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MATERIALS RESEARCH INSTITUTE BULLETIN FALL 2007

FOCUS ON BIOMATERIALS

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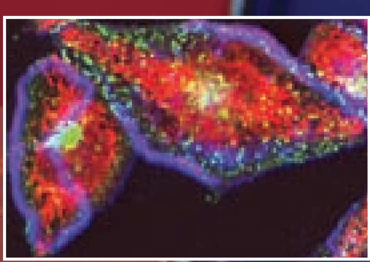

ENGINEERING THE BRAIN

MATERIALS RESEARCH INSTITUTE

Focus on Materials is a bulletin of the Materials Research Institute at Penn State University. Visit our website at **www.mri.psu.edu**

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Graphic Design by
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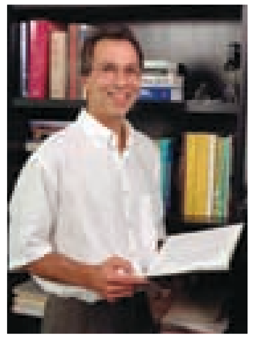


Message from The Director

Welcome to our biomaterials issue of *Focus on Materials*. In this issue you will read about the many ways the materials and life sciences are working together to gather new understandings of the incredibly complex systems within our body, systems that have evolved over vast scales of time, space, and organization. The physical principles that govern these multi-scale phenomena are common to the life, computational, engineering, and social sciences and provide the bridge for solving global problems in healthcare.

In our feature story, the director and associate director of the new Center for Neural Engineering discuss the problems involved with understanding the complex systems of the brain, and how collaborations with Penn State researchers in electrical engineering and materials science will aid them in sensing and controlling diseases of the brain. Neuroscience is one of the fastest growing fields of research, offering the possibility that in the not too distant future we may find treatments for such malfunctions as Alzheimer's, Parkinson's, epilepsy, and major depression, among others.

In this issue you will also read about a nanoengineering method to combat blood clotting. These dangerous clots form on most materials when they come into contact with blood, and the drugs that inhibit clot formation can be both expensive and dangerous to some patients. Our surface chemists are using nanotexture to thwart the clot formation without the need for drugs. Other chemists at Penn State are finding new ways to investigate the intra-molecular interactions of living cells, and are using nanofabrication methods to mimic the molecular processes that create and control cell membranes.

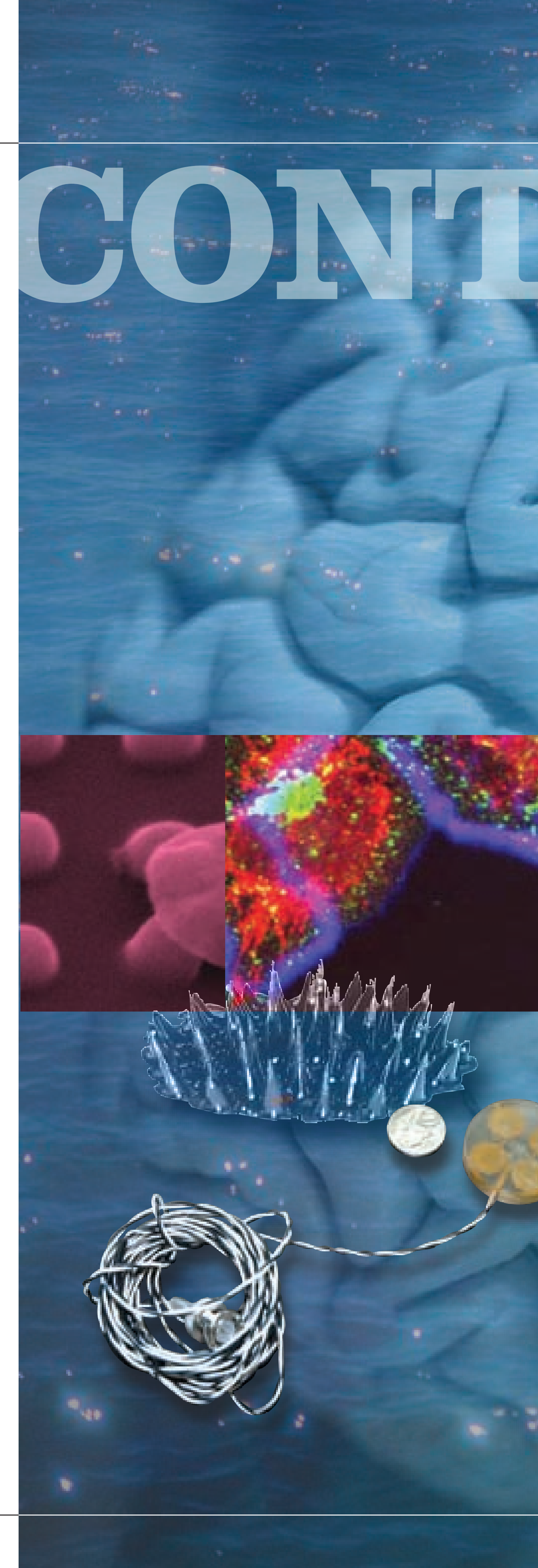
Ultrasound technology was first developed for naval sonar, then for detecting defects in materials, and subsequently applied for the imaging of fetuses, hearts and other living organs; now, our bioengineering faculty are using ultrasound to treat diabetes and other chronic diseases.

