VA RESEARCH CURRENTS

RESEARCH NEWS FROM THE U.S. DEPARTMENT OF VETERANS AFFAIRS • OCTOBER 2007

Brain-imaging tool may offer quick mental-health diagnostics

esearchers at the Minneapolis VA have found that a brainimaging technology called magnetoencephalograpy, or MEG, may be a fast, accurate, non-invasive way to diagnose mental-health and neurological disorders such as Alzheimer's disease, schizophrenia and multiple sclerosis.

"The test takes only three minutes, and it's totally non-invasive," said Apostolos P. Georgopoulos, MD, PhD, director of the Brain Sciences Center at the Minneapolis VA and professor of neuroscience, neurology and psychiatry at the University of Minnesota.

see MEG on pg. 7



Apostolos P. Georgopoulos, MD, PhD, is seen here with a patient about to undergo a MEG scan at the Brain Sciences Center at the Minneapolis VA.

Message from the CRADO

Extra \$32.5M for OIF/OEF research

By Joel Kupersmith, MD, chief research and development officer

This past spring, VA received a supplemental appropriation from Congress that included \$32.5 million for research specifically targeted to the needs of veterans of operations Iraqi Freedom and Enduring Freedom (OIF/OEF). Some of the areas that have been funded as a result of this extra appropriation include the following:

• **Traumatic brain injury**—This is the signature condition of the current conflict. Funded research is directed toward improved diagnostic criteria, better methods for screening for TBI and assessing treatment effectiveness, and new treatments to lessen the emotional, behavioral and psychomotor complications of TBI.

• **Spinal cord injury**—Research in this area is directed toward developing improved understanding and treatment of spinal cord injury.

• Sensory loss—Blast and impact injuries often result in hearing and vision loss, including, very commonly, tinnitus. Studies will explore new methods for diagnosis, evaluation and treatment.

• **Post-deployment mental health**—Chronic PTSD, as well as PTSD complicated by or possibly confused with

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The brochure pictured here, about VA research on the health needs of OIF/OEF veterans, can be previewed at www. research.va.gov/resources/pubs/default.cfm and obtained by contacting VA Research Communications at (410) 962-1800, ext. 223, or research.publications @va.gov.



Studies find some benefits to limits on new doctors' work hours

tudies by VA investigators and colleagues have found modest benefits—and no apparent ill effects—to nationwide regulations enacted in 2003 to limit work hours for medical residents in U.S. teaching hospitals, in the hope of preventing fatigue-related medical errors.

The most recently published studies appeared in the Sept. 5 *Journal of the American Medical Association*. One study looked at VA hospitals, while the other was based on Medicare data from non-VA hospitals.

"We can say there's some evidence of benefit in terms of mortality outcomes," said Kevin G. Volpp, MD, PhD, of the Center for Health Equity Research and Promotion at the Philadelphia VA Medical Center and the University of Pennsylvania, lead author on both studies. He stressed that neither study found evidence that outcomes had worsened. Some experts have feared the new policy could harm patients by reducing continuity of care.

Rules limit weekly hours to 80

The rules, developed by the Accreditation Council for Graduate Medical Educa-

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The study on VA hospitals included data on nearly 319,000 patients at 131 sites. It compared the three-year period before the regulations with the two-year period following the implementation. All the patients had been admitted for surgery or one of the following medical conditions: heart attack, congestive heart failure, gastrointestinal bleeding, or stroke.

Benefits seen in second year

The researchers found no significant change for the first year the new rules were in place, but by year two, the risk of dying had decreased in more teaching-intensive VA hospitals—those with more residents per hospital bed. But the improvement seemed to affect only medical patients, and not those admitted for surgery. Volpp suggested that for surgery patients, the benefits of the policy may have been offset to a greater extent by a reduction in continuity of care.

The other study by the same group, an analysis of Medicare data on more than eight million non-VA patients, found no significant worsening or improvement in mortality.

Volpp said the differences in findings between the VA and Medicare studies may have been due to "the markedly greater mean resident-to-bed ratios at VA teaching hospitals compared with non-VA teaching



Under rules enacted in 2003, medical residents can work no more than 80 hours per week.

hospitals, and better information systems within VA that may have mitigated some of the potential downsides of the work-hour regulation in terms of continuity of care."

