Neuroscientists, engineers, psychiatrists, applied mathematicians, surgeons, and other experts explore how we hurt, how we fear, how we see, how we connect, and how we learn.

**NOT QUITE A DECADE AGO**, when Professor of Neuroscience Diane Lipscombe P’14 began to look into the neurological roots of pain, she briefly thought that she must be overlooking seminal swaths of literature. “It’s a really difficult problem, and so pervasive,” she says. “You think ‘Oh, we must know a lot about pain, I must not be reading the right things, this must already be known...’ but there are, in fact, fundamental aspects of pain that are unknown.”

Indeed, Lipscombe would discover that remarkably little was understood about how perception of pain is “produced” at the neuronal or synaptic level—a lack of knowledge that, she believes, may inform a societal tendency to dismiss the phenomenon. “Pain is sometimes described as being ‘all in your head,’” she says. “Well, of course it’s in your head. But that doesn’t mean it’s not real.”

The prospect of exploring a vast landscape of uncharted scientific territory, in an area with enormous clinical and social implications, drew Lipscombe in. “Pain is a major public health problem,” she says. “It crosses so many major disorders and diseases, from HIV to diabetes. It erodes productivity, and it can destroy quality of life. There’s an increased suicide rate among people who suffer with chronic pain. There’s a real need for new ideas and new treatments.”

Lipscombe is best known for her research on the cellular mechanisms that drive the function of calcium ion channels, which regulate many critical neuronal functions such as transmitter release, nerve growth, and synaptic plasticity. She believes that the work will enhance understanding of mental illness, as well as pain—while
possibly helping to identify new drug delivery methods.

ILLUMINATING PAIN

For the past year, Lipscombe has also been collaborating with Professor of Medical Science Julie Kauer to overcome a major technical obstacle that has impeded researchers’ progress in the study of pain. The two, soon to be joined by Associate Professor of Neuroscience Christopher Moore, are investigating a method for isolating the neural pathways that carry the pain response from those that transmit other sensations, such as touch or warmth, so that they can be clearly observed and tested.

“We’re exploring use of optogenetic techniques to study pain pathways using a light source,” Lipscombe explains. “That will allow us to look at the synapse during the pain response and see what the signal looks like, how effective the synapse is, and if the synapse changes its efficacy in response to different types of activity.”

Lipscombe and Kauer are particularly interested in the process that converts acute pain to chronic pain—a remodeling of the pain pathways, commonly experienced by people with spinal cord injuries and peripheral neuropathy, among other conditions, that can generate chronic pain from the physical echo of a previous acute episode or injury. They suspect that their research may also carry implications for other disease processes that “rewire” the neural pathways, such as addiction.

“No one has ever shown what happens when pain travels from, say, the finger to the spinal cord to the brain, and nobody really even knows if there are distinct pain pathways,” says Kauer. “Exploring the basic cellular mechanisms would open the door to understanding and possibly addressing the physiological changes underlying a number of neurological and psychiatric disorders.”

The work has been supported by seed funding from the University’s Office of the Vice President for Research and by the Brown Institute for Brain Science (BIBS), an interdisciplinary enterprise that encompasses 19 academic departments, involves more than 100 faculty members, and extends from the College to the Medical School to its affiliated hospitals. Representatives of more than 10 departments sit on the executive committee that drives the Institute’s strategic direction.

The interdisciplinary model being developed by Kauer, a molecular pharmacologist, and neuroscientists Lipscombe and Moore, as well as their use of basic science to solve problems that may affect a range of clinical areas, epitomizes the collaborations that BIBS aims to encourage. “I’m interested in receptors, Julie is an expert in the hippocampus and spinal cord, and Chris works in brain imaging,” Lipscombe says. “We will be able to follow the pain response all the way from the surface of the skin to the brain. Who knows what we might find?”

ENDOGENOUS STRENGTHS

“BIBS grew out of Brown’s culture,” says Henry Merritt Wriston Professor of Neuroscience John Donoghue PhD’80 P’09, ’12MD’16, the Institute’s director. “It sounds cliché, but things really do happen here that don’t happen in other places. We have a history of being interdisciplinary and collaborative ... of attacking interesting problems that call for diverse skills and perspectives.”

