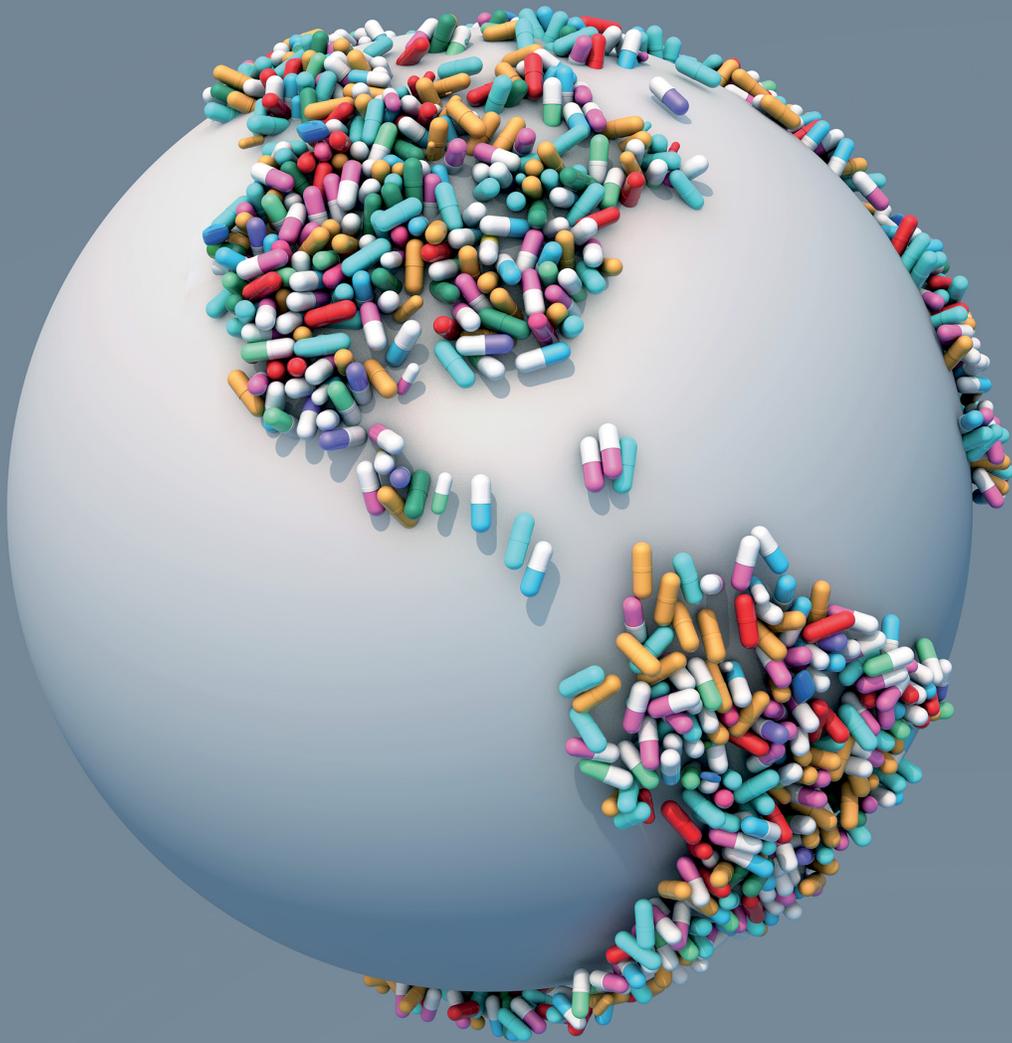


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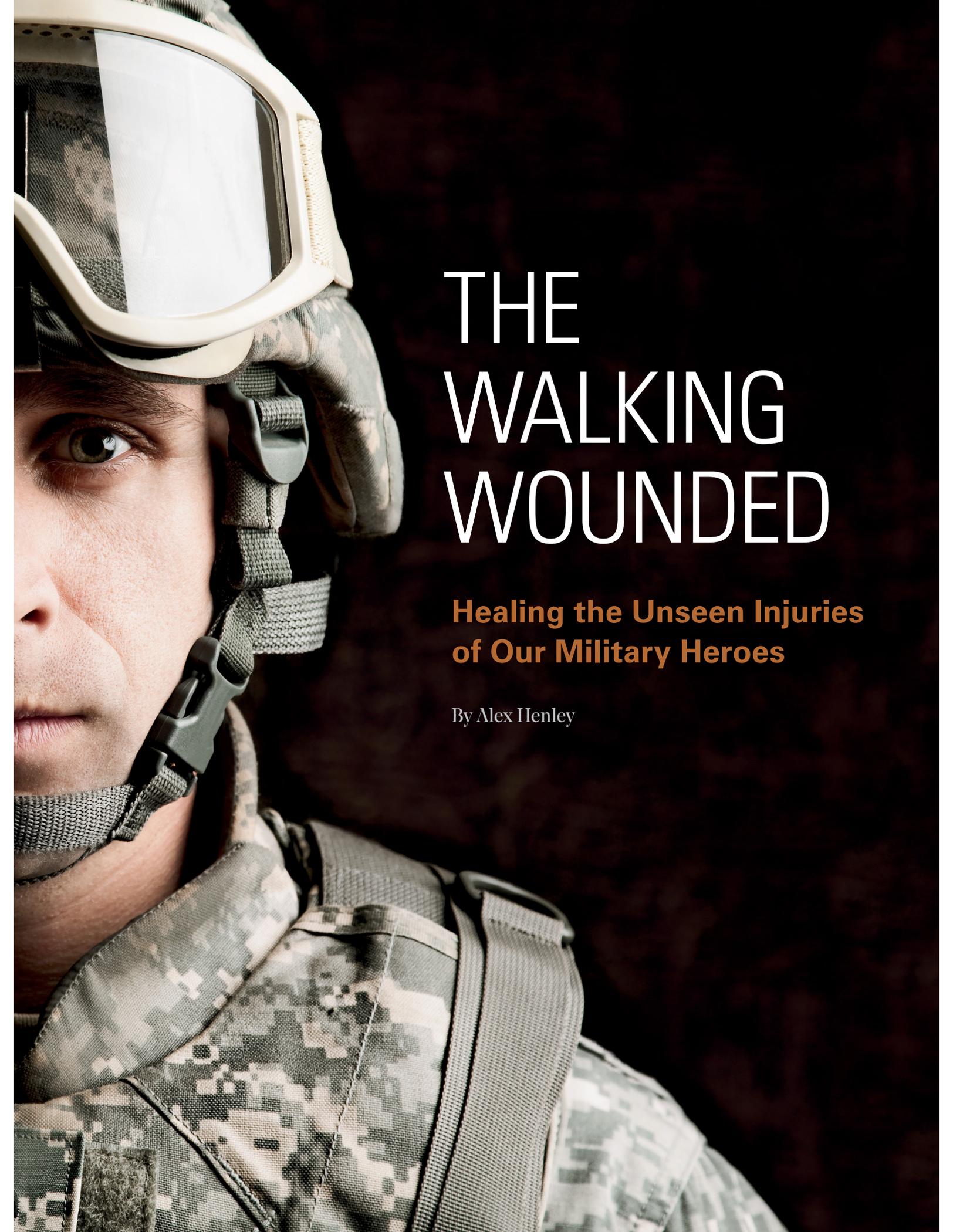
The Future of Discovery at VCU Health

Spring 2020



Medicines for All

REVOLUTIONIZING THE GLOBAL SUPPLY CHAIN



THE WALKING WOUNDED

**Healing the Unseen Injuries
of Our Military Heroes**

By Alex Henley

Imagine waking up after being knocked out by an IED. You're on the ground, face in the dirt, and not sure what just happened. Despite being groggy and confused, you must act quickly because you're in enemy territory. After a quick assessment, you find yourself one of the lucky ones — there's no external bleeding or other visible injuries. There's a piercing pain in your head, your ears are ringing, and you can't get your eyes to focus, but you force yourself to stumble around and check on the rest of your unit so you can all move to safety.

