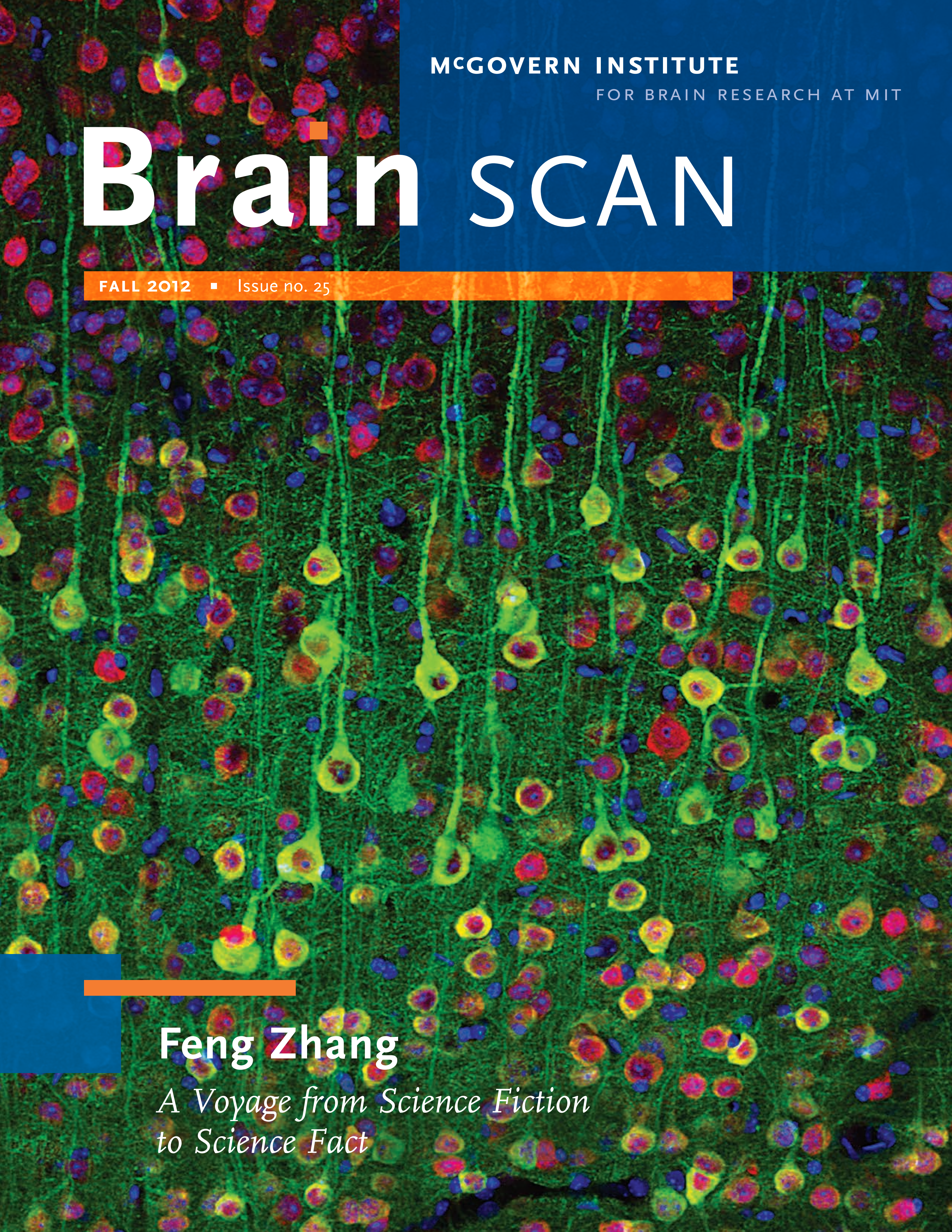
McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Brain SCAN

FALL 2012 ▪ Issue no. 25



Feng Zhang

A Voyage from Science Fiction to Science Fact

FROM THE DIRECTOR

The past decade has been a golden era for human genome research, and one of the fruits of this work has been a growing list of genes associated with brain diseases such as schizophrenia, bipolar disorder and autism. But finding these genes is only the first step toward understanding and treating disease – ultimately we must learn *how* they affect the brain.

Feng Zhang, whose work we feature in this issue, is developing revolutionary new methods to approach this challenge. His work takes inspiration from nature, adapting natural proteins for new functions that will make it possible to edit the genome and to switch genes on or off at will.

Feng's work is already helping to create new disease models by introducing disease-causing mutations into cultured cells and animals. In the future, these methods may also lead to new therapeutic approaches, perhaps even making it possible to repair damaged genes within the body.

