Brain SCAN

MCGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Issue no. 3 Summer 2006

From the Director

Just as the invention of the telescope revolutionized our understanding of outer space, the invention of functional brain imaging is beginning to revolutionize our understanding of inner space.

Bob and An An Desimone

In May, the dream of having our own brain imaging facility at MIT became a reality when our Siemens 3T MRI (magnetic resonance imaging) machine produced its first images of functional activity in the human brain. In fact, the first images were of the "face processing region" in the brain of Nancy Kanwisher, a McGovern Institute faculty member! In recognition of the central role the new Martinos Imaging Center at the McGovern Institute will play in the future of neuroscience, we are devoting this issue to how brain imaging helps us investigate cognition, one of the major research topics of the McGovern Institute.

In the last issue of *Brain Scan*, our feature article focused on perception and described how the brain undertakes very difficult perceptual tasks seemingly effortlessly and automatically. How different the situation with cognition! Cognition includes mental operations such as decision making, planning, drawing inferences, attention, and learning, all of which seem to take considerable mental effort on our part. Not surprisingly, these difficult cognitive operations are vulnerable in many psychiatric diseases and brain disorders, including ADHD, Parkinson's Disease, autism, schizophrenia, and Alzheimer's Disease. Non-invasive brain imaging technology is proving critical to our ability to understand how cognition goes awry in these disorders.

In this issue, you will read how some of our faculty members are using brain imaging. John Gabrieli, for example, uses it to investigate learning disabilities, mental disorders, and aging, as well as the brain systems responsible for normal cognition in healthy people. The Imaging Center will soon have a more powerful machine for animal studies that can link the findings from human fMRI to those from detailed recordings of neural activity in research animals. These studies are easier to conduct than ever, now that the Imaging Center is just downstairs from the research labs. Meanwhile, Alan Jasanoff is developing next-generation imaging technologies that can visualize specific types of molecules in the brain. I hope these stories will convey some of the excitement we are feeling as we enter this new chapter in the McGovern Institute's research.

Bob Desimone, Director

The McGovern Institute at MIT is a neuroscience research institute committed to improving human welfare and advancing communications. Led by a team of world-renowned, multi-disciplinary neuroscientists, The McGovern Institute was established in February 2000 by Lore Harp McGovern and Patrick J. McGovern to meet one of the great challenges of modern science—the development of a deep understanding of thought and emotion in terms of their realization in the human brain.

Additional information is available at: http://web.mit.edu/mcgovern/

ON COGNITION — IMAGING THE MIND

John Gabrieli, Director, Martinos Imaging Center at the McGovern Institute

As a species, we take pride in our cognitive abilities, but until recently we have had a hard time studying them in the brain. Take, for example, seeing a child about to touch a hot stove. We can measure the perceptual input and how it is decoded by the brain: the sight of her hand nearing the stove. We can measure the output from the brain: the shouts of "No, no!" But what goes on between stimulus and response in the brain?

That in-between area belongs to the proverbial "black box" of cognition. Traditionally, people studied cognitive processes by conducting behavioral studies, the domain of psychology. Careful behavioral observations and insightful cognitive theories are essential for understanding the mind. But what are the underlying brain mechanisms?

One way to study brain mechanisms is to study what happens when parts of the brain malfunction or are injured. As an analogy, if you had no idea how a radio worked, you could open it, remove a piece to see what happens to the radio's performance, and thus deduce how that piece functions. You could use tools to make measurements on some components, and gradually arrive at a theory of how the radio works.

Similar methods work for cognition. For example, studying people with aphasia, a language processing disorder that results from damage in the prefrontal cortex, yielded valuable clues about a brain region that controls some aspects of language. But strokes and brain damage from trauma typically affect so many different brain regions, as well as the connections between areas, that it is often difficult to dissect the critical functions. Taking the radio analogy again, it might be difficult to conclude much about the functioning of its parts following a short circuit that melted the power supply and many of the internal wires.

Brain imaging tools fill that gap, by snon-invasively allowing scientists to peer inside the brain. Functional Magnetic Resonance Imaging (fMRI) provides measurements of activity in regions throughout the brain as people perform tasks, such as reading, listening, and speaking.

