



MCGOVERN INSTITUTE

FOR BRAIN RESEARCH AT MIT

Brain SCAN

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Rethinking Mental Illness Treatment

*The Poitras Center supports research into how
brain scans can personalize psychiatric medicine*



FROM THE DIRECTOR

This year we celebrate the 10th anniversary of the Poitras Center for Affective Disorders Research, which was established in 2007 with a landmark commitment of \$20M from our longtime supporters Jim and Pat Poitras.

Over the past 10 years, the Center has enabled a long list of discoveries and technical advances. Some have involved animal models, including the development of new genetic technologies for studying psychiatric disorders such as autism, schizophrenia and bipolar disorder. Other projects have focused on human patients, including the work of my colleagues Sue Whitfield-Gabrieli and Satrajit Ghosh, which you can read about in this issue.

Sue and Satra, who are affiliated with the lab of John Gabrieli, are working to identify ways that human neuroimaging can be translated into practical applications that can directly impact patient care. For example, they have shown that brain scans can help improve predictions about who will respond best to a given treatment, and they are now working toward predicting before the onset of symptoms who is most likely to develop a given disorder—opening the door to earlier and potentially more effective interventions.

It is exciting to see the powerful new technologies of neuroimaging applied to these important clinical challenges, and we are deeply grateful to Jim and Pat Poitras for their visionary gift that has made this work possible.

Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

On the cover:

Cells of the mouse hippocampus visualized using expansion microscopy—a technique developed in Ed Boyden's lab in which brain tissue is physically expanded to reveal fine structural details.

Image: Yosuke Bando, Fei Chen, Dawen Cai, Ed Boyden and Young-Gyu Yoon



McGovern researchers are finding neural markers that could help improve treatment for psychiatric patients.

Ten years ago, Jim and Pat Poitras committed \$20M to the McGovern Institute to establish the Poitras Center for Affective Disorders Research. The Poitras family had been longtime supporters of MIT, and because they had seen mental illness in their own family, they decided to support an ambitious new program at the McGovern Institute, with the goal of understanding the fundamental biological basis of depression, bipolar disorder, schizophrenia and other major psychiatric disorders.

The gift came at an opportune time, as the field was entering a new phase of discovery, with rapid advances in psychiatric genomics and brain imaging, and with the emergence of new technologies for

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genome editing and for the development of animal models. Over the past ten years, the Poitras Center has supported work in each of these areas, including Feng Zhang's work on CRISPR-based genome editing, and Guoping Feng's work on animal models for autism, schizophrenia and other psychiatric disorders.

This reflects a long-term strategy, says Robert Desimone, director of the McGovern Institute who oversees the Poitras Center. "But we must not lose sight of the overall goal, which is to benefit human patients. Insights from animal models and genomic medicine have the potential to transform the treatments of the future, but we are also interested in the nearer term, and in what we can do right now."

One area where technology can have a near-term impact is human brain imaging, and in collaboration with clinical researchers at McLean Hospital, Massachusetts General Hospital and other institutions, the Poitras Center has supported an ambitious program to bring human neuroimaging closer to the clinic.

Discovering Psychiatry's Crystal Ball

A fundamental problem in psychiatry is that there are no biological markers for diagnosing mental illness or for indicating how best to treat it. Treatment decisions are based entirely on symptoms, and doctors and their patients will typically try one treatment, then if it does not work, try another, and perhaps another. The success rates for the first treatments are often less than 50%, and finding what works for an individual patient often means a long and painful process of trial and error.

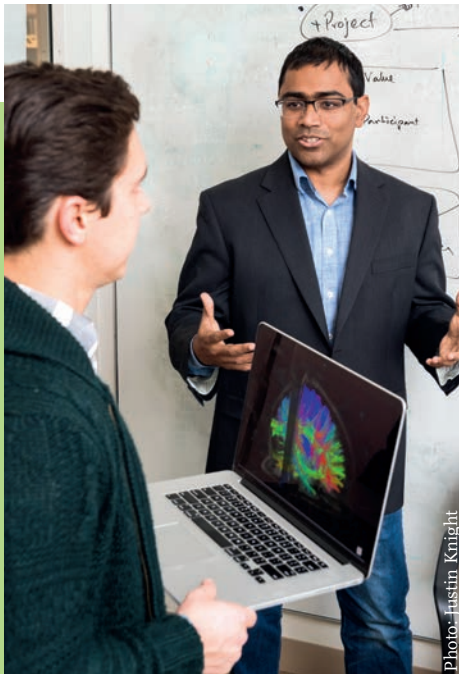
McGovern research scientist Susan Whitfield-Gabrieli and her colleagues are hoping to change this picture, with the help of brain imaging. Their findings suggest that brain scans can hold valuable information for psychiatrists and their patients. "We need a paradigm shift in how we use imaging. It can be used for more than research," says Whitfield-Gabrieli, who is a member of McGovern Investigator John Gabrieli's lab. "It would be a really big boost to be able use it to personalize psychiatric medicine."



