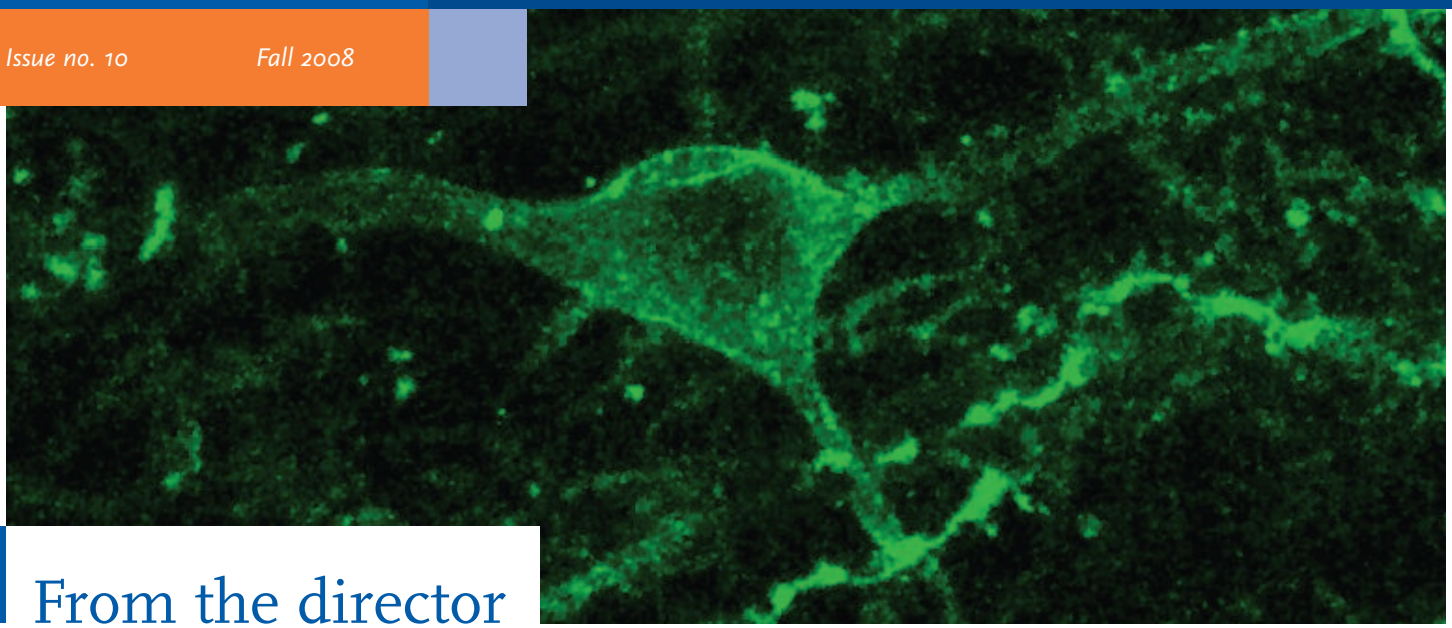
Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Issue no. 10 Fall 2008



From the director

Advances in neurotechnology are giving us powerful new tools to study the brain, and many of these same technologies also provide new therapeutic opportunities.

In this issue of *Brain Scan*, you will read about a dynamic young researcher, Ed Boyden, who is making revolutionary advances in neurotechnology. Ed has been a leader in developing a remarkable technology that combines genetic and optical methods to manipulate neural activity with a precision far beyond what was previously possible. This new method is rapidly enhancing our understanding of brain function, and also allows us to contemplate entirely new clinical approaches to treating a wide range of brain disorders, from brain injury and epilepsy to schizophrenia and blindness. Many of his colleagues, myself included, are eager to apply these potent methods in our own research. Equally important, Ed is training a new generation of creative neuroengineers to address long-standing problems in basic and clinical neuroscience. I am certain that Ed's work will continue to transform the field in the years ahead.

Cover image: Ed Boyden used a viral vector to introduce a light-activated protein into monkey neurons. This protein, visible here in green, allows him to control brain activity with pulses of light.

In other news, we have been awarded two new grants from an anonymous donor. One of these is a challenge grant that will help us to create a magnetoencephalography (MEG) facility in the Martinos Imaging Center at the McGovern Institute that will greatly enhance our human neuroimaging capabilities. The challenge requires us to raise matching funds, and we plan to launch a major campaign later this year so that we can take advantage of this wonderful opportunity. The other award will help the McGovern Institute and the Picower Institute establish a shared core facility for viral vector production. These vectors provide researchers with valuable new tools to genetically manipulate the brain, and the new core will make them widely available to the MIT neuroscience community.