Whether for healthcare, environmental remediation, food production, or national security, the ability to understand and integrate organic, biological, and inorganic systems is certain to advance our lives in many different ways. In this issue, we will explore just a few of the many ongoing biomaterials research projects underway at Penn State.

Sincerely,

Carlo Pantano
Director of the Materials Research Institute,
and Distinguished Professor of Materials Science and Engineering

To access the materials expertise at Penn State, please visit our Materials Research Institute web site at **www.mri.psu.edu** or the Industrial Research Office web site at **www.techtransfer.psu.edu/iro/**



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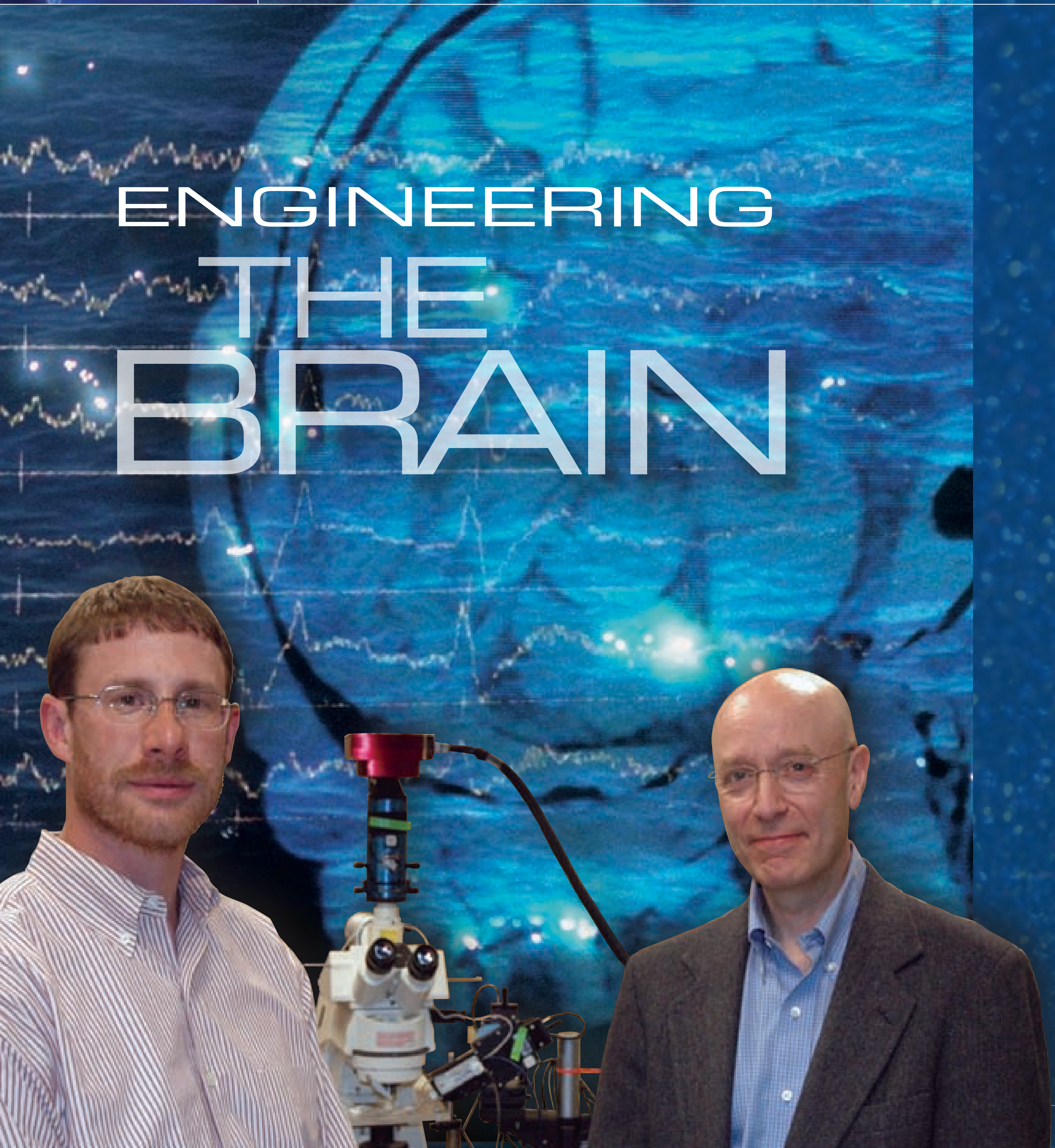