This is what countless military heroes have faced in the course of battle, some of them many times. It's what medical professionals call a mild traumatic brain injury (mTBI), commonly known as a concussion.

As the weapons of warfare have changed, with blast injuries on the rise, military personnel have returned from battle with different types of injuries. Since 2000, the U.S. Department of Defense reported more than 383,947 military personnel have sustained a traumatic brain injury, and 82.3% of these are mild.¹ Actual numbers are likely much higher as many mTBIs go unreported.

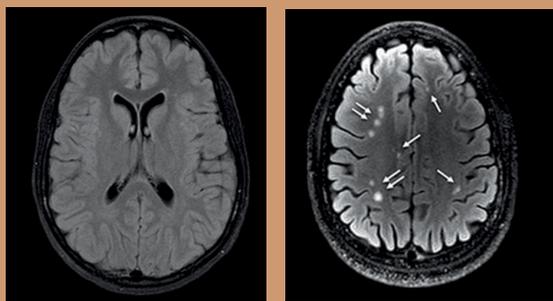
"No one stops in the middle of a battle and gets assessed for a concussion," said David Cifu, M.D., chair and professor of the VCU School of Medicine's Department of Physical Medicine and Rehabilitation and senior traumatic brain injury specialist for the U.S. Department of Veterans Affairs. "Service members want to and need to keep fighting."

WHAT IS A CONCUSSION?

A concussion is the mildest form of a traumatic brain injury usually resulting in no loss of consciousness or, rarely, in a brief loss of consciousness under 30 minutes. It involves a disruption in the normal function of the brain caused by a sudden force, bump or blow to the head that forces the brain to rapidly accelerate and then decelerate.

"The brain is made up of white and gray matter," Dr. Cifu explained. "If you imagine a Jell-O fruit dessert, the white part of the brain is like the fruit. It's fairly firm in consistency, is located deep inside the brain and is the communication system — it connects the different parts of the brain to the spinal cord. The gray matter does the thinking, creates the actions and generates our feelings. Its consistency is soft and wobbly like Jell-O and it is on the outside, surrounding the white matter.

"Where the gray and white matter come together offers a significant difference in tissue density, just like the difference between the Jell-O and the fruit ('the gray-white junction'). If you've ever shaken up Jell-O, you've seen the Jell-O move or wobble, while the fruit sits there, and if you look closely you'll see the separations and air bubbles where the Jell-O and fruit meet ('the Jell-O-fruit junction'). That's sort of how a concussion occurs — the force causes rapid bursts of movement and the differences in tissue density stretch the brain tissue beyond its capacity, causing the gray and white matter to separate, tear and become



Two MRI scans show a healthy brain on the left and a brain that has suffered an mTBI on the right. The arrows on the right point to areas where the force of the concussion caused the white matter in the brain to twist and tear beyond its ability to stretch. While it's helpful for physicians to confirm a traumatic brain injury with an MRI, many concussions do not show up on scans and must be diagnosed by a patient's symptoms. Photos: Courtesy of VCU Health and Dr. David Cifu

“No one stops in the middle of a battle and gets assessed for a concussion. Service members want to and need to keep fighting.”

David Cifu, M.D., chair and professor of the VCU School of Medicine’s Department of Physical Medicine and Rehabilitation

dysfunctional. If it tears a lot, it bleeds and you have a more significant injury, but the majority of the time it’s either just small tears or simply overstretching that temporarily alters the brain’s abilities and leaves the person feeling confused and disoriented.”

The vast majority of people who have a concussion make a full functional recovery, often within days or weeks. However, if a person has had multiple concussions, gets tears in just the wrong locations or has had a more severe injury that is undiagnosed or untreated, the person may experience ongoing symptoms, such as headaches, dizziness, irritability, sleep disruptions, memory issues, anxiety, and sensitivities to light and sound, which are collectively called “persistent, post-concussion symptoms.”

CHRONIC EFFECTS OF NEUROTRAUMA CONSORTIUM (CENC)

As U.S. veterans began returning home from the wars in Iraq and Afghanistan and reporting post-concussion symptoms, research into traumatic brain injuries increased. In 2013, the Departments of Defense and Veterans Affairs awarded Virginia Commonwealth University a \$62.2 million grant to lead the Chronic Effects of Neurotrauma Consortium (CENC), making it the largest grant in VCU’s history.

