New research center to focus on returning veterans

A new research program based at the Waco campus of the Central Texas Veterans Healthcare System will study brain and mental-health conditions common among troops returning from Iraq and Afghanistan: posttraumatic stress disorder, traumatic brain injury, depression, and substance abuse.

The Center for Excellence for Research on Returning War Veterans, supported by Veterans Integrated Service Network (VISN) 17, will be led by psychologist Suzy Gulliver, PhD, former director of outpatient mental health care at the Brockton (Mass.) VA. The program will feature a $3.5-million mobile functional MRI machine that will travel between Waco, the Temple VA, and nearby Fort Hood, the largest Army base in the U.S., from which more than 40,000 troops have deployed to Iraq. The fMRI machine, one of few such mobile research units in the world, will be used to correlate activity in different areas of brain with patients’ PTSD symptoms and with the effects of treatment.

According to Gulliver, the center will emphasize translating research findings into practice so that veterans can be helped as soon as possible.

“There is a reputation that scientists are hiding out in the ivory tower, and that is just not going to do for this center,” she told the Waco Tribune-Herald. “We are going to be in the trenches. We are going to be making the practice better.”

Keith Young, PhD (right), seen here with colleague Willy Bonkale, PhD, will be studying the genetic and biological underpinnings of PTSD as part of VA’s new Center for Excellence for Research on Returning War Veterans in Waco, Tex.

Study sheds doubt on pain rating scale

The most common method for pain screening may only be modestly accurate, reported VA investigators and colleagues in the Oct. 2007 Journal of General Internal Medicine.

In a study involving 275 adult clinic patients, the researchers tested the pain numeric rating scale, which asks patients to rate their current pain from 0 (“no pain”) to 10 (“worst possible pain”). The researchers also verified patients’ pain using other clinical measures.

Though easy to use, the numeric rating scale failed to identify about one in three patients with pain serious enough to interfere with everyday functioning. “Even
When a team led by John Donoghue, PhD, and Leigh Hochberg, MD, PhD, published results from their pilot study of the BrainGate system in *Nature* in 2006, the headline in one Canadian newspaper proclaimed, “Movement by Thought: Science Fiction to Fact.” A London newspaper referred to the trial participant as “the first bionic man.” The editors at an Oakland daily were equally impressed, running the headline: “Paralyzed Man Moves Mountains with Mind.”

It was hard for even the most serious science journalists to ignore the fascination surrounding the researchers’ stunning achievement. The scientists—from Brown University, VA and other institutions—had enabled a 25-year-old man with quadriplegia to operate a computer cursor and perform other tasks solely through his thoughts.

The technology, called BrainGate, uses a tiny sensor implanted in the motor cortex, the part of the brain that controls movement. The sensor, about the size of Lincoln’s head on a penny, has 100 hair-thin electrodes that pick up brain signals. The signals are sent to an external decoder that turns them into commands for electronic or robotic devices. For now, the brain implant is wired to a computer, but the researchers hope to go wireless in the future.

Development of the system is spearheaded by Donoghue, a Brown neuroscientist who became affiliated with VA when the agency established its Providence-based Center for Restorative and Regenerative Medicine in 2004. Donoghue is also chief scientific officer at Cyberkinetics Neurotechnology Systems, a company formed by Donoghue and colleagues in 2001 to bring BrainGate to market.

A ‘nascent science’

Hochberg, lead author on the landmark *Nature* paper and the principal investigator on current trials involving BrainGate, admits there has been some hype in media coverage of the technology, but says most reports have been balanced and accurate.

“Overall, many people have been captivated by the potential of the technology. But thankfully, the media has generally been responsible in describing these as early trials [and making clear] that this is a nascent science—that we’re really at the beginning of a tremendous period of learning and opportunity in terms of restoring lost function for people with paralysis or limb loss.”

Notwithstanding Hochberg’s tempered view, it may be fair to say that in the case of brain-computer interfaces, yesterday’s science fiction—for example, the 1938 Andre Maurois novel *The Thought-Reading Machine*—has indeed become today’s reality.

Even so, what’s been realized by researchers to date has clear boundaries. BrainGate and similar technologies have little applicability with regard to “higher” functions of the human mind: that which is uniquely individual, such as memory, emotions, creativity. “For the moment, that’s a theoretical discussion,” notes Hochberg. “The technology is not even close to being able to read into memories or thoughts in the general sense. The leading edge of the field is the ability to extract a neural signal that’s related to the intention to move one’s limb—and thereby a computer cursor—in a particular direction.”

And even the notion of “reading thoughts,” while not wholly inaccurate, is more a handy catchphrase for the media than a precise description of what the technology is designed to do.
Leigh Hochberg, MD, PhD, is lead investigator on two clinical trials of a brain-computer interface called BrainGate.

