Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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From the director

I normally use this space to highlight the work of my colleagues in the McGovern Institute. However, I have recently been honored to be named to the newly endowed Doris and Don Berkey Professorship, and I would like to use this opportunity to give some context to the Berkey's generous gift by telling you about my own research interests.

It may come as a surprise to some people that I still spend time at the lab bench amid my responsibilities as director of the McGovern Institute. But I firmly believe in the importance of administrators remaining close to the science. As you will read in the following pages, I began my career as a researcher hoping to help people with mental illness some thirty years ago. Since then, I have witnessed the evolution of new opportunities for treating brain disorders that were unimaginable at the time that I entered the field. We now have the opportunity to make real progress in treating these intractable diseases, and one of my most important goals as director is to promote the translation of basic scientific understanding into new therapeutic approaches.

In introducing this issue, I want to acknowledge the contributions of my junior colleagues, past and present. As faculty members we are the public faces of our laboratories and of the McGovern Institute, but our research is always a team effort, and none of it would be possible without the many talented students, postdocs and staff members whose energy and enthusiasm drive the work of the institute. I am particularly grateful to the generous donors whose support helps these young researchers, two of whom you can read about on page 8 of this issue. Despite the difficulties with the current federal funding climate, I firmly believe that the outlook for young neuroscientists is bright. The need is great, the opportunities are boundless, and there has never been a better time for young scientists to enter this field.

Bob Desimone, Director

Robert Desimone, Director, McGovern Institute; Doris and Don Berkey Professor of Neuroscience

ROBERT DESIMONE: SYNCHRONY IN RESEARCH AND ADMINISTRATION

As director of the McGovern Institute, Bob Desimone divides his time between his administrative responsibilities and his own research on the control of attention. His career has reflected the evolution of the field, as basic research has begun to provide new insights into disease mechanisms.

Robert Desimone, Ph.D., director of the McGovern Institute and first incumbent of MIT's Doris and Don Berkey Professorship in neuroscience, entered Macalester College in 1970 determined to become a psychotherapist. He majored in psychology and worked in a halfway house for the mentally ill, dealing with nighttime emergencies and suicide attempts. After graduation, he spent a year as a mental health counselor.

"These experiences convinced me that therapy was not my strong suit," he reflects. "I wanted to help people directly, but my talent was in basic research."

With redirected goals, he earned a Ph.D. at Princeton University under the guidance of neuroscientist Charles Gross. He then accepted a position at the National Institute of Mental Health (NIMH), where he ran his own research lab. He rose through the ranks to become director of Intramural Research, overseeing both basic and clinical research. He revitalized the NIMH's clinical research agenda, creating programs on the genetics of psychosis and on mood and anxiety disorders. He also strengthened the translational programs that connect the research lab to the clinic. The emphasis on translational research continues at the McGovern Institute, which under Desimone's leadership has established a major new center for psychiatric disease research.

Desimone's own research focuses on attention, which researchers now understand is critical in education and learning, and is disturbed in many psychiatric conditions. "Attention is a cognitive function that is impaired in depression, schizophrenia, attention deficit disorder (ADD) and other forms of brain disorders," he says."

"When I first entered the field, basic neuroscience research appeared quite removed from patients suffering from mental illnesses," Desimone continues. "But to my satisfaction, neuroscience has grown much more relevant to psychiatry. In my administrative capacity, at NIH and now at the McGovern Institute, I have been involved in translational research with clinical applications. My own research has also come full circle and I'm now seeing potential applications to mental illness that I could never have imagined when I started my career."

The challenge of attention

Our brains are constantly flooded with sensory information, most of which is usually irrelevant—the feel of our shoes, traffic sounds, patterns on the wall, and so on. The brain's attentional control system allows us to filter out these irrelevant distractions and focus on the task at hand.

The ability to ignore distractions and stay on task is an essential skill that most of us take for granted. But some people find this very challenging, and attentional difficulties can be profoundly disruptive for many aspects of everyday life.