Dr. Cifu was named the principal investigator for CENC, a five-year study that brought together more than 70 of the top brain researchers in the country across 30 universities, 15 Veterans Affairs Medical Centers and 12 military treatment facilities.

CENC Accomplishments

- CENC researchers successfully recruited more than 2,300 veterans and service members, who served in the wars in Afghanistan and Iraq, as active study participants. These post-9/11 individuals, including those with mild traumatic brain injury (most with multiple concussions), PTSD, chronic pain, depression and other symptoms, are now available to participate in a series of planned treatment studies. More than 1,700 of these individuals (and another 1,300+) are also continuing as participants in an ongoing longitudinal study that allows researchers to follow their health outcomes over the course of their lives.
- CENC developed a standardized mild traumatic brain injury research assessment protocol. This is particularly important because concussions can be challenging to diagnose after the fact and hard to characterize — in fact, they show no abnormalities on MRIs or other

imaging tools in more than two-thirds of cases. CENC researchers have created the gold-standard, diagnostic clinical interview and overall approach to assessing and following these individuals that includes learning about the patient’s symptoms and blast exposure event(s), and performing balance testing, blood biomarker and other tests.

- CENC combined nine military, veteran and federal databases into a single, searchable mega-database with the health, medication, benefits and administrative information from more than 2 million service members and veterans, which will allow researchers to complete epidemiologic studies using big data analyses.
- CENC researchers published more than 70 peer-reviewed papers, completed 11 research studies and participated in more than 150 lectures internationally.



As faculty members of the VCU School of Medicine's Department of Physical Medicine and Rehabilitation, Dr. David Cifu and Dr. Ronald Seel have helped veterans and service members heal for decades. Now, they are partnering to make the CENC research understandable and accessible to everyone. *Photo: Kevin Schindler*

“VCU has a long history as a leader in traumatic brain research,” said Ronald Seel, Ph.D., executive director of the VCU Center for Rehabilitation Science and Engineering. “The roots of our Department of Physical Medicine and Rehabilitation go back more than 150 years to the Civil War. In addition to our capabilities as an academic health center, we’re proud to serve veterans through a partnership with the Hunter Holmes McGuire VA Medical Center in Richmond. David Cifu has a national reputation as an energetic leader that can make things happen. Those were all contributing factors in VCU being named the coordinating center and receiving this grant.”

Beginning in October 2013, CENC researchers launched multiple studies with service members and veterans to better understand both the immediate and longer-term issues associated with combat-related blast concussions to develop better treatment protocols.

The accomplishments made by CENC researchers since 2013 have been substantial. While it is impossible to cover the entirety of their work, a few key accomplishments and findings are highlighted below and on page 22.

CENC KEY RESEARCH FINDINGS

The good news is that more than two-thirds of the post-9/11 service members and veterans in the ongoing longitudinal study (1,700 participants) who have experienced one or

more combat-related traumatic brain injuries are doing well. They are high-functioning members of society who are employed and active with their families and in their communities. While they may have some issues with headaches or other symptoms, they are receiving treatment and able to manage these symptoms and live full lives. A little less than one-third of this population is having more significant symptoms that are not allowing them to return to the full function they had before military service. A positive takeaway is that this group is following up with their physicians and seeking the care that they need.

In more good news, none of the post-9/11 longitudinal study participants have shown signs of dementia or Parkinson’s disease, and there have been no suicides. These study participants are, on average, 11 years out from their last combat-related traumatic brain injury and more than 20 years from their first one.

One CENC study involved 322 post-9/11 veterans and service members and looked at whether mild traumatic brain injury was related to ongoing difficulties with balance. Researchers used their intake interviews to categorize participants into groups of those with no mTBI, 1-2 mTBIs, and more than 3 mTBIs. Results showed no difference in balance between participants with no mTBI and 1-2 mTBIs, but they did find that service members who suffered 3 or more mTBIs had poorer balance, with pain as a contributing



Researchers are investigating whether the presence of certain proteins in the blood can be used as biomarkers to indicate whether a combat-related concussion has affected a person's brain health. *Photo: Julia Rendleman, VCU University Marketing*

factor.² This helps alert physicians to focus on possible risks for dizziness and balance issues when treating a veteran or service member who has multiple mTBIs.

