McGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

Brain SCAN

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Inside the Autistic Mind

New approaches to studying brain development are reshaping our understanding of autism

FROM THE **DIRECTOR**

In this issue we focus on autism, a major area of research at the McGovern Institute and elsewhere at MIT. Autism is among the most mysterious of all brain disorders, affecting those aspects of brain function, such as social cognition, that are most distinctively human.

Autism is strongly influenced by genetic factors, and animal models are essential if we are to understand how these genes affect brain function. But if we are to truly conquer autism, we must also understand how human genes interact with our complex social environments and life histories to shape our own brains. In this issue, you will read about some of our "molecules-to-mind" approaches. I am encouraged that several clinical trials are now underway for syndromes with autism-like features, inspired in part by work conducted here at MIT.

Our work in this area depends heavily on both government and philanthropic support. We are grateful for private donors, the Ellison Foundation, and most recently the Simons Foundation, which has enabled us to establish the Simons Center for the Social Brain at MIT. Directed by Mriganka Sur, the Simons Center will benefit McGovern researchers along with many others throughout MIT. Ultimately, we believe it will also benefit the millions of families for whom autism is now part of their daily lives.

Bob Desimone, Director
Doris and Don Berkey Professor of Neuroscience

On the cover:
Neurons in the mouse cerebellum, expressing the synaptic protein SAPAP-4.

Image: Louis Tee and Guoping Feng

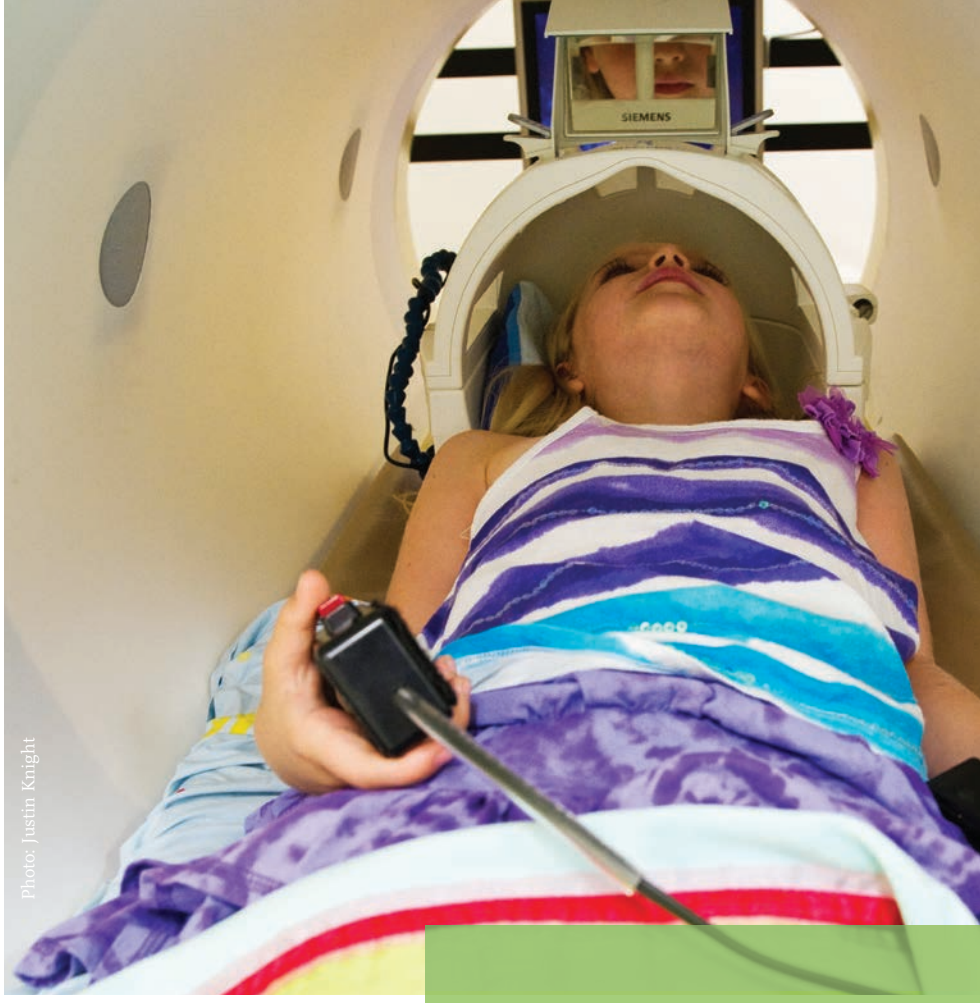


Photo: Justin Knight

New approaches to studying brain development are reshaping our understanding of autism.

