



RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs



Photo by Kevin Walsh

MEG brain scans play a big role in neuroscience research at the San Diego VA

6

WHAT'S INSIDE

Fast Findings

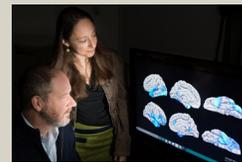
2



The loneliness factor: How much does it drive depression in Veterans? **10**



'Mystery shopper' model being used to boost VA care **13**



PTSD and accelerated aging: How advanced is the science? **14**



Suicide prevention: They've got each other's backs **16**



Advisory committee key to shaping VA research initiative **19**



VA Researchers Who Served: Dr. Gina McCaskill **20**



Lab study suggests curcumin could improve memory, mood in Gulf War illness

Curcumin may lead to better cognitive and mood for those with Gulf War illness, according to a rat study by Olin E. Teague Veterans' Medical Center and Texas A&M researchers. Curcumin is a natural antioxidant compound found in turmeric and other plants, and is sometimes sold as an herbal supplement. Rats with simulated Gulf War illness symptoms were treated with either curcumin or a placebo for 30 days. Those in the curcumin group had better cognitive and mood function, based on behavioral tests. They also had better neurogenesis (growth and development of nerve tissue) and lower inflammation than the placebo group. The researchers hypothesize that changes in gene expression caused by curcumin could improve memory and mood symptoms related to Gulf War illness. (*Brain, Behavior, and Immunity*, March 2018)

The print edition of
VA Research Currents
 is published quarterly by:
VA Research Communications
U.S. Department of Veterans Affairs
 31 Hopkins Plaza, Ste. 102
 Baltimore, MD 21201
 443-759-3456
varesearchcurrents@va.gov

Read the expanded online edition of
 VA Research Currents at www.research.va.gov

 facebook.com/VAResearch

 twitter.com/VAResearch

Editor/writer: Mitch Mirkin
 Writers: Mike Richman, Tristan Horrom
 Layout: Robert Williams

Any health information in this newsletter is strictly for informational purposes and is not intended as medical advice. It should not be used to diagnose or treat any condition.



Photo: ©iStock/onairjw

VA



U.S. Department
 of Veterans Affairs



Photo: ©iStock/g-stockstudio

One-day workshop shows promise for migraine sufferers

A one-day behavioral intervention workshop for Veterans with migraine improved symptoms and pain acceptance, found a Houston VA HSR&D Center for Innovation and Baylor College of Medicine study. Twenty-five Veterans with migraines along with depression or anxiety attended the workshop, which featured education and elements of acceptance and commitment therapy, a type of cognitive behavioral therapy. Participants said that the workshop helped them better understand their condition and

empowered them to better manage their headaches. The training led to greater awareness of how stress can make headaches worse. At a three-month follow-up, participants had significantly improved depressive and anxiety symptoms, general functioning, and headache-related disability. Findings of this small trial suggest that educational workshops could have important benefits for treating migraines, pending replication in a more rigorously designed large-scale study. (*Military Medicine*, Feb. 6, 2018)

Steroid drug may help PTSD symptoms

The drug dexamethasone improved PTSD symptoms when paired with trauma memory activation, in a VA North Texas Health Care System study. Dexamethasone is a glucocorticoid—a type of steroid involved in glucose metabolism and the immune system. It is commonly used to treat a number of conditions, such as rheumatoid arthritis, allergies, and asthma, because of its anti-inflammatory properties. Fifty-four male Veterans with PTSD received either dexamethasone or placebo. The first group was given the drug while doing a trauma memory reactivation task in four weekly sessions. Those treated with the drug had significantly lower PTSD symptoms at one- and three-month follow-ups. They also had lower symptoms six months later, but the results were no longer significant relative to the placebo group. The drug is thought to facilitate the extinction of fear memories—meaning that the memory is replaced with new learning. Extinction is impaired in people with PTSD. The drug has an “excellent high-dose safety profile,” according to the researchers, although it could have side effects such as increased appetite, insomnia, heartburn, and muscle weakness, and increased blood sugar. One study participant was hospitalized because of leg swelling that possibly resulted from the drug. Further trials are needed to explore the drug’s potential role in PTSD treatment, say the researchers. (*Psychiatry*, Winter 2017)

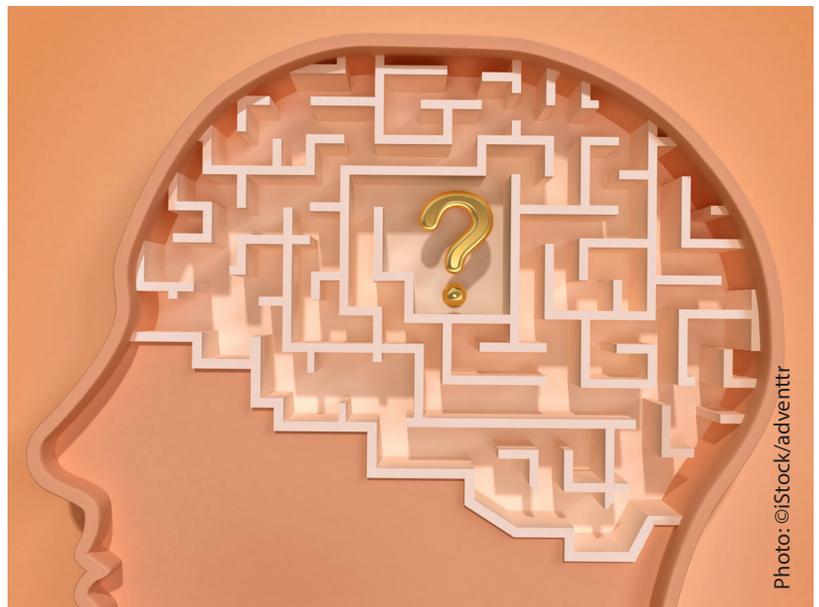


Photo: ©iStock/adventtr



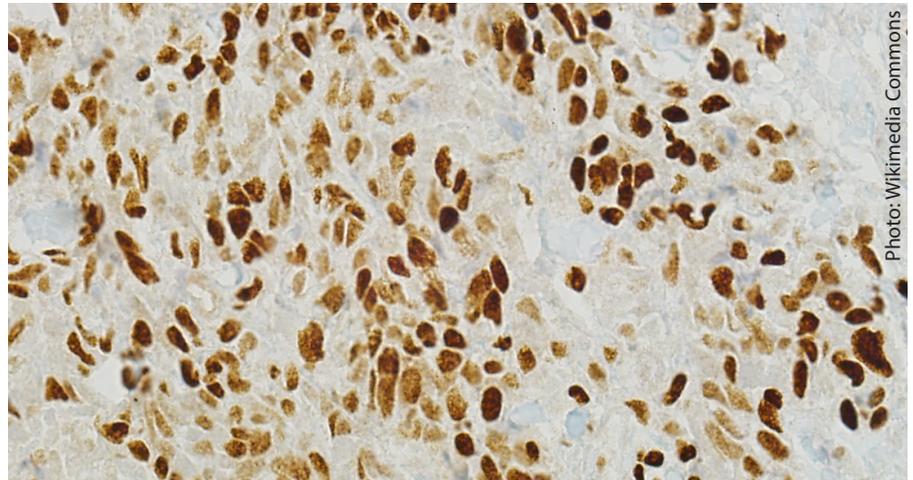
Non-specialists do as well as specialists at treating sleep apnea

