Chronicle of a Field Retold:

Autism Science in Profile

SPECTRUM

PROFILES

CONTENTS

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INTRODUCTION

"Most people say that it is the intellect which makes a great scientist," Albert Einstein famously said. "They are wrong: It is character." Arguably, it's a mix of both—but there is something to be learned from looking at scientists beyond their published works. That's exactly what we set out to do for our fifth annual book. Instead of reflecting on autism through studies, theories or statistics, we sought a more personal lens: the lives of the people who study it.

The scientist profiles that fill these pages reveal that autism researchers are, perhaps unsurprisingly, a heterogeneous bunch. Not only do their academic areas of interest vary widely, but outside of the lab they are marathon runners, mountaineers, bicyclists and basketball coaches; foodies, yogis, musicians and spelling-bee champions; former teachers, farmers, Peace Corps volunteers and emergency medical technicians. The end pages of this book feature more vignettes of life "beyond the bench" (page 190).

For all of their differences, though, more than a few share deep connections to autism and disability, and core descriptions about these researchers recur—creative, persistent, adaptable and collaborative. *Spectrum* previously highlighted collaborations in the field, creating a network map that can be viewed by following the QR code below. For this collection of scientists, we also built a family tree of mentors and mentees across eight decades, which we hope to expand in the future (page 70).

The book begins at the base of that tree. In "The new history of autism," journalist David Dobbs draws the roots of the autism field back to women and other scientists whose forgotten work predated or enabled that of Leo Kanner and Hans Asperger, long credited as the sole founders of the field (page 7). To look out beyond the tree's branches, we asked our profile subjects about the most promising young scientists they have worked with in recent years—an exercise that led to our list of "40 under 40" autism researchers (page 112).

We also asked our profiled scientists for updates, including career shifts and significant accomplishments since their profiles appeared on *Spectrum*. And for each one, we compiled a list of their highly cited papers, using Clarivate's Web of Science. For some researchers, we included their full profile as it originally appeared; for others, we included a QR code back to their profile on our website.

We hope these pages show autism research in an exciting time of flux, propelled by what these scientists care about, what questions drive their work and where they think the field is headed next.

— the *Spectrum* team

Researcher Connections
https://connections.spectrumnews.org





THE NEW HISTORY OF AUTISM

For decades, two figures have dominated the history of autism studies. Today, newly excavated documents are calling into question the primacy of these men as founders of the field.

BY DAVID DOBBS

with fact checking by Yvonne Bang

For 40 years, Leo Kanner and Hans Asperger have dominated virtually every story about the 'pioneers of autism research.'

These two men published in 1943 and 1944, respectively, what were long accepted as the first descriptions of, as Kanner's seminal paper claimed, "children whose condition differs . . . markedly and uniquely from anything reported so far."

Both papers are absorbing, touching and authoritative. Both describe young people whose challenges defied the known diagnoses of the time but clearly fall into what we now call autism. And both offered a new diagnostic category for such people.

Kanner's 1943 paper, "Autistic Disturbances of Affective Contact," drew almost immediate attention. Within a year, he renamed the condition these children shared, dubbing it 'early infantile autism,' which soon became known as 'autism' or 'Kanner's syndrome.' His articulation of the condition, based on observations of 11 children he and his associates treated in his Baltimore, Maryland, clinic, remained the standard well into the 1980s and involved three elements: Autism was a condition marked by: (1) emergence early in childhood, (2) deficits in communication and social interaction, and (3) restricted or repetitive behaviors and a desire for sameness. Even today, these three elements anchor the official diagnostic criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, as well as the widely used International Classification of Diseases and Related Health Problems.

Asperger's 1944 paper, which presented case studies on four children he and his colleagues had seen in his clinic in Vienna, Austria, made its impact far more slowly. In fact, because Asperger published in German (and in a German journal in the middle of a war that had essentially halted transatlantic scholarly exchange), the paper went largely unnoticed outside Europe for decades. Asperger's descriptions resembled Kanner's in many ways, although he outlined a wider apparent range of intelligence and capabilities than Kanner

did, with some of his study participants reaching prominence in their fields. Asperger coined the diagnostic term 'autistic psychopathy.'

Scholars quietly debated how much the two conditions actually diverged: Were they fundamentally different or just different sets of variations in certain traits? Asperger later acknowledged the similarities between his and Kanner's syndromes, but he considered them different: He saw Kanner's infantile autism as a psychotic process of disintegrating capabilities, often resulting from physical issues during birth, but regarded his autistic psychopathy as a stable 'personality type' present early in childhood.

The two descriptions finally merged in 1981 in the astonishingly influential paper "Asperger's Syndrome: A Clinical Account," by British psychiatrist Lorna Wing. Wing argued that Kanner's autistic clients and those Asperger described, who had a condition she dubbed 'Asperger's syndrome,' were part of a wider range of people—soon known as 'the spectrum'—who shared some mix of impairments in social interaction; deficits in comprehension and use of language; and the presence of 'repetitive, stereotyped pursuits.'

Wing's paper prompted a rush of scholarly interest in Asperger's syndrome and autism in general. It also ushered in a decade during which popular works both about and by autistic people, such as the 1988 movie "Rain Man" and Temple Grandin's 1986 hit autobiography, "Emergence: Labeled Autistic," drew broad public attention to the condition for the first time. Asperger became as well known as Kanner in academia and a household name in popular culture, cementing the two men's reputations as the dual founders of autism studies—or "the two great pioneers," as Adam Feinstein called them in his 2010 "A History of Autism."

In the past decade or so, however, the excavation of several long-overlooked papers and other archival material has called into question the primacy of Kanner and Asperger as 'founders.' It's now clear that at least one researcher beat them to their discoveries. And others have played key, previously unrecognized roles in Kanner's and Asperger's own work.

The ongoing revelation of these contributions does more than add to a list of 'discoverers' or 'pioneers.' It also reminds us that, as historian Stephen Haswell Todd has noted, science and medicine usually advance not via eureka moments or individual discoveries, but by an accrual and evolution of observations and ideas—"a gradual process of interpretation and reinterpretation"—that leads to new ways of recognition or thinking.

As we'll see, autism, as a particular and remarkable condition, was not just noted but depicted in detail more than once before Kanner codified it in 1943. And although Kanner himself may have missed some of these descriptions (and enjoyed his status as the field's founder), he recognized that autism was a collection of visible traits, even if seeing it was a matter of being in the right place at the right time, and with a certain set of questions in mind.

"I did not discover autism," he said in a 1969 talk. "It was there before."

Beating Kanner to the punch

Descriptions of people who were likely autistic go back at least as far as the 13th century. At that time, Lorna Wing notes, a monk named Brother Juniper—a follower of St. Francis of Assisi who was described as "naively innocent and lacking in any social intuition or common sense" and nicknamed "the renowned jester of the Lord"—may well have been autistic. Another 36 people who

probably had autism turned up among records that a pair of Russian-speaking scholars at the University of Michigan examined in 1974. All of these "holy fools" had lived in self-isolation, "unhampered by society's preconceptions," and been declared saints by the Russian Orthodox Church as long ago as the 1400s. And there "can be no doubt," Wing wrote, that Victor, a boy found living in the woods of Aveyron in France in the late 1700s and educated by physician Jean Marc Gaspard Itard, was autistic. The medical literature occasionally notes roughly similar cases beginning in the 1800s—for instance, John Langdon Down, a British physician and superintendent of an asylum, who first described the genetic syndrome that bears his name, gave a 1887 lecture about several children distinguished by what we would now recognize as Aspergian powers of memorization.

The recognition of autism—of an 'infantile' or childhood condition—depended partly on an understanding of childhood as a distinct period of life. In the West, this way of thinking began in the mid-1700s, when philosophers John Locke and Jean-Jacques Rousseau were among the first to frame childhood as a time of sanctuary and education before the trials of adulthood. When the industrial revolution all but enslaved many children in factories, reformers pushed not just for protections from such exploitation but for schools and specialized medical care for children.

By the 20th century, the rise of pediatrics had merged with the Victorian-age growth of psychiatric asylums to produce the first psychiatric clinics specifically for children—a requisite for the insights of early autism researchers. One of the first of these clinics was established in Moscow, where in the early 1920s a young Jewish child psychiatrist treated 11 children—6 boys and 5 girls—with what she initially called 'schizoid psychopathy' and later renamed 'autistic psychopathy.' Grunya Sukhareva published her findings about the children in two German papers—one in 1926, about the boys, and a 1927 paper about the girls—in which she stated that the cases represented a previously unrecognized group of disorders. Today, these case studies read as descriptions of children with autism; their traits match both Kanner's and Asperger's criteria as well as today's official diagnostic guidelines in the Diagnostic and Statistical Manual of Mental Disorders and elsewhere.

Sukhareva went on to publish more than 150 papers and several books, becoming the most prominent Soviet psychiatrist of her generation. That her work has been almost invisible for nearly a century is one of the oddest things in the odd history of autism studies. The biggest puzzle, as British child psychologist Sula Wolff notes in her 1996 English translation of Sukhareva's 1926 paper, is how Kanner and Asperger could have been unaware of that earlier and most relevant work when they wrote their own pivotal accounts of autism in 1943 and 1944.

That neither Kanner nor Asperger knew of Sukhareva seems possible but unlikely. Both men read almost anything they could find about withdrawn, schizophrenic, 'schizoid' or 'psychopathic' children. Both men had well-read staff who likewise might have come across Sukhareva's work. Both cited other articles from the journal in which Sukhareva published her 1926 and 1927 papers, the Berlin-based *Monatsschrift für Psychiatrie und Neurologie (Monthly Journal of Psychiatry and Neurology),* which was prominent among the handful of European journals covering autism and schizophrenia. In a 1949 article, Kanner even refers to another of Sukhareva's autism papers, from 1932,

saying that autism "is so intimately related to the basic nature of childhood schizophrenia as to be indistinguishable from it, especially from the cases with insidious onset discussed by Ssucharewa." So how had he and Asperger overlooked her work six years earlier?

Addressing this conundrum raises uncomfortable possibilities. Several scholars posit that Asperger, anyway, immersed in European journals, probably came across one or two of Sukhareva's autism papers but did not mention them (or works by other Jews) because of the institutionalized antisemitism of 1930s and 1940s Austria. Likewise, given the depth of sexism in Western culture, it's possible that Kanner and/or Asperger found it convenient to ignore Sukhareva's work simply because she was a woman. Anti-Soviet feelings might also have played a role.

"I did not discover autism. It was there before." —Leo Kanner

Sukhareva's larger and ongoing obscurity may also rise partly from the messy nomenclature surrounding autism. Today (and generally since Kanner's 1943 paper), the term 'autism' refers to a broadly defined but distinct syndrome that emerges in early development, produces deficits or peculiarities in social interaction, and features repetitive or restricted patterns of behavior, interests or activity. But from the word's 1908 coinage by psychiatrist Eugen Bleuler until the 1940s, 'autistic' had a much simpler but broader meaning: It referred mainly to the self-absorption and withdrawal often seen in schizophrenic people. Until Kanner's usage came along, in other words, 'autism' didn't denote a condition or syndrome; it simply referred to a symptom often accompanying schizophrenia or similar states.

Another confusing term from those early days of autism studies—and in the title of Sukhareva's 1926 and 1927 papers—is 'schizoid,' a word defined vaguely in 1922 that in practice covered so wide a range of mental illness that it could seem to refer to almost anything. The closest thing to a core definition is social withdrawal, particularly if associated with schizophrenia (note the confusing overlap with Bleuler's 'autistic'), but often it meant schizophrenia-*like* instead. To make matters worse, the differences between 'schizoid' and 'schizoid type,' and between 'schizophrenia' and 'schizophrenic,' were also indistinct. A diagnosis called 'schizoid personality disorder,' for example, referred to (and still does) someone detached from personal relationships and limited in their expression of emotions—traits in common with the social withdrawal element of autism.

Finally, the word 'psychopathy,' as Sukhareva used it, referred not to antisocial psychopaths or psychosis, but merely to disturbances of mental health (*psycho-* meaning mental, *path-* meaning disease). One 1919 definition says psychopathy "refers

to cases situated on the boundary between mental illness and mental health"—an *-ish* sort of word.

So although Sukhareva's title for her 1926 paper—translated as "Schizoid Psychopathy in Children"—may today suggest to us young schizophrenic sociopaths, it was actually about a mental disturbance involving social withdrawal in children. Sukhareva later, in fact, referred to them as cases of 'autistic psychopathy'—which was precisely the term Asperger gave to the condition he described. Kanner, meanwhile, opined that Asperger's and others' usage of 'autistic psychopathy' referred to autism. One of the most thorough Sukhareva scholars, Charlotte Simmonds, who translated one of Sukhareva's papers and wrote a dissertation on Sukhareva for her Ph.D. in philosophy at the Victoria University of Wellington in New Zealand, considers Sukhareva's work on schizoid psychopathy "a far more detailed clinical picture of the syndrome than Asperger's paper of 1943," which was published 1944.

Sukhareva had observed these children at the small hospital school her Moscow clinic ran. As with Asperger's and Kanner's clinics, Sukhareva's allowed the clinicians to spend extended time with their patients and get to know them well. And like Asperger and Kanner, Sukhareva wrote clinical descriptions rich in detail and almost novelistic in their attention to the conflicts between the children's seemingly regimented inner lives and their place in a more chaotic society.

Ten-year-old M.R., for instance, is "unsociable, isolating himself from other children." Another patient is extremely talkative, with conversation "marked by repetitive, obsessional themes," yet never takes part in the school's communal games, has a "flattened" affective life with muted reactions to almost everything, and "lives in a fantasy world" of obsessional states and compulsive counting. Another child, distinctly Aspergian in his obsessions, began speaking rhymes at age 3 but is nicknamed "the talking machine" by the other children, whose games he avoids.

In her summary, Sukhareva identifies several traits that distinguish this group: an "odd type of thinking" marked by abstraction and "a tendency to . . . absurd rumination"; an "autistic attitude" that steers them away from others and leaves them "never fully themselves among other children"; and tendencies toward obsessive-compulsive behavior.

But Sukhareva didn't merely describe an Aspergian-like autism. By detailing a specific but broad view of autism, she anticipated not just Kanner and Asperger but the rise of the 'spectrum' view of autism that would be spurred 55 years later by Wing and by the activism of an increasingly connected autistic community.

Sukhareva's pivotal papers, then, were far ahead of her time. Yet even as the autism field expanded postwar, even after Kanner had cited her paper in 1949, even as she remained active in the field into her 70s and lived to 89, her work remained sparsely cited and, outside the Soviet Union (and later Russia), scarcely noticed.

"Citations," wrote bibliometrician Blaise Cronin in 1981, "are frozen footprints in the landscape of scholarly achievement, footprints which bear witness to the passage of ideas." And, as other scholars have noted, "citation is coloured by a multitude of factors. . . . Social and psychological factors play a part, along with 'subconscious remembering as well as forgetting.'" The scarcity of Sukhareva's footprints in the autistic literature is a dark mystery, as Wolff suggested in 1996, that "remains unanswerable."

Forgotten collaborators

Also faint are the prints left by two other pioneers in early 20th century autism research who, Zelig-like, managed to be present in both Asperger's and Kanner's labs at critical points in those men's work. Anni Weiss and Georg Frankl, both born in 1897, started their careers in the mid-1920s as key clinicians and researchers at a children's psychiatric clinic at the University of Vienna. Weiss, who studied child psychology and social work, was there from 1927 to 1934; Frankl, a psychiatrist specializing in children's issues, held a post there from 1925 to late 1937. Though their roles were critical to the identification of autism, their very existence was almost completely obscure until 2015, when journalist Steve Silberman and historian Stephen Haswell Todd, respectively and independently, discovered and then wrote of them in Silberman's book 2015 best-selling "Neurotribes" and Haswell Todd's 2015 dissertation, "The Turn to the Self: A History of Autism, 1910-1944."

The Heilpädagogik Children's Clinic, founded and headed by psychiatrist Erwin Lazar, was one of Europe's earliest and most innovative child psychiatry clinics. It had both a day clinic, which saw children referred from all over Austria, and a 21-bed inpatient ward—more like a boarding school, with staff so devoted they were like family—that treated and educated children who had psychiatric issues of research interest.

Asperger joined this clinic in 1932 as a freshly minted doctor. He completed his training under Lazar and Frankl, who was the only physician and psychiatrist on staff other than Lazar.

As front-line clinicians, both Weiss and Frankl had constant contact with the young patients. Along with a psychologist and a nun named Sister Viktorine, Weiss and Frankl wrote many of the patient-observation records that Asperger would draw on heavily in writing his pivotal 1944 paper. Of note, Frankl and Weiss also wrote papers on these patients that predated Asperger's—Frankl in 1934 and Weiss in 1935.

Frankl's paper focused on a dynamic that he spent the next decade exploring in ways that almost certainly influenced Asperger's view. He first distinguished "word language," words said aloud, from what he called "emotional language," which encompassed tone of voice, body language, facial expression, general presence—everything beyond the actual words that communicate what someone is trying to say. When we listen to someone, Frankl wrote, we "acquire two different sets of information." If a clinician hears a child's description of a series of occurrences, for instance, "he learns *what happened, the objective facts.* At the same time, he recognizes *how the child actually feels about these events,* although [the child's] feelings are not verbalized." Yet some children (such as those Asperger would come to call autistic) process emotional language differently than non-autistic children do. Asperger later described how this other kind of processing required teachers and parents to present requests or orders with a lack of affect in their voices.

Weiss, in her paper, drew heavily on the clinical notes describing a 9-year-old patient, Gottfried K., to describe the Lazar clinic's approach to intelligence testing. Dry fare, it would seem, but in Weiss' hands the paper reveals not just the testing regime's innovative flexibility, but her own sensitivity to Gottfried's challenges and assets—and a recognition that he had certain traits seen in other patients.

She describes a child who is clearly autistic. Once Gottfried learned the clinic school's routines, for instance, he grew comfortable there, but he would become "thoroughly upset" if the routines were disrupted the slightest bit. He showed

12

13

Ambulanz.

zero interest in making friends. Although on initial impression he seemed "feeble-minded," he usually did well on lessons when Weiss phrased questions or problems in ways that matched his way of communicating or thinking. Instructions had to be given as straightforward imperatives; offer him instructions that were vague or posed as suggestions, and he would struggle.

Weiss concluded that "the intelligence defect found in him is not due to a developmental retardation only, neither can it, strictly speaking, be considered as the usual mental inferiority. But it is a disorder within the deeper regions of mental life." Then, calling on her experience with similar children, she outlined approaches and accommodations that teachers and parents could use to maximize such a child's learning, function and quality of life: a peaceful, predictable atmosphere; a recognition that "in this type of child some special talent may be found"; and a commitment to locating that talent and building upon it as the foundation of a trade or profession.

Neither Frankl's nor Weiss' paper attempted to define a new diagnostic category or syndrome. Yet both papers provided close, sensitive studies of a "type of child" they already seemed to know—characterized by what today would be seen as autism traits. And Weiss' paper, in which she described the clinic's testing method and what the tests revealed about the patient being discussed, was a veritable prototype, "in both form and substance," as Haswell Todd observes, of the one Asperger wrote a decade later.

Frankl's and Weiss' papers also reflect an apparently staff-wide fascination with autistic children at a time when Asperger was looking to Frankl (and doubtless to Weiss as well) for guidance in making sense of them. At the clinic's weekly staff meetings, these and other cases would have sparked discussions crucial to Asperger's growing understanding of what he was seeing in some of the clinic's young charges.

Possibly even more important, Haswell Todd argues, were the individual "pieces of description," or "descriptive motifs," that Viktorine, Weiss and Frankl used to portray these children. These motifs—noting the children's social remove, lack of affect, desire for routine or peculiarities of language and intellect—implicitly outlined the distinctive traits Asperger (and Kanner) would later use to define the autistic "types." Indeed, Asperger's and Kanner's papers both contain frequent and sometimes lengthy passages taken directly from patient records written by Frankl and Weiss. These excerpts, Haswell Todd asserts, represent not just the textual material of those papers but some of the conceptual building blocks Asperger and Kanner used to construct their theories about 'autistic psychopathy' and 'infantile autism.'

How important were Frankl and Weiss to Asperger's theory of autism? As suggested above, their contributions were easily large enough that, under today's more inclusive standards of scientific and medical authorship credit, both would have been listed (along with Sister Viktorine and others) on the long, thorough and brilliant 1944 paper that made Asperger's name.

Shortly after Frankl's November 1937 departure, Asperger gave a talk in which he spoke about the "autistic psychopathy" he and his colleagues were seeing in a handful of young patients. He soon published it as "Das Psychisch Abnormale Kind" ("The Psychically Abnormal Child"). This was essentially a rough draft of his later paper, with key parts of the picture still missing. Yet it clearly marks a new direction in his thinking, one that would lead to the completion six years later

At left: Pirquet Children's Hospital, in the General Hospital, Vienna, 1921.
Credit: MediUni Vienna / Josephinium

of his dissertation, which would be published the following year.

Alas, Asperger's paper lists no co-authors and only 13 references, most of them from giants in the field. This paucity of citations looks unseemly today, when a 54-page paper such as Asperger's would typically have dozens of references and give co-author bylines to those who contributed patient data or key ideas. But this "was a time," says Christine Borgman, director of the Center for Knowledge Infrastructures at the University of California, Los Angeles, "when it wasn't uncommon for professors who headed departments to take credit for the department's work and used the royal 'we'" instead of identifying collaborators as co-authors. No matter how collaborative the actual work was, it was often a boss-takes-all game.

History, of course, would and did intrude. During that particularly fruitful time at the Lazar clinic, the Nazism that had been growing more prevalent in Austria increasingly made itself felt in universities. Anti-Jewish rhetoric grew ever more virulent. Universities began to refuse to hire or promote Jews such as Frankl and Weiss, and sometimes sacked them outright. In 1932, when clinic director Erwin Lazar died, the head of the hospital, an ardent Nazi named Franz Hamburger, replaced Lazar not with the highly experienced psychiatrist Frankl but with an immunologist, Valerie Bruck. When Bruck retired two years later, Hamburger tapped Asperger, then just 28 and on staff for only three years, to head the clinic, elevating him over Frankl. This promotion meant that when Asperger published his dissertation—for that was what his 1944 paper was—he did so not as an underling but as chief of the clinic. In the meantime, two of the people who had helped him most had moved on: Weiss left in 1934, the year of Asperger's promotion, for the United States. Frankl followed not long after, resigning from the clinic in November 1937 to join (and marry) Weiss in New York.

The birth of Kanner's autism

Having left one of the most renowned child psychiatry clinics in Europe, Frankl landed in one of the most notable in the U.S., which had been founded and was presided over by 43-year-old Leo Kanner. Kanner, who two years before had published the textbook "Child Psychiatry," was easily the most prominent child psychiatrist in the country. Like Asperger, he was from Austria-Hungary. He was born in 1894 in a Yiddish-speaking village on the border with Russia, in what is now Ukraine. At age 12 he moved to Berlin for school, but he suspended his medical studies when the army drafted him into World War I. He finished his medical degree in 1921 and in 1924 moved to the U.S. with his wife and daughter to escape the inflation and recession the war had triggered in Austria and Germany. Soon after, Johns Hopkins Hospital in Baltimore hired him to lead the Children's Psychiatric Service, the country's first child psychiatry clinic.

Kanner's clinic in many ways resembled Lazar's facility in Vienna. It had a day clinic that handled referrals from all over Maryland and beyond; an inpatient ward that took in some cases to treat, school and study; and a sharp, deeply engaged staff who got to know the children well and thoughtfully discussed and recorded their cases. Frankl, joining the staff in November 1937, made a major addition to this team. He worked alongside the unit's senior clinical psychiatrist, Eugenia S. Cameron, to evaluate and then follow and write up some of the more difficult or intriguing cases.

These patients, as it happened, would soon include a 5-year-old boy named Donald T., who

in October 1938 became the first of the 11 children whom Kanner described in his 1943 paper, "Autistic Disturbances of Affective Contact." In the first sentence of that paper, Kanner pinpointed the year he and his staff first made note of these cases:

> Since 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities.

This sentence stands out for two reasons. The first is Kanner's use of "our attention," which implies or acknowledges that this was a team perception. Further, his mention of the year, 1938, marks the point when several factors might have coalesced to suggest that Donald T. had a syndrome that no one had ever heard of.

What was special about 1938? Both European and American child psychiatry had for several years been giving increased attention not just to Bleuler's 'autism,' or separateness, but also to the growing and increasingly baggy diagnosis of schizophrenia, which included many people whom today would be diagnosed as autistic. It thus seems fairly likely that if neither Asperger nor Kanner had discerned and defined what became modern autism, some other midcentury child psychiatrist would have. This isn't to say the air was filled with the notion of modern autism. But it held whiffs.

In October 1938, for instance, the same month Donald T. showed up at Kanner's clinic in Baltimore, Asperger in Vienna gave and then published his previously mentioned talk describing "autistic psychopaths." Given that both Vienna and Baltimore were then prime nodes in child psychiatry's conference and professional networks, it is conceivable that Kanner (a native German speaker) could have received a description or even a copy of Asperger's lecture.

Meanwhile, 1938 was Frankl's first full year in the Kanner lab. And Frankl, having seen, written about and discussed with his Vienna colleagues the same children Asperger was seeing, presumably would have shared with his Baltimore colleagues memories or insights about those cases. After all, his wealth of experience was precisely what Kanner had hired him for. (This is not to say that Kanner lifted case accounts from Asperger. But Kanner's mention of "a number of children" with autism traits coming to his attention in 1938 could have easily encompassed reports of cases from other clinics.) And at least three occasions for such conversations would come while Frankl was at the clinic. For in addition to Donald T., two more patients Kanner described in his paper arrived at his clinic during the three years Frankl worked there.

Finally, Frankl also brought to Baltimore something more tangible in 1938: the draft of a paper, "Language and Affective Contact," which he eventually published in 1943 alongside Kanner's paper on 'infantile autism' in *Nervous Child.* At least two scholars who have studied this period closely believe this manuscript profoundly shaped Kanner's concept of autism.

"Language and Affective Contact" advances some of the concerns Frankl explored in his 1934 paper on 'emotional language.' Its last and most focused section centers on a boy named Karl K., almost certainly from Asperger's lab, whose disregard for spoken and all other language had produced an apparently total "lack of contact with other persons," cut off from the human connections built and maintained by full conversation or even mutual presence. He wandered around his

schoolmates "like a strange being," Frankl wrote, and "even when amid a crowd of people . . . behaved like a solitary person."

All of Asperger's staff, of course, and doubtless Kanner's, too, had noticed that some of their young patients were remote and detached. But it was Frankl who put a term and a theoretical framing to that detachment by identifying a crucial connection between people—the almost unconscious exchange, communication and sharing of affective information—that seemed to be missing in these children.

Kanner was excited about Frankl's idea of affective contact as early as 1938, when, as historian Haswell Todd describes, he wrote to neurologist Bernard Sachs: "I have become very much interested in a special and, I can say, original piece of work that Dr. Frankl is engaged in. I have gone over with him his formulation of the topic and was struck by its newness as well as soundness. The plan is concerned with a practical and concrete study of what Dr. Frankl calls the affective contact of children." This concept, wrote Kanner, "opens a new, objective and practically useful avenue of approach."

Haswell Todd argues convincingly that "the ideas that Frankl brought from Vienna—chiefly his own original concept of 'affective contact'—were critical in starting and guiding the research that led to Kanner's epochal 1943 autism paper." Kanner's autism, he asserts, "was not discovered all at once" but built up from a combination of concepts and "descriptive motifs" from patient observations—and the foundational concept was Frankl's notion of 'affective contact' as a vital feature disrupted in certain (autistic) children. Frankl saw this disruption create a distinctive type of social isolation; Kanner looked at a growing number of patients displaying that type of isolation, saw it often associated with repetitive behaviors and a desire for sameness (as documented by Frankl and others), and declared this combination "a highly specific and rare disorder."

In 1941, the *Nervous Child* editors asked Kanner to create a special section for the journal, centered on his work. Kanner invited Frankl to contribute, urging him to submit his long-unpublished "Language and Affective Contact." Kanner originally planned to have Frankl's piece appear right before his own "Autistic Disturbances of Affective Contact." But for reasons unclear, the order was reversed, with Kanner's coming first—even though Frankl's paper was both chronologically and conceptually its predecessor.

John Elder Robison, author of the autism memoir "Look Me in the Eye" and neurodiversity scholar-in-residence at the College of William & Mary in Williamsburg, Virginia, harbors no doubt that Frankl's theory of affective contact played a central role in shaping Kanner's theory of autism. In a sharp, well-documented 2017 paper in *Autism,* "Kanner, Asperger, and Frankl: A Third Man at the Genesis of the Autism Diagnosis," Robison, like Haswell Todd, argues convincingly that the "disturbance of affective contact" that Kanner's paper describes, having come to him from Frankl, was the kernel around which Kanner's theory of autism coalesced.

As it happened, Frankl would largely abandon his work on autism after his and Kanner's papers were published in 1943. Haswell Todd thinks Frankl may have already decided to abandon that work by the time Kanner invited him to submit his article to *Nervous Child.*

Why would Frankl wish to drop the subject of affective contact? A hint is in a letter, found by Haswell Todd in the Melvin Sabshin Archives of the American Psychiatric Association, that Frankl

Dr. Hans Asperger works with a young boy at the Children's Clinic at the University of Vienna in the 1930s. Courtesy of Maria Asperger Felder

Undated photo of Grunya Sukhareva. Courtesy of the Scientific and Practical Center for Mental Health of Children and Adolescents n.a. G. Sukhareva

Painting of Leo Kanner, Johns Hopkins University

Hans Asperger, bottom right, appears with the staff of the Vienna Children's Hospital in 1933. Courtesy of Maria Asperger Felder

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wrote to Kanner while the two were exchanging edits of Frankl's *Nervous Child* paper. Frankl refers to a time five years before—in 1937—when he was fleeing an Austria gone mad, narrowly escaping the roundup of Jews a year later:

> To tell the truth, I have become loath of this paper. Most of it was written in Europe five years ago, the first desperate attempts in English language were made translating it, then I rewrote it time and again, obstinately thinking that its publication was imminent. I had my fun with it five years ago, but now I have become negatively conditioned to it. . . . This publication will, after all, be an official termination of a peculiar and rather difficult period in my life.

As Haswell Todd notes, evidence suggests that Frankl's mother was killed in the Holocaust. In August 1942, a 73-year-old woman with her maiden name, Franziska Adler, was put on a train in Vienna that arrived the next day at the Theresienstadt concentration camp. She died in Treblinka a month later. This loss was perhaps part of what Frankl hoped to put behind him when he dropped his work on affective contact.

Frankl had already left Kanner's lab for a more remunerative job in Buffalo, New York, in 1941. From then on, his career focused mainly on treating children rather than studying them, though he did take up autism again in the 1950s, when he wrote but never published a long paper on the subject. By then, of course, autism was Kanner's thing, and would remain almost exclusively so until the day he died in April 1981, mere months after Lorna Wing brought Hans Asperger's work to wide attention.

Frankl, meanwhile, had died of lung cancer six years earlier, in 1975, at age 77. He was survived by Weiss, who died in 1991, a month shy of her 94th birthday. Neither gets more than a rare mention in articles about the history of autism. As of this writing, in fact, neither has even a Wikipedia page.

Refinements and expansions

The basic conceptual framework of the autism spectrum was largely built by the 1980s, but four developments since then have had fundamental effects on our picture of autism. The first arose from a 1977 paper by psychiatrists Susan Folstein and Michael Rutter that finally quashed the harmful notion, dating back to the 1950s and popularized in the 1960s, that autism was caused by 'refrigerator mothers' who lacked the warmth to raise healthy children. Folstein and Rutter studied autism rates among twins and found "important hereditary influences" underlying some of autism's signature traits. The study was convincing enough to do away with a theory that had aggrieved many families and sometimes even removed autistic children from their mothers' care.

The view of autism, meanwhile, was also broadened by Wing's 1981 paper, discussed above, that declared the autistic world was populated not just by Kanner's deeply disabled children and a sprinkling of Aspergian savants but by an entire spectrum of presentations in which autism's traits might appear in different combinations at different strengths.

This understanding, which spread slowly but steadily through both the research and autistic communities, helped lay the foundation for the autistic community's largely successful recasting, beginning in about 2000, of autism as a syndrome not of 'deficits' but of 'neurodiversity'—a breadth and variety of traits that, like most in the human palette, can be liabilities in some contexts and assets in others. The term originated in "Odd People In," a 1998 undergraduate honors thesis

At left: Pirquet Children's Hospital, in the General Hospital, Vienna, 1921.
Credit: MediUni Vienna / Josephinium

by autistic writer and advocate Judy Singer, who later wrote the book "NeuroDiversity: The Birth of an Idea."

Robison sees the term as a way for autistic people to both own and celebrate their condition, as it "did not carry the stigma of disability. Because where *autism* was exclusively a characterization of how we were less than other people, *neurodiversity* allows for the possibility that we are more than the average person in some domains and less in others."

Finally, the most notable development in autism research as a venture has been the increasing presence of autistic researchers who are diversifying research staffs and expanding the focal points of study.

Their goal is to steer research away from searches for 'causes' or 'cures' and toward work on the sorts of interventions, programs, practices and information that can help autistic people manage their places in the world—and help non-autistic people understand what *they* can do differently to improve mutual comprehension. "Nothing about us without us," has been a battle cry of this movement.

As many research centers and funders begin to heed this call, they are shifting their autism research agendas to produce more experience-centered studies. One line of study led by autistic researcher Damian Milton, lecturer in intellectual and developmental disabilities at the University of Kent in England, for instance, explores what he dubbed "the double-empathy problem," which involves the failure of non-autistic people to see that they are often at least as bad at understanding autistic people as autistic people are at understanding them.

Another recent paper, led by Tomisin Oredipe and Bella Kofner, who worked on the study as undergraduate students at the College of Staten Island in New York City, found that telling children at a younger age that they are autistic improves their well-being and function compared with autistic children who are told later. As their collaborator, Steven Kapp, senior lecturer at the University of Portsmouth in England, put it, this "helps people understand themselves and also helps them connect with other people like them."

Breadth brings depth

The history of autism studies is a troubled one, with critical passages full of fog that may never lift. But what's clear amid that fog is that science advances by being inclusive, recognizing diversity and widening its scope.

"Ultimately," wrote author Lina Zeldovich in a 2018 *Spectrum* story about Sukhareva, "it took a spectrum of these researchers to define autism's full spectrum." Sukhareva, Frankl, Weiss and Sister Viktorine all played crucial roles in recognizing autism as a distinct syndrome, but all went unfairly and spectacularly ignored for decades. This deprived them of recognition that would have produced not just rewards to them, but a fuller and more accurate history of autism—and the real workings of science. These names, along with Wing, Folstein, Rutter, Robison and others we lack room for here, belong alongside Kanner and Asperger as pioneers of this field—which, like all science, remains a frontier, now being explored by people who vary more in origin, experience and perspective than ever before.

SPECTRUM

PROFILES

Ralph Adolphs: Setting the pace for cognitive research

BY VIRGINIA HUGHES / 9 SEPTEMBER 2010

The summer of 1993 would turn out to be a turning point in Ralph Adolphs' life.

That summer, he moved from sunny California to a massively flooded Iowa City, and began working with several people who would leave an indelible mark on his career. Antonio Damasio—a neuroscientist and book author famous for linking emotion and reason in the brain—was Adolphs' postdoctoral fellowship mentor at the University of Iowa. Dan Tranel, a young professor in the department, would become Adolphs' co-author on dozens of scientific papers, not to mention his running partner and best friend.

And then there was S.M.

A friendly and childlike woman in her late 20s, S.M. would become one of the most famous patients ever cited in the psychological literature. She has a rare genetic condition called lipoid proteinosis, in which calcium deposits eat away at the brain tissue. Unlike in other patients with this disease, however, S.M.'s lesions are localized to just one spot on each side: the amygdala, an almond-shaped mass of tissue sitting deep behind the eyes.

For nearly two decades, using any technique he can, Adolphs has been trying to figure out how S.M.'s mind—and, by extension, the human amygdala—works. An avid outdoorsman, Adolphs, 47, has run a dozen 50- and 100-mile races, and his colleagues say he approaches science with the same stamina and intensity. He has already published more than 100 scientific papers, several of them revealing intriguing ties between S.M. and people with other brain conditions, including autism.

Tranel first published S.M.'s case report in 1990, to little fanfare. She was just one of hundreds listed in the university's world-famous registry of patients with brain lesions.

That collection lured Adolphs—a foodie and wilderness lover—to the flatlands of the Midwest: he was convinced it would help him understand how the brain generates and understands emotions in people, rather than in animal models.

FAST FACTS

Current position: Bren professor of psychology, neuroscience and biology, California Institute of Technology
Main areas of interest: Emotion and social cognition • **Lab URL:** emotion.caltech.edu
Notable mentors: Mark Konishi, Antonio Damasio

Within a year of meeting S.M., he had published a paper in *Nature* showing that she cannot identify fear in facial expressions. Years later, using an eye-tracking machine, he discovered why: she doesn't look people in the eyes.

These cognitive problems are similar to what's commonly seen in autism—people with the condition have trouble gauging others' beliefs, and avoid eye contact.

That connection wasn't lost on Adolphs when he launched his lab at the California Institute of Technology in 2004. He decided to systematically investigate the similarities and differences between adults with autism and two rare groups: those with amygdala damage, like S.M., and those with agenesis of the corpus callosum (ACC), who are missing the large bundle of fibers that bridges the two sides of the brain.

Adolphs is known for this kind of experimental creativity. "Most people in science just build on what other people have done. But he will take a completely new approach," says Joe Piven, professor of psychiatry at the University of North Carolina, Chapel Hill.

The Adolphs lab is in a shiny building that is striking against the lush and serene backdrop of Caltech's campus. His office has an air of understated sophistication—one of two flat-screen monitors displays a color-coded calendar, and the only visible scrap of paper is the napkin underneath a small pile of potato chips.

A miniature stuffed white owl on his desk is a kitschy reminder of his Ph.D. dissertation, a connectivity map of the barn owl's auditory system. That project didn't satisfy his real intellectual interests. "At the end of that, I just felt like I still was very far away from the really difficult, interesting questions about the human mind," he says.

He was fascinated in particular by social cognition—the thinking that comes between social perception and social behavior. For example, when people look at others' faces, they immediately begin making inferences about who they are, what they think, what they may say or do next. "We do something with respect to thinking about people that we just don't do when thinking about coffee cups or books," he says.

But in the early 1990s, before the advent of functional magnetic resonance imaging, there were few options for studying the human brain. Around that time, Adolphs saw Damasio give a guest lecture about Iowa's growing collection of people with brain lesions. Adolphs was immediately intrigued, and a year later—after defending his thesis and getting married—found himself in Iowa.

Months before he met S.M., Adolphs encountered Boswell, a man with severely damaged frontal and temporal lobes, including the amygdala. Boswell had no sense of smell and his short-term memory had a limit of about 45 seconds.

Adolphs found that Boswell had trouble recognizing facial expressions, particularly fear. Because animal work had connected the amygdala to fear, Adolphs began looking for patients with selective amygdala lesions, which led him to S.M.

Adolphs and Tranel studied Boswell for years,

even after Adolphs ascended to professor in the department and expanded his research interests. On many occasions, Tranel and Adolphs would drive an hour and a half to the care facility where Boswell lived. They chatted with him, trying to soak up as much as possible about the way his mind worked, and sometimes performed informal experiments to tap into his emotional reactions.

Adolphs convinced Tranel to train with him on his 100-mile ultra-marathons. On many weekends, they ran together in a hilly region of Iowa for eight hours at a time. That gave them a lot of time to talk—mostly about work. "We'd be halfway through a 50-mile training run and have some great insight about how to reanalyze some data," Tranel says.

It takes a certain kind of personality to take on that kind of sport. "You're basically doing something that's really extreme just for the experience of having done it," Tranel says. "Ralph's done that a lot in his life."

In his research, Adolphs' adventurous spirit has led him to some unconventional experiments.

For example, when he was in Iowa, Adolphs recorded brain signals directly from electrodes inserted in the brains of people undergoing brain surgery to remove epileptic tissue. He found that both the prefrontal cortex and the amygdala respond differently when people look at aversive pictures, say a snarling dog or a violent war scene, compared with pleasant ones, such as a smiling baby or a delicious plate of food.

In his first year at Caltech, Adolphs got a phone call from Lynn Paul, a researcher and the head of the National Organization for Disorders of the Corpus Callosum. Paul had studied the psychological aspects of ACC for years, and wanted Adolphs to help her scan the brains of this rare group.

"Within a week, [Adolphs] had gotten seed money to start the program," says Paul, a senior research fellow at Caltech. "I didn't have an appointment, or any title here, but that's Ralph. He just thought, 'Well, this is a good topic. We should study this.'"

As it turned out, the ACC group fit in nicely with the experiments Adolphs was planning for adults with autism.

Adolphs had stumbled on autism many years earlier. In 1998, he showed that S.M. and two other individuals with amygdala lesions rate photographs of faces that look untrustworthy—such as a scowling man wearing sunglasses—as trustworthy.

Joe Piven, then a brain-imaging expert in Iowa's psychiatry department, convinced Adolphs to repeat the experiment in high-functioning adults with autism. In 2001, they reported that this group, like S.M., tends to be more trusting than healthy controls are.

With access to three rare groups—those with autism, ACC or damage to the amygdala—Adolphs is in a unique position to test two long-standing cognitive theories of autism: one that argues that social impairments of the disorder arise from abnormal amygdala activity, and the so-called 'connectivity hypothesis', which says autism stems from weak long-range connections in the brain.

Participants from each group perform a long battery of tasks, ranging from having conversations while Adolphs' team measures their eye-gaze patterns, to playing a virtual slot machine while the researchers image their brain activity.