Yet another method for restoring communication—this one focused on patients who’ve lost their speaking ability—is being developed by a private Georgia-based company called Neural Signals, Inc., the only other neuroprosthetics group worldwide, to Hochberg’s knowledge, that is using recording sensors inside the brain. Their product is a computer-controlled prosthetic device that would be controlled by brain signals and reproduce the sounds of natural speech.

Brain waves may drive natural or artificial limbs

As for enabling movement, BrainGate has already enabled research participants to open and close a robotic arm. This aspect of the work—using brain signals to activate limbs—may benefit from a new $6.5 million grant from the National Institutes of Health to Cyberkinetics, Brown and the Cleveland Functional Electrical Stimulation (FES) Center, which is sponsored jointly by VA and Case Western Reserve University.

The partnership with the FES Center represents an intriguing melding of approaches. Most past FES work has involved people with intact but non-functioning limbs—such as those with spinal cord injury or stroke. Electrodes are implanted not in the brain but in the weakened or paralyzed muscles that would normally move the limb. Small electrical currents from external or implanted devices activate the muscles and restore movement and function. Only recently, research there has expanded to prosthetics applications. In one project, electrodes would be implanted onto intact arm and shoulder muscles near the amputation and pick up brain signals to drive an artificial hand.

The new FES-BrainGate collaboration is “potentially very promising,” says Hochberg, in that two groups of patients might benefit: those using prosthetics limbs, and those whose natural limbs are intact but disconnected from the brain and nervous system. Either way, what BrainGate inventor John Donoghue has described as the ultimate goal of the technology—to reconnect brain to limb”—may eventually be within reach.
Below is a brief sampling of recent scientific publications and presentations by VA investigators. Only VA-affiliated authors are listed here, due to space constraints.

“Amyloid-Beta Precursor Protein Expression and Modulation in Human Embryonic Stem Cells: A Novel Role for Human Chorionic Gonadotropin.” Prashob Porayette, MBBS, MS; Miguel J. Gallego, MS; Maria M. Kaltcheva; Sivan Vadakka-Porayette, MBBS, MS; Miguel J. Gallego, PhD. Biochemical and Biophysical Research Communications, Dec. 2007.


“The Burden of Stroke Scale (BOSS) Provided Valid, Reliable, and Responsive Score Estimates of Functioning and Well-Being During the First Year of Recovery From Stroke.” Patrick J. Doyle, PhD; Malcolm R. McNeil, PhD; Katherine Ross, PhD; Julie Wambaugh, PhD; William D. Hula, MS. Pittsburgh, Phoenix, Salt Lake City. Quality of Life Research, Oct. 2007.


“Does Compensation Status Influence Treatment Participation and Course of Recovery From Post-Traumatic Stress Disorder?” Craig S. Rosen, PhD; Paula P. Schnurr, PhD; Matthew J. Friedman, MD, PhD. Palo Alto, White River Junction. Military Medicine, Oct. 2007.

“Experimental Examinations of Cognitive Psychopathology in PTSD.” Suzanne Pineles, PhD; Jillian Shepherd, PhD.


“Race and Dialysis-Free Mortality Among Patients With Diabetes and Advanced CKD.” Chin-Lin Tseng, DrPH; Anjali Tiwari, MBBS, MS; Elizabeth F. O. Kern, MD, MS; Donald Miller, ScD; Miriam Maney, MA, CPHQ; Leonard Pogach, MD, MBA. East Orange, Cleveland, Bedford. The 5th National Health Disparities Conference, Nov. 12, 2007.


Wes Ely, MD, MPH, was quoted in an Oct. 17 Wall Street Journal article about hospitals’ efforts to prevent the complication of delirium. Ely is founder of the ICU Delirium and Cognitive Impairment Study at the Nashville VA and Vanderbilt University Medical Center. The group studies brain dysfunction in critically ill patients. Ely is also associate director of research for the Nashville VA’s Geriatric Research Education and Clinical Center.

Gregory Goodrich, PhD, a research psychologist at the VA Palo Alto Health Care System, was quoted in a Nov. 14 USA Today article on the effects of traumatic brain injuries on vision. A study by Goodrich “found that 40 to 45 percent of patients with mild traumatic brain injuries suffered vision loss even though their eyes were physically healthy. The biggest problem was an inability for both eyes to operate precisely together,” which “can lead to eye strain and blurred vision.”

Ross Fletcher, MD, chief of staff and a researcher at the Washington, DC, VA Medical Center, was cited in a Nov. 12 Los Angeles Times news brief on his study that found that high blood pressure can be tougher to control in winter than in summer. The study included more than 443,000 veterans in 15 cities, from Anchorage to San Juan. Fletcher said the “trend may be driven by weight gain, different eating habits and less exercise during winter.”

