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 initiated a faculty search during spring 2007. Although we reviewed over 100 applications, we ultimately decided not to make an offer and will instead run the search again in 2007–2008.

We held our second annual imaging symposium at the McGovern Institute on May 15, 2007. The co-organizers of this year's event were Christopher Moore, Alan Jasanoff, and Charles Jennings. The theme, "Plumbing the Mind: Brain Activation and the Regulation of Cerebral Blood Flow," brought together people working on the physiological mechanisms of neurovascular coupling with others interested in the development of brain imaging technology, especially (but not exclusively) fMRI. Held in the brain and cognitive sciences complex, it was an oversubscribed event that was incredibly well received.

The Institute's Annual Scolnick Prize lecture and dinner was held May 21, 2007. The winner, Dr. David Julius, gave a late afternoon talk, followed by a well-attended dinner at the McGovern Institute. The Scolnick Prize recognizes an outstanding discovery or significant advance in the field of neuroscience.

The McGovern Institute held its 5th annual retreat June 3–5 at the Newport Marriott in Newport, Rhode Island. The format was similar to that of past years, with postdocs and students giving talks, a keynote address, and a poster session. The keynote speaker, Bai Lu from the National Institutes of Health, gave a well-received talk on memory and disease and other invited outside guests spoke as well. A special activity for the group was a sail on America's Cup racing boats.

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.

The McGovern board of directors meets quarterly, in July, October, January, and April. The membership of the board has not changed since its inception and consists of

Patrick McGovern; Lore McGovern; Elizabeth McGovern; Gerald Fischbach, Columbia University; Robert Langer, MIT; Edward Scolnick, Broad Institute; Robert Silbey, MIT; 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 Schatz, Harvard Medical School; Charles Stevens, Salk Institute; and Robert Wurtz, National Eye Institute.

Awards and Honors

Emilio Bizzi was appointed president of the American Academy of Arts and Sciences. In addition he was named chair of the Scientific Advisory Board of the Italian Institute of Technology.

Ed Boyden was awarded the Fannie and John Hertz Foundation Top PhD Thesis Prize in 2006. He also received a (MINT) award and was named one of *Technology Review*'s TR35 "Top 35 Innovators Under Age 35." In early 2007 he was awarded the Wallace H. Coulter Early Career Award.

Robert Desimone was named a fellow of the Association for Psychological Science (APS) for distinguished contributions to psychological science.

Ann Graybiel was awarded the NARSAD Distinguished Investigator Award, an honorary doctorate of philosophy from the Hebrew University of Jerusalem, and an honorary doctorate in medical science from Queens University, Belfast, all in 2007.

Alan Jasanoff, an associate member of the McGovern Institute, received a 2006 Technological Innovations in Neuroscience Award from the McKnight Foundation, which will support in vivo testing of the new family of MRI calcium sensors his laboratory has developed. He is also the recipient of the Dana Foundation Brain and Immuno-Imaging Grant and the N.C. Rasmussen Career Development Chair in Nuclear Science Engineering.

Tomaso Poggio was the guest of honor at the symposium "A Journey through Computation" organized in Genoa, Italy by Alessandro Verri, Federico Girosi, and Gadi Geiger for Poggio's 60th birthday. Poggio gave the 2007 Rockwood lecture at the University of California at San Diego. In addition, Dr. Poggio was the keynote speaker at several other conferences such as TK60 at Carnegie Mellon University.

Research

Bizzi Lab

Dr. Bizzi's research focuses on the study of the physiological mechanisms underlying complex, coordinated arm movements. His investigations deal with the mechanisms by which the central nervous system simultaneously controls the large number of muscles

involved in arm and hand movements. The presence of many muscles in the limbs of vertebrates is the basis of their remarkable ability to perform different tasks in a wide range of environmental conditions. However, the large number of muscles creates a complex computational problem for the nervous system. Dr. Bizzi has explored this problem experimentally and theoretically. His results have demonstrated the presence of a modular organization in the vertebrate spinal cord based on groups of interconnected interneurons. When active, these modules control groups of muscles as a unit. Through this neural architecture the central nervous system achieves a significant reduction of controlled variables.