"Still, soft, and super-duper!" This is what researchers at the McGovern Institute tell kids as they prepare to step into the MRI scanner. Getting a 5-year-old to lie still, relax, and pay close attention for an hour, the duration of a typical experiment, is quite a trick.

But details like this are the key to success for scientists who study children, including McGovern Investigators Nancy Kanwisher, Rebecca Saxe and John Gabrieli. These researchers are using the latest scanning technologies to learn how the human brain develops through the early years of life. They are also hoping to detect changes that might explain the origins of autism and other brain disorders that begin during childhood.

Inside the Autistic Mind

In the United States, an estimated 1 in 88 children are affected by autism spectrum disorders, yet there are no physical tests that can detect it. Autism is diagnosed purely by observation, a process that is complicated by the fact that symptoms vary widely and can include difficulties with communication, social deficits, and repetitive movements and speech.

The development of new treatments is also complicated by the fact that the brain changes responsible for these heterogeneous symptoms are still largely unknown. Understanding the origins of autism is an important goal at the McGovern Institute, whose researchers are taking a variety of approaches, from scanning the brains of children to studying animal models of the disease. Ultimately, they hope that insights from this work will eventually lead to new treatments and individualized interventions for patients with autism.

Creative Scanning

In a typical brain imaging experiment, a volunteer subject views pictures or reads stories while lying in the scanner. Kanwisher, for example, shows images of faces in order to study the brain regions responsible for face recognition. Saxe sometimes presents stories involving moral judgments, to learn how we reason about the mental states of other people.

In the case of autism, one of the primary deficits is in social cognition, so Saxe and Gabrieli decided several years ago to incorporate real social interactions into their scans. They developed a system that allows subjects in the scanner to interact with the experimenter through a live video feed. Communicating only through eye movements, the participants played a game called "catch the mouse" in which they cooperate to find a mouse hidden somewhere on the computerized display. To solve the task quickly the subject must follow the experimenter's gaze, a process known as joint attention.

Photo: Justin Knight

John Gabrieli, director of the Martinos Imaging Center at MIT.

This ability, which feels automatic and effortless for most of us, is well-developed in a typical 2-year-old, yet people with autism often have difficulty initiating and reciprocating joint attention. Using their new system, Saxe, Gabrieli and Elizabeth Redcay, a former postdoctoral fellow in Gabrieli's lab now at the University of Maryland, were able to confirm that interaction with a real person elicits patterns of brain activity that are not seen when subjects respond to computerized stimuli. Moreover, these patterns differed between autistic and typical individuals, notably in several brain areas previously implicated in social cognition.

Through experiments like these, researchers hope to understand which brain regions are involved in the different symptoms of autism, and to find clues that could lead to better treatments. Current treatments address behavioral symptoms rather than fundamental mechanisms because, for the most part, those mechanisms are unknown. "It's a huge mystery in the field because the symptoms on the surface seem unrelated," says Gabrieli. "It could be that different elements of autism are treatable in different ways."

One key to successful treatment may be to intervene early in at-risk children, in ways that could guide the developing brain away from the path toward autism. This is the rationale behind another project at the McGovern Institute, in which Kanwisher and Saxe are using brain imaging to study brain development in young children, and to search for the earliest signs of autism.

Working with colleagues at MGH and with funding from the Ellison Medical Foundation, the MIT researchers have adapted their scanning equipment to fit the heads of young children. This has allowed them to visualize the developing brain at a level of detail not previously possible. One early result has been Kanwisher's discovery that the part of the brain responsible for face recognition is already fully formed by age five. In the future she plans to examine the same region in children with autism, who often experience difficulties in recognizing faces.

"Autism is a huge mystery because the symptoms on the surface seem unrelated. But different elements of autism may be treatable in different ways."

—John Gabrieli

Understanding Genetic Underpinnings

Human brain imaging is important for understanding which parts of the brain are affected in autism, but to understand the root causes of the condition, researchers must also turn to animal models. In conditions similar to autism, this approach is already paying off. MIT researchers discovered that in Rett's syndrome, a single gene mutation prevents synapses from maturing. That insight has led to the development of an experimental drug to block the effects of that mutation.

For autism, however, hundreds of genes may be involved, and understanding how each individual gene contributes to the risk of autism is a considerable challenge.

One researcher who is undaunted by that challenge is McGovern Investigator Guoping Feng. Feng's work is driven by the finding that many of the genes implicated in autism are known to affect synapses, the microscopic structures through which neurons are connected to each other. In earlier work, he had discovered that mutations in one of these synapse-building genes could cause dramatic behavioral effects in mice, causing them to show repetitive behaviors reminiscent of human obsessive-compulsive disorder (OCD).

