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Monitoring and Assessment Technologies

Cognitive changes and dementia risk after traumatic brain injury: Implications for aging military personnel☆

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Abstract Traumatic brain injury (TBI) is recognized as an important risk factor for the long-term cognitive health of military personnel, particularly in light of growing evidence that TBI increases risk for Alzheimer's disease and other dementias. In this article, we review the neurocognitive and neuropathologic changes after TBI with particular focus on the potential risk for cognitive decline across the life span in military service members. Implications for monitoring and surveillance of cognition in the aging military population are discussed. Additional studies are needed to clarify the factors that increase risk for later life cognitive decline, define the mechanistic link between these factors and dementia, and provide empirically supported interventions to mitigate the impact of TBI on cognition across the life span.

Keywords: Alzheimer's disease; Traumatic brain injury; Risk factors; Military medicine; Dementia

1. Introduction

There is growing evidence that a history of traumatic brain injury (TBI) places individuals at greater risk for developing neurodegenerative diseases such as dementia of the Alzheimer's type (DAT) and other dementias across the life span [1–5]. Although much of the research has focused on the increased risk associated with moderate-to-severe brain injuries, emerging evidence suggests that mild head injuries, particularly repeated mild injuries, may also serve as a risk factor [6–8]. Both the Department of Defense (DoD) and the Department of Veterans Affairs (VA) have recognized the importance of better understanding this relationship, particularly given the incidence of TBI in the military resulting from combat exposures, the growing evidence of dementia risk after TBI, emotional disorders and other nonspecific factors, and concern for the implications of these factors on the aging service member [9,10].

The purpose of this article is to review neurocognitive and neuropathologic changes after TBI, with a focus on the potential risk for cognitive decline across the life span in military service members with a history of TBI. We will begin by defining TBI and summarizing expected short- and long-term cognitive and behavioral outcomes. Next, we will summarize evidence for increased risk of dementia, particularly DAT and chronic traumatic encephalopathy (CTE), after a history of TBI. We will review TBI assessment protocols, outcomes, and lessons learned within the military and will end with a discussion of implications for monitoring and surveillance of cognition in the aging military population.

2. TBI overview

Similar to the definition of TBI from the Centers for Disease Control and Prevention [11], the VA/DoD [12] define

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TBI as a traumatically induced structural injury and/or physiological disruption of brain function resulting from an external force that is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event: any period of loss of or decreased level of consciousness; any loss of memory for events immediately before or after the injury; any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.); neurologic deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient; or intracranial lesion. Relevant to the military and veteran populations, this definition further specifies that external forces may include the head being struck by an object, the head striking an object, the brain experiencing acceleration/deceleration movement without external trauma to the head, a foreign body penetrating the brain, or forces generated from events such as a blast or explosion.

TBI ranges in severity from mild to moderate to severe and results in some disturbance in cognitive, behavioral, emotional, or physical functioning. These effects may be transient, long lasting, or permanent depending on injury characteristics and severity. Initial presentation of TBI varies greatly; thus, classification of injury severity is one of the most important predictors for immediate and long-term outcomes. Severity of TBI is most commonly determined by depth of coma (e.g., via Glasgow Coma Score [GCS]), duration of unconsciousness after injury (e.g., loss of consciousness [LOC] or time to follow commands), or duration of confusion after injury (e.g., length of post-traumatic amnesia [PTA]). GCSs are commonly used to define injury severity, with postinjury GCS scores <8 indicating a severe injury and GCS scores between 9 and 12 indicating a moderate injury. For a TBI to be considered mild, most definitions require GCS scores to be no less than 13; LOC and PTA, if present, to be brief (e.g., <30 minutes and <24 hours, respectively); and neuroimaging studies to have no abnormal findings [13–15]. The label, complicated mild TBI (mTBI), has been used to indicate an injury that meets the mTBI definition with the presence of abnormal neuroimaging findings [16]. Although TBI occurs in all demographic groups, particular risk factors for TBI include age (i.e., very young or aging individuals) [17], being male [17], lower socioeconomic status [18], being from a minority racial/ethnic group [19], history of alcohol or other substance abuse [20], and history of TBI [21]. Additionally, military service members are at particular risk for TBI, with prevalence rates estimated to be between 10% and 20% of those currently serving in the military [22–24].

TBI is a leading cause of death and disability among civilians in the United States with an estimated 1.7 million people sustaining a TBI annually [17]. However, these rates do not include military personnel who sustained a TBI abroad or who received care in federal, military, or VA hospitals. According to the Defense and Veterans Brain Injury Center, more than 270,000 TBIs have been documented in military medical records from January 2000 through the first quarter of 2013 [25]. Although combat- or weapon-related TBI is often considered the signature injury among service members serving in Iraq and Afghanistan since 2001, the rate of TBI occurring in the nondeployed population actually exceeds that of combat-related TBI [25,26].

Most TBIs diagnosed in the DoD and VA are consistent with mTBI (82%), with the primary etiology being blast related [25]. The other major causes of TBI are consistent with those observed in the civilian population and include motor vehicle accidents or land transport accidents, falls, and sports and recreational injuries [25]. In those with severe and penetrating TBI, the four most common etiologies are blast, motor vehicle accident, falls, and gunshots to the head or neck [27].

