Brain SCAN

John Gabrieli

From Brain Imaging to Personalized Medicine

In a recent speech at the White House, President Obama announced a new initiative to understand the brain, which he described as one of the grand challenges for the scientific community and for the nation as a whole. The President's initiative will focus especially on the development of new technologies, a goal that we at MIT can embrace wholeheartedly. Progress in neuroscience is critically dependent on technological advances, and one of my early decisions as director was to establish our own neurotechnology program, to support collaborations with researchers from other disciplines and to take advantage of the extraordinary range of expertise and opportunities that surround us. Through this program we have already funded over 20 seed projects, some of which have now grown into major research efforts.

One technology that has had an especially profound effect on neuroscience is magnetic resonance imaging (MRI), which allows us to observe the workings of the living human brain with ever-greater precision. My colleague John Gabrieli, who is featured in this issue, has been central to our efforts in this area, both as director of our Martinos Imaging Center and as a leading advocate of human neuroimaging for the study of normal brain function and its impairment in disease. As you can read here, John has an exceptionally wide range of scientific interests, and there is almost no area of cognitive neuroscience that has not been influenced by his work.

Bob Desimone, Director
Doris and Don Berkey Professor
of Neuroscience

On the cover:
A bundle of spiny apical dendrites, reconstructed from a series of ultra-thin slices of mouse cortex.

Courtesy of Daniel Berger and Sebastian Seung (MIT); based on data from Jeff Lichtman and colleagues (Harvard).

Photo: Justin Knight

John Gabrieli uses brain imaging to understand the origins of mental disorders and search for better treatments.

The summer after John Gabrieli finished college with a literature degree from Yale, he found himself in a store in Harvard Square, wondering what to do next.

"I was looking at books and found this," he says, walking to a shelf in his cluttered office at the McGovern Institute and pulling down a book with a tattered red cover. He points to the title, *Human Neuropsychology*. "I thought, that sounds interesting. It's about people, like literature, but with a science-y edge and a humanitarian side."

He shared his newfound interest with a family friend who happened to know the chief of neurosurgery at Massachusetts General Hospital. One phone call later, Gabrieli was connected with Suzanne Corkin, now MIT professor emerita of Brain and Cognitive Sciences.

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He began work in her lab soon after. "I took to it like a duck to water," he says.

For the next several years, as a graduate student at MIT, Gabrieli was among the privileged group of scientists invited to study Henry Molaison, known in his life-time only as HM, yet perhaps the most famous patient in the history of neurology.

In 1953, at the age of 27, Molaison had undergone a surgical procedure to prevent epileptic seizures. After removal of his hippocampus the seizures vanished, but so did his ability to form new memories.

Molaison, who died in 2008, happily cooperated with Corkin and her colleagues for several decades, providing groundbreaking insights into the basis of human memory. The experiments were exciting, recalls Gabrieli, not only because HM was such an unusual and delightful person, but also because the questions were timely. "This work coincided with an explosion of ideas about how different forms of memory exist in different neural systems in the brain, so there was a lot to examine."

After completing his PhD, Gabrieli moved to Stanford University, where he became interested in the emerging technology of brain imaging, applying it to study memory and other areas of psychology such as emotion, intelligence and language.

While at Stanford, Gabrieli met his future wife, Susan Whitfield-Gabrieli, who had a longstanding interest in psychiatry. They began to collaborate, studying patients with schizophrenia, bipolar disorder and other neuropsychiatric conditions. "Our interests complement each other nicely," says Whitfield-Gabrieli, now a research scientist in the Gabrieli lab. "Between our work and our two young daughters, there's no shortage of lively conversations."

Gabrieli returned to MIT in 2006, to become Grover Hermann Professor in Health Sciences and Technology and Cognitive Neuroscience, and to direct the newly established Martinos Imaging Center at the McGovern Institute. By this time he had worked with many different patient populations, including people with attention

Photo: Justin Knight

Postdoc Elizabeth Norton prepares a child for the MRI scanner.

deficit disorder, traumatic memories, Alzheimer's disease, Parkinson's disease and dyslexia.

Many of these studies had been designed to address basic questions about normal brain function or its disruption in disease. Since returning to MIT, however, Gabrieli's goals have evolved toward more direct therapeutic applications of imaging technology. "Now that we have a better understanding of the brain, we are focusing on learning how to help patients," he says.

One of his major goals is to apply brain imaging to guide and personalize treatment choices. For many psychiatric patients, the choice of treatment is a matter of trial and error, and clinicians often have no way to predict in advance what will work for any individual patient. Finding an effective treatment can be slow, inefficient and frustrating for patients and their families. "It seems we should be able to do better," says Gabrieli.