FMRI uses the same MRI machine that is used to diagnose soft tissue damage, such as following a sports injury or a stroke. That machine has a powerful magnet that detects the differing magnetic fields of the tissues, and computers convert the data to images. FMRI requires additional hardware and software to detect changes in the neural activity of different brain regions. More active regions recruit more blood, which increases the oxygenation of tissues, altering the magnetic field. The fMRI signal is translated into illuminated spots on a brain image, which are colorized to indicate activity level.

Researchers can compare the active regions that differ, for example, in good and poor readers in an effort to understand underlying brain abnormalities in disorders like dyslexia. FMRI has revolutionized the study of cognition by connecting brain anatomy to brain function, and brain function to human behavior.

Learning the Sound of Language

To John Gabrieli, the most exciting aspect of brain imaging is the ability to watch the brain as it learns and processes information—literally glimpsing the organization of the mind. Sometimes, these studies confirm what people might have guessed about how the mind works. Other times, they reveal unanticipated brain mechanisms at work.

For example, if we were promised a reward for remembering a piece of information, we might expect parts of our brain involved in motivation and learning to become active—and to be visualized by using fMRI. Indeed, Gabrieli showed that anticipating a reward activated not only the medial temporal lobe (MTL) involved in long-term learning, but also the dopamine-driven reward circuit containing the nucleus acumbens. He could even predict who would remember the information based on how active these regions became.

But his recent studies, published in May's *Neuron*, went even further. He showed the sequence of when these reward regions turned on (in anticipation of receiving the information), when they turned off (after receiving the information), and when MTL brain regions took over to record the information into memory. These findings have relevance to teaching and education, as well as to addiction, in which misguided motivations hold a destructive grip on brain function and behavior.

FMRI can also give us important insights about how children learn, which parts of the brain become involved as we master skills, and what happens differently in the brain of children with learning disabilities such as dyslexia. Based on his previous studies of people learning to read mirror-reversed text, Gabrieli speculates that when children first learn to read, letters are just scribbles to memorize and do not represent the sounds of spoken language. Most people have assumed that children with dyslexia, who commonly reverse letters and words in reading and writing, have visual processing problems.

However, Gabrieli's work, including a study published in the December 2005 *Annals of the New York Academy of Science*, supports an alternative, more controversial explanation. Language learning relies on the temporal processing of short auditory syllables. Dyslexic children have difficulty associating the auditory sounds of language with written letters and words because they have problems with auditory processing.

Moreover, this hypothesis may relate to the so-called "Mozart effect," which refers to evidence that listening to music can enhance non-musical cognition. Some studies have reported that music enhances verbal skills, although no one could explain a possible mechanism for such a connection. Gabrieli showed that music training helps people distinguish more fine-tuned differences in syllables. He is now investigating whether a musician's skill in processing rapidly changing sounds bolsters the quick perceptions required for language learning. If so, would music training help children with language processing difficulties?

In other research, Gabrieli is collaborating with McGovern Institute's Nancy Kanwisher and the Cambridge, Massachusetts school system to study visual word discrimination in children who are learning to read. The team is planning the first studies to examine the development of a brain region Kanwisher identified as responding selectively to printed letters in dyslexic and non-dyslexic children.

Reward-motivated learning:

Brain activation in the hippocampus, shown with arrows, that occurred when people were highly motivated to learn information and also successfully learn the information.

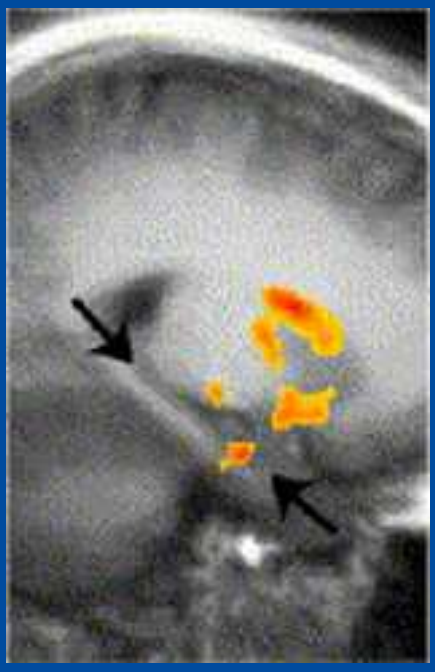

Image: Adcock, Thangavel, Whitfield-Gabrieli, Knutson, Gabrieli: Stanford University

