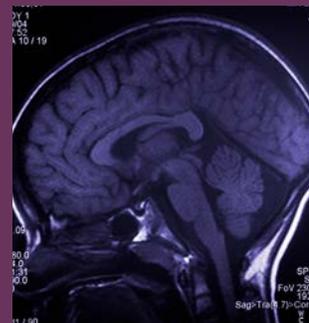
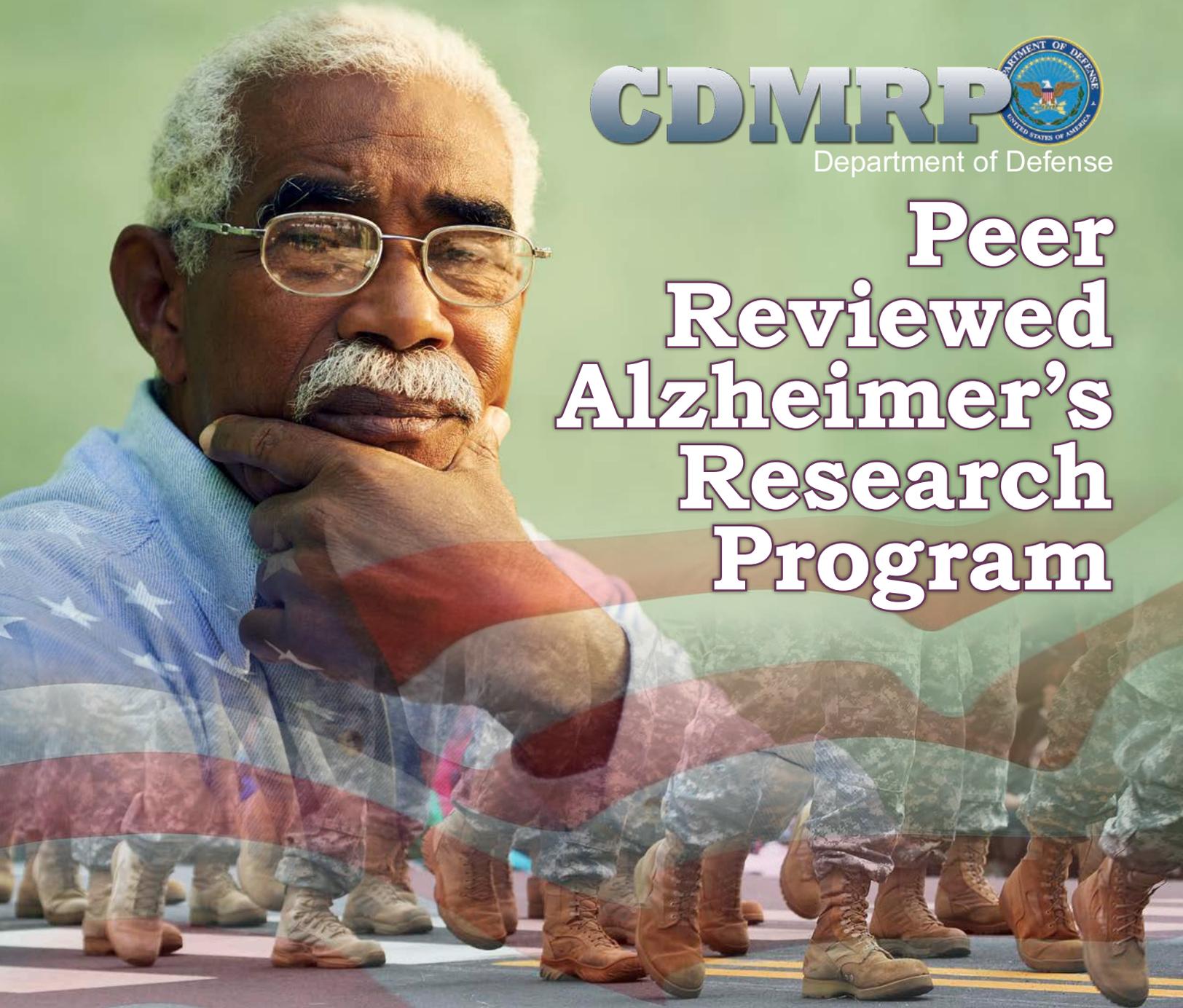