3. Cognitive outcome after TBI

The effect of TBI on cognition and subsequent recovery varies as a function of injury severity. Individuals sustaining a mTBI will typically experience transient cognitive (e.g., mild confusion, difficulty maintaining attention, and forgetfulness), emotional (e.g., tearfulness, irritability), and physical symptoms (e.g., headaches, sensitivity to light, blurred vision) that begin immediately after the injury and improve over a period of days to weeks, as illustrated in Fig. 1. Most available research shows that individuals with uncomplicated mTBI typically recover to baseline levels of cognitive functioning within 1 to 3 months after injury and are expected to have a favorable long-term outcome [28,29]. Prolonged recovery course has been associated with more severe acute injury indicators (e.g., unconsciousness, PTA, or initially more severe symptoms) [30], and there is evidence that repeated mTBI or complicated mTBI may also place individuals at risk for a prolonged or atypical recovery course [31,32]. Although persisting symptoms may remain

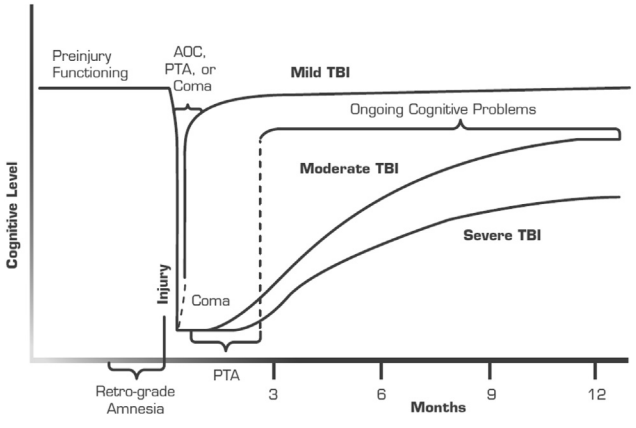

Fig. 1. Hypothetical cognitive function recovery paths. Reprinted, with permission, from Employee Education System. Traumatic Brain Injury: Independent Study Course. Department of Veterans Affairs; 2010: p. 17. AOC, alteration of consciousness; PTA, posttraumatic amnesia; TBI, traumatic brain injury.

in a minority of individuals outside of this window [33], evidence indicates that incomplete recovery from mTBI may be associated with or complicated by preexisting or comorbid psychiatric, medical, psychosocial, or litigation factors [34,35]. The etiology of persistent complaints in some military service members after mTBI is poorly understood and will be discussed in more detail in Section 5.

In contrast, individuals with moderate-to-severe TBI may have persisting or even chronic impairments that limit their ability to return to previous levels of functioning (See Fig. 1 for illustration). Compared with individuals with mTBI, these individuals are much more likely to require acute hospitalization, inpatient [36] or post–acute rehabilitation [37], and outpatient care related to their injuries. The early recovery period after moderate-to-severe TBI includes a series of predictable stages during the initial recovery period. Although the order of progression through these stages is constant, some stages may be absent and duration varies. Impaired consciousness is typically seen immediately after injury, with coma and persistent vegetative state (PVS) representing the most extreme end of the spectrum. When present, resolution of coma and PVS is typically followed by a period of PTA, in which the individual is responsive but markedly confused and amnestic [38]. After resolution of PTA, most individuals with moderate-to-severe TBI demonstrate continued cognitive and neurobehavioral impairments, which are variable and dependent on factors such as severity of injury, premorbid functioning, comorbid neurologic and psychiatric status, and length of time since injury. Characteristic cognitive impairments include impaired fine motor speed; attention; cognitive processing speed, learning, and memory; complex language and discourse; and executive functions (e.g., [38,39]). Circumscribed or localized cognitive impairments, such as language or visual spatial impairment, may be seen in individuals with focal injuries but are generally superimposed on global cognitive dysfunction resulting from diffuse injury. Although not described in detail in this article, moderate-to-severe TBI may also result in a number of neurobehavioral changes in addition to these cognitive changes, including, but not limited to, decreased awareness, disinhibition, impulsivity, impaired social pragmatics, and decreased judgment [40].

Cognitive and neurobehavioral functioning typically improves in those with moderate-to-severe injuries with the most recovery seen in the first 6 months after injury and continuing for 18 months or longer [28,39]. Improvement in basic cognitive skills, such as immediate attention and orientation, precedes improvement in more complex cognitive skills, such as problem solving and executive functioning [39,41]. In large-scale prospective studies, almost all patients with moderate or severe TBI have detectable cognitive impairments at 1 month after injury [42]. By 1 year, almost all individuals with very severe injuries display cognitive impairment, and more than half with moderate-to-severe impairment have some residual deficits [43]. Recovery of cognitive functioning usually reaches a plateau at 18 to 24 months, but a subgroup will improve beyond this point, whereas another subgroup may show late decline [39,44]. Greater age at the time of injury and increased levels of depression may be associated with increased risk of late decline. There is also significant literature indicating that a history of TBI leads to increased risk for dementia later in life [1–5]. This will be discussed in more detail in Section 6.