Patients with obstructive sleep apnea receive similar quality of care from sleep specialist physicians and non-sleep specialists, found a Minneapolis VA Health Care System review. Four studies found that sleep specialist physicians and non-sleep specialists performed equally well at diagnosing obstructive sleep apnea and classifying its severity. Eight other studies showed that patients with both types of providers had similar quality of life, adherence to

treatment, and symptom scores. Using dedicated sleep specialist physicians can be expensive and inefficient. The researchers believe that more research is needed on the best and most efficient care models for sleep apnea. (*Annals of Internal Medicine*, Feb. 6, 2018)

Natural language processing accurate at analyzing bladder cancer reports

Natural language processing was successful at identifying details on patients with bladder cancer from medical reports. Researchers analyzed 600 reports on patients with bladder cancer from the VA's Corporate Data Warehouse using a computer engine that looks at language. They used this set of reports to develop and evaluate the computer program. Researchers then applied the natural language processing engine to more than 10,000 other reports. The program was able to accurately detect pathologic characteristics—such as tumor structure, depth, and grade—in 99 percent of patients. This technology could be used to group cancer patients together by similar characteristics for future studies. (*Urology*, December 2017)



Neuropeptide Y may not be good biomarker for PTSD

Neuropeptide Y levels were not found to indicate PTSD risk, in a Dutch and American study including a VA San Diego Healthcare System researcher. Neuropeptide Y is a neurotransmitter associated with the stress response. Previous research had suggested that high neuropeptide Y levels might protect against PTSD. The researchers looked at neuropeptide Y levels in 3,319 U.S. Marines and Dutch service members both before and after deployment. They did not find any connection between neuropeptide Y levels and level of PTSD symptoms at either time point. The results suggest that neuropeptide Y may not be a useful biomarker for PTSD risk, say the researchers. (*Biological Psychology*, April 2018)



Study: Written exposure therapy as effective as cognitive processing therapy

Written exposure therapy had similar effects to cognitive processing therapy for treating PTSD, found a VA Boston Health Care System study. Cognitive processing therapy is considered the gold standard for PTSD treatment. Written exposure therapy involves five weekly sessions, compared with 12 sessions in cognitive processing therapy. The researchers assigned 63 patients to written exposure therapy and 63 to cognitive processing therapy. Participants in written exposure therapy had similar improvements in PTSD symptoms as cognitive processing therapy participants after 36 weeks. The findings suggest that written exposure therapy could offer an efficient PTSD treatment for patients unlikely to complete longer-term therapy, say the researchers. (*JAMA Psychiatry*, March 1, 2018)





Dr. Mingxiong Huang prepares to do a MEG brain scan on a “healthy control” who has participated in his neuroimaging research.

Studies using electrical stimulation, neuroimaging aim for new insights on TBI, PTSD

VA scientists are studying an experimental electrical brain-stimulation technique, coupled with neuroimaging, to learn how mild traumatic brain injury interacts with PTSD in specific areas of the brain.

VA scientists are studying an experimental electrical stimulation technique, coupled with neuroimaging, to learn how mild traumatic brain injury interacts with PTSD in specific areas of the brain.

Researchers at the VA San Diego Healthcare System are carrying out a double-blind study on the procedure in collaboration with the University of California, San Diego.

The study involves 200 Veterans with chronic effects of mild traumatic brain injury (mTBI), which is a concussion, and PTSD. Half will undergo a form of non-invasive transcranial electrical stimulation called IASIS that sends low-intensity pulses to the brain, combined with an EEG (electroencephalography) to monitor brain activity. The pulses are aimed at reducing abnormally slow brain waves, as well as post-concussion and PTSD symptoms.

The rest of the Veterans are in a control group. They will not get IASIS treatment but will be scanned multiple times to assess the test-retest reliability of the MEG measurements.

Three MEG scans are being performed for the IASIS group, one at baseline, one in the middle of the six-week treatment course, and the third at follow-up. MEG is a neuroimaging process that can detect changes in abnormal slow waves in specific areas of the brain.

Dr. Mingxiong Huang, a research scientist at VA San Diego, is leading the study, which is expected to be completed in 2021. He says he and other MEG researchers have learned that the brains of people with mTBI generate abnormal slow waves. Slow-wave MEG source imaging is a promising marker for detecting specific regions of the brain that are impaired by a mild TBI, with an 85 percent accuracy rate, he says.

More conventional imaging tools, such as a CT scan or a structural MRI, have an accuracy rate of only about 5 percent in detecting mTBI, he says.

“This makes MEG a good functional imaging technique not only for assisting in the diagnosis of mTBI, but also for assessing the efficiency of mTBI treatments, such as drugs,” says Huang, who is also a professor in the department of radiology at the University of California, San Diego (UCSD). “The results from the study may provide information that could lead to large-scale clinical use of low-intensity transcranial electrical stimulation.”

An example of how alternative therapies can be tested

MEG-based studies are rare, Huang says, most likely because only 20 to 30 MEG scanners are available in the United States. In addition to the VA San Diego, VA medical centers in Minneapolis, Albuquerque, Boston, Seattle, Philadelphia, and San Francisco have also performed MEG research.

“There’s a huge population of Veterans with chronic mTBI and PTSD,” he says. “In fact, studies show that pre-existing mild TBI might double the likelihood of PTSD. The question is why. Treating the mild TBI components might also improve PTSD symptoms. That’s why this research is necessary to understand the interaction between mild TBI and PTSD.”

Huang and his team believe that Veterans in the IASIS group will show much greater declines in post-concussion and PTSD symptoms between the baseline and post-treatment MEG scans.

“Dr. Huang is one of our leading innovative MEG investigators,” says Dr. Stuart Hoffman, scientific program manager for brain injury in VA’s Office of Research and Development, which is sponsoring the study. “This ongoing early phase clinical study is a perfect example how alternative therapies can be tested with scientific rigor and validated methods. If efficacy is found in this early-phase study, a future phase 3 trial could be possible.”

IASIS, the Greek word for healing or cure, is one in a family of low-intensity, pulse-based electrical brain stimulation techniques. It differs from its counterparts, such as LENS and FNS, mainly because it has a lower pulse rate. The low-intensity pulses that IASIS delivers are thought to be more beneficial than LENS, for example, for normalizing brain signals, reducing abnormal slow waves, and speeding up the recovery process, according to Huang.

