Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Issue no. 13 Summer 2009

From the director

It is always exciting when insights about one aspect of the brain, such as its early development, turn out to be relevant to other aspects, such as learning—especially when they also help to explain brain disorders at a very basic level.

This issue of *Brain Scan* features the work of my colleague Martha Constantine-Paton, whose pioneering research on synaptic plasticity has changed the way we think about brain development and learning.

Martha's earliest studies as an independent investigator vividly demonstrated the role of neural activity in molding our brain circuitry to our experiences of the world. At the same time, she showed a previously unsuspected link between plasticity during development and adult plasticity during learning—something we now take for granted. She has made many other important discoveries about how the brain becomes "wired up" over the years, and she is now applying her expertise to understand how synapses go awry in brain disorders, both early and late in life.

We have had a busy spring at the McGovern Institute, with several major events, including our annual symposium and our Scolnick Prize award, which this year honored Jeremy Nathans of Johns Hopkins University for his contributions to the understanding of human color vision. Especially gratifying to me was our own annual retreat, during which each of the McGovern labs presented their work to their colleagues. In these difficult economic times, it is good to be reminded that our young researchers are continuing to push the frontiers of our field.

Artwork: "The Synapse Revealed" by Graham Johnson of www.fivth.com for HHMI ©2004

I would like to end with two notes of appreciation. First, we thank Howard Finkelstein for agreeing to join the McGovern Institute Leadership Board and commit his time, talent and resources to advancing the Institute's mission. Second, we thank Kay and Ted Poitras for their lead-off gift to meet the challenge grant we've received to acquire an advanced magnetoencephalography (MEG) instrument for our brain imaging center. This technology has the potential to transform our research on the coordination of neural activity in the human brain, and we are deeply grateful to Kay and Ted for bringing us closer to our goal.

Bob Desimone, Director

Martha Constantine-Paton, a founding member of the McGovern Institute.

Photo courtesy Kent Dayton

MARTHA CONSTANTINE-PATON: SEEING BRAIN DEVELOPMENT IN A NEW LIGHT

Children can learn much faster than their otherwise more skillful parents because their brains are more easily rewired by experience. Martha Constantine-Paton looks at plasticity during development to understand how our aging brains lose this flexibility and how faulty brain wiring may cause brain disorders.

At birth, our brain already contains most of its 100 billion neurons. The enormous changes that occur early in life arise not from adding new neurons but from changing the trillions of connections between them. Everything a newborn baby experiences—a mother's touch, a father's lullaby, the motion of a mobile above the crib—elicits new patterns of activity within the brain. These experiences shape the connectivity pathways within the brain's nascent wiring diagram.

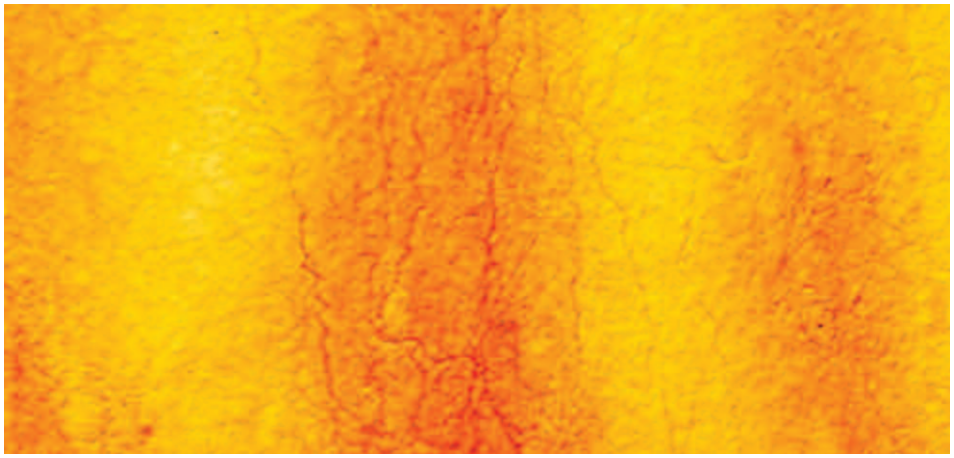
This ability to be molded by experience is called plasticity, and Martha Constantine-Paton wants to understand how it works. "Kids' brains have incredible plasticity so they can adjust to every new thing they confront," she says. "It also gives them an amazing ability to learn and great powers of recuperation—a baby can fully recover from the kind of stroke that would leave an adult paralyzed for life. I want to know why our aging brains lose this flexibility and whether we can prevent the decline in plasticity that contributes to brain disorders like Alzheimer's disease, schizophrenia, and ALS."

