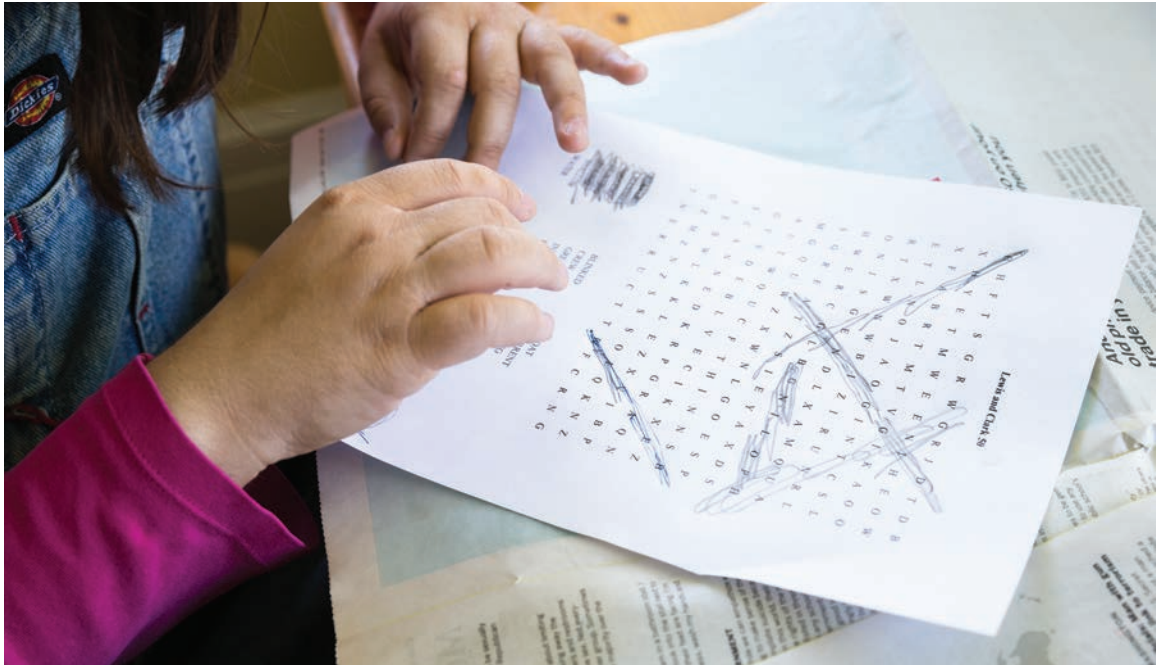
“
**She spots the
backwards and
diagonal words as
fast as she does
the regular ones.
She crushes me.**
”

BERNARDO PACE

Today, Bernardo recognizes that Gina is lucky, as these things go, and significantly more capable than many people with CDD. Yet getting the diagnosis then "was devastating," he says, and part of him initially refused to accept it. Much would fall away in the months and years to come, including his marriage to Gina's mother. At first, though, there was grief. "There were a lot of tears there. There still are sometimes," he says. "You have this idea of what's possible in your child's life. It's a really hard thing to let go of."

BLOOD NOON

The morning before our dinner at Abate's, Gupta had tried to coax Gina into a brain scanner so she could record Gina's brain-activation patterns as she viewed faces and objects. Structural brain



Hidden surprises: Although she rarely speaks more than two words in a row, Gina is lightning-fast at word-search puzzles.

scans have so far found nothing physical that distinguishes the brains of people with CDD. But as part of the research in which Gina is participating, a long-running study of about 30 people with the condition over the past 30 years, Gupta is trying to see if people with CDD show any distinctive patterns of brain activation — that is, in the way the brain works. Unfortunately, when she asked Gina to climb into the scanner — a noisy, narrow tube — Gina declined. “She bolted, actually,” says Gupta good-naturedly.

Now, on the second day of testing, Gupta is hoping things will go more smoothly. The morning’s schedule calls for some cognitive and social-skills testing with psychologist Wolf, then a blood draw so that Gupta can look for any genetic distinctions that might help explain CDD. The skills testing — well-established assessments called the Differential Ability Scales and the Autism

Diagnostic Observation Schedule, about 90 minutes altogether — is first. The blood draw will come last; Gina, like many people, does not like needles.

For days, Bernardo has been gently preparing Gina for the blood draw. He has shown her pictures of how blood is drawn, promised a reward at lunch, and established that Daddy will have his blood drawn first, three vials of it, to demonstrate that it doesn’t last long or hurt too much. By the time I meet them that morning at the Child Study Center, Bernardo is wondering if maybe he has oversold the procedure. Gina, dressed brightly in pink jeans and a pink tank top over a long-sleeved T-shirt, keeps asking to see the schedule. Every time she looks at it, she taps the soft, pale skin inside her elbow, then types “Blood Noon” on an app on her iPad, which voices the words: “Blood. Noon.” Then she resumes nervously pacing the room.

Finally, someone fetches us. They lead Gina and Bernardo to a testing room, where Gina sits across a small table from Wolf. Bernardo sits behind Gina, while Gupta and I watch from an adjacent room through one-way glass. Wolf exudes a calm, intelligent warmth, to which Gina responds by giving prompt responses to Wolf's questions via her iPad app. She goes off-task only to occasionally tap the inside of her arm and type out "Blood Noon" again, and, twice, when Wolf pulls supplies from a drawer and leaves the drawer

“
**The funding was
already hard to get.
This makes it
even harder.**
”

ABHA GUPTA

open, Gina gets up and walks clear around the table to close the drawer properly.

Gina's social skills are impressive compared with those of most people with severe autism, according to Wolf. She makes a fair amount of eye contact, and she reliably follows Wolf's gaze to locate an object when Wolf looks at it. And she kills the math. Gina, facing a multiple-choice list of possible answers to double-digit arithmetic problems, can "solve and select the correct answer ... faster than the examiner was even able to read/process what was written on the screen," Wolf later writes in her report.

But the morning's evaluations also reveal how trying Gina's life can be. In verbal comprehension, vocabulary and matching pictures, she performs

like a typical 3-year-old. She copies or constructs foam-block patterns like a 4-year-old. She readily recognizes objects identified by name ("Give me the cat") or category ("Give me all the pets") but cannot identify objects described by prepositions ("Give me the cat that's behind the barrel") — an ability usually present by age 4. In the section of the report listing age equivalences, Gina's all fall between 2 and 4 — the ages during which her CDD emerged.

Blood Noon does not go well. Gina and Bernardo are both tired by then, and because the vein-prickers are running behind, an anxious and increasingly hungry Gina must wait a full half-hour.

Finally, the receptionist calls her name. Bernardo, Gina and two technicians crowd into the phlebotomy room. I watch from the doorway. At the far end of the narrow room, Bernardo sits in a chair and rolls up his sleeve. With Gina looking on, Bernardo gives up three fat ruby vials.

When Gina's turn comes, she moans, a rising pitch of anxiety, but lets herself be seated, and then lets her arm be held and turned pale side up, swabbed with alcohol, and tied with a tourniquet. She moans louder when the tech inserts the needle and removes it to tape the cannula into place, louder still when the tech snaps on the first vial. Yet she stays put. Bernardo, talking with her steadily, stands and relaxes just a bit. The first vial fills.

But just as the tech snaps on the second vial, Gina says something loudly, lunges out of the chair, inadvertently knocking Bernardo smack back against the wall two feet behind him, and makes a break for the door.

Bernardo is with her in two quick strides.

"It's okay, baby," he says, holding and calming her. "It's okay."

The blood collected will probably be enough, Gupta says later, for some simple genotyping, but probably not for the sequencing she had hoped to do. She shrugs and says, "Maybe next time."

WHAT REMAINS

After saying goodbye to the Paces, Gupta and I run into Wolf, who has just finished scoring Gina's evaluations. Her brief description of the results — Gina as a 2-to-4-year-old, which somehow does not seem quite right to either Wolf or Gupta — inspires a discussion between them about one of CDD's most unsettling puzzles: Among the apparent erasures in CDD's cruel reversal, what remains?

Wolf and Gupta both say many people with CDD have assets that standardized autism screens do not reveal. Gina's language skills seem beyond the 3-year-old level the test perceived. Ditto with the fast math, the solitaire, the word-finding puzzle prowess. And with the connections of trust and comfort she makes with people such as Wolf, Gupta and me after knowing us for only a few hours.

The 8-year-old boy in Gupta's video is now in his teens, and also speaks mainly in two-word phrases. "Then all of a sudden he'll be like, 'No, I don't want to do that,'" Wolf tells us.

Are his and Gina's skills truly gone, Wolf and Gupta ask, or just obscured, like memories we can't recall?

"You feel like it's still in there," Gupta says quietly. "Don't you?"

Wolf nods.

Later that afternoon, Gupta and I sit down with her colleague Kevin Pelphrey to discuss the CDD study that he and Gupta have repeatedly been overhauling for more than three years. (Pelphrey has since moved from Yale to George Washington University, in Washington, D.C., but he and Gupta continue to collaborate on this project.)

Gupta, Pelphrey and the many collaborators on this CDD study face a difficult problem: They're studying a condition about which science knows almost nothing. The very things that distinguish

it — its severity, rarity and opacity — make it ludicrously hard to study. This is science at its earliest, most difficult, and most confounding. It's mostly bumping into strange shapes in the dark and trying to figure out what they mean.

The study draws together data from psychological and cognitive testing, family histories, eye tracking, genetic analysis and brain imaging in more than two dozen people with CDD. Progress has been slow, they explain, partly because, like Gina, few people with CDD can lie still in scanners or tolerate blood draws. It has also taken time because Gupta and Pelphrey kept finding things that defied their expectations. "There was a lot of 'This can't be right ...,'" says Pelphrey.

Given CDD's severity, for instance, they had hoped to find a few powerful genes at fault, but did not. They had thought they might find brain activity disrupted in ways characteristic of the severest cases of classic autism, but did not. In general, they had thought they'd find the underlying neurobiology of an especially debilitating sort of autism. They did not.

Instead, says Pelphrey, their findings suggest a fairly typical brain — that is, the brain of a person without autism — with key processes halted at, or perhaps pushed back to, early developmental stages.

In eye-tracking studies, for instance, he and Gupta had expected people with CDD to scan faces much as most people with autism do: by paying more attention to the mouth than to the eyes. Instead, the participants with CDD scanned faces as typical infants do between 4 and 12 months of age, according to one leading model of face processing.

This theory holds that between about 4 and 6 months, an infant moves from one way of looking at faces to another. Baby-eye-gaze geeks call these stages of gaze during infancy 'conspec' and 'conlern;' we can think of them as 'eyes-only'

and ‘eyes-plus.’ In the eyes-only stage, up to 4 to 6 months, a baby looking at a face looks almost solely at the eyes. In the eyes-plus stage, which begins after 6 months, the baby still looks frequently at the eyes, but also begins glancing quickly elsewhere around the face, presumably to collect social information.

The participants with CDD looked at eyes as if they were infants who were just starting to use the eyes-plus mode; they still devoted most of their attention to the eyes. People with autism generally follow neither of these patterns. They give the eyes no more attention than they give to the mouth, nose or hairline. The gaze of the CDD participants suggests not a loss of social interest, but a return to an earlier form of facial and social processing. What does this mean? Pelphrey and Gupta’s answer is essentially a prolonged head-scratch; they can only speculate that some developmental pathway devoted to reading faces has suffered a big reversal.

That’s just one small study, of course. (Only 5 of their 25 participants would sit still for eye tracking.) Gupta and Pelphrey might have ignored it if their brain imaging work did not also suggest that people with CDD are more like neurotypical infants or toddlers than like adolescents or adults on the spectrum. For instance, when seven of their CDD participants got in the brain scanner and looked at faces versus houses, their brain activity more closely resembled that of typically developing children between 1 and 3 years of age than that of people on the spectrum. This finding too suggests that specific developmental reversals may be at work in CDD.

A third stream of data, from genetics, seems to point the same way. In an analysis of 15 participants with CDD, Gupta found that 14 carry rare mutations in one or more of 40 genes. The genes stand out for three reasons: They have never been

linked to autism; they are expressed not in brain regions usually associated with autism, but rather in those Pelphrey found altered in brain scans of people with CDD; and postmortem studies of gene expression have shown that 11 of the 40 genes surge in activity in those areas between ages 3 and 8 – the period during which CDD usually emerges.

These results seem to support the idea that mutations in these genes contribute to CDD’s emergence – and perhaps to the reversals Gupta and Pelphrey found in their eye-tracking and brain scanning studies.

Gupta looks pained as she acknowledges that with so few people studied, these findings are merely suggestive. Yet she and Pelphrey say their results strongly support the idea that CDD is a distinct sort of autism with unique biological underpinnings, and that it’s important to follow these new clues about what may be going amiss.

Neuroscientist Rebecca Saxe of the Massachusetts Institute of Technology applauds this effort, amid autism’s vast heterogeneity, to bear down on particular processes in “the smaller, more specific group” with CDD. Understanding CDD, she says, is important both as a reminder of autism’s huge variations, “and because it may provide a clue to one of autism’s most mysterious and emotionally devastating symptoms in some cases of autism: regression.”

As it happens, the deeper biological investigation that Gupta and Pelphrey propose would constitute a return of sorts to CDD’s beginnings. In the decades after Heller wrote up CDD, most scientists thought the condition arose from some biological anomaly. When the crude tools of that time found nothing biological, theory and research moved elsewhere, but with little effect. Now, with new tools and these new clues in hand, Pelphrey and Gupta may be able to follow strands of biological evidence that simply weren’t visible before.



Happy trails: Following in her father's wake, Gina bicycles confidently near their Staten Island home.

ON THE ISLAND

Bernardo thinks a lot lately about how and where Gina will live when he is gone. Bernardo's father is in his 90s, and Bernardo himself is quite fit at 61, so that day may be slow in coming. Yet increasingly it presses on his mind.

Where, for instance, will Gina live? Wolf's report, arriving a few weeks after Gina's testing, recommends that Bernardo start looking for a good residential placement where Gina can learn to manage relationships with non-family members while she still has Bernardo to lean on. Bernardo was already working on this. Gina spends 35 hours a week in an adult day program at Eden, a school near their home on Staten Island for people with developmental issues. A

board member at the school, Bernardo hopes to convince state, city and private benefactors to help build a residential center for women with disabilities along the same lines.

In the here and now, he has other worries. As connected as he is to Gina, he often wonders about his daughter's inner life. Does she experience the gap between herself and others as something painful? What do those findings of Wolf's mean? Can it really be that Gina does not recognize prepositional relationships? If she can't perceive the-cat-behind-the-barrel, can she also not perceive the-father-who-stands-beside-her?

Two days after I saw them in New Haven, I joined Bernardo and Gina at their home for lunch and a bike ride. Gina was noticeably more relaxed, and after a delicious lunch of pasta and homemade wine in their charming yellow house, we extracted bikes from their backyard shed and took off to visit Snug Harbor, a park a couple of miles away. Bernardo, leading, kept an eye on Gina with a rearview mirror on his handlebar. Gina, in front of me, tailed Bernardo at a steady distance.

This was worrying to watch. We rode part of the way in the street, with the occasional car passing us.

But Gina looked as engaged, confident and secure as I had yet seen her. She tracked Bernardo perfectly, staying in his jet-trail, following his path and his example, avoiding obstacles fixed and moving. She clearly took much strength and safety from the father who rode before her. The only question is whether she can get that from others someday.



chapter

**RESEARCH
FRONTIERS**

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THE TREASURES OF MONKEY ISLAND

On Cayo Santiago island, scientists track the alliances and power struggles of a colony of feral monkeys — collecting data to generate new insights into the social challenges that people with autism face.

by

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4 IN SITS ALONE UNDER THE WAXY leaves of a bay rum tree. When he hears us approaching, he looks up from the ground and smacks his lips as though he has peanut butter on the roof of his mouth. The gray hair on his chest hides his identifying tattoo, but this 16-year-old rhesus macaque is hard to mistake: He has freckles on his face and smears of red extending horizontally from his eyes like war paint. Because March is the breeding season here on Cayo Santiago — Puerto Rico’s so-called ‘Monkey Island’ — his face and genitals are tinted a garish coral hue.

For Michael Platt, a neuroscientist who is normally stuck in his lab at the University of Pennsylvania in Philadelphia, this moment was the first time he was able to match a face to a gene. 41N is one of 40 macaques on Cayo Santiago that Platt’s group identified last year as carrying a naturally occurring variant of a gene called SHANK3. This gene codes for a protein that strengthens the connections between neurons. About 1 percent of people with autism have a mutation in SHANK3; on Cayo Santiago, potentially one out of every

eight monkeys possesses this SHANK3 variant. As in people, a disruption of this gene affects the monkeys’ social lives. “Are those autistic monkeys?” Platt says, immediately answering his own question with a scientist’s allergy to hype: “I don’t know.”

What makes Cayo Santiago special is that it is a haven for social diversity. Most traditional research colonies would have weeded out uncooperative monkeys or ones with behavioral issues, but the monkeys here are left to themselves. The island was first stocked with macaques from India for medical research in the late 1930s, and now has more than 1,500 crammed into an area the size of around eight city blocks. The primate population density here rivals that of the New York City metropolitan area. The monkeys, slightly larger than house cats, make friends, raise families and mourn the loss of their loved ones. They have formed six tightly knit groups, and within those groups there are defined pecking orders. The social butterflies, for instance, spend time with other social butterflies — forming a popular in-group.

41N and his ilk are neither more nor less gregarious than run-of-the-mill macaques. Rather,

they are more adventurous when it comes to picking their friends. Instead of joining a pre-existing social clique, they form relationships with monkeys that don't necessarily spend time with one another, creating a bridge between cliques. That may be because they're not skilled at reading social cues, or because they simply choose to find friends outside the norm. It's too early to tell.

In 2007, Platt launched a wide-ranging research effort here to elucidate the role that genes and the environment play in shaping these animals' social lives. Over the next five years, he hopes to bring monkeys with natural or engineered genetic variants into the laboratory, probing their atypical brains and testing drugs in experiments that would be impossible to conduct with people.

A decade ago, few in the research community would have anticipated that some of the most intriguing advances in understanding autism might come from feral monkeys on a Caribbean island. Monkeys are not the most convenient research animals: They are expensive to raise and take a long time to study. Many consider it unethical to conduct research — invasive or not — on primates. The result has been that most autism research is conducted using rodents as models.

But Platt and other researchers have begun to draw attention to the limitations that come with that mouse-sized package, namely that rodent brains are different from our own. Mice don't form societies, and the critical bond between mother and child concludes at weaning. These differences may explain why the majority of clinical trials for neurological drugs based on mouse studies have failed.

Platt's work has focused on the descendants of wild macaques on Cayo Santiago and in his Philadelphia lab, but he also has plans to study transgenic macaques in China whose genomes have been modified with a man-made mutation in SHANK3 along with the top autism gene, CHD8.

A handful of other such transgenic monkeys have recently been engineered for autism research, promising insight into genetic influences on brain development and, potentially, a new platform for testing drugs that influence social behavior. "Mice are great for a lot of things," Platt says, "but to study social behavior, you really have to study primates."

MIGHTY MOUSE

From the earliest days of medical science, rats and mice have been the top testing ground for lifesaving vaccines and treatments. Mice are easy to care for and mature in just six to eight weeks.

But 75 million years of evolution separate the house mouse, *Mus musculus*, from people. Researchers can alter the mouse genome to recreate some of the features of a human genetic disease by knocking out a healthy gene or slotting in a defective one, but for conditions such as autism, which are caused by many genes, it's not so simple.

In people, autism diagnoses are based on interviews and observations, which can reveal whether someone avoids looking into other people's eyes or following their gaze. But how exactly do you diagnose a mouse? Researchers videotape animals placed together in cages and score their social interactions, such as how often they sniff each other, and how often they show repetitive behaviors, such as grooming obsessively or running in circles. To test a mouse's social interest, researchers might score how much time it spends with another mouse versus a wire cup.

But there can be many reasons why one mouse, say, sniffs less than another, including the possibility that it is simply less active. The upshot is that it's just too difficult to know what a mouse is thinking, says Karen Parker, who studies

primates and humans at Stanford University's Autism Center in California. "I'd be hard-pressed to measure theory of mind in mice."

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**Are those
autistic monkeys?
I don't know.**
”

MICHAEL PLATT

Even mouse models of the most promising autism gene candidates have shown inconsistent responses in social assays. Since 2012, PsychoGenics, a company based in Tarrytown, New York, has tested five of the top mouse models using a battery of standardized behavioral tests. The only mouse that has shown a noticeable problem in sociality is a mouse lacking a large chunk of SHANK3, and even that difference is not statistically significant compared with social behavior in typical mice. "Studying social behavior in a mouse is a very difficult task," says the leader of this effort, behavioral scientist Dani Brunner.

FUNKY MONKEYS

Michael Platt never planned to study autism; he was just a boy who loved monkeys. "Every time I did a school project, it was about evolution," he says. It was an obsession that wasn't necessarily encouraged in the working-class Catholic neighborhood just outside of Cleveland where he grew up. Platt was the captain of his high school

football team and in 1985 was recruited to play for Yale University. When he arrived, however, he quickly realized he didn't want to be a jock. He took a course in primate evolution and soon got hooked, sorting through monkey bones in the drawers of the university's Peabody Museum of Natural History.

After his third year at Yale, Platt spent three weeks in a summer field course on Totogochillo Island in Mexico's Lake Catemaco, which hosted an introduced colony of stump-tail macaques. The experience gave him an appreciation of the richness of the social lives of monkeys. It was also where he met his future wife, Elizabeth Brannon, whose work now focuses on the behavior of human infants. While in graduate school, Platt tried to study wild wedge-capped capuchin monkeys in the seasonally flooded forests of Venezuela. It rained so much there that the trails disappeared under three feet of water teeming with anacondas, and the forest was so leafy he could hardly see the treetops where the monkeys were. One day in July 1991, he shot a pregnant monkey with a tranquilizer dart, aiming to catch her on a sheet. But he lost track of her in the canopy, and she crashed to the ground. She survived but the fetus did not.

Devastated, Platt fled from field work. He joined Paul Glimcher's lab at New York University as a postdoctoral fellow, learning to record the activity of neurons in monkey brains in order to better understand how monkeys make decisions about what to look at. Platt was probing a murky region of the brain that sits between the visual and motor areas of the parietal lobe. He found that neurons in this region, called the lateral intraparietal area, fire more frequently when the monkey expects either a reward or a high probability of receiving the reward. His 1999 paper on this finding launched a new paradigm called neuroeconomics, which marries economic theory to the study of brain activity.

Platt took this nuts-and-bolts approach with him when he joined the faculty of Duke University in Durham, North Carolina. His goal then was to unlock the neurobiology underlying the social behavior of a dozen macaques he kept in the lab. Whom we look at—and who watches us looking—is a fundamental part of human relationships. During a conversation, when one person looks to the left, the other person reflexively follows the gaze. The reflex develops in early infancy, setting the stage for our complex social lives. Platt knew that primates, including macaques and chimpanzees, also seem to develop this behavior, but children with autism often do not. (Unlike mice, dogs and some birds also pay attention to the human gaze.)