In recent years, the medical community has focused increasing attention on non-invasive brain-stimulation technologies, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). The former applies an electrical current to the skull and brain, while TMS makes use of a magnetic field that the brain translates into electrical activity. Both techniques have the potential to positively impact

“In the past, we observed that people with mild TBI had pathological slow waves, and with that we were able to localize the site of the injury.”

Continued on next page



Ashley R. Swan, a research associate with Dr. Mingxiong Huang's team, demonstrates how IASIS is administered. The therapy sends low-intensity pulses to the brain.

neurons, brain cells that carry electrical impulses, and can help treat such conditions as depression.

These technologies are being tested on patients with mild TBI. But, as in the case with IASIS, more evidence is needed from clinical trials before they can get FDA approval and come into routine use.

Mild traumatic brain injury is a leading cause of chronic health problems in Veterans, active-duty service members, and civilians. VA has diagnosed TBI in more than 93,000 Vets who suffered brain injuries from blasts and other forms of trauma in the wars in Iraq and Afghanistan.

Mild TBI symptoms include headaches, mood changes, confusion, slow thinking, nausea, loss of smell, sleep disturbance, poor memory, and a sensitivity to light and sounds. In most people with mTBI, symptoms resolve within days after an injury, but they can persist for months or longer. Few treatments are available, partly because the pathology of the chronic effects isn't fully understood.

Decline in abnormal waves, post-concussive symptoms

Huang's research follows a VA-funded pilot study in which MEG scans revealed a sharp decline in abnormal brain waves in six mTBI Veterans who underwent the IASIS procedure. The findings appeared in the

journal *Brain Injury* in September 2017.

Huang, who led the study, says it was the first neuroimaging evidence of changes produced by a pulse-based brain stimulation technique in Veterans with traumatic brain injury.

Six Veterans with mild mTBI took part in the study, five of whom were post-9-11 Vets. Three of the participants had a blast-related mTBI, two from a car accident, and one from blunt trauma. Scientists at VA San Diego and USCD carried out the IASIS and MEG procedures.

A baseline MEG scan showed abnormal brain waves in all six Veterans. They then underwent six weeks of IASIS, receiving weak electrical currents via scalp electrodes during two 30-minute sessions per week. The pulses were well below the sensory threshold so the patients couldn't feel them. The process involved simultaneous EEG monitoring.

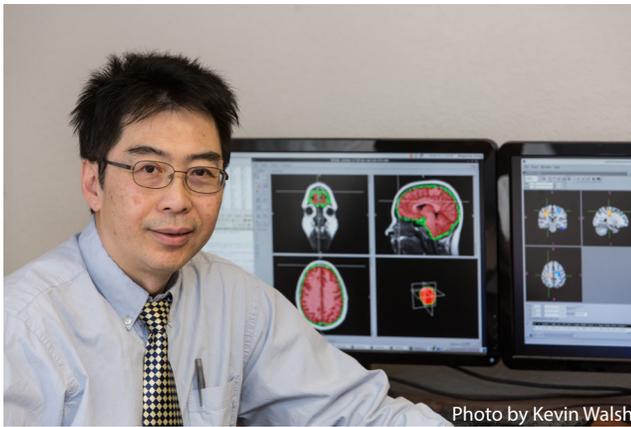
The typical length for IASIS treatment is 10 weeks. But the number of participants and the limited availability of MEG resources forced Huang and his team to reduce the length of the testing.

The MEG scans were performed while the Vets were awake but had their eyes closed. Evidence has been rising in support of resting-state MEG slow-wave imaging during wakefulness as an imaging marker for brain abnormalities in people with mTBI.

The researchers performed follow-up MEG scans to investigate the neuronal changes. The scans showed an average decline of 54 percent in abnormal slow waves in approximately the same regions that had abnormal waves during the baseline exam. The pre-frontal lobe is the most common brain area that generated abnormal slow-waves in the Veterans with mTBI, suggesting that region is quite vulnerable to combat-related brain injuries, Huang says.

He notes that it's important to be able to see the abnormal waves.

"In the past, we observed that people with mild TBI had pathological slow waves, and with that we were able to localize the site of the injury," he says.



Dr. Mingxiang Huang is a neuroscientist with VA and the University of California, San Diego.

“To be able to see the reduction in slow waves is key because now we can start looking at why people get better. So the neuroimaging that documents the neuronal changes due to the reduction in slow waves helps us substantially in understanding the way the brain recovers from TBI.”

The researchers also learned three to six months after the treatment that post-concussive symptoms dropped an average of 53 percent, supporting the investigators’ hypothesis that the MEG slow-wave changes would correlate with the decrease in post-concussive symptoms. The symptoms that declined the most included headaches, dizziness, sleep disturbance, fatigue, nausea, and memory.

Researcher cautions that pilot study produced limited data

Huang says it is unclear if the Vets in the study will see a permanent reduction in abnormal waves and post-concussive symptoms.

“We’re still in the process of collecting information for longer-term windows,” he says. “So we can’t tell for sure right now if the abnormal slow waves or the post-concussive symptoms will be reduced forever, or for that matter, whether the benefits will continue to occur, even with booster treatments.”

Huang and his colleagues say the pilot study set the stage for a new line of research that can advance the understanding of low-intensity, pulse-based transcranial electrical stimulation and its possible benefits for people with mTBI. However, he cautions that the research produced limited data because there were only six participants. He says his double-blind study with 200 Veterans should produce more evidence on the possible benefits of IASIS.

“Pulse-based transcranial electrical stimulation has been used in the past to treat depression, headaches, and traumatic brain injury on an experimental basis,” he says. “However, our pilot study was the first functional neuroimaging study that documents neuronal changes, in terms of abnormal brain waves, in people who underwent transcranial electrical stimulation. It was a small study, but it suggests new potential for effectively speeding the healing process in mild TBI.”

Want to hear about the latest in VA research, *direct* from the experts?