4. Neuropathologic changes and neurometabolic cascade after TBI

Pathology resulting from TBI is heterogeneous and typically categorized as focal or diffuse. Focal injuries, by definition, are typically associated with moderate-to-severe TBI and most often occur from direct impact to the head or brain (e.g., blunt force, gunshot wounds, etc.). Focal injuries include cortical or subcortical contusions and lacerations, as well as intracranial bleedings (e.g., subarachnoid hemorrhage and subdural hematoma). Contusions to the brain after TBI are common and often occur in a characteristic distribution involving the frontal and temporal poles, the lateral and inferior aspects of the frontal and temporal lobes, and less commonly the inferior aspects of the cerebellum [45]. Diffuse brain injury refers to widespread stretching and tearing of brain tissue, including a number of pathologies such as hemorrhages and tissue tears throughout the brain. It is commonly seen after acceleration/deceleration injuries (e.g., motor vehicle accidents). The main form of diffuse injury is called diffuse axonal injury (DAI) and involves shearing of neuronal axons. The cerebral commissures and other white matter tracts of the brainstem are particularly vulnerable to stretching and shearing as a result of mechanical forces. The extent of DAI may be the principal pathologic substrate responsible for decreased arousal levels and the range of neurologic deficits after brain injury [46].

Despite clear transient cognitive and behavioral changes, brain trauma resulting from mTBI is typically not observable on standard structural neuroimaging. There is no dispute, however, that mTBI results in some diffuse and likely microscopic trauma or metabolic alteration of the brain. Recent animal studies indicate that cognitive and behavioral changes observed after mTBI are most likely the result of a multifaceted neurometabolic cascade. The initiating event is believed to be stretching and disruption of neuronal and axonal cell membranes resulting in abrupt and indiscriminant release of neurotransmitters and ionic shifts, which include increases in extracellular potassium and sodium and intracellular calcium. Enhanced release of excitatory neurotransmitters, particularly glutamate, which binds to N-methyl-D-aspartate receptors, results in further depolarization, influx of calcium ions, and widespread suppression of neurons and glucose hypometabolism. Glucose consumption is raised as membrane pumps increase activity to restore

ionic balance, further depleting energy stores. This is coupled with decreased cerebral blood flow and glucose availability resulting from endothelial accumulation of calcium. The discrepancy between glucose supply and demand leads to a generalized cellular crisis [47,48]. This overall process is transient with an ultimate return to homeostasis within a few days.

5. Effects of TBI in military

Most studies presented previously describe TBI in civilian populations. Given the high rates of TBI seen in veterans and military service members, the cognitive and behavioral sequelae of TBI among military personnel have been a primary focus of research in recent years. These studies build on the knowledge gained from civilian literature, while recognizing the unique characteristics of this special population who may have different injury mechanisms, risk factors, and comorbidities. Studies have examined both the acute and chronic symptoms of TBI as well as commonly occurring comorbid conditions.

The acute effects of mTBI in military personnel have been documented. Similar to civilians, the most commonly reported postconcussive symptoms include headaches, dizziness, memory problems, balance problems, and irritability [49,50]. Cognitive deficits are observed on computerized testing in the *acute* postinjury phase (i.e., within 3–10 days after injury) in deployment-related mTBI [51–54]. Consistent with civilian research, these prospective studies show that cognitive deficits resolve within days to weeks. Additionally, retrospective studies of more remote history of mTBI (e.g., months to years after injury) during deployment typically do not show persisting cognitive effects or noncognitive symptoms [55–57]. For example, self-reported TBI during deployment did not increase the risk of cognitive impairment on postdeployment cognitive testing for individuals who had returned from deployment in the last 2 years [55]. Likewise, a history of TBI did not affect outcomes in a study of the effects of deployment on cognition [58]. In a study of cognitive change from baseline to routine postdeployment cognitive testing [59], 70% of service members reporting a history of mTBI during deployment showed no change in cognitive functioning. Compared with a control group, however, declines in performance were observed in a subset of individuals who reported both mTBI and ongoing noncognitive symptoms. Whether these declines are due to persistent effects of mTBI or some other comorbid condition is unknown from this study, particularly given the high degree of comorbidities in service members with TBI history [22,23,60], particularly posttraumatic stress disorder (PTSD) and mood disorders. Other retrospective studies of the *chronic* effects of mTBI show that a subset of individuals with a history of mTBI continue to report persistent cognitive complaints and somatic symptoms consistent with concussion [22]. There is evidence, however, that these enduring symptomatic complaints may be misattributed to mTBI and may, in fact, be the result of other nonneurologic issues such as emotional distress or PTSD [22,24,57,61–63].

Others argue that the specific nature of military-related TBI (i.e., blast injury, repetitive injuries, etc.) may explain persistent or atypical cognitive and noncognitive recovery of symptoms. Given extended and repeated deployments, the risk for repeated mTBIs is high. There is support within civilian literature that repeated mTBIs, particularly in close proximity, lead to greater magnitude of symptoms and slower recovery rates for individuals with a history of multiple concussions [32,64]. Initial studies in service member and veteran populations suggest that multiple mild brain injuries do increase symptoms reported in the acute period after the most recent injury and are associated with more symptom complaints associated with postconcussion syndrome compared with those who incurred only one injury [50,65]. Animal studies have led some to speculate that blast injury, commonly experienced in deployment settings, may lead to more severe and potentially persistent neuropathologic changes in the brain (for review, see [66]). However, studies to date have not documented clinical differences in the acute or chronic effects of blast injury compared with nonblast injury on cognitive performance or somatic symptoms [52,67–71].