There is no more important time in a scientist's career than the first years of independence, and we are deeply grateful to the donors who have supported Feng and other young researchers during these critical years.

Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

On the cover:

Neurons in the brain of a transgenic mouse engineered to express a protein that emits light when neurons become active.

Image: Qian Chen, Guoping Feng

Photo: Justin Knight

Feng Zhang, a pioneer in the emerging field of synthetic biology, is editing the genome to understand the biological basis of brain disease.

Feng Zhang was born in China in the early 1980s, a period of reform when the country was opening itself to outside influences, and its people were becoming fascinated with science. During that time, Chinese writers started dabbling in a new genre: science fiction.

Zhang, who joined the McGovern Institute in 2011, was hooked. "Chinese writers were opening their minds and imagining what the future might be like," he recalls. In those days, if he wasn't busy building things with Lego-like toys, he had his nose buried in sci-fi books.

Fast-forward twenty years or so, and Zhang's work now reads as if sprung from the pages of a sci-fi novel. His first major

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research project, as a graduate student at Stanford, was to control the brains of mice using laser light. Now, he is adapting proteins from microorganisms and using them to edit the genome – a "find/replace" tool for DNA sequences, which he hopes will make it possible to change the genome of any organism, and to switch genes on and off at will. This would have profound implications for many fields of research, but Zhang himself hopes to use it to understand the brain. In particular he hopes to create new ways to study the origins of brain disorders.

To Boldly Go

Zhang, who holds a joint appointment at the Broad Institute, credits a high school mentor for setting him on the path to success. At age 11 he had moved from China to Des Moines, Iowa, and through a school science program he had the opportunity to work in a local lab that was researching gene therapy. His mentor gave him a piece of advice that has stuck with him ever since.

"He told me I should work on things that are on the sexy side of practical," recalls Zhang. "It was a good way to put it. I want my work to be useful without ever being dull."

From Iowa, Zhang went on to Harvard, where he majored in chemistry and physics, bedrock subjects for modern science. But after graduation, he was ready for a new challenge and decided to study the brain. "Neuroscience seemed like a frontier," he explains. "There was so much that was still unknown."

He moved to Stanford University and in 2005 joined the newly formed lab of Karl Deisseroth, who along with Ed Boyden (now a McGovern Investigator) had recently begun to develop a revolutionary new method for controlling brain activity with light. The method, which came to be known as optogenetics, involved taking light-sensitive proteins from microorganisms and expressing them in neurons, making it possible to control the neurons' electrical activity with extraordinary precision.

Image: Le Cong

Structure of a TAL-effector protein wrapped around a DNA double helix. Image based on data from Mak et al., Science *2012.*

Zhang's first assignment as a starting graduate student was to find a way to express channelrhodopsin reliably in neurons, using technologies based on gene therapy with which he was already familiar. The project succeeded beyond all expectations, and it transformed Zhang's career. Within five years he had published 11 papers, an impressive track record for any student. His work attracted wide recognition; by the time he completed his PhD, optogenetics had been named by *Nature Methods* as its 2010 "Method of the Year" and by *Science* magazine as one of the most important tools of the past decade.

Fast, Cheap, and Ingenious

On the strength of his track record as a student, Zhang was awarded a prestigious Harvard Junior Fellowship, allowing him to bypass the usual postdoctoral apprenticeship and to begin to do independent research. Optogenetics had opened his eyes to the power of "synthetic biology," the idea of engineering living organisms based on tools borrowed from nature. But to take full advantage of the potential of optogenetics, further technical advances would be needed. The brain contains hundreds, perhaps thousands, of cell types, packed together and connected in networks of extraordinary complexity. To make sense of this complexity, Zhang needed a way to specifically target the light-sensitive proteins to certain cells but not others.

Photo: Justin Knight

Zhang in his laboratory with graduate student Silvana Konermann.

The best way to do this was by modifying the genome, taking advantage of the organism's own ability to express different genes in different cell types. While this was possible in certain species such as mice, it was still a painstaking process. Zhang wanted a better method.