Listen to the Voices of VA Research podcast series:

www.research.va.gov/podcasts



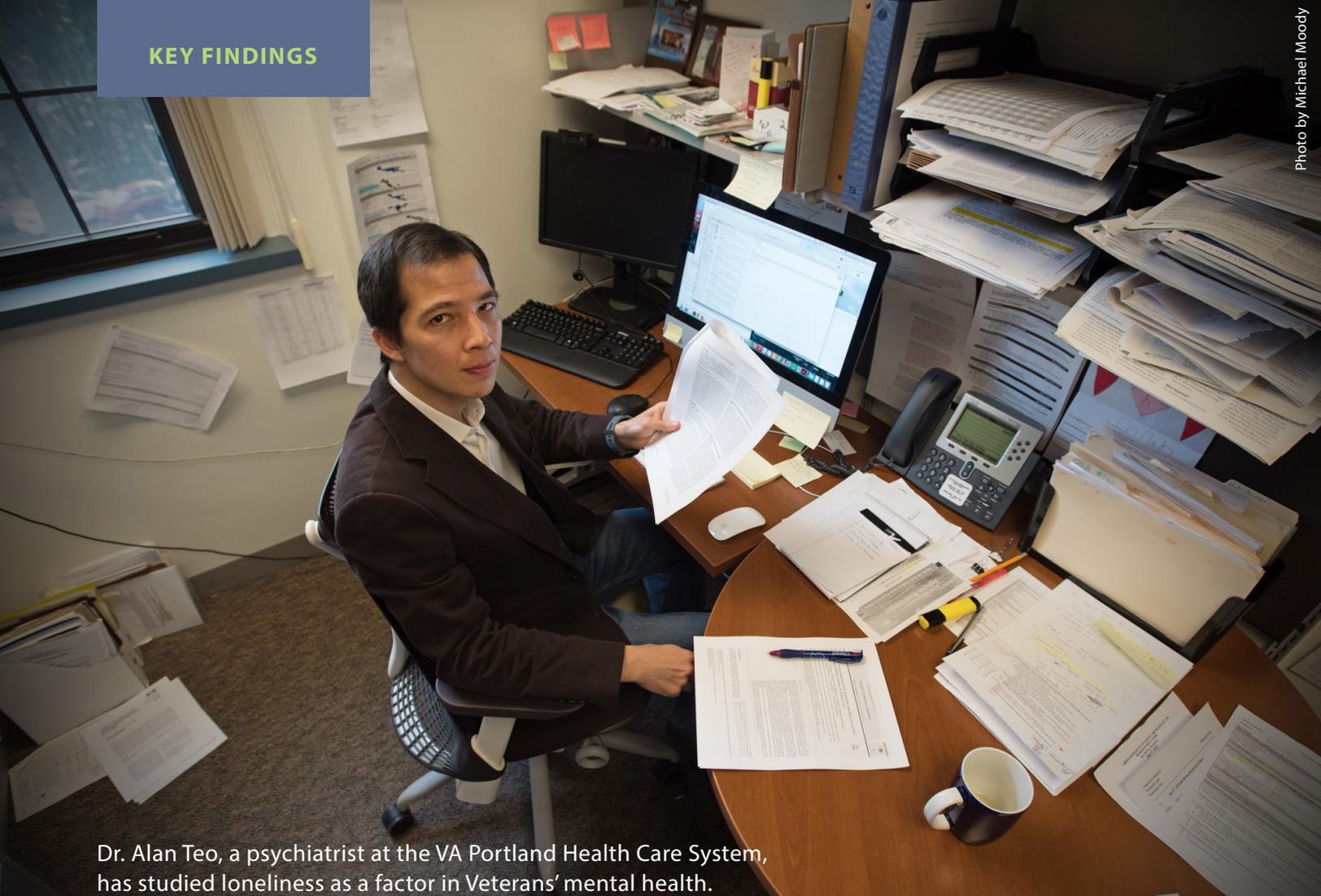


Photo by Michael Moody

Dr. Alan Teo, a psychiatrist at the VA Portland Health Care System, has studied loneliness as a factor in Veterans' mental health.

The loneliness factor: How much does it drive depression in Veterans?

To what extent does loneliness contribute to depression in Veterans? A VA-funded study has addressed that relatively unexplored question.

There has been a wealth of research on the ties between depression and loneliness. In fact, loneliness has been linked to depression perhaps more than any other psychiatric problem. The two are not synonymous, but they interact with one another.

But to what extent, if any, does loneliness contribute to depression in Veterans?

A VA-funded study has addressed that relatively unexplored question. The researchers tried to learn which facets of social connectedness, including loneliness, are linked the most to depression in former service members. Social connectedness refers to relationships and support networks and is vital to a person's health and self-esteem.

Among five forms of social connectedness, loneliness was tied to the highest levels of depression and suicide ideation, or thoughts of committing suicide, the researchers found. Loneliness was also associated with the lowest levels of patient efforts to manage their health and to seek help.

Dr. Alan Teo, a psychiatrist at the VA Portland Health Care System, led the study, which is now online and will appear in the April 2018 *Journal of Affective Disorders*.

He explains that the project didn't begin as an evaluation of loneliness as it relates to depression in Veterans, but that loneliness became the "takeaway message."

"I wanted to do it from a perspective where almost nothing is known," he says. "I looked at different facets of social connectedness to see which one sticks out as being the most important, or conversely whether they are equally important."

Dr. Somnath Saha, a staff physician at VA Portland and a co-author of the study, isn't surprised by its main conclusions. He sees many patients experiencing depression and loneliness.

"Humans are social beings, and connection to others is part of what buoys us in a stressful world," Saha says. "When people are cut off from others—whether they are truly socially isolated and are alone or just feel isolated and are lonely—they are navigating their lives without the stabilizing ballast of friends and loved ones. That can lead to major depression and its cardinal symptoms: feeling down, fatigued, overwhelmed, and unmotivated.

"Being cut off from others is like not being connected to your battery," he adds. "You lose an important source of energy. Unfortunately, that loss of energy often results in less motivation to engage with others and to seek help. So the isolation and loneliness worsen, and a vicious cycle is created, whereby loneliness leads to depression, which leads to more loneliness and so on. Breaking that cycle is difficult but important."

According to the American Psychiatric Association, loneliness isn't necessarily the same as being alone. It usually refers to the distress people feel when their social involvement and relationships are not what they want them to be, such as feeling left out or alone when they'd prefer to be involved or interacting with others.

Teo is unaware of any other studies that have analyzed the connection between depression and loneliness in Veterans treated in primary care.

"There has been a lot of research on loneliness," he says. "But it's relatively novel to look at it in relation to the Veteran population. How do we tackle depression in primary care? In other words, people may be surprised to know that most depression is diagnosed and treated by primary care doctors. It's not the psychiatrists. It's

not the psychologists. Primary care folks see many more patients with depression. It's a common issue."

He adds: "Looking at this population of Veterans in primary care is an issue that's important to VA. We're now shining light on the importance of paying attention to loneliness within that important patient population."

Loneliness not on the 'radar' of primary care providers

At the same time, Teo thinks loneliness is often not on the "radar screen" of primary care doctors when they are treating Veterans with depression. Homeless Veterans and rural Veterans are two groups in the VA population that are vulnerable to loneliness and a lack of social connections, he says.

"This is something that primary care folks are probably not aware of or thinking about," he says. "So it raises real discussion about how we might tackle this among Veterans in primary care. Primary care doctors are sort of aware that loneliness is a problem when you probe. But it's probably not at the top of their mind."

Saha agrees that loneliness is not a top priority for primary care providers.

"We typically think of loneliness as a consequence of depression, rather than a cause," he says. "We try to address depression using our standard treatments, such as medications and psychotherapy, thinking if we can tackle the depression, people will regain their motivation to engage with others.