More than 50 million Americans are affected by neurological illness each year. A million people in this country are living with Parkinson's disease. Autism affects four percent of children in the United States. Besides Parkinson's and autism, diseases of the nervous system include cerebral palsy, multiple sclerosis, Alzheimer's, ALS (Lou Gehrig's disease), and epilepsy. In addition, almost twenty percent of the population suffers from serious depression that affects their ability to function normally. Add to these schizophrenia and obsessive compulsive disorder, attention deficit hyperactivity disorder, addictions, and bipolar disorder; include massive brain trauma due to injury or stroke, and the costs of brain malfunctions to our quality of life and our national productivity are staggering.

Bruce Gluckman and Steven Schiff are building the new Penn State Center for Neural Engineering.

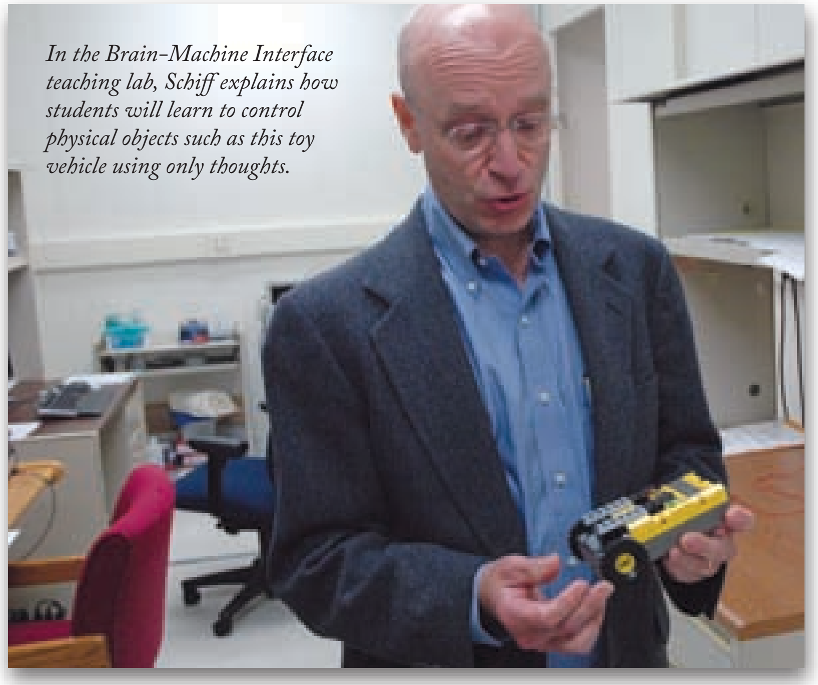
Steven Schiff and Bruce Gluckman are among those who would like to find new and better ways to relieve some of the multitudinous problems that arise when the brain malfunctions. Schiff, a pediatric neurosurgeon with over 20 years of experience in the physics of dynamical diseases of the nervous system (diseases in which the structures of the organ malfunction), is working to find less destructive methods than the standard surgical procedures for treating diseases such as Parkinson's, cerebral palsy, and epilepsy. His colleague for the past ten years in this search is experimental physicist Bruce Gluckman. Gluckman's expertise is in the group dynamics of individual systems, with a special focus on how various parts of the nervous system interact. In 2006, the two highly regarded researchers were recruited by Penn State to form the new Penn State Center for Neural Engineering. A third faculty member, Corina Drapaca, has just been hired to add expertise in image analysis and the biomechanics of hydrocephalus.

