McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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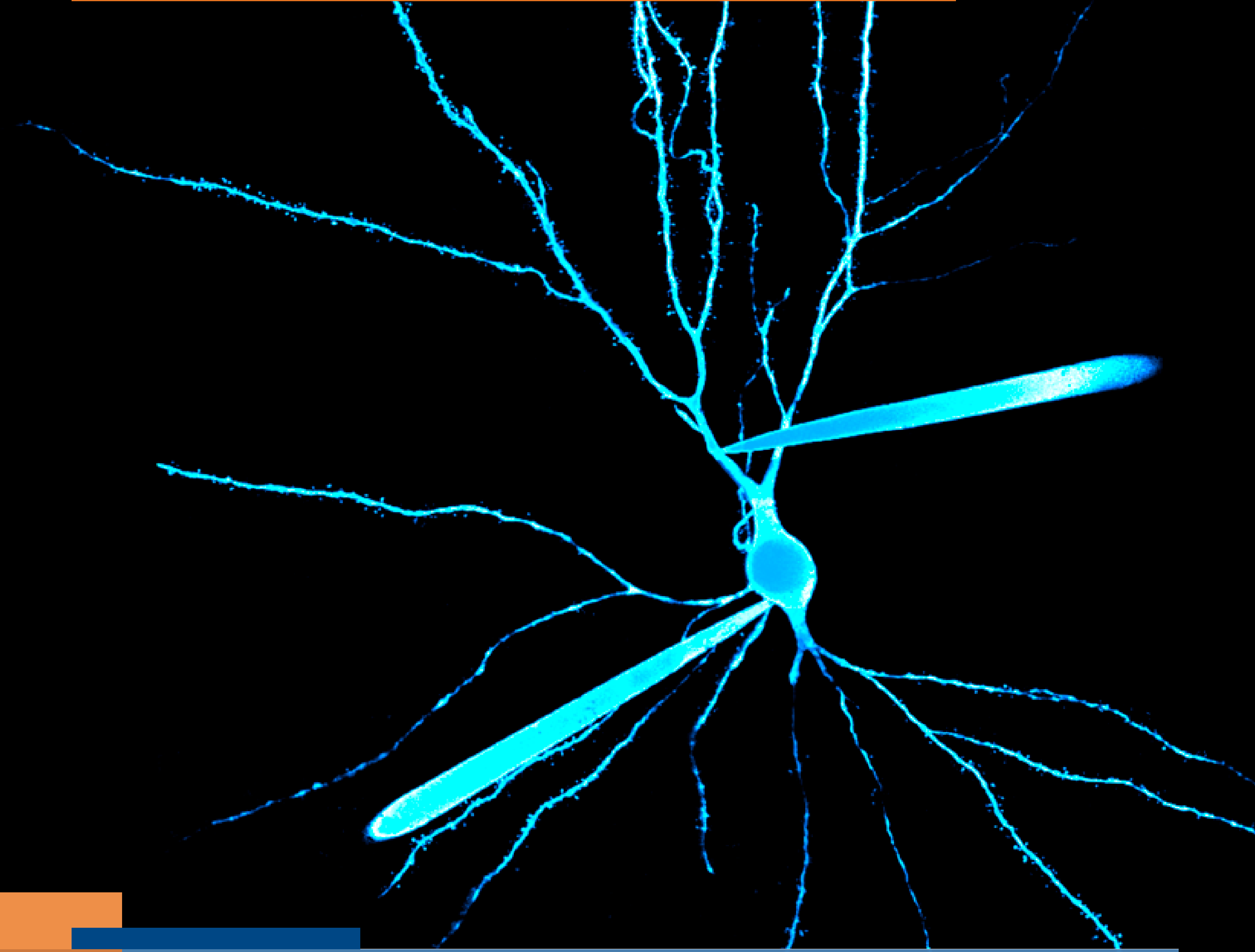

Listening to Neurons

The Harnett Lab is investigating how the brain's elemental units give rise to the mind