We are also very grateful to the Michael J. Fox Foundation for a new grant to Ann Graybiel's lab that will support work aimed at discovering new drug treatments for Parkinson's disease. In all, we have much to celebrate and much to strive for as we start this new academic year.

Bob Desimone, Director

Ed Boyden, Associate Member, McGovern Institute

ED BOYDEN: ENGINEERING THE BRAIN

Ed Boyden—neuroscientist, engineer and inventor—develops new strategies for manipulating brain activity. He hopes these methods will lead to new approaches to treating epilepsy, Parkinson's disease and mood disorders.

Ed Boyden entered MIT just after his 16th birthday, and he graduated with a BS in physics and BS and Master's degrees in electrical engineering and computer science in 1999, at the age of 19.

During his final year at MIT, he spent 3 months at Bell Labs in the laboratory of Michale Fee, who is now at the McGovern Institute, studying birdsong and building devices for recording brain activity. "Like me, Michale was a lapsed physicist, and he opened my eyes to a new frontier—neuroscience," Boyden recalls. "I became fascinated with the vast unknown of the brain, partly because it was an area where technology could have a big impact."

Boyden decided to do a pure biology Ph.D. in order to learn how to study brain function through animal behavior. He went to Stanford University, where he worked with Dick Tsien, a leader in the field of synaptic physiology, and with Jennifer Raymond, who studied memory in the cerebellum.

But he still dabbled in engineering, and as a side project with Karl Deisseroth, he developed a radically new method for stimulating neurons using light. Before even finishing his dissertation on memory in 2005, he and Deisseroth published their findings. Their new method was immediately recognized as a major advance and has been adopted by dozens of labs worldwide.

Within a year of finishing his Ph.D., Boyden was offered a faculty position at the MIT Media Lab, a hotspot for innovation in the interface between people and machines that has become increasingly involved in life sciences. At 27, he became one of the youngest professors at MIT—a remarkable achievement in a field where the median age for faculty appointments is 36. Boyden already has more than 100 existing or pending patents to his name, and he has received numerous honors, including a Sloan Research Fellowship and an NIH Director's New Innovator Award.

Controlling neurons with light

Boyden's ambitious vision for his lab at MIT—"To engineer intelligent, targeted control interfaces for neural circuits, in order to repair pathology, augment cognition, and reveal new insights into the human condition"—began to take shape as he was applying to graduate schools. He asked neuroscientists how he could best use his physics training to have an impact in the field. The answer: learn where existing methods break down.

He chose to focus on neural stimulation, an important research tool with many clinical applications but also many inherent limitations.

The traditional method of stimulation involves inserting a thin wire electrode into a selected brain region and using it to deliver a current that activates nearby neurons. The method allows researchers to manipulate neural activity in a brain region of interest and to look for effects on behavior. Clinically, deep brain stimulation (DBS) is used to treat movement disorders such as Parkinson's disease. DBS is also being evaluated for obsessive-compulsive disorder, depression, epilepsy and certain brain injuries.

But these implanted electrodes tend to stimulate large numbers of neurons indiscriminately, making the results difficult to predict or control. Moreover, electrical stimulation can only activate neurons, not inactivate them. So although it can disrupt the normal function of a brain region, it cannot shut down unwanted activity.

The optical method developed by Boyden and his colleagues at Stanford and MIT provides an elegant solution to these problems. It works by using genetic technology to introduce light-activated protein 'switches' into neurons. These proteins, which occur naturally in certain microorganisms, are delivered into the targeted neurons using a harmless virus, engineered to infect neurons without damaging them. Then, a thin, flexible fiber-optic cable implanted in the brain delivers millisecond pulses of light to control neural activity.