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”
MICHAEL PLATT

In an early study, Platt and a postdoc in his lab, Robert Deaner, tracked how long it took people and monkeys to move their eyes to a yellow target that randomly appeared on the left or right side of a screen. Before the target flashed, an image of a monkey face would appear, gazing to either

the left or the right. People and monkeys both shift their gaze more quickly in the correct direction when the image of the monkey face is also looking in that direction. Platt also recorded involuntary eye movements called microsaccades that are thought to indicate a shift in attention and expectations. The data from people and monkeys were almost identical, suggesting to Platt that both species process gaze the same way.

Platt grew convinced that monkeys, with their stripped-down cultures and customs, hold the key to cracking open fundamental questions about how our social brains develop—and, potentially, what happens when this typical development goes awry. In an experiment published in 2005 that he called “Monkeys Pay Per View,” he found that male monkeys were willing to forgo a juice reward to look at a photo of a high-ranking male or a female’s rear end (the equivalent of monkey smut). But he had to bribe them with an extra squirt of juice to get them to look at the lowliest members of their group. He later monitored which neurons were firing and found that the lateral intraparietal area is also involved in keeping tabs on the social hierarchy.

Soon, parents of children with autism began showing up at his talks and asking him the kind of question he was never trained to answer as a scientist: “What does this mean for us?” The pressure made Platt think about how to make his experiments more relevant to people, he says. “It was the first time I began thinking more seriously about the clinical implications of my work.” One of the people who witnessed this transformation was Geraldine Dawson, former chief science officer for the research and advocacy group Autism Speaks, which began to fund his research. “Michael’s interest in autism went from being strictly scientific to one that moved him emotionally,” she says.

When Platt was up for tenure at Duke, his department chair encouraged him to switch his

focus to mice in order to take advantage of new genetic tools. Platt ran a study of decision-making in mice, but his heart wasn't in it, and he never published the results. "I had no feeling for that organism at all," he says. He was convinced that monkeys could provide answers mice never could. But he couldn't keep more than two monkeys in a single cage at his lab — severely limiting his ability to study how monkeys socialize.

His best bet was to return to the field.

MONKEY ISLAND

The story of how Cayo Santiago came to be sounds like the plot of a science-fiction film. In the late 1930s, India was tightening restrictions on the export of its rhesus macaques for lab research. With the threat of World War II looming, scientists in the United States were concerned that their monkey supply would be cut off. Columbia University negotiated the purchase of Cayo Santiago and dispatched Clarence Ray Carpenter, a dashing young primatologist, to obtain macaques for the new colony. Carpenter's benefactors had hoped to study tropical diseases, but he always envisioned the island as a natural laboratory for studying social behavior.

The expedition to India, Carpenter later recalled in an address to the University of Puerto Rico, was a "nervy business." He had to negotiate with animal traffickers in Calcutta and bribe a ship captain to accept his cargo. He accompanied 500 monkeys back to New York and then on to Puerto Rico aboard the steamship S.S. Coamo. "I worked 14 or 15 hours a day," he said. "I cleaned cages or fed animals all day long, exhausted, in rough weather or calm, then I went to sleep."

Carpenter released a total of 409 monkeys on the island in December 1938 and January 1939,

and established six feeding stations to keep the animals spread out. One of the early caretakers on the island, Angel Figueroa, who is now 85, recalls cooking huge vats of root vegetables during the 1950s. It was never enough. "They were always hungry," he says.

When you set foot on Monkey Island even now, it's hard not to feel like you've arrived on a Hollywood set. The island is just a five-minute boat ride from the mainland, but the perimeter is surrounded by 'Do Not Enter' signs that warn "Peligro, Estos monos muerden! Danger, these monkeys bite!" Before visiting, I had to sign a form acknowledging the risk of exposure to herpes B — a virus harmless to monkeys but potentially deadly to people.

From the dock, I follow Platt and colony manager Giselle Caraballo-Cruz through a dry stand of mangroves. Platt, a muscular man with a white goatee and a bald head, looks like a college coach heading out to practice. As we approach the island's headquarters — basically a storage shed and picnic table surrounded by steel diamond mesh — a monkey scurries across the corrugated metal rooftop. Platt doesn't bat an eye. He opens the door and invites me inside. "Out here," he says, "the cages are for the people."

The island is still strewn with the ruins of abandoned buildings, including stone shelters meant to give courting monkeys privacy, and an old cabin where the first manager and his wife lived. Today, no one sleeps on the island, and the monkeys have sex wherever they like. Researchers and caretakers come almost every day. They know the relationships of every monkey on the island and pedigrees dating back to the 1950s.

Owned and managed by the University of Puerto Rico, the island supplies some monkeys for medical research, but it is primarily a semi-wild laboratory where social interactions have consequences. (It's where E.O. Wilson developed his

theory of sociobiology in the 1970s.) A veterinarian treats any injuries that occur during the annual census, when workers trap hundreds of monkeys, clip their ears and tattoo their chests with a three-digit code, and draw blood for genetic work. Young ones also get vaccinated for tetanus. Other than that, the monkeys are left to fend for themselves, and the results can be gruesome. One monkey on the island today had his nose ripped off in a fight, leaving a hole between his eyes.

NAME GAME

Platt and I hike to the highest point of the island, a rocky summit known as El Morillo, and greet one of his graduate students, Sam Larson. Larson is standing inside a chain-link-fenced hexagon the size of a baseball diamond. Around him, two dozen macaques hunched on the ground meticulously sort through soap-sized bars of food, as though one piece of this commercial chow were measurably superior to another. Larson has just finished testing his new assistant on his ability to identify more than 200 individual monkeys by sight. “He passed,” Larson says.

Larson himself got a handle on the monumental task by naming them after characters in the television series “Game of Thrones.” The monkey Tyrion has a scar running across his face, while Jaime has a short, deformed arm. “Everyone else just calls him ‘Chicken Wing,’” Larson says. Monkeys are not just notable for their physical attributes. An old male who regurgitates his food into his cheek pouches and swallows it again is universally known as The Great Disgusto.

In addition to giving them all names, the researchers keep track of their social lives. All six groups are led by powerful females and their daughters and sisters. The largest and most dominant by far is Group F, with more than 300

members. When other monkeys see them coming, they get out of the way — fast. The members of group S are known as the hippies, because they tend to be more relaxed around people than the other groups are. Then there’s the V group, made up of what Caraballo-Cruz calls the “trash-can monkeys,” who don’t seem to fit in anywhere else.

Because this is a rare chance for Platt to see his study subjects firsthand, he asks the team about some of the monkeys with unusual behaviors. Caraballo-Cruz mentions 13H, who had plucked two perfect lines of fur from the base of her child’s tail. Over-grooming seems to run in the family.

“That’s really interesting, because the SHANK₃ variant in mice leads to over-grooming,” he says, tapping out a note for himself on his smartphone. Platt doesn’t know if 13H has the SHANK₃ variant, but he says the team needs to keep better track of aberrant grooming behaviors to hunt for genetic correlates.

Whereas Platt’s laboratory work gets its power from doing technically difficult studies with a handful of monkeys, his work on the island is based on collecting simple pieces of information from hundreds of them. In the summer, the island can be packed with up to 10 of Platt’s students, postdocs and collaborators. Even during the academic year, several assistants stay in Puerto Rico to observe the monkeys.

Each morning, they draw up a ‘hit list’ of individual monkeys to watch during a 10-minute block. Then they head out to the field with a handheld computer to record those animals’ social interactions, such as whom they spend time with, whom they groom and whom they threaten. Over time, these data have allowed Platt to map out the social networks and dominance hierarchies on the island, along with behavioral characteristics of individual monkeys.

In 2013, Lauren Brent, Platt’s former postdoc and field research guru who is now at the University of Exeter in the United Kingdom, reported that a



Rules of the game: The animals have six cliques, with pecking orders within each group.

monkey's social tendencies can be passed down from parent to child. She used techniques developed in human behavioral genetics to collect data suggesting that monkeys with few grooming buddies tend to have specific variants of two genes that govern serotonin levels in the brain. One of these genes, *TPH2*, has been implicated in depression and autism. The more recent discovery of a natural *SHANK3* variant is particularly intriguing, because it shows that even the most complex and subtle social behaviors can have a clear genetic signature.

Platt and his colleagues have presented the *SHANK3* findings at scientific meetings as a demonstration of the promise of the Cayo Santiago monkeys, but they say it's too early to draw solid conclusions from the work. Rather than

singling out one gene at a time, their goal is to conduct a genome-wide analysis of autism-related genes and their impact on monkey social behavior. They have sequenced the whole genomes of 220 monkeys and plan to add another 200 in the near future.

In a paper published in May, they described how the gaze-following reflex develops in 481 macaques on the island. The study, led by Alexandra Rosati of Harvard University, found that gaze-following begins to emerge at 5 months — the equivalent of an 18-month-old human infant — and declines with old age. Following puberty, females seem to follow gazes more than males, which aligns with patterns seen in people.

But these observations are only true of typical monkeys. It turns out that about one in every three



Social studies: More than 1,500 feral macaques roam Cayo Santiago, creating a natural lab for social behaviors.

monkeys at 1 year of age don't follow gazes at all. "That's what I'm most interested in," Platt says. His goal now, he says, is to hunt for connections between gaze-following and genetic variants that might be relevant for understanding conditions ranging from social anxiety and schizophrenia to autism.

MODEL COLLABORATORS

In 2013, as Platt's team was busy collecting field data in Puerto Rico, a monkey unlike any other was born in a laboratory in the southern Chinese city of Kunming. An independent team of researchers there had inserted a mutated gene, MeCP2, into the one-celled zygotes of rhesus macaques and crab-eating macaques, another southeast Asian primate. Mutations in this gene cause most cases

of Rett syndrome, which has similarities to autism and can be difficult to study in rodents. Mice with mutations in MeCP2 are anxious and eventually develop seizures, but they don't look much like people with the syndrome.

One female macaque was born 162 days later, becoming the first-ever transgenic monkey model for autism, but the researchers haven't described its behavior. In February, a second group of Chinese researchers used a different technique to create macaques with multiple copies of the human MeCP2 gene. MeCP2 duplication syndrome, like Rett syndrome, shares fundamental features with autism. The researchers have reported that the mutant monkeys pace in circles and let out anxious grunts. They also seem to be less social than controls: In a rudimentary behavioral test, the researchers found that the transgenic animals spend less time with other monkeys than controls do.

These tools are part of a resurgence in interest in monkey models, particularly as the gene-editing technique known as CRISPR has allowed quick and precise engineering. Guoping Feng, a neuroscientist at the Massachusetts Institute of Technology, has created a mouse in which SHANK3 has been rendered inoperative with a point mutation. He plans to insert the same mutation into the common marmoset, a palm-sized New World monkey with a white shock of fur around each ear. Marmosets weigh less than a pound and converse with each other using distinctive squeaks. “We say they are talking,” Feng says.

They are also fast breeders: Each pair produces twins or triplets twice a year. Over the past two years, Feng has bred a colony of 120 animals in Cambridge, Massachusetts. “We cannot say that the marmoset will be a better model than the mouse,” he says. “We don’t have proof of that yet, but based on the structure of their brains and their evolution, we think so.”

Platt’s group has also begun working with transgenic monkeys. In May, one of his graduate students visited the Chinese Academy of Sciences, where collaborators have engineered crab-eating macaques with a SHANK3 mutation and are making one with a mutation in CHD8, the top autism candidate gene.

Laboratory monkeys are also being recruited in basic research studies looking at how drugs may affect social behavior. Katalin Gothard, a researcher at the University of Tucson in Arizona, has identified neurons in the monkey amygdala — an emotional center of the brain — that respond specifically to eye contact. Gothard has shown that the strength of the gaze-following reflex in one monkey depends on the facial expressions of the monkey it is watching in a video. In a study submitted for publication, she found that giving male macaques oxytocin increases their likelihood of gaze-following. Gothard says oxytocin

could ultimately help people with autism connect to their families and communities.

Platt has seen this struggle to connect firsthand as he has become more involved in the autism community. In November 2014, he visited the Marcus Autism Center in Atlanta, where he met children who had been placed in padded rooms and restrained in order to prevent them from punching themselves in the face. Platt says he hopes his work will directly improve the lives of people with autism, but Cayo Santiago has also given him a lens to think about the spectrum in the context of evolution.

The close monitoring of monkey social life — Platt’s boyhood passion — continues to elicit deep questions. One of the most remarkable monkeys on the island is a male named Pinocchio, who sits near the bottom of the dominance hierarchy, ranked 39 out of 48 males in the powerful Group R. He was originally born into group F in 1999, but has bounced in and out of it twice over the past six years. Pinocchio is one of the floaters that have been observed since the island’s early days but never formally studied. Although Pinocchio has fathered a few children, he is no longer able to reproduce due to an injury, possibly from a fight. He spends a lot of his time alone, which is where we find him.

“Is living outside of groups adaptive?” Platt wonders. His research has been built on the idea that the failure to develop social behavior could be a pathology. But he says he can also see how living outside of the group has some advantages, particularly for a low-ranking male such as Pinocchio.

All that time alone over the years has given Pinocchio time to innovate: He is the only monkey on the island who knows how to open a coconut. When he finds one, he goes down to the concrete dock and tosses it up in the air again and again for hours until it finally breaks open. For this particular monkey, solitude holds sweet rewards.

Children with autism
are often clumsy,
physically awkward
or uncoordinated.
This understudied
and nearly ubiquitous
feature has researchers
contemplating a new
idea: Could motor
problems be one source
of autism's social
difficulties?

AUTISM IN MOTION

by

**NICHOLETTE
ZELIADT**

photograph by

MATTHEW HOPPER

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FOR 6-YEAR-OLD MACEY, LUNCHTIME at school is not so much a break from reading and math as it is an hour rife with frustration.

Here's how Macey's mother, Victoria, describes Macey's typical lunch break: In her special-education classroom an hour north of San Francisco, Macey's classmates gather at a big square table, chattering away and snatching one another's food. Macey, meanwhile, is sequestered away at a small white table in a corner, facing a bookshelf. She grabs the handle of a spoon using the palm of her right hand, awkwardly scoops up rice and spills it onto her lap. She wants to be at the big table with her peers, but she sits with an aide away from the other children to minimize distractions while she eats. (Victoria requested that

we use her and Macey's first names only, to protect their privacy.)

After lunch, the children spill out onto the playground. Macey, wearing a helmet, trails behind, holding her aide's hand. She can walk, but she often trips on uneven surfaces and falls over. She tends to misjudge heights, and once pulled a muscle while climbing on playground equipment. When she was 3, she tripped and fell headfirst out of a sandbox, scraping her face, chipping one tooth and dislodging another.

Macey has little trouble moving around the house because it has few stairs and her mother never changes the layout of the rooms. Victoria's biggest concern is that Macey's movement troubles interfere with her social life.

Macey is naturally social: She likes interacting with adults but sometimes gets frustrated when they don't understand her. It's even more difficult with her peers. One afternoon last year, Macey watched her older brother and her cousins ride their bicycles in front of the house. When her brother took a break and laid his bicycle down on its side, Macey shuffled over and tried to climb on. "But there was no way," Victoria recalls. "She's wobbly, and I was afraid she would fall off and hurt herself." Victoria gently led her daughter away from the bicycle. Tears began to stream down Macey's face as she shouted, "I want bike!"

Macey will probably have these motor problems her entire life. They are a characteristic feature of her condition: She has an extra copy of a small stretch of DNA on chromosome 15, which causes a condition called dup15q syndrome. Like most children with the syndrome, Macey also has autism.

About 80 percent of people with autism have some sort of movement problem, ranging from clumsiness or a mechanical style of walking to more profound difficulties like Macey's. "It is very, very common for children with autism to have

clear impairments in their motor control,” says Stewart Mostofsky, director of the Center for Neurodevelopmental and Imaging Research at the Kennedy Krieger Institute in Baltimore, Maryland.

Despite their prevalence, movement problems are not considered a core feature of autism — that is, they are not required for an autism diagnosis. And they are understudied compared with the social difficulties and repetitive behaviors that define the condition. “For many years, it has been ignored as a challenge that children with autism experience,” says Nicole Rinehart, director of the Deakin Child Study Centre at Deakin University in Melbourne, Australia.

A few scientists, including Rinehart and Mostofsky, are precisely measuring the movements of children like Macey to find brain features that might underlie motor difficulties. Because motor problems often emerge in infancy, well before other features of autism, some researchers are pursuing a provocative idea: Movement problems might be one source of the social difficulties in people with autism.

The theory goes like this: Children who have trouble exploring their environments miss out on opportunities for social interactions, making it difficult for them to learn communication and social skills. Later on in childhood, their clumsiness prevents them from participating in group activities, worsening their social problems. This is a controversial idea, but if true, it means that therapies that teach people with autism how to move more fluently could also help them interact with others.

MOVERS AND SHAKERS

In 1943, Leo Kanner chronicled the medical histories of the 11 children who were the first to be

diagnosed with autism. Some of the parents told him that their children had learned to walk late. And that when the parents reached for their babies to pick them up, the children did not raise their arms or tuck their legs — as babies typically do when they are picked up. A year later, the Austrian pediatrician Hans Asperger also described odd gestures and posture in four boys with autism. He described one boy, Fritz, as having “no mastery over his body” and “atrocious” handwriting, according to an English translation of his written account. About another boy Asperger wrote, “He could not possibly catch a ball, however easy one tried to make it for him.”

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NICOLE RINEHART

In the ensuing decades, scientists focused on other, more consistent and troubling, features of autism, such as social problems and difficulties with communication. But in the 1980s, standardized tests of motor skills began to confirm these initial observations.

The movement problems vary from person to person, but most people with autism have some

difficulty coordinating their movements — such as turning their head while reaching for an object — as well as trouble with balance. Perhaps as a result, they also have trouble with many everyday tasks, from fine-motor tasks such as buttoning a shirt to gross-motor skills such as running, jumping or catching a ball.

The research available so far suggests that these difficulties begin early in life. Home-video analyses reveal that children later diagnosed with autism tend to have trouble turning over and sitting up as infants, and are late in learning to crawl. Their movements are also often asymmetric: When walking or crawling, the limbs on one side of the body do not mirror those on the opposite side. Parents echo these observations: They tell doctors that their child lagged behind their typical peers in learning to walk, or has trouble learning complex, coordinated movements, such as pedaling a tricycle. “If you ask any parent of a child with autism, you get near-universal agreement that this is an issue,” Mostofsky says.

Victoria knew something wasn’t quite right when Macey didn’t learn to walk until she was 2. Even after Macey began walking, she remained unsteady. “She looked like a drunken sailor,” Victoria says.

It is unclear why children with autism have these problems, but emerging research is beginning to provide some clues. An unpublished study of more than 2,400 children with autism suggests that, compared with other children on the spectrum, those who carry certain rare mutations strongly linked to autism are more likely to have motor problems. This suggests that some motor problems in people with autism have genetic underpinnings.

Others researchers are using computational methods that reveal which parts of the body are not moving properly during certain tasks. When people with autism perform the tasks, they have

characteristic difficulties that suggest the brain areas or circuits affected — information researchers can use to identify exactly what goes awry.

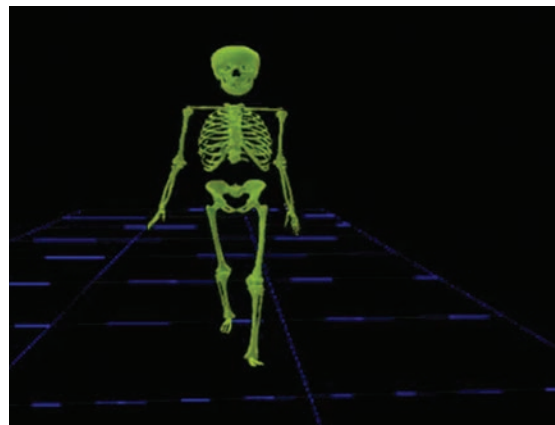
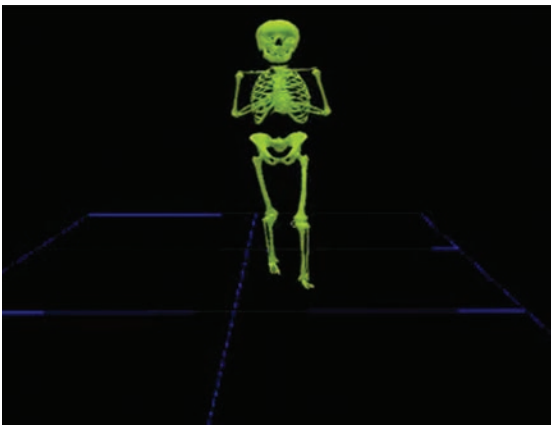
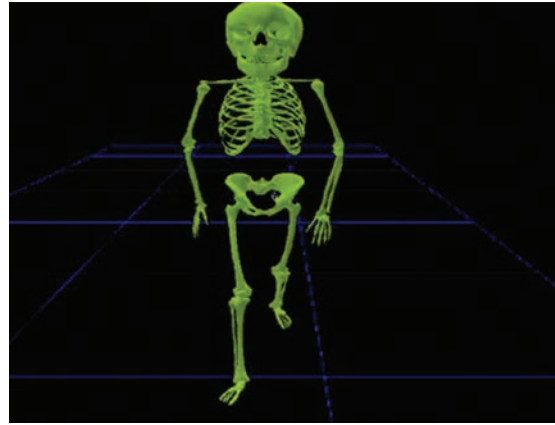
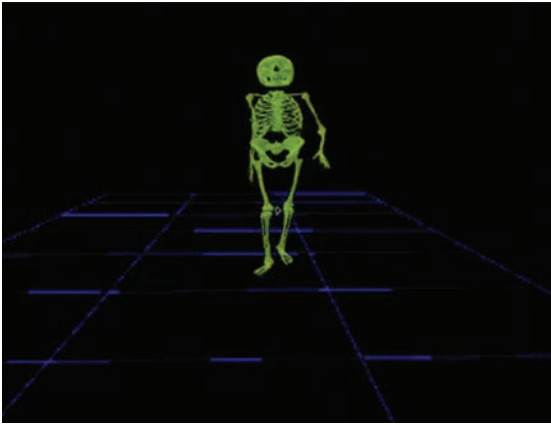
BUSY BODIES

Inside a small, dark lab in Melbourne on a December morning, Rinehart watches as a girl named Catherine, then 12, walks the entire length of a brown floor mat that spans the room diagonally.

Pressure sensors in the mat detect the girl’s footsteps. Wires connect the mat to a computer in the corner, which collects data in real time and calculates Catherine’s walking speed, her stride length, and the distance between her feet. Rinehart uses the automated system to compare the gait of children who have autism with that of their typical peers. (Catherine is Rinehart’s daughter, and does not have autism; Rinehart conscripted her to demonstrate the technology.)

The length and width of Catherine’s stride are highly consistent. By contrast, Rinehart says, children with autism tend to have a wide stance, and their stride length and width vary from step to step. These patterns may explain why some people with autism seem to have an unusual walking style — even if it’s difficult to pinpoint exactly what’s odd about their movements.

