Brain SCAN

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FOR BRAIN RESEARCH AT MIT

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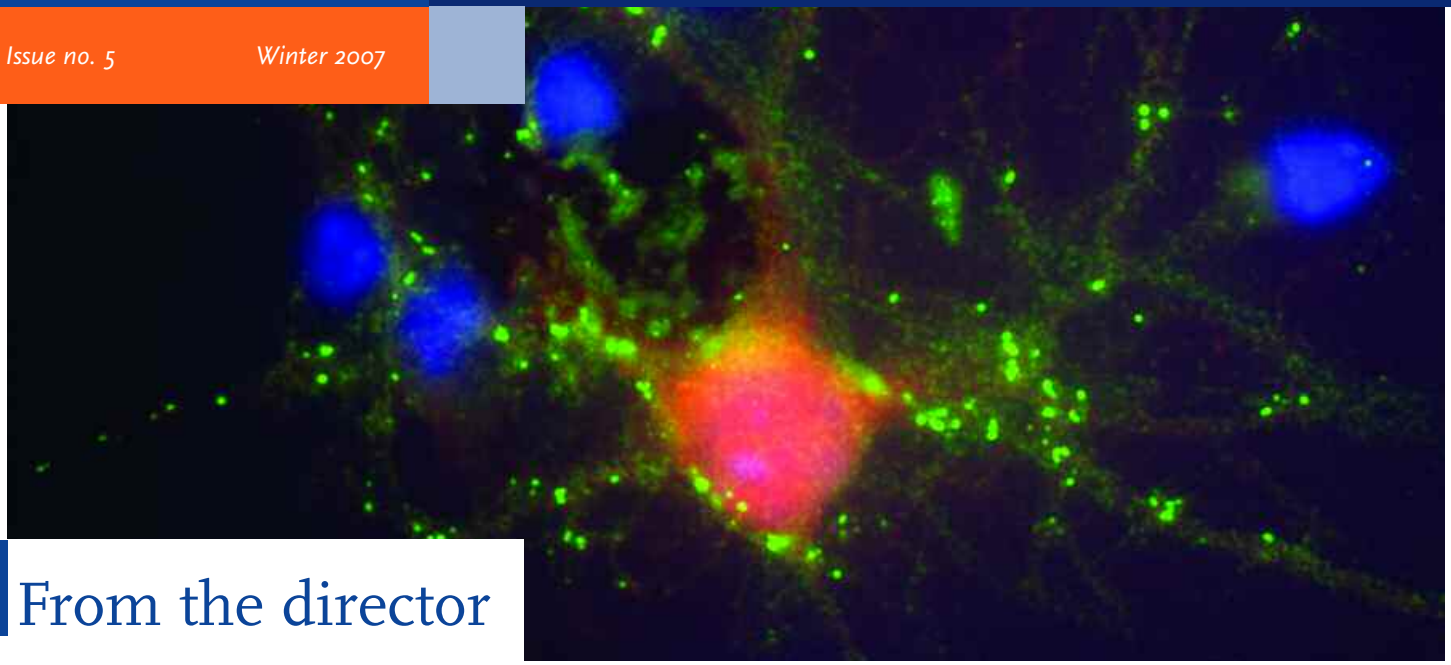


From the director

It is often the case that basic research leads to unforeseen new insights into clinical disorders.

Above: Cultured neurons from the striatum, the largest of the basal ganglia. The cells have been stained to reveal the presence of two signaling molecules (DARPP-32 in red and GABA A receptor in green) that play key roles in regulating the behavior of these neurons in the intact brain.

Image courtesy of Jill Crittenden and Anna Borkowska, McGovern Institute

Our feature article in this issue of *Brain Scan* focuses on one such instance of basic research yielding insights into psychiatric illnesses—Ann Graybiel's groundbreaking work on the brain structure known as the basal ganglia.