Photo: Justin Knight

Above left, Sue Whitfield-Gabrieli, whose research on psychiatric imaging is supported by the Poitras Center, which was established in 2007 by Jim and Pat Poitras (above).

One of Whitfield-Gabrieli's goals is to find markers that can predict which treatments will work for which patients. Another is to find markers that can predict the likely risk of disease in the future, allowing doctors to intervene before symptoms first develop. All of these markers need further validation before they are ready for the clinic, but they have the potential to meet a dire need to improve treatment for psychiatric disease.



Satrajit Ghosh (right) with graduate student Kevin Sitek.

A Brain at Rest

For Whitfield-Gabrieli, who both collaborates with and is married to Gabrieli, that paradigm shift began when she started to study the resting brain using functional magnetic resonance imaging (fMRI). Most brain imaging studies require the subject to perform a mental task in the scanner, but these are time-consuming and often hard to replicate in a clinical setting. In contrast, resting state imaging requires no task. The subject simply lies in the scanner and lets the mind wander. The patterns of activity can reveal functional connections within the brain, and are reliably consistent from study to study.

Whitfield-Gabrieli thought resting state scanning had the potential to help patients because it is simple and easy to perform. “Even a 5-minute scan can contain useful information that could help people,” says Satrajit Ghosh, a principal research scientist in the Gabrieli lab who works closely with Whitfield-Gabrieli. Whitfield-Gabrieli and her clinical collaborator Larry Seidman at Harvard Medical School decided to study resting state activity in patients with schizophrenia. They found a pattern of activity strikingly different from that of typical brains. The patients showed unusually strong activity in a set of interconnected brain regions known as the default mode network, which is typically activated during introspection. It is normally suppressed when a person attends to the outside world, but schizophrenia patients failed to show this suppression. “The patient isn’t able to toggle between internal processing and external processing the way a typical individual can,” says Whitfield-Gabrieli, whose work is supported by the Poitras Center for Affective Disorders Research.

Since then, the team has observed similar disturbances in the default network in other disorders, including depression, anxiety, bipolar disorder, and ADHD. “We knew we were onto something interesting,” says Whitfield-Gabrieli. “But we kept coming back to the question: how can brain imaging help patients?”

fMRI on Patients

Many imaging studies aim to understand the biological basis of disease and ultimately to guide the development of new drugs or other treatments. But this

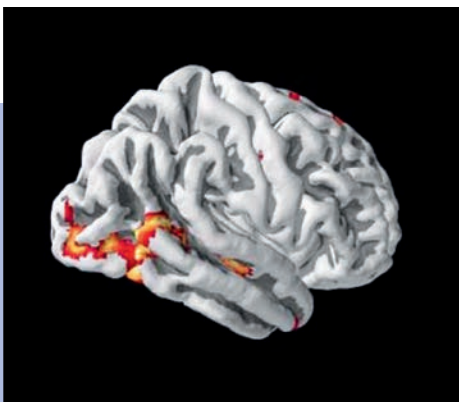
is a long-term goal, and Whitfield-Gabrieli wanted to find ways that brain imaging could have a more immediate impact.

So she and Ghosh decided to use fMRI to look at differences among individual patients, and to focus on differences in how they responded to treatment. “It gave us something objective to measure,” explains Ghosh. “Someone goes through a treatment, and they either get better or they don’t.” The project also had appeal for Ghosh because it was an opportunity for him to use his expertise in machine learning and other computational tools to build systems-level models of the brain.

For the first study, the team decided to focus on social anxiety disorder (SAD), which is typically treated with either prescription drugs or cognitive behavioral therapy (CBT). Both are moderately effective, but many patients do not respond to the first treatment they try.

The team began with a small study to test whether scans performed before the onset of treatment could predict who would respond best to the treatment. Working with Stefan Hofmann, a clinical psychologist at Boston University, they scanned 38 SAD patients before they began a 12-week course of CBT. At the end of their treatment, the patients were evaluated for clinical improvement, and the researchers examined the scans for patterns of activity that correlated with the improvement. The results were very encouraging; it turned out that predictions based on scan data were 5-fold better than the existing methods based on severity of symptoms at the time of diagnosis.