He and Paul have already shown that people with ACC have trouble identifying fearful faces and, when they make these judgments, they don't look preferentially at the eyes. People with

> “I’d like to understand what kind of mind counts as a mind of autism.”
> —Ralph Adolphs

autism process faces in a similar way, suggesting that they may have weakened long-range connections just as those with ACC do.

Adolphs is also investigating how individuals with amygdala lesions or ACC score on standardized tests of autism. Last fall, he reported that S.M. has a skewed sense of personal space, a trait that has been anecdotally observed in people with autism. This month, however, he reported that neither S.M. nor another patient with amygdala lesions come close to meeting diagnostic criteria for autism.

“The amygdala has probably gotten too much attention, frankly, in large part because of our own work,” Adolphs says. “The story is much more complex.”

Pinpointing which brain circuits are at fault is the first step in designing effective treatments for autism, Adolphs says. But he is equally interested in studying a disorder that’s never the same in any two individuals.

“To really get a sense for the boundaries and potential subtypes within autism—it’s philosophically challenging,” he says. “I’d like to understand what kind of a mind counts as a mind of autism.”

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A

Simon Baron-Cohen: Theorizing on the mind in autism

BY MOHEB COSTANDI / 9 MAY 2011

One of the key concepts in autism research—that people with autism have difficulties interpreting the actions and intentions of others—owes its existence to Simon Baron-Cohen, a British researcher and among the most provocative thinkers in the field.

So does the first screening instrument for the infant siblings of children with autism, which Baron-Cohen developed in 1992. And the controversial hypothesis that autism is a manifestation of the 'extreme male brain,' which, according to Baron-Cohen, explains why the condition affects four times as many boys as girls.

Few scientists have a career that spans as wide a spectrum in autism research as Baron-Cohen, professor of developmental psychopathology at the University of Cambridge in the U.K. And fewer still garner effusive compliments from those who don't agree with them.

"He is extremely prolific and has been hugely influential, both in the U.K. and worldwide," says Francesca Happé, professor of cognitive neuroscience at King's College London.

Given that Happé and Baron-Cohen are on opposite sides of one of the most controversial debates in autism—the decision to merge Asperger syndrome into the autism spectrum in the forthcoming edition of the Diagnostic and Statistical Manual of Mental Disorders—the compliment is particularly weighty.

Shortly after graduating with a master's degree in human sciences from the University of Oxford in 1981, Baron-Cohen worked as a teacher in a small school for children with autism. He was fascinated by the children, who showed clear signs of intelligence but at the same time appeared oblivious to normal rules of social interaction.

"These puzzling behaviors made me want to explore the disconnect between intelligence and social skills," Baron-Cohen says.

The job led him to a Ph.D. at the Medical Research Council-funded Cognitive Development

FAST FACTS

Current position: Professor of developmental psychopathology, Cambridge University
Recent significant work: Foetal oestrogens and autism, Baron-Cohen S. *et al. Molecular Psychiatry* 25, 2970-2978. https://doi.org/10.1038/s41380-019-0454-9 • **Other major achievements:** Knighted for services to autistic people
Main areas of interest: Cognitive neuroscience, sex differences, prenatal sex steroids
Lab URL: https://www.autismresearchcentre.com/ • **Notable mentors:** Uta Frith

Unit, under the supervision of the pioneering autism researcher Uta Frith.

"Simon was one of those rare students who could make a success out of a rather sketchy idea which still had many question marks," says Frith, professor of cognitive neuroscience at University College London. "He impressed me with his willingness to design his own test materials and to work hands-on with children."

At the time, theory of mind—the ability to attribute mental states to others and interpret their actions—was a new concept, and it was thought that mind blindness, or the lack of theory of mind, might be the underlying cause of some aspects of autism.

Baron-Cohen and Frith recruited 4-year-old children with autism to test this idea. They showed the children a scenario involving two dolls. In the scenario, one of the dolls places a marble into her basket and leaves the scene. The second doll then moves the marble into her own basket. The researchers then ask the children where the first doll should look for her marble when she returns.

Typically developing children and those with Down syndrome pick up on the plot very quickly, and realize that the first doll doesn't know what has happened. But children with autism say the first doll should look for the marble in the second doll's basket.

This landmark study provided the first evidence that theory of mind is affected or delayed in children with autism.

"Baron-Cohen's early research is the foundation of a whole field which has been growing exponentially in the last decade," says Rebecca Saxe, assistant professor of cognitive neuroscience at the Massachusetts Institute of Technology. "It has transformed both autism research and treatment practice."

Still, it didn't go far enough for Baron-Cohen.

"In those early years we took a very narrow view of theory of mind," says Baron-Cohen. "The mind blindness theory had something going for it, but it missed a lot, particularly the role of emotions."

In the late 1990s, Baron-Cohen began to explore the idea that the autism spectrum might be defined by sex differences. He developed the Empathy Quotient, a measure of the ability to identify with another person's feelings.

Women generally score higher on the empathy scale, whereas men tend to score higher on the systemizing scale, a measure of the drive to analyze and construct systems that follow rules. Children with autism also tend to score low on empathy and high on systemizing, Baron-Cohen has found.

Seeing this same pattern of results on psychological tests, Baron-Cohen in 1997 proposed the extreme male brain hypothesis, which characterizes people with autism as hyper-systemizers—focusing more on systems and repeating patterns than on other people's thoughts and actions.

"Initially people were wary of it because of the long history of sex differences being taboo in science," Baron-Cohen says. "But increasingly, the

research community is recognizing that we might need to take sex-linked factors into account to understand autism."

To better understand the skewed sex ratio in autism, Baron-Cohen started measuring testosterone levels in amniotic fluid taken from hundreds of pregnant women during routine testing procedures. The project is nearing its end; the children are about 10 years old, and Baron-Cohen's group has studied around 500 of them so far.

"We found correlations between early hormones and later behavior," he says, "and are now inviting children to climb into the brain scanner, so that we can look for correlations in the brain."

Many in the field are skeptical of this hypothesis, however. "It isn't clear if the theory predicts that fetal testosterone is sufficient to cause autism or whether fetal testosterone levels interact with other markers of genetic vulnerability," notes David Skuse, professor of behavioral and brain sciences at University College London.

Most of the analyses carried out by Baron-Cohen's group are based on the mothers' perceptions of their children's behavior, and not on objective measures, Skuse adds.

In the past year, Baron-Cohen has taken on yet another controversial idea: that Asperger syndrome and autism should be merged under one diagnosis.

Baron-Cohen is a prominent critic of this decision, arguing that Asperger syndrome should remain a distinct diagnostic entity.

"My suggestion was that it is premature to delete it," Baron-Cohen says. "I don't think there have been enough studies comparing Asperger syndrome to other types of autism to be able to say there's no difference."

Still, he is quick to dismiss the idea that autism is a mental illness. Instead, he says, it is both a disability and a difference.

"The disability is in relation to social functioning and adapting to change," he says. "But the child is processing information in an intelligent, albeit different, way, with attention to detail and an ability for spotting patterns."

He compares the way in which autism is viewed today with how left-handedness once was, and says he hopes it will eventually be regarded as another variation.

"There are lots of different routes to adulthood," he says. "The profile we call autism might just be one of those routes."

BARON-COHEN'S HIGHLY CITED PAPERS:

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Raphael Bernier: Decoding the mysteries of the autistic brain

BY MICHELE SOLIS / 16 MARCH 2009

Given the unconventional approach to his own life, it's no surprise Raphael Bernier is focused on the atypical brain signals seen in people with autism.

In the spring of 2002, as a new graduate student at the University of Washington, Raphael Bernier was charged with introducing his advisor, Geraldine Dawson, before her lecture to a room of about 40 people from the psychology department. To Dawson's astonishment, Bernier sang his introduction to the tune of *On Top of Old Smokey*. "[It was] a pretty gutsy thing for a first-year student to do," Dawson says.

Bernier's *curriculum vitae* is sprinkled with other surprises: one year spent counseling troubled teenagers, another year with the Peace Corps, and almost three years on the board of a local yoga center.

A little over a year ago, Bernier became an assistant professor of psychiatry and behavioral sciences at the University of Washington in Seattle, delving into what makes the brain of a person with autism different from that of someone without the condition. He has found atypical brain signals in people with autism related to a difficulty in imitating others, which may explain some of the social and language impairments associated with the disorder.

Because these signals are more quantifiable than most measures of behavior, Bernier's research refines the picture of autism, and helps bridge the gap between autism-like behaviors and their underlying causes.

Trained as both a scientist and a clinician, Bernier has tremendous energy that carries him to the conclusion of his projects, rather than fizzling in their diversity.

"Raphe has a lot of good ideas," says Dawson, now chief science officer for Autism Speaks. "Just as important, though, is the fact that he gets things done. He is highly productive."

B

FAST FACTS

Current position: Scientist at Apple
Recent significant work: My involvement in the identification and characterization of individuals with disruptive mutations to CHD8.
Main areas of interest: Behavioral phenotypes
Notable mentors: Geraldine Dawson, Susan Folstein

"I realized autism was the coolest way to study [social difficulties]." —Raphael Bernier

Bernier's career path did not lead straight to autism research, however. In the early 1990s, as an undergraduate studying psychology at Tufts University, he moonlighted as an emergency medical technician. Motivated to help young people struggling with behavioral problems, he went on to get a master's degree in counseling psychology from the University of Wisconsin in Madison.

In 1996, he took a job as a counselor in Boston, where he worked with teenagers who either had attention deficit hyperactivity disorder, were victims of sexual abuse, or were themselves sexual offenders. Bernier realized all these teens had something in common: social difficulties. "What was going on with their social interactions, their social communication?" he asks.

He began to contemplate how the brain mediates social behavior, and turned to autism as an interesting case study. "I realized autism was the coolest way to study [social difficulties]," he says.

This interest led him to answer an ad for a research study coordinator posted by Susan Folstein, the scientist at Boston University who, in 1977, first identified genetic factors associated with autism.

Over the following two years, Bernier discovered that he enjoyed many aspects of autism research, from conducting clinical interviews of families to thinking about its genetics, and he began to plan for graduate school.

He put these plans on hold to join the Peace Corps with his wife, Kimberly. "In the U.S. here, we're just so encapsulated from how the rest of the world works," he says. "I felt it was an important personal experience that I needed to have." Stationed in the Solomon Islands in the South Pacific, Bernier taught first aid and clinic management to nurses in a village on a beach, a place that he describes as "paradise."

He left research with some trepidation, however. "I was nervous they were going to find the genes for autism when I was away," he says, laughing. A few months after he returned, in 2001, he began graduate school in clinical psychology, conducting research in Dawson's lab at the University of Washington.

One Wednesday in December, Bernier, who has a marathon runner's frame and an equally spartan office at the University of Washington's Autism Center, talked animatedly about his research. Easygoing, yet intense, he referred to his study participants as "kiddos" while describing the technical details of his studies.

To understand what has gone amiss in the brains of autistic people, Bernier uses electroen-

cephalography (EEG), a non-invasive technique that picks up electrical activity from the brain through the skull. Participants in EEG studies wear a stretchy white cap, similar to a swimmer's cap, out of the top of which rises a bundle of wires headed toward a bank of computers. Inside the cap, 128 electrodes sense tiny electrical signals generated by the brain.

One signal detected in this way is the mu rhythm, a brain wave whose voltage rises and falls about 8 to 13 times per second. The wave pattern—which resembles the Greek letter μ—appears when a person is at rest and dampens when a person moves or observes someone else moving. This 'mu attenuation' reveals a change in neural activation somewhere inside of the sensorimotor cortex, a large brain region that processes sensory stimuli as well as motor movements.

Because the brain region generating the mu rhythm is sensitive to both observing and making movements, it is suspected to be involved in imitation. Some people with autism have difficulty imitating another person's actions—such as using a pencil to draw a line—and mimicking gestures and facial expressions.

As a graduate student in Dawson's lab, Bernier found that the mu rhythm is not fully suppressed in adults with autism when they observe others making a movement. This might reflect an inability to relate to others and cascade into imitation impairments, he says.

To explore this idea, Bernier measured the imitation abilities of the study participants by videotaping their imitations of hand gestures, facial expressions and actions on objects. The quality of each imitation was scored using a standardized scale developed by Sally Rogers and her colleagues at the University of California, Davis. For example, the researchers scored finger placement and orientation separately during hand gesture imitation.

Bernier found a connection between imitation and mu attenuation: the worse people with autism are at imitating, the less their mu attenuation when observing someone else.

This link to behavior "extended substantially" the understanding of the mu rhythm in autism, says Jaime Pineda, an associate professor of cognitive science at the University of California, San Diego.

Pineda's group had found a similar impairment in mu attenuation in people with autism in a 2005 study, but had not related it to behavior. "It's important to correlate [the finding] with the behavioral dysfunctions," Pineda says, "so I'm glad he's in the field."

Now in his own lab, Bernier is trying to understand how malleable mu attenuation is. Because his earlier study links mu attenuation to imitation, he is testing whether behavioral therapy that improves imitation skills can affect brain activity.

"We know kids with autism aren't attending to social information," Bernier says. "In an intervention, we're pushing attention to that social information and we're forcing experience that might not normally occur for [them]."

Bernier is obtaining EEGs from children who have completed two years of an intensive intervention that stresses imitation skills. If the intervention affects the part of the brain responsible for mu attenuation, he expects a difference in mu attenuation in these children compared with those who receive standard treatments.

If the children show behavioral improvement, but no difference in mu attenuation, then other brain systems may be stepping in to compensate, Bernier says. Either way, he adds, the results may help understand the effect of the intervention.

Tracking brain wave patterns such as mu attenuation may eventually help clinicians diagnose autism, identify subtypes, or even monitor treatment progress in the brain before behavioral changes are apparent.

"That's the ideal down the line, once you know enough about mu," Bernier says cautiously. "At this point, it remains to be seen."

Bernier's clinical skills also contribute to the search for autism's genetic roots. He and his team are conducting the behavioral testing of children with autism who provide DNA to the Autism Genome Project and to the Simons Simplex Collection databases, measuring qualities such as their social responsiveness, repetitive behaviors, cognitive abilities and vocabulary.

Bernier also carries his expertise into the community. Last year, he almost single-handedly scripted and directed an informational video for all parents in Washington State whose child had received a diagnosis of autism. He also helped develop a program with Felice Orlich of Seattle Children's Hospital to train teenagers to be mentors to peers with autism.

Beyond autism, Bernier has helped administrate a yoga center in Seattle, organizes donations of time and money to a youth gardening outfit, and analyzes data *pro bono* for a nonprofit that promotes sustainability education to students and teachers.

He is also busy building his family. Five months ago he and his wife had their first child, a daughter, Sadie. "We did our first race together," Bernier says proudly of a 5-kilometer race that he ran in December with Sadie in the stroller.

Bernier's diverse experiences might explain his tendency to solicit different opinions at work, from junior and senior people alike. "He loves to discuss things and he really wants to encourage everyone coming together and sharing their ideas," says Jen Varley, a graduate student mentored by Bernier. "It feels very collaborative."

With an office adjacent to Bernier's at the University of Washington, Sara Jane Webb is frequently caught up in his swarm of ideas. A recent three-hour conversation with him about future experiments left her whiteboard covered in lists and diagrams. "Raphe's favorite saying to me all the time is, 'Teamwork never seems [like] work,'" she says.

Teamwork aside, Bernier's individuality is still very much a part of his work. For one, he has kept up his infamous musical ditties, which enliven thesis defenses, going-away parties and other special occasions.

"I work hard and the other folks here at the UW Autism Center work hard, so it's fun to lighten that up," Bernier says. "I just like to be goofy periodically, and music is one way to show that."

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Elizabeth Berry-Kravis: Running a marathon for fragile X syndrome

BY ESTHER LANDHUIS / 26 MAY 2021

In April 2020, as the world went into lockdown and laboratories shuttered, Elizabeth Berry-Kravis was on the move.

Her team's clinical trial of a potential treatment for fragile X syndrome—one of the most common inherited forms of intellectual disability and a leading genetic cause of autism—was nearly complete. But she and her colleagues had to collect critical data from two participants in the coming days. One man had been scheduled to travel from Oklahoma to Berry-Kravis' lab at Rush University Medical Center in Chicago, Illinois, in late April.

But the pandemic derailed those plans. So Berry-Kravis, professor of child neurology, and two study coordinators hopped in her car for a more than 10-hour drive through pouring rain to meet him at his farm. Wearing masks and wielding disinfected tablets, the researchers tested his cognition in a camping trailer. A few hours later, they retraced their nearly 700-mile route north, returning to Chicago around 2 a.m. The next day, the exhausted researchers flew to Florida to meet up with another trial participant.

"But we got the data!" Berry-Kravis says.

FAST FACTS

Current position: Professor of pediatrics, Rush University Medical Center
Main areas of interest: Translational neuroscience for neurogenetic disorders of childhood
Notable mentors: Peter Huttenlocher

The rationale for the new drug dates back to analyses Berry-Kravis, 63, did more than 30 years ago. In the late 1980s, she made an unexpected discovery linking fragile X syndrome to a learning mechanism involving the signaling molecule cyclic AMP. The findings catapulted Berry-Kravis into the fragile X field.

Since then, Berry-Kravis has authored more than 250 peer-reviewed publications. Her productivity is unparalleled, her colleagues say. "She gets more stuff done than any other researcher I know," says Randi Hagerman, medical director of the MIND Institute at the University of California, Davis.

No matter how busy she is, Berry-Kravis wakes up to run 4 to 6 miles almost every morning, something she has done since running track in high school. She has completed two marathons, including one in 2014 that she ran as a symbol of the long road to fragile X drugs.

She shows endurance in both races. She is best known for her efforts to apply lessons from unsuccessful clinical trials in fragile X to new studies of the condition. "Her work has moved the needle on targeted treatments and translational research in fragile X syndrome perhaps more than any other single person," says David Hessl, professor of clinical psychiatry at the University of California, Davis.

The 2020 trial data would move that needle once again. They showed promise for an experimental drug for fragile X syndrome after more than a decade of failed attempts.

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Berry-Kravis has known since seventh grade that she wanted to be a neurologist. Never mind that women made up less than 10 percent of doctors in the United States back then. "I had been interested in how the brain wires and connects and speaks to itself," she says.

Among the first few women to enroll at the University of Notre Dame in Indiana in 1975, Berry-Kravis earned a B.S. in chemistry in 1979 and then an M.D.-Ph.D. from the University of Chicago for her studies of molecular pathways regulating cyclic AMP in neurons.

In the 1980s, several studies had linked low cyclic AMP with impaired learning in fruit flies and sea slugs. So in 1987, during her pediatric neurology fellowship, Berry-Kravis decided to test whether cyclic AMP deficiency might also relate to cognition in people. At first, she aimed to study people with a rare endocrine condition called pseudohypoparathyroidism, who are known to have low cyclic AMP. She decided to also measure cyclic AMP in people with fragile X syndrome, initially as a control group.

To her surprise, she found that blood cells from some people with fragile X syndrome had even less cyclic AMP than those from people with pseudohypoparathyroidism, hinting that lack of the signaling molecule might be key to understanding fragile X. She submitted an abstract to the 1990 Child Neurology Society meeting—only to realize, upon hearing it was accepted, that the meeting coincided with her second child's due date.

As fate would have it, her son was born early. So within a few days of giving birth, she popped into her lab to do the final cyclic AMP assay, and a few days after that, gave her talk.

To confirm and expand her initial findings—for example, to examine different cells and tissues—Berry-Kravis needed to recruit more people with fragile X, so she reached out to local support groups. At their meetings, Berry-Kravis learned about families' confusion about the science. A key 1991 paper had just identified FMR1

as the culprit gene in fragile X, but its inheritance patterns were baffling. Mothers who did not have fragile X were being told they were carriers, and they did not understand why.

Berry-Kravis explained that it depends on the number of repeated DNA segments the gene contains. Typical FMR1 has fewer than 45 of these 'CGG repeats.' Having more than 200 of them turns off the gene, suppressing production of its protein, FMRP, and leading to the syndrome. But the gene can expand over generations: Mothers with 55 to 200 CGG repeats have what is known as a premutation. They may not have fragile X traits, but their children are more likely to. At one meeting, Berry-Kravis says, "I wound up staying there for four hours."

Families were also frustrated about the lack of care. "As I met the families, it was clear they were desperate to have a place to go where someone would know everything about fragile X syndrome," Berry-Kravis says. So in 1991 she and her team set up a fragile X clinic. It grew rapidly, fueled by word of mouth about Berry-Kravis' expertise, and now treats more than 700 people. "She is so knowledgeable," Hagerman says. "She also has a great memory and sensitivity to what the families are going through."

In the mid- and late 1990s, Berry-Kravis presented her findings linking low cyclic AMP to fragile X syndrome at various conferences. "This was such a novel thing," she says. Whereas much of the field was focused on genetics, "this was an actual mechanism for why fragile X neurons were not working right."

In 1998, she and her colleagues published a paper in which they showed that overexpressing FMR1 in a neurotumor cell line could rescue the cells' cyclic AMP deficit—providing support for the involvement of this pathway in the cognitive difficulties of fragile X.

If a lack of cyclic AMP underlies fragile X syndrome, Berry-Kravis reasoned, then raising levels of the molecule might be a way to treat it. She considered the strategy of blocking phosphodiesterase, an enzyme that breaks down cyclic AMP—but quickly dismissed the idea. Phosphodiesterases are present throughout the body, so inhibiting them would likely lead to serious side effects. "There was no drug that would do that without causing major havoc," Berry-Kravis says.

In the early 2000s, Berry-Kravis saw that fragile X research was converging on another drug target: a receptor called mGluR5, which sits on the surface of neurons. FMRP acts as a brake on parts of the mGluR pathway, which controls protein production. In people with fragile X, the absence of FMRP leads mGluR signaling—and protein synthesis—to proceed unchecked, suggesting that blocking mGluR could correct the problem.

By 2012, studies from more than 20 labs showed that mGluR inhibitors could reverse fragile X traits in mice, rats and flies. "It was probably the largest body of evidence that any genetic disorder has ever amassed on a type of drug reversing the disorder by the time we went to trials," Berry-Kravis says. What is more, a few of these drugs looked promising in early-phase human testing.

Yet mGluR blockers did not show benefit in larger human trials, which Berry-Kravis and Hagerman helped design. In 2014, both Novartis and Roche disbanded their programs.

But Berry-Kravis had not given up on the drugs. Instead, she began to question the way they were vetted. For starters, the trials enrolled adolescents

and adults, but fragile X is a developmental condition. "You probably have to treat kids to find out whether the drug works," she says. And although learning difficulties are central in fragile X, the trials did not assess cognitive outcomes. "We were like, 'Hey, wait a minute, what were we doing? We don't even know if these drugs don't work or if we just did the trials wrong,'" Berry-Kravis says.

In 2015, Berry-Kravis—working with Hagerman, Hessl and others—applied for a grant from the U.S. National Institutes of Health to fund "the trial we wanted Novartis to do," she says. The NeuroNEXT study is testing Novartis' mGluR blocker AFQ056 in 3- to 6-year-old children with fragile X syndrome. All children in the trial receive intensive language treatment, and the researchers plan to assess whether outcomes are better in children who are taking the drug than in those given a placebo.

Alongside her research, Berry-Kravis co-directs the Molecular Diagnostics Section of the Genetic Laboratory at Rush University, which tests people for fragile X and other genetic disorders. She also works as a doctor about 20 hours per week at the fragile X clinic. "Most people would tell you that I don't sleep as much as other people," Berry-Kravis jokes. (She gets just four to six hours of sleep per night.)

Her naturally high energy gets a boost from another habit: Tab soda. She used to chug three to four cans a day but has capped daily consumption at two cans since production of the caffeinated drink stopped last December.

Her tireless drive is what kept the clinical trial on track in April 2020. The drug under scrutiny was a re-imagined phosphodiesterase inhibitor. By solving the crystal structure for a phosphodiesterase important for brain function, scientists from the biotech firm Tetra Therapeutics were able to design a drug that blocks only this form of the enzyme. The specificity radically improves its safety profile, says Mark Gurney, Tetra's chief executive officer.

In April 2021, Berry-Kravis, Gurney and their colleagues published the results of the trial: significant improvement in language, daily function and cognition in 30 men with fragile X syndrome. For Berry-Kravis, it was a result three decades in the making—and yet the potential therapeutic still has to clear large-scale trials. To the fragile X community, she recommends patience in the search for treatments. "We need to have the stamina of a marathoner," she says.

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Michael Boland and Soo-Kyung Lee: The most personalized medicine

BY LYDIA DENWORTH / 7 JULY 2022

The day Michael Boland's son was born in July 2018 was blissfully normal. It had been a routine birth, and little Lukas aced the Apgar, a standard health test given to newborns. The next day, Boland made a quick trip home. As he walked back into the hospital room, he saw Lukas move in a sudden, odd way.

"What was that?" he said to his partner, Maja Horn.

"We saw him do that earlier," Horn said.

A first-time mother, she wondered if the brief, jerky movements were typical of newborns. Or maybe it was hiccups?

Boland suspected otherwise. A cell biologist at the Institute for Genomic Medicine at Columbia University, he studies developmental and epileptic encephalopathies. He knew what seizures looked like in infants. When Lukas moved the same way again an hour later, Boland alerted the doctors. They whisked Lukas to the neonatal intensive care unit and put him on antiseizure medication. Two and a half weeks later, genetic testing revealed a mutation in a gene called STXBP1.

"Oh my God, I was devastated," Boland says. "I had an idea what we were facing."

He had not studied STXBP1, or syntaxin binding protein 1, but he knew that it plays a critical role in the transmission of electrical signals between neurons. Researchers had identified mutations in STXBP1 that reduce that signaling as a cause of infantile epileptic encephalopathy in 2008. Since then, increases in genetic testing have revealed STXBP1 encephalopathy in about one in 33,000 children. Clinical symptoms vary, but include epilepsy and, often, severe cognitive impairment; about 20 percent of children with the condition exhibit autism traits. Of the most affected children, Boland says, "they're not going to be potty trained ever, they're not going to learn to dress themselves."

A couple of months after Lukas' birth, Boland sat down with his colleagues at the Institute, David Goldstein and Wayne Frankel, and told them what was going on with Lukas.

"Wayne was like, 'You've got to be kidding me!'" Boland remembers. "David's jaw hit the table."

"When do we start working on STXBP1?" Boland asked them.

"Immediately," they responded.

With that, Boland became one of a handful of scientists in an unenviable but potentially important position: He would turn his heartbreak into hard data and study his own child's condition. "I'm a scientist. . . This is my son. We have all of the tools here to do this," he says. "It just feels like that's what I was trained to do."

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In the world of rare autism-linked genetic syndromes, parents are already playing a central role, pushing to raise funds and advance investigations into their children's conditions. "Parents are essentially kick-starting, and frankly, de-risking the research," says Charlene Son Rigby, who in 2017 cofounded the STXBP1 Foundation, which has three parents on its science advisory board, including Boland.

Attracting parents who are also scientists to the cause only turbocharges those efforts. Nasha Fitter, a cofounder of the FOXG1 Research Foundation, a parent-led foundation for research on an autism-linked condition called FOXG1 syndrome, could hardly believe it when she stumbled on a 2017 Facebook post by FOXG1 parent Soo-Kyung Lee about a grant she and her husband, Jae Lee, both respected neuroscientists, had secured. "Hold up, you guys are parents and you're scientists?" she remembers thinking, even before she knew of their expertise and reputation for rigor. The Lees now lead the FOXG1 Center of Excellence at the University at Buffalo in New York State and receive considerable funding from the foundation. FOXG1 families are unfortunate in many ways, Fitter says, "but we're very fortunate with Soo and Jae."

Experts see little risk in the personalized

FAST FACTS

Soo-Kyung Lee's current position: Empire innovation professor of biology, University of Buffalo, SUNY
Recent significant work: Our research program is aimed at understanding the pathophysiology of neurodevelopmental disorders associated with congenital brain deficits, such as FOXG1 syndrome, using our new mouse models and various therapy developments.

research of people like Boland and the Lees, noting that ethical review boards and the peer review process help protect against conflicts of interest. Meanwhile, the upside of the urgency and commitment parent-scientists bring may be considerable. "Being extra super smart is great," says William Dobyns, a pediatric neurologist and medical geneticist at the University of Minnesota in Minneapolis who has helped identify many single-gene brain disorders, "but focus and motivation, that's one of the difference makers. That gets progress."

STXBP1 and FOXG1 represent two of an ever-growing list of genes implicated in autism-related neurodevelopmental conditions over the past 15 years. Where once children might have been diagnosed with autism, severe intellectual disability, epilepsy or some combination of the three, genetic testing now pinpoints a causative mutation in about 40 percent of cases, according to Dobyns. (For autism without co-occurring conditions requiring high support, that number is far lower, in the low single digits, he says.)

The more profound a person's traits, the more likely it is that an explanation can be found in their DNA. Having a genetic diagnosis fine-tunes the prognosis for a child and reveals whether other family members are at risk. It also allows hope.

"Once we recognize a specific genetically defined disorder, then the possibility of developing targeted therapy is here," Dobyns says.

Soo Lee understood that better than most. When her daughter Yuna was born in 2010, Lee was a rising star in the world of neurodevelopmental biology. Her research focused on the role of transcription factors, which regulate genes, during brain development. The demands of her career were intense—so much so that when her infant daughter showed signs of profound developmental delays, she worried it was somehow her fault for working too much. Yuna missed every milestone, had enormous trouble feeding and sleeping and had seizures beginning soon after birth. Magnetic resonance imaging (MRI) revealed microcephaly, a small brain, but genetic testing did not initially turn up any mutations. Yuna was diagnosed with congenital Rett syndrome, a catchall for children who have clinical similarities to the autism-linked condition.

The Lees pressed to keep searching for a genetic culprit. Soo Lee took to carrying Yuna's MRI results wherever she went, including a multiday meeting for the National Institutes of Health held in San Francisco, California. There, she talked about her then 2-year-old daughter's condition with a researcher who offered to consult a radiologist colleague who had deep experience reading pediatric neurological MRI results. A few days later, that radiologist reported that the abnormalities in Yuna's brain structure might be tied to FOXG1, a gene so critical to brain development that mice lacking both copies do not develop a functional brain and die shortly after birth. (The same is true of STXBP1.)

The idea that her own daughter might have a condition related to a neurodevelopmental gene, encoding a transcription factor no less—the very thing Lee studied—seemed almost too coincidental to be believed. Although FOXG1 was well known, the syndrome related to FOXG1 muta-

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Main areas of interest: Neurodevelopment. I am a neurodevelopmental biologist who wants to combine basic science expertise with a translational research program.
Lab URL: http://www.myfoxgirl.com/ • **Notable mentors:** Samuel L. Pfaff

tions had only been named in 2011 and wasn't yet widely recognized. When the Lees had Yuna tested for it specifically, the radiologist was proved right. Soo Lee reviewed the raw sequencing data herself to be sure. She estimates that Yuna was the 20th child in the world to be identified with FOXG1 syndrome. There are still fewer than 1,000 known cases, although there are likely to be many more who have not been identified.

The hallmarks of the syndrome include microcephaly, cortical atrophy and weak or missing connections between brain hemispheres, as well as seizures, cognitive disabilities, absence of language, movement disorders and, sometimes, autism. Children who have a completely inactivated copy of the gene, like Yuna, have more disabling traits than those with a more mildly affected version that produces faulty FOXG1 protein.

Yuna's diagnosis prompted Soo Lee to make FOXG1 a centerpiece of her research. "I thought, this is what I have to do," she says. Jae Lee, who had done important work on gene regulation of metabolism, joined her. "I was more than glad to drop everything else," he says.

Much of the Lees' home on a quiet cul-de-sac near the university is organized with Yuna in mind. The house features wide-open spaces and hardwood floors that can be readily navigated with a wheelchair. Construction on a small indoor swimming pool is underway, because Yuna enjoyed the hotel swimming pools they frequented when they drove across the country from Oregon to Buffalo to start their center in 2019.

Small and thin for a 12-year-old, Yuna usually wears soft clothing such as sweatpants and a fleece top, with her hair pulled into a ponytail atop her head with a fuzzy scrunchie. (Her dad has gotten very good at doing her hair in the morning.) She cannot walk or speak, but her family know what she likes—including stuffed animals and toys that light up or play music. After she gets home from her specialized school, she spends a lot of time in a play area they've created for her in an alcove off the kitchen. Her poor motor control means that she is constantly moving, but when her caregiver puts a sticker on the couch and encourages Yuna to go get it, the girl rocks and reaches her way to the couch. The Lees credit years of therapy and hard work. Her movement has become "more purposeful because she has better control," Jae Lee says.

They take heart from other small, hard-won changes. Yuna never used to make eye contact with her parents. Recently she began glancing out the school bus window at them as they waved goodbye in the morning. One day when Jae did not join Soo in the driveway, Yuna looked far longer than normal. Soo says she believes Yuna was searching for her father. The next day Jae was back in position and Yuna, presumably satisfied, resumed her usual glance. "She's doing much better than what I thought [was possible] 5 years ago," Soo Lee says. "It's a very subtle thing. Nowadays, I can tell what she likes, that she's happy. It's just so much easier to know who Yuna is."

The research that Boland and the Lees have conducted so far differs in the specifics but offers a basic science primer on how to tackle monogenetic conditions. First, establish viable models,

FAST FACTS

Michael Boland's current position: Assistant professor of neurology, Columbia University, Irving Medical Center
Main areas of interest: Stem cell/organoid models of cortical malformations and developmental and epileptic encephalopathies; transcriptomics; neurophysiology
Notable mentors: Kristin Baldwin, Jeanne Loring

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beginning with mice, and use those models to investigate what exactly the genes of interest do in the brain. Because these conditions are developmental, address the pivotal question of whether the work of the gene is complete at birth or whether it continues and offers an opportunity to intervene. Finally, ask the ultimate question: Is it possible to reverse the damage and rescue what has been lost—in humans, not just in mice?

The Lees have focused their efforts on mouse models. The first one they analyzed lacked one copy of the FOXG1 gene and showed altered brain structure and behavior that mimicked the movement, learning and memory deficits seen in children with FOXG1 syndrome. The Lees have since made multiple mouse models that mimic various mutations found in people. And they have shown that FOXG1 helps establish the brain's cortical layers and create the corpus callosum, which connects the left and right brain hemispheres.

Boland, too, is working with a mouse model of STXBP1, with help from Frankel, who has decades of experience in the field. But Boland also grows human pluripotent stem cells, which he coaxes into two different models: two-dimensional neuronal networks that look like lacy latticework, and three-dimensional brain organoids, which look like chickpeas yet faithfully recapitulate

> "As a parent, I'm less of the poker player. I'm more like, these are my cards. If you can learn from me, then maybe that'll help you develop a therapy faster than mine."
> —Michael Boland

the early cell growth in developing brains. He has even created models using Lukas' cells and his own. "[That's] a 3D model of my son's brain in a dish," he says during a tour of the lab. The three models—neuronal networks, organoids and mice—trade biological complexity for granularity and together, Boland says, allow more nuanced comparisons of how typical and STXBP1 neurons communicate.

Fortunately, FOXG1's work appears to be incomplete at birth, the Lees have found, and STXBP1 is critical to how neurons communicate throughout life. That leaves open the possibility of drug treatments or gene therapies. Boland and Frankel are focusing on testing two gene therapies for STXBP1: a traditional replacement therapy that adds back a functional copy of STXBP1 and an adaptation of CRISPR technology that upregulates the gene's expression. (That work is supported by a grant from The Simons Foundation, *Spectrum*'s parent organization, and Boland is a part-time consultant for the foundation.) Unpublished work in other labs has successfully stopped seizures and rescued learning and memory deficits in mice, Boland says.

The Lees are using their mice as platforms for drug screening. One therapy they tried in an unpublished experiment reversed some of the traits in FOXG1 model mice. "We wanted to confirm whether FOXG1 syndrome can be fixed," Jae says. "The answer seems to be yes. We were just completely stunned."

Despite the promise, treatment is not imminent for either of these conditions. At home, these scientists focus on being parents, not researchers. Half of Boland and Horn's Manhattan living room is given over to a colorful rug with toys stacked around its edges. At first glance Lukas, at nearly 4 years old, looks like any child his age, with a cherubic round face. He sits tall on the rug (therapists compliment his posture) and gazes at his parents. But it's soon evident that his behavior is more like that of a 1-year-old. His feeding issues mean everything he eats must be pureed. He doesn't talk. He only recently learned to crawl. He might be able to walk by age 6 or so, though it won't be coordinated walking, Boland says.

Each new skill—head control, sitting up, pulling up, crawling—was the work of many months or even years. Boland and Horn call them "inchstones" not milestones. Nonetheless, they say, Lukas is easygoing and engaged. He loves spinning tops, musical toys and board books. Lying on the floor with an Elmo book, he dips his head to the page and touches it with his lips, giving Elmo a kiss. Such social behavior feels like a gift, Boland says, while mashing up sweet potatoes, spinach and quinoa for Lukas' dinner. "When he can give you those big beautiful brown eyes that stare into your soul, it makes it easier."

During her pregnancy, Horn, who was over 40 and at increased risk for having a child with a disability, worried a little bit about that possibil-

ity. "Will you do everything you can?" she asked Boland. He said he would. But that was a hypothetical conversation, and the reality of Lukas' condition was a shock. Over time, however, says Horn, a professor of Spanish literature at Barnard College in New York City, she has come to fully accept Lukas for who he is, and the experience of raising him has changed her "in every imaginable way." She, too, has shifted her academic interests to think about perceptions of ability and disability. She is glad Boland is studying STXBP1—that he is, in fact, doing everything he can. But she is not willing to try anything too risky on her child. Her focus is on cherishing Lukas as he is, "a child that's so lovely and happy," and facing the immediate future. "My hope is that he will be able to express his needs and wants on his [communication] device. . .to be able to say I'm hungry, I'm thirsty," she says. "I think that's totally within reach."

Boland and the Lees have been changed as well, for better and for worse.

One Sunday afternoon, when Yuna was 5 years old, Soo Lee collapsed in the living room. She had developed vestibular neuritis, a destabilizing condition caused by inflammation, which Soo attributes to stress. Seven years later, she manages her condition with medication but must limit work hours, screen time and some daily activities like driving. When her 9-year-old son, Joon, "wants to show me a YouTube video, he says, 'Wait, wait, let me lower the brightness,'" she says with a laugh.

Science is famously competitive and ego-driven; there is only so much money and recognition to go around. For Boland and the Lees, however, ego has less to do with it these days. Regardless of funding or support, Jae Lee says, "this is what we would be doing." Interactions with other scientists are different, too. It used to be "like holding a poker hand," Boland says. No more. "As a parent, I'm less of the poker player. I'm more like, these are my cards. If you can learn from me, then maybe that'll help you develop a therapy faster than mine."

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B

Wendy Chung: Genetic sleuth is advocate for families

BY DEBORAH RUDACILLE / 21 JULY 2011

A few months ago, a young woman walked into Wendy Chung's office with a notebook and a flash drive. She said, "Here's my medical history, here's my genome, now you figure out what caused all this."

This is exactly the kind of challenge that Chung relishes. A skilled genetic detective, she is adept at tracing an individual's symptoms to a particular genetic anomaly, teasing out its molecular ramifications and identifying the associated syndrome.

According to those who know her well, that analytical bent is accompanied by a rare sensitivity.

"I've known a lot of brilliant doctors and though she's at the top of the brilliance list, she also has a humanistic philosophy that animates everything she does," says Hamilton Cain, the father of one of Chung's patients. "She's not only thinking on all cylinders, but also feeling on all cylinders. She really connects with patients and their stories and their lives."

Chung, who began her research career studying diabetes and obesity, is director of the clinical genetics program at Columbia University Medical Center in New York as well as the university's fellowship program in clinical and molecular genetics. Two years ago, she moved into the autism field, accepting an invitation to serve as the principal investigator of the Simons Variation in Individuals Project (VIP), launched by the Simons Foundation, *Spectrum's* parent organization. The project aims to identify and study individuals with an autism-associated deletion or duplication on chromosome 16p11.2.

Chung also teaches many core medical courses at Columbia. Her talent for teaching and mentorship has won her the prestigious Presidential Teaching Award and other prizes. She is what an earlier generation of researchers called "a triple threat"—skilled clinician, ambitious researcher and gifted teacher, says Rudolph Lei-

FAST FACTS

Current position: Kennedy Family professor of pediatrics and medicine, Columbia University
Recent significant work: Establishing SPARK • **Main areas of interest:** Genetics
Notable mentors: Gerry Fischbach

bel, head of the division of molecular genetics in the department of pediatrics at Columbia University Medical Center.

"She's certainly one of the brightest of her generation of physician-scientists," says Leibel, who was Chung's doctoral advisor at Rockefeller University in New York before both moved to Columbia. "In many ways, she is the poster child for physician-scientists."

Chung began her career as a basic scientist. "I was a classic academic scientist: Lab-based, cloning genes, looking for very rare pathologies," she says. "It was very abstract but it was what my mentor had done and what I thought a successful scientist should do."

A family tragedy led her to change her plans. Very late in pregnancy, Chung miscarried for reasons that remain a medical mystery. Chung, who has two surviving sons, says, "As that kind of experience often does, it totally changed my life."

She says she began to wonder what she would leave behind if she were to die the next day. "I realized that I would be very disappointed if, at the end of my life, all people would say is that I had published a certain number of papers," she says. "I wanted to make sure that what I do is making a difference in patients' lives."

Her goal became making discoveries that would have a direct application to human disease. Leibel says he believes that transformation would have occurred in any event, although the tragedy may have sped it up.

Chung's substantial gifts were evident early in her career, when she was a postdoctoral researcher working in his lab at Rockefeller University, Leibel recalls.

