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# Military traumatic brain injury: A review☆

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**Abtsract** Military mild traumatic brain injury (mTBI) differs from civilian injury in important ways. Although mTBI sustained in both military and civilian settings are likely to be underreported, the combat theater presents additional obstacles to reporting and accessing care. The impact of blast forces on the nervous system may differ from nonblast mechanisms, mTBI although studies comparing the neurologic and cognitive sequelae in mTBI survivors have not provided such evidence. However, emotional distress appears to figure prominently in symptoms following military mTBI. This review evaluates the extant literature with an eye towards future research directions.



*Keywords:* Traumatic brain injury; Concussion; Blast injury; Veterans; Military personnel; Combat

## 1. Introduction

Traumatic brain injury (TBI) is a frequent source of morbidity and mortality in both the civilian and military populations. Hyder and colleagues [1] estimated the global incidence of TBI at 10 million cases annually, with 1.7 million emergency department visits yearly among U.S. civilians [2]. Because these rates do not include injuries cared for in military or Veterans Affairs (VA) hospitals, outpatient clinics, doctor's offices, or at home, it is probable they underestimate the true incidence of TBI [3].

In a military combat setting, the incidence of TBI is likely to be higher. Hoge and colleagues [4] surveyed two Operation Iraqi Freedom (OIF) Army combat brigades with validated clinical instruments, generating 2525 surveys with usable data. Approximately 15% of respondents had sustained a TBI with either loss of consciousness (LOC) (4.9%) or altered mental status (10.3%). Terrio and colleagues [5] screened an OIF Army combat brigade (n = 3973) and clinically evaluated those reporting injury. Clinician-confirmed brain injuries, most in the mild range, were found in 22.8% (n = 907) of the total sample. Similarly, Schell and Marshall's [6] work suggested incidence rates of 19.5% (upper limit estimate, 22.7%) among personnel serving in either Operation Enduring Freedom (OEF) (Afghanistan) or OIF, based on questionnaires administered upon return from deployment.

There is a paucity of data on the prevalence of chronic TBI with persisting symptoms, and little information available on individuals who sustain multiple TBIs. A recent study of military conscripts in Sweden [7] used the national patient registry and concluded that, of 811,622 men with a mean age of 18 years at the time of conscription, 34,698 sustained one mild TBI, 4569 sustained two mild TBIs but no severe TBI, and 5982 sustained at least one severe TBI during a mean follow-up of 33 years.

In both civilian and military populations, most (76%–83%) injuries are classified as mild TBI (mTBI) [8,9]. The identification and treatment of a moderate to severe brain injury is more straightforward in many ways than a mild injury because of the obvious objective findings and clear history, which are usually documented in acute care records. With mTBI, the signs of injury overlap with other conditions, such as acute stress reaction, posttraumatic



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stress disorder (PTSD), and depression, which frequently coexist with mTBI. The lack of objective markers on neuroimaging or laboratory evaluations can also lead to delayed diagnosis and inappropriate disposition. As such, this article focuses on mild brain injury.

We first review the conceptual history and current diagnostic criteria for mTBI, including both the injury event and the postinjury sequelae. In the remainder of this article we review elements specific to military brain injury.

## 2. Conceptual history and diagnosis of mTBI

### 2.1. Conceptual history

Frequently, the lack of objective findings from neurological examination and computed tomography (CT) scans after mild brain injury result in spurious conclusions about the nature of persisting symptoms. Such symptoms are often attributed to functional disorders or desire for secondary gain, either conscious or unconscious. Recently, results from advanced neuroimaging studies of brain abnormalities after mTBI have revised this view, and raised concerns about possible unreported or undetected mTBIs. These concerns take on particular importance with the realization that professional athletes and military service members commonly experience multiple mTBIs during their careers, and a much larger number of subconcussive blows to the head that do not result in mTBI. Recent evidence [10,11] has suggested that a subgroup of patients with multiple mTBIs may experience progressive neurodegenerative symptoms during subsequent years and decades.

