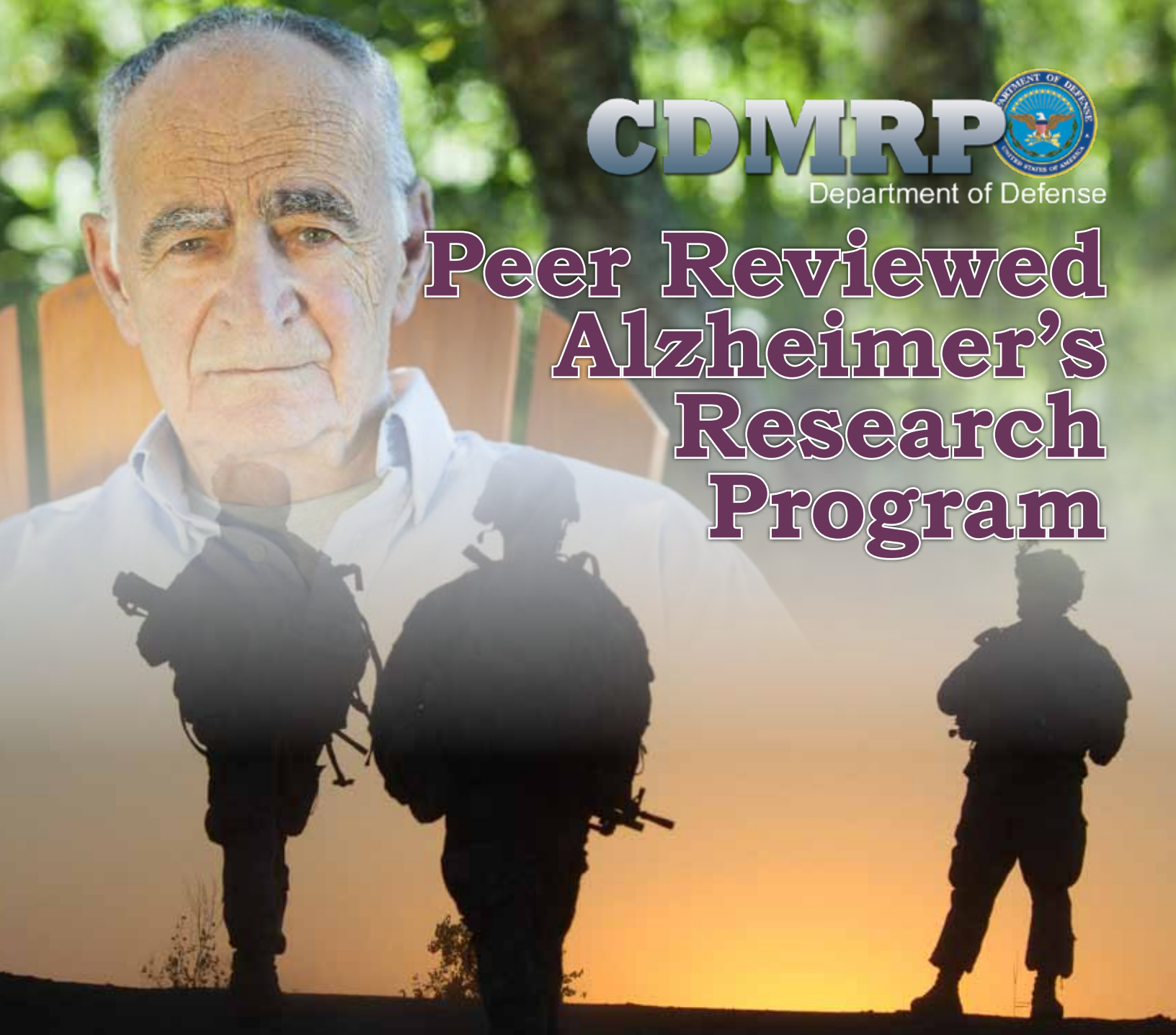# CDMRP
## Department of Defense

# Peer Reviewed Alzheimer's Research Program

*U.S. 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 $8.7 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 is 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 disease survivors. 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 Program Steering Committee, are composed of leading scientists, clinicians, and consumer advocates. The Program Steering Committee members make recommendations for funding based on a number of scientific criteria. The criteria can include not only the 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.

