Title
Military-related risk factors for dementia

Journal
Alzheimer's & Dementia, 14(12)

ISSN
1552-5260

Authors
Snyder, Heather M
Carare, Roxana O
DeKosky, Steven T
et al.

Publication Date
2018-12-01

DOI
10.1016/j.jalz.2018.08.011

Peer reviewed

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Alzheimers Dement. 2018 December ; 14(12): 1651–1662. doi:10.1016/j.jalz.2018.08.011.

Military Related Risk Factors for Dementia

Heather M. Snyder[1,*], **Roxana O. Carare**[2], **Steven T. DeKosky**[3], **Mony de Leon**[4], **Derek Dykxhoorn**[5], **Li Gan**[6], **Raquel Gardner**[7], **Sidney R. Hinds II**[8], **Michael Jaffee**[3], **Bruce T. Lamb**[9], **Susan Landau**[10], **Geoff Manley**[7], **Ann McKee**[11], **Daniel Perl**[12], **Julie A. Schneider**[13], **Michael Weiner**[14], **Cheryl Wellington**[15], **Kristine Yaffe**[7], **Lisa Bain**[16], **Anthony M. Pacifico**[17,^], and **Maria C. Carrillo**[1]

[1.]Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA

[2.]Clinical Neuroanatomy, Equality and Diversity Lead, University of Southampton, Southampton, United Kingdom

[3.]Department of Neurology and Neuroscience, University of Florida, Gainesville, FL, USA

[4.]Department of Psychiatry, New York University Medical Center, New York City, NY, USA

[5.]Department of Microbiology and Immunology, Miami University, Miami, FL, USA

[6.]Gladstone Institute, University of California, San Francisco, San Francisco, CA, USA

[7.]Department of Psychiatry, Neurology & Epidemiology, University of California, San Francisco, San Francisco, CA, USA

[8.]Blast Injury Research Program Coordinating Office, United States Army Medical Research and Material Command, Frederick, MD, USA

[9.]Stark Neurosciences Research Institute, Indiana University, Indianapolis, IN, USA

[10.]Helen Willis Neuroscience Institute, University of California, Berkley, Berkley, California, USA

[11.]Department of Neurology and Pathology, Boston University, Boston, MA, USA

[12.]Department of Pathology, Uniformed Services University, Bethesda, MD, USA

[13.]Neurology Department, Rush University Medical Center, Chicago, IL, USA

[14.]Department of Radiology, University of California San Francisco, San Francisco, CA, USA

[15.]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

[16.]Independent Science Writer, Philadelphia, PA, USA

[17.]Program Manager, Congressionally Directed Medical Research Programs, Frederick, MD, USA

[*]Corresponding author: Tel.: 11-312-335-5184; Fax: 11-866-875-2553. hsnyder@alz.org.

[^]"The paper does not reflect Department of Defense (DoD) policy or opinion on Alzheimer's or traumatic brain injury (TBI) research."

Abstract

INTRODUCTION: In recent years, there has been growing discussion to better understand the pathophysiological mechanisms of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) and how they may be linked to an increased risk of neurodegenerative diseases including Alzheimer's disease (AD) in veterans.

METHODS: Building on that discussion, and subsequent to a special issue of *Alzheimer's & Dementia* published in June, 2014, which focused on military risk factors, the Alzheimer's Association convened a continued discussion of the scientific community on December 1, 2016.

RESULTS: During this meeting, participants presented and evaluated progress made since 2012 and identified outstanding knowledge gaps regarding factors that may impact veterans' risk for later life dementia.

DISCUSSION: The following is a summary of the invited presentations and moderated discussions of both the review of scientific understanding and identification of gaps to inform further investigations.

1. Introduction and Background

In 2012, the Alzheimer's Association and the Veterans' Health Research Institute (NCIRE) brought together experts from civilian and military research centers to discuss evidence suggesting that the pathophysiological mechanisms of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) may be linked to an increased risk of neurodegenerative diseases including Alzheimer's disease (AD) in veterans (1). At the time of this meeting, several projects had been funded by the Department of Defense (DoD) and the Department of Veterans Affairs (VA) to better understand the prevalence of these conditions and factors that may increase the risk of dementia in veterans, identify biomarkers that may elucidate pathogenic mechanisms, and characterize mild and moderate TBI and PTSD resulting from the various etiologies of head trauma, including blunt force trauma and blasts from Improvised Explosive Devices (IEDs).

Building on that discussion, and subsequent to a special issue of *Alzheimer's & Dementia* published in June, 2014, which focused on military risk factors (2-19), the Alzheimer's Association convened a continued discussion of the scientific community on December 1, 2016, to evaluate progress made since 2012 and identify outstanding knowledge gaps regarding factors that may impact veterans' risk for later life dementia. The following is a summary of the invited presentations and moderated discussions of both the review of scientific understanding and identification of gaps to inform further investigations.

2. TBI and PTSD in civilian and military populations

TBI is extremely common and costly, especially among veterans (20). In 2012, the Congressional Budget Office (CBO) estimated that the cost of Traumatic Brain Injury (TBI) and TBI/ Post Traumatic Stress Disorder (PTSD)-specific care by the Veterans Health Administration was roughly $430M (in FY11 dollars) between 2004-2009 for the first year

of treatment for veterans of overseas contingency operations. The Centers for Disease Control (CDC) estimated medical costs for domestic TBI was $76.3B in 2010 (21, 22).

The Defense and Veterans Brain Injury Center (DVBIC) estimates that more than 350,000 service members were diagnosed with TBI between 2000 and 2016. The vast majority of these cases were mild, involving either a loss of consciousness (LOC), alteration of consciousness (AOC), or post-traumatic amnesia (PTA) and were diagnosed in non-deployment settings (23). Moreover, about half of all recruits experienced at least one TBI prior to their military career, although the cause of the prior TBI is generally unknown.

Concern about the long-term health consequences of TBI in both military and civilian populations has been increasing in recent years in parallel with an increased understanding of the pathological features and possible mechanisms involved (24). These concerns have prompted interagency collaborations among the DoD, VA, and National Institutes of Health (NIH), including: longitudinal studies by DVBIC , the Center for Neuroscience and Regenerative Medicine (CNRM, a congressionally mandated intramural research collaboration on TBI bringing together expertise of investigators from the DoD and the NIH) and the Chronic Effects of Neurotrauma Consortium (CENC) to determine the long-term cognitive, physical, and mental health effects of mild TBI as well as risk factors for poor outcome and impact of interventions. DoD established the Peer-Reviewed Alzheimer's Research Program (PRARP) in 2011 (25). The PRARP currently addresses the paucity of clinical and epidemiologic studies examining the relationship between TBI and subsequent AD and related dementias, the inadequacy of research resources, and the need for new technologies and assessments for diagnosis, detection of progression, and interventions to benefit patients and caregivers living with these conditions.

In 2012, President Obama issued an executive order on “Improving Access to Mental Health Services for Veterans, Service Members, and Military Families” (26), which resulted in a National Research Action Plan, and subsequent funding of the CENC (27). CENC is a multicenter collaboration of DoD, VA, academic universities, and private research institutes that has established 5 research cores and multiple projects in order to conduct epidemiologic, basic research, and clinical studies on TBI.

Many deployment-related TBIs occur as a result of exposure to an explosive blast, resulting in a range of clinical, bio-physical, and neuropathological effects (10, 28, 29). It is extremely difficult to distinguish the “pure” effect of a blast wave on the brain in a deployed setting because secondary, tertiary, quaternary and/or quinary effects are known to occur with blast. These have been described by Department of Defense Directive (DoDD) 6025.21E and the Blast Injury Research Program Coordinating Office and are recognized as confounders in studying pure blast effects on the CNS (30-32). To summarize this concept, prior DoD investigators coined the term “blast plus” to illustrate the fact that many combat injuries were not caused by blast in isolation (33). The majority of TBIs in service members are not sustained during combat and are single mechanism impact injuries such as training injuries.