FROM THE **DIRECTOR**

The computing power of the human brain is in many ways more impressive than the largest supercomputer, yet it achieves this with an energy consumption no bigger than an electric lightbulb. One key to this remarkable efficiency is the computational power of individual neurons, of which there are almost 100 billion in a human brain. As you can read in this issue, my colleague Mark Harnett is studying how information is processed by individual neurons, and how they work together to form functional circuits within the living brain. Mark has assembled a talented team of young researchers whose technical skills allow them to make electrical recordings from the tiny branches of individual neurons, known as dendrites. Their work is helping to reveal computations within individual dendrites that represent the fundamental building blocks of brain function.

One of Mark's questions is whether and how human neurons are different from those of mice and other experimental animals. The only way to answer this is by studying live human brain tissue, pieces of which can sometimes be obtained through epilepsy surgery. We are fortunate to be collaborating with a world-class neurosurgical team at Massachusetts General Hospital, who share our interest in understanding the fundamental workings of the human brain and its implications for both science and medicine.

Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

On the cover:
Two patch clamp electrodes are positioned on a human cortical neuron (one on the cell body and the other on a dendrite) to assess its biophysical properties.

Image: Lou Beaulieu-Laroche and Mark Harnett

By zeroing in on the neuron—the brain's most basic computational unit—Mark Harnett is beginning to untangle fundamental questions about the human mind.

When McGovern Investigator Mark Harnett gets a text from his collaborator at Massachusetts General Hospital, it's time to stock up on Red Bull and coffee.

Because very soon—sometimes within a few hours—a chunk of living human brain will arrive at the lab, marking the start of an epic session recording the brain's internal dialogue. And it continues non-stop until the neurons die.

"That first time, we went for 54 hours straight," Harnett says.

Now two years old, his lab is trying to answer fundamental questions about how the brain's basic calculations lead

Listening to Neurons

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to the experience of daily life. Most neuroscientists consider the neuron to be the brain's basic computational unit, but Harnett is focusing on the internal workings of individual neurons, and in particular, the role of dendrites, the elaborate branching structures that are the most distinctive feature of these cells.

Years ago, scientists viewed dendrites as essentially passive structures, receiving neurochemical information that they translated into electrical signals and sent to the cell body, or soma. The soma was the calculator, summing up the data and deciding whether or not to produce an output signal, known as an action potential. Now though, evidence has accumulated showing dendrites to be capable of processing information themselves, leading to a new and more expansive view in which each individual neuron contains multiple computational elements.

Due to the enormous technical challenge such work demands, however, scientists still don't fully understand the biophysical mechanisms behind dendritic computations. They understand even less how these mechanisms operate in and contribute to an awake, thinking brain—nor how much the mouse models that have defined the field translate to the vastly more powerful computational abilities of the human brain.

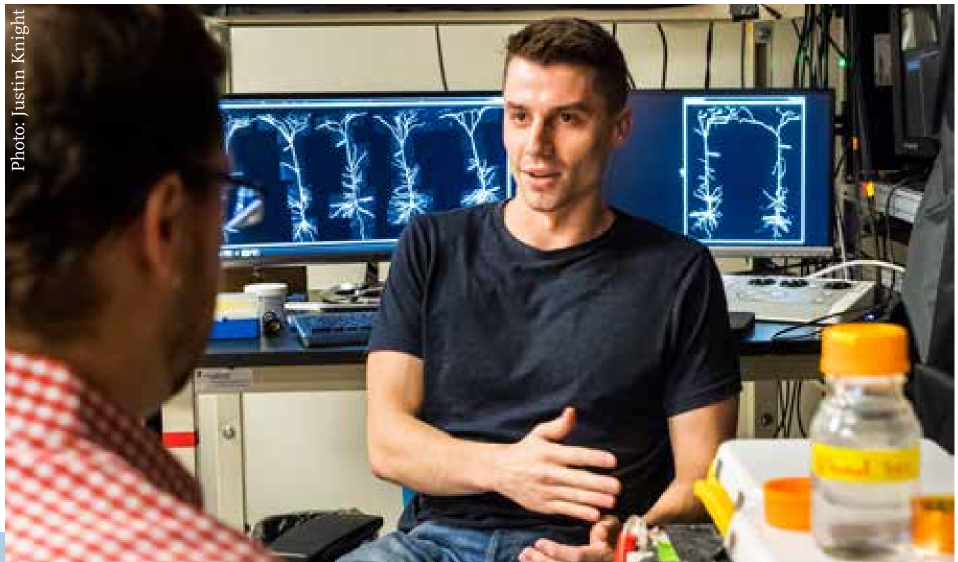
Harnett is in an ideal position to untangle some of these questions, owing to a rare combination of the technology and skills needed to record from dendrites—a feat in itself—as well as access to animals and human tissue, and a lab eager for a challenge.

