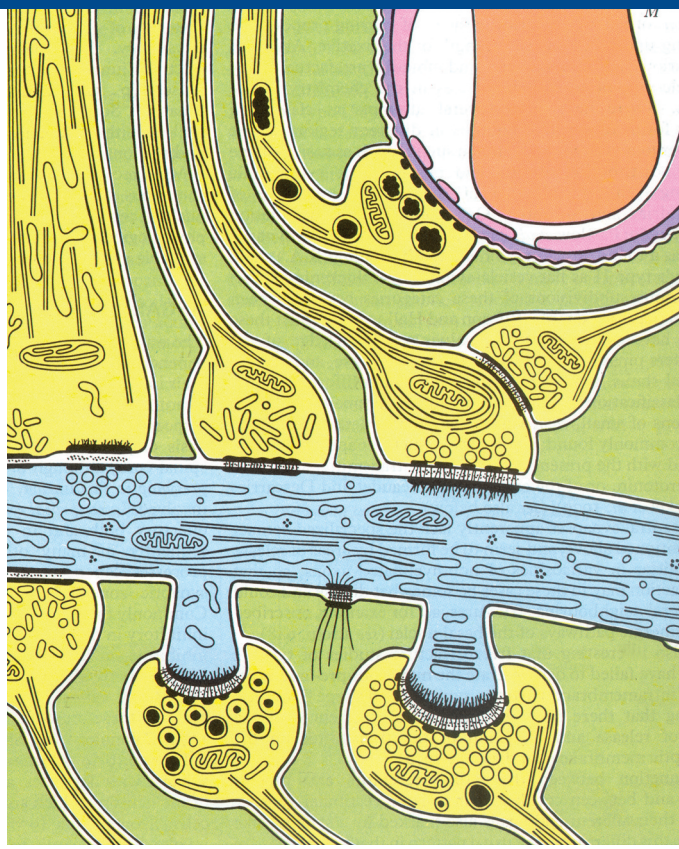
Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Issue no. 16 Spring 2010

From the director

The work of our newest faculty member, Guoping Feng, demonstrates once again that basic research can have unexpected clinical implications. While hunting for genes involved in building synapses, he engineered a mutant mouse with behaviors similar to obsessive-compulsive disorder in humans.



Cover art: Structures of synapses in the central nervous system.

Image reprinted from Gray's Anatomy,

I am delighted to welcome Guoping Feng and his research team to the McGovern Institute. Guoping, who joins us after ten years on the faculty of Duke University, is one of the world's leading experts on the development and function of synapses. He is also a pioneer in the development of new technologies for visualizing neurons in the living brain. I am especially excited about the relevance of his work to psychiatric disorders—he has created animal models for conditions such as obsessive-compulsive disorder, bipolar disorder and autism, allowing researchers to explore the mechanisms underlying these disorders in unprecedented detail. Guoping will become the first recipient of the Poitras Professorship of Neuroscience in the Department of Brain and Cognitive Sciences, thanks to the generous support of our long-standing supporters Jim and Pat Poitras.

This May, we hosted our sixth annual symposium, *Cells, Circuits, and Behavior*, which featured talks from eight exceptional researchers including a keynote from Steven Paul, former VP for research at Eli Lilly, who discussed the importance of basic research to developing new treatments for Alzheimer's disease. Also in May, we awarded the seventh annual Scolnick Prize in Neuroscience to Lily and Yuh-Nung Jan, whose research on fruit fly genetics has taken them into the realm of neurological disorders.

I am also pleased to introduce Roberta Sydney, the new chair of the Friends of the McGovern Institute. I am delighted that Roberta accepted our invitation to serve as Chair of the Friends and I look forward to working with her to engage more people in our mission.

Bob Desimone, Director

Guoping Feng, a pioneer in the study of synapses, joined the McGovern Institute in June.

Photo courtesy of Kent Dayton

LISTENING TO SYNAPSES

Guoping Feng studies the molecular building blocks of synapses. His work is leading to new animal models for psychiatric conditions such as obsessive-compulsive disorder, bipolar disorder and autism.

Guoping Feng is interested in how neurons talk to each other. "Unlike other cells, neurons don't function autonomously," says Feng, who joins McGovern Institute after 10 years on the faculty of Duke University. "Neurons must communicate with each other, and the apparatus for neural communication is the synapse."