Feng saw this as a clue not only to OCD but also to autism, which also involves repetitive behaviors. Accordingly, he decided to create a mutant mouse with an alteration

Photo: Justin Knight

Guoping Feng (right) studies how the disruption of synaptic connections can lead to behavioral disorders such as OCD or autism.

Photo: Justin Knight

McGovern Institute researchers use animal models to study the genetic and molecular underpinnings of autism.

in a gene called Shank3, which had previously been implicated both in human autism and in the building of synapses.

Sure enough, the Shank3 mutant mice showed several behaviors that are characteristic of autism. They groomed themselves obsessively, and they also showed reduced social interactions, preferring to retreat to the far corner of their cage rather than interact with an unfamiliar mouse, as healthy mice readily do. Feng examined their brains and found changes in the striatum, a part of the brain involved in habitual and repetitive behaviors. "By localizing the abnormality to a specific group of cells," says Feng, "we're one step closer to knowing where in the brain we need to intervene to treat the disorder."

Feng plans to study more autism-like mutations in a series of mouse models. He hopes that similarities will emerge, and that different genetic defects will turn out to affect similar brain circuits in ways that can explain their common behavioral effects. "If by studying multiple models we can find a common circuit, then we can possibly also find a common molecular pathway which can be a drug target," he says.

Finding a Way In

McGovern Investigator Martha Constantine-Paton is also looking to mice for clues, but from a very different starting point. For 35 years, she has studied the development of the synapses in the visual system. But working on developmental disorders such as autism had never been a priority for her. "I saw no way in," she says.

That changed recently, however, when she happened upon a mutant mouse with a naturally occurring genetic defect that affects myosin Va, a protein involved in building synapses. She found these mice exhibit many behaviors characteristic of autism, including anxiety, reduced social contact, poor spatial learning and obsessive grooming.

Constantine-Paton hopes to study these mice further to find out which brain structures and cell types are affected. "If we can eliminate this mutation in the prefrontal cortex, for example, we may see recovery from symptoms," she says. "It's a whole new way of looking at neurocognitive disorders."

Confluence in the Clinic

The studies on Shank3 or myosin Va may lead to fundamental advances in understanding autism, but the path to new therapies is likely to be a long one. Meanwhile, though, other animal research suggests that the hormone oxytocin, which surges in young mothers as they care for their newborns and has been shown in animal and human research to stimulate social and nurturing behavior, may be helpful for people with autism.

In the fall of 2012, Gabrieli will begin a study, in collaboration with Aude Henin, Janet Wozniak and Gagan Joshi of MGH, to test the effectiveness of oxytocin and cognitive-behavioral therapy for promoting social skills in young adults with autism. Gabrieli will also scan the brains of the participants to see if the scans can predict which individuals benefit from either treatment. Similar approaches are being used in other trials of psychiatric treatments, because the complexity of these disorders makes it hard for doctors to predict how well a particular patient might respond. "There must be something different between those who benefit and those who don't," says Gabrieli.

This study illustrates how animal models can suggest novel therapies, and how human imaging can reveal the effects of these therapies on brain activity. The hope is that over time, all of these approaches together to will begin to carve a path towards the development of earlier, more individualized therapies for this very individualized disorder. ■