Human Interest

Most previous research on dendrites has been done in rats or mice, and Harnett's collaboration with MGH addresses a deceptively simple question: are the brain cells of rodents really equivalent to those of humans?

Researchers have generally assumed that they are similar, but no one has studied the question in depth. It is known, however that human dendrites

Mark Harnett (top) studies how information is processed within single neurons, whose complex shapes reflect their sophisticated computational capacities.



Lou Beaulieu-Laroche, a graduate student in Harnett's lab, uses a technique called patch clamping to record electrical activity in individual neuronal branches, known as dendrites.

are longer and more structurally complex, and Harnett suspects that these shape differences may reflect the existence of additional computational mechanisms.

To investigate this question, Harnett reached out to Sydney Cash, a neurologist at MGH and Harvard Medical School. Cash was intrigued. He'd been studying epilepsy patients with electrodes implanted in their brains to locate seizures before brain surgery, and he was seeing odd quirks in his data. The neurons seemed to be more connected than animal data would suggest, but he had no way to investigate. "And so I thought this collaboration would be fantastic," he says. "The amazing electrophysiology that Mark's group can do would be able to give us that insight into the behavior of these individual human neurons."

So Cash arranged for Harnett to receive tissue from the brains of patients undergoing lobe resections—removal of chunks of tissue associated with seizures, which often works for patients for whom other treatments have failed.

Logistics were challenging—how to get a living piece of brain from one side of the Charles River to the other before it dies? Harnett initially wanted to use a drone; the legal department shot down that idea. Then he wanted to preserve the delicate tissue in bubbling oxygenated solution. But carting cylinders of hazardous compressed gas around the city was also a nonstarter. "So, on the first one, we said to heck with it, we'll just see if it works at all," Harnett says. "We threw the brain into a bottle of ice-cold solution, screwed the top on, and told an Uber driver to go fast."

When the cargo reaches the lab, the team starts the experiments immediately to collect as much data as possible before the neurons fail. This process involves the kind of arduous work that Harnett's first graduate student, Lou Beaulieu-Laroche, relishes. Indeed, it's why the young Quebecois wanted to join Harnett's lab in the first place. "Every time I get to do this recording, I get so excited I don't even need to sleep," he says.

First, Beaulieu-Laroche places the precious tissue into a nutrient solution, carefully slicing it at the correct angle to reveal the neurons of interest. Then he begins patch clamp recordings, placing a tiny glass pipette to the surface of a single neuron in order to record its electrical activity. Most labs patch the larger soma; few can successfully patch the far finer dendrites. Beaulieu-Laroche can record two locations on a single dendrite simultaneously.

"It's tricky experiment on top of tricky experiment," Harnett says. "If you don't succeed at every step, you get nothing out of it." But do it right, and it's a human neuron laid bare, whirring calculations visible in real-time.

The lab has collected samples from just seven surgeries so far, but a fascinating picture is emerging. For instance, spikes of activity in some human dendrites don't seem to show up in the main part of the cell, a peculiar decoupling mice don't show. What it means is still unclear, but it may be a sign of Harnett's theorized intermediary computations between the distant dendrites and the cell body.

