DIFFERENT

If there's one thing Ralph Adolphs wants you to understand about autism, it's this: "It's wrong to call many of the people on the autism spectrum *impaired*," says the Caltech neuroscientist. "They're simply different."

These differences are in no way insignificant—they are, after all, why so much effort and passion is being put into understanding autism's most troublesome traits—but neither are they as inevitably devastating as has often been depicted. They are simply differences; intriguing, fleeting glimpses into minds that work in ways most of us don't quite understand, and yet which may ultimately give each and every one of us a little more insight into our own minds, our own selves.

What makes autism so fascinating, Adolphs notes, is what also makes it so difficult to study, to get a good grasp on: the diversity of the population itself. If you've met one person with autism, the saying goes, you've met one person with autism.

Still, there are characteristic tendencies and traits, gifts and gaps. According to psychiatry's diagnostic bible, familiarly known as the *DSM-IV*, autism involves an "impairment" in social interaction and communication, as well as "restricted repetitive . . . patterns of behavior, interests, and activities." What this means to the rest of us is some combination of these: Lousy eye contact. Social awkwardness. Hand flapping. Toe walking. Late-talking babies. Kids who can't seem to get the hang of playing cops and robbers with friends, yet can talk for an hour about Egyptian gods, elevators, or elephants. Adults who speak in flat tones, who come off as rigid, uncomfortable, brilliant.

Or not. The fact that there are few absolutes is part of why the set of disorders—autism, Asperger's, pervasive developmental disorder not otherwise specified (PDD-NOS)—that fall under autism's umbrella are referred to as a spectrum. As with the spectrum of visible light—where red morphs into orange, which morphs into yellow—it is difficult to draw sharp lines between the various diagnoses in the autism spectrum.

And, like the autism spectrum itself, the spectrum of autism research at Caltech also runs a gamut. Adolphs, for example, studies brain differences between adults on the high-functioning portion of the autism spectrum and the general public—the so-called neurotypical population. Neurobiologist John Allman's work on a particular set of neurons is providing insight into a possible basis for some of autism's social quirks. And then there's neurobiologist Paul Patterson, who literally has just finished writing the book on the connection between the immune system and autism, and who is collaborating with biologist Sarkis Mazmanian to explore the connections between gastrointestinal symptoms and the brain in autism spectrum disorders.

They and half a dozen or so of their colleagues have come together in a sort of informal Autism Working Group, which meets regularly to talk about their individual findings and to brainstorm together. "People don't think of Caltech when they think about autism research," says Patterson. "But we have a lot going on here; a lot of insight to offer."

AN INFECTIOUS THEORY

Much of that insight comes from Patterson, who pioneered the study of the connections between the brain and the immune system in autism, schizophrenia, and depression a decade ago.