Synapses are the connections that allow information to pass from one neuron to the next. The presynpatic neuron releases chemical messengers, or neurotransmitters, that diffuse across the gap and bind to receptors on the receiving or postsynaptic neuron. This binding can trigger the postsynaptic neuron to release its own neurotransmitters, thus allowing the signal to continue on to other neurons.

Feng was looking for genes involved in building synapses when, almost serendipitously, he engineered a mutant mouse that shows behaviors similar to human obsessive-compulsive disorder (OCD), and which may provide new insights into the underlying biology of this condition.

He plans to continue this work in his new laboratory at MIT, where he will hold the Poitras Professorship of Neuroscience, established by by James W. Poitras '63 and Patricia Poitras to support psychiatric research within the Department of Brain and Cognitive Sciences.

A random beginning

Feng grew up during Mao Zedong's Cultural Revolution near Hangzhou "the most beautiful place in China. We say above you have heaven and below you have Hangzhou." For millenia, the city of Hangzhou was a center for scholars—until Mao suppressed scholarship, closed universities, and sent many children to work in the field instead of the classroom. Somehow, 17-year-old Feng acquired enough knowledge that, upon Mao's death in 1976, he earned a rare spot at a university. He had dreamed of engineering big things, but a random placement system sent him instead to a medical university.

Feng chose a pediatric hospital internship because he loved children, but he was tortured by the suffering of children with terminal diseases. "I went to graduate school for biomedical studies in pharmacology because I naïvely thought we could develop drugs that could save these children.

As a student in China, Feng was randomly assigned to a medical university.

Image courtesy of Guoping Feng

Then I realized that we needed to understand the fundamental processes before we could design effective drugs."

As a graduate student at SUNY Buffalo, Feng became interested in neuroscience and wanted to learn more about the underlying basis of psychiatric diseases, but that seemed impossible without reliable animal models. Scientists often create animal models to investigate diseases of the human body for the purpose of better understanding disease mechanisms and exploring new treatment methods. But what about diseases of the mind?

"It's inherently difficult to model psychiatric disease because they have no known physical diagnostic markers and no clear pathological mechanism," explains Feng. "Besides, animals cannot talk. Mice can't tell us about their disturbed thoughts, dreams, or obsessions."

Undermining the scaffold

One approach to understanding psychiatric disorders is to identify a gene linked to a human disorder, and then mutate the same gene in mice to see what effect it has on the mouse's behavior. But Feng came from the opposite direction, first studying how a gene works in the mouse brain and then realizing it might be linked to a human psychiatric disorder.

Feng was interested in genes that produce what are called scaffold proteins. These proteins, as their name suggests, provide the structural framework on which other components of the synapse are assembled, including the receptors that allow neurons to respond to incoming signals. Given their structural importance, Feng suspected that mutations in scaffold proteins might disrupt this communication between neurons and thus produce behavioral effects.

He chose to study a gene called SAPAP3, which is specifically expressed in a brain region called the striatum. The striatum is the largest of the basal ganglia, a group of structures that have been implicated in many human disorders, including OCD, autism, addiction, ADHD, Parkinson's and Huntington's disease.

Repetitive grooming

The result of the experiment was dramatic. The mice that lacked the SAPAP3 gene developed normally for the first three months, but they began to develop large lesions on their faces and necks. Surveillance video of the mutant mice revealed that they were grooming themselves so much that they actually scratched their own hair off.

"It reminded us of the repetitive behaviors in OCD in people," Feng recalls. OCD is characterized by recurrent thoughts, aimless rituals, and repetitive actions—including excessive grooming, hair pulling, nail biting, and skin picking.

Another common feature of OCD is anxiety, and these mice exhibited anxiety-like behaviors, including avoiding open or unfamiliar areas. Since about half of OCD patients respond to Prozac, Feng wondered if Prozac would reduce either the excessive grooming or the anxiety in the knockout mice. It did both, and following six days of treatment with Prozac, the lesions began to heal.

For final proof that the mutated SAPAP3 gene was responsible for the abnormal mouse behavior, Feng used a genetic trick to add healthy copies of the gene back into the striatum of adult mice. This mouse version of gene therapy "rescued" the mice, preventing both excessive grooming and anxiety, and proving that the brain deficits caused by the genetic mutation are potentially reversible. Feng is now using this rescue method to determine precisely which synapses are responsible for the defect.