It has long been known that the basal ganglia are important for motor control, such as moving the arms and legs, and in learning habitual actions. Damage to the basal ganglia can cause loss of control over body movements and can impair the learning of new motor skills, as happens in Parkinson's disease. Ann's new research, however, shows that the basal ganglia also play a critical role in forming 'habits' of thought and emotion, which can settle into dysfunctional states. Her work suggests that certain disorders of the basal ganglia might lead to compulsive behaviors, irrational anxieties, and chemical addictions.

In the previous issue of *Brain Scan*, we discussed the importance of promoting new technologies to accelerate brain research and to link the lab bench to the bedside, where research can benefit patients. In this issue, I'm happy to introduce the person who will help us make that happen, Charles G. Jennings, Ph.D., who is directing our newly created McGovern Institute Neurotechnology (MINT) program. We're excited about Charles's goal of promoting new collaborations between neuroscientists, engineers, and clinical researchers, both within MIT and in the broader scientific community in and beyond Boston.

I'm also pleased to announce a wonderful new gift to the Institute from Bard Richmond, MIT class of 1972. Bard has chosen to support an important research initiative here in a way that holds personal significance to him, having three school age children. He is supporting a new project (described inside) led by Nancy Kanwisher and John Gabrieli to study dyslexia in children who are learning to read. This project provides another example of how basic research on brain functions can enhance our understanding of brain dysfunctions, or in this case, a learning disorder that affects millions of children.

Bob Desimone, Director

HABITS, ADDICTIONS, AND HUNTINGTON'S DISEASE

By following the trail of rats in a maze, Ann Graybiel has discovered a surprising source of human emotional 'habits' in the brain. That discovery also has bearing on psychiatric and neurodegenerative disorders.

Ann Graybiel

For the past 30 years, Ann Graybiel has studied the basal ganglia, a cluster of structures that lie buried deep within the brain. Less well known than the cerebral cortex, and difficult to study because of their concealed location, the basal ganglia are nevertheless turning out to be of profound importance to brain function.

Clinical neurologists have long been interested in these brain structures because of their role in a variety of brain disorders, including Parkinson's and Huntington's disease.

Graybiel's fascination with the basal ganglia traces back to 1978, when she first showed that the striatum, the largest of these ganglia, is actually composed of two intermeshed tissue types, which she termed the 'striosomes' and 'matrix'. She has continued to study these structures ever since, using techniques ranging from anatomy to molecular biology to electrophysiology, to understand what the basal ganglia do and how they go awry in disease.

The traditional view of the basal ganglia, which dates back at least a century, was that they are mainly involved in the control of movement. Graybiel's work, however, suggests a broader view. It now appears that the basal ganglia are involved in a much wider range of behaviors than previously appreciated, including the formation of many types of habits, not only of movement but also of thought and emotion.

In Search of Chocolate

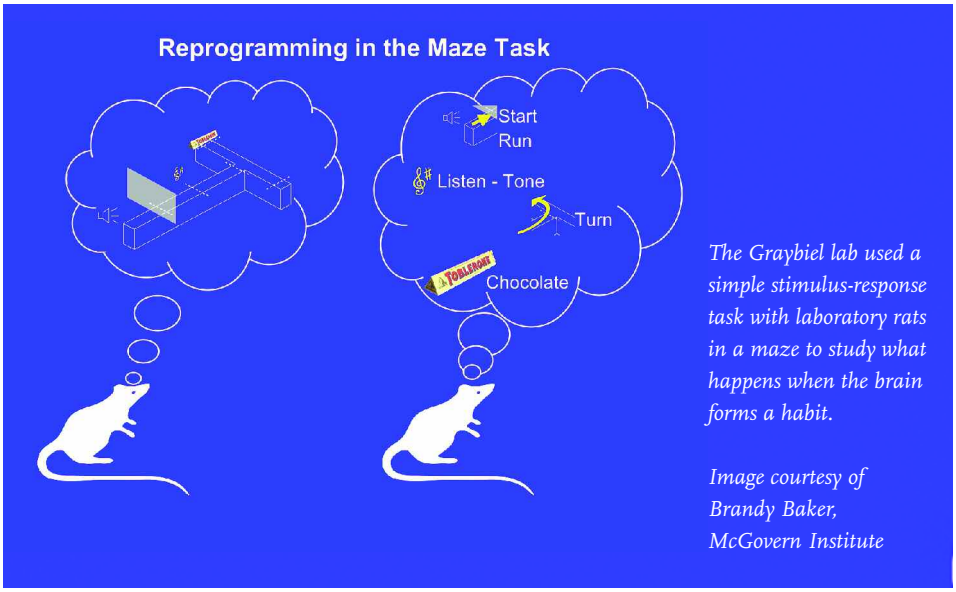
A key piece of evidence for the importance of the striatum in habit formation comes from a 2005 paper that Graybiel published in the journal *Nature*. This study was based on a recent technological advance, the development of miniature recording devices known as tetrodes that can monitor the activity of hundreds of neurons

