Brain SCAN

McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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From the director

I have often commented on how basic research can have unexpected relevance to human brain disorders. But even I am amazed at how much Michale Fee's work on songbirds is telling us about the brain circuits that underlie complex motor behaviors and which are disrupted in many brain disorders.

Michale Fee's basic research on song learning in zebra finches has broad implications for understanding trial-and-error learning, and promises to shed new light on a variety of brain disorders. Photo: Dimitri Vasiliou (Troon, Scotland)

Many scientists study songbirds because they are one of the few animals that learn their vocalizations, similar to human language learning. But Michale Fee shows us that birdsong is also a versatile model for many other learned behaviors. Insights from the songbird brain may help us understand the origins of Parkinson's disease, obsessive compulsive disorder and many other brain disorders.

Like birdsong and speech, many of the abilities that we value most are complex sequential behaviors. These include skills such as playing a sport or a musical instrument, but also mundane activities like getting dressed or brushing our teeth. We have to learn how to do these things, step by step, until the movements flow seamlessly together. We could not get through the simplest task without the brain circuitry that underlies this sequential learning.

Unfortunately, these brain systems are often compromised, whether by movement disorders, psychiatric disease or substance abuse, imposing great difficulties in daily living and in the pursuit of higher goals.

I am very excited that Michale's work on songbirds is showing how these brain pathways work, because similar human pathways are involved in many of the disorders that we do not yet understand well enough to develop better treatments. Work on the song system will give us valuable new research tools that will improve our understanding of many brain disorders.

The link to Parkinson's disease is particularly exciting, because Ann Graybiel's lab is also getting a big boost to its work in this area through a generous grant from the Sydney family. The Sydneys have personal experience of both Parkinson's disease and stroke, and understand only too well the impact of brain disorders on individuals and their families. We are deeply grateful for their support. We are also grateful to the Ellison Medical Foundation for a new grant that will support our efforts to understand two other major brain disorders—dyslexia and autism. These developmental disorders are typically diagnosed in early childhood, but affected individuals often struggle with these conditions throughout life. Nancy Kanwisher and John Gabrieli will head this multi-institutional project.

I hope you are excited by these promising developments, described on the following page.

Bob Desimone, Director

MICHALE FEE: LEARNING FROM BIRDSONG

Charles Darwin once noted that songbirds closely model how human babies progress from babbling to recognizable speech. Now, Michale Fee's research on the songbird brain suggests that song learning also provides a fruitful opportunity to examine what goes wrong in Parkinson's disease and many other brain disorders.

Michale Fee

Today, Michale Fee's lab at McGovern Institute is filled with colorful zebra finches and with the sounds of birdsong. It seems far removed from his original training in atomic physics and engineering. But the transition came naturally to Fee.

"Physicists are generally interested in understanding how the brain works because we think of it as circuits," he explains. "It's appealing to think that if there's a circuit, then I can figure out how it works."

Fee was working at Bell Labs when he heard a talk on birdsong learning. He was fascinated by the challenge of explaining a complex learned behavior in terms of its underlying brain circuitry, and he began applying his engineering expertise to build new instruments that would allow him to study the song system in unprecedented detail.

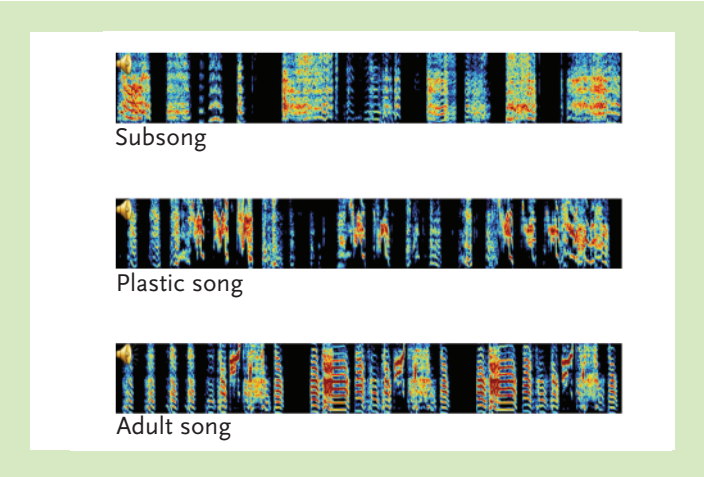
Neuroscientists have long been interested in songbirds as an animal model for language learning and speech. "But these bird vocalizations actually model a much more general process for learning and producing complex sequential behaviors," Fee explains.