Furthermore, screening-based survey data reflect a large degree of overlap between TBI and a number of comorbidities, including PTSD, anxiety, and mood disorders and other mental health diagnoses. Rates of comorbid PTSD and mTBI are estimated to be about 30% of all those who screen positive for TBI [22,23,72]. Increased odds of PTSD symptoms have been associated with a history of TBI [73]. Veterans with a confirmed diagnosis of TBI were more likely to have clinical diagnoses of PTSD, other anxiety disorders, and adjustment disorders [74]. It is believed that co-occurrence of these two disorders may result in additive effects on the brain leading to longer symptom duration and greater cognitive difficulties after TBI [22,75]. Other studies demonstrate a specific increased risk for depression after TBI across the spectrum of TBI severity [22,76], which is important to document as depression can slow recovery, worsen neuropsychological impairment, and contribute to worse global outcomes [77]. Increased suicide risk after TBI is equivocal with some studies showing increased risk [78,79], even among those with milder injuries [80] and other studies [81–83], including a large review by the Institute of Medicine (IOM) [84], concluding no association between TBI and suicide.

Other factors such as ongoing pain and sleep disturbance may impact cognitive functioning and, when present, exacerbate the effects of TBI. A meta-analysis found prevalence rates of pain disorders in the military to be 43.1% with TBI demonstrating an independent correlation with pain disorder diagnosis, even when mental health diagnoses were controlled [85]. In a study of veterans with TBI, 70% had

a comorbid diagnosis of head, back, or neck pain [86]. Sleep disturbance is a frequent complaint after TBI [87]. Studies have found that sleep problems are significantly related to TBI in military populations [88–90] and that risk for sleep disturbance increases with a history of multiple mild TBIs [91].

6. Risk for dementia after TBI

The link between TBI and risk for dementia later in life has been repeatedly established in the literature [1–8,92–97]. Specifically, a prospective study of World War II veterans [2] found a two- to fourfold increase in dementia in veterans with a history of moderate-to-severe TBI. Other retrospective studies show that a history of moderate-to-severe TBI earlier in life is reported more frequently in individuals with dementia compared with controls [3,98–100]. Systematic reviews [8,84] conclude an increased risk of dementia in individuals with a history of at least one moderate-to-severe TBI compared with those with no TBI history. However, consensus is not complete given that some epidemiologic studies failed to show an association between TBI and later dementia [4,101–106]. Although some conflicting findings have been reported, subsequent reanalysis of these studies confirmed the positive association between development of DAT and a history of previous head trauma [1,6]. Other studies provide evidence that a history of TBI accelerates DAT onset at younger ages [95,107,108] and that risk for developing DAT increases with increasing severity of TBI [2,3].

The risk for dementia after mTBI is less conclusive. Previous systematic reviews and an IOM report conclude there is no increased risk for DAT later in life after a history of mTBI without LOC [8,84]. There was also no increased risk for dementia in World War II veterans with a history of mTBI [2]. However, there is evidence that *repeated* mTBI may result in accumulated neuropathology, chronic neurologic problems, and ultimate dementia [109]. Links between professional boxing and later dementia pugilistica have been established since the 1920s [110,111], with corresponding neuropathologic changes reported as early as the 1970s [112].

More recently, similar chronic cognitive and neurobehavioral problems have been described in athletes in contact sports with a history of repeated concussions [113–116]. A series of autopsy reports of such athletes have reported neuropathologic changes similar to those seen in boxers with dementia pugilistica [113,116]. These neuropathologic changes include, among other things, accumulated neurofibrillary tangles (NFTs), which are believed to be a result of repeated mechanical and rotational forces on the brain. The more general term, chronic traumatic encephalopathy (CTE), is being used to describe this chronic brain syndrome believed to result from repetitive mild brain trauma. CTE is regarded as a chronic neurodegenerative condition that occurs in midlife, years or decades after a sports career has ended, and is clinically associated with many behavioral changes, including irritability, impulsivity, aggression, depression, cognitive changes (e.g., memory and executive functioning) [117], and heightened suicidality [116,118]. However, the clinical course and symptoms reported in patients believed to have CTE are variable, and there are no generally accepted guidelines for a clinical diagnosis of CTE or for how to distinguish it from other types of dementias [109]. As of yet, there are no prospective or case-controlled studies to verify specific or causal relationships between the behavioral syndrome of CTE and the underlying neuropathologic findings. A recent study [119] confirmed higher rates of cognitive impairment in a sample of retired National Football League (NFL) athletes (35%) than would be expected in the general population with comparable age ($\sim$5%). However, the pattern of neurocognitive impairments in those retired NFL athletes with probable mild cognitive impairment (MCI) did not differ from a demographically matched clinical sample of amnestic MCI patients, suggesting a similar underlying pathophysiology. Thus, it was concluded that cognitive dysfunction in retired NFL athletes is best explained by the presence of diminished cerebral reserve leading to earlier clinical expression of late-life neurodegenerative diseases rather than CTE. A number of research groups have reported recent progress toward identification of imaging agents for in vivo imaging of tau deposition in the brain [120–125]. These efforts will facilitate much needed research regarding tau pathophysiology in CTE and other neurodegenerative dementias.