Much of what is known about the long-term consequences of mild TBI has come from the study of concussion in athletes, particularly boxers and American football players. One

concept emerging from these studies that may have relevance for the military population is sub-concussion, a condition where head impact results in no obvious immediate clinical symptoms or neurological dysfunction despite exposure of the brain to substantial acceleration and deceleration forces, but which can cause cumulative injury and functional impairment over time (34). It is also important to distinguish mild TBI from moderate to severe TBI, as the findings from these studies may be different and give rise to unique mechanisms and specific long-term consequences. However, research in the area remains unclear. Importantly, a recent study from the CENC epidemiology project reported that increasing TBI severity was associated with increasing risk of developing dementia and that even mild TBI without loss of consciousness carried a small increase in risk for later dementia. The clinical and scientific communities are investigating the thresholds, technology used to measure sub-concussion, and objective medical data for both blunt and blast exposure (35). Beyond this, literature on the incidence and prevalence of AD subsequent to all types of TBI in military populations is sparse.

3. Risk factors for dementia in military and civilian populations

Veterans face a unique set of exposures in addition to normal health risk factors and comorbidities that may lead to an increased risk of developing late-life dementia (36). Many, but not all studies have identified moderate-severe TBI as an independent risk factor for dementia (37-40). In one retrospective cohort study of older veterans, TBI was associated with a 60% increase in the risk of developing dementia over a 9-year follow-up period (41). Diagnosis of TBI and dementia in this study was not based on self-report but rather on physician electronic medical records (EMR) diagnosis. Plassman et al. evaluated Navy and Marine World War II (WWII) veterans retrospectively, including 548 veterans diagnosed with non-penetrating head injuries at time of hospitalization and found that both moderate and severe but not mild TBI were significant risk factors for the development of both AD and dementia. In this study, mild TBI was defined as loss of consciousness (LOC) or post-traumatic amnesia (PTA) for less than 30 minutes, moderate as LOC or PTA ranging between 30 minutes to 24 hours, or severe if the symptoms persisted for more than 24 hours (42). One limitation of this landmark study was that AD was diagnosed clinically and did not use AD biomarkers such as amyloid positron emission tomography (PET) scans or cerebrospinal fluid (CSF) measurements of amyloid-β (Aβ) and tau. More recent studies of elders with prior TBI using neuropathology at autopsy (38) or AD biomarkers (43) have not shown a relationship between prior TBI and the development of AD pathology.

In addition to TBI, veterans have a high burden of cardiovascular disease (44), depression (45), and PTSD, all of which have been shown to be associated with increased dementia risk (41, 45-50). Furthermore, these risks appear to be additive (41). Among veterans with TBI, more than half also have depression, PTSD, and/or a substance use disorder (51), and studies suggest a longitudinal relationship among PTSD, TBI and cognitive impairment (52). However, preliminary results from studies funded by the DoD in conjunction with the Alzheimer's Disease Neuroimaging Initiative (DOD ADNI) indicate that neither TBI nor PTSD are associated with increased AD biomarkers (amyloid PET or medial temporal lobe atrophy assessed by MRI) (43). Emerging evidence also suggests that sleep disturbances and poor sleep quality increase the risk of dementia in older adults (53), including veterans (54).

Sleep disturbances are common in veterans, particularly among those with PTSD (55). Prior TBI increases the risk for repeated TBI, and repeated TBI is associated with worse outcomes (37, 56, 57). In addition, another variable is the severity of TBI in each instance and how this may contribute to the overall impact of the TBI on the underlying biology. Compared to civilians, older veterans report higher rates of repeat vs. single TBI (50). Finally, the impact of TBI on development of dementia could also be affected by the age at which the TBI occurred, with younger adults being more resilient than older adults to the effects of mild TBI (49).

Post-TBI dementia may also not be of the pure Alzheimer's type. For example, following remote TBI with loss of consciousness for >30 minutes, military veterans may show a different pattern of cognitive deficits than are typically see in AD, i.e., impaired motor (58) and executive function and processing speed but no impairments in memory and language (50). These latter findings regarding lack of impairment in memory and language following remote TBI have been replicated in a nationally representative sample of civilians as well (59). Recent pooled data from several large brain banks suggests that TBI with loss of consciousness could be associated with Lewy body pathology, cerebral microinfarcts and progression of parkinsonism rather than amyloid plaques and tau tangles (38). Further, repetitive head injury has been associated with chronic traumatic encephalopathy (CTE), although the incidence and prevalence in various forms of brain injury is still being investigated. Finally, it remains unclear how the variety of different neurodegenerative diseases and related brain changes, including AD, PD, CTE and others are related to one another following TBI (60, 61) and how repeat TBI may serve to alter or even accelerate the progression of a pre-existing neurodegenerative disease in the brain.

4. Biological underpinnings

Animal models are important proxies for studying TBI, providing biospecimens under controlled conditions, allowing pre- and post-injury assessments, and facilitating hypothesis testing experiments from basic mechanistic studies to drug development. Many different animal models have been generated, validated, and used widely to study different aspects of TBI pathophysiology (62), with various levels of both face and construct validity. While these model systems provide an important way to study the effects of TBI, there are limitations and caveats to each model that should be considered in its application. For instance, current models recapitulate some of neurodegenerative-related brain changes, including increased phosphorylation of tau, but in general neurofibrillary tangles do not form.

4.1 Tau

Hyperphosphorylated tau, found in neurofibrillary tangles in AD, CTE, and many other neurodegenerative diseases, known collectively as tauopathies, has also been identified in the postmortem brains of veterans with known blast exposure or concussion (63). Animal models of TBI have shown an increase in tau immunoreactivity and tau phosphorylation, which correlates with injury severity (64). In both human and animal models, the accumulation and aggregation of tau is thought to reflect an imbalance between production

and clearance of toxic forms of the protein, which may be affected by complex post-translational modifications (65). However, it remains to be determined whether the pathologic species in acute and chronic TBI are the same as those in other tauopathies. One area of growing research is to compare and contrast tau deposition among mild, moderate and severe TBI. Repetitive mild TBIs, sustained in both military and domestic settings are a growing concern as well. Tauopathy research currently suffers from a lack of high-quality diagnostics, although several are under development (66-68). A drug called salsalate, which inhibits tau acetylation and protects against deficits in spatial memory and hippocampal atrophy (69), is currently being tested in two Phase 1 studies in AD and progressive supranuclear palsy (PSP), another tauopathy.

4.2 Amyloid

Early studies of head injury suggest the likelihood of Aβ42 as the predominant form of Aβ generated in response to injury; this study included 19 individuals with severe TBI (70). Surgically resected temporal cortex was analyzed for levels of soluble Aβ 40 and 42. These individuals had higher levels of soluble Aβ42 but not Aβ40 in addition to observed cortical plaques (71). TBI also exerts changes in axonal pathology to include accumulations of amyloid and amyloid precursor protein (APP) in swollen axons in a wide variety of head injuries (72) that can be adjacent to plaque formation (73).

There have been both acute and chronic findings of Aβ demonstrated in animal models and human studies. Investigators are attempting to better understand the variability in the chronic finding of cortical amyloid plaques. There are ongoing studies regarding variability in the dynamics of Aβ to understand its role in chronic injury (74) For instance, chronic injury response in the axonal and cortical brain regions may require both Aβ40 and 42 (75). These areas require further study.

Several CSF and plasma biomarker studies of Aβ42 published observations suggesting TBI is associated with cortical amyloid changes. Mondello and colleagues evaluated 12 individuals with severe TBI and found that Aβ42 levels in the CSF were significantly lower after injury, while levels in the plasma were elevated. CT imaging showed an equal distribution of diffuse injury and focal lesions across the cohort with no correlation between CSF and plasma levels of Aβ42. While limited data on survival was published on this cohort, the study did show that low levels of CSF Aβ42 and high levels of plasma Aβ42 correlated with mortality (76). Gatson and colleagues found similar results and have shown that increases in CSF oligomeric species could be used to predict poorer outcome (77). Other studies suggest that the Aβ42 decrease may be long-lasting (78, 79). Further, Franz and colleagues evaluated 29 individuals over the course of 1 and 284 days post-trauma with cognitive disorders and headache; they found that concentrations of Aβ42 were significantly lower in individuals with traumatic brain injury (TBI) than in control groups over this duration (79). Studies indicating that TBI significantly increases the amount of Aβ42 measured in human CSF are also reported in the literature, but these studies have very small n values, vary greatly between patients and lack rigorous controls.