"But depression and loneliness are more like chicken and egg," he adds. "It's not always clear which came first, or which is the cause and which is the effect.

"We typically think of loneliness as a consequence of depression, rather than a cause."

Continued on next page

If we start seeing depression and loneliness as a cycle, each contributing to the other, we'll start to think of loneliness as an area where we might try to intervene to break the cycle."

Number of confidants not a factor with depression

Teo's study included 301 patients being treated for probable major depression at the Portland VA and its community-based outpatient clinics (CBOCs). Eight-four percent of the participants had at least moderately severe symptoms of depression, and 28 percent had screened positive for suicide ideation.

The participants were mainly men of a wide range of ages and income levels. Just over half were married or partnered; the rest were separated, divorced, or widowed. Nearly 80 percent of the Veterans identified a spouse or other family member as one of their confidants.

Teo and his colleagues examined five elements of social connectedness—number of confidants, social support, interpersonal conflicts, social norms, and loneliness—in relation to five depression-related outcomes: depression symptom severity, suicide ideation, patient efforts to manage their health and to seek help, and medication adherence.

The patients answered questions according to scales that shed light on their social connectedness. For instance:

- How often in the last month confidants "don't listen when I ask for help" and "let me down when I am counting on them."
- How often in the last month "I feel alone and apart from others," and "I feel left out."
- "Looking back over the last six months, who are the people with whom you discussed matters that are important to you"?

Based on their statistical methods, Teo and his

team determined that loneliness, by far, was linked to depression symptoms more than any of the other forms of social connectedness.

"The number of confidants didn't matter with depression symptom severity," Teo says. "It didn't matter whether you had one close friend of the family, or whether you had 10. People would intuitively think that if you had 10 friends and family you felt really close to, that your depression would be under much better control. Instead, we found it was the loneliness that really mattered. If you feel like you're missing out on social relationships, that you don't have companions and you don't have friends, regardless of the actual number of people, it's that feeling of loneliness that stands out."

The researchers also concluded that two forms of social connectedness—social support and social norms—were associated with stronger patient efforts to manage their health and to seek help.

Older Veterans at risk for loneliness

As Teo sees it, loneliness can affect every type of person no matter his or her age, gender, or race. He adds that the condition is especially common among older adults and, in the case of Veterans, is prevalent among those who fought decades ago.

"As people age, there are a lot of changes in their physical mobility, changes in losing people around them," he says. "So it doesn't mean you're pre-ordained to be lonely just because you're aging. But it's a risky period, and people are very worried about loneliness in the older population. Guess what: Most of our Veterans are in the older age group. Our Vietnam-era Veterans may have had experiences earlier in life that set them up to become lonely in this more vulnerable stage of life."

Read more at www.research.va.gov/currents ★

‘Mystery shopper’ model being used to boost VA care



Amy Binns-Calvey, who today works at VA’s Center for Innovation for Complex Chronic Healthcare, had previously parlayed her acting experience into a stint as an unannounced standardized patient in research projects.

If you’ve ever worked in retail, you may be familiar with the concept: A “mystery” or “secret” shopper comes through the store, pretending to be just another customer, and later reports back to the company on how good the service was.

Thanks to the research of Dr. Saul J. Weiner and colleagues, based at the Jesse Brown VA Medical Center in Chicago, the same model is being used to improve VA care and services.

One version uses what Weiner’s team calls “unannounced standardized patients,” or, in the case of non-medical settings, “unannounced standardized Veterans.” These are actors trained to appear as real Veteran patients or clients. There’s a lot that goes into orchestrating this; more on that below.

Another version relies on actual VA patients who agree to audio-record their visits with VA doctors—ideally, surreptitiously—to help improve the care they and their fellow Veterans receive.

At first glance, these methods might seem to raise ethical flags. Don’t these participants—whether actors pretending to be Veterans, or real Veterans secretly recording their visits—have to lie to, or at least be less than open with, the staff who are earnestly working to take care of them?

One point to counter the concern is that VA staff know ahead of time that a “mystery shopper” will be coming through their clinic or office. They have agreed to it as part of research or quality improvement. They just don’t know who it will be, or when exactly.

There are other important factors that have not only made the approach acceptable to VA doctors and other providers, but also caught the attention of top policy-makers in the agency who are excited about using it to get an honest, real-world picture of how VA is doing, and to detect problems that need fixing.

First off, says Weiner, doctors know that “this will never come back to bite them. It’s confidential.” His team scrubs the real identities—both the patient’s and the doctor’s—from the data, and reports gets aggregated across multiple providers. “The only way we share provider-identifiable data is that we send providers individualized reports for their own benefit.”

Second, in an age when doctors often feel overwhelmed by administrative chores, they are happy that Weiner’s approach to quality improvement does not add to their workload. “It’s not burdensome,” he says. “We’re not asking them to do anything other than provide usual care.”

Read more at www.research.va.gov/currents ★



Photo by Derrick Morin

PTSD and accelerated aging: How advanced is the science?

Two psychologists with VA's National Center for PTSD are at the forefront of understanding the long-term biological impacts of PTSD, including accelerated aging at the cellular level.

Evidence is growing in the scientific community that people with PTSD are aging at an abnormal pace. The link between the two is a hot topic, as is the connection between other forms of psychological and environmental stress and accelerated aging.

Two Boston-based clinical research psychologists with VA's National Center for PTSD—Dr. Mark Miller and Dr. Erika Wolf—are at the forefront in dissecting the nexus between PTSD and accelerated aging.

They are examining the theory that the stress of PTSD and its other symptoms speed up the aging process, with biological age exceeding chronological age. They and other researchers surmise that this phenomenon could lead to an early onset of age-related diseases, such as dementia and chronic pain, and even premature death.

The key question Miller and Wolf are trying to answer is what traumatic stress does to make someone age at a rate faster than normal.

“Everyone wants to know how traumatic stress ‘gets under the skin,’” Wolf says. “My view is that psychiatric symptoms are paired with biological reactions that are manageable in the acute phase but become problematic when

they occur chronically. These include inter-related processes, such as increased heart rate, inflammation in the brain, and oxidative stress, as well as decreased immune system functioning, abnormal stress reactivity, and metabolic irregularities that disrupt basic bodily functions.”

Oxidative stress is tissue damage resulting from an excessive amount of pro-oxidants and an insufficient level of antioxidants.

“Collectively, these problems take a toll on the body via cellular aging and reduced blood brain barrier functioning, as well as other processes,” Wolf says. “In addition, behaviors such as smoking, substance use, and poor sleep, nutrition, and exercise contribute to some of the same biological problems. My hope is if we can identify this process early on and see who is at risk for which negative outcomes, we can prevent or delay the risk of disease by matching treatments to the person.”

