Brain SCAN

MCGOVERN INSTITUTE
FOR BRAIN RESEARCH AT MIT

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From the director

In this issue we highlight the work of Alan Jasanoff, who is developing imaging technologies that will provide an entirely new view of brain activity.

Magnetic resonance imaging (MRI) has been critical to our understanding of brain function, and Alan Jasanoff is working to take this technology to an entirely new level. He is designing new molecular sensors that can reveal far more about brain activity than conventional functional MRI, which is based on changes in blood flow and oxygen levels within the brain. Alan's work draws on nuclear engineering, protein engineering, chemistry and cognitive neuroscience, and exemplifies the interdisciplinary approach that is at the heart of our mission.

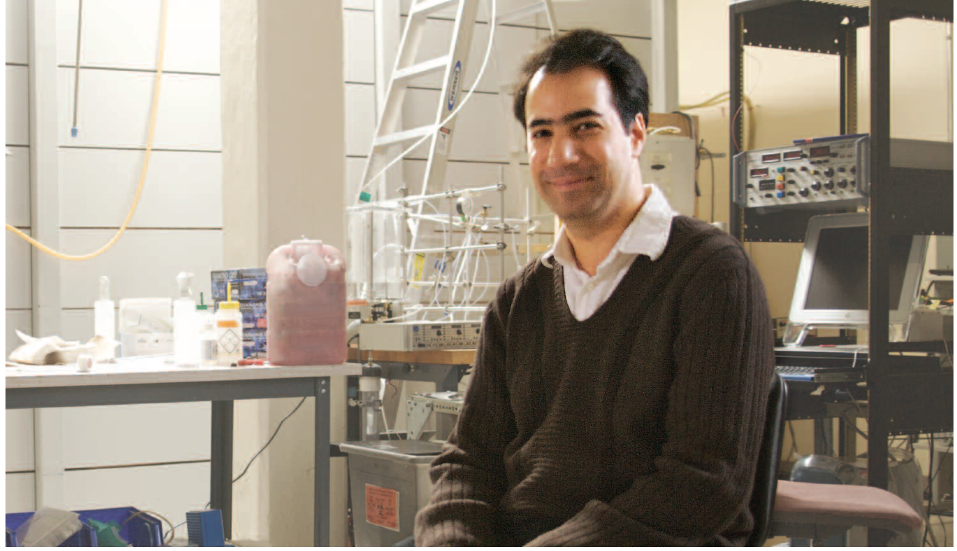
I am also pleased to announce the appointment of a new faculty member, Feng Zhang, who will be joining the McGovern Institute in January 2011. Feng, who received his PhD from Stanford University and who is now a Harvard Junior Fellow, is an expert on optogenetics and stem cell applications. I am especially pleased that, in addition to his appointment in the McGovern Institute and the Department of Brain and Cognitive Sciences, Feng will also be a core faculty member of the Broad Institute. His appointment strengthens our ties to the world's foremost center for genomics research in medicine.

Finally, we are preparing to celebrate our tenth anniversary on October 14th. We are honored to be joined by two prominent public advocates for science–Alan Alda and Jane Pauley–and by our longtime friend and advisor Gerald Fischbach, scientific director at the Simons Foundation. I look forward to seeing many of you there.

Bob Desimone, Director

Cover art: Feng Zhang, who will join the Institute in 2011, is an expert in manipulating brain activity with light.

Image courtesy of Feng Zhang, Stephen Dixon, and Karl Deisseroth



Alan Jasanoff, an associate member of the McGovern Institute and a faculty member in MIT's Department of Biological Engineering.

Photo courtesy of Kent Dayton

PUSHING THE FRONTIERS OF MRI

Alan Jasanoff is developing molecular tools that promise to provide an unprecedented view of brain activity, and which could some day transform the diagnosis and treatment of brain disorders.

Alan Jasanoff came of scientific age during the genomics revolution in the late 1990s, when genome researchers were decoding the entire human DNA sequence in the hope of eventually understanding the genetic basis of human diseases.

"It struck me that we needed a similarly comprehensive approach in neuroscience, to measure everything that's happening in the brain at once," Jasanoff recalls. "I thought one way I could help was to adapt magnetic resonance imaging so that it could reveal molecular changes in the living brain."