Since joining the McGovern Institute in 2003, he has made discoveries about the song system that have unexpected relevance to the human circuits involved in many learned complex behaviors—the same circuits that become disrupted in a wide range of human brain disorders.

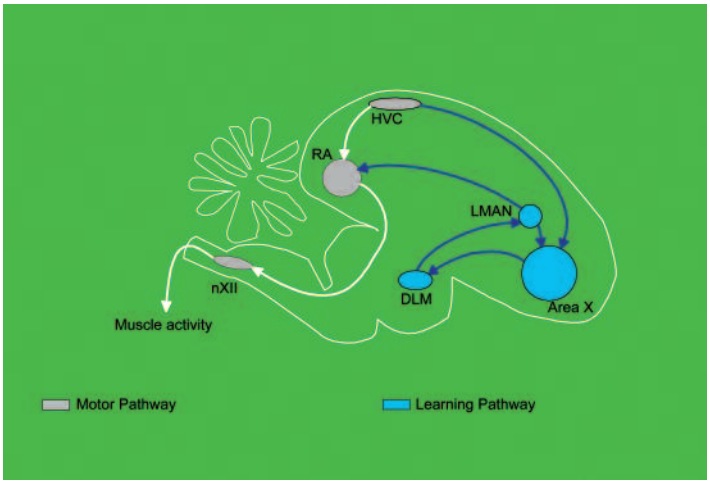
For example, when these circuits degenerate in Parkinson's disease, people lose control of their learned movements. Patients have trouble initiating and timing movements such as stepping out of a chair or producing speech—sometimes with devastating consequences for normal life. Surprisingly, birdsong is poised to become a valuable tool in understanding the brain mechanisms behind this loss of movement control.

Sequences of movements

Just as new golfers must practice their swings before they can hit a hole in one, a young songbird must try and try again before it can sing like its father. In each case, the novice must learn to string together many individual movements in just the right sequence and with precise timing.



These recordings of audio frequencies, called spectograms, show the progression of three stages of song learning in the zebra finch.



Song pathways in the zebra finch brain; The motor pathway (white/grey) controls timing and song production. The learning pathway (blue) drives the exploration required for trial-and-error learning. Similar pathways exist in the human brain.

"Many behaviors that we consider uniquely human are complex sequences that must be learned by trial and error," explains Fee, "and bird song is one of the best systems in which to understand how this works."

Young zebra finches learn to sing on a predictable schedule. At around 5 weeks, they start attempting to imitate the song they hear from their father or other 'tutor.' Their first attempts, known as subsong, are erratic and highly variable—like the babbling of human infants, as Darwin presciently observed. With time and practice, the subsong evolves into a more structured plastic song as individual syllables come together in sequences that increasingly resemble the tutor's song. By about 3 months of age, the variability disappears as the song crystallizes into its mature, adult form.

"These stages are analogous not just to speech but also to other forms of learning," Fee explains. "For instance, infants first flail their arms and legs, and then learn to crawl and toddle, and finally to walk."

Fee's lab focuses on two related questions: How does the adult bird's brain control song production, and how does a young bird learn its song in the first place? Work from many groups, including Fee's, has revealed the existence of distinct brain circuits for these two processes. One pathway underlies learning, while a second pathway is responsible for the production of the mature song in the adult brain.

Both the learning and production pathways also exist, with analogous brain regions, in humans. Defects in these pathways are implicated in Parkinson's disease and other movement disorders, obsessive compulsive disorder, addictive behavior, Tourette syndrome and possibly schizophrenia and depression.

Setting the tempo

Fee's discoveries about how the motor circuit controls the production of the adult song have intriguing implications, for birds and people. By recording from individual neurons as the bird sings, he has helped clarify the distinct contributions of the two key areas involved in the production of song, known as HVC and RA, that resemble human cortex.

HVC appears to act as a timekeeper, like the conductor of an orchestra setting the tempo of the music. It does so by coordinating the entries of the individual players (the RA neurons), which in turn control the muscles that produce the song.