"The brain is a material that is very challenging for us to deal with," says Schiff, the Center's director, choosing his words carefully, as well he might. Tinkering with the brain sets off alarm bells in many people. Far more than any other organ, the brain is who we are, storing our memories, maintaining our identity, expressing our emotions. Engineering the brain raises questions of our humanity, the potential of becoming more – or less – than human.

Schiff will approach that issue later, but for the moment he sketches the outlines of brain research. "The brain is electrical, but not like a typical circuit board. Yes, there are wires and cables and computational elements, but it is really more like a city. There is an energy supply, which is wet, and there is a lot of refuse to be collected, and that refuse, which can be

Our brain, the wet computer

The adult human brain weighs about 3 pounds and contains some 100 billion brain cells, called neurons. Neurons communicate with each other by an electrochemical process through wires, called dendrites and axons, at connections called synapses. There are an estimated one quadrillion synapses in the human brain, so there are plenty of places where things can go wrong. One American in six is affected by a neurological illness each year. Deep brain stimulation (DBS) is a recent development in the field of neuroengineering that offers the potential for alleviating a number of diseases of the brain, as well as the possibility of enhancing the brain's normal functions, such as memory and concentration.



In the Brain-Machine Interface teaching lab, Schiff explains how students will learn to control physical objects such as this toy vehicle using only thoughts.

simple ions, needs to be redistributed through fluid channels. It's like that book that shows all those things that are hidden under the streets and buildings of New York City that make it run."

Bruce Gluckman, the engineer to Schiff's clinician, adds another layer of metaphor. "I look at it this way – if you consider a business in a big office complex, if the plumbing backs up, everyone leaves the building and no work gets done. The success of the business depends on the plumbers and the garbage collectors. The whole support structure has to be designed well. When parts of that break down, the whole business fails." In the brain, the support system can fail in subtle ways. It's not all about measuring the electrical activity connected with computation, Gluckman says, it's also about the support structure that keeps the brain functioning correctly – the metabolism.

Materials for neural engineering

The new Center for Neural Engineering will be a bridge between the clinical researchers at the Penn State Hershey School of Medicine and the engineering and materials disciplines at University Park. Neural engineering relies on materials science as well as computation and electrical engineering to attempt to restore brain functions. There is the potential that cognitive disorders such as depression, obsessive/compulsive disorder, and other things that plague people might be related to rhythms in the brain that could be modulated with systems that can sense, then compute, and then actuate stimuli which could alter how the brain is functioning in ways that simply bathing the brain in drugs can't, Schiff says.