Rinehart’s colleague, Jennifer McGinley, guides Catherine through a series of increasingly challenging tasks. The girl walks smoothly along a narrow black line on the mat as if balancing on a tightrope, placing the heel of her lifted foot directly in front of the planted one with each step. Children with autism might instead stumble off of the line or walk along it without lining up their feet heel to toe as instructed — a classic sign of problems in the cerebellum, a brain region that coordinates movement.



Walking through: Murphy’s study distinguishes the walking styles of children with autism from those of controls.
Courtesy of Anna Murphy

Catherine is then asked to walk as fast as she can while naming types of pets or items of furniture typically found in a home. This test reveals whether multitasking can cause difficulties to emerge. “When you look at a playground, you don’t often see kids walking along slowly and silently by themselves,” McGinley says. “So we need to look at how they cope when they’re doing other things as well.” On this task, Catherine walks slightly more slowly than she did when she was not required to answer questions. People with autism walk even more slowly or are wobblier than usual, which suggests that problems with attention may also factor into their movement challenges.

To provide a more complete picture of gait, Rinehart’s team uses a 3-D tracking system, housed at the nearby Kingston Centre clinic, to measure the movement of the limbs and torso. Researcher Anna Murphy demonstrates how it works with her 7-year-old son, Liam, who does not have autism. “Mom’s going to turn me into a skeleton,” Liam says as his mother peels off his shirt and attaches small reflective markers to his bare shoulders, elbows, chest and back, as well as his hips, thighs, knees, calves and ankles. Murphy slides a stretchy headband with four additional sensors around his forehead, and places a smaller band with two sensors around each of his wrists.

As Liam walks along a black strip of plastic affixed to the floor, a series of eight infrared cameras connected to a computer near the back of the room track the movement of the markers. Liam's body appears as a neon-green skeleton strutting across the computer screen. The system measures parameters such as the angle of the torso and that of the pelvis, as well as the overall degree of movement of his upper body. Murphy's unpublished data indicate that the upper bodies of people with autism tend to tilt forward as they walk, and that they have more bounce in their step than their typical peers do. These findings align with the results of the two-dimensional footstep analysis. "If you've got more movement in your trunk, you tend to be more unstable at the bottom, so you account for that by widening the step," Murphy says.

From these types of studies, Rinehart and her colleagues ultimately hope to be able to identify movement patterns that distinguish autism from other conditions. The team is recruiting children with autism as young as 2 years old to see if the same patterns of altered gait turn up in toddlers with the condition.

"What this group has done is remarkable," says Shafali Jeste, associate professor of psychiatry and neurology at the University of California, Los Angeles. "Many of us see that children with autism have motor impairments, but it has remained a clinical observation; they're taking that clinical observation and turning into something measurable and quantifiable."

MOVING FORWARD

Babies typically learn to talk in large part by moving their bodies first — or so one leading theory goes. When babies reach out to their parents

or bring them a toy, the parents may respond verbally, which helps the babies learn to communicate. Infants who explore less than usual "are not experiencing words in the same way," says Anjana Bhat, associate professor of physical therapy at the University of Delaware in Newark.

In babies with autism, motor problems become apparent early — well before social and communication difficulties, which typically aren't noticeable until after a child's first birthday. These observations come from studies of so-called 'baby sibs,' the younger siblings of children with autism, who are at increased risk of the condition. As early as 3 to 6 months of age, infants later diagnosed with autism show delays in rolling over and holding up their heads. They also don't reach for things around them as often as typical babies do, and have trouble grasping and manipulating toys.

Even though the children may eventually acquire these abilities, "it's not irrelevant that a baby has these postural control and grasping challenges," says Rebecca Landa, director of the Center for Autism and Related Disorders at the Kennedy Krieger Institute, who has led some of the studies. Delays or disruptions in learning to stand and walk limit a child's ability to explore her surroundings and interact with others. "These simple little things that might seem inconsequential can add up over time, and put the child at risk for other delays, like in language or social interaction," Landa says.

A few studies have found that baby sibs with motor delays in infancy have trouble learning to speak and understand words. The severity of motor difficulties also predicts the extent of their social problems. Bhat and others say that movement problems in infancy have cascading effects on communication and social development.

But not everyone agrees with this hypothesis. Motor problems may develop before social ones, but that doesn't mean they are causal, argues

Mostofsky: “I don’t think that argument holds up to scrutiny.” In his view, movement problems only appear to precede social difficulties because motor skills develop earlier than social skills. “Motor development is much more prominent in the first year of life,” he says. At that early stage, “you might not detect signs in social communicative development, because there isn’t much at that point to detect.”

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STEWART MOSTOFSKY

Instead, Mostofsky says, motor and social deficits are both manifestations of a deeper problem: faulty connections between certain brain regions. The disrupted connections make it difficult for people with autism to incorporate visual information when they plan movements. Being able to do this is key to social interactions — for example, making appropriate gestures and facial expressions in response to another person’s words or actions.

In support of this idea, his team reported in 2009 that when children with autism learn to control a robotic arm, they rely primarily on proprioception — that is, sensations gleaned from their own muscles — rather than on visual information,

as typically developing children do. The less the children depend on visual information, the more severe their problems with social skills. He also reported in 2015 that children with autism have more difficulty catching a ball than do children with attention deficit hyperactivity disorder. “This is a task where you have a projectile coming at you, and you have to quickly adjust your movements based on that visual input,” he says.

Mostofsky also has data from imaging studies that support his theory: Typical children with the most synchronization between visual and motor brain regions tend to have the best imitation skills. These regions are often out of sync in children with autism; and those least in sync have the most severe autism features.

FIELD DAY

Even researchers such as Mostofsky who don’t generally believe that movement problems disrupt social skills say that treatments that improve motor skills may help people with the condition socially. Several small studies hint that movement-based therapies boost social skills, communication abilities, attention and behavior.

Parents of children with autism are gravitating toward programs that promise to teach physical skills. For example, a summer program to teach children with autism how to ride a bicycle was filled to capacity in a matter of days, says the program’s leader Megan MacDonald, assistant professor at Oregon State University in Corvallis. “It clearly indicated to us a need for opportunities like this,” she says.

Other researchers have also launched similar programs. Mostofsky’s team is developing a video game that helps children with autism learn to dance by imitating an avatar, with the goal of



Play time: Team sports, such as Australian-rules football, might ease social difficulties in children with autism. Courtesy of AllPlay

strengthening connections between the visual and motor areas of their brain. Mostofsky predicts that the game will boost both motor abilities and social skills. He is scanning the brains of the children with autism before and after they play the video game to assess the results.

A few programs more overtly combine both physical and social training. Shafali Jeste's ACEing Autism program, which teaches basic tennis skills, launched in 2008. The coaches teach children with autism social cues, including how to follow and interpret a partner's movements to predict his next move. Jeste is launching a pilot study, intended to include at least 20 children with autism, that will use standardized tests and other quantitative measurements to assess whether the program improves children's motor skills, eye contact and other behaviors.

Along similar lines, Rinehart and her colleagues have partnered with the Australian Football League to create AllPlay, a program that teaches children with autism or other developmental conditions to play the sport. The coaches modify activities and drills: A coach may position the child closer to the goal line or use a lighter football, for example. The program naturally combines physical education with social training, as parents and children have the opportunity to meet new people, play in groups, learn to cope with crowds and prepare for physical contact with others. Rinehart's team plans to measure the walking patterns and social skills of children with autism before and after the program.

As much as Victoria would like to sign Macey up for something like this, her daughter is too young. "She's 6, but she has the mentality of a 3-year-old," Victoria says. Until three years ago, Macey attended a Sunday school program for toddlers, where she could interact with children of her emotional or intellectual age. But the church decided that Macey is too big to play with children who are years younger than her. "The other parents were afraid that she was going to fall over and hurt them or something," Victoria says.

For now, she and her husband are doing the best they can on their own. They are thinking about purchasing an adaptive bike, a three-wheeled contraption that does not require balance. It would keep Macey safe — and still allow her to play with other children.

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THE CURIOUS CONNECTION BETWEEN AUTISM AND CANCER

A surprising number of genes associated with autism also have links to cancer. Does that mean cancer drugs can treat autism?

by

ALISA OPAR

illustrations by
NICK OGONSKY



FIVE YEARS AGO, ON CHARLIE RYAN'S second birthday, a big lump mysteriously formed on the side of his abdomen. At the emergency room his parents took him to, doctors suggested the lump was a hernia caused by some unknown trauma, and referred the family to a surgeon. The surgeon told them it was a benign tumor, and sent them home.

Charlie already had a host of medical issues. He'd been born with an abnormally large head and other features of autism, including being nonverbal. Now this.

Like many a baffled and worried parent, his mother, Autumn Ryan, turned to Google, typing in Charlie's ailments and coming up with a possible cause: a mutation in PTEN, a gene that reins in cell growth. Further searching led her to websites dedicated to families whose children have PTEN mutations. It all looked familiar — and worrisome. "I read stories of little boys who haven't lived, descriptions of these children with a multitude of bumps all over their bodies," Ryan recalls. "I was freaked out."

Two years later, after visits to multiple doctors and the nine months it took for his genetic test to be analyzed, her hunch proved right. Charlie has a mutation in PTEN. Ryan immediately faxed the results to Charis Eng, a PTEN expert at the

Cleveland Clinic in Ohio, whose name she had come across in her research. A few months later, the family made their first trip from their home in Tulsa, Oklahoma, to see Eng and her colleague, autism expert Thomas Frazier. Together, Eng and Frazier have treated more than two dozen children like Charlie — who all have PTEN mutations, autism and large heads.

In Eng, Ryan finally found someone who understood Charlie's condition. "It's like going to the person who has all the knowledge in the world, and you can ask her any question," Ryan says of Eng.

Eng was first and foremost a cancer geneticist, and stumbled upon PTEN-linked autism through her work in that field. In 1997, she discovered the genetic root of Cowden syndrome, a rare condition characterized by tumor-like growths and a high lifetime risk of many cancers. Following people with the syndrome, as well as their unaffected family members, she noticed that a few relatives of people with Cowden syndrome have an autism diagnosis. She thought little of it; it was probably a coincidence. But then Eng noticed a few more children with autism in the families. And then a few more. "We started going, 'Huh, how come there's all this autism in the family members?'" she recalls.

Curious to see if this trend was more than a fluke, Eng teamed up in 2004 with Merlin Butler, a clinical geneticist at the University of Kansas Medical Center in Kansas City. Eng and Butler screened 18 children with an autism diagnosis and macrocephaly, because enlarged head size is a hallmark of both Cowden syndrome and autism. They found that 3 of the 18 children have mutations in PTEN. Mutations in PTEN have been linked to dozens of cancers, but the gene had never before been shown to have any effect on social skills or behavior. “Wow,” Eng recalls thinking. “PTEN plays a role in a neurodevelopmental disorder, too.”

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CHARIS ENG

The finding was so unexpected that it was a tough sell. *The Lancet* and the *New England Journal of Medicine* both rejected the paper. “They didn’t believe us,” says Eng, now head of the Cleveland Clinic’s Genomic Medicine Institute. “Their reaction was: ‘It’s a cancer gene. How can this be?’”

To Eng, it was perfectly plausible that a mutation in the gene could lead to autism as well as to the many cancers of Cowden syndrome. Cancer arises when PTEN mutations release their brake

on cell growth and proliferation, and cells grow out of control. When PTEN mutations cause an overgrowth of nerve fibers in the brain, Eng reasoned, they might instead lead to autism.

The *Journal of Medical Genetics* ultimately published the study in 2005. Other groups soon confirmed the findings, and today the subtype of autism with PTEN mutations and macrocephaly — called PTEN-ASD — is estimated to represent up to 2 percent of all autism cases.

The unexpected connection between cancer and autism isn’t limited to PTEN. In the past decade, many cellular pathways involved in cancer have been found to overlap with those implicated in autism, and dozens of genes have been linked to both.

“We didn’t know, when we started out, how [the autism genes] would look,” says Michael Wigler, a molecular biologist at Cold Spring Harbor Laboratory in New York who became involved in autism research after 25 years as a cancer scientist. “It turns out that they are all over the place,” says Wigler. “The body doesn’t invent each cellular system from scratch.”

The findings have sparked investigations into whether autism treatments can piggyback off of approved cancer drugs that target specific genes. They also raise concerns that Charlie and other children with autism who have mutations in known cancer genes might be at increased risk for developing malignancies. So far, scientists have no concrete answers to address this worry. “We’ve barely scratched the surface,” says Eng.

SURPRISE FINDS

Most researchers agree that a combination of genetics and environmental factors lead to autism. Hundreds of genes are involved in autism, though

only a fraction of these are strong candidates for the condition. Mutations are typically categorized as either ‘germline,’ meaning that someone is born with the mutation and carries it in nearly every cell of the body, or ‘somatic,’ meaning that the mutation occurs after birth and affects only a subset of the body’s cells.

Cancer is usually a disease of aging, caused by somatic mutations; autism, a developmental condition, is usually linked to germline glitches. So it was a surprise when autism studies started picking out genes in pathways typically associated with cancer. In several instances, the crossover emerged in much the same way it did with Cowden syndrome – with scientists noticing autism traits in people they were treating for other conditions.

That’s what happened with tuberous sclerosis complex (TSC), a rare condition caused by mutations in *TSC1* or *TSC2*. Both genes are located downstream from *PTEN* on a pathway known as mTOR (for mammalian target of rapamycin). In people with this condition, benign tumors grow in the brain and other organs, causing seizures, lung and kidney disease and other health problems, and occasionally turn malignant. Around 20 years ago, as autism diagnoses started to rise, clinicians began to recognize that autism was strikingly common among people with TSC. Today, up to half of people with TSC are estimated to have autism.

Something similar also happened with RASopathies, a group of five disorders characterized by developmental issues, tumors and skin discoloration. Katherine Rauen, chief of genomic medicine at the University of California, Davis, identified mutations in the RAS-MAPK pathway, a well-studied cancer pathway, as the cause of RASopathies. Around 15 years ago, Rauen began to notice that many people with RASopathies are diagnosed with autism or have autism-like features. “When you see rare syndromes, and you see

a lot of them, you start picking out patterns,” she says. In 2013, Rauen and her colleagues reported that 27 percent of people with RASopathies meet the criteria for autism.

Other researchers hit upon the cancer connection directly, through deep dives into the genome. Geneticist Evan Eichler and his collaborators are sequencing the DNA of tens of thousands of children with autism as well as their unaffected family members to show that genetic mutations underlie autism. Among the first genes that popped up in their quest was *CHD8*, a gene that is involved in arranging DNA into tightly packed chromosomes. *CHD8* also interacts with the WNT signaling pathway, which translates messages from outside cells into changes in gene expression, and has strong cancer ties. Eichler and his colleagues found that spontaneous, or *de novo*, mutations in *CHD8* seem to cause a distinct subtype of autism with specific physical traits. When they looked at children with *CHD8* mutations and autism, they noted that the children have broad foreheads, large heads, wide-set eyes and gastrointestinal issues.

The growing number of cancer genes linked to autism piqued the curiosity of Janine LaSalle, an autism researcher at the University of California, Davis. In a study published in March, she and her colleagues reported that at least 43 genes thought to be involved in autism are also associated with cancer. Of those, 16 genes, including *PTEN* and *CHD8*, have strong autism links, and 8 others lead to autism-related conditions such as Rett syndrome and TSC.

“Some themes jumped out” from the list, says LaSalle. She saw genes involved in chromatin – the DNA-protein complex that forms chromosomes – DNA repair and the transmission of signals that alter cell activity. Nine genes involved in the WNT pathway alone showed up; all are involved in genome maintenance, or fighting damaging assaults on DNA – and that’s a clue.

The thinking is that early in brain development, errors in pathways that maintain the genome's integrity may lead to autism. If the mistakes happen later in life, says LaSalle, they may occur in cell types prone to tumors.

There may be more to it than timing and cell type. Eng and others are delving into the specific types of mutations, too, to see whether certain kinds of mutations contribute to autism, whereas others shift the balance toward cancer.

SIMILAR, BUT DIFFERENT

When Eng first made the autism connection in 2005, she knew she'd hit upon a mystery she couldn't solve alone. She needed to find the right partner.

As it turns out, someone else was looking for a similar meeting of minds.

Clinical psychologist Thomas Frazier had just shifted his focus from attention deficit hyperactivity disorder and bipolar disorder to concentrate on autism, after his son was diagnosed with autism. Frazier and Eng, who had just moved to the Cleveland Clinic, clicked immediately. "Had we met 20 years before, we would've shaken hands, and that would've been it," says Frazier, who now runs the Cleveland Clinic's Center for Autism. "There would have been no reason for us to collaborate."

Eng invited Frazier to attend her weekly lab meetings. After publishing on PTEN-ASD in 2005, Eng's autism research had stalled, and she was eager to get it moving again. For his part, Frazier needed a mentor to guide him through genetics. When he showed up for Eng's lab meetings, he initially had to look up words on his phone. Eng's team would talk about the chemical modifications of DNA that alter gene expression, for example. "I had no idea what methylation was. The first

year was really brutal like that," he says, laughing.

Frazier's hard work paid off, and Eng was impressed with how deeply he came to understand genetics. "That's really rare," she says.

The two now partner to explore what PTEN mutations do in people with autism, and hope to use their knowledge to find targeted treatments. In 2009, for instance, they began hunting for biological markers of autism, comparing people with PTEN-ASD and those who have autism but no PTEN mutation.

To understand how mutations in PTEN cause autism features, they compared 17 children who have PTEN-ASD with three other groups: 16 children with autism and large heads, 38 with autism alone, and 14 controls.

Compared with the other groups, children with PTEN-ASD had lower PTEN protein levels. Magnetic resonance imaging scans revealed that they had enlarged volumes of white matter, the fibers that brain cells use to communicate. The children also had poorer working memory and slower processing skills than the children in the other groups. Taken together, says Frazier, the findings indicate that low PTEN protein levels drive white matter abnormalities, which in turn impair cognition.

The next step, says Frazier, will be to pin down the exact molecular effects of the loss of PTEN protein — an endeavor that other groups are working on as well. PTEN typically cycles between the cytoplasm (the fluid inside the cells) and the nucleus (the control center where the DNA is stored). The protein plays different roles in each location: In the nucleus, PTEN stabilizes DNA strands and plays some role in the cell cycle, whereas in the cytoplasm it plays multiple roles, including controlling cell proliferation and helping to suppress tumor activity. Eng's lab created mice in which the PTEN protein clusters in the cytoplasm rather than in the nucleus, hoping to understand how the location of the protein influences brain physiology

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THOMAS FRAZIER

and behavior. Mice with most of the protein in the cytoplasm perform better in maze trials but display abnormal social behavior, traits that line up with those seen in people who have mild features of autism. Eng and Frazier haven't thoroughly studied mice with PTEN primarily in the nucleus, but the mice appear to perform poorly on memory tasks and be socially withdrawn.

Eng's lab and others are also working to tease apart how PTEN mutations in autism and cancer differ. So far, they've found that PTEN mutations associated with autism tend to be missense mutations, in which one amino acid is replaced by another. That change drastically lowers, but does not halt, its key activity. A variety of mutations seen in cancers, by contrast, entirely disrupt PTEN, effectively halting its activity and releasing a brake that prevents tumors. Eng's group is developing stem cell models that could pinpoint more specific differences.

In cases of autism caused by mutations in other genes, it appears that the same mutation sometimes occurs in people with autism and those with cancer; the difference is in when and where in the body the mutation occurs. For example, the same germline mutation in a person with

RASopathy-related autism might also be found in someone with bladder cancer — but only in the cells lining the bladder, and accompanied by mutations in other genes.

Likewise, mutations of the TSC genes seem to have different effects in neurons than they do in other cells of the body, says Mustafa Sahin, director of the Translational Neuroscience Center at Boston Children's Hospital. In cancer cells, the genes control cell growth and proliferation through the mTOR pathway, but in neurons, they appear to regulate connections between the cells. In mice missing one of the TSC genes, the axons — the long, thin part of nerve cells that conduct electrical impulses — “go to the wrong places in the brain,” Sahin says. Diffusion tensor imaging, which maps nerve fibers, also reveals abnormalities in the wiring of the corpus callosum — the bridge between the two hemispheres of the brain — and in language pathways in people with TSC. For now, however, the precise series of events that push development off track remain a mystery. “That's really what we're focusing on right now,” Sahin says.

SEARCHING FOR TREATMENTS

There are no drugs approved to treat autism's core features, but the cancer link offers at least one clear possibility for leapfrogging forward. Billions of dollars devoted to cancer research have produced treatments that zero in on specific mutations — shutting down defective enzymes, for instance, or checking overactive proteins. Autism researchers are looking to borrow from cancer's medicine cabinet.

Targeted therapies devised for cancer could become “incredibly effective” for the subtypes of autism that arise from a single mutation, says Luis Parada, director of the Brain Tumor Center

at Memorial Sloan Kettering Cancer Center in New York. Parada has made mouse models for both cancer and autism, with the mice lacking genes including PTEN, TSC1, TSC2 and NFI, a gene linked to autism and pediatric cancers.

In support of this hope, Sahin and others found in 2012 that mice missing TSC1 or TSC2 display autism-like behaviors, including atypical social interactions and repetitive behaviors. Rapamycin, a compound that blocks the mTOR pathway, halts these behavioral problems and seizures.

Buoyed by these results, researchers then moved into clinical trials. In 2016, Sahin completed a three-month trial of 47 people with TSC, aged 6 to 21 years. One-third of the participants received a placebo, while the rest were given everolimus, a safer analog of rapamycin that is frequently used to treat pancreatic cancer. Neither the participants nor the clinicians knew who was receiving the drug.

The researchers are still analyzing the results, but so far they do not see marked improvement in cognitive function in the everolimus group compared with the placebo group. The team hasn't yet looked at autism features such as impaired social behavior and communication. Even so, Sahin is already thinking about next steps. In mice, he says, "we can rescue autistic-like behaviors if we start the treatment early, in the first days or weeks after birth, but often not if we start much later." So a short-term treatment may not be enough to improve autism features in the age range tested. "We may have to redesign the trial to potentially look at the effects of everolimus in younger children," he says.

Eng and Frazier plan to launch their first trial of everolimus in people with PTEN-ASD early in 2017. Rapamycin and related compounds have been shown to prevent the overgrowth of brain cells that leads to macrocephaly and autism-like behaviors in mice lacking PTEN. Their trial will

last two to three years, with participants taking the drug for six months. "We want to give the medicine time to actually show an effect," says Frazier. The aim is to enroll 40 participants, also between 6 and 21 years of age. Judging from the people Frazier and Eng have seen at their clinic in Cleveland, however, they anticipate that the participants will skew young. "That's when the brain is most malleable," says Frazier. "We'll certainly look at age as a possible moderator of treatment outcome."

He emphasizes that although he is hopeful the drug will prove safe, and that the participants show at least a small improvement in brain function, he can't predict the outcome of the trial. "In a wild, wild scenario, maybe their autism symptoms get better," he says.

CALCULATING RISK

Autumn Ryan hopes Charlie will participate in the trial, but she knows that's not a given. Eng, ever the straight shooter, has told her that Charlie, who is now 7, may be too intellectually disabled to participate.