He continues: “Different disorders of the nervous system seem to have common fundamental causes, and what we do well at Brown is look at those fundamental mechanisms, which gives us insight into a broad spectrum of diseases.” He cites as an example mechanisms that seem to be shared between memory and muscular dystrophy, which Professor of Medical Science Justin Fallon P’07, ’09 is studying. “We don’t deploy major resources to target a single disease. Instead, we pursue what might on the surface seem to be wildly disparate areas that provide mechanisms that underlie a set of human diseases.”

Donoghue has been building bridges between disciplines at Brown for nearly three decades. He founded the University’s interdisciplinary Brain Science Program, BIBS’s precursor, in 1999. He has also launched and shepherded a variety of research projects—most prominently BrainGate®, an investigational technology that aims to help people who are silenced or paralyzed by stroke, neurodegenerative disease, or other challenges to communicate through the power of their brain waves, using a computer and an implanted device. BrainGate is the product of years of research by a team of neuroscientists, neuroengineers, and clinicians convened by Donoghue.

BIBS is formalizing that approach. “We make a deliberate effort to interweave our research, making it easy to collaborate, physically getting people from different fields in the same room on a regular basis, applying for grants together,” Donoghue adds. “That kind
of interaction is very special, and a real strength of Brown.”

“Brown has a long history of outstanding research in many areas of brain science,” says John Davenport, who joined Brown as associate director of the Brain Science Program in 2005 and guided its transformation to an Institute in 2009. “The most insightful advances require researchers of different backgrounds to team up, and BIBS has brought people together in fundamental science, brain health, and neurotechnology. Brown’s renewed investment means we’ll continue to take advantage of this fantastic environment and make great discoveries.”

Provost Mark Schlissel believes that, over and above its contributions to brain science, BIBS may be a model for future big-picture collaborations at Brown. “BIBS really highlights what we’re good at … bringing together bright people with a passion for problem-solving and a talent for collaboration. Significantly, BIBS brings together our whole community … those based on campus and at Alpert Medical School and our affiliated hospitals … in a seamless, very effective way. I’m hopeful that it’s the first of many initiatives to follow this model.”

In addition to providing the infrastructure to support the faculty who currently collaborate under the BIBS umbrella, the University has committed to the near-term hiring of seven additional scholars working in areas of strategic importance. (Longer-term plans call for recruitment of 14 additional faculty positions when the University can provide appropriate laboratory space to support them.) New faculty will be at once affiliated with BIBS and based in individual academic departments. BIBS’s executive committee, which participates in the search process, will seek scientists “who support the BIBS mission by bridging disciplines even as they contribute to the disciplinary strength of their home department,” explains Davenport.

“Our goal is to recruit the best people, working in fields that are most fertile for growth and discovery at any given time,” says Schlissel.

BEING HUMAN

Before backing additional investments in the Institute, Schlissel did his homework.

In 2011, freshly arrived from the University of California, Berkeley, where he was dean of biological sciences, Brown’s new Provost commissioned an objective panel of national experts to assess the strengths of BIBS and its constituent departments and to evaluate the potential for scientific contribution that a full-blown Institute might have.

“Our goal was to confirm that we did actually have something special here, and that the opportunity was as significant as we thought it was,” says Schlissel. “The conclusion was that there is an overwhelming discovery opportunity in brain science, and that our strength in the neurosciences, in psychiatry, and in other established and emerging areas positions Brown very well for important things to happen here.”

For Schlissel, himself a physician and researcher, BIBS reflects Brown’s deep commitment to exploration of the whole of the human condition while at the same time offering life-enhancing and lifesaving insights for people struggling with disease and disability.

“There is no doubt that we have the potential to help relieve millions of people from the enormous burden of devastating diseases and conditions, from psychiatric disorders to Parkinson’s disease to spinal cord injuries to learning disorders,” Schlissel says. “But it’s much broader than that. It can help us discover how the healthy brain functions, as well. BIBS provides a home for almost any scholar at Brown … whether he or she is based at Alpert Medical School or at the Granoff Center. It can show us how we see, how we experience the world, how we discern beautiful music from cacophony. It can show us how we are human.”

Finding the essence of humanity within the impossibly complex and elegant structure of the brain resonates deeply with Professor of Neurosurgery G. Rees Cosgrove, the inaugural chair of the Department of Neurosurgery at Brown Medicine.
“One of the goals of all of our collective efforts in neuroscience, from a research perspective, is to discover what makes us uniquely human.”

