

Introduction: Evolution of military and veterans brain health research[☆]

Recent military conflicts have resulted in a new focus on brain injury and brain health of service members and aging veterans. The wars in Iraq and Afghanistan have been characterized by injuries from improvised explosive devices, including nearly a quarter million cases of mild traumatic brain injury (mTBI) since 2000 [1]. Brain injuries represent a higher proportion of injuries compared with previous conflicts such as the Vietnam War, in part because the modern body armor has altered the pattern of combat injuries. Although most patients with mTBI recover, persistent mTBI can include incapacitating multisensory and neuropsychological symptoms and other delayed problems include depression and behavioral dysfunction [2–4]. In 2011, there were 1,542,625 veterans receiving compensation for tinnitus and hearing loss problems alone. These injuries are combined with high rates of psychological trauma, including > 100,000 new combat-related cases of posttraumatic stress disorder (PTSD) in service members since 2000 and more than one half million veterans from all wars receiving compensation for unresolved PTSD in 2011 [1]. As a result of the Vietnam and first Gulf War experiences, PTSD is better recognized and treated than ever before, whereas some Korean War veterans are only now being diagnosed for long untreated conditions [5]. Stigma has also been reduced for some mental health issues. Military leaders have helped to change a culture that previously labeled PTSD as a personal failing. When General Peter Chiarelli was the Vice Chief of Staff of the Army, he initiated Army-wide education campaigns on suicide and mental health issues, promoting a new perspective that it was possible for anyone to break under stress, and it was important for soldiers to seek medical help, be restored to full function, and continue their military career [6]. Just as soldiers with lower limb amputations have now returned to function with prosthetic legs and are leading troops in Afghanistan [7], soldiers who have suffered from PTSD have also been treated and continue to serve. These new priorities have been substantially promoted by

Congressional funding for brain research to benefit both service members and veterans.

The first Gulf War in 1990 to 1991 launched this brain health focus. Of a large deployed force of 697,000 troops, there were 147 combat deaths and relatively few injuries [8], unmasking a form of chronic multisymptom illness now referred to as “Gulf War Syndrome” characterized by pain, fatigue, and neurocognitive symptoms that have probably presented in some form after every major conflict [9–11]. To ensure that the Department of Defense (DoD) and Veterans Affairs (VA) met the needs of veterans with undiagnosed symptoms of Gulf War Illness, Congress provided >\$150 million for medical research to investigate virtually every testable hypothesis concerning deployment health [12,13] and more funding for medical care. The findings led to new health monitoring policies, a new emphasis on electronic medical records and exposure databases, health risk communications, and major investigations into neurologic health and neurotoxic threats [10]. In 2006, there was a resurgence of Congressional interest in military health-care needs and Congress provided \$300 million for research on traumatic brain injury (TBI) and PTSD (FY2007), followed by >\$100 million each year to continue the research (>\$1 billion to date). In June 2008, the Secretary of Defense, Robert Gates, directed the military services to refocus the medical research program to advance “the state of medical science in those areas of most pressing need and relevance to today’s battlefield experience, particularly in the area of mental health and traumatic brain injury” [14]. In FY2010, there was an additional large increase in the Pentagon’s annual budget for medical research (\$400 million/y). These huge funding increases for medical research for service members and veterans have largely focused on near term health-care needs of injured and ill service members [15], but other Congressional appropriations provided for longer term concerns.

There is a large, parallel, DoD-funded effort on investigation of long-term consequences of war-related brain injury (Fig. 1). The costs of delayed action, in terms of quality of life and post hoc medical research investigations, have been well demonstrated in the continuing investigations of Vietnam veterans exposed to Agent Orange and the Gulf War Illness cohorts. Congress prodded the DoD and VA into action on militarily-relevant Parkinson’s disease research with annual funding for the Army’s

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K.E.F. received licensing royalties for a patent bundled with other patents pertaining to the neuropsychological test that the DoD uses (United States Patent 7,837,472 B1).

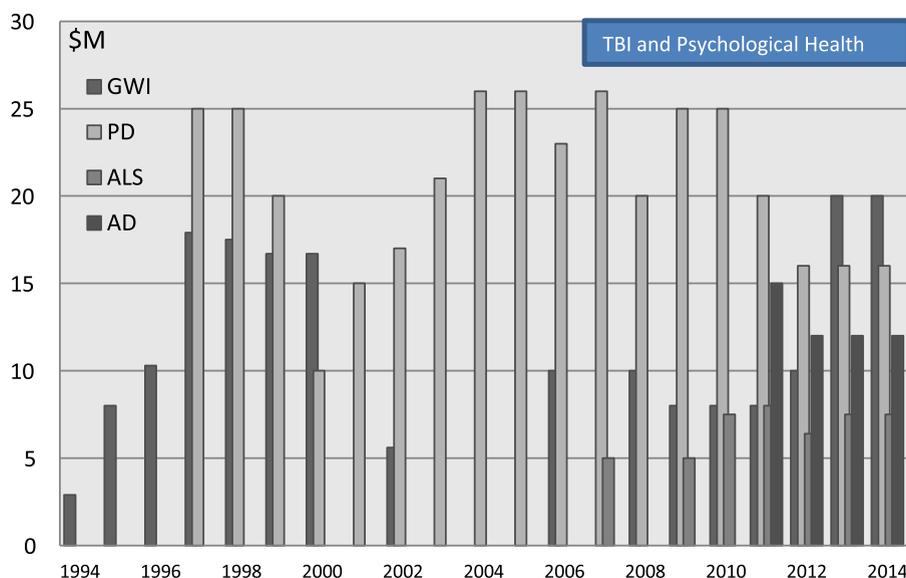


Fig. 1. DoD funding profile for Gulf War illness (GWI), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD) medical research programs that preceded and now parallel major funding surges exceeding \$1 billion in traumatic brain injury (TBI) and psychological health research since 2007.