Nuclear imaging of Aβ has been completed in a number of civilian and military cohorts. A recent radioimaging study using 11C-Pittsburgh compound B (11C-PiB)-PET in addition to

structural and diffusion MRI evaluated individuals 11 months to 17 years after moderate-severe TBI and demonstrated that increased PiB binding was observed in the posterior cingulate cortex (PCC) and cerebellum despite lack of clinical dementia symptoms. The PCC result correlated with decreased fractional anisotropy. PiB binding in AD patients without TBI was lower in neocortical regions but increased in the cerebellum, suggesting a distinct amyloid burden for TBI versus AD. About half of the individuals with TBI also presented focal lesions (80). Other studies using PiB have shown contrasting results. A study of Operation Iraqi Freedom/Operation Enduring Freedom male combat veterans revealed reduced global cerebral blood flow (gCBF) in those who had sustained a TBI but no amyloid burden even years post-injury (81). Studies of other amyloid tracers such as Florbetapir (F-18) have been shown to be of significance in chronic traumatic encephalopathy (82).

Hong and colleagues evaluated 15 individuals within a year of TBI occurrence before and after death with a PET autopsy study using PiB imaging prior to death further adds to the contours of the TBI-AD interrelationship. Post-mortem results showed significantly increased PiB distribution in cortical gray matter and the striatum, while regions such as white matter and thalamus did not show significant differences from the controls. Although no PiB binding was observed in the white matter, Aβ and APP were detected by immunohistochemistry. These individuals with TBI scored normally on the MMSE (83).

In summary, there is evidence from neuropathology, neuroimaging, and fluid biomarkers to suggest that amyloid accumulation in the brain contributes to the pathophysiology of those who develop a progressive dementia following either moderate-severe TBI or repetitive brain trauma. There are ongoing investigations to better understand the exact mechanisms that trigger the chronic accumulation in those patients that develop this long-term sequela. It is hoped that better identifying these mechanisms can inform treatment strategies for both TBI patients and AD patients.

4.3 Clearance of intracranial fluids

Apart from the blood, there are two fluids in the cranium that could be affected after TBI: CSF and interstitial (ISF) fluid. ISF drains out of the brain along basement membranes surrounding arterial smooth muscle cells, the intramural periarterial drainage pathway (IPAD) (84). CSF communicates with the ISF via glial-pial basement membranes, a pathway dependent upon the glial aquaporin 4 (85). With ageing and possession of *APOE4* allele, there are changes in the cerebrovascular basement membranes that lead to a failure of the IPAD to properly clear the ISF, as well as impairing the glymphatic pathway (86). In TBI there are changes in the composition of the extracellular matrix, likely affecting the cerebrovascular basement membranes as well as both IPAD and the glymphatic pathways (87). Mouse models of adult and juvenile TBI have both demonstrated that brain injury causes long-term impairment of the glymphatic pathway resulting in the deposition of Aβ and tau, but to date no experimental data has evaluated the changes in the intramural periarterial drainage after mild, moderate or severe TBI (86, 87). Emerging evidence suggests that the glymphatic system may be particularly relevant during sleep (88). However much more research is needed to clarify the biochemical changes that regulate clearance of pathological proteins and the disruptions of both the IPAD and glympathic pathways that

occur following TBI, in particular in association with post-traumatic stress disorder (PTSD) (86).

Aging and presence of the *APOE4* allele have also been linked to changes in the basement membranes involved in the glymphatic pathway that lead to impaired clearance of Aβ (89, 90). Together, these findings have important implications for the development of therapeutics, particularly since immune complexes formed in response to immunotherapy also appear to interfere with perivascular drainage (91). This suggests that more attention should be attributed to the effects of TBI on both the IPAD and the glymphatic pathways

4.4 Inflammation

Inflammation provides another link between neurodegeneration and TBI, since inflammatory and immune pathways are known to be important in neurodegeneration (92, 93) and brain trauma induces early, robust, and long-lasting inflammation in the brain (94). Genome wide association studies (GWAS) have also provided evidence linking inflammatory pathways to AD (95). One gene implicated in AD that may also play a role in the inflammatory response after TBI is the triggering receptor on myeloid cells 2 (*TREM2*) gene. In neuropathologic studies, TREM2 has been shown to be expressed on the macrophages that are found surrounding amyloid plaques (96). Recent studies using the lateral fluid percussion injury platform in mice suggest that *TREM2* expression is upregulated at early but not late time points following injury. In *TREM2*-deficient mice, activated macrophages have been shown to accumulate near the injury site but not at more distal sites and these mice have a reduction in post-injury hippocampal volume loss and behavioral impairments compared to their wild type counterparts (97). Unpublished studies further indicate that the role of *TREM2* is dependent on both age and type of pathology (i.e., amyloid versus tau). While TREM2 may serve as a potential biomarker for TBI, there are many unanswered questions as to whether *TREM2*-expressing macrophages originate from the brain or periphery.

4.5 Genetics and epigenetics

Genetic studies have proven powerful in identifying genes that influence the development of AD and other dementias, including the genes involved in TBI (98). The majority of genetic studies in TBI have focused on candidate gene associations (99). Among the genes studied, the apolipoprotein E (*APOE*) gene has garnered the most attention largely due to the strong genetic association between *APOE* and AD (100) and the important role that this gene plays in promoting repair and growth of neurons, synaptic functioning, and modulating inflammatory responses (98). Although the results of these studies have been conflicting, the majority of studies have shown that the *APOE4* allele adversely affects recovery following TBI, particularly in dementia-related outcomes (101). For example, a meta-analysis by Zhou et al. (2008) of 14 cohort studies showed that, although no effect was seen on the initial severity of the TBI, the *APOE4* allele increased the risk of poor long-term outcomes as measured by the Glasgow Outcome Scale (GOS) (102). Further analysis by Zeng and colleagues found that the association between *APOE4* and poor prognoses was limited to severe TBI (103). Additional candidate gene studies (reviewed in (104) have examined genes associated with response to neurotrauma (such as angiotensin converting enzyme

(*ACE*) and Interleukin 1β (*IL-1β*)), neuronal repair and plasticity (such as brain-derived neurotropic factor (*BDNF*)), and pre- and post-injury cognitive capacity and reserve (such as dopamine D2 receptor (*DRD2*) and catechol-O-methyltransferase (*COMT*)). These studies, as well as the nature and severity and frequency of TBI, may help explain much of the heterogeneity in outcome following neurotrauma (104). Replication studies are needed to help strengthen the association of many of these candidate genes with TBI-associated neurological outcomes. However, this has been complicated by the lack of uniformity in the clinical assessments performed, the heterogeneous nature of TBI, and the small sample sizes being examined in most studies. Generally, these associations have been of small to modest effect size suggesting the involvement of additional, as yet unidentified, genetic loci. To overcome these limitations, there is a need for comprehensive genetic studies to examine the role of common and rare genetic variants in TBI-related clinical outcomes (e.g. AD and other dementias) using well-defined study populations with sufficient numbers of participants to permit robust statistical analyses.

The cellular and molecular mechanisms that shape outcome to any kind of stress including TBI may also be affected by a variety of environmental exposures through epigenetic modifications (105). Epigenetics helps explain at a molecular level “the structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states” (106). Epigenetic mechanisms include chemical modification at the level of the nucleotide (e.g., DNA methylation) as well as post-translational modification of the N-terminal tails of histones, nucleosome remodeling, and RNA interference. The vast majority of studies examining the impact of TBI on epigenetic changes in the brain have focused on animal models. In rat models of TBI, injury induces perturbations in DNA methylation, histone methylation, and histone acetylation in the brain (107-109). For example, Zhang et al (2007) found that there was a global hypomethylation of DNA in injured brain regions of rats following a weight-drop contusion. This hypomethylation of DNA was most profound in a subset of activated microglia/macrophages whose accumulation is known to follow TBI contributing to post-injury inflammation. If it goes unchecked, prolonged microglia activation can have destructive effects on CNS tissue. (110) Following a controlled cortical impact in rats, Schober and colleagues found DNA hypermethylation within the Insulin-like growth factor 1 (*IGF-1*) gene promoting the expression of the IGF1B isoform shown to play a role in neuroprotection (108). This alteration in *IGF-1* DNA methylation was correlated with altered histone methylation and acetylation changes including increased histone H3 lysine 36 trimethylation at the *IGF-1* promoter region 1 (PR1). Little is known about the impact of TBI-induced epigenetic changes in the human brain. This is largely due to a paucity of post-mortem brain tissues for analysis. Epigenetic modifications also influence other mechanisms important in TBI, such as inflammation. These processes are being studied in the peripheral blood and CSF for application of potential biomarkers.

