McGovern Institute for Brain Research

The McGovern Institute for Brain Research at MIT is a research and teaching institute committed to advancing human understanding and communications. The goal of the McGovern Institute is to investigate and ultimately understand the biological basis of higher brain function in humans. The Institute is conducting interdisciplinary research that combines and extends the results of recent breakthroughs in three major, interrelated areas: systems and computational neuroscience, imaging and cognitive neuroscience, and genetic and cellular neuroscience.

Activities

We conducted a faculty search during spring 2008. We reviewed over 100 applications and made one offer, to Yingxi Lin, currently a postdoc at Harvard Medical School. She has accepted our offer and will begin as an assistant professor January 1, 2009.

The Leadership Board met on April 14, 2008, beginning with a luncheon and concluding with the Institute's Annual Scolnick Prize lecture and dinner. The Scolnick Prize recognizes an outstanding discovery or significant advance in the field of neuroscience. The board heard a presentation from Ann Graybiel and met privately with the Scolnick prizewinner, Dr. Michael Davis, from Emory University. Dr. Davis gave a late afternoon talk, followed by a well-attended dinner at the Institute. Davis, who is the Robert W. Woodruff professor of psychiatry and behavioral sciences at Emory University School of Medicine, received the prize for his work on the neural basis of fear and its clinical applications in psychiatry, particularly posttraumatic stress disorder. His work represents one of the best examples of bench-to-bedside translational research in psychiatry.

On Monday, April 28th and Tuesday, April 29th, the McGovern Institute hosted a two-day symposium on the biological basis of psychiatric disease, co-sponsored by the Martinos Imaging Center at the McGovern Institute and by the newly established Poitras Center for Affective Disorders Research. The symposium covered both animal models and human clinical research, especially (although not exclusively) neuroimaging. The symposium was very successful and we were pleased with the turnout—over 150 people over the course of the two days.

The McGovern Institute held its 6th annual retreat June 1–3 at the Newport Marriott in Newport, Rhode Island. The format was similar to that of past years, with a keynote address, talks by postdocs and students, and a poster session. Jeff Lichtman, from Harvard University, gave a fantastic keynote address. As in years past, we invited people from outside McGovern with whom we collaborate or are interested in collaborating with. A special activity for the group was a sunset cruise and lobster boil in Newport Harbor.

The McGovern Institute Neurotechnology (MINT) program was created in 2006 to capitalize on faculty interaction and opportunities. By reaching out to researchers from other disciplines, within and beyond MIT, we hope to establish collaborations and build a community around the shared goal of technical innovation that will help to transform the future of neuroscience. With support from the Institute's founding donors Patrick and Lore

McGovern, the MINT program provides seed funding for collaborative projects that seek to develop new tools and technology platforms for neuroscience research. Five projects were funded during FY2008, and we anticipate funding a further six projects in FY2009.

The McGovern board of directors meets quarterly, in July, October, January, and April. The membership of the board consists of Patrick McGovern; Lore McGovern; Elizabeth McGovern; Gerald Fischbach, Columbia University; Marc Kastner, MIT; Robert Langer, MIT; Edward Scolnick, Broad Institute; Sheila Widnall, MIT; and Torsten Wiesel, Rockefeller University.

A distinguished scientific advisory board composed of some of the world's most prominent neurobiologists also guides the Institute. The board last met on April 23, 2007 and will meet again in spring 2009. Members are John Duncan, Medical Research Council, England; Eric Kandel, Columbia University; Nikos Logothetis, Max-Planck Institute for Biological Cybernetics; Carla Shatz, Stanford University; Charles Stevens, Salk Institute; and Robert Wurtz, National Eye Institute.

Awards and Honors

Ann Graybiel was named the Marsden Award lecturer of the Movement Disorder Society this summer, and was a plenary speaker at the American Academy of Neurology in the spring.

H. Robert Horvitz received the Mendel Medal from the Genetics Society (UK) and was also the recipient of the Eli Lilly Lecturer Award, 2007.