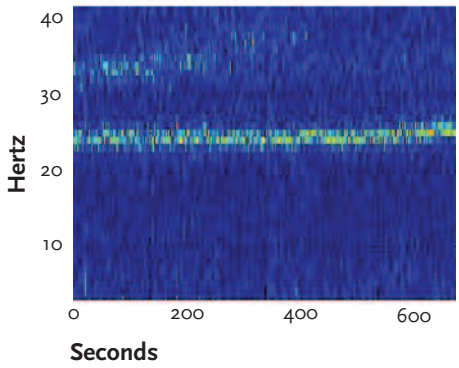
One of these proteins, channelrhodopsin-2, allows neurons to be activated by blue light. A second protein, halorhodopsin, allows them to be switched off by yellow light. A neuron carrying both proteins can be rapidly activated and inhibited by alternative pulses of different wavelengths, giving researchers an unprecedented degree of control over neural activity in a living, behaving animal.

Illuminating new therapies

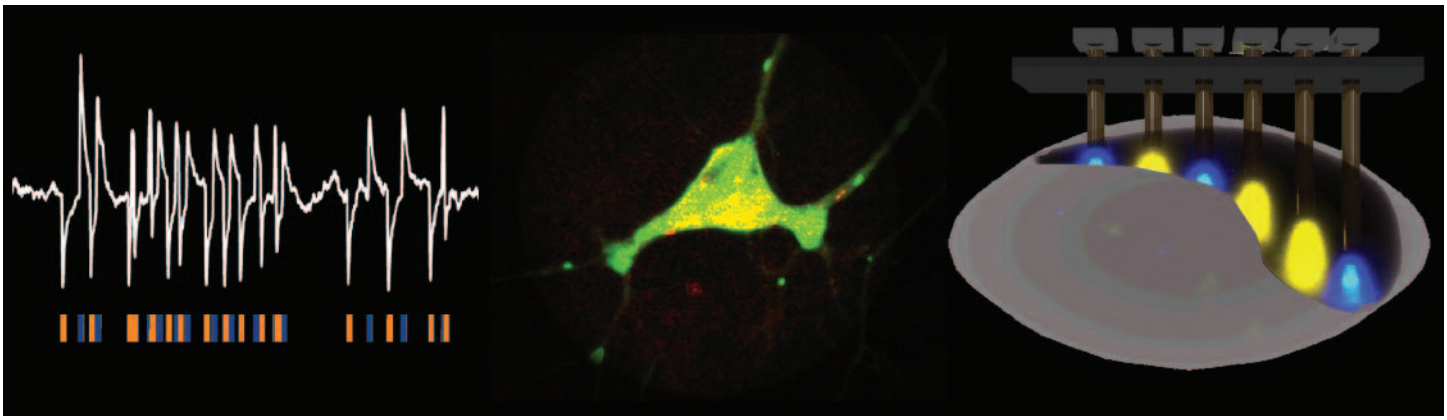
This combination of genetic and optical methods, already extremely useful in research, has the potential to improve upon clinical brain stimulation applications involving electrodes. It could even lead to entirely new applications, by targeting very specific populations of cells with far greater precision than can be achieved with current electrical methods.

Before it can be applied to humans, however, Boyden's method must be tested in animal models, including non-human primates, to show that the method is effective and that light-activated proteins can be delivered safely to the brain without producing unwanted side-effects. In a collaboration supported by the McGovern Institute Neurotechnology (MINT) program, Boyden has been working with Robert Desimone and Ann Graybiel to test the method in monkeys. As in human gene therapy, the researchers have used viral vectors to introduce light-sensitive proteins into the monkey brain. The early results have been encouraging, and suggest that Boyden's method will be an important research tool for studying primate models of human brain function. Given the rapid rate of progress in the field of human gene therapy, Boyden is also optimistic that it will eventually be possible to use his method in a clinical setting.

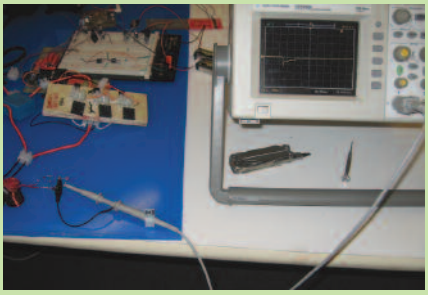
continued, page 4

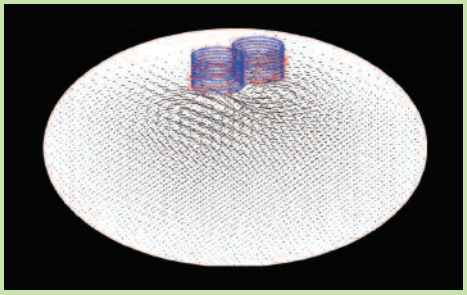


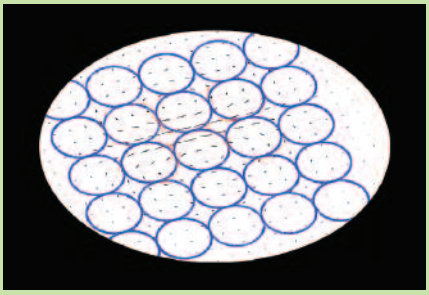
A recording of neural activity in brain tissue stimulated by chemicals that mimic natural brain activity. Boyden will compare such recordings to results obtained by optically stimulating neurons.