CDMRP
Department of Defense



Peer Reviewed Alzheimer's Research Program



US Army Medical Research and Materiel Command



Congressionally Directed Medical Research Programs

HISTORY

The Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 by a powerful grassroots effort led by the breast cancer advocacy community. This initiated a unique partnership between the public, Congress, and the military. Since then, the number of national and military health programs has grown. Over the course of its history, the CDMRP has managed over \$11.9 billion (B) in congressional appropriations for both military and domestic health research programs. The research spectrum supported by the CDMRP extends from basic science to large, multi-institutional consortia. The spectrum for each program is tailored to meet the specific research priorities envisioned by its stakeholders. Funds for the CDMRP are added annually to the Department of Defense (DoD) budget in order to support individual programs such as the Peer Reviewed Alzheimer's Research Program (PRARP) and are allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation. Both tiers involve dynamic interaction between scientists and consumers. Examples of consumers can be disease survivors or those responsible for the care of someone living with a disease. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the research program's stakeholders. The stakeholders, collectively referred to as the PRARP Programmatic Panel, are composed of leading scientists, clinicians, and consumer advocates. The Programmatic Panel members make recommendations for funding based on a number of programmatic review criteria. These criteria include not only scientific merit, but also potential for innovation, potential impact of the research, and portfolio composition. The programmatic review allows the stakeholders to select the particular science that will best satisfy the mission and vision of the program.

Peer Reviewed Alzheimer's Research Program

VISION: To address the long-term consequences of traumatic brain injury (TBI) as they pertain to Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD).

MISSION: The PRARP's mission is devoted to (1) understanding the association between TBI and AD/ADRD and, (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities. Support for the PRARP's mission is anticipated to be delivered by the research community through a combination of mechanistic and preclinical studies.

ABOUT THE PROGRAM

Military personnel and other individuals living with traumatic brain injury (TBI) face an increased risk for developing several long-term health problems. These include Alzheimer's-like dementia, aggression, memory loss, depression, and symptoms similar to those of other neurological diseases. Many of these injuries, both military and civilian, can be life-long injuries that impact the individual living with the injury, as well as their loved ones. The PRARP was initiated in 2011 to address the long-term consequences of TBI as they pertain to Alzheimer's disease (AD) in both the civilian and military communities. In FY16, the program was expanded to include AD-related dementias (ADRD) research pertaining to TBI. Appropriations for the PRARP from FY11 through FY16 totaled \$78 million (M). The PRARP has funded 73 Awards between FYs 11-16.

The PRARP Strategic Plan to address the long-term consequences of TBI-related dementias has evolved to look at six key areas, called the PRARP Overarching Challenges. The Overarching Challenges represent long-standing research goals for the program. For FY17, these include the following:

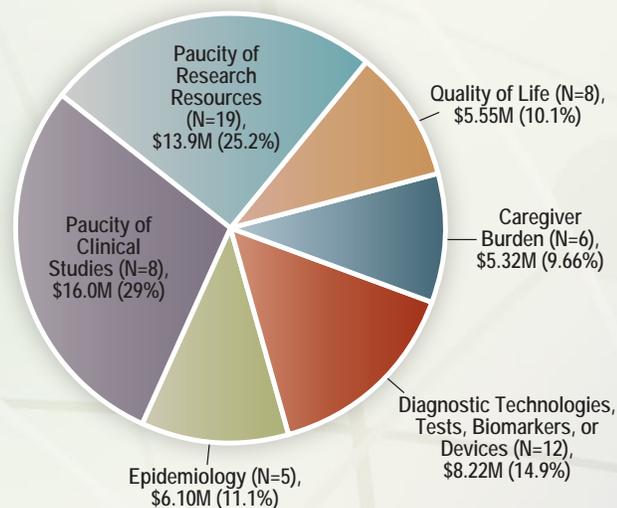
- **Paucity of Research Resources:** The paucity of research resources to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities
- **Paucity of Clinical Studies:** The paucity of clinical studies to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities
- **Diagnostic Technologies, Tests, Biomarkers or Devices:** The need for technologies, tests, or devices to detect the progression to AD/ADRD subsequent to TBI
- **Epidemiology:** The paucity of epidemiological research to examine the interrelationship between TBI and