5. Neuropathology

Much of what is known about the neuropathological consequences of mild TBI come from studies of athletes. What is now known as CTE has been identified in boxers, American football players, and other athletes, both professional and amateur (111, 112). Neuropathological analysis of an initial cohort of 85 brains from athletes and military

veterans with a history of repetitive head injury (RHI) reported the key diagnostic feature of CTE as a perivascular hyperphosphorylated tau lesion deposited in neurons and astroglia around small blood vessels in the cortical sulci, distinguishing it from the typical tau lesions seen in AD. While there is debate on the specific pathway of tau related pathology changes, several studies suggest that tau pathology initiates in the cortex and spreads to adjacent cortical regions, eventually progressing to widespread degeneration of most areas of the cerebral cortex and medial temporal lobe. It is not known whether the order of tau-related pathology changes is similar across neurodegenerative diseases, and this is an important question to understand. In these studies, CTE stage and potentially severity is significantly correlated with age at death and length of playing football.

In 2014, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) held the first consensus meeting to evaluate the preliminary pathological criteria for diagnosing CTE. Seven neuropathologists were given slides from 25 cases of various tauopathies with no clinical or demographic information or information on gross neuropathology. 91.4% of the total responses correctly identified CTE, rising to 95.7% after clinical information and gross neuropathological features were revealed (113). A second consensus meeting in 2016 confirmed the validity of the pathological criteria. Clinical criteria, as well as research diagnostic criteria for “traumatic encephalopathy syndrome” (TES) have also been proposed (114) but there are currently no consensus clinical or research criteria for TES (115). Recently Crane et al. published a seminal paper on this topic (38). In conclusion, this large neuropathological study showed that prior history of concussion was not a risk factor for development of AD pathology but did increase risk for development of Parkinson’s disease pathology including Lewy Bodies and increased deposition of alpha synuclein.

5.1 Blast injuries vs. impact injuries

The pathology seen in athletes with TBI is also seen in veterans, which is not surprising given that most TBIs among veterans occur off the battlefield through contact sports, motor vehicle accidents, falls, or fights. However, a unique pathological signature has been observed in veterans who sustained blast injuries such as those from improvised explosive devices (IEDs). The blast wave produces a short (approximately 10 milliseconds) pulse of high pressure that spreads in all directions at greater than the speed of sound, penetrating the skull and entering the brain. Service members with blast exposure report common and persistent physical, cognitive, behavioral and emotional post-concussive symptoms following the blast injury. However, diagnostic tools such as neuroimaging are needed to identify the pathologic lesions *in vivo.*

Several neuropathological studies have explored the long-term effects of blast exposure among a small number of veterans exposed to blast, however, their findings have been mixed in showing either axonal damage and/or tau pathology (63, 116, 117). A more recent neuropathological study compared the brains of individuals with chronic blast exposure, acute blast exposure, chronic impact TBI, exposure to opiates, and a control group with no history of brain injury (29). Although this study had a relatively small sample size, those with chronic blast exposure showed characteristic interface astroglial scarring of the subpial

glial plate, penetrating cortical blood vessels, grey-white matter junctions, and structures lining the ventricles, a pattern that adheres to the basic principles of blast biophysics (29). Acute blast exposure showed early astroglial scarring in the same brain regions; however, civilian cases with or without a history of TBI or opiate use showed no signs of astroglial scarring. Only the oldest and longest latency case among the chronic blast injury group had tau staining and met the criteria for CTE, while another case had a few tau tangles but did not meet the neuropathological criteria. One possible explanation is that scarring around the subpial plate and penetrating blood vessels impairs cerebrovascular function including glymphatic clearance (118), thus predisposing blast injured individuals to subsequent tau neurodegeneration.

5.2 Civilian TBI

Neuropathological studies in civilian populations not enriched for TBI have only recently begun to look for CTE pathology, so the prevalence of long-term consequences related to TBI are still incompletely understood. At a routine neuropathology service in Canada, approximately one-third of cases had CTE pathology (119), while in a series of 268 cases studies at the Queens Square Brain Bank in the UK, 32 (12%) had neuropathological diagnoses of CTE, and of these, 94% had a history of TBI. At the University of Washington Alzheimer's Disease Research Center, which is enriched for cases of AD, 200 consecutive autopsies identified 17% with probably or definite CTE pathology (unpublished data). Autopsy data from the Adult Changes in Thought (ACT) study revealed no strong evidence of a link between self-reported TBI and AD pathology, but an increase in risk for Lewy body dementia, microvascular brain injury, and Parkinson’s disease (38). However, this cohort included mostly individuals with mild TBI but no dementia and was based on the individual’s self-report with limited exposure history available. Whether TBI is also associated with other AD (amyloid plaques, inflammation, etc.) and non-AD pathologies (alpha synuclein, TDP43, etc.) is an area of active and ongoing investigation (71, 120). To understand the true prevalence may require applying standardized neuropathological criteria to an unbiased community or population-based cohort with detailed exposure history and clinical data, including psychiatric measures.

6. Biomarkers

Biomarkers could be used clinically for diagnosis, progression monitoring, and treatment management if they qualify as surrogates, and have the potential to provide mechanistic insight as well. Mild TBI usually produces minimal or no structural damage to the brain that can be visualized with computed tomography (CT); there is a clear need for fluid biomarkers that can be measured in the CSF and plasma. Candidate fluid biomarkers identified for assessing brain injury include those that detect axonal injury, such as neurofilament light (NfL) (121); and those that indicate neurodegeneration, such as tau (122). Increased concentrations of tau can also be detected in the plasma of individuals with brain injury, although NfL levels in the plasma and CSF are highly correlated (66), elevated tau levels in the blood do not persist as long in the blood as in the CSF (123). CSF biomarker levels are affected by CSF clearance pathways (124), and reduced CSF clearance may be related to tau pathology. Reduced levels of CSF Aβ have also been detected in patients with post-

concussion syndrome (PCS), suggesting amyloid deposition (125). Indeed, increased amyloid deposition has been reported in a subset of mainly older individuals with CTE, particularly those who are carriers of the *APOE4* allele (126).

Tau PET tracers may also be useful as progression biomarkers for tauopathies, and for distinguishing the tauopathy of AD from others (127). Such patterns are beginning to emerge with further experience with tau tracers, matching patterns of tau PET ligand retention with known neuropathological distribution (128). However, the currently available tau PET imaging of Vietnam War veterans with TBI and/or PTSD studied in the ADNI-DoD study suggests that there may be significant variability between individuals while not much group variation. This may be due to insufficient sensitivity of existing tau PET tracers to differentiate tau pathology in individuals with TBI with or without PTSD from those who do not have TBI and/or PTSD, or because current analytical techniques have not yet identified a tau "signature" associated with TBI/PTSD. A final possibility is that the individuals with TBI and/or PTSD may overlap in the extent and regional locations of their individual tau burden. In PTSD individuals with and without TBI, however, an association between elevated medial temporal tau and PTSD severity has been observed (129). This finding, while preliminary, extends previous work linking the hippocampus and medial temporal regions to stress (130) and PTSD, and provides a potential target for therapeutic intervention.

PET imaging of the translocator protein TSPO, a marker of neuroinflammation, may also be a useful tool however it is unclear how sensitive this tool is to measure neuroinflammation (131). The field, and in particular in military and veteran population studies, needs to develop tools with broad applicability to measure tau-related brain changes in neurodegenerative diseases.

Diffusion tensor imaging for TBI has been examined in multiple studies with mixed results to date. The varying reports illustrate the challenge of a structural neuroimaging biomarker with adequate sensitivity and specificity especially for mild TBI, which is associated clinically with a transient disruption in neuronal function (132-134).