Earlier this year, a study by researchers at the Palo Alto VA and Stanford University School of Medicine, published in the July 17 *Annals of Internal Medicine*, yielded similar results: The authors found somewhat lower death rates in high-risk medical patients in community-based teaching hospitals after the enactment of the new regulations, but no improved outcomes for surgical patients. "It's difficult to say, based on our findings, that the regulations are good for everyone," said lead author Kanaka Shetty, MD. "But they do appear to have a modest impact on some."

Another study published in the same edition of *Annals*, this one by a group at Yale University School of Medicine and the West Haven VA, found improved outcomes in some measures but not others, and "no evidence of adverse unintended consequences after the institution of workhour regulations."

Scientist traces genetic ties between alcoholism, anxiety

ats that love to drink alcohol are kept quite busy in the lab of Subhash C. Pandey, PhD, a neuroscience investigator at the Jesse Brown VA Medical Center in Chicago and the University of Illinois.

"This is a very good animal model—it really mimics human alcoholism," says Pandey of the alcohol-preferring rodents—otherwise known as P rats—that he uses in much of his research. "These animals really drink heavily. If we can learn why, this could lead to the development of new treatments for alcoholism."

Pandey and his colleagues have already revealed part of the answer. Their work made headlines a few years ago when they showed that P rats appear to drink because of anxiety, and discovered a genetic and biochemical pathway linking the two behaviors. Pandey's team has continued to probe this area, and is coming closer to identifying promising new drug targets for both conditions.

Clinically, alcoholism and anxiety often occur together, and pose a significant double-blow to many veterans in VA's health system. Last year, among VA outpatients alone, more than 31,000 had both diagnoses.

The anxiety-alcohol link

The connection might seem like a no-brainer: Because alcohol is relaxing, people with anxiety are more likely to start drinking. But that's only the case with some alcoholics, according to Pandey. Other people drink initially for pleasure. They develop anxiety only after they try to stop drinking and experience withdrawal. "One of the early withdrawal symptoms is anxiety," explains Pandey. "At this point, the person may drink again only to self-medicate the anxiety that developed during withdrawal. This can be a crucial factor in the continued consumption of alcohol and in relapse."

In either scenario, anxiety and alcoholism appear to be linked by the same genes and proteins. Pandey's queries over the past few years have focused on a molecule called CREB (cAMP responsive element binding protein). It's a transcription factor, which means it turns various genes on or off. So while several dozen genes have been implicated over the past decade as playing a role in alcoholism—some with relatively modest influence—CREB may be a kind of "team captain." Alcoholism is thought to be 40 to 60 percent hereditary, or gene-dependent.

CREB also affects other brain functions and is thus a big topic in mental health research, says Pandey. So far, he has compelling evidence that CREB is the hub of the metabolic pathway linking



Subhash C. Pandey, PhD, measures anxiety in rats and mice by observing their behavior in a device called the elevated plus-maze. It has two enclosed arms, which the animals perceive as more secure, and two open arms, which they perceive as potentially dangerous.

alcoholism and anxiety. His team has found that by modulating CREB activity up or down—and thereby altering the levels of brain chemicals controlled by CREB—they can change the anxiety level of rodents and their tendency to drink alcohol.

A 2003 study by the group showed that when rats experienced withdrawal symptoms, CREB activity went down and anxiety shot up. The researchers followed with an experiment to see what would happen in mice that were genetically engineered to lack CREB. In short, these rodents behaved just like the P rats, which had been selectively bred—but not genetically engineered per se—to prefer alcohol.



Recent publications and presentations by VA investigators

Below is a brief sampling of recent publications and presentations by VA investigators, based on notifications received from the field by VA R&D Communications. (Reporting requirements for VA investigators can be viewed at www. research.va.gov/resources/ policies/pub_notice.cfm.) Only VA-affiliated authors are listed here, due to space constraints.

"Alternative Splicing and Nonsense-Mediated mRNA Decay Regulate Gene Expression of Serum Response Factor." Jeanne Wei, MD. Little Rock. *Gene*, Oct. 1, 2007.