Another CENC study used the mega-database of 2 million veterans and service members to examine the relationship between traumatic brain injury and Parkinson's disease. Researchers used the records of 325,870 veterans, with an average age of 48, some of whom had 1 or more TBI and others who never experienced a TBI. The results showed that patients with a history of any severity of TBI had twice the rate of eventually developing Parkinson's disease compared to those with no history of TBI. Those who had only sustained a prior mild TBI had a nearly 1.5 times higher risk than those without any TBI history. The overall incidence of developing Parkinson's disease is quite small for all veterans, less than one in 100; however, the results illustrate both the strength of "big data" research and that there is a significantly increased risk for developing Parkinson's disease in service members who have suffered a TBI.³

Another big data study examined the relationship between mild traumatic brain injury and dementia. Investigators compared the records of 357,588 veterans, average age of 49 years old, half of whom had experienced 1 or more TBI and half who had no history of TBI. Veterans with any TBI history developed dementia at a rate of 6.1%, compared to only 2.6% of veterans with no TBI history — a nearly 2.5 times increase in incidence. After adjusting for factors that could influence dementia rates, the chance of developing dementia was 2.4 times greater for veterans who had experienced a mild TBI without loss of consciousness,

2.5 times greater for mTBI with loss of consciousness, and 3.8 times greater for more severe TBI. While the overall incidences are still small, they again point to the value of this CENC research and the need for individuals with TBI histories and their healthcare providers to be aware of this connection.⁴ Ongoing research by the CENC team includes identifying lifetime approaches to brain health and cognitive wellness (e.g., plant-based diet, daily exercise, stress reduction, high blood pressure treatment, weight loss, improved sleep patterns, managing mental illnesses, etc.).

An exciting area of research is looking at fluid biomarkers to measure the health and recovery of the brain. One such biomarker is tau protein, which is found in the blood and saliva and, therefore, easily tested. In a healthy person, tau proteins normally help stabilize a part of brain cells called microtubules. However, in people with neurodegenerative disorders, like Alzheimer's disease, tau proteins pull away from the microtubules and stick to each other, eventually forming filaments and tangles that disrupt communication between brain cells. Elevated levels of tau protein in the blood are indicative of declining brain health.

Researchers conducted a study with 195 participants, average age of 40, from four CENC Veteran Affairs Medical Centers, and examined the tau protein levels in their blood plasma to determine if mTBI caused any change in those biomarker levels. Researchers noted there were no changes in tau protein levels in veterans who had 1–2 concussions as compared to veterans with no concussions, but tau levels were elevated for veterans who had experienced 3 or more concussions.⁵ This marker could identify patients at risk for neurodegenerative disorders in the future and help them seek preventative measures.

Many of the CENC studies were pilot or proof of concept trials; researchers were testing the feasibility of the study or its hypothesis on a smaller population. The next phase of research involves clinical trials with a much larger patient population that will measure results over a longer period of time. That's where the next phase of CENC begins.

LONG-TERM IMPACT OF MILITARY-RELEVANT BRAIN INJURY CONSORTIUM (LIMBIC)

This fall, VCU announced it received another \$50 million federal grant to pursue the CENC research and further study the long-term impacts of concussions on service members and veterans. This ongoing study is called the Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC). Dr. Cifu will continue as the principal investigator.

"We've narrowed the focus from 11 studies to 2 major, multi-tiered epidemiologic studies," said Dr. Cifu. "The first study will increase our longitudinal cohort of 1,700

Helping Out Our Future Military Brothers and Sisters

“I knew something bad had happened, but being deployed you just keep driving on,” U.S. Army veteran Joe Montanari told us. “I didn’t even know I had experienced a concussion until I started working with CENC.”