Traditionally, the time course of brain injury has been described as occurring throughout two phases: (1) a primary or mechanical injury, which is a discrete injury event, followed by (2) a secondary, longer duration injury related to the activation of molecular and biochemical pathways originated by the primary event. The secondary injury was initially believed to be limited to hours or days postinjury. However, new findings indicate that the abnormal signaling and inflammatory processes activated during the secondary injury persist for much longer.

Historically, TBI has been classified into three broad mechanism categories: focal, diffuse, or mixed. Focal injuries emanate from blows to the head (e.g., assault with a weapon, hit from another player's helmet, striking an object or the ground during a fall) that may involve direct impact of the brain's surface on the bony protuberances of the skull. Focal mechanisms can result in laceration, contusion, and hemorrhage. A special type of focal injury termed a coupe contracoupe injury occurs when the head accelerates in one direction striking an object (e.g., windshield), which in turn propels the head in the opposite direction, striking another object (e.g., headrest). Coupe contracoupe injuries are common in motor vehicle accidents.

Diffuse injury refers to the stretching and twisting of axons and blood vessels by shear forces resulting from acceleration, deceleration, and rotation of the brain. Primary axotomy is rare during the initial mechanical insult and usually occurs during the secondary injury phase. The immersion in cerebrospinal fluid and attachment to the spinal cord render the brain vulnerable to centrifugal motion on acceleration and deceleration (e.g., falls) that can also occur during focal injuries.

The mixed mechanism simply refers to the involvement of both focal and diffuse mechanisms in a brain injury. Both blast and nonblast brain injuries commonly involve mixed mechanisms.

### 2.2. Diagnosis of mTBI

#### 2.2.1. The injury

Chief among the diagnostic challenges presented by mTBI are heavy reliance on patient self-report or witness accounts. Loss or alteration of consciousness and posttraumatic amnesia are inherent features of mTBI, and in the absence of eyewitnesses, ascertainment of duration of reduced consciousness is imprecise. The cognitive and emotional difficulties that can result from TBI may also reduce awareness and interfere with reliability of self-report [12]. Last, symptoms resulting from mTBI, such as headache, dizziness, depression, and anxiety, are nonspecific and, although frequently exacerbated by injury, are also common premorbidly (in the population at large). These factors underscore the need for objective measures that would improve diagnostic accuracy and provide a substrate for monitoring treatment.

Although based largely on self-reported information, the basic definition and severity indicators for TBI have general conceptual agreement among a broad array of institutions, both civilian and military. However, the diagnostic criteria for determining whether an mTBI has occurred is separate from the criteria for diagnosing persisting symptoms attributed to such an event (e.g., postconcussion syndrome). Hoge and colleagues [13] noted that the Department of Defense (DOD) and the Department of Veterans Affairs (DVA) postdeployment health care initiatives were more focused on injury event determination than on current symptoms and level of impairment. These investigators asserted that a unitary definition for TBI—including symptoms, time course, and level of impairment in addition to the injury event criteria—would improve the utility of diagnosis.

Several professional societies and federal agencies have developed diagnostic criteria for TBI, ascribing to some version of disruption of brain function by an external force. However, for the purposes of coding and remuneration, numerous diagnostic codes have emerged to cover the wide range of specific insults that can be involved in the injury event. In medical settings, any of several hundred codes from the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) [14] can indicate a head injury.

The high incidence of multiple mTBIs in military veterans of combat theaters, and the accumulating evidence that

multiple concussions may result in neurodegeneration, led the DOD and to adopt a common definition, and to develop screening criteria and practice guidelines. In May 2007 [15], the DOD and DVA agreed jointly to an adaptation of American Congress of Rehabilitation Medicine [16] definition of brain injury as follows: "Any traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:

1. Any period of loss of or a decreased level of consciousness
2. Any loss of memory for events immediately before or after the injury
3. Any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking)
4. Neurological deficits (e.g., weakness, balance disturbance, praxis, paresis/paraplegia, change in vision, other sensory alterations, aphasia) that may or may not be transient
5. Intracranial lesion″ [15]

In addition, the DOD/DVA formalized their consensus-based criteria for severity determinations [15] for closed head injury (Table 1).

