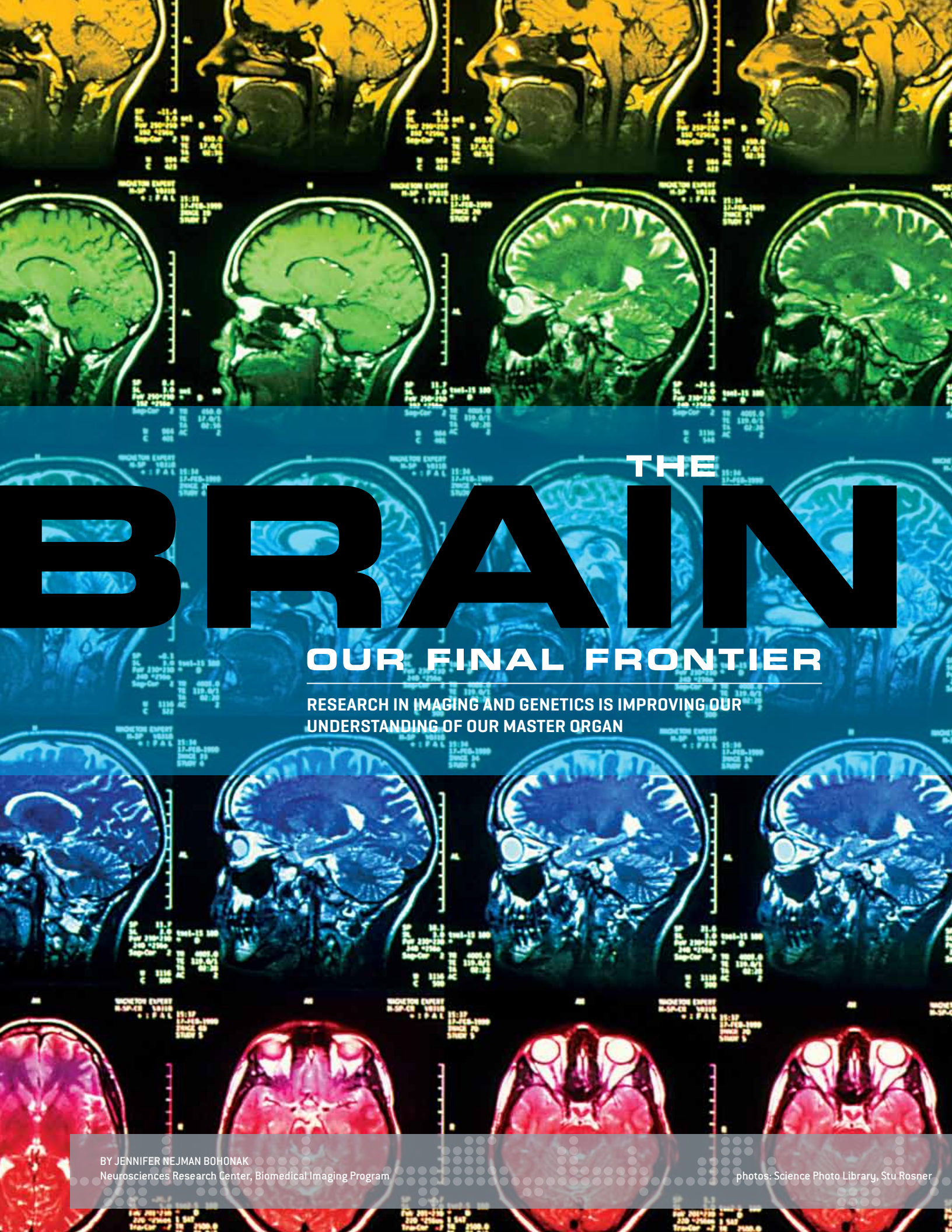


THE BRAIN

OUR FINAL FRONTIER

RESEARCH IN IMAGING AND GENETICS IS IMPROVING OUR UNDERSTANDING OF OUR MASTER ORGAN

BY JENNIFER NEJMAN BOHONAK
Neurosciences Research Center, Biomedical Imaging Program

photos: Science Photo Library, Stu Rosner

The brain is maestro of the body's orchestra of nerves, organs, and limbs. With grace and precision, this master organ inspires and coordinates performance after performance, every moment of our lives.

Through our brain, we interact with the world outside our bodies, and we guide ourselves.