The researchers then turned to another condition, ADHD, which presents a similar clinical challenge, in that commonly used drugs—such as Adderall or Ritalin—work well, but not for everyone. So the McGovern team began a collaboration with psychiatrist Joseph Biederman, Chief of Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital, on a similar study, looking for markers of treatment response. The study is still ongoing, and it will be some time before results emerge, but the researchers are optimistic. “If we could predict who would respond to which treatment and avoid



Social anxiety patients with more activity in visual processing areas (right) responded better to subsequent cognitive behavioral therapy than patients with lower activity (left).

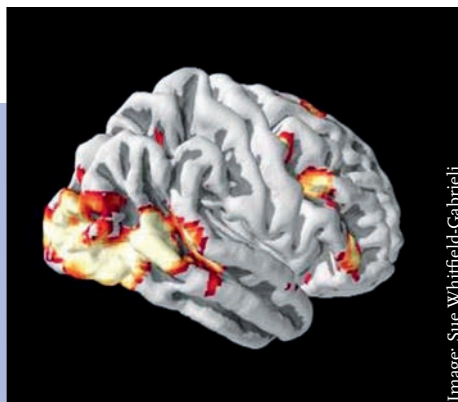


Image: Sue Whitfield-Gabrieli



Photo: Justin Knight

Sue Whitfield-Gabrieli and Satrajit Ghosh use computational methods to build models that relate brain patterns to clinical outcomes.

months of trial and error, it would be totally transformative for ADHD,” says Biederman.

Another goal is to predict in advance who is likely to develop a given disease in the future. The researchers have scanned children who have close relatives with schizophrenia or depression, and who are therefore at increased risk of developing these disorders themselves. Surprisingly, the children show patterns of resting state connectivity similar to those of patients. “I was really intrigued by this,” says Whitfield-Gabrieli. “Even though these children are not sick, they have the same profile as adults who are.”

Whitfield-Gabrieli and Seidman are now expanding their study through a collaboration with clinical researchers at the Shanghai Mental Institute in China, who plan to image and then follow 225 people who are showing early risk signs for schizophrenia. They hope to find markers that predict who will develop the disease and who will not.

“While there are no drugs available to prevent schizophrenia, it may be possible to reduce the risk or severity of the disorder through CBT, or through interventions that reduce stress and improve sleep and well-being,” says Whitfield-Gabrieli. “One likely key to success is early identification of those at highest risk. If we could diagnose early, we could do early interventions and potentially prevent disorders.”

From Association to Prediction

The search for predictive markers represents a departure from traditional

psychiatric imaging studies, in which a group of patients is compared with a control group of healthy subjects. Studies of this type can reveal average differences between the groups, which may provide clues to the underlying biology of the disease. But they don’t provide information about individual patients, and so they have not been incorporated into clinical practice.

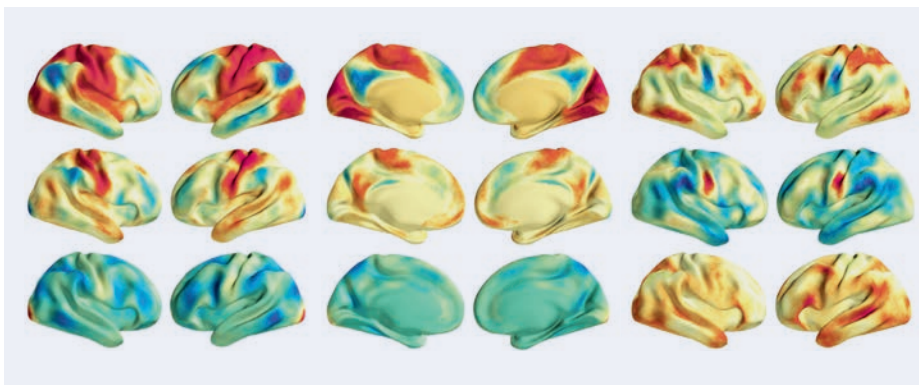
The difference is critical for clinicians, says Biederman. “I treat individuals, not groups. To bring predictive scans to the clinic, we need to be sure the individual scan is informative for the person you are treating.”

To develop these predictions, Whitfield-Gabrieli and Ghosh must first use sophisticated computational methods such as ‘deep learning’ to identify patterns in their data and to build models that relate the patterns to the clinical outcomes. They must then show that these models can generalize beyond the original study population—for example, that predictions

based on patients from Boston can be applied to patients from Shanghai. The eventual goal is a model that can analyze a previously unseen brain scan from any individual, and predict with high confidence whether that person will (for example) develop schizophrenia or respond successfully to a particular therapy.