simultaneously. Tetrodes are small enough that they can be attached to the head of an experimental animal such as a rat without impeding its ability to move around and explore its environment. Using such a device, Graybiel and her colleagues were able to listen in on the activity of the striatum as the rats learned to navigate a simple maze in search of a reward—in this case, a small piece of chocolate.

As the rats approached the decision point, they heard a brief sound, either high or low in pitch, which indicated the location of the chocolate. Their task was to discover by trial and error which way to turn in response to these different cues.

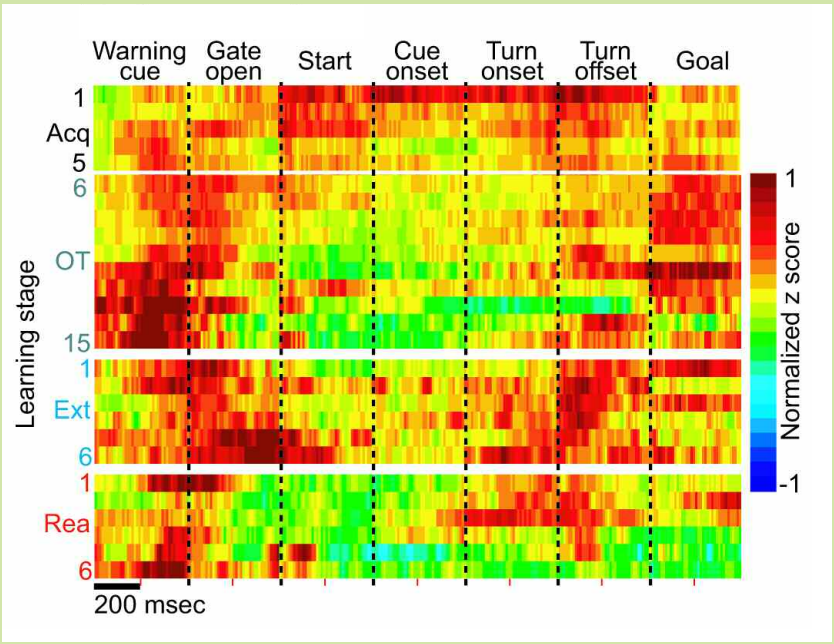
In the early trials, when the rats were still uncertain what to do, many striatal neurons were strongly active throughout the task period. As the animals mastered the task, however, the level of neuronal activity was much reduced, particularly during the middle phase of the task when the animals were making the critical choice between the correct and incorrect paths. If the researchers confused the rats by taking away the chocolate, the striatum once again became active when the animals reached the decision point. The researchers were able to do this repeatedly, and with each cycle they found that the activity of the striatum tracked the unlearning and relearning process.