"The brain mediates and underlies all thought and feeling and every sphere of human experience," says David Silbersweig, MD, chair of the Department of Psychiatry at Brigham and Women's/Faulkner Hospitals and chair of the Institute for the Neurosciences. "It is what, through evolution, makes us who we are, and allows us to be able to even ask questions about who we are."

To understand the conductor of our mind and body, we need to be able to see what is going on. With imaging machines, we can safely look inside to study the brain, heart, and other organs. The hope is that through imaging research, we might be able to find connections between disease processes in seemingly unrelated conditions, such as depression and heart disease.

By harnessing imaging and genetic research tools, one day we may be able to alert patients of their risks and intervene—long before they experience symptoms.

If we could intervene in schizophrenia, multiple sclerosis, and Alzheimer's disease before these conditions have taken their toll, we might be able to ease suffering and help people live longer, healthier lives. For mental illness, improved treatments could mean preventing suicides, hospitalizations, mental suffering, family turmoil, and loss of income from disability.

FIGHTING STIGMA WITH SCIENCE

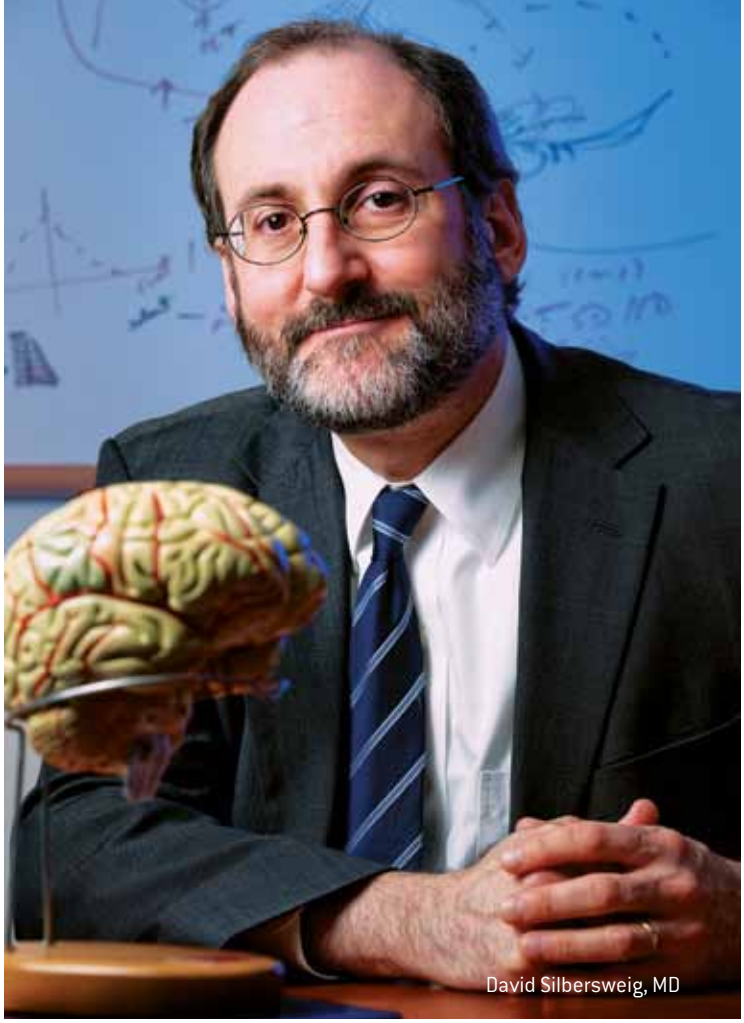
In the United States, one in four adults, 57.7 million Americans in total, will have a diagnosable mental disorder during any given year, according to the U.S. National Institute of Mental Health.

Sadly, even today disorders of the mind carry a stigma that affects both those who live with mental illness and their loved ones.

"If someone has a psychiatric disorder, they have a double hit. They not only suffer tremendously and poignantly, but they're misunderstood and blamed very often—as if it's some moral failing or some weakness, or they should pull themselves up by their bootstraps or snap out of it. That's just as ridiculous as saying that someone with a kidney stone should snap out of it," Silbersweig says.

He believes that one of the most effective ways to reduce societal stigma is through science. If we can understand the biology of mental illness, we can create better treatments, shatter stereotypes, and objectively examine the disease process.