Ryan is reassured to know that even if Charlie doesn't take part in the trial, Eng and Frazier will continue to care for him, answering questions by phone or email, and seeing him once a year when the family visits the Cleveland Clinic. It's an arduous trip that requires two plane rides and wears out both Charlie and his mom. Yet Ryan wouldn't skip it. "I won't travel all day to go on vacation with Charlie," she says, "but I will to go to the Cleveland Clinic." As Charlie gets older, these visits will involve more invasive tests to screen for cancer, such as colonoscopies beginning when he's 9. Ryan worries about breast cancer, too: People with PTEN mutations have an 85 percent lifetime risk



of developing that malignancy, and a drug Charlie is on to treat aggressiveness and hyperactivity, risperidone, is causing him to develop breasts. “All we can do is watch and wait,” she says.

Ryan’s concerns are shared by other parents whose children are on the spectrum and have mutated cancer genes. They can’t help but worry: Are their children also at heightened risk for malignancies?

In short, nobody knows for certain.

A handful of studies indicate that the genetic overlap might not increase these individuals’ odds of developing cancer. In one analysis of the medical records of thousands of people with autism in California, cancer didn’t make the list of the conditions these individuals are most likely to develop. In fact, some evidence suggests that they might have an unusually low cancer risk. In another large-scale analysis, University of Iowa researchers compared the medical records of 1,837 people who have an autism diagnosis with those of 9,336 controls. They found that people with autism have a lifetime cancer risk of 1.3 percent versus 3.9 percent in the control group.

There’s not enough evidence to say that mutations in cancer genes that contribute to autism prevent malignancies, Eng cautions. No study has specifically analyzed cancer risk in people with autism who have mutations linked to cancer pathways.

Eng and Frazier are collaborating with researchers at four other institutions to follow up to 100 children with PTEN-ASD long term. They might not have to wait decades to get a signal for risk, because thyroid cancer, which can be detected with a simple ultrasound, can develop in children as young as 4. (To date, none of the 30 children with PTEN-ASD seen at the Cleveland Clinic has developed thyroid cancer.)

If people with PTEN-ASD do develop cancer, there are several effective drugs that might be able to combat it — some of which, like rapamycin, are the very same therapies being tested for autism.

Even if Eng is successful in finding targeted treatments for people with PTEN-ASD, however, she would be helping only a small fraction of people with autism. “That’s how precision therapy works,” she says. But given her years of experience in cancer biology, Eng inevitably thinks of the parallels: Just as cancer drugs developed for one type of cancer have turned out to be effective at fighting other types, perhaps a treatment for one subtype of autism will follow a similar arc.

The everolimus trial is a first step to testing this optimistic scenario. Eng’s team is looking for gene variants, or even novel pathways, that haven’t yet been identified as being important to autism. Should they hit upon anything promising, they plan to scour the enormous inventory of existing cancer drugs. “Some drug companies may have these therapies already,” Eng says. “Maybe there’s a drug they’ve shelved because it didn’t work as they’d hoped, and voilà, it targets the underlying mechanism we don’t even yet know exists.”

Ryan, meanwhile, says she knows Eng and Frazier are in for the long haul — and so is she. “Charlie will be a part of any study that he qualifies for,” Ryan says. “We want to get as much information about this condition as possible, and to help other families as much as we can.”

3

chapter

**TOWARD
BETTER
TREATMENTS**

WHY DON'T WE HAVE BETTER DRUGS FOR AUTISM?

Clinical trials for autism drugs have been plagued with problems: bad design, the wrong measures, too broad a range of participants.

All that is finally starting to change.

by

RACHEL ZAMZOW

photographs by

**VANESSA
MCKEOWN**



TAYLOR STEVENSON'S FAMILY NEVER left him out of conversations, but they never expected him to participate, either. His contributions, if he made any, were a few random words — gibberish or a Big Bird quote.

So when Taylor started speaking his mind in his squeaky, singsongy voice, his mother, Debbie Stevenson, was stunned. “It was such a huge shock,” Stevenson says. She cried tears of joy. This was in late 2012, when Taylor was 16. Over the next year, his once-cursory answers spun into three-to-five-word sentences. Phrases such as “I’m okay, thank you” became part of his repertoire.

Taylor has fragile X syndrome, a genetic condition that causes lifelong intellectual disability. One in three people with the syndrome also have autism. Taylor is not one of them, but he does have some autism-like features, such as difficulties with language. At first, Stevenson wasn’t sure

what was triggering her son’s changing behavior. Perhaps Taylor’s new high school had sparked the improvement, or perhaps the countless hours of intensive therapy he had endured were finally paying off.

Stevenson began to suspect that a new drug Taylor was taking was responsible. A few months earlier, Taylor had enrolled in a clinical trial exploring the effects of an experimental drug called mavoglurant, manufactured by the pharmaceutical giant Novartis, for people with fragile X syndrome. Stevenson had heard about the trial through her volunteer fundraising work with the nonprofit FRAXA Research Foundation, a fragile X research and advocacy organization. Because there are no approved drugs to treat fragile X, she eagerly signed Taylor up.

Taylor enrolled in the 12-week trial in September 2012 and began taking either mavoglurant or an inactive placebo twice a day. (Neither the

Stevenson nor the researchers knew which drug Taylor was taking.) The family flew from their New York City home down to Atlanta, Georgia, once a month for questionnaires and behavioral testing at Emory University, one of the trial's 38 sites.

Within a few months, Stevenson noticed a slight shift in Taylor's behavior. He started asking her for help when he needed it, and his anxiety diminished. These improvements persisted even after he switched to the second, long-term phase, during which he and the other participants took mavoglurant for more than a year. Stevenson became convinced that Taylor's improvement really was due to the drug.

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ELIZABETH BERRY-KRAVIS

To Stevenson's surprise, however, rumors that the trial wasn't going well began to spread through FRAXA circles in February 2014. When the family showed up at Emory for another testing session a few months later, the researchers told them Novartis was suspending the trial. "I was beyond shocked," Stevenson says. "I thought that even if only 25 percent of the population has seen what

I've seen, of course they'll approve it — because we have nothing else."

When Taylor's supply of the drug ran out, his strides forward reversed. Within a few months, his sentences diminished to single words, and now he mostly ignores questions, as he did before the trial.

Stevenson, who took Taylor's regression the hardest, wished the study had been able to capture Taylor's progress. But it would become clear to her that the trial had been poised to fail even before it got off the ground. Deeper issues — the wrong design and inadequate tests — crippled the study from the start. For the families who heard about the trial's failure in June 2014 via FRAXA, this revelation came as a shock. "I was pretty horrified," Stevenson says. "Do we have a drug that is getting slammed because we didn't measure this properly?"

As it turns out, this trial's misfire wasn't an isolated incident. The same problems have dogged major trials exploring three of the most promising drugs for fragile X, including ventures launched within the past decade by Roche and the now-defunct Seaside Therapeutics. Stunted by flawed designs, each of the trials flopped, and by late 2014 all three drugs had been yanked from the research pipeline. To date, no drugs are approved to treat fragile X syndrome.

In the case of autism, too, few drugs have proven effective in trials, and several have failed due to poor design. Just two drugs, risperidone and aripiprazole, are approved by the U.S. Food and Drug Administration (FDA) for autism and are intended to relieve irritability. A few others treat attention deficit hyperactivity disorder and epilepsy, which often accompany autism. But none have passed muster for treating the condition's core social impairments or repetitive behaviors.

For example, in 1998 a preliminary report suggested that the gut hormone secretin boosts the language abilities of children with autism. But

the excitement fizzled when larger studies did not confirm those findings. Experts also proposed that antidepressants such as citalopram and fluoxetine would reduce repetitive behaviors in children with autism, but clinical trials of these ideas did not show improvements.

This series of disappointments has left families like the Stevensons with limited options. Most people with autism or fragile X rely on behavioral therapy. In desperation, others end up trying alternative treatments such as marijuana, which lack scientific support. Stevenson says she fears the high-profile failures will discourage families from participating in clinical trials.

Problems with study design and improper measures have continued to plague autism clinical trials, leading to the deaths of once-promising drugs. Many of these studies also continue to test drugs in broad groups of participants, a practice that is inappropriate for conditions as heterogeneous as autism and fragile X, says Eric London, director of the Autism Treatment Research Laboratory at the New York State Institute for Basic Research in Developmental Disabilities. “That’s the number one reason drug trials fail,” he says.

But a new way of approaching drug research has started to shift this pattern of failure and frustration. In an attempt to overhaul autism clinical trials, scientists have teamed up with partners in industry and federal agencies to create better study designs and smarter ways to cluster participants and measure their symptoms. They hope to redesign how trials are done.

TRIAL AND ERROR

In the early 2000s, a small community of researchers sought to try and curb the symptoms of fragile X syndrome by offsetting its primary mechanism.

The mutations that cause fragile X lower the supply of a protein called FMRP, and some mutations cause people to lack FMRP altogether. This releases a brake on the production of other proteins, causing them to be produced in excess at synapses, the sites where neurons interact. The surplus of these proteins disrupts neuronal connections, and is thought to underlie the learning difficulties and behavioral features of fragile X.

The researchers thought that blocking a protein called mGluR5, which counters the normal role of FMRP, might restore the balance of synaptic proteins in people with fragile X syndrome. To their delight, the idea worked — in mice. A string of studies showed that in mouse models of fragile X, mGluR5 blockers normalize synapse function and improve learning. More than 30 papers thus far have shown the benefits of mGluR5 blockers in animal models, says Elizabeth Berry-Kravis, professor of pediatrics, neurological sciences and biochemistry at Rush University in Chicago. “That’s one of the biggest bodies of basic science evidence for a mechanism ever amassed.”

Emboldened by this bulk of evidence, several drug companies launched clinical trials in people with fragile X syndrome. In 2009, a 12-person trial sponsored by Neuropharm Ltd., a U.K.-based company now owned by Autism Therapeutics, found that an mGluR5 blocker called fenobam eases oversensitivity to sounds, a common feature in people with fragile X. That same year, Novartis’ mavoglurant showed early promise for treating hyperactivity, social difficulties and repetitive behavior in seven people with fragile X who lack FMRP. And an early Roche-sponsored trial, which also began in 2009, found that the drug basimglurant, another mGluR5 blocker, seemed to alleviate anxiety.

However, as Novartis and Roche prepared to launch much larger trials to test these drugs further, Berry-Kravis, who ran studies at Rush

for both companies, grew concerned. The drugs target connections between neurons, which have the most capacity for change during early brain development, so they should work best in children. But both proposed trials were focused on adults and adolescents, which is the typical first step for large clinical trials. If these trials failed to show a benefit, the chances that the companies would launch studies in children were slim, Berry-Kravis says. (The companies ran early studies to test the drugs' safety in children but didn't include children in larger trials.)

Berry-Kravis also had reservations about how the companies planned to judge the drugs' effectiveness. The FDA requires companies to specify these so-called 'outcome measures' before a trial begins. Novartis decided to rely on the Aberrant Behavior Checklist (ABC), a questionnaire that asks parents to rate their child's problem behaviors, including irritability and hyperactivity. Some participants in an earlier mavoglurant trial had improved on the ABC, and the test had also been the measurement of choice in trials of risperidone and aripiprazole.

The FDA's approval of those two drugs made the ABC a logical choice for future trials, says Florian von Raison, therapeutic area head for Novartis, who led the company's later mavoglurant trials. Roche also included the ABC in its trials of basimglurant, though it picked an anxiety survey as its primary measure. A spokesperson from Roche declined to comment on the trials.

However, a behavioral test might not be the best measure of drugs that affect communication between brain cells, notes Berry-Kravis. The greatest benefit, if any, would probably be related to cognition and learning, she says, so outcome measures should ideally track how well participants pick up new skills or language abilities.

Walter Kaufmann, who was involved in research for both mGluR5 trials, says he had similar doubts based on his own research. He was

also collecting data for trials of arbaclofen, a drug Seaside Therapeutics had tested since 2008 for people with fragile X and, later, for those with autism. The company had chosen the ABC as its goalpost, but researchers leading the studies had begun to suspect that the measure didn't detect the behavioral changes, such as gains in language, they saw in the participants. Results from later trials for both conditions showed that the drug didn't shift participants' ABC scores any more than the placebos did. (In May 2013, Seaside announced



plans to terminate its arbaclofen studies, and the company subsequently went under.) With the mGluR5 inhibitor studies, "we were in some way repeating the same mistakes from the arbaclofen trial," says Kaufmann, director of the Center for Translational Research at the Greenwood Genetic Center in South Carolina. "It was a very unfortunate situation."

The researchers voiced their concerns about the trials' design to Novartis and Roche, but the companies wouldn't budge. Beginning in 2010, hundreds of adults and teens, including Taylor, enrolled in the trials. During each study session, the participants' parents completed the ABC and

several other questionnaires, gauging traits such as social impairment and anxiety. But none of the measures seemed to capture Taylor's extraordinary progress. Stevenson was concerned. "All those amazing things I had just seen in the last month and then I'd told the clinicians about at Emory, none of it translated to what I was putting down on this piece of paper," Stevenson says.

When the results of the trials rolled in, Stevenson's fears were confirmed. The effects of the drugs did not differ from placebo based on the ABC or any of the other behavioral measures. In the eyes of the drug companies, the trials had failed. Novartis announced plans to shut down development of mavoglurant in April 2014, and Roche shuttered its program five months later. Families like the Stevensons were left empty-handed.

LIMITING FACTORS

The failure of these trials, with their repetition of earlier mistakes, is a source of enormous frustration for scientists. "It's very possible that we could have drugs that work really well on development, and we've missed them because of the way we develop drugs," Berry-Kravis says.

As with the ABC, many measures are ill-equipped to track shifts in key autism features in response to the drug being tested, experts say. Panels of researchers convened to evaluate existing measures for this purpose and could recommend only a few — such as the Vineland Adaptive Behavior Scales, a test of social, communication and daily living skills — and even those were suggested with reservations. Other assessments used in some trials, such as the Autism Diagnostic Observation Schedule, are designed to diagnose autism or measure its overall severity, not necessarily to detect behavioral changes over time, says Gahan Pandina, senior director of neuroscience at

Janssen Research and Development. The ABC and many other tests are completed by parents, whose ratings of the effects may be swayed by their hopes.

These limitations leave researchers without the precise, sensitive measures needed to capture subtle changes in language or social interaction in response to drugs. Mavoglurant was helping Taylor, but the ABC couldn't detect it, even when it was scored using modified criteria designed to be more sensitive to fragile X symptoms, such as hyperactivity and social withdrawal.

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Given the weaknesses of traditional questionnaires, some researchers are turning to brain waves and other biological signals to identify potential responders. Many drug studies now include biomarkers such as eye tracking, electroencephalography (EEG) and levels of various molecules in the blood, says Craig Erickson, associate professor of psychiatry at Cincinnati Children's Hospital Medical Center in Ohio. Erickson is using some of these biomarkers in ongoing trials of the drug acamprostate, which is thought to block mGluR5, in people with autism or fragile X syndrome.



“We call it the bells-and-whistles approach, but I think it’s what we need to do to really discover what are these drugs doing and whom do they potentially help the most,” Erickson says.

Researchers may also need to adopt unconventional trial designs to tease out drug effects. Some experts propose N-of-1 trials, in which researchers or families carefully track the effects of a drug in a single person. This approach keeps the focus on whether the drug improves the lives of individual people, as opposed to a broad and heterogeneous group of participants, says Randall Carpenter, chief scientific officer of the Rett Syndrome Research Trust, a funding organization based in Connecticut. (Carpenter previously co-founded Seaside Therapeutics.) “As many people have said, ‘If you’ve seen one child with autism, you’ve seen one child with autism,’” he says. “We need to start treating it that way.”

FORGING FORWARD

Learning from the long string of failures, autism researchers are collaborating with drug companies and federal agencies to revamp the way clinical trials are conducted.

One team of researchers spanning multiple centers has embarked on a \$28 million initiative

to put autism measures and biomarkers through rigorous testing. In this project, called the Autism Biomarkers Consortium for Clinical Trials, the researchers plan to follow 200 children with autism for six months and carefully chart their behavior and brain functioning with a specific set of candidate biomarkers. The four-year project, which began recruiting in October, aims to provide a set of measures that can precisely detect changes in trial participants. These tools may help researchers better track how participants respond to treatments, as well as predict who is most likely to benefit, says lead researcher James McPartland, associate professor of child psychiatry and psychology at the Yale Child Study Center. As a bonus, when the project ends, its five sites will be equipped to run high-quality trials.

Taking a different approach, researchers at Janssen Research and Development are creating a web-based and mobile application for parents to record aspects of their children’s behavior, from mood to moments of social engagement. The idea is to help parents gather rich information for researchers in an easier and more comprehensive way than traditional paper-and-pencil questionnaires, says Pandina, the project’s leader. Janssen is also developing wearable sensors to track sleep and repetitive movements, much like a fitness tracker logs steps. Pandina hopes to hone these components, which are still undergoing initial

testing, into a standardized system that can be shipped off for use in clinical trials.

Another project, launched in 2012 in Europe, aims in part to pinpoint subtypes of autism. The nearly 30 million euro (about \$32 million) endeavor, called European Autism Interventions – A Multicentre Study for Developing New Medications (EU-AIMS), merges the efforts of academic researchers and industry players such as Roche and Pfizer. In one piece of the five-year project, researchers are tracking about 450 children with autism for up to two years, collecting detailed genetic, brain imaging and behavioral data, to help define meaningful subgroups of individuals.

EU-AIMS and the Autism Biomarkers Consortium are both working with government agencies such as the FDA in the hopes of finding biomarkers that the regulators are more likely to accept. This way, drug companies will have more objective measures than the questionnaires, such as the ABC, that have previously been used, McPartland says. “It will put us in a position of being proactive instead of reactive,” he says.

These efforts may bolster plans to revive some of the drugs from the failed trials: Arbaclofen is slated for new autism trials funded by the Simons Foundation (*Spectrum’s* parent organization). A new study led by researchers at the Children’s Hospital of Philadelphia aims to test arbaclofen with a measure of brain activity, as opposed to traditional questionnaires such as the ABC. The researchers plan to examine the drug’s effects using a technique called magnetoencephalography— which maps magnetic signals produced by neurons — to predict who might respond to the drug in subsequent trials.

Mavoglurant is also getting a reboot. Berry-Kravis plans to launch a new trial in June that she hopes will address the flaws of previous studies. The study, sponsored by the U.S. National Institutes of Health, will involve children, because the drug is expected to affect how the brain

establishes connections. In addition to tracking behavior with questionnaires, Berry-Kravis and her colleagues plan to observe how well the participants respond to a language-training program while taking mavoglurant or an inactive placebo for six months. They also plan to test mavoglurant’s effects on brain functioning using eye tracking and EEG.

This is the trial Berry-Kravis had envisioned from the beginning: one that may pick up on improvements in learning or behavior — a few extra words, a meaningful response — and one that might have caught the gains Stevenson had seen in her son. Taylor, now 20, is too old to participate in the new trial, but Stevenson says she wouldn’t hesitate to enroll him in future studies. She says she still believes in the power of research, and helps FRAXA raise funds for new studies. “Clinical trials are huge,” she says. “We need them.”

Taylor still uses words sparingly and fixates on unusual things, such as the compact discs that go into his beloved portable DVD player. But he likes being around other people and making them laugh with a funny look or a non sequitur. He lives at a residential school for people with disabilities on farmland a couple of hours away from his family’s home in New York City. In November, he moved into the adult house at the school, and Stevenson drove up to help him get settled. “It’s huge, because this is where he could really stay for the rest of his life,” she says.

Given all of his difficulties, Taylor may need a whole cocktail of drugs, Stevenson says, and so may many others like him. The trick will be getting enough drugs on the market to try out different combinations. In the meantime, she is open to anything that might help her son navigate his world, like his new adult program. Everyday skills, such as brushing his teeth and cooking himself dinner, are still challenging for Taylor. Learning little things like this, she says, would dramatically change his life.

by
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HOW 'SHOCK THERAPY' IS SAVING SOME CHILDREN WITH AUTISM

Given its reputation, the most shocking thing about electroconvulsive therapy might be how beneficial — and banal — it actually is.



FOR A BOY WHO NEEDS ROUTINE, THIS day is off to a bad start. It's early, just before 8 a.m., and unseasonably warm for June. Kyle, 17, has been up since 6:20 a.m., which isn't all that unusual. But already, enough has happened to throw him off balance. His mother has driven him to Johns Hopkins University in Baltimore, as she does every week. But today she is wearing makeup and fancy clothes rather than her usual exercise gear. When they get to the hospital, the hallway is not empty as it usually is, and his mother walks away from him to talk to someone else.

Kyle starts to bounce on the balls of his feet. Just a small bounce at first, but higher and faster and louder as the minutes pass. He twirls the long shoelace of his toy, a tiny teal Converse sneaker speckled with white stars. When his mother comes back to check on him, he's too agitated to even look at her. He walks away, turns his head and nips at the underside of his upper arm, then bounces some more, winding and unwinding the lace. He jiggles the handle of a door labeled 'ECT Suite,' trying to get in, but it's locked.

Finally, it's time. Melinda Walker, the nurse he adores, comes out of the room and gives him a hug. After a brief conversation with him, she says softly, "Come on in, Kyle."

And with that, Kyle's routine is restored. He goes into the room holding Walker's arm. Once the door shuts, he slips off his soft, gray shoes, as he always does, and hands his glasses to his mother. He lies down on the bed. Walker kneels by his feet, holding his hand. His mother stands behind his head, covers his eyes and whispers, "It's okay, it's okay," over and over, as an anesthesiologist Kyle knows inserts an intravenous line into his right arm. Kyle's left hand clutches his sneaker. Another nurse places an oxygen mask on his face.

Once Kyle is under, his mother leaves the room. A psychiatry resident places electrodes on Kyle's temples and a brown bite block in his mouth to protect his tongue. A nurse compresses a green bag, sending oxygen into Kyle's lungs and pushing carbon dioxide out — essentially hyperventilating him to lower his seizure threshold. Then, Irving Reti, the chief psychiatrist in the room, presses an orange button on a small machine in the corner,

sending an electric pulse of 800 milliamps at a frequency of 30 hertz into Kyle's brain for eight seconds. A few seconds later, Kyle's chin clenches, his lips quiver, and his index finger starts to vibrate. A minute in, the nurse suctioned some fluids out of Kyle's mouth. Exactly 107 seconds after it began, the seizure is over.

THE WAY WE LIVE NOW

As medical procedures go, electroconvulsive therapy (ECT) is underwhelming. Kyle's entire session, from when he lay down on the bed to when he woke up and was taken to the recovery room, lasted about 15 minutes. While the seizure lasted, he was under the effect of anesthetics and a muscle relaxant — not awake, aware or thrashing around in pain, as the movies would have you believe. In fact, the version of ECT shown to powerful effect in the 1975 film "One Flew Over the Cuckoo's Nest" hasn't been practiced in the United States or most other countries since the 1950s. Still, it's what comes to mind when most people think about ECT.

While public perception remains stuck in the past, hundreds of psychiatrists worldwide employ the treatment, most often for bipolar disorder or depression that hasn't responded to anything else. "[ECT] is practiced at every large psychiatric medical center in the United States and most around the world," says Charles Kellner, director of the ECT service at Mount Sinai Hospital in New York. An estimated 100,000 people in the U.S. and more than a million people worldwide receive ECT each year, he says. "Overall in history, millions and millions of people have benefited from it."