"We think individual HVC neurons activate each other in a chain reaction, like a sequence of falling dominoes," explains Fee. He is developing new technologies to test this idea so that he can watch the entire chain of dominos as it falls during a song. He is also asking what controls the initiation of a song sequence—what pushes the first domino in each cascade, as it were. The answer seems to lie in another area, known as UVA, that is closely connected to HVC. Understanding how these two areas work together could provide an unprecedented insights into how similar cascades of 'neural dominos' control the timing and pace of human movements, and how that system may fail in movement disorders.

UVA could even harbor clues about the control of consciousness, Fee suggests, referring to recent news that a brain injured patient in a minimally conscious state was aroused by stimulation of a human brain area that closely resembles the bird's UVA. "Maybe there's a deeper relationship between the control of movement and the control of conscious states," he wonders. "It's a very intriguing question."

Variability and creativity

Fee's research on the song learning pathway also suggests a fascinating interplay between learning, exploration, and creativity. The songbird learning pathway contains a region dubbed Area X, equivalent to the mammalian basal ganglia, large structures that are involved in initiating and regulating movement, and also in trial and error learning and habit formation. Area X in turn receives connections from LMAN, which is similar to the prefrontal cortex, an area that is highly developed in humans, where it is associated with reasoning, intelligence, attention, planning, temper and even personality

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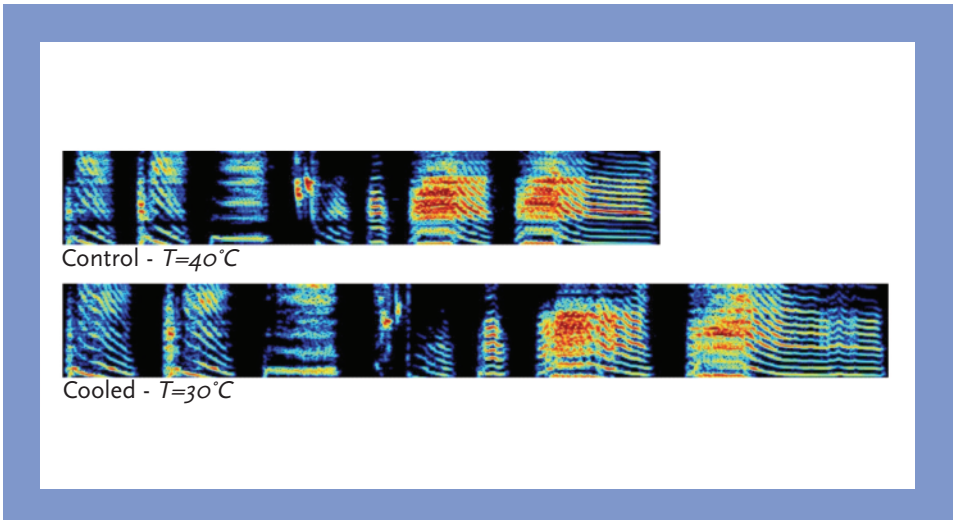


Fee's research shows that HVC in the motor pathway is the songbird's timekeeper. Cooling neurons in the HVC slows down the tempo of the song without altering the pitch or frequency.

The zebra finch songbird is the perfect model for studying complex learned sequential behaviors like those that fail in people with Parkinson's disease.

and a sense of self. A third structure, known as DLM, completes the song learning loop, and the entire circuit closely resembles its human counterpart.

Several years ago, Fee discovered that LMAN serves as the source of the trial-to-trial variability that a bird needs to perfect its song. Scientists had previously observed that disabling LMAN in a young bird stopped its song learning in midstream. The bird still sings, but because it loses the ability to try out new variations, its song becomes frozen in an immature form. Fee wants to understand the origin of this variability, which is so critical for continued learning. "A young bird is being creative" he says, "exploring many different sounds through trial and error. If that ability is lost, you see stereotyped behavior instead—very much like what happens in some human psychiatric disorders."

"We were particularly excited because LMAN is probably related to the human prefrontal cortex (PFC)," he continues. "Thoughts and emotions generated in the PFC also happen in sequences and are likely also subject to trial-and-error learning. I like the idea that PFC produces variability in learning, not only in movement, but also in thinking. This could well be a key feature of creativity."

From bird song to human disorders

Although song learning has great intrinsic interest, Fee stresses that the real importance of this work comes from the generality of the problem and from the parallels between the brains of songbirds and mammals, including humans. Trial and error learning is a fundamental part of our behavioral and cognitive development, and the underlying brain structures have been implicated in a wide range of neurological and psychiatric disorders.