A Brain's Eye View

Alan Jasanoff imagines one day having access to very specific information about what the 10 billion neurons are doing across all parts of a person's brain. One obstacle in the way of that goal is the trio of limitations facing current fMRI technology: time, space, and specificity. Jasanoff's laboratory is developing new chemical sensors, detectable by MRI machines, to overcome these limitations. These sensors will provide more detailed information, at a much finer resolution—in some cases down to a single neuron—in real time. He plans to test their utility in a classic paradigm of conditioning behavior and reward learning. In these experiments, rats learn to press a lever in order to earn rewarding experiences.

continued, page 4

Alan Jasanoff

Conventional fMRI shows which regions of the brain are recruited as rats learn the rules of the game. Those images, however, are indistinct in both time and space.

That's because current technology can only measure brain activity indirectly, through increased blood flow to regions of the brain that become more active during a certain task. This blood flow occurs about two seconds after the neurons actually fire, which is too slow to study precise neural activity or, for instance, the sequence of excitatory and inhibitory neurons. Likewise, the spacing of the capillaries limits the spatial resolution of the image to roughly 1,000 neurons at best, too coarse to discriminate highly specialized functional areas within a brain region.

Moreover, fMRI cannot distinguish among populations of different types of neurons, such as those that produce dopamine (a neurotransmitter at the root of reward learning) or the sequence of their interactions with other neurons.

Jasanoff is overcoming these obstacles with contrast agents (the MRI equivalent of dyes) that directly measure what neurons are doing while the brain works. Previously, scientists could only measure these cellular properties through invasive means, by inserting electrodes or other measurement devices physically into the brain.

His favorite new contrast agent detects calcium, which flows into the cell as the neuronal firing rate increases. His lab is now developing methods to deliver this contrast agent to the brain, either homogeneously throughout the brain or to specific targeted areas.

Eventually, contrast agents can target specific types of cells, such as dopamine neurons, and will show how they project their axons and dendrites throughout the brain to form neural circuits. Currently, scientists can use optical imaging to trace such projections in slices of brain images.

Jasanoff's goal is to establish similar techniques suitable for seeing the whole brain noninvasively, including the brain stem and other deep structures. Scientists can then build up a complete wiring diagram of the connections and circuits in the brain, annotated with the existing fMRI information about how those circuits function.

A related goal is to develop chemical sensors able to relay other important information besides calcium, such as voltage membrane potential, changes in protein expression, modifications of proteins that accompany learning, and the synaptic transmission of neurotransmitters and gene transcription underlying longer-term changes in brain structures.

Jasanoff predicts that chemical imaging sensors will help establish a new comprehensive approach in neuroscience—"neuroinformatics"—by compiling data about many characteristics of cells across the brain during various functions. That tool will transform the way scientists learn about cognition and other facets of mind and behavior. ■

In (A), a specialized contrast agent complex (yellow and gray) binds to a target molecule (red), which exposes the agent's paramagnetic center (green) and increases contrast on the MRI. In (B), the presence of a target molecule (red) induces aggregation of contrast agents (green), which also enhances contrast. Contrast agents may also be directed against specific cells, generally by means of antibodies or cell-surface receptors. In (C), contrast agents (green) accumulate and enhance MRI contrast in the neighborhood of their cellular targets (red), but not near untargeted cells (gray).

"Smart" Contrast Agents and Physiological Targets

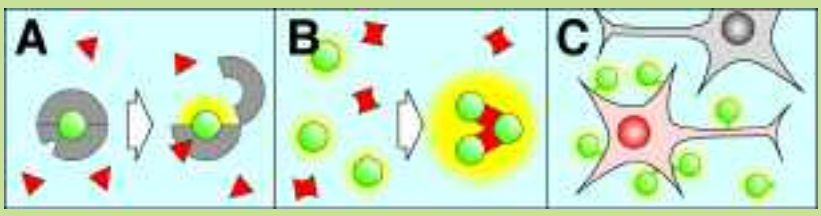

Image: Jasanoff

Brain Imaging Symposium

Scientists and guests gathered at the McGovern Institute for a symposium entitled "Imaging the Human Brain in Health and Disease" on May 30, 2006. The symposium, co-hosted with the Harvard-MIT Health Sciences and Technology Department (HST), marked the opening of the new Martinos Imaging Center at the McGovern Institute.