While working on her thesis project, for example, Chung made a discovery that would have slipped by many experienced researchers, he says. She noticed that one of the animals in a diabetes study had an unusual gait, and set out to determine whether a mutation in the colony had led to the peculiar trait. She did this on her own, taking videos of the animals and working them up carefully.

Ultimately, she cloned a gene from the animal that affects conductance in the heart and can lead to lethal arrhythmias. "That kind of thing has been repeated many times over in her career," Leibel says. "She has a good sense of what is worth pursuing."

At Columbia, Chung is involved in a broad range of research projects, investigating the genetic basis of diabetes, cardiac disorders, neuromuscular disease and neuropsychiatric disorders. She also sits on the advisory board of the master's program in bioethics and has co-authored multiple papers with faculty in that program, exploring the ethical and social implications of genetic medicine.

"She is the go-to person for genetic issues at Columbia," says pediatric cardiologist Teresa Lee, who was a fellow in Chung's lab and still works there, researching genetic factors in cardiac disease. "She pretty much manages any patient in the hospital with a genetic disorder."

As a mentor, Chung pushes her students as hard as she pushes herself, Lee says. A few years

ago, her graduate students and postdocs hosted a dinner to celebrate Chung winning the Presidential Teaching Award. Each presented Chung with a book for her two sons that reflects lessons he or she had learned from Chung. Lee's choice was "The Little Engine That Could"—"because she believed in me sometimes more than I believed in myself," Lee says.

Chung builds equally strong relationships with her patients and their families. In fact, Cain, the father of one of her patients, is writing a nonfiction book about genetic medicine with Chung as the protagonist.

"She was a great advocate for us," says Cain, whose son Owen, now 8 years old, was born with spinal muscular atrophy, a neuromuscular disease that is the most common genetic cause of death in infants.

The family endured months of agony and uncertainty until Chung diagnosed the disease just as Owen celebrated his first birthday. Chung's support and advice meant a great deal to the family as they navigated the complex details of his treatment, Cain says. "It really empowered us to make the right decisions for our son."

Genetic medicine can pose difficult questions for both clinicians and parents. For example, deletions and duplications in the 16p11.2 region almost always produce some symptoms of autism, but only about 30 percent of individuals with a deletion warrant a diagnosis.

The Simons VIP study aims to understand the full spectrum of the 16p11.2 phenotype, or collection of traits. Until it does, however, it is tricky to advise parents on whether to opt for prenatal tests for the region and other less well-characterized genetic anomalies.

"One way of thinking about this is people can make their own decision," Chung says. "On the other hand, I can tell you the flip side, the patients who got the intensive arrays and say afterwards, 'Boy, I really regret making this decision.'"

Still, whenever there is a question about sharing information with families, Chung invariably comes down on the side of patient autonomy, says Christa Lese Martin, director of the genetics laboratory at Emory University in Atlanta, and a co-investigator on the Simons VIP. "She's always got the family's needs in mind."

Leibel adds that Chung also serves as a sounding board for physicians wrestling with such difficult issues at Columbia.

"She's not talking about theoretical constructs," he says. "She's lived them herself, in terms of losing a child for reasons that still remain unknown. I think that's one of the reasons she's so sensitive on these points and so effective."

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Hollis Cline: Leapfrogging over gaps in autism research

BY LAURA DATTARO / 1 FEBRUARY 2022

Early in her first postdoctoral position, Hollis Cline first showed her hallmark flair for creative problem-solving.

Cline, who goes by Holly, and her adviser, neuroscientist Martha Constantine-Paton, wanted to study the brain's 'topographical maps'—internal representations of sensory input from the external world. These maps are thought to shape a person's ability to process sensory information—filtering that can go awry in autism and other neurodevelopmental conditions.

No one knew just how these maps formed or what could potentially disrupt them. Cline and Constantine-Paton, who was then at Yale University and is now emerita professor of brain and cognitive sciences at the Massachusetts Institute of Technology, weren't sure how to find out.

But as a first step, the pair decided to take the plunge with an unusual animal model: the frog—specifically, a spotted greenish-brown species called *Rana pipiens,* or the northern leopard frog. The amphibians spend two to three months as tadpoles, a span during which their brains change rapidly and visibly—unlike in mammals, which undergo similar stages of development inside of the mother's body.

These traits made it possible for Cline and Constantine-Paton to introduce changes and repeatedly watch their effects in real time.

"That's an extended period when you can actually have access to the developing brain," Cline says.

The unorthodox approach paid off. Cline, 66, now professor of neuroscience at the Scripps Research Institute in La Jolla, California, worked out that a receptor for the neurotransmitter glutamate, which had been shown to be important for learning and memory, also mediated how visual experiences influence the developing topographical map. She later created a novel live imaging technique to visualize frog neurons' development over time and, sticking with frogs over the ensuing decades, went on to make fundamental discoveries about how sensory experiences shape brain development and sensory processing.

Such innovation and persistence characterize Cline's prolific career—and have made her an especially collaborative scientist, colleagues say. "One of the great things about Holly has always been that she's been able to work and find solutions to problems others have made into obstacles," says Scott Fraser, professor of biology at the University of Southern California in Los Angeles.

As a reward for her efforts, Cline served as president of the Society for Neuroscience from 2015 to 2016; has published more than 200 papers, which have been cited more than 17,000 times, according to Google Scholar; and has been recognized with several mentorship awards. And she continues to extend her scientific reach and innovate, including a recent turn to stem-cell models in search of answers about Rett syndrome.

"There's no limit," says Linda Van Aelst, professor of cancer research at Cold Spring Harbor Laboratory in New York. "She goes for it, if that will answer a question."

Cline's love for the lab started young. As a child, she was captivated by her mother's work as a lab technician, which she started as soon as Cline, the youngest of three, entered school. Cline so wanted to be in the lab that she regularly faked being sick to miss school and tag along. (Her mother, who earned a doctorate in biochemistry in 1965, let her get away with the ruse.)

Cline studied biology at Bryn Mawr College in Pennsylvania and made plans to follow in her mother's footsteps. But in 1977, during her final year, she took a neurobiology course and switched gears. "I was totally enamored with it," Cline says.

So enamored, in fact, that she set aside her graduate school applications and instead took a job as a research technician in endocrinologist Martin Sonenberg's lab at Memorial Sloan Kettering Cancer Center in New York City. She often walked across the street to attend neuroscience seminars at Rockefeller University. And in 1979, she was ready for graduate school—this time in neuroscience, at the University of California, Berkeley, where another chance encounter once again redirected her career.

Cline, who was studying the role of cell lineage in brain development, had to write a paper outside of her direct area of interest to fulfill a school requirement. She focused on the development of

FAST FACTS

Current position: Professor and chair of neuroscience, Scripps Research
Recent significant work: Identification of activity-induced changes in protein synthesis in genetically defined brain cell types suggests additional components of plasticity pathways.
Other major accomplishments: Election to the National Academy of Sciences

the visual system and happened upon a question that would motivate her entire career: How does sensory experience help shape the brain's development? After reading Constantine-Paton's 1984 paper on the visual system's development in frogs, Cline decided to return to the East Coast in 1985 to study with her.

Initially they decided to try to unpack how tinkering with the glutamate receptor alters visual system development in frogs, which other teams had demonstrated in goldfish and cats. They found that when they blocked the same receptor in optical cells in the tadpoles' brains, visual signals no longer shaped the map. What's more, the axons of signal-transmitting cells called retinal ganglion cells spread across a wider area and produced a more "scattered" topographical map.

Visual input to the eye, Cline and Constantine-Paton proposed, activates glutamate receptors on certain optical cells, prompting them to form, test and re-form the map's connections. However compelling, though, the model was based on still images of tadpole brains at various time points. Without a method to watch the process unfold in real time, Cline says she felt she would have to abandon her research. "That was a pretty dramatic thought."

The solution came while flipping through the August 1990 issue of the journal *Neuron,* which featured a study describing a method of dyeing a frog's neurons and recording how they grow and form connections. Cline ran to her phone and called Fraser, the study's lead investigator, who offered to teach Cline his techniques. Cline also switched to a genus of frogs called Xenopus, albino specimens of which are transparent.

"I just remember reading that paper and saying, 'Oh my God, this is amazing,'" Cline says. "That really opened up a brand-new world, actually, and I started to do everything in live imaging."

After a second postdoctoral fellowship in Richard Tsien's lab at Stanford University in California, Cline set up her first lab at the University of Iowa in 1990 and then moved to Cold Spring Harbor Laboratory in 1994. There she created a technique to introduce light-emitting molecules into individual frog cells. "Holly really pioneered this area of in-vivo imaging in the frog," says Elly Nedivi, professor of brain and cognitive sciences at the Massachusetts Institute of Technology.

When Cold Spring Harbor Laboratory began hosting a series of meetings on fragile X syndrome in the 1990s, Cline started to see how her work might support studies of neurodevelopmental conditions. Among the attendees was Michael Tranfaglia, a doctor whose son had recently been diagnosed with fragile X, a condition often accompanied by autism.

Tranfaglia was on a mission to persuade developmental neuroscientists to study the syndrome. "One name kept coming up over and over again, and that was Holly Cline," he says. He convinced Cline to devote some of her time to investigating how mutations in the FMR1 gene, which cause fragile X syndrome, affect brain development.

"It motivated me to be much more broadly informed about various human conditions," Cline

C

Main areas of interest: Neuronal plasticity during brain development and aging • **Lab URL:** https://www.clinelab.org/
Notable mentors: Martha Constantine-Paton, Gunther Stent, Carol Mason

"I really think people work best when they're driven by their own inspiration and their own curiosity, and so I try to foster that in my group."
—Hollis Cline

says. "That was definitely very rewarding for me."

In 2008, Cline moved her lab to the Scripps Research Institute, where she continues to oversee research on inhibitory and excitatory neurons and conditions in which their balance is disrupted, as in autism and related conditions. And in 2014, she discovered that frogs that lack FMRP make fewer neurons than frogs that have working copies of the gene.

Since 2016, Cline has been director of the Dorris Neuroscience Center at the Scripps Research Institute, an airy, open lab environment that is home to 11 scientists. She sees mentoring younger women as crucial, she says. Her lab meetings regularly include discussions of how to improve representation in science, and she has received both the Scripps Research Institute Outstanding Mentor Award and the Society for Neuroscience's Mika Salpeter Lifetime Achievement Award specifically for promoting the advancement of women in science.

Her job, as she sees it, is to provide "the intellectual environment and scholarly environment for people to do the work that is most motivating for them," she says. "I really think people work best when they're driven by their own inspiration and their own curiosity, and so I try to foster that in my group."

Cline actively encourages event organizers, grant committees and others in positions of power to feature women in their programs, colleagues say.

Nedivi—who did postdoctoral research with Cline—says Cline taught her "everything." Cline and Nedivi worked together for only two years, more than two decades ago, yet Nedivi says she still considers Cline one of her closest friends. Others among Cline's colleagues and former students describe her as a respectful, supportive leader who doesn't see herself as being above others.

As her investigative scope and responsibilities have expanded, Cline says she has continued to consider herself a basic science researcher. Just as much as her work studying autism-related genes has elucidated some of the condition's underpinnings, it has also enabled her to gain a better understanding of the brain as a whole.

Studying Rett syndrome, for example, helped Cline answer a fundamental question about cell communication in the brain—a discovery that could, in turn, lead to a treatment for the genetic condition, which predominantly affects girls and often co-occurs with autism. She'd heard a talk by geneticist Huda Zoghbi, who discovered the gene that, when mutated, causes Rett syndrome. Cline was perplexed by how the girls lost previously acquired skills in early childhood.

Admittedly based on little more than a hunch—what she describes as "like an idea you

have in the shower"—Cline theorized that brain cells' typical process of exchanging information using exosomes, or packages of protein, DNA and RNA, goes awry in children with Rett, causing widespread regression in brain function.

To test the idea, she enlisted neuroscientist Alysson Muotri, who had built a human stem-cell model of Rett syndrome. Her hunch turned out to be right: In a dish, Rett syndrome neurons form few synapses on their own, but given exosomes from control neurons, they flourish.

"The strategy in science is: You observe something, you see something happen, and then you kind of push it to change it," Cline says. "Based on how it responded to your push, you learn something new."

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Eric Courchesne: Reaching for the rings in autism research

BY SARAH DEWEERDT / 4 SEPTEMBER 2017

Eric Courchesne's career in autism research began with an elevator pitch.

It was around 1980, and Courchesne had just started his first faculty job in the neuroscience department at the University of California, San Diego. In the elevator at Rady Children's Hospital one day, he met a clinical psychologist. They exchanged what-do-you-do pleasantries, and Courchesne explained that he was studying the brain's electrical responses to novelty—sights and sounds that a person has not experienced before.

"She said, 'Well you should study autism, because autistic children don't seem to be interested in novelty; they seem to be interested in repeating the same stimuli again and again,'" recalls Courchesne, who is now professor of neuroscience at the university and co-director of its Autism Center of Excellence.

The psychologist introduced Courchesne to a 15-year-old boy with autism, and Courchesne recorded the boy's brain waves. He discovered that the boy, along with nine other adolescents and young adults with autism, indeed turned out not to show the typical brain response to new things.

"That was it," Courchesne says. "I said, 'Oh finally, this is the developmental disorder that I'm going to study.'"

At the time, few neuroscientists were studying autism; some scientists had never even heard of the condition. But Courchesne had a long-standing interest in the development of the nervous system: He had contracted polio at age 4, which paralyzed the muscles in his legs. It took six surgeries over five years for him to stand and walk on his own again.

Courchesne doesn't shy away from talking

FAST FACTS

Current position: Professor of neuroscience and co-director of the Autism Center of Excellence, University of California, San Diego

Recent significant work: Neural responses to affective speech, including motherese, map onto clinical and social eye tracking profiles in toddlers with ASD. Courchesne E *et al. Nat Hum Behav.* 6, 443-454. (2022)
DOI: 10.1038/s41562-021-01237-y

about his disability; on the contrary, it's one of the first things he mentions when he meets someone new. And his repeated references to polio suggest that the illness has influenced not only his interest in autism, but his entire scientific career.

Today, Courchesne walks with a splayed-out, twisting gait but has the powerful upper body of a former gymnast. He has also made huge strides in understanding autism. He is best known for his findings on brain size. In 2001, his team reported that the brains of children with autism are larger than those of their typical peers in the first few years of life, but smaller later on. He led a large imaging study that confirmed the findings in 2010.

This pattern of brain growth affects only a subset of people with autism, but it is one of the most consistently replicated anatomical findings related to the condition. It helped to solidify the idea of autism as a biological condition with roots in the brain, rather than one that is purely psychological.

His discoveries extend beyond brain growth. Courchesne "has an encyclopedic knowledge of neuroscience," says Lisa Eyler, professor of psychiatry at the University of California, San Diego, who collaborates with Courchesne on imaging studies. Over the years, Courchesne has brought that knowledge to bear on topics as disparate as the function of the cerebellum and how the brains of preverbal children respond to language.

Courchesne was born and raised in Berkeley, California, in a family with a love of learning that slanted toward the humanities. His father had a rich trove of poems committed to memory. His mother spoke a half-dozen languages and played piano and violin, performing around the Bay Area.

His first taste of scientific research came when he was an undergraduate at the University of California, Berkeley in the late 1960s. He and a friend studied hermit crabs in local tide pools with the aim of understanding aggression in animals. (It was the Vietnam War era, after all, and Berkeley was a hotbed of antiwar protests.)

Courchesne started taking classes at the university in his final year of high school, at age 16. One day after class, the gymnastics coach noticed him hanging around the gym and invited him to try out for the team. It was a powerful experience of inclusion. "The coach wasn't bothered by the disabilities part. He said, 'Well, come on in,'" Courchesne says.

Courchesne competed on the pommel horse, and one year won the Pac-10 Conference on still rings. Years later, he realized that the uneven strength in his arms, a legacy of the polio infection, had forced him to start his routine on rings with a move that is considered unusually difficult, so he often garnered high scores. Without being conscious of it, he had not only adapted to his disability, but turned it into a competitive advantage.

Others see a similar adaptability, and a willingness to take on difficult challenges, in his scientific career.

"He isn't stuck in a particular method, approach, or even question," says Elizabeth Redcay, assistant professor of psychology at the University of Maryland, who was a graduate student in Courchesne's

Main areas of interest: Developmental molecular, cellular and systems neurobiology of autism
Lab URL: https://autism-center.ucsd.edu • **Notable mentors:** Steven A. Hillyard, Robert Galambos

lab from 2002 to 2008. “His goal is to understand autism, and often that means seeking well beyond his current work and comfort zone.”

In casual conversation, Courchesne has an easygoing manner that suits his shaggy hair, salt-and-pepper stubble and wardrobe staple—graphic T-shirts. His lab, which he shares with his wife Karen Pierce, who is also an autism researcher, is on a street with a sleepy, beach-town feel, just blocks from the Pacific Ocean in La Jolla. Lab members are known to take breaks from their experiments to ride the waves. “My surfboard lived in the office for a while,” Redcay says.

But the lab’s trappings belie its leader’s combative streak: Courchesne can be sensitive to criticism, quick to dismiss questioning from colleagues and competitors—and slow to let it go. Asked about a time when he’s been wrong scientifically, he only mentions ideas that didn’t gain traction at first, such as the role of the cerebellum in autism, but have since been vindicated.

In the past 15 years, Courchesne has been trying to trace the origins of the abnormal brain growth in autism, and the mechanisms that govern it. For this work, he needed brain tissue from children with autism.

Postmortem brain tissue is scarce, and that from young children even more so. It took five years for Courchesne to gather samples. In 2011, his team reported that seven boys with autism had an excess of neurons in their prefrontal cortex, a brain region involved in complex thought and planning. All of the nerve cells in this region appear before birth, so the results point to a prenatal origin for altered brain growth in autism, Courchesne says.

Three years later, Corchesne’s team analyzed brain tissue from 11 children with autism and 11 controls and found patches of immature cells, and disruptions of the characteristic layered structure of the brain’s outer region, the cerebral cortex, in the children with autism. This finding suggests that autistic brains have excess neurons because too many of them form, not because too few are pared back in a process called pruning, Courchesne says.

Other researchers in the field were skeptical of these studies because of the small number of brains and the focus on a few areas of the cortex. But the critique doesn’t faze Courchesne, who says other advances in autism research are also based on small sample sizes.

Courchesne has since reported more evidence to support his theory. For example, neurons made from skin cells of toddlers with autism who had enlarged heads divide faster than those of typical toddlers. The larger the child’s brain, the more rapidly the neurons proliferate.

Other researchers praise the diverse set of approaches Courchesne has used to explore these questions. Konstantinos Zarbalis has not met or worked with Courchesne but says his work helped him interpret his own results. Zarbalis’ research on mutant mice showed many of the same brain anomalies—increased head size, excess neurons, patches of abnormal cortex—that Courchesne identified in people with autism. Courchesne’s findings “tied everything together,” says Zarbalis, associate professor of pathology at the University of California, Davis.

Courchesne and Pierce met when she was a postdoctoral fellow in another lab at the university.

They have a 14-year-old daughter and a 12-year-old son, and work closely together. Pierce sat in during the interview of Courchesne for this article; the two sometimes finish each other's sentences and talk in a clipped, almost coded way when, for example, discussing the maximum strength of a magnetic resonance imaging magnet or calculating exactly how long they have been a couple.

Pierce studies eye tracking as an indicator of the chances of having autism and has pioneered an approach to identify children more likely to be autistic as early as 12 months of age. Together, she and Courchesne study how the brains of children more likely to be autistic respond to language.

"It's great that [he is] this massively awesome basic science researcher and me a little more clinically minded," Pierce says. "We can kind of feed off of each other and push the research forward together."

The couple's imaging studies have involved many late nights because they scan children while the children are sleeping. Courchesne doesn't shy away from the long hours.

"Usually you have a senior scientist and they develop the study, and then when the data collection comes around they're pretty hands-off," Eyler says. "That's not how Eric works, that's never been how he works; he always wants to meet the families and interact with the participants."

Courchesne says he can't imagine doing otherwise. His own experience with polio left him with particular empathy for what parents of children with autism might experience. "Some parents feel the way my parents felt," he says. "I became a champion gymnast, a successful scientist. And to the end of my parents' lives, they still cried every time they thought of the beginning; it was a trauma that they never stopped feeling."

He lists things that may seem out of reach for some children with autism, especially those with significant disabilities: being on a soccer team, running over to a friend's house to watch a movie, joining a game on the playground. In some ways, the goal of his research is to help them experience some of the very things he missed out on.

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Lisa Croen: Autism's first dedicated epidemiologist

BY RACHEL NUWER / 28 MARCH 2022

Lisa Croen's career took a sharp left turn toward autism research about 30 years ago, when she was working as an epidemiologist at the California Birth Defects Monitoring Program. Until then, she had largely studied the prevalence of physical birth defects, such as spina bifida and cleft palate. But in the 1990s, her boss asked her to examine figures on cerebral palsy.

Studying a condition that affects both brain and behavior intrigued Croen. So when the cerebral palsy study was finished, she and a colleague drummed up a new plan to examine intellectual disability from an epidemiological point of view. Before launching the project, they sought input from Mary Lu Hickman, a pediatrician specializing in children with special needs, who worked at the state's Department of Developmental Services.

"Yeah, you could do that," Croen recalls Hickman saying. "But what you should really look into is pervasive developmental disorder"—then an umbrella term for a suite of conditions that included autism. One of Croen's nephews had been diagnosed with autism a few years earlier, so the suggestion hit home.

Ever since then, Croen, 62, has focused almost exclusively on autism research—a subject she says she finds "incredibly fascinating and motivating. Every aspect of life that we encounter is concentrated in the study of autism—everything from behavior, biology, physiology and hardcore science to politics and ethics."

Croen, who now directs autism research at Kaiser Permanente's Northern California Division of Research in Oakland, was one of the first scientists to bring an "epidemiology tool box to autism

FAST FACTS

Current position: Senior research scientist, Division of Research, Kaiser Permanente Northern California, and director, Kaiser Permanente Autism Research Program

Main areas of interest: Epidemiology of autism and other neurodevelopmental disorders

Notable mentors: Judith Grether

research," says Eric Fombonne, professor of psychiatry at Oregon Health and Science University in Portland. "Environmental research was lagging behind, and she has been a pioneer in realigning etiological enquiries in the last 20 years."

Croen led one of the first large-scale studies to try to unravel potential environmental contributors to autism, and how genetics may modify their influence. She helped connect activation of the immune system during pregnancy to increased odds of having an autistic child. "This is important for our field, since this may direct strategies that can reduce risk during pregnancy," says Daniele Fallin, chair of the mental health department at the Johns Hopkins Bloomberg School of Public Health.

And Croen went on to document a significant gap in health outcomes between autistic and non-autistic adults. The work was a "tour de force" and a crucial wake-up call that prompted other labs to investigate such health disparities and find solutions, says Elizabeth Weir, a research associate at the Autism Research Centre at the University of Cambridge in the United Kingdom.

In recognition of Croen's many contributions to the autism field, in May 2021 the International Society for Autism Research (INSAR) named her a fellow—the highest honor that INSAR gives.

"Lisa is an absolutely outstanding epidemiologist," Fallin says. "Due to her careful choices about what to study, her rigorous approach to research and her ability to communicate findings in meaningful ways, her results have helped shape the field of autism epidemiology."

Croen is driven, Fallin says, "by a deep desire to improve people's lives."

Croen grew up in Palo Alto, California, the daughter of a neurologist and a social worker. Inspired by her parents, she considered becoming either a specialist in primate behavior or a teacher. A precocious violin player, she also thought about a career in music. At the University of California, Berkeley, though, she ended up majoring in environmental science because, she says, "I got to do all sorts of science and also continued taking anthropology, political science, philosophy and music."

Croen found her calling after graduation when her brother, a physician, introduced her to an epidemiologist. Talking with her brother's colleague reminded her of lessons that had fascinated her as an undergraduate—how major development projects, such as the Aswan Dam in Egypt, can lead to unexpected infectious disease outbreaks, or how a hospital building's features, such as having many windows, can improve patient outcomes. "Oh my God," she recalls thinking at the time, "this field allows you to study all these different things, and it's health related."

Croen enrolled in a master's program at Berkeley's School of Public Health and then, in 1986, took a job at the California Birth Defects Monitoring Program. After her pivot to focus on autism a decade later, she was energized by the fact that so little was known about the condition at the time. "I saw quickly that there were very few people studying autism—and what an incredible opportunity!" she says. In 1996, the same year she began her work in autism, she earned a

doctorate in epidemiology from the University of California, Berkeley.

From the beginning, Croen wanted to look for biological signatures that could be measured at birth to predict an eventual autism diagnosis—an interest that led to the first study to look for such markers among newborns. Croen and her colleagues tested infant blood samples for eight molecules involved in brain development and found a specific signature that distinguished those who were later diagnosed with intellectual disability or autism. The results, published in 2001, provided some of the field's first clues about the condition's underlying mechanisms.

The long-term goal of that study and many that have followed, Croen says, is to identify markers that enable clinicians and families to intervene as early as possible and improve a child's outcomes. "I am a scientist, but I'm not just this bench scientist," she says. "I really like the application."

In 2001, Croen moved to Kaiser Permanente to oversee a range of research on children admitted to the neonatal intensive care unit, but within two years she again chose to focus on autism. "Quickly it became my sole focus," she says.

Croen launched a landmark population-based effort to dig up clues to the condition's environmental and genetic drivers, the Early Markers for Autism (EMA) study. The team analyzed nearly 1,500 blood samples from pregnant women and newborns for immune markers, hormones, chemicals and genetic factors, and connected them to child outcomes.

The results have spawned more than 20 papers, linking autism to prenatal exposure to certain endocrine disruptors, such as PCBs, and weakening its association with vitamin D levels in a woman or her child. Several analyses showed that immune markers in a woman can influence the chances of autism in her baby. One published in 2019 used health records to link infection and fever during pregnancy to elevated odds of having a child with autism.

"It's funny, because people now are like, 'Oh, well, we know autism and the immune system have things to do with each other,'" says Judith Van de Water, an immunologist at the University of California, Davis and Croen's frequent collaborator. "I think the work we've done has really helped remove that barrier."

One summer Friday afternoon in 2015, Croen joined Van de Water at her cluttered office in Davis, with views overlooking Mount Diablo. Their goal: to brainstorm a new study that would build upon the EMA findings and more thoroughly untangle the relationship between a child's outcomes and a woman's immune or cardiometabolic profile during pregnancy. Three hours later, the two had "worked through the bones of what we thought the study should be," Van de Water says.

The grant proposal they submitted spelled out how they would draw data from Kaiser's patient population, giving them access to detailed medical records. Unlike the EMA data they had collected, the Kaiser records contain rich information about clinical diagnoses a woman may have received during pregnancy, as well as blood samples collected during her first and second trimester.

The study, launched in 2019, is now well underway, and Croen, Van de Water and their colleagues have finished genotyping maternal DNA samples and are conducting an array of immune and metabolic laboratory assays.

"I'm always seeking different people to collaborate with, from all these different points of view,"

Croen says. "I like to learn new things, I like to talk to people, and I really like to work together."

This multidisciplinary approach has been particularly useful for studying autism because of the condition's astounding diversity, she says.

> "All those people diagnosed as kids are becoming adults," she says. "No one was really paying attention to that."
> —Lisa Croen

"It's not just one thing."

For her nephew, who has been her inspiration from the start, autism has meant declining health with age, including challenges with seizures, anxiety, sleep and gastrointestinal problems, among other issues. Not only is there a lack of services for autistic adults like him, Croen says, scientists seem to ignore them, too.

"All those people diagnosed as kids are becoming adults," she says. "No one was really paying attention to that."

So a few years ago, Croen set out to investigate the health of autistic adults on a large scale and confirmed that there is a glaring gap. The work has had a significant impact, says Christina Nicolaidis, professor of social work at Portland State University in Oregon. "[It] has allowed us to say, with greater confidence, that autistic young adults experience increased rates of co-occurring health conditions, greater overall health expenses and lower rates of preventative services such as Pap smears."

Croen is working with clinicians on one solution: a pediatric-to-adult-care transition protocol for doctors and their autistic patients, which provides evidence-based guidelines and creates an open line of communication between pediatric and adult care providers. "[Croen] is a huge advocate for autistic people and sees this work as a way to provide insights that can help maximize health and abilities during child development," Fallin says.

Croen continues to draw inspiration from her nephew, a talented piano player now in his 30s who holds a part-time job hosting sing-alongs for children and is active in the Special Olympics. "I have a perspective that's larger than just a scientific one," she says. "I had a personal connection, and that's really fueled my passion for what I do."

CROEN'S HIGHLY CITED PAPERS:

Croen L.A. *et al.* The health status of adults on the autism spectrum. *Autism* **19**, 814-823 (2015) https://doi.org/10.1177/1362361315577517

Croen L.A. *et al.* Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch. Gen. Psychiatry* **68**, 1104-1112 (2011) https://doi.org/10.1001/archgenpsychiatry.2011.73

Zerbo O. *et al.* A study of physician knowledge and experience with autism in adults in a large integrated healthcare system. *J. Autism Dev. Disord.* **45**, 4002-4014 (2015) https://doi.org/10.1007/s10803-015-2579-2

Kuzniewicz M.W. *et al.* Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. *J. Pediatr.* **164**, 20-25 (2014) https://doi.org/10.1016/j.jpeds.2013.09.021

Zerbo O. *et al.* Immune mediated conditions in autism spectrum disorders. *Brain Behav. Immun.* **46**, 232-236 (2015) https://doi.org/10.1016/j.bbi.2015.02.001

Additional A–C Profiles

Thomas Bourgeron:

Pioneering rare paths in autism genetics

https://www.spectrumnews.org/news/profiles/thomas-bourgeron-pioneering-rare-paths-in-autism-genetics/

Aravinda Chakravarti:

Not everything we do is biology

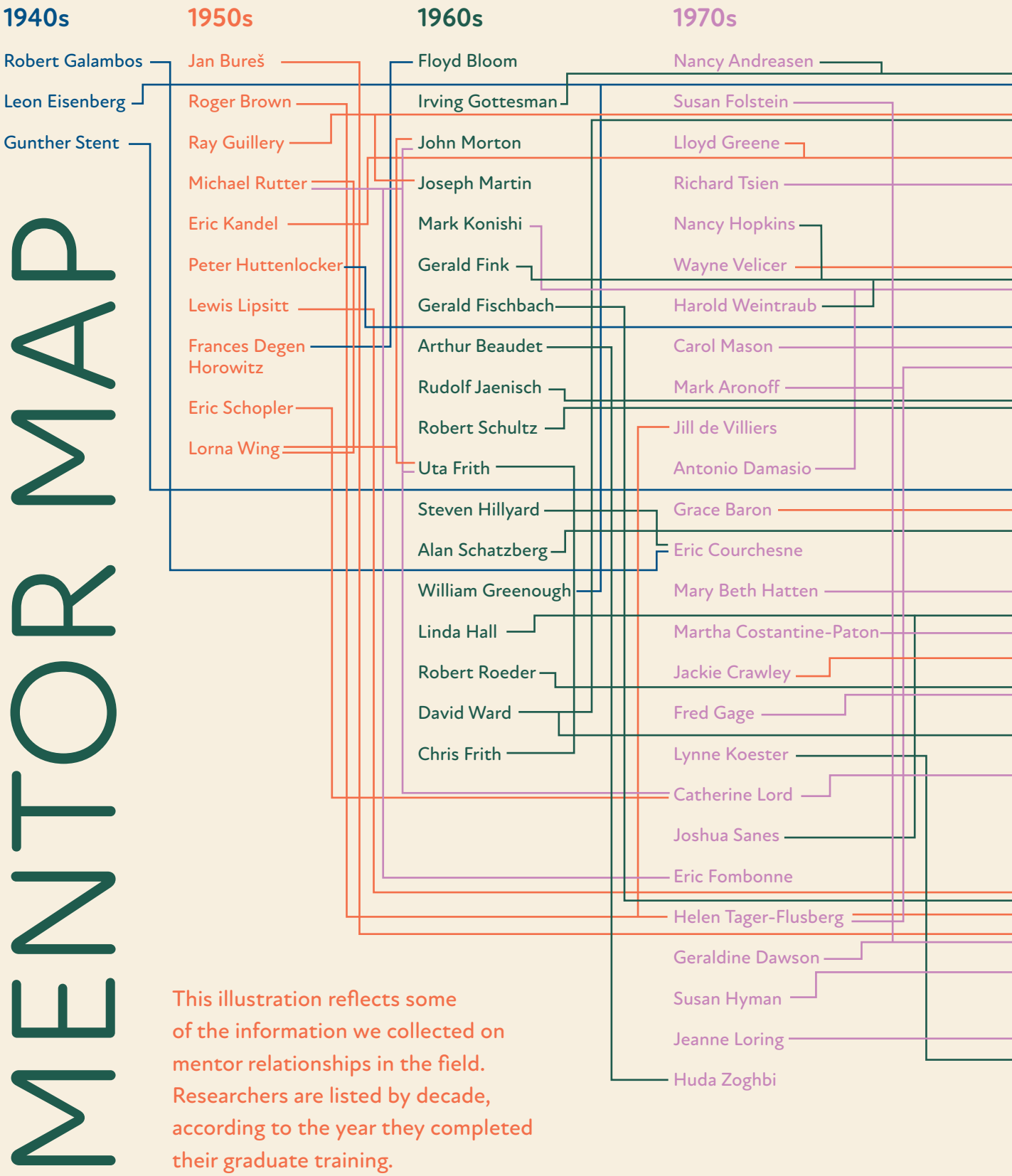
https://www.spectrumnews.org/news/profiles/aravinda-chakravarti-not-everything-we-do-is-biology/

John Constantino:

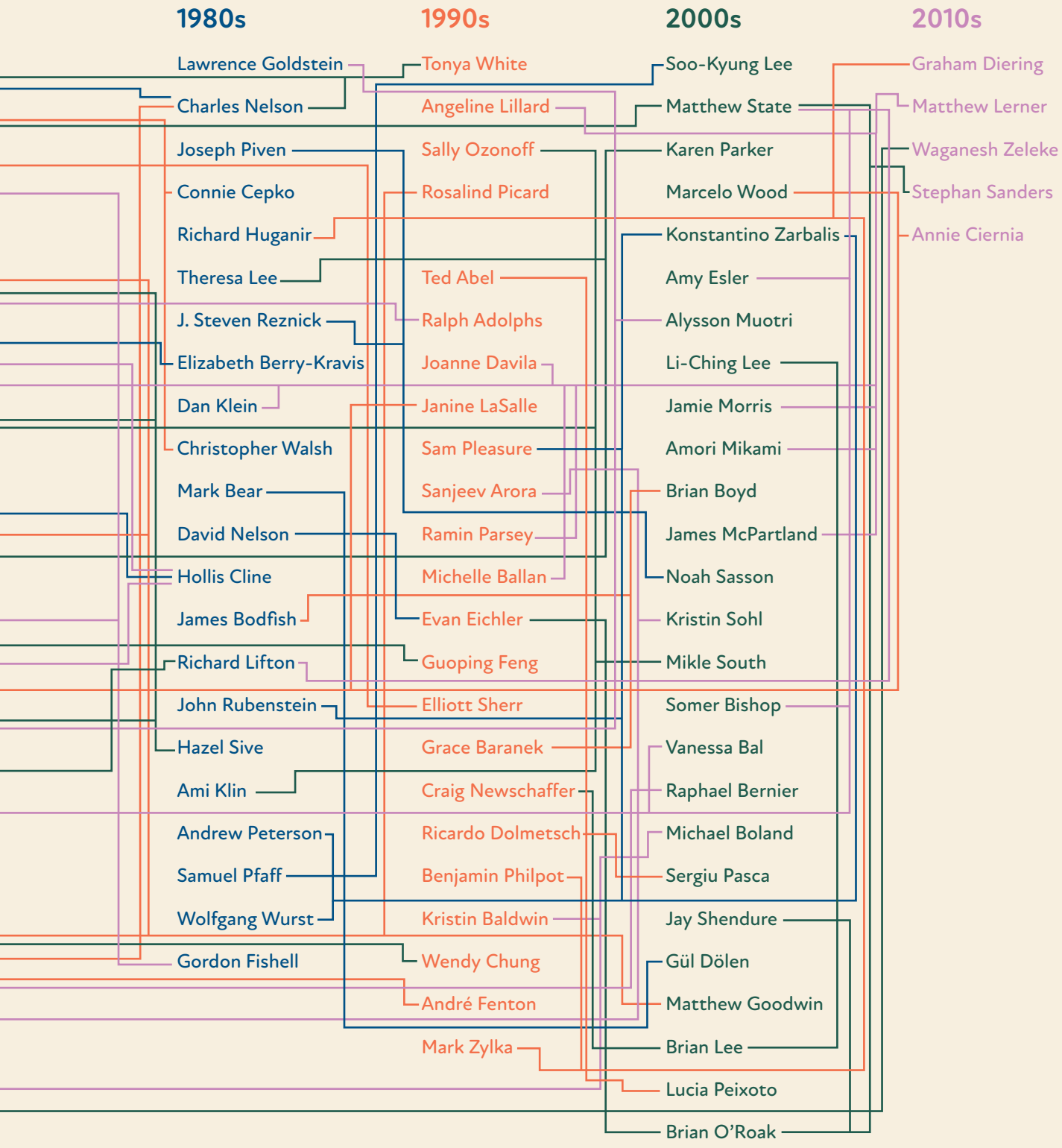
Educating communities
about autism's complexities

https://www.spectrumnews.org/news/profiles/john-constantino-educating-communities-about-autisms-complexities/

MENTOR MAP



This illustration reflects some of the information we collected on mentor relationships in the field. Researchers are listed by decade, according to the year they completed their graduate training.


1980s
1990s
2000s
2010s
Lawrence Goldstein
Charles Nelson
Joseph Piven
Connie Cepko
Richard Huganir
Theresa Lee
J. Steven Reznick
Elizabeth Berry-Kravis
Dan Klein
Christopher Walsh
Mark Bear
David Nelson
Hollis Cline
James Bodfish
Richard Lifton
John Rubenstein
Hazel Sive
Ami Klin
Andrew Peterson
Samuel Pfaff
Wolfgang Wurst
Gordon Fishell
Tonya White
Angeline Lillard
Sally Ozonoff
Rosalind Picard
Ted Abel
Ralph Adolphs
Joanne Davila
Janine LaSalle
Sam Pleasure
Sanjeev Arora
Ramin Parsey
Michelle Ballan
Evan Eichler
Guoping Feng
Elliott Sherr
Grace Baranek
Craig Newschaffer
Ricardo Dolmetsch
Benjamin Philpot
Kristin Baldwin
Wendy Chung
André Fenton
Mark Zylka
Soo-Kyung Lee
Matthew State
Karen Parker
Marcelo Wood
Konstantino Zarbalis
Amy Esler
Alysson Muotri
Li-Ching Lee
Jamie Morris
Amori Mikami
Brian Boyd
James McPartland
Noah Sasson
Kristin Sohl
Mikle South
Somer Bishop
Vanessa Bal
Raphael Bernier
Michael Boland
Sergiu Pasca
Jay Shendure
Gül Dölen
Matthew Goodwin
Brian Lee
Lucia Peixoto
Brian O'Roak
Graham Diering
Matthew Lerner
Waganesh Zeleke
Stephan Sanders
Annie Ciernia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In deep water with Gül Dölen

BY PETER HESS / 3 AUGUST 2022

As a child visiting her grandparents in Turkey, Gül Dölen was terrified to swim in the Mediterranean. She could see through the clear water all the way to the bottom, where scores of sea urchins lived. "I was like, 'I'm not gonna go in that water; those spiky things are gonna hurt me,'" she recalls. Her grandmother, a zoologist and high school biology teacher, knew how to transform Dölen's fear: She plucked one of the spiny echinoderms out of the water and dissected it right there on the beach. She showed her 8-year-old granddaughter its mouth, its little teeth, its stomach.

"I wasn't scared anymore," Dölen says. "I was just curious."

Dölen's office decor at Johns Hopkins University in Baltimore, Maryland, where she is associate professor of neuroscience, recalls that teachable moment. Sea urchin skeletons line the long windowsill, alongside snail shells and an ammonite fossil—even a preserved octopus. But there are also items that hint at her more recent work, including Mayan stone mushroom sculptures, a grinning ceramic peyote cactus and a framed photograph of Dölen with the late chemist Alexander Shulgin, who invented and self-assayed hundreds of psychedelic compounds. Her lab walls bear images by Alex Grey, the psychedelic artist whose work has been associated with the progressive-rock band Tool.

The decor reflects where Dölen's mind is these days: deep in the ocean, with its weird and wild creatures, and focused on the healing power of

FAST FACTS

Current position: Associate professor of neuroscience, Johns Hopkins University

Recent significant work: Discovered a novel critical period for social reward learning as well as a novel method for reopening it (with MDMA) (Nardou et al 2019 Nature); discovered parallel processing circuit for social behaviors, as well as implicated one arm of this parallel circuit in the pathogenesis of social deficits for 60+ autism-linked risk genes (Lewis et al, 2020 Neuron)

psychedelics. But her lab is also upending long-held scientific views of the brain, on a mission to improve quality of life for autistic people and those with neurological conditions.

Yet, as recently as 2018, Dölen was thinking about quitting science. For years prior, she had gone all in on her career, following a path familiar to many researchers. As an M.D./Ph.D. student in Mark Bear's lab, first at Brown University in Providence, Rhode Island, and then at the Massachusetts Institute of Technology in Cambridge, Dölen arrived so full of new research ideas that Bear's main goal was to rein her in; he recalls telling her to "narrow your worldview a little bit, and try to pick something we can make some progress on." She began work on fragile X syndrome in mice. The syndrome arises from a mutation in the gene FMR1 and is a leading genetic cause of autism.