Achieving this will be challenging, because it will require scanning and following large numbers of subjects from diverse demographic groups—thousands of people, not just tens or hundreds as in most clinical studies. Collaborations with large hospitals, such as the one in Shanghai, can help. Whitfield-Gabrieli has also received funding to collect imaging, clinical, and behavioral data from over 200 adolescents with depression and anxiety, as part of the National Institutes of Health’s Human Connectome effort. These data, collected in collaboration with clinicians at McLean Hospital, MGH and Boston University, will be available not only for the Gabrieli team, but for researchers anywhere to analyze. This is important, because no one team or center can do it alone, says Ghosh. “Data must be collected by many and shared by all.”

The ultimate goal is to study as many patients as possible now so that the tools can help many more later. “Someday, a person will be able to go to a hospital, get a brain scan, charge it to their insurance, and know that it helped the doctor select the best treatment,” says Ghosh. “We’re still far away from that. But that is what we want to work towards.” ■



Scans of resting brain activity reveal different patterns of connectivity between brain regions in individual subjects.

Image: Satrajit Ghosh and Georg Langs



Lisa Yang (left) and Hock Tan '75 SM '75.

Tan-Yang Center for Autism Research Established at the McGovern Institute

The McGovern Institute is pleased to announce the establishment of a new center dedicated to autism research. The center is made possible by a kick-off commitment of \$20 million, made by Lisa Yang and MIT alumnus Hock Tan '75.

The Hock E. Tan and K. Lisa Yang Center for Autism Research will support research on the genetic, biological and neural bases of autism spectrum disorders, a developmental disability estimated to affect 1 in 68 individuals in the United States. Tan and Yang hope their initial investment will stimulate additional support and help foster collaborative research efforts to erase the devastating effects of this disorder on individuals, their families and the broader autism community.

“With the Tan-Yang Center for Autism Research, we can imagine a world in which medical science understands and supports those with autism—and we can focus MIT’s distinctive strengths on making that dream a reality,” says MIT President L. Rafael Reif. “Lisa and Hock’s gift reminds us of the impact we envision for the MIT Campaign for a Better World. I am grateful for their leadership and generosity, and inspired by the possibilities ahead.”

“I am thrilled to be investing in an institution that values a multidisciplinary collaborative approach to solving complex problems such

as autism,” says Hock Tan, who graduated from MIT in 1975 with a bachelor’s degree and master’s degree in mechanical engineering. “We expect that successful research originating from our Center will have a significant impact on the autism community.”

Originally from Penang, Malaysia, Tan has held several high-level finance and executive positions since leaving MIT. Tan is currently CEO of chipmaker Broadcom, Ltd.

Research at the Tan-Yang Center will focus on four major lines of investigation: genetics, neural circuits, novel autism models and the translation of basic research to the clinical setting. By focusing research efforts on the origins of autism in our genes, in the womb and in the first years of life, the Tan-Yang Center aims to develop methods to better detect and potentially prevent autism spectrum disorders entirely. To help meet this challenge, the Center will support collaborations across multiple disciplines—from genes to neural circuits—both within and beyond MIT.

“MIT has some of the world’s leading scientists studying autism,” says McGovern Institute director Robert Desimone. “Support from the Tan-Yang Center will enable us to pursue exciting new directions that could not be funded by traditional sources. We will exploit revolutionary new tools, such as CRISPR and optogenetics, that are transforming research in neuroscience. We hope to not only identify new targets for medicines,

but also develop novel treatments that are not based on standard pharmacological approaches. By supporting cutting-edge autism research here at MIT as well as our collaborative institutions, the Center holds great promise to accelerate our basic understanding of this complex disorder.”

“Millions of families have been impacted by autism,” says Yang, a longtime advocate for the rights of individuals with disabilities and learning differences. “I am profoundly hopeful that the discoveries made at the Tan-Yang Center will have a long-term impact on the field of autism research and will provide fresh answers and potential new treatments for individuals affected by this disorder.” ■

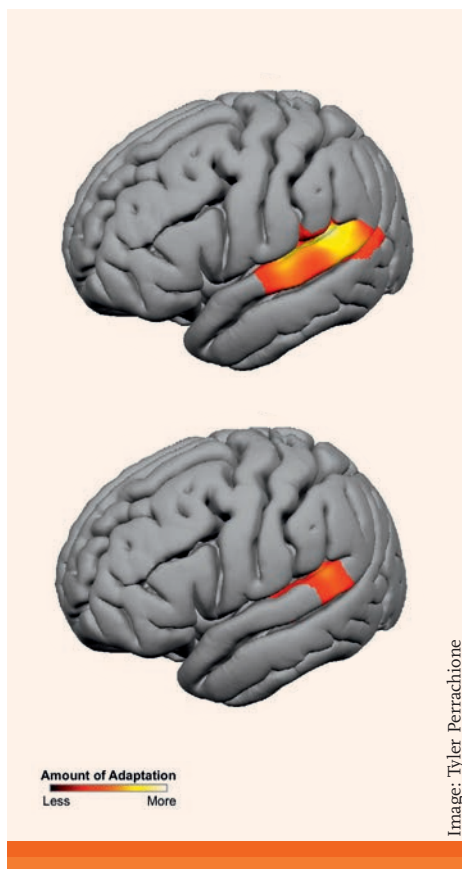
McGovern Institute Awards Scolnick Prize to Catherine Dulac