Joe proudly served as a weapons specialist in the U.S. Army from 1999 to 2008, deployed to locations in Germany, Kosovo and Iraq. He was medically discharged after six years of active duty and four years in the National Guard.

“In talking with my friends, a few of us returned home with the same symptoms — headaches like crazy, not sleeping at all and lightheadedness. Your balance really goes sometimes — it’s like standing in a parking garage on the rubber joints when a car goes by and you can feel the shakiness and instability for a couple seconds,” Joe explained.

Joe is currently serving as a CENC military coordinator, where he is responsible for both recruiting and retaining service members and veterans as participants in the LIMBIC-CENC longitudinal study. He is also a participant in this research study. For him and veterans like him, it’s not just about returning home, it’s working hard to return to the fullest capacity possible to be there for their families.

It was through his training and participation with CENC that he learned he was experiencing post-concussion symptoms from two combat-related mild traumatic brain injuries. “I’m the type of person that if something happens with my health, I like to break

Joe Montanari is pictured in 2002 during his military service as a U.S. Army weapons specialist. *Photos: Courtesy of Joe Montanari*



Joe Montanari returns home to his wife Micah following his first deployment to Iraq in 2005.

it down and know what’s going on so I can get the right treatment. Knowledge is empowering.”

Joe also hopes to be of service and use his experience to help future military service members. “I’ve already been through everything and experienced the injuries, so if I can help someone else out, I’m all about that. I know a lot of people I’ve talked to feel the same way. It’s just helping out a future brother or sister who might sustain a mild traumatic brain injury in combat.”

If you’re a veteran or service member interested in speaking with Joe to learn more about the LIMBIC-CENC research or become a study participant, please email him at joseph.montanari@vcuhealth.org.

Joe Montanari, a U.S. Army veteran who suffered a traumatic brain injury while serving in Iraq, not only works as a military coordinator for the CENC and LIMBIC research grants but is also engaged as a study participant. *Photo: Julia Rendleman, VCU University Marketing*



LIMBIC Sites

Cores

Coordinating Center

– Virginia Commonwealth University, Richmond, VA

Imaging Core

– VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

Clinical Studies Core

– Virginia Commonwealth University, Richmond, VA

Biomarkers Core

– Uniformed Services University of the Health Sciences/National Institutes of Health, Bethesda, MD

Data Management Biostatistical Core

– Hunter Holmes McGuire VA/Virginia Commonwealth University, Richmond, VA
 – VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

Studies

Prospective Longitudinal Study Enrollment Sites

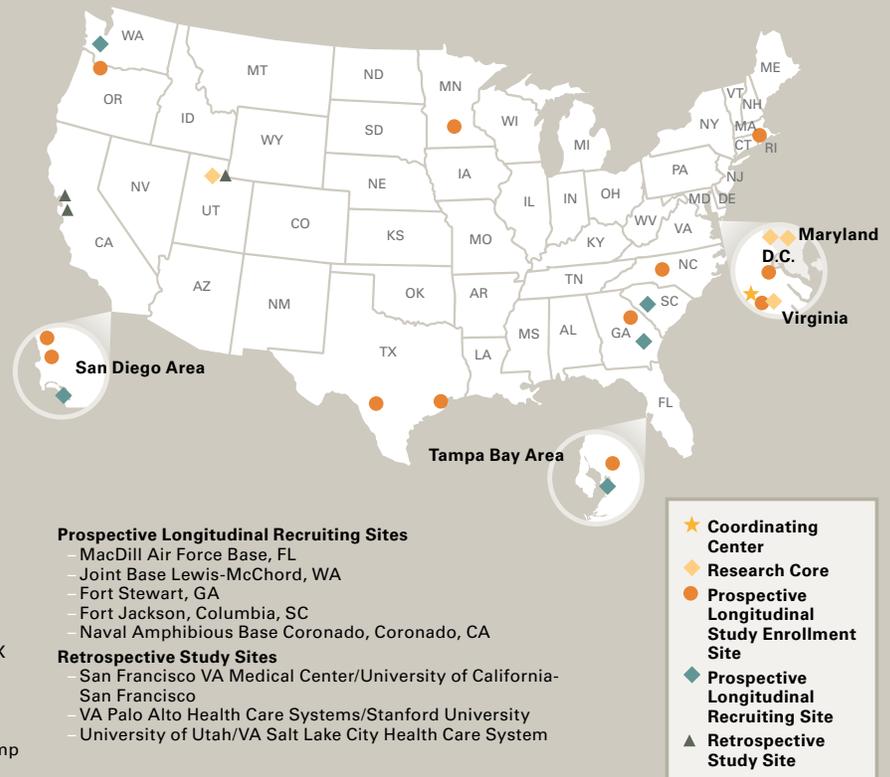
– Hunter Holmes McGuire VA, Richmond, VA
 – James A. Haley Veterans Hospital, Tampa, FL
 – VA Boston Healthcare System, Boston, MA
 – VA Portland Health Care System, Portland, OR
 – Michael E. DeBakey VA Medical Center, Houston, TX
 – South Texas Veterans Healthcare Center, San Antonio, TX
 – WG Hefner VA Medical Center, Salisbury, NC
 – Minneapolis VA Health Care System, Minneapolis, MN
 – Eisenhower Army Medical Center, Fort Gordon, GA
 – Fort Belvoir Community Hospital, Alexandria, VA
 – VA San Diego Health System/University of California/Camp Pendleton, San Diego, CA