Alan Jasanoff was awarded a 2007 NIH Director's New Innovator's Award, a highly competitive $3.5 million grant. He was promoted to associate professor without tenure.

Tomaso Poggio was the distinguished speaker at DARPA-IPTO, Washington, April 5, 2008. He gave the keynote address at Cosyne 2008, Salt Lake City, Utah, February 28, 2008 (http://cosyne.org/c/images/1/1b/Poggio.pdf "Models of Visual Recognition in the Ventral System"). Professor Poggio was the tutorial speaker at the Twenty-first Annual Conference on Neural Information Processing Systems (NIPS) Conference 2007, Vancouver, British Columbia, Canada, December 3, 2007 (http://nips.cc/Conferences/2007/Program/event.php?ID=574 "Visual Recognition in Primates and Machines").

Research

Bizzi Lab

Dr. Bizzi's research examines how the brain translates our general intentions into the detailed commands needed to control muscle movements. One of his key discoveries is that not every muscle needs to be controlled individually. Instead, groups of muscles are activated synergistically by circuits of neurons in the spinal cord, and Bizzi proposes that these synergies represent the fundamental building blocks for assembling a repertoire of complex movements.

To understand how the brain accomplishes even a simple task, such as picking up a glass of water, Bizzi is studying how movement commands are represented by electrical activity in the motor cortex, and how this representation changes as new skills are acquired through practice. His work has implications both for normal learning and also for rehabilitation after brain injuries. Patients who lose motor control after a stroke or other in jury often show some recovery over time, and Bizzi is exploring ways in which this recovery might be enhanced, for instance through virtual reality training or magnetic stimulation of the brain.

Boyden Lab

Ed Boyden is developing tools to manipulate brain function at many levels, by using a wide variety of technologies in his work, with the common thread of finding new and more potent ways to alter brain function for both research and therapeutic purposes. A major goal of the Boyden lab is to manipulate individual nerve cells using light. By doing this he will be able to develop on/off switches for brain activity. This will be a powerful way to test theories of brain function in experimental animals, and could also open the door to new clinical therapies for conditions such as epilepsy, Parkinson's disease or blindness. The Boyden lab is also working on transcranial magnetic stimulation (TMS), a noninvasive method for manipulating human brain activity widely used both as a research tool and as clinical therapy for promoting recovery after stroke.

Dr. Boyden, an associate member of the McGovern Institute, is also developing new approaches to psychotherapy. Cognitive and behavioral therapies can be effective but their applications tend to be limited due to cost and availability of therapists. Boyden is collaboratively testing, with Harvard Medical School, a web-based system for helping people to learn strategies for handling uncontrolled emotions and subjective states such as pain and anxiety.

DiCarlo Lab

Professor James DiCarlo's lab continues to focus on their work on understanding the high-level neuronal representations that support the brain's remarkable ability to recognize objects under a very wide range of viewing conditions. In one line of work they have been examining the role of real-world visual experience in constructing the neuronal representations that underlie this ability. They have discovered a novel form of rapid visual plasticity that may point to the brain's underlying solution to this problem. Specifically, they found that specific, subtle alterations in the visual world that are invisible to human subjects can predictably alter a key computational property of their visual recognition that was previously assumed to be rock solid—the ability to recognize objects in different positions. They are continuing their exploration of this very exciting research, using both neurophysiology and computational modeling.

The DiCarlo lab also recently completed their first studies using fMRI in nonhuman primates to gain new understanding of the spatial organization of shape information in the high-level visual cortex. They developed a novel high-resolution stereo x-ray method that is allowing them to study those fMRI-determined responses at the neuronal level.