Desimone's research helps explain why we have little awareness of things we are not paying attention to, and it is leading to a greater understanding of the role of attentional difficulties in learning and psychiatric disorders.

Grandmother cells

Desimone came to the study of attention indirectly, through his interest in visual perception. His early research focused on the first stages of visual processing, as information enters the brain from the retina. He and his colleagues set out to map the connections between different parts of the visual cortex, and to understand how visual information is transformed as it passes from one area to the next.

Neurons in the early visual areas respond to edges, corners and other simple visual features, but as researchers looked deeper into the brain, they found neurons with preferences for more complex patterns. In the early 1980s, while recording neural activity in the relatively uncharted temporal lobe of the monkey, Desimone and Gross made the remarkable discovery that some neurons respond exclusively to faces.

The response was overwhelmingly skeptical, he recalls. "Even though we knew that damage to the temporal lobe could impair face recognition in people, a condition called prosopagnosia, scientists didn't believe face cells were possible. They said we must be misinterpreting. One NIH reviewer told me, 'Even if it is true, you should drop it because no one will believe you.'"

Indeed, neuroscientists had mocked the notion that cells could have such a precise sensitivity by invoking the so-called 'grandmother cell'—a hypothetical neuron that could respond only to one's grandmother. The grandmother cell was intended as a straw man, but today it is clear that exquisitely specialized cells do in fact exist within the brain—indeed a recent study reported two different neurons that responded selectively to the actresses Jennifer Aniston or Halle Berry. Modern neuroimaging techniques, not yet developed when Desimone made his discovery, have confirmed that, far from being an isolated curiosity, this specialization is a general organizational principle within the brain. For example, Desimone's McGovern colleague Nancy Kanwisher has identified distinct brain regions that respond to faces and to body parts.

The wheel of attention

Desimone might have continued to study object recognition, but a serendipitous discovery led him to shift his research to the problem of attention. While recording neural activity in the monkey visual system, he found that some neurons behaved inconsistently, sometimes responding strongly to a visual stimulus and other times showing little response. Could the difference depend on whether the monkeys were paying attention to visual stimulus?

As with most vision studies at the time, Desimone's monkeys only needed to look passively at the screen before their eyes. No one could tell when a monkey was paying attention to the objects on the screen, or whether its mind was wandering. "It was as if a steering wheel was spinning out of control" recalls Desimone. "If I could get control of that wheel, I thought I could get more consistent results."

To gain that control, he trained monkeys to perform tasks requiring them to attend to a particular stimulus—for instance, tracking a red dot while ignoring a green one nearby. He realized that attention was something worth studying in its own right. "We saw

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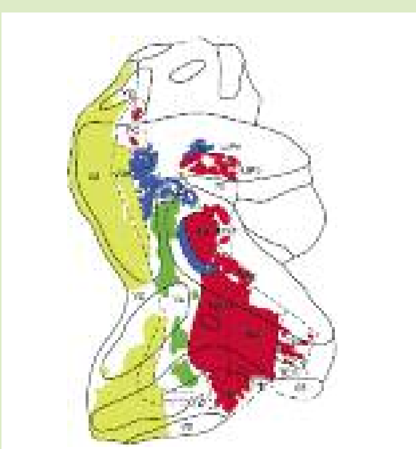
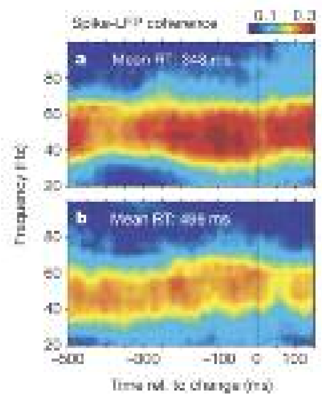


Distribution of neural connections in the monkey visual system

*Visual signals from lower cortical areas (*yellow*) pass through intermediate areas (*green and blue*) to the higher areas where specific classes of objects are represented (*red*). Desimone's work has shown that the flow of information through intermediate areas such as V4 (*green*) is strongly influenced by attention.*

Graphic: Leslie G. Ungerleider, Thelma W. Galkin, Robert Desimone and Ricardo Gattass; NIMH



Graphic representation of synchronous neural activity in the visual cortex

Darker red signifies greater synchronization of rhythmic activity among large numbers of neurons. The stronger synchrony seen in the upper panel is associated with faster behavioral responses to a visual stimulus.