Emily Stern, MD, director of the functional neuroimaging laboratory at BWH, is using imaging to study premenstrual dysphoric disorder


David Silbersweig, MD

(PMDD), a condition some people have claimed is not real or tagged as only psychological. The disorder—more severe than the better-known PMS—causes disabling mood and behavioral changes, resulting in women having problems at work and in relationships. PMDD is estimated to affect between 2 and 8 percent of women.

Stern and her colleagues are studying women diagnosed with the disorder and women who have steady emotions. In this ongoing National Institutes of Health–funded study, they are seeking information about the location of hormonal changes; how the brain responds; individual predispositions; and where dysfunction exists.

The women's brains are scanned when they are premenstrual and postmenstrual using a technique called functional magnetic resonance imaging (fMRI). While in the fMRI, the women view words that evoke emotions and press buttons. Similar to a stress test that measures the heart's capacity, through fMRI, researchers test the brain's systems, circuits, and functions.

FMRI allows researchers to look noninvasively at the pattern and location of brain activity—at rest, and in response to particular mental tasks—and begin the creation of brain maps. With the advanced technology and analytic tools, Stern and her colleagues track blood flow and oxygen changes that occur when the brain's neurons are active and using more energy, blood, and oxygen.

Stern and her colleagues proved that parts of the brain's frontal lobe (the section that sits behind your forehead) are more active during a

woman's premenstrual phase, even if the woman has no symptoms. These areas help to regulate emotion, which remains stable in women who do not have PMDD. Stern explains that the brain works harder during a woman's premenstrual phase, so women who do not have the disorder will not experience symptoms.

The study found abnormalities in the brains of women diagnosed with premenstrual dysphoric disorder. Researchers pinpointed changes within the orbitofrontal cortex, in an area that mediates the interaction of emotion and behavior, particularly negative emotions and the inability to control impulses. They also found abnormalities in the amygdala, an area associated with fear-conditioning and negative emotions, and in the nucleus accumbens, which is involved in positive emotions and rewards.

BWH's Jill Goldstein, PhD, and her research colleagues are also using fMRI. They are investigating how fetal antecedents—risk factors for diseases that develop during pregnancy—relate to sex differences in psychiatric disorders.

Her team is studying fetal antecedents to sex differences in adult psychoses and depression, as well as shared fetal antecedents to depression and cardiovascular disease. The findings will be important for the development of sex-specific hormonal and immunoregulatory treatments and also for sex-specific prevention strategies.

INSIDE OUR MINDS

FMRI uses thousands of pictures and mathematics to pull out patterns and highlight areas in the brain associated with a change in cognition, emotion, perception, behavior, or interactions of these processes, as well as what happens when something goes awry.

BWH researcher Seung-Schik Yoo, PhD, MBA, who directs fMRI services, plans to use fMRI to gather data from people in real time. His theory is that if you know what's happening in the brain because you can see a high-resolution image as the person is in the fMRI scanner, then you can work on a better rehabilitation strategy.

Yoo gives the example of a stroke patient. Often, a stroke patient will have trouble moving one arm due to damage in the responsive brain area.

When the patient tries to grab something with the nonresponsive hand, the patient often unwittingly engages the opposite, undamaged part of the brain to assist with that movement. But if the patient could see a functional image of the brain, the patient might be able to figure out where and how to get the correct brain cells working to take over the role of the damaged brain cells.

This theory might also have implications for controlling addictions because it examines modifying brain function associated with substance abuse, Yoo says.

LINKS BETWEEN DISEASES, INFLAMMATION, AND GENES

At BWH, physicians and scientists are working together on common research themes, says Martin Samuels, MD, neurologist-in-chief of BWH's Department of Neurology. "I don't think there is another place that has a truly integrated program in neurology, neurosurgery, psychiatry, neuroradiology, and neuropathology that spans clinical care, training, and research," he says.

He points to two theories researchers are investigating that link diseases in a broader way than previously considered—inflammation and shared genes.

One collaborative goal is to study the effect of neuroinflammation on brain-mind disorders. Neuroinflammation may play a role in a wider range of neuropsychiatric conditions than previously thought, which could open the door to new therapeutic possibilities, Silbersweig says.