It seems, then, that the striatum is somehow involved in this trial-and-error learning, and in the process by which a learned behavior eventually becomes automatic. Graybiel suspects that the human striatum is doing something similar. Like rats, humans learn through trial and error, and it is an everyday experience that many tasks that initially require intense concentration—driving, for example—eventually become almost subconscious. A role for the striatum in habit formation may also account for the effect of drugs of abuse such as amphetamine or cocaine. These drugs profoundly affect the striatum, along with other basal ganglionic structures. If the drugs somehow 'hijack' the striatum's normal role in the formation of new habits, this could explain why experimentation with these drugs—which are often described as 'habit-forming'—leads so easily to addictive behavior.



The Graybiel lab used a simple stimulus-response task with laboratory rats in a maze to study what happens when the brain forms a habit.

Image courtesy of Brandy Baker, McGovern Institute



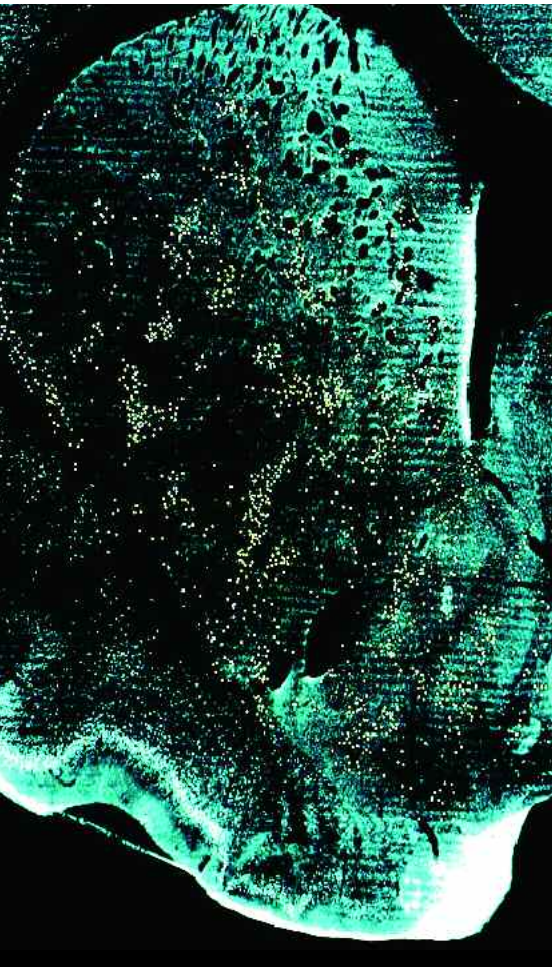
Graphic representation of neural activity in the rat striatum during maze learning (red is highest activity, blue is lowest). The stages of the task (hearing the tone, finding the chocolate, etc) are depicted along the horizontal axis. Each row corresponds to one trial, and the vertical axis corresponds to the progression of learning, unlearning, and re-learning over the course of many trials.

Image courtesy of Terra Barnes et al, McGovern Institute

A Role In Mood Control

The importance of the basal ganglia in the control of action is well established. But the basal ganglia make connections not only to the motor parts of the cortex, but also to the limbic areas that control our emotional state. This would seem hard to explain if the sole purpose of the basal *con*ganglia is to control movements. But it may help to make sense of a longstanding puzzle. Although Huntington's and Parkinson's disease are primarily movement

continued, page 4



Microscopic image of a section through the rat striatum, a brain region that is an important target for many drugs of abuse. The white dots indicate where a gene called fos is switched on after the animal receives a shot of amphetamine. The dots are clustered in particular structures within the striatum known as striosomes, which were first described by Graybiel.

Image courtesy of Ann Graybiel

disorders, they are sometimes accompanied by disorders of mood—not merely the natural despondency that is to be expected after receiving a diagnosis of a serious disease, but also psychiatric symptoms such as obsessive behaviors, irrational anxieties, or clinical depression. Could damage inflicted by the disease on the basal ganglia also explain these symptoms?