Prospective Longitudinal Recruiting Sites

– MacDill Air Force Base, FL
 – Joint Base Lewis-McChord, WA
 – Fort Stewart, GA
 – Fort Jackson, Columbia, SC
 – Naval Amphibious Base Coronado, Coronado, CA

Retrospective Study Sites

– San Francisco VA Medical Center/University of California-San Francisco
 – VA Palo Alto Health Care Systems/Stanford University
 – University of Utah/VA Salt Lake City Health Care System



veterans and service members to more than 3,000 from all eras of military combat (Vietnam to the present). Approximately 80% of this group will have experienced at least one mTBI, while the remaining 20% will be the control group who were exposed to combat but didn't have a concussion. Participants from both groups are likely to have other common conditions associated with combat, such as PTSD, depression, chronic pain and anxiety. The control group will allow us to see what's caused by having been exposed to the combat setting versus what's attributable to the additional mTBI.

"As with the research started in CENC, we'll be getting a 360-degree overview of every possible aspect of these participants, from their brain and nervous systems, to their endocrine and cardiovascular systems. We'll continue to follow this group annually over the course of their lives to search for any evidence of decline in function, including dementia and Parkinson's disease."

The second set of LIMBIC studies will expand the use of the CENC mega-database of more than 2 million veterans and service members to look for further associations and relationships that can then be cross-validated in the longitudinal study. Researchers will use this massive dataset to investigate whether mTBI is linked to higher incidences of dementia, Parkinson's disease, depression, opioid use, chronic pain, PTSD or suicide risk.

"We have initial analyses revealing that significant trends can be seen in these mega-data supporting the

linkage between higher rates of these conditions in veterans and service members with mTBI," Dr. Cifu explained. "We're going to apply what we learn from this massive database to the ongoing longitudinal study of more than 3,000 participants. We'll be able to see if we find these problems occurring at the individual level, better analyze their causes and then apply clinical trials as cutting-edge treatments to help members of this group. It's all about translating findings from big data to longitudinal data so that actual preventative and treatment interventions can be applied in real-time."

Over the next five years, the LIMBIC longitudinal study will include multiple intervention trials to examine treatments for common issues associated with combat-related mTBI, including headaches, insomnia, PTSD and memory issues.

"As clinicians, we want to take the theoretical and apply it to our patients and help them get well and improve the quality of their lives, as well as reduce their risk for problems in the future. Knowing the future risks enables us to take bold steps now to maintain wellness," said Dr. Cifu.

The research findings of LIMBIC-CENC will also be applicable to nonmilitary members of the general public. According to the CDC, in 2014 there were approximately 2.5 million TBI-related visits to emergency departments across the U.S. The most common injuries were falls, especially in older adults, motor vehicle accidents and sports-related injuries.⁶

LOVING YOUR BRAIN

For veterans, service members, athletes and anyone who has suffered a concussion or even multiple concussions, Dr. Cifu has a positive message.