"Associations in Sense of Coherence and Depresion in Caregivers of Stroke Survivors Across Two Years." Neale R. Chumbler, PhD; Maude R. Rittman, PhD, RN: Samuel S. Wu, PhD. **Gainesville.** Journal of Behavioral Health Services and Research, Sept.12, 2007.

"Characteristics of VA Patients Who Use Low-Quality Private Sector CABG Centers in New York." William B. Weeks, MD, MBA; Elliott S. Fisher, MD, MPH. White River Junction. Medical Care Research and Review, Sept.18, 2007.

"A Closer Look at Pain and Hepatitis C: Preliminary Data from a Veteran Population." Amy K. Silberbogen, PhD; E. Amy Janke, PhD; Claire Hebenstreit. **Boston, Hines.** Journal of Rehabilitation Research & Development, Vol. 44, No. 2 (2007).

"Cost-Effectiveness of Universal Bone Densitometry Followed by Treatment of Those with Osteoporosis Compared to No Densitometry or Treatment in Elderly Caucasian Men." **Minneapolis.** *Journal of the American Medical Association,* Aug. 8, 2007.

"Declines in Invasive Breast Cancer and Use of Postmenopausal Hormone Therapy in a Screening Mammography Population." Karla Kerlikowske, MD. **San Francisco.** *Journal of the National Cancer Institute*, Sept. 5, 2007.

"Demographic, Clinical, and Quality of Life Variables Related to Embarrassment in Veterans Living with an Intestinal Stoma." C. Max Schmidt, MD, PhD; Clifford Y. Ko, MD; Christopher Wendel, MS; Robert S. Krouse, MD. Indianapolis, Los Angeles, Tucson. Journal of Wound, Ostomy and Continence Nursing, Sept./Oct. 2007.

"Effect of an Oral Iron Chelator or Iron-Deficient Diets on Uroporphyria in an Animal Model of Porphyria Cutanea Tarda." Nadia Gorman, MS; Adrian Zaharia, MD; Heidi S. Trask, PhD; Jacqueline F. Sinclair, PhD; Peter R. Sinclair, PhD. **White River Junction.** *Hepatology*, Sept.13, 2007.

"Ethnic Differences in Alcohol Treatment Outcomes and the Effect of Concurrent Smoking Cessation Treatment." Steven S. Fu, MD, MSCE; Molly Kodl, PhD; David B. Nelson, PhD; Sean Nugent; Amy A. Gravely, MA; Anne M. Joseph, MD, MPH. **Minneapolis.** *Drug and Alcohol Dependence*, Aug. 3, 2007.

"Fracture Risk Following Parathyroidectomy Among Chronic Hemodialysis Patients." Annemarie Dooley, MD; Bessie Young, MD, MPH. **Seattle.** *Journal of the American Society of Nephrology,* Aug. 2007.

"Patient, Physician, Pharmacy and Pharmacy Benefit Design Factors Related to Generic Medication Use." Steven M. Asch, MD, MPH. Los Angeles. Journal of Internal Medicine, Sept. 2007.

"Prevalence and Factors Associated with Dry Skin in HIV Infection: The FRAM Study." Carl Grunfeld, MD, PhD; Rebecca Scherzer, PhD. **San Francisco.** *AIDS*, Oct. 1, 2007. "Problem-free Drinking over 16-years Among Individuals with Alcohol Use Disorders." Mark A. Ilgen, PhD; Paula L. Wilbourne, MS; Bernice S. Moos; Rudolf H. Moos, PhD. **Ann Arbor, Palo Alto.** *Drug and Alcohol Dependence,* Aug. 22, 2007.

"Screening for Post Traumatic Stress Disorder in VA Primary Care Patients with Depression Symptoms." Martha S. Gerrity, MD, MPH, PhD; Kathryn Corson, PhD; Steven K. Dobscha, MD. **Portland.** *Journal of General Internal Medicine*, Sept. 2007.

Researchers at veterans' conventions

This past summer, VA's Office of Research Development coordinated speaking engagements for VA researchers at the national conventions of several Veterans Service Organizations (VSOs). Below is a list of the speakers, their VA site, the topic they addressed, and the VSO meeting they attended:

• Judith Long, MD, Philadelphia—"Diabetes and You." Montford Point Marines Association.

• Joe Maino, OD, Kansas City, Mo.— "When is 20/40 not 20/40?" Blinded Veterans Association.