In a paper published in January 2007 in the journal *Brain*, Graybiel has begun to test this idea. In collaboration with a group of clinical researchers in New Zealand, she decided to investigate why some Huntington's patients develop mood disorders while others do not, and to see if the basal ganglia might somehow explain this difference.

The New Zealand team, led by Richard Faull at the University of Auckland, had a longstanding interest in Huntington's disease, and over the years had accumulated a large collection of postmortem human brains. Graybiel and her collaborators examined brain tissue from 35 Huntington's patients, comparing these samples with control brains from patients of similar age who had died of unrelated causes. They knew that the Huntington's patients would show damage to the striatum, but they were now seeking differences in the detailed pattern of damage that might explain the different clinical symptoms. In particular, they looked for differential effects on the two components of the striatum that Graybiel had described some thirty years earlier—the striosomes and the matrix. Sure enough, these components were not affected equally in every patient. In some cases the damage was mainly confined to the striosomes, in others it was mainly in the matrix, while a third group showed similar levels of damage to both areas.

To find out whether these different types of damage might explain the different symptoms, a second group of researchers conducted interviews with the families of the deceased patients. By using a carefully structured interview, the researchers were able to reconstruct the patients' symptoms. They recorded detailed accounts of the patients' motor problems and the presence or absence of mood abnormalities – anxiety, depression, obsessive behaviors, irritability, and so forth—and were able to rank the deceased patients according to the severity of both classes of symptoms.

To avoid unconsciously biasing the results, neither team was allowed to know the other team's findings as they were collecting their own data. Only at the end, when the measurements were complete, did the researchers break the code. When they did so, a clear pattern emerged. The samples that showed the most striosome damage were from the patients with more severe mood dysfunction, and less severe motor problems. This finding suggests that the patients' symptoms during the course of their disease differ depending on which specific circuits within the striatum are disrupted by the degenerative process.

So what does maze learning in rats have in common with the disorders of movement and mood that afflict Huntington's patients? More than you might think, according to Graybiel. Habits are not just about movement; we also develop habits of thought and of emotion. Just as we perform many sequences of actions as if on auto-pilot, we also follow particular trains of thought, and even feel certain emotions, habitually and unthinkingly. Even though the mental content of these brain functions seems quite different, a common thread uniting them may be that complex sequences, whether of movement or thought or feeling, are initially learned and eventually become automatic. This, Graybiel suspects, may be the true purpose of the basal ganglia.

Understanding the role of the basal ganglia, in health and disease, is a lifelong quest for Graybiel. Their importance in Parkinson's and Huntington's disease is well established, as is their role as targets for many drugs of abuse. But there are many other conditions—Tourette's syndrome, obsessive-compulsive disorder, and autism, for example—that involve stereotypical sequences of movement or thought, and the basal ganglia may also hold the secret to understanding these conditions. And in addition to helping us understand some diseases, Graybiel believes, the basal ganglia have much to teach us about our own personalities—for example, why old habits die so hard. ■

Article by Charles Jennings

You can read a new release about the habit study at: http://web.mit.edu/mcgovern/html/News_and_Publications/0510_graybiel.shtml.

Charles Jennings At Helm of Institute's New Neurotechnology Program

In December 2006, the McGovern Institute welcomed Charles G. Jennings, Ph.D., as Director of the newly created McGovern Institute Neurotechnology (MINT) program. The MINT program is an evolving concept, based on the vision that progress in neuroscience is driven by the development of new technologies. The McGovern Institute hopes MINT can drive this process through collaborations with labs from other disciplines, both inside and outside MIT. The new program will help to establish these collaborations and will provide seed funding for new projects.

"Progress in brain research has always gone hand in hand with the development of new tools," explains Jennings. "If you trace back the history of today's technology, you find it often came from people in other fields who were also interested in neuroscience and brought their expertise to bear on technical challenges."

A key goal of the MINT program, says Jennings, will be to develop new methods for measuring, stimulating, and imaging brain activity. He also hopes to take advantage of advances in human genetics, and to establish collaborations with geneticists and clinical researchers who are studying brain diseases. "One of our hopes is to develop technologies that will be useful to the biopharma industry and that can contribute to the development of new therapies."