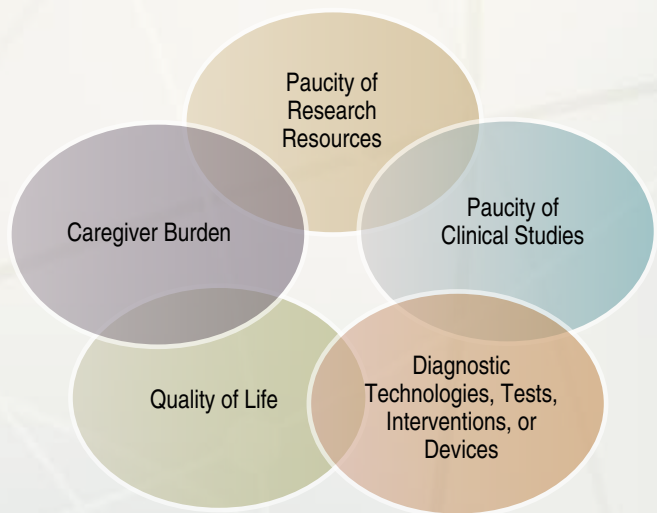# Peer Reviewed Alzheimer's Research Program

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

**MISSION:** The PRARP is devoted to (1) understanding the association between TBI and AD; and (2) reducing the burden on caregivers and individuals affected by TBI-AD symptoms, especially in the military community
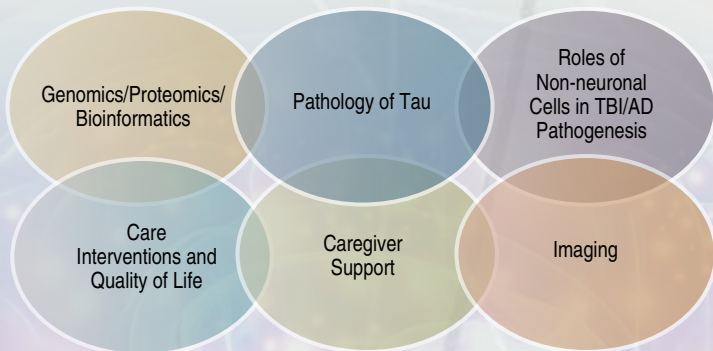
## ABOUT THE PROGRAM

The PRARP (formerly the Militarily Relevant Peer Reviewed Alzheimer's Disease Research Program) was initiated in 2011 to build a program devoted towards understanding the association between TBI and AD. In order to achieve its mission, the PRARP faces 5 Overarching Challenges:



- Paucity of Research Resources
- Caregiver Burden
- Paucity of Clinical Studies
- Quality of Life
- Diagnostic Technologies, Tests, Interventions, or Devices

In order to answer these overarching challenges, the PRARP has identified six scientific focus areas which support innovative and systematic research:



- Genomics/Proteomics/Bioinformatics
- Pathology of Tau
- Roles of Non-neuronal Cells in TBI/AD Pathogenesis
- Care Interventions and Quality of Life
- Caregiver Support
- Imaging

Between fiscal year 2011 (FY11) and FY13, the program has administered $39 million in funding across 29 grants that are intended to address at least one overarching challenge. Currently, the PRARP research portfolio is balanced between pathological studies, epidemiology, new diagnostics, and quality of life research.

## OUR PROGRAM STEERING COMMITTEE

Members of the PRARP Program Steering Committee provide unique insights into the research funded through the program. The panel is comprised of experts from the National Institutes of Health, U.S. Department of Veterans Affairs, DoD, and not-for-profit entities such as the Alzheimer's Association. The panel provides guidance regarding funding recommendations for new projects, and research progress of current projects. The panel also sets the tone for future strategic initiatives by identifying funding overlaps and identifying 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 Alzheimer's disease.

## FACTS ABOUT AD AND TBI

- More than 5 million Americans are living with AD.
- In 2013, 15.5 million caregivers provided an estimated 17.7 billion hours of unpaid care valued at more than $220B for AD.
- A 2007 report noted that AD was the 3rd most common neurological disease or disorder after migraine and stroke in the United States (Hirtz 2007).
- While there is likely more than one cause for AD, evidence suggests that closed head injuries may contribute to the number of AD cases.