Image: Robert Desimone

a dramatic difference. If the monkey was attending to the stimulus, there was a big response. If the monkey was not attending, the neuron had no response, as if the unattended information was deleted. We could actually show where unattended things were taken out of the visual pathway."

Biased competition

What guides the hand on the steering wheel? When Desimone first entered the field, most scientists thought that attention was related to the control of eye movements—that an attentional 'spotlight' illuminates a point in the visual field and direct the eyes to move there. But he realized that attention is not necessarily directed to any particular location; it can also be driven by higher level cognitive processes, such as memories, instructions or internal plans, that are independent of a stimulus's location. For example, attention allows us to search for a specific person in a crowd even if we don't know where to look. In his most cited paper, a 1995 review article, Desimone and his coauthor John Duncan proposed a new view of attention which they termed 'biased competition'. The brain cannot process all the sensory signals that it receives, so these signals must compete for neural resources. A winner emerges either because of its inherent salience (the brightest object, the loudest noise) or because it is selected through a top-down biasing influence (the person we were looking for). Desimone argued that a likely origin of these biasing signals was the prefrontal cortex, the seat of higher cognitive functions and of working memory.

Again, after initial skepticism, this view of attentional bias is now generally accepted. Desimone and others are now mapping out the underlying brain pathways to understand how attention normally functions and how it malfunctions in brain disorders.

All together now

In recent years Desimone's research has moved from studying individual cells to surveying the synchronous activity of many neurons distributed across multiple brain structures. When a monkey pays attention to a stimulus, the neurons responding to that stimulus do not merely become more active, they also coordinate their activity. By firing in synchrony with each other, they gain a competitive edge, increasing the likelihood that other brain regions will detect their message.

"It's like being in a crowd of people who are all talking at once," explains Desimone. "An individual voice gets lost, and if people simply raise their voices it just increases the noise. But if a group starts chanting in unison, their voices rise above the background and get noticed."

Desimone is now studying the same phenomenon in humans, using a non-invasive brain-imaging method called magnetoencephalography (MEG). This technology uses sensitive detectors outside the head to monitor tiny magnetic fluctuations that originate from underlying brain activity. When large populations of neurons synchronize their activity, they produce high-frequency oscillations in the magnetic field that can reveal large-scale patterns of activity thought to underlie attention and other cognitive processes. Desimone's MEG work is currently done in collaboration with colleagues at NIMH, but he hopes in the future to acquire a state-of-the-art MEG scanner at MIT.

Applications to human disorders

"We want to know whether these basic mechanisms that we are learning about in monkeys also apply to humans, and we also want to look for disease effects," says Desimone. "There's growing evidence that neural synchrony may be impaired in disease conditions like schizophrenia, epilepsy, autism and Alzheimer's and Parkinson's disease. If this proves to be true, we could use MEG to help identify the dysfunctional circuits, and if we find them, it may be possible to restore synchrony therapeutically."

This intervention might come in the form of new drugs, or through direct manipulation using new optical and genetic technologies that Desimone's colleagues Ed Boyden and Xue Han have helped develop. Desimone is exploring that possibility with Han and Boyden, an associate member of the McGovern Institute.

Desimone is enthusiastic that neuroscience can now explicitly study issues related to psychology and human behavior. "When I entered the field, the opportunities for neuroscience research to impact mental illness were far behind where we are today. The trajectory of my own research parallels that of the entire field. It is extremely satisfying that 38 years into my career, I am right in the middle of what I originally set out to do!" ■

Bob Desimone Named to Doris and Don Berkey Professorship

Donald and Doris Berkey

Doris and Donald ('42SB, '43SM) Berkey of Naples, Florida have donated $3,000,000 to endow a MIT Professorship in neuroscience, with Robert Desimone, Director of the McGovern Institute, as the first incumbent.