subsequent AD/ADRD for the military, Veteran, and civilian communities

- **Quality of Life:** The need for technologies, assessments, interventions, or devices to benefit individuals living with the common symptoms of TBI and AD/ADRD
- **Caregiver Burden:** The need for technologies, assessments, interventions, or devices with the goal of reducing the burden for caregivers of individuals living with the common symptoms of TBI and AD/ADRD

Applications submitted to the PRARP must address one of these challenges, which are developed and updated at each year's Vision Setting meeting. The Overarching Challenges are used in conjunction with the PRARP Focus Areas as the framework for Program Announcements of funding opportunities. The Program Announcements help investigators understand the types of science the PRARP Programmatic Panel is interested in funding to fulfill its mission and vision.

FY12-FY16 PRARP Research Investment by Overarching Challenge



THE PRARP PROGRAMMATIC PANEL

Members of the PRARP Programmatic Panel provide unique insights into the research funded through the program. The panel is comprised of experts from the National Institutes of Health, Department of Veterans Affairs, DoD, universities, and not-for-profit entities such as the Alzheimer's Association. The panel provides guidance regarding funding recommendations for new projects and the research progress of current projects. The panel also sets the tone for future strategic initiatives by identifying funding overlaps, as well as gaps in research that must be addressed. By carefully monitoring the research from concept to outcome, the panel ensures that the PRARP will bridge the gaps between the long- and short-term consequences of TBI with respect to AD.

FACTS ABOUT TBI and AD

- More than 5 million Americans are estimated to be living with AD.¹
- In 2016, 15 million caregivers provided an estimated 18.2 billion hours of unpaid care, valued at more than \$230B, for AD.¹
- A 2007 report noted that AD was the third most common neurological disease or disorder after migraine and stroke in the United States.²
- While there is likely more than one cause for AD, evidence suggests that closed head injuries may contribute to the number of AD cases.³
- The Defense and Veterans Brain Injury Center (DVBIC) reported more than 350,000 cases of TBI in the U.S. military since 2001.⁴
- Domestically, TBI resulted in more than 2M estimated emergency room visits in 2010,⁵ with costs for care estimated to be over \$70B in that year alone.⁶

¹ http://www.alz.org/documents_custom/2017-facts2017_infographic.pdf

² Hirtz D, Thurman D J, Gwinn-Hardy K, Mohamed M, Chaudhuri A R, and Zalutsky R. 2007. How common are the "common" neurologic disorders? *Neurology* 68(5):326-337.

³ <https://www.alz.org/dementia/traumatic-brain-injury-head-trauma-symptoms.asp>

⁴ <https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi>

⁵ https://www.cdc.gov/traumaticbraininjury/get_the_facts.html

⁶ <https://www.cdc.gov/cdcgrandrounds/pdf/grtbi20sep2011.pdf>



Improving the Quality of Life of Veterans with Amnesic Mild Cognitive Impairment

J. Kaci Fairchild, Ph.D., Palo Alto Veterans Institute for Research

As individuals age, there is a propensity for increases in subjective memory complaints. Some of the research aimed at alleviating these deficits has become more interested in the concept of “aging in place.” This is the concept that one can positively adjust their lifestyle to maintain or improve their overall mental and physical health as they age. Exercise has long been proposed as an important component of aging in place, yet many questions about the role of exercise in healthy aging remain unanswered. One of the key challenges in understanding how exercise can benefit aging individuals is characterizing the types of exercise that are most beneficial to aging individuals, especially individuals showing signs of memory impairments. Dr. Kaci Fairchild compared aerobic versus balance/flexibility exercise in a Veteran population that was diagnosed with mild cognitive impairment (MCI). The goal of this study was to evaluate whether there were any differences between the two study arms in terms of cognitive performance. Both groups did benefit, but not equally. The study showed some evidence that individuals in the aerobic exercise arm did better on some cognitive tests after the intervention when compared to the balance/flexibility training arm, but there were some benefits to the balance/flexibility training as well. Fewer people dropped out of the balance/flexibility training arm of the study, and their overall physical health improved. This study has provided a preliminary framework for future studies with veterans to improve their quality of life.



