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Military risk factors for Alzheimer's disease

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Abstract Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are signature injuries of the wars in Iraq and Afghanistan and have been linked to an increased risk of Alzheimer's disease (AD) and other dementias. A meeting hosted by the Alzheimer's Association and the Veterans' Health Research Institute (NCIRE) in May 2012 brought together experts from the U.S. military and academic medical centers around the world to discuss current evidence and hypotheses regarding the pathophysiological mechanisms linking TBI, PTSD, and AD. Studies underway in civilian and military populations were highlighted, along with new research initiatives such as a study to extend the Alzheimer's Disease Neuroimaging Initiative (ADNI) to a population of veterans exposed to TBI and PTSD. Greater collaboration and data sharing among diverse research groups is needed to advance an understanding and appropriate interventions in this continuum of military injuries and neurodegenerative disease in the aging veteran.

Keywords: Alzheimer's disease; Risk factors; Military medicine; Traumatic brain injury; Posttraumatic stress disorder; Tau; Beta-amyloid; Apolipoprotein E e4; Biomarkers; Alzheimer's Disease Neuroimaging Initiative; Vietnam; Veterans; Chronic traumatic encephalopathy; Blast injury

1. Introduction

Mounting evidence suggests that traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) resulting from military exposures increase the risk of developing neurodegenerative diseases such as Alzheimer's disease (AD). Therefore, understanding the mechanisms underlying this association has become a high priority, not only for the Department of Defense (DoD) and the Department of Veterans Affairs (VA), but for the Alzheimer's research community as well, which has recently intensified its focus on identifying individuals at high risk and preventing disease in its presymptomatic stages. Recognizing their shared priorities,

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stakeholders and researchers from these communities came together on May 8, 2012, at a meeting hosted by the Alzheimer's Association to strategize about research partnerships to move the field forward quickly. The meeting was co-sponsored by the Veterans' Health Research Institute (NCIRE).

This *Perspective* article summarizes information presented at this meeting, including population-level evidence that TBI and PTSD in early life (i.e. postnatally) increases the risk of developing AD later in life; current evidence and hypotheses regarding the pathophysiological mechanisms that may underlie and link TBI, PTSD, and AD; and research efforts that are needed or are underway to advance our understanding of these mechanisms. These research communities have not traditionally collaborated or considered related mechanisms and markers of disease.

2. Soldiers and civilians at risk for TBI, PTSD, and AD

Since the beginning of the Iraq War in March of 2003, more than 200,000 U.S. service members deployed to Iraq and Afghanistan as part of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) have been diagnosed with TBI [1]. The vast majority of these cases were classified as mild TBI (mTBI), also known as concussion [2]. In the same period of time, nearly 67,000 deployed U.S. military personnel, as well as more than 16,000 nondeployed U.S. military personnel, were newly diagnosed with PTSD [3]. Approximately 22% of Iraq and Afghanistan veterans entering the VA health care system between 2002 and 2008 were diagnosed with PTSD [4]. TBI and PTSD have been called "invisible wounds," yet they are also considered the "signature injuries" of these 21st century wars [5]. TBI and PTSD are distinct disorders with different causes, but they may occur together and share some symptoms such as deficits in attention and memory, irritability, and sleep disturbances.

Moreover, both of these conditions raise the risk of substantial and severe long-term sequelae, including dementia. A recent cohort study of more than 180,000 veterans from the VA's own National Patient Care Database found that those diagnosed with PTSD were more than twice as likely to develop dementia [6]. Also, a prospective study of World War II veterans found that moderate and severe, but not mild, head injury was associated with 2- to 4-fold increased risk of AD and other dementias in late life [7].

The association of TBI with dementia has also been documented in many studies involving nonveteran populations (reviewed in [8]). Dementia pugilistica was first recognized in professional boxers in 1928 [9]. This condition, now referred to as chronic traumatic encephalopathy (CTE), has now been identified not only in boxers, but also in American football and other contact sports as well [10], and it has been linked to subsequent development of dementia [11]. CTE is thought to result from repeated multiple head injuries or subclinical impact to the head [12]. CTE manifests initially with emotional and behavioral symptoms; cognitive changes, including memory loss and executive dysfunction, later become apparent. With increasing age, individuals with CTE often develop overt dementia, gait problems, parkinsonism, and speech abnormalities. Approximately 12% also develop an amylotrophic lateral sclerosis (ALS)-like condition called chronic traumatic encephalomyelopathy. The relationship of CTE to the development of AD pathology is unknown.