Of the multiple publications Dölen and Bear co-authored on the topic, perhaps the most significant was a 2007 paper in *Neuron* demonstrating that the brains of mice with half the normal level of FMRP (the protein encoded by FMR1) have overactive synaptic plasticity, forming too many connections between neurons. Reducing the amount of the protein mGluR5 in mice helped level out overactive signaling in their brains, primarily correcting the synaptic plasticity issue. This singled out mGluR5 as a treatment target for fragile X syndrome.

During this time, Dölen's perspective on neuroscience began to shift. As a neuroscientist working with mice, she took consistent control of their lives—housing, food, cagemates, and even the lengths of day and night—so she could monitor their core brain mechanisms. But once a month she visited the genetics clinic at Massachusetts General Hospital, where she watched clinicians work with people who had autism, fragile X syndrome or a neuropsychiatric condition. She observed that the developmental trajectory for an autistic person living with 10 people in a two-bedroom apartment was different from an autistic person living in the country and receiving plenty of personalized care. This was a key realization. "So much of what makes human behavior interesting is not the stuff that we're born with," she says. "It's the stuff that we're born ready to learn—and in cases like autism, born unable to learn."

From there, Dölen joined the lab of Robert Malenka as a postdoctoral researcher in 2009. Malenka is professor of psychiatry and behavioral sciences at Stanford University in California, and at the time his lab was focused on the mesolimbic reward pathway, a brain circuit involved in motivation. Malenka was investigating how that circuitry is implicated in depression and addiction, and in particular the role of the neurotransmitter dopamine, but Dölen thought perhaps the social hormone oxytocin could be important to this pathway in mice. Malenka was not optimistic about the project's prospects, and he gave her six months to generate meaningful data.

"It was a little bit of a dare," Dölen says.

She took him up on it and found that not only are oxytocin receptors present in the mouse nucleus accumbens (part of the mesolimbic pathway), but also that they are involved in peer-

Main areas of interest: Social behaviors, psychedelics, autism, octopuses, MDMA

Lab URL: www.dolenlab.org • **Notable mentors:** Mark Bear

to-peer social reward behavior in mice. Perhaps most surprisingly, she demonstrated that oxytocin controls the release of the brain chemical that moderates this relationship: serotonin. The results appeared in *Nature* in 2013.

This finding boosted Dölen's career. She moved to Baltimore and started her own lab at Johns Hopkins University. Her newfound autonomy was both exhilarating and scary, and she quickly secured three private foundation grants, including a prestigious Searle Scholarship, to study autism via the brain circuitry of social reward—the positive feelings that motivate people and animals to be social. But the bigger money and recognition of National Institutes of Health (NIH) research grants proved more elusive. Her department and the university tweaked budgets to help keep her staff intact and the lab running, which felt "wonderful, on one hand," she says, but "on the other hand, it also felt like, God, I'm an immigrant—we don't rack up credit card debt." She wondered how she could really be perceived as a leader if she couldn't financially stabilize her team.

When Dölen reached her 10th NIH rejection, she began to fear she might not make it as a lab head, or even as a scientist. Her outside-the-box thinking had yielded impactful findings during her graduate and postdoc years, but her approach didn't seem to fly with the NIH, and she felt the mounting pressure to prove that she could run a world-class lab. "Even if the department isn't literally putting pressure on you to get it done or get out, it's implied," she says.

Grant rejections are part of doing science, and the need to chase money for research can be distressing. This is a feeling Malenka is familiar with. "I think the challenge of getting and maintaining grant support is the major reason investigators leave academia," he says. Something similar was happening to Dölen. Her confidence was beginning to wane, and she wondered if she knew how to come up with meaningful projects, or if she could generate evidence to support her ideas. She wondered if her work had the potential to make an impact. Finally, she began to wonder if she still loved science.

"The transition from postdoc to [principal investigator] is very challenging," Bear says. "An entirely new skill set needs to be mastered, particularly multi-tasking, and the first grant review is usually a bitter pill to swallow."

Bear gave her a pep talk at the time, but ultimately it was a road Dölen had to walk herself. Her fears persisted, and her grant proposals became more conservative to fit with what the NIH seemed to want. She felt the joy and curiosity that had initially attracted her to science slipping away. If this was going to be her career—disappointing, stifling and frustrating—then she should have chosen a job with more free time and a 9-to-5 schedule.

She also began to feel resentful. She was a woman living on her own, whereas her male colleagues seemed to have the benefit of spousal support for their long hours. She also had no children and found that she was the de facto dinner host for visiting scientists—as if she had nothing waiting for her at home. In the face of her growing NIH grant rejections, she felt a creeping suspicion that her ambitious ideas would not be so uniformly dismissed if she were a man, that she would not have to overcome such a large credibility gap.

Dölen fell into a depression that extended beyond the lab. She stopped doing the things that brought her joy outside of work: going to jazz concerts, taking long walks in the woods. And her

dimmed spark made it even harder to keep pushing at work.

When she'd been in Bear's lab at MIT, he had stressed the importance of science being fun. "If you lose sight of the fun in science, it's hardly worth continuing," he used to say. Dölen decided that if she was indeed going to give up a life of science, she would go out on her own terms. She would do one final project—a fun one, just to see what would happen, and it would have only a tenuous relationship to everything else she had been studying.

The idea was this: Dölen wondered whether octopuses would make friends while on ecstasy.

She had read a 2015 paper about the octopus genome, which got her wondering whether serotonin signaling in octopus and human brains share any similarities—even though the two species' last common ancestor lived hundreds of millions of years ago. She got in touch with Eric Edsinger, who had worked on the paper as a postdoctoral researcher at Woods Hole Oceanographic Institution in Falmouth, Massachusetts. And as luck had it, Woods Hole had seven of the animals and was willing to lend them out.

Woods Hole shipped the octopuses down, and Dölen hosted Edsinger in Baltimore, bestowing upon him an air mattress in her living room. She sent her students and postdocs home for the week, and Dölen and Edsinger played mad scientist, toiling in the lab from early morning until late at night, breaking only for coffee or food. Using Edsinger's team's octopus genome, they found that octopuses have genes that encode a serotonin transporter, the protein whose response to MDMA likely leads to the psychedelic drug's prosocial effects in people.

Bathing the octopuses in a solution of MDMA, they found that the psychedelic drug seemed to make the usually solitary animals interested in socializing with other members of their species. This finding indicated that the octopus, whose brain structure is nothing like a mammal's, has a serotonin system in its brain that plays an important role in social interaction—just as humans have.

Dölen was shaken by the finding. Conventional neuroscience wisdom says that brain structure is what matters when it comes to translating animal findings to humans—if MDMA exerts its effects by way of the amygdala in rats, for instance, then it probably affects the human amygdala, too. But an octopus doesn't have an amygdala. It doesn't even have a cerebral cortex. It has one central donut-shaped brain in its head and one subordinate 'mini-brain' in each of its eight legs. If Dölen and Edsinger's results were reliable, they suggested that compounds such as MDMA were acting on a cellular level, not a structural level. "It challenges not a specific result, but a whole framework of how to approach how to understand the brain," Dölen says.

The paper was published in September 2018, and it immediately got attention. Popular news outlets covered it, late-night comedians joked about it, and academics paid attention, too; it has been cited 49 times, according to Altmetric. But what mattered to Dölen was that it got her excited about science again.

"It kind of brought me back," she says. "I had spent three years feeling like I had a boot on my chest, and when the octopus paper came out, instead of an elephant wearing that boot, it was a horse."

While the octopus study was in progress, Dölen began to build on what she had learned, investigating a potential role for MDMA as a therapeutic for people with autism. To this end, she used an assessment of social-reward learning

> "When you feel joyful, when you feel like you're participating in science in a curiosity-based, 'let's see where this goes' thing, then suddenly all of the different connections become obvious."
> —Gül Dölen

to demonstrate that MDMA, through its effects on oxytocin, can reopen the critical period for social-reward learning in mice. Scientists long assumed that any compound powerful enough to reopen a critical period, the timespan when the brain's connections can reshape in response to learning, would wreak havoc on the brain, either causing seizures or amnesia. But now she had done it: Her work showed that adult mice, which are typically too old to learn social reward, suddenly became open to it after treatment with MDMA. The paper appeared in *Nature* in 2019.

After that success, she began to suspect that using psychedelics to reopen a critical period could be the missing piece in other areas of study. Though drugs targeting mGluR5 have been investigated in clinical trials, they have not yet yielded the results researchers had hoped for. Dölen remains confident that mGluR5 might be a treatment for fragile X syndrome, especially if MDMA is included with the therapy to prime trial participants to respond. And in other work, she and her team are exploring whether classic psychedelics such as psilocybin and LSD can have similar effects. She also suspects that other critical periods, such as that for stroke recovery, can be reopened by this class of drugs, which would be a massive scientific breakthrough.

During her slump, Dölen had slid into a conservative approach to science. The octopus breakthrough demonstrated to her the power of questioning conventional thinking around brain research. Since then, she has secured three NIH grants, and now, as the self-styled creative director of her lab, the conservative bent that dampened her research questions is nowhere to be found.

This creative, elegant approach was apparent in Dölen's previous work, says Catherine Dulac, professor of molecular and cellular biology at Harvard University, who has known her since the 2013 *Nature* paper came out. In that one paper, Dölen had brought together three different circuit components in a way that nobody had before, Dulac says: the nucleus accumbens that regulates reward, serotonin that regulates the nucleus accumbens and oxytocin that regulates it all at the synaptic level.

"She's a little bit like an artist," Dulac says. "It's great to have somebody like this in the field."

Theory of mind is the idea that a person or animal can attribute to another individual a state of mind different from one's own. Impairment in theory of mind was once thought to be

a core autism trait. That idea has mostly fallen out of favor, but Dölen thinks that studying it in the octopus has important implications for our understanding of how theory of mind evolved in the first place.

Many suspect it arose from social living, where animals watch and learn from one another, but it also exists in the solitary pygmy zebra octopus. The animal uses theory of mind to hunt, tailoring its approach based on the type of prey: attacking directly from behind for crabs, for instance, or setting a trap for quick shrimp. For the pygmy zebra octopus, theory of mind seems to have "evolved out of predatory rather than social-selection pressure," she says.

It was the neuroscientific and philosophical questions around theory of mind that initially got Dölen interested in autism, and her work with the octopus reinvigorated her interest in psychedelic therapies. It also turned her career around. The fact that the octopus exhibits theory of mind is just one more thing Dölen loves about these asocial creatures with nine brains. Her work is once more bringing her happiness.

"Part of that feeling of joy is that you can see all the connections again," she says. "When you feel joyful, when you feel like you're participating in science in a curiosity-based, 'let's see where this goes' thing, then suddenly all of the different connections become obvious."

DÖLEN'S HIGHLY CITED PAPERS:

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Nardou R. *et al.* Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature* **569**, 116-120 (2019) https://doi.org/10.1038/s41586-019-1075-9

Edsinger E. and Dölen G. A conserved role for serotonergic neurotransmission in mediating social behavior in octopus. *Curr. Biol.* **28**, 3136-3142 (2018) https://doi.org/10.1016/j.cub.2018.07.061

Lewis E.M. *et al.* Parallel social information processing circuits are differentially impacted in autism. *Neuron* **108**, 659-675 (2020) https://doi.org/10.1016/j.neuron.2020.10.002

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Evan Eichler: Following his instincts to autism 'hotspots'

BY MICHELE SOLIS / 22 MARCH 2010

One day before his interview for a faculty position at Case Western Reserve University, in December 1996, Evan Eichler was wrangling with a decision that, really, should have been made days, or even weeks, earlier: Which job talk to give?

One option was to tell his audience, the entire genetics department, about his work on fragile X syndrome, which is characterized by intellectual disability and, often, autism. This was a hot topic because just five years earlier, scientists had discovered that the syndrome stems from the silencing of a single gene, FMR1. As a graduate student, Eichler had studied what makes the gene prone to mutation.

"The other talk was about this crazy duplication idea," he says, referring to 'segmental duplications'—stretches of DNA 10,000 or more nucleotides long, whose sequences are repeated

FAST FACTS

Current position: Professor of genome sciences and Howard Hughes Medical Institute investigator, University of Washington

Recent significant work: Completion of the human genome

Other major accomplishments: Application of long-read sequencing to characterize patients with autism

nearly verbatim elsewhere in the genome. Segmental duplications are fixtures of the genome in humans and other organisms.

At the time, many scientists dismissed segmental duplications as useless hiccups in the DNA code. But Eichler recognized that they could instigate genomic change, throwing off the alignment of paternal and maternal chromosomes as they trade bits of DNA during the division of germ cells. This improper positioning leads to missing or extra pieces of DNA, called copy number variations (CNVs), in the resulting sperm and egg cells. When passed on to the new generation, the mutations can also drive evolution.

Unable to decide between the two topics, he asked his wife, Marla, for her opinion. "She said, 'Do the crazy one. Whatever you actually feel more passionate about, do that one,'" Eichler recalls. So he did. "I went with my instincts instead of thinking through it logically."

He got the job.

In the decade since, Eichler has continued to follow his instincts—with spectacular success. In 2002, he was the first to map the locations of all segmental duplications in the human genome. He then used that map to identify hotbeds of mutation. With an openness to collaboration and a healthy dose of daring, he has turned his offbeat interest in segmental duplications into a new understanding of how genomes evolve, expediting the search for genes disrupted in disorders such as autism.

"Much of scientific advance comes from these strange ideas," says Aravinda Chakravarti, director of the Center for Complex Disease Genomics at Johns Hopkins University, who helped recruit Eichler to Case Western Reserve. "Evan pursued his hypothesis in a very dogged way, with a lot of passion and a huge amount of hard work, at a point in time when many others thought this was a bogus idea," Chakravarti says.

In the past year, Eichler has turned his attention to the Simons Simplex Collection (SSC), a repository of well-characterized samples from 2,000 children with autism and their families. Rather than screening the entire genome for defects linked to the disorder, he is targeting segmental duplications because of their predisposition to create CNVs. Several studies in the past few years have implicated CNVs in autism and other diseases.

"He's made a compelling case that we should look at these regions for autism [mutations]," Chakravarti says.

Early on an overcast October morning in Seattle, Eichler sits in his office at University of Washington. Beyond the open door, machines whirr and hum as his lab members show up for work.

Despite having just returned from a three-day trip to Australia, Eichler brims with energy as he describes his work, occasionally springing up to draw something on a whiteboard littered with older sketches, making the boyish cowlicks above his forehead bounce.

"I'm still close enough to the pulse, the science stuff," he says about running his lab. "It's the greatest place to be."

Main area of interest: Autism genetics, structural variation, gene duplication, evolution
Lab URL: https://eichlerlab.gs.washington.edu/ • **Notable mentors:** David Nelson

When he's not traveling (he made at least 27 trips in 2009), Eichler lives in North Bend, a small community in the foothills of the Cascade Mountains in Washington, with his wife and four children. He skis the nearby slopes, he says, "probably more often than I should."

No stranger to the outdoors, Eichler was raised on a farm in Manitoba, Canada. He got his first taste of genetics there, breeding angora rabbits with different colored coats for his mother's yarn. By the time he was in high school, he knew he wanted to study human genetics. But these plans were put on hold when he enrolled at University of Saskatchewan, where the biology curriculum emphasized evolution.

In 1991 he headed to Houston, Texas, to pursue a doctorate in human genetics at Baylor College of Medicine. With his characteristic clarity, he applied to join the lab of David Nelson, who had just discovered that mutations in FMR1 cause fragile X syndrome.

"[Eichler] came up to me and said, 'I'd really like to understand how genomes evolve.' Full stop," Nelson recalls. "That's very unusual for a student."

Unfortunately, the tools weren't yet ready to study and compare whole genomes. The Human Genome Project had been launched just a year before, and DNA microarray technology was still getting off the ground. Still, Nelson did not discourage him.

"It was so clear that he was very passionate about where he wanted to go," Nelson says, adding with a laugh that Eichler basically needed something to do in graduate school while he waited for the tools to become available.

FMR1 contains repeating trios of CGG nucleotides, and the number of repeats can vary between parents and offspring. When there are more than 200 repeats, FMR1 gene expression halts, triggering fragile X syndrome. The instability of the repeats fueled Eichler's interest in whether other parts of the genome are similarly prone to radical changes in the DNA code. "I got fascinated not so much in the gene or what the gene did, but actually the mechanism of mutation," he says.

For his thesis, Eichler showed that stretches of triplet repeats that are not briefly interrupted by other sequences are particularly vulnerable to gene silencing.

From his four years in Nelson's lab, Eichler eventually produced 15 papers, including one on segmental duplication of a piece of the X chromosome. He also managed to find an evolutionary angle to his research, comparing the sequence of FMR1 across 44 different species, wrangling samples of platypus DNA from Australia and bat DNA from Texas.

After Baylor, Eichler started a postdoctoral fellowship at Lawrence Livermore National Laboratory in California, where he sequenced parts of chromosome 19, which is packed with segmental duplications.

In 2000, from his own lab at Case Western Reserve, he finally got a genome-wide view of segmental duplications. As the publicly-funded Human Genome Project finished its first draft, the organizers tapped Eichler to map the duplications.

"I said, 'Well, I'm all set up, I can do this now'—which was a total lie," he says, chuckling.

Eichler quickly cobbled together 15 computers to analyze the sequences. After a false start, followed by a tricky collaboration with both the public venture and the competing private biotech company, Celera, he and his team precisely located

the repeated sequences in the human genome.

Although segmental duplications were once considered rare, Eichler's search showed that they make up more than 5 percent of the genome, and occur on all chromosomes. What's more, unlike in most mammals, the majority of duplications in humans are interspersed, meaning that they have blocks of unique sequence between them.

Eichler predicted that an interspersed duplication would be a 'hotspot' prone to genetic accidents, and he wanted to systematically search these hotspots to fast-track the discovery of disease-linked CNVs.

This targeted search required a collaboration, and Eichler forged one at a pub in Oxford, England, during a conference in 2000. Over a beer, he convinced geneticists Daniel Pinkel and Donna Albertson to help him develop a DNA microarray to detect CNVs in these hotspots.

"He's driven by biological questions, and he looks for ways to approach those wherever he can find them," says Pinkel, professor of laboratory medicine at University of California, San Francisco. "If that takes collaborations, he does it."

The microarray the researchers developed probed 130 hotspots, consisting of segmental duplications separated by 50 to 10,000 kilobases of unique DNA sequence. Standard microarrays typically miss these repeat-rich regions because the signals are harder to interpret than those from unreplicated, unique portions of the genome.

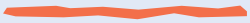
The results, published in 2006, revealed CNVs that can cause intellectual disability in a sizable 5 percent of children with the condition. "We hit pay dirt there," Eichler says.

The high yield confirmed that these hotspots are prone to mutate, and that screening them increases the likelihood of finding 'recurrent' mutations that crop up in more than one person.

Scientists have had not much luck finding recurrent mutations, making it hard to definitively link a particular genetic defect to a disease. But in Eichler's study, 4 of the 290 children have the same mutation: a small deletion on chromosome 17. This argues strongly that the mutation caused their intellectual disability and unusual facial features.

This hotspot approach also discovered previously unrecognized phenotypic similarities among people carrying the same mutation. For example, Eichler's team has documented a recurrent deletion in chromosomal region 15q24 in multiple individuals who have intellectual disability combined with delayed growth, and a recurrent deletion in 15q13.3 in individuals with intellectual disability combined with seizures.

"It's not like it's magical," Eichler says about the abundance of disease-related mutations in his hotspots. "Lots of areas of the genome can result in disease if you delete or duplicate them. It's just that we're sampling regions we think are really hot for new mutation."



Eichler is bringing his methodology to autism, with a plan to screen up to 800 hotspots in individuals from the SSC.

Most of these will be what Eichler calls 'mini- or micro-hotspots'—regions that contain a unique sequence as small as one kilobase between duplications. He suspects that CNVs found in the collection will be small, affecting only a few genes, because participants have narrowly defined autism that doesn't usually include other difficulties, such as intellectual disability or physical abnormalities.

"And the beauty of it is, if we do [find CNVs in]

these minis and micros, we get it down to the level of the gene practically instantaneously," he says.

Eichler then plans to widen his search to look at a broadly defined population of people with developmental delays, because the same mutations could take on different forms.

For example, the 15q13.3 deletion he identified in cases of intellectual disability with seizures has also been related to epilepsy, schizophrenia, autism and, in some cases, no disease at all.

Screening a group burgeoning with an array of symptoms might seem like another one of Eichler's offbeat ideas. After all, many genetic studies go to great lengths to limit the variability in their study population.

But studying a diverse population is a valuable "flipside" to gene discovery because it acknowledges the winding and variable pathway that leads from a particular mutation to behavior, says Matthew State, associate professor of child psychiatry and genetics at Yale University. State is canvassing the entire genomes of SSC individuals for CNVs, which he then plans to sequence to pinpoint autism-related mutations.

"We've got to be humble about our phenotypic categorizations," State says, pointing out that they are made without an understanding of the genetics behind them.

Eichler plans to initially identify CNVs in the SSC's tightly-defined autism group, and then look for the same mutations in the developmentally delayed group. This 'genotype-first' approach will help find the variety of phenotypes that can stem from the same mutation, and promises to blur the distinction between various brain conditions, he says.

If that sounds like another one of Eichler's crazy ideas, chances are it will pay off in spades.

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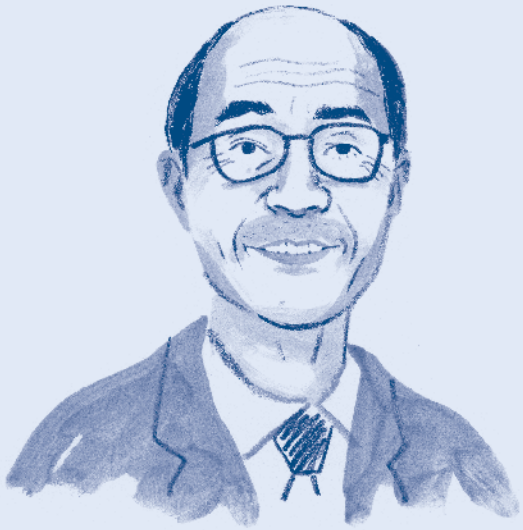
O'Roak B.J. *et al.* Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nat. Genet.* **43**, 585-589 (2011) https://doi.org/10.1038/ng.835

Many scientists dismissed segmental duplications as useless hiccups in the DNA code, but Eichler recognized that they could instigate genomic change . . .

Guoping Feng: Unearthing the roots of compulsive behavior

BY VIRGINIA HUGHES / 4 JANUARY 2010



Guoping Feng never gives up. In or out of the lab, as a teenager in China or a successful neuroscientist in the US, healthy or in debilitating pain, Feng has approached every obstacle in his life with dogged persistence.

Perhaps that's because he has faced so many obstacles in his life.

"He is sort of infinitely optimistic and infinitely energetic. Because of those two features, he has an extremely low barrier to trying out new projects, new techniques, and learning what needs to be learned," notes Joshua Sanes, Feng's postdoctoral advisor and director of the Center for Brain Science at Harvard University.

Feng's perseverance has proven a boon to the hundreds of neuroscientists who rely on his most celebrated scientific achievement: two dozen mouse strains engineered to have brightly colored brain cells, allowing scientists to choose from a library of animals that each light up a specific component of the cell. In the past couple of years, Feng's efforts have also made waves in the autism field. By creating the first robust mouse model of obsessive-compulsive disorder (OCD), Feng has found a way to study the genetic underpinnings of repetitive behaviors, one of the three core characteristics of autism.

Even these successes came only after years of failed attempts.

In early 1995, Feng was a new postdoctoral fellow in Sanes' neurobiology lab, then at Washington University in St. Louis. Feng's project involved trying to label cells in the mouse nervous system so that their workings could be observed under a microscope.

Using tricks of genetic engineering, Feng first induced certain cells to produce an enzyme called beta-galactosidase. Previous studies in bacteria had shown that when mixed with two other compounds, the enzyme turns blue, marking the cells that express it.

Unfortunately, Feng's experiments with the

FAST FACTS

Current position: Poitras Professor of Neuroscience, Massachusetts Institute of Technology
Recent significant work: Development of nonhuman primate models for autism research; development of gene therapy approaches for SHANK3 mutation; discovery of a neural circuit mechanism of attention-deficit/hyperactivity disorder and sleep disruption in autism models.

mouse cells failed. The beta-galactosidase only works in fixed tissue, so it couldn't be used in a live mouse brain. But the setback didn't affect his morale.

"With most people, if something doesn't work, they go into a bit of a funk for awhile," Sanes says. "With Guoping, if something didn't work, he'd start three new projects."

Sure enough, following the failed project, Feng took up numerous unrelated lines of research, which resulted in several high-profile publications. But he never dropped the labeling idea. Three years later, taking advantage of a new molecular tool, he finally succeeded—ultimately producing a large collection of mutant mice with red-, blue- and green-glowing brain cells.

"The fact that the first seven ways didn't work did not diminish his enthusiasm for keeping at it until he finally cracked it," Sanes says.

Now in his own lab at Duke University—and with an imminent move to the Massachusetts Institute of Technology in the spring of 2010—Feng is applying the same tenacity to autism research.

In 2007, his team described the first well-characterized mouse model of OCD, a condition defined by recurrent thoughts and seemingly aimless rituals. Feng's team deleted the gene for a key protein that supports the synapse—the junction of brain cell communication—effectively turning normal mice into compulsive, round-the-clock groomers that scratch the hair right off their faces.

The behaviors Feng uncovered in the mutant mice are also seen in some people with autism. "All behaviors are basically outputs of basic circuits," Feng says. "So even if there are many different genes and many different pathways [involved], the repetitive behaviors in autism, in [attention deficit hyperactivity disorder and] in OCD may all have a common circuitry."

Feng is scanning the genes of children with autism for mutations in genes related to those circuits. The work will contribute to a much larger undertaking: distinguishing the rare genetic changes that are part of normal human variation from those that have unwanted functional consequences in the brain. This slow, yet steady, approach, he says, will be key to understanding the complex disorder.

In 1976, the year Feng graduated from high school, Mao died, taking with him the forces of the revolution. Feng spent a year working as a farmer until the country's universities slowly reopened. He was lucky to have the opportunity to go to college, but he had to apply at the same time as millions of Chinese citizens who had for a decade been denied that chance.

To meet the sudden demand, the government assigned applicants to colleges based on test scores. Feng was the only one from his high-school class of 180 students who scored above the cutoff for college placement. He was randomly assigned to medical school.

Still set on engineering, however, the then 17-year-old was extremely disappointed. "I had no choice. And I said to my mom, 'I really don't want to go'," he recalls. She eventually convinced him to go.

F

Main areas of interest: Synapse and circuit function and dysfunction in neurodevelopmental and psychiatric disorders
Lab URL: https://fenglaboratory.org/ • **Notable mentors:** Linda M. Hall, Joshua R. Sanes

During a pediatrics internship in his last year of medical school, Feng became deeply frustrated by the dearth of cures for childhood cancers and other chronic illnesses.

"I was very naïve, and decided that I really needed to study pharmacology, to make more effective drugs," he says. After getting his bachelor's degree in medical sciences, he completed a master's in pharmacology. "But the more you study, the more you realize that you cannot just go develop a drug without understanding the basic processes behind [the diseases]," he says.

In 1989, Feng moved 7,000 miles to begin a doctorate program in molecular genetics at the State University of New York at Buffalo. There, working in the lab of neuroscientist Linda Hall, he finally became an engineer—of fruit fly genes. His dissertation culminated in a paper, published in *Cell* in 1995, showing that a known *Drosophila* gene is crucial for neuronal firing.

F

By 1998, three years had passed since Feng's failed attempt with the neuron-labeling project. Since then, a new molecule had hit the scene: green fluorescent protein (GFP), the natural substance that makes jellyfish glimmer.

After GFP was first sequenced in 1992, biologists had uncovered several related fluorescent proteins, and used them to stain a variety of cells in a test tube.

Over the following two years, Feng practiced many ways to use the GFP family to tag brain cells in a living animal. He created 25 lines of mice, each of which developed different subsets of glowing neurons.

The methods paper describing the mice, published in 2000, has been cited in hundreds of publications. "These animals are in use in probably at least 200 labs. And I know that because we continue to send them out to this day," Sanes says.

That same year, Feng launched his own lab at Duke University, where he continued to study the complex interactions of synaptic proteins and look for better ways to visualize brain cells.

Feng enjoyed the next few years settling into his new home in warm and friendly North Carolina. Around that time, he and his wife, Ning, were happily surprised to find out that she was pregnant with their second son—14 years after the first. Just after the baby, Daniel, was born, however, Feng began having debilitating back pain.

"It was so severe, he talked about not holding Daniel for several years," says Maria Donoghue, who met Feng when they were both working in Sanes' lab, and is still a close friend. The pain worsened to the point where Feng could no longer come into the lab. Undaunted, he advised his team from home.

"I called him every couple of weeks to check in, and every time he'd say, 'Oh, things are great'. Meanwhile, he's lying on the floor of his living room," Donoghue recalls. He refused most pain medications, she adds, "because he didn't like what it did to his intellect."

While he was on medical leave between 2004 and 2006, Feng published more than a dozen papers. He eventually had successful surgery, although he still has mild back pain. In addition to running his lab, he now travels often—including at least one trip to China every year—and works in the garden.

"I love seeing seeds grow—it's an interesting developmental process," he says with a chuckle. "I always tell my wife that when I retire, I'm going to buy a farm."

Many projects in Feng's lab focus on the role of scaffolding proteins that assemble near a synapse. A couple of years ago, studying one family of these proteins—called SAPAPs—inadvertently led him to psychiatric disease.

Feng had planned to create mice carrying specific mutations in SAPAP genes, to see whether and how various synaptic changes affect the animals' behavior. Anticipating subtle differences, he formed a large collaboration with scientists who specialize in measuring mouse behaviors. As it turned out, for the mutants lacking SAPAP3, he didn't need any help from the experts.

"The behavior was so obvious—they're basically grooming their skin off. It's very gross," Feng says. The mice are the first robust animal models of compulsive behavior.

Since then, Feng has partnered with several teams of geneticists to search for SAPAP3 variations in people. Earlier this year, one such collaboration reported that SAPAP3 variants crop up in 4.2 percent of people with OCD or trichotillomania—compulsive hair-pulling—compared with 1.1 percent of healthy controls. A later study found that human SAPAP3 variants are also associated with pathologic nail-biting and skin-picking.

Feng is looking for mutations in SAPAP3 and about 20 other synaptic genes in 400 samples from the Simons Simplex Collection, a gene bank of children with autism and their families.

Although he hasn't collected enough data for statistical analysis, Feng says these variations are likely to be associated with autism. SAPAP3 interacts directly with SHANK3, another synaptic protein that several studies have tied to autism.

SAPAP3 and SHANK3 are expressed almost exclusively in synapses located in the striatum—the deep, central brain region that is known to go awry in people with OCD. Some studies have also found abnormally large striatal volumes in people with autism.

If the synaptic gene variants turn out to be more common in autism than in controls, Feng plans to tackle the bigger project of determining exactly how these aberrations affect striatal circuitry, and how those changes in turn lead to the telltale behaviors of autism.

Not surprisingly, he's up for the challenge.

"It will probably take us a long time to reach that goal, with a lot of trial and error," he says. "But I'm very optimistic."

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André Fenton: Playful problem-solver

BY CHARLES Q. CHOI / 9 NOVEMBER 2015

On the Fourth of July in Woods Hole, Massachusetts, you might find André Fenton dressed up as a neuron, surrounded by students pretending to be calcium ions and electrical signals. You might also find him quietly pondering the meaning of 'reality.'

Fenton, professor of neural science at New York University (NYU), is equal parts fun and philosophical. At the Marine Biological Laboratory in Woods Hole, where he co-directs an eight-week course on the neural basis of behavior, he mixes deep discussions of the mind with water-balloon fights. "He really gets into it, and has really good aim, too," says Hans Hofmann, professor of integrative biology at the University of Texas at Austin, who co-directs the course with Fenton. "I think that tells you that whatever he does, he does with a passion and a vengeance. And he also has a very strategic mind."

Fenton funnels this passion and planning into his research. At NYU, he is teasing out the role of the brain's memory center, called the hippocampus, in autism. He has helped design experimental tasks that scientists worldwide use to investigate memory. In 2006, *Science* magazine heralded a discovery that he and his colleagues had made about long-term memories as one of that year's biggest breakthroughs.

"He's really at the forefront of research into how patterns of firings of neurons encode different types of memories—why we remember this and not that, and how memories can get confused and mixed up," says his long-time collaborator, Todd Sacktor, professor of physiology, pharmacology and neurology at the State University of New York (SUNY) Downstate in Brooklyn.

Fenton is now exploring how the behavior of neurons in the hippocampus might be different in autism. With a focus on this memory center, he is trying to better understand why the brain of a person with autism may be less capable of

FAST FACTS

Current position: Professor of neural science, New York University Center for Neural Science

Recent significant work: Cognitive control training to ignore distracting stimuli, changed synaptic excitation and inhibition within an entorhinal-hippocampal subcircuit causing learning to learn (improved and generalized future learning) that persisted with the circuit changes for at least two months. See Chung, et al. Cognitive control persistently enhances hippocampal information processing. Nature 600, 484–488 (2021).

adapting to changing circumstances, with an eye toward making it more flexible.

Images of how memory and the brain work surround Fenton as he tries to answer such questions. In Fenton's lab stands a 15-foot-long table topped with a half-ton slab of glass. Embedded in the glass is an orange, black and white image—a fragmented cityscape meant to resemble a memory.

Fenton was born in Guyana in 1967. His family moved to Toronto when he was 7 after his mother got a job with IBM, so he learned at an early age to go with the flow.

"The kids in Toronto were nice, but none played anything I knew how to play; nobody knew how to play cricket," Fenton says. "So I learned to play hockey and ice-skate."

Fenton's adaptability has carried him through an eclectic career, from neuroscientist to inventor to entrepreneur, says Clifford Kentros, professor of medicine at the Norwegian University of Science and Technology, who worked with Fenton at SUNY Downstate. Fenton developed tiny devices that wirelessly record brain data from rodents. A start-up Fenton helped form, BioSignal Group, advanced this concept by miniaturizing electroencephalography (EEG) machines to measure brain activity in people. In 2012, the U.S. Food and Drug Administration approved the device, called the MicroEEG, which Fenton says could one day help doctors routinely check the brain function of people in hospitals.

"[Fenton] has reinvented himself again and again, moving into new fields with ease," Kentros says. "And each time he's remade himself, he brings something from other fields he knows."

Fenton's first field of choice was literature. In high school, he gravitated toward novelists such as Albert Camus and Joseph Conrad, who celebrated what he calls "lives of the mind." Fenton recalls, "I was obsessed with the nature of reality and how we understand the world."

He planned to major in English at McGill University in Montréal, but happened to take a biology course. He rarely attended that early-morning class during the cold winter term, but made it to one lecture on a paper titled "What the Frog's Eye Tells the Frog's Brain."

The landmark paper, by the late cognitive scientist Jerome Lettvin, revealed that frogs are limited in what they see because of how their eyes communicate with their brains. For instance, frogs can easily detect dark moving dots, such as flies, but cannot see dark, still objects.

When he heard that, Fenton realized that reality is simply a construct of the brain. "It just blew my mind," he says.

Fenton quickly swapped English for biology, focusing on the neurobiology of crickets for his senior thesis. After graduating in 1990, he took a job as a research assistant at the Institute of Physiology in Prague in the Czech Republic, in the lab of the late neuroscientist Jan Bures. There, he became enchanted by the hippocampus, which he considers "one of the most philosophical brain regions."

Other major accomplishments: As of 1 September, direct/Chair NYU's Center for Neuroscience.
Chair of NIMH Board of Scientific Counselors
Main areas of interest: Neurophysiology, synaptic plasticity, memory, spatial cognition, autism, neuropsychiatric dysfunction
Lab URL: www.fentonlab.com • **Notable mentors:** Jan Bureš, Robert Muller

"Mostly we observe a behavior, such as a rat avoiding an area, and infer from that behavior that the animal has a memory it is recalling. I'd like to take memory research away from such indirect measures to actually looking at what the brain is doing when it is remembering." —André Fenton

Beyond its role in memory and learning, the hippocampus also helps people to navigate their surroundings. Famed philosopher Immanuel Kant speculated that space and time are concepts that a person understands innately, not through experience.

"The fact that brain cells knew something about space, when space might not even exist, was very interesting to me," Fenton says.

In Bures' lab, Fenton invented the rotating arena—a large spinning platform designed to study how long rats can keep track of where they are. Neuroscientists worldwide use the device for experiments on memory.

In 1992, Fenton pursued a Ph.D. at SUNY Downstate. There, he studied 'place field neurons,' which are crucial for remembering locations. He discovered, for example, that these cells operate as part of a cohesive network, and that cognitive factors such as attention can influence their firing patterns in ways that can explain their variability.

After receiving his degree, he collaborated with Sacktor to investigate molecules that help the brain store long-term memories. Using the rotating arena, the researchers discovered that blocking a certain enzyme makes rats forget where the shock zone is. *Science* heralded this finding as 1 of 10 breakthroughs of 2006. The enzyme, PKM-zeta, was the first molecule linked directly to storage of long-term memories.

"There's no question that was the right behavioral task to use for the cleanest and most beautiful result that was also easy and fast," says Sacktor. "Whenever I tie myself up into knots and can't figure out a problem, I just talk to André, and he solves it quickly."

Fenton's calm demeanor and problem-solving skills come in handy outside the lab, too. On a kayaking trip in 1997, in the Channel Islands off the coast of Los Angeles, a rising tide trapped him and Kentros in a sea cave.

"We noticed that the high-tide line in the caves was well over our heads," says Kentros. "André thought rationally that as the tide came in, it'd get scarier, but also easier to paddle out, and that was indeed the case."

Fenton's disposition has helped him in his career, too. "I feel I'm pretty easygoing when there are challenges, because they're not that scary in the end," he says.

On the wall of his office at NYU, where he arrived in 2008, is a large piece of art that represents a view of the brain through the eye—an image that evokes the frog's-eye lecture that inspired his foray into neuroscience.

With a lab of about 10 people, Fenton has a number of ongoing projects. For example, the team is investigating whether neural activity in the hippocampus is slower to organize into patterns that represent a memory in mouse models of autism than it is in control mice. They are also exploring whether they can make the brains of these mice more adaptable, either by stimulating their brains electrically or by manipulating certain genetic pathways in neurons.

Fenton says he hopes to change the way scientists study memory—paving the way for them to look at neurons directly rather than just at behavior. "Mostly we observe a behavior, such as a rat avoiding an area, and infer from that behavior that the animal has a memory it is recalling," he says. "I'd like to take memory research away from such indirect measures to actually looking at what the brain is doing when it is remembering."

This research continues the interest in the inner life of the mind that first brought Fenton to neuroscience.

"How many thoughts do we enjoy that involve very little in the way of behavior?" Fenton asks. "We may sit in a chair with wonderful thoughts and magnificent ideas, and no outside observer will recognize that. Most of my thoughts, my contributions to the world, are like that—unrecognizable by explicit behavior."

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Gordon Fishell: Oracle's gift to autism

BY VIRGINIA HUGHES / 7 DECEMBER 2007

Friends say 'Gord' Fishell is the poster child for collaboration.

In May 2002, on an isolated hilltop in Delphi overlooking the Aegean Sea, several dozen scientists convened to discuss how the cerebral cortex, the brain's outer layer, develops. It was there, at the site of the legendary Greek oracle, that Gordon Fishell reached a turning point in his career.

Fishell, then 42, had been studying how the developmental environment in a mouse embryo influences how stem cells turn into different types of interneurons—the intriguing cells that dampen electrical signaling in the brain. But he needed help understanding the next step: measuring the activity of fully developed interneurons.

He found his answer in conference organizer Arnold Kriegstein, then a Columbia University physiologist renowned for his brain-cell recording techniques. Soon after the Delphi meeting, on a much noisier island five thousand miles west, the two scientists began what Fishell now calls the "taxi cab collaboration."

Downtown at his New York University lab, Fishell transplanted different kinds of interneurons, tagged with fluorescent green molecular markers, into mouse embryos. Once the transplanted mice were born, he transported them uptown by taxi to Kriegstein's Columbia lab.

"As you might imagine, the taxi bills were killing us," Fishell—'Gord' to his friends—jokes in his tidy office overlooking the East River. "So eventually we moved it all down here."

Along with answering fundamental questions about mammalian brain organization, watching interneurons' "handshake" with other brain cells is the key to understanding autism, Fishell says. "When you look at the 30-odd genes that are linked to autism, a remarkable number of them turn up in interneurons," he says.

FAST FACTS

Current position: Professor of neurobiology, Harvard Medical School • **Recent significant work:** We have had three really exciting papers: 1) Allaway *et al. Nature* 2021, in which we examined the genetic and epigenetic divergence of parvalbumin (PV) and somatostatin (SST) interneurons that arise from a common progenitor and both of which are likely affected in autism (PV, which utilizes the MEF2C gene, which this paper focuses on). 2) Favuzzi *et al. Cell* 2021, which examined the intimate and previously unsuspected role of microglia in the selective pruning of inhibitory synapses. This work showed that the GABAb receptor (and a risk gene for both autism and schizophrenia) functions as a quorum-sensor [and] as a "find me" signal in the pruning of inhibitory synapses, and that selective removal of this gene from microglia differentially

This summer, the Simons Foundation gave Fishell a SFARI pilot grant to explore how disruption of five of these genes in mice might lead to brain and behavioral abnormalities similar to those seen in individuals with autism.