Going in Circles

"So now we had a mouse model for OCD, but would it help us understand the human disorder? Although OCD is highly heritable, we don't know the genetic basis, so we wanted to find out if variations of SAPAP3 in humans might explain some of that heritability," Feng says.

Working with physicians and genetists studying human OCD, his team has preliminary evidence that certain variants of SAPAP3 are indeed more prevalent in patients with OCD–like behaviors. Although SAPAP3 alone cannot explain the inheritance of OCD, Feng's results suggest that other similar genes involved

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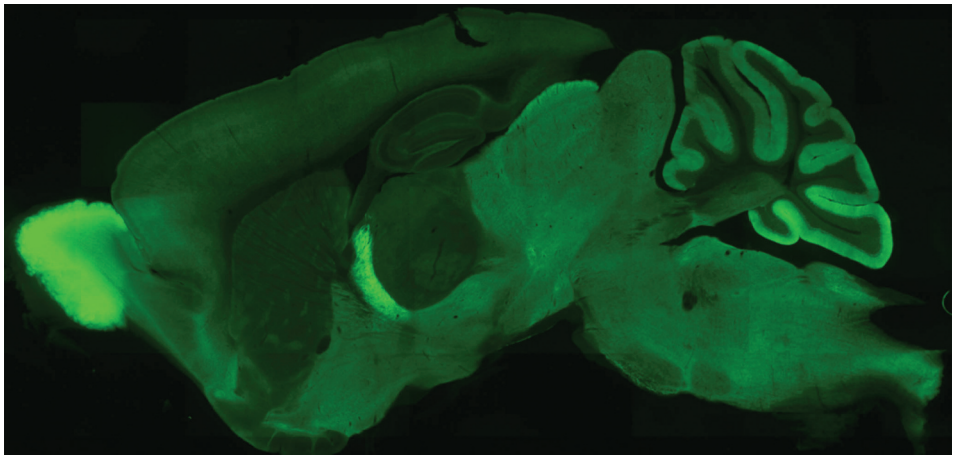


A mouse brain that has been genetically engineered to express fluorescent protein in specific regions.

Image courtesy of Guoping Feng

in synaptic function in the basal ganglia circuitry could also contribute to the development of OCD or similar conditions.

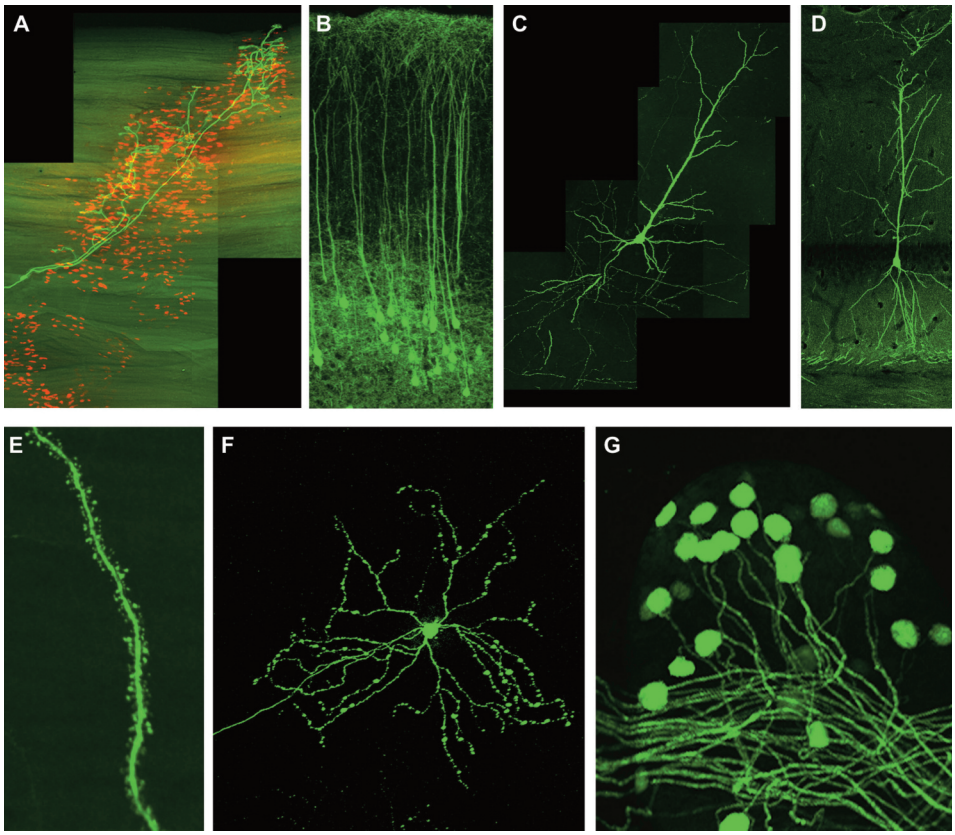
Indeed, Feng is now studying another scaffold protein called Shank, and has found that deleting this protein causes mice to develop autism-like behaviors. About 30% of autism patients have OCD, and repetitive behaviors is one of the defining characteristics of autism. Feng hopes that studying genes like SAPAP3 and Shank may reveal how synaptic dysfunctions contribute to autism and may possibly suggest new therapeutic approaches to this common developmental disorder.