3. TBI

TBI is defined as an injury resulting from external force to the head, which results in an alteration or loss of consciousness. Most military or combat-related TBI occurs as a closed head injury as a result of exposure to an explosion (via primary blast wave, rotational brain injury, or brain contusion), motor vehicle accident, fall, or athletic activity. TBIs are classified as mild, moderate, or severe on the presence and duration of loss of consciousness (LOC), alteration of consciousness or mental state, and post-traumatic amnesia. The Glasgow Coma Scale (GCS) is the most common instrument used to assess the consequences of TBI. Other instruments include concussive scales such as the Cantu or Colorado scales.

The widespread use of improvised explosive devices (IEDs) in Iraq and Afghanistan has produced a high prevalence of TBI, reported to be as high as 23% of clinician-confirmed cases in one brigade combat team of nearly 4000 soldiers [13]. Although controversial, a unique TBI condition caused by a blast has been characterized by a different clinical pattern than TBI caused by other mechanisms [14–16], and the implications of these differences in terms of diagnosis, prognosis, and treatment are under investigation. The predominant neuropathological signs of TBI include diffuse axonal injury (DAI) and microhemorrhage [17]. Service members also frequently have a combination of injuries resulting from blast and nonblast (noncombat) events such as sports and motor vehicle accidents. Indeed, the vast majority (84%) of military TBIs occur in nondeployed settings from accidents, falls, sports, or training. Other factors that may influence the clinical and pathological presentation of TBI include the presence of polytrauma, PTSD, or other comorbidities as well as the frequency, severity, and cumulative effect of injuries. Genetic differences are also thought to play an important role.

To facilitate research on TBI across military, civilian, and veteran populations, a working group representing multiple federal agencies proposed a core set of outcome measures. This resulted in a set of common data elements (CDEs) that would enable comparison of findings across studies [18]. A 2-year multicenter study to test and refine these CDEs, the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, was funded by the National Institute of Neurological Disorders and Stroke (NINDS) in 2010. TRACK-TBI is also collecting data to support standardization of neuroimaging and genomics and proteomics tests for dementia. At the time of the meeting, TRACK-TBI had enrolled and collected imaging

or biospecimen data from more than 600 patients who presented to an emergency department within 24 hours of having a head injury. Most of these head injuries were mild; however, more than one quarter of individuals with mild TBI screened positive for PTSD, suggesting that the findings in this population may be applicable to military populations.

4. PTSD

In contrast to TBI, PTSD connotes a psychological condition in which an emotionally distressing event led to a constellation of symptoms. In patients with PTSD, there appear to be changes in synaptic connectivity associated with learning, such as fear conditioning, as well as alterations in central and peripheral hormones and regional atrophy of both gray and white matter. Veterans with PTSD have been shown to have reduced hippocampal volume that correlates with impaired memory, and functional imaging studies indicate that patients with PTSD have impaired brain function in the medial prefrontal cortex, amygdala, and hippocampus [19]. Brain atrophy in PTSD is also affected by PTSD severity [20,21]. However, chronic stress due to PTSD has also been shown to cause hypertrophy of the amygdala, an area of the brain that has evolved to deal with stressful, dangerous, and threatening situations. Thus, it may be that hippocampal atrophy represents an adaptive change in response to high stress rather than a form of brain damage.

Another possibility is that individuals with smaller hippocampi are at higher risk of developing PTSD. A study in Gulf War veterans [20] showed that current but not lifetime PTSD symptoms were associated with smaller hippocampal volume. This may mean that hippocampal size reverts to normal when PTSD symptoms abate or that individuals with small hippocampi fail to recover from PTSD. However, another study of identical twin pairs discordant for combat exposure in Vietnam found that hippocampal diminution was shared by the combat-unexposed twins of combat veterans with PTSD [22].

Studies also suggest that genetic factors and early life adversity may also influence the subsequent development of PTSD, possibly through neuroendocrine mechanisms involving glucocorticoid receptor responsiveness [23].