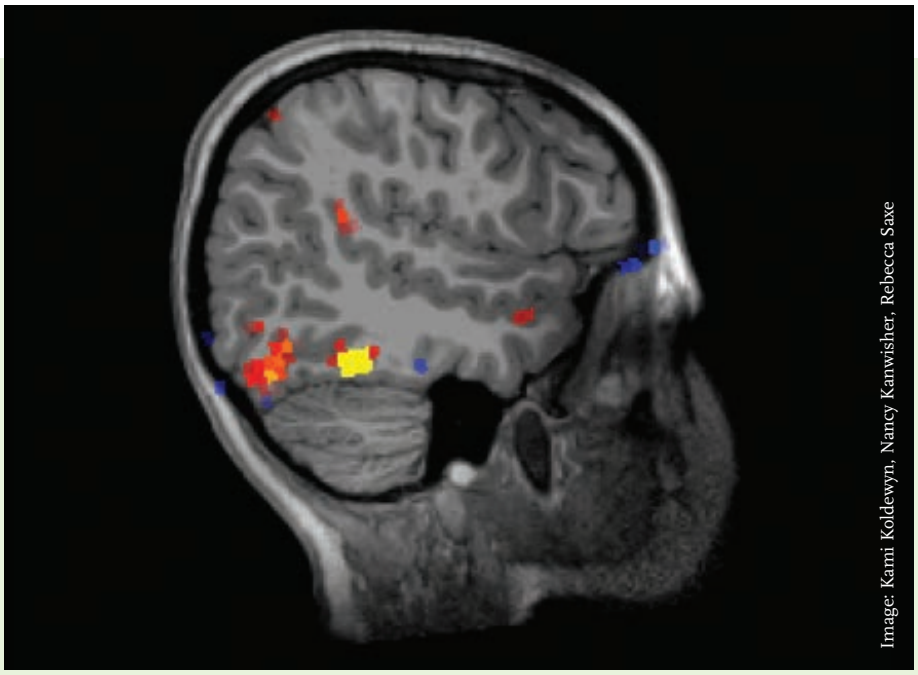
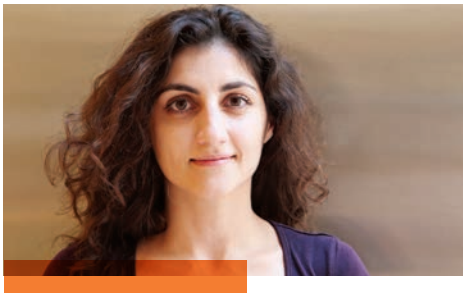


Image: Kami Koldewyn, Nancy Kanwisher, Rebecca Saxe

fMRI image of a child with autism showing the response of the brain to dynamic moving faces.

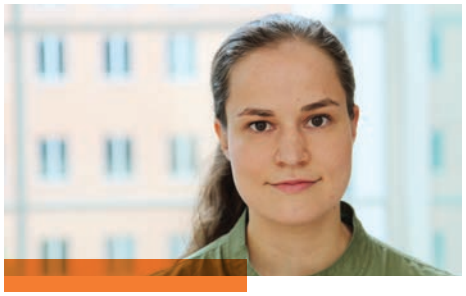
McGovern Institute Names New Graduate Fellows

The Friends of the McGovern Institute Fellowship has been awarded to **Joel Leibo** for his work in Prof. Tomaso Poggio's lab. Leibo is applying his background in neuroscience and mathematics to ask two key questions: How do we learn to recognize faces? And how can we build machines to do the same? He plans to use the McGovern Institute's newly acquired magnetoencephalography (MEG) scanner to decode face-related activity in the human brain.



Nuné Lemaire, a graduate student in Prof. Ann Graybiel's lab, was awarded the Mark P. Gorenberg '76 Fellowship for her research involving the cortico-basal ganglia loop, a brain circuit thought to underlie habit formation. Lemaire hopes that her work will lead to a better understanding of how habits are controlled by the brain, and potentially to new ways to prevent or treat addiction and other pathological habits.

The Janet and Sheldon Razin Fellowship has been awarded to **Amy Chuong**, a graduate student in Prof. Ed Boyden's lab. The fellowship will support her work to engineer faster and more powerful neural silencers—light-sensitive proteins that can be used to suppress electrical activity in specific brain circuits. Her work promises to yield new tools for understanding how brain circuits control behavior and how their disruption can lead to disease.



Silvana Konermann, a second year graduate student in Prof. Feng Zhang's lab, is the recipient of this year's Hubert Schoemaker Fellowship. Konermann is developing a new method for manipulating brain gene expression using light. The brain expresses around 20,000 genes, and a method to regulate their activity with precision would be of great value as a research tool. Konermann's goal is to use this technology to study the genetic basis of depression. ■

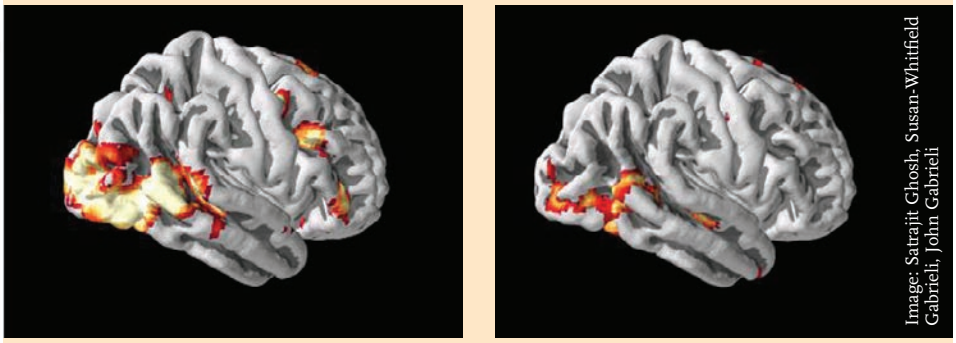
GabLab Summer Reading School

The Gabrieli Lab hosted a summer reading school as part of an ongoing project to study how children learn to read.