He chose to work with George Church at Harvard Medical School, a pioneer in DNA research and one of the leaders of the human genome project. On the lookout for ideas, Zhang learned through a pair of papers published in *Science* in 2009 about a protein from bacteria that infect rice plants. This protein, known as a TAL effector or TALE, is used by bacteria to subvert the plant's natural defenses. It does this by binding to specific DNA sequences in the plant genome, switching on plant genes that are helpful to the bacterium. The protein was of particular interest because its DNA-binding domain had a simple modular structure – much like the Lego pieces Zhang played with as a child – raising the possibility that it could be

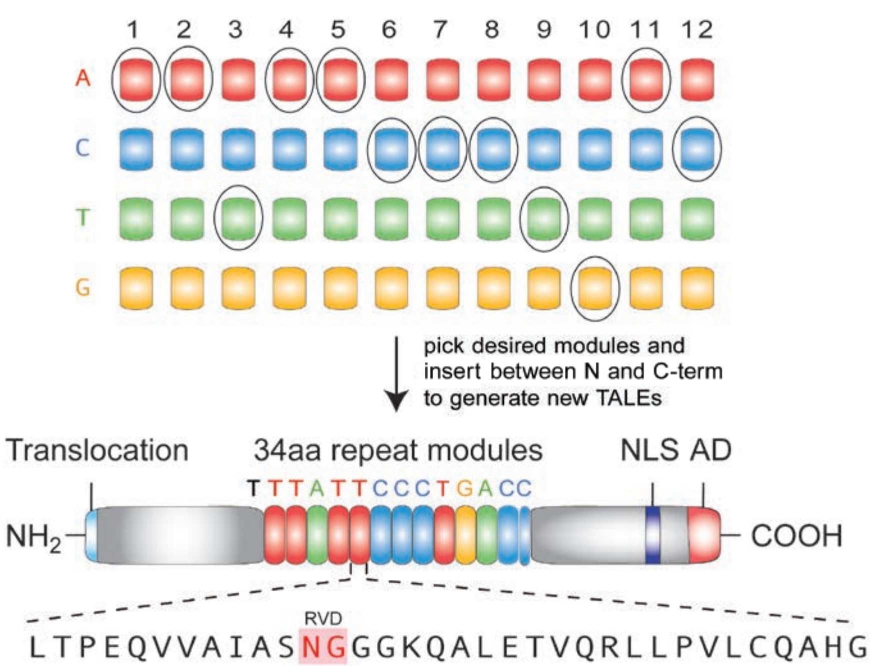


Image: Feng Zhang

TAL effectors can be engineered to bind to any desired DNA sequence.

artificially engineered simply by rearranging the order of the individual modules.

"We were hunting for something like this but never expected to find it in nature," says Le Cong, a graduate student who collaborated with Zhang at Harvard and later followed him to MIT.

Working together in Church's lab, Zhang and Cong devised a way to build artificial TALEs with the modules assembled in any desired order. Their method was much faster and cheaper than any existing alternative, and it allowed them to uncover a set of simple design rules for building TALEs that would recognize any desired DNA sequence. "It was as if for any given lock we could design a key to fit," says Zhang.

New Frontiers

The potential is enormous, and goes far beyond their original idea of targeting light-sensitive proteins to specific neurons. TALEs can be used to switch genes on or off, allowing cells to be reprogrammed. They can also be used as "molecular scissors" to make targeted cuts in the DNA sequence, and to introduce genetic changes that will be passed to the next generation.

There are many potential applications, but Zhang's immediate goal is to enable basic research including the creation of new disease models. For example, once human disease genes are identified, Zhang's method will allow researchers to express them in animals and to understand how they work to cause disease. TALEs may also be useful for creating stem cells that could be used to study, and perhaps even treat, human disease.

Perhaps the most exciting possibility is that TALEs could be used therapeutically to treat patients with genetic disorders, by silencing a mutant gene or activating its healthy counterpart, or even by editing the genome to correct the damaging mutation. Treating brain disease in this way will be challenging, but Zhang is undeterred. He points to the example of gene therapy, recently approved in Europe for the first time, to treat a rare metabolic disorder. "The idea of gene therapy in any form would have been considered science fiction until recently," says Zhang. "We should not be near-sighted when looking to the future."

Making History from Fantasy

For all its engineering sophistication, Feng's approach is simple in its essence. "To understand how biological systems work, we need tools to perturb them," he says. "My goal is to make that possible."

Guoping Feng, a long-time collaborator and now a McGovern colleague, says Zhang "thinks in terms of bigger questions than a single disorder, and he wants to develop tools across the board, not just for neuroscience." He adds, "It fits his personality. He is ambitious, creative, and pragmatic."

He is also a good citizen, making his methods freely available to other researchers. He created a website devoted to making TALEs widely available and to sharing his own lab's expertise with other researchers worldwide. "As a tool builder, you want your tools to be used," says Zhang. "Otherwise, what are you really contributing?"