Several concerns about these criteria relate to specificity and timing. The type of neuroimaging used (CT vs. magnetic resonance imaging [MRI]) is not specified, nor is any guidance on the timing. CT scans, frequently used in emergency rooms, are generally less sensitive than MRI. The timing of neuroimaging is another important issue; early signs of injury can resolve within days, in both CT and MRI. Specific guidance is also not provided for classification of patients when indicators place them in different severity categories (e.g., patients who experience only a few minutes of LOC but report posttraumatic amnesia of several days).

#### 2.2.2. *Postinjury diagnostics*

Symptoms after brain injury are frequently categorized by their timing during the recovery period as either acute or persisting, following the general template for phases of recovery: acute, subacute, or chronic. Most symptoms are present for just days or, at most, weeks after mild brain injury. The operational definitions of these time periods, particularly acute and subacute, differ from study to study. However, the outer limits of the chronic period are generally considered to begin 3 to 6 months postinjury. Although idiographic variations are the rule in recovery timing, 3 months has been viewed traditionally as the outer limit of the time period in which the brain repairs itself from mild brain injury (the natural recovery period) [15].

Once thought to be a rare occurrence, a substantial number of military personnel and veterans report symptoms from mild brain injury persisting long after the 3-month mark. The prevalence of persisting symptoms appears to range from 20% to 48% in veterans [17]. In civilian mTBI, evidence [18] suggests that persisting symptoms are present in only 3% to 5%. As discussed later, persisting (chronic period) symptoms in veterans and military personnel have been linked to both mTBI and coexisting mental health conditions.

The set of symptoms that can follow and persist after mTBI are defined differently by the ICD-9-CM and the *Diagnostic and Statistical Manual for Mental Disorders*, fourth edition, Text Revision (*DSM-IV*-TR)[19]. The ICD-9-CM criteria include a history of mTBI and the presence of three or more of the following eight symptoms: (1) headache, (2) dizziness, (3) fatigue, (4) irritability, (5) insomnia, (6) concentration or (7) memory difficulty, and (8) intolerance of stress, emotion, or alcohol. However the *DSM-IV*-TR, criteria require evidence of attention or memory difficulty from quantifiable cognitive evaluation. One of the limitations of both sets of diagnostic criteria is their focus on symptoms and signs and exclusion of mechanism-based information [20].

## 3. Military TBI

### 3.1. *Combat theater factors*

Military TBI (TBI occurring during deployment to a combat zone) differs from civilian brain injury in several important ways. Although the incidence of TBI, particularly mild injuries, are believed to be underreported in both the military and civilian populations, the unique nature of the combat theater presents additional obstacles to reporting, accessing care for, and documenting such injuries [3,21]. Tanielian and Jaycox's findings suggested "poor documentation of blast exposures and failure to identify individuals with probable TBI" [21, p. xxvi].

Table 1
DOD/DVA Consensus-based Classification of Closed TBI Severity [15].

| Severity index | Mild | Moderate | Severe |
|---|---|---|---|
| Neuroimaging findings | Normal structural imaging | Normal *or* abnormal structural imaging | Normal *or* abnormal structural imaging |
| Initial Glasgow Coma Scale score, pt | 13–15 | 9–12 | <9 |
| Duration of loss of consciousness | 0–30 min | >30 min *and* <24 h | >24 h |
| Duration of AOC | A moment up to 24 h | AOC >24 h (use other criteria) | |
| Duration of posttraumatic amnesia, days | 0–1 day | >1 and <7 | >7 |

Abbreviation: AOC, alteration of consciousness.

In the combat theater, brain and other injuries are frequently embedded in longer, continuous missions rather than occurring as discrete events, as is often the case in civilian brain injury (e.g., motor vehicle accidents, falls, and so on). Removing oneself from active combat to report mild injury or to access care often does not occur.

Military service members who experience TBIs are frequently sleep deprived and operating under high levels of physiological stress and emotional trauma. The stress and ongoing sensory experience of the combat environment can impede the ability to identify or recognize postinjury symptoms significantly and can interfere with the encoding of details for future recall. These factors may also diminish resilience and reduce the ability to recover from seemingly mild injuries.