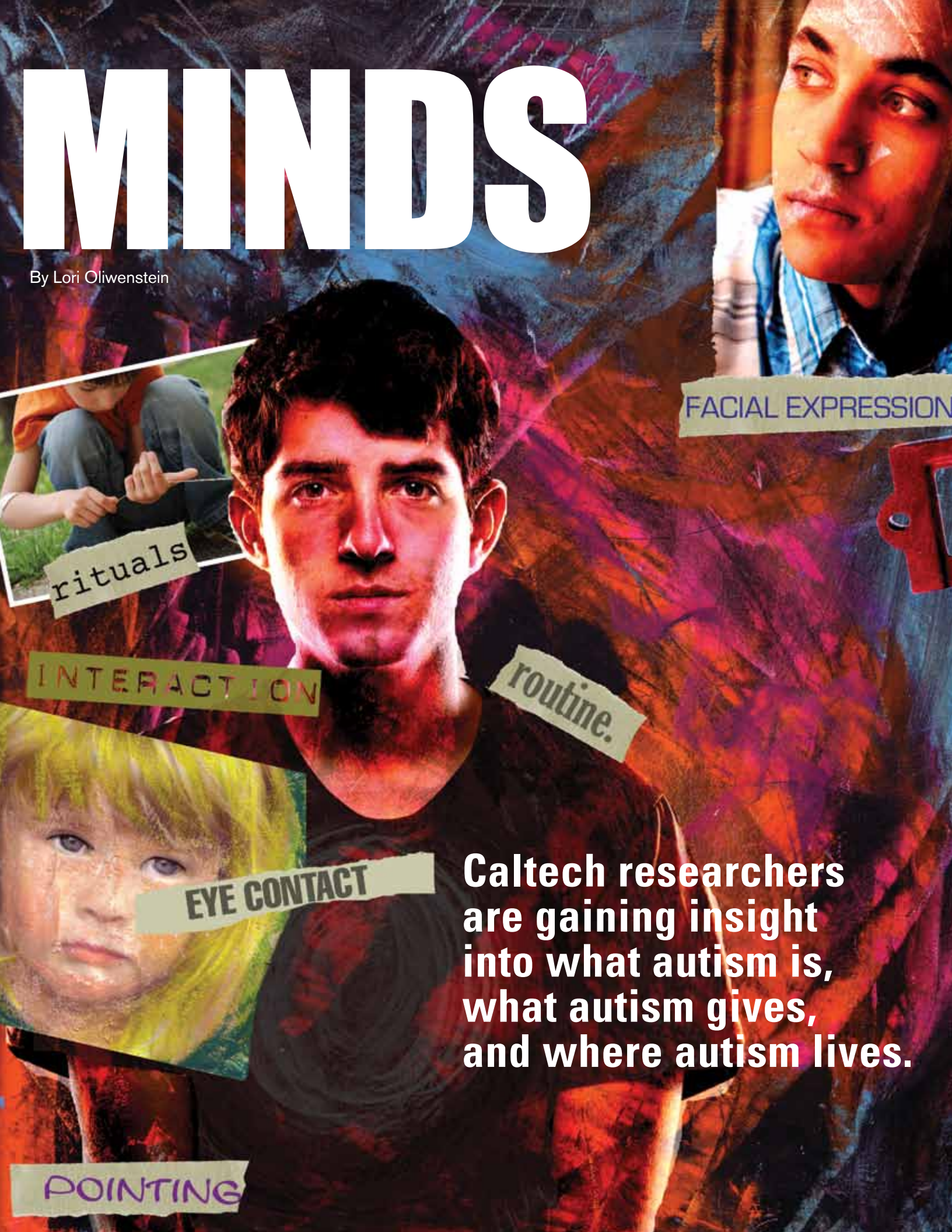
The main focus of that connection? Some kind of viral infection during pregnancy, Patterson explains. Or, rather, the immune response that infection inevitably engenders.

To bolster his argument, Patterson points to a recent study by Hjordis O. Atladottir of Aarhus University, Denmark, and colleagues—"an extraordinary look at over 10,000 autism cases" in the Danish Medical Register, which is a comprehensive database of every Dane's medical encounter from cradle to grave—that showed a strong epidemiological link between autism in a child and a first-trimester viral infection in the mother. "And we've found that if you give a mouse the flu during pregnancy, or activate the mother's immune system directly without a pathogen, the offspring will show a neuropathology characteristic of autism, as well as the three cardinal symptoms of autism."

In mouse terms, that means exhibiting repetitive behavior such as excessive self-grooming and compulsively and furiously burying marbles placed on its bedding. Freaking out, rather than making friends, when faced with an unfamiliar mouse. And communicating much less as a young pup with its mother, or as an adult with other mice. (Mice "talk" to one another at ultrasonic frequencies, requiring a special microphone and recording equipment to make their conversations audible to human ears.)

MINDS

By Lori Oliwenstein



Caltech researchers are gaining insight into what autism is, what autism gives, and where autism lives.

Patterson observed the same neuropathology and behavior in mice who had never had an infection, but were instead given synthetic molecules that mimic the presence of a virus. In other words, Patterson found that simply mounting an immune response may be enough to steer a fetus down a path that could eventually lead to an autism-like condition after birth.

That "may" is key. There is definitely a connection between infections during pregnancy—especially the early months of pregnancy—and increased risk of autism (and, as Patterson has also shown, schizophrenia) in the offspring, he says, but that is not the same as saying it's a direct, 100 percent, if-you-get-sick-while-you're-pregnant-your-baby-will-have-autism correlation.

How does it all work? Patterson thinks cytokines—proteins produced by the body in response to an infection—play a role. In fact, grad student Steve Smith (PhD '08) found that giving pregnant mice one cytokine in particular, called interleukin-6 (IL-6), leads to offspring who exhibit autistic and schizophrenic features. "It was really unexpected that a single injection of a single cytokine would exert such a powerful effect," Patterson notes.