Given the different etiologies and symptoms, different diagnostic and treatment strategies are needed for subjects with PTSD compared with those with TBI; however, the overlap in symptoms causes problems with diagnosis. Moreover, any type of physical injury, including even mild TBI, increases the risk for PTSD [24–26], and PTSD can exacerbate cognitive and other symptoms of TBI [27]. However, PTSD can and usually does occur in the absence of TBI, and TBI is neither necessary nor sufficient for PTSD.

5. Identifying and managing TBI

Evaluating someone who has experienced head trauma to determine the extent of the injury is critical to limiting further brain damage. Rapid assessment is needed in the military theater and on the playing field to determine if it is safe for the soldier or athlete to return to his or her unit or team. Indeed, studies in high school and college football players suggest that there may be a period of increased vulnerability to repeat concussion for 7–10 days after a concussion [28]. In the military theater, screening is complicated because TBI occurs in the context of sleep deprivation, nutritional changes, emotional stress, polytrauma, and difficult environmental factors. In addition, service members may hide symptoms so they can return to action quickly. However, imaging studies show that there may be substantial brain injury even in the absence of self-reported symptoms [29].

In 2007, the DoD adopted a common diagnostic criterion set for TBI reporting to include any period of loss or a decreased level of consciousness, loss of memory for events immediately before or after the injury, or alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.) [30]. The Military Acute Concussion Evaluation (MACE) was developed in 2006 by the Defense and Veterans Brain Injury Center (DVBIC) to assess in-theater combat-related TBI [31]. The MACE is used in conjunction with clinical algorithms, both of which were further modified in 2012 to incorporate standards for in-theater concussion care centers. These standards were based on recommendations from the Gray Team, a multiservice team formed by the Chairman of the Joint Chiefs of Staff.

Despite these efforts to improve the identification of TBI in theater, studies suggest that many cases of mild TBI are missed [24]. This indicates the need to come up with better early detection procedures in theater that rely on objective measures and mandatory reporting. New operational rules that are more event driven than symptom driven represent a paradigm change for the military. These rules require a 24-hour rest period after an incident, with prolonged rest in cases of multiple concussions over 12 months. Specific recommendations are provided for issues such as sleep problems and headache. Injured personnel must refrain from sports or other activities that increase the risk of concussion until medically cleared. MACE documentation is required after the event and as part of the return-to-duty evaluation. If symptoms do not improve, service members are moved to a concussion center. Medical screening is also required for all persons in any damaged vehicle, anyone within 50 m of blast, or anyone who receives a direct blow to the head.

6. Links between TBI, PTSD, and AD: Mechanisms, biomarkers, and neuroimaging

There are several possible mechanisms that could link PTSD and TBI with late-life dementia. Identification of common underlying biological mechanisms is essential to an improved understanding of military risk factors for the development AD and for the design of effective prevention and treatment strategies.

Brain injury may cause earlier onset or acceleration of Alzheimer's pathology [32]. For many years, β-amyloid

(Aβ) has been considered the dominant driver of AD. Scientists have also been investigating other molecular and cellular pathways and processes that contribute to AD pathogenesis. Abnormal phosphorylation of tau, which forms the neurofibrillary tangles characteristic of the AD brain, has been implicated as a mechanism of AD pathology for decades [33]. In the early stages of CTE, massive deposition of phophorylated tau (phospho-tau) is seen, particularly in the frontal cortex [11], and this tauopathy is distinct from that seen in AD. The connection between phospho-tau deposition in CTE and AD pathology is unknown. One possibility is that the tauopathy induced by brain injury may predispose an individual to later development of AD. Further, in neuropathological studies of blast-exposed veterans, changes were seen that were similar to those in young athletes with CTE [34].

A well-established risk factor for development of AD is the presence of an apolipoprotein E ε4 (*APOE* ε4) allele [35], which encodes for a protein gene product that regulates Aβ metabolism. The presence of the *APOE* ε4 allele is also associated with increased risk of poor outcome after TBI [36], suggesting a link between *APOE* ε4 and aberrant Aβ metabolism in the wake of head trauma. However, it is interesting to note that it is the *APOE* ε2 rather than the *APOE* ε4 allele that appears to be associated with impaired memory and worsening PTSD symptoms in combat-exposed veterans [37].