Comorbid mental health symptoms and conditions are more prevalent in those who experienced a military mTBI compared with their civilian counterparts. Such symptoms are difficult to differentiate from mTBI sequelae. Like many of its comorbidities, mTBI relies upon patient self-report for diagnosis, limiting diagnostic accuracy [22].

A disproportionate fraction of military TBIs are associated with high-energy explosions, which may impact the brain in novel ways. Multiple mTBIs are common in combat settings, and multiple deployments are often the rule during a prolonged conflict [23,24]. Repeated mTBIs and/or exposures to subconcussive blasts increase concern about vulnerabilities with aging and emerging neurodegeneration or chronic traumatic encephalopathy (CTE).

### 3.2. Blast vs. nonblast TBI

Both nonblast- and blast-related brain injuries are heterogeneous in their mechanism. DePalma and colleagues [25] reported a conceptual schematic of blast-related brain injury mechanisms, which when combined, include the potential for any number of focal and diffuse cerebral injuries. For example, the primary blast mechanism refers to the overpressurization shock wave associated with high-energy explosives. Additional insults can result from secondary (flying debris) or tertiary (body displacement) mechanisms. Crush injuries from structure collapse and burns are classified as quaternary mechanisms.

Given the forces present in the overpressurization shock waves that emanate from high-energy explosives, which can travel at the speed of sound with the potential to be multiplied by reflection [26], it has been hypothesized that the damage from this mechanism may differ substantially from that of nonblast origin. However, in its natural state, this mechanism is highly complex, with multiple mediating and moderating variables that have presented challenges to experimental modeling.

The very method of transmission through which the blast contributes to brain injury is currently a topic of vigorous debate. Proposed transmission modes have included direct neural transmission [27], vascular propagation [26] and, more recently, acceleration/deceleration of the head [11]. Although acceleration/deceleration also occurs frequently in nonblast TBI, the velocity is likely significantly greater during a blast.

Despite the inherent logic of greater acceleration/deceleration velocity as a critical difference between blast and nonblast mechanisms, the few studies completed to date have not found consistent evidence that blast and nonblast mTBI sequelae differ substantially. These studies have examined neuroimaging metrics, neuropsychological performance, and self-reported symptoms that are accounted for by blast and nonblast mechanisms. This research is confounded by the very low incidence of isolated primary blast. With vanishingly rare exceptions, service members who report mTBI associated with a blast exposure also report secondary or tertiary injury mechanisms.

Very few neuroimaging studies have compared blast and nonblast mTBI directly. Davenport and colleagues [28] executed a diffusion imaging study that hypothesized blast-related mTBI would be associated with subtle axonal damage that was spatially disparate between individuals. Compared with nonblast, blast mTBI was related to a greater number of voxels with low fractional anisotropy in hypothesized tracts and across the white matter mask. An interaction effect showed that the presence of a prior nonblast mTBI was only associated with a greater number of these voxels in the absence of blast mTBI.

Several investigators have examined differences in these mechanisms through performance on neuropsychological tests. Belanger [29] found an absence of main effects between those with mild or moderate-to-severe blast-related TBI compared with individuals with the same severity levels from the nonblast group. Cognitive domains tested included speed/flexibility and verbal and visual learning and memory. An interaction effect for visual memory showed stronger performance in those with blast-related mTBI and poorer performance for those with blast-related moderate-to-severe TBI vs. same-severity non-blast TBI groups.

Lange and colleagues [17] reported an absence of neuropsychological differences between a group with blast-related mTBI plus secondary blunt trauma ($n = 35$) compared with a nonblast blunt trauma group ($n = 21$) after controlling for depression and stress. These groups showed no differences on the clinical scales of the Personality Assessment Inventory.

Several investigative groups have conducted high-quality record reviews or surveys comparing differences in persisting symptoms between those sustaining blast and nonblast mTBIs. Wilk and colleagues [30] surveyed 3952 U.S. Army personnel several months after returning from OIF. Five hundred eighty-seven soldiers (14.9%) had self-reported concussion, 201 with LOC (34.2%) and 373 with alteration of consciousness (63.5%). Four hundred twenty-four (72.2%) reported the mTBI as blast related and 150 (25.6%) as nonblast related. The blast mechanism was

associated with headaches and tinnitus, but only for those with LOC. However, among the entire concussion group, the blast mechanism was not related to mental or physical health outcomes. Nonblast mTBI was associated significantly with self-reported concentration and memory problems, and abdominal symptoms.