Participants received 6 weeks of free instruction from trained teachers, and their brains were scanned at the beginning and end of the program. This will enable researchers to study how the children's brains are changed by the intervention, and perhaps to identify brain signals that can predict in advance which individuals will benefit most from the program. ■

Image: Patricia Saxler

RESEARCH NEWS



Brain scans of patients with social anxiety disorder can predict which patients will benefit most from cognitive-behavioral therapy. Left, pattern of activity in patients with better outcomes; right, patients with worse outcomes.

John Gabrieli and colleagues have used brain imaging to study patients undergoing treatment for social anxiety disorder (SAD), and to predict in advance which patients will respond best to cognitive-behavioral therapy. This approach holds promise for SAD and many other psychiatric conditions for which the choice of therapy is still often a matter of guesswork.

Feng Zhang has engineered a DNA-binding protein, known as a TAL-effector, that can bind to any sequence of DNA. He has also linked the DNA-binding region to a repressor domain—making it a potentially useful technique for switching off genes at will.

Guoping Feng's lab, in collaboration with colleagues at New York University and elsewhere, has described a new way to monitor electrical activity in the living brain. Their method is based on a genetically engineered protein that emits light in response to the increased calcium concentration that accompanies neuronal activity.

H. Robert Horvitz examined worms that lack normal levels of dopamine, a neurotransmitter that is also depleted in Parkinson's disease. Like human Parkinson's patients, these mutant worms showed abnormal movement control, suggesting a possible connection between the role of dopamine in humans and worms.

AWARDS AND HONORS

Ann Graybiel has been awarded the 2012 Kavli Prize in Neuroscience. The $1 million prize, which is awarded every two years, is among the most prestigious awards that a neuroscientist can receive. Graybiel shares the Kavli Prize with Cornelia Bargmann of the Rockefeller University and Winfried Denk of the Max Planck Institute for Medical Research "for elucidating basic neuronal mechanisms underlying perception and decision."

Tomaso Poggio was a guest speaker at the Fourth Israeli Presidential Conference, *Facing Tomorrow 2012*. The event, held in June, was hosted by President Shimon Peres. ■

Ann Graybiel celebrates with members of her laboratory.

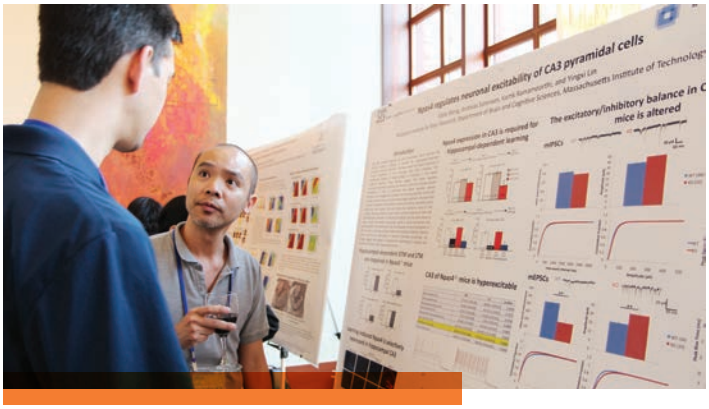
Science Teachers Visit McGovern Institute

In June, the McGovern Institute hosted a visiting group of K-12 science teachers, as part of MIT's Science and Education Program for Teachers. The 55 participants spent the morning learning about neuroscience research at MIT, and their visit included a tour of the Martinos Imaging Center. The session was part of a one-week program to help teachers stay in touch with the frontiers of science and technology.

Visiting teachers met with McGovern researcher Emile Bruneau, who demonstrated how hand-eye coordination adapts to prism glasses—a vivid example of rapid brain plasticity.

Annual Retreat Features Work of Young Scientists

The tenth annual McGovern Institute retreat took place at the American Academy of Arts and Sciences in Cambridge, MA. Students and postdocs from McGovern labs presented 13 talks, followed by a poster session and dinner at the Academy. Photos from the event are available on our website.



Eddie Weng, a postdoc in Yingxi Lin's lab, presents his findings at the retreat.

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, who is the Doris and Don Berkey Professor of Neuroscience at MIT and former head of intramural research at the National Institute of Mental Health.

Further information is available at: http://mcgovern.mit.edu

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