Before non-invasive brain imaging, neuroscientists had few tools available to unravel the enigma of the human brain, recalled Associate Member John Gabrieli, who co-organized the event with Principal Investigator Nancy Kanwisher and who directs the Martinos Imaging Center at the McGovern Institute. Robert Desimone, Director of the McGovern Institute, joined the other speakers in thanking Pat and Lore McGovern and the Martinos family for their gifts that made the Imaging Center possible. The Martinos family helped fund the Center as part of a Harvard-MIT alliance for developing an enabling technology to advance human health. Martha Gray, Director of the HST, said that brain imaging has emerged as a transforming technology, leading to entirely new lines of inquiry. Bruce Rosen, head of the Martinos Center that includes both the MIT Center and the Center at Massachusetts General Hospital, spoke of the many benefits for cooperation between MIT and Harvard in the future development of brain imaging.

continued, page 6

Symposium Speakers and Topics

- **Marcus Raichle (Washington University):** "The brain at work: An evolving perspective."
- **Brian Wandell (Stanford University):** "Maps and tracts: Reading development in visual cortex."
- **Marlene Behrmann (Carnegie Mellon University):** "About faces: Imaging neural correlates of face processing in pathological populations."
- **Nora Volkow (NIH/NIDA):** "Imaging the addicted brain: From molecules to behavior."
- **Daniel Weinberger (NIH/NIMH):** "Imaging genetics: An approach to validating genetic associations in the brain."
- **Randy Buckner (Harvard University):** "Imaging human memory in health and disease"
- **Bruce Rosen (Harvard Medical School):** "The future of brain imaging."

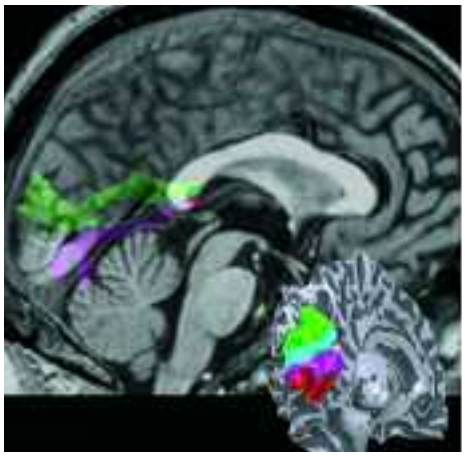

Figure 1: Reading Pathways using DTI
Diffusion tensor imaging (DTI) shows where pathways connecting the two occipital lobes pass through the posterior part of the corpus callosum (main image). Damage to these pathways can cause a specific inability to read (alexia). The small inset (right) shows the destination on the cortical surface for these fibers. It is thought that the fibers colored in red are essential for reading.

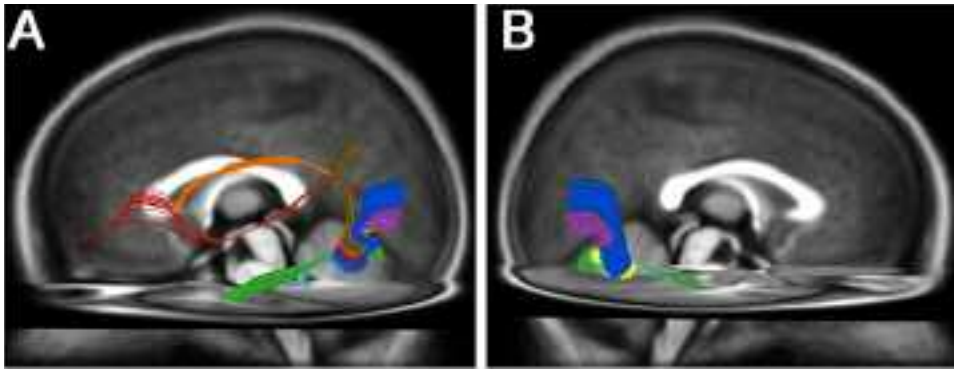

Figure 2: Asymmetry in Reading Pathways
On the left side of the brain (A) long fiber tracts connect a region in occipito-temporal cortex (essential in reading) to inferior-parietal and frontal language regions. The right side of the brain (B) has similar temporal connections, but no frontal/parietal ones. This asymmetry may reflect the specialization of the left hemisphere for reading and language.