Lippa and colleagues [31] examined postconcussive symptoms and PTSD scores in the medical records of 339 OEF/OIF veterans with mTBI. Veteran scores on the Neurobehavioral Symptom Inventory (NSI) [32] and the Posttraumatic Stress Disorder Checklist (PCL) [33] were analyzed by type of mTBI: (1) blast related only (n = 148), (2) nonblast related only (n = 56), or (3) both, having sustained at least one blast-related mTBI and one nonblast-related mTBI (n = 145). The two blast-related mTBI groups were younger and had more PTSD symptoms than the nonblast group. However, no differences were found among these groups for severity of postconcussive symptoms. Neither the number of blast-related mTBIs nor the estimated distance from the blast was related statistically to postconcussive symptoms. PCL scores accounted for a greater amount of unique variance (46.6%, $P = .001$) in the total postconcussive symptoms than LOC (1.6%, $P = .02$). It should be noted that, as a result of the fact that blast-related mTBI includes both blast and nonblast mechanisms in the great majority of cases [34], the blast-only group likely did not differ from the both blast and nonblast group.

Belanger and colleagues [35] compared self-reported symptoms on the NSI and PCL between clinician-diagnosed blast (n = 292) and nonblast (n = 92) mTBI groups. Results showed that neither mechanism of injury (blast vs. nonblast) nor type of reduced consciousness (LOC versus alteration of consciousness) accounted for significance amounts of variance in total NSI symptom scores. Greater symptoms were reported by those injured more than 1 month ago (compared with less than 1 month) and by those endorsing more PTSD symptoms. Hearing difficulty was the only individual symptom that differed between groups.

Overall, these results suggest an integral role for emotional distress in persisting symptoms from military mTBI, whether from blast or nonblast mechanisms. However, several other factors must also be considered. First, although insignificant in one of the previously mentioned studies, basic physics dictates that, in high-energy explosions, distance from detonation is a key, but frequently indeterminate, factor in the assessment of brain injury presence. In addition, rather than a graduated dose effect between mild vs. moderate-to-severe blast TBI, the blast mechanism may operate through a threshold effect, with symptomatic differences in mechanism emerging with moderate injuries that are more proximal to the point of detonation. Other factors may mediate or moderate blast TBI in ways that are not currently understood. Few blasts occur in the open field, on which older models are based.

Second, if emotional factors are the primary etiology for postconcussive symptoms, then we should expect this same symptom set in many individuals with PTSD from trauma exposures with features similar to those experienced in combat. Evaluation of multiple study groups such as the military units described here would help to identify and rank candidate features (e.g., traumas with long duration, with persistent or semipersistent stressors, occurring in unfamiliar surroundings, and so on) associated with combat PTSD. An investigation of individuals with civilian PTSD from analog stressor experiences could produce informative convergent or divergent validity with respect to the presence of postconcussive symptoms and whether they are accounted for by PTSD symptoms.

Third, many of the aforementioned studies used self-report measures. Although self-report is an important element in the diagnostic process, human judgment and memory are subject to certain limitations and individual perceptions. For example, although neural changes after blast-related mTBI may impact functioning negatively, they may be experienced and/or reported in ways inconsistent with their origin. The most salient feature to an individual may be the fear that he/she feels rather than the subtle cognitive difficulties resulting in that fear. In this way, self-report instruments capture only the variance related to symptoms that are foremost in the mind of the reporter. Indeed, outcomes research in recent years has prioritized "patient-related outcomes" over "disease-related outcomes"—meaning, the experience of the patient is of primary importance. Although this view should not be discounted, it also should not be left unchecked by objective data, given the abundant evidence of the limitations of the former. The careful integration of objective and subjective data is likely to produce ground truth. Furthermore, such integrative solutions may be possible only through machine learning strategies.