7.0 Conclusions

Moving towards therapies for the short-term and the long-term consequences of TBI will require a better understanding of basic biological mechanisms, including cell types involve and their activation states at different stages of disease-related changes, through the use of blood biomarkers, neuroimaging, and neuropathology. Most importantly, these finding need to be linked to clinical presentation and positively impact diagnosis, prognosis, treatment, and management. There is a growing amount of research to support the suggestion that TBI-related neurodegeneration is more broadly tauopathy and not only AD, however, this may depend on the type and level of severity of the TBI, other contributing risk or resilience factors, and there may also be individuals that develop AD as a result of independent biological underpinnings. This workshop identified the following gaps and research priorities:

7.1 Gaps

There is limited knowledge about the determinants of post-TBI resiliency and vulnerability, as well as the biological mechanisms of chronic effects of single versus repeat TBI. Mild verses moderate versus severe TBI studies are needed to explore the contribution of genes, exposures, comorbidities, lifestyle factors and disease modifiers. Most studies have been cross-sectional and therefore have not been able to establish whether post-TBI cognitive impairment and dementia result from static non-progressive effects of TBI in the context of normal aging, from progressive neurodegeneration that is seeded or accelerated by TBI, or from pre-existing sub-clinical dementia that led to the TBI itself rather than the reverse (reverse causation). Knowledge is also limited with regard to how pathology relates to phenotype, for example, the exposure type, exposure threshold, latent disease, clinical criteria, and biomarkers. Finally, evolving definitions and classifications make it difficult to integrate findings from different studies.

7.2 Research priorities

At the infrastructure level, an interdisciplinary framework is needed to integrate clinical care and research to provide better care for individuals while continuing to improve understanding of the mechanisms that link brain injury, PTSD, cardiovascular disease, and sleep with neurodegeneration. Some progress has been made in breaking silos and contexts between AD and TBI through data sharing. The Global Alzheimer's Association Interactive Network (GAAIN) (135) and the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System (136) have helped facilitate this progress. Data sharing through FITBIR is now a condition of receiving a grant from DoD for almost all human TBI studies. To advance the field through better informed resource use, an effort to develop a single web location to query TBI related research is needed. NIH and many federal organizations use the Federal RePORTER as a means to track research studies (137). An easily accessible system of this nature would provide researchers with potential collaborators and provide protocol review committee information on similar research endeavors.

Goals over the next five years are to build more translational partnerships and leverage resources to enable moving from bench to bedside with improved understanding of mechanistic pathways and triggers, earlier antemortem diagnosis, and effective multi-modal therapeutic interventions. Other more specific goals include:

- Identification of immune-based blood, plasma, and CSF fluid biomarkers, as well as PET ligands, such as for microglia, to clarify the role of inflammation, facilitate the cross-over between animal models and human studies, and illuminate the potential for intervening in inflammatory pathways.
- Development of novel genetic animal models of neurodegeneration for TBI studies could provide insights into biological disease mechanisms, biomarkers and potentially individual susceptibility loci. The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) Center, a National Institute of Aging funded consortium between Indiana University, Jackson Laboratories, and Sage Bionetworks, has been established for this purpose. Deep phenotyping and

biomarker studies in these models could provide valuable information relevant to human TBI. However, given the numerous biological, structural and physical differences between rodents and humans, the face validity of these models remains to be assessed and will be critical for determining the success of this strategy. A small animal model with a gyrencephalic brain would be immensely helpful, more closely mimicking brain movement in human TBI.

- Continuing investigation of modifiable risk factors in veterans to understand the interplay of medical and psychiatric comorbidities, which will require validated measures to capture exposure.
- Conduct studies investigating military risk factors among women and racial/ethnic minorities in order to determine if there are particular profiles of vulnerabilities or resilience
- Integration of results from current studies regarding threshold and cumulative exposures, natural history, risk factors, and the relationship of TBI, CTE, AD and other neurodegenerative disorders.
- Development of novel animal and human cell-based models that faithfully replicate the cellular and molecular underpinnings of epigenetics and phenotype.
- Establishment of biorepositories and brain banks as well as standardized methods for rapid specimen procurement, analytical validation and clinical validation of biomarkers and mechanisms.
- Development of a cohort of older veterans for studies, to include additional development and clinical phenotyping of cognitive and psychological tests to help identify the long-term effects of TBI and PTSD.
- Development of longitudinal cohorts for long-term follow-up, similar to the Rush Religious Orders Study (RROS) to better understand at-risk veterans with TBI or PTSD by following them longitudinally with clinical evaluations, cognitive testing and ultimately, brain donation.
- Improve understanding post-TBI trajectories, with prospective multi-year longitudinal studies of post-TBI clinical and biological trajectories, ideally with pre-TBI baseline measures.

Acknowledgements

This meeting was organized and funded by the Alzheimer’s Association. Investigators presented work funded by numerous funding sources, including National Institutes of Health and the U.S. Department of Defense. Thank you to all the study participants in the studies discussed throughout this manuscript.

9.0 References

1. Weiner MW, Friedl KE, Pacifico A, Chapman JC, Jaffee MS, Little DM, et al. Military risk factors for Alzheimer's disease. Alzheimers Dement. 2013;9(4):445–51. [PubMed: 23809365]
2. Byers AL, Yaffe K. Depression and dementias among military veterans. Alzheimers Dement. 2014;10(3 Suppl):S166–73. [PubMed: 24924668]

3. Chapman JC, Diaz-Arrastia R. Military traumatic brain injury: a review. Alzheimers Dement. 2014;10(3 Suppl):S97–104. [PubMed: 24924680]
4. Durazzo TC, Mattsson N, Weiner MW, Alzheimer's Disease Neuroimaging I. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimers Dement. 2014;10(3 Suppl):S122–45. [PubMed: 24924665]
5. Fiandaca MS, Mapstone ME, Cheema AK, Federoff HJ. The critical need for defining preclinical biomarkers in Alzheimer's disease. Alzheimers Dement. 2014;10(3 Suppl):S196–212. [PubMed: 24924671]
6. Friedl KE. Introduction: Evolution of military and veterans brain health research. Alzheimers Dement. 2014;10(3 Suppl):S94–6. [PubMed: 24924679]
7. Greenberg MS, Tanev K, Marin MF, Pitman RK. Stress, PTSD, and dementia. Alzheimers Dement. 2014;10(3 Suppl):S155–65. [PubMed: 24924667]
8. Khachaturian AS, Khachaturian ZS. Military risk factors for Alzheimer's dementia and neurodegenerative disease. Alzheimers Dement. 2014;10(3 Suppl):S90–1. [PubMed: 24924677]
9. Little DM, Geary EK, Moynihan M, Alexander A, Pennington M, Glang P, et al. Imaging chronic traumatic brain injury as a risk factor for neurodegeneration. Alzheimers Dement. 2014;10(3 Suppl):S188–95. [PubMed: 24924670]
10. McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. Alzheimers Dement. 2014;10(3 Suppl):S242–53. [PubMed: 24924675]
11. Meziab O, Kirby KA, Williams B, Yaffe K, Byers AL, Barnes DE. Prisoner of war status, posttraumatic stress disorder, and dementia in older veterans. Alzheimers Dement. 2014;10(3 Suppl):S236–41. [PubMed: 24924674]
12. Mohlenhoff BS, Chao LL, Buckley ST, Weiner MW, Neylan TC. Are hippocampal size differences in posttraumatic stress disorder mediated by sleep pathology? Alzheimers Dement. 2014;10(3 Suppl):S146–54. [PubMed: 24924666]
13. Sibener L, Zaganjor I, Snyder HM, Bain LJ, Egge R, Carrillo MC. Alzheimer's Disease prevalence, costs, and prevention for military personnel and veterans. Alzheimers Dement. 2014;10(3 Suppl):S105–10. [PubMed: 24924663]
14. Tanner CM, Goldman SM, Ross GW, Grate SJ. The disease intersection of susceptibility and exposure: chemical exposures and neurodegenerative disease risk. Alzheimers Dement. 2014;10(3 Suppl):S213–25. [PubMed: 24924672]
15. Villemagne VL, Okamura N. In vivo tau imaging: obstacles and progress. Alzheimers Dement. 2014;10(3 Suppl):S254–64. [PubMed: 24924676]
16. Vincent AS, Roebuck-Spencer TM, Cernich A. Cognitive changes and dementia risk after traumatic brain injury: implications for aging military personnel. Alzheimers Dement. 2014;10(3 Suppl):S174–87. [PubMed: 24924669]
17. Weiner MW. Military Risk Supplement. Preface. Alzheimers Dement. 2014;10(3 Suppl):S92–3. [PubMed: 24924678]
18. Weiner MW, Veitch DP, Hayes J, Neylan T, Grafman J, Aisen PS, et al. Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's Disease Neuroimaging Initiative. Alzheimers Dement. 2014;10(3 Suppl):S226–35. [PubMed: 24924673]
19. Yaffe K, Hoang TD, Byers AL, Barnes DE, Friedl KE. Lifestyle and health-related risk factors and risk of cognitive aging among older veterans. Alzheimers Dement. 2014;10(3 Suppl):S111–21. [PubMed: 24924664]
20. Veitch DP, Friedl KE, Weiner MW. Military risk factors for cognitive decline, dementia and Alzheimer's disease. Curr Alzheimer Res. 2013;10(9):907–30. [PubMed: 23906002]
21. Congressional Budget Office. The Veterans Health Administration's treatment of PTSD and traumatic brain injury among recent combat veterans. 2012.
22. McGuire LC, Wright DW, Kellermann AL. Reducing severe traumatic brain injury in the United States2011.
23. Defense and Veterans Brain Injury Center (DVBIC). DoD Worldwide Numbers for TBI. Accessed 1/15/18 at: http://www.dvbic.org/dod-worldwide-numbers-tbi 2017 [