Neurotoxin Exposure Treatment (Parkinson's) Research program starting in 1997 (totaling \$372 million to date) and with the establishment of the VA Parkinson's Disease Research, Education, and Clinical Centers in 2001 with an initial focus on deep brain stimulation therapy for veterans. Connections between head trauma and longer term risks for dementia, Alzheimer's disease (AD), and Parkinson's disease were already suspected, with highly visible cases in boxers and football players. Parkinson's disease also had a strong association with neurotoxic chemical exposures with overlapping chemicals of concern in the investigations of Gulf War illness, as highlighted in this issue by Carlie Tanner and her colleagues. After intensive epidemiologic investigation of amyotrophic lateral sclerosis (ALS) in Gulf War veterans [16], the VA determined that ALS was a Gulf War deployment-associated disease and provided compensation to affected veterans, and Congress provided funding for a new DoD ALS research program. More recently, Congress has provided annual funding for a militarily-relevant AD program (totaling \$51 million in 3 years). The Vietnam veterans Alzheimer's Disease Neuroimaging Initiative (ADNI) study, described in this issue, was the first effort established under this new program, seizing the opportunity to leverage the existing ADNI research infrastructure to identify potential long-term AD risks associated with PTSD or TBI originating with service in the Vietnam War. Most recently, the VA has made AD and Parkinson's disease presumptive for TBI connected with military service [17].

The association of psychological trauma, depression, and mental resilience in the development of dementia and neurodegenerative diseases has emerged in recent research but is still complicated and awaiting mechanistic explanations. Depressive illness is an important concern in service mem-

bers and has been related to brain injury and psychological stress as highlighted in articles in this issue. Chronic stress conditions, such as being held as a prisoner of war, have also been associated with Parkinson's disease [18] and with AD and other dementias (described in this issue by Meziab et al.). The mechanistic links between depression and neurodegenerative disease are beginning to fill in with the foundational Army-funded work of researchers such as Paul Greengard [19,20]. The Army Parkinson's program preceded the huge budget increases for TBI and psychological health research by a decade and provided a foundation of research on military risk factors such as TBI and chemical exposures, as well as development of tools such as the neuropsychological test used by the DoD [21] and development of biomarkers of neurodegenerative disease (both described in this issue by Vincent and Fiandaca). The Parkinson's program and the other militarily-relevant disease programs (ALS and AD) have been particularly useful in advancing research that served both military medical needs and neurodegenerative disease objectives. These programs highlight changing military medical research needs, influenced by changing problems and biomedical advances especially related to common medical diagnostic and treatment needs across the wide continuum of service members and veterans. The development of tau protein neuroimaging capability is one important example of a common tool that may be important to breakthrough diagnostic capability for young head-injured soldiers, as well as injured veterans (articles by McKee and Villemagne in this issue).

Much of the DoD clinical research funding has gone to VA researchers where the critical research capabilities, expertise, and relevant patient populations reside. VA research centers are recognized as the national resource for treatment and rehabilitation of deployment-related brain injury and illness and

have received >\$120 million of the DoD funding appropriated for TBI and behavioral health, more than twice the amount spent in DoD clinical research studies. The DoD continues to institute improvements in protection of service members, including avoidance of neurotoxic chemical exposures, development of brain injury models to guide helmet design, and programs to promote psychological resilience; develop strategies for brain health monitoring throughout a service member's career; and validation of assessment methods to detect mTBI, PTSD, and other behavioral health changes [15]. These DoD brain health protection strategies include consideration of long-term consequences for veterans from a continuum of military risk factors. Just as DoD research demonstrated that stress fractures prevalent in basic training were associated with the same risk factors as osteoporosis in aging veterans, brain health and resilience are likely associated with the type of brain aging that military veterans will face. When the VA and the DoD finally resolve issues concerning the President's request for the creation of a virtual lifetime electronic record [22], special registries will be a thing of the past and many interrelated etiologic factors, including medical history and genetics, military exposures and experiences, and health outcomes will become clearer. The current Surgeon General of the Army, LTG Patricia Horoho, is leading the services on a new forward-looking health path, focusing on brain health and resilience of service members through modifiable health habits as seemingly pedestrian as exercise, nutrition, and sleep [23]. Articles in this issue address lifestyle factors and specifically sleep and smoking roles in later brain health status.

This special issue presents current concepts on the continuum between military risk factors of current importance and high prevalence and development of neurodegenerative disease in veterans. The articles illustrate the highly collaborative nature of this DoD and VA cooperation to better prevent and treat brain injuries in young service members, with the potential to dramatically reduce the risk for later neurodegenerative disease in military veterans.

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