Given the high incidence of comorbid PTSD with TBI in military populations, researchers have begun to examine the relationship between PTSD and dementia risk. In two separate studies, Yaffe et al. [126] and Qureshi et al. [127] found a nearly twofold increased risk of dementia associated with PTSD in veteran samples after controlling for confounding factors. Mechanisms proposed for this increased risk included decreased cognitive reserve and stress-related sequelae, including damage to the hippocampus due to chronic stress or inflammation related to changes in the hypothalamic-pituitary-adrenal axis due to acute stress. However, further research is warranted to understand the independent contributions of TBI and PTSD to risk of dementia and the associated risk in comorbid TBI/PTSD.

Table 1 provides a summary of the onset and course of the primary cognitive and neurobehavioral effects associated with the conditions discussed in this section. Of significance is the high degree of overlap of clinical symptoms between these conditions. Despite this overlap, the prominence of clinical symptoms and their onset and course differ significantly. It should be highlighted that mTBI and TBI show immediate effects that typically recover over time as opposed to variable onset and course of symptoms seen in PTSD. Lastly, although the clinical symptoms of DAT and CTE may appear to be similar to those of TBI,

Table 1
Comparison of clinical symptoms, onset, and course in mild traumatic brain injury (mTBI), moderate-to-severe traumatic brain injury (TBI), posttraumatic stress disorder (PTSD), dementia of Alzheimer's type (DAT), and chronic traumatic encephalopathy (CTE)

Condition	Onset	Course	Primary cognitive effects	Primary neurobehavioral effects
mTBI	Immediate	Recovery within days to weeks; persisting symptoms often accounted for by psychosocial factors	Mild effects seen in attention, processing speed, and short-term memory	Minimal
TBI	Immediate	Recovery over months to years; possible chronic effects	Global cognitive effects most pronounced in attention, processing speed, memory, and executive functioning	Often pronounced and may include decreased awareness, disinhibition, impaired social skills, poor judgment, and others
PTSD	Variable	Variable; may see recovery of symptoms with treatment	Most pronounced in attention; variable effects in learning, memory, and executive functioning	Often pronounced and may include hypervigilance, anxiety, avoidance, flashbacks/nightmares
DAT	Delayed	Progressive	Specific to memory but progresses to be global	Minimal early in course and progress to include anosognosia and other variable problems
CTE	Delayed	Progressive	Executive functioning and memory but progresses to be more global	Significant early in course and may include irritability, impulsivity, aggression, depression, and heightened suicidality

they occur later in life and follow a progressively deteriorating course.

7. Pathology of dementia after TBI

Although evidence is accumulating that DAT risk is increased after TBI, the specific underlying pathology driving this increased risk is still unclear. Most mechanistic explanations focus on a presumed neuropathologic trigger that is activated at the time of injury that persists and evolves over time, ultimately resulting in progression to dementia. Axonal damage is a key manifestation of both Alzheimer's disease (AD) and TBI, thus many have pursued this as a possible link between TBI and the development of dementia. Evidence from both human studies and animal models has demonstrated that the key protein most commonly associated with AD, amyloid-β (Aβ), accumulates within neuronal cell bodies and injured axons [128,129] within hours to days after TBI [130–135]. In response to trauma, increased amyloid precursor protein (APP) is expressed within both neuronal cell bodies [136] and injured axons [137] leading to increased generation of its metabolite, Aβ. This accumulation of APP and Aβ is hypothesized to be a key factor in the subsequent Aβ plaque formation [138], which is one of the hallmarks of AD. Furthermore, it is hypothesized that the *APOE* ε4 genotype may affect amyloid pathology and outcome after TBI, putting those with this allele at particular risk for AD [3,139,140].

NFTs are also considered to be a major pathologic hallmark of AD. NFTs are composed of abnormally phosphorylated tau proteins, which are believed to be neurotoxic and can be the cause of neuronal death. Tau accumulation has been observed after TBI in animals [132,141,142] and humans [130,131]. However, unlike Aβ, NFTs have not been found to be acutely increased after a single TBI [141]. Instead, accumulated tau protein pathology, with little to no deposition of Aβ, appears to be implicated in the increased risk for early-onset behavioral and cognitive decline as a result of multiple repetitive mTBIs [133].