24. DeKosky ST, Ikonomovic MD, Gandy S. Traumatic brain injury: football, warfare, and long-term effects. Minn Med. 2010;93(12):46–7.
25. Department of Defense. Peer Reviewed Alzheimer's Research Program (PRARP) [Available from: http://cdmrp.army.mil/prarp/.
26. Obama PB. Executive Order - Improving access to mental health services for veterans, service members, and military families. In: Secretary TWHOotP, editor. Washington, DC2012.
27. Consortium CEoN. [Available from: https://cenc.rti.org/.
28. Armonda RA, Bell RS, Vo AH, Ling G, DeGraba TJ, Crandall B, et al. Wartime traumatic cerebral vasospasm: recent review of combat casualties. Neurosurgery. 2006;59(6):1215–25; discussion 25. [PubMed: 17277684]
29. Shively SB, Horkayne-Szakaly I, Jones RV, Kelly JP, Armstrong RC, Perl DP. Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series. Lancet Neurol. 2016;15(9):944–53. [PubMed: 27291520]
30. MacDonald CL, Johnson AM, Nelson EC, Werner NJ, Fang R, Flaherty SF, et al. Functional status after blast-plus-impact complex concussive traumatic brain injury in evacuated United States military personnel. J Neurotrauma. 2014;31(10):889–98. [PubMed: 24367929]
31. Defense Do. Directive No. 6025.21E: Medical research for prevention, mitigation, and treatment of blast injuries. . 2006.
32. Department of Defense Blast Injury Research Program Coordinating Office. What is blast Injury?
33. Moore DF, Jaffee MS. Military traumatic brain injury and blast. NeuroRehabilitation. 2010;26(3): 179–81. [PubMed: 20448307]
34. Talavage TM, Nauman EA, Breedlove EL, Yoruk U, Dye AE, Morigaki KE, et al. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. J Neurotrauma. 2014;31(4):327–38. [PubMed: 20883154]
35. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin J, Yaffe K. JAMA Neurol. 2018;in press.
36. Asken BM, Sullan MJ, Snyder AR, Houck ZM, Bryant VE, Hizel LP, et al. Factors Influencing Clinical Correlates of Chronic Traumatic Encephalopathy (CTE): a Review. Neuropsychol Rev. 2016;26(4):340–63. [PubMed: 27561662]
37. Dams-O'Connor K, Guetta G, Hahn-Ketter AE, Fedor A. Traumatic brain injury as a risk factor for Alzheimer's disease: current knowledge and future directions. Neurodegener Dis Manag. 2016;6(5):417–29. [PubMed: 27599555]
38. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Keene CD, et al. Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings. JAMA Neurol. 2016;73(9):1062–9. [PubMed: 27400367]
39. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry. 2003;74(7):857–62. [PubMed: 12810767]
40. Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. J Neurosurg. 2016;124(2):511–26. [PubMed: 26315003]
41. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology. 2014;83(4):312–9. [PubMed: 24966406]
42. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55(8):1158–66. [PubMed: 11071494]
43. Weiner MW, Harvey D, Hayes J, Landau SM, Aisen PS, Petersen RC, et al. Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary Report. Alzheimers Dement (N Y). 2017;3(2):177–88. [PubMed: 28758146]
44. Selim AJ, Berlowitz DR, Fincke G, Cong Z, Rogers W, Haffer SC, et al. The health status of elderly veteran enrollees in the Veterans Health Administration. J Am Geriatr Soc. 2004;52(8): 1271–6. [PubMed: 15271113]

45. Byers AL, Covinsky KE, Barnes DE, Yaffe K. Dysthymia and depression increase risk of dementia and mortality among older veterans. Am J Geriatr Psychiatry. 2012;20(8):664–72. [PubMed: 21597358]
46. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004;292(18):2237–42. [PubMed: 15536110]
47. Zeki Al Hazzouri A, Vittinghoff E, Byers A, Covinsky K, Blazer D, Diem S, et al. Long-term cumulative depressive symptom burden and risk of cognitive decline and dementia among very old women. J Gerontol A Biol Sci Med Sci. 2014;69(5):595–601. [PubMed: 24097423]
48. Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, et al. Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry. 2010;67(6):608–13. [PubMed: 20530010]
49. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. JAMA Neurol. 2014;71(12):1490–7. [PubMed: 25347255]
50. Peltz CB, Gardner RC, Kenney K, Diaz-Arrastia R, Kramer JH, Yaffe K. Neurobehavioral Characteristics of Older Veterans With Remote Traumatic Brain Injury. J Head Trauma Rehabil. 2016.
51. Taylor BC, Hagel EM, Carlson KF, Cifu DX, Cutting A, Bidelspach DE, et al. Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War Veteran V.A. users. Med Care. 2012;50(4):342–6. [PubMed: 22228249]
52. Vasterling JJ, Aslan M, Lee LO, Proctor SP, Ko J, Jacob S, et al. Longitudinal Associations among Posttraumatic Stress Disorder Symptoms, Traumatic Brain Injury, and Neurocognitive Functioning in Army Soldiers Deployed to the Iraq War. J Int Neuropsychol Soc. 2017:1–13.
53. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Tranah G, Cauley JA, et al. Measures of Sleep-Wake Patterns and Risk of Mild Cognitive Impairment or Dementia in Older Women. Am J Geriatr Psychiatry. 2016;24(3):248–58. [PubMed: 26964485]
54. Yaffe K, Nettiksimmons J, Yesavage J, Byers A. Sleep Quality and Risk of Dementia Among Older Male Veterans. Am J Geriatr Psychiatry. 2015;23(6):651–4. [PubMed: 25794635]
55. Alexander M, Ray MA, Hebert JR, Youngstedt SD, Zhang H, Steck SE, et al. The National Veteran Sleep Disorder Study: Descriptive Epidemiology and Secular Trends, 2000–2010. Sleep. 2016;39(7):1399–410. [PubMed: 27091538]
56. Dams-O'Connor K, Spielman L, Singh A, Gordon WA, Lingsma HF, Maas AI, et al. The impact of previous traumatic brain injury on health and functioning: a TRACK-TBI study. J Neurotrauma. 2013;30(24):2014–20. [PubMed: 23924069]
57. Dams-O'Connor K, Gibbons LE, Bowen JD, McCurry SM, Larson EB, Crane PK. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. J Neurol Neurosurg Psychiatry. 2013;84(2):177–82. [PubMed: 23172868]
58. Gardner RC, Peltz CB, Kenney K, Covinsky KE, Diaz-Arrastia R, Yaffe K. Remote Traumatic Brain Injury Is Associated with Motor Dysfunction in Older Military Veterans. J Gerontol A Biol Sci Med Sci. 2017;72(9):1233–8. [PubMed: 28329183]
59. Gardner RC, Langa KM, Yaffe K. Subjective and objective cognitive function among older adults with a history of traumatic brain injury: A population-based cohort study. PLoS Med. 2017;14(3):e1002246. [PubMed: 28267747]
60. McKee AC, Alosco ML, Huber BR. Repetitive Head Impacts and Chronic Traumatic Encephalopathy. Neurosurg Clin N Am. 2016;27(4):529–35. [PubMed: 27637402]
61. Stern RA, Riley DO, Daneshvar DH, Nowinski CJ, Cantu RC, McKee AC. Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. PM R. 2011;3(10 Suppl 2):S460–7. [PubMed: 22035690]
62. Namjoshi DR, Good C, Cheng WH, Panenka W, Richards D, Cripton PA, et al. Towards clinical management of traumatic brain injury: a review of models and mechanisms from a biomechanical perspective. Dis Model Mech. 2013;6(6):1325–38. [PubMed: 24046354]

63. Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med. 2012;4(134):134ra60.
64. Tran HT, LaFerla FM, Holtzman DM, Brody DL. Controlled cortical impact traumatic brain injury in 3xTg-AD mice causes acute intra-axonal amyloid-beta accumulation and independently accelerates the development of tau abnormalities. J Neurosci. 2011;31(26):9513–25. [PubMed: 21715616]
65. Morris M, Knudsen GM, Maeda S, Trinidad JC, Ioanoviciu A, Burlingame AL, et al. Tau post-translational modifications in wild-type and human amyloid precursor protein transgenic mice. Nat Neurosci. 2015;18(8):1183–9. [PubMed: 26192747]
66. Blennow K, Brody DL, Kochanek PM, Levin H, McKee A, Ribbers GM, et al. Traumatic brain injuries. Nat Rev Dis Primers. 2016;2:16084. [PubMed: 27853132]
67. Collins-Praino LE, Corrigan F. Does neuroinflammation drive the relationship between tau hyperphosphorylation and dementia development following traumatic brain injury? Brain Behav Immun. 2017;60:369–82. [PubMed: 27686843]
68. Koliatsos VE, Xu L. The problem of neurodegeneration in cumulative sports concussions: Emphasis on neurofibrillary tangle formation In: Kobeissy FH, editor. Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects Boca Raton, FL: CRC Press/Taylor & Francis; 2015.
69. Min SW, Chen X, Tracy TE, Li Y, Zhou Y, Wang C, et al. Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. Nat Med. 2015;21(10):1154–62. [PubMed: 26390242]
70. Gentleman SM, Greenberg BD, Savage MJ, Noori M, Newman SJ, Roberts GW, et al. A beta 42 is the predominant form of amyloid beta-protein in the brains of short-term survivors of head injury. Neuroreport. 1997;8(6):1519–22. [PubMed: 9172166]
71. DeKosky ST, Abrahamson EE, Ciallella JR, Paljug WR, Wisniewski SR, Clark RS, et al. Association of increased cortical soluble abeta42 levels with diffuse plaques after severe brain injury in humans. Arch Neurol. 2007;64(4):541–4. [PubMed: 17420316]
72. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. J Neurotrauma. 1995;12(4):565–72. [PubMed: 8683607]
73. Smith DH, Chen XH, Iwata A, Graham DI. Amyloid beta accumulation in axons after traumatic brain injury in humans. J Neurosurg. 2003;98(5):1072–7. [PubMed: 12744368]
74. Johnson VE, Stewart W, Smith DH. Traumatic brain injury and amyloid-beta pathology: a link to Alzheimer's disease? Nat Rev Neurosci. 2010;11(5):361–70. [PubMed: 20216546]
75. Sengupta U, Nilson AN, Kayed R. The Role of Amyloid-beta Oligomers in Toxicity, Propagation, and Immunotherapy. EBioMedicine. 2016;6:42–9. [PubMed: 27211547]
76. Mondello S, Buki A, Barzo P, Randall J, Provuncher G, Hanlon D, et al. CSF and plasma amyloid-beta temporal profiles and relationships with neurological status and mortality after severe traumatic brain injury. Sci Rep. 2014;4:6446. [PubMed: 25300247]
77. Gatson JW, Warren V, Abdelfattah K, Wolf S, Hynan LS, Moore C, et al. Detection of beta-amyloid oligomers as a predictor of neurological outcome after brain injury. J Neurosurg. 2013;118(6):1336–42. [PubMed: 23540266]
78. Bagnato S, Andriolo M, Boccagni C, Galardi G. Prolonged changes in amyloid-beta metabolism after a severe traumatic brain injury. Neuroreport. 2017;28(5):250–2. [PubMed: 28178070]
79. Franz G, Beer R, Kampfl A, Engelhardt K, Schmutzhard E, Ulmer H, et al. Amyloid beta 1–42 and tau in cerebrospinal fluid after severe traumatic brain injury. Neurology. 2003;60(9):1457–61. [PubMed: 12743231]
80. Scott G, Ramlackhansingh AF, Edison P, Hellyer P, Cole J, Veronese M, et al. Amyloid pathology and axonal injury after brain trauma. Neurology. 2016;86(9):821–8. [PubMed: 26843562]
81. Ponto LL, Brashers-Krug TM, Pierson RK, Menda Y, Acion L, Watkins GL, et al. Preliminary Investigation of Cerebral Blood Flow and Amyloid Burden in Veterans With and Without Combat-Related Traumatic Brain Injury. J Neuropsychiatry Clin Neurosci. 2016;28(2):89–96. [PubMed: 26548655]

82. Barrio JR, Small GW, Wong KP, Huang SC, Liu J, Merrill DA, et al. In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging. Proc Natl Acad Sci U S A. 2015;112(16):E2039–47. [PubMed: 25848027]

83. Hong YT, Veenith T, Dewar D, Outtrim JG, Mani V, Williams C, et al. Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. JAMA Neurol. 2014;71(1): 23–31. [PubMed: 24217171]

84. Engelhardt B, Carare RO, Bechmann I, Flugel A, Laman JD, Weller RO. Vascular, glial, and lymphatic immune gateways of the central nervous system. Acta Neuropathol. 2016;132(3):317–38. [PubMed: 27522506]

85. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med. 2012;4(147):147ra11.

86. Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. J Neurosci. 2014;34(49): 16180–93. [PubMed: 25471560]

87. Jullienne A, Roberts JM, Pop V, Paul Murphy M, Head E, Bix GJ, et al. Juvenile traumatic brain injury induces long-term perivascular matrix changes alongside amyloid-beta accumulation. J Cereb Blood Flow Metab. 2014;34(10):1637–45. [PubMed: 25052558]

88. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013;342(6156):373–7. [PubMed: 24136970]

89. Hawkes CA, Hartig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, et al. Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta Neuropathol. 2011;121(4):431–43. [PubMed: 21259015]

90. Hawkes CA, Sullivan PM, Hands S, Weller RO, Nicoll JA, Carare RO. Disruption of arterial perivascular drainage of amyloid-beta from the brains of mice expressing the human APOE epsilon4 allele. PLoS One. 2012;7(7):e41636. [PubMed: 22848551]

91. Carare RO, Teeling JL, Hawkes CA, Puntener U, Weller RO, Nicoll JA, et al. Immune complex formation impairs the elimination of solutes from the brain: implications for immunotherapy in Alzheimer's disease. Acta Neuropathol Commun. 2013;1:48. [PubMed: 24252464]

92. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388–405. [PubMed: 25792098]

93. Kokiko-Cochran O, Ransohoff L, Veenstra M, Lee S, Saber M, Sikora M, et al. Altered Neuroinflammation and Behavior after Traumatic Brain Injury in a Mouse Model of Alzheimer's Disease. J Neurotrauma. 2016;33(7):625–40. [PubMed: 26414955]

94. Barone FC, Feuerstein GZ. Inflammatory mediators and stroke: new opportunities for novel therapeutics. J Cereb Blood Flow Metab. 1999;19(8):819–34. [PubMed: 10458589]

95. Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry. 2015;77(1):43–51. [PubMed: 24951455]

96. Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. J Exp Med. 2015;212(3):287–95. [PubMed: 25732305]

97. Saber M, Kokiko-Cochran O, Puntambekar SS, Lathia JD, Lamb BT. Triggering Receptor Expressed on Myeloid Cells 2 Deficiency Alters Acute Macrophage Distribution and Improves Recovery after Traumatic Brain Injury. J Neurotrauma. 2017;34(2):423–35. [PubMed: 26976047]

98. Bennett ER, Reuter-Rice K, Laskowitz DT. Genetic Influences in Traumatic Brain Injury In: Laskowitz D, Grant G, editors. Translational Research in Traumatic Brain Injury Frontiers in Neuroscience. Boca Raton (FL)2016.