"It could be that the dendrite network of a human neuron is a little more complicated—maybe a little bit smarter," Beaulieu-Laroche speculates. "And maybe that contributes to our intelligence."

Active Questioning

The human work is inherently limited to studying cells in a dish, and that gets to Harnett's real focus. "A huge amount of time and effort has been spent identifying what dendrites are capable of doing in brain slices," he says. Far less effort has gone into studying what they do in the behaving brain. It's like exhaustively examining a set of tires on a car without ever testing its performance on the road.

To get at this problem, Harnett studies spatial navigation in mice, a task that requires the mouse brain to combine information about vision, motion, and self-orientation into a holistic experience. Scientists don't know how this integration happens, but Harnett thinks it is an ideal test bed for exploring how dendritic processes contribute to complex behavioral computations. "We know the different types of information must eventually converge, but we think each type could be processed separately in the dendrites before being combined in the cell body," he says.

Graduate student Marie-Sophie van der Goes (left) and postdoc Mathieu Lafourcade.

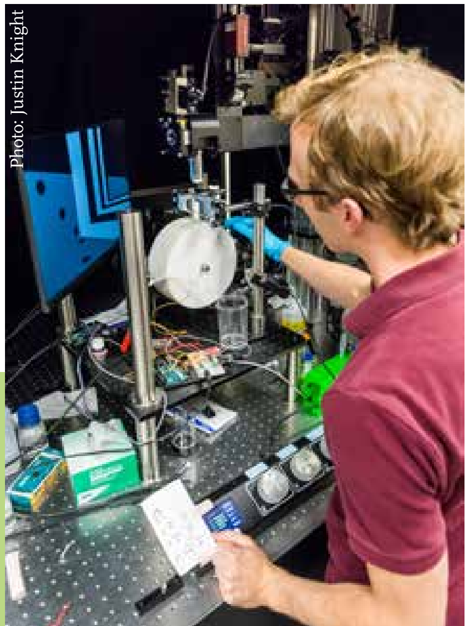


Photo: Justin Knight

Postdoc Lukas Fischer is developing ways to record brain activity in mice as they navigate a virtual reality environment.

The difficult part is catching neurons in the act of computing. This requires a two-pronged approach combining fine-grained dendritic biophysics—like what Beaulieu-Laroche does in human cells—with behavioral studies and imaging in awake mice.

Marie-Sophie van der Goes, Harnett's second graduate student, took up the challenge when she joined the lab in early 2016. From previous work, she knew spatial integration happened in a structure called the retrosplenial cortex, but the region was not well studied.

"We didn't know where the information entering the RSC came from, or how it was organized," she explains.

She and laboratory technician Derrick Barnagian used reverse tracing methods to identify inputs to the RSC, and teamed up with postdoc Mathieu Lafourcade to figure out how that information was organized and processed. Vision, motor and orientation systems are all connected to the region, as expected, but the inputs are segregated, with visual and motor information, for example, arriving at different locations within the dendritic tree. According to the patch clamp data, this is likely to be very important, since different dendrites appear to process information in different ways.

The next step for Van der Goes will be to record from neurons as mice perform a navigation task in a virtual maze. Two other postdocs, Jakob Voigts and Lukas Fischer, have already begun looking at similar questions. Working with mice genetically engineered so that their neurons light up when activated, the researchers implant a small glass window in the skull, directly over the RSC. Peering in with a two-photon microscope, they can watch, in real time, the activity of individual neurons and dendrites, as the animal processes different stimuli, including visual cues, sugar-water reward, and the sensation of its feet running along the ground.

It's not a perfect system; the mouse's head has to be held absolutely still for the scope to work. For now, they use a virtual reality maze and treadmill, although thanks to an ingenious rig Voigts invented, the set-up is poised to undergo a key improvement to make it feel more life-like for the mouse, and thus more accurate for the researchers.