“The PRARP is the only program focused on the relationship of military risk factors to the development of dementia and improvements in quality of life for those affected as well as their caregivers. These resources promote collaborations between researchers from dementia and traumatic brain injury across a variety of disciplines. The program has an impressive track record of scientific discovery that has opened windows for all dementia research and is fortunate to have the collaboration of key federal agencies and the Alzheimer’s Association.”

Michael Jaffee, M.D., FY17 Programmatic Panel Chair



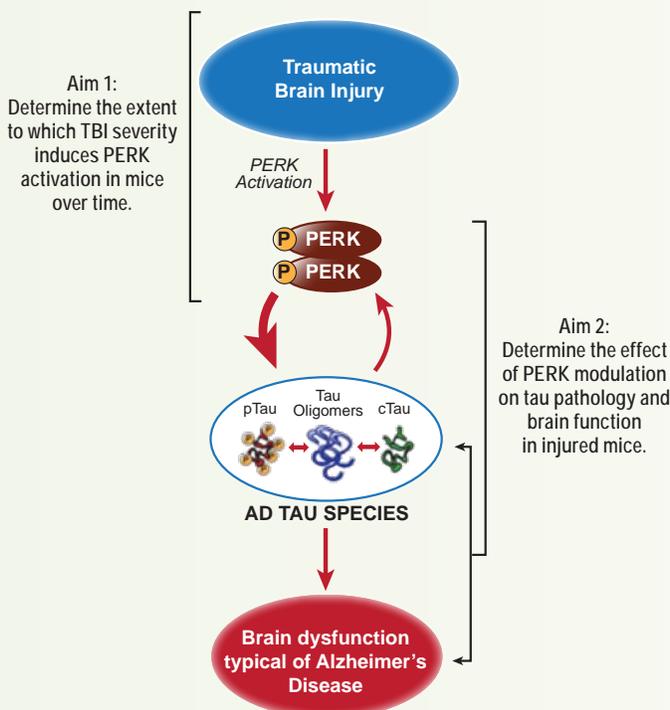
Left to right: back row, Grant Nation, Blain Weiss, Emad Chishti, Joe Abisambra; front row, Chiara Lanzillotta, Shelby Meier, and Sara Galvis

The Impact of PERK on Post-Traumatic Tauopathy in Alzheimer's Disease

Jose Abisambra, Ph.D., University of Kentucky

Novel biomarkers can start in a variety of places, perhaps as a newly discovered molecular pathway that requires more characterization as a potential molecular target. The biology of Tau, the protein found in “tangles” within brains showing signs of either injury or neurodegenerative disease, still remains largely a mystery in terms of how Tau exerts its deleterious effects. Tau is a putative fulcrum between brain injuries and long-term diseases such as AD. Dr. Abisambra was awarded an FY14 Convergence Sciences Research Award to examine whether TBI

activates the Protein Kinase R-like ER Kinase (PERK). He hypothesizes that PERK activation may be a marker of cellular stress that may ultimately influence how Tau can negatively impact the brain after TBI. As a result of this study, Dr. Abisambra has shown early and sustained activation of PERK after TBI in a model animal system. Furthermore, Dr. Abisambra’s study has shown that he can modulate the effects of PERK activation, since this study has identified some of the other signaling molecules involved in the PERK response. He has also identified that neurons are the cells that are most affected by PERK activation. These signaling molecules respond to small molecule inhibitors, paving the way for potential preclinical research. Further work is needed to understand how this mechanistic research can be extended to Tau pathology. In addition to the mechanistic work, this study will also couple those findings with state-of-the-art magnetic resonance imaging (MRI), which will accelerate future research.