Magnetic resonance imaging, or MRI, is widely used in medicine as a noninvasive way of viewing the body's internal structure. It has also been adapted by neuroscientists to reveal the brain's activity, through a method knows as functional MRI or fMRI. But fMRI detects changes in the brain's blood supply, and provides only a limited view of brain activity.

Jasanoff wants to change that. He is developing entirely new classes of chemical agents that promise to provide a radically new view of activity in the living brain, one that will allow researchers to track brain activity in real time at the molecular level. It is an ambitious agenda, but after six years at MIT he is well on his way to achieving it.

Looking for an adventure

Jasanoff grew up in a family of academics—they joke that the only family member who is not yet a professor at Harvard or MIT is Alan's 4-year-old daughter. But Jasanoff did not originally plan to become a neuroscientist. He had studied the structure of proteins, first as a Harvard undergraduate, then for a master's degree at Cambridge University, before returning to Harvard for a PhD in biophysics. "But I was interested in having an adventure," he explains, "so when I became an independent fellow at the Whitehead Institute I decided to change fields and to begin studying the brain."

Neuroscience was a new field for Jasanoff, but he came to it with a biophysicist's understanding of nuclear magnetic resonance, the natural phenomenon that underlies human brain imaging. Jasanoff was struck both by the power and problems of magnetic resonance-based neuroimaging. "We use fMRI to study brain activity, but what it actually measures is changes in blood flow and blood oxygen," Jasanoff explains. "It's a very indirect method."

When a part of the brain becomes more active during a mental task, it uses more oxygen and blood flow to that site increases. MRI can detect these events because of the unusual properties of hemoglobin, the iron-containing protein that carries oxygen and gives blood its color. The iron atoms within hemoglobin make it magnetically active, and its magnetic "signature" changes when it releases its oxygen. Hemoglobin therefore serves as a natural "contrast agent" to monitor the brain's metabolic activity. Functional MRI exploits this opportunity and has provided invaluable insights into human brain function since its invention 18 years ago.

Jasanoff discusses a new research result with technical assistant Yelena Gluz.

Photo courtesy of Patricia O'Loughlin

But changes in blood flow happen much slower than the brain events that cause them. The spatial resolution is also limited by the density of blood vessels, which are large compared to neurons. Perhaps most important, fMRI cannot distinguish between different types of neurons or different chemical events. All activity looks the same, and so much of the brain's complexity—the huge variety of neural cell types, the constantly fluctuating signals carried by dozens of different neurotransmitters—is invisible to current methods.

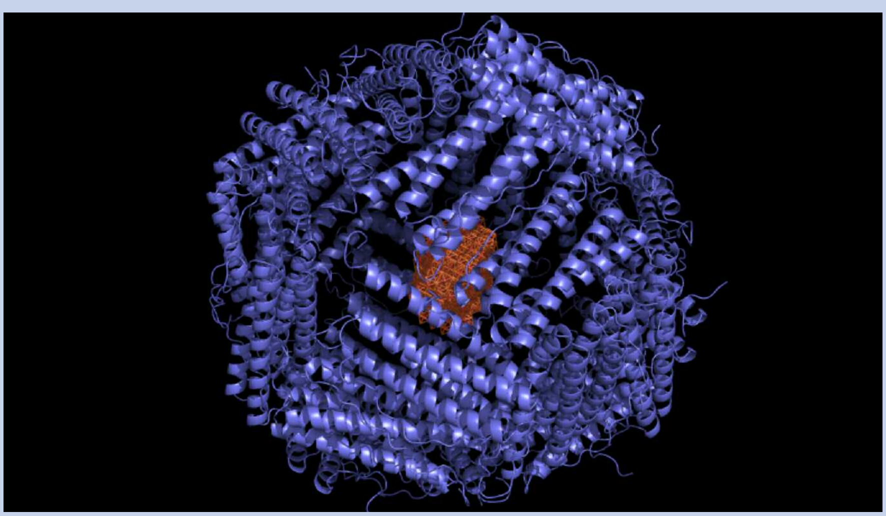
"If we could see this hidden level of complexity, it would be a huge benefit for basic research," says Jasanoff. "It would be like moving from black-and-white to color photography." Although Jasanoff cautions that human applications are further off, "we could imagine using contrast agents to investigate conditions like schizophrenia or depression, where it is very difficult to monitor whether a therapy is working."