• Lisa Rubenstein, MD, MPH, Sepulveda—"PTSD and Mental Health in Women Veterans." American Legion.

• Jennifer Strauss, PhD, Durham—"PTSD and Military Sexual Trauma in Women Veterans of the Conflict in Iraq." AmVets.

• Elizabeth Yano, PhD, Sepulveda— "Setting Evidence-Based Priorities to Improve the Health and Health Care of Women Veterans." Disabled American Veterans.

• Tara Zaugg, AuD, Portland—"Hearing Loss in Veterans." Veterans of Foreign Wars.



Tampa VA researcher receives 'Service to America' medal

avid Vesely, MD, PhD, a physician-researcher at the Tampa VA Medical Center and University of South Florida, has won a 2007 Service to America Medal, or "Sammie," for his discovery and subsequent studies of three cardiac hormones that have shown extraordinary cancer-fighting abilities in lab experiments.

The annual awards, started by the Partnership for Public Service in 2002, go to 10 federal employees whose work has made—or promises to make—a significant impact in the lives of Americans, in areas ranging from national security to health science. Vesely was cited for "Career Achievement" for his pioneering research.

Cardiac hormones may help cancer

Vesely, with the Tampa VA since 1987, focused his early research on congestive heart failure and kidney failure. When he lost his wife to breast cancer in 2002, he expanded his studies to look at cancer. He has since found that the heart-produced hormones he discovered may not only help heart and kidney failure, but cancer as well.

His lab research shows that giving these heart hormones to cancer cells eliminates up to 97 percent of all cancers in 24 hours. This includes some cancers that are nearly untreatable or have a very low survival rate, such as brain tumors and malignant pancreatic and ovarian tumors.

Published in the May/June 2007 issue of the journal *In Vivo*, Vesely's latest research showed that up to 80 percent of adenocarcinomas (tumors in glands) growing in lab mice can be cured with these hormones—particularly atrial natriuretic peptide, or ANP. Of those human pancreatic cancers that weren't cured, the tumors shrunk to a tenth the size of tumors in untreated mice.

"Significantly, even in the carcinomas it didn't cure, it decreased the volume of these cancers to less than 10 percent, and the animals didn't die of cancer—they died of old age," said Vesely. "Thus, this is a new concept in cancer treatment. Even if you don't cure every cancer, some can be treated like a 'chronic disease' which one lives with, but doesn't die from."

Vesely also pointed out that the hormones would be basically nontoxic as a human therapy, especially compared with conventional chemotherapy. "Since these peptides are made by your own body, they have almost no side effects. The body doesn't recognize them as foreign, and thus, it doesn't develop antibodies which can



David Vesely, MD, PhD, is a researcher and chief of endocrinology, diabetes and metabolism at the James A. Haley VA Medical Center in Tampa.

Career milestones

Andrew Goldberg, MD, director of the Geriatric Research, Education and Clinical Center (GRECC) at the Baltimore VA Medical Center, received the 2007 Joseph T. Freeman Award from the Gerontological Society of America for his research, clinical and mentoring contributions in the areas of exercise physiology, obesity and metabolism.

Hugh Herr, PhD, of the Media Lab at the Massachusetts Institute of Technology (MIT) and the Providence-based Center for Restorative and Regenerative Medicine, a collaborative research initiative among VA, Brown University and MIT, received the 13th annual Heinz Award for Technology, the Economy and Employment. Herr, a double amputee and widely known bioengineer who has led efforts to develop new prosthetic devices that merge body and machine, was one of six distinguished Americans to receive a \$250,000 award from the Heinz Family Foundation. "Everything about Dr. Herr is an expression of the triumph of the human spirit over adversity," said foundation chair Teresa Heinz.

John Donoghue, PhD, also with VA's Center for Restorative and Regenerative Medicine, won the K.J. Zulch Prize from Germany's Max Planck Society for his work on a new brain implant and decoding system that has allowed research volunteers with paralysis to control robotic and electronic devices using only their thoughts. The award is one of the highest international honors for neurological research.



Health issues common among combat troops returning from Iraq and Afghanistan, such as traumatic brain injury, are the focus of a recent \$32.5M funding supplement from Congress for VA research.