Another possible mechanism involves an association of PTSD and TBI with reduced cognitive reserve (CR). The concept of CR posits that intelligence, education, or other life experiences are in some way protective against neurodegeneration [38]. CR may influence the likelihood of developing PTSD [39], and in a study of children and adolescents with mild TBI, the occurrence of postconcussive symptoms was shown to be linked to CR [40]. It is possible that TBI earlier in life damages neurons, reduces connections between neurons, or otherwise diminishes the brain's capacity to function. Thus, later in life when Alzheimer's pathology may develop, an individual who had experienced TBI may develop symptoms at an earlier stage of pathology than someone who had not been exposed to TBI. Thus, TBI could be a risk factor for AD by both mechanisms: acceleration of Alzheimer's pathology and reduction of CR.

Biomarkers should be helpful in clarifying these mechanisms, in identifying endophenotypes of disease, and in assessing soldiers after a blast exposure to determine if intervention or removal from theater is needed. Using boxing as a human model of TBI, Zetterberg and colleagues studied biomarker changes in the cerebrospinal fluid (CSF) of amateur boxers [41] and later in Olympic boxers [42]. They showed that two markers of neuronal and axonal injury—neurofilament light (NFL) protein and total tau—as well as the astroglial injury marker glial fibrillary acidic protein (GFAP) were increased in boxers after bouts in which they had received many hits, but that only NFL and GFAP remained elevated after a period of rest, suggesting that boxing is clearly associated with profound signs of subcortical axonal injury. Tau, the protein most often linked to neuronal damage in AD, did not remain elevated in these subjects, suggesting a different pathological mechanism in CTE compared with AD. The finding of increased NFL protein would be consistent with reduction of CR. The same team of investigators also assessed CSF biomarkers in army officers who had been exposed to blast overpressure from repeated explosions of firing heavy weapons and found no evidence of brain damage [43].

Neuroimaging of military personnel who have experienced TBI has also provided important clues about the mechanisms of injury and the possible relation to subsequent development of dementia, although many questions still remain. Diffusion tensor imaging (DTI) is particularly useful in identifying DAI, and studies using DTI support the hypothesis that blast-related TBIs may involve axonal injury [44].

7. ADNI and DoD-ADNI

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an ongoing, longitudinal, multicenter study supported by the National Institutes of Health (NIH) and private industry sponsors. Launched in 2003, ADNI is a public-private partnership among federal agencies (NIH, U.S. Food and Drug Administration), pharmaceutical companies, and nonprofit philanthropic organizations, including the Alzheimer's Association. The primary goal of ADNI is to develop, validate, and standardize the use of neuroimaging as an AD biomarker for use in clinical trials. Data generated by ADNI is made available on a public database (UCLA/LONI/ADNI). This database includes clinical data and the imaging data archive from where investigators may upload MRI and PET scans. The ADNI/LONI database is available to all qualified scientists and has supported the publication of more than 300 papers [45].

The first phase of ADNI, now known as ADNI-1, was completed in October 2010. More than 800 participants were enrolled at 57 sites in the United States and Canada. Data were collected from clinical exams, cognitive tests, structural magnetic resonance imaging (MRI), and blood tests. In addition, approximately half of the subjects also had fluorodeoxyglucose (FDG) positron emission tomography (PET) scans and lumbar punctures (LP) for CSF biomarker testing. As a result of add-on funding from the Alzheimer's Association and General Electric, approximately 100 participants had amyloid imaging PET scans with Pittsburgh compound B (PiB). ADNI-1 enrolled three groups of subjects: those with MCI, those with mild AD, and a control group who were cognitively normal. Subsequently, a Grand Opportunities (GO) grant and a continuation grant (ADNI-2) enabled the enrollment of an additional cohort of early MCI (eMCI) participants because it had become clear that the MCI population enrolled in the original ADNI cohort were too far advanced to capture changes that reflect the early stages of AD. In addition to exploring a broader range of severity, ADNI-2 is using an expanded set of imaging tools, including DTI, arterial spin labeling (ASL)

perfusion imaging, resting blood oxygen-level dependent (BOLD) MRI, and analysis of hippocampal subfields.