There are lingering concerns about the therapy's side effects — its ability to produce short- and long-term memory loss, in particular. But ECT's

champions say that in cases where people are depressed enough to be suicidal or otherwise desperately ill, the benefits far outweigh the risks.

In the past few years, some psychiatrists have stumbled upon a new purpose for the therapy: calming the brains of children with autism who, like Kyle, would otherwise pinch, bite, hit and harm themselves, perhaps fatally. The numbers are small, no more than 50 children treated in the U.S. in any given year, although no one knows the exact figure. But for this group of children, who are driven by uncontrollable, unrelenting impulses to hurt themselves, ECT grants a reprieve. "For some of these children who have tried every other treatment modality," says Kellner, "ECT can be dramatically helpful and sometimes life-saving."

HARD TIMES

There was a time when Kyle's mother, Alison, thought he would not live to adulthood.

Kyle was diagnosed with autism when he was just 15 months old. His identical twin, Jake, also has autism, but as their older sister, Callie, likes to say, "Jake has a little bit of autism and Kyle has a lot."

When he was around 8, Kyle began hurting himself. It was never clear to his parents what the trigger was, but it seemed to happen hundreds of times a day, without a clear cause or conclusion, and sent him into paroxysms of crying. Videos of Kyle from that time are difficult to watch. They show a boy who seems compelled by forces he cannot control to smack his face, rapidly and repeatedly, turning his cheek a deep crimson. (Alison says, in a tone that suggests she's still coming to terms with it, that he sometimes hit himself more than 100 times an hour.) Kyle also tore up his arms with his teeth, dented the wall and pounded

“
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coma right now.**
”

ALISON

the concrete floor with his head, and pinched his thighs and abdomen hard enough to draw blood.

Kyle was lucky enough to find a spot in a private school with an autism program, but “he was always unhappy and never, ever available to learn anything,” says Alison. “He’d go to school and all they’d basically do is make sure he didn’t hit himself.”

At the time, Kyle weighed only about 35 pounds, a weight low enough to be categorized as ‘failure to thrive.’ Desperate for help, his parents spent hundreds of thousands of dollars on a laundry list of therapies, from reputable behavioral interventions to quack treatments they read about on the internet. “We did just about everything you could possibly do. We flew all over the country for doctors that specialize in autism and other things,” says Alison. None of it helped.

When Kyle was 11, he was admitted to the Neurobehavioral Unit at the Kennedy Krieger Institute in Baltimore, a long-term in-patient facility for children with intractable behavioral problems. He was at the unit for nine months,

but the doctors there had no success. When he was discharged, he had a floor mat to cushion the blows when he hammered his head on the ground, splints on his arms to prevent him from hitting his face, and thick tights to protect his thighs and abdomen from his pinching.

The gear created its own problems. Kyle is nonverbal and communicates using sign language, but the arm splints made that difficult to do. The splints, the socks he had to wear underneath and the tights all had to be removed, and his limbs rubbed, every two to three hours to restore his circulation and prevent sores and swelling. Worst of all, none of it eased the misery that compelled him to hurt himself in the first place.

It was around then that Alison, a yoga teacher, struck up a rare personal conversation about her son’s troubles with a client. As it turned out, the client knew of a solution that she had heard did wonders for children like Kyle: ECT.

Alison is still angry that not a single doctor she met had brought up ECT to her as an option for Kyle. Even after she heard about it and discussed it with Lee Wachtel, medical director of the Neurobehavioral Unit, there was no easy path to ECT. Wachtel referred the family to Kellner, whose office in Manhattan was a full four-and-a-half-hour drive from their home in suburban Maryland. Kyle needed three treatments a week — typical for ECT’s acute phase — for the first few months, followed by maintenance therapy every 7 to 10 days.

Undaunted, Alison put in place an exhausting schedule of long-distance drives and handoffs of the other two children with her husband twice, sometimes three times, a week. She kept this up for 17 months. Wachtel then connected her to a psychiatrist in Philadelphia. His clinic was closer, two and a half hours away. Alison and Kyle made this drive to Philadelphia once a week for two and a half years before Johns Hopkins’ Reti agreed to treat Kyle. Their trip now is an easy hour each way.

Altogether, Kyle has been receiving ECT for about five years. In that time, Alison says, she has worn down three cars and years off her life. From her perspective, every minute has been worth it.

“Once Kyle’s treatment started, a whole new person emerged,” she says. “As time went on, he just kept on getting better and better.” He has learned to sign new words. He is a healthy 145 pounds for his 5-foot-8-inch height. At school, he delivers mail and newspapers to the staff, and helps with the recycling. He has done so well, in fact, that his teachers are starting him on a four-hour shift maintaining an off-site park once a week. He goes hiking, bowling, swimming or simply to a restaurant with his family. In May, he was invited to attend a school dance for the first time ever. And he hurts himself just a few times a day, if at all. He’s at his best the first few days after a treatment: calm, present and interactive. “I think that’s huge, because people think you’re going to get a zombie [after ECT], and you don’t,” says Alison. But as the days go on, the treatment’s effects seem to wear off, and he becomes increasingly agitated — until his next session.

It’s entirely possible that Kyle will need to keep this up for the rest of his life — and Alison is more than okay with that. “Well, what is the alternative in my son’s case?” she asks. Without ECT, she says, “he’d be dead right now; he’d be in a coma right now; he’d have a detached retina right now. So in my opinion, having him alive and enjoying his life is way better than anything anybody else can say.”

A BEND IN THE RIVER

The version of ECT that debuted in 1937 is every bit deserving of its shocking reputation. Although the idea of inducing seizures, rather than treating

them, seems odd and counterintuitive, a Hungarian psychiatrist called Ladislas Joseph von Meduna hit upon it as a possible treatment for schizophrenia. Beginning in January 1934, von Meduna first used camphor and then a drug called metrazol to induce seizures in people with schizophrenia. His remarkable success — he claimed that 95 percent of individuals with acute schizophrenia recovered — inspired Italian researchers Ugo Cerletti and Lucio Bini three years later to pursue electric shock as a safer and more effective way to induce seizures.

In those early years, the patients were neither anesthetized nor sedated and their *grand mal* seizures sometimes broke their bones. But by the mid-1950s, the routine use of general anesthesia and muscle relaxants had made ECT much safer. And by the 1970s, doctors began triggering the seizure with a brief square-wave electric pulse rather than the harsher sine wave currents that emerge from an electrical socket.

At the same time, antipathy to ECT rose apace. During World War II, many psychiatrists in the U.S. were acolytes of Sigmund Freud and held up psychotherapy and psychoanalysis as the gold standard treatments for psychiatric illness. They published statements opposing ECT, which they said damages the brain. Among the general public, there were waves of protest against ECT in general and its use in children in particular. “It just became inconceivable that one would pump electricity into the developing child’s brain,” says Edward Shorter, Jason A. Hannah Professor of the History of Medicine at the University of Toronto. “ECT in children became very badly stigmatized.”

Part of ECT’s image problem is that nobody knows how it works: The idea that shocking the brain would somehow restore its health seems so profoundly paradoxical as to be disturbing. The stigma against it only intensified with “One Flew Over the Cuckoo’s Nest.” The scene in which Jack

Nicholson is forcibly held down and zapped with electricity as he screams became etched in the minds of everyone who saw it. ECT became second only to abortion in its vilified public image.

At least partly in response, several states enacted laws around the procedure — mandating the consent of two psychiatrists, or forbidding it altogether in children under 14 or 16. “As though it was the role of the state legislators to practice medicine and to protect the children from psychiatrists,” says Shorter.

In the late 1990s, after the hubbub over antidepressants had subsided, there was a resurgence in interest in ECT to treat severe depression and other conditions. But the damage to its reputation had endured. It wasn’t until 2008 that Wachtel, along with Reti and others, reported that ECT can treat self-injury associated with autism. The case study describes a young woman called “J” who had autism and ‘psychomotor retardation,’ meaning she was slow-moving — “except that sometimes she would pound herself into oblivion,” says Wachtel.

J’s slow movements were the manifestation of catatonia, which can overlie many conditions across the psychiatric spectrum, from deep depression to tic disorders such as Tourette syndrome. But the classic idea of a mute, motionless person is just one side of catatonia; the flip side is ‘psychomotor agitation’ — repetitive, uncontrolled and purposeless movements, as if driven by a motor gone awry.

What Wachtel and other experts say now is that the self-injury seen in some people with autism is an expression of catatonia’s agitated side. (Some children can show both aspects of catatonia at once: In one video of Kyle, one of his arms is wooden like a tree branch, and the other is repeatedly whacking his head.)

The experts owe this theory to Max Fink, a psychiatrist who has, formally or informally,

served as a mentor to most of them. Fink, 93, lives in Nissequogue, New York, in a rambling old house by the water, with exactly the kind of ornate rugs and book-lined shelves you would expect to see in a learned psychiatrist’s home. Over the course of an hours-long conversation, Fink details the long and troubled history of ECT, replete with dates, occasionally shuffling in his bent gait to his formidable library to bring out a relevant manuscript or a book.

Fink is the world’s leading expert on catatonia and ECT, and many of his ideas have become mainstream. Psychiatric diagnostic manuals now describe both kinds of catatonia, as well as the idea that catatonia can accompany any number of other conditions. Case studies suggest that both sides of catatonia are exquisitely responsive to ECT. If the therapy — which Fink prefers to call “induced seizures” — helps some children with autism, he says, it’s because it relieves their catatonic self-injurious behaviors.

One of Fink’s protégées, a Belgian researcher called Dirk Dhossche, deserves the credit for solidifying this link between autism and catatonia. Dhossche trained with Fink at Stony Brook University in the 1990s. “At that time, there was very little talk about catatonia in children; we didn’t even talk about autism much, for that matter,” recalls Dhossche. When working in the Netherlands, he had seen two adolescents, one with autism and the other with Prader-Willi syndrome, an autism-related condition. Both boys had catatonia and responded to lorazepam — a benzodiazepine that is the standard first-line therapy for catatonia. (In fact, ‘the lorazepam challenge test,’ or response to the drug, has come to be known as proof of catatonia.) Dhossche set out to search the literature for more reports of children with catatonia and found about 30.

In 2001, Dhossche moved to the University of Mississippi, where he is now medical director of

the child psychiatry inpatient unit. Shortly after his move, he saw a 9-year-old boy who had for months stayed mute and bedridden, and was not eating or drinking — all criteria for catatonia. After exhausting various treatment options, including benzodiazepines, Dhossche suggested using ECT. The response was nothing short of “spectacular,” Dhossche says. “This boy started speaking again, eating again, walking again.”

Even though the boy didn’t have autism, some of his characteristics even prior to the catatonia reminded Dhossche of autism. “This was my first realization that actually, autism and catatonia, they seem to overlap at some point,” he says. Repetition is a hallmark of catatonia; by that token, the echolalic speech and repetitive movements — including self-injurious behavior — characteristic of autism could be seen as catatonic. Dhossche’s publications on this topic prompted Wachtel to contact him, and eventually led to the 2008 case report. Since that success, Wachtel has referred about 20 children with autism who seemed to meet the criteria for catatonia to clinics that offer ECT, including the one at Johns Hopkins. Like Kyle, these children were a danger to themselves. Like him, they are doing well, some still receiving ECT as maintenance therapy, others on lithium or antipsychotic drugs to keep their self-injury in check.

“The reward of diagnosing catatonia is that it’s treatable,” says Dhossche. “Not with the easiest type of treatment, not the most popular one, but that’s just unfortunate at this point.”

Because of his publications on the topic, parents come to Dhossche from as far away as California or Texas — two states that have banned ECT in children under a certain age. But the numbers are still vanishingly small. In total, he says, he has treated perhaps 10 children with autism.

One thing Dhossche has noticed among the children he has treated is that the catatonia seems

to appear after a stressful event of some sort. One 14-year-old boy with autism from Texas, for example, developed unusual finger movements and grimacing expressions after a particularly severe episode of bullying at his school. “It often starts with an incident, with an event, and then it gets worse,” says Dhossche.

THINGS FALL APART

Doug DiPrisco was diagnosed with autism in 1993, when he was 3. He had some speech, reading and math abilities, and could do many things for himself. But in November 2009, his parents went to Europe without him to visit his brother, Greg, at college. In retrospect, they suspect Doug thought they were never coming back, perhaps creating the traumatic trigger Dhossche describes. Doug became catatonic — moving slowly and barely talking — although his parents wouldn’t know to call it that for a while.

By 2011, the catatonia was much worse, recalls Lori DiPrisco, Doug’s mother. “Every day was torture, from the minute he woke up until the minute he went to bed at night.” Any change from one position to another — getting out of the car, for instance — would take Doug ages. He would pose — the official term is ‘posturing’ — in strange ways, standing for 20 minutes like an airplane poised to fly, for example. He stopped talking, wasn’t eating or drinking and lost 18 pounds in two months. He had been toilet-trained since age 3, so when he began wetting himself, it pushed his parents to take him to the emergency room. The doctors there had no answers, but by chance, they gave Doug lorazepam to keep him still for the CT scan.

“When they gave him that injection, it was like a miracle, he stopped all the [unusual] movements,” recalls Dom DiPrisco, Doug’s father. That



Gentle soul: Kyle, 17, used to hit, pinch and bite himself hundreds of times a day.

little tidbit became important later on when, after many futile visits to other psychiatrists, Doug's parents took him to see Wachtel. Even before the visit, Wachtel suspected that Doug had catatonia after seeing his home videos. In one, Doug tries to eat, but his arm meanders to somewhere near his mouth and then flails about without making contact, all with excruciating slowness — as if he is moving through molasses or performing an extreme version of tai chi. Wachtel told the DiPriscos about the lorazepam challenge, and about catatonia.

She prescribed the drug for him again. He responded well, as he had before, but like most

people, became tolerant to the drug. Over the next few years, he reached 19 milligrams a day, close to the maximum dose Wachtel was comfortable prescribing.

The first time Wachtel broached the possibility of ECT, Doug's parents were horrified. "We said no way, we're not doing that," recalls Dom DiPrisco. "It's not marketed well, let's say that."

"We didn't know what it would do to [Doug's] brain," he adds. "Would it create many more problems than he has?"

Then, last year, Doug seemed to stop responding to the highest dose of lorazepam. One horrible day in November, Lori DiPrisco says, it took Doug

about an hour and a half to walk from the kitchen counter to the dining table. His parents began considering ECT. His mother read “Each Day I Like It Better,” a book by writer Amy Lutz about the remarkable response her son with autism had to the therapy. Parents and psychiatrists praise the book as the definitive introduction to the topic. It convinced the DiPriscos to give it a try.

Doug had seven ECT sessions over three weeks at NewYork-Presbyterian/Columbia University Medical Center, but his parents did not like the way Doug was treated there. They halted Doug’s therapy. In March, they began anew at Long Island Jewish Medical Center. “It was like going from the worst-case scenario to the best-case scenario,” says Dom DiPrisco. Doug was calm, happy, talking. The posturing became almost unnoticeable. Doug now gets ECT every two weeks, and lithium in between. And he is back to being able to eat, talk and be his cheerful self.

IN SEARCH OF LOST TIME

Most people, including mental health professionals, would not have connected either Kyle’s self-injury or Doug’s classic catatonia with ECT. Psychiatrists who administer the therapy typically work with older people who are severely depressed. In the past few years, psychiatrists’ interest in the approach has been rising. Wachtel and others have regularly led well-attended sessions on ECT at psychiatric conferences for the past six years. Still, for many doctors, the stigma around the therapy is a tough mental hurdle to overcome — especially when it comes to children, and even more so those with developmental disabilities. “It recalls connotations of torture and I guess brain injury,” says Dhossche. “But in all the cases that we’ve treated, we’ve never seen it.”

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CHARLES KELLNER

One of the major side effects reported for ECT is memory loss. But psychiatrists and families who have experience with the therapy say the memory loss, when it occurs, is minor and reversible. Even in the rare cases where it is significant, they say, it is infinitely better than the alternative.

“I have one patient who has had over 700 ECT [sessions] over the past eight years, maybe. If you ask him now what he had for breakfast, he cannot tell you,” says Wachtel. “But on the other hand, without ECT he would try to remove his eyeballs from his head.”

Still, no one knows whether and how much of an issue memory loss might be for children with autism who might receive maintenance therapy for years. Reti has published two case studies of individuals with autism or intellectual disability who have been treated with ECT for years, showing that cognitive testing did not show any memory loss or other damage. But those data are limited, says Matthew Siegel, director of the Autism & Developmental Disorders Inpatient Research Collaborative in Maine. “I think it speaks to the need to do a rigorous study of this,” Siegel says. “Getting that kind of study funded by the federal government would be a challenge, but it’s necessary.”

Even for psychiatrists who are convinced that ECT's benefits outweigh its risks, setting up a practice is no easy task. "There is resistance at every level — within the institution, outside of the institution, from colleagues, from other professionals," says Neera Ghaziuddin, associate professor of psychiatry at the University of Michigan in Ann Arbor. "They have some very exaggerated and dramatic idea of what might be going on in the treatment."

Public reactions are worse still. There are demonstrations against ECT at meetings of the American Psychiatric Association and an online "Hall of Shame" listing practitioners' names (rumored to be set up by the Church of Scientology, which openly opposes ECT). Articles in the media inevitably provoke intense vitriol from commenters. "It's just unbelievable, the amount of hate that's out there on the internet," says Kellner, who has borne more than his share of nasty comments.

Families are only too familiar with the unforgiving censure of the internet. Alison asked that her last name not be published because the comments on a prior article left her feeling attacked and unsafe. But she and other parents are adamant that people should not judge them for their choices.

"They have no idea what it's like to have a child like mine and have lived through that and think about the alternatives, which would be institutionalization, coma or death," Alison says. "Those were our three choices; we had no other choices." The DiPriscos echo that sentiment: "I'd like them to spend a day with Douglas the way he was before," says Dom DiPrisco. "It was no quality of life at all."

Many people with autism may hurt themselves, but often they are acting out for a particular goal. For example, a child might have learned that if he punches himself in the face, his mother will stop insisting that he finish his schoolwork,

and offer him a treat or a hug instead. But self-injury in children like Kyle is usually not intentional. "There's nothing manipulative about it, there's nothing deliberate about it," says Reti.

Behavioral therapists spend a great deal of time making sure that a child's self-injury has no purpose. Even then, most children receive behavioral therapy and try at least two drugs before a practitioner will mention ECT. There may be some fallout from waiting so long. Ghaziuddin says that when she first started offering ECT for young people, "we were treating people who had failed everything." But the longer someone is sick, the less likely that they will recover fully, she says, so she now recommends ECT sooner than she used to.

In a way, the number of deterrents for ECT may be a good thing. "It's a problem for the kids who need it, but it's good in only one way, which is that it causes people to really pause and consider if this is the appropriate treatment — so you don't have ECT clinics opening on back roads like you have chelation clinics," says Siegel.

Wachtel says there are fewer than 15 ECT clinics in the U.S. to which she would refer children on the spectrum. About half of the children with autism who receive ECT begin in Wachtel's care. Kennedy Krieger does not offer ECT, so she refers them to clinics across the country. All of the clinicians know each other, and a phone call to one is quickly relayed to the others. They're each careful to clarify, repeatedly, that ECT is in no way a treatment for autism per se, but rather for a specific set of self-injurious or catatonic behaviors that some children on the spectrum display. Kellner puts it bluntly: "This is not for kids with moderate autism who are talking but have difficulty socializing; this is for kids who are going to be dead if they're not restrained."

Some researchers are focused on learning more about how ECT works — and based on that, developing more palatable alternatives. What



Better days: Kyle's mother, Alison, says ECT has been enormously beneficial for him.

scientists know so far is that in the long term, ECT stimulates the birth and growth of neurons. In the short term, it floods the brain with neurotransmitters — in particular, GABA, the chemical messenger that tamps down brain activity. This is the same effect that taking an antidepressant or benzodiazepine might have, but much more rapid and powerful. Perhaps, one theory goes, triggering a seizure forces the brain to release a torrent of GABA, which in turn calms other aberrant brain activity.

“If you take a benzodiazepine and imagine that as a drip of GABA, then ECT would be like turning the faucet on full force,” says Wachtel.

Reti has led about 10,000 ECT treatments over the past decade, although Kyle is one of only

three children with autism he treats. He is trying to develop a stimulator that could be implanted in the brain and switched on as needed. For people like Kyle, who might need maintenance therapy for years, perhaps their lifetime, this would be a welcome alternative.

THE SUN ALSO RISES

It's the evening before Kyle's first ECT session in nine days. This week has been more challenging than usual, because Kyle was at a sleepaway camp for children with disabilities — a big break in his routine. Alison scheduled one session for the

day before she dropped him off, and one for the day after she picked him up. Kyle is restless. He's humming — the sound is more like gargling, really — and bouncing loudly, 1, 2, 19 times, as his mother makes him a turkey sandwich.

"Look at me," she says. "It's time to stop. I want you to go down and eat it." Bounce, bounce, bounce, bounce. "Get your water." Bounce, bounce. "I love you." Bounce, bounce, bounce.

Kyle goes downstairs with his aide, Brittany. The television is on, but he lies facedown on the couch, playing with another small sneaker, this one light gray with bright yellow smiley faces. When his mother comes downstairs, he gets up, signing that he wants to go out. He smacks himself, hard, on his left cheek, which is still a purplish brown — a permanent relic of his years of self-abuse, along with the keloids and scars on his limbs.

"Kyle, Kyle, Kyle," Brittany says, moving to touch and calm him. She pours out a small plastic container of dry pasta and makes him count the penne: The tedium of the task is supposed to deter him from hitting himself. Kyle completes it, but a couple of minutes later, he hits himself again. Whack. Bounce, bounce, bounce. Whack, whack. Bounce, bounce, bounce, bounce, bounce. Whack, whack. Bounce. Whack. "He hasn't been O-U-T in the C-A-R today, that's why," Alison says.

Eventually, Alison and Brittany get Kyle outside and into the car. He loves to go on drives, and the park is among his favorite destinations. Kyle swings for a long stretch, looking off into the distance, his adult-sized body incongruous in the little children's section. When he stops swinging, he hits himself again. Whack, whack, whack.

Alison and Brittany are unfazed by his agitation. "I just know that when it's been over a week [after ECT], when he's not been in his regular environment, that this is to be expected. I don't get discouraged because I know it's not permanent,"

Alison says. "[The ECT tomorrow] is going to make a big difference."

The next morning, at Johns Hopkins, Kyle still seems agitated. But he doesn't hit himself, only bounces restlessly in the hallway as he waits for his session to start. Once the seizure ends and the oxygen mask is off his face, a nurse takes him to the recovery room, where he dozes for half an hour. As he stirs, Alison stands by his side, whispering, "Mommy's here." She hands him his glasses. Nurse Walker helps Kyle sit up. She flaps the back of his sweat-soaked shirt, saying, "Always got to cool the back off." Alison slips his shoes back on his feet.

A few minutes later, Kyle stands up and holds his mother's hand. "Say goodbye, Kyle," she says, and he does, turning to look at Walker, and waving. He and Alison walk down the hallway. Kyle runs his hand along the wall. Alison stops once and kisses Kyle on his head. He touches his nose to hers. Then he spins, once, and continues walking, holding her hand the whole way.