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.

"Research portfolios that investigate the impact of traumatic brain injury and post-traumatic stress disorder and their impact on current and future military and veteran populations, will make a significant contribution to a greater understanding about Alzheimer's and related dementias. The Alzheimer's Association strongly supports this very important program that we believe will generate new insights into the causes of dementia as well as potential treatments and risk reduction strategies."
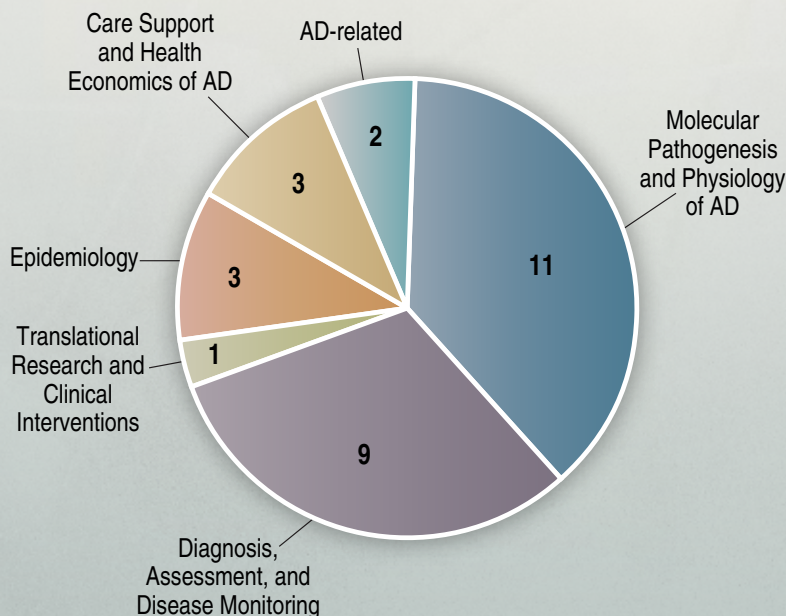
**Dr. Maria Carrillo**
**Alzheimer's Association**
**Chief Science Officer, Medical and Scientific Relations**

## FY11–FY13 PRARP Portfolio by International Alzheimer's Disease Research Portfolio (IADRP) Ontology Criteria



Pie chart segments:
- Care Support and Health Economics of AD
- AD-related: 2
- 3
- Epidemiology: 3
- Molecular Pathogenesis and Physiology of AD: 11
- Translational Research and Clinical Interventions: 1
- Diagnosis, Assessment, and Disease Monitoring: 9

The International Alzheimer's Disease Research Portfolio, or IADRP (http://iadrp.nia.nih.gov/cadro-web/), is an online database that attempts to capture AD and AD-related research projects worldwide. IADRP is a joint effort between the National Institute on Aging and the Alzheimer's Association. Research projects included in IADRP are organized around the Common Alzheimer's Disease Research Ontology (CADRO) (http://www.nia.nih.gov/research/dn/cadro-outline), a three-tiered classification system created to capture the complete range of AD and related research and research resources. To date, IADRP includes research supported from almost 30 organizations with approximately $4B in research funding dispersed among more than 6,000 research projects and 2,500 unique investigators—all searchable across the three tiers of the CADRO for in-depth portfolio analyses. All PRARP research projects from FY11 to FY13 are included in IADRP.

## Oligomeric Neuronal Protein Aggregates as Biomarkers for TBI and AD

### Dr. Michael Sierks, Arizona State University

Dr. Michael Sierks is designing a novel, and potentially cost-effective, strategy for detecting the early events after TBI and for long-term monitoring. Dr. Sierks uses a combination of two technologies, atomic force microscopy and phage display, to generate a highly sensitive assay for detecting signs of TBI and long-term neurodegeneration associated with AD. Dr. Sierks uses a virus called a bacteriophage (which infects only bacteria) to first isolate nanobodies that selectively bind toxic protein variants implicated in AD and TBI. He also developed a simple modified ELISA assay to detect the toxic protein aggregates in human samples with femtomolar sensitivity. The nanobody is used to capture the target antigen, and a phage-displayed version of a second nanobody is used to amplify the detection signal. The assay is readily customized for selective analysis of TBI and AD targets. The modified phages are nontoxic and self-assembling; hence, they have potential use as a cost-effective diagnostic.