Inflammatory response in the brain after TBI has been extensively documented [143,144]. And although Aβ formation and associated tauopathy might appear to sufficiently explain the potential link between TBI and dementia, these same proteins can trigger processes leading to inflammation. Although acute inflammation is to be expected after TBI, there is also accumulating evidence that the inflammatory response from TBI may persist over time demonstrating that the initial effects of TBI may be more long lasting than previously believed. Studies document persistent inflammation in the brain after TBI in animal models for at least a year [145,146] and in postmortem human studies for many years after TBI [147]. A recent study using positron emission tomography to examine in vivo the inflammatory response after brain injury demonstrated increased microglial activation up to 17 years after injury, with activation in the thalamus being associated with more severe cognitive impairment [148]. Thus, TBI may trigger an inflammatory response, particularly in subcortical regions, that may persist and further evolve over time. This persistent inflammation may be an initial trigger of a larger cascade ultimately leading to TBI-related dementia, neurodegenerative, or cerebrovascular disease. The presence of inflammation is foreboding, given findings that elevated inflammatory markers are predictive of cognitive decline decades later [149]. Additionally, persisting inflammation in TBI may offer explanation for more recently published findings of increased stroke risk in individuals with a history of TBI [150,151].

8. Lessons learned from current military TBI monitoring programs

Given obvious immediate effects of the injury (e.g., LOC, marked confusion, coma), moderate-to-severe TBIs are

often easy to identify leading to treatment. Both the DoD and the VA are actively following these injured service members, longitudinally, in empirical studies [152,153]. Many service members suffer not only brain injury but also other systemic injuries (e.g., amputation, sensory loss), and longitudinal follow-up and data monitoring will help to clarify initial care that helped to improve outcome and the natural course of brain injury and polytrauma over the lifespan.

In contrast to moderate-to-severe TBI, the immediate symptoms of mild TBI can be subtle and difficult to detect. This is particularly true within a combat situation when symptoms of mTBI may be mistaken for the stresses of deployment or other psychological trauma/shock. To aid in the detection of mTBI and its sequelae in the deployed environment, multiple policies and programs were initiated by the DoD, including the implementation of a neurocognitive baseline assessment program at predeployment that allows for postinjury comparison [154,155]. In the deployed environment, the DoD enacted a policy to require screening after potentially concussive events, standardized evaluation of symptoms, and documentation of the event, symptoms, and resultant diagnosis [156]. After the enactment of this policy, the DoD increased training of medics in appropriate screening for concussion and modified their clinical care algorithms to reflect recent evidence from theater-based research. The DoD continues to emphasize detection of mTBI by requiring screening at multiple time points (e.g., point of injury, before medical evacuation to the United States, and before redeployment). Survey questions targeting TBI detection at postdeployment and at postdeployment reassessment (see Section 8.1) were recently refined to encourage symptom reporting to connect service members to care [156–158]. Additionally, there are concerted efforts to screen for the presence of TBI in polytrauma centers where other critical or life-threatening multisystem injuries may mask initial symptoms of mTBI [159]. Looking forward, research efforts are underway to evaluate the efficacy of biomarkers, neuroimaging, and other novel approaches for unequivocal diagnosis of TBI [160].

8.1. Potential underreporting of mTBI on postdeployment screening

Because of the growing concern over the health consequences of TBI, all service members returning from combat are screened for TBI using the Post-Deployment Health Assessment/Post-Deployment Health Re-Assessment (PDHA/PDHRA) from the DoD or the Veteran's Health Administration's TBI Screening Questionnaire [80]. These measures screen for potential exposure to risk events and ongoing symptomology. However, the timing of administration of these measures can play an important role in what the service member is willing to report. Some service members may minimize symptoms so as not to delay their return home with lengthy follow-up evaluations [24,80]. Others may not recognize the extent of their symptoms or may minimize the impact of their symptoms until they return home to their regular activities. Any delays in the initiation of treatment can negatively affect the path of symptom resolution and recovery; therefore, continued efforts to better identify injuries as close to the time of injury as possible are critical. As the DoD continues to develop its care model in theater, there are now mandatory evaluations in place for those who are felt to be at risk for TBI [161], with prescribed algorithms for follow-up care. Refinements of the questions asked during the PDHA and PDHRA are also focused to address underreporting and to encourage acknowledgment of symptoms to connect Service members to care [156]. The attention to screening and follow-up evaluation provides documentation of diagnosis of TBI, records multiple exposures and/or injuries in the population, and provides a better basis from which one can evaluate long-term outcomes and dementia risk.

8.2. Value of baseline testing

In 2008, Congress mandated a baseline predeployment neurocognitive assessment for all US service members [155] to address increasing concern surrounding the risk of cognitive insult during military deployment. Recently, the empirical validity of baseline cognitive testing within concussion monitoring and management programs for preventing or mitigating concussion risk has been questioned [162]. Although some studies have suggested no added value of baseline testing in civilian concussion monitoring programs [163,164], there is evidence that baseline testing reduces the possibility of false-positive detection of concussion in healthy service members. In a large study of military service members (n = 8002), Roebuck Spencer et al. [165] found that when norm-referenced postdeployment scores were considered in isolation, 66% of individuals classified as "atypical" actually showed no change from baseline. Baseline testing, especially testing that can be repeated over the life span, allows for longitudinal tracking of an individual's cognitive trajectory and detection of factors that cause a change from baseline. Monitoring of these results over time and controlling for effects of aging or other normative causes of cognitive change could improve the sensitivity of dementia monitoring protocols.