"Our decision to endow this chair reflects our belief that a better understanding of the brain will help to prevent some of the suffering caused by psychiatric disease," the Berkeys say. "We were delighted to learn that Bob Desimone and the McGovern Institute share this goal."

For Don Berkey, attending MIT was a childhood dream come true. Here he studied mechanical engineering at the undergraduate and masters level. "My mind was mechanical and I wanted to understand how things work," he explains. After receiving his SM in 1943, he joined General Electric to work on jet engines during World War II. He rose through the managerial ranks, becoming General Manager of the Jet Engines Department and he holds several patents in jet engine design, including the high by-pass turbine engine. GE had won a $465 million military contract to design a more efficient engine for the C5A, a large military transport plane that had long-range requirements. "Our engine was 30% more fuel efficient," he says, "and it's the basic design for all the high-bypass jet engines that you see today with their big fans enclosed on the wings."

For his last 7 years at GE, Don headed the Energy Systems and Technical Division as Vice-President, working to advance technologies for solar energy, coal, nuclear and other forms of energy during President Carter's "war on energy" years. When that focus receded during the Reagan presidency, he retired in 1982 at the age of 62. Don and Doris divided their time between Cape Cod and Florida, and have taken up golfing, boating and competitive duplicate bridge. They keep abreast of technology developments by reading the *Technology Review* and other publications.

"In thinking about how we could focus our philanthropy," explains Don, "we decided to support research related to mental illness because our family, like so many others, has been touched by these issues. We went to the Internet to learn about research in this area, which ultimately led us to the McGovern Institute. In speaking with Bob Desimone, we were impressed by his experience in mental health research and by his accomplishments at the National Institute of Mental Health. We were also encouraged by the direction he has been leading the McGovern Institute and in particular by the focus of the new Poitras Center for Affective Disorders Research."

Finally, after speaking with MIT's Provost, Rafael Reif, the Berkeys decided to create the Don and Doris Berkey Professorship naming Desimone as the first incumbent.

"I agreed that Bob Desimone was the perfect choice for this professorship, given his long track record of achievements in basic neuroscience research that is beginning to have clinical relevance to psychiatric disorders," comments Reif.

Desimone adds that he feels profoundly grateful for the Berkeys' generosity. "This professorship will support my ongoing efforts to nurture a new generation of neuroscientists dedicated to linking basic research to improving the lives of people struggling with psychiatric disorders." ■

Leadership Board Meeting and Award Dinner

The McGovern Leadership Board held its spring meeting on April 14, 2008. The board welcomed two new members, Robert Buxton of New York and Robert (Bard) Richmond ('72 EE; '63 SB) of Seattle. McGovern Institute director Bob Desimone provided an update on major initiatives, including the Poitras Center for Affective Disorders Research and the McArthur Foundation's Law and Neuroscience project. This was followed by a lively discussion about communications strategy for the institute. The board members also met with Michael Davis of Emory University, the winner of this year's Scolnick Prize, who gave a preview of his prize lecture (see next page). Board members then attended the lecture, reception and dinner in honor of Dr. Davis. ■

Michael Davis and Bob Desimone

Fear, Anxiety and PTSD

Michael Davis, a neuroscientist at Emory University School of Medicine in Atlanta, Georgia received the McGovern Institute's 5th annual Edward M. Scolnick Prize in Neuroscience on April 14, 2008. In his award lecture, "The Neurobiology of Fear, Anxiety and Extinction: Implications for Psychotherapy," he described his bench-to-bedside translational research in psychiatry.