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THE PIONEERS

Meet the backyard
marijuana growers and
home chemists who
are rushing in where
scientists fear to tread.

by

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SHAWN RECORDS

HOW PARENTS ARE EXPERIMENTING WITH MARIJUANA FOR AUTISM



KARLEE LIVES IN A QUIET TOWN IN southeastern Washington. Last year, she put in a new cedar fence around her home. The fence is 6 feet tall, and behind it Karlee grows tomatoes, zucchini and marijuana. As it matures, the sweet smell of pot starts to waft into the neighborhood. This is Karlee’s cue that it’s time to pick the leaves and have them processed into oils. She gives these to her 13-year-old son, who has autism. (Karlee requested that her last name not be used, to protect her son’s privacy.)

Spencer, her boy, was having increasingly aggressive tantrums and was becoming harder to control. By the age of 11, he was lashing out with “run-by slappings” of his sisters, and threatening to take his own life and his parents’. Terrified that his aggression might force the family to consider other housing options, Karlee turned to marijuana two years ago, cast as a miracle cure in an internet success story she had read. She suspected the story was “baloney,” but she was desperate. She soon became a believer: A twice-daily dose of marijuana dramatically alleviated Spencer’s anxiety within a week. He stopped hitting his sisters and, earlier this year, shocked his mother by asking to attend a middle-school dance. Karlee watched in

the corner, crying, as he danced for the first time with a girl.

Meanwhile, neurologist Gregory Barnes keeps his marijuana derivative inside a lockbox, stored inside a biometric safe, inside a locked pharmacy. This year, Barnes plans to start the first clinical trial to test the effect of cannabidivarin (CBDV) on children who have both autism and epilepsy. (CBDV is one of marijuana’s many active ingredients.) In the nearly two years Barnes has been trying to get his trial off the ground, agents from the U.S. Drug Enforcement Agency (DEA) have paid two visits to inspect his facility — and he’s expecting a third.

Medical marijuana is legal in many states, including Washington, but the federal government still bans its use. The DEA ranks all compounds extracted from marijuana as Schedule 1 drugs — meaning they have “no accepted medical use and high potential for abuse.” CBDV and the closely related cannabidiol (CBD) do not produce the high associated with marijuana. Still, their Schedule 1 status put them in the same league as heroin and LSD, a more dangerous one than cocaine or oxycodone.

In 2011, the then-governors of Rhode Island and Washington petitioned the DEA to reclassify

medical marijuana as a Schedule 2 drug. The change would have enabled states to regulate safe access to medical marijuana for those who need it without violating federal law. But in August, the DEA reaffirmed its stance, based on a recommendation by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse. The DEA did relax some rules, however, inviting universities to apply to grow marijuana for “research purposes.”

These stark contrasts leave the state of marijuana research for autism in a bizarre state of flux: Marijuana is simultaneously legal and illegal, easy to obtain and heavily restricted, a miracle cure and a completely untested treatment navigating the first rounds of clinical trials.

At the crux of the contradictions lie important questions: Is marijuana a legitimate treatment for autism? And is it safe to give to children? Many families feel they already know the answers. But researchers say these questions need to be addressed in a controlled, rigorous way.

“I’m OK with approving these things and making them accessible for people with treatment-resistant problems,” says Orrin Devinsky, a neurologist at New York University who is studying the effect of CBD on epilepsy. “By the same token, we as a political, medical and scientific society should be moving for high-quality scientific data. If it’s safe and effective, people should be able to use their prescription plans and get it; if it’s dangerous or if it’s ineffective, nobody should get access to it.”

HOME COOKING

California became the first U.S. state to legalize medical marijuana, mainly for adults with severe chronic illness such as cancer or AIDS. Since

California’s decision in 1996, 24 states and the District of Columbia (Washington, D.C.) have followed, and since 2012, four states and Washington, D.C., have legalized recreational use of the drug. So far, only Pennsylvania specifically permits medical marijuana use for autism, but in the past few years, parents of children with epilepsy across the nation have adopted this approach.

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pioneers in this.
We’re the newbies.**
”

Much of this enthusiasm stemmed from the widespread media coverage in 2013 of Charlotte’s Web, a marijuana strain with high levels of CBD. The strain reportedly helped its namesake, Charlotte — a young girl with a form of epilepsy called Dravet syndrome — go from having hundreds of seizures a week to being practically seizure-free. Perhaps because epilepsy frequently accompanies autism, parents soon began giving marijuana to their children with autism, and reporting great successes. Medical societies warned that these claims were only anecdotal. But to some parents, marijuana was no worse than the conventional drugs that didn’t work and triggered terrible side effects.

Around that time, Karlee was at her wits’ end. A visit to doctors had yielded only a prescription for Risperdal (risperidone), which Spencer, then 11,

had tried before. That and similar drugs had “put a wet blanket” over her son and had done little to help him. Spencer tried behavioral therapy, but driving to the closest clinic took Karlee more than three hours each way. So after reading the article about marijuana, she drove to Seattle, nearly 300 miles away, in search of a doctor willing to prescribe it for a child. Even though Washington’s approved indications for marijuana use don’t include autism, it does allow use for severe gastrointestinal issues, which Spencer has in abundance.

Giving her son marijuana was not an easy decision for Karlee. “Growing up, it was: ‘Drugs are bad, drugs are bad, marijuana is terrible, it’s a gateway drug for heroin and meth and so on,’” she says. “I still have that wrestle in my head thinking, ‘Oh my gosh, you’re doing it to get him high.’” Ultimately, she says, she realized that if she didn’t give him marijuana, she’d end up giving him something even more dangerous.

With her prescription in hand, Karlee was able to visit a for-profit medical dispensary that sells marijuana oils and tinctures — marijuana extracts steeped in alcohol. At these dispensaries, customers are greeted by a bewildering variety of choices. Marijuana includes a mix of hundreds of bioactive compounds, and plant breeders have created hundreds of strains, each of which harbors a different proportion of these chemicals.

Tetrahydrocannabinol (THC), the chemical that creates the high, is the best-known compound. It acts on the CB₁ receptor in brain cells that regulate pain, mood and appetite. By contrast, CBD does not lead to a high and has been well studied in animal models for its anti-seizure properties. Unlike THC, it binds to multiple receptors, but it’s unclear which of these pathways mediates its effect on seizures.

Families must choose a strain based mainly on the dispensaries’ advice or on internet lore — a fact that makes some researchers extremely

nervous. “I worry a lot about a physician sending a child, or a child’s parents, to a dispensary to have a conversation about what type and dose and route of administration of cannabis should be given to a kid,” says Ryan Vandrey, associate professor of behavioral sciences at Johns Hopkins University in Baltimore. “To me, that’s completely backwards,” he says. Vandrey studies the effects of marijuana exposure on adults.

Spencer responds best to tinctures that contain roughly a 3-to-5 ratio of THC to CBD, Karlee says. She continually experiments with this ratio, and when and how often to dose, to find the most effective treatment. As Spencer has grown, she has needed to give him more and more of the compounds. To counteract his rising tolerance, she sometimes tapers the drug concentration down for a week, then raises it back up. She has also used a high-THC oil at night to help Spencer sleep.

Meanwhile, there is no guarantee that what a dispensary says is in a product is really there. Plants, tinctures or oils obtained from dispensaries may also contain pesticides or other potentially dangerous byproducts. The FDA issued six warning letters in 2015 and eight in 2016 to companies that market CBD products, saying the products did not contain the CBD levels the companies claimed, and some had none at all. Karlee has a workaround for this problem: She sends her homegrown oils to a private laboratory to confirm the levels of CBD and THC.

This option is not available to Leslie Johnson, who lives in New Jersey and gives medical marijuana to her adult son, John, to help him cope with severe epilepsy and autism. Devinsky prescribed marijuana for Johnson’s son in January 2015 after a seizure medication lowered John’s white blood cell count to a dangerous point. But New Jersey permits dispensaries to sell only the dried plant, lozenges and topical treatments. So Johnson has to figure out how to turn the plant into something

more appropriate than a joint to give to her son. “I have no idea why New Jersey came up with their policy,” says Devinsky.

Without official guidance, parents in New Jersey form informal support groups, sharing recipes designed to enhance CBD levels in a plant extract while minimizing the THC. Johnson, who says she dislikes even the smell of marijuana, was at first completely overwhelmed. “Here I am, a goody two-shoes, I never tried it before myself,” she says. But nearly two years later, she is an expert — receiving as many as three calls a week for her marijuana recipe. Her method involves a process called ‘decarbing,’ which bakes \$500 worth of the plant in turkey roasting bags, supposedly bringing the CBD to the surface. She then uses a MagicalButter machine — a \$200 contraption that infuses herbs into butter or, in Johnson’s case, marijuana leaves into a mixture of soy lecithin granules and organic coconut oil.

“You’re basically searching for as close to a version of Charlotte’s Web, which is out in Colorado, that has the highest CBD,” Johnson says. But she can’t confirm that her home chemistry experiment enhances CBD at the expense of THC: There are no testing labs available to parents in New Jersey, and it is illegal to ship marijuana oils across state lines.

Still, the drug has worked better than she expected, Johnson says. Her son became calmer and more content after the first 1-milliliter dose. During the year and a half he has used the drug, Johnson has lowered the dosage of his seizure medications significantly. She says he has had, at most, three severe seizures, compared with at least one per month before. In the past few months, she has been experimenting with strains that have slightly more THC, which she says seems to have the best calming effect. “You do anything you can for your son, if it’s going to help him,” she says. “Mothers like me, we consider ourselves pioneers in this. We’re the newbies.”

BAD VIBES

Marijuana’s effects on a child who takes it regularly are unknown. Many parents assume the drug is safe simply because they have taken it themselves, but occasional use by a young adult is not the same as a child taking it daily for years. In fact, little is known about how the chemicals it contains work in the brain at all. In a 2013 study, researchers in Italy reported that blocking the CB1 receptor alleviates seizures as well as memory problems in a mouse model of fragile X syndrome, an autism-related condition.

This finding suggests that CBD, which may also block the CB1 receptor, would be beneficial for treating autism. THC — which activates the receptor — might exacerbate the condition, says lead researcher Andrés Ozaita Mintegui, at the Universitat Pompeu Fabra in Barcelona, Spain. On the other hand, a study last year found that drugs that activate the endocannabinoid system, as THC does, improve learning and memory in fragile X mice. To complicate matters further, a study published in April found that CBD might turn into THC when it comes into contact with stomach acids.

Most studies in people have looked at the effects of long-term marijuana use as a recreational drug, and raise some concerns. A 2012 study showed that 19 recreational marijuana users who began smoking before age 16 had problems with cognitive function. A 2014 study by the same team found changes in brain connectivity that tracked with impulsiveness in 25 regular marijuana smokers. Another study followed more than 1,000 people from birth to 38 years of age and found that those who used marijuana regularly as adolescents showed a decline in their intelligence quotients in adulthood.

These kinds of data may — or may not — apply to medical uses of marijuana, says Vandrey. “You’re not going to have a 5-year-old autistic kid smoking

a 5-inch blunt, having a competition with his buddies to see how much he can smoke,” he says. “So the consequences that we associate with cannabis right now — addiction, brain changes, vomiting, paranoia, panic attacks, acute psychosis — all of that kind of stuff may be completely irrelevant to the 5-year-old with autism. But we have no idea.”

Sometimes, the effects are unpredictable even from one month to the next. Shafali Jeste, a child neurologist at the University of California, Los Angeles (UCLA), treats a 13-year-old boy with autism who was given marijuana by his family to help him sleep. It’s not clear exactly what happened, but the parents were trying different plant strains, and at some point the concentration of THC may have been much lower than usual, plunging the boy into withdrawal, Jeste says. The boy, who is nonverbal, ended up in the emergency room seemingly in the throes of severe hallucinations. He needed to be physically restrained and sedated with drugs. Despite this scare, the parents resumed treating the boy with marijuana.

Jeste does not endorse the use of marijuana, but makes sure she knows if children are taking it, so she can try to track its effects with other medications she prescribes. She says she understands parents’ desperate search for something that might work. These parents urgently need research that can guide them through their choices, she says. “It’s our job to do the trials. I’m not going to say, ‘Oh there’s no evidence, I’m just going to pooh-pooh the whole thing,’” she says. “We need to do studies.”

INTO THE WEEDS

Some studies are underway for treating epilepsy with marijuana. Shaun Hussain, a pediatric neurologist at UCLA, studies a rare form of epilepsy called infantile spasms that halts a child’s



The harvest: Karlee regularly gives marijuana oils to her 13-year-old son with autism.

development. One of the best conventional treatments for infantile spasms costs \$150,000 per course and hampers children’s immune systems so severely that even an ordinary ear infection can kill them.

Over the past few years, many families that Hussain treats instead began turning to marijuana. Some families saw no benefit, but others reported that their children went from having hundreds of seizures a day to being seizure-free, Hussain says. “I thought, ‘This is wishful thinking, these are anecdotal seizures, they are misleading themselves,’” he says. So he performed electroencephalograms, which detect the erratic brain activity that occurs during seizures, and confirmed these reports. He was also impressed by a survey of parents who treat their children’s epilepsy with marijuana, which suggested that the drug could be effective.

Intrigued by this evidence, in 2014, Hussain launched his ‘upside-down’ clinical trial — in which research follows widespread use rather than the other way around. He did an online survey of the parents of 117 children who were

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ORRIN DEVINSKY

trying high-CBD marijuana strains to curb their child's epilepsy. About 85 percent of the parents said their child had fewer seizures after taking the drug, and 14 percent said their child had become seizure-free. Hussain emphasizes that the survey is uncontrolled, prone to placebo effects and bias. But he was encouraged enough by the results that he decided to partner with Insys Therapeutics, a pharmaceutical company based in Chandler, Arizona, that makes a synthetic form of CBD. He is recruiting children with infantile spasms to test the product.

Devinsky was similarly thrust into the world of medical marijuana by families, and was also initially skeptical. But after seeing hints of the drug's positive effects, he says, he felt the need to follow up these reports with actual research. He partnered with GW Pharmaceuticals, which manufactures Sativex, a compound containing both CBD and THC. Sativex is approved for multiple sclerosis tremor in many nations, but not in the United States; GW is based in the United Kingdom.

Devinsky and his colleagues tested a new CBD compound made by GW in nearly 200 children and adults across 11 epilepsy centers in the U.S. The participants all had severe childhood epilepsy that had not responded to conventional treatment. By the end of the trial, 20 of the participants were free of seizures. But 20 participants had severe side effects, such as diarrhea and nausea; 9 of them showed a dangerous spike in seizure frequency called 'status epilepticus' that may have stemmed from the drug. The trial was open-label, meaning that participants knew what they were taking and why — so it's possible these reports were influenced by a placebo effect.

In the meantime, GW has been conducting a clinical trial that is yielding promising results. The company reported in March that in a late-stage trial, its CBD compound Epidiolex reduced the frequency of seizures by 39 percent in 60 participants with Dravet syndrome. By contrast, the placebo lowered seizures by 13 percent. In June, GW reported similarly promising results for children with another form of epilepsy, Lennox-Gastaut syndrome. The company has launched a late-stage trial of Epidiolex for tuberous sclerosis, an autism-related condition, and aims to file a New Drug Application — the first step to getting drug approval — with the FDA in 2017.

SPARK IT UP

Marijuana has direct effects on autism features as well — at least, according to anecdotal reports from parents. Some parents say their children seem calmer, more contented and aware when given marijuana. Some doctors prescribe medical marijuana for children who have severe aggressive outbursts and do not respond to antipsychotics. Jeste says many of the children with autism she knows are given marijuana to help them sleep —

as in the case of the boy who ended up in the emergency room.

One of the challenges when designing marijuana studies for autism will be finding a way to objectively measure these anecdotal observations, Jeste says. “Are we trying to improve social communication, are we trying to improve sleep, are we trying to improve irritability? What are we trying to move?”

It’s also unclear whether marijuana research for autism would focus primarily on CBD, which has been shown to be safe, or include THC, which many parents of children with autism say is most beneficial. The compound Barnes is testing in his small trial is made by GW and is almost entirely made up of CBD. A tiny fraction of THC comes along for the ride when CBD is purified from plants, but too much THC might be toxic to the developing brain, Barnes says. He plans to recruit 10 children who have both autism and epilepsy. The trial aims to primarily measure whether the drug reduces the frequency of seizures, but Barnes also plans to look at autism features such as repetitive behaviors and sensory sensitivity, and the drug’s effect on sleep.

To launch the trial, Barnes first had to apply for a license with the DEA for permission to work on a Schedule 1 drug, a process that includes at least one visit from DEA agents. The agents ensure that the compound is kept in a secure facility that only certain personnel can enter and has electronic security measures — something Barnes did not initially have. He also needed to fill out a new form for each stage of his study, and for any changes to the study design.

Hussain says he knew setting up his clinical trial would be difficult, but it proved even more challenging than he had expected. Apart from getting the DEA’s permission, he had to have his protocol approved by the California State Department of Justice and the FDA. He also needed to navigate university politics, convincing staff

there that the study would be legal, and wouldn’t damage their reputation. “You need buy-in from your colleagues who are helping you recruit patients — who are helping you conduct studies; you need buy-in from your department at your university; you need buy-in from the university-wide establishment; you need buy-in from the legal folks at your university,” he says. “As this goes forward, you keep getting new layers of bureaucracy.”

Hussain says that on his own, the barriers might have seemed unnavigable. He and Barnes both got help from their pharmaceutical company partners, which provided their compounds as well as consultants for the mess of federal forms. Researchers without pharma partners must apply to receive marijuana through the federal government. The entire federal supply comes from a single site at the University of Mississippi in Oxford, although the new DEA policy may change that. Last year, the government approved 23 requests for marijuana for research projects.

Parents, meanwhile, are continuing to lead the way in testing marijuana. When Barnes was involved in the Dravet syndrome trial, he was deluged with calls from parents eager to enroll their children. He anticipates getting as many as five calls a day for the 10 spots in his autism trial.

Some parents aren’t waiting for trials. Karlee has a permit to grow marijuana in her backyard, so she no longer has to drive for hours to a dispensary. But when Washington state legalized the sale of recreational marijuana in July 2014, it also tightened restrictions on dispensaries and on individuals growing the plant. “We’re trying to make sure we’re obeying the law, but it’s a little vague,” Karlee says.

Last year, Karlee harvested enough marijuana to provide oil for Spencer for the entire year. In the next few weeks, she will be starting her second harvest, stripping the plant’s leaves to make the medicine she says changed everything for her family.

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chapter

**LIVED
EXPERIENCES**

ORIGINALLY PUBLISHED 3 MAY 2017

SEX AND OTHER FOREIGN WORDS

People with autism
fall in love. They
marry. They even
(gasp) have sex. Yet
these deeply human
needs have mostly
gone ignored by
scientists.

by

ANN GRISWOLD

illustrations by

JULIEN PACAUD



MUCH OF WHAT STEPHEN SHORE knows about romance he learned in the self-help aisle of a bookstore near the Amherst campus of the University of Massachusetts.

In college, Shore, who has autism, began to wonder if women spoke a language he didn't understand. Maybe that would explain the perplexing behavior of a former massage student with whom he traded shiatsu sessions, who eventually told him she had been hoping for more than a back rub. Or the woman he met in class one summer, who had assumed she was his girlfriend because they spent most nights cooking, and often shared a bed. Looking back, other people's signs of romantic interest seemed to almost always get lost in translation.

Shore turned to the self-help shelves to learn the unspoken language of love: He pored over chapters on body language, facial expression and nonverbal communication.

By the time he met Yi Liu, a woman in his graduate-level music theory class at Boston University, he was better prepared. On a summer day in 1989, as they sat side by side on the beach, Liu leaned over and kissed Shore on the lips. She embraced him, then held his hand as they looked out at the sea.

"Based on my research," he says, "I knew that if a woman hugs you, kisses you and holds your hand all at the same time, she wants to be your girlfriend; you better have an answer right away."

The couple married a year later, on a sunny afternoon in June 1990.

RELATIONSHIP STATUS

Shore was diagnosed with autism around age 3, about a year after he lost his few words and began throwing tantrums. Doctors advised his parents to place him in an institution. Instead, they immersed him in music and movement activities, and imitated his sounds and behavior to help him become aware of himself and others. He began speaking again at 4 and eventually recovered some of the social skills he had lost.

Shore, now 55, recalls his classmates dating in middle and high school, but at the time he didn't understand love's allure. "I couldn't really make sense out of it," he says.

Society teaches many people with autism from a young age that they are incapable of love, says Jessica Penwell Barnett, assistant professor of sexuality studies in the Women, Gender,

and Sexuality Studies program at Wright State University in Dayton, Ohio. Barnett leads sexual education sessions for college students with autism. The stereotype of children with autism as cold, emotionless robots is painful, pervasive and entirely misleading, she says. “Some are very aware of this social representation — it’s like a cloud that hovers over all of their thinking about whether they can be in a relationship or whether another person is going to want to be with them.”

In fact, many people with autism both desire and sustain lasting relationships. “There’s no incompatibility with being on the spectrum and being in a romantic relationship, being in love, being part of a committed partnership,” Barnett says. Like Shore, an estimated 47 percent of adults with the condition share their home — and their life — with a romantic partner.

That doesn’t necessarily mean relationships are easy for people on the spectrum. Some features of autism, such as inflexibility, anxiety, sensory overload, difficulty communicating one’s own — and sensing others’ — personal needs and limits, would seem to lend themselves to relationship disasters. But that thinking is based almost entirely on conjecture. Scientists have been slow to study how and why people with autism form satisfying relationships. Until this decade, many adults with autism went undiagnosed, and those who had the social prowess to forge romantic relationships were considered “vanishingly rare,” says Matthew Lerner, assistant professor of psychology, psychiatry and pediatrics at Stony Brook University in New York.

As that stereotype falls away, researchers are scrambling to piece together a realistic portrait of romance and sexuality in people with autism. Through small studies and anecdotal evidence, they now know scant facts: that many more people with autism desire romantic relationships than achieve them; that autism features such as rigid

thinking, anxiety and social awkwardness can create barriers to dating, sex and relationships; that gender variances, including non-binary genders and bisexuality, are more common among people with autism than in the general population.

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The only thing I knew to do was to play the role of a girlfriend.

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AMY GRAVINO

Having identified some problems, researchers are still grappling with how best to help people with autism achieve lasting relationships. “This has become a sort of screaming priority,” Lerner says. “It’s one of the areas with perhaps the largest gap — I might go so far as to say it’s the area with the largest gap — between community interest and need, and empirical research.”

DATING DILEMMAS

For most people, a healthy love life underpins psychological health and an overall sense of well-being. Depression and anxiety tend to ebb in women with satisfying relationships.

Scientists say these same benefits apply to people with autism — and when romantic relationships are lacking, a key piece of social and emotional health goes missing, too. That can beget a sense of isolation: Depression and anxiety are more than three times as common in adults

with autism as in people without the condition. “There is a big problem with loneliness in this population,” says Katherine Gotham, a clinical psychologist at Vanderbilt University Medical Center in Nashville, Tennessee.

Step one in solving this problem: Dating.