Alpert Medical School and chief of neurosurgery at Rhode Island Hospital and The Miriam Hospital.

Cosgrove says that the University’s capacity for discovery in this realm—along with the unique opportunity for growth, innovation, and collaboration that individual scientists find within BIBS—were his major incentives to come to Brown from Tufts University School of Medicine, where he served as a professor of neurosurgery, and the Lahey Clinic, where he chaired the Department of Neurosurgery after previous appointments at Harvard Medical School and Massachusetts General Hospital.

“One of the goals of all of our collective efforts in neuroscience, from a research perspective, is to discover what makes us uniquely human,” says Cosgrove.

Cosgrove also serves as clinical director of the Norman Prince Neurosciences Institute (NPNI) at Rhode Island Hospital, with which BIBS has a strategic partnership.

“With the recent decision to expand brain science through BIBS, the formation of the Norman Prince Neurosciences Institute at Rhode Island Hospital, and the recruitment of new leadership in Brown’s three clinical neuroscience departments [Neurosurgery, Neurology, and Psychiatry and Human Behavior], the blocks are being assembled to support a new era of interdisciplinary, collaborative brain research at Brown,” says John Robson, who is both administrative director of NPNI and associate director for medical research and clinical programs of BIBS.

“The many combinations that are possible between basic neuroscience and engineering, and among other fields, are really limitless,” says Cosgrove. “Because we have this large group of committed and experienced individuals who communicate with each other and collaborate in meaningful ways, you have the opportunity to build on one discovery after another, and to ask and answer essential questions about how the brain informs the different facets of our experience as human beings. This work goes to the fundamental purpose of the University.”

THOUGHT MADE MANIFEST

In a surgical suite at Rhode Island Hospital, Associate Professor of Psychiatry and Human Behavior Benjamin Greenberg leads a patient through an assessment that will determine the precise placement of an electrode that may change his life. Soon, guided by Greenberg’s assessment and computerized imaging technology, Rees Cosgrove will place the electrode that will stimulate a pushpin-sized piece of brain—with the aim of liberating the patient from the most severe symptoms of debilitating, treatment-intractable obsessive-compulsive disorder (OCD).

“We’re very conscious that this is brain surgery, with its inherent risks, and therefore this intervention is only open to about 1 percent of the people who seek it,” explains Greenberg. “We select people whose primary diagnosis is OCD, whose OCD is fundamentally disabling, and whose symptoms have persisted despite receiving all reasonable treatments over a five-year period.”

“It’s not a cure,” he continues. “Deep brain stimulation, or DBS, works in addition to medication and ongoing behavior therapy.”

Patients generally recover at home after a one-night hospital stay following placement of the electrode. About two weeks later, they return for intensive outpatient testing and then begin a regimen of stimulation supervised by their treating psychiatrist. For long-term DBS, patients receive rechargeable brain stimulators (Rhode Island Hospital was the first in New England to use them), which are expected to last eight years.

People who receive DBS at Brown (see Brown Medicine, Spring 2006) are part of an eight-site national study, sponsored by the National Institute of Mental Health, designed to test the efficacy of the treatment and better understand how it may work. Greenberg, the principal investigator on the study, collaborates with a Butler Hospital colleague, Interim Chair of Psychiatry and Human Behavior Steven Rasmussen.
TRIPLE THREAT

Rasmussen, Greenberg, and Cosgrove (left to right) discuss MRI images of brain pathways targeted in neurosurgery.
Rasmussen is quick to point out that continued advances in neurological approaches to intractable psychiatric disorders are dependent on interdisciplinary collaborative efforts that bring expertise from different perspectives. That, he says, is the potential of BIBS. “I arrived at Brown as an undergraduate in 1970, and this is the most exciting time for brain science here in 40 years,” he says. “There is tremendous synergy between people based on campus and in the affiliated hospitals, working together to develop new approaches to treatment in an academic environment that is truly unique.”

Exciting Times

Ask Rasmussen to remember a patient with OCD whose life was dramatically improved after surgical intervention, and he will tell you about the young man from the Midwest who was the first patient he treated in 1993 with a gamma knife procedure—the precursor to today’s deep brain stimulation therapy.

