

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

The leadership board met on November 7, 2008 and April 27, 2009. Both meetings were well attended. The April meeting concluded 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 met privately with the Scolnick prizewinner, Dr. Jeremy Nathans from Johns Hopkins University. Dr. Nathans gave a late afternoon talk, followed by a well-attended dinner at the institute. Nathans won the prize for his contributions to the understanding of color vision, brain development, and retinal disease.

On February 24th and 25th, the McGovern Institute sponsored a symposium held at Tsinghua University in Beijing, China. Five McGovern Institute faculty members attended (Edward Boyden, Robert Desimone, Michale Fee, Ki Ann Goosens, and Yingxi Lin). There were 19 talks over two days and the symposium was well attended, with over 300 people each day.

On May 7th, the McGovern Institute hosted a symposium on the biological functions of the basal ganglia in health and disease. The symposium covered both animal models and human clinical research, including neuroimaging and deep brain stimulation. The symposium was very successful and we were pleased with the turnout—over 150 people over the course of the day.

The McGovern Institute held its seventh annual retreat on June 18 at the American Academy of Arts and Sciences, Norton's Woods, in Cambridge, MA. Attendees enjoyed a full day of talks by postdocs and students, a popular poster session, and an evening dinner. Yingxi Lin, the newest faculty member in the McGovern Institute, gave the keynote address. As in years past, we invited people from outside McGovern with whom we collaborate or are interested in collaborating with.

The McGovern Institute Neurotechnology (MINT) program, created in 2006, provides seed funding for interdisciplinary collaborations that aim to develop new technologies for neuroscience research. The program funded six projects in FY2009, bringing the total to 14 since the program was established in 2006. Collaborators have been drawn from multiple MIT departments, as well as several external organizations; these include the Departments of Mechanical Engineering, Chemistry, Electrical Engineering and Computer Science, Chemical Engineering, and Materials Science and Engineering, plus

the MIT Center for Biomedical Engineering, Navia Systems, Inc., and the Broad Institute. Several papers have been published within the past year based on MINT-supported collaborations.

A viral vector core facility was established as a shared resource between the McGovern and Picower Institutes. The core opened in fall 2008, under the directorship of Rachael Neve, who was recruited to MIT from a faculty position at McLean Hospital. It has already provided over 25 vector constructs to users in 12 different labs at MIT.

The McGovern board of directors meets quarterly, in July, October, January, and April. 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 fall 2009. Members are John Duncan, of the Medical Research Council in England; Nikos Logothetis, from the Max-Planck Institute for Biological Cybernetics; Carla Shatz, of Stanford University; Charles Stevens, with the Salk Institute; and Robert Wurtz, from the National Eye Institute.

Awards and Honors

Edward Boyden was named one of *Discover* magazine's 20 Best Scientists Under Age 40 and received a National Science Foundation (NSF) Emerging Frontiers in Research and Innovation Grant (Cognitive Optimization and Predication: From Neural Systems to Neurotechnology), an NSF Small Grant for Exploratory Research, the MINT Award, a Congressionally Directed Medical Research Program Post-Traumatic Stress Disorder Concept Award, and an MIT Alumni Class Funds Award for Excellence in Educational Innovation.

Ann Graybiel was named an Institute Professor in November 2008. She also received the Vanderbilt Prize in Biomedical Science and was invited to give the Lord Adrian Lecture at the University of Cambridge and Mildred Trotter Lecture at Washington University in St. Louis.

H. Robert Horvitz was elected as a foreign member of the Royal Society of London.

Tomaso Poggio was named an honorary member of the IEEE Symposium on Computational Intelligence for Financial Engineering. He was the distinguished speaker at NSF in Washington, DC, on August 14, 2008 and the main speaker at the inauguration of the Werner Reichardt Centre for Integrative Neuroscience at the University of Tübingen, Germany, in December 2008. Poggio also served as the distinguished multidirectorate speaker at NSF in May 2009.

Research

Bizzi Lab

Dr. Emilio 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 injury 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

The Boyden group has developed a new optical silencer, named Arch, which is about five times better than older reagents at mediating light-induced inhibition of neurons. Their paper describing Arch is currently under review. The Boyden lab has also developed some fusion proteins that combine multiple opsins to enable bi-directional control of neurons using single genes. They have also been working on the integration of optical control with functional magnetic resonance imaging (fMRI) to enable the first-ever method for parsing out neural circuits across the entire brain using fMRI. The lab also isolated a target in the brain that, when optically modulated, can accelerate recovery from fear extinction.

Dr. Boyden, an associate member of the McGovern Institute, is collaborating with Bob Desimone on probing the means of gamma oscillations for attention. In addition, he is collaborating with Ann Graybiel and Christopher Moore to invent a new technology, opto-fMRI, for optical control of neural circuits coupled to fMRI readout, and working with Ki Goosens to use optical neuromodulation to accelerate fear extinction, revealing new therapeutic targets.