His track record of innovation has landed Zhang many awards, including a McKnight Technological Innovations in Neuroscience Award, a National Institutes of Health Transformative Research Award, the Perl /UNC Neuroscience Prize (shared with Ed Boyden and Karl Deisseroth) and, most recently, in 2012, one of ten NIH Director's Pioneer Awards, which aim to fund exceptionally creative scientists with pioneering approaches to research.

Meanwhile Zhang spends as much time as he can where he is happiest, working in the lab to test his latest ideas. He appreciates having lab space both at the Broad and the McGovern Institutes, surrounded by experts in both genomics and neuroscience, where ideas can be cross pollinated between different fields. "You never know where the next idea will come from," he says. As someone who has made a career taking natural inventions from the microbial world and using them to manipulate the brain, Zhang's own success provides strong support for his argument – and an illustration of how, in the hands of the right scientist, history can be created from fantasy. ■

"As a tool builder, you want your tools to be used. Otherwise, what are you really contributing?"

— Feng Zhang

For their summer retreat, the Zhang Lab camped on Lovells Island in the Boston Harbor Islands.

Mehrdad Jazayeri to Join McGovern Faculty


Photo: Mehrdad Jazayeri

The McGovern Institute has appointed a new faculty member, Mehrdad Jazayeri, who will join the institute in January 2013. He will also be an assistant professor in MIT's Department of Brain and Cognitive Sciences.

Jazayeri is currently a postdoctoral researcher at the University of Washington, Seattle, where he studies the neurobiology of interval timing and how temporal regularities in the environment influence the brain's estimate of elapsed time. His research exploits multiple techniques including human psychophysics, computational modeling and monkey physiology. His most recent work combines electrophysiology with optogenetics in order to analyze neural function in the primate brain.

Jazayeri will pursue two long-term research themes at MIT. One line of research will examine how neurons track time, an ability that is crucial for mental capacities such as anticipating events, inferring causes and sequencing thoughts and actions. The other line of research will exploit timing tasks to understand the neural basis of sensorimotor integration, a key component of cognitive functions such as deliberation and probabilistic reasoning.

Originally from Iran, Jazayeri obtained his BSc in electrical engineering from Sharif University of Technology in Tehran. He received his PhD from New York University, where he studied with J. Anthony Movshon, winning the dean's award for the most outstanding dissertation in the university. After graduating, he was awarded a Helen Hay Whitney fellowship to join the laboratory of Michael Shadlen at the University of Washington, where he has been since 2007. ■

First Annual Gathering for Friends and Circle of Willis Society

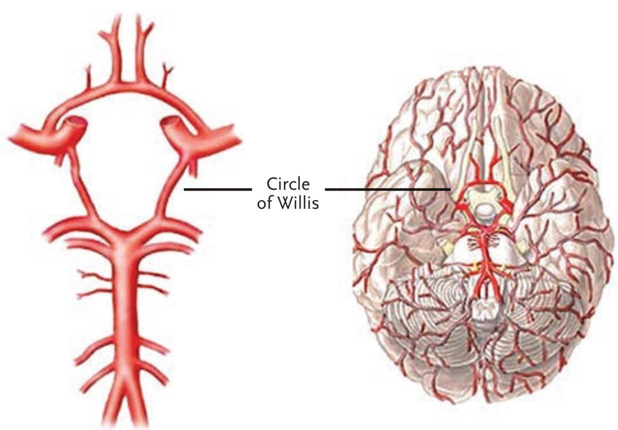


Image: ADAM.com

The Circle of Willis is a system of arteries that supplies blood to the brain.

Friends of the McGovern Institute and members of the new Circle of Willis Society joined the McGovern community for a special event featuring economist Karl Case, co-creator of the S&P/Case-Shiller Home Price Index. His afternoon talk, "Reflections on 22 Years of Living with Parkinson's Disease," was followed by group tours of McGovern labs and an evening reception in the atrium.