The overarching hypothesis of this work is that TBI activates PERK, which induces tau pathogenicity typical of Alzheimer's disease. This hypothesis is being tested in two aims. In Aim 1, the extent to which TBI severity induces PERK activation in a mouse model of head injury over time will be established. The data so far suggest that severe TBI substantially activates PERK throughout the brain. In Aim 2, the effect of PERK modulation on tau pathology and brain function in injured mice will be determined. So far this work has shown that head injury promotes aggressive deposition of tau into tangles at very early stages. Preliminary results suggest that PERK inhibition alters tau pathology; however, it is not clear yet whether PERK inhibition promotes functional brain improvement. Surprisingly, treatment with the PERK inhibitor ameliorated astrocytic reactivity, suggesting that this compound could promote molecular changes that have never been measured before. Dr. Abisambra's team is currently investigating whether these changes can offer neuronal benefits.



Sleep, Traumatic Brain Injury, and Chronic Traumatic Encephalopathy

Maiken Nedergaard, M.D., D.M.Sc., University of Rochester

The brain's physiological response to stressors such as lack of sleep has recently been discovered to be mediated by an intricate network of channels called the glymphatic system. The glymphatic system is key to restoring the brain's proper function as you sleep by removing toxins or waste products, such as proteins associated with AD. Tau, a pathological hallmark of many neurological diseases and disorders, is not only associated with AD, but also with chronic traumatic encephalopathy (CTE). CTE is becoming more closely associated with TBIs. One hallmark of CTE is the deposit of Tau in the brain. Dr. Nedergaard was awarded an FY15 Convergence Science Research Award to study how TBI affects sleep and how some aspects of the pathology of TBI, namely reactive gliosis, compromise the removal of toxins normally removed by the glymphatic system. Dr. Nedergaard's findings thus far suggest that sleep disorders associated with TBI can significantly decrease the removal of proteins such as Tau by negatively altering the glymphatic system. In addition to the careful mechanistic studies necessary to characterize the physiology of the glymphatic system, Dr. Nedergaard's team will evaluate how the alterations impact cognition. While this work is in its early stages, it is conceivable that this research will result in a novel diagnostic platform for neuroscience in the coming years. It is also hoped that this study may provide new ways to improve how the glymphatic system works, so as to overcome the effects of aging, injury, or disease.





Tau and Beta-Amyloid Deposition, Microhaemorrhage and Brain Function After Traumatic Brain Injury in War Veterans

Christopher Rowe, M.D., University of Melbourne

International partners make up a small but important component of the PRARP's research portfolio. This study, in conjunction with the larger DoD Alzheimer's Disease

Neuroimaging Initiative (ADNI) studies, has increased understanding of some of the subtle changes that occur in military populations as they age. The aging of military populations is different from their civilian counterparts, since comorbidities that can be sustained in combat (such as TBI and post-traumatic stress disorder [PTSD]) can be sustained on the battlefield. Dr. Christopher Rowe was awarded an FY13 Convergence Science Research Award to study the relationship between TBI and PTSD in Australian Veterans who served in Vietnam. More than 116 Australian Veterans have participated in this study. Australian Veterans with PTSD and/or TBI, as well as those who did not sustain either injury, took part. The study used state-of-the-art imaging (MRI and nuclear imaging) to characterize each arm of the cohort. Early results hint at subtle differences between the groups, but a more robust data analysis is still required to fully appreciate the long-term effects of TBI and PTSD in terms of Alzheimer's disease. Both the Australian and American (DoD ADNI) studies used methods that are interchangeable, so this permits comparisons between the groups that may reveal even more subtle differences among the three cohort arms. It is anticipated that data from both the Australian and DoD ADNI studies will be made available to the scientific research community so that these datasets can be used as the basis for further research.



“It is only through research that we will find ways of preventing and effectively eliminating the devastating effects of Alzheimer's and dementia. The Alzheimer's Association is proud of our collaboration with the PRARP funding program. The scientific investigations made possible through this program are critical to advancing our understanding of dementia risk in those who served in the military. These efforts are not only essential to supporting individuals in our military and Veteran communities as they age, but may help lead to improvements in diagnosis and treatment for all who are affected by dementia.”

**Heather M. Snyder, Ph.D.,
Senior Director of Medical and Scientific Operations
at the Alzheimer's Association**



For more information, please visit

<http://cdmrp.army.mil/prarp>

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