This is an important clue connecting the mother's immune reaction to the fetus's brain development. It's known that the interleukins are inflammation-boosters, and inflammation is all well and good when you need to wake up the immune system and get it to pour white cells into an infected area. But it has its unintended side effects as well; the inflammatory response often takes a scattershot approach, meaning that healthy tissues can also get caught up in the onslaught.

For instance, grad student Elaine Hsiao is finding that IL-6 and other cytokines not only work directly on the fetal brain, but can also alter the function of the placenta, which would have indirect effects on fetal development.

Why does an immune response sometimes result in a developmental disability—and sometimes not? Patterson thinks it could be the timing of the infection, or the genetic makeup of the mother, or her fetus that modulates the outcome.

The questions Patterson is asking about inflammation and the brain might apply to other parts of the body as well. So he and biologist Sarkis Mazmanian are looking at the gastrointestinal problems somewhat commonly found in kids with autism, and how those might be related to the development of autism.

"The evidence that there are gastrointestinal issues in children with autism is pretty good," Patterson notes. "You test it by feeding a child a molecule that gets broken down in the gut; if the gut is leaky—if there is some dysfunction there—then the breakdown product gets into the bloodstream. And research has indeed found that this happens more often in kids with autism than in typical kids."

There's similarly strong evidence, he says, implicating our normally helpful and cooperative intestinal bacteria—as it turns out, the various types of bacteria found in the digestive systems of typical and autism spectrum kids tend to differ.

But while the bowel-bacterium-brain connection is clear, it's still not known just how widespread it is. "Estimates of the percentage of people with autism who are affected by these gastrointestinal differences vary from 20 to 70 percent," Patterson says. "Clearly, the science is lagging; there's still a lot of work to be done."

Which is why the science-and-advocacy group Autism Speaks recently brought Patterson and Mazmanian together with immunologist Paul Ashwood at UC Davis and pediatrician Alessio Fasano from the University of Maryland to explore the gut-brain-immune connections in mice and in kids with autism spectrum disorders.

"You have Sarkis's and Alessio's expertise in the human gastrointestinal system, you have Paul's expertise in children with autism, and then you have our mouse model," says Patterson. "That makes for a pretty exciting consortium. It should allow us to look at autism in new and unprecedented ways."

LOOKING AND CONNECTING

Ralph Adolphs, too, is looking at autism in new ways—and looking at *looking* in autism as well.

Adolphs, who runs the Autism and Asperger Syndrome Research Program at Caltech, spends most of his time working with high-functioning adults with autism. "We're exploring the social differences people with autism have," says Adolphs. "We're looking at every-

thing from eye-tracking, to reasoning, to complex theory-of-mind stuff, which is about understanding what others feel or think. We hope one day to be able to tell a story about the roles of particular brain areas, and how the white-matter connections between them look abnormal, and how that causes the effects we see."

For example, people with autism look at faces differently—focusing not on the other person's eyes, the way a neurotypical person would, but on the center of the face or on a point beside the face. Several research groups, including Adolphs's lab, have discovered that this is linked to the brain's amygdala, which is known to play roles in face recognition and in the processing of emotions—both our own and others'.

The amygdala is also involved in social interactions, so Adolphs's team is looking at how being aware of other people affects behavior. In one set of experiments, volunteers were asked to make charitable donations (with their own money!) in the presence or absence of an observer. As expected, neurotypical people gave bigger sums when other people were watching. By contrast, the people with high-functioning autism gave the same amount either way. "For most of us, when other people are watching, we act differently," he says. "But we've found that people with autism lack that behavioral change. They don't seem to think about what other people think of them."

But at its root, this seems to be more about what you notice around you, and how you respond to it, rather than a lack of caring. "What's interesting is figuring out what people with autism pay attention to," says Adolphs. "It's not that their amygdala doesn't work, it's that it works differently."