‘A cascade of biological consequences’

Wolf and Miller, who are also affiliated with the Boston University School of Medicine, have been pursuing this line of research for several years.

Initially, the duo conducted studies that showed major links between Veterans with PTSD and accelerated aging. Some of the former service members were in their early 30s, suggesting that relatively young Vets with PTSD have the potential to age fast and develop age-related health conditions.

“The idea that traumatic events can have a physical effect on people has been around for a long time,” Miller says. “Observations suggest that traumatic stress starts a cascade of biological consequences that can produce visible signs of aging. [Further] research shows how this is happening on a cellular level, and for the first time we have the methods to actually see it in a person’s DNA.”

“We have examined the extent to which a person’s DNA methylation age is greater than or less than their chronological age.”

As they examine accelerated aging in relation to PTSD, Miller and Wolf have come to focus on an index of biological or cellular age referred to as DNA methylation (DNAm) age. Methylation is one of the main ways the body switches genes on and off, and certain patterns of DNA methylation change normally with a person’s age.

Investigators have developed calculations for predicting cellular age from DNA methylation data. Some researchers have linked abnormal DNA methylation to adverse outcomes, including human diseases.

Miller and Wolf are taking it a step further by researching PTSD in relation to abnormalities in DNA methylation age.

“We have examined the extent to which a person’s DNA methylation age is greater than or less than their chronological age,” Wolf says. “We have shown in analyses focused on Veterans that PTSD was linked to accelerated methylation age. We also showed that Veterans with accelerated DNA methylation age were more likely to display subtle signs of neurodegeneration in a region of the brain important for transmitting information across the cerebral cortex—and that they were more likely to die prematurely.”

The cerebral cortex plays a vital role in memory, attention, cognition, awareness, language, and consciousness.

In a study published in July 2017 in the journal *Psychosomatic Medicine*, Wolf and colleagues evaluated ties between trauma exposure, PTSD symptoms, and accelerated versus decelerated DNAm aging in 241 trauma-exposed Veterans. The team also examined if accelerated DNA methylation age predicted death over the course of a 6.5-year medical review period.

Read more at www.research.va.gov/currents ★



Jesse Brown (center) and Chris Murray (second from right) are part of a suicide-prevention group led by Drs. Marianne Goodman (third from right) and Kalpana Nidhi Kapil-Pair (left) at the Bronx VA Medical Center.

They've got each other's backs

While group therapy sessions for those with issues like PTSD or anger are commonplace at VA hospitals, clinics, and Vet Centers, a research team at the Bronx VA is doing relatively pioneering work by running a group for suicidal Veterans.

When Jesse Brown thinks back on his life, there's a sharp dividing line around that grim day in September 2001 when terror struck the U.S.

"Before 9-11, I was happy. I was good."

Brown, then with the New York Army National Guard's 145th Maintenance Company out of Staten Island, took part in search and rescue at ground zero. He took in nightmarish scenes of victims in the rubble.

Then came his deployments to Iraq, three in all.

"Two of my guys getting killed. Hearing voices in your sleep. Going through the PTSD, the anger."

Brown, now 58, received an honorable discharge in 2012, after 32 years of service, with deep wounds no one could see. The storm raging inside was more than he could bear. He eventually tried to take his own life.

"I've been going through a lot of trials and tribulations. I was on a suicide ward."

That's when things began to turn around, just enough to give him some hope.

"They came and saved me. It's been excellent."

The “they” he refers to is Dr. Marianne Goodman and her team. Goodman is a psychiatrist and researcher who’s co-leading a suite of suicide-prevention projects at the James J. Peters VA Medical Center in the Bronx, New York. The work is part of the Mental Illness Research, Education, and Clinical Center at the site.

‘Project Life Force’ treads new ground with group format

One study is Project Life Force. The idea is to bring together a cadre of Vets who all have a recent history of suicidal thinking and a completed suicide plan, provide them with group psychotherapy, and have them revise their safety plans as they incorporate the new skills they are learning.

While group sessions for those with issues like PTSD or anger are commonplace at VA hospitals, clinics, and Vet Centers, Goodman’s crew is doing relatively pioneering work by running a group for suicidal Veterans.

“This is new ground,” says Goodman, who is also with the Icahn School of Medicine at Mount Sinai. “This is the only manualized group therapy that specifically targets suicide. In the literature, there is a one-session inpatient safety planning group and an unstructured psychotherapy group, but otherwise, people have been reluctant to place suicidal individuals in a group together, for fear of contagion. Even DBT discourages discussion about active suicidal feelings.”

In other words, therapists have feared that allowing suicidal patients to mix with other suicidal patients and talk about their thoughts and feelings could actually increase risk. Goodman and her team are finding otherwise, at least with their Veterans cohort. She says the very power of the intervention appears to be the group.

“Veterans no longer feel alone,” says Goodman. “They feel someone understands their impulses and urges.”

The study was originally funded by VA’s Rehabilitation Research and Development Service, and

now the Clinical Science R&D Service is supporting its expansion to a multisite trial. It uses elements from dialectical behavior therapy (DBT). This form of psychotherapy helps people cope with painful emotions and improve their relationships by teaching skills in mindfulness, distress tolerance, emotional regulation, and interpersonal effectiveness.

Goodman’s 10-session manualized version is slightly modified from classic DBT. It does not use the mindfulness component. It emphasizes friendship-building, and improving ties to family and the treatment team, as part of the interpersonal work. It adds education on gun safety, and minimizing access to other lethal means. And it shows the Vets how to use a mobile app to help them stick to their safety plan.

‘I go to the group and lay it out on the table’

Jesse Brown started attending the group in 2016. He completed 12 sessions as a research participant but has continued attending, almost every week. He’s not out of the woods yet, but he’s making progress.

“If I’ve had a bad week, if something’s going on, instead of me trying to hurt myself, I go to the group and lay it out on the table. I let them know how I’m feeling. I get their feedback. I’ve got a great bunch of guys who are working with me. They help me, and I help them too.”

Brown says it’s important to him that the other men in the group are also Veterans.

“They are going through the same stuff I’m going through. You come back from the war, and you ask yourself, where do I fit in now?”

Goodman says it’s almost like the participants are back in the military, in terms of how they bond.

“The group cohesion, much to my surprise, has been an incredibly powerful factor in the intervention’s success. The Veterans recreate ‘units’ and come to group to make sure their ‘brothers and sisters stay alive.’ Just like in the military, their actions toward each other can save lives.”

The psychiatrist points out that many of the men

Continued on next page

and women in her groups lack family support—that can be part of the problem in the first place. In another clinical trial, called SAFER (Safe Actions for Families to Encourage Recovery), her team is involving families in suicide safety planning. Though it might seem surprising, families are typically not part of the process.

“Exactly how to communicate distress around suicidal feelings is very problematic for Veterans,” explains Goodman. “We were surprised to learn how difficult it is for Veterans to ask for help, and the fears about appearing vulnerable and ‘weak.’”