The intricacies of dating — striking up a conversation with a stranger or trying to gauge another person’s interest based on body language or facial expressions, for example — aren’t specific to people with autism, but they’re more difficult for people with the condition to navigate. “We all have the same sorts of struggles, but folks with autism struggle even more,” Barnett says. “The differences are a matter of degree, not kind.”

Cultural factors can complicate courtship. In the United States, for example, dates typically unfold in noisy bars, busy restaurants or loud movie theatres. These environments can worsen anxiety and even be painful for people with sensory sensitivities.

Another complication is that most people tend to have a certain ‘type,’ whether it’s men with beards, for example, or tall women. But people with autism are sometimes unwilling to compromise, Gotham says. “I can think of five people off the top of my head who are frustrated because they don’t have what they want,” she says. The problem is that these people want not just someone they can connect with, but someone with a specific list of attributes. This rigidity can diminish dating prospects.

Dave, a single man living in Nashville, Tennessee, says that for most of his life he has felt anxious about interacting with women. (Dave requested that his last name not be used.) He has had a couple of romantic relationships — but what he really wanted was a girlfriend who resembled someone like Jennifer Aniston; he didn’t want to settle for anything less. He reasoned that because he didn’t have a girlfriend who fit that description,

he must have been doing something wrong.

Dave attributed his struggles to a hearing impairment, his physical appearance and the scarcity of Aniston look-alikes in his area. Until he was diagnosed at age 45, he says, “it never occurred to me that it was autism.” After Dave was diagnosed, his therapist helped him hone his social skills. Before long, he had learned a few ground rules for casual conversation, such as taking turns speaking and choosing topics both people are interested in.

The nuance and subtlety of courtship can be especially confusing for people who have trouble recognizing social cues. It’s one of the most challenging social experiences that people with autism face: “Dating involves flirting, it relies on a lot of nonverbal behaviors,” Barnett says. “You don’t say what you’re thinking in the way that you’re thinking it.”

Last year, a team of researchers at University College London reported that women with autism tend to overlook subtle cues signaling a man’s interest, and mirror men’s flirtatious behavior without meaning to. About one-third of the women in the study said they didn’t notice platonic interactions escalating into something more sexually charged, so they often found themselves fending off unwelcome advances.

For Shore, too, the difficulty of recognizing social cues landed him in his first romantic encounter before he even realized what was happening.

After his first year of college, Shore began spending long hours with the woman he met during summer classes — talking, cooking and watching movies. “Then one day she tells me she really loves hugs and back rubs,” Shore recalls. “I remember sleeping over at her house, sharing a bed, and that was exactly what we did. Then she seemed to get pretty upset.”

During a lengthy conversation, Shore realized the woman had wanted to be his girlfriend. He wasn’t interested in dating, so the couple parted

ways. But the experience stirred Shore's curiosity about social cues. "That suggested to me that there's this whole area of communication that we call nonverbal, which became fascinating to me," he says. He started logging long hours in bookstores and libraries.

GIRLFRIENDS' GUIDE TO ROMANCE

Whereas Shore read books to learn to detect a budding romance, Amy Gravino mostly relied on Hollywood to decode the rules of long-term relationships.

Like many women with autism, Gravino often masked her social difficulties by adopting the mannerisms of neurotypical women. When she entered her first relationship at age 19, she mimicked the girlfriends she had seen in television shows and movies. "I didn't know what in the world I was doing," she says. "The only thing I knew to do was to play the role of a girlfriend — what I thought a girlfriend was supposed to do: I'm supposed to laugh at his jokes even if they're not funny; I'm supposed to meet his parents." Looking back, she says, "I didn't realize that I just needed to be myself."

Gravino says she found it difficult to forge a deep bond with her partner, in part because she didn't feel comfortable being herself. The relationship stumbled over rocky terrain for a few months before she finally broke it off.

Her experience isn't unusual, researchers say. For people with autism, developing a deep and lasting emotional connection is often more difficult than attracting a mate. That may be because a strong relationship depends on partners being both self-aware and aware of others, maintaining emotional stability and being able to learn from past experiences — three domains that

prove challenging for some people with autism, Lerner says.

The condition doesn't necessarily prevent children from forming deep friendships, as Lerner's team found last year after analyzing the literature — a total of 18 studies — on friendships of boys with autism. But it may constrain the depth and closeness of those friendships — a finding that doesn't bode well for romantic relationships later in life.

Relationships between a person with autism and a neurotypical person often falter over a specific problem: 'able-ism,' an unconscious or overt bias toward people deemed socially or physically 'able.' It can be difficult for a neurotypical partner to "understand what it feels like to exist in the world as a person on the spectrum, and be respectful of that and see [their partner] as a whole person," Barnett says.

Unsurprisingly, long-term relationships are sometimes easier to navigate when both partners have autism. Barnett's research suggests people on the spectrum are often accepting of each other's quirks — a craving for deep touch, say, or no touch at all. "They felt that their relationships were higher quality when the partner was on the spectrum; they felt like their partner really got them," she says. These observations jibe with those from a study of 26,000 adults with autism and 130,000 controls in Sweden, which found that most people with autism prefer partners on the spectrum.

The people with autism who form successful long-term relationships are the ones who have learned to negotiate arrangements that respect their needs — whether a prolonged period of quiet time after work, a relationship with cuddling but no sex, or even a sparsely decorated home that forestalls sensory overload.

Shore's first relationship lasted a little more than two years. His second ended after just six months, when he discovered that his girlfriend



liked to fall asleep to rock music. Shore, who had studied music education in college, found the music too distracting. The couple's incompatible sleep preferences broke their relationship.

TOUCHY SUBJECTS

Beyond dating and love, sexual satisfaction — alone or with a partner — is important to well-being. But only a smattering of studies have explored the nature of sexual experiences of people on the spectrum. “Sexuality isn’t taboo in the research community, but it’s still kind of the last topic to the table — which isn’t really fair because it could be key to understanding quality of life and emotional health in people with autism,” Gotham says.

Shore says in his experience, there are two hurdles for a person on the spectrum to be sexual. The first is noticing a partner’s interest in sex. When a date made sexual advances, he often missed them.

Once he caught on, a second hurdle appeared: He enjoyed sex but found the sensations overwhelming. Often his girlfriend would have to remain still while he waited for the sensations to pass.

The sounds and sensations of physical intimacy can overwhelm some people with autism. In a 2015 study, Barnett found that for some women with autism, these sensitivities manifest as vaginal muscle spasms, known as vaginismus, that make penetration painful or impossible. “Since [penetration] is considered the default for heterosexual sex in our population, some of them felt the obligation to provide sexual pleasure to their partners, but they also felt this painful coitus,” Barnett says.

Some women with autism don’t realize vaginismus is a common concern and may consider it a personal setback. Instead, she says, they need to use explicit language to describe their discomfort. “Sometimes you just have to say, ‘Vaginal sex just ain’t going to be our thing,’ and negotiate other activities that you can do for sexual pleasure and release.”

That may be easier said than done, however. In the University College London study, the researchers found that many women struggled to articulate their sexual desires and limits. Half of the women said they had acquiesced to unwelcome sexual encounters because they wanted to feel accepted, to receive affection or because they thought they were obliged to perform sexually in a relationship. These patterns also hold true for many neurotypical women, but women on the spectrum may be even less likely to stand up for themselves.

Healthy sexuality draws upon three factors — positive psychological and physical function, a supportive view of self and a strong knowledge base — says Shana Nichols, director of the ASPIRE Center for Learning and Development in Long Island, New York. The first factor comes naturally to people with autism who feel positive about their sexual function. And men with the mildest features of autism report the highest levels of sexual desire, performance, satisfaction and assertiveness, particularly when in a relationship.

The second has to do with self-acceptance and self-love: For some people with autism, romance could promote that positive view of self; for others, it may ultimately lead to the conclusion that life is best lived alone. About five years ago, Dave enrolled in ballroom dancing classes and began to practice interacting with women. Now he says he feels comfortable around his dance partners, and he enjoys socializing with them. “The key is to not worry so much about how someone else responds to me, but for me to be okay in how I’m responding to them,” he says. “Others see that I feel good about myself and it draws people to me.”

Dave insists he’s no longer actively looking for romance — he says he prefers to keep his dance partners at a safe, platonic distance. “I think one of the mistakes people make, including myself, is thinking they have to find somebody in order to

be fulfilled,” he says. “A relationship with yourself is really everything.”

When it comes to the third factor — knowledge of sex — people with autism often have little information about sexually transmitted illnesses, contraceptives and sexual behaviors. What little they do know tends to be gleaned mostly from television shows, pornography or the internet. Neurotypical people, by contrast, generally learn about sex from friends, parents or teachers.

Dave says he used to think sex defined a relationship, and he wasn’t particularly interested in compromising on that point. “When you don’t have a lot of sexual experience, you tend to value that more than you actually should,” he says. “I thought that unless I was having those experiences, I wasn’t getting anything out of a relationship.” After working with his therapist, he understands that romantic relationships can mean different things, depending on each partner’s interests, desires and needs.

DARK SIDE

Many parents feel compelled to educate their teenagers on the spectrum about sexuality, but need expert advice, according to a 2016 survey. Last year, researchers at Cardiff University in Wales uncovered one source of this squeamishness: Although studies of healthy sexuality are few and far between, there are more than 5,000 published studies linking autism to inappropriate behavior such as stalking, public fondling or sexual obsessions. A closer look at 42 of these studies reveals that those problems often arise in people with severe autism, perhaps due to difficulty sensing when other people are uncomfortable.

Problematic behaviors also tend to crop up in children who are caught off guard by the physical

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**Sexuality isn't taboo
in the research
community, but it's
still kind of the last
topic to the table.**
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KATHERINE GOTHAM

changes of puberty, prompting the researchers to propose that sexual education may help stave off misconduct. Still, mainstream sex education classes may not address the needs of students with autism.

One program in the Netherlands, called Tackling Teenage Training, individualizes sex education for young people with autism. Enrolled teens have private counseling sessions every week for about six months, focusing on areas such as safe sex, respecting boundaries, and sexual preferences. A small clinical trial earlier this year found that the program helps teens with autism improve their sexual knowledge, build confidence and prevent inappropriate behaviors. One year after completing the program, teens still showed improvements in sexual knowledge, social behavior and problematic sexual behavior.

Sex education programs may also help reduce the alarming rates of sexual exploitation of people with autism.

The researchers at University College London uncovered a “shockingly high incidence” of sexual vulnerability: They found 9 of the 14 women in their study had a history of sexual abuse and 3

had been raped by a stranger. More than half of the women had felt trapped in an abusive relationship at some point in their life. The women also said uncertainty about social norms and trouble sensing ‘creepiness’ or red flags made them vulnerable to sexual exploitation.

Beyond protecting the vulnerable and deterring deviant behavior, these programs aim to guide people with autism toward strong, satisfying relationships.

Sometimes romance blooms without formal training, Nichols says, especially for people such as Shore, who are naturally motivated to notice subtle social cues. “It’s the greater awareness — that social awareness of others and also of themselves — that is really important,” Nichols says. “And the right fit of a partner is huge.”

Shore recalls the moment he realized Liu was the right fit. As he drove her across town one morning in the spring of 1989, Liu looked over at him and said she felt like they were already married. “I thought about it and realized she was right,” he says. In that moment, he says, they became engaged — without a diamond ring, a bended knee or other trappings of a traditional marriage proposal. “It was new territory, taking our relationship to a new level,” Shore recalls. “It was very exciting.”

Shore married a fellow musician, something he always expected he would do. But Liu grew up in China, which upended Shore’s long-held assumption that he would marry someone who shared his New England traditions and customs. He realized it didn’t matter at all that this expectation would not come to pass.

On the afternoon of 10 June 1990, about 150 friends and family members gathered in Cape Cod, Massachusetts, to celebrate Shore and Liu’s wedding. The couple exchanged vows roughly 40 miles down the coast from where they had shared their first kiss.

Conventional wisdom
holds that people
with autism don't get
hooked on alcohol or
other drugs, but new
evidence suggests
otherwise.

AUTISM'S HIDDEN HABIT

by

MAIA SZALAVITZ

illustrations by

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SHANE STONER'S ADDICTION BEGAN in 2008. He lost a factory job, his parents divorced, his father died — and then a relative introduced him to heroin. “I felt like heroin gave me confidence,” Stoner says. “I could get out of bed in the morning and do the day. No matter what happened, it made me feel like it was going to be all right.” It erased his constant anxiety.

Stoner, now 44, eventually entered detox in 2013 after he was arrested for stealing copper from an abandoned house. It was obvious at that point that he was addicted to heroin. But it would take several more years for him to get the diagnosis that truly helped him understand himself: autism.

The new label came as a relief. It explained Stoner's sensitivity to things such as tags on his T-shirts, and his succession of obsessive interests. It clarified why he had such a difficult time fitting in as a child, his problems with roommates in college — and why he continued to struggle with social connections as an adult. “I can't believe nobody ever mentioned it before, because I started

thinking back and there's pictures of me, like, 3 years old, and I'm honestly flapping my hands.”

Stoner is now three years into recovery from his addiction. “I like my autism now that I know what it is,” he says. “I don't like all parts of it — I don't like the anxiety — but it's like it all made sense.”

Until recently, researchers held that addiction among people with autism is rare, although there wasn't much solid evidence for this view. It seemed plausible, though: Many people with autism have a penchant for strictly following rules, which would seem to make them less likely to try alcohol or illegal drugs. Because people with autism are often isolated from their peers, this could protect them from the peer pressure that can lead to youthful experimentation. And many people diagnosed with autism decades ago had severe features; a person who can't live independently has few opportunities to become addicted.

A new study in Sweden, however, suggests that people with autism who have average or above-average intelligence quotients (IQs) are

more than twice as likely to become addicted to alcohol or other drugs as their peers are. The risk is even higher for people who also have attention deficit hyperactivity disorder (ADHD). This study is the first to look at the general risk for addiction among people with autism.

Other research is also finding unexpected biological and psychological commonalities between the two conditions. “These two fields have really developed independently, but I think there could be a lot of cross-fertilization,” says Patrick Rothwell, assistant professor of neuroscience at the University of Minnesota Twin Cities in Minneapolis. In 2016, Rothwell opened a lab focused on studying the biological and behavioral parallels between addiction and autism.

There are similarities in the way people with either condition use repetitive behaviors to cope with emotional problems, as well as in their impulsivity and compulsions. The two conditions affect some of the same brain regions and involve some of the same genes. These connections are spurring a new area of research that could eventually help improve both autism care and addiction treatment and prevention.

NEW NUMBERS

For much of the 20th century, most of those who received an autism diagnosis were on the severe end of the spectrum. In this largely nonverbal population, addiction seemed unlikely. But in 1994, when the “Diagnostic and Statistical Manual of Mental Disorders” added Asperger syndrome as a category, the spectrum extended to people who had much more opportunity to access alcohol and other drugs. Still, for years, the assumption remained that addiction was one concern the autism community could safely ignore.

When Espen Arnevik reviewed the literature for a paper he published last year, he found only 18 studies that looked at the overlap between autism and addiction. Each of them looked mainly at select samples — such as people being treated for addiction, or those caught up in the criminal justice system — rather than at the general population.

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SHANE STONER

Arnevik found that the combined prevalence of alcoholism and addiction in people with autism ranged from 0.7 percent to 36 percent. Because the data were so varied, the range couldn’t be narrowed down any further. Overall, however, “most studies suggest a significantly lower prevalence than in the general population,” says Arnevik, associate professor of psychology at the University of Oslo in Norway. In the United States, the lifetime prevalence of alcoholism is 14 percent; for other substance addictions, the figure hovers around 2 to 3 percent (there is some overlap between these groups).

Given the prevailing impression that addiction is uncommon among people with autism, the findings of the Swedish study came as a surprise



to many. The study analyzed national health registry records of the 1.3 million Swedes who were born between 1973 and 2009, and identified 26,986 people diagnosed with autism. The researchers also determined how many of those with autism had an additional diagnosis of intellectual disability, substance use disorder or ADHD.

Overall, an autism diagnosis doubles the risk of addiction, the researchers found. Elevated risk is concentrated among those with an IQ of 100 or above. But across the spectrum, ADHD is a great multiplier of risk: Among those with autism and intellectual disability, having ADHD increases the risk of addiction fourfold; among those with an IQ in the typical range or above, ADHD increases the risk eightfold.

Parents and siblings of people with autism also have a higher risk of addiction, suggesting a genetic link.

These findings don't necessarily conflict with earlier data showing lower addiction risk among people with autism, says Paul Lichtenstein, professor of genetic epidemiology at the Karolinska Institute in Sweden, who worked on the study. The main takeaway, he says, is that risk varies with level of intellectual ability. Previous research often included a much higher proportion of people with intellectual disability, which would have skewed the results.

On the other hand, autism is often diagnosed later in Sweden than in the U.S., and the proportion of people at the milder end of the spectrum may be higher. That may cause the increase in addiction risk to look larger than it is, notes Jeremy Veenstra-VanderWeele, associate professor of psychiatry at Columbia University. "I would want to see whether this paper's findings hold up when [autism] follows the typical pattern of relatively

early recognition, rather than quite late diagnosis.” Another possibility: Given the wide variety of people on the spectrum, it is possible that some types of autism raise risk, whereas others lower it.

The Swedish finding comes as less of a surprise to people with autism. Matthew Tinsley, now 55, had always looked to alcohol and prescription drugs to reduce his anxiety. Tinsley is author of “Asperger Syndrome and Alcohol: Drinking to Cope,” one of the few books on this subject. (He has been sober since 2004.) From an early age, he would take his mother’s anxiety medications when he felt overwhelmed. “I found being amongst groups of people very stressful,” he says.

In college, he discovered that alcohol also helped ease socializing. “Everyone else is drinking, it’s socially acceptable, and if you drink, you fit in because everyone else is doing it,” he says. “It took the edge off.” By the time he was in his 40s, Tinsley adds, he was drinking “lethal” amounts of alcohol: 3 liters of gin every day. This led to cirrhosis, and he entered rehab in 2004. As in Stoner’s case, his autism diagnosis in 2005 came as a relief. Once he realized there was an explanation for his sensory and social difficulties, he began to be kinder to himself and found healthier ways of coping.

The link between autism and addiction is also unsurprising to clinicians who work with people on the spectrum. Valerie Gaus, a psychologist in the New York City area, says of her clients with autism who have drinking or drug problems, many of the older ones turn to alcohol, whereas the younger ones tend to use marijuana.

Eric Hollander has seen a similar pattern. However, he says he treats more behavioral addictions, such as gambling. “I work with a lot of people with [autism] who have all kinds of impulsive behaviors,” says Hollander, director of the Autism and Obsessive Compulsive Spectrum Program at Albert Einstein College of Medicine in New York. “In fact, that’s one of the main targets

when people come in for treatment. Either they’re out of control in terms of shopping on the internet or gaming, or they’re just addicted to the internet.”

Hollander has looked at similarities between obsessive compulsive disorder, addiction, and the impulsive and compulsive behaviors that occur in people with autism. He proposes that these conditions, all characterized by repetitive thought and behavior, should be grouped together as ‘obsessive compulsive spectrum disorders’ in the diagnostic guidelines.

Impulsivity — acting quickly without thinking — and compulsivity, or being unable to stop an activity once it has started, are both problems of self-control, or ‘executive function.’ Impulsivity is strongly linked with the risk for becoming addicted; addiction is defined as compulsive drug use that persists despite negative consequences. People with autism show signs of both impulsivity and compulsivity. For example, they frequently engage in repetitive, compulsive behaviors — dubbed ‘stimming’ — to address either a lack of sensory stimulation or a surfeit of it. In the case of addiction, different types of addictive drugs can enhance or reduce sensation.

Tanea Paterson, a mother of two who lives in New Zealand, used drugs to deal with social stress, but also to cope with her sensory problems. A mixture of heroin and other illegal opioids, her drug of choice, “wound down my senses to a more bearable level,” she says. Using drugs also gave Paterson routines, she says. “They were predictable in an unpredictable world.”

Paterson kicked her addiction more than 10 years ago, but didn’t find out she has autism until 2015. Her son had previously been diagnosed with autism, and she convinced the therapist who had helped him to evaluate her. For Paterson, too, the diagnosis brought relief: “It was a lifting of so much guilt and shame in many, many ways,” she says.

Paterson had been bullied and excluded as a teenager before she found peers who used marijuana and were more accepting. In this group, she felt safer, she says. Others with autism and addiction also report that drug culture helps them feel accepted: Unusual behavior is expected when people are high, so they don't stand out.

DEEPER LINKS

Addiction is known to be linked to changes in the striatum, a central region of the brain involved in pleasure, motivation and habitual behavior. During a period of addiction, control over drug-related behavior shifts from one region of the striatum to another.

Before drug use devolves into addiction, drug-related brain activity occurs primarily in the ventral area, which is involved with motivation and seeking pleasure. At this stage, people take drugs mainly because they offer either comfort or joy. The ventral region seems especially connected to impulsive behavior. But as addiction progresses, some of the action moves toward the dorsal striatum, a region involved in automating behavior into more programmed patterns, which can be set off by specific cues. This automation can be useful when it processes a complex dance move or other skill into a single, willed action — but it can also create a compulsion that, once unleashed, becomes difficult to restrain.

The compulsion could be drug use, but it could also be the repetitive behaviors of autism. In both cases, the striatum drives the persistent behavior. It's possible that in people with autism or addiction, the striatum is more prone to getting stuck in a repetitive pattern. “[Behavioral patterns] become very difficult to change once they're well-practiced,” says Rothwell, who is among the

few researchers who studies both autism and addiction. “That's definitely a concept that I think is very relevant both to the repetitive symptoms of autism and the habitual patterns of addiction.”

Paterson, the New Zealand woman who formerly used opioids, says she sees these patterns in her own behavior: “I think of autistic inertia — can't start, can't stop — comfort in consistency, predictability and obsessiveness.”

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Addiction and autism may also share genetic connections. For example, Rothwell has found that *NLGN3*, a candidate gene for autism, is highly active in the nucleus accumbens, a region in the ventral striatum that is linked to desire and drug use. “That was striking because that's very much also an addiction hotspot,” Rothwell says.

Chromosomal region 16p11.2 is deleted in some cases of autism — and mice with this deletion show enlargements in the nucleus accumbens. *CNTNAP4*, another autism candidate gene, is also



active in the striatum; mice that lack the protein have elevated levels of dopamine in the nucleus accumbens, which is a brain state that is common at the start of addiction.

There are also intriguing neurochemical connections between autism and addiction. Interactions between oxytocin, dopamine and the brain's natural opioids in the striatum appear to be important in both conditions: Oxytocin is thought to connect the memory of specific people to pleasure, thereby creating social bonds. This process may go awry in some people with autism, and they may find socializing unrewarding or unpleasant. There may be parallels with addiction here as well. People with addiction often report feeling that

social connection is difficult or even impossible, until they find solace in drugs.

Addiction also affects the brain's endogenous opioid system, which produces the experience of pleasure and comfort most people feel when they socialize. Mice lacking genes involved in this system are less sociable than usual and engage in stereotyped behavior reminiscent of autism. "There's some very interesting data out there that suggests there could be a deficiency in opioid signaling that might be a factor in autism," says Rothwell.