Human Questions

As much as the lab has accomplished so far, Harnett considers the people his greatest achievement. "Lab culture's critical, in my opinion," Harnett says. "How it manifests can really affect who wants to join your particular pirate crew."

And his lab, he says, "is a wonderful environment and my team is incredibly successful in getting hard things to work."

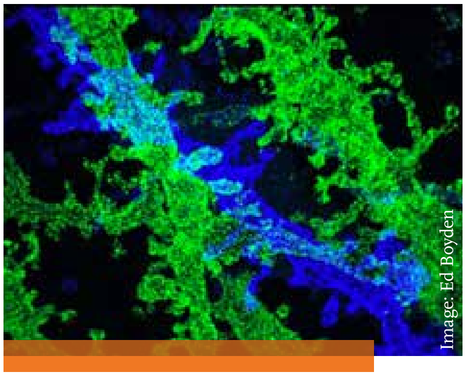
Everyone works on each other's projects, coming in on Friday nights and weekend mornings, while ongoing jokes, lab memes, and shared meals bind the team together. Even Harnett prefers to bring his laptop to the crowded student and postdoc office rather than work in his own spacious quarters. With only three Americans in the lab—including Harnett—the space is rich in languages and friendly jabs. Canadian Beaulieu-Laroche says France-born Lafourcade speaks French like his grandmother; Lafourcade insists he speaks the best French—and the best Spanish. "But the Germans never speak German," he wonders.

And there's another uniting factor as well—a passion for asking big questions in life. Perhaps it is because many of the lab members are internationally educated and have studied more philosophy and literature than a typical science student. "Marie randomly dropped a Marcus Aurelius quote on me the other day," Harnett says. He'd been flabbergasted, "But then I wondered, what is it about the fact that they've ended up here and we work together so incredibly well? I think it's that we all think about this stuff—it gives us a shared humanism in the laboratory." ■

Photo: Justin Knight

Mark Harnett (front, second from right) with members of his lab.

Three McGovern Researchers Receive NIH Director's Awards



Neurons in the hippocampus, imaged with Ed Boyden's expansion microscopy (ExM) technique.

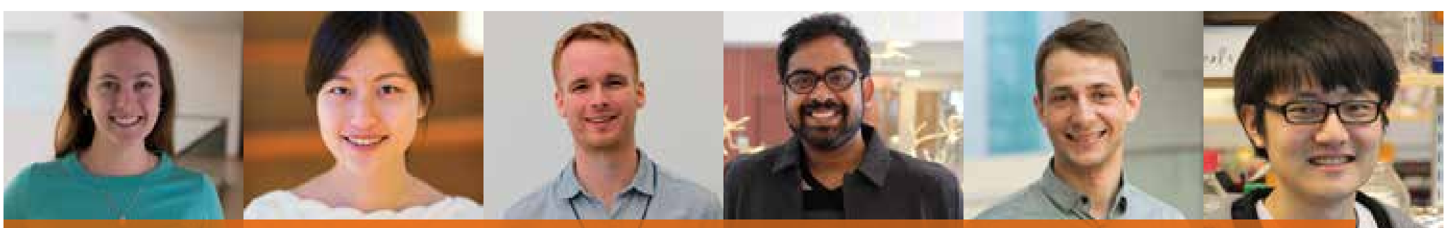
The High-Risk, High-Reward Research (HRHR) program, supported by the National Institutes of Health (NIH) Common Fund, has awarded 86 grants to scientists with unconventional approaches to major challenges in biomedical and behavioral research. Ten of the awardees are affiliated with MIT, including three from the McGovern Institute. The NIH typically supports research projects, not individual scientists, but the HRHR program identifies specific researchers with innovative ideas to address gaps in biomedical research. The program issues four types of awards annually—the Pioneer Award, the New Innovator Award, the Transformative Research Award and the Early Independence Award—to "high-caliber investigators whose ideas stretch the boundaries of our scientific knowledge."