After struggling for years with life-threatening OCD rituals, the 17-year-old boy weighed 80 pounds. He could not eat. He could not go to school. His desperate parents, eventually reduced to force-feeding him a dietary supplement to keep him alive, brought him to Rasmussen at Butler Hospital. Within a year of treatment, the boy had returned to school. He went on to college, where he graduated magna cum laude, and then to graduate school. Today, he is an accomplished professional.

But Rasmussen is quick to point out that continued advances in neurosurgical approaches to intractable psychiatric disorders are dependent on interdisciplinary collaborative efforts that bring expertise from different perspectives. That, he says, is the potential of BIBS. “I arrived at Brown as an undergraduate in 1970, and this is the most exciting time for brain science here in 40 years,” he says. “There is tremendous synergy between people based on campus and in the affiliated hospitals, working together to develop new approaches to treatment in an academic environment that is truly unique.”

Doctor of Engineering

Leigh Hochberg is an associate professor of engineering at Brown. He is also an attending physician on the Stroke and Neurocritical Care Services at Massachusetts General Hospital and Brigham & Women’s Hospital and a member of the consulting staff at Spaulding Rehabilitation Hospital. So he’s well positioned to see the clinical potential of
BrainGate team has demonstrated that the neural signals associated with the intent to move a limb can be “decoded” by a computer and used to operate external devices—such as moving a computer cursor simply by thinking about it. The work has been featured in *Nature*, among other journals.

The team has now moved on to BrainGate2, which is investigating the feasibility of giving people even more control over their environment through use of cortically controlled prosthetic limbs and assistive movement and communication devices. Professor of Engineering and Physics Arto Nurmikko, co-director of Brown’s Center for Biomedical Engineering and a BrainGate team member, is working to develop a new generation of wireless medical technologies.

Leigh Hochberg is reluctant to theorize about what goes through the minds of the people who have helped to test the BrainGate devices, or to imagine what they might think about the possibilities his team may be creating for them.

But he does have a story to tell.

A few years ago, the BrainGate team brought a video of a participant in the study with them to the annual meeting of the Society for Neuroscience. The woman, who had been left paralyzed and unable to communicate by a brain stem stroke, delivered her message to the distinguished assembly. Slowly, using the still-potent force of her brain, she tapped out three words:

*There is hope.*

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**BIGGER THAN THE SUM OF ITS PARTS**

The Brown Institute for Brain Science brings together faculty members, graduate students, undergraduates and staff from 19 academic departments. Their areas of expertise are different but they have a shared mission: to understand, heal, and unlock the awesome power of the brain.

- **APPLIED MATHEMATICS**
- **BEHAVIORAL AND SOCIAL SCIENCES**
- **BIOSTATISTICS**
- **COGNITIVE AND LINGUISTIC SCIENCES**
- **COMPUTER SCIENCE**
- **DIAGNOSTIC IMAGING**
- **ENGINEERING**
- **ENGLISH**
- **EPIDEMIOLOGY**
- **HEALTH SERVICES, POLICY AND PRACTICE**
- **MOLECULAR BIOLOGY, CELL BIOLOGY AND BIOCHEMISTRY**
- **MOLECULAR PHARMACOLOGY, PHYSIOLOGY AND BIOTECHNOLOGY**
- **NEUROLOGY**
- **NEUROSCIENCE**
- **NEUROSURGERY**
- **PATHOLOGY AND LABORATORY MEDICINE**
- **PHILOSOPHY**
- **PHYSICS**

BIBS’s work every day. Some of his patients are “locked in”—conscious and cognitively intact, but unable to communicate, move, or perform routine tasks—by stroke, traumatic brain injury, or degenerative neurological disorders.

After graduating from Brown in 1990 with an ScB (Honors) in neural science, Hochberg earned an MD and a PhD in neuroscience at Emory University. He returned to Brown in 2004 to work with his college professor, John Donoghue, on the BrainGate project, later accepting a faculty appointment in Brown’s School of Engineering.

After implanting an array of electrodes (one array of 96 electrodes is the size of a baby aspirin) in the brain, the

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**Eileen O’Gara-Kurtis** is the founder and president of Silver Branch Communications. She is a frequent contributor to Brown Medicine.