With respect to motor learning, Professor Bizzi has investigated the problem of consolidation of motor memories. Bizzi has found that the memories of learned movements initially exist in a vulnerable state. He has evidence indicating that these vulnerable memories gradually become consolidated. These results provide the first indication that motor memories are transformed by a process of consolidation.

The studies of motor control and motor learning in Bizzi's laboratory have already led to the development of a system for the rehabilitation of patients affected by stroke.

Boyden Lab

Ed Boyden invents and applies tools to the analysis and engineering of brain circuits in humans and in research animals. He designs new technologies to help treat human brain disorders while improving our understanding of the human mind. He is developing new strategies for systematically repairing brain pathologies, such as epilepsy, anxiety, and Parkinson's disease, and also for augmenting cognition in diseases like Alzheimer's. His research integrates nanotechnological, molecular, optical, and other technologies into interfaces for the precise control of neural circuit dynamics and function. He and his colleagues created a genetically targeted way to activate and shut down neurons using millisecond-timescale pulses of light. This innovation is now being widely used in neuroscience and neuroengineering.

Dr. Boyden will became an associate member of the McGovern Institute in July 2007. In 2006, he joined the MIT Media Lab as a visiting scientist, where he is now an assistant professor (jointly with the Biological Engineering Division). He received a PhD in neuroscience from Stanford University in 2005. He holds a double BS in physics and electrical engineering and computer science and an MEng in electrical engineering and computer science from MIT. In 2006 he was named one of the world's "Top 35 Innovators Under Age 35" by *Technology Review*. In 2007, he received a Wallace H. Coulter Early Career Award to develop new approaches for treating epilepsy and Parkinson's disease.

DiCarlo Lab

Professor James DiCarlo's lab continues to focus on understanding the neuronal representations supporting the brain's remarkable ability to recognize objects under a very wide range of viewing conditions. In one line of work they are examining the role of visual experience in the real world in supporting this ability. Last year, they discovered that specific, subtle alterations in the visual world, which are invisible to the human subjects, can alter a property of their visual recognition previously assumed to be

rock solid—the ability to recognize objects in different positions. This year the DiCarlo lab completed a neurophysiology study that revealed that related effects of visual experience are found in high-level neuronal patterns of activity in nonhuman primates. The lab is continuing our exploration of this line of work, using both neurophysiology and computational modeling. The lab has several ongoing collaborations with other groups in the McGovern Institute. Along with Professor Tomaso Poggio's group, the group is working to better understand how object information is represented along the ventral visual stream, and they have made important progress on the relationship between selectivity for visual objects and tolerance for viewing those objects in cluttered scenes. In collaboration with Professor Nancy Kanwisher's group, the DiCarlo Lab has recently completed studies using fMRI in both human and nonhuman primates to gain new understanding of the spatial organization of shape information in high-level visual cortex.

Goosens Lab

Mammals have a highly conserved system for detecting and responding to danger cues in the environment. This system integrates information from multiple neuronal circuits to produce a coordinated, adaptive fear response. The fear response is derived both from circuits that produce hardwired, reflexive behaviors and from circuits that exhibit tremendous plasticity. Although it is highly adaptive to acquire information about potentially dangerous stimuli, fear learning can also enter a pathological state, where the level of fear expressed is inappropriate given the circumstances.