Hypothetical examples of the benefits of longitudinal monitoring are provided in Fig. 2A and B. These examples illustrate how longitudinal testing might aid in diagnosis and clinical management of service members. The y-axis represents standardized cognitive testing scores (mean = 100; standard deviation [SD] = 15). Fig. 2A includes a representation of an individual who experienced an mTBI during deployment. This individual demonstrates a drop in cognitive performance of approximately two SDs after injury, which then improves to baseline functioning over time and remains at this level at routine postdeployment testing illustrating expected recovery of functioning as

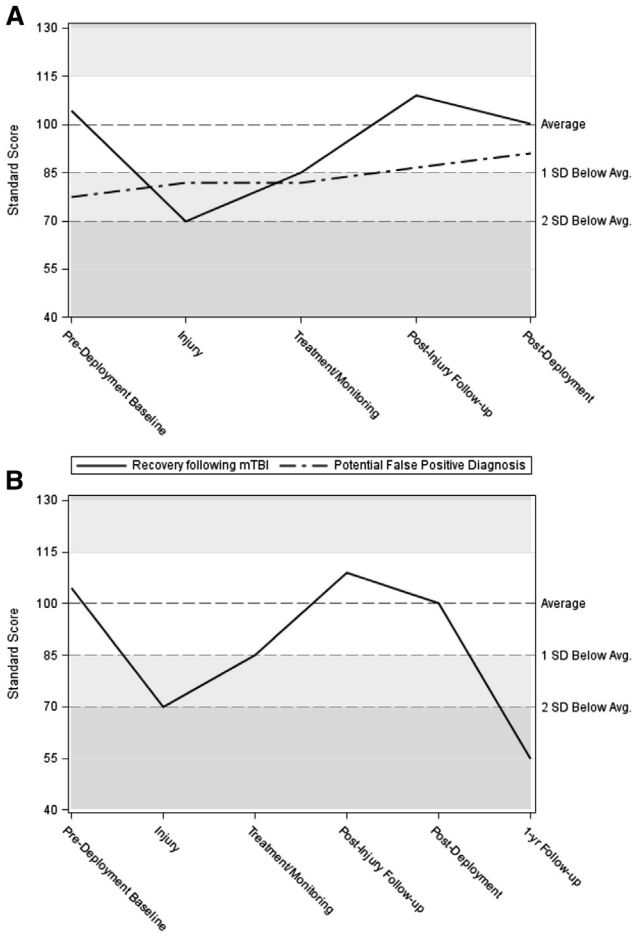

Fig. 2. (A) Hypothetical cognitive function courses depicting (1) successful recovery after mild TBI and (2) potential false-positive diagnosis in an individual with below average baseline performance. (B) Hypothetical cognitive function course depicting recovery after mild TBI with successful recovery followed by late-onset cognitive symptoms. SD, standard deviation; mTBI, mild traumatic brain injury.

documented in civilian and military literature [53,54,166]. Fig. 2A also provides an example of a possible false-positive error in someone with premorbidly below-average predeployment functioning. After an injury with suspected concussion, this individual performed two SDs below the mean on cognitive testing. In the absence of other information, postinjury performance might be interpreted to represent cognitive impairment related to a concussion injury. However, longitudinal assessment reveals that the individual showed no change from baseline and that cognitive functioning remained stable at follow-up testing points. Without the advantage of longitudinal testing including a baseline assessment, this individual may be misdiagnosed as having had a concussion and may receive unnecessary treatment. Finally, Fig. 2B provides a hypothetical example of late-onset symptoms in an individual with a prior mTBI. Longitudinal testing clearly shows a successful cognitive recovery after the documented mTBI. Without the benefit of longitudinal testing, late-onset symptoms might erroneously be attributed to the previous mTBI. With the availability of routine cognitive screening, the clinician would be better equipped to explore and treat more accurate etiologies of these symptoms. Finally, although not shown here, longitudinal cognitive testing over the lifetime, when corrected for expected effects of aging, would allow for identification of future declines in functioning that, if found to be progressive in nature, might signal the onset of a neurodegenerative process.

8.3. Role of effort and motivation in assessment protocols

Confirming that test results are valid and representative of true abilities/functioning is an essential part of any (neuro)psychological evaluation but is of particular importance for military and veteran populations in whom invalid performance may increase risks of misdiagnosis, have implications for determining readiness to perform, and may lead to overutilization of resources. Research with veterans demonstrates discrepancies between subjective symptom reporting and objective deficits on neuropsychological test performance [167], indicating that symptom report alone may be an unreliable way to establish cognitive functioning. High failure rates on performance validity tests during neuropsychological evaluations have been reported in service members and veterans [168,169], with rates ranging between 8% and 67% depending on evaluation context [69,169–171]. Although the possibility of intentional deception should be considered and ruled out, noncredible symptom reporting may result from misattribution of symptoms [172] or the effects of other comorbid risk factors (e.g., pain, sleep loss, PTSD, etc.). Research on novel performance validity indices for cognitive and neurobehavioral assessment in military samples is emerging [173,174], including an embedded performance validity indicator within the Automated Neuropsychological Assessment Metrics (ANAM) [165], a computerized measure of cognition used routinely for establishing baseline cognitive functioning in service members before deployment.