Last, as discussed in the following sections, symptoms of physiological or emotional stress associated with exposure to combat can be highly variable within the same individual, emerging and submerging in an idiographic pattern, and presenting challenges in measurement and interpretation. Substantial and meticulous work must ensue before conclusions can be drawn about blast vs. nonblast mechanisms.

### 3.3. Psychiatric comorbidities

Psychiatric and substance-abuse related conditions occur frequently with military brain injury. An archival study [36] of 12,056 OEF/OIF veterans diagnosed with deployment-related brain injury through the DVA standardized diagnostic procedure, the Comprehensive TBI Evaluation, examined patient records for psychiatric diagnoses and neurobehavioral symptoms. PTSD or a depressive disorder was found in 67% and 34% of this sample, respectively, with 29% having both. Thirty-four percent had been diagnosed with alcohol- (26%) or drug-related (8%) conditions.

Attribution of symptoms after mTBI to brain injury vs. other frequently comorbid conditions such as PTSD and

depression has been difficult [30,37,38]. Diagnosis for all these conditions relies heavily on patient self-report of events and symptoms, limiting diagnostic accuracy. In the case of mental health conditions, the potential reluctance to discuss painful or stigmatizing details can impede accuracy [22,39,40]. In addition, the shared symptoms between mTBI, PTSD [12], and depression complicate differential diagnosis further.

Exposure to emotional trauma is more likely in the combat theater, as is the development of PTSD. Among U.S. civilians, approximately 61% of men and 51% of women will be exposed to trauma during their lifetime, but only about 8% (5% of men and 10% of women) will develop PTSD, based on the National Comorbidity Survey [41]. As would be expected, PTSD occurs more frequently among military personnel deployed to combat zones than within the civilian population. The general stress of deployment combined with the greater incidence of trauma exposure likely accounts for these higher rates. PTSD prevalence for those serving in OEF and OIF has been estimated at 14% [6]. These investigators also found that fully one-third of OEF/OIF veterans with probable TBI also had probable PTSD. A review by Carlson and colleagues [42] reported that, although comorbidity rates for mTBI and PTSD among military personnel vary widely (0%–89%), the largest studies cited figures between 33% and 39%. In contrast, the largest civilian studies of mTBI showed that PTSD comorbidity ranged from 12% to 27%.

Despite the association of PTSD with physical or postconcussive symptoms in some studies comparing blast vs. nonblast mechanisms, other studies have found that having both diagnoses accounts for greater variance in persisting symptoms than either condition alone. Brenner and colleagues [43] conducted a retrospective analysis of the sample reported on by Terrio and colleagues [5]. The injured soldiers (n = 1247) from a combat brigade included 907 with one or more clinician-confirmed TBIs and 385 with other injuries (not TBI). After adjustments for demographics, having both mTBI and PTSD was related more strongly to postconcussive symptoms (adjusted prevalence, 6.27) than either mTBI (adjusted prevalence, 4.03) or PTSD (adjusted prevalence, 2.74) alone.

The same factors creating challenges in diagnosis of mTBI are encountered again in treatment. Decisions related to the timing and monitoring of treatments and transitions are complicated by the absence of objective markers. Evidence linking PTSD and chronic stress to cardiovascular disease and dementia has accumulated [22] in tandem with findings linking multiple concussions to CTE [10].

## 4. Chronic traumatic encephalopathy

CTE, formerly called "punch drunk" or "dementia pugilistica," was first described by Dr. Harrison Martland [44] in a 1928 article discussing the punch drunk state of many retired boxers. The condition was termed "dementia pugilistica" by Millspaugh [45] in 1937, and "chronic progressive encephalopathy of the boxer" by Critchley [46]. In 1973, Corsellis and colleagues [47] described three stages of symptoms that appeared to typify the degeneration associated with CTE. Affective and psychotic symptoms characterized the first stage. The second stage comprised social volatility, memory loss, unpredictable behavior, and the early presentation of Parkinson's disease. The third stage was marked by cognitive changes leading to dementia, gait disorders, and, in many cases, advanced parkinsonism.