Researchers want to know: Is inflammation a common underlying pathophysiologic mechanism in many neuropsychiatric conditions? Are people depressed because they have heart conditions, are stressed, and don't feel well? Or are they depressed because the mechanism that is contributing to their heart problem is also making them depressed by affecting circuits in the brain that control mood?

For conditions like multiple sclerosis, evidence already exists of an inflammatory process in the body. But for others like epilepsy, schizophrenia, or psychotic disorders, finding a link to inflammation would be a breakthrough.

In essence, excess inflammation is a miscalculation by the body of how much help it needs to heal itself. While some inflammation is natural, too much can have disastrous effects.

BWH researchers use tools such as positron emission tomography (PET) to scan the brain to study the inflammatory process.

Stern and her colleagues use 11C-PK11195—a radioactive molecule that helps them to make images of neuroinflammation in the brain with PET. Magnetic resonance imaging (MRI) techniques are also used to study neuroinflammation. BWH's Martha Shenton, PhD, analyzes neuroinflammation in patients through the use of diffusion imaging, a novel MRI procedure. With funds from a recently awarded traumatic brain injury grant, Stern and Shenton, the grant's principal investigator, will use imaging to study patients who have head injuries caused by vehicle accidents or sports.

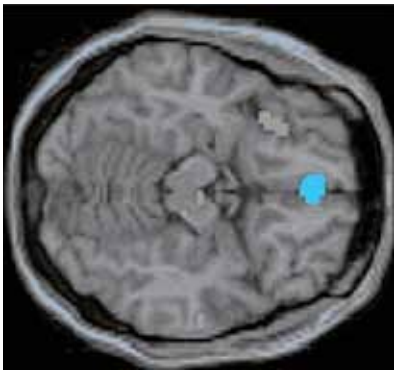
The goal is to study inflammation, over time, in injured patients. Stern says if researchers learn that too much inflammation is harmful, possible treatments include anti-inflammatory drugs or other interventions. Many soldiers with traumatic head injuries, who are otherwise young and healthy, are returning home from Iraq and Afghanistan and could benefit from improved treatments, Shenton says.

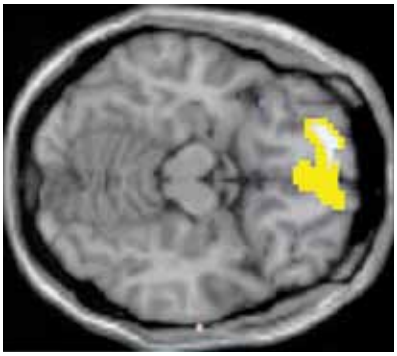
THE FUTURE

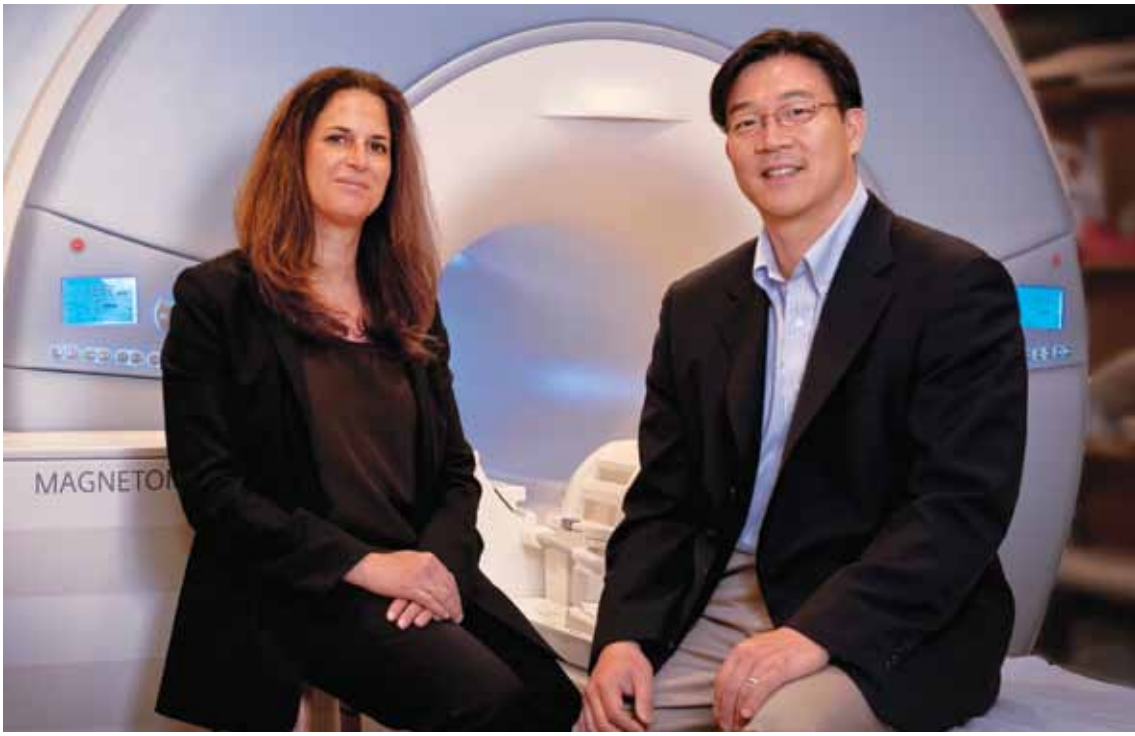
The hope for all of medicine, and especially for clinical neuroscience, is that in the future, physicians will have the ability to treat a person based on individual genetic and biological profiles.