Figures 1 and 2: Ben-Shachar, Dougherty, Wandell, Stanford University

Imaging Symposium, *continued*

During the daylong symposium, seven guest speakers (see box on previous page) shared their discoveries and visions for using brain imaging to understand how the brain works and what goes wrong in brain disorders. Their interests ranged from basic research to clinical practice and technology development, in areas as diverse as dyslexia, addiction, and Alzheimer's Disease (AD).

Several speakers described how refinements in brain imaging technologies are linking functional brain imaging to the underlying biology and structure of the brain, including the architecture of the cortex and the white matter fibers that connect brain regions. A new technology called diffusion tensor imaging (DTI) may help fill in some gaps left in fMRI studies by outlining the physical "wiring" of the white matter (figures 1 and 2).

Positron Emission Technology (PET) imaging, while an older technology, is using new tracers for specific molecular targets in the brain to reveal events at the level of synapses, neurotransmitters, and genes (figure 3). Finally, genetic analyses are linking molecular, genetic, and biological events to behaviors like addiction or to susceptibility for depression and schizophrenia that can be studied via brain imaging.

The symposium ended with coming attractions of imaging technologies that can provide new types of real-time information. Ideally, we will one day have a machine that takes movies of the brain. Ultimately, though, we need basic research to close the "translation gap" and interpret what those images reveal about the human brain.

Edward M. Scolnick Prize and Lecture

The McGovern Institute presented the third annual Edward M. Scolnick Prize in Neuroscience on Tuesday, April 25, 2006 to Dr. Michael Greenberg. Greenberg is the FM Kirby Director of the Program in Neurobiology within the Children's Hospital/ Harvard Medical School Department of Neurology. A crowded auditorium listened to his lecture, entitled "Signaling Networks that Control Synapses Development and Cognitive Function."

Greenberg explained how research on molecular and genetic events is providing insights into the underlying basis of neurological diseases involving cognitive deficits. He investigates the signaling molecules called transcription factors that regulate the development of synapses and the dendritic spines of neurons in response to activity.

One important developmental process involves synaptic refinement – pruning away the initial overabundance of synapses. This refinement requires a fine balance between excitation and inhibition of neural activity, and mechanisms that upset that balance may lead to the pathologies involved in neurological diseases. Greenberg found that one gene (MeCP2) when over-expressed can cause the thin, immature spines that occur in Rhett Syndrome, a human disorder of cognitive function. A knockdown of expression of another gene (MEF2) increases the number of synapses beyond normal levels. These findings may provide new insight into the process of human cognitive development.

The McGovern Institute awards this prize, named in honor of Dr. Edward M. Scolnick, formerly the President of Merck Research Laboratories, to recognize an outstanding discovery or significant advance in the field of neuroscience.

Figure 3: Default Patterns and Alzheimer's Plaques
FMRI studies identified a "default program" of background brain activity that occurs during passive states like daydreaming, and that appears to replay experiences and perhaps imbeds them in long-term memory. PET images, using a new tracer for the amyloid plaque that accumulates in Alzheimer's Disease, show plaque formation along that very default pattern. Here, the brain areas active in young adults during passive states (blue) are those that show early changes in AD patients (red).

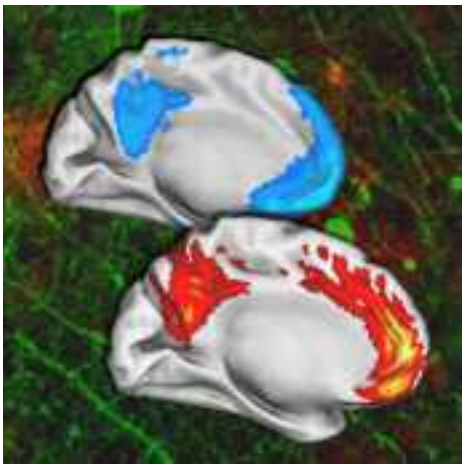

Image: Buckner, Harvard University; Benjamin Shannon, Washington University in St. Louis

Neurotech Conference

McGovern Institute co-founder Lore Harp McGovern addressed neuroscience executives and investors at the sold out "Neurotech Industry Investing and Business Conference," organized and hosted by NeuroInsights on May 18th in San Francisco. The conference featured scientists, executives, and investors analyzing critical factors driving the development of new drugs, devices, and diagnostics for brain and nervous system disorders. Lore's keynote speech highlighted the McGovern Institute's progress in discovering the underlying mechanisms of neurological and psychiatric diseases, including an overview of the Institute's Advanced Neuroscience Technologies Initiative.