Predictive Pictures

For patients with social anxiety disorder, Gabrieli already has evidence to back up this belief. With support from the Poitras Center for Affective Disorders Research, he was able to team up with clinicians at Massachusetts General Hospital and Boston University who were preparing to conduct a study on the effectiveness of cognitive behavioral therapy.

Before starting the therapy, a group of patients were scanned at MIT. As they lay in the scanner, they were shown images of

angry or neutral faces, which the researchers expected might be processed differently by patients with social anxiety. After the course of treatment, the researchers want back to the brain scans to look for variations in activity that may predict how well each patient would respond to treatment. They found varying levels of activity in several brain regions associated with high-level visual processing; most significantly, they found that individuals with more activity in these regions tended to show better treatment responses.

Although the brain scans were able to predict treatment responses more accurately in each individual than existing clinical assessments, the new approach still needs to be validated on a larger group of patients, according to Satrajit Ghosh, a research scientist in Gabrieli's lab and a co-author on the study. "We also hope to extend this work to other types of therapy such as anti-depressants and anti-anxiety drugs," he says. "If our algorithm predicts that a treatment is unlikely to work well for a given patient, we'd also like to point that person to some other treatment that is more likely to work."

Reading the Signs

Gabrieli is also exploring predictive imaging for dyslexia, a longstanding interest that goes back to his days at Stanford. He had previously found that the brains of children with dyslexia show a distinctive pattern of brain activity during reading, and also that there are anatomical differences in the white matter between dyslexic and non-dyslexic individuals.


Boston-area schoolchildren participate in a dyslexia study in the Gabrieli lab.

Dyslexia is common—affecting 5 to 17% of children by some estimates—but it often goes unrecognized until a child is already struggling at school, by which time the opportunity for early intervention has already been missed. Even when a problem is identified, dyslexic children may not receive the special reading education they need. "We want to do a better job of assigning children to interventions by predicting which intervention is most likely to work for a given child," says Joanna Christodoulou, a postdoc in the Gabrieli lab who is also affiliated with the learning disabilities program at Boston Children's Hospital.

Last year, Gabrieli and Christodoulou recruited a large group of children from the Boston area to participate in a study that involved a 6-week program of intensive reading instruction. They scanned over 70 of the children, some with dyslexia and some without, before and after the program. For four hours a day, five days a week, a group of 6- to 8-year-olds descended on MIT for summer camp. "We decorated our offices and turned them into classrooms," says Christodoulou. "It was so much fun."

It soon became clear that the intervention was working. "Compared to the kids who hadn't yet received the intervention, the children who did receive it showed benefits," says Christodoulou.
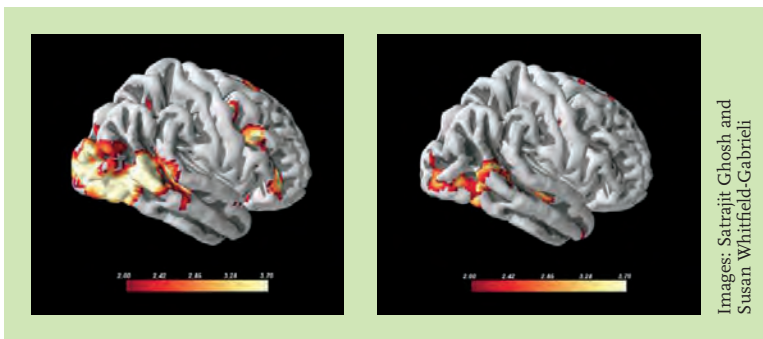
Images: Satrajit Ghosh and Susan Whitfield-Gabrieli

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

The key question, still under analysis, is whether it is possible to find signs in the brain that could predict in advance which children would benefit most; or brain changes at the end of the study that might be correlated with an improvement in reading performance.

Answering this question requires a massive data-crunching process, and the analysis is proceeding slowly to meet the researchers' exacting standards. "The combination of neuroscience and education is new terrain," says Christodoulou. "We want to be systematic in exploring its potential."

Photo: Justin Knight

John Gabrieli with members of his lab.

Rest Assured

One challenge in using brain imaging therapeutically is that many brain measurements require the patients to perform a behavioral task in the scanner, something that is difficult to standardize in a clinical setting.

"These types of experiments where you show faces, every investigator does them differently, so it's hard to compare results from one study to the next," says Gabrieli. "Doctors want a test that gives them a number, but performing a brain scan is a lot more complicated than running a blood test."

A possible solution, which he and his colleagues are now pursuing, is to scan the patients when they are doing nothing except lying in the scanner and allowing their minds to wander.

Even when resting, our brains are still at work, explains Whitfield-Gabrieli. Activity across different brain regions rises and falls in concert like the sections of an orchestra, the violins and cellos playing in harmony as the wind instruments are silent. These patterns of correlated activity reveal functional connections between brain regions, whose disruption can be a sign of disease.