In Parkinson's disease, for example, specialized neurons in the basal ganglia begin to degenerate. These neurons produce dopamine, a brain signaling chemical that helps coordinate movements—and which is also well known for its role in motivation, attention and learning. Without these dopamine neurons, the patient's motor control deteriorates, causing trembling of the limbs, jaw and face; stiffness of the arms, legs and trunk; slow movement; and poor balance and coordination.

In another basal ganglia disorder, Tourette syndrome, patients have a compulsion to produce unwanted movements and sounds, known as tics. Problems with the basal ganglia may also underlie obsessive compulsive disorder (OCD), which affects more than two million Americans in a given year. OCD patients report recurrent, unwanted thoughts (obsessions) and may perform repetitive behavioral sequences (compulsions), such as hand-washing, counting or cleaning.

Songs of hope

Fee started his career as an engineer determined to understand how the songbird's brain circuitry drove its complex behavior. Now that his research is showing that the songbird's circuitry mimics the biology involved in many complex human behaviors, researchers can contemplate using the songbird to model a variety of common brain disorders.

Because these brain pathways are well-defined in the bird and because it is relatively easy to analyze changes both in brain activity and behavior, the bird offers the possibility of modeling human disorders at a level of detail that would be impossible in the mouse or rat. Eventually, Fee hopes, in addition to helping understand the pathology of these diseases, the songbird model may prove to be a good testing ground for new therapies. ■

The Sydney Family's Challenge for Parkinson's Research

Stanley H. Sydney (SB '52, SM '54) and his wife Sheila of Brookline, Massachusetts have committed $500,000 to the McGovern Institute to support Ann Graybiel's research on Parkinson's disease. They and their daughter Roberta Sydney (SM '88) have challenged other donors to match their gift.

The Sydneys have experienced first hand the impact that brain disorders can have on families. Stanley has had Parkinson's disease for many years. With five children, the youngest age 1, Sheila suffered a stroke at age 38 that left her paralyzed on one side and affected her speech.

The Sydneys were inspired to make their gift after visiting Graybiel, a leading Parkinson's disease expert, and members of her laboratory. Parkinson's disease results from the degeneration of dopamine-containing neurons within the basal ganglia, brain regions that are the focus of Graybiel's research.

"If we can motivate others to join us in supporting the work of Dr. Graybiel and her team that helps to improve the quality of life for people like Dad, then we will have made a big difference," says Roberta, who succeeded her father in running his real estate business and who, with her brothers and sisters, advocates for his care.

"We were profoundly moved by this family's heroism and courage," recalls Graybiel. "When Parkinson's enters a family, it is a devastating blow. The Sydneys had already confronted and overcome the consequences of Mrs. Sydney's stroke. They have a wonderful attitude, and they appreciate the value of basic research in understanding and treating brain disorders."

During the visit to Graybiel's laboratory, Stanley demonstrated devices that help him move and speak. A deep brain stimulator, resembling a pacemaker for the brain, helps control the involuntary movements resulting from his Levo-DOPA drug treatment. He still struggles with speaking, a frustration to this successful MIT-educated businessman. Remarkably, he can improve his speech by rhythmically touching a series of pegs, and when singing, his communication becomes fluent. These are among the mysteries of basal ganglia function that the Graybiel lab studies.

Roberta urged the captivated researchers to find better treatments and ways to prevent side effects for people like her father. "It was a magical moment," recalls Graybiel. "We'll never forget the plight of Stanley Sydney, and we are all inspired to redouble our determination to make a difference in Parkinson's disease."

Sheila and Stanley Sydney of Brookline, MA

Graybiel's lab combines systems neuroscience methods with gene-based methods. They use electrical recordings to investigate how the symptoms of Parkinson's disease reflect the influence of the basal ganglia on other parts of the brain. They also use genetic techniques to explore the molecular changes that may accompany the disease symptoms. "We are excited because we discovered two genes whose expression levels are proportional to the dyskinesias resulting from Levo-DOPA" says Graybiel. "This work is close to the hearts of the Sydney family."

Because federal funding for basic research has declined sharply, Graybiel says, she could not pursue these expensive studies without support from donors like the Sydneys. To make a matching gift for the Sydney Challenge, contact Laurie Ledeen (617-324-0134; ledeen@mit.edu) or Judy Sager (617-253-6463; jsager@mit.edu).