To date, Dr. Sierks has used the assay to detect early stages of AD in post-mortem tissue, cerebral spinal fluid, and serum samples. He is currently investigating whether the assay can be used with human cerebral spinal fluid and serum samples. If successful, the results may provide a novel, cost-effective diagnostic for TBI and AD. Other neurological disorders such as Parkinson's disease may also benefit from this technology.

> "Support from the DoD has been critically important in enabling our lab to develop an analytical assay capable of detecting the low concentrations of aggregated protein variants present in complex human samples."
>
> **Dr. Michael Sierks**
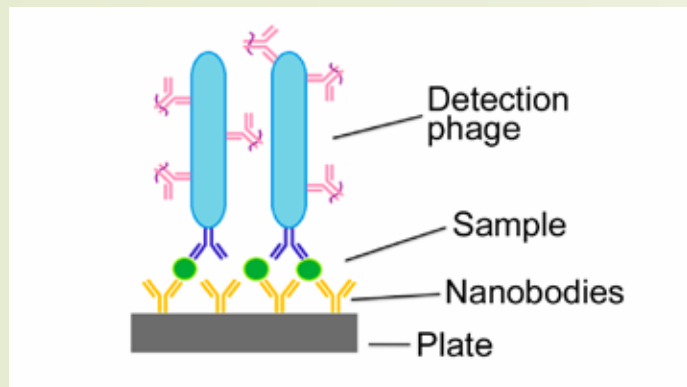


*The disease marker (green) is captured by nanobodies (yellow), and then labeled with phage (blue). The phage can then be detected by a standard assay known as ELISA.*
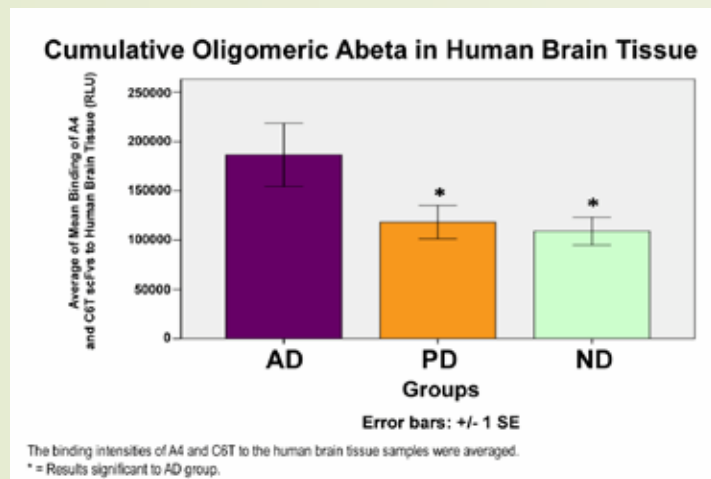


*Early work showing the detection of a toxin specific to Alzheimer's disease (AD). The toxin, Abeta was not detected in brain tissue from Parkinson's patients (PD) when compared to controls (ND).*

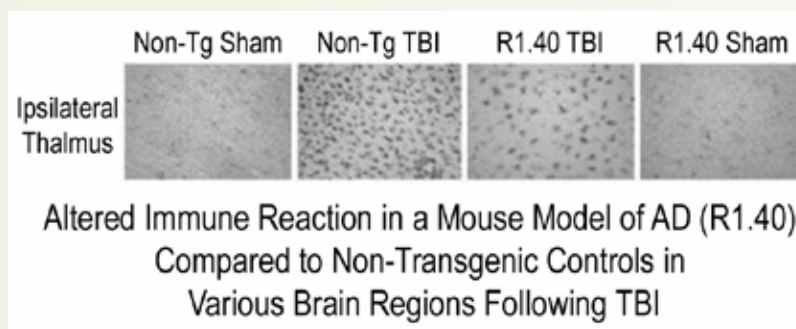## Novel Genetic Models to Study the Role of Inflammation in Brain Injury-Induced Alzheimer's Pathology

**Dr. Bruce Lamb, Cleveland Clinic**

The mechanisms that link TBI with neurodegenerative conditions such as AD remain a mystery. Dr. Bruce Lamb hypothesizes that one of the key bridges between TBI and AD is the inflammatory cascade that occurs after TBI. After carefully considering this hypothesis, Dr. Lamb and colleagues developed sensitive measures to detect neurological changes attributed to TBI. Dr. Lamb and his team collected data using mice prone to developing AD after TBI. The idea is that Dr. Lamb's experiments will track two different sources of inflammation, namely, the peripheral monocytes of the bloodstream and the microglia innate to the brain. Both can contribute to neuroinflammation, but the extent that each plays in outcome following TBI remains unknown.