“Concussions and related injury factors contribute to less than 1% of all dementia and ‘bad genes’ may add another 5–8% at most. On the other hand, at least 50% of all dementias are the result of common lifestyle factors that are within everyone’s control. Additionally, it’s not the one-time concussion that typically causes long-term issues, if it was treated appropriately,” Dr. Cifu explained.

“People who have a concussion improve and can return to their lives 99% of the time with the right diagnoses and care, and it’s important to let them know that — YOU WILL GET WELL! For anyone who is still having ongoing symptoms, work with your primary care clinician to get additional information and care. The brain, the tissues around the neck and skull, and the other areas affected have remarkable abilities to heal and adapt, and you can be taught to control your symptoms and enjoy your lives.

“Our LIMBIC-CENC team at VCU and the McGuire VAMC (and nationwide) want to take this opportunity to educate people (injured individuals, their loved ones, clinicians) how to ‘love’ and nurture their brains and take care of their overall health over the long-term.

“Eating a vegetable-based diet, getting the right amount of sleep, finding a form of exercise that you enjoy and will do consistently, managing your weight and blood pressure, having good social support, keeping your mind active and engaging in a spiritual practice — these are the most important ways to support your whole health and offer your brain optimal wellness as you age.

“I’d like to acknowledge all the amazing researchers who are diligently working across the country, and most

importantly, I’d like to thank our military veterans and service members who have risked their lives and sacrificed so much and are now helping us by participating in these studies,” said Dr. Cifu.

If you would like to read more about the LIMBIC-CENC studies, please visit www.cencstudy.org.

If you would like to support traumatic brain injury research at VCU Health, please contact Brian Thomas, MCV Foundation vice president and chief development officer, at 804-828-0067 or brian.thomas@vcuhealth.org.

1. According to the Defense and Veterans Brain Injury Center for the time period 2000–2018 Q1: <https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>.
2. William C. Walker, Kayla J. Nowak, Kimbra Kenney, Laura Manning Franke, Blessen C. Eapen, Karen Skop, Harvey Levin, Amma A. Agyemang, David F. Tate, Elisabeth A. Wilde, Sidney Hinds & Tracy L. Nolen (2018). Is balance performance reduced after mild traumatic brain injury? Interim analysis from chronic effects of neurotrauma consortium (CENC) multi-centre study. *Brain Injury*, 32:10, 1156–1168, doi: 10.1080/02699052.2018.1483529.
3. Raquel C. Gardner, Amy L. Byers, Deborah E. Barnes, Yixia Li, W. John Boscardin, Kristine Yaffe. Mild TBI and risk of Parkinson disease: A Chronic Effects of Neurotrauma Consortium Study. *Neurology*. 2018;90(20):e1771-e1779. doi:10.1212/WNL.0000000000005522.
4. Deborah E. Barnes, Amy L. Byers, Raquel C. Gardner, Karen H. Seal, W. John Boscardin, Kristine Yaffe. Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in U.S. Military Veterans. *JAMA Neurol*. 2018;75(9):1055-1061. doi:10.1001/jamaneurol.2018.0815.
5. Kimbra Kenney, Bao-Xi Qu, Chen Lai, Christina Devoto, Vida Motamedi, William C. Walker, Harvey S. Levin, Tracy Nolen, Elisabeth A. Wilde, Ramon Diaz-Arrastia, Jessica Gill and the CENC Multisite Observational Study Investigators. Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury. *Brain Injury*. June 2018;32(10):1276-1284. doi:10.1080/02699052.2018.1483530.
6. According to the Centers for Disease Control and Prevention: www.cdc.gov/traumaticbraininjury/data/tbi-ed-visits.html.



U.S. Army Veterans (left and right) Kevin Sickinger and Joe Montanari work with Dr. Cifu (center) at the Hunter Holmes McGuire VA Medical Center to recruit LIMBIC research participants. Photo: Julia Rendleman, VCU University Marketing