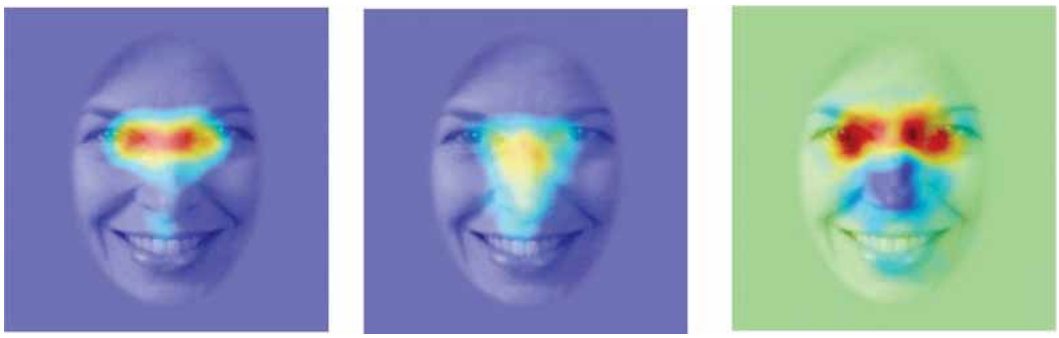
Neurobiologists John Allman and Atiya Hakeem (BS '93) have also been focusing on a component of the brain that may work differently in people with autism. Called the von Economo neurons, these cells are thought to play a key role in your ability to quickly and intuitively assess a situation—say, for example, when you meet someone for the first time, and come to an immediate conclusion about how to respond to their greeting. Those sorts of snap judgments, Allman says, are much more difficult for people with autism, who tend to have trouble realizing that what you say when you first meet a new client is very different from the way you should respond upon first meeting your brother's new girlfriend or your long-lost Aunt Sadie.

And that, he posits, may well be due to abnormalities in the connections these neurons make or where they wind up in the brain. The latter notion has since begun to gain traction elsewhere—a recent study led by Micaela Santos of the Mount Sinai School of Medicine in New York has found that children with autism have an oversupply of von Economo neurons in the fronto-insular cortex relative to another type of neuron. This brain structure is linked not only to your emotional awareness and empathy, but also to your internal awareness—of the state of your digestive system, the sensation of pain, and the like. This fits well with the known tendency of people with autism to be hypersensitive to sound, light, temperature and other stimuli.

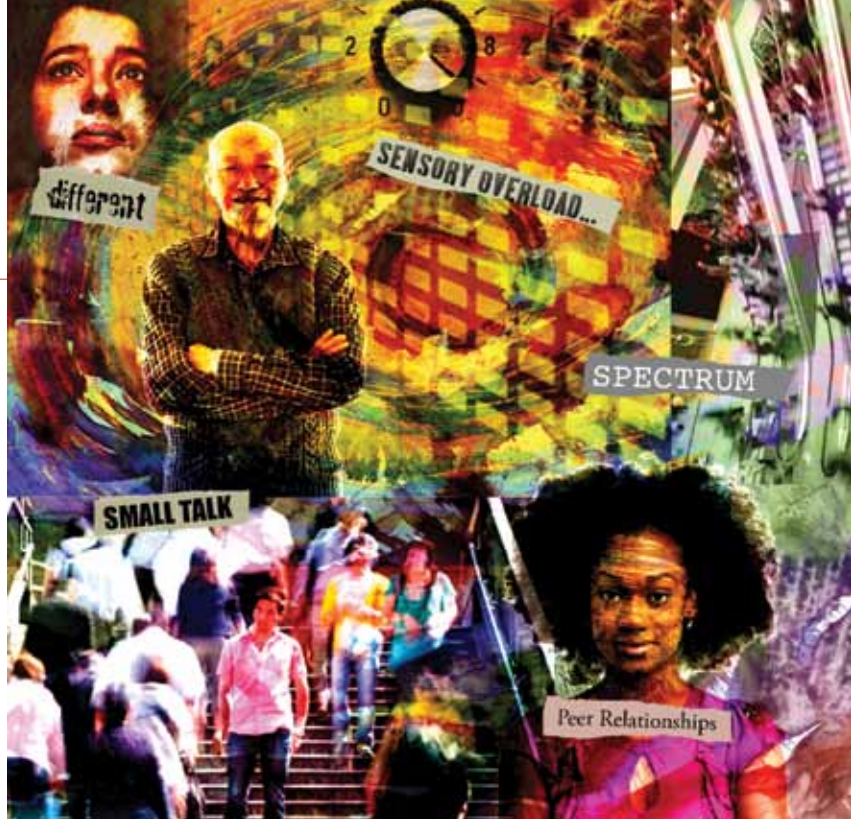
The missed or unusual connections both Adolphs and Allman are looking at may be a critical part of the story, Adolphs adds. Indeed, he says, there's a sort of "globally abnormal connectivity in the brains of people with autism."

Which is why Adolphs and Caltech psychology researcher Lynn Paul have been studying a group of people born without a corpus callosum—the bundle of nerve fibers that connects the brain's two hemispheres. Intriguingly, a full third of such people also meet the diagnostic criteria for having an autism spectrum disorder.