The research goal of the Goosens Lab is to understand the neuronal mechanisms for encoding and expressing fear and anxiety, and to determine the pathways by which chronic stress can trigger pathological fear and anxiety. In the last year, her laboratory has focused on three areas related to this goal:

- Replicating the potentiating effects of chronic stress on amygdala function. Dr. Goosens previously showed that chronic stress facilitates the function of the amygdala, one of the brain areas central to learning about fearful stimuli. Because of differences in animal housing, available rodent suppliers, and other parameters, it was important to demonstrate that her lab could reliably replicate their previous results here at MIT. They have now replicated their basic findings and have started to extend these findings. For example, they have examined the influence of the duration of stress (spanning several days to several weeks) on amygdala function.
- Building viral vectors to probe the role of growth hormone (GH) in amygdala function. Goosens previously demonstrated that locally synthesized GH is upregulated in the amygdala after chronic stress. To probe the role of growth hormone in normal and stress-potentiated amygdala function, the Goosens Lab is cloning and testing several viral vectors designed to manipulate growth hormone levels. They have cloned a vector that overexpresses rat GH. They are currently cloning a second vector to overexpress constitutively secreted GH. They are also currently cloning a vector that expresses hairpin RNAs and will produce targeted degradation of GH. They will be testing these vectors in primary neuronal culture to quantify the degree of overexpression or knockdown produced by the

vectors. They are particularly excited about the development of these tools, as there is almost nothing commercially available that can be used to probe the role of GH in brain function.

- Probing the role of ghrelin in amygdala function. Ghrelin is a hormone that potently stimulates GH release, and has been shown to cause dendritic expansion in the hippocampus. They believe that its trophic role is due to its effects on GH release. They have now shown that ghrelin infused prior to fear conditioning increases fear memory during testing. These effects are temporally specific, and are largest when GH release is maximal. They are also not produced when ghrelin is infused immediately postconditioning, suggesting the effect is on the acquisition of the memory itself, and not the consolidation.

Graybiel Lab

The Graybiel Lab's research is focused on brain regions that become disabled in Parkinson's disease, Huntington's disease, and dystonia, and that also are disabled in a range of neuropsychiatric disorders including Tourette syndrome, obsessive-compulsive disorder, and some autistic syndromes. These brain regions are the basal ganglia and corresponding cortico-basal ganglia loops. Remarkably, these same brain regions and circuits underlie normal habit learning and, with drug use, addictive states. These circuits are thus of fundamental importance to us as humans in guiding both our normal behavior as well as our behavior in clinical disorders.

The lab is taking two main approaches to studying these circuits. The first is through research directly related to human disorders. During the past year the Graybiel Lab found, with their New Zealand colleagues, that one subsystem in the basal ganglia is particularly affected in Huntington's disease patients, in which disabling mood symptoms predominate at early stages of the disease process. This is particularly notable because Huntington's disease reflects a disorder in a single gene, yet different symptom complexes can occur in different patients. Their work identified differential vulnerability of brain subcircuits associated with these different symptoms. During the last year they also have found that in a model of Parkinson's disease, a gene that they cloned in our laboratory, CalDAG-GEFII, is upregulated very strongly. This is a very new finding, but is of real interest because the gene could contribute to aspects of Parkinson's disease pathophysiology. Third, they are developing a model of abnormal stereotypic behavior that they are investigating as a possible model of stereotypes in autism and also in drug-induced states in which repetitive movements and thoughts occur. This model is based on a genetically engineered mouse that they produced in their laboratory in which another gene that they cloned in the lab, CalDAG-GEFI, has been knocked out. All three of these disease-oriented studies involve a major genetic component as well as thoroughgoing analyses of behavior and in some instances electrophysiology.

The second approach is to analyze, as deeply as possible, the basal ganglia-related neural circuits themselves. This work predominantly involves recording from large ensembles of neurons in the neocortex and striatum of monkeys, rats, and mice as they learn tasks and then perform them. During the last year they have confirmed, both in rats and mice, their finding of the previous year that widescale changes in the patterns

of neural activity occur in the striatum during behavioral "habit learning." They are investigating the mechanisms that lead to this striking brain plasticity. This work involves recording from multiple tetrodes (4-channel electrodes) chronically implanted in the striatum. They are also recording, with multiple electrodes, in the brains of macaque monkeys as they acquire and perform tasks. They have mounting evidence that a totally naive monkey can spontaneously develop a habit in a simple visual search task (the "habit" is the monkey's way of searching—we do not teach it, it develops this itself). The Graybiel Lab was startled and interested to find that the pattern that is developed is the optimal search pattern as determined by computational analysis. They are just beginning to analyze neural data recorded during the entire time that the acquiring this "habit."