Although originally described in boxers, other contact sports have been implicated in CTE as well. After a number of professional football players retired early as a result of postconcussion syndrome, the National Football League created the National Football League Committee on Mild Traumatic Brain Injury in 1994. In a recent article, McKee and colleagues [10] reported results from the postmortem pathological examinations of 85 cases with a history of repetitive mTBIs and 18 control subjects without such history. The cases included 64 athletes and 21 military veterans. Of the 21 veterans, many (n = 16) were athletes and only four were exposed to a blast. McKee and colleagues [10] found CTE in 68 of the 85 cases and in zero of the control subjects. This investigation was not designed to address incidence of CTE and, at this time, such estimates are unknown. Incidence can only be estimated with prospective longitudinal studies.

It is hypothesized that CTE can be comorbid with other neurodegenerative conditions such as Alzheimer's disease, Lewy body disease, frontotemporal dementia, or motor neuron disease [39,40,48–50]. However, as McKee and colleagues [10] noted, CTE appears distinguishable pathologically from other neurodegenerative diseases, especially with respect to topographical dispersion and, to a lesser degree, type of pathological entity (although see Hong and colleagues [51]) and course (e.g., slower rate of progression through stages [10]). In addition, although CTE often begins with clinical symptoms of behavior and personality changes similar to frontotemporal dementia, the timing of psychiatric symptoms differs significantly from the more prevalent Alzheimer's disease.

From the close assessment of the studied cases, McKee and colleagues [10] refined earlier pathological and clinical characterization of CTE stages. Clinical characterization was completed by interview with family and review of medical records. Specifically, McKee and colleagues [10] detail four stages. During stage I, multifocal and frequently perivascular axonal varicosities are found in the frontal cortex, subcortical white matter, and deep fiber tracks in the diencephalon. The most common clinical symptoms in stage I include headache and loss of attention/concentration. During stage II, axonal disruptions extended to the temporal cortices, and the clinical symptoms added, are mood swings/depression, explosive episodes, and short-term memory loss. During stage III, macroscopic findings include mild atrophy, abnormalities of the septum, lateral and third ventricle dilation, and mild to moderate depigmentation of the locus coeruleus and substantia nigra. Axonal loss and

severe distortion are more diffuse than in earlier stages, and are found in the subcortical white matter, particularly in the frontal and temporal cortices. Clinical symptoms include cognitive impairment with memory loss, executive dysfunction, loss of attention/concentration, depression, explosivity, and visuospatial deficits. Last, stage IV is described as a progression of macroscopic findings, diffuse and marked axonal loss, and distortion found in the subcortical white matter. Clinical symptoms extended from stage III to frank dementia, with some cases displaying paranoia and impulsivity.

Within McKee and colleagues' [10] cohort with pathologically confirmed CTE, 11% were asymptomatic, with many of these cases in stage II at death. As they note, this finding raises the possibility that, in some affected persons, CTE may not produce symptoms, or that CTE may not progress. In addition, data from McKee [10] and Goldstein [11] suggested that CTE can occur after a single TBI of mild or greater severity. Taken together, these results heighten the imperative to conduct careful and thorough prospective, longitudinal investigations of TBI.

## 5. Conclusion

Based on our review of the military mTBI literature, several important themes emerge. First, a large body of evidence indicates that there are important differences between civilian and military TBI. Second, the important role of emotional distress after military mTBI must be incorporated into study designs and treatment approaches. Third, attempts should be made to determine the roles associated with dose and threshold effects for the blast mechanism of TBI. Fourth, analogs of combat PTSD could be identified and tested for the presence of postconcussive symptoms and whether they can be accounted for by PTSD. This type of study would inform the importance of the mTBI component. Fifth, the amalgam of symptoms emanating from OEF/OIF/Operation New Dawn (OND) military personnel and veterans may represent an injury/trauma syndrome. Sixth, objective and subjective measures should be integrated in very large samples through machine learning procedures. Based on the linkages among TBI, PTSD, and neurodegenerative conditions, identification of objective markers for receding, persisting, and emerging symptoms is critical. Treatment approaches should be based upon the results of these inquiries.

We have reported previously on the links among TBI, PTSD, Alzheimer's Disease, and other dementias [52]. This special issue updates the evidence that links military TBI to emerging symptoms.

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