Davis used the conditioned learning paradigm made famous by Pavlov's dogs to trace the brain pathways that underlie learned fear. By studying rats, he showed the importance of synaptic changes in fear learning and discovered that this form of learning depends on molecules known as NMDA receptors, acting within a brain structure called the amydgala. He went on to show that the loss of fearful memories, known as extinction, is not merely the gradual decay of memory but rather is an active process that also depends on NMDA receptors.

Drugs that enhance NMDA receptor activity can enhance this suppression of fearful memories in rats, suggesting that they might also enhance the beneficial effects of human psychotherapy. Davis and his collaborators have tested this approach in patients suffering from fear of heights, with encouraging results. He is now conducting a larger study of Iraq veterans with post-traumatic stress disorder (PTSD), and several other trials are also underway. This approach holds great promise for treating obsessive-compulsive disorder, social phobia, panic disorder and many other conditions.

The McGovern Institute awards the annual Scolnick Prize of $50,000 to recognize an individual who has made outstanding advances in the field of neuroscience. The prize was endowed by Merck & Co, Inc. and named in honor of Dr. Edward M. Scolnick, who served as President of Merck Research Laboratories until 2002. Scolnick now directs the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard and is a member of the McGovern Institute's governing board. ■

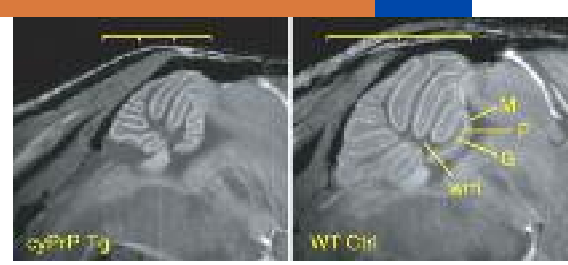
Michael Davis has developed a way to combine drug treatment with behavioral therapy in order to extinguish fearful memories. He is testing this approach on Iraq veterans with PTSD, using virtual reality to recreate the context in which traumatic memories were first acquired.

Image: Michael Davis, Emory University

RESEARCH NEWS

MRI Scanner Update

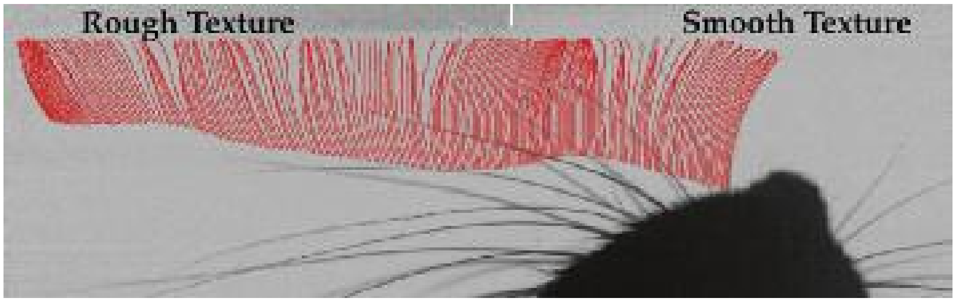
One year ago, the Martinos Imaging Center at the McGovern Institute acquired a new state-of-the art MRI machine for imaging experimental animals. This instrument is now fully operational, and is a shared resource not just for the McGovern Institute but also for the entire biomedical research community at MIT and beyond. For example, Alan Jasanoff, an associate member of the McGovern Institute, has been collaborating with Susan Lindquist, a former director of the Whitehead Institute for Biomedical Research, to study a mouse model of 'mad cow disease,' a neurodegenerative disease of humans and cattle. The new machine, with its powerful 9.4T magnet, provides a detailed view of the disease process in living mice. ■



These images illustrate the shrinkage of the cerebellum and brain stem of the mice with 'mad cow disease' (left) compared to normal controls (right).