"Gord is one of the most creative scientists I know," says Kriegstein, who now heads the Program in Developmental and Stem Cell Biology at the University of California, San Francisco. "He's among a small handful of people who are applying the latest molecular and genetic technologies to the problems of cortical development."

The upper layers of cortex in the mammalian brain house a complicated circuit of cells that transmits information via electrical signals. The signals come from excitatory neurons, cells that originate in these layers and stay there. Interneurons, in contrast, arise deep within the brain and migrate to the upper cortex in the later stages of embryonic development.

Around birth, "a vast army of interneurons comes streaming up and invades the brain," Fishell says. The cells' role is to prune synapses—the relay points between neurons—and thus dampen the signaling in ways that aren't fully understood. In a formed mammal, about one in every five brain cells are interneurons.

This delicate balance of excitatory and inhibitory signals is the brain's way of filtering the constant barrage of sensory information from the outside world—and what's probably missing in people with autism, according to Fishell.

"Their filtering mechanism, of being able to decide what it is they want to attend to in the world and what they want to ignore, really doesn't work properly," Fishell says. A malfunctioning in interneurons could disrupt this balance and trigger the "noisy brains" characteristic of autism, Fishell says.

Bolstering this hypothesis is the fact that about 30 percent of those with autism have epilepsy, meaning that their neurons fire electrical impulses at a rate that's up to four times higher than normal. "You can easily imagine this has something to do with the balance of excitation and inhibition," Fishell says.

Fishell sees the various types of interneurons as "widgets and gadgets of the brain," meaning that each contributes a specific function in the brain. He identified five types whose genes have been linked to autism. When one of these five 'widgets' is knocked out, he's betting the result will be a mouse with autism.

"Of course, there's a soft underbelly to all of this," Fishell says wryly. "What the hell would an autistic mouse look like?"

In September, Thomas Südhof and his colleagues debuted mice with the same mutation in the neuroligin 3 protein that's been found in some autistic individuals. These knockouts are more likely to have enhanced spatial memory and to associate with inanimate objects—behavior Südhof suggests is comparable to those seen in autism.

"The problem with that is I'm not a mouse. I don't know what mice like," Fishell says. "So how can I come in and say it looks like my mouse isn't paying attention to something?"

affects behavior in male versus female mice. Finally 3) Ibrahim et *al. Neuron* 2021, which showed that bottom-up thalamic signals are needed for the maturation of top-down signals in layer 1 interneurons, a finding that I believe is important for the initialization of brain function, as well as being an early interaction that may be perturbed in psychiatric disease.
Other major accomplishments: More of a focus on the assembly and function of developing cortical circuits as they related to inhibitory interneuron function. Also a separate effort to create virally based tools to target specific interneuron types (and now with Paola Arlotta, excitatory pyramidal cell types as well). • **Main areas of interest:** Genetics, circuit assembly and cortical inhibition
Lab URL: https://fishelllab.hms.harvard.edu • **Notable mentors:** Mary Beth Hatten and Richard Tsien

"[Fishell] is the poster child of collaboration. He shares all of his reagents. And everything he publishes is immediately available to anybody who asks."
—Stewart Anderson

Rather than observe mouse social behavior, Fishell advocates looking for more quantifiable measures, or endophenotypes, of autism—such as the frequency of neuronal firing—in both mice and humans. "Then we're no longer talking about some vague behavior," Fishell says. "We're talking about, say, a gamma frequency of X, in this part of the cortex."

Mouse models such as Südhof's could still prove very useful in understanding autism.

Because scientists do not have access to the brains of humans with autism, pinpointing what goes wrong in the autistic brain is like looking for a needle in a haystack. Having mouse models that mimic the disease "makes the haystack much, much smaller," says Weill Cornell Medical College psychiatry professor Stewart Anderson. "To some extent, it doesn't actually matter if the mouse is autistic."

Once researchers have a better grasp on the human pathology, he says, "then they can focus on potential treatments that would be useful, and use the mice to test those treatments."

Complete understanding is only likely to emerge from the joint effort of multiple models and approaches—something Fishell fully endorses.

A few years before the Delphi conference, Fishell, Kriegstein and Anderson organized a New York City 'Progenitor Club,' where they'd hop from lab to lab to discuss their unpublished results over beer and pizza.

"[Fishell] is the poster child of collaboration," Anderson says. "He shares all of his reagents. And everything he publishes is immediately available to anybody who asks."

At the same time, Fishell has a track record of attempting novel, even risky, experiments. "Gord's not afraid to build a ladder that nobody's ever used before, climb up the tree, and pull off something very special," says Anderson. "A lot of people wouldn't be willing to try."

But if Fishell's at all anxious about his experiments working, it's masked by the palpable enthusiasm in his voice and demeanor. "My lab is

a lot of fun," he says. Asked what makes it so, he tells the story of a friend of his who was recently tenured: "I said to him, 'Why does tenure matter?' And he said, 'Well, you can take up golf, or you can do something you never would have had the guts to do before.'

"This," Fishell says, pointing to the video of his caged autistic mice playing on his computer monitor, "is what I never would have had the guts to do before."

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Eric Fombonne: Crossing continents to expand autism science

BY SARAH DEWEERDT / 7 SEPTEMBER 2021

The Arabic sign-language interpreter stood at the front of the auditorium, his gestures perfectly in sync with the presenter's passionate, French-accented speech.

The audience—more than 2,000 people assembled for the First Gulf Autism Conference in January 2020—sat with rapt attention. "All these people were so quiet," remembers Watfa Al-Mamari, a developmental pediatrician at Sultan Qaboos University in Oman and a conference organizer.

"You could hear a pin drop," recalls Stephen Scherer, a geneticist at the University of Toronto in Canada.

The speaker was child psychiatrist Eric Fombonne, describing how he and others had, in the 1990s, debunked the erroneous idea that vaccines cause autism.

Fombonne pitched his talk at people with little scientific background. His listeners included politicians, policymakers, autistic people and their families, and the general public. Yet even the scientists and clinicians in the auditorium learned something new: Scherer took out his cell phone to snap photographs of Fombonne's slides—something he says he had never done before—so that he could look up the references later.

In many ways, the talk was itself a snapshot of Fombonne's four-decades-long career: a mix of rigorous science and public engagement, delivered with the kind of human warmth that makes him a respected colleague and sought-after clinician. Al-Mamari says she remembers seeing him later at the conference, surrounded by autistic people and their families.

Fombonne, 66, is best known for his studies of the patterns of autism distribution and prevalence. "Whenever I had any question about epidemiology, he was the one I would turn to," says Uta Frith, professor emeritus of cognitive development at University College London in the United Kingdom.

But his contributions to the field are wide-rang-

FAST FACTS

Current position: Professor of psychiatry, Oregon Health & Sciences University
Recent significant work: The development of epidemiological monitoring/surveillance of autism worldwide and the constitution of now very large cohorts/databases (for example, SPARK) that provide improved power to understand and dissect the heterogeneity of the autism phenotypes and of its multiple etiological pathways.
Main areas of interest: Child psychiatry, neurodevelopmental disorders, epidemiology • **Notable mentors:** Michael Rutter

ing. He has published on topics from genetics to assessment tools, and his curriculum vitae, which includes academic positions in four countries, runs to 94 pages. Within the research community, colleagues say, Fombonne has been unusually good at forging international partnerships and unusually willing to stake out bold positions on the cause, prevalence and nature of autism.

Last year, for example, he waded into a debate about camouflaging, publishing an editorial arguing that the term—often used to describe how some autistic people change their behavior to appear neurotypical—has not been rigorously defined. The editorial prompted a lengthy response from scientists studying the phenomenon, but it wasn't entirely unwelcome.

Fombonne "challenged the field of camouflaging research in a very constructive manner," says William Mandy, a psychologist at University College London and one of the authors of the rebuttal. "[His] intervention is helping clarify areas of disagreement and misunderstanding, and is shaping the questions that future camouflaging research should address."

Fombonne was born in Paris and grew up in an affluent suburb. He was a strong student, interested in mathematics and science. He was also politically engaged and participated in student demonstrations in the late 1960s—activism he attributes to his parents, devout Catholics involved in social justice causes.

In medical school at the University of Paris, Fombonne chose to specialize in child psychiatry. At the time, there was "intellectual excitement about psychiatry because [of] the mystery of the mind," he says, and child psychiatry seemed to hold the most therapeutic potential.

Another factor, too, helped guide Fombonne's decision: Around the time he entered medical school, his older sister, Dominique, was diagnosed with schizophrenia. As a young medical student, he accompanied her to hospital emergency rooms on several occasions; after grappling with the illness for more than a decade, she died by suicide in 1986.

The experience left him keenly aware of the limitations of psychiatric care—and skeptical of theories that didn't offer any practical help for patients and their families. "It certainly shaped my later sense that I needed to pursue research and to ask questions and challenge the views of the current establishment," he says.

To that end, in the late 1980s Fombonne launched the first study of the prevalence of child psychiatric conditions in France while on staff at a psychiatric hospital in Paris. His work attracted the attention of a French association of families with autistic children, who inspired him to conduct the first epidemiological studies of autism in France. He soon became an advocate for improved autism care, speaking at conferences and lobbying the French government on the topic.

Fombonne's epidemiological studies earned him recognition as a rising star, and in 1993 he was recruited to join a group at the Institute of Psychi-

atry in London led by Michael Rutter, renowned as the 'father of child psychiatry.'

There, Fombonne joined a community of like-minded clinician-researchers for the first time, he says. "There still are very, very exquisite relationships with some of my peers who I met during that period."

His position in London also put him at the epicenter of child psychiatry when, in 1998, a bombshell hit: Now-discredited gasteroenterologist Andrew Wakefield published a paper in *The Lancet* alleging a link between the measles-mumps-rubella (MMR) vaccine and the onset of autism.

Fombonne was immediately skeptical. Within weeks of learning about the paper and before its publication, he had marshaled data from two existing datasets to refute Wakefield's claims. And after the paper came out, Fombonne conducted multiple studies to test Wakefield's hypotheses, always with the same result: Wakefield's science was "completely bogus," he says, vaccines were safe, and there was no connection between the MMR vaccine and autism.

Wakefield's paper was later retracted—he had falsified his data—but Fombonne "was really almost prescient in understanding that this was going to have a big effect on families and on our field, and understanding the importance of bringing really rigorous science to evaluate whether that hypothesis was correct," says Sally Ozonoff, a child psychologist at the MIND Institute at the University of California, Davis, who has known Fombonne for many years.

Fombonne gave talks on the vaccine controversy at medical conferences and at meetings of the Institute of Medicine in the United States. Despite death threats from anti-vaccine activists, he served as an expert witness in vaccine-injury trials. "I was not prepared to do all that in my career," he says. "I remember I was so shy when I first gave talks in public, and then to be speaking in the court in Texas in English!"

However challenging, the work was fulfilling, he says, because he knew that widespread acceptance of an incorrect explanation of autism's origin would harm people with autism and their families—and that there was a broader public health risk if people abandoned vaccines.

"It made me sense that the path that I had chosen for my career had a social impact," he says.

Fombonne expanded his epidemiological work with another big move in 2001, becoming the Canada Research Chair in Child Psychiatry at McGill University in Montreal and head of the child psychiatry department at Montreal Children's Hospital. From this post, he led a World Health Organization-sponsored review of how geographical and cultural variations impact autism prevalence estimates—work that has been cited more than 2,300 times.

Although Fombonne's research documented an increase in autism prevalence worldwide, he is skeptical of the 'autism epidemic' framing that has dominated some discussions. Instead, he argues that other factors likely contribute to the uptick, such as a broader definition of autism and greater clinical recognition of it—another instance of his insistence on a careful accounting of the data before drawing flashy conclusions, Ozonoff says.

In Canada, Fombonne developed an autism research and clinical program, as well as a training program—the first of its kind in the country. Over the course of a decade, the program educated at least 150 early-career scientists, many of whom are now prominent autism researchers. "It had the reputation, even within the first few years, that you want to be seen there," says Scherer, who taught in the program.

Al-Mamari participated in the training program in the mid-2000s and trained under Fombonne, as did Mayada Elsabbagh, a neuroscientist at McGill University who worked on the World Health Organization review and now directs a similar training program.

"Eric had a big influence in terms of my research trajectory and opened up opportunities that were quite nice and exciting, and ones that I still pursue today," says Elsabbagh, who has been his frequent collaborator since.

Fombonne's collaborations and epidemiological studies have taken him around the globe, to Mexico, China, Oman, Qatar, Kazakhstan, Morocco and Brazil.

"He is the 'active ingredient' in research teams now internationally," Elsabbagh says. "I don't know anybody who has done the same scale of international partnerships."

And since 2011, he has been working to build another autism research program and clinical center at Oregon Health & Science University in Portland—a relocation prompted by his then-wife, who had lived in the city previously.

"I said, 'Portland? Where is it, first? What is there for me?'" Fombonne recalls jokingly.

In each new country where he contributes to an epidemiological study or takes up an academic post, Fombonne aims not only to capture autism prevalence, but to build regional research and clinical capacities, and provide data that local policymakers need to develop autism services.

Fombonne builds partnerships not just on good science, but on good company, Elsabbagh adds. After a regional International Society for Autism Research meeting in Chile in 2019, for instance, political unrest forced them to road-trip out of the country, along with several other scientists. "In theory the circumstances were not very pleasant, but we actually had a really good time," she says.

The coronavirus pandemic has put a temporary damper on Fombonne's scientific travels, but he's finding new ways to engage in social issues. Every weekend from March through June, he volunteered at a mass vaccination clinic at the Portland airport: "I put Pfizer, Moderna and J&J shots in thousands of arms," he says. "Older arms at first, and later, younger and younger arms!"

Like his more usual work, it afforded him a mix of clinical practice and big-picture impact. "I enjoyed the experience," he says. "Contacts with people were relatively brief, but I could see a cross-section of society and many interesting facets of human experience."

If you or someone you know is having suicidal thoughts, help is available. Here is a worldwide directory of resources and hotlines that you can call for support. https://findahelpline.com/i/iasp

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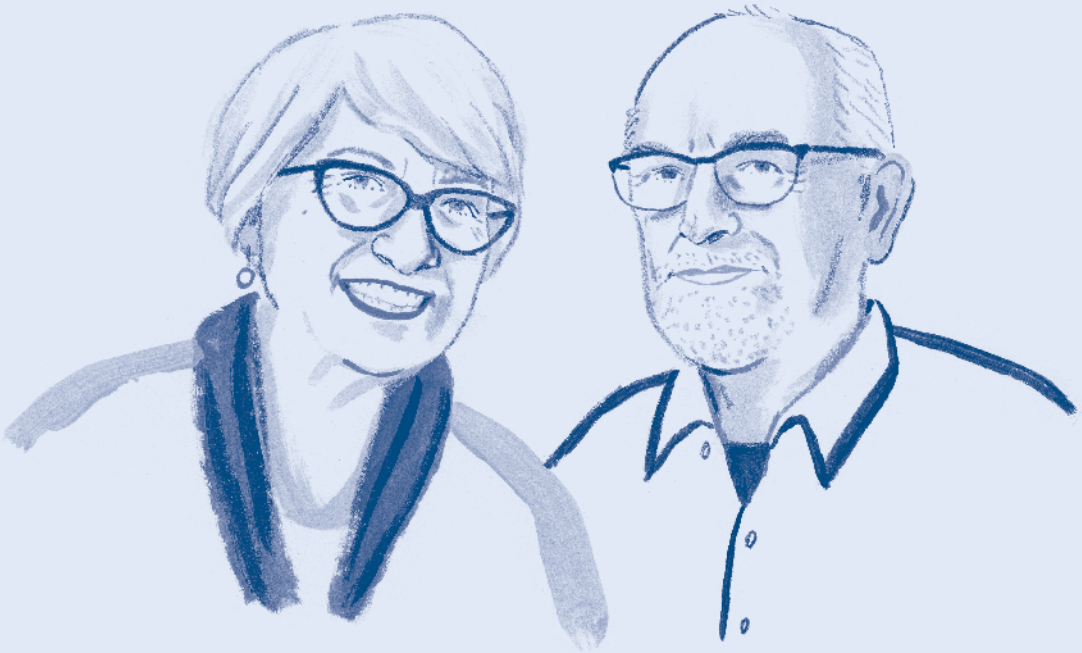
Uta and Chris Frith: A partnership of the mind

BY MOHEB COSTANDI / 28 AUGUST 2014



Autism can be baffling, appearing in various forms and guises and thwarting our best attempts to understand the minds of people affected by it. Anything we know for sure about the disorder can probably be traced back to the pioneering research of the developmental psychologist Uta Frith.

Frith was the first to propose that people with autism lack theory of mind, the ability to attribute beliefs, intentions and desires to others. She also recognized the superior perceptual abilities of many with the disorder—and their tendency to be unable to see the forest for the trees. Frith, now affiliated with the Institute of Cognitive Neuroscience at University College London (UCL), has shaped autism research for an entire generation of investigators.

Meanwhile, her husband Chris Frith formulated a new view of schizophrenia, a mental illness marked by hallucinations, disordered thinking and apathy. His work explored how the disorder affects the experience of agency, the sense that we are in control of our bodies and

FAST FACTS

Uta Frith's current position: Emeritus professor of cognitive development, University College London
Recent significant work: An attempt at improving science communication: a graphic non-fiction book about social cognitive neuroscience, written with Chris Frith and Alex Frith, and illustrated by artist Dan Locke, called "Two Heads: A Graphic Exploration of How Our Brains Work with Other Brains."
Main areas of interest: Cognitive theories of autism

responsible for our actions. And his innovations in brain imaging helped researchers examine the relationship between brain and mind.

Independently, husband and wife explored the social and cognitive aspects of these psychiatric disorders. Together, they helped lay the foundations of cognitive neuroscience, the discipline that seeks to understand the biological basis of thought processes.

Trevor Robbins, a cognitive neuroscientist at the University of Cambridge in the U.K., calls them "tremendously influential pioneers," in particular because both brought a social perspective to cognitive neuroscience.

"Uta and Chris are generally regarded as the matriarch and the patriarch of cognitive neuroscience," says Karl Friston, professor of neuroscience at the Wellcome Trust Centre for Neuroimaging in London, and an occasional collaborator. "They've had a profound effect in terms of intellectual content, but they've also enabled, encouraged and nurtured many others along the way."

The couple first met in 1965, when the young Uta Aurnhammer moved to London after graduating from the University of Saarbrücken in Germany. Uta was drawn to psychology by the work of Hans Eysenck, whose ideas about intelligence and personality were highly influential. "He was kind of a hero of mine," she says, "because his books debunked psychoanalysis and described new behavioral therapies for psychological disorders."

She took an internship at the Institute of Psychiatry in London, where Eysenck worked, and met Chris Frith in a course on clinical psychology. "It was just a meeting of minds," Uta recalls. "We seemed to have the same taste in art, poetry, film, literature and music." Both also felt that abnormal psychology could reveal much about the human mind.

They married the following year, and both stayed on at the Institute of Psychiatry. Uta had met children with autism, or 'childhood psychosis' as it was then known, during her training. When Eysenck proved to be elusive and uninspiring, she decided to make the condition the subject of her thesis. "People with autism can be excellent at some things and very poor in others, and this variation fascinated me," she says.

At the time, autism was still thought to be caused by cold, uncaring parenting, but a series of twin studies carried out by the developmental psychologist Michael Rutter in the early 1970s revealed the genetic basis of the condition. Encouraged, she pursued her hunch that autism has a biological basis.

She studied language and visual processing in children with autism, finding that they have excellent perception of fine details, but fail to grasp the gist of a scene or sentence. She would later formalize this observation as the 'weak central coherence theory,' the idea that people with autism have difficulties consolidating streams of information.

After she finished her Ph.D., her advisor Neil O'Connor hired Uta at the Medical Research Council Developmental Psychology Unit in cen-

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Lab URL: http://frithmind.org/ • **Notable mentors:** Beate Hermelin, Neil O'Connor, Lorna Wing, Michael Rutter, John Morton

tral London—"my absolute dream job," she says. She remained there for the rest of her career, cultivating many graduate students and making a string of discoveries about social impairments in children with autism.

In the mid-1980s, she developed the Sally-Ann test with her student Simon Baron-Cohen, now professor of developmental psychopathology at the University of Cambridge. The test uses puppets to measure children's capacity to understand that others have beliefs that might be different from their own. Together, Uta and Baron-Cohen showed that children with autism lack theory of mind, and hypothesized that this was at the root of their social impairments—an idea that guides the field to this day.

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From the beginning, Chris was interested in schizophrenia. "I had met some patients while working in these huge, old-fashioned south London asylums, and became fascinated by how seemingly intelligent people could have such bizarre ideas," he says.

His early work transformed the view of this mental illness. The cognitive processes underlying its symptoms were poorly understood, until his studies revealed that people with schizophrenia sometimes have poor awareness of their own actions and thoughts. This is why they misattribute their own actions to external sources, and mistake hallucinations as originating from the outside world.

By the early 1990s, Chris had moved to the Medical Research Council Cyclotron Unit at Hammersmith Hospital in London. He used neuroimaging methods such as positron emission tomography to investigate the neural basis of mental processes and schizophrenic symptoms. "Chris did the very first sophisticated cognitive experiments using noninvasive brain imaging with humans," says Friston.

In 1992, the Friths' lines of research began converging. The insight that both schizophrenia and autism involve social difficulties led the two to suggest that the brain has a dedicated system devoted to social cognition that malfunctions differently in each disorder. In 1999, they co-authored a paper proposing to identify a biological basis for social interactions. In so doing, they established social cognitive neuroscience as a discipline in its own right.

The Friths have both received countless awards for their work. This year, the two were jointly recognized with the Jean Nicod Prize, awarded to a leading philosopher of mind or cognitive scientist. Both have been elected to the Fellowship of the Royal Society, and last year Uta was made an honorary Dame of the British Empire. Both are now retired, but continue to pursue research with emeritus positions at UCL.

Although autism was thought to be rare when she began her career, Uta is now concerned that it might be overdiagnosed, because the current diagnostic criteria are so broad.

"There was a time when autism was underdiagnosed and we wanted to raise awareness of it," she says. "But people with autism-like behaviors are now diagnosing themselves incorrectly, and I'm

FAST FACTS

Chris Frith's current position: Emeritus professor of neuropsychology, Wellcome Centre for Human Neuroimaging, University College London • **Recent significant work:** See preceding page
Main areas of interest: Social cognition, consciousness, culture • **Notable mentors:** Uta Frith

worried about over-extension of the diagnosis."

Chris continues to explore the interactions of minds, studying how people follow instructions and exploring thought insertion, a symptom of schizophrenia in which people believe that their thoughts are put in their minds by somebody else.

Uta has been a fierce advocate for women in science and technology, and both Friths have had a lasting influence on the careers of dozens of other scientists, many of whom are now regarded as experts in their own fields.

Sarah-Jayne Blakemore, professor of cognitive neuroscience at UCL, studied for her Ph.D. with Chris as one of her advisors. "He always gave me brilliant advice which I still adhere to," says Blakemore. "I also became friends with Uta, who immediately became a mentor, and with her encouragement I became independent quite early in my career."

The Friths' advice extended beyond intellectual life, says Blakemore. "Even today, when I find myself in a difficult situation, I often find myself thinking, 'What would Chris do?'"

Sociable people, both Chris and Uta document their ongoing research through social media such as Twitter and blogs. "Their own social brains are also highly developed," quips Robbins. "They wear their preeminence lightly and with a sense of humor, adding to their popularity as role models, mentors, icons and sages for young scientists worldwide."

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F

Matthew Goodwin: Bridging disciplines for autism care

BY EMILY SINGER / 8 APRIL 2013

Here's a scenario that Matthew Goodwin is all too familiar with. A child with autism is sitting at a desk, seemingly checked out, staring into space. A teacher asks the child to get back to work, and the child stands up, flips over the desk and runs out of room.

"One second he's fine and the next he's having a tantrum," says Goodwin, assistant professor of health sciences at Northeastern University in Boston.

But looks can be deceiving: Goodwin has shown that some children sitting and looking calm may actually be deeply anxious, with a pulse racing at 120 beats per minute. And the child's apparent 'spacing out' may be an attempt to self-regulate his physiology.

"If I knew the child's internal state, I wouldn't place a demand on that kid. I might encourage him to relax or take a walk," says Goodwin. "I would adjust my interaction style to calm him back down."

The problem is that many children on the more severe end of the autism spectrum are nonverbal, and even those who can talk often have difficulty identifying and expressing how they feel. Goodwin is trying to develop alternative ways to measure these children's internal states and in turn help teachers and parents modulate their interactions with them.

Goodwin is tackling this task with myriad monitors—from ceiling cameras and microphones to wearable sensors that track heart rate, temperature and sweat—and computer algorithms. Together, these may be able to determine when a child is stressed and what triggered the episode, and to evaluate the most effective strategy for making him feel better.

Similar tools could be used to assess treatments as well—automated monitoring may provide a way to more quantitatively measure changes in hyperactivity, for example, and even

FAST FACTS

Current position: Interdisciplinary associate professor, Northeastern University
Recent significant work: Demonstrated that challenging behavior (aggression to others, self-injury, tantrums) can be predicted three minutes in advance using wireless biosensors and machine learning algorithms in minimally verbal individuals with autism.

irritability and aggression, which are typically measured by short questionnaires.

Researchers who have worked with Goodwin uniformly comment on his unique ability to think about how to apply technology to autism care.

"Many people are experts in the autonomic nervous system, signal processing and hardware design, but he is able to bring these roles together and think about how we can develop methodologies that can ultimately impact care," says James Rehg, professor of interactive computing at the Georgia Institute of Technology and a collaborator.

Goodwin began working with children who have autism early in his career, volunteering at a school for children with autism for 20 hours a week during a year of college spent at Oxford University in the U.K.

"He's an experimental psychologist but also really tuned in to the kids—I've been in this field for 30 years, and there are not a lot of people like that," says Terry Hamlin, chief of staff at the Center for Discovery in Harris, New York, a residential facility on a farm in the Catskills for people with autism and other disabilities. "He also makes wonderful connections and brings people together."

The children at the Oxford center had challenges making eye contact and with joint attention, classic features of autism, Goodwin recalls. "But after showing up repeatedly and just spending time together, they would start to look at me and talk to me and show some empathy toward me," he says. "Around then, I started reading the literature, which says these kids have no theory of mind, but that didn't match the behavior I saw."

Goodwin returned to the U.S. for college in 1995 and began interning at the Groden Center in Rhode Island, a day and residential program that serves profoundly impaired children with autism.

He noticed that stress and anxiety often aggravated the children's behavioral problems. The clinical staff would try to calm the children down using a variety of methods, such as deep breathing or cognitive exercises. Goodwin says he wanted to understand what triggered the anxiety in the first place, and how effective the different methods were.

"That requires some measure of how stressed or non-stressed a person is," says Goodwin. But if children can't identify or communicate how they feel, how can a scientist adequately measure it? Or efficiently treat it? "Most stress research is based on surveys or direct behavioral observation, and herein lies the problem," Goodwin says.

Fortunately for Goodwin, two technology trends were then beginning to be incorporated into the study of human health.

The first was wearable computing—sensors on the body or in clothing or accessories that can measure an individual's biology or behavior. These are especially advantageous for studying children with autism, who often have sensory and movement issues that make traditional mon-

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Main areas of interest: Computational behavioral science, personal health informatics, ambulatory psychophysiology
Notable mentors: Grace Baron, June Groden, Lewis Lipsitt, Wayne Velicer, Rosalind Picard

itoring technologies unsuitable. They can be also used in real-world settings, such as the home or classroom, and can monitor a child for hours, days or weeks, rather than in a limited lab session.

The second trend was ubiquitous computing, in which sensors built into spaces, such as classrooms, record what's going in the environment.

One of Goodwin's first targets was hand flapping, a repetitive behavior seen in 70 percent of children with autism. "We don't know why kids do this. We don't know if it's stimulatory or self-soothing," says Goodwin. "It's certainly socially stigmatizing."

Hand flapping and other repetitive behaviors are a hot-button issue among families, educators and clinicians. Some education programs try to stop children from engaging in these behaviors, but that can make the child agitated or aggressive.

Goodwin is passionate about trying to understand these behaviors. "We ignore them, restrain them or medicate them," says Goodwin. "But before we decide what to do about it, let's try to decide why they do it."

Preliminary research suggests that people with autism engage in repetitive behaviors for a variety of reasons—sometimes to calm down, sometimes to excite themselves. Hand flapping may even act as form of communication, showing happiness when they get something they want or frustration when they can't get out of a situation they don't like.

"If this is how they communicate, regulate stress and sensation, and feel their body, the last thing I want to do is stop them from doing it or medicate them," says Goodwin.

Most studies measuring restricted and repetitive behaviors in autism use either parent report or direct observation, both of which can be unreliable. Two observers rating repetitive behaviors in real time agree only a third of the time, says Goodwin, largely because the behaviors can start and stop so quickly. Video recording is more accurate but is slow and expensive.

For his doctoral dissertation, Goodwin analyzed data from children with autism who wore three accelerometers—small devices that detect movement—one on each wrist and one around the waist. He created algorithms that, after a short training period, can automatically detect when a child is flapping or rocking, and found that the three devices together have an accuracy of 90 percent.

Goodwin's latest work incorporates more complex sensors, which can track skin conductance—an indirect measure of the autonomic nervous system—as well as heart rate, movement and body temperature.

Goodwin strapped one such device around my wrist when I visited his lab, and we watched as it conveyed a stream of data to a laptop. A set of lines on the screen rose and fell throughout the conversation as my attention focused or wavered.

One of the biggest challenges of the project is to figure out how to interpret the sensor's signals. Unlike, say, an electrocardiogram, which records electrical signals from the heart, there is no standard pattern for skin conductance.

Goodwin and his colleagues are analyzing data collected from ten children with autism wearing accelerometers and heart rate monitors in a classroom during a variety of tasks and emotional states. Their goal is to determine whether repetitive behaviors are triggered by particular activities or internal states. The answer is unlikely to be simple: According to their preliminary find-

ings, repetitive movements appear to be linked to physiology in some children but not in others.

Goodwin is also part of a five-year, $10 million project, funded by the National Science Foundation, to create automated tracking technology to help diagnose people with autism and track the outcome of therapies. The project involves bringing together a mix of sophisticated technologies, including cameras, sensors and machine learning—computational techniques that learn from data—to solve clinical problems.

He is also working with Hamlin on a pilot project at the Center for Discovery, set in a classroom outfitted with ten ceiling cameras and two microphones. The children and staff all wear wireless monitors that record their heart rate, temperature and movement.

The researchers are creating algorithms to automatically identify problem behaviors, such as wandering off or self-injury, based on data from the sensors. They can also look at the physiological data leading up to a behavioral outburst, as well as the physiological consequences of the behavior.

Hamlin says they have been recording for about a year and that the computers are now able to automatically recognize different behaviors.

The next challenge will be figuring out what to do with the enormous volume of data being collected. "We have to get it into the hands of clinicians to figure out which measures are predictive," Goodwin says. He is also setting up instruments at his own testing center at Northeastern.

Goodwin has also helped launch a new graduate program at Northeastern that bridges technology and medicine.

"I was trained as a behavioral scientist and got interested in computer science late in life," says Goodwin. (At 36, late is a relative term.) "The idea of the program is to train the next generation simultaneously, so they will be able to do what we can't."

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Additional D–H Profiles

Petrus de Vries:

Architect of the autism research field in Africa

https://www.spectrumnews.org/news/profiles/petrus-de-vries-architect-of-the-autism-research-field-in-africa/

Ricardo Dolemetsch:

Regenerating the cells of autism

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Jacob Ellegood & Jason Lerch:

Meet the dynamic duo scanning every autism mouse brain

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In dogged pursuit of autism's off switch

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https://www.spectrumnews.org/news/profiles/simon-fisher-hunting-on-the-foxp2-trail/

Daniel Geschwind:

On the trail of autism's genetics

https://www.spectrumnews.org/news/profiles/daniel-geschwind-after-many-detours-on-the-trail-of-autisms-genetics/

40 UNDER 40

We asked our profile subjects and sources to flag rising stars in their labs or among their former students. The result is this list of 40 young researchers who are working on autism-related science across the globe.

To read more about early-career researchers, subscribe to our Spectrum Launch newsletter.

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Broadening the autism spectrum: Q&A with Oluwatobi Abubakare

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Rising Star: Vanessa Bal traverses fine work-life balance

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Whitney Guthrie
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Clare Harrop
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How to safeguard online data collection against fraud

Desiree Jones
Doctoral student
University of Texas at Dallas
Dallas, Texas, United States
How to support Black scientists and clinicians in autism research

Erin Kang
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Montclair, New Jersey, United States

Ann Kennedy
Assistant professor
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Evanston, Illinois, United States
Rising star: Ann Kennedy bridges gap between biology, computational theory

Yinqing Li
Associate professor
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Brenna Maddox
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UNDER 40

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Gabriela Rosenblau
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George Washington University
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Beyond the bench: A Conversation with Gabriela Rosenblau

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Novel protocol captures autism voices across the spectrum

Constantina Theofanopoulou
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Visiting associate professor at Rockefeller University
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Beyond the bench: Learning new moves with dancer-scientist Constantina Theofanopoulou

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Alex Tsompanidis
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Tychele Turner
Assistant professor
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Focus on function may help us unravel autism's complex genetics

Kandice Varcin

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Assistant professor
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Madison, Wisconsin, United States
Webinar: Donna Werling on gene-expression differences in the brains of autistic people

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Vanderbilt University
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A new hub for participatory research: Q&A with Zachary Williams

Helen Willsey

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University of California, San Francisco
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Brian Lee: Pushing the limits of autism epidemiology

BY PETER HESS / 14 OCTOBER 2021

Brian Lee did not set out to be an autism researcher. Thinking mathematically (as he does), he wonders about the probabilities. "If I were growing up now, I might be some sort of Bitcoin trader, working my quant skills," says Lee, associate professor of epidemiology and biostatistics at Drexel University in Philadelphia, Pennsylvania. "If you flicked one little switch early on, life would be so different now."

Lee says he fell into the study of autism because he likes dealing in complexity, and he found that his quantitative skills could help unearth the various environmental and genetic contributions to the condition. In 77 peer-reviewed papers penned over a decade, he has revealed how perinatal factors such as gestational age at birth and prenatal factors such as maternal infection or vitamin D consumption affect a person's chances of having autism. He has also shown a correlation between autism and prenatal antidepressant use, as well as autism and family history of psychiatric conditions.

Teasing these variables apart from other factors requires both careful statistics and large datasets, Lee says. Part of his numerical wizardry comes from his connections to scientists in Scandinavian countries, where universal healthcare records grant insights into individuals' lives and exposures dating back generations. "It's the stuff that epidemiologists' dreams are made of," Lee says.

The other part is his penchant for playing mathematical defense against potentially confounding variables, issues with ascertainment and modest effect sizes. "Brian's contributions in that were elevating those challenges and making sure we tried to explicitly address them head-on, as opposed

FAST FACTS

Current position: Associate professor of epidemiology and biostatistics, Drexel University
Notable mentors: Craig Newschaffer, Li-Ching Lee

to pushing them aside," says Craig Newschaffer, professor of biobehavioral health at Pennsylvania State University in State College. (Newschaffer served on Lee's master's thesis committee.)

Lee has developed powerful statistical methods for disentangling the complicated webs of genetic and environmental factors that may contribute to autism, his colleagues say. "He is a really skilled methodologist. He represents a new generation of analysts with updated quantitative skills," says Lee's longtime collaborator Cecilia Magnusson, director of the Centre for Epidemiology and Community Medicine at the Stockholm County Council in Sweden.

Growing up in Minot, North Dakota, a town of about 35,000 at the time, Lee won piano competitions and, at age 12, came in second in the 1994 National Spelling Bee. It was the first year that the event was televised. "I'm pretty sure I'm one of the few epidemiologists who has ever been on ESPN for more than a split second," he says.

Lee's mother, a librarian, encouraged him to read widely, and his father, a physician, inspired him to consider health and medicine as a career, he says.

And so, as an undergraduate student at Harvard University starting in 1999, Lee found himself on a pre-med track—but he quickly realized his heart was not in treating people. He switched to biological anthropology, the study of human evolution, and designed an experiment for a class to test a hypothesis about primate diets. "It got my feet wet in terms of independent research," Lee says.

Lee dove into more experimentation, this time with the brain. He took a job in Harvard neurologist Alfred Geller's lab, modifying DNA to enhance learning in rats. After graduating in 2003, Lee headed to the University of California, San Francisco for a loosely designed internship in which he coded web pages, among other tasks. There, he crossed paths with an epidemiologist named Jonathan Showstack, who opened his eyes to a field that would make use of his mathematical abilities.

Lee's facility with numbers had been apparent since middle school, when he won city and state math competitions. He had also just read Jared Diamond's book "Guns, Germs, and Steel," which describes how environmental advantages set the stage for some cultures to dominate others throughout history. The idea that health and environmental factors may play invisible roles in life outcomes spoke to Lee. So as Showstack broke down the basic divisions of his field—disease surveillance, environmental epidemiology and so on—a switch flicked on in Lee's brain. "All of a sudden, I was like, 'Hey! Maybe I could think about epidemiology as a career direction.'"

Lee applied to epidemiology Ph.D. programs and ended up at Johns Hopkins University in Baltimore, Maryland, where he wrote his thesis on how neighborhoods influence cognitive function in older adults, as part of the Baltimore Memory Study. His overarching curiosity was: Why do people's lives end up the way they do?

While working on the neighborhood study, he found another opportunity to answer that question—involving autism. In a study published in

2008, he used a statistical technique to help identify seasonal patterns in the likelihood that a newborn will go on to have an autism diagnosis.

After earning his Ph.D. in 2009, Lee was offered a postdoctoral fellowship at the Karolinska Institutet in Sweden, working with the Swedish health registries. It was a tantalizing opportunity for a budding epidemiologist, "millions of records, spanning multiple tables in a complex database," he says. At the same time, Newschaffer recruited him for a tenure-track position at Drexel University.

So Lee did both—sort of. Newschaffer gave him the go-ahead to spend the first month of his time at Drexel living in Stockholm and working pro bono with a biostatistics research group at the Karolinska Institutet. There, Lee and his colleagues used Swedish health data to examine the link between blood type and risk of preeclampsia. During his time in Sweden, Lee earned the trust of his Swedish colleagues, who invited him to use the prized Scandinavian health registry data.

Through those connections, Lee and his colleagues later used the Swedish National Patient Register to establish a modest but significant association between prenatal infections and autism, described in a 2014 paper. "Not everyone gets their fingers into the jar, so to speak, but he does because he's trustworthy and very nice," Magnusson says.

Magnusson is not the only one of Lee's collaborators to cast his personality as an asset. "To have him at Drexel is an incredible draw for many of us, and having him in our immediate orbit, in our atmosphere, he bolsters our research experiences," says his Drexel colleague Lindsay Shea, director of the Policy and Analytics Center at the Drexel Autism Institute. In August, when Shea reached out to tell Lee their latest manuscript had been rejected, Lee responded immediately—even as he was moving into a new home. He said that the rejection was actually a good thing, because the comments would help redirect and improve the work. "That sort of interaction can really shift how you work through your day," she says.

Lee's collaborative style also shows up in his own laboratory—which makes him an outstanding leader and mentor, Shea says. One of his graduate students, Jessica Rast, says that Lee respects the goals of his mentees, even when they differ from his own. Rast says she wanted to work on a project that was just outside the scope of Lee's grant. Instead of rejecting Rast's request, Lee found a way for her to pursue her interests under his guidance. "He's not interested in fitting me within his program; he's interested in giving me experience to learn," Rast says.

Lee taught himself to repair computers as a child, fixing a broken sound card with scavenged parts so he could play multiplayer "Doom" over his 56k modem. He bolstered his self-taught skills with a few programming classes and a stint at Harvard's computer help desk as an undergraduate student. He was then prepared to tackle all manner of hardware and software challenges. "Kind of like a guy who knows how to fix his car, I'm that guy who never needs to call tech support," he says.

But it wasn't until he had to grapple with the massive Swedish databases that his real lessons in coding began. With millions of records and hundreds of variables, crunching data can be a monumental task. "That was a much bigger problem to solve than a broken sound card," he says.

One of Lee's early epiphanies was just how many possible associations there are between data points in a real-life database. As a graduate

student, for example, he recognized that a neighborhood represents much more than an address. Wealth, education and race all affect the likelihood that someone will live in a certain locale, and each of these factors has its own associations with lifelong health.

Using his computing skills to decipher these webs of influence has come to define Lee's career. In doing so, he has reshaped how autism epidemiology is done, Newschaffer says. One of Lee's core contributions is an improvement, based on machine learning, on a statistical method called propensity score weighting. This strategy debuted in a 2010 paper, which remains his most cited work. It helps distinguish exposures such as drugs and diet from the factors that lead to those exposures—a potential source of confounding. For example, prenatal antidepressant use is usually accompanied by a psychiatric diagnosis, and that diagnosis may independently affect a child's outcome. Propensity score weighting works by making two groups—mothers who were either exposed or unexposed to an antidepressant, for instance—as statistically similar as possible in every way except for the exposure in question.

In a 2017 study, Lee and his colleagues used a related technique called propensity score matching to identify a small but significant association between women taking certain antidepressants during pregnancy and autism in children. Later that year, Lee, Magnusson, Newschaffer and others used the same technique to parse Swedish registry data for more than half a million people, revealing lower chances of autism among the children of mothers who took prenatal multivitamins.

Lee's newest work extends beyond the womb to lifestyle, health and policy factors that affect autistic people as they develop and age. This year, he and Shea are examining Medicaid data on the use of psychotropic medications by people with autism to determine the safety of such usage, an understudied area. They are also developing a tool for Pennsylvania state officials that helps autistic adults enrolled in Medicaid navigate life changes or issues such as contact with the criminal justice system, Shea says.