To create a strategic 'taxonomy' of areas for technological collaboration and to prioritize them for the MINT program, Jennings is talking to McGovern researchers about their challenges and future aspirations. Meanwhile, he is also looking outward, with an eye towards identifying potential collaborators. "It will be about relationship building," he says of the program. "We need to get people excited about what we do, and about the opportunity to have an impact on understanding the brain and brain disorders."

Jennings already knows something about neuroscience at MIT, thanks to his graduate and post-graduate training as a neuroscientist and his 11 years as editor at the journal *Nature*. Before becoming an editor, he was a postdoctoral researcher in the Biology department at MIT. While at *Nature*, he launched the journal *Nature Neuroscience*. As a result, he says, "I got to know many of the top people in the field, including most of the McGovern faculty members. So I'm already feeling quite at home here."

After he left *Nature*, Jennings was recruited to Harvard University to become the first executive director of the new Harvard Stem Cell Institute, where he helped to set up the institute and to shape its scientific strategy. He then did a year-long stint as a private consultant; his clients included the Seattle-based Allen Institute for Brain

Charles Jennings, Ph.D., Director, McGovern Institute Neurotechnology Program

Science and several other academic organizations and biotech companies. He continues to serve on the advisory committee for the Connecticut Stem Cell Research Program.

For Jennings's creation of the MINT follows a logical path, given the increasingly interdisciplinary nature of modern biomedical research. "Traditional boundaries are breaking down," he says, "and a lot of the most exciting stuff happens at the edges." ■

Read more about Jennings's plans in the February 5, 2007 Technology Review. http://www.technologyreview.com/Biotech/18137/

On December 7, 2006, Bob Desimone joined Debra Wise, artistic director of the Underground Railway Theater, for a post-performance conversation about the play "On Ego", a play about the neural basis of the self.

Image courtesy of Henry Hall, McGovern Institute

Emilio Bizzi: Taking the Helm of the American Academy of Arts and Sciences

When Emilio Bizzi was elected President of the prestigious American Academy of Arts and Sciences last year, he had already served the Academy as Secretary from 1998 to 2005. He joins a long, distinguished roster of scholars in this national honor society. The Academy was founded by John Adams and other 'scholar-patriots' in 1780. In the 227 years since, it has examined issues at the interface of science, technology, and policy, as well as the arts and humanities. "I like this organization because it brings together excellent people from every walk of life for the public good," says Bizzi, who is an MIT Institute Professor and and member of the National Academy of Sciences and Institute of Medicine. "It's also independent and is not influenced by external powers."

Emilio Bizzi
President, American Academy of Arts and Sciences
Photo by Martha Stewart, AAAS

Bizzi plans to draw on the Academy's tradition of offering cross-disciplinary, informed analyses of persistent problems and new challenges facing the nation and the world. In recent years, for example, the Academy became involved in the issues of nuclear disarmament and universal childhood education. Bizzi will guide the Academy in constructing projects and studies in areas where the interaction of academic, business, and government leaders can have the greatest impact. "The Academy is good at this because it can rely on its very diverse members," he explains.

One of Bizzi's first projects as President was to organize a symposium at the Academy on the use of brain imaging for truth detection. Strong claims have been made for the potential of functional magnetic resonance imaging (fMRI) to determine whether or not a person is telling the truth, notes Bizzi, so it is important to evaluate the evidence scientifically. The symposium, which was held on February 2nd and was cosponsored by the McGovern Institute and Harvard University, convened a panel of scientific and legal experts to examine the scientific feasibility of fMRI-based truth detection, as well as the legal, ethical and privacy issues that such technology would raise.

