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Review Article

Military-related risk factors for dementia

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Abstract

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

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

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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.

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 estimated that the cost of TBI and TBI/PTSD-specific care by the Veterans Health Administration was roughly $430M (in FY11 dollars) between 2004 and 2009 for the first year of treatment for veterans of overseas contingency operations. The Centers for Disease Control estimated medical cost for domestic TBI was $76.3 B in 2010 [21,22].

The Defense and Veterans Brain Injury Center 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, or post-traumatic amnesia (PTA), and were diagnosed in nondeployment settings [23]. Moreover, about half of all recruits experienced at least one TBI before 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 Defense and Veterans Brain Injury Center, the Center for Neuroscience and Regenerative Medicine (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 in 2011 [25]. The Peer-Reviewed Alzheimer's Research Program 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 five research cores and multiple projects 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, biophysical, 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 6025.21 E 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]. Most 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 subconcussion, 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 an LOC carried a small increase in risk for later dementia. The clinical and scientific communities are investigating the thresholds, technology used to measure subconcussion, and objective medical data for both blunt and blast exposures [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 to 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 diagnosis. Plassman et al. evaluated Navy and Marine World War II veterans retrospectively, including 548 veterans diagnosed with nonpenetrating head injuries at the 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 LOC or PTA for less than 30 minutes, moderate as LOC or PTA ranging from 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 is 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 versus 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, after remote TBI with an LOC for >30 minutes, military veterans may show a different pattern of cognitive deficits than are typically seen in AD, that is, 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 after remote TBI have been replicated in a nationally representative sample of civilians as well [59]. Recent pooled data from several large brain banks suggest that TBI with an LOC could be associated with Lewy body pathology, cerebral microinfarcts, and progression of parkinsonism rather than amyloid plaques and tau tangles [38]. Furthermore, 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 after TBI [60,61] and how repeat TBI may serve to alter or even accelerate the progression of a preexisting neurodegenerative disease in the brain.

4. Biological underpinnings

Animal models are important proxies for studying TBI, providing biospecimens under controlled conditions, allowing preinjury and postinjury 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 validity and construct validity. Although 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 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, 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 Aβ40 and Aβ42. 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 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 Aβ42 [75]. These areas require further study.

Several CSF and plasma biomarker studies of Aβ42 published observations suggesting that 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. Computed tomography imaging showed an equal distribution of diffuse injury and focal lesions across the cohort with no correlation between CSF and plasma levels of Aβ42. Although limited data on survival were 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]. Furthermore, Franz and colleagues evaluated 29 individuals over the course of 1 and 284 days after trauma with cognitive disorders and headache; they found that concentrations of Aβ42 were significantly lower in individuals with 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 PET in addition to structural and diffusion MRI evaluated individuals 11 months to 17 years after moderate to severe TBI and demonstrated that increased PiB binding was observed in the posterior cingulate cortex and cerebellum despite lack of clinical dementia symptoms. The posterior cingulate cortex 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 in those who had sustained a TBI but no amyloid burden even years after 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 with a PET autopsy study using PiB imaging both before and after death; this study further adds to the contours of the TBI-AD interrelationship. Postmortem results showed significantly increased PiB distribution in cortical gray matter and the striatum, whereas 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 amyloid precursor protein 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 after either moderate to 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 fluid (ISF). 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 aging 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 have 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 glymphatic pathways that occur after TBI, in particular in association with 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 because 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 because 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 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 after 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 postinjury 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 vs. tau). Although 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 to be powerful in identifying genes that influence the development of AD and other dementias, including the genes involved in TBI [98]. Most 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, most studies have shown that the *APOE*4 allele adversely affects recovery after 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 [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 the study by McAllister [104]) have examined genes associated with response to neurotrauma (such as angiotensin-converting enzyme and interleukin 1β), neuronal repair and plasticity (such as brain-derived neurotropic factor), and preinjury and postinjury cognitive capacity and reserve (such as dopamine D2 receptor and catechol-O-methyltransferase). These studies, as well as the nature and severity and frequency of TBI, may help explain much of the heterogeneity in outcome after 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 after 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 postinjury inflammation. If it goes unchecked, prolonged microglia activation can have destructive effects on the CNS tissue [110]. After 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. Little is known about the impact of TBI-induced epigenetic changes in the human brain. This is largely due to a paucity of postmortem 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 comes 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 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 potential severity is significantly correlated with age at death and length of playing football.

In 2014, the National Institute of Neurological Disorders and Stroke and the National Institute of Biomedical Imaging and Bioengineering 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" have also been proposed [114], but there are currently no consensus clinical or research criteria for traumatic encephalopathy syndrome [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 versus 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. The blast wave produces a short (approximately 10 ms) 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 postconcussive symptoms after 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, gray-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, whereas 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 case studies at the Queens Square Brain Bank in the United Kingdom, 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 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]. Understanding 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; 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 [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 neurofilament light 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 postconcussion syndrome, 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 there is 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, although 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. Conclusions

Moving toward therapies for the short-term and the long-term consequences of TBI will require a better understanding of basic biological mechanisms, including cell types involvement and their activation states at different stages of disease-related changes, through the use of blood biomarkers, neuroimaging, and neuropathology. Most importantly, these findings 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 who 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 nonprogressive effects of TBI in the context of normal aging, from progressive neurodegeneration that is seeded or accelerated by TBI, or from preexisting subclinical 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 [135] and the Federal Interagency Traumatic Brain Injury Research Informatics System [136] have helped facilitate this progress. Data sharing through Federal Interagency Traumatic Brain Injury Research 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 5 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 multimodal therapeutic interventions. Other more specific goals include the following:

- 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 crossover 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 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 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

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 multiyear longitudinal studies of post-TBI clinical and biological trajectories, ideally with pre-TBI baseline measures.

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RESEARCH IN CONTEXT

1. 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 article is the summary of the invited presentations and the moderated discussion from this meeting.
2. 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 (traumatic brain injury–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.
3. 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.

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