McGovern Institute research affiliate Fei Chen has received a New Innovator Award, which supports "unusually innovative research" from early career investigators. As a postdoc with Ed Boyden, Chen pioneered novel molecular and microscopy tools to illuminate biological pathways and function. In his own lab at the Broad Institute, he will use one of these tools, expansion microscopy, to explore the molecular basis of glioblastomas, an aggressive form of brain cancer.

McGovern Investigator Feng Zhang has won a Pioneer Award, which challenges recipients to pursue "groundbreaking, high-impact approaches to a broad area of biomedical or behavioral science." Zhang, who developed the gene-editing technology known as CRISPR, plans to develop a suite of tools designed to achieve precise genome surgery for repairing disease-causing changes in DNA.

McGovern Investigator Ed Boyden is a recipient of the Transformative Research Award, which promotes "cross-cutting, interdisciplinary approaches that could potentially create or challenge existing paradigms." Boyden, who develops new strategies for understanding and engineering brain circuits, will use the grant to develop high-speed 3-D imaging of neural activity. ■

McGovern Institute Names Six Graduate Fellows



Six McGovern Institute graduate students have been awarded fellowships for the 2017-2018 academic year.

Three students, Sara Beach, Julia Juong and Steven Sando, have received Friends of the McGovern Institute fellowships. Beach is a graduate student in John Gabrieli's lab who is using neuroimaging to understand the brain basis of language, including language-learning aptitude, aphasia and dyslexia. Juong, a third-year graduate student in Feng Zhang's lab, is planning an ambitious project to identify transcription factors that drive the differentiation of specific neuronal cell types. Sando, who studies *C. elegans* behavior in Bob Horvitz's lab, has already discovered new behaviors in the worm and has successfully employed a variety of techniques to analyze these behaviors.

Ishan Gupta, a graduate student in Ed Boyden's lab, has been awarded the Janet and Sheldon Razin Fellowship for his work imaging the activity of the living brain with unprecedented precision. Gupta will explore ways to manipulate the optical properties of the living brain, allowing its dynamical activity to be imaged in real time.

The newly established Hock E. Tan and K. Lisa Yang Center for Autism Research has awarded its first student fellowship to Tobias Kaiser, a graduate student in the lab of Guoping Feng. Kaiser studies the mechanisms underlying psychiatric disease and his thesis research focuses on developing gene therapy tools for Shank-3-related autism.

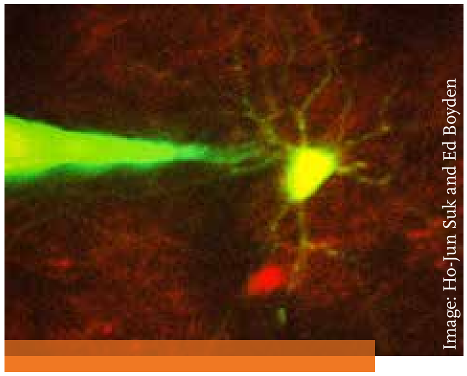
Xaiochen Sun, a graduate student in Yingxi Lin's lab, is the recipient of this year's Hugo Shong Fellowship. Sun's thesis project aims to genetically identify neurons that are involved in encoding sensory and behavioral information, and to understand how these neurons are modified by experience. ■

RESEARCH NEWS

Recording electrical signals from inside a neuron in the living brain can reveal a great deal of information, but it is very difficult, and only a handful of labs worldwide have the expertise to perform such recordings. To make this technique more widely available, **Ed Boyden** and his collaborators have devised a way to automate the process, using a computer algorithm that analyzes microscope images and guides a robotic arm to the target cell. This technology will allow more scientists to study single neurons and learn how they interact with other cells to enable cognition, perception, and other brain functions.

Mothers who experience an infection severe enough to require hospitalization during pregnancy are at higher risk of having a child with autism. Two new studies from the lab of **Gloria Choi** and collaborators at the University of Massachusetts Medical School shed more light on this phenomenon and identify possible approaches to preventing it.