*Optical control of neurons: On the left, blue and yellow bars indicate the timing of pulses of light. Blue light activates neurons (*upward deflections of white trace*), and yellow light inhibits neurons (*downward deflections*). Middle: A neuron bearing light-activated proteins. Right: Design of an implantable fiberoptic device for optical control of neurons.*







Boyden's lab has developed what may be the world's smallest transcranial magnetic stimulator (TMS) device. Rather than using a single large figure-of-eight coil, as is traditional, Boyden's device consists of an array of small coils, lying over the surface of the scalp in a honeycomb arrangement. Each coil can be programmed separately, giving the operator much greater control over the shape of the resulting magnetic field within the brain.

Boyden is pursuing this possibility through collaborations with several groups within and beyond MIT. For example, he is working on epilepsy with Eric Leuthardt, a neurosurgeon at Washington University in St. Louis, developing ways to use optical control to suppress seizures.

In another collaboration with Clifford Wolff, a pain expert at the Massachusetts General Hospital, Boyden is developing an improved version of the chronic pain therapy known as dorsal column stimulation (DCS). The dorsal column of the spinal cord contains the nerve fibers that carry touch and pain sensations to the brain. An implanted stimulating electrode in the spine can sometimes reduce chronic pain. But the results are mixed and DCS is a therapy of last resort. Boyden and Woolf hope that optical methods can silence the pain fibers more specifically and effectively, with fewer side effects.

Magnetic appeal

The invasiveness of the optical-genetic method means that it will require extensive development and testing before it can be approved for human clinical use. In the meantime, though, Boyden is also applying his engineering skills to other, less invasive ways to manipulate brain circuits.

One of these methods is transcranial magnetic stimulation (TMS). In this approach, magnetic coils close to the surface of the head are used to generate magnetic pulses that pass through skull and influence activity in the underlying brain region. TMS is used as a research tool and as an experimental therapy for promoting recovery after stroke and for treating depression and migraine. But the inherent imprecision of today's TMS devices has led to inconsistent results. Stimulating the right prefrontal cortex, for example, can improve symptoms of depression, but can also increase undesirable risk-taking behavior.

To achieve more honed results, Boyden's lab has devised a stimulator with multiple small coils, tiled in a honeycomb arrangement (instead of the usual two coils in a figure-eight configuration) to focus the magnetic field within the brain. "The idea came to me while stuck in an airport," he recalls, "so I sat there and wrote a MATLAB script in the departure lounge." Back at his MIT lab, he gave the project to an undergraduate student, who has now built a prototype that may be the smallest and most precise TMS device yet constructed. He is now seeking industry and clinical collaborators to help take this device to patients.

Training new neuroengineers

Boyden credits much of his success to the energy and enthusiasm of the MIT students who come to his lab, and he places high priority on teaching and mentoring the next generation of neuroengineers. He has developed a popular hands-on teaching course in which students design a never-before-seen method to solve a problem in basic or clinical neuroscience. They then build a prototype to validate their design. Several projects have grown into graduate theses, and some are evolving into business ventures. Meanwhile, the first generation of post-docs are ready to leave his lab and strike out on their own.

Boyden has high hopes for their future careers. "They know the importance of controlling brain processes and functions, and how to identify problems and create new solutions from the ground up," he says. "And they've seen first hand how basic science leads unexpectedly to practical applications." ■

All graphics courtesy Ed Boyden, MIT Media Lab

Challenge Grant for MEG Brain Imaging

MEG is a child-friendly mode of brain imaging, making it ideal for studies of learning disabilities and developmental disorders.

Photo courtesy of Elekta, Inc.

An anonymous donor has presented the McGovern Institute with a $2M challenge grant toward the creation of a magnetoencephalography (MEG) facility for human brain scanning that will serve researchers at MIT and throughout the Boston community.