Complex agents

Designing a contrast agent is difficult challenge—comparable in many ways to designing a new drug. First, the agent must bind reversibly to a target molecule that is directly related to brain activity. It must also contain a so-called paramagnetic metal (such as iron or manganese) that changes the agent's magnetic properties when it binds to the target molecule, so that it produces a different MRI signal depending on whether the target molecule is present or absent.

The agent must also be stable within the brain and must not interfere with normal brain function. And if the contrast agent is used to detect changes that occur inside neurons, it must cross the surface membrane that separates the neuron from its surrounding environment.

Designing a molecule that meets all these criteria can take years of work. "It requires teamwork," says Jasanoff. "I'm lucky to be at MIT so I can work with experts in chemistry and molecular biology to help me find solutions."



Jasanoff uses protein engineering methods to construct MRI contrast agents. The protein ferritin, shown here, forms the starting point for several contrast agents developed in his lab.

Image courtesy of Alan Jasanoff

Sensing dopamine

If asked what chemicals they would most like to see within the living brain, most researchers would probably pick neurotransmitters—the signaling molecules that carry information across synapses from one neuron to another. Among neurotransmitters, dopamine is an especially attractive target because of its role in appetite and reward learning, and also because dopamine signaling is disrupted in many brain disorders, including Parkinson's disease, schizophrenia, and substance abuse.

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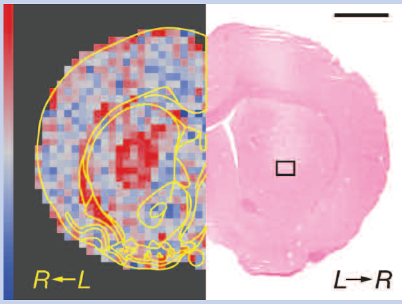


Changes in brain dopamine (red areas in left panel) revealed by a contrast agent.

Image courtesy of Alan Jasanoff

Designing a sensor for dopamine is one of Jasanoff's major goals. But rather than starting from scratch, he and his colleagues borrowed a trick from evolution. In collaboration with Frances Arnold at Caltech and Robert Langer at MIT, they chose a magnetically active protein similar to hemoglobin, and then "evolved" it through rounds of artificial mutation and selection to bind specifically to dopamine. Eventually, after five rounds, they had a working prototype for an entirely new class of sensor.

In a first test of the new sensor, Jasanoff's group has confirmed that they can detect dopamine release in the rat brain in response to injections of potassium. It can also reveal changes caused by an injection of cocaine, which is known to work by enhancing dopamine signaling. The real goal, though, is to use the sensor to monitor changes in dopamine during normal behavior. The lab is already using conventional fMRI to understand how animals evaluate and respond to a rewarding stimulus. "We know that dopamine is involved somehow—we want to watch dopamine in action so that we can relate its changes to the animal's behavior."

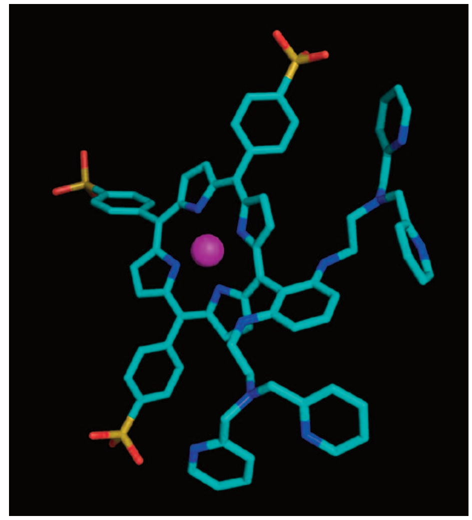
Metal detectors

Jasanoff is also developing MRI sensors for calcium and zinc, two metal ions that are of great interest to neuroscientists. In collaboration with Stephen Lippard, a faculty member in MIT's Department of Chemistry, he has recently built a prototype zinc sensor, and confirmed that it can reveal the distribution of zinc within the rat brain (see page 7). The team is now working to produce a similar agent that can detect calcium. "Almost everything that neurons do involves changes in calcium," explains Jasanoff. "If we could see those changes in the living brain, that would be incredibly useful."