Rajiv Jain, MD, chief of staff and an investigator at the Pittsburgh VA Medical Center, was quoted in an Oct. 24 Associated Press article about hospitals’ battles against the spread of methicillin-resistant Staphylococcus aureus, commonly known as MRSA. Jain led a successful pilot study at the Pittsburgh VA that cut infection rates by 50 percent and served as the model for VA’s nationwide MRSA prevention program.

Jonathan Shay, MD, PhD, a staff psychiatrist with the VA Boston Healthcare System, was profiled on National Public Radio’s “Morning Edition” on Sept. 25 as one of 24 winners of a 2007 fellowship from the John D. and Catherine T. MacArthur Foundation. The fellowships, commonly referred to as the “genius awards,” include $500,000 over five years. They recognize “individuals who show exceptional creativity in their work” and who have a “track record of significant achievement.” Shay has combined his treatment of combat trauma with critical and imaginative interpretations of the ancient accounts of battle in Homer’s Iliad and Odyssey. His 1994 book Achilles in Vietnam: Combat Trauma and the Undoing of Character draws parallels between the depiction of the epic warrior-hero Achilles and the experiences of individual Vietnam veterans whom he treated. In his 2002 work Odysseus in America: Combat Trauma and the Trials of Homecoming, Shay focuses on the veteran’s experience upon returning from war and highlights the role of military policy in promoting the mental and physical safety of soldiers.

Tony Wyss-Coray, PhD, an investigator with Stanford University and the Geriatric Research, Education and Clinical Center at the VA Palo Alto Health Care System, was interviewed by Ira Flatow on National Public Radio’s “Talk of the Nation” show on Oct. 19 regarding a new blood test that Wyss-Coray’s team is developing to screen for Alzheimer’s disease. The researchers reported in the Nov. 2007 issue of Nature Medicine on a set of 18 proteins in the blood—all of them “signaling” molecules that enable communication between cells—that appear to predict the onset of the disease. The test is now undergoing further study.
Journal issue focuses on brain injury, polytrauma

The current issue of the *Journal of Rehabilitation Research and Development* (JRRD), an international, peer-reviewed journal published by VA, focuses on traumatic brain injury (TBI) and polytrauma. Guest editor is Henry L. Lew, MD, PhD, director of Physical Medicine and Rehabilitation at the VA Palo Alto Health Care System and a noted expert in research and care related to these topics.

“The conflicts in Iraq and Afghanistan have resulted in a new generation of combat survivors with complex physical injuries and emotional trauma including post-concussive symptoms, posttraumatic stress, poor cognitive performance, head and back pain, auditory and visual symptoms, and problems with dizziness or balance,” said Lew. “The purpose of this special issue is to document lessons learned that will enhance the identification and treatment of veterans with polytrauma across the country.”

Articles in the issue cover topics such as treatment of patients with posttraumatic stress disorder and mild TBI; military and VA telemedicine systems for patients with TBI; an operational description of the VA Palo Alto Polytrauma Network Site; a neuropsychiatric perspective on TBI; hearing, vision, awareness and balance problems following TBI; and community-integrated rehabilitation for TBI.

The journal is available for free viewing and download at www.rehab.research.va.gov. Printed copies can be requested by emailing dore.mobley@va.gov.

TBI conference planned

It is estimated that at least 20 percent of U.S. troops wounded in Iraq or Afghanistan have suffered some degree of traumatic brain injury. To help advance research and care on this issue, VA’s Office of Research and Development is planning a “state-of-the-art” conference for spring 2008 titled “Research to Improve the Lives of Veterans: Approaches to Traumatic Brain Injury Screening, Treatment, Management, and Rehabilitation.” VA and non-VA investigators, clinicians, managers, and policymakers taking part in the invitation-only event will work to develop a research agenda that will help promote optimal care for veterans with traumatic brain injury.

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a pain screening cutoff of 1 missed nearly a third of patients with clinically important pain,” wrote the authors.

The study was the first to test the scale in a general population in primary care. According to study leader Erin Krebs, MD, MPH, “These measures were developed for use in patients with pain, and their reliability and validity were evaluated in patients with chronic and acute pain. Their reliability and validity as screening measures to identify the presence of pain in a general population was not assessed before they were widely implemented.” She emphasized that “validity is not just a characteristic of a measure—it’s a characteristic of a measure in a certain population for a certain purpose.”

Krebs is with the Center on Implementing Evidence-Based Practice at the Roudebush VA Medical Center in Indianapolis. She is also with Indiana University School of Medicine and the Center for Health Services and Outcomes at the Regenstrief Institute.

The pain scale—which is sometimes accompanied by graphics such as smiling or grimacing faces, especially in pediatric settings—is ubiquitous in U.S. medical care. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the nation’s main body for standard-setting and accreditation of hospitals and clinics, requires routine assessment of all patients for pain. VA’s health system, which is accredited by JCAHO, uses the scale as part of its “Pain as the Fifth Vital Sign” campaign.