For instance, in their social anxiety study, Ghosh and Whitfield-Gabrieli found a network connected to the amygdala, often described as the brain's fear center. When compared to healthy controls, patients with social anxiety show stronger connections from the amygdala to other brain regions,

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— John Gabrieli

and this can be used to predict how well they will respond to therapy. "It turns out that our resting state metrics are better at predicting outcomes than the existing behavioral scales doctors use," says Whitfield-Gabrieli, who is in the process of publishing these findings.

There are many other projects going on in Gabrieli's lab, yet he somehow manages to find quality time for each one. The magic, says Christodoulou, is Gabrieli's deep trust of the people in his lab. "What that translates to for me is license to explore, knowing I have his full support and encouragement."

"Independence helps people follow their passions," says Gabrieli, who learned this lesson himself in graduate school three decades ago. ■

Photo: Susan Whitfield-Gabrieli

Susan Whitfield-Gabrieli, John Gabrieli and their two daughters, Christina and Isabella.

MIT Researchers Join Obama for Brain Announcement

Ed Boyden (left) and Robert Desimone at the White House for the BRAIN Initiative announcement.

Robert Desimone and Ed Boyden were invited to the White House on Tuesday, April 2, when President Barack Obama announced a new initiative to understand the human brain.

The McGovern researchers, along with MIT faculty colleagues Emery Brown and Sebastian Seung, were among a group of leading neuroscientists who joined Obama for the announcement, along with Francis Collins, director of the National Institutes of Health, and representatives of federal and private funders of neuroscience research.

In unveiling the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, Obama highlighted brain research as one of his administration's "grand challenges"—ambitious yet achievable goals that demand new innovations and breakthroughs in science and technology.

"There is this enormous mystery waiting to be unlocked," Obama said, "and the BRAIN Initiative will change that by giving scientists the tools they need to get a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember. And that knowledge could be—will be—transformative."

A key goal of the BRAIN Initiative will be to accelerate the development of new technologies to visualize brain activity and to understand how this activity is linked to behavior and to brain disorders.

To jump-start the initiative, the NIH, the Defense Advanced Research Projects Agency, and the National Science Foundation will invest some $100 million in research support beginning in the next fiscal year. Planning will be overseen by a working group co-chaired by Cornelia Bargmann PhD '87, now at Rockefeller University, and William Newsome of Stanford University. Emery Brown, an MIT professor of computational neuroscience and of health sciences and technology, will serve as a member of the working group.

The detailed goals of the initiative are still being worked out, but Desimone is optimistic that McGovern researchers will be well placed to contribute. "Many of our researchers are leaders in technology development, and there's no better place than MIT to push the neurotechnology field forward," he says. "One example is optogenetics, a method for controlling brain activity with light that is already revolutionizing the field. We're also exploring many other areas through the McGovern Institute Neurotechnology (MINT) program, which supports collaborations with engineers, computer scientists, materials scientists and so on. We are very fortunate in having so much expertise on campus, and we want to take full advantage of the opportunities around us." ■
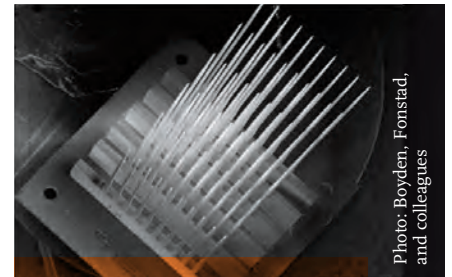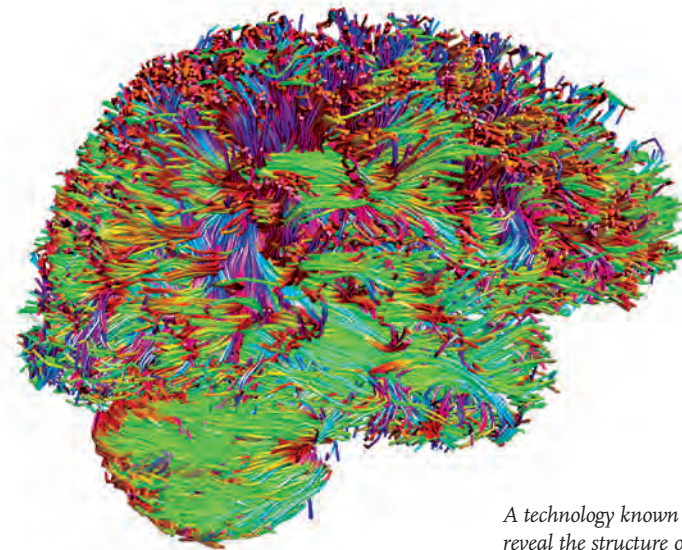