8.4. Comorbidities and TBI

TBI is a complex injury that is closely associated with a number of co-occurring disorders and conditions (described earlier). These comorbidities each may have independent and specific effects on cognition and symptom reporting, presenting a continuing challenge for clinicians working with military service members with TBI. These patients should be approached as individual cases, with an understanding that co-occurring factors including, but not limited to, PTSD and other mental health disorders, ongoing acute or chronic pain, sleep disturbance, and potential sensory dysfunction will contribute to the clinical presentation [175], and discerning the effects of these factors from those of TBI may be difficult.

9. Implications for assessment and monitoring of aging military service members

Studies of previous cohorts of service members have provided a window by which to view the lessons learned and advances made in TBI screening, diagnosis, and treatment. For example, the Vietnam Veterans Head Injury Project monitored individuals who incurred penetrating head injuries during the Vietnam War [176] and tracked their health status, functional outcomes, and reintegration into the community. Although limited in sample size, the study has helped to demonstrate the potential for neuroplastic repair, provided a time course for development of posttraumatic epilepsy, and yielded findings even from its initial publications that influenced in-theater triage and surgical intervention. This serves as a framework to consider the current information base within the cohort deployed to current theaters of operation and informs future efforts to monitor an aging population of service members who deployed to the combat theater.

Primary to any major longitudinal monitoring effort is definition of key data elements that allow for integration of data from multiple studies and shared ontologies associated with that data to allow for reliable analysis and interpretation. DoD, VA, the National Institute on Disability and Rehabilitation Research, and the National Institutes of Health (NIH) have contributed to the development of common data elements for use in research related to TBI [177], and many of these agencies now require the use of those data elements for their funded research. In addition, the NIH and DoD have sponsored a collaborative database aimed to integrate findings from funded research, especially clinical trials, that will be available on request for aggregated analysis and publication (https://fitbir.nih.gov). Similar to efforts in aging and autism, this increases available data to examine effective treatments, novel contributors to positive outcome, or evaluation of devices or methods for diagnosis and detection. Furthermore, ongoing studies in DoD and VA, to include the 15 Year Study sponsored by the Defense and Veterans Brain Injury Center [178] and the TBI Model Systems effort within VA [152] will allow for long-term monitoring of not only moderate-to-severe TBI patients but also those who have suffered mild injuries. These efforts will contribute to the systematic monitoring of service members and veterans over their life span and will lay the groundwork for tracking of dementia onset, type, and course for those individuals with premorbid brain injury.

Not all data for monitoring are contained in research studies, and studies cited within this article reflect the need for clinical data, at the administrative level, to be available for analysis and monitoring of specific cohorts of patients who were either exposed to risk for brain injury or incurred brain injury. Recent policies in DoD that require documentation in the clinical record using automated forms provide a substantial lesson learned and provide the initial documentation of injury, which allows for accurate follow-up and long-term monitoring. Health systems research and clinical monitoring studies based on these data, both in DoD and VA, will allow investigators to chart the natural course of recovery in routine care and ultimately may provide insights into the development of dementia associated with this risk factor alone and/or in combination with other comorbid conditions.

As noted in previous paragraphs, the starting point is accurate diagnosis and early intervention. This has implications not only for diagnostic techniques and the need to incorporate objective biometric diagnostics, but also for improvements in the timing and nature of the screening protocols currently in use by health-care providers in DoD and VA. By encouraging acknowledgment of current symptoms, early interventions can be offered and chronic conditions may be prevented. Education of the service member, their command, and medical personnel on the effectiveness of treatment, especially for mild injury, and the expected recovery from current symptoms may improve ultimate outcome.

Finally, to understand if there are changes that may indicate the onset of dementia, monitoring programs need to consider and incorporate expected change and variability in targeted areas of functioning, especially those affected by age. This is especially true for cognition, in which there are known specific effects of normal aging in various cognitive domains. Incorporating the effects of normal aging (and other relevant demographic factors) into ongoing monitoring could be accomplished through development of normative reference databases that use longitudinal modeling and risk ratios based on performance decrements compared with an individual's own premorbid performance and to the performance of similar demographic groups. Although implementing such monitoring programs may initially increase the costs associated with TBI treatment for the DoD and VA, the benefits of early detection of cognitive changes and more accurate understanding of potential causal factors allow for earlier and more focused treatment and would be expected to improve outcome and reduce long-term costs in many cases.

10. Conclusion

In summary, TBI is known to lead to transient or chronic effects on neurobehavioral and cognitive functioning, which vary according to severity, mechanics, and timing of injury. Growing research documents that a history of TBI may place some individuals at risk for dementia later in life, either because of genetic vulnerability or diminishing of cognitive reserve leading to earlier onset of neurodegenerative changes. Military service members are at particular risk for TBI, leading to significant implications for monitoring programs not only to detect these injuries and their effects at their onset but also for monitoring potential long-term effects across the life span. This article highlights research on the cognitive effects and risks for later life dementia from TBI in civilian and military populations. Many lessons have been learned from current military TBI monitoring

and management programs with significant implications for continued monitoring of aging service members and veterans.

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