She looks for answers to these questions at the synapses, the connections among neurons whose strengths are constantly being adjusted in response to activity. Understanding synaptic plasticity is central to the study of brain development and learning, and to explaining the loss of abilities with age and disease.

Critical Periods in Development

Just as babies learn to walk and talk, they must also learn to see. The visual system requires visual experience—exposure to the lights and sights of the world—in order to become properly wired. The synapses are highly plastic at particular developmental stages, called critical periods.

Many aspects of brain function have critical periods. For example, we learn language during a particular developmental stage and baby animals learn to recognize their mothers—a phenomenon called imprinting—during a critical period after birth or hatching. Babies will not develop normal vision if they are deprived of visual experience in early life. Scientists have extensively studied critical periods in the visual system because the key brain regions are well-known and because they can precisely control and measure visual stimuli.



Experimentally produced 'ocular dominance' stripes in the brain of a frog following grafting of an extra eye during early development. The connections from different eyes form alternating stripes within the frog's visual system, providing an opportunity to study fundamental mechanisms that underlie the formation of wiring patterns within the brain.

Image courtesy Martha Constantine-Paton

"By manipulating the timing and intensity of light and pattern exposure," explains Constantine-Paton, "I can track how neural activity shapes the synaptic connections at different developmental stages."

The Third Eye

Constantine-Paton began her career studying tadpoles, whose large eyes and slow development made them a convenient experimental system for studying visual development. In 1976, soon after starting her lab at Princeton University, she amazed her colleagues when she discovered a remarkable plasticity in the developing tadpole brain.

The most dramatic demonstration was a three-eyed frog, which she produced by grafting a third eye during embryonic development. In a normal frog, the two eyes make connections to opposite sides of the brain without overlapping. But when a third eye is introduced, its connections must compete with those of the two normal eyes for space within a region of the brain called the tectum. Where the connections from two eyes overlap, they segregate into a zebra-like pattern of stripes from alternate eyes. A similar pattern occurs naturally in the brains of mammals, whose two eyes converge on the same brain region to produce binocular vision.

Constantine-Paton showed that the formation of these stripes depended on visual activity, and that it required the activation of a molecule known as the NMDA receptor. The function of these receptors is to sense glutamate, the brain's most important signaling molecule. NMDA receptors are also implicated in the formation of new memories. By showing that NMDA receptors are involved in activity-dependent developmental plasticity in the frog brain, Constantine-Paton established a link between memory and development, and changed the way neuroscientists thought about both processes.

"It makes sense, because every developmental milestone, like reaching or crawling, involves learning," she explains. "When we learn as adults, we are also rewiring our brains and pruning our synapses, so it's not surprising that we use many of the same molecules and mechanisms."

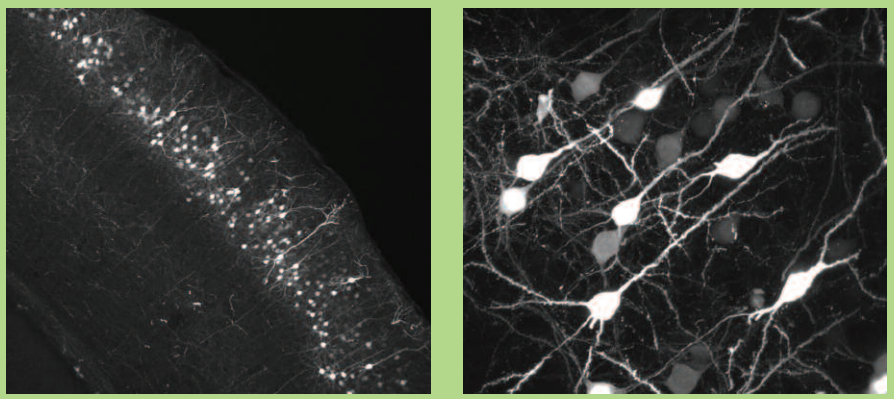
Eye Opening

Constantine-Paton continued to explore visual development at Princeton and later at Yale University, where she began studying mice and rats. She then moved to MIT, joining her husband and sometime research collaborator H. Robert Horvitz as a founding member of the McGovern Institute in 2000. For the past decade, she has been using genetic, biochemical, and electrophysiological methods to study light-induced synaptic plasticity at the molecular level. "We are finding that these pathways overlap with those being worked out for learning," Constantine-Paton explains.