The new facility will be integrated into the Martinos Imaging Center at MIT, one of the few places in the world where researchers can conduct comparative brain imaging studies of humans and animals. The MEG machine will represent a major expansion of the Center's existing functional magnetic resonance imaging (fMRI) brain imaging capabilities. MEG has the potential to revolutionize the study of both normal human cognition and disorders of the brain in children and adults.

Magnetoencephalography is based on detecting the very weak magnetic fields that originate from electrical activity within the brain. MEG is fundamentally different from fMRI, and the two techniques are highly complementary. MEG signals provide very high (sub-millisecond) temporal resolution that is essential for studying rapid brain events that underlie mental processes. fMRI lacks this precise timing, but provides higher spatial resolution for pinpointing specific brain regions involved in an activity. Ideally, the two methods are combined in the same subjects. This will be possible when the new MEG machine comes to the MIT Martinos Center.

MEG is completely noninvasive and raises no safety issues for volunteer subjects, who wear a snug helmet fitted with detectors. It is quick to perform, almost silent, and allows the subject to sit comfortably and interact with other people. These advantages make it feasible to study large numbers of subjects, including young children and elderly people. MIT researchers hope to use MEG for studies of normal cognition as well as disease research. For example, what differs when an autistic child interacts with another person, when an elderly patient responds to a question, or when someone with schizophrenia watches and describes a scene?

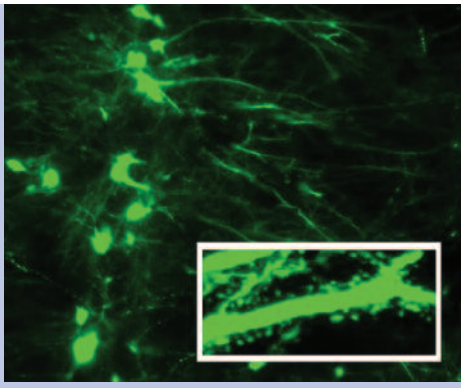
Having MEG at MIT will be a major resource for MIT's many research programs in systems and cognitive neuroscience, and for our academic and clinical collaborators throughout the Boston area. It will also help identify new biomarkers for brain disorders that are currently diagnosed purely based on behavioral symptoms. Although MEG is still primarily a research tool, it will likely become important in clinical neurology, neurosurgery and potentially psychiatry. MIT is well placed to promote such translational applications, given its ties to industry, its experience with technology transfer and its proximity to major clinical research centers.

To make this vision a reality, we must raise an additional $2M to match the challenge grant. A formal fundraising campaign will be launched in the fall; meanwhile, anyone interested in making a donation or learning more about this opportunity is invited to contact Laurie Ledeen at ledeen@mit.edu. ■

Viral Core Facility Comes to MIT

The McGovern Institute and the Picower Institute for Learning and Memory have received a joint grant from an anonymous donor to establish a new viral core facility. The new facility, which will serve the entire MIT neuroscience community, will produce viral vectors used to manipulate gene expression in the brains of experimental animals. Viral vectors are widely used in basic and translational neuroscience research, and they are also being developed for human gene therapy. (One example is Ed Boyden's work on light-activated ion channels, as described on pages 2-4.) Because the production of these viruses requires special expertise that is not often found in neuroscience labs, the new core facility will be an important enabling resource for McGovern neuroscientists and their collaborators.

Rachael Neve, the former director of the Molecular Neurogenetics Laboratory at McLean Hospital, will direct the core, and a steering committee will include representatives from McGovern and Picower Institutes. The core is expected to begin operations later this year.



Neurons in rat hippocampus, labeled using a herpes viral vector system developed by Rachael Neve

Image courtesy of Ki Ann Goosens, McGovern Institute

Michael J. Fox Foundation Grant

Ann Graybiel's laboratory at the McGovern Institute is one of 9 research teams to receive funding from The Michael J. Fox Foundation's $2.4M Target Validation initiative. This annual MJFF program provides intellectual and financial resources to help push potential drug targets forward towards clinical trials and ultimately to help the nearly 5 million Parkinson's patients worldwide.

The discovery of a new potential therapeutic target generates great excitement among patients and researchers, says Katie Hood, CEO of The Michael J. Fox Foundation. But to attract an industry sponsor who will pay for clinical testing, researchers must demonstrate through animal studies that the target is involved in the disease and that manipulating it impacts disease symptoms or progression. The target validation initiative supports the necessary preclinical studies to determine whether a molecule or mechanism of interest is a promising drug target and whether it should be prioritized within the drug development pipeline. By funding this essential yet historically under-resourced phase of drug development, MJFF aims to remove a major roadblock to the development of new therapies for Parkinson's disease.