Goosens Lab

The Goosens lab studies the relationship between fear, anxiety, and stress, hoping that understanding the brain's response to stress will lead to new therapeutic strategies for anxiety disorders, depression, and other psychiatric diseases. Goosens uses a method known as viral-mediated gene transfer to manipulate the expression of specific genes in the brain. By combining gene transfer with a powerful new technology termed RNA interference (RNAi), which makes it possible to block the effect of specific genes in the living organism, she hopes to determine which genes are of greatest importance in modulating the brain's fear pathways. In addition to understanding how stress affects the brain, the Goosens lab hopes this work will lead to potential targets for the development of new psychiatric drugs.

Graybiel Lab

The Graybiel lab focuses on the habit system of the brain, which, remarkably, turns out to be the same brain complex that is disordered in neurologic disorders such as Parkinson's disease, Huntington's disease, and dystonia; "motor-plus" disorders; and neuropsychiatric disorders such as obsessive-compulsive disorder and Tourette syndrome and likely also in attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) and aspects of schizophrenia.

They have made a major effort to understand the paradox that l-DOPA, which is the main pharmacologic therapy for Parkinson's disease, can virtually abolish the symptoms of dopa-responsive dystonia (DRD), a hypokinetic disorder that is associated with very different symptoms than those of Parkinson's disease. Their research, conducted with Japanese collaborators, demonstrates that in a mouse model of DRD, there is prominent and differential loss of the neurotransmitter dopamine in striosomes. Striosomes are neurochemical compartments in the basal ganglia that the Graybiel lab previously discovered, and showed with collaborators to be differentially spared in the onset of symptoms of Parkinson's disease in the so-called MPTP model of parkinsonism. This work is in press in the *Proceedings of the National Academy of Sciences*.

The lab's interest in the potential compartmental aspect of neuronal vulnerability in Parkinson's disease and related disorders has been heightened by their new finding, in research led by Dr. Jill Crittenden in the lab, that two compartmentally distributed genes discovered by the Graybiel lab in collaboration with MIT biologist David Housman are dysregulated in a model of Parkinson's disease in which the dyskinesias are induced by prolonged use of l-DOPA therapy. These two new findings are of great clinical interest and the Graybiel lab and their collaborators are conducting new experiments to pursue these leads.

In their work on habit formation, the Graybiel lab has focused on the question of how it is that even though habits are repeated behaviors, and nearly automatic, the striatum of the basal ganglia is the central part of the brain's habit system. The striatum is also essential for switching from one type of behavior—habit or otherwise—to another. They recorded neural activity in the striatum throughout the time that two different habits were learned in succession, and asked what happened at the switch from one to the other. They have found a remarkable dual representation of the habits in the striatum.

One is quite fixed and stable across the switch, but the other is more adaptable and can change when conditions change. These new findings suggest that such coexisting representations may underlie the co-occurrence of cognitive flexibility and yet cognitive stability as we acquire and modify our habits. Dr. Graybiel published a major compendium on habit formation entitled, "Habits, Rituals and the Evaluative Brain," in the *Annual Review of Neuroscience*.

Dr. Graybiel has much collaboration. One, with Bob Desimone's lab, focuses on trying to activate and inactivate neurons in the primate brain with light using the methods that Ed Boyden helped to develop. A second collaboration, with John Gabrieli, is trying to bring together experimental work in animals with human fMRI, by having tasks that are applicable to both. If this were successful, it would be a major step forward in allowing the insights of basic science to be used in relation to human brain conditions. The third collaboration is with Chris Moore, trying to push forward the limits of resolution of fMRI imaging to allow detection of the compartments of the striatum and to understand the patterns of co-activation of the cortex and striatum. Success with this work would be groundbreaking technically, and also scientifically, in allowing for the first time the fundamental units of the striatum to be viewed functionally.