Ann Graybiel in her laboratory

McGovern Researchers to Lead $8.5M Project to Study Autism and Dyslexia

McGovern Institute researchers Nancy Kanwisher and John Gabrieli, both prominent experts in human brain imaging, will head an ambitious, multi-institutional project to study the origins of autism and dyslexia, supported by a $8.5M grant from the Ellison Medical Foundation. Kanwisher will lead the work on autism, and Gabrieli will head the dyslexia component.

Autism and dyslexia are complex brain disorders that first appear in early childhood. Autism impairs social interactions and communication, and affected individuals may engage in bizarre and repetitive behaviors. Dyslexia is a learning disorder that manifests itself as reading difficulty despite adequate education and otherwise normal perceptual and intellectual abilities.

Little is known about the causes of either disorder, although both are highly heritable, and it is thought that the earlier treatments begin, the more effectively they help the child compensate. Thus, it is important to develop methods for early diagnosis, and scientists believe that non-invasive brain imaging may be a means to this end.

A major emphasis of the new project will be to translate recent advances in brain imaging to children, which presents many technical and practical challenges. The McGovern researchers will collaborate with Larry Wald, Bruce Fischl and Ellen Grant at Massachusetts General Hospital (MGH), who will develop scanning coils designed specifically for children's heads, new procedures to shorten scan times for fidgeting children, and methods to analyze data from developing brains.

"We expect these technological advances to radically improve pediatric neuroimaging and help us make major strides in understanding typical and atypical human brain development," comments Kanwisher.

The researchers plan to scan young children at regular intervals to examine the development of brain systems that have been implicated in social cognition (for autism) or reading (for dyslexia). By comparing autistic or dyslexic children with control groups, they will look for telltale markers that could help to diagnose these disorders and track their progression. They also plan to look for markers of improvement in response to therapy, which could in turn lead to better therapies. Eventually, linking their findings to future genetic discoveries about these disorders could lead to genetic tests that will be easier and less expensive than brain scans, says Gabrieli.

One collaborator, Rebecca Saxe of the MIT Department of Brain and Cognitive Sciences, will focus on the development of social cognition to identify the earliest stages at which infants' brains become specialized to perceive other people and understand language. Other collaborators are Laura Schulz at MIT, April Benasich at Rutgers University, Maryanne Wolf at Tufts University, David Pauls and Matti Hamalainen at MGH, and Glenn Rosen and Albert Galaburda at Beth Israel Deaconess Medical Center.

About the Ellison Medical Foundation

The Ellison Medical Foundation was established in 1998 by Lawrence J. Ellison, the founder and CEO of Oracle. The Foundation supports basic biomedical research on aging relevant to understanding lifespan development processes and age-related diseases and disabilities, as well as scientific advancement in other research areas not sufficiently funded by traditional sources in the U.S. ■

Collaborative Agreement with Tsinghua University

Robert Desimone, Director of the McGovern Institute (left), gave a keynote speech at a symposium at Tsinghua University in China in January 2008. While there, he and Tsinghua's President, Binglin Gu (right), signed an agreement establishing collaborative neuroscience research between the McGovern Institute and Tsinghua University. This cooperative research program is supported by a gift from Hugo Shong (center), an International Data Group (IDG) executive who recently raised his commitment to McGovern Institute from $500,000 to $800,000. ■

Photo: Tsinghua University

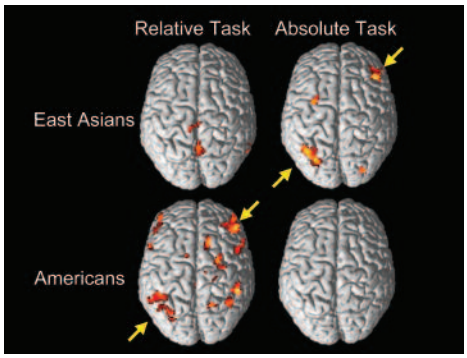
IN THE NEWS

John Gabrieli's fMRI studies have been receiving widespread attention. His recent finding that people from different cultures use their brains differently to solve the same visual perceptual tasks was covered by *NBC, Fox News, The Times of India* and many other news outlets. Some perceptual tasks come more easily to Americans, others to East Asians. For judgments that are less culturally preferred, the brain's attention system has to work harder, Gabrieli told *NBC*. "The harder you have to think about something, the more it will be activated."

Gabrieli's work was also featured on *NBC*'s special series *The Truth About Boys and Girls* on January 17, 2008, in which Gabrieli discussed the differences in emotional memory between men and women.