She adds: “Sometimes, family members are part of the stress leading to suicidal feelings. Learning to resolve these conflicts is important.”

Learning how families can be part of solution

Through SAFER, the researchers hope to learn more about how families can be part of the solution for Vets at risk for suicide.

“There is very little information on how family members can support their Veteran who is suicidal,” says Goodman. “Most of the information is on how to recognize suicide risk, but not how best to handle it.”

Chris Murray, 33, a participant in Project Life Force, is perhaps lucky on that point. It was his wife who reached out to the friends of the former Marine and National Guardsman when he tried to take his life in 2016. Those friends, mainly from Murray’s military days, would form a potent support network.

“After my suicide attempt, my wife had reached out to a bunch of my friends,” says Murray, who had two combat deployments to Iraq and two to Afghanistan. “A lot of them came from all around New York State to visit me in Westchester Presbyterian Hospital. Some of them came multiple times during the two weeks I was there. A lot of them came or called as often as they could.”

One of the things Murray says he has learned in Project Life Force is to carry his suicide safety plan

with him at all times, along with a crisis line number. Another is to call on his friends when he needs them. He says he learned it is a powerful way to combat isolation.

“In the [Project Life Force] group, everyone admitted to some form of isolation. I picked up on that. And so one thing I started to do is, whenever I feel depressed, or am not feeling all there, I’ll reach out to one of my friends. And we’ll have a conversation for an hour or two, just about random things. And it will get me out of that funk. I’ll completely forget about why I was in that mood, and what I wanted to do. I’ll start to feel normal again.”

He says friends will also text him on a regular basis. “They’ll check in on me. They’ll text, Hey, how’s everything going? How you feeling? I’ve got a really good support network.”

Bonding between Vets crosses generations

But it’s also his buddies at the Bronx VA who keep him going strong. He made one friend in particular, a Vietnam Veteran, who he says helped him through tough times.

“He is closer to my Dad’s age. But some of the stuff he experienced in combat, I experienced. When I was talking about certain things, he could relate, and when he was talking about certain things, I could relate. He would talk about ways he would help himself, and I was like, I never tried that. I would try it and it would work for me. I thought, this is awesome. And I would tell him about certain things, and he would say, let me try that, and it would help him as well. To this day, when I see him at the VA, we’ll stop and get coffee and talk.”

Murray says that’s what he likes best about Project Life Force: having the support of other Veterans. “There are other Veterans there to help you, regardless of what you’ve been going through. They’ll be there for you, even though they’re going through stuff as well.” ★

Advisory committee key to shaping VA research initiatives



Photo by Mitch Mirkin

NRAC member Dr. Andrew Guccione addresses his colleagues during the group's winter 2018 meeting.

Advisory committees have long played a critical role in shaping the policies, programs, and direction of federal agencies. Composed mostly of experts from academia and the private sector, these committees give government officials and the public advice and access to information on many issues affecting federal initiatives.

Nearly 30 advisory committees help guide VA programs and policies. One of them is the National Research Advisory Council, or NRAC, which was created in 1999 to provide external review of VA's research mission. NRAC advises the VA secretary on research sponsored or conducted by the agency, including policies and programs of VA's Office of Research and Development (ORD), and makes recommendations to ORD.

Normally consisting of 12 members with distinguished scientific backgrounds, the council brings a wealth of experience that helps shape new programs and priorities for VA research. That research targets the high-priority health care needs of Veterans.

"This group is absolutely critical both to respond to ideas that may be emanating from VA staff and to suggest priorities," says NRAC member Dr. Andrew Guccione, chair of the department of rehabilitation

science at George Mason University in Virginia. "Certainly in the last two years, we've stressed the importance of getting the message out. That has made ORD increase its public communications."

He adds: "There is much good that happens through VA research but, even if the public finds out about it, they may not know it came from VA. There has been the desire that Congress also know what is coming out of the VA research programs. VA is such a large system and a huge research enterprise."

Scientific diversity a hallmark of NRAC panel

NRAC falls under the purview of VA's Advisory Committee Management Office, which oversees the agency's 29 advisory committees, 17 of which were mandated by Congress. NRAC is one of the 12 that was established at the direction of the VA secretary.

Council members are appointed to a two-year term, with the option to be chosen for another two years. Five of the 12 members serving in the 2018 to 2020 session are in their second term, such as Guccione.

[Read more at www.research.va.gov/currents](http://www.research.va.gov/currents) ★



Photo by Mitch Mirkin

The NRAC is one of nearly 30 advisory committees that help guide VA programs and policies.



VA researcher Dr. Gina McCaskill, based in Birmingham, Alabama, is an avid endurance cyclist in her free time. She wears a mask to avoid respiratory symptoms.

VA Researchers Who Served: Dr. Gina McCaskill

Birmingham, Alabama VA Medical Center

Dr. Gina McCaskill, an Army Veteran, is a junior investigator in the Geriatric, Research, Education, and Clinical Center (GRECC) at the Birmingham, Alabama VA Medical Center. She focuses on improving the quality of life and well-being in older Veterans with chronic health conditions. She's also interested in reducing health disparities among older Veterans. In her doctoral dissertation at the University of Alabama, she developed an instrument for assessing self-care among older African-Americans with type 2 diabetes. She served for more than four years in the U.S. Army Signal Corps, which supplies information systems and worldwide networks for the Army, the Department of Defense, and allied nations in coalition operations.

What drove you to military service?

Initially, I wasn't interested in military service. After enrolling in college, my mother became terminally ill. So I returned home to care for her. My mother planted the seed. My father, who was from a military family, was also on board. My parents sold the idea to me as an opportunity to see the world and serve our country! I was the first woman in my family to join the military.

What inspired your research career?

My research career has been inspired by intelligent and incredible people engaged in research to improve the lives of

older adults. As a graduate student at the University of Alabama, I had the opportunity to serve as a research interviewer for the study of aging at the University of Alabama, Birmingham (UAB). Dr. Richard Allman was the principal investigator at UAB. His work inspired me and gave me ideas for my future dissertation research. I have also been inspired by the researchers at the Birmingham VA GRECC, such as Dr. Patricia Goode, Dr. Kathryn Burgio, and especially Dr. Cynthia Brown. They care a great deal about improving the lives of Veterans!

Did you have mentors who inspired you in life, the military, or your research career?

Yes. I had mentors who inspired me during my military service, especially Sgt. Edna Sloan. I have also been fortunate to have had mentors throughout my academic and research career, too many to mention. My mentors have served in different roles. They are all on speed-dial on my cell phone.

When and where did you serve in the military? Describe your military experience.

In a little more than four years in the Army, I served in South Korea and then-West Germany. I also had a couple of posts in the U.S. When I was honorably discharged from the Army, I had no idea that my military service would be life-changing. I have friends from the Army with whom I remain in contact. When I earned my doctorate in social work at the University of Alabama in 2013, my friend Sgt. First Class David Nelson was right there with me 20 years after we served in the military together!