Glowing neurons

One consistent theme in Feng's research has been technological innovation. While he was a postdoctoral researcher at Washington University in St. Louis, he devised a method for labeling individual neurons in different colors in the living brain—a technique that has now been used by hundreds of laboratories. He was among the earliest adopters of optogenetics—a method for manipulating neuronal activity using light – and the first to demonstrate that it could be used in the intact mouse brain. He has now developed a range of cell type-specific optogenetic mice, which will help him and many others to examine the brain circuits that underlie specific behaviors.

Prozac's secrets

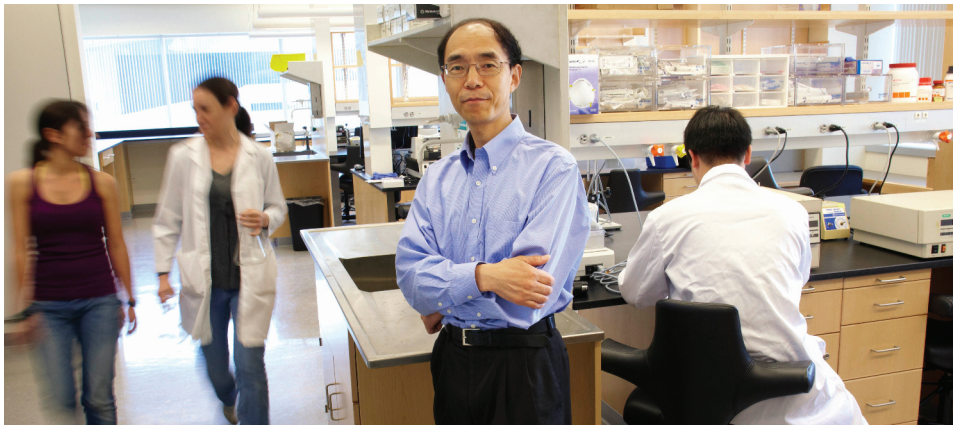
Through the use of these and other techniques, Feng hopes to dissect the altered brain circuits that underlie psychiatric diseases and their treatment by drugs such as Prozac. For example, he has found that Prozac enhances the communication between the cortex and the SAPAP3 neurons in the striatum, at the same synapses that are disrupted in his OCD mice. Perhaps by learning direct ways to improve synaptic communication, researchers can design more widely effective drugs.



Feng uses fluorescent proteins to label subsets of neurons, revealing their different shapes and allowing researchers to identify them in living animals.

Image courtesy of Guoping Feng

Feng thinks being at MIT—"an incredible place for neuroscientsts"—will accelerate this work. "I love the McGovern Institute's commitment to improving the understanding of brain disorders to benefit patients. At MIT I can apply innovative technologies in genetics to neural systems in psychiatric disease, and also work with the Broad Institute on genetic links to psychiatric disorders. I'm passionate about research that could lead to a deeper understanding of the underlying processes involved in these disorders." ■



Many of Feng's lab members have joined him in moving to MIT, and the new lab at the McGovern Institute is already up and running.

Photo courtesy of Kent Dayton

Roberta Sydney Becomes Chair of Friends, Welcomes New Members

Roberta Sydney SM '88, Leadership Board member and new Friends Chair.

The McGovern Institute is pleased to announce that Roberta Sydney SM '88, a member of the McGovern Leadership Board, has accepted the invitation to serve as Chair of the Friends of the McGovern Institute with the goal of expanding the group and broadening its mission.