Horvitz Lab

Bob Horvitz has devoted most of his career to studying the nematode worm *C. elegans*. With fewer than 1,000 cells, this worm is remarkably informative for studying many biological problems, including the genetic control of development and behavior and the mechanisms that underlie neurodegenerative disease. Future research in the Horvitz lab, understanding how certain genes operate, might lead to new treatments for certain retinal degenerative diseases as well as for Alzheimer's, Parkinson's and Huntington's diseases, stroke and traumatic brain injury. Horvitz has recently begun to study the genetic basis of aging, and one of his lab's aims is to understand how aging drives the degenerative process in conditions such as Alzheimer's disease.

In addition to the lab's work on *C. elegans*, Horvitz also has a longstanding interest in human neurodegenerative disease. He was a principal member of the team that in 1993 identified the first gene to cause familial amyotrophic lateral sclerosis (ALS), and in collaboration with colleagues at Massachusetts General Hospital he continues to work on the search for additional ALS genes.

Jasanoff Lab

In the past year, the Jasanoff laboratory continued to make progress in the development of MRI contrast agents for molecular imaging of brain activity. Work on an MRI dopamine sensor is now being completed by graduate student Mikhail Shapiro and postdoc Gil Westmeyer, including *in vivo* studies, which are among the first to demonstrate real-time noninvasive monitoring of dopamine transport in living animals. Next steps will use the sensor to examine patterns of dopamine released during rewarding stimulation in animals. A zinc sensor developed last year in collaboration with Steve Lippard's laboratory is being applied to detect labile zinc distributions in mice; ongoing work being performed by postdoc Xiao-an Zhang may ultimately allow functional imaging of neuronal activity using sensors of this family. Much of the newest

work of the lab now concentrates on genetically encoded contrast mechanisms. These methods will allow functional imaging of targeted neuronal elements. A recent step toward this goal has been the creation of ferritin-based protein contrast agents sensitive to neuronal signal transduction pathways (work of Mikhail Shapiro).

Poggio Lab

The Poggio lab's research is on the problem of learning in both biological organisms and computers. They believe that learning is at the heart of the problem of both building intelligent machines and of understanding how the brain works. Thus, they work in three main research directions: mathematics, engineering, and neuroscience of learning. The last one is gaining in importance and internal emphasis since they increasingly believe that neuroscience can now lead to new developments in artificial intelligence and establish new bridges between computer science and brain and cognitive sciences. In the mathematics area, they are continuing to work on a new mathematical formulation of the model of visual cortex developed at the Center for Biological and Computational Learning in collaboration with Steve Smale (University of Chicago and TTI) and others. In engineering, they are working on speech synthesis and computer vision, especially in the areas of surveillance and image search.

Their main effort is in neuroscience of vision/learning. They continue to develop their model of the feedforward path in visual cortex, which reproduces and predicts properties of neurons in several visual areas (see Serre, T., A. Oliva and T. Poggio. A feedforward architecture accounts for rapid categorization, *Proceedings of the National Academy of Sciences* (PNAS), Vol. 104, No. 15, 6424-6429, 2007; see Kouh, M . and T. Poggio. A canonical neural circuit for cortical nonlinear operations, *Neural Computation*, 2008;20:1427-1451, early access. Posted Online February 6, 2008. [doi:10.1162/neco.2008.02-07-466]. The Poggio Lab recently extended it to the recognition of action in videos with very good results (see Jhuang H., T. Serre, L. Wolf and T. Poggio. A Biologically Inspired System for Action Recognition, In: Proceedings of the Eleventh IEEE International Conference on Computer Vision (ICCV), 14-21 October 2007, 1–8.).

The Poggio lab has made several notable accomplishments since the last report. They have extended the model of the ventral stream to incorporate neuroscience data on back projections and control of attention and eye movements in collaboration with Bob Desimone. Preliminary results show that this extended model can predict human eye movements in top-down tasks better than other standard models of saliency. They are also in the process of developing more neuroscience details of an extension of the model to the dorsal stream for the recognition of actions. They have used the system above to phenotype mice behavior—developing a vision system that could be developed into a useful tool for biologists.

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More information about the McGovern Institute for Brain Research can be found at http://web.mit.edu/mcgovern/.