For instance, Gluckman and Schiff have learned that low frequency electrical stimulation can modulate parts of the brain in order to turn off the seizures and symptoms of Parkinson's disease or epilepsy. However, to truly take advantage of this knowledge, they need to understand where the electrical signals come from and how they affect the brain. That has proven to be a problem. The interpretation of EEG (electroencephalography) results, which record the electrical activity of the brain using electrodes placed on the scalp or within the brain, are no clearer now than when Schiff was in medical school. "In the last ten years we've thrown an enormous amount of computer cycles at trying to understand the electrical activity of the brain through better signal processing, and we've learned, what would you say, Bruce – nothing?" Schiff says with a shrug.

> ***"We're understanding now that the computer of the brain is really three pounds of a couple of billion gooey elements that gets hot and spits out chemicals and needs chocolate."***
>
> ***– Steven Schiff***

Without a good physical model of how the brain works, the interpretation of electrical activity remains guesswork based on the superficial resemblance of patterns that show up on an EEG. "You spend a year or two in a dark room," Schiff says of the training physicians receive on the electroencephalograph. "When you see the same patterns as on a medical diagnosis, you're allowed to graduate."

Gluckman and Schiff came to Penn State, at least in part, because they felt that here was a place ideally situated to solving the mystery of how the brain works, especially those subterranean systems that provide the brain's infrastructure. So far, no one has designed the sophisticated sensing devices to show what's going on in the brain. They don't know where to place the sensors or how large they should be. Do they all have to be in the head or can they pick up enough information outside the head and avoid the need for surgery? With what Schiff calls Penn State's "enormous sophistication" in testing the electrical and magnetic properties of materials, "if they knew how to apply that knowledge to nervous systems, then, who knows? In a perfect world, we could be the two people who could help them make that bridge."

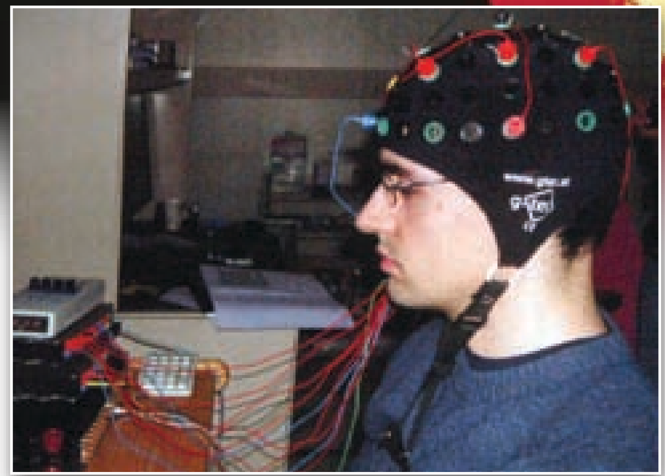
(In a new Materials/Life Science complex, expected to open in the next three years, the Center for Neural Engineering's researchers will work alongside materials scientists and engineers expert in nanotechnology and microfabrication.)

It isn't rocket science

Neural engineering is the techie side of neuroscience, says Gluckman. Its earliest big success was the development of the electroencephalogram, which has been in wide use for over half a century and gave neuroscientists at least a blurry blueprint of the electrical activity of the brain.

More recently the major advances have occurred in devices and prosthetics, especially the cochlear implant for hearing loss, first developed in 1969 and now worn by over 100,000 users worldwide. Other active projects involve other sensory inputs, such as retinal implants, and artificial limb implants. Recently, a great deal of effort has gone into developing the brain-computer interface, a closed loop system in which signals feed back and forth from the brain to the computer, in effect training both.

"It has been five years since animal studies showed monkeys controlling robotic arms or cursors on a screen through measurements out of the motor cortex," says Gluckman. Similar experiments have been performed



A student is wired up to a computer in the teaching lab. "Locked-in" patients without the ability to move may learn to use such devices to communicate.

with human volunteers, with electrodes implanted that allow some control of computers. This has also been done for "locked-in" individuals who through brain trauma or disease have completely lost the ability to move or communicate. In those cases, the computer-brain interface is made in a noninvasive fashion that uses EEG-type recordings.