"We are delighted that Roberta accepted our invitation," says Robert Desimone, director of the McGovern Institute. "She brings to the Friends extensive executive and organizational experience, as well as a personal commitment to neuroscience research and to the mission of the McGovern Institute."

Roberta's commitment to neuroscience research is indeed personal. Her father, Stanley H. Sydney, SB '52, SM '54, was diagnosed with Parkinson's disease more than twenty years ago and her mother, Sheila Sydney, suffered a stroke when Roberta was only 13 and her four brothers and sisters ranged in age from 1 ½ to 14. In 2007, after visiting the McGovern Institute, Roberta and her family created a fund to support Ann Graybiel's research on Parkinson's disease. (See Spring 2008 issue of *Brain Scan*).

"While my family has faced significant challenges, we have also been most fortunate," explains Roberta, who is President and CEO of Sydney Associates, a real estate development company in Brookline, Mass. "We continue to be involved in the causes in which we believe. After meeting Ann Graybiel's talented team, we felt compelled to support her Parkinson's disease research become directly involved with the McGovern Institute."

A graduate of Wellesley College with an MBA from Harvard Business School and a master's degree from MIT's Center for Real Estate, Roberta excels in bringing people together for a common goal. She admits that her current goal is an ambitious one—she aims to double the number of McGovern Friends by the Institute's tenth anniversary celebration on October 14, 2010.

Established by founding chairs Regina Pyle, and her late husband, Thomas Pyle, the Friends of the Institute provide members with special access to the latest developments in neuroscience research. By supporting the Institute's scientific mission, Friends interact directly with McGovern scientists and they receive regular research updates as well as invitations to private lectures, seminars, and symposia.

"I believe that we have much to gain from dialogues between McGovern scientists and individuals beyond the scientific community." Together with the Friends Executive Committee, Roberta is developing new ideas about Friends programming that she hopes will encourage even more engagement with the Institute's faculty and research initiatives.

Roberta's enthusiasm for the Institute is infectious. Since becoming Chair in March, Roberta has already recruited 20 new Friends and is well on her way towards reaching her goal. ■

Become a Friend

If you are interested in becoming a Friend of the Institute, please visit our website and become a Friend online.

Metcalfe Gift Supports Undergraduate Research in Goosens Lab

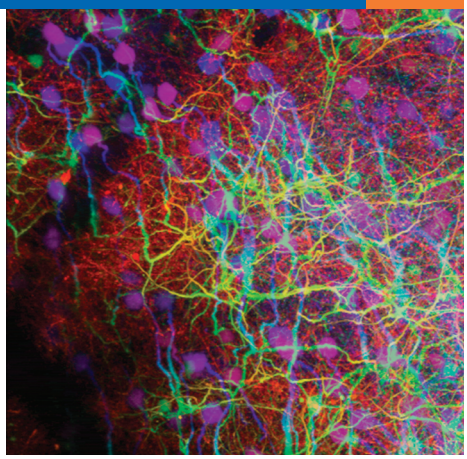
*Ki Goosens (*right*) with undergraduate researcher and Rhodes Scholar Ugwechi Amadi.*

Ki Goosens is passionate about training the next generation of neuroscientists, and a new gift by Robert Metcalfe '68, will make it possible for four undergraduate students to benefit from her leadership and guidance this summer. Metcalfe, who formerly chaired the McGovern Institute leadership board, gave $25,000 in support of undergraduate research in Goosens' lab. His generous gift follows a similar donation in 2007 (see summer 2007 issue of *Brain Scan*) in which he funded two undergraduate researchers in Goosens' lab through MIT's Undergraduate Research Opportunity Program (UROP). ■

McGovern Institute To Acquire a Two-Photon Microscope

The McGovern Institute will soon be creating a new core facility, with help from the federal stimulus package. A team of MIT researchers led by Martha Constantine-Paton has been awarded a $1.4M stimulus grant from the National Institutes of Health to acquire a two-photon microscope, a powerful tool for imaging individual neurons in the living brain. The machine, built by Prairie Technologies Inc. of Middleton, Wisc., will include two workstations customized to MIT's needs, and will allow researchers to visualize neurons in the brains of live animals with unprecedented detail.