She relates how one young scientist in her lab, Akira Yoshii, a pediatric neurologist from Japan, made an intriguing discovery. "He noticed that a 'scaffold protein' that anchors glutamate receptors at synapses increased dramatically at visual synapses about two weeks after birth. We wondered what could account for this sudden increase. Then we realized the change coincides with the time at which baby rats and mice open their eyes."

Nobody had studied the brain's response to normal eye opening before, but Constantine-Paton realized that eye opening, like birth, represents a sudden and massive increase in brain stimulation. By looking at molecular changes at the synapses before and after eye opening, she has learned how the NMDA receptor plays different roles during these two developmental phases.

continued, page 4



Constantine-Paton uses molecular and genetic tools to study early brain development. In these images, DNA encoding fluorescent protein was injected into the developing mouse brain to label specific neurons in the visual cortex.

Images courtesy Martha Constantine-Paton

Martha training the next generation of neuroscientists in her lab; undergraduates Sam Clark '09 and Diana Lusk '09.

Photo courtesy Patricia O'Loughlin/MIT

Reinforcing or Weakening Synapses

"The brain starts out with many more synapses than it needs, and it eventually eliminates the ones that are not useful," Constantine-Paton explains. "This refinement continues even into adulthood, as we learn new things and forget others. We want to know what role NMDA receptors play in these processes."

She discovered that after eye opening, NMDA receptors help to strengthen synapses that have made proper connections and to eliminate those with less effective connections. When light stimulates a neuron, the number of receptors at its synapses are increased, making that neuron more responsive to future light stimulation. The effect is like a fast-flowing river, whose strong currents carve deeper channels that in turn allow more water to flow. Less active synapses do not receive this boost, and like slow-flowing channels blocked with silt, they become even less active, eventually withering away.

Scientists had assumed that NMDA receptors play the same role before eye opening. At this stage in young rodents, the eyes receive only low level diffuse light—similar to what a human fetus experiences prior to birth. Since no one had examined what happens around the time of eye opening, Constantine-Paton decided to explore this great developmental divide.

She found that prior to eye opening, NMDA receptors had a different and unsuspected effect. Instead of strengthening the well-connected synapses, receptors tend to weaken the ones with the poorest connections. "During this earliest phase, the brain does not have enough experience to know which connections are good, but it can already tell that some are wrong," she explains.

Miswiring in Brain Disorders

For Constantine-Paton, the excitement in developmental brain research arises not only because the development of vision shares mechanism with learning and memory, but also because many of these cell and molecular interactions are also implicated in developmental and neuro-degenerative disorders.

She believes that problems in establishing the brain's initial wiring may result in early disorders such as autism. But the human brain continues to develop through the teens and early twenties, so initial wiring problems may be suppressed until later trauma or hormonal irregularities stress the circuits beyond their ability to compensate further, resulting in disorders that emerge later in life such as schizophrenia.

"In this way late onset diseases could result from very early imbalances in circuits that for many years are masked but which eventually reveal themselves in maladaptive behavior or cognition," Constantine-Paton explains. "So it may be important to identify the earliest manifestations of a disease process in order to develop new therapies that could prevent its progression later in life."

For example, ALS (Lou Gehrig's disease) causes motor neurons to degenerate in middle age, with most patients dying roughly four years after diagnosis. But using a mouse genetic model of ALS, Constantine-Paton found that synapses mature too soon in the affected animals, causing excessive neural activity as the earliest manifestation of the disease.

"If we can show how a disorder impacts circuitry, we can understand how it arises clinically," she says. "Once we know how these circuits behave, we can design new therapies and invent new ways to screen promising drug candidates."