Genes involved in the autism-related conditions Rett syndrome and fragile X syndrome also show up in addiction research. Neuroscientists

were startled to find that MeCP2 — which is mutated in Rett syndrome — becomes highly active in the brain when rats are given access to large amounts of cocaine. FMR1, the gene mutated in fragile X syndrome, seems to have a similar relationship to cocaine addiction.

A better understanding of the connections between autism and addiction could provide important therapeutic insights into both, says Robert Malenka, professor of psychiatry at Stanford University in California, who worked with Rothwell on the NLGN3 research. “Clinicians in one field should pay attention to what is going on in the other field,” he says.

Autism and addiction research have already converged on one medication: baclofen, a drug approved in the U.S. for treating muscle spasms. A version of baclofen is in trials for treating autism and the related fragile X syndrome. The drug is also widely used in France to treat alcoholism, although clinical trials have shown mixed results. And preclinical research suggests it may help treat opioid and cocaine addiction.

For people on the spectrum who have addictions now, however, getting help can be challenging. There is not a single study on the best way to treat these individuals. In fact, there’s reason to believe that most addiction treatments are poorly suited to people with autism.

Addiction therapy is mainly conducted in group sessions, with strict rules requiring members to participate and articulate emotional problems. People with autism may respond to these expectations with anger and anxiety, which counselors may misinterpret as defiance. For those who are obligated to participate by the criminal justice system, failure to comply can even lead to incarceration.

Stoner, for one, says he had difficulty with rehab because he was made to spend many hours in group therapy and 12-step programs,

including Narcotics Anonymous and Alcoholics Anonymous. “I’ve had a really hard time getting into that,” he says. When faced with speaking in front of a group or at an Alcoholics Anonymous meeting, “my mind goes blank,” he says. He also had difficulty connecting with other members. He was rejected twice before he found someone to be his ‘sponsor,’ or recovery mentor.

Given these difficulties, programs to help people with autism who have addictions may need to rely less on group therapies and more on individualized care.

Stoner now works as a peer specialist at the Kenmore Club, a government-funded project of the Rappahannock Area Community Services Board in Fredericksburg, Virginia. He says the organization’s more personal approach is better suited to his needs. The staff train people with various forms of developmental and psychiatric disabilities to help one another. Until more research is done, he says, people with both autism and addiction will have to find their own way to the best care.

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LIVING BETWEEN GENDERS

'Trans' people with autism express a gender at odds with societal expectations, or reject the male-female divide entirely. Many are breaking new ground on how identity is defined — and what it means to also have autism.

by

**DEBORAH
RUDACILLE**

illustration by

PEP BOATELLA

photographs by

J.M GIORDANO



SITTING BY A TEXAS CREEK ONE afternoon, 6-year-old Ollie turned to his mother and said, “Mama, I think that I am half boy and half girl.”

Ollie’s mother, Audrey, wasn’t particularly surprised by the comment. (Audrey and the other parents in this article have requested that we use only their first names to protect their children’s privacy.) By age 2, Ollie had been drawn to “sparkly stuff and tutus.” On a shoe-shopping expedition when he was 3, Ollie had rejected his usual brown slip-on shoes in favor of pink, saying emphatically, “I need clothes in every color.” After that, Audrey says, when they went shopping she let him choose clothes in whatever colors he liked, whether they were from the ‘boys’ or ‘girls’ department. At 5, Ollie began playing ‘dress up’ at home and shortly afterward started wearing dresses in public.

“That was scary, because we were living in Texas and I didn’t know what would happen when we walked out our front door,” Audrey says.

Ollie’s parents wondered if his gender nonconformity — behavior that doesn’t match masculine and feminine norms — might have something to do with his autism. Ollie had been

diagnosed with sensory processing disorder at age 2: An extreme sensitivity to sounds, light, the texture of some foods or the feel of a particular fabric can send children like Ollie into a meltdown. He also had difficulty falling asleep and staying asleep. It would take his parents four more years to find a doctor who recognized the classic symptoms of Asperger syndrome — above-average intelligence combined with social and communication deficits, and restricted interests. (Ollie was diagnosed with Asperger syndrome before the diagnosis was absorbed into the broader category of autism spectrum disorder in 2013.)

Audrey didn’t think autism was causing Ollie to like the color pink or want to wear dresses, but she did wonder whether her extremely logical child might reason that the fact that he liked those things meant he wasn’t a real boy — “like, ‘these are the rules of society,’” she says. Her husband, who serves in the U.S. military, thought that because of Ollie’s autism, the child might not understand that a boy dressing in girls’ clothes was not socially acceptable.

Ollie’s parents are not alone in pondering this puzzle. A handful of studies over the past five years — and a series of case reports going back to 1996

— show a linkage between autism and gender variance. People who feel significant distress because their gender identity differs from their birth sex — a condition known as gender dysphoria — have higher-than-expected rates of autism. Likewise, people with autism appear to have higher rates of gender dysphoria than the general population.

Between 8 and 10 percent of children and adolescents seen at gender clinics around the world meet the diagnostic criteria for autism, according to studies carried out over the past five years, while roughly 20 percent have autism traits such as impaired social and communication skills or intense focus and attention to detail. Some seek treatment for their gender dysphoria already knowing or suspecting they have autism, but the majority of people in these studies had never sought nor received an autism diagnosis. What's more, roughly the same numbers of birth males and females appear to be affected — which is surprising, given that in the general population, autism skews male.

At this early stage of research into the overlap between autism and gender dysphoria, much remains unknown — for example, whether gender identity develops differently in people with autism. This lack of information challenges both clinicians and families who want to do what's best for transgender children.

The combination of autism and gender dysphoria represents not just a doubling of challenges but “a multiplication of challenges,” says John Strang, a pediatric neuropsychologist at Children's National Health System in Washington, D.C., and author of a 2014 paper exploring rates of gender dysphoria among children with autism.

Gender-dysphoric people need to clear many hurdles to live comfortably in the world. They must articulate an identity at odds with their sexual anatomy and the social expectations for that anatomy, plan and execute some form of

transition, and deal with incomprehension or outright hostility as they navigate the perilous territory between genders.

“That involves a lot of transitions, flexibility, self-advocacy,” says Strang. “Those are all the weakest areas for people with autism.”

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**I'm in-between and
I'm comfortable
being in-between.**

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OLLIE, AGE 9

At the same time, people with autism have characteristics that can make this process easier, he says. They tend to be less worried about what other people think and less concerned about their social status or reputation.

Now 9 years old, Ollie bears out that assessment. He has endured teasing, bullying and the loss of friends and classmates; he has had to drop certain activities, such as taekwon do, because instructors or the parents of other students are uncomfortable with his gender expression. He sees a counselor to help him deal with the way that other people sometimes treat him. “It makes me want to scream sometimes,” he says. He also has appointments each week with autism specialists to address his sensory sensitivities, fine motor skills and auditory processing.

On a late winter day, at home with his mother, his dog and his cat, Ollie is busy with Star Wars Lego, acting out a mock battle between Stormtroopers and the Rebel Alliance. He is wearing pale pink sweatpants with a glittery dark pink stripe and

a pink barrette. “I’m not meant to be squeezed in that box. I’m beside it,” he says. “I’m in-between and I’m comfortable being in-between.”

DIAGNOSTIC OVERLAP

Over the past decade, people with gender dysphoria have developed new ways of expressing their sense of self. Whereas many once identified as transsexual or transgender, some now call themselves ‘genderqueer’ or ‘non-binary.’ Rates of autism and autism traits appear to be higher in those identifying as genderqueer. Like Ollie, these people generally say they don’t feel fully masculine or feminine, and explicitly reject the notion of two mutually exclusive genders. The word ‘trans’ is often used to encompass all of these identities and the phrase ‘affirmed gender’ to convey a person’s sense of self.

Although some trans people opt to alter their bodies via hormones or surgery, others — particularly those who identify as genderqueer or non-binary — may adopt a name and pronouns that better reflect their sense of self, without physically changing their bodies. (Ollie briefly experimented with using a feminine variant of his name and female pronouns, but it didn’t feel quite right, so he switched back.)

As with autism, the causes of gender dysphoria are poorly understood. Biological factors such as genetic predisposition, prenatal exposure to hormones, environmental toxins, and various social and psychological factors have all been proposed, but none have been confirmed. Like autism, gender dysphoria is heterogeneous, meaning that there is no one profile or presentation common to all those who identify as trans.

Only recently have researchers begun systematically exploring the overlap between gender

dysphoria and autism; the first study to assess the convergence of the two conditions was published just six years ago. It included 231 children and adolescents who had been referred to the Gender Identity Clinic of the Vrije University Medical Center in Amsterdam between April 2004 and October 2007. The researchers found the incidence of autism among the children was 7.8 percent, 10 times higher than the rate in the general population. Among the adolescents in the sample, the incidence was even higher, at 9.4 percent.

Another group reported last year that more than half of 166 young people referred to the Gender Identity Development Service, a specialized British National Health Service clinic, in London between December 2011 and June 2013 had features of autism, as measured by the Social Responsiveness Scale, a screening tool for autism. Of that number, nearly half of those who scored in the severe range had not previously been assessed for autism.

Strang says he is not surprised by those results. He trained as an autism specialist, but had sampled other specialties for his internship, including at the gender clinic, and he’d seen a similar overlap there. “As soon as I started to do the evaluations, I felt like I was back in the [autism] clinic,” he says.

Inspired by the Dutch study, Strang and his colleagues approached prevalence from another angle. Instead of measuring the incidence of autism among gender-dysphoric children and adolescents, they assessed gender variance — defined as a child “wishing to be the other sex” — in children with autism. “We found rates that were 7.5 times higher than expected,” Strang says.

The researchers don’t have an explanation, but they do have a few theories. First, children with autism might be less aware of social restrictions against expressing gender variance. Second, the kind of rigid black-and-white thinking that is



Close connection: Jes Grobman, here with her partner Lane Balassie, is now a transgender rights activist. Many of her friends are also trans people with autism.

characteristic of autism might lead people with mild or moderate gender nonconformity to believe that they are not the sex they were assigned at birth. Third, there might be a biological connection between autism and gender dysphoria.

These are only hypotheses, as is the theory that gender identity may unfold differently in people with autism — there is little data to either support or refute them.

REBEL ALLIANCE

Jes Grobman, 23, is a trans person with autism who is less concerned about the causes of the autism/trans overlap than about building a society that

does not punish difference. Diagnosed with Asperger syndrome at 11, Grobman says many of her trans friends and acquaintances also have autism diagnoses. “I think there’s a lot of overlap between autistic people and trans people,” she says. “I am probably friends with more autistic trans people than just trans people.”

Still, it took Grobman a long time to find a community where she felt understood. Throughout much of her childhood in Chicago, she says, she felt isolated and lonely. “In middle school, I had no friends. In freshman year of high school, I spent every lunch period in the library, reading.” Middle school was particularly hellish, she says: “I was bullied and picked on.”

She began coming out of her shell at age 16, when she made friends in a Jewish youth group.

But it wasn't until she started college at American University in Washington, D.C., that she began tentatively exploring what she calls "gender feels" — admitting to herself and others that she had never really felt like a boy, without really grasping exactly what that meant. "I was able to formulate it as more of an intellectual thing," she says. "Like, 'what is gender, really?'"

The idea that she might be trans both intrigued and terrified her. For two years, she alternately explored and repressed her feelings. "I was very, very afraid. The narratives about trans women scared me," she says. "I always basically understood that it would kill me, that I would be a pariah, sick and diseased, and I would lose everyone that cared about me. So I pushed it down deep inside me."

Grobman has struggled with anxiety and depression, which are common among both transgender people and those with autism. "It's impossible for me to separate my trans-ness and my autism from my issues with depression and anxiety," she says. She also had conflicted feelings about her autism diagnosis: "I used to feel very, very shameful about it and tried to hide it from other people."

It wasn't until she began exploring her trans identity and building relationships with others in that community that Grobman was finally able to "remove all the shame and stigma and embrace the fact that I have autism," she says. She attributes this to the confidence she developed by talking to people about being trans and being accepted for who she is without having to hide any aspect of her identity.

At first, Grobman resisted identifying as either male or female and asked her family and other people to refer to her using the gender-neutral pronouns 'they' and 'them.' Her parents were supportive up to a point, she says. But in November 2013, in the midst of an argument, her mother said,

"I refuse to refer to you as 'they.' Realize what you are and be it."

This was, Grobman says, "one of the most important things that anyone has ever said to me but also one of the most hurtful things anyone has ever said to me." She decided to adopt the statement as her motto and began using feminine pronouns and taking estrogen soon afterward.

Before graduating last December, Grobman helped found a support and advocacy group called DC Trans Power. In February, she helped write a joint statement by LGBT and disability rights groups on the death early that month of Kayden Clarke, a 24-year-old trans man with autism who was shot to death by police responding to a suicide call at his home in Mesa, Arizona. Police claim that Clarke brandished a knife, and they fired in self-defense. Clarke had posted emotional videos on YouTube prior to his death, describing the challenges he faced as a person with autism seeking to begin hormone therapy. One therapist had informed him that he could not start on hormones until his autism was 'fixed,' Clarke said, an assertion that filled him with despair.

The statement, co-authored by Grobman and posted on the website of the Autistic Self Advocacy Network, charges that lack of adequate medical care for Clarke's gender dysphoria precipitated a mental health crisis that led directly to his death. People with autism and other developmental disabilities and mental health issues often face resistance when seeking transition-related medical care, the activists say — a form of discrimination. "Autistic people's gender identities are real and must be respected," they write.

Grobman views Clarke's death as a murder, just as she views the deaths of trans people who take their own lives due to discrimination and prejudice as murder. "The entire system is complicit in their deaths," she says.

DO NO HARM

Clinicians who work with trans people who have autism say that although some individuals do encounter difficulties transitioning, healthcare providers are not always to blame. The standards of care promulgated by the World Professional Association for Transgender Health do not bar individuals with autism or other developmental disabilities from access to treatment, including hormones and surgery.

“The same criteria that applies to anybody else looking into trans medical care would apply to people on the spectrum,” says Katherine Rachlin, a clinical psychologist who has worked with adult transgender people in New York City for 25 years and is co-author of a 2014 paper on the co-occurrence of autism and gender dysphoria. “Are they informed consumers? Do they fully understand the medical procedures and treatments they are requesting? Is their experience of gender stable and enduring?”

Even people with autism who are severely affected can meet these criteria, says Rachlin, who serves on the board of directors of the World Professional Association for Transgender Health. “My experience is that even if their interpersonal deficits are severe, people are still more comfortable in their affirmed gender, no matter what else is going on in their life.”

People with autism sometimes have difficulty getting their needs met by healthcare providers due to the social and communication deficits associated with autism, says Rachlin: They may not keep their appointments, for example. “It’s not necessarily that professionals are discriminating against them on the basis of their autism,” she says.

Also, those who struggle to understand that others have beliefs, desires and perspectives that differ from their own — an impairment in ‘theory

of mind’ common in people with autism — may not comprehend that others do not see them in the same way they see themselves. A person with autism may not realize, for example, that to be seen by others as a woman, they must adjust their grooming and appearance. Some of Rachlin’s clients resist taking even small steps in that direction, she says, insisting that they don’t care what other people think at the same time that they express great distress at not being correctly identified in their affirmed gender. Some also complain of deep loneliness and isolation, yet avoid social situations, refusing to attend even trans-related events and support groups.

Still, she cautions that sometimes, what looks like autism may actually be untreated gender dysphoria. “So much of the experience of being trans can look like the spectrum experience,” she says. People who don’t want to socialize in their birth genders may seem to have poor social skills, for example; they may also feel so uncomfortable with their bodies that they neglect their appearance. “That can sometimes be greatly alleviated if you give that person appropriate gender support,” she says.

Others agree with these insights. A 2015 study by researchers from Boston Children’s Hospital reported that 23.1 percent of young people presenting with gender dysphoria at a gender clinic there had possible, likely or very likely Asperger syndrome, as measured by the Asperger Syndrome Diagnostic Scale, even though few had an existing diagnosis. Based on these findings, the researchers recommend routine autism screening at gender clinics.

But they also note that some symptoms, such as feeling different and being isolated, are associated with both conditions. Other symptoms in common include not maintaining eye contact and spending a lot of time online, according to Amy Tishelman, assistant professor of psychology

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”

KATHERINE RACHLIN

at Harvard Medical School, who worked on the study. Even the preoccupation with gender is analogous to the obsessive interests common in autism.

Tishelman says better screening and diagnostic tools, as well as specific interventions, are required for children who have both autism and gender dysphoria. “We need to develop interventions that will help them with the even more complex navigation of social circumstances,” she says.

The resistance of some parents to dual diagnoses also presents challenges. At Children’s National in Washington, D.C., some parents of children being treated for gender dysphoria were reluctant to accept that their child might also have autism, Strang says. Conversely, parents of children and teens previously diagnosed with autism wonder whether what looks like gender dysphoria may simply be an obsessive interest that will disappear in time. “Parents have expressed concerns that for some kids, gender can become a passing fixation, just like trains used to be,” Tishelman says. “There can be hesitation [about allowing their child to transition] on the part of some families because of that.”

DIFFICULT CHOICES

Kathleen and Brad, parents of a teenager with Asperger syndrome, were flummoxed when Jazzie (Brad’s nickname for his daughter), then 14, told first her school counselor and then her mother that she was trans and that she wanted to begin hormone therapy to physically transition to the female gender. Jazzie had been diagnosed with Asperger syndrome at age 3. Her parents, particularly Kathleen, had fought a seemingly never-ending battle with public school administrators and teachers to get her the legally mandated services and accommodations she needed.

From her parents’ perspective, Jazzie’s announcement came out of the blue. They were cautious about approving irreversible medical interventions such as hormone therapy, in the event that gender proved to be a passing fixation. “[Jazzie] never said, ‘I’ve been feeling this way for years,’ or that she’d felt like this since elementary school,” says Kathleen.

But for Jazzie, it felt like her parents were “being idiots” and refusing to trust her. She spent much of her 15th and 16th years feeling resentful. “I felt like time is running out, my body is destroying itself and you are not letting me fix it,” she says now, at age 18.

Jazzie began taking hormones and using a feminine name and pronouns her last year of high school, when she was 17. “It does feel to me like if I had started sooner, I would be more me. But now, since I started so late, it’s harder to physically become as I should be,” she says. “I’m more half-formed than I should be physically.”

Brad attributes Jazzie’s assumption that her parents should have known about her gender dysphoria to Asperger syndrome. The difficulty people with autism sometimes have understanding other people’s beliefs and emotions made it hard for her to grasp that her parents could not have known

about something so clearly evident to her, even though she never articulated her feelings of gender dysphoria. “She felt like we should have known,” Brad says. “But we had to tease it out of her.” Having helped a colleague transition on the job more than 20 years ago, Brad was better informed than many parents about the process, but like his wife, he felt it best to proceed cautiously.

In retrospect, Brad and Kathleen can identify a couple of incidents that might have pointed to childhood gender dysphoria — such as the time they found Jazzie, then 6, under the bed wearing pantyhose. Kathleen then found that Jazzie had stashed her old pantyhose in a desk drawer, but she assumed that Jazzie wore them because they provided the same kind of sensory comfort as the compression suit she sometimes wore at school.

Meanwhile, Jazzie insists that she has experienced gender dysphoria since early childhood. “I felt like I wasn’t a guy,” she says now. “But it wasn’t until middle school that I started feeling super distressed about it.” She has been Googling words related to gender and its variations since she was 8 or 9, she says.

Once Jazzie’s parents were sure gender wasn’t a temporary obsession, they helped smooth her transition at school by speaking with teachers, guidance counselors and administrators. They already knew how to advocate for her; their experience with autism had prepared them for this new challenge.

The parents of 5-year-old Natalie are just embarking on that journey. Referred to the autism clinic at Children’s National when she was less than 1 year old due to developmental delays, Natalie exhibited signs of gender nonconformity from a young age. When their grandmother took the family on a cruise and provided miniature captain’s suits for all the kids to wear, her brothers strutted proudly around the cabin when told how handsome they looked. Natalie, then 4, burst into

tears, saying, “I don’t want to be handsome, I want to be pretty.” That year, she insisted on dressing as Queen Elsa from the Disney movie “Frozen” for Halloween.

Natalie’s father watched these developments with foreboding. “I’ve known something was up since she was 1 and a half,” he says. Natalie’s choice of toys and fantasy roles, her style of play and her mannerisms all pointed in the feminine direction, even before she was able to articulate her gender identity in words. It disturbed him, he says: “I wanted her to be a boy.” For a year, the two battled it out, but faced with a deeply unhappy and recalcitrant child, “finally, I said, ‘Okay, be a girl.’”

Since then, Natalie has been much happier, he says. He and his partner are still working out the details of Natalie’s transition to her new name and pronouns at school, and wrestling with their own feelings about the challenges ahead. Making decisions on her behalf, and supporting and advocating for her in school and in the community, is more difficult due to the lack of data on outcomes for gender non-conforming children on the autism spectrum. “Right now, we’re just taking our cues from her,” her father says. “She is still trying to find her space.”

Although science provides little help to parents of children like Natalie right now, that may soon change. Until now, all of the published studies on the co-occurrence of autism and gender dysphoria have been incidence studies, confirming that the two conditions appear together more often than expected by chance. Hoping to move the science to the next level, Strang contacted all those who have published on the phenomenon, as well as experts at gender clinics around the world. For the past two years, this group has discussed their experiences and ideas online. The result is a position paper and set of initial guidelines for diagnosis and treatment supports for people with co-occurring gender dysphoria and autism spectrum disorders.



Finding herself: Grobman, who has autism, was initially terrified to consider she might also be trans. Today, both aspects are part of her identity.

This document will lay out best practices, perhaps preventing the kind of clinical misunderstanding that drove Kayden Clarke to despair.

Strang hopes the paper will be published within the next six months. “These kids need support,” he says.

In March 2016, North Carolina legislators passed a law barring trans people from bathrooms and locker rooms that do not match the gender on their birth certificates. For trans people with autism, who are often socially naïve and unaware of how they are perceived by others, such laws present a very real threat of the kind of confrontation they are ill-equipped to manage. Strang’s group works to help the children and teens in their

program deal with such challenging situations. “We focus a lot on safety,” says Strang, “what it means to be trans in different types of communities.” Autism can create blind spots around those issues, he says, but he and his colleagues also recognize its gifts, such as intense focus and concentration.

Grobman too sees those aspects of autism as integral to her effectiveness as an activist. Her intense focus on trans and disability rights may be an obsession of sorts, she admits, but unlike her childhood preoccupation with the game Pokémon, this fixation is not trivial. Living with the threat of being bullied, assaulted or arrested for using the ‘wrong’ restroom generates near constant anxiety. Grobman says she feels driven to work for the kind of social change that will make the world a safer place for people like Ollie, Natalie, Jazzie and herself. “We need to create an understanding of the validity of trans experience and autistic experience,” Grobman says. “You are fighting for your own existence.”

Ollie seems to share that belief. Immersed in the struggle between the Rebel Alliance and the Galactic Empire on his dining room table, he keeps up a running commentary that seems an oblique reference to the challenges he faces. “They need reinforcements,” he says. “This is the last squad of troops, and they are trying to survive.”