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. Particularly, they found that specific, subtle alterations in the visual world that are invisible to human subjects can predictably alter a key computational property of visual

recognition previously assumed to be rock solid—the ability to recognize objects in different positions. They are continuing exploration of this very exciting research using both neurophysiology and computational modeling.

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, 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; neuropsychiatric disorders such as obsessive-compulsive disorder and Tourette syndrome; and likely also in attention deficit disorder/attention deficit hyperactivity disorder and aspects of schizophrenia.

The Graybiel lab has made several important discoveries during the past year. They found that two genes that they had previously identified were differentially dysregulated in the brains of rats exhibiting dyskinesias induced by prolonged L-DOPA therapy, suggesting new therapeutic methods to prevent or minimize the unwanted side effects of this widely used treatment. This work was published in the *Proceedings of the National Academy of Sciences*. In mice, they discovered ensemble activity of neurons in the sensorimotor region of the striatum that relates to both stability of the global framework of a preestablished behavioral procedure and flexibility of detailed representation of individual sensory and motor events. The results of this study are in press in the *Journal of Neurophysiology*. In primates, they continue to study neural mechanisms underlying preplanning of future sequential actions, development of visual scanning paths that approach the most efficient pattern without instruction, and decision-making under conditions of emotional conflict.

The Graybiel lab collaborated with many labs in the McGovern Institute. A study with Bob Desimone's lab, in which neurons in the primate brain were activated and inactivated with light using the methods that Ed Boyden helped to develop, has been published in *Neuron*. They also collaborated with Chris Moore and Ed Boyden to develop methods to measure activation patterns using fMRI in rodents in response to optical activation of cortical regions. They continue to collaborate with John Gabrieli to bring together experimental work in animals with human fMRI by having behavioral tasks that are applicable to both. With Chris Moore, they push forward the limits of resolution of fMRI imaging to allow detection of the compartments of the striatum and to understand the patterns of coactivation of the cortex and striatum. The Graybiel lab works with Emery

Brown on development of new analytical tools for behavioral and neuronal data. Finally, they collaborate with Ki Goosens to interactions between the striatum-mediated reward system and the amygdala-related fear system.

Horvitz Lab

Bob Horvitz has devoted most of his career to studying the nematode worm *Caenorhabditis 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.

Lin Lab

The Lin laboratory focuses on understanding how neuronal activity regulates the development and function of GABAergic synapses. Despite being key elements of neural circuit plasticity and stability, the mechanisms governing GABAergic synapse development are relatively poorly understood because the molecules involved are largely unknown. The lab recently discovered a novel activity-regulated transcription factor, *Npas4*, as a crucial molecular link between neural excitation and GABAergic synapse development. The lab currently uses forward genetics to characterize the transcription programs downstream of *Npas4* that are important for the development of inhibitory circuits. This work will be followed by a combination of molecular, biochemical, electrophysiological, and mouse genetic approaches to extend gene discovery to an in-depth understanding of the molecular mechanisms underlying inhibitory circuit development and function. Lin lab research will address fundamental questions in neuroscience and identify potential therapies for neurological disorders.

The Lin lab collaborates with the Poggio lab, the Center for Biological and Computational Learning, to help them develop software to automatically phenotype mouse behaviors.

Poggio Lab

The Poggio laboratory's research is focused on the problem of learning in both biological organisms and computers. The Center for Biological and Computational Learning, which Poggio directs, is based on the belief that learning is at the heart of the problem of both building intelligent machines and of understanding how the brain works. The lab works in three main research directions: mathematics, engineering, and neuroscience of learning.

The last one is gaining in importance and internal emphasis since neuroscience can now lead to new developments in artificial intelligence and establish new bridges between computational science and brain and cognitive sciences.

In the mathematics area, they are obtaining an increasingly general mathematical formulation and characterization of a hierarchical model of learning inspired by visual cortex. This work is a collaboration with Steve Smale at the University of Hong Kong, and others. In engineering, they have been working on bioinformatics (regulatory gene networks in *Drosophila* development) and computer vision, especially in the areas of object recognition, surveillance, and image search.

The lab's main effort is in the neuroscience of vision/learning. They continue to develop a model of the ventral stream path in visual cortex, which reproduces and predicts properties of neurons in several visual areas (see Kouh M and Poggio T. A canonical neural circuit for cortical nonlinear operations, *Neural Computation* 2008 20:1427–1451). This model was recently extended to the recognition of action in videos with very good results.

The Poggio lab's main accomplishments over the last 12 months are:

- Extending 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, match old and new data on the physiology of attention, and improve recognition performance in natural images.
- Developing—with neuroscience details—an extension of the model to the dorsal stream for the recognition of actions. This system has been used to phenotype mice behavior, developing a vision system that could be developed into a useful tool for biologists.
- Formulating a mathematical theory of hierarchical networks for learning. This framework may lead to results about a variety of learning architectures, including convolution networks, HMX-like models of cortex, and dynamic Bayesian networks.

Robert Desimone

Director

Doris and Don Berkey Professor of Brain and Cognitive Sciences

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