These are possibilities that she could not have imagined when she began her career looking at the visual system of frogs. As she continues to study how our brains produce the shifting patterns of connections that allow us to live in an ever-changing world, she hopes her work will also provide the basis for a better understanding of disorders that cripple the lives of so many people. "Basic research is indeed the 'basis' of all research." she says. "It's the intellectual key that frequently, and often unexpectedly, opens the gates to new advances in health." ■

*Tracing of individual neurons reveal how visual activity affects development of connections. Axons form many branches prior to eye opening (*top*). After the eyes open, branches disappear from the shaft but proliferate near the tip (*middle*). When eyelids remain shut, synapses become less active and branches eventually disappear (*bottom*).*

Image courtesy Martha Constantine-Paton

Leadership Board Welcomes New Member

Howard M. Finkelstein, President of Finkelstein & Co. and newest member of McGovern Institute Leadership Board.

This April, the McGovern Institute Leadership Board welcomed its newest member Howard M. Finkelstein '75.

"I was drawn to the McGovern Institute because the brain is the least understood part of the human body and because we have so much to learn," says Finkelstein, who is President of Finkelstein & Company in Greenwich, Connecticut. "We've all been affected by disorders of the brain—whether it is our friends or our own families—and advances in neuroscience could make a huge difference in the lives of many people."

Finkelstein earned his bachelor's degree in life sciences from MIT in 1975 followed by his Master of Science in management from MIT's Sloan School in 1977. He spent the majority of his career in the telecommunications industry, including a 19-year association with Metromedia Company. He credits his lifelong interest in science among his key reasons for joining the Leadership Board.

Finkelstein was initially introduced to the McGovern Institute by his brother Stan Finkelstein '71, a Senior Research Scientist at the Harvard-MIT Division of Health Sciences & Technology, and was impressed both by the newness of the Institute and by the tremendous potential of the research going on here. "It is exciting to be a part of something that is so new," Finkelstein says. "We've conquered an awful lot of areas of science but we still know relatively little about the brain." ■

Leadership Board Meeting and Award Dinner

The McGovern Leadership Board held its spring meeting on April 27. The board welcomed new member Howard Finkelstein '75 (see above). Director Bob Desimone discussed the Institute's progress towards its strategic goals and funding priorities, stressing the $2 million challenge grant to support the acquisition of a magnetoencephalography (MEG) system for human brain scanning. The afternoon session featured presentations by faculty members Bob Horvitz and Christopher Moore. Horvitz discussed his Nobel Prize-winning research on programmed cell death in the nematode worm, and its implications for clinical problems such as autoimmunity and neurodegenerative disease. Moore talked about how the dynamics of brain activity give rise to our sensory perceptions, and he also provided guests with a tour of his lab.

At the end of the day, board members met with Jeremy Nathans, the winner of this year's Scolnick Prize (see page 7), who talked about the origins of retinal blindness and the ways in which it might be prevented. They then attended Nathans' prize lecture, followed by a reception and dinner in his honor. ■

Poitras Gift Supports MEG Campaign

The McGovern Institute has received a donation toward its campaign for a magnetoencephalography (MEG) brain scanner at MIT. The new gift comes from Kay and Ted Poitras, and follows a family tradition of support for MIT that was begun by Ted's father Edward J. Poitras '28 SM'29 and continued by Ted's brother Jim Poitras '63, who is also chair of the McGovern Institute Leadership Board. In 2007, Pat and Jim Poitras established the Poitras Center for Affective Disorders Research, whose research will be greatly enhanced by the planned MEG facility.

Kay and Ted Poitras hope that their gift will encourage others to join them in meeting the $2M challenge grant from an anonymous donor, which must be completed by December 2009 (see Fall '08 issue of *Brain Scan*). ■

Magnetoencephalography (MEG) is a powerful and noninvasive method for studying human brain activity.

Photo courtesy Elekta, Inc.

In the Media

Institute director **Robert Desimone** was featured as the key expert in a *New York Times* article and related blog about the science of paying attention. "Ear Plugs to Lasers: The Science of Concentration," was the most emailed story of the day and attracted over 150 questions from readers—some of which Desimone answered publicly on the *NYT* web site. In a segment on *CNN's Lou Dobb's Tonight* about the dangers of texting while driving, Desimone discussed the limitations of the brain's processing capacity, calling this kind of multitasking the "perfect storm" of attentional problems. *Wired.com* ran an article about Desimone's recent *Science* paper, which examined the brain mechanisms by which we attend to specific features of our visual world.