OIF/OEF (from pg. I)

TBI, depression and other psychiatric disturbances, are matters of great concern to veterans and the nation. Projects funded via the supplemental appropriation will include research on early interventions, psycho-physiological reactivity, enhancing resilience and prevention of PTSD, evaluating access to care, vocational rehabilitation, and potential genetic markers for development of PTSD and response to treatments. This last group of projects also advances us toward the goal of personalized medicine for veterans with PTSD.

• **Prosthetics and amputation healthcare**—Funded projects include those related to proper fitting, rehabilitation and functional use of prosthetics by amputees. In addition, there will be new efforts geared to improving understanding of wound healing and tissue regeneration to minimize the need for amputation in the first place.

• **Chronic pain**—About a quarter of returning OIF/OEF veterans report chronic pain that interferes with daily activities. Funding will include a variety of pain-research initiatives to assess, manage and treat chronic pain; assist a seamless transition to civilian life; develop novel therapies for neuropathic pain; and develop new coping strategies to improve rehabilitative outcomes.

• Smoking and other substance-use disorders—Smoking cessation is particularly important among returning veterans due to the strong association of smoking with deployment. Interventions designed to predict post-deployment needs and facilitate recovery from other substance-use disorders will also be funded.

This is by no means a complete list of all the areas that are deemed relevant to the needs of OIF/OEF veterans, but it does give examples of topics that are considered high priorities to VA. The Office of Research and Development is dedicated to conducting research that will contribute to optimal care for these brave men and women, as well as for all our nation's veterans.



VA-tested shingles vaccine now available for veterans

A vaccine for shingles, tested by VA and the National Institutes of Health (NIH) in one of the largest adult vaccine trials ever, is now available to veterans at VA medical facilities nationwide.

VA physicians will offer the vaccine to appropriate patients—usually those who are 60 years of age or older and have healthy immune systems. A single dose of the vaccine offers protection against shingles, or herpes zoster. The disease, marked by a painful blistering rash, is caused by a reawakening of dormant chickenpox virus in the body. It can affect anyone who had chickenpox as a youth—virtually all middle-aged and older Americans.

The VA-NIH clinical trial, led by Michael Oxman, MD, of the San Diego VA Healthcare System, involved nearly 39,000 older adults. The vaccine reduced the incidence of shingles by 51 percent and dramatically lessened its severity in the cases that did occur. Moreover, vaccine patients were only one-third as likely to develop a complication known as post-herpetic neuralgia, a form of severe chronic nerve pain. Findings from the study appeared in the *New England Journal of Medicine* in 2005, and the vaccine was approved by the Food and Drug Administration last year.

SERVICE (from pg. 5)

affect a person's immune system. Also, the hormones don't have the side effects of cancer drugs currently being used. In the lab, we gave these peptide hormones 24 hours a day for an entire month at the concentration which eliminates cancers growing in living tissue, without a single side effect."

The next step in Vesely's research will be clinical trials testing the cardiac hormones in congestive heart failure and cancer.



Joel Kupersmith, MD, is chief research and development officer for VA.

MEG (from pg. I)

His team recently published a study involving 142 volunteers—one group of healthy controls, and six groups representing six different brain conditions: Alzheimer's, schizophrenia, alcoholism, Sjogren's syndrome, multiple sclerosis, and facial pain. The researchers showed that each condition corresponds to a particular pattern of neural activity in the brain, as recorded by MEG. The results appeared in the Aug. 27 issue of the *Journal of Neural Engineering*.

The MEG machine itself resembles a giant, space-age salon hair dryer. It has hundreds of sensors that pick up miniscule magnetic signals that result when brain cells "talk" to each other through electrical impulses.

The setup at the Minneapolis VA costs about \$2 million, almost a quarter of which funded the construction of a special shielded room, made of a nickel-iron alloy and aluminum, to reduce magnetic interference from the outside. "If you're in a place like downtown New York City, with subways running underground, you need a lot of shielding," said Georgopoulos. "We're extremely quiet here in Minneapolis, and we were able to get away with the first tier of shielding, which costs about \$400,000."