Ed Boyden has collaborated with Clif Fonstad, a professor of electrical engineering and computer science, to develop arrays of miniature electrodes that can record from thousands of neurons simultaneously.
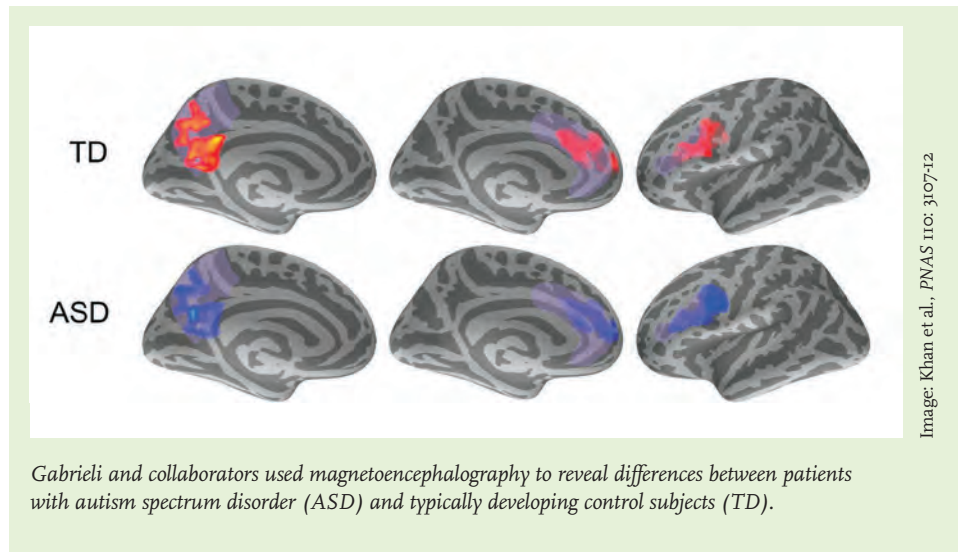

A technology known as diffusion imaging can reveal the structure of long-range connections in the living human brain. Image courtesy of Zeynep Saygin (MIT).

John Gabrieli collaborated with colleagues at Massachusetts General Hospital and Boston University to study how brain connectivity is altered in autism. They used magnetoencephalography to measure how strongly different brain regions are communicating with each other, and found that both local and long-range connections are weaker in people with autism.

The key hallmark of Parkinson's disease is the loss of dopamine in part of the brain known as the striatum. A new study from **Ann Graybiel**'s lab provides insight into how the activity of the striatum is disrupted by this loss of dopamine, and how these changes are reversed by the drug L-DOPA, commonly used to treat Parkinson's disease.

Image: Khan et al., *PNAS* 110: 3107-12

Gabrieli and collaborators used magnetoencephalography to reveal differences between patients with autism spectrum disorder (ASD) and typically developing control subjects (TD).

A study from **Nancy Kanwisher**'s group challenges the commonly held view that people with autism are less able to process global information relative to local information. The authors report that autistic children are equally able to process global patterns when so instructed, but prefer to focus on local information when given the choice—a distinction that may have important implications for remediation therapies. ■

AWARDS AND HONORS

Photo: Kent Dayton

Martha Constantine-Paton has been elected to the American Academy of Arts and Sciences.

Martha Constantine-Paton is among nine MIT faculty members elected to the American Academy of Arts and Sciences. The new class, which includes leaders from academia, business, public affairs, the arts and humanities, will be inducted at a ceremony on October 12 in Cambridge, MA. Constantine-Paton was also awarded the Dean's Medal from Tufts University School of Arts and Sciences.

Ed Boyden has been named a recipient of the 2013 Grete Lundbeck European Brain Research Prize. The 1-million-euro prize is awarded for the development of optogenetics, a technology that makes it possible to control brain activity using light. Boyden will share the prize with five other researchers.

Boyden has also received the Gabbay Award in Biotechnology and Medicine from Brandeis University, along with two other pioneers in optogenetics, Karl Deisseroth of Stanford University and Gero Miesenbock of the University of Oxford.

Suhasa Kodandaramaiah, a postdoc in **Ed Boyden**'s lab, has been named by *Forbes Magazine* among the top 30 rising stars in science and health. ■

Photo: Pete Souza

Thomas Jessell Delivers the Scolnick Prize Lecture

On April 1, Thomas Jessell of Columbia University delivered the 10th annual Scolnick Prize Lecture in Neuroscience. Jessell received the award for his research on the embryonic development of the spinal cord. A video of the lecture is available on our website. ■

Ann Graybiel Invited to the White House

President Obama met on March 28 with the six U.S. winners of the 2012 Kavli Prizes—including Ann Graybiel (fourth from right) and two MIT colleagues, Mildred Dresselhaus, and Jane Luu. Graybiel shared the Neuroscience Prize for "elucidating basic neuronal mechanisms underlying perception and decision." ■

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