Finally, an important spin-off of their gene cloning work is that one of the genes cloned, CalDAG-GEFI, turns out to be absolutely critical for the kind of platelet aggregation that stops bleeding (the formation of a thrombus). Platelets in the lab's CalDAG-GEFI knockout mouse have lost the ability to aggregate, and thus if the mouse is cut it will bleed uncontrollably. The Graybiel Lab has worked with colleagues at Harvard Medical School on this research and has identified the molecular pathway responsible for this effect. Moreover, lab members have worked with other colleagues who were analyzing bleeding disorders (LAD III syndromes) in children. It seems highly likely that an abnormality in CalDAG-GEFI leads to at least one LAD III syndrome. Thus this work with the genes may have potential to help such children.

Jasanoff Lab

The Jasanoff Lab has made significant progress on its core focus of developing molecular probes for next-generation functional imaging in animals. They introduced a new family of calcium sensors for MRI, and are now in the process of applying them in single cells and intact organisms. They also collaborated with Steve Lippard's group to develop porphyrin-based cell-permeable contrast agents that address the key problem of in vivo delivery, and could be important for future neuroimaging work. Newer projects have focused on several types of genetically controlled contrast agents; most advanced is their work on a protein dopamine sensor that we plan to use for mapping reward-related signaling in rodents. The lab recently completed a project to study development of neural connectivity and hemodynamic responses in juvenile rats in collaboration with Martha Constantine-Paton's lab. They found that systematic changes in BOLD time courses take place from P13-adulthood, and may be related to changes in carbonic anhydrase expression that occur at this age; the changes also coincided with gross repatterning of neural activity in response to somatosensory stimuli in these animals.

Kanwisher Lab

The Kanwisher Lab continues their collaboration with Jim DiCarlo, which has proven exciting and fruitful, and will soon submit a second joint paper, this one on fMRI scanning in monkeys. In the last year the lab has developed new behavioral methods to study reorganization of visual cortex in adulthood, and continues fMRI work on this topic. The lab has also developed a new method for asking which pattern data in visual cortex participate in perceptual discrimination tasks. Finally, the lab may have

discovered a new kind of evidence for precise feedback to primary visual cortex. All of these studies are ongoing at the moment, along with many other projects.

Poggio Lab

The Poggio Lab focuses their research 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. In the mathematics area, they are working on a new learning theory formulation of the model of visual cortex developed at CBCL in collaboration between Andrea Capponnetto, Steve Smale (at the Toyota Institute in Chicago), and Tomaso Poggio. In engineering, they are working on speech synthesis and computer vision, especially in the areas of surveillance and image search. Stan Bileschi has graduated with a PhD thesis focused on developing a system for Scene Understanding in the domain of StreetScenes and is now involved in several projects for image understanding for surveillance, which they expect to be funded by DARPA.

The Poggio Lab main effort is now in neuroscience of vision and learning. As mentioned, their model of the feedforward path in the visual cortex, which reproduces and predicts properties of neurons in several visual areas, is performing well in recognition tasks in complex, natural images. The model also mimics human performance in difficult image categorization tasks.

The Poggio Lab consists of about 20 researchers, including students, postdocs, visitors, and staff.

The lab's main accomplishments since the last report are the development of a hierarchical feedforward architecture for object recognition based on the anatomy and the physiology of the visual cortex, showing that the resulting performance on several databases of complex images is as good or better than the best available computer vision systems (Serre T, Wolf L, Bileschi S, Riesenhuber M, Poggio T. Robust object recognition with cortex-like mechanisms. *PAMI* 2007 29(3):411–426). They also showed, for the first time, that a neurobiological model of the cortex does as well as humans for short presentations on a difficult natural image recognition task (Serre T, Oliva A, Poggio T. A feedforward architecture accounts for rapid characterization. *PNAS* 2007 104(15):6424–6429).

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