A running start

Looking beyond these current projects, Jasanoff hopes to develop sensors for many different molecules, including genetically-encoded sensors that could be targeted to specific cell types, or used to monitor long term changes in gene expression in the living brain. "Our ultimate goal is to have a whole panel of MRI contrast agents that can allow us to detect events both inside and outside of neurons," he says. "If we can do this, we will truly begin to understand how brain regions interact and respond to experience."

The earliest payoffs of these new imaging tools will be for basic research, but they also have great potential for studying disease mechanisms. For example, Jasanoff has previously collaborated with Susan Lindquist of the Whitehead Institute to study a mouse model of mad cow disease. They were able to track the progressive neurodegeneration in these mice using conventional MRI methods. But, he says, "we could learn much more about neurodegenerative disease if we had contrast agents to measure changes in neural activity during the course of the disease."



A contrast agent designed to detect zinc ions in the brain. The arms (pointing outward) bind to zinc; the pink ball (center) is a manganese ion that changes its magnetic properties when the agent binds to zinc.

Image courtesy of Alan Jasanoff

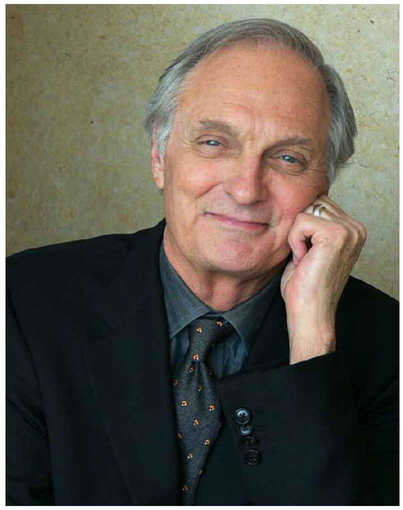
Eventually, he hopes it will be possible to inject contrast agents into human patients as a way to diagnose disease and monitor responses to treatment. Such a technology could transform the treatment of many brain disorders. This is a long-term goal, but Jasanoff's successes to date have already brought this vision a few steps closer to reality. ■

Taekwan Lee, a research associate in Jasanoff's lab, uses the 9.4T MRI scanner in the Martinos Imaging Center to test new contrast agents.

Tenth Anniversary Celebration to Feature Distinguished Speakers

The McGovern Institute will celebrate its tenth anniversary on October 14th. The event will feature keynote addresses from two prominent public advocates for science research: actor Alan Alda, host of the PBS documentary series *Scientific American Frontiers* and *The Human Spark*; and TV journalist Jane Pauley, a member of the McGovern Leadership Board and an outspoken proponent for mental health research. The anniversary celebration will also include an address by Dr. Gerald Fischbach, scientific director of the Simons Foundation.

Following a reception and dinner for McGovern supporters, there will be a presentation by performance artist Nick Cave. Seating will be limited and by invitation only, but the event will be recorded and made publicly available on our website. ■



Actor Alan Alda (left) and broadcast journalist Jane Pauley (top right) will give keynote addresses at the McGovern 10th anniversary event. An evening 'Soundsuit' presentation will be given by Nick Cave (bottom right), Chair of the Fashion Department at the School of the Art Institute of Chicago.

Photos courtesy of Alan Alda, Andrew Eccles, and James Prinz

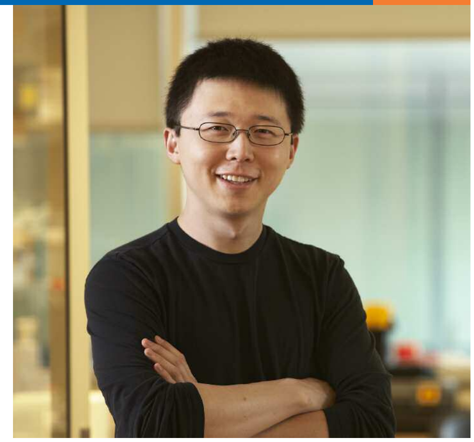
Pat and Jim Poitras Interviewed for Video Profile

During a recent visit to the McGovern Institute, Pat and Jim Poitras '63, sat down for a video interview to discuss their motivation for supporting research at the McGovern Institute and for establishing the Poitras Center for Affective Disorders Research.