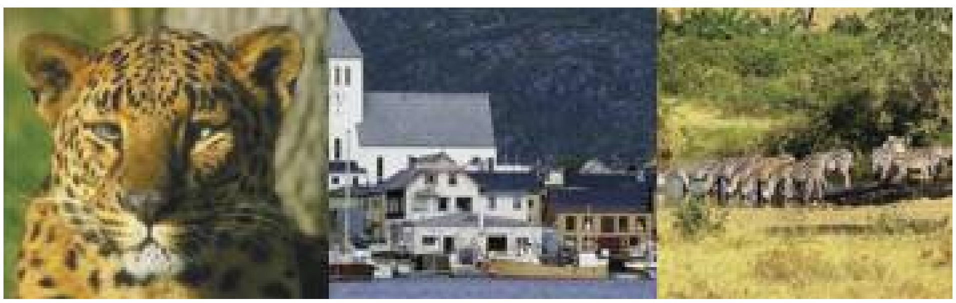
Image: Henryk Faas, McGovern Institute
Walker Jackson, Whitehead Institute

In the News



Christopher Moore published a paper in *Neuron* that received wide coverage in the popular press, including *Time*, *Scientific American*, *MSNBC* and many other publications.

Image: Jason Ritt, McGovern Institute



Tomaso Poggio's brain-inspired computer models of human vision, which may lead to better systems for machine vision, were featured in *Scientific American* and in the *BBC* television documentary "*Visions of the Future*". A computer model developed in Poggio's lab matched human performance in categorizing images after just a fleeting glimpse.

Image: Thomas Serre, McGovern Institute

Nancy Kanwisher's work on face recognition was featured in the *Wall Street Journal*. Kanwisher, who has argued that our attraction to faces may reflect an innate aspect of brain wiring, was also cited in recent articles in the *Scientific American MIND* and the *New York Times*.

For links to media coverage, go to http://web.mit.edu/mcgovern/html/News_and_Publications/media_coverage.shtml.

Ed Boyden Named Sloan Research Fellow

Ed Boyden, an associate member of the McGovern Institute, was one of seven junior MIT faculty to win a 2008 Alfred P. Sloan Foundation Research Fellowship. The fellowships are intended to enhance the careers of the very best young faculty members in specified fields of science at a pivotal stage in their work. Boyden invents new tools for analyzing and manipulating brain circuits. In addition to research applications, he hopes that these new technologies will contribute to the development of new therapeutic approaches to brain disorders such as epilepsy and schizophrenia.

Boyden also received the MIT Alumni Class Funds Award for Educational Innovation and his lab was featured in the "Best 5 Science Moments of 2007" by the *Discovery Channel*.

New Brochure

A new 36-page brochure about the McGovern Institute is now available. The brochure summarizes the work of the institute and includes profiles of each faculty member. To request a copy, email Laurie Ledeen at ledeen@mit.edu.

Supporting Young Scientists

Aaron Andalman in Michale Fee's lab received the 2007–2008 graduate student fellowship of the Friends of the McGovern Institute. Andalman studies the basal ganglia, a set of brain structures that degenerate in Parkinson's and Huntington's diseases. He focuses on how the basal ganglia help us acquire new motor skills, using songbirds as a model. "This fellowship has allowed me to develop a new behavioral technique in which birds rapidly learn to change the pitch of a particular note in their song," he explains. "I'm using this technique to ask how the brain makes adjustments to a previously learned behavior."

Aaron Andalman

Ana Fiallos

Ana Fiallos, a graduate student in Alan Jasanoff's lab, holds the Schoemaker Fellowship for the 2007–2008 year. She studies the brain circuitry involved in positive reinforcement. When rats are rewarded for performing a task, specialized reward-responsive neurons release the chemical dopamine. Fiallos is combining behavioral studies with non-invasive brain imaging using the new 9.4T MRI magnet in the Martinos Imaging Center (see page 6). "Dopamine signaling pathways in the brain are essential for reinforcement learning and motor control, and dysfunctions in this system occur in drug addiction, Parkinson's disease and many other disorders," Fiallos explains. "I hope our work will lead to a better understanding of what goes wrong in these conditions and how they might be treated."

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/

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