Christopher Moore's recent study in *Nature* was covered in *Scientific American* and *Seed* magazine. The study used laser light to induce gamma waves in the mouse brain. These brain waves play a crucial role in attention, consciousness, and memory, and are disrupted in people with schizophrenia and other disorders.

Wired.com and *Technology Review* ran articles about **Ed Boyden**'s new technology for manipulating brain activity. In collaboration with Robert Desimone and Ann Graybiel, Boyden introduced a light-activated protein into the brains of rhesus monkeys, allowing the activity of specific neurons to be controlled by laser light. This is first demonstration of the optical technique in primates, and may pave the way for its eventual therapeutic use in human brain disorders.

John Gabrieli appeared on the *PBS* special *New Science of Learning: Brain Fitness for Kids*, discussing the role of brain plasticity in child development and learning. The program airs nationally this summer. ■

Horvitz, Constantine-Paton Visit Italian Earthquake Region

*Onna, Italy, the village near L'Aquila hit hardest by the earthquake (*left*); Martha Constantine-Paton presenting her research in a tent at the University of L'Aquila (*right*); all of the university buildings were damaged by the earthquake.*

Photos courtesy H. Robert Horvitz

During a visit to Italy in May, **Martha Constantine-Paton** and **Bob Horvitz** visited the Abruzzo capital L'Aquila to explore the region where Martha's paternal grandparents had resided. One month earlier, L'Aquila was rocked by a magnitude 6.3 earthquake that killed 295 people, including 55 students and at least one faculty member at the university. With 70% of its staff homeless, the University of L'Aquila had begun to work again—and they invited the couple to speak at an event that marked the first renewal of research activities. Martha gave a presentation about synapses and neuronal connections. "I ended the talk with my search for my own lineage in that region and emphasized our mutual affiliations." Bob discussed his Nobel Prize-winning research on programmed cell death. "We were invited to show scientific solidarity with people who have survived in a community that has suffered losses on so many levels."

McGovern Class Reunion

Edwin "Bick" Hooper '59, Bob Desimone, Pat McGovern '59, and David Weisberg '59.

On June 5, Pat McGovern hosted a tour of the Institute for 125 fellow alumni and guests of the class of 1959. Nancy Kanwisher, Yingxi Lin, and Ann Graybiel opened their labs to guests and John Gabrieli gave tours of the Martinos Imaging Center. ■

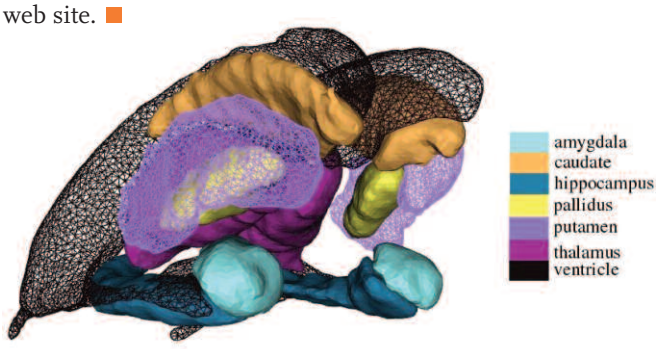
Annual Symposium: Basal Ganglia in Health and Disease

Symposium speaker Roshan Cools poses a question. To her right are co-organizer Ann Graybiel and speakers Okihide Hikosaka, Andres Lozano, and Peter Brown.

On May 7, the McGovern Institute held its fifth annual symposium, bringing together leading researchers from the US, Canada, Europe, and Japan to discuss progress towards a unified understanding of the basal ganglia in health and disease.

The basal ganglia are involved in many aspects of behavior, including reinforcement learning, habit formation, and motor control. They are also implicated in Parkinson's disease, Huntington's disease, drug addiction, and many psychiatric conditions. The clinical importance of the field was emphasized by Andres Lozano, a neurosurgeon at the University of Toronto and an expert on deep brain stimulation, who addressed the graduate students in the audience: "Your work is helping us treat patients with disorders. We can apply the understanding of circuitry and neural function to develop novel therapies."