99. Lipsky RH, Lin M. Genetic predictors of outcome following traumatic brain injury. Handb Clin Neurol. 2015;127:23–41. [PubMed: 25702208]

100. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921–3. [PubMed: 8346443]

101. Lawrence DW, Comper P, Hutchison MG, Sharma B. The role of apolipoprotein E episilon (epsilon)-4 allele on outcome following traumatic brain injury: A systematic review. Brain Inj. 2015;29(9):1018–31. [PubMed: 25915580]
102. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. J Neurotrauma. 2008;25(4):279–90. [PubMed: 18373478]
103. Zeng S, Jiang JX, Xu MH, Xu LS, Shen GJ, Zhang AQ, et al. Prognostic value of apolipoprotein E epsilon4 allele in patients with traumatic brain injury: a meta-analysis and meta-regression. Genet Test Mol Biomarkers. 2014;18(3):202–10. [PubMed: 24475734]
104. McAllister TW. Genetic factors modulating outcome after neurotrauma. PM R. 2010;2(12 Suppl 2):S241–52. [PubMed: 21172686]
105. Klengel T, Binder EB. Epigenetics of Stress-Related Psychiatric Disorders and Gene x Environment Interactions. Neuron. 2015;86(6):1343–57. [PubMed: 26087162]
106. Bird A Perceptions of epigenetics. Nature. 2007;447(7143):396–8. [PubMed: 17522671]
107. Haghighi F, Ge Y, Chen S, Xin Y, Umali MU, De Gasperi R, et al. Neuronal DNA Methylation Profiling of Blast-Related Traumatic Brain Injury. J Neurotrauma. 2015;32(16):1200–9. [PubMed: 25594545]
108. Schober ME, Ke X, Xing B, Block BP, Requena DF, McKnight R, et al. Traumatic brain injury increased IGF-1B mRNA and altered IGF-1 exon 5 and promoter region epigenetic characteristics in the rat pup hippocampus. J Neurotrauma. 2012;29(11):2075–85. [PubMed: 22413999]
109. Zhang ZY, Zhang Z, Fauser U, Schluesener HJ. Global hypomethylation defines a sub-population of reactive microglia/macrophages in experimental traumatic brain injury. Neurosci Lett. 2007;429(1):1–6. [PubMed: 17996371]
110. Kempermann G, Neumann H. Neuroscience. Microglia: the enemy within? Science. 2003;302(5651):1689–90. [PubMed: 14657479]
111. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain. 2013;136(Pt 1):43–64. [PubMed: 23208308]
112. Bieniek KF, Ross OA, Cormier KA, Walton RL, Soto-Ortolaza A, Johnston AE, et al. Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. Acta Neuropathol. 2015;130(6):877–89. [PubMed: 26518018]
113. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol. 2016;131(1):75–86. [PubMed: 26667418]
114. Stern RA, Daneshvar DH, Baugh CM, Seichepine DR, Montenigro PH, Riley DO, et al. Clinical presentation of chronic traumatic encephalopathy. Neurology. 2013;81(13):1122–9. [PubMed: 23966253]
115. Reams N, Eckner JT, Almeida AA, Aagesen AL, Giordani B, Paulson H, et al. A Clinical Approach to the Diagnosis of Traumatic Encephalopathy Syndrome: A Review. JAMA Neurol. 2016;73(6):743–9. [PubMed: 27111824]
116. Omalu B, Hammers JL, Bailes J, Hamilton RL, Kamboh MI, Webster G, et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. Neurosurg Focus. 2011;31(5):E3.
117. Ryu J, Horkayne-Szakaly I, Xu L, Pletnikova O, Leri F, Eberhart C, et al. The problem of axonal injury in the brains of veterans with histories of blast exposure. Acta Neuropathol Commun. 2014;2:153. [PubMed: 25422066]
118. Nedergaard M. Neuroscience. Garbage truck of the brain. Science. 2013;340(6140):1529–30. [PubMed: 23812703]
119. Noy S, Krawitz S, Del Bigio MR. Chronic Traumatic Encephalopathy-Like Abnormalities in a Routine Neuropathology Service. J Neuropathol Exp Neurol. 2016.
120. Ikonomovic MD, Uryu K, Abrahamson EE, Ciallella JR, Trojanowski JQ, Lee VM, et al. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. Exp Neurol. 2004;190(1):192–203. [PubMed: 15473992]

121. Neselius S, Brisby H, Theodorsson A, Blennow K, Zetterberg H, Marcusson J. CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. PLoS One. 2012;7(4):e33606. [PubMed: 22496755]
122. Zetterberg H, Hietala MA, Jonsson M, Andreasen N, Styrud E, Karlsson I, et al. Neurochemical aftermath of amateur boxing. Arch Neurol. 2006;63(9):1277–80. [PubMed: 16966505]
123. Zetterberg H, Blennow K. Fluid markers of traumatic brain injury. Mol Cell Neurosci. 2015;66(Pt B):99–102. [PubMed: 25659491]
124. Chen L, Elias G, Yostos MP, Stimec B, Fasel J, Murphy K. Pathways of cerebrospinal fluid outflow: a deeper understanding of resorption. Neuroradiology. 2015;57(2):139–47. [PubMed: 25398655]
125. Shahim P, Tegner Y, Gustafsson B, Gren M, Arlig J, Olsson M, et al. Neurochemical Aftermath of Repetitive Mild Traumatic Brain Injury. JAMA Neurol. 2016;73(11):1308–15. [PubMed: 27654934]
126. Stein TD, Montenigro PH, Alvarez VE, Xia W, Crary JF, Tripodis Y, et al. Beta-amyloid deposition in chronic traumatic encephalopathy. Acta Neuropathol. 2015;130(1):21–34. [PubMed: 25943889]
127. Li Y, Tsui W, Rusinek H, Butler T, Mosconi L, Pirraglia E, et al. Cortical laminar binding of PET amyloid and tau tracers in Alzheimer disease. J Nucl Med. 2015;56(2):270–3. [PubMed: 25572087]
128. Pullman MY, Dickstein DL, DeKosky ST, Gandy S. Antemortem biomarker support for a diagnosis of clinically probable chronic traumatic encephalopathy. Mol Psychiatry. 2017;22(5):638–9. [PubMed: 28070125]
129. Rissman RA, Staup MA, Lee AR, Justice NJ, Rice KC, Vale W, et al. Corticotropin-releasing factor receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation. Proc Natl Acad Sci U S A. 2012;109(16):6277–82. [PubMed: 22451915]
130. Chao LL, Yaffe K, Samuelson K, Neylan TC. Hippocampal volume is inversely related to PTSD duration. Psychiatry Res. 2014;222(3):119–23. [PubMed: 24742925]
131. Coughlin JM, Wang Y, Munro CA, Ma S, Yue C, Chen S, et al. Neuroinflammation and brain atrophy in former NFL players: An in vivo multimodal imaging pilot study. Neurobiol Dis. 2015;74:58–65. [PubMed: 25447235]
132. Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME. Diffusion tensor MR imaging in diffuse axonal injury. AJNR Am J Neuroradiol. 2002;23(5):794–802. [PubMed: 12006280]
133. Matsushita M, Hosoda K, Naitoh Y, Yamashita H, Kohmura E. Utility of diffusion tensor imaging in the acute stage of mild to moderate traumatic brain injury for detecting white matter lesions and predicting long-term cognitive function in adults. J Neurosurg. 2011;115(1):130–9. [PubMed: 21417709]
134. Niogi SN, Mukherjee P, Ghajar J, Johnson CE, Kolster R, Lee H, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. Brain. 2008;131(Pt 12):3209–21. [PubMed: 18952679]
135. Alzheimer's Association. Global Alzheimer's Association Interactive Network 2013 [Available from: http://www.gaain.org/.
136. National Insitutes of Health. Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System [Available from: https://fitbir.nih.gov/.
137. NIH. Federal RePORTER [Available from: https://federalreporter.nih.gov/.

Research in Context – Military Risk Factors

Systematic Review:

Building on a 2012 meeting, the Alzheimer's Association convened a state of the science meeting to evaluate the growing evidence on military related risk factors in dementia. This manuscript is the summary of the invited presentations and the moderated discussion from this meeting.

Interpretation:

During this one day meeting, speakers and presenters delved into the military relevant risk factors, including learning from civilian and military population studies; evaluating the relevant biological underpinnings in military populations (TBI related biology, tau, brain fluid clearance, inflammation); learning from neuropathology in population based studies including athletic populations, military and civilian studies; and focusing on the state of biomarkers including fluid, neuroimaging and emerging biomarker measures.

Future Directions:

During this meeting, participants presented and evaluated the progress made since the 2012 meeting and focused on identifying the outstanding knowledge gaps regarding factors that may impact Veteran and military risk for later life dementia.