The consensus of the panelists, including McGovern Investigator Nancy Kanwisher, was that this approach is at best premature. Summarizing their discussions in a letter to the *New York Times*, Bizzi wrote "The consensus view...is that one should be careful not to invest too much faith in the capacity of brain imaging to reveal individuals' true motives and motivations; it is far from the silver bullet for law enforcement, prosecutors or defense attorneys that its champions claim." The Academy plans to issue a report for Congress and other policy makers based on the symposium.

For a summary of the symposium see the MIT Tech Talk article at http://web.mit.edu/newsoffice/2007/lying.html.

Recent Events

- Sheng He, Ph.D., (University of Minnesota) discussed on March 14, 2007 how the visual system processes 'invisible' visual information without our conscious awareness.
- Yves Agid, M.D., Ph.D., (Hôpital de la Salpêtrière, Paris) spoke on February 13, 2007 about the role of the basal ganglia in emotional disorders and how new deep brain stimulation devices provide a means to treat some of these disorders.
- Ed Callaway, Ph.D., (Salk Institute for Biological Studies) described on November 29, 2006 a new genetic method he is developing to study the intricate sub-networks of cortical neurons at level of detail barely imaginable a few years ago.
- The McGovern Institute and the MIT Department of Brain and Cognitive Sciences sponsored a symposium on Scene Understanding on February 1-2, 2007.

Save the Date

The McGovern Institute will sponsor a Brain Imaging Symposium on May 15, 2007. Details are posted at: http://www.mit.edu/mcgovern.

In Other News

Nancy Kanwisher's research was described in special issues on the brain in the December 23, 2006 *Economist Magazine* and the January 29, 2007 *Time Magazine*. She also appeared on the Charlie Rose Science Series in late October 2006 to discuss cutting edge neuroscience. http://www.pfizer.com/pfizer/think/mn_think_cr_science.jsp.

Bard Richmond Gives to Dyslexia Research

A generous donation by Bard Richmond, class of 1980, is funding a 3-year, first-of-its-kind research project at the McGovern Institute exploring the brain mechanisms underlying dyslexia. The project will study what happens to a recently discovered brain region that selectively recognizes written letters as children learn to read. Project leaders Nancy Kanwisher and John Gabrieli will compare that brain region, called the Visual Word Form Area (VWFA), in children with typical reading abilities to those with dyslexia. (See article on back cover.)

"Bard Richmond's donation and involved curiosity catalyze our efforts to understand how reading ability develops in the brain, and how this development goes astray in children who have difficulty in learning to read," says Gabrieli.

"I have three children approaching the age of reading, so this dyslexia project piqued my interest," Bard explains. "Also, reading and education problems are often politicized and not always handled scientifically, with real data." He was impressed that the project could be expanded as the investigators make their findings, and that it could lead in many directions for exploring other brain mechanisms. Bard named the grant the Martin Richmond Memorial Fund for his father, Martin Richmond, a "profoundly intuitive engineer" with more than 30 patents in radar electronics.

Bard Richmond with his wife, Julie, and sons Eli (6), Owen (4), and Max (6).

Bard has not only met with investigators about the project, he has also had the same fMRI testing at the Martinos Imaging Center at the McGovern Institute that the children in the project will undergo. "I lay in the scanner and had to tell whether sequences of either letters or nonsense characters were the same or different," he recalls. "Some were hard, and I suspected my VWFA was not lighting up. When they were easy, it seemed I was feeling a natural ability in my brain."

Bard entered MIT with the Class of 1972, but left to play bass guitar with the Road Apples. The band had a hit record and opened at the Boston Garden for the band Boston (founded by Tom Scholz, '69 ME). Bard returned to MIT to finish his degree in computer science and engineering. In 1983, he co-founded Active Voice Corporation, which became the leading manufacturer of PC-based voice processing systems and went public in 1993. It was named among the best small companies by *Forbes* and *BusinessWeek*. In 1999, Bard received the Presidential Service Award for establishing the free Community Voice Mail Program, which gave the homeless phone numbers for retrieving messages from potential employers. Cisco Systems bought Active Voice for nearly $300M in 2001.