In addition to inflammation, the interplay of variation in an individual's genes and environmental risk factors can ultimately trigger the disease process, says Philip De Jager, MD, PhD, director of the Program in Translational Neuropsychiatric Genomics in BWH's Department of Neurology and Psychiatry.

photo: Stu Rosner







[Left] These functional magnetic resonance imaging (fMRI) pictures illustrate differences in brain activity between women experiencing premenstrual dysphoric disorder (PMDD) and those who do not have the disorder, which can cause disabling mood and behavioral changes. Women with PMDD (top image) show decreased activity in their frontal lobe, displayed in blue. In women who do not have PMDD (bottom image), there is more activity, shown in yellow, in areas that are helpful in regulating negative emotions and controlling impulses.

[Right] Emily Stern, MD, and Seung-Schik Yoo, PhD, MBA, in a BWH lab with the fMRI equipment they use to study brain activity.

"One fascinating story that's emerged over the past few years is that while diseases like type 1 diabetes, multiple sclerosis, and lupus, for example, look very different and affect different organ systems, they share a remarkable number of genetic risk factors," De Jager says.

Strides have been made for certain breast cancer genes, but for mental illness treatment, doctors must rely on descriptive categories, not biological markers, when prescribing medication. Antidepressants can take four to six weeks to kick in. If the medicine prescribed doesn't work, it becomes a race against time, Silbersweig explains. The healthcare provider could try another medication, but by then weeks could have passed—and the patient may be suicidal.

Today, new approaches to treating depression and other brain disorders are being developed at BWH as well, including neurological deep-brain stimulation of key brain circuits using mild electrical signals that can help manage symptoms of mental illness.

And BWH researchers are working on ways to predict who might be at risk for mental illness. If doctors could alert patients of their genetic risk earlier, then patients could seek treatment when they first notice symptoms. Healthcare providers could offer cognitive therapy, a process of teaching a person how to alter negative thought patterns. One day, there may even be personalized treatments to prescribe.

We live in an era in which we can continue to pose the questions about life that philosophers and scientists have asked for thousands of years, Silbersweig says. Why do some people get sick? Why do we react differently to traumatic situations? We ask these questions because, through evolution, we have developed a brain with the ability to do so, he says.

And today, we have the imaging and research tools that allow us to better understand and help our maestro. ●

HISTORIC STRIDES

BWH has a long history of leading advances in the fields of neurology, neurosurgery, and psychiatry. In 1913, the Peter Bent Brigham Hospital, one of BWH's founding institutions, named Harvey Cushing, MD, who is considered the founder of modern neurosurgery, its surgeon-in-chief. One of Cushing's first interns at the Brigham, Stanley Cobb, MD, helped create the field of modern neurology and psychiatry in the United States. He was the first to classify anorexia nervosa as a disease in its own right, and not a manifestation of schizophrenia. Today, David Silbersweig, MD, is chair of the Department of Psychiatry at Brigham and Women's/Faulkner Hospitals and the Stanley Cobb Professor of Psychiatry at Harvard Medical School.

To make a gift to benefit mental illness treatment or other brain research, please contact Kristin Garrity in the BWH Development Office at 617-424-4325 or **kgarrity1@partners.org**.