Krebs said that if screening tests are inaccurate and don’t provide information that can be used to improve care, “doctors learn to tune out the numbers.” She said physicians might need to adopt other ways of assessing pain in primary care patients.

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ing sure that what we are finding out in the laboratory makes it into clinical practice.”

She expects the center to eventually be home to some 10 core faculty members and between 50 and 60 staff to assist them. One of the core investigators will be Keith Young, PhD, co-director of the Neuropsychiatry Research Program at the Temple VA and Texas A&M University Health Sciences Center College of Medicine. With $5.7 million in funding from the Department of Defense, along with other support, his team is studying the role of genes and brain anatomy in PTSD. The study will screen and follow 1,400 troops from Fort Hood. In another study, Young is seeking to identify blood and brain markers of traumatic brain injury.

According to Rep. Chet Edwards (D-Waco), who led the effort to secure funding for the PTSD research, “This groundbreaking research project is an important part of realizing our goal of making the Waco VA a world-class PTSD and mental health care research center, and it is one of the few programs in the country focused on the links between genes and brain anatomy in the development of PTSD and mental illness in our combat soldiers.”

Suzy Gulliver, PhD (left), of VA consults with study collaborator Matthew Dolan, MD, of the San Antonio Military Medical Center and the Infectious Disease Clinical Research Program of the Uniformed Services University of Health Sciences.

Two genes found to play major role in progression of HIV to AIDS

Vir al load—the amount of virus in the blood of a person infected with HIV—has long been seen as the main factor in how fast HIV infection progresses to full-blown AIDS. Now, an international team including researchers with VA and the University of Texas Health Sciences Center (UTHSC) in San Antonio has confirmed that two genes also figure largely in the process, and could eventually play a role in how AIDS risk is assessed or how new vaccines are evaluated. The findings appear in the Dec. 2007 issue of Nature Immunology.

Researchers led by Sunil Ahuja, MD, of VA and UTHSC examined genetic information from more than 3,500 people, nearly half of whom were infected with HIV-1, the main virus that causes AIDS. They found that those who had specific combinations of two genes—CCR5, which helps HIV enter cells; and CCL3L1, an immune response gene—were more likely to have reduced immune responses and a greater decline in CD4 T cells, the two main signs of progressive disease. In HIV-infected subjects, viral load contributed only 9 percent to the variability in rate of progression to AIDS, whereas variations in CCR5 and CCL3L1 together accounted for 6 percent.

“What we show is that genetic variations in [CCR5] and [CCL3L1] contribute nearly as much to the extent of inter-individual variability in AIDS progression rates as does HIV-1 viral load,” said Ahuja, director of the VA Research Center for AIDS and HIV Infection in the South Texas Veterans Health Care System and a professor of medicine, microbiology, immunology and biochemistry at UTHSC.

Ahuja said physicians “should become familiar with the notion that although viral entry, replication and spread [as reflected
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by viral load] are important determinants of AIDS progression rates, host factors [such as variations in the genes CCR5 and CCL3L1] can have an equal or even greater impact on AIDS progression rates.”

First author Matthew Dolan, MD, from the San Antonio Military Medical Center and the Infectious Disease Clinical Research Program of the Uniformed Services University of Health Sciences in Bethesda, said the finding could have major implications for the care of HIV-positive patients. “It brings us closer to the possibility of using genetic information along with laboratory tests such as the CD4 count and viral load to assess AIDS risk.” Furthermore, he said, the research suggests how genetic information could be used to evaluate potential new vaccines. On that point, Ahuja noted that “clinical trials of potential vaccines certainly need to look at other endpoints than reduction of viral load, and may need to account for the disease-modulating effects of host genotype.”

Their study was funded mainly by VA and the National Institutes of Health.

VA Research Week 2008 on the way

Scenes like the one at the right, from an event last May at the VA Pittsburgh Healthcare System, will be repeated this coming spring as VA medical centers nationwide commemorate VA Research Week 2008. The exact dates will be announced and posted on the VA research website (www.research.va.gov) in the near future.

Veterans, their families and other members of the community, as well as VA staff and other stakeholders, will have an opportunity to learn more about local and national VA research through laboratory tours, lectures, exhibits, poster presentations, contests and other educational activities.

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“Universal pain screening has become widespread despite a lack of research evaluating its accuracy and effectiveness. We know that pain is a serious problem in primary care, but pain screening may not be the best way to address this problem,” said the researcher.

Collaborating with Krebs were Timothy Carey, MD, MPH, of the University of North Carolina School of Medicine; and Morris Weinberger, PhD, of the University of North Carolina School of Public Health and the Center for Health Services Research in Primary Care at the Durham VA Medical Center. The study was funded by the Robert Wood Johnson Foundation.