What kinds of research are you involved in? How does it potentially impact Veterans?

My research relates to older Veterans. I'm especially interested in improving the quality of life and well-being of older Veterans who have multiple chronic conditions, such as hypertension, diabetes, and osteoarthritis. For instance, I set Veterans up in their home with a chair exercise program that they can do at any time of the day. I provide hand weights, resistance bands, an exercise ball, a DVD player, and a DVD

program.

Did your military experience inspire you to pursue a career as a VA researcher? Is your military experience connected in some way to your VA research?

Initially, my military experience did not inspire my career as a VA researcher. However, once I began to connect with Veterans through my professional life, I became inspired by their stories and concerned about their welfare. I began to think about ways that I could improve their lives.

How do you feel about the possibility of making life better for Veterans through your research?

I am incredibly grateful for each and every Veteran that decides to participate in my research. The possibility to improve the lives of older Veterans is my priority and my passion. At the end of each day, I go home and sleep well knowing that my research will make a difference in the lives of older Veterans.



In this photo taken in Brooklyn, New York, in 1983, Dr. Gina McCaskill is seen with her father, Charles W. McCaskill, who passed away in 2011.



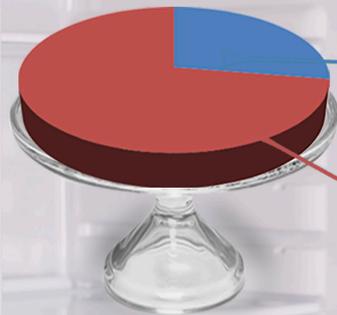
PUNCHING WALLS

‘An under-recognized form of self-injury’

- ✊ In a group of **1,143 Veterans** seeking PTSD treatment, **43%** reported **punching walls or objects** within the past two weeks.
- ✊ The behavior was **twice as common in male Veterans**, compared with female Veterans.
- ✊ Wall/object punching was more likely to result in **emotional relief** than were other forms of non-suicidal self-injury, such as cutting, biting, or burning oneself. It was also strongly related to **current suicidal thinking**.
- ✊ The researchers recommend **more study** of this “**important but under-recognized form**” of nonsuicidal self-injury.

Source: “Wall/Object Punching: An Important but Under-Recognized Form of Nonsuicidal Self-Injury,” *Suicide and Life-Threatening Behavior*, online Sept. 19, 2017. Infographic by VA Research Communications, March 2018. Photo: © iStock/Smitt

Food insufficiency among women using VA care



27.6%

Reported food insufficiency
(inadequate amount of food intake
owing to lack of money or resources)

72.4%

Did not report food insufficiency

Those reporting **food insufficiency** were **more likely** to report or screen positive for:

- Delayed or missed care**
- Anxiety**
- Depression**
- Fair to poor health**

Findings based on survey responses from 818 women who had at least three visits to VA primary care or women's health providers between December 2013 and November 2014. Source: "Access to Care and Health Outcomes Among Women Veterans Using Veteran's Administration Health Care: Association With Food Insufficiency," *Women's Health Issues*, Feb. 20, 2018. Infographic by VA Research Communications, March 2018. Photo for illustrative purposes only. © iStock/Goldfaery

Check out more VA Reseach infographics at:

<https://www.research.va.gov/pubs/infographs>

The high burden of 'subthreshold' PTSD

Those with subthreshold PTSD have some PTSD symptoms but not enough to meet the criteria for a PTSD diagnosis.

Data from the National Health and Resilience in Veterans Study.

Subthreshold PTSD	Probable PTSD (meets full diagnostic criteria)
Libraries are being used 22.1%	Libraries are being used 14.2%
Four months 13.5%	Four months 12.5%

Conclusion: "The results of the study suggest that a strikingly high proportion of U.S. veterans experience clinically significant PTSD symptoms in their lifetime."

Source: "The high burden of subthreshold PTSD among U.S. veterans," *World Psychiatry*, June 2018. Infographic by VA Research Communications, February 2018. Photo for illustrative purposes only. Photo © iStock/WITMCORG

Individual Placement and Support for Veterans with PTSD

Individual placement and support helps Veterans with PTSD find employment through job coaching based on their interests and backgrounds, rather than traditional one-size-fits-all vocational rehabilitation and transitional work placements.

The results below are from the Veterans Individual Placement and Support Towards Advancing Recovery (VIP STAR) study of 543 Veterans.

	Transitional Work	Individual Placement and Support
Found steady work	23%	39%
Found competitive jobs	57%	69%
Average income for study period	\$10,989	\$14,642

Conclusion: "Individual placement and support is more successful than transitional work at helping unemployed Veterans with PTSD obtain and sustain competitive employment."

Source: "Effects of the Veterans Individual Placement and Support (IPS) Program on Employment and Postsecondary Education in Veterans with PTSD," *Psychiatry*, Feb. 28, 2018. Infographic by VA Research Communications, February 2018. Photo for illustrative purposes only. © iStock/ianphillips WALET

Firearm training among U.S. adults

Findings from a study by VA researchers and colleagues:

- The percentage of U.S. firearm owners who reported receiving formal firearm training showed little change between 1994 (24 - 28%) and 2015 (21%).
- The most commonly reported combination of training topics was self-loading, safe storage, and accident prevention.
- Only 11% of owners said their training occurred within a professional setting.
- Conclusion: The proportion of U.S. firearm owners with formal fire arm training has not meaningfully changed in two decades. Training programs vary widely. Efforts are needed to **expand and standardize** the effectiveness of training.

Source: "Prevalence and Characteristics of Firearm Training Among U.S. Adults," *Journal of Traumatic Stress*, June 2018. Infographic by VA Research Communications, February 2018. Photo for illustrative purposes only. Photo © iStock/PhotoLibrary



RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs

Accepting hepatitis C-positive liver transplants could improve life expectancy

Patient without hepatitis C needing a liver transplant may have increased life expectancy if they are willing to accept a donated liver that is positive for the hepatitis C virus, according to a mathematical model. A team including a researcher from the Michael E. DeBakey VA Medical Center used data from published studies to create a simulated trial. They found that accepting any liver regardless of hepatitis C status resulted in increased life expectancy over waiting for a liver free of the hepatitis C virus. Although infected livers could have adverse outcomes, the virus can now be treated very effectively post-transplant using direct-acting antivirals. (*Hepatology*, Dec. 9, 2017)



VA



U.S. Department
of Veterans Affairs

VA Research Communications | 31 Hopkins Plaza, Ste. 102 | Baltimore, MD 21201
varesearchcurrents@va.gov | 443-759-3456



Read the expanded online edition of
VA Research Currents at www.research.va.gov



facebook.com/VAResearch



twitter.com/VAResearch