Feng Zhang, who first harnessed CRISPR for genome editing, has engineered a new CRISPR-based system for editing RNA in human cells. This method makes it possible to repair mutated RNAs and proteins without altering the genome itself. In a paper published in *Science*,



A pipette guided by a robotic arm approaches a neuron identified with a fluorescent stain.

Zhang describes the new system, called RNA Editing for Programmable A to I Replacement, or "REPAIR." The system can change single RNA nucleotides in mammalian cells in a precise fashion. REPAIR has the ability to reverse disease-causing mutations at the RNA level, with profound implications for both research and disease treatment.

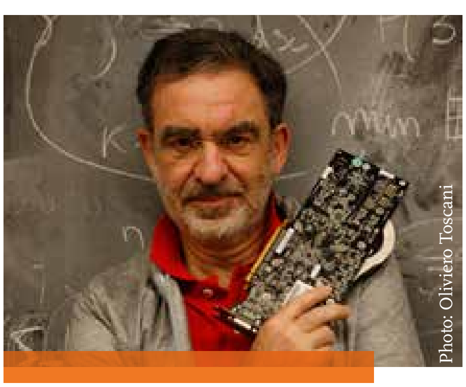
Nancy Kanwisher's lab collaborated with neurosurgeons in Japan to examine the coding of visual information in the human cerebral cortex. An epilepsy patient was implanted (for clinical reasons) with an array of cortical electrodes, allowing the researchers to locate regions that respond specifically to faces or to colors. When these areas were electrically

The new REPAIR system developed by the Zhang lab edits RNA, rather than DNA.

stimulated, the patient reported seeing illusory faces or rainbow colors, with no other perceptual effects, supporting the idea that these regions are specifically involved in single mental processes.

Making decisions is not always easy, especially when choosing between two options that have both positive and negative elements. Researchers in **Ann Graybiel**'s lab have now discovered that making decisions in this type of situation, known as a cost-benefit conflict, is dramatically affected by chronic stress. In a study of mice, they found that stressed animals were far likelier to choose high-risk, high-payoff options. ■

AWARDS & HONORS



McGovern Investigator Tomaso Poggio.

Tomaso Poggio was presented with the sixth Azriel Rosenfeld Lifetime Achievement Award at the International Conference on Computer Vision this October in Venice, Italy. The award was established to "honor outstanding researchers who are recognized as making significant contributions to the field of computer vision over longtime careers."

Feng Zhang a pioneer of the revolutionary CRISPR gene-editing technology, TAL effector proteins, and optogenics, is the 2017 recipient of the $500,000 Lemelson-MIT Prize, the largest cash prize for invention in the United States. The prize honors outstanding mid-career inventors who improve the world through technological invention and demonstrate a commitment to mentorship in science, technology, engineering and mathematics (STEM). ■

Ed Boyden signs the Book of Members at the American Academy of Arts and Sciences induction ceremony on October 7, 2017.

Boyden Inducted into American Academy

McGovern Investigator Ed Boyden was among 11 MIT researchers inducted into the American Academy of Arts and Sciences this October. ■

The Gabrieli Lab won first prize at the Halloween party for their portrayal of McGovern Investigator John Gabrieli (third from left).

McGovern Halloween Party

This Halloween, the McGovern Institute headquarters hosted its annual bash for the neuroscience community at MIT. Visit our website to see some of the costumes worn by members of our creative community. ■

The McGovern Institute for Brain Research at MIT is led by a team of world-renowned neuroscientists committed to meeting two great challenges of modern science: understanding how the brain works and discovering new ways to prevent or treat brain disorders. The McGovern Institute was established in 2000 by Lore Harp McGovern and the late Patrick J. McGovern, with the goal of improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, who is the Doris and Don Berkey Professor of Neuroscience at MIT and former head of intramural research at the National Institute of Mental Health.

Further information is available at: http://mcgovern.mit.edu

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