Graybiel's project will investigate new targets for possible alleviation of dyskinesias, the abnormal movements that often as a result from treatment with L-DOPA, the most widely prescribed medication for Parkinson's disease.

INSTITUTE NEWS

In the News

In May, **Michale Fee**'s study in *Science* of how juvenile songbirds learn to sing—much the way human babies learn to talk—received coverage in the *New York Times*, the *Boston Globe*, *National Geographic News*, the Canadian Broadcast Center and many other outlets.

In July, *The Guardian* wrote about **Patrick McGovern**, co-founder of the Institute, and his company IDG Communications. *PC Magazine* also covered **Tomaso Poggio**'s research in developing computer models to understand how the brain processes visual information.

Adult and juvenile zebra finches in the Fee lab

Photo courtesy of Aaron Andalman, McGovern Institute

Media coverage can be found on the McGovern Institute's website: http://web.mit.edu/mcgovern

Next Issue

The winter issue of *Brain Scan* will profile our new faculty member, Yingxi Lin, who joins us from Harvard University. It will also include an update on the McGovern Institute Neurotechnology (MINT) program.

Awards

*Ann Graybiel with Serge Przedborski (*left*) and Christopher Goetz of the Movement Disorders Society*

Photo courtesy of Ann Graybiel

Ann Graybiel received the C David Marsden award from the Movement Disorders Society. She presented an award lecture at the society's 12th annual congress in Chicago on June 25.

Ed Boyden received a 2008 Young Investigator Award from NARSAD, the world's leading charity dedicated to mental health research. He will receive $60,000 over the next two years to develop new methods to study schizophrenia.

McGovern Symposium on Psychiatric Disease

The McGovern Institute's annual symposium, *The Biological Basis of Psychiatric Disease*, on April 28-29 drew an overflow audience of researchers and clinicians from Boston and beyond. The event was co-sponsored by the Martinos Imaging Center and the Poitras Center for Affective Disorders Research.

The 17 speakers discussed recent progress in understanding psychiatric diseases such as schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder and anxiety disorders. Unlike many conferences on psychiatry, each session combined talks on human psychiatric diseases with others on animal models of disease.

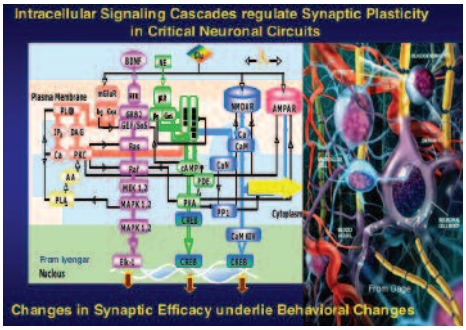
As with other human diseases, researchers need animal models to understand psychiatric disease mechanisms and to develop new therapies. Yet developing animal models based on human pathology is challenging because there are no physical diagnostic tests for any psychiatric illness. As we identify human disease genes, though, the technologies of mouse genetics enable researchers to study the roles of these genes within the brain. Using genetic mouse models, we can ask: How does a gene contribute to the disease process? How do psychiatric drugs affect signaling pathways? Can this understanding lead to new therapeutic strategies?

Speakers also stressed the importance of human brain imaging in studying psychiatric disease. Both genetic and environmental factors affect the risk of developing disease. But to understand how these factors interact, researchers must study the human brain directly. Functional MRI is a key technology in psychiatric research, and improvements in imaging methods will accelerate progress.

Brain imaging can also help 'road test' hypotheses about a drug's affect on the brain's functional networks, explained Ed Bullmore, who holds appointments at Cambridge University and GlaxoSmithKline. Finding new drugs for brain disorders is among the pharmaceutical industry's most difficult challenges. But Bullmore said new collaborations between industry and academia will help in validating the candidate drugs and in finding predictable biomarkers for measuring drug efficacy.