Lore McGovern and Jack Lynch

DVD of Opening

McGovern Institute Director Robert Desimone's presentation at the November 4, 2005 opening ceremony is available on DVD, and as a download from the website. To receive a copy, contact Laurie Ledeen at ledeen@mit.edu.

Awards and Honors

Ann Graybiel

James DiCarlo

Alan Jasanoff

H. Robert Horvitz

Emilio Bizzi

Patrick McGovern

GRAYBIEL HONORED FOR PARKINSON'S RESEARCH

Principal Investigator Ann Graybiel was named the Harold S. Diamond Professor by the National Parkinson Foundation (NPF) in recognition of her contributions to the understanding and treatment of Parkinson's Disease. The professorship, which is external to her Walter A. Rosenblith Professorship of Neuroscience at MIT, was created in honor of Miss Lynn Diamond of New York City and named after Miss Diamond's late father.

DICARLO AND JASANOFF HONORED BY MCKNIGHT FOUNDATION

Principal Investigator James DiCarlo received a 2006 McKnight Scholar Award for his work on the neuronal mechanisms underlying object recognition during natural viewing. The award is $75,000/year for 3 years starting in July.

Associate Member Alan Jasanoff received a 2006 McKnight Technological Innovations in Neuroscience Award, which provides up to $100,000 per year for two years and will fund Jasanoff's development of methods to apply MRI calcium sensors for cellular-level functional imaging in living animals. *See article on pages 3–4.*

HORVITZ: A PRIZE PROFESSOR

Principal Investigator H. Robert Horvitz received MIT's James R. Killian Jr. Faculty Achievement Award for 2005-2006, in recognition of his extraordinary professional accomplishment as an MIT faculty member. Over his 27-year tenure, Horvitz, a Nobel Laureate and the David H. Koch Professor of Cancer Biology, is credited with teaching thousands of students the fundamentals of genetics and mentoring graduate students and postdocs who have become top-rated faculty.

BIZZI: A PRESIDENT

Principal Investigator and MIT Institute Professor Emilio Bizzi was elected President of the American Academy of Arts and Sciences. Previously, he served as Secretary from 1983-1987.

PATRICK MCGOVERN: A VOICE OF INNOVATION

The May 1, 2006 issue of *Business Week* featured McGovern Institute co-founder Patrick J. McGovern as a Voice of Innovation for his role as chairman of International Data Group (IDG).

2006 RETREAT IN NEWPORT, RI


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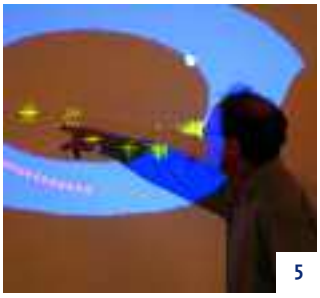
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McGovern Institute faculty, researchers, graduate students, and staff enjoyed good weather, fine dining, smart company, and dazzling science at their annual retreat held this year at the historic Hotel Viking in Newport, Rhode Island from June 4-6, 2006.

After the opening reception and dinner Sunday evening, newly appointed Principal Investigator Ki Ann Goosens from Stanford University spoke about her research on the systems and molecular approaches to the study of fear memory. Goosens will join the McGovern Institute at the start of the new academic year.

Attendees then enjoyed dessert while perusing 15 posters on current research and spoke to fellow scientists about their lab projects. On Monday, researchers from each of the labs made presentations about their work.

1 Ki Ann Goosens
2 Chris Moore and Ed Vul
3 Bob Horvitz and Jill Crittenden
4, 5 Andrew Schwartz
6 Bob Metcalfe and Bob Desimone
7 Hu Dan and Pat Harlan
8 Bob Horvitz and Martha Constantine-Paton with researchers

Andrew Schwartz of the University of Pittsburgh gave the keynote address on using signals from motor cortex to guide a mechanical arm, which could help people suffering from paralysis. He showed movies illustrating realistic neuroprosthetic devices using his techniques.

Tuesday morning brought more presentations from McGovern labs and a talk by John Gabrieli before the closing lunch.

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Writer: Cathryn M. Delude
Photos: Gabrieli, Moore, Jasanoff, P. McGovern, Goosens by Kent Dayton; Cover and retreat by HF Hall, Graybiel Laboratory

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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