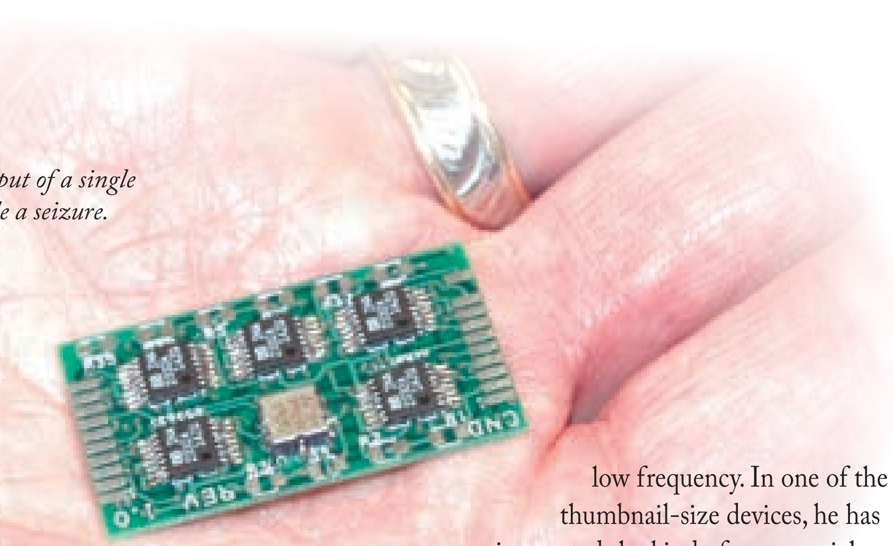
"There are also successes in neural engineering for neurological problems such as Parkinson's disease and epilepsy, which I have been studying for the past ten years, and Steve for more like 20 years," says Gluckman. Schiff adds, "Neural engineering has been around for a long time, but the applications were spotty. There have been a few examples of very successful implementations, but it has been in the last 10 years that we have been able to blend what we know about materials engineering, electronic engineering, and computer engineering with working with a soft and wet three-pound computational organ."

Despite these recent successes, sensing and control systems for the brain are still unsophisticated. The cruise control system in your car is probably substantially more sophisticated than any neural control system that's been designed so far. "It's not rocket science," Schiff says, speaking quite literally. "Back in the sixties, rocket science reached a level of engineering theory that allowed it to do all those things we know about from the space program, sending rockets throughout the solar system and landing humans on the moon. We've never applied a whit of that knowledge to working with neural control systems of the brain."

The purpose of sensing and control devices is to treat diseases in which the dynamics of the brain are malfunctioning. In such cases the brain is like a turbine that's beginning to wobble, and scientists such as Schiff and Gluckman use control pulses to try to stabilize its frequency. "We're beginning to understand that associated with cognitive disorders of the brain there seem to be changes in rhythmicity" Schiff says. "Broadly speaking, how do you sense that a nervous system is not functioning properly, that its rhythms are wrong, and how can you readjust those rhythms by stimulation? The obvious case that comes to mind is Parkinson's disease."

Into the lab

The Neural Engineering Center is made up of three connected laboratories on the floor with Gluckman's and Schiff's offices in the Earth-Engineering Sciences Building, one of the cluster of new research buildings on the west end of campus. The first lab is a small shielded room with hardware and software devoted to computer/brain interface experiments. On a table on one side of the lab, a toy vehicle is attached by wires to a computer. Here students and postdocs wearing electrode-studded skull caps attempt to control the movements of the truck using only the electrical signals from their brain. "In the future," says Schiff, "we are going to have a course where our students play neural ping pong as one of the laboratory exercises. We want to guide students into projects that lead into the unknown." This room serves to prototype coursework and equipment for a future Brain-Machine Interface teaching laboratory at Penn State – space for it is already reserved in the future Materials/Life Sciences II building. Penn State will be one of the first sites in the world to offer such a course for its engineering students.



Gluckman's chips measure the output of a single neuron or the motions that precede a seizure.

