THE AUTISM SEX BIAS
Boys are diagnosed with autism at more than four times the rate of girls. Scientists are trying to figure out why, but this much is becoming clear: 

All that we think we know about autism is only half the story.

When Frances was born, she was an undersized but easy baby—healthy, happy, social.

As she got older, she was slow to roll over, to crawl and to take her first steps. She didn’t always respond to her name. And while she could seem somewhat disinterested in the people around her, she was consumed with Henry the octopus from the kids show *The Wiggles*. And it was a stuffed Henry toy that finally, at age 3½, coaxed out her first word—a full phrase, actually: Frances had excitedly just opened the gift when her mom teasingly claimed the doll as her own. Frances screamed: “Henry! That’s my Henry.”

Her father, Kevin Pelphrey, was a recently minted PhD in psychology from the University of North Carolina at Chapel Hill, working as a postdoc studying cognitive neuroscience at Duke. He’d often discussed his daughter and her struggles with his -

STORY BY Kristen Mitchell
I had a degree in child psychology, and I was willing to accept the answer, ‘She’ll grow out of it,’ because I liked hearing that,” Dr. Pelphrey says.

But fathers can be forgiven a little wishful denial. And physicians are reminded over and over in their training that when they hear hoofbeats, look for a horse not a zebra—that an ailment is likely the garden-variety thing, not the exotic exception. A girl with autism was a zebra.

Today, boys in the U.S. are affected at four-and-a-half times the rate of girls: 1 in 42 versus 1 in 189, according to the Centers for Disease Control and Prevention. As a result, for decades it’s been the boys with autism who overwhelmingly are the ones enrolled in studies, and it’s boys for whom treatments and interventions are designed. Now researchers are realizing that the textbook definition of autism—the repetitive behaviors, impaired communication and social interactions—might pertain only to boys, too.

Shorty after the suggestion that Frances may have autism, Dr. Pelphrey took her for a day of testing at Yale University’s Child Study Center. After evaluations by a psychologist, a social worker and a speech pathologist, she was officially diagnosed with autism.

The mysteries surrounding her condition and the meandering path to a diagnosis eventually would become the driving force of Dr. Pelphrey’s career.

He was studying the human brain and how it comprehends other humans, but “never really cared about its application. It was just knowledge for knowledge’s sake,” he said in an emotional speech at GW in October, eyes red with stifled tears. “[I]t was my daughter Frances that shaped my career into something that’s been incredibly, incredibly valuable for me.”

Dr. Pelphrey became a professor at the Yale Child Study Center, where Frances
was diagnosed, and the founding director of a center for developmental neuroscience at Yale. Then last year, he came to GW to launch its Autism and Neurodevelopmental Disorders Institute and to fill a new endowed professorship (the Carbonell Family Professor in Autism and Neurodevelopmental Disorders), bringing along $20 million in grants, including a $15 million grant from the National Institutes of Health to mine the conundrum of girls with autism.

“He’s now really known as the go-to person in the field,” says Lisa Gilotty, a program chief at the NIH’s National Institute of Mental Health who oversees autism research, including Dr. Pelphrey’s grant.

His unprecedented explorations into the brains of kids with autism now lead him to believe that the boy-to-girl ratio is probably more like 2 to 1, instead of 4.5 to 1, and that what we think we know about autism is certainly only half the story. The differences in autism between the sexes, he says, is “actually very fundamental to what autism is.”

FRANCES PELPHREY IS NOW 13 and, in a lot of ways, is a typical middle-schooler. She’s in love with Zac Efron, she likes her music loud and she’s inseparable from her phone.

Dr. Pelphrey has said that 10 years earlier, when doctors were stymied by her symptoms and inclined to wait it out, they would have been more proactive were she a boy. The problem is that time in those first years is crucial.