"The new microscope will be a great boost to the MIT neuroscience community," says Constantine-Paton. "This is a state-of-the art machine whose cost far exceeds what most individual labs could afford. By setting it up as a shared core facility, we can make the newest technology available to the entire MIT neuroscience community." The machine is expected to arrive by the end of this year. ■



The 2-photon microcope from Prairie Technologies reveals an extraordinary level of detail about the fine structure of the brain.

Image courtesy of Prairie Technologies, Inc.

McGovern Video Wins Telly Award

We are pleased to announce that our feature video, Welcome to the McGovern Institute, has won a 2010 Telly Award. Produced by Emmy nominated John Rubin Productions, the twenty-minute video shows how research at the Institute is pushing the frontiers of technology and providing new insights into brain disorders such as autism, Parkinson's disease, and mental illness. The video, which is freely available on our website, won top honors in the fundraising category. ■

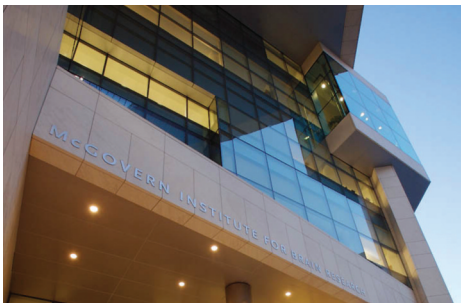
The Silver Telly is the highest honor given by the annual Telly Awards.

Construction Underway for New MEG Scanner

Construction is now underway for the space that will house the new magnetoencephalography (MEG) scanner. The scanner will be installed later this year.

Photo courtesy of Goody Clancy

Save the Date: McGovern 10th Anniversary



Join us on October 14th as we celebrate the 10th anniversary of the founding of the Institute. Details of the event will be announced soon. ■

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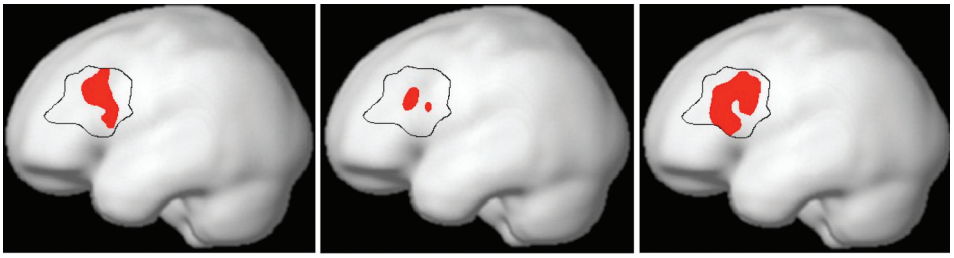
RESEARCH NEWS



*Brain activations of the left frontal language area (*shown in red*) varies considerably between three subjects.*

Image courtesy of Evelina Fedorenko / MIT

Tomaso Poggio's lab has developed a new mathematical model to describe how the human brain visually identifies objects. The model accurately predicts human performance on certain visual perception tasks (which suggests that it's a good indication of what actually happens in the brain) and it could also help advance artificial intelligence research.

Bird song learning is a model system for studying general principles of learning, but attempts to draw parallels between learning in birds and mammals have been hampered by anatomical brain differences between the two species. A new study from **Michale Fee**'s lab helps solve this problem, by identifying specific classes of neurons within the brains of songbirds and matching them to their mammalian counterparts.

Although many human brain regions are known to be associated with language, it has proved very difficult to localize these areas precisely or to understand what they are doing. **Nancy Kanwisher**'s team has found a new method for identifying brain areas involved in specific tasks such as language—one that may reveal a clearer picture of how these areas work together to produce this uniquely human behavior.

Driving to work is a habit for many people. But before our commute became routine, we had to learn the new route through trial-and-error exploration. **Ann Graybiel**'s lab has found that there are two brain circuits involved with this kind of learning and that the patterns of activity in these circuits evolve as our behaviors become more habitual.

Video Spotlight

Scanning the brains of young children helps us understand how the human brain develops during childhood, and may also provide new clues to the origin of developmental disorders such as autism and dyslexia. In a series of talks for lay audiences, **Nancy Kanwisher** and her colleagues, Daniel Dilks and Rebecca Saxe, discuss what they've learned about brain development—including when we learn to identify faces—through their neuroimaging studies. Visit our website to watch these talks online.

A proud subject holds a picture of her own brain.