The winner of the 2017 Scolnick Prize is Catherine Dulac of Harvard University. Dulac is recognized for her discovery of mammalian pheromone receptors and for tracing the pathways by which pheromones act on the brain to control behavior. In work that began while she was a postdoc, Dulac identified two large families of pheromone receptors, which are expressed in a specialized part of the olfactory epithelium known as the vomeronasal organ. She has gone on to study the mechanisms by which sensory neurons respond to pheromones, and the neural circuits by which these volatile chemical signals control a range of stereotypic and sex-specific behaviors, including courtship, mating, parental behavior and aggression. ■



Catherine Dulac, winner of the 2017 Scolnick Prize.

RESEARCH NEWS



These fMRI images show the amount of adaptation in the brains of individuals with dyslexia (below) and those without (top) when hearing a repeated voice. The dyslexia group showed significantly less adaptation than the control group.

John Gabrieli and colleagues have used MRI to identify brain differences that may underlie dyslexia. When a stimulus is presented repeatedly, the brain response decreases with each repetition, a phenomenon known as neural adaptation. The researchers, led by Tyler Perrachione, found that this effect was diminished in people with dyslexia, including both adults and children. The difference was seen in multiple brain regions, suggesting that the deficit responsible for dyslexia affects many different brain functions. The authors speculate that reading may be especially sensitive to subtle deficits, because it involves so many brain processes.

Synthetic biology allows scientists to design genetic circuits that can be placed in cells, giving them new functions such as producing drugs or other useful molecules. **Ed Boyden** and colleagues have now demonstrated that these circuits can be encapsulated within synthetic cell-like structures known as liposomes, preventing them from disrupting each other. The researchers can also control communication between these cells, allowing for circuits or their products to be combined at specific times.

Tomaso Poggio and colleagues have developed a new computational model for how the brain learns to recognize faces. Their model, which is based on known properties of neurons, takes

account of the symmetry of faces and, like real brains, learns to recognize faces as they turn to either the left or right.

Alan Jasanoff's lab has devised a new class of probes that allow scientists to image brain molecules without using any chemical or radioactive labels. The new sensors consist of proteins designed to detect a particular target, which causes them to dilate blood vessels in the immediate area. This produces a local change in blood flow that can be imaged with magnetic resonance imaging (MRI) or other imaging techniques. ■



A computational model developed by the Poggio lab suggests how the brain can recognize faces from different viewpoints.

AWARDS & HONORS



Feng Zhang has been named the Patricia and James Poitras Professor in Neuroscience.

Feng Zhang has been named the inaugural chairholder of the Patricia and James Poitras (1963) Professorship in Neuroscience. He was also among five CRISPR scientists named to *TIME Magazine's* shortlist for 2016 Person of the Year. ■

EVENTS



Photo: Justin Knight

From left to right: Elizabeth McGovern, Hugo Shong, Walter Boyd, Patrick McGovern III, Lore Harp McGovern, Brett Liu and Robert Desimone.



Photo: Justin Knight

Symposium participants pose for a photo outside the McGovern Institute.

IDG Sale

International Data Group Inc., founded by the late Patrick J. McGovern, announced on January 19 that it was being acquired by China Oceanwide Holdings Group and IDG Capital, the investment management firm run by IDG China executive and McGovern supporter Hugo Shong. Proceeds of the sale will benefit the McGovern Foundation, which supports neuroscience research at the McGovern Institute. ■

Joint Symposium with IDG/McGovern Institutes

On Nov 8, the McGovern Institute hosted a joint symposium with our three sister institutes in Beijing. The event, which was supported by Hugo Shong, featured nine speakers from the IDG/McGovern Institutes at Peking University, Tsinghua University, Beijing Normal University and MIT, along with poster presentations by young researchers from all four institutes. Videos of the talks can be viewed on our website. ■

■ *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 Lore Harp McGovern and the late Patrick J. McGovern, with the goal of 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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