His son Lowell, the youngest of three biological kids (he and his wife, Annie, have five children altogether), was ½ when he came to the attention of doctors. He was about to participate in a control group made up of the typically developing siblings of children with autism when Yale researchers discovered Lowell wasn’t making appropriate eye contact for his age. He was diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified, or PDD-NOS, a gray area under the autism umbrella in which a person typically has social or communication impairments but not all of the features of the more defined subgroups.

He began an intense weekly regimen of 32 hours of behavioral therapy and after four years, Lowell, now 8, was no longer considered to be on the autism spectrum, although he does tend to shy from social interactions, Dr. Pelphrey says, and to speak in a “direct and precise,” almost scholarly cadence.

Coming off the spectrum is rare, but studies have shown that an early jump on therapy can give kids with ASD critical developmental and social boosts, and the American Academy of Pediatrics recommends screening children as early as 18 months old in order to get them into the treatment pipeline.

But girls, historically, have not had the benefit of that early and often life-changing intervention because their symptoms go overlooked.

Girls with ASD tend to have better social skills and often are less disruptive than boys with ASD, and even their typically developing male peers, Dr. Pelphrey says. Frances, for instance, has always sustained good eye contact, while difficulty with that is considered one of the hallmark red flags of ASD. Instead, he says, for Frances and some other girls with autism, difficulty regulating emotions is more of a distinguishing feature.

Obsessive lining up or ordering of objects is common, too, but may be more apparent in boys because of the inanimate objects, like cars and trains, that a boy might be more prone to play with, Dr. Pelphrey says.

“If a girl is more likely to be interested in dolls and is lining up dolls, it looks more typical because she’s lining up social objects when really she is just lining them up like they’re dominos,” he says.

The issue of girls with autism being underidentified by doctors and teachers and little-understood by researchers became a self-perpetuating cycle.

Donna Werling, a postdoctoral researcher at the University of California-San Francisco, worked in Dr. Pelphrey’s Yale lab a decade ago as an undergraduate. “At that time, everyone would report there was a sex bias in autism diagnosis,” she says, “but they would go on to use that as an excuse not to include girls.”

Today Dr. Werling studies how typically developing boys and girls are different on a genetic level, and how those differences relate to autism. The underdiagnosis of girls makes her work difficult.

“Inherently, the work that we’re doing is challenged by the fact that the samples we have available to us are more biased toward boys than they should be,” she says. “Hopefully, time will fix that.”

Funding for studies focused on sex and gender differences in people with autism is on the rise. In 2015, some of the top organizations funding autism research designated more than $6.4 million for 11 projects on sex differences, compared to slightly more than $300,000 on two projects in 2008, according to an analysis by Spectrum, an autism news site that is an editorially independent wing of the Simons Foundation Autism Research Initiative.

Dr. Pelphrey predicts it will take at least another decade for the information about girls with ASD to match the mass of information available about boys with ASD.

Part of the obstacle in gathering that has been the way autism is diagnosed. Most children with autism are diagnosed through observation and an intensive, hourslong oral exam with their parents, who are questioned about their child’s behavior. Answers are scored on a scale and plugged into a formula to determine where on the spectrum a child might be.

The infinitely individualized nature of autism has so far eluded any singular biological signature—a gene, a chemical disruptor, a brain wave—that can be screened for. Instead there’s a growing list of promising biomarkers, each indicative of some piece of the autism equation, for some people with autism.

It’s an effort to understand autism from the inside out, and the intellectual abyss of the brain and genetics offers an opportunity for scientists of just about any stripe to bring their chops. There is no scientifically
agreed-upon cause of autism, and people on the spectrum range from those with severe language and mental impairments to those who live and thrive independently.

Dr. Pelphrey got involved as a side project while he was a postdoc at UNC; he was working in developmental psychology, building a wearable camera for infants that would track the direction of their gaze.