The January 24, 2008 *Scientific American* ran a story about **Christopher Moore**'s novel hemoneural hypothesis, published in the October 2007 *Journal of Neurophysiology*. Moore's theory that blood actively modulates how neurons process information, rather than just delivering 'supplies' to neurons, has clinical implications for diseases involving vascular abnormalities such as Alzheimer's, schizophrenia, multiple sclerosis and epilepsy.

Links to the above stories can be found on the McGovern Institute web site at: http://web.mit.edu/mcgovern/ ■



Left: Brain activity in East Asians and Americans as they make relative and absolute judgments. The arrows point to brain regions involved in attention that are engaged by more demanding tasks. Image: Trey Hedden, McGovern Institute

Right: Christopher Moore proposes that changes in blood flow in the brain can affect how neurons function. Photo: Donna Coveney, MIT

EVENTS

Leadership Board and Friends Celebrate Poitras Center Opening

The Leadership Board meeting on November 16, 2007 preceded the opening celebration for the McGovern Institute's new James W. and Patricia T. Poitras Center for Affective Disorders Research later that day. Bob Desimone gave an overview of the strategic plan and Charles Jennings updated the members on the MINT program for developing neurotechnology. Rebecca Schwarzlose, the first recipient of the Janet and Sheldon Razin Fellowship, presented her research. Schwarzlose is a graduate student in Nancy Kanwisher's lab.

The luncheon keynote speaker set the stage for celebrating the Poitras Center (Fall 2007 *Brain Scan*). Janet Wozniak (Harvard Medical School and Director of the Pediatric Bipolar Clinical and Research Program in Pediatric Psychopharmacology at Massachusetts General Hospital) addressed the controversial issue of bipolar disorder in children.

In the afternoon, John Gabrieli outlined plans for initial Poitras Center brain imaging projects, including collaborating with Wozniak to better understand pediatric bipolar disorder. Sebastian Seung (MIT Department of Brain and Cognitive Sciences and the Department of Physics) discussed the value of studying connectivity in the brain. Ed Boyden described new tools he is developing for controlling brain activity. Pamela Sklar (Broad Institute of Harvard and MIT) discussed her genetic studies of schizophrenia and bipolar disorder. Christopher Moore explained his hypothesis that blood flow in the brain influences neural activity.

Patricia and James Poitras receive a glass brain at a dinner honoring their generosity in establishing the Poitras Center for Affective Disorders Research. Photo: Henry Hall, McGovern Instiute

The Poitras Center celebration ended with dinner and a champagne toast to Pat and Jim Poitras for their generosity in establishing this center. The Provost of MIT, Rafael Reif, represented President Susan Hockfield, who was unable to attend but who had hosted a dinner the previous week to honor Pat and Jim Poitras. ■

SAVE THE DATE

Symposium—The Biological Basis of Psychiatric Disease
Monday April 28 – Tuesday April 29, 2008

On April 28–29, the McGovern Institute will host a two-day symposium on the biological basis of psychiatric disease. The symposium will cover both animal models and human clinical research, with an emphasis on neuroimaging. Speakers will also discuss genetics, neurobiology, molecular and translational approaches, and drug discovery.

John Gabrieli, Ki Ann Goosens and Charles Jennings are organizing the Symposium. The Martinos Imaging Center and the newly established Poitras Center for Affective Disorders Research are co-sponsoring the event. This event is free and open to the public. For registration and other information, please visit the McGovern Institute web site (http://web.mit.edu/mcgovern).

Confirmed Speakers

James Blair (National Institute of Mental Health)
Ed Bullmore (Cambridge University & Glaxosmithkline)
Cameron Carter (University of California Davis)
Joe Coyle (McLean Hospital & Harvard Med School)
Guoping Feng (Duke University Medical Center)
Jay Gingrich (Columbia University)
Maria Karayiorgou (Columbia University)
Sonia Lupien (McGill University)
Husseini Manji (National Institute of Mental Health)
Ruth McKernan (Pfizer)
Andreas Meyer-Lindenberg (ZI Mannheim)
Karoly Mirnics (Vanderbilt University)
Greg Quirk (University of Puerto Rico)
Trevor Robbins (Cambridge University)
Akira Sawa (Johns Hopkins University)
Paul Thompson (University of Califoria Los Angeles)
David Zald (Vanderbilt University)

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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