The center was established in 2007 to support research into the causes of bipolar disorder, depression, and other serious psychiatric diseases. "The mission of the Poitras Center and the McGovern Institute are totally congruent," says Jim Poitras. "I'd like to think of it as a model for other centers to be established within McGovern. I'd love to see more people step forward and make an equal commitment—that would accelerate the research here even more." The Poitras' interview, including their visit to the laboratory of Guoping Feng, will be available on our website this fall.

Pat and Jim Poitras '63, visit the laboratory of Guoping Feng (left), who holds the Poitras Professorship of Neuroscience in the Department of Brain and Cognitive Sciences.

Feng Zhang to Join McGovern Faculty



Feng Zhang, an expert on genetic control of brain function, will join the McGovern Institute in spring 2011.

Image courtesy of Kent Dayton

We are pleased to announce the appointment of Feng Zhang as a McGovern Investigator, starting in spring 2011. Zhang, an expert on genetic control of brain function, will also become an assistant professor in the MIT Department of Brain and Cognitive Sciences and a Core Faculty Member of the Broad Institute.

Zhang is currently a Junior Fellow at Harvard University's Society of Fellows, and obtained his PhD from Stanford University.

While working with Karl Deisseroth at Stanford, he helped to pioneer the use of optogenetic tools for manipulating brain activity with light. Zhang's current work focuses on applying synthetic biology methods to the study of brain function. He also plans to develop new ways to use stem cells for the treatment of brain disease and injury. A full profile of Zhang and his work will appear in a future issue of *Brain Scan*. ■

Ki Goosens Inspires Philadelphia High School Students

Ki Goosens speaks about her research with students at the Friends' Central School in Philadelphia.

Students from the Friends' Central School after their tour of the McGovern Institute.

Earlier this year, Ki Goosens took her enthusiasm for neuroscience to the Friends' Central School in Philadelphia, Pa., where she was invited to speak as part of the school's distinguished visiting scientist program. Goosens spoke to a large audience about her research on fear, anxiety, and stress. Science teacher John Gruber was impressed with her colloquium-style lecture. "She spoke to the students like intelligent and capable beings; she never talked down to them," said Gruber. "It was very much a vote of confidence, inviting them to be participants in her neuroscientific research, and I loved that collaborative sense of welcome."

In June, a group of students from the school paid a return visit to the McGovern Institute. They were given tours of Goosens' lab and the Martinos Imaging Center, and heard presentations by Charles Jennings, director of the neurotechnology program, and Claire Ahn, an undergraduate researcher in Ed Boyden's lab. ■

Progress on MEG Lab

Dimitrios Pantazis has been recruited from the University of Southern California to run the new MEG lab.

A staff scientist, Dimitrios Pantazis, has been recruited to run the new magnetoencephalography (MEG) lab at the Martinos Imaging Center. Pantazis is currently a research assistant professor at the University of Southern California, and an expert on the complex statistical methods that are used to analyze MEG and other brain imaging data. Pantazis will join the McGovern Institute toward the end of the year.

Meanwhile, pre-installation renovations of the MEG lab are almost complete. The next step will be the assembly of a special three-layered magnetically shielded room to block out external magnetic interference, enabling the MEG scanner to detect the tiny magnetic signals that emanate from the human brain. The shielding, which has been custom-fabricated in Germany, will be in place by early fall.

The human amygdala responds to first impressions of people's faces, including the perceived trustworthiness of strangers. In a new study, **John Gabrieli** and collaborators at Tufts University tested whether these brain responses can be validated by objective criteria. The team examined brain activity as participants viewed the faces of Fortune 1000 CEOs. The strongest responses were evoked by executives who were actually most successful (as measured by company profits), suggesting that successful CEOs may be judged to be better leaders because their faces are more effective at eliciting emotional brain responses in others.