When Lee and Shea work with policymakers, Lee does not flex his Ph.D. or push his ideas, Shea says. Rather, he asks how he can help. "There are few ways that you can engage with policymakers that would be more effective," she says. "I'm eager to get Brian in as many of those conversations as possible."

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Cathy Lord: Setting standards for autism diagnosis

BY VIRGINIA HUGHES / 30 JUNE 2008

In the late 1960s, as an undergraduate student in psychology at the University of California, Los Angeles, Cathy Lord spent a couple of hours a day teaching two young boys with autism.

She was working for clinical psychologist Ole Ivar Lovaas, one of a few doctors who believed in behavioral therapy for autism. Lovaas had plucked the boys out of a state hospital for his unconventional treatment, which focused on positive reinforcement—from M&Ms to animated clapping—of good behaviors.

One of the two boys Lord worked with improved tremendously. "He had been a little terror," Lord recalls, and had been institutionalized

FAST FACTS

Current position: George Tarjan Distinguished Professor of Psychiatry, Semel Institute of Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles
Notable mentors: Michael Rutter, Eric Schopler

for years. But after a few months of intense therapy, his disruptive behaviors stopped.

The approach didn't work so well with the second boy, however, who had severe intellectual disability as well as autism. "I was supposed to teach him to talk, but he didn't understand anything about what I was trying to do," Lord says. She was happy just to be able to teach him to wash his hands and press an elevator button.

Lord came away from that experience with two lessons: that children with autism are better off outside mental institutions, and that behavioral therapy is inadequate. She went to graduate school, she says, "to figure out what else you can do for them."

Since then, Lord has acquired a reputation for rigorous study of the autism phenotype. She's worked with thousands of children in nine schools and clinics in the United States, Canada, and England. She and her colleagues have developed the field's gold standard for autism diagnoses and in 2001, she launched the University of Michigan Autism & Communication Disorders Center (UMACC).

"She's probably the smartest person I've ever worked with," says long-time colleague Pam DiLavore, assistant director of the Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH) Center in Raleigh. "[Lord] is one of the few psychologists I know who can go into an evaluation room with someone of any age, on any part of the autism spectrum, and develop an immediate rapport," DiLavore says.

Lord has also developed solid relationships with her colleagues, staff and students. Although she's perpetually juggling a dozen projects, they say, she still makes time for her graduate students and for her family.

"She got me involved in writing a couple of papers at a very early stage," recalls John McLennan, who was a medical student when he met Lord at the University of Alberta in the late 1980s. "Her standards are very, very high. But she pushed people in a positive way, and always looked for opportunities to promote her students," he says.

Lord began her doctorate studies in psychology and social relations in 1971 at Harvard University. Three years later, when her husband took a job at Dartmouth, she finished her dissertation there and worked part-time at a school for children with disabilities.

None of the eight children, who ranged in age from 2 to 8 years, had been in a school before. On the first day of class, the scheduled teacher didn't show up. Lord took over for the day, and then for the rest of the year, while the school tried to find a replacement. "It was horrifying," she recalls. "I had no idea what I was doing."

One girl was so developmentally delayed that she could not sit up consistently. Four of the eight children had autism: "These four were so different from one another, and I thought that was so interesting," she says.

That experience was still on her mind in 1976, when she finished her Ph.D. and began a clinical

internship at the TEACCH program at the University of North Carolina.

At the time, children who usually received autism diagnoses were severely handicapped. "If a child talked, we would debate whether they could really have autism," she says. But as time went on, clinicians became more and more aware of children with milder forms of autism, even those who were quite verbal. "So for me, the question became: What about them?"

In 1982, Lord went to London to work with world-famous psychologist Sir Michael Rutter on a diagnostic tool that would distinguish children with autism from those with other kinds of mental impairments.

Together, they came up with the ADOS—the Autism Diagnostic Observation Schedule—which comprises a few hours of tasks that require verbal social interaction, such as make-believe play with action figures. Each task is scored by a trained examiner, and the scores are totaled at the end.

Lord and Rutter then tweaked the ADOS so that it included only the tasks that best predicted whether a child would receive an autism diagnosis. They published their protocol, the first of its kind, in 19891. That version was designed for children aged 5 to 12 with fairly high verbal skills. In the following few years, Lord modified the procedures for younger children.

The new version, called the Pre-Linguistic ADOS (PL-ADOS), focused on non-verbal tasks such as watching balloons being blown up, that tested for social abilities.

Lord had one personal problem while working on the development of PL-ADOS: she couldn't blow up a balloon. "This was so funny to us because there aren't many things that were hard for her," jokes DiLavore.

Over several years, DiLavore and her colleagues gave Lord lessons, starting with balloons that had already been blown up halfway. She finally got it. "She was so proud of herself," DiLavore recalls with a chuckle. "When I look at the UMACC website now there's even a photo of her blowing up a balloon."

> "Every once in awhile I sit back and say, 'How does she manage all of this?' It's just amazing what one woman can do."
> —Susan Risi

In 1999, Lord combined the two previous versions of ADOS, creating a new one with four different modules based on a child's language ability. This comprehensive version became popular very quickly with other researchers: tens of thousands of people have since attended ADOS training workshops organized by Lord and her staff.

Lord made the kits herself, buying 150 baby dolls at a time from local toy stores, and enlisting her adolescent son to help stuff the kits. "He never let me forget because his fingers hurt from unwrapping those packages," she says, joking.

She is almost finished with the fourth and final version, the 'Toddler ADOS,' which is designed for

non-verbal children whose development is lower than that of a normal 15-month-old. A database of ADOS-tested children that Lord launched in 1990 holds more than 2,000 families. Within it is one group of 14-year-olds that she's been following since age 2. "We can actually use their PL-ADOS data to predict what their behaviors are like now," she says. "It doesn't mean it's perfect, but it works pretty well."

There is only one way Lord can accomplish everything she does, friends and colleagues suspect: she must get very little sleep.

"If you go to work at 8:00 in the morning, she's already written half a chapter and there'd be a handful of messages waiting for you about your data," DiLavore says. "She doesn't give the impression of someone who works all the time, but she certainly fills every moment of her life with her family and her work."

At just after 7 a.m. one Thursday this May, while making a cappuccino in the lobby of her Manhattan hotel, Lord apologized for being four minutes late. Her email client had been down all morning, she explained, preventing her from sending out a new grant proposal to the US National Science Foundation—one she had written earlier that morning.

"Every once in awhile I sit back and say, 'How does she manage all of this?'" says Susan Risi, a clinical psychologist at UMACC who first worked with Lord at the University of Chicago in 1996. Now at UMACC, working under Lord with about 30 other researchers and staff, Risi is still amazed at Lord's administrative abilities.

UMACC was the first of 13 centers to contribute to the Simons Simplex Collection—a shared catalog of the genes, medical histories, and behavioral patterns of 2,000 autistic families. Lord is the principal investigator of the entire project. "It's just amazing what one woman can do," Risi says.

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Alysson Muotri: Audacious plans for brain organoids

BY HANNAH FURFARO / 12 AUGUST 2019

It is nearly sunset, and Alysson Muotri ducks into a small, cluttered room in his expansive laboratory at the Sanford Consortium for Regenerative Medicine in La Jolla, California. An incubator the size of a mini-fridge houses unusual residents—and he wants to make introductions.

"This is the factory of mini-brains," says Muotri, cracking a smile. His colleague holds a glass tray up to the light, and pink spheres the size of caviar whirl into view.

The spheres are 3D balls of human cells, called brain organoids—and Muotri spends his days thinking up ways to use them to study the human brain's complexity.

The cells of these spheres form layers, just as human brains do, and show brain-like activity, passing electrical signals from one cell to the next. But they do not have the anatomical complexity of a real brain. They also cannot think or feel—at least, not yet.

Muotri coaxes stem cells to develop into globes of about 1 million cells of the types seen in the brain. He aims to understand how these quasi-brains mature—and how their patterns of activity match up to those in a human brain. To the extent they do, he hopes to use them to unravel what goes awry in autism and related conditions—and find leads for treatments.

Muotri created his first brain organoids in 2014 with stem cells from the father of an autistic boy. Two years later, he found that organoids made using stem cells from autistic children have different network dynamics than those from neurotypical controls. He has made organoids from

FAST FACTS

Current position: Professor of pediatrics and cellular and molecular medicine, University of California, San Diego
Recent significant work: Trujillo *et al Science* 2021.
Other major accomplishments: Became director of the UCSC Stem Cell Program and Archealization Center
Main areas of interest: Human brain organogenesis, brain evolution, stem cells, gene therapy
Lab URL: muotri.ucsd.edu • **Notable mentors:** Fred (Rusty) Gage, Lawrence Goldstein

cells toting Neanderthal DNA and those infected by the Zika virus. In July, he helped send the first brain organoids to space. The ultimate goal, he says, is to create organoids that can learn.

Some critics contend that Muotri is prone to overinterpreting his data, but most of his colleagues admire his determination to push the limits of this technology, even when that work is controversial.

"His name carries a lot of weight in trying to do things with organoids that no one has yet done," says Ferid Nassor, assistant professor of stem cell and genetic engineering at Institut Sup'Biotech de Paris in France. "He is really trying to push the boundaries with what can be done."

Muotri's steadfast optimism has won over many skeptics, in fact—and won him several awards and many millions of dollars in grants.

Muotri was preoccupied with how things work even as a child. He remembers his "first deep thought," around age 7, when he tried to figure out how a lightbulb works: "My idea was that the lightbulb was not there to send light but to suck up the darkness," he says.

As a teenager in São Paulo, Brazil, he often immersed himself in nature, capturing fireflies in jars so he could "have light forever." He created a time-lapse series of photos of flickering light from fireflies—one of many projects that earned him the nickname 'The Scientist' from family members.

As an undergraduate at the University of Campinas in São Paulo, he excelled in molecular biology, although he was always interested in the brain—and in memory in particular. But Brazil was not a hotbed of neuroscience research, so Muotri studied cancer for his graduate work at the University of São Paulo, picking up the basics of cell biology.

While at the university, Muotri tried to develop a topical gene therapy for xeroderma pigmentosum, a rare skin disease that causes extreme sensitivity to sunlight and often leads to cancer. The project required making models of skin in a dish. He traveled to biologist Alain Sarasin's lab in France in 2001 to learn a technique that involves mixing stem cells from the skin with 'feeder cells' that provide support as the stem cells multiply and produce layers of skin.

But he soon realized that if he wanted to pursue neuroscience, he would need to leave Brazil altogether. In 2002, he joined Fred Gage's team in San Diego, California, a nexus of developmental neuroscience, as a postdoctoral researcher.

"He likes to be out there on the edge," says Gage, president of the Salk Institute for Biological Studies in La Jolla, California.

The transition from skin to brain involved a steep learning curve for Muotri. Besides, embryonic stem cells were in limited supply, as was funding for the research, because of a 2001 federal law that banned public funds for studies using the cells.

At Gage's lab, Muotri's work was confined to a specially equipped room supported by private

donors. The plan was to turn stem cells into neurons, but that was hardly straightforward.

"Nobody knew exactly how to do that," Muotri says. Simply keeping the stem cells alive was a challenge.

After three years of effort, Muotri reported in 2005 that he and his colleagues had transplanted human embryonic stem cells into the brains of mouse embryos. They found functioning human neurons integrated into networks in the newborn mice's brains.

In his haste, Muotri had missed a step: He had not sought approval from the Salk Institute's institutional review board, which vets human research for potential harm. He received a warning.

"This was my first connection with these ethical issues," Muotri says. "I learned two lessons: There were many people angry about these experiments and many people happy about these experiments."

Among the happy people was cell biologist Larry Goldstein, who was convinced Muotri's work would speed up the stem-cell field.

"I've been around the block a few times; I know a lot of scientists, and I know which ones are unusual in their creativity, drive and insight—[Muotri] is one of them," says Goldstein, scientific director of the Sanford Consortium for Regenerative Medicine.

Three years later, Goldstein recruited Muotri to join him at the University of California, San Diego, where he is a professor.

In his new lab, Muotri moved away from embryonic stem cells, and their ethical issues, to a type called 'induced pluripotent stem cells,' which are made using skin and other body cells as a starting point.

In 2010, he reported that stem cells made from the skin cells of people with Rett syndrome, an autism-related condition, generate fewer neurons than those from typical people. One television interview about this work caught the attention of Andrea Coimbra, a Brazilian woman whose son Ivan, then 5, has severe autism.

"I decided to tell him that I was living better after knowing his work and his research," Coimbra recalls. After exchanging emails for a year, Coimbra and Muotri met at a scientific conference in Brazil—and fell in love. They married in 2016.

As he got to know Ivan, Muotri became more and more invested in finding ways to translate his work into therapies for autism.

Organoids and stem cells are not the only tools Muotri is using to study autism and to screen therapies. In unpublished work, he has found differences in neuronal activity in organoids grown from cells with the Rett syndrome mutation. After four months of growth, when the organoids are the size of mustard seeds, their cells show an electrical pattern that resembles one seen in preterm infants. This suggests, he says, that the organoids are good models of human development.

Some researchers say this conclusion is hasty.

"Just finding intermittent activity in the neural networks doesn't mean it's a model of a preterm brain," says clinical neurophysiologist Sampsa Vanhatalo, who led the work on preterm infants.

Muotri shrugs off the criticism. Not only that, he has set his sights on an even more ambitious project: creating an organoid that can learn.

The idea of an organoid learning or having consciousness elicits skepticism from some experts, however.

Suggesting the balls of cells have the ability to recapitulate any kind of complex thought crosses

a line, says organoid expert Flora Vaccarino, professor of neuroscience at Yale University.

But others say that setting such goals pushes boundaries of science in ways that only make science better.

> "I've been around the block a few times; I know a lot of scientists, and I know which ones are unusual in their creativity, drive and insight—[Muotri] is one of them."
> —Larry Goldstein

"As science progresses, it leaves questions that make people think, give people pause," says Hongjun Song, professor of neuroscience at the University of Pennsylvania. "That is very good for the field."

While others debate the merits of his ambition, Muotri is forging ahead. A video stored on his phone features a 1-foot-wide spidery robot cloaked in neon wires scuttling back and forth across a room. Unseen, the robot's biological puppeteer directs its every move: The robot's limbs move in response to a computer which, in turn, receives signals from an organoid in an incubator.

The robot steps at random, often bumping into walls, suggesting that the signals are not coordinated. Someday, Muotri says, he will create organoids that produce meaningful signals. With sensory feedback from the robot (say, from hitting an obstacle), the organoid might alter its firing patterns—'learn,' that is—to direct the robot around the obstacle.

"Maybe he has some kind of trick up his sleeve," says Nassor. "I believe if someone can actually do something like that, it might be in Muotri's lab."

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Charles Nelson: Searching for early signs of autism

BY VIRGINIA HUGHES / 23 JULY 2012

Cross-eyed toddlers running up to strangers with their arms outstretched. A boy with a head as big as a basketball. Another with a narrow head who sits sedated in a chair all day. A 1-year-old child in the body of a 1-week-old. A room full of babies, each lying in a crib and staring at a white ceiling.

This is what Charles Nelson saw in 1999, on his first visit to the eerily silent St. Catherine's Orphanage in Bucharest, Romania.

Nelson knew what to expect before the trip, but was still not emotionally prepared. "It was so heartbreaking," he says. "We had to make a rule that we were not allowed to cry in front of the kids."

Ten years had passed since the execution of Romanian dictator Nicolae Ceaușescu, and his infamous network of state-run orphanages was

FAST FACTS

Current position: Professor of pediatrics and neuroscience; Richard David Scott Chair in Pediatric Developmental Medicine Research, Harvard Medical School, Boston Children's Hospital

Recent significant work: Using electroencephalography, we are inching closer to being able to predict, in early infancy, which children will [be diagnosed with] autism by the time they are 2-3 years old.

Other major accomplishments: Serving as co-principal investigator on the coordinating council of the Healthy Brain and

beginning to disintegrate. As these children came under international scrutiny, the MacArthur Foundation funded the Bucharest Early Intervention Project. Led by Nelson and several other scientists, the longitudinal study would randomly place some children in foster care and then compare their fates to those of children who stayed in the institutions.

Nelson's team found that even when institutionalized children receive adequate food and decent living conditions, their social and physical neglect results in stunted growth, motor delays, anxiety, attention deficit, repetitive behaviors and low intelligence quotients. But they also found an encouraging trend: Many of these symptoms can be at least partially reversed if the children enter foster homes before age 2.

Famous for his sense of humor and easygoing charm, Nelson's personality is a natural fit for interacting with families. The work is an intellectual fit, too. Whether it is studying how infants learn to recognize faces (his self-described obsession), or measuring the brain effects of premature birth or maternal diabetes, Nelson says he has always been fascinated with the question of how early experience alters development.

From his lab at Boston Children's Hospital, he is asking the same thing about autism: How do different risk factors—whether a single mutation, a family history or extreme social deprivation—lead to different manifestations of the diverse disorder?

His strategy is to analyze brain waves in babies with autism syndromes caused by a single genetic glitch, as well as in infant siblings of children with the disorder. He aims to find patterns, or biomarkers, that can predict not only which babies are likely to develop autism, but how severe their symptoms will be and what treatments might work best.

Nelson's scientific curiosity germinated as a child growing up in Long Island, New York, when he and his father dissected roadkill in their basement—despite his mother's exasperation with the smell of decaying flesh. "They were always dead first. I wasn't one of those people who went out and tortured animals," he says with his characteristic grin.

Nelson first became interested in how experience shapes the brain as an undergraduate student in psychology at McGill University in Montreal. But his mentors told him there was no way to study that in people. "The advice I got was, to do neuroscience you're going to have to work with rats or mice," he says.

As it happens, he is terribly allergic to rats, cats and rabbits, and instead decided to study developmental psychology. When he received his Ph.D. in 1981, electroencephalography (EEG)—a technique in which non-invasive electrodes measure brain waves—was just emerging.

"My first epiphany was when I put electrodes on babies' heads and saw their brain activity," Nelson says. "It was like this is what I was meant to do."

In 1986, Nelson launched a lab at the University of Minnesota. Over the following 19 years, he used EEG to show that babies produce different

Childhood Development project; principal investigator on a major new initiative focused on the neural correlates of executive functions in the first 1,000 days, funded by Welcome Leap.

Main areas of interest: Developmental cognitive neuroscience, neurodevelopment and neurodevelopmental disorders

Lab URL: https://www.childrenshospital.org/research/labs/nelson-laboratory-research

Notable mentors: Frances Degen Horowitz , Floyd Bloom, Leon Eisenberg , William Greenough

> “ . . . so much attention has been paid to genetics, and too little to the environment.” —Charles Nelson

brain responses to objects as well as to the faces of monkeys, strangers and their own mothers.

Several of Nelson’s colleagues attribute his success partly to his good nature, rare in academia’s competitive culture.

Sara Webb, who was a graduate student in Nelson’s lab from 1996 to 2001, says she will always remember Nelson’s cheeky contribution to her otherwise stressful dissertation defense.

Webb’s project was about how memory works in the infant brain. “Out of nowhere, Chuck asked me about what type of memory systems his dog had, giving me some illustration of what his dog had just done,” Webb recalls, laughing. “Looking back, it was a fantastic question. For one, it broke the ice. But also, I couldn’t have expected it, and yet I was prepared to answer it.”

Nelson is also known for his openness to collaboration—even when that means sharing preliminary data. “He is extraordinarily kind and non-dogmatic about his science,” says Nathan Fox, distinguished professor of human development at the University of Maryland, who has known Nelson since the early ’80s. “He puts new data out there because he wants people to respond to it and interact with it. It broadens his own thinking.”

In the late 1990s, Fox, Nelson and nine other researchers were part of the MacArthur Foundation’s Research Network on Early Experience and Brain Development. For nine years, the group met a few times a year to share ideas and launch pilot projects. One of these studies investigated the effects of maternal separation on rhesus macaque monkeys.

The results showed that it all comes down to timing: When 1-week-old monkeys are separated from their mothers, they tend to develop severe social deficits. If they are separated when they’re 1 month old, they wind up anxious and nervous, and if at 3 or 6 months, have no problems at all.

In 1999, at Nelson’s request, Dana Johnson, one of Nelson’s colleagues at the University of Minnesota, spoke to the group about Johnson’s work on international adoptions. “He showed us these videos of kids in Romanian institutions, and they looked just like the baby monkeys,” Nelson recalls. “It was really unnerving.”

Inspired, in 2000 the group launched the Bucharest study on the effects of foster care. The years since have seen growing international awareness about the dangers of institutional care, in large part because of the highly publicized sci-

entific reports from the project. "When I travel to other countries, like Russia and China, they're aware of the Bucharest study," says Johnson, professor of pediatrics at the University of Minnesota. "There's been a real change in attitudes."

In 2005, Nelson moved from Minneapolis to Boston and launched an autism research program. Although he had never studied the disorder before, his science had influenced the field a great deal.

Geraldine Dawson, chief science officer of the autism science and advocacy organization Autism Speaks, remembers sitting on a park bench with him one day many years ago in Seattle, discussing how she could apply EEG to children with autism. That conversation led in 2002 to the first EEG study of face processing in children with the disorder, and dozens of others since. "What makes him exceptional is his ability to integrate developmental psychology with basic neuroscience," Dawson says.

His search for brain-based biomarkers in autism is also beginning to bear fruit. In June he reported that brain imaging can distinguish children with the genetic syndrome tuberous sclerosis and autism from those who have tuberous sclerosis alone. And last year he showed that EEG recordings can identify infant siblings of children with autism.

Back at St. Catherine's, Nelson maintains a lab of about ten people who are following the lives of the original group of orphans. Now that those children are reaching adolescence, he says, he wants to find out whether their early social isolation affected their brain development into the teen years, a volatile period even for the most privileged children.

All of his work, Nelson says, suggests that the environment shapes the brain just as much as the genome does. And that has big implications for the autism field.

"The simplistic model that there is a genetic vulnerability, whatever that means, and some environmental hit, whatever that means, is probably the right one," he says. "But so much attention has been paid to genetics, and too little to the environment."

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Brian O'Roak: Bringing his 'A' game to autism genetics

BY SARAH DEWEERDT / 21 JANUARY 2016

Brian O'Roak is rarely seen without a baseball cap. As a postdoctoral researcher, he was known for being intense and focused, sometimes responding to questions with a raised eyebrow beneath the bill of the cap, along with a noncommittal "Hmm . . ."

He may be no less intense or focused these days at Oregon Health and Science University (OHSU) in Portland, where he is assistant professor of molecular and medical genetics, but he's also known as an unpretentious team leader who is willing to get his hands dirty in the lab. In lieu of rolling up his sleeves, he flips his trademark ball cap to the back of his head.

Eric Fombonne, a professor of psychiatry at OHSU who works closely with O'Roak, says he is impressed by his colleague's mission to make an impact on the lives of people with autism. "It's very nice to have a collaboration with a geneticist who is not only brilliant in his work, but is also compassionate and empathic," Fombonne says.

The first in his family to earn a four-year college degree, O'Roak has, at 34, already become a serious player in autism genetics—a field with no shortage of stars. In fact, this die-hard baseball fan is the scientific equivalent of a five-tool player, a baseball player who excels at throwing, fielding and base-running, and hits balls hard and often.

"He knows the big problems, he knows the technology, he's gifted at applying it. And he's really, really good analytically," says Matthew State, chair of psychiatry at the University of California, San Francisco and O'Roak's graduate adviser.

O'Roak's combination of skills has already paid off with some impressive wins, including papers in top journals such as Science and Nature. He has helped to steer some of the largest, most complex studies of autism genetics to date, managing the sequencing and analysis of reams of DNA from more than 2,000 individuals. Colleagues also credit him with the inspiration that many of the genes altered in autism belong to a network involved in DNA packaging.

O'Roak was raised in California's Central Valley

FAST FACTS

Current position: Associate professor of molecular and medical genetics, Oregon Health & Science University
Recent significant work: Large, deep mutation-scanning dataset and clinical implications for autism and cancer risk gene PTEN. We are now developing stem cell/brain organoid models, which is new for the lab.
Main areas of interest: Neurogenomics, neurodevelopment, induced pluripotent stem cells, brain organoids
Lab URL: www.ohsu.edu/oroak-lab • **Notable mentors:** Matthew State, Jay Shendure, Evan Eichler

by a single mother who often drove him and his brother three hours each way to the Bay Area to attend the San Francisco Giants' baseball games. In high school, a charismatic teacher sparked his interest in biology and genetics, and he spent the summer after his sophomore year in the lab of Timothy Ramsay, then at Louisiana State University in Baton Rouge, working with cells from genetically engineered obese mice.

"Nothing I did worked. Everything got contaminated," O'Roak recalls. "But it was still a great experience."

As his high school graduation drew near, O'Roak was unsure what to study in college. Then the nearby Fresno campus of California State University offered him a tuition-free spot in its new undergraduate honors program, an opportunity that O'Roak found impossible to turn down. He joined a plant genetics lab and investigated the molecular genetics of a tiny worm that wreaks havoc on crops.

On his first day at Fresno State, in 1999, O'Roak met his future wife, Erin, a fellow honors student with an interest in business and marketing. The couple married after their junior year.

By his senior year, O'Roak knew he wanted to stay in research, but he wasn't sure what exactly he wanted to work on or where. He applied to several programs, including one at Yale University because his undergraduate advisor, Alejandro Calderon-Urrea, had earned his Ph.D. in biology there. "I had never been to the East Coast and just really had no sense of what that would be like," O'Roak says.

At the time, Matthew State had a lab at Yale and was looking for rare genetic variants associated with a range of psychiatric and neurodevelopmental disorders. O'Roak joined State's lab in mid-2004 and jumped right into one of its trickiest projects.

His colleagues identified a chromosomal rearrangement in a child with Tourette syndrome, a condition characterized by vocal and motor tics, but puzzled over how to determine the significance of the genetic change. "He came up with a lot of the underlying ideas about how we thought about evaluating what we found," says State.

In casual conversation, O'Roak has an easygoing manner and a dry sense of humor. But when talk turns to the details of a scientific topic, he can become intense.

State recalls a series of conversations late that year with O'Roak and Jesse Abelson, another graduate student, as they wrestled with the logic and statistics needed to prove that the gene disrupted by the rearrangement, SLITRK1, can cause Tourette's. "I remember those really vividly because they were some of the most interesting and exciting and challenging interactions that a [scientist] can have with his or her trainees," State says.

The researchers detailed their findings in a 2005 paper in *Science*—O'Roak's first scientific publication. "That kind of set the bar pretty high, I guess, moving forward," he says with a wry grin.

Next, O'Roak got involved in the search for rare genetic variants in a gene known as CNTNAP2. The gene had been linked to autism and lan-

guage impairments, but it wasn't easy to replicate the success of the Tourette syndrome work. DNA sequencing methods at the time were laborious and time-consuming. Despite spending more than two years sequencing the gene in 2,000 people, O'Roak came up with frustratingly ambiguous results.

By 2009, when O'Roak was finishing his Ph.D., sequencing technology began to catch up with his ambitions. That November, he became a postdoctoral fellow at the University of Washington in Seattle, jointly assigned to the labs of Evan Eichler, a geneticist, and Jay Shendure, who develops tools for analyzing genomic data. There, O'Roak used the new faster and cheaper methods to sequence the protein-coding regions of the genome, or exomes, in families affected by autism.

As a trial run, O'Roak deciphered 60 exomes belonging to 20 children with autism and their unaffected parents. Four of the children had *de novo* mutations—genetic aberrations not inherited from either parent — that could potentially explain their autism. O'Roak and his colleagues reported the results in a 2011 paper in *Nature Genetics.*

The finding hinted that *de novo* mutations contribute to autism, and that exome sequencing is a good way to find them. So O'Roak and his colleagues scaled up their efforts, decoding exomes from 209 families affected by autism.

As he was connecting genetic mishaps to autism, O'Roak was also forging human ties. "He was kind of a glue between our lab and Evan's lab," Shendure says. "There are a lot of friendships and collaborations there that I think were really made possible by having him as that kind of common ingredient."

He was also good at making molecular connections. At first, he says, he was "somewhat naïve," assuming that all of the *de novo* mutations would land in a small set of genes. Instead, the mutations turned out to affect dozens of genes, rarely striking the same one twice.

As O'Roak read up on each of these genes, however, connections emerged. "Very strangely, I kept coming across the fact that gene A binds to gene B, and then later on I'd be reading about gene C and it would say it binds to gene B," he says. He recalls thinking, "Hmm, that gene kind of seems familiar."

This led O'Roak to wonder whether autism-linked mutations affect a large number of proteins that interact in a network—in particular, one that governs the packaging of DNA, a process known as chromatin remodeling.

Eichler was skeptical. The literature on protein-protein interactions is notoriously unreliable —incomplete and rife with purported connections between proteins that don't really interact.

What's more, at the time, most autism researchers were focused on synapses—the junctions between neurons. The idea that defects in DNA packaging might be important in the condition came out of left field.

Undaunted, O'Roak persevered in his theory. As he and his colleagues sequenced more exomes, they were able to show that only the people with autism in their study, and not those individuals' siblings or parents, may have mutations in DNA-packaging genes. "I think that one of the most innovative things that he did when he was working in the lab is this idea of the pathways," Eichler says.

The results of this second exome sequencing study were published in the April 2012 alongside two other related papers in *Nature*. The trio of studies blew open the field by suggesting that there might be hundreds of genes involved in autism.

Eight months later, the researchers published a still larger study in *Science* in which they looked for *de novo* mutations in 44 genes in 2,446 individuals with autism. "That was a busy year," says O'Roak, who also welcomed a baby boy in May 2012.

For the *Science* study, O'Roak drew on a technology known as a 'molecular inversion probe' that Shendure's lab had developed but rarely used. The technique allows researchers to rapidly home in on and 'resequence' specific genes in a large number of individuals.

"That's something that Brian basically brought back from the dead in my lab, and turned it into a really scalable platform," Shendure says. "And that continues to be used in my lab and Evan's lab and other labs around the world."

Using the technique, O'Roak and his colleagues uncovered 17 severe *de novo* mutations, all but one of which affect genes in the chromatin remodeling network, confirming the importance of the network in autism.

The elegant work has made a mark even outside of autism genetics. "I started thinking about ways I could apply the same approach," says Aaron Gitler, associate professor of genetics at Stanford University, who studies the genetics of neurodegenerative diseases.

In 2013, O'Roak landed a faculty position at OHSU, where he continues to develop technologies to aid his hunt for mutations. He's also working to parse the function of autism risk genes, aiming to eventually turn these insights into targeted treatments for autism.

In his free time, O'Roak brews beer and plays Gaelic football, a fast-paced mashup of sports that resembles rugby. "I haven't sequenced my genome yet, but we definitely confirmed my Y chromosome was Irish when I was in Matt's lab," he quips.

Free time is scarce, however, and it's about become more so: O'Roak and his wife are expecting another baby in February.

It isn't easy to balance the demands of a growing family with those of a growing lab. O'Roak compares leading a lab as a young principal investigator to shepherding an underdog baseball team. He embraces baseball's 'moneyball' approach, which involves the use of rigorous but unconventional statistics to identify passed-over players with promise—and to build a winning team on a budget. "How do you find really talented people who may have been overlooked by others?" he asks. He may have some perspective here: O'Roak was exactly that kind of player not long ago.

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Sergiu Pasca: Scientist at play

BY SARAH DEWEERDT / 19 FEBRUARY 2015

Sergiu Pasca set up his first science lab at the age of 11, in the basement of his parents' 150-year-old house in Aiud, Romania. At an age when most children want to play sports or hang out with friends, Pasca's chosen pastime looked a lot like work—but Pasca could hardly tell the difference.

"I was getting all kinds of reagents from wherever I could," says Pasca, now assistant professor of psychiatry and behavioral sciences at Stanford University in California. "Of course, the first thing that I wanted to make was gunpowder."

Those preadolescent chemistry experiments set the stage for his future. In his final year of high school, Pasca won a national chemistry prize—a prestigious award that came with a full scholarship to any university in the country. This accolade was just the first of many. At 33 years old, Pasca is already the recipient of at least a dozen scientific prizes and the author of just as many publications, including a paper that made the cover of *Nature Medicine* when he was still a postdoctoral fellow. That work, conducted in Ricardo Dolmetsch's lab at Stanford, debuted the first model of autism built from neurons made from people with the disorder. The feat opened a new avenue for teasing out the biochemical underpinnings of specific forms of autism.

Yet Pasca's trajectory has been an untraditional one. "He was an M.D. who had very little real lab experience," says Dolmetsch, who is now global head of neuroscience at the Novartis Institutes for BioMedical Research in Boston. "But what he had to make up for it was a real passion for autism and the [people with autism] that he knew."

Pasca was born in 1982, about six years before the collapse of Communism in Romania. He remem-

FAST FACTS

Current position: Uytengsu director of Stanford Brain Organogenesis and professor of psychiatry and behavioral Sciences, Stanford University

Recent significant work: The profile was done as I was starting my lab; since then, we have introduced instructive signals to generate organoids resembling multiple domains of the nervous system, pioneered the development of assembloids, and developed models of disease, evolution and injury to the nervous system.

bers televised broadcasts of hours-long speeches on the country's greatness by dictator Nicolae Ceausescu, and nightly blackouts during which his mother, a schoolteacher, would read to him by candlelight.

Pasca's family valued learning and he himself doggedly carried that banner. He sat for the grueling chemistry exam several years in a row, gradually working his way up from a classroom prize to a national one. Even today he carries himself with a confidence born out of hard work rather than cocky self-regard.

"The truth is, I don't think I was very good," Pasca says of winning the chemistry prize. "Actually, I failed repeatedly."

Pasca was the first member of his family to attend college. (His sister, six years his junior, followed in his footsteps to become a psychotherapist for children with autism.)

From the spoils of his chemistry award, Pasca attended a six-year program to get his M.D. at Iuliu Hatieganu University of Medicine and Pharmacy in Cluj-Napoca, Romania. As a busy medical student there, he begged his biochemistry professor, Maria Dronca, to let him help her with research. Dronca told him he could join her team if he got the highest marks in his first year of medical school, a stipulation that didn't faze Pasca.

From Dronca, Pasca learned a strategy that would be key to his success: to balance what is necessary with what is possible. The two of them spent long hours reading papers and "thinking about what we could do.

Not just what would be an interesting question, but what we could do with what we had," Pasca says. "I think that was actually quite useful, when I look back on it."

Their initial plan was to study heart disease. But they realized that such a common condition would require huge numbers of people to yield significant results. Funding was scarce in post-Communist Romania and Dronca was using her own salary to buy research supplies, so their sample size would have to be quite limited. Those concerns led them to autism, which was then considered rare in Romania.

They managed to recruit 12 children with autism, and tested their blood for elevated levels of an amino acid called homocysteine, an indicator of possible metabolic problems that could affect the brain. They found that the children with autism had higher levels compared with the nine typically developing controls. They soon expanded their study, recruiting dozens more children with autism and broadening their search to include other blood-borne chemicals that might indicate metabolic differences in autism.

Over the course of the study, Pasca got to know many parents of children with autism. Some blamed themselves for their child's condition, and most were desperate for help. "It was so frustrating for me as a physician-in-training to see how little you could do for these patients," he says. Meeting those individuals cemented his drive to figure out what causes autism and to find better treatments.

Pasca also made a difference to the families

Main areas of interest: Modeling of human brain development and disease
Lab URL: www.pascalab.org • **Notable mentors:** Ricardo Dolmetsch

“His presence in our life truly changed the course of my son’s evolution,” says Dragu, a former journalist who is now the coordinator of an autism resource center in Romania. “Finding that lab scientists also have hearts and really care about their subjects is a huge help at a psychological level.”

he met, says Ana Dragu, who sought Pasca’s help in finding interventions for her son Eduard, or “Dudu,” who has autism.

“His presence in our life truly changed the course of my son’s evolution,” says Dragu, a former journalist who is now the coordinator of an autism resource center in Romania. “Finding that lab scientists also have hearts and really care about their subjects is a huge help at a psychological level.”

Soon after Pasca finished medical school in 2007, researchers developed induced pluripotent stem (iPS) cell technology, which enables scientists to reprogram skin cells into any type of cell in the body—including neurons. At the time, Dolmetsch had begun to experiment with stem cells with an eye toward probing the origins of autism.

Once again, however, Pasca’s path was not easy. Dolmetsch wanted Pasca to secure his own research funding—an unlikely feat for a foreign student, especially one from an isolated country such as Romania. Pasca applied for grant after grant, fellowship after fellowship—until he got one.

Many researchers were skeptical that such a complex brain disorder could be modeled in a dish and doubted that abnormalities seen in people would persist in the reprogrammed stem cells. Pasca was undeterred.

“Sergiu was willing to bet his career on it,” says Kristen Brennand, assistant professor of psychiatry and neuroscience at the Icahn School of Medicine at Mount Sinai in New York, who uses iPS cells to study schizophrenia.

Pasca and his colleagues chose to study Timothy syndrome—a rare disorder caused by a single base change in a gene called CACNA1C, which causes heart abnormalities, intellectual disability and, usually, autism. The mutation affects a calcium channel—a protein the Dolmetsch lab had both the tools and expertise to study. In this way, he could look at one cause of autism through a narrow lens.

Over time, Pasca became an expert at conjuring neurons from iPS cells—a weeks-long process that involves dosing dishes of cells with different cocktails of chemicals at precise times. At one point he managed to have 15 different cell lines in various stages of development at once, Dolmetsch recalls.

In his *Nature Medicine* cover story in Novem-

ber 2011, Pasca unveiled the first proof that iPS cells can be made to recreate some of the characteristics seen in people with neurodevelopmental disorders. The researchers reported that neurons derived from the iPS cells of people with Timothy syndrome show the overactive calcium signaling that is known to be a consequence of the mutation.

The team later uncovered details about how this simple mutation leads to complex changes in the cells, hinting at how it can result in a multifaceted disorder such as autism.

Now in his own lab, which opened last May, Pasca continues to work with iPS-derived neurons from people with autism-related disorders, including individuals with Timothy syndrome and those who carry deletions of the chromosomal region 22q11—a genetic defect that leads to autism in perhaps 20 percent of cases.

Acknowledging the limitations of producing a single layer of neurons in a dish, he has developed a way to coax iPS cells to differentiate into neurons that grow in spheres, more accurately modeling the layered structure of the brain's outer rind. His method is not yet published, but Pasca says it yields more mature cells than did past efforts to culture neurons from iPS cells, either in a single layer or in three dimensions.

Pasca continues his scientific tinkering as if he has no need to do anything else. "I don't think he's ever been sighted outside the lab," says Ben Barres, professor of neurobiology, developmental biology and neurology at Stanford. Barres is collaborating with Pasca to generate star-shaped brain cells called astrocytes from people with autism.

The natural comingling of work and play in Pasca's life brought Anca, now his wife, to the young man's attention during microbiology class in their second year of medical school. Anca is currently a neonatology fellow at Stanford and does research in Pasca's lab, appearing as a coauthor on many of his papers. A photo on the lab's website shows the couple's almost-2-year-old son, Darius, perched atop a lab bench, playing with a pipette.

Pasca says Darius sees the lab as "a playground," and it's clear that discovery in the lab remains a primary source of pleasure for Pasca as well. "If I could just take one form of autism and figure out the really detailed signaling mechanisms and find a target and find the small molecules and maybe bring that to the clinic," he says, "then I think I would feel happy."

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Lucia Peixoto: Breaking down the interplay between sleep and autism

BY ANGIE VOYLES ASKHAM / 9 MAY 2022

Lucia Peixoto vividly remembers how she felt when she gave her first academic talk.

It was September 2006, and she had traveled to Woods Hole, Massachusetts, as a graduate student to present her work on the genetics of the parasite *Toxoplasma gondii*. Her lab mates at the University of Pennsylvania attended this meeting for parasitologists every year, and she was proud to get to share her work there, too.

Peixoto had always been comfortable in front of a crowd and understood English, but, having grown up in Uruguay, she primarily spoke Spanish. To prepare, she put in place a series of practice sessions, drawing on the determination and focus she had honed as a competitive volleyball player in high school. She rehearsed her slides with her adviser, biologist David Roos, poring over the details and discussing exactly what to communicate.

As Peixoto stepped onto the stage at the meeting, she felt a familiar thrill—excitement, adrenaline—the same rush she had experienced at the start of a big volleyball match. "You train, you train, you train, and you go play that important match in the finals," she says.

It was an easy ace: She won the "Best Student Talk" award and, with it, the opportunity to present her work at a larger conference later that year.

Peixoto's instinct to break down a challenge and drill the component skills has continued to serve her well as an autism researcher. Now age 43 and assistant professor of translational medicine and physiology at Washington State University in Spokane, she is busy laying the groundwork to serve up a better understanding

FAST FACTS

Current position: Assistant professor of translational medicine and physiology, Elson S. Floyd College of Medicine, Washington State University
Main areas of interest: Sleep, learning, chromatin/transcriptional regulation
Lab URL: https://labs.wsu.edu/peixoto-lab/ • **Notable mentors:** Ted Abel

of the interplay between sleep and brain development. Her research on a mouse model of autism, for example, has provided some of the earliest evidence that sleep disruptions in the condition have a genetic basis.

"She thinks so deeply about what you can really learn from animal models when you're trying to study autism," says fellow sleep researcher Matthew Kayser, associate professor of psychiatry and neuroscience at the University of Pennsylvania in Philadelphia.

For all her drive, Peixoto is also a true team player, supportive mentor and a champion for increased diversity and inclusivity in science, her colleagues say. She doesn't shy away from discussing the difficulties she has faced as a woman in science "and why she wants to support the next generation," says Elizabeth Medina, a third-year graduate student in Peixoto's lab.

Propelling Peixoto forward is the knowledge that, whether on the court or in the lab, success rarely springs from luck alone, she says. "There is always work involved."