Dr. Lamb and his team made a recent discovery using mice that overproduce beta-amyloid, the toxic species often associated with formation of senile plaques in AD. As expected, they discovered that both monocytes and microglia were present a few days after injury. What came as a surprise was that the injury continued to grow in the mice that overproduced beta-amyloid. This was also accompanied by a reduction in the immune response in these mice when compared to injured controls. The injured mice that overproduced beta-amyloid also showed worsened behavioral outcomes, including time-dependent spatial working memory. This work shows that key risk factors associated with AD can modulate how the immune system functions after TBI, thus contributing to the worsening and severity of these injuries.

> "The research conducted under this study may provide the basis for controlling damage due to inflammation in the brain, be it from TBI or AD."
>
> **Dr. Bruce Lamb**



Altered Immune Reaction in a Mouse Model of AD (R1.40) Compared to Non-Transgenic Controls in Various Brain Regions Following TBI
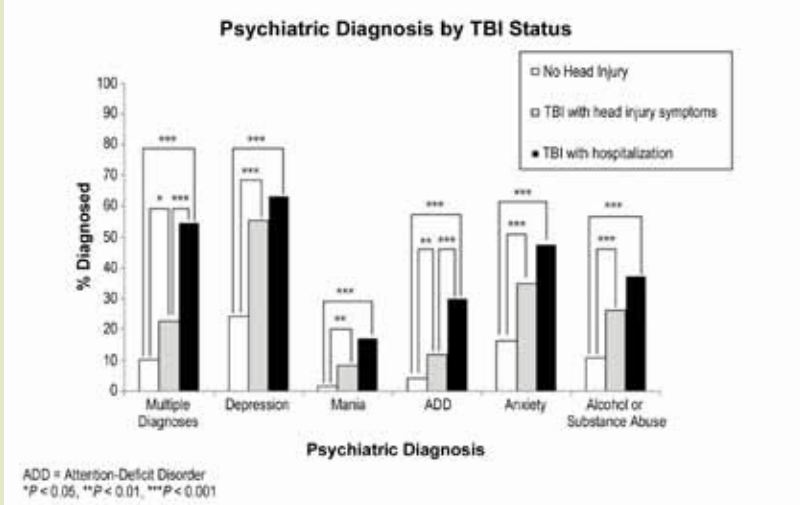
### Endophenotypes of Dementia Associated with Traumatic Brain Injury in Retired Military Personnel

**Dr. Kristine Yaffe, Northern California Institute for Research and Education**

Dr. Kristine Yaffe has launched a study that examines the psychiatric symptoms (e.g., depression, anxiety) and cognitive profiles of aging veterans affected by TBI. Despite an association between TBI and increased risk of dementia such as AD, much remains unknown about the relationship between the two conditions. This study extends previous research by focusing on veterans, a population with a high prevalence of TBI, and looks at common psychiatric disorders. These disorders may be indicative of individuals suffering dementia. The first part of the study is now complete. Dr. Yaffe's team surveyed nearly 300 veterans at two veteran retirement homes, located in Washington, DC, and Northern California. The results from the study showed that 56% of those surveyed had a history of TBI. Further, TBI was associated with psychiatric symptoms such as depression, anxiety, and post-traumatic stress disorder (PTSD). Compared to controls, more TBI participants reported subjective memory complaints.

The second part of the study is ongoing and involves obtaining neuropsychological testing on 150 veterans with and without a history of TBI. This study will begin to offer a better grasp of the relationship between TBI and AD. If successful, it would provide some of the groundwork for comprehending how TBI facilitates the onset of AD, or it may provide some of the underpinnings on how TBI represents its own distinct pathological entity. The project also posits overlaps with other neurological disorders, such as Chronic Traumatic Encephalopathy, which may be part of the TBI/AD signature.