MEG is relatively rare technology

The scientist points out that there are fewer than 100 MEG instruments in the world, and only about a dozen that are as high-density as the one in his lab. Density is a function of the number and positioning of the super-conducting sensors in the unit; the higher the density, the more sensitive and accurate the instrument.

Electroencephalography, or EEG—an older, more commonplace technology—also eavesdrops on the brain's electrical activity. But the signals get distorted as they pass through the skull and the soft tissue surrounding the brain.



Other types of brain scans, such as functional MRI and PET, measure metabolic factors such as blood flow or oxygen use in the brain. Other scans, like CT and conventional MRI, offer static images of structure. None of these shows how neurons communicate with each other, which in some brain diseases is the only evidence of abnormality. Some of these techniques, however, can be used in conjunction with MEG to provide a fuller picture of brain function.

Perhaps the key difference between other brain-imaging technologies and MEG, says Georgopoulos, has to do with speed. MEG records brain activity essentially in real time—down to a thousandth of a second. That's how fast brain cells talk with each other. Other types of scans involve lags of three seconds or longer. In trying to understand brain function, says the researcher, that difference is critical.

"From the time you see the red light to the time you step on the brakes, everything happens in a fraction of second. The whole brain—the cerebellum, the visual cortex, the motor cortex—is involved in an extremely fast loop of processing. So if you're waiting three seconds to get an integrated picture of what's happening in the brain, there's a lot of potentially valuable information you've lost." Dr. Georgopoulos foresees a great demand for MEG as a screening and diagnostic tool—especially in cases involving subtle progressions of a disease over time.

Georgopoulos' lab is now collecting MEG data from patients with other conditions, such as PTSD, Parkinson's disease and depression. "We need about 100 per group to really develop the template and start using this as a diagnostic test," he says.

Tracking Alzheimer's disease

The VA researcher foresees a great demand for MEG as a screening and diagnostic tool—especially in cases that involve subtle progressions of a disease over time. He offers the example of tracking the brain-cell-firing patterns of older patients with signs of memory loss. "Some people with mild cognitive impairment will develop frank Alzheimer's, and others will not. The outcome of our MEG analysis is a continuum. We differentiate between normal and a particular diagnosis if there's a probability of more than 50 percent. Say you have an older person who tends to forget, and you get a reading of .2 Alzheimer's and .8 normal. After six months or a year, that reading could change, and you would have a good objective measure of whether the person is progressing toward Alzheimer's or remaining stable."

In his research with chronic alcoholics, he was able to detect subtle improvements in their neural patterns as they went successive days without drinking. "By day seven, they were much closer to normal," he said.

The work recently published in the *Journal of Neural Engineering* was funded mainly by the University of Minnesota, VA and the American Legion.



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ALCOHOLISM (from pg. 3)

"If CREB is so crucial, we wanted to see how CREB-deficient mice would behave," says Pandey. "We found that even from birth, they're particularly anxious, and they consume more alcohol."

That research, the first direct evidence of a CREB link, was followed by other studies in which Pandey's team implicated a particular region of the brain in the process: the amygdala, which is involved in reward, reinforcement and motivation. They also traced CREB's effects further along the metabolic pathway to some of the proteins it controls. Two examples are neuropeptide Y (NPY), a brain chemical that interacts with neurotransmitters such as serotonin and dopamine and protects against stress and anxiety; and BDNF, a nerve-nourishing protein that also fights anxiety and appears to be involved in the action of Prozac and similar antidepressants.

Today, Pandey and colleagues are continuing to make strides in demonstrating the effects of CREB and its related proteins on anxiety and alcoholism. Now that he knows the specific area of the brain



Dr. Subhash C. Pandey's research has been funded by VA and the National Institute on Alcohol Abuse and Alcoholism.

involved—in fact, his group has honed in on two of the amygdala's three subregions—he would like to eventually explore how brain-imaging technology, such as functional MRI, can be used to extend these findings to clinical studies.

Other areas he aims to study in relation to anxiety and alcoholism are how environmental factors alter the expression of CREB-dependent genes, and how CREB and its related proteins affect not only the function of brain cells, but their actual structure, or morphology. It's an ambitious goal, but the dedicated scientist keeps his eye on the endgame: "Linking gene, to protein, to morphology of the neuron, to behavior," says Pandey—"this is how we can discover the best drugs to treat these conditions."