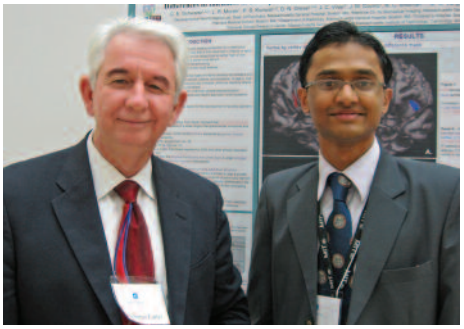
The symposium closed with a reminder from Akira Sawa of Johns Hopkins University that translational approaches for disorders like schizophrenia must understand why the symptoms do not appear until early adulthood when the risk events may occur early in life. Understanding these early events could lead to prevention strategies, while better understanding the pathophysiology that occurs in the young adult brain could lead to more effective treatments.

The webcast of the symposium is available on the McGovern Institute web site. ■



Husseini Manji (National Institute of Mental Health) *compared the challenge of understanding the molecular pathways underlying bipolar disorder to finding one's way through a big-city subway system.*

Image courtesy Husseini Manji, NIMH



Cameron Carter (UC Davis, left)*, a speaker at the symposium, and Jyoti Ballabh, a participant.*

McGovern Institute To Visit New York

On October 6th, McGovern Leadership Board member, Robert Buxton, will host an event entitled "The Future of Brain Disorders Research" at the Knickerbocker Club in New York City. Fellow Board member, Jane Pauley, will be the guest speaker, along with Institute director, Bob Desimone, and faculty members Ann Gaybiel and John Gabrieli. For more information, contact Laurie Ledeen at ledeen@mit.edu (617-324-0134).

Luncheon Honoring Sydney Gift

In the spring 2008 *Brain Scan*, we announced Stanley (SB '52, SM '54) and Sheila Sydney's $500,000 commitment to Parkinson's disease research in the lab of Ann Graybiel. On June 12, we hosted a luncheon honoring the Sydneys along with their family members, friends—including several of Stanley's MIT classmates—and members of the Graybiel lab. Michael Sydney, Ann Graybiel and Bob Desimone spoke at the luncheon.

Stanley Sydney (seated) *and fellow members of the MIT class of 1952*

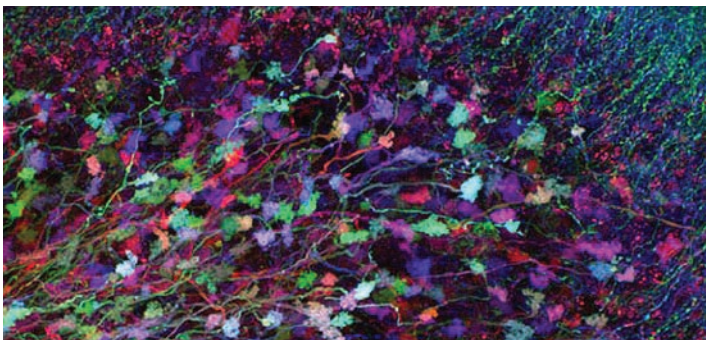
Sixth Annual McGovern Institute Retreat

Beautiful weather graced the 6th Annual McGovern Institute Retreat, which was held in Newport, Rhode Island on June 1-3, 2008. Institute co-founder Lore Harp McGovern and Leadership Board member Bob Metcalfe joined some 120 members of the McGovern Institute and their collaborators to hear presentations by students and postdocs from the McGovern labs. In addition to the formal agenda of 14 talks and 22 posters, attendees enjoyed a visit to the famous Breakers mansion and an evening cruise and dinner on Newport harbor.

The guest keynote speaker was Jeff Lichtman of Harvard University, whose talk on connectivity in the brain included many spectacular images based on his 'brainbow' method for labeling individual neurons within the mouse brain. Other guests included M. Fatih Yanik and Rahul Sarpeshkar from the MIT department of Electrical Engineering and Computer Science, both of whom are collaborating with McGovern researchers through the McGovern Institute Neurotechnology (MINT) program.

Lore Harp McGovern, Mriganka Sur, Bob Desimone

Photo courtesy Julie Yoo, MIT



Genetically labeled neurons in the mouse brain

Image courtesy of Tamily Weissman and Jeff Lichtman

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://web.mit.edu/mcgovern/

Brain SCAN
Quarterly Newsletter of the McGovern Institute

Editor: Charles Jennings
Writer: Cathryn M. Delude
Development Officer: Laurie Ledeen
Design: Sametz Blackstone Associates, Boston

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Massachusetts Institute of Technology
77 Massachusetts Avenue 46-3160
Cambridge, MA 02139