**Veterans Home of California Yountville, CA**

**Armed Forces Retirement Home Washington, DC**



Psychiatric Diagnosis by TBI Status

- No Head Injury
- TBI with head injury symptoms
- TBI with hospitalization

*P < 0.05, **P < 0.01, ***P < 0.001

ADD = Attention-Deficit Disorder

"We hope our study will improve the healthcare of veterans, especially those with history of TBI, by improving our understanding of how TBI affects cognitive aging and impairments such as Alzheimer's disease."
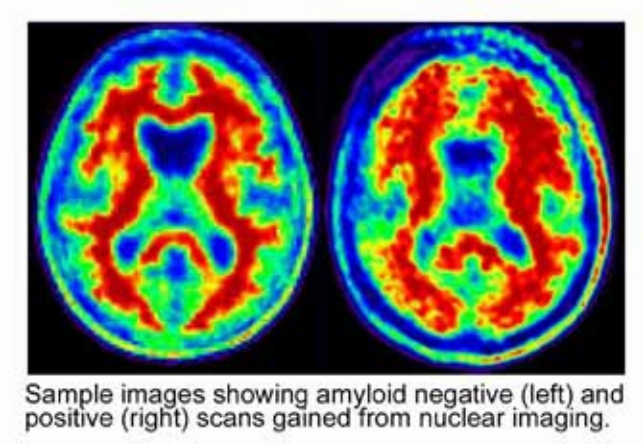
**Dr. Kristine Yaffe**

## Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder on Alzheimer's Disease in Veterans Using Imaging and Biomarkers from the Alzheimer's Disease Neuroimaging Initiative

**Dr. Michael Weiner, Northern California Institute for Research and Education**

Loss of consciousness and post-traumatic amnesia associated with TBIs are well-recognized risk factors for neurodegenerative diseases like AD. Dr. Michael Weiner evaluates Vietnam veterans with a history of TBI or PTSD to investigate the relationship between pathological markers of AD and cognitive decline. Dr. Weiner posits that TBI and/or PTSD may lead to some of the same pathological changes as those seen in AD. The investigation takes advantage of the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multi-million dollar study that developed common research protocols for researching AD. The ADNI harmonizes researchers across the nation so that results can be compared and new insights gleaned regarding AD.


Sample images showing amyloid negative (left) and positive (right) scans gained from nuclear imaging.

The Vietnam Veteran ADNI study uses many of the imaging modalities common to the original ADNI studies, including nuclear (commonly known as positron emission tomography [PET] imaging) and magnetic resonance imaging. The study captures data regarding psychological and cognitive measures. Biological samples are also collected (blood and cerebral spinal fluid). The idea is that the careful collection and combination of all of these measures and tests may reveal changes that no single measure by itself could characterize. Ultimately, the data captured from this study could reveal if and how individuals who have sustained TBI and/or PTSD from today's conflicts are susceptible to longer-term cognitive issues from diseases such as AD. The data may provide the basis for assessing cognitive decline before it starts in veterans who were injured.

Dr. Weiner has recently received additional funding for this research. The subsequent study, "Effects of TBI and PTSD on AD in Veterans with Mild Cognitive Impairment (MCI) using the ADNI," will investigate a subset of the original study population. It is not known what the risk for developing MCI is after TBI or PTSD, and it is hoped that characterizing these individuals may provide the basis for controlling cognitive decline or preventing its rapid progression.

Since the inception of the Vietnam Veteran ADNI study, more than 10,000 individuals were contacted. As a result of these efforts, accrual has been robust, with the first 124 veterans having completed the baseline testing.

> "The Department of Defense-funded project concerning the effects of traumatic brain injury and post-traumatic stress disorder on the development of Alzheimer's disease in Vietnam veterans will help establish the role of military risk factors for Alzheimer's-related dementia, and will be a major step in our long-term goal to prevent cognitive decline and dementia in veterans."
>
> **Dr. Michael Weiner**

For more information, please visit
*http://cdmrp.army.mil/prarp*
or contact us at:
*usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil*
(301) 619-7071