Peixoto was born in Montevideo, Uruguay. Her father worked as an economist and her mother trained as an architect but did not practice much after the birth of Peixoto's younger sister, who has Down syndrome. "Taking care of my sister took a lot of her time," she says.

Peixoto did well in high school and loved the idea of helping people, so she decided to train for a career in either science or medicine. She enrolled in an undergraduate program at Universidad de la República in her hometown in 1997 and soon joined a biochemistry lab, giving her an early taste of benchwork.

At a scientific conference in Uruguay in 2001, she met her future husband, Marcos Frank, then a postdoctoral researcher studying the role of sleep in visual development. "We have the geekiest meetup story," she says. She asked him a question about his talk, and they kept in touch and both moved to the University of Pennsylvania two years later.

There she pursued a Ph.D. in biology, focusing on genomics and computational biology, inspired by advances in genome sequencing that she had learned about in college. "I thought, 'This genome thing is going to be something,'" she says.

Within genomics, she had initially decided to focus on infectious diseases—something that particularly affects South America. But after earning her Ph.D. in 2009, she decided instead to study conditions like her sister's and applied to a postdoctoral training program in neurodevelopment at Children's Hospital of Philadelphia (CHOP).

"We had to give her bad news," says Mike Robinson, professor of pediatrics at CHOP, who led the training. Peixoto's Ph.D. work was under review at a journal but not yet published, making her ineligible for the program. The paper was expected to make a splash, though, and so Robinson met with her and encouraged her to reapply once the work was officially out—which she did. Robinson admitted her later that year.

"She's passionate for the science that she's doing and passionate for the goals that she has,"

Robinson says. "That's infectious."

With the program's funding, Peixoto took a postdoctoral position in Ted Abel's lab, then housed at the University of Pennsylvania. The lab was studying how the neural mechanisms of learning and memory falter in animals that model autism and other neurodevelopmental conditions. Abel brought Peixoto on to evaluate how learning and sleep deprivation affect the animals' gene-expression patterns, using next-generation sequencing technology.

Peixoto says she initially felt out of place in the Abel lab. "I had never touched a mouse in my life! I was the most inexperienced person. I got bitten a lot."

But again, she trained. After about six months of practice—with coaching from more senior lab members—she honed her handling techniques. And when it came time to interpret her data, her experience studying gene expression in parasites proved beneficial, Robinson says. The skills she had refined working in a simple system were directly applicable to the more complex animal model.

Still, Peixoto couldn't shake the idea that before she tackled atypical development, she needed to master the "fundamentals" of typical development. "Coming from a background of genomics, I felt like we didn't know enough about baseline," she says. "So, I spent most of my postdoc thinking about how learning and memory regulate gene expression" in wildtype mice.

Peixoto and her colleagues discovered that different histones—the proteins that help package DNA into the nucleus in the form of chromatin—are expressed differently after wildtype mice form new long-term memories. Her team also pinpointed how gene expression fluctuates in mice after they learn to associate a sound with an electric shock. The work elucidated molecular pathways that spring into action to store different types of memories to help a mouse learn.

After presenting some of her postdoctoral research at a conference, Peixoto met Geraldine Bliss, president of the nonprofit organization CureSHANK, whose son has Phelan-McDermid syndrome, an autism-related condition caused by mutations in the SHANK3 gene. Peixoto was surprised to find out that Bliss and other parents in the organization were more concerned about the condition's effect on their children's sleep than on learning and memory.

That conversation and several others like it eventually persuaded Peixoto to again pivot her research focus. "I understood the journey of having a child that is different, and the challenges that that brings," she says, referring to her mother's experience raising her sister. "So I always wanted to work on something that really mattered to parents."

In 2015, Peixoto started her own lab at Washington State University to probe how genetics shapes sleep in neurodevelopmental conditions. Her husband, who now collaborates with her, had started his own adjoining lab at the university the year before.

Peixoto began studying mice with a mutation in SHANK3. The animals have trouble falling asleep, as children with Phelan-McDermid syndrome do, and the mutation seems to be the cause, she and her team reported in 2019. The discoveries relied on detailed characterizations of sleep patterns and circadian rhythms in mice and people to ensure the team was measuring the same thing across species, Kayser says.

During the pandemic, Kayser and Peixoto began hosting joint lab meetings, he says. During one virtual session, she and her colleagues discussed how they had recorded electroencephalography signals from wildtype and SHANK3

mice at different ages, revealing how the animals' sleep changes throughout development and how the mutation affects that development.

"Those are painstaking experiments in a mouse," Kayser says—in part because some of the experiments need to be run at the crack of dawn when mice naturally go to sleep. How much sleep an animal gets after learning something new or what time of day they are tested can sway an experiment's results, Peixoto's group and others have found.

For all her careful work in mice, Peixoto has a deep concern for how her findings apply to people, her colleagues say.

Other researchers often manipulate a gene associated with the human disease and call it a model, Kayser says. "But [Peixoto] puts so much rigor into making sure that that's really a valid model, and that it's going to be useful for understanding mechanisms."

After Peixoto read a study on sleep in autism, she reached out to the lead investigator, Annette Estes, professor of speech and hearing sciences at the University of Washington in Seattle, and the pair started collaborating on a grant proposal. "She doesn't want her work, I think it's fair to say, to only be about mice," Estes says. "She wants it to connect to clinically meaningful questions and outcomes."

As part of connecting her work to people, Peixoto also spends time thinking about how to increase racial and ethnic diversity in academia. She has served as co-chair of the Equity, Diversity and Inclusion Committee of the International Society for Computational Biology since 2019, and she regularly tweets about how existing biases harm the future of research.

Medina, who is her first graduate student, and whose parents immigrated to the U.S. from Mexico, says she appreciates that Peixoto understands what it's like to be a woman in science from an underrepresented background. "I feel comfortable having her in my corner," Medina says.

As a mentor, Peixoto also talks about the importance of 'work-life balance,' although she hates that particular phrase: "My work is not the opposite of my life!" she says. Instead, she refers to the challenge as a "juggle of priorities."

Like every challenge, she builds on fundamentals. Living in Spokane, a location that is "close to nature," affords a slower pace of life and helps her manage that juggling act, she says. And now that knee injuries have put her volleyball days behind her, she tries to squeeze in 30 minutes of exercise each day—from hiking to yoga—sometimes alongside her son and daughter.

Yoga in particular, she says, gives her the chance to let her perfectionism slide. "It's not going to be the perfect yoga practice" when a 6-year-old is involved, she says. "But it's better than no yoga practice."

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Additional I – P Profiles

Shafali Jeste:

Early autism meets its match

https://www.spectrumnews.org/news/profiles/shafali-jeste-early-autism-meets-its-match/

Warren Jones & Ami Klin:

Melding art and science for autism

https://www.spectrumnews.org/news/profiles/ami-klin-warren-jones-melding-art-and-science-for-autism/

Patricia Kuhl & Andrew Meltzoff:

Joint attention to mind

https://www.spectrumnews.org/news/profiles/andrew-meltzoff-patricia-kuhl-joint-attention-to-mind/

David Mandell:

How losing a parent helped shape Mandell's approach to autism research

https://www.spectrumnews.org/news/profiles/how-losing-a-parent-helped-shape-david-mandells-approach-to-autism-research/

Kevin Pelphrey:

Charting the course of the social brain

https://www.spectrumnews.org/news/profiles/kevin-pelphrey-charting-the-course-of-the-social-brain/

Benjamin Philpot:

Managing risks to reap big rewards

https://www.spectrumnews.org/news/profiles/benjamin-philpot-managing-risks-to-reap-big-rewards/

Tim Roberts: Sounding out a signature for autism

BY JESSA NETTING / 24 OCTOBER 2013

It's about 10 a.m. on a warm August day and Tim Roberts is already in full-throttle public-speaking mode. His shock of blond hair—and the espresso he immediately brews in his desk-side machine—only heighten the intensity he radiates.

Roberts is a gifted speaker, and a reflexive educator, whether breaking down medical concepts to a group of physicists, clinicians, grade-school children or a visiting reporter. He's also warm and funny, with a disarming British wit employed chiefly to poke fun at himself.

He needs this energetic persona to tackle his ambitious list of projects. At the Children's Hospital of Philadelphia, where he is vice chair of pediatric radiology, his work knits together physics, neurology, computing, autism, epilepsy and linguistics. He is integrating these disparate fields to try to unravel the neurological basis of hitches in language processing, a hallmark of autism.

The goal, he says, is to identify a telltale signature, or biomarker, for autism, which would help doctors spot and treat the disorder early.

"This biomarker work is leading us toward not really personalized, but stratified therapies," Roberts says. By that, he means that biomarkers might help identify subtypes of autism with various biological origins, which might each call for a different treatment approach.

This sort of multimodal thinking is rare among scientists, notes Howard Rowley, professor of radiology, neurology and neurosurgery at the University of Wisconsin, Madison and Roberts' longtime collaborator and friend.

"[Roberts] is a translational medical practitioner, a scientist who helps bring ideas into practice," says Rowley. "That's his signature; that's his gift, where he has impact and will have a lasting impact."

For his work on autism, Roberts relies on novel

FAST FACTS

Current position: Professor of radiology and Oberkircher Family Chair in Pediatric Radiology, Children's Hospital of Philadelphia, University of Pennsylvania

Recent significant work: MEG-detected Auditory Evoked Response Latencies Prolonged in ASD, Roberts *et al. Autism Res.* 3: 8-18. 2010 doi: 10.1002/aur.111

and retooled magnetic encephalography (MEG) and magnetic resonance imaging (MRI) machines. While MRI gives a snapshot of brain structures using radio-wave pulses and a magnetic field, MEG captures the electrical activity of neurons by measuring the magnetic fields they produce over time, on the order of tens of milliseconds.

In 1999, Roberts and his team used MEG to show for the first time that the brains of children with autism lag behind those of their peers in response to tones they hear. Later, they quantified this delay for vowel sounds to about 50 milliseconds. A delay in processing one vowel sound could interfere with the next, piling up like train cars to derail a whole sentence.

"With MRI, there are various software packages for analysis and for delivering stimuli—it's in some ways more turnkey. But for MEG, you really have to know how the machines work and the physics in order to get the results," says Ted Abel, professor of biology at the University of Pennsylvania. "What's impressive to me about Tim is his energy for it all."

In the past few years, Roberts and his collaborator Steven Siegel have documented this same kind of hearing glitch in several animal models of autism.

Siegel, a self-described "schizophrenia guy," says Roberts was a gracious and enthusiastic tutor of autism. "He is a bridge to the other communities, and he brought my lab and division to autism," Siegel says.

Roberts' attention to detail is apparent in the rooms he has set up for his experiments. For example, two of the lab's three extraordinarily sensitive MEG instruments are in what he calls "the quietest room in the hospital," a custom-built fortress against wayward magnetic signals.

The room is entirely encased in sheets of aluminum sandwiched between two layers of Mu-metal, a nickel-iron alloy that attracts and captures magnetism. "We planned for this seven years ago," says Roberts. "This is the largest magnetically shielded room, I believe, on the planet."

If they weren't in this shielded environment, the instruments could capture a magnetic signal several miles away. Even within the room, the sensors can pick up the magnetic signal of a mother's beating heart if she hovers too close to her child in the scanner.

And yet, it looks much like a child's bedroom, with cameras hidden beneath friendly sea creatures, wires concealed in the floor and cables nested inside cabinets cleverly disguised as a chest of drawers. A plush frog holds 'MEG dollars' in its mouth, premiums for the children's cooperation in putting on their pajamas or lying quietly in the machine. Even the two MEG instruments are entirely encased in curving white plastic that gives one the look of a giant cartoon microscope and the other a sort of small clown car.

"The point is, we've got all this super technology, but it's all worthless if we can't get the child to go anywhere near it," says Roberts.

The book that prepares children for the study introduces the two machines as "Max the MEG and his little brother." But inside 'Max' are 275 magnetic field detectors, arrayed on the inside of a small dome that fits the heads of 97 percent of people.

Main areas of interest: magnetoencephalography/diffusion tensor imaging/magnetic resonance spectrography in autism and neurodevelopmental disorders • **Notable mentors:** Laurie Hall, Mike Moseley

"[Roberts] is a translational medical practitioner, a scientist who helps bring ideas into practice. That's his signature; that's his gift, where he has impact and will have a lasting impact."
—Howard Rowley

The heads of children aged 3 or younger are generally too small for these machines, so most labs scan only older children. But Roberts was insistent that the lab acquire a baby MEG, so that the team could study the brains of children at just the age when language is seeding in the brain.

Three years in the making and custom-built by a firm in San Diego in close consultation with Roberts, the baby MEG has 123 detectors squeezed into its smaller helmet. "It's North America's first and, one could argue, the world's first dedicated infant MEG scanner," Roberts says.

Roberts' first full exposure to imaging equipment was a far cry from the fortress of quietude he has set up. As an undergraduate at Cambridge University in the United Kingdom, he had managed to spice up his restrictive schedule of mathematics, physics and chemistry with courses in cell biology, an unheard-of addition.

But Roberts found himself underwhelmed by his choices for an undergraduate research project, a roster heavily weighted with diode or liquid crystal experiments. "That list of projects, I'm not going to say it's on stone tablets, but it's pretty old," he recalls.

And again in graduate school, only one project that seemed novel and had a biological element intrigued him: Laurance D. Hall, professor of medicinal chemistry at the university, had amassed a graveyard of dead machines, which his lab was supposed to fix and improve. The students worked alongside medicinal chemists in a lab housed in the school of clinical medicine, applying principles of physics and engineering to MRI scanners.

"This is the birth of Tim: the multimodal, interdisciplinary, not-quite-fitting-in-anywhere scientist," Roberts says.

Roberts eventually went to the University of California, San Francisco to work as a postdoctoral fellow in the lab of Michael Moseley, now

at Stanford University and an MRI pioneer. Roberts then got a chance to work on MEG when the department got a loaner machine to evaluate its applicability for clinical research.

This was in the early 1990s, when no one knew much about MEG's capabilities, and Roberts and Rowley—who first met at that time—lurched from one project to another, at one point attempting presurgical mapping of tumors with MEG and at another trying to trace the origin of nausea in the brain. The latter involved their donning prism glasses from the National Aeronautics and Space Administration, spinning in a chair and getting violently ill. (They decided they had had enough of this line of inquiry after one publication.)

Over large amounts of sushi and sometimes copious quantities of beer, Rowley came up with clinical questions and Roberts generated ideas for solving them using MEG, MRI or other imaging tools.

"[Roberts] is exceptionally brilliant," Rowley says. "He's able to keep all that in his mind and make the kind of connections that others simply can't make."

Not long after that, Roberts became interested in the neural correlates of language. His work on the brain's response to pitch caught the attention of Eric London, founder of an autism advocacy group. Cruising by Roberts' poster at a Society for Neuroscience meeting in the late 1990s, London asked Roberts, "How much do you know about autism?" Roberts recalls, and told him to apply for a grant.

Roberts immediately saw this would be a way to make his research useful, using a superbly sensitive technology to investigate a key feature of a disorder. "It was turning autism on its head," says Roberts. "Instead of going to the behavioral endpoint of autism—the result—the clinical exam tells you all the things that are going wrong [in the brain]."

Since then, Roberts hasn't stopped moving, combining that intense energy with compassion for patients and a lecture schedule that takes him all around the country. "If I were not a scientist," he says, "I would write books on how to navigate airports and frequent-flyer programs."

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Stephan Sanders: Accidental geneticist

BY APOORVA MANDAVILLI / 6 NOVEMBER 2014

In May 2009, about 20 of the brightest minds in autism genetics gathered in Chicago. The goal was to figure out how to handle the reams of data emerging from big sequencing projects.

In this assembly of bigwigs, Stephan Sanders, a neophyte, steered the discussion.

"At first I thought, 'Who is this brash young man?'" recalls Bernie Devlin, professor of psychiatry and human genetics at the University of Pittsburgh. "But he led the meeting with aplomb, and by the end convinced me that this was someone who deserved respect and who could be a great researcher."

Even now, Sanders is often the youngest researcher at power-packed conferences. But at 35, he is already credited with bringing a measure of clarity to autism genetics. Working with his advisor Matthew State, Devlin and other stalwarts, he has developed tools to sift through the sea of sequences pouring in and pin down mutations that lead to autism.

As if that were not compelling enough for a resume, Sanders is also a pediatrician and co-author of a series of bestselling how-to books for medical students in the United Kingdom. He has served as an expedition medicine expert, leading troops of teenagers into the Andes, Patagonia and Tanzania for a BBC television series. And he is an avid mountaineer, hiker, bicyclist, boater and enthusiast of sundry other outdoor pursuits.

By all accounts, he is good at everything he sets out to do, and a thoroughly nice fellow to boot.

"Stephan is the complete package," says State. "I fully expect him to be one of a handful of people moving this field forward."

Most recently, as assistant professor of psychiatry at the University of California, San Francisco—a status so new that he has neither a lab nor a team—Sanders is exploring the reasons for autism's gender bias.

What makes autism so compelling, he says, is

FAST FACTS

Current position: Professor of paediatric neurogenetics, Oxford University, Institute of Developmental and Regenerative Medicine
Recent significant work: Identifying numerous genes associated with autism
Main area of interest: Autism genetics and neurobiology
Lab URL: https://sanderslab.github.io • **Notable mentors:** Matthew State

this link to bigger questions of difference: between men and women, between well and unwell. "Why do humans get ill? Autism is a really good entry to that issue," he says. "It's a really important model for understanding complex diseases."

Before Sanders was a graduate student in State's lab, he was a postdoctoral fellow—yes, you read that right.

Sanders was a doctor in the U.K. in 2007 when his wife, art historian Imogen Hart, won a postdoctoral fellowship at the Yale Center for British Art. He dutifully followed her to New Haven, Connecticut without a plan for what he would do next.

Hart's boss happened to live next door to Rick Lifton, chair of Yale's genetics department. That eventually led Sanders to poke his head into the State lab, even though he had no background in human genetics.

Somewhat serendipitously, State had seen Sanders in a number of his adrenaline-filled televised expeditions, and meeting him in person only reinforced State's sense of him as an unflappable person.

"He definitely gave the impression that he could take on and tackle pretty much anything without getting the least bit flustered," State says. One expedition into Patagonia later, Sanders joined the State lab as a postdoc in February 2008.

A year earlier, researchers at Cold Spring Harbor Laboratory in New York had reported that people with autism are especially vulnerable to massive mistakes in their genomes, with entire chromosomal chunks either missing or multiplied. (This was a landmark paper in autism, and has since been soundly validated.)

But the data on these so-called copy number variations (CNVs) is extremely noisy because people who have no obvious symptoms can also harbor them. It was clear that to find a signal, researchers would need to muffle the noise.

Chris Mason, another postdoc in the State lab, showed Sanders a few lines of computer code aimed at doing just that. To most biologists, the code was completely foreign and impenetrable. To Sanders, it was a revelation. "It was like discovering a language I had always known," he says.

Within weeks, Sanders mastered coding and started to sift through the copy number data. He and Mason together developed CNVision, a program that cleans up raw data to reveal clear, annotated CNVs. They used the program to confirm a region on chromosome 16 implicated in the landmark paper—a rare feat in science. "To actually see something which someone else has found and independently to verify it, that was absolutely fantastic," he says.

They also implicated a slice of chromosome 7 that is key in the autism-related disorder Williams syndrome.

The team began sequencing the exomes—the genomic units that comprise the code for all genes—of hundreds of people with autism and their unaffected family members. Two years ago, they estimated that autism risk is expansive, with

contributions from nearly 1,000 genes. Last week, based on an analysis of more than 2,500 families, they homed in on 27 of the most likely culprits.

At some point in the course of these trailblazing studies, Sanders decided that he would benefit from formalized training in genetics and enrolled in a Ph.D. program.

"It was a unique situation, where in my second year of grad school, my postdoc mentor became a grad student," says Jeremy Willsey, now a postdoc in State's lab. But Willsey still looked to Sanders for advice and direction in the lab and beyond. Following Sanders' lead, he even switched his choice of caffeinated beverage from coffee to Diet Coke.

Sanders' foray into genetics wasn't entirely accidental. As a pediatrician, he always wanted to understand why some children had developmental delay or language problems. "I think there's a benefit in parents knowing that, because there's a natural degree of blame that goes on there, and actually being able to understand that can be therapeutic," he says.

He brings this same empathy and broad perspective to his interest in autism's gender bias. Autism is diagnosed in four times as many boys as girls. But there are big, unresolved questions about whether this ratio is accurate and whether and how the disorder manifests in men versus women.

This dovetails nicely with Sanders' wife's interest in art and feminism—although in feminism, as he notes, the impetus is usually to minimize the differences between men and women. One leading model holds that women are protected from autism because they can tolerate more mutations.

But if this theory should prove to be limited, Sanders is ready to change course. "There are times when you have to accept this is a problem, where I just do not have the data or the ability to address this," he says.

In April 2003, Sanders was climbing in the Himalayas when he realized his ice screws—his only tether to the mountain—were unsuitable for the deep snow. He was tired and hot, and his glasses were foggy. His climbing companion wanted to keep going, but Sanders decided to stop.

"I had this revelation that I really didn't need to get to the top that much," he says. "I was sitting there and enjoying the view and thinking that it was a much nicer way to experience the mountain."

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“There are times
when you have
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I just do not have the
data or the ability
to address this.”

—Stephan Sanders

Noah Sasson: Connecting with the autistic community

BY RACHEL ZAMZOW / 15 SEPTEMBER 2022

On a hot May evening in Austin, Texas, Monique Botha stepped into the opening reception of the 2022 International Society for Autism Research (INSAR) meeting. Botha, who is autistic and uses they/them pronouns, had traveled from the University of Stirling in Scotland to attend the large annual gathering of autism researchers for the first time. The room was crowded with hundreds of people, and the bustle was overwhelming.

But Botha soon found Noah Sasson, professor of psychology at the University of Texas at Dallas, who was chatting with a couple of graduate students. Botha had been in contact with Sasson through Twitter for years but had never met him in person, and the two had planned to meet up at INSAR. After chatting for a while, the group migrated to a nearby taco place for dinner. The conversation bounced from research trends to movies, to reality TV, to what it's like to be neurodivergent in a predominantly neurotypical field—something everyone at the table except Sasson had experienced.

Botha noticed that sometimes Sasson just listened quietly, but when he did chime in, it was from a place of genuine interest. Soon Sasson mentioned an unfinished paper he was struggling to revive, and Botha helped him find a way to reframe it. Botha sometimes feels tokenized when talking with neurotypical researchers, who often seem to want only cursory approval from an autistic person for their latest study. But from Sasson, Botha instead felt a lack of defensiveness and a rare intellectual reciprocity.

"That kind of allyship is really appreciated,"

FAST FACTS

Current position: Professor of psychology, University of Texas at Dallas
Main areas of interest: Social cognition and social interaction
Lab URL: https://labs.utdallas.edu/sassonlab/
Notable mentors: J. Steven Reznick, Joseph Piven

Botha says, because it means autistic academics aren't alone in their fight for research that can truly make a difference for autistic people.

Sasson, 47, grew up in Chapel Hill, North Carolina, in a house where the news was always on. His mother has an activist streak, his father is a Syrian immigrant, and "civil rights issues were always talked about in my household," says Sasson, who remembers watching the documentary "Eyes on the Prize: America's Civil Rights Movement" on PBS with his parents.

Judging from his family, it would seem that Sasson was destined for life in academia. His father was a professor of religious studies at the University of North Carolina at Chapel Hill and later at Vanderbilt University, and he is renowned for his work on ancient Near Eastern civilizations. His mother has a Ph.D. in English and directed the masters in liberal studies program at Duke University. One of Sasson's two brothers earned a Ph.D. and studies reproductive behavior in horseshoe crabs at the South Carolina Department of Natural Resources in Charleston.

But early on, Sasson wasn't sure what he wanted to do. It wasn't until his junior year at Franklin & Marshall College in Lancaster, Pennsylvania, that he declared English literature as his major, because he enjoyed getting class credit for reading novels. After graduation, he worked for a few years as a teaching assistant at an elementary school near his hometown, a career path spurred by an interest in child development and summers working as a counselor at a YMCA camp in Chapel Hill. But long teaching days required high energy, and he decided he couldn't see himself corralling elementary students for the coming decades. "I kind of was more of a quieter type that wanted to think about ideas," he says.

Sasson had already been considering how a child's background shapes their development, and he shared this growing interest with his parents. Through academic connections, they arranged for him to meet Steven Reznick, a developmental psychology professor at the University of North Carolina at Chapel Hill. The two bonded over a shared affinity for early rock 'n' roll music (Sasson now has hundreds of the late Reznick's old vinyl records), and Reznick took a chance and invited Sasson to volunteer in his lab.

Sasson started working with autism researcher Kevin Pelphrey, who was a graduate student at the time.

"He just seemed so brilliant to me," says Sasson, who enjoyed tinkering with equipment alongside Pelphrey and mulling over ideas in the lab; it was the kind of deep thinking he'd been searching for.

Sasson officially joined Reznick's lab as a graduate student in 2000 and helped Pelphrey test out a new eye-tracking system in autistic adults. That study, led by Joseph Piven, professor of psychiatry and pediatrics at the university, found that people with autism spend less time looking at others' facial features than non-autistic people do, and it resulted in one of the seminal facial scanning papers in autism research. It also proved that Sasson, though a newcomer to research, could hold his own. He doesn't self-promote, and he's never "the loudest guy in the room," Piven says, "but he just always really understood stuff at a deeper level than most people."

The eye-tracking paper garnered a lot of attention, and Sasson's interest in autism research grew. He became fascinated by the early papers of Simon Baron-Cohen exploring theory of mind. And he began to interact with autistic people directly, most notably during his dissertation on how face processing develops. Sasson drove all over North Carolina testing autistic participants as part of his research and came away thinking they "had this unique, really interesting perspective on the world," he says.

Sasson moved over to Piven's lab in 2005 for a postdoctoral fellowship, where he continued his eye-tracking work, but a year and a half later he followed his then-girlfriend (now wife), Amy Pinkham, to Philadelphia, where she was studying social cognition in schizophrenia. They both did postdoctoral fellowships at the University of Pennsylvania in neuroscientist Ruben Gur's lab, and the following year, Sasson began work on eye-tracking with autism researcher Robert Schultz at the Children's Hospital of Philadelphia.

The couple moved to Texas in 2009, after Sasson found a home at the University of Texas at Dallas and Pinkham landed at Southern Methodist University (in 2014 she joined Sasson at the University of Texas at Dallas). Sasson began setting up his own lab, which proved to be challenging at first. He'd come from autism research powerhouses at the Children's Hospital of Philadelphia and University of North Carolina, where the infrastructure is well established, but at the University of Texas at Dallas, he was starting from scratch. He leaned into collaborations, including work with Piven exploring autism-related traits in families, and he continued honing the eye-tracking skills that had made him an attractive hire for the university.

But after a few years, eye-tracking work began to lose its meaning for Sasson, and by 2013 he had hit a wall.

The problem, Sasson says, is that he realized these studies are often detached from the actual experiences of autistic people. Looking over his body of work, he sometimes wondered if anything would change if all of his papers suddenly disappeared. This research "didn't strike me as actually ever trickling down to having any impact whatsoever on the world," he says. It was comforting to be able to secure funding, but he was already feeling burned out.

At home, Pinkham knew he was questioning his direction. The couple have two children, often collaborate on research and have published two dozen papers together—a reflection of how the fields of autism and schizophrenia often cross-pollinate. Pinkham and Sasson had admired each other's work even before they were a couple, back when they were classmates in graduate school, and now they were forging their careers alongside each other. The issue, Pinkham says, was that Sasson needed to decide if he still wanted to "get funding, sometimes for what seems like funding's sake, and not necessarily for good scientific reasons," or branch out and try something new.

As he mulled over his future, Sasson joined Twitter. At first, it was so he could see what others were saying about his research, but then he started following autistic people (including Botha), and it exposed him to research he might not have come across otherwise. In particular, he read the papers of Damian Milton, who developed the double empathy problem, which conceptualizes social difficulty as a two-way issue between autistic and non-autistic people.

This was a lightbulb moment for Sasson, who found himself wondering why this idea wasn't being explored more expansively. He thought that

this was where empirical work should go, and that it would be not only intellectually interesting, but also truly beneficial for autistic people.

He began applying those concepts to his own work. In his 2015 study that originally intended to test whether non-autistic people misperceive the facial expressions of autistic people, Sasson detected subtle hints of stigma from non-autistic people. In truth, non-autistic people accurately identify the emotions of autistic people, but they tend to rate these expressions as overly intense and less natural-looking than those of non-autistic people.

And in a study of college roommates, Sasson found in 2016 that a mismatch in social style, rather than the style itself, negatively affects relationship quality. For example, pairs of roommates who both scored high for aloofness on a questionnaire assessing autism-related traits, rated their relationship as more satisfying than pairs in which only one roommate was aloof.

Sasson began to view social disability as a lack of compatibility between a person and their social environment. And that, in turn, caused him to question the "idea of autistic people having some inherent social deficit about them specifically that needs to be rectified," he says.

This concept revived his academic drive. Over nearly a decade, Sasson has followed this thread in subsequent studies, digging deeper into how external factors, such as stigma, weigh heavily on the ways autistic people are perceived. In a 2017 paper, for example, Sasson and his team showed that non-autistic people tend to form negative first impressions of autistic people after just a few seconds, based on how they act and sound rather than on their conversational content.

Then, in 2019, Sasson's team found that non-autistic people prefer interacting with other non-autistic people versus autistic people, and that autistic people tend to share more about themselves when they interact with each other. Preliminary data from the same study also reveal empirical evidence of masking: Some autistic people adapt their behavior to meet the social demands of non-autistic people.

Sasson and his colleagues have even shown that standard measures of social skills fail to accurately predict how well autistic people fare in real conversations. These findings highlight an important gap within the field, Sasson says. "Even though social interaction is core to the diagnosis, autism research really hasn't studied real social interaction very well."

It is this kind of work that has won Sasson praise from voices within the neurodiversity movement. "Noah is one of the first and one of the most vigorous and creative researchers" honoring neurodiversity-driven perspectives, says Steve Silberman, author of "NeuroTribes," the 2015 autism history tour de force. "And not just by saying nice phrases like 'social model of disability' or 'a difference, not a disorder.' But actually by doing the hard work of quantifying and extending those thoughts into the empirical realm of science."

For Botha, Sasson's work is "evidence that, actually, there are some researchers out there who are actually willing to understand autistic people in context, which shouldn't be as radical as it is."

These days, Sasson spends most of his time working on manuscripts and texting or emailing with members of his lab. In a given year, he has two doctoral students, a masters student or two and a gaggle of undergraduates. There are always several autistic students.

Danny Dunn, who completed an honors thesis while an undergraduate in Sasson's lab and today is a masters student at Texas Woman's University in Denton, says this level of represen-

tation would be harder to establish elsewhere, but the University of Texas at Dallas' campus has a huge autistic student population, possibly formed through an intersection with the university's LGBTQ+ friendly culture and its propensity to attract "nerds." Dunn explains, "We don't have a football team, [but] our chess team is top notch, and our esports team is winning nationals."

Sasson has fully embedded himself in this community. Not just as a researcher, but as an ally. He serves as a faculty advisor for the student-run For Autistic Empowerment organization, and he is a member of the university's Neurodiversity Working Group, which works to support the needs of neurodiverse students. And he actually listens to the autistic students in his lab, Dunn says. But Sasson thinks that's just part of the job. If he is going to study autism, then he has to be comfortable having his work "consumed and critiqued by autistic people," Sasson says.

His sense of justice extends beyond autism, however. He is working with doctoral student Desi Jones on her upcoming dissertation, exploring the intersection of racial issues and autistic experiences—research Jones doesn't think she'd be able to do elsewhere. Sasson is also searching for ways to mitigate the double empathy problem. Too often, he says, "all the burden, the whole entire onus, is on autistic people to figure out how neurotypical people work and then basically mask to do that."

His team has instead focused on non-autistic people through video trainings aimed at increasing their understanding of autistic people—helping to explain stimming, for example. This approach seems to improve non-autistic individuals' self-reported attitudes about autism and boosts their interest in interacting with autistic people, the researchers found in 2021. That said, the non-autistic people's implicit biases about autism didn't budge, suggesting that more internalized attitudes may be harder to shift.

Perhaps the best way to move toward more fruitful connections between autistic and non-autistic people, Sasson thinks, is through the development of long-term relationships. This is something he'd love to test with a longitudinal study someday. "The only things that really seem to break down racial, discriminatory attitudes and things like that," Sasson says, "is protracted, meaningful interaction with people."

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Elliott Sherr: Coaching teams to tackle autism's mysteries

BY SARAH DEWEERDT / 10 OCTOBER 2013

At first glance, you wouldn't peg Elliott Sherr as a basketball player—he's not particularly tall or lanky. But basketball has been his sport ever since he was a schoolboy in southern California. More recently, he coached his three children's community basketball league teams for nine years.

Sherr hung up his coach's whistle last year (his children are all old enough to play on school teams now). When he looks back on his experience as a coach, he takes particular pride in games in which every member of the team scored.

That inclusive yet disciplined approach also translates to his lab at the University of California, San Francisco, where Sherr is a child neurologist and geneticist.

Rather than focus on just one disorder, his lab is trying to unravel the effects of genetics and brain structure in a handful of disparate disorders that each illuminate some aspect of autism. He is among only a few autism researchers who evaluate children with autism in the clinic.

He is also probing changes in brain wiring that may be akin to those present in autism, working out how autism symptoms can derive from either duplications or deletions of the same genes, and characterizing animal models of the disorder.

"Being overcommitted is one of my flaws," he says.

Sherr lets the self-deprecating joke hang there for a long beat. His sense of humor is so dry, colleagues say they can't always tell whether he's joking.

Sherr has good reason for having so many

Current position: Professor of neurology, University of California, San Fransisco
Recent significant work: Gene discovery in disorders of the corpus callosum
Main area of interest: Gene discovery, phenotype/genotype correlations, animal and cell-based models
Lab URL: brain.ucsf.edu • **Notable mentors:** Lloyd Greene, Eric Kandel

FAST FACTS

irons in his scientific fire, however.

"There are probably two main hypotheses that are out there about autism so far," he says. "One is that autism is a disruption in neuronal connectivity, and the other is that autism is an imbalance of excitation and inhibition."

Two of Sherr's primary research interests, the corpus callosum and epilepsy, directly address these two hypotheses.

The corpus callosum is the thick bundle of nerve fibers that connects the two hemispheres of the brain. People born without this structure often have social deficits, and Sherr and his colleagues have found that 45 percent of children with this defect, known as agenesis of the corpus callosum (AgCC), meet the criteria for autism.

The connectivity theory of autism holds that people with autism have defective long-range connections in the brain. Lacking a corpus callosum is an extreme example of having impaired long-range connections, Sherr notes. He and his collaborators have shown that the absence of a corpus callosum results in a broad rewiring of the brain's structural connections.

Sherr has also helped to suss out genomic regions associated with the birth defect.

"That's a small field where he's made really seminal contributions," says Elysa Marco, assistant professor of clinical neurology at the University of California, San Francisco and a former student and longtime collaborator.

Sherr and his colleagues assembled a group of 374 individuals who were born without the brain structure, including 100 who had never been studied before. They identified 12 areas of the genome associated with the defect, as well as overlaps with genetic causes of other brain malformations.

Sherr also studies the genetics of epilepsy, a condition in which surges of excitatory nerve impulses in the brain cause seizures. Epilepsy affects about 30 percent of people with autism, and some researchers believe that a less extreme imbalance of excitatory and inhibitory nerve impulses underlies autism itself.

Some researchers might pick a favorite theory about autism up front and look for evidence to support it, but Sherr's work explores both views of autism.

He shows a similar open-mindedness in the clinic, says Marco, who first met Sherr when she was a medical student and he was completing a child neurology fellowship. Sherr still sees patients at the university's Benioff Children's Hospital, mostly children with severe epilepsy or brain malformation.

"We would be on rounds, and it wouldn't be unusual to take a 15-minute interlude to check out some articles about a subject so that we could make a really well-founded decision," Marco recalls. In other words, he didn't need to have all the answers. "He's got a humble approach."

Since the earliest days of his career, Sherr has been unafraid of what he doesn't know.

"In his thesis work, Elliott took on a project on which neither he nor I had much background or familiarity with the required methodologies," says Lloyd Greene, professor of pathology and cell biology at Columbia University in New York, and Sherr's Ph.D. adviser. "Elliott proceeded to master the subject and the methodologies largely on his own."

Greene's lab focused mainly on neuronal differentiation, but for his dissertation, Sherr sequenced the genes for a family of small myosins, molecular motors related to the proteins involved in muscle contraction, and mapped their expression in the mouse brain.

Overcommitted from the beginning, Sherr was part of an M.D./Ph.D. program. "I got interested in autism and intellectual disability through my work as a clinician," he says.

He says he hoped that studying the biology underlying these conditions might not only help people with disorders, but also yield broader insights into why people think and behave the way they do. To learn more, he began to get involved with family support groups for rare neurodevelopmental disorders.

"In some ways, I've learned more by seeing families that way, in a more natural setting, than in a very formalized setting inside of a clinic room," Sherr says.

The goodwill and rapport he developed this way are also key to the success of his research. "He's able to attract relatively large numbers of people so that they will come from across the country or even other countries to be involved in these studies," says Pratik Mukherjee, associate professor of radiology at the University of California, San Francisco, who collaborates with Sherr on brain imaging studies of AgCC and other conditions.

Most recently, Sherr has gotten to know families of children with deletions or duplications of a chromosomal region called 16p11.2. These genetic defects increase the risk for autism and are the subject of the Simons Variation in Individuals Project, which is funded by *Spectrum's* parent organization. Together with a consortium of European researchers, the project has reported that carriers of the deletion have lower intelligence quotients than unaffected relatives, and 15 percent also have autism.

Of course, teasing out the relationships between autism symptoms and genetics isn't always straightforward. A study in Sherr's lab of BTBR mice, which lack a corpus callosum and show autism-like behaviors, failed to find a genetic link between these two conditions.

Sherr says the experience spurred him to look beyond mouse models of autism. He is now part of a team working to develop a monkey model of the disorder. "I think I was more sanguine about being able to use mice earlier on than I am now," he says.

This constantly expanding set of research questions and methodologies also requires an equally diverse set of collaborators—something that plays to Sherr's strengths.

"He's a really good team player," says Karen Parker, assistant professor of psychiatry at Stanford University in California, and a collaborator. "He's very good at including everyone—I like how he treats everyone on the team, from technicians to postdocs."

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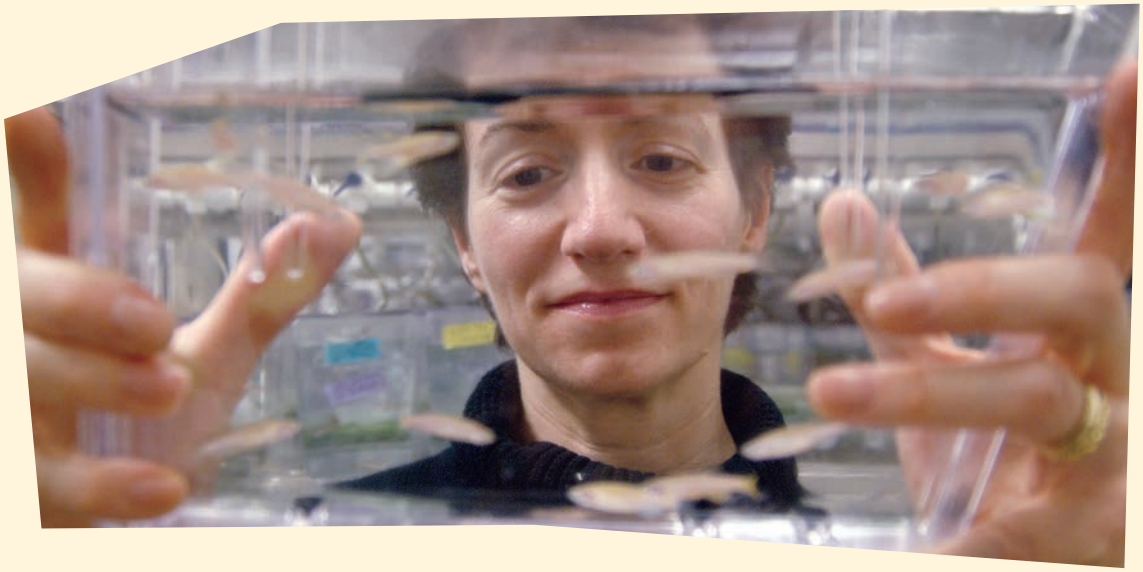
Hazel Sive: A fish tale

BY EMILY SINGER / 29 NOVEMBER 2010



Every morning in Hazel Sive's lab begins with an act of creation. In a compact room stacked high with tubs of zebrafish, a researcher selects one tub and pulls out the clear plastic divider separating an eager male fish from several waiting females. The darting creatures quickly release sperm and eggs, and fertilized embryos rain down to the bottom.

These small, transparent fish embryos are being used for research on autism—an unusual choice, as they obviously lack the complex behavioral repertoire seen in the condition.

But zebrafish share many genes with people, allowing researchers to study the function of candidates identified in human genetic screens of autism. And an arsenal of tools is available to manipulate those genes, making them an ideal system in which to probe the genetics of autism.

Sive, professor of biology at the Massachusetts Institute of Technology and member of the Whitehead Institute in Cambridge, Massachusetts, is a classically-trained embryologist and developmental biologist, and an expert in zebrafish genetics.

"She is a leader in the field of developmental biology," says Mriganka Sur, head of MIT's department of brain and cognitive sciences. "To have someone like her who has made many important discoveries about how the body and brain of zebrafish is put together, that's a big coup for the autism field."