A mentor, UNC professor Joe Piven, who heads the Carolina Institute for Developmental Disabilities, suggested he use the tool to study people with autism. The result, in 2002, was the first study—albeit a very small one—to compare the eye movements of five adult males with autism and five without as they looked at a photo of another person’s face, which has been cited 900 times in the years since.

While the path of movement for the control group generally formed a triangle across the eyes, nose and mouth, the eyes of the group with autism tended to roam less—revealing facial features, like an ear or chin, Dr. Pelphrey and his colleagues wrote. The findings, they said, could point to a reason why people with autism experience difficulty with facial perception and with reading a person’s affect, or it may be the result of a broader information-processing issue.

Dr. Pelphrey was still primarily interested, though, in more broadly understanding the so-called “social brain,” the parts that process things like facial expressions, posture, movement—the nonverbal signaling we absorb and use to make sense of other people.

Occasionally that veered into autism research over the years, including, in a big way, in 2010. Dr. Pelphrey and a team from Yale compared the brain activity of kids and teens with autism with that of their unaffected siblings and of typically developing kids as each group watched a video of familiar human movement, like someone playing pat-a-cake.

They found brain regions where there was reduced activity only in the autism group, and they found areas of the brain where both the autism group and their unaffected siblings had reduced activity—indicative, they suggested, of some shared genetic risk for neurodevelopmental disorders.

But most intriguing: Only among the unaffected siblings, they also found heightened activity in areas of the brain that aren’t typically involved in processing that kind of visual data. It was almost as if the brains of the unaffected siblings had found an alternate route, compensating for deficits by circumventing them.

“Development is an active process,” Dr. Pelphrey says of the brain, drawing an analogy to rivers carving through a landscape. “It’s not just an unfolding plan; it’s not just the unfolding of a preconceived destiny. And with that, you’ve got the opportunity for flexibility. This one gene is pushing you, but the rest of your body is constantly trying to get back [on track].”

Exploring this kind of issue through the engines of genetics and brain imaging at once was an intensely powerful tool—one autism researcher, who was not part of the study, told a reporter at the time that using them to reach this finding was “nearly unprecedented.”

The next step for Dr. Pelphrey would be to add people and time. He wants to build a data set that might even be considered, in his words—those of a man who scraps daily with the love, the pain, the elation and the biological wonder of autism—“a national treasure.”

Eventually, he has said, “I would like for anyone in the D.C. area who Googles ‘autism’ to see that they have a place to come that has everything they need.”

That place, a 10,000-square-foot clinical center that Dr. Pelphrey’s institute is building at GW’s Virginia Science and Technology Campus in Ashburn, is expected to open in the fall. It will be a place for diagnosis and therapy, with specialists onhand from mental health and medicine to nursing, occupational therapy and speech and hearing sciences, working together, as well as with clinical and research partners from Children’s National Health System.

Also planned are training opportunities for graduate students and undergrads, and a second location in Monroe Hall on the Foggy Bottom Campus.

The idea is to take what’s learned in the lab—from a molecular level on up—and use that to build more targeted autism treatments and interventions for use in the clinic. When one of those works, or doesn’t,
The team will break it down to its molecular level again to figure out why, and then push that knowledge into even-more-tailored treatments and, possibly, translate it outward into efforts to influence public policy.

At the moment, though, it’s the basic science that’s giving the young institute its oomph and confident stride into a competitive field.

“Kevin has always been very innovative,” says Dr. Piven, the mentor from his days at UNC. “He’s not doing the 10th study of some idea, he’s often doing the first study.”

In 2012, Dr. Pelphrey, while still at Yale, was awarded a five-year, $15 million grant from the National Institutes of Health to lead a network of researchers in trying to understand the nature of autism in girls and how it differs from that of boys. It was part of a $100 million assault on autism’s vagaries that year by the NIH, funding nine centers and networks, with Dr. Pelphrey’s the only one exploring sex differences.