AWARDS AND HONORS

*Christina Triantafyllou (*middle row, third from left*) was among the winners of MIT's Infinite Mile Award.*

Photo courtesy of MIT

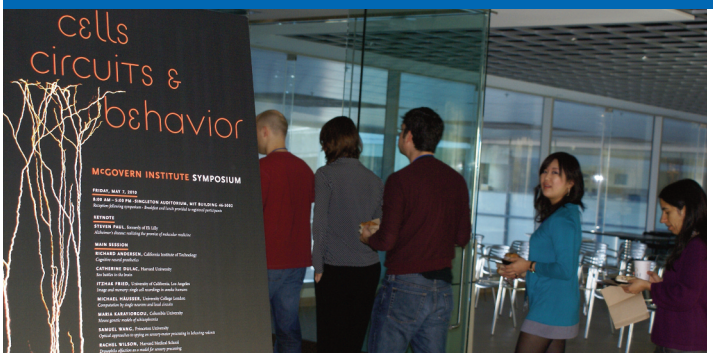
Robert Desimone won the Helmholtz Award of the International Neural Network Society. The award recognizes outstanding contributions in the field of sensation and perception.

Yingxi Lin received MIT's James H. Ferry Fund to support her research into inhibitory circuitry in the brain. She was also awarded the prestigious John Merck Scholarship, which supports gifted young scientists as they pursue research into the neurobiology of developmental disabilities.

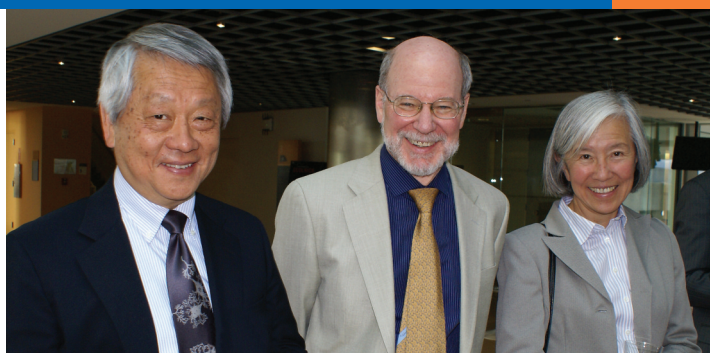
Kartik Ramamoorthi, a research assistant in Lin's lab, was awarded the Norman B. Leventhal Presidential Graduate Fellowship, which recruits "the most outstanding students worldwide to pursue graduate studies at the Institute." Ramamoorthi will begin his studies at MIT this fall.

Christina Triantafyllou, Associate Director of the Martinos Imaging Center, is among this year's recipients of MIT's Infinite Mile Award. The annual award recognizes individuals who have made extraordinary contributions to help MIT carry out its mission.

Nicolas Pinto, a PhD student in James DiCarlo's lab, was awarded the NVIDIA Graduate Fellowship for 'cutting edge multimedia innovation.' The fellowship is awarded to ten students annually—this is Pinto's second year in a row as an NVIDIA Fellow.



McGovern's sixth annual symposium was well attended by the local neuroscience community.



*Lily and Yuh-Nung Jan with H. Robert Horvitz (*center*), who introduced their lecture.*

Annual Symposium: Cells, Circuits, and Behavior

On May 7, the McGovern Institute held its sixth annual symposium, bringing together leading experts from the US and abroad to discuss neural circuits, their relationship to behavior and implications for therapy. The speakers covered a range of topics, from computational powers of single neurons, the complexity of gene regulation in the brain, and the development of neural prosthetic devices. A keynote talk by Steven Paul, formerly VP for research at Eli Lilly, discussed recent advances in Alzheimer's disease and the road from basic research to new treatments.

The symposium can be viewed on the McGovern Institute website.

McGovern Institute Honors Pioneers in Neurogenetics

The McGovern Institute awarded the seventh annual Scolnick Prize in Neuroscience to Lily Jan and Yuh-Nung Jan of the Howard Hughes Medical Institute and the University of California, San Francisco. The Jans were honored for their lifelong contributions to neuroscience, in particular their genetic research on fruit flies which has provided many key insights into the brain function and development.

The Jans delivered their joint prize lecture on Friday, May 28 to a packed auditorium. Their talk, entitled "Dendrite morphogenesis and channel regulation: implications for mental health and neurological disorders" can be viewed on our website.

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, formerly the head of intramural research at the National Institute of Mental Health.

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

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