



Peer Reviewed Alzheimer's Research Program

The linkage between Traumatic Brain Injury (TBI) and Alzheimer's disease (AD) and AD-related dementias (ADRD) is complex in Service member populations. Understanding the complex interrelationship between TBI and AD/ADRD has required unique, multi-disciplinary approaches to understand the risk factors and comorbidities that drive or accelerate the consequences of TBI toward dementia. Both TBI and AD/ADRD share a variety of common symptoms. These include memory disorders, aggressivity, depression, and executive functioning deficits. How these symptoms worsen or become associated with AD/ADRD subsequent to TBI has been the focus of the Peer Reviewed Alzheimer's Research Program (PRARP).

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 understanding the association between TBI and AD/ADRD and to reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities.

PROGRAM HISTORY

The PRARP was initiated in fiscal year 2011 (FY11) per a request and funding from Congress. Experts from the U.S. Army Medical Research and Materiel Command, Alzheimer's Association, National Institutes of Health, Tri-Services, and the Defense and Veterans Brain Injury Center met to discuss the PRARP's vision and mission. They agreed that there was enough evidence to focus the PRARP on the relationship between TBI and AD while meeting the needs of the civilian community at large. This was based on a variety of existing studies, including an Institute of Medicine report that showed an increased risk for dementia from moderate and severe TBI.

In FY16, the program was expanded to include ADRD research as it pertains to TBI. This was done to highlight the complexity of the TBI-dementia connection and the need for an expanded scope outside of traditional AD research into other areas such as Lewy body, frontotemporal, and vascular dementias. It is hoped that this revised focus will expand our knowledge of the complex pathology of TBI as it pertains to dementia. The PRARP concentrates its initiatives on large programmatic gaps or Overarching Challenges and asks researchers to identify how they will address these gaps using the PRARP's identified Focus Areas.

FY19 OVERARCHING CHALLENGES

- Paucity of Research Resources
- Paucity of Clinical Studies
- Diagnostics and Prognostics
- Epidemiology
- Quality of Life
- Family and Care Support

FY19 FOCUS AREAS

- Mechanisms of Pathogenesis
- Biomarkers
- Quality of Life
- Family and Caregiver Support
- Epidemiology
- Novel Target Identification
- Nonpharmacological Interventions and Devices
- Bioinformatics



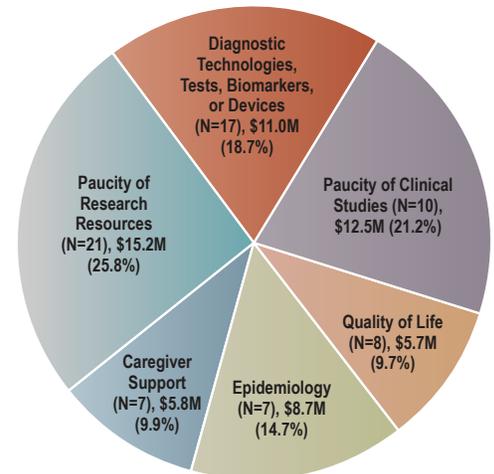
FACTS ABOUT TBI AND AD

- More than 5 million (M) Americans are estimated to be living with AD.
- In 2016, 15M caregivers provided an estimated 18.2 billion (B) hours of unpaid care, valued at more than \$230B, for AD.
- A 2007 report noted that AD was the third most common neurological disease or disorder after migraine and stroke in the United States.
- While there is likely more than one cause for AD, evidence suggests that closed head injuries may contribute to the number of AD cases.
- The Defense and Veterans Brain Injury Center reported more than 350,000 cases of TBI in the U.S. military since 2001.
- Domestically, TBI resulted in more than 2M estimated emergency room visits in 2010, with costs for care estimated to be over \$70B in that year alone.

PRARP RESEARCH INVESTMENT

Currently, the PRARP research portfolio is balanced among pathological studies, epidemiology, new diagnostics, and quality of life research. The FY13 to FY17 PRARP investment by Overarching Challenge is shown at the right.

FY13-FY17 PRARP Investment by Overarching Challenge



N = number of awards funded by the PRARP



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 associated with both AD and 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 these 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, and 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 Department of Defense (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 AD. 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.

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