Our Circle of Willis Society was established to recognize contributors who support our research efforts with annual gifts of $1,500 or more. To learn more, contact Kara Flyg at kflyg@mit.edu or (617) 324-0134. ■

Gift to Support New Scanner

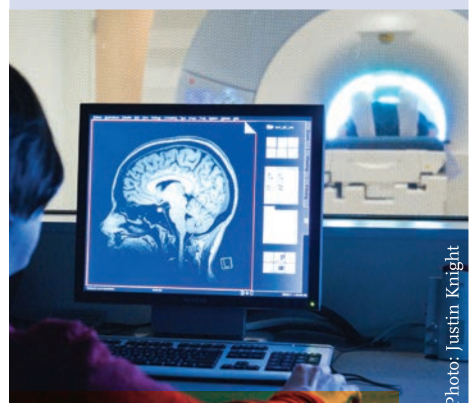
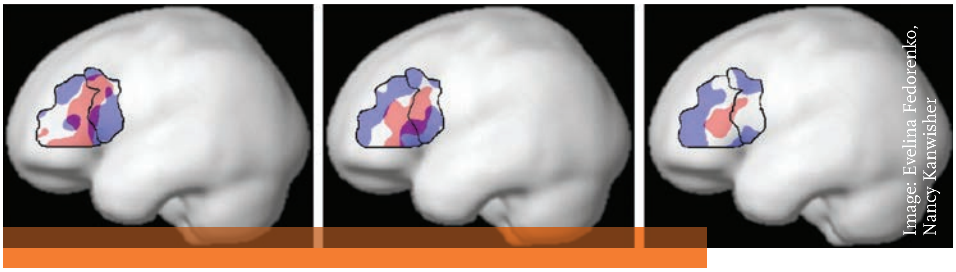


Photo: Justin Knight

A generous gift from Nancy and Jeffrey Halis '76 will support the McGovern Institute's acquisition of a new MRI scanner. The scanner will be installed in the Martinos Imaging Center at MIT, and will be used for a wide range of studies on human brain function in children and adults. ■

RESEARCH NEWS

Evelina Fedorenko, a research scientist in **Nancy Kanwisher**'s lab, has found that Broca's area – a region long believed to be the "speech center" of the brain – may actually consist of two distinct subregions. One of these is specialized for language but the other, unexpectedly, appears to act like a "central processing unit" that is involved in many different cognitive functions.



Brain scans showing language-selective (red) and domain-general (blue) subregions of Broca's area.

A team led by **Guoping Feng** has developed a way to monitor the activity of many brain cells simultaneously, using a protein that is genetically engineered to glow in the presence of calcium. The new imaging technique will allow researchers to study the brain circuits that underlie normal behavior, and could also provide new insights into the origins of autism, obsessive-compulsive disorder and other psychiatric diseases.

Ann Graybiel's lab has used optogenetics to identify a region of the rodent brain that can switch between new and old habits. The work suggests that it is possible to suppress habitual behaviors even though they appear to be deeply ingrained – encouraging news for anyone trying to kick a bad habit.

Emilio Bizzi and colleagues have found that after a stroke, the brain's ability to coordinate muscle activity is disrupted in specific ways. The pattern of disruptions depends on the severity of the stroke and the length of time since its occurrence. The findings could lead to improved rehabilitation for stroke patients, as well as a better understanding of how the motor cortex coordinates movements. ■

AWARDS AND HONORS

Martha Constantine-Paton (left) has won a lifetime achievement award from the Society for Neuroscience.

Martha Constantine-Paton received a lifetime achievement award from the Society for Neuroscience. The award recognizes individuals with outstanding career achievements in neuroscience who have also actively promoted the professional advancement of women in neuroscience.

Feng Zhang has received one of 10 NIH Director's Pioneer Awards, which support exceptionally creative scientists working to solve major challenges in biomedical and behavioral research. The award will fund Zhang's work on developing new genomic technologies to understand brain disorders.

Guoping Feng is the recipient of Indiana University's 2012 Gill Young Investigator Award. The award recognizes "exceptional scientists who have emerged as international leaders in cellular, membrane or molecular neuroscience." ■

Ed Boyden delivers the Harvey Prize lecture at the McGovern Institute.

McGovern researchers gave over 70 presentations at the recent meeting of the Society for Neuroscience in New Orleans.

Ed Boyden Honored for Optogenetics Work

Ed Boyden has been named by the Institute of Engineering and Technology as the first winner of the newly established A. F. Harvey Prize. The award was given to recognize Boyden's pioneering work on optogenetics, a method for controlling brain activity with light. Boyden delivered his prize lecture at the McGovern Institute on October 22. A video of the lecture will be made available on the McGovern Institute website. ■

McGovern Researchers in New Orleans

In October, McGovern researchers joined more than 30,000 participants at the world's largest conference on the brain – the Society for Neuroscience's annual meeting in New Orleans, Louisiana. The McGovern Institute was strongly represented, with researchers giving over 70 presentations during the five-day event. ■

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 Patrick J. McGovern and Lore Harp McGovern, who are committed to 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

Brain SCAN
Quarterly Newsletter of the McGovern Institute

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