Bard hopes the project will enhance the understanding of how dyslexia is related to the VWFA's development, how normal processes are subverted, and possibly how to train the dyslexic brain for better reading. "It would also be nice to know why the ability to recognize written letters migrates to that specialized area of the brain," he adds. "And how did evolution favor the mental equipment that enables reading?"

New Gifts

We are grateful to the following donors for recent gifts to the McGovern Institute:

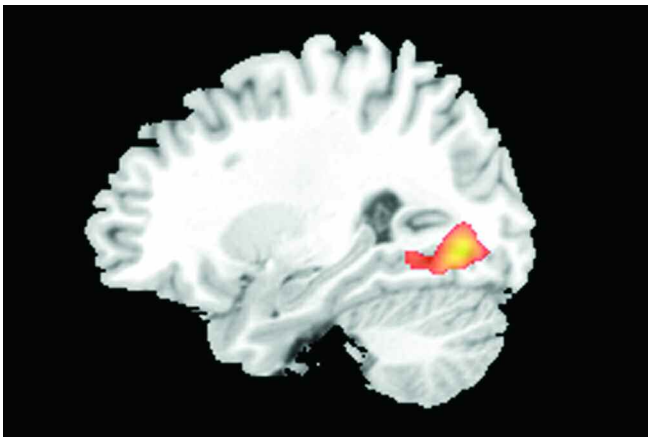
David Bleakman
Kelly and Elizabeth Conlin
Eric Cosman
Patricia and Robert Dettmer
Howard Finkelstein
Richard Hargeaves of Merck
Ira Jaffe
Paul Marcus
Carina Ryan
Gary and Jane Trudeau
Michael and Andrea Norkus
Geoffrey Sholkin
Howard Sholkin

THE DYSLEXIA PROJECT

Dyslexia is a complex learning disorder that manifests itself as reading difficulty despite adequate education and otherwise normal perceptual and intellectual abilities. A functionally and anatomically distinct brain region called the Visual Word Form Area (VWFA), which responds selectively to letters, may help explain the brain mechanisms involved. Surprising, no one has compared the development of the VWFA in typical children and dyslexic children as they learn to read. Now, Bard Richmond ('80 CS and Eng) is making such a study possible by funding a collaboration between Nancy Kanwisher, who has expertise in discovering the neural organization of high-level vision, and John Gabrieli, who uses brain imaging to study the brain basis of learning disorders.

The precise role of the VFWA in reading has been under intense debate, but Kanwisher's recent discoveries provide an opportunity to study it more systematically. She showed that the VFWA responds selectively to learned language characters—rather than to other meaningful stimuli such as line drawings, or to characters from unknown languages. Therefore, this area must grow to be specialized for letters as children learn to read.

The project will first determine baseline information about the VWFA by examining how it develops in typical-reading children from age 7-18, and relate the growth of this area to standardized tests of reading and language ability. Next, the researchers will compare the VWFA between children with and without dyslexia, ages 8-10, along with reading skills. They will also relate the fMRI and reading skill to measurements of cortical thickness throughout the brain as well as diffusion tensor imaging (DTI) of the white matter connectivity in the brain. The results may tell whether VFWA is the perceptual gate that initiates specialized processing of letters and words and reading.



In typical children, the VWFA activates during reading, while fMRI scans show virtually no activation in dyslexic children.

FMRI image (sagittal view) courtesy of Fumiko Hoeft in John Gabrieli's former lab at Stanford University.

The McGovern Institute at MIT is a neuroscience research institute committed to improving human welfare and advancing communications. Led by a team of world-renowned, multi-disciplinary neuroscientists, The McGovern Institute was established in February 2000 by Lore Harp McGovern and Patrick J. McGovern to meet one of the great challenges of modern science—the development of a deep understanding of thought and emotion in terms of their realization in the human brain.

Additional information is available at: http://web.mit.edu/mcgovern/

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