In another imaging study published this summer, **Gabrieli**'s group explored a new method to examine the brain basis of social interaction and attention. Using a video feed, participants engaged in live interactions with other individuals while inside the scanner. This method resulted in strong activation of brain regions involved in social cognition and reward, and could open up new avenues of research in social cognitive neuroscience.

Alan Jasanoff published a paper in *Chemical Biology* describing a noninvasive method for detecting metal ions in the brain using MRI. Jasanoff's team modified a naturally occurring molecule called a porphyrin, making it sensitive to zinc, a metal that has been implicated in memory formation and stroke damage. They tested their sensor in living animals, and found that it accurately revealed the distribution of zinc within the brain.

The left amygdala region responds strongly to faces of executives who run profitable companies.

Image courtesy of John Gabrieli

AWARDS AND HONORS

Sarah Weigelt was awarded the Otto Hahn medal for her doctoral work in illusory perception.

Sarah Weigelt, a postdoctoral fellow in **Nancy Kanwisher**'s lab, was awarded the Otto Hahn medal of the Max Planck Society for her doctoral work in illusory perception. At MIT, Weigelt is combining psychophysics and functional magnetic resonance imaging to understand the development of face perception in children with and without autism.

Chris Moore's 2009 *Nature* paper, in which he used optogenetic methods to induce high frequency activity in the brains of mice, has been cited by Thomson Reuters *ScienceWatch* as a featured New Hot Paper in the field of neuroscience and behavior. According to *ScienceWatch*, Moore's paper was one of the most cited papers in this discipline published in the past two years.

Our feature video, *Welcome to the McGovern Institute*, has won a 2010 CINE Golden Eagle Award. Winners of the CINE competition are chosen based on storytelling, production value, artistry, purpose, and overall excellence. This is the second industry award for the McGovern video; in June, it won a Telly Award for outstanding programming in the fundraising category.

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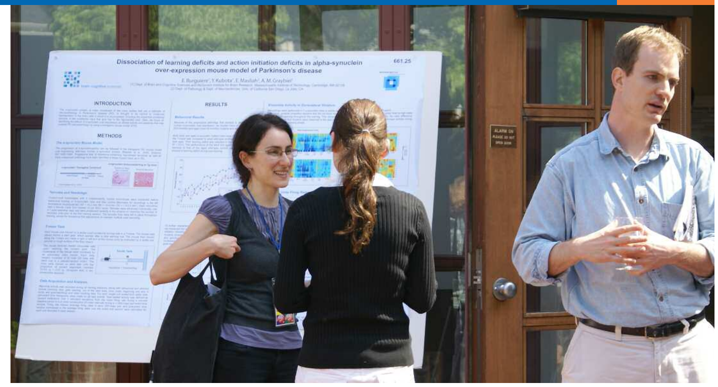
Video Spotlight

Functional magnetic resonance imaging (fMRI) has revolutionized our understanding of the human brain, but the method is now approaching the limits of its capabilities. In this five-minute video, **Alan Jasanoff** describes how his lab is developing new technologies that will greatly improve the specificity and resolution of future brain imaging procedures (see page 2). Visit our website to watch this video profile online.

Nearly 150 people attended the McGovern Institute retreat at the American Academy of Arts and Sciences this June.



This year's retreat featured 13 talks and 26 poster presentations.

8th Annual McGovern Institute Retreat

McGovern Institute faculty, researchers, and staff enjoyed spectacular weather and a full day of scientific talks at the eighth annual retreat, held this year at the American Academy of Arts and Sciences in Cambridge. Institute founders Pat and Lore McGovern and Leadership Board member emeritus Bob Metcalfe '68 joined members of the McGovern Institute to hear presentations by students and postdocs from McGovern labs. The event featured thirteen talks, followed by an indoor/outdoor poster session and dinner at the Academy. ■

Retsina Meyer, a graduate student in Ki Goosens' lab, explains her research to Institute founders Pat and Lore McGovern.

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