FAST FACTS

Current position: Dean, College of Science, and professor of biology, Northeastern University
Recent significant work: Identification of FAM57B as an autism risk gene that controls cellular lipid cohorts and metabolism in 16p11.2 deletion syndrome cells and zebrafish model. Suggests possible therapies that involve interventions into lipid metabolism.

Over the past few years, scientists have identified a number of genetic regions linked to autism, thanks in large part to gene chips that make it possible to survey the entire genome in large numbers of people.

Researchers have yet to figure out which genes within these genomic chunks are responsible for an increased risk for autism, however. For example, one notable region on chromosome 16, linked to one percent of autism cases, contains about 25 genes. But scientists know very little about the function of these genes.

"It's easy to discover genes as the tools of genetics get better and better, but much harder to discover what they do," says Sur. "There's only so many ways you can look at them using a mouse or human brain."

Once Sive and her team find specific neural defects linked to candidate genes in zebrafish, they can look for ways to remedy those defects.

"This is where the fish is really fantastic," says Sive. "They are small so we can put them in wells in tissue-culture dishes and look for them getting better with a particular chemical."

When Sive describes her work with zebrafish, she is careful to call them 'tools' rather than 'models.' The distinction may seem subtle, but Sive notes that she is using the fish specifically to assess gene function and potential treatments.

"The point is not to get something in fish that happens in humans," she says. "The point is to get a handle on gene function that we can use to assay human [candidate genes]."

Her perspective is still somewhat unique; most people studying animal models of disease aim to mimic the human versions as closely as possible. But the approach is likely to become more popular as the need grows for relatively simple methods of understanding gene function.

"I think it is really a creative thing that she's trying to do," says Nancy Hopkins, a biologist at MIT who devised technologies to study zebrafish, identifying hundreds of genes vital for development. "It's a risky project, but with huge possible outcomes," Hopkins says.

About seven years ago, Sive, who is from South Africa, became interested in the architecture of the brain. She became particularly intrigued by the neural tube, a structure unique to vertebrates. The center of the neural tube develops into ventricles, which form an internal circulatory system that bathes the developing nervous system in cerebrospinal fluid.

Because zebrafish embryos are transparent, scientists can observe development, including the formation of the neural tube, as it unfolds in live animals. Sive quickly realized that she could use the transparent fish to study human brain disorders, such as hydrocephalus, characterized by the accumulation of cerebrospinal fluid in the ventricles.

"Human mental health disorders are extremely poorly understood, so we started wondering whether fish could be a tool to address some of the functions of the genes that might be involved," Sive says.

For autism research, her approach became

Main areas of interest: Neurodevelopmental disorders, including autism
Notable mentors: Robert Roeder, Harold Weintraub , Gerald Fink, Nancy Hopkins, Rudolf Jaenisch

> "Science doesn't allow enough of this kind of exploration because we are so geared to funding stuff we know is going to work. If this really works and becomes a paradigm, it would be fantastic." —Hazel Sive

useful only after geneticists began identifying segments of DNA harboring a number of candidate genes for the disorder. In January 2008, Mark Daly, a geneticist at the Broad Institute in Cambridge, Massachusetts, identified the deletion on chromosome 16. "Then we had a set of genes we could really work with," Sive recalls.

Amid the gurgling tanks in the fish storage room, a researcher collects a newly-created embryo and whisks it away to a microscope. While the embryo is still at the single-cell stage, it is injected with a molecule designed to reduce the function of a single target gene by about 50 percent—roughly mimicking an individual with just one functional copy.

Just 24 hours later, the zebrafish embryo resembles a small, transparent snake curled tightly around a ball, the yolk cell. The developing spinal cord stretches down its length, and both the flow of blood and the beating heart are visible under a simple light microscope.

At this stage, the zebrafish's brain is the approximate equivalent of a 5-week-old human embryo. Red dye injected into the ventricles reveals a characteristic outline of peaks and valleys representing the normal structure of the forebrain, midbrain and hindbrain. Although it can't yet swim, a healthy day-old embryo flinches when poked, providing a simple method for detecting motor deficits. Fluorescent dyes highlight the shapes of neurons and their projections, or axons.

To date, Sive's team has identified 28 zebrafish homologs—sequences that resemble gene sequences in humans—of the genes in the chromosome 16 deletion linked to autism. Researchers in her lab have knocked out 11 of the genes, and discovered that 10 of them appear to play vital roles in the brain.

In some cases, mutations in the genes cause the brain to be misshapen and small. In others, they cause nerve cells to grow in the wrong direction or in the wrong pattern. For example, in a healthy fish, the nervous system looks like a ladder, with two parallel strands and a series of regular rungs. But fish that lack PPP4CA, one of the genes in the 16p deletion, do not have specific midbrain structures and part of the optic tract, and their spinal cord neurons are jumbled.

"That is quite extraordinary," says Sive. "We were quite surprised to see so many really devastating brain abnormalities in the fish."

Sive feeds this information back to Daly, who continues to study these genes and others in people in autism. "We tell Mark [Daly] what we're learning, and he tells us about what he's learning," says Sive.

"We're quicker than him because human genetics is so slow."

Sive and her colleagues also aim to find ways to fix these defects by testing a number of small-molecule drugs on zebrafish embryos.

It's too early to identify any promising candidates, but colleagues in both the zebrafish and autism fields hope Sive's gamble proves successful.

"Science doesn't allow enough of this kind of exploration because we are so geared to funding stuff we know is going to work," says Hopkins. "If this really works and becomes a paradigm, it would be fantastic."

SIVE'S HIGHLY CITED PAPERS:

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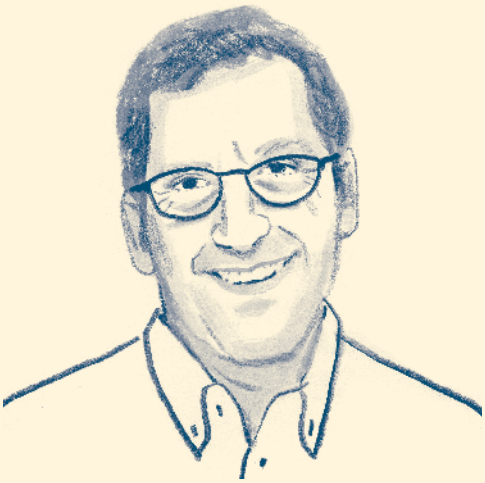
Matthew State: Bridging the gap between bench and bedside

BY DEBORAH RUDACILLE / 24 FEBRUARY 2011

Soon after arriving at Yale University in 1999 to begin work on a doctoral degree in genetics, Matthew State found his way to a community mental health center in Branford, Connecticut, a small town eight miles north of New Haven.



He signed on as the center's only child psychiatrist, treating low-income children for anxiety disorders, depression, autism, schizophrenia and psychosis.

These days, as co-director of the Program on Neurogenetics and deputy chair of research in psychiatry at Yale, he commutes weekly between Manhattan, where his wife and 13-year-old daughter live, and New Haven. But he still spends every Wednesday at the center, from 1 p.m. well into the night, and remains on call for his patients there.

"Matt will take a call at any time of the day or night," says Maggy Trapazzo, clinical director of the Branford Counseling Center. "We've woken him out of a sound sleep to renew a prescription when he was in Indonesia—we didn't know he was there," she recalls. "But he gets right up and does it."

Dedicated child psychiatrists may not be a rarity, but State is among the few who can also lay claim to a career as a world-class scientist, delivering breakthroughs in autism genetics.

State's work in 2005 on the SLITRK1 gene, associated with some forms of Tourette syndrome, was cited as a top scientific breakthrough that year by *Science* magazine. In autism research, he is best known for identifying the risk gene CNTN4. His laboratory is one of two teams sequencing and analyzing samples and data from the Simons Simplex Collection (a project run by *Spectrum's* parent organization), a repository of genetic samples and clinical profiles from more than 2,500 families.

State is not only a fine researcher himself, but a stellar team player, notes Bernie Devlin, professor of human genetics at the University of Pittsburgh, and State's collaborator.

"Matt is one of a handful of exceptional collaborators who inspire me," Devlin says. "He has

FAST FACTS

Current position: Oberndorf Family Distinguished Professor and Chair, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco • **Recent significant work:** I led the Simons Simplex Collection Genetics Consortium (SSCGC), which made key methodological breakthroughs in the early study of de novo copy number variants (CNVs), replicated their contribution to risk, and discovered that duplications in the Williams syndrome region are associated with autism. My lab was the first to establish SCN2A as an autism-associated gene. We demonstrated the first systematic approach to autism gene discovery through exome sequencing (simultaneously with Michael Wigler, Evan Eichler & Mark Daly labs), proposed and undertook (with Sestan) one of the first spatio-temporal analyses of high confidence autism risk

a knack for helping you dig deeper into a problem than you had ever considered before."

Ironically, State never intended to become a physician or biomedical researcher at all. Growing up in a politically active family, he intended to build a policy career in Washington D.C. While still an undergraduate at Stanford University, he landed internships with Senator Ted Kennedy and at the Carnegie Endowment for International Peace.

But after graduation, while he was working on arms control as a staff member for Senator Gary Hart, "I had an epiphany," he says, realizing that D.C. wasn't for him. "It's a tremendously adversarial environment. My personality wasn't well-suited to Washington."

Deciding that he wanted to have a more personal impact on people's daily lives, he returned to Stanford for his M.D., and did a residency in child psychiatry at the University of California, Los Angeles.

Even so, the negotiating skills State picked up during his stint on Capitol Hill, combined with a temperament that naturally seeks to reconcile different points of view, have become key factors in his success as a researcher, physician and administrator.

Just about everyone who works with State comments on his almost uncanny ability to drill through to the nut of a problem and to integrate disparate perspectives to find workable solutions.

"His ego is never in the game," says John Krystal, chair of psychiatry at Yale. "He is remarkably generous and also tremendously generative, stimulating people to get involved."

Krystal was so impressed by State's energy and capacity to engage people that he asked State to be his deputy chair two years ago. At Yale, child psychiatry and psychiatry are separate departments, Krystal notes, so having a child psychiatrist serve as his second-in-command is quite an anomaly.

State has since worked to bring together a research council of senior investigators across disciplines at Yale. "Our goal was to break down those intellectual silos and look for common interests and opportunities," Krystal says.

Ellen Hoffman, a child psychiatry resident who came to Yale, says that soon after her arrival, State quizzed her about her interests and encouraged her to collaborate with a genetics lab—using zebrafish to investigate how rare genetic variations contribute to autism. "Because I expressed an interest in model systems, he identified this project, which didn't exist before I came here."

For his part, State lists training physicians like Hoffman to do basic research in genetics as his most satisfying career accomplishment so far. "I've got three child psychiatrists and a pediatrician who are doing beautiful, sophisticated work," he says. "In my field, there are really just a handful of people doing basic molecular genetics."

State's perspective on this approach came from another epiphany of sorts—when he was training to be a psychiatrist at Stanford.

"I was taking care of kids with severe illness

genes (simultaneous with the Geschwind lab) and demonstrated, for the first time, genetic risk convergence in deep layer cortical glutamatergic neurons in mid-fetal human development. We discovered that estrogens are protective against multiple high-impact autism de novo, likely gene-disruptive mutations (with Antonio Giraldez in a zebrafish model and with Helen Willsey & Jeremy Willsey in xenopus and human neurons), and most recently demonstrated that defects in neurogenesis are a convergent autism molecular and cellular phenotype (with Helen & Jeremy Willsey). I also co-founded the National Institutes of Health-funded autism sequencing consortium (with Joseph Buxbaum & Thomas Lehner) • **Main areas of interest:** Genetics, genomics and neuroscience • **Lab URL:** https://www.mstatelab.com • **Notable mentors:** Richard Lifton, David Ward

and thought that I really needed to understand genetics," he says. With no background in science, "I felt like I had to start from the beginning." He decided to get a Ph.D. in genetics.

Donald Cohen, then chief of child psychiatry at Yale, was among the only people open to this approach. He allowed State to get his Ph.D. while he was a junior faculty member in the department.

"[Cohen] had thought for a long time that it was important for child psychiatrists to have a stronger grounding in science, so he created this really unusual situation for me," State recalls.

Early in his research career, State was a staunch believer in the importance of rare variants. "I like rare variants because they have big effects," he says. "Finding one extremely rare variant that can point to the center of a biological process can be more powerful in my view than finding out a ton about 30 different alleles that contribute a tiny bit of information, which is what we're seeing in a lot of common alleles."

Over the years, however, he's come to recognize that no one approach is likely to identify the causes of autism. "The genetic architecture of autism is likely to include both common and rare variants," he says.

Still, State believes that genetics can only take autism research so far. "It's the biological mechanisms that are going to be a target for treatment," he says, "not the particular variation in one person versus someone else."

State says he spends much of his time at clinical conferences persuading physicians to screen for genetic disorders. This is important for families both medically—because carrying certain chromosomal deletions can result in severe medical issues—and emotionally.

"In psychiatry we went through this awful period where moms were being blamed for autism," he notes.

"At least you can inform people who might still have this notion what we understand about heritability, and how it's similar to other medical disorders."

This sort of sensitivity to the emotional needs of families at the Branford Counseling Center has impressed Trapazzo even more than State's encyclopedic knowledge of genetics and disease.

"He has the capacity to get down and be with these families around the truth of their world," she says. "He's willing to be involved from molecules and DNA right down to the concrete things that make life better for our kids."

STATE'S HIGHLY CITED PAPERS:

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"He has the capacity to get down and be with these families around the truth of their world. He's willing to be involved from molecules and DNA right down to the concrete things that make life better for our kids."

—Maggy Trapazzo

Helen Tager-Flusberg: Decoding the language of autism

BY VIRGINIA HUGHES / 24 NOVEMBER 2011

Of the thousand or so individuals with autism Helen Tager-Flusberg has studied since the 1970s, one sharply stands out in her memory: a 13-year-old boy whose special education teachers had been helping him recognize different emotions.

When the boy walked into Tager-Flusberg's small research room, she asked him, "How are you doing today?"

He looked her straight in the eye, and with a poker face said, "I'm happy, mad, glad and sad!"

Tager-Flusberg still remembers how much his response startled her.

"I couldn't decide—did he understand these words? Did he actually experience all of this? Was it that he had just learned these words? Did he pick these words because of their rhyming? Was there, in fact, a little bit of irony in all of this?" Tager-Flusberg recalls. "I was clueless. But it opened my eyes that perhaps there's a lot more to some people, that you can't take them at face value."

The language deficit in autism is complex and diverse: Many children have language delay, some speak in a monotone or repeat others' words, and some don't speak at all. Tager-Flusberg, professor of psychology at Boston University and president of the International Society for Autism Research, has devoted her career to sorting it all out.

"If you asked somebody, 'Who are the famous people studying language in autism?' she's the first name to come to mind," says Ken Wexler, professor of brain and cognitive science at the Massachusetts Institute of Technology (MIT).

Since moving from London to Boston nearly 40 years ago, Tager-Flusberg has investigated the linguistic abilities of people with autism using a

FAST FACTS

Current position: Professor of psychological and brain sciences, Boston University

Recent significant work: Over the last decade, I began a new and, in my view, most important direction for my research on language in autism: investigating the approximately one-third of children who fail to acquire spoken language and remain minimally verbal. We have developed methods and measures for how to study language and related cognitive functioning in this challenging population and explored some of the explanations for why they fail to acquire spoken

wide variety of approaches: psychological tests, eye tracking, brain imaging and, most recently, by studying younger siblings of children with the disorder. She now proposes that most language-related deficits in verbal children with autism are no different from those seen in other language disorders—with one exception.

"Where you see the difference in autism is in those aspects of language that really entail a theory of mind," she says, referring to the ability to understand other people's beliefs and intentions. "Their ability to use language effectively and appropriately in a social context is what's significantly impaired."

Tager-Flusberg was born in England, but did her graduate work in the infamously serious and almost entirely male experimental psychology department at Harvard University. This was in the 1970s, and she shared the hallways with the likes of B.F. Skinner, perhaps most famous for devising a box that delivered electrical shocks to rats.

"It was very serious psychologists who mostly did not deal with live human beings. They were famous for being extremely rigorous and not pleasant," says Cathy Lord, who overlapped with Tager-Flusberg at Harvard, and is now director of the Institute for Brain Development at New York-Presbyterian Hospital.

Still, Tager-Flusberg, who is known for her no-nonsense British sensibility, had no trouble holding her own. "She toughed it out," Lord says.

Lord and Tager-Flusberg both did their graduate work with the late Roger Brown, who stood apart from his colleagues for his long-term observations of children during language development. Tager-Flusberg applied the same approach to children with autism, a disorder that had received little attention at the time.

For her dissertation, for example, she investigated whether children with autism understand syntax, or the grammatical rules of language, by giving them sentences—such as *'The boy pushes the girl'* and *'The girl was pushed by the boy'*—and asking them to act out each sentence using toys.

Healthy children and those with autism both use a simple word-order strategy, which assumes that the subject precedes the object, she found. In other words, children with autism seem approach language much the same way healthy children do.

This was a surprise, especially because linguists at that time were deeply focused on the importance of syntax. Tager-Flusberg spent the following two decades using psychology to delve deeper into the language deficit in autism.

In a 1992 study, for example, she analyzed recordings of children having conversations with their mothers in their homes over two years. She found that children with autism make fewer references to psychological states, as measured by their infrequent use of verbs such as believe, figure, forget and trick, compared with either typical controls or those who have Down syndrome.

These days, her team at Boston University is using a similar study design to explore how children with autism use pronouns. So far, their data suggest that children with the disorder often use

language (for example, auditory processing impairments; speech-motor deficits/childhood apraxia of speech), as well as highlighted the enormous heterogeneity even within this group.

Other major accomplishments: Received the INSAR Lifetime Achievement Award in 2021

Main areas of interest: Language and communication • **Lab URL:** www.bu.edu/autism

Notable mentors: Roger Brown, Jill de Villiers, Charles Nelson

pronouns without the right context. For instance, if there were three women in a story, they might refer to each of them as 'she.'

Both these studies suggest that children with autism speak without taking their audience into account, Tager-Flusberg says.

"When you tell a story, it's not about you telling a story, it's about your listener hearing it," she says. "To have theory of mind, you've got to appreciate that that's what you're doing."

Not everyone agrees that the language deficit in people with autism stems only from social cognition, however. Wexler, for instance, has unpublished results showing that children with autism struggle with certain grammatical rules. "I think it's going to turn out that the linguistic deficit in autism is much worse" than previously assumed, he says.

To resolve some of these discrepancies, Wexler and Tager-Flusberg, along with MIT's John Gabrieli, plan to scan the brains of children with autism or other language disorders while they make grammatical judgments or repeat strings of made-up words.

This willingness to use a wide range of technologies distinguishes Tager-Flusberg from most experimental psychologists.

"She's always interested in using something new," says her collaborator Susan Folstein, professor of psychiatry at the University of Miami. "[Tager-Flusberg] has brought together all kinds of collaborations, and put together people with unusual skills—often unrelated to her own."

For example, Tager-Flusberg began working with Charles Nelson, research director at Children's Hospital Boston, after a chance meeting on the elbow of Cape Cod in the summer of 2004. The two launched a project on the so-called 'baby sibs' of children with autism, who have a higher-than-normal risk of developing the disorder.

In March, they reported that electroencephalography can distinguish 9-month-old baby sibs from typical controls with 80 percent accuracy.

Tager-Flusberg is able to juggle so many projects at once is because she is so "organized and compulsive," says Nelson. "She can be very British sometimes. I have to needle her to lighten up."

Tager-Flusberg says she considers herself lucky to have access to this wide variety of technologies—tools that weren't available years ago, when she was puzzling through that 13-year-old boy's poker face.

"I could never have imagined where we would be, what kind of research we would be doing today, when I first started out," she says. "That would have been a dream. So that's been the most rewarding aspect of a career in science."

TAGER-FLUSBERG'S HIGHLY CITED PAPERS:

Hadjikhani N. *et al.* Anatomical differences in the mirror neuron system and social cognition network in autism. *Cereb. Cortex* **16**, 1276-1282 (2006) https://doi.org/10.1093/cercor/bhj069

Tager-Flusberg H. and Kasari C. Minimally verbal school-aged children with autism spectrum disorder: The neglected end of the spectrum. *Autism Res.* **6**, 468-478 (2013) https://doi.org/10.1002/aur.1329

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"I could never have imagined where we would be, what kind of research we would be doing today, when I first started out. That would have been a dream. So that's been the most rewarding aspect of a career in science."

—Helen Tager-Flusberg

Christopher Walsh: Solving mysteries of the mind in the Middle East

BY EMILY SINGER / 13 MAY 2008

At first glance, the waiting room at the Ministry of Health Hospital in Muscat, Oman, may look different than that of your average American hospital.

Men dressed all in white and women in black burqas wait in separate rooms, even if they are members of the same family. But talking to these families soon reveals just how similar they are to their American counterparts, says Christopher Walsh, a neurologist who has studied neurodevelopmental disorders in the Middle East for nearly 10 years.

Recalling one father seeking treatment for his child with autism, Walsh says, "His questions could have been the same as those I might hear from suburban parents at a Boston hospital."

Since 2004, Walsh's team has traveled regularly to the Middle East, carefully phenotyping children with autism.

"We met considerable skepticism initially that 'autism' would mean the same thing in Arabic cultures as in European or American cultures," says Walsh. "Our results indicate that it is highly similar if not exactly the same."

In fact, unpublished evidence from Walsh's lab suggests that there is some overlap between the genes that carry recessive mutations in Middle Eastern children with autism and those found by other scientists to have de novo structural variations—which occur spontaneously in the sperm or the egg of the parent.

Walsh's scientific journey to the Middle East began a decade ago with his quest for patients with recessive genetic disorders. After scanning

FAST FACTS

Current position: Chief of Genetics and Genomics, Boston Children's Hospital, and investigator, Howard Hughes Medical Institute

Recent significant work: We have found that the human brain is a mosaic of cells that each have a unique genome due to the ubiquitous occurrence of somatic mutations that occur during development and those that continue to accumulate in neurons with age. We found that somatic mosaic copy number variants (present in some but not all neurons) contribute

the literature, Walsh called Saad Al Shahwan at the Armed Forces Hospital in Riyadh, who had published a paper about a recessive condition in which the brain was malformed, called "lissencephaly with cerebellar hypoplasia."

As Al Shahwan explained to Walsh, in many Middle Eastern countries intermarriage between first and second cousins is a common social custom. And as a result, recessive genetic disorders occur more frequently and are easier to identify.

"If you go to a genetics clinic in Saudi Arabia, more than 98 percent of families have parents that are related," says Walsh, who is chief of genetics at Children's Hospital Boston. "You can track the gene back to a common grandparent or great-grandparent, which means you can get lots of information from one family."

Over the past decade, Walsh has traveled to Turkey, Saudi Arabia, Jordan, Dubai and Oman, working with doctors there to find families in which children suffer from different disorders.

His team has collected more than 1,500 DNA samples from families with children affected by an assortment of neurological diseases, including intellectual disability, epilepsy, cerebral palsy, brain malformations, and degenerative diseases.

"The vast majority of them are genetic, but we do not know the genetic cause as yet," says Walsh. "The diversity of genetic brain conditions to which humans are subject still amazes me."

Walsh's team has so far identified 12 genes linked to brain developmental disorders, including several types of intellectual disabilities and malformations of the brain that are linked to epilepsy and cerebral palsy.

"This work has given us great insight into the development of human cerebral cortex," says Daniel Geschwind, a neuroscientist at University of California, Los Angeles.

Walsh knows full well all that can go wrong with the brain: brain folds important for language that grow abnormally tiny, clumps of neurons can get stuck in the wrong part of the brain, triggering learning disabilities and seizures.

"Anything you can imagine can go wrong has gone wrong," he says.

These days, he's applying his approach to autism, which is characterized by impairments in language and social function. "Autism is a disorder that seems to be telling us something very important about how the brain works," says Walsh.

Language and social abilities are the most recent cognitive functions that have appeared in human evolution, he notes, "And those are the abilities that are disrupted in autism."

Identifying the genetic bases for autism has not been not easy, however.

Autism is thought to be the result of many different genetic variations, each of which may be extremely rare. Even large, genome-wide association studies—which dramatically boost the power of genomic studies by scanning the DNA of thousands of people—have yielded variations that explain only a small proportion of autism cases.

to about 0.4 percent of autism cases, while mosaic single nucleotide variants (SNV) contribute to as many as 5 percent of autism cases.

Main area of interest: Human genetics relating to brain development and autism spectrum disorders

Lab url: www.walshlab.org • **Notable mentors:** Ray Guillery, Connie Cepko, Jos Martin

> "The diversity of genetic brain conditions to which humans are subject still amazes me."
> —Christopher Walsh

"Disorders that are genetically heterogeneous are hard to study because no two genes are the same in two kids," says Walsh. "One family will lead us to one chromosome, and another will lead us to a different one."

Walsh is a physician scientist, and runs a joint clinic specializing in children with difficult neurological cases. He completed a residency in neurology in 1989 and a fellowship in genetics at Harvard University in 1992 before launching his own lab at Beth Israel Deaconess Medical Center in 1993.

Within the first five years, his team had uncovered several genes linked to neurodevelopmental disorders in American, European and Australian families.

Suspecting that there were myriad disorders yet to be discovered, he began searching for disorders linked to recessive mutations, meaning that the disease only develops when someone has two disabled copies of the gene.

"When you identify a recessive mutation, the connection between the mutation and the syndrome is clearly established, so it gives a good place to start for functional studies," says Geschwind.

Walsh's careful work characterizing these disorders has required both the clinical finesse of a physician and the deep knowledge of brain development that came from his animal research.

As a post-doctoral researcher at Harvard Medical School, he published seminal work demonstrating how far neurons migrate in the developing brain in rats. His lab now develops mouse models of the genes that they identify in human brain disorders in order to understand their mechanism of action.

With that combination, Walsh has shown that disruptions in multiple genetic pathways can lead to the same outcome—such as intellectual disability.

"He has shown that even common diseases are a collection of rare diseases," says Huda Zoghbi, a neurologist at the Baylor College of Medicine in Houston, Texas.

For his work on autism, Walsh has so far collected DNA samples from about 200 families, some of which have up to four children diagnosed with autism, and is expected to publish the first set of results in the next few weeks.

Still, the search has only just begun, Walsh says.

"It will take more than five years to understand even half of the families we have recruited so far, to say nothing of other families that may enter research," he says. Although there is no cure for autism, the researchers offer the families genetic counseling and customized genetic testing.

As he has in the past, Walsh plans to decode the role that the genes he identifies play in the brain. In that regard, his approach gives him an advantage over most autism researchers, who focus on finding more common variants.

"Will we need to perform gene therapy for each gene we find, or do they organize into pathways, with many genes in a pathway potential affected by a smaller set of drugs?" asks Walsh. "I am hoping for alternative number two, and our recent work suggests that this might be the case."

WALSH'S HIGHLY CITED PAPERS:

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Evrony G.D. *et al.* Single-neuron sequencing analysis of L1 retrotransposition and somatic mutation in the human brain. *Cell* **151**, 483-496 (2012) https://doi.org/10.1016/j.cell.2012.09.035

Huda Zoghbi: Taking genetic inquiry to the next level

BY RACHEL ZAMZOW / 25 JUNE 2021

Most mornings, Huda Zoghbi, 67, climbs a glass-encased, curling staircase to reach her lab on the top and 13th floor of the Jan and Dan Duncan Neurological Research Institute in Houston, Texas. The twisting glass tower, which she designed with a team of architects, echoes the double helix of DNA—a structure that has been central to her career-long quest to uncover genes underlying neurological conditions.

As the institute's director—and as a scientist— she is known for going beyond the standard job description. Genetics researchers often cast a wide net and sequence thousands of genes at a time. But in her prolific career, Zoghbi has focused on a handful of genes, methodically building up an understanding of their function one careful step at a time.

Thanks to that approach, Zoghbi has made a

FAST FACTS

Current position: Distinguished Professor and Director, Duncan Neurological Research Institute, Baylor College of Medicine and Texas Children's Hospital

Recent significant work: Discovery that early training during pre-symptomatic [stages] improves function and delays disease onset in a mouse model of Rett syndrome, which implies early diagnosis for Rett before symptom onset will provide an opportunity for training that might improve outcomes. We also discovered that a subtype of inhibitory

number of landmark discoveries, including identifying the genetic roots of Rett syndrome, an autism-related condition that primarily affects girls, as well as the genetic mutations that spur spinocerebellar ataxia, a degenerative motor condition. She has authored more than 350 journal articles.

Her accomplishments have earned her almost every major biology and neuroscience research award, including the prestigious Breakthrough Prize in 2017 and the Brain Prize in 2020. "She's clearly the international leader in the field," said the late Stephen Warren, professor of human genetics at Emory University in Atlanta, Georgia.

Zoghbi never set out to lead a large research center, she says—her heart is in the lab. That said, she has excelled at it: Since the institute's inception in 2010, it has grown to host more than 200 scientists and fostered more than 70 new disease gene discoveries.

Part of that success may be due to the high expectations she sets for her trainees. They work long hours in what some call "the lab that never sleeps," says Vincenzo Alessandro Gennarino, a former postdoctoral fellow in the lab, now assistant professor of genetics and development, pediatrics and neurology at Columbia University. But many say she is also endlessly empathetic and caring toward her 'lab family,' as she describes it. "She really kind of sees them as her scientific children in a way," says her son, Anthony Zoghbi, assistant professor of clinical psychiatry at Columbia.

For more than a decade now, this family has worked toward turning the deep biological mechanisms they have uncovered into treatment targets for Rett syndrome and other autism-related conditions. Finding effective therapeutics for such complex conditions is a tall order, Warren said. "But she's got good model systems, good ideas, and she attracts very talented people in her lab, so I think she has a crack at it."

Zoghbi grew up in the vibrant city of Beirut, Lebanon, in the 1950s and '60s. Her father filled the family's home with books, which fueled an early passion for Arabic and English literature. She considered studying English literature when she entered the American University of Beirut in 1973, but she switched to biology, swayed by her mother, who saw her talent for the sciences. This path led Zoghbi to medical school at the same institution.

During her first few months of medical training in 1975, the Lebanese Civil War that had erupted earlier that year escalated. Constant bombings made it too dangerous to commute, so Zoghbi and her 62 classmates took shelter on campus. She lived in a closet inside a women's bathroom until the school year ended.

When flying shrapnel injured her 16-year-old brother, Jamal, in the spring, Zoghbi's parents decided to send her and her younger siblings to live with their older sister in the United States for the summer. By mid-September, the war had only worsened, and Zoghbi scrambled to find a medical school that would accept a transfer student from another country.

neurons, oriens-lacunosum moleculare (OLM) neurons, receives decreased excitatory input, and this, in turn, contributes to hippocampal circuit dysfunction and learning and memory dysfunction in the mouse model of Rett syndrome.
Main areas of interest: Neurodevelopmental disorders, Rett syndrome, autism, neurodegenerative disorders.
Notable mentors: Arthur Beaudet

Within weeks, she landed an interview at Meharry Medical College, a historically Black institution in Nashville, Tennessee, and started classes the next day. She spent the rest of the year catching up and feeling achingly homesick, she says, taking solace only in letters from William Zoghbi, a classmate she had started dating before she left Lebanon. "Those books were soaked with tears," Zoghbi says. "I literally cried my way through that year."

William—whom she says she admired for his captivatingly kind smile—joined her at Meharry the following year. They later married. (William Zoghbi is now chair of cardiology at Houston Methodist Hospital.)

Zoghbi sought a future in pediatric cardiology at the start of her residency at Houston's Baylor College of Medicine in 1979. "And then I rotated in neurology, and everything changed," she says. "I fell in love with neurology."

But her excitement wore off soon after she started a neurology fellowship in 1982. It was incredibly frustrating, Zoghbi says, to diagnose children with rare neurological conditions and be unable to provide their families with any information about a cause or hope for a treatment.

This helpless feeling came to a point in October the following year, when she encountered a little girl with a particularly devastating and puzzling condition: Ashley Fry, a 3-year-old girl with sparkling brown eyes, had developed typically for the first 18 months of her life but then suddenly started losing language skills and wringing her hands, rubbing her left hand over and over with her right.

"That pain was very tangible to me—like, to have a girl, she's healthy, and she's beautiful, and you're enjoying her, and then to see her robbed of that," Zoghbi says. "I felt that agony."

Zoghbi and her attending physicians diagnosed Ashley with Rett syndrome. Ashley was the first case diagnosed in Texas and among only a handful identified in the U.S. at the time. But a week later, Zoghbi found another case—a girl who arrived at a cerebral palsy clinic wringing her hands. Zoghbi pulled more charts from the clinic describing similar symptoms—a stark regression, intellectual disability, seizures and hand-wringing—and found a few more cases.

Soon Zoghbi and her colleagues started publishing papers on Rett syndrome, and children with suspected cases came in from all over the country. "One after the other they looked the same, and I was like, 'It has to be a gene,' and that's when I decided I'm going to go into research," Zoghbi says.

In 1984, she approached the renowned geneticist Arthur Beaudet at Baylor about doing a postdoctoral fellowship in his lab. She had collected blood samples from 200 children with Rett syndrome, and she wanted to try to find the gene underlying the condition. Zoghbi had virtually no laboratory experience, but "she was just extremely talented and bright and motivated," says Beaudet, now chief executive officer of the Houston-based prenatal genetic testing company Luna Genetics. "She was the kind of trainee every scientist hopes to encounter one day."

Beaudet took Zoghbi on but, to her disappointment, said she couldn't focus on Rett syndrome, which he deemed too difficult to trace genetically. Zoghbi agreed instead to study a family in Texas with spinocerebellar ataxia—work that later led to a groundbreaking co-discovery of the gene underlying a subtype of the condition.

Even as Zoghbi's spinocerebellar ataxia work accelerated, she continued thinking about Rett syndrome.

Her urge to help grew even stronger when she had her first child, a daughter named Roula, in 1985. She did little experiments here and there, sometimes under the radar, searching for clues that the causative gene was on the X chromosome, or X-linked. If so, it would explain why all the cases she'd seen so far were girls. If a mutation disrupts a gene on the X chromosome, girls, who have two Xs, still have a functioning copy. But boys, who have only one X chromosome, might not survive.

She was able to pursue her ideas further when she started her own lab at Baylor in 1988. With help from geneticist Uta Francke at Stanford University in California, Zoghbi and her team eventually ruled out more than two-thirds of the genes along the X chromosome. That left hundreds of genes to explore, which they started sequencing one by one, taking about a year's worth of work each time. "Every gene was a labor of love," Zoghbi says.

Negative results piled up, and funding slowed. But Zoghbi kept at it, persistent as ever. Sometimes, during long weekends in the lab, her two children, Roula and Anthony, tagged along, peering into petri dishes or practicing pipetting while she worked.

One afternoon in August 1999, Zoghbi's phone rang just as she and her family were returning home from their annual summer trip to Lebanon. She raced to the phone, and on the other end was Ruthie Amir, a postdoctoral fellow in the lab.

"I think I found it," Amir said.

Poring over the data together at Zoghbi's house later that day, the pair saw that five girls with Rett syndrome all carried a spontaneous mutation in the same gene on the X chromosome. The gene, MECP2, encodes a protein known as methyl-CpG binding protein 2, which regulates the expression of thousands of other genes throughout the body and brain.

The team published their results two months later in *Nature Genetics,* 16 years after Zoghbi first met Ashley. Zoghbi invited Ashley and her family to the press conference announcing the discovery. She didn't have to explain why she was asking them to come to Houston, recalls Ashley's father, Clifford Fry. "I knew it in my heart that she had found the gene."

Zoghbi has meticulously probed the far-reaching effects of MECP2 ever since, tracking the results of removing the gene from different areas or cell types in the brain. Each of these 'conditional knockouts' has helped to account for a subset of Rett-related traits. Deleting MECP2 from the hypothalamus, for example, produces mice that eat uncontrollably and are aggressive and easily stressed, not unlike traits seen in boys with less severe mutations in MECP2.

Knocking out MECP2 in inhibitory neurons recapitulates almost all the traits of Rett syndrome. The mice even clasp their forepaws repeatedly, which mirrors the girls' hand-wringing. And by removing MECP2 from each of two subtypes of inhibitory neurons, or from inhibitory versus excitatory cells, Zoghbi has demonstrated how the gene supports the function of whole brain circuits, not just individual neurons.

Zoghbi and her team also engineered mice with an extra copy of MECP2 to use as controls in Rett experiments. But the animals developed severe seizures, and about a third died prematurely. This unexpected result, published in 2004, showed that a surplus of MECP2 protein can be

> “I learned a lesson from that. Always go back and take a second look. You never know.”
> —Huda Zoghbi

just as problematic as a deficiency. The following year, another team described some of the first cases of MECP2 duplication syndrome, which causes autism, intellectual disability and seizures—mostly in boys.

Zoghbi is particularly attached to her MECP2 duplication work because Tropical Storm Allison nearly washed it away. When the storm slammed into Houston in June 2001, it flooded the animal facility where some of Zoghbi’s MECP2 duplication mice lived. Zoghbi and one of her graduate students suited up in waders and went searching with a flashlight through the chest-high water for any surviving mice. They found a lone survivor in a top rack of the cages. That mouse is the founder of one of the MECP2 duplication colonies the lab studies to this day.

“I learned a lesson from that,” Zoghbi says. “Always go back and take a second look. You never know.”

Zoghbi holds a steady focus on finding what will truly help people with Rett syndrome and the other conditions she studies. “It’s clear that her approach is not ‘Okay, I’ve discovered the gene, I’ve done my job,’” says Michela Fagiolini, associate professor of neurology at Harvard University, who also studies Rett syndrome. And that drive is Zoghbi’s true legacy: “She has built not just an empire in Texas but also created a school of thinking.”

In one ongoing line of work, Zoghbi’s team has used snippets of genetic material, called antisense oligonucleotides, to silence the extra MECP2 gene copy in duplication mice. A drug delivering these genetic strands reverses problems with movement, learning and memory in mice with two human copies of MECP2, suggesting that it might also be effective in people.

The key to these types of treatments, Zoghbi says, will be titrating the dosage of MECP2 expression so that it normalizes protein levels without tipping them too far in the direction of Rett syndrome. As such, Zoghbi is searching for

biomarkers that signal when MECP2 levels have reached a 'safe zone.'

Zoghbi has also worked with colleagues at Baylor to show that deep brain stimulation applied to the hippocampus improves learning and memory in a mouse model of Rett. They are exploring whether stimulating motor circuits can similarly ease motor deficits in the mice. And Zoghbi has also tried mimicking the effects of deep brain stimulation in the form of intensive behavioral training to activate some of the same circuits.

Training Rett mice on motor and memory tasks early in life postpones the onset of difficulties in these areas, according to results published in March. If the same holds true in human clinical trials, it would help build the case to offer genetic screening for Rett syndrome in newborns, Zoghbi says. "Let's give these girls the maximum opportunity, and let's hopefully delay the disease onset by a year or year and a half or two," until more effective genetic treatments become a reality, she says.

Zoghbi stopped working as a clinician a couple of years ago, but a photo of Ashley, now 41, sits on the windowsill in her office, reminding her of where it all started and what she's working toward. When Ashley and her family are in town, Zoghbi sometimes meets them at their hotel, just to say hi to Ashley and give her a hug and a gift, such as an ornate purple and gold shawl.

Giving people like Ashley a chance to fully engage in their world is at the heart of Zoghbi's inexhaustible work ethic, says Laura Lavery, a postdoctoral associate who has worked with Zoghbi for the past seven years. "She's the most driven person I've ever met, and underlying all of that is really her love and empathy for humankind. She is just not going to stop until she figures out how to help."

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BEYOND THE BENCH

"When I started to seek out my own identity in science and life, I discovered a new me. I discovered that my mental strength, to a certain extent, highly correlated with my physical strength and endurance."

—MU YANG, DIRECTOR OF THE MOUSE NEUROBEHAVIOR CORE, COLUMBIA UNIVERSITY

"Like a lot of scientists, I live for the moment when new data have dropped and we can make our first tentative interpretations."

—ETHAN SCOTT, PROFESSOR, UNIVERSITY OF QUEENSLAND

"I jumped last and I vividly remember feeling as if I were stuck in the air. I saw the other parachutes below me, decreasing in size and moving toward the earth. I seemed to be stuck above everyone. I thought I'd never reach the ground — time just stopped. And then, suddenly, I saw the ground approaching really, really fast. It was such a relief."

—LILIA IAKOUCHEVA, ASSOCIATE PROFESSOR, UNIVERSITY OF CALIFORNIA, SAN DIEGO

"We had hookups for our clothes washer and dryer put in upstairs when we moved into our house so that I could convert my entire basement utility room into a hydroponic garden and seed-starting space. I grow greens, peas, strawberries and other fruits and vegetables inside in the winter. I start approximately 200 plants annually in this space to plant in our outdoor garden."

—HOLLY STESSMAN, ASSISTANT PROFESSOR, CREIGHTON UNIVERSITY

"My imposter syndrome, that feeling of self-doubt, has decreased over time. It's partly because I'm not doing brand-new things anymore. Medical school and residencies and post-docs and being a new PI (principal investigator), those are all new experiences in which you only see the tips of everyone else's success icebergs, and you wonder how they manage when you can't."

—AUDREY BRUMBACK, ASSISTANT PROFESSOR, UNIVERSITY OF TEXAS AT AUSTIN

"When I was 7, I broke my arm and had to spend the night in a hospital. My roommate there had been in a car accident and had extensive burns over her whole body. Watching her resilience and joy, despite the hurt, really moved me. Since then, I've never veered from my passion to be a physician."

—KRISTIN SOHL, PROFESSOR, UNIVERSITY OF MISSOURI

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