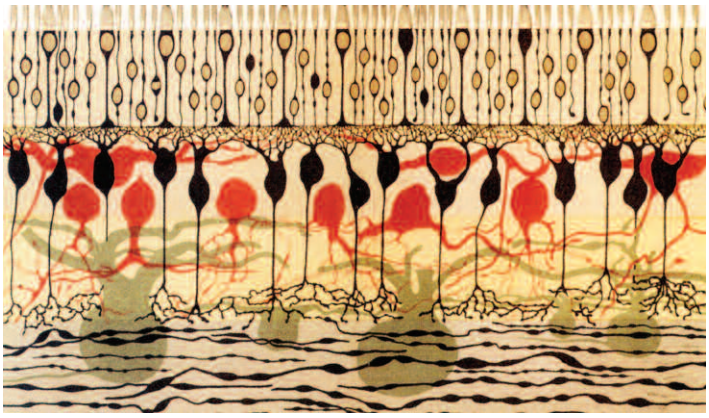
The entire symposium can be viewed on the McGovern Institute web site. ■



Components of the human basal ganglia.

Image courtesy Anqi Qiu/National University of Singapore

Scolnick Prize Lecture on Color Vision



Anatomy of the retina.

Image courtesy Jeremy Nathans/Johns Hopkins University

The McGovern Institute awarded the 2009 Scolnick Prize to Jeremy Nathans of Johns Hopkins University School of Medicine for his work on color vision, brain development, and retinal disease. Nathans '79 delivered his prize lecture entitled "The Evolution of Trichromatic Color Vision" to a packed auditorium on April 27. He described how he identified the genes for the color-sensitive pigments of the retina, and how mutations in these genes lead to color blindness. He went on to discuss how color vision arose in our primate ancestors, and speculated about its possible advantages. He ended by describing an experiment that recapitulates this proposed evolutionary history; by introducing a human color pigment gene into a mouse, he was able to endow it with the ability to distinguish colors that mice cannot normally perceive. Nathans' lecture can be viewed on the McGovern Institute web site. ■

Awards and Honors

Nancy Kanwisher was elected a Fellow of the American Academy of Arts and Sciences. Kanwisher also delivered the keynote address, *The Specialized Brain*, at the annual convention of the Association for Psychological Science in San Francisco. A video of her talk can be seen on the McGovern Institute web site.

James DiCarlo was awarded tenure at MIT in May. His work will be featured in a future issue of *Brain Scan*.

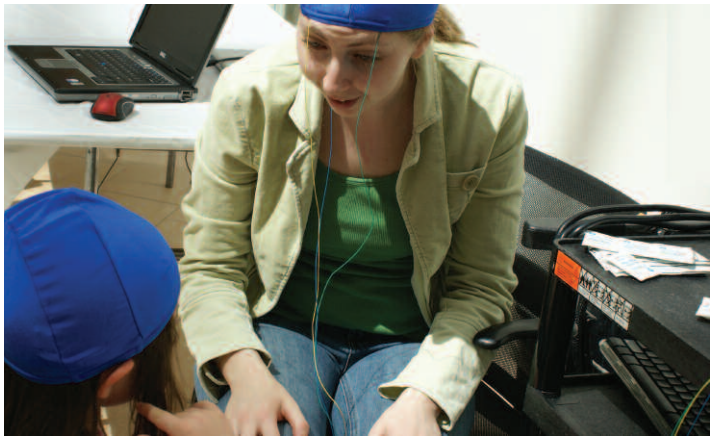
Yingxi Lin received two research grants (from the Whitehall Foundation and from an anonymous donor) to investigate how neural inhibition is regulated.

7th Annual McGovern Institute Retreat

American Academy of Arts and Sciences, Cambridge, MA.

This year, the annual McGovern Institute Retreat was held locally at the American Academy of Arts and Sciences in Cambridge, rather than at Newport Beach as in previous years. But the agenda for the June 18 meeting was as packed as ever, with 12 talks from McGovern labs, including a keynote presentation from Yingxi Lin, the newest faculty member at McGovern Institute. The talks were followed by a poster session and dinner at the Academy.

Cambridge Science Festival



Michelle Machon '09 demonstrates how electroencephalography (EEG) measures activity in a young volunteer's brain.

This spring, researchers from the McGovern Institute participated in the Cambridge Science Festival. Now in its third year, the week-long festival showcases hundreds of free events throughout the City of Cambridge that are designed to excite, engage, and educate the public. Yingxi Lin and Ki Goosens each gave public talks about their work, and visitors participated in a variety of hands-on activities and demonstrations about the brain, including tours of the Martinos Imaging Center.

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

Editors: Charles Jennings, Julie Pryor
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