In the second lab, two students are studying small slices of brain under microscopes. Gluckman explains the purpose of brain slice research. "About a decade ago, Steve and I rediscovered that if instead of using pulses like in most deep brain stimulation, we used some very low frequency electrical fields or electrical current, meaning a constant electrical field that lasts longer than the firing of a single neuron, then we could shift the set point of the cell so that slightly more or less input is required to fire the next signal. This modulates the response of that neuron to its input." For instance, they can make the neurons less responsive to the electrical firestorm of a seizure.

After years of brain slice experiments, the two scientists discovered they were able to simultaneously record the activity of the system as they were modulating the response – creating, in effect, a closed loop. The feedback system allowed them to control seizure-like activity in the brain slices, and eventually to create control devices to interact with seizures in implanted animals.

In the third lab, the researchers translate the knowledge gained in the brain slice experiments to understanding the complexities of electrical activity in living subjects. Here Gluckman builds small implantable electronic circuits to record the firing of single neurons under low frequency. In one of the thumbnail-size devices, he has integrated the kind of commercial accelerometer that can be found in auto airbags into a circuit designed to measure the tilt of a lab animal's head, which helps determine behavior (sleeping, drinking) when combined with the EEG. One goal is to use such data to predict a seizure before it happens. Also in this lab, with a grant from the Grace Woodward endowment at Penn State, they are developing an X-ray CT scan analysis algorithm to diagnose temporal lobe epilepsy in children in sub-Saharan Africa that would normally require costly MRI equipment.

The implications are huge

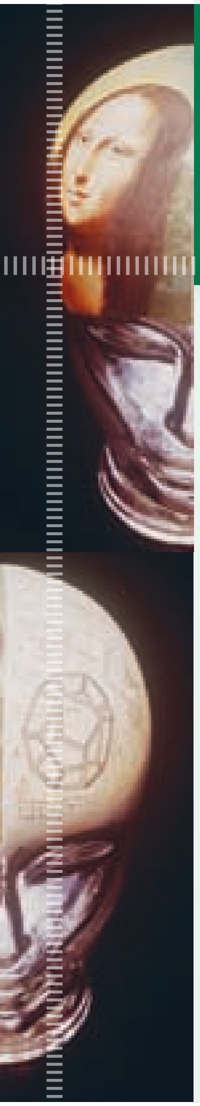
Nanotechnology and microengineering are highly advanced research areas at Penn State that can speed the progress of neural engineering. Gluckman predicts that the techniques of nanotechnology will help them develop the elusive model of the brain that is currently lacking. "We think that the whole science that is developing around creating different surfaces with different textures and structures and materials is one that is extremely important for neural engineering," Gluckman says. "We are deeply involved with sensing, using nanosensors to study analytes in microdomains of the brain in both space and time. What we mean by that is you need to know the level of metabolites that change the excitability of electrical components of the brain. By using various technologies to do sensing on very small scales, and knowing the anatomical structure, we can see how materials are transported and build computational models to understand how that alters the stability in parts of the brain." (Cont'd on p.11)

What are the risks and what are the benefits of placing electrodes into the brain?

Where does therapy stop and enhancement begin?

Given the expense of neural engineering, how are the costs and benefits of neurosurgery shared by society?

These were some of the issues debated at what some billed as the first international conference on the ethics of neural engineering – *Implanting Change: The Ethics of Neural Prosthetics* – held at Penn State in September 2007. If none of the answers was entirely conclusive, that may be because the debate is just beginning. The ability to make truly revolutionary improvements in the functioning of the brain has only recently been proven.



Therapy vs. Enhancement:

The Ethics of Neural Engineering

"We decided several decades ago that psychosurgery was immoral in many ways," says Penn State neurosurgeon Steven Schiff. "We shut down whole areas of destructive neurological surgery trying to alter the minds of people. We had no effective treatment for those we felt needed treatment or institutional care. We've stopped doing lobotomies, and now we're about to revive it under the guise of the technological capability of being able to stimulate almost any place in the brain with what are 'probably' acceptable risks. We really need to define very carefully for any of these treatments what are the risks and what are the potential benefits."