The team recently found that despite the missing 200 million or so connections between neurons that the corpus callosum normally provides, these folks' left and right hemispheres still manage to carry on communications with one another. "This finding really amazed us," says Adolphs, "and it shows that you can generate remarkably normal functional networks that communicate between different parts of the brain even when the wiring is all scrambled. There must be some fundamental principle about how the brain orga-



These eye-tracking studies show how we "read" other people's faces. Left: Neurotypical people look at the eyes. Middle: People with autism tend to focus on or around the bridge of the nose. Right: Superposing the two, with red being the neurotypical folks and blue being people with autism.



nizes itself functionally during development, such that it can do so even when the corpus callosum is entirely missing."

Although the corpus callosum study looked at a specialized population, most of Adolphs's other findings have come about thanks to the cooperation of some 40 adult volunteers with diagnoses of high-functioning autism, Asperger's, or PDD-NOS.

Why study high-functioning adults? Adolphs admits that at least some of the impetus is purely practical. It's much easier to get adults to sit through long hours of testing and MRI scanning than it is to get any child—with or without autism—to do the same. But the payoff is worth it. Those hours they've spent lying motionless in the MRI mean that Adolphs knows these people inside and out.

And there are other draws as well. For one thing, the overwhelming majority of autism research is done on children and is about children. "You hear a great deal about children with autism, but not so much about adults," Adolphs says. "In fact, although autism starts to be noticed in childhood, it's not a childhood disorder. Instead, it's a disorder of development, and those children who have autism become adults with autism, and eventually elderly adults with autism. We know extremely little about how autism interacts with the aging process, for instance."

Indeed, he notes, while some of autism's symptoms are most apparent in childhood—delayed speech, for instance—others don't make themselves known until later in life and are a direct result of the atypical development that came before. "Autism affects development," Adolphs says, "and in turn, development affects autism. And so we want to look at the interaction of autism with the entire developmental lifespan."

They also want to look at the way autism interacts to create not only deficits, but benefits. "One of the things we're getting with such detailed assessments is a profile of peaks and valleys of ability," says Adolphs. "People with autism have strengths and they have weaknesses, just as we all do."

Mapping these peaks and valleys will not only help academics like Adolphs and his Caltech colleagues learn the ins and outs of autism, it will help society as a whole understand how best to help people with autism exploit their strengths and work around their weaknesses.

And lest anyone think these lessons apply only to those with a diagnosis that falls clearly onto the autism spectrum, Adolphs has a few words of caution. "Autism is just one extreme of this broad spectrum of individual differences that stretch across the general population," he says. For instance, in a 2008 paper published in *Current Biology*, Adolphs and colleagues showed that the parents of children with autism—who were not themselves autistic—frequently respond to faces in a manner similar to children with autism, spending more time looking at other people's mouths than at their eyes.

"It turns out that what we're learning about autism," Adolphs notes, "may be relevant to almost anyone who is a little bit different, who does things differently."

That means you over there in the corner, who hates large parties and small talk. And you, the person who plugs your ears at a concert, because you feel physically assaulted by the noise. And you, spending hours upon hours fixing up old computers, or old cars, or organizing your model-train collection.

Not diseased. Not impaired. Just different. Just like you and me. E&S

Paul Patterson is the Anne P. and Benjamin R. Biaggini Professor of Biological Sciences at Caltech. His research on autism and schizophrenia is funded by Autism Speaks, the International Rett Syndrome Foundation, the National Institute of Mental Health (NIMH), the U.S.-Israel Binational Science Foundation, the Simons Foundation, the McGrath Foundation, the Weston Havens Foundation, the Della Martin Foundation, the Department of Defense, and the Caltech Innovation Initiative. His book,* Infectious Behavior: Brain-Immune Connections in Autism, Schizophrenia, and Depression*, was published in September by the MIT Press.

Ralph Adolphs is the Bren Professor of Psychology and Neuroscience and professor of biology, as well as director of the Caltech Brain Imaging Center. His research is supported by grants from Autism Speaks, NIMH, and the Simons Foundation.

John Allman is the Frank P. Hixon Professor of Neurobiology. His research is funded by the James S. McDonnell Foundation, NIMH, and the Simons Foundation. He and neuropsychiatrist Peter Williamson are the coauthors of* The Human Illnesses: Neuropsychiatric Disorders and the Nature of the Human Brain*, published in January 2011, by the Oxford University Press.