Since then, Dr. Pelphrey—along with collaborators at Harvard University, Seattle Children’s Hospital, the University of California-Los Angeles, the University of Southern California, Yale and, now, GW—is building what the team of researchers is calling an unparalleled study sample: 250 girls with autism and 250 boys, 100 each of sisters and brothers of people with autism, and 100 each of typically developing girls and boys, all within the range of 6 to 17 years old.

They’ve been stratified by their observable, behavioral characteristics; they’ve had extensive brain imaging; their genomes are being sequenced and their gene expression—the turning on or off of a gene, and when—is being analyzed.

So far they’ve used that data to generate some 50 peer-reviewed articles, which have been cited nearly 2,000 times. Among them is a 2016 study that found brain imaging can predict which kids with autism will benefit from one of the only evidence-based therapies, called pivotal response treatment.

Another study, published in 2016 by Dr. Pelphrey and others, turned again to brain activity in the regions responsible for processing biological motion. The researchers found that they could look at that brain circuit and predict with 76 percent accuracy who was affected by ASD—but it only worked on the boys. The technique could not distinguish a girl with autism from a typically developing girl.

“This was incredibly important for us to understand, because it might be that everything we thought we knew, really, was specific to boys,” Dr. Pelphrey said last year during a public lecture through the Interactive Autism Network.

“We’re doing a great job of characterizing the neurocircuitry that’s disrupted in boys. Our whole field should be proud of that,” he said. “But we’ve overlooked the girls.”

Still, the findings could have enormous implications for diagnosing boys with autism and getting them earlier access to treatments. It also gets researchers one step deeper into the fog of the girl question. They’re hunting now for the equivalent biomarkers in girls. But if girls are somehow being shielded, or even compensating for autism’s deficits, the answers stand to benefit both sexes.

Entering the final year of the grant, which Dr. Pelphrey hopes to renew, he’s anxious to begin tracking the study group through the transition into adolescence and adulthood, and to see how the childhood data bears out over time.

Similar to the all-absorbing brains of newborns and toddlers, and the emphasis on early intervention for them, he says, neurologists are finding that adolescence brings a second window of brain plasticity and potential growth. “You’ve got this massive reorganization in the brain as well as this reorganization of societal demands,” Dr. Pelphrey says. “So it’s a time when you can either get worse or be doing better. We’re hoping to understand how that transition happens.”

And whether he’s looking for them or not, similar changes will be underway at home, too, as Frances transitions into adolescence.

Fixations with children’s TV shows have given way to fixations with boys, and requests for him to print out photos of Zac Efron for her. The answer is always no.

But he’s come to appreciate her bare honesty, and that it keeps open a window that might be abruptly shut for other fathers of teenage girls.

“Growing up, my sister never discussed boys with our dad,” Dr. Pelphrey says. “Frances tells me more than I want to know. It’s cute.”
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Sometimes things don’t work out. Colombian-born Corcoran professor Juana Medina knows this as well as anyone. But the children’s book illustrator and author also knows that sometimes they do, and that's enough to keep her cheery in the face of gloom.
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Speaking of drinks (p. 48), what’s your go-to beverage?

“Nitro stout. The robust flavors and dense, smooth texture—it’s like settling into a pillow of beer.”

“Club soda with apple cider vinegar. Every morning.”

“A glass of viognier. Good ones are more vibrant and rich than most white wines, plus ordering it makes me feel like a sophisticated fancy lady. ‘Vee-own-yay, please.’”

“I fell in love with rosé on a springtime trip to Paris—brings back great memories!”

“Horchata, from a SoCal taco truck at approximately 1am. It is the drink of its time and place.”

“Thai ice tea, because it’s practically a dessert.”

“Sicilian white wines. Sicily is known mostly for reds, but I think the whites are refreshing and surprisingly affordable.”

“Moscow mule. I love the flavor and the ritual of the copper mug.”

“Diet Coke is probably tearing a hole in my stomach. I don’t even want to think about what the bourbon’s doing.”

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