By the early 1950s, according to Joseph Fins of Weil Cornell Medical College, a noted medical ethicist and one of the conference speakers, 50,000 psychosurgery procedures had been performed, many of them on shell shocked and depressed veterans returning from World War II. Lobotomies dwindled in popularity in the late fifties and early sixties with the advent of Thorazine, the first nonsedating tranquilizer. However, long-term studies of the harmful effects of lobotomies left a lingering anti-psychosurgery legacy with the public. Dr. Fins noted that the public is largely unaware of the differences between the deliberately destructive psychosurgery of fifty years ago, and the far more localized and minimally destructive deep brain stimulation (DBS) practiced today. He predicts that in the future nanotechnology and new materials will further reduce the side effects of implantation.

With the proper safeguards, neural engineering for therapeutic purposes should develop with little opposition, the participants concluded. The public seems to be in favor of implants for the control of Parkinson's tremors and epileptic seizures. Where the controversy begins is when therapy edges over into human enhancement. For instance, placing computer interfaces inside the skull raises the question of what is strictly human and what is artificial. Are the risks of a neural implant worth the potential benefits of increased attention and wakefulness, or a 20-point gain in IQ? It may come down to individual cases. The benefits to a person with much below normal intelligence might be greater than for someone who is already functioning capably in society. We might decide that an airline pilot has greater need for concentration and wakefulness than a student studying for an exam.

Neural engineering is especially problematic in the context of the military. Here there may be special risk versus benefit balances that are uncommon in civilian life. Is it justified to improve a soldier's capabilities to enable his or her survival in circumstances that would otherwise carry a high risk of death? Customary medical ethics would want the risk of the device to be significantly less than the risk without it. On the other hand, if the neural prosthetic were intended to largely increase the effectiveness of creating injury to others, is this beyond the acceptable scope of medical care?

The technologies of neural engineering now place us at the threshold of the abilities to increase human intelligence, control moods with stimulation, ameliorate depression, increase wakefulness, and enhance concentration. This means that the challenges for the Penn State Center for Neural Engineering will extend well beyond the technical arena at which Penn State excels, and into the domain of the personal and societal implications of brain research where scientists are often reluctant to tread. Clearly, the researchers in this new Center are eager for the challenge, both ethical and scientific, that the emerging field of brain engineering creates. Soon we will find out if we are able and willing to improve on the hand that Nature has dealt us.

Even without a clear understanding of how the brain works, dramatic possibilities are opening up, says Schiff. "There have been very high profile papers coming out in the scientific press in the last couple of years showing you can modify memory in people by applying electrical current to the brain. A recent paper showed you can disrupt cancer cells with modestly high frequency fields that are focused properly. Because it is not well understood why this works, it is important to get better models. It's something we feel we can provide here at Penn State."

Functional magnetic resonance imaging (fMRI) is one of the important new tools for neural research. Rather than measuring electrical activity (EEG), the fMRI measures blood flow, indicating areas of the brain that are presumably involved with mental and physical activities. Penn State is about to get a new magnetic resonance imaging tool on campus for human use. The ability to make magnetic and electrical fields is enormously expanded by that addition, Schiff says. One example of the utility of fMRI is a paper that appeared in the journal Neuron about a year and a half ago, showing that a very small target very deep in the brain when stimulated for most of the day could substantially help the majority of the small handful of patients they tested with serious depression. They picked the target for stimulation based on functional magnetic resonance imaging of people who were or were not depressed, and determined from such images who was a good candidate to stimulate.

Amazingly, it worked, Schiff says. We can look for an explosion of such technology following on the heels of this study.

Schiff argues for caution in the rush to harvest the benefits of neural engineering. "We've made a big push here to be very careful to study the damaging effects of putting something into the brain, and to be very careful about how even our electrical stimulation can damage it. We want the things we make here at Penn State to be safe for the patients that we treat. All medical decision-making balances risks and benefits. We're very focused here on paying attention to both. I hope over time we can collaborate with the experts on campus to do things none of us could ever do on our own."

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For more information on the Center, visit:
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