The major accomplishment of ADNI thus far has been to show that brain atrophy, especially in the hippocampus, is the most sensitive and robust measure of change that can be detected in AD and that it correlates with neuropsychological and functional changes. Another major finding from ADNI has been to show that amyloid deposition as measured by PET imaging predicts a high rate of conversion to MCI and AD [46]. CSF amyloid correlates with amyloid imaging, and acquisition of CSF allows the measurement of other biomarkers. A hypothetical model of biomarker changes as AD progresses was proposed in 2010 [47]. This model predicts lower CSF levels of β-amyloid 42 (Aβ42) as an early sign of AD, followed by elevation of tau and phospho-tau, which signal neuronal injury, and these biomarker changes have been linked to cognitive changes in healthy older adults [48]. Recent ADNI data show that approximately 20% of patients with clinically diagnosed AD appear not to have high levels of brain amyloid detected by amyloid PET imaging. Furthermore, using amyloid PET imaging, approximately 60% of subjects with MCI are positive (indicating MCI due to AD) and 30% of normal subjects in their middle 70s are positive (suggesting preclinical AD). ADNI has been a model for widespread sharing of scientific data without embargo. The World Wide ADNI project (sponsored by the Alzheimer's Association) links U.S. ADNI to similar projects in Australia, Japan, Europe, China, Taiwan, Argentina, Brazil, and Korea [49].

The Vietnam Veterans ADNI Project (DoD-ADNI) is the newest addition to ADNI. This project, funded by DoD, will enroll 210 Vietnam war veterans between the ages of 60 and 80 to examine the effects of TBI and PTSD on AD using imaging and biomarkers.

The primary hypothesis to be tested in DoD-ADNI is that veterans with combat-associated TBI and/or PTSD have increased risk for AD compared with veteran controls as measured by (1) increased florbetapir uptake on amyloid PET scans; (2) decreased CSF Aβ; (3) increased CSF tau and phospho-tau; (4) increased atrophy in several regions in the brain; and (5) reduced cognitive function, particularly delayed recall. The study will also examine the role of brain reserve and *APOE* genotype as well as the correlation between severity of TBI and severity of PTSD or cognitive impairment. The ultimate goal, as in the broader ADNI study, is to enable clinical trials and provide data to other investigators studying AD and TBI.

Subjects in DoD-ADNI will undergo a battery of imaging tests, structural (T1-weighted, T2-weighted, fluid attenuated inversion recovery [FLAIR] MRI, and DTI) and functional (ASL, functional MRI [fMRI], FDG-PET), as well as amyloid imaging with florbetapir. One of the advantages of DoD ADNI is that baseline data are available because of the armed forces qualifying exam and other examinations given at the time of induction. These assessments will enable investigators to determine how many of the veterans fulfill biomarker and imaging criteria for AD or other dementias, such as frontotemporal dementia (FTD) or vascular dementia, and whether dementia-related biomarker or imaging patterns correlate with a history of CTE or PTSD.

The VA has launched two other efforts aimed at improving outcomes for veterans with TBI and PTSD through its three War-Related Illness and Injury Centers (WRIISCs). The Markers for the Identification, Norming, & Differentiation of TBI and PTSD (MIND) study is designed to evaluate the prevalence of TBI and PTSD in OEF/OIF veterans and the effectiveness of screening instruments as well as to identify sensitive and specific objective markers for TBI and PTSD and develop prediction models. The MIND study includes multiple assessments: neuroimaging (DTI, PET, and fMRI); endocrine, neurologic, sensorimotor, and immunologic function; and angiogenic, genomic, and cognitive metrics. A second study, the Blast Injury Outcomes (BIO) study, aims to characterize mild and moderate TBI and PTSD resulting from blast injuries and to examine the relationship between these disorders using multiple measures, eventually leading to a diagnostic prediction algorithm. A convenience sample will be enrolled from multiple sites, including VA medical centers, college campuses, and community-based outpatient clinics. Subjects will be evaluated using neuroimaging; a full cognitive battery; and neurobehavioral, psychosocial, and physiologic measures. The VA and DoD recently released two Requests for Applications for grants concerning TBI and PTSD. Millions of dollars will be awarded to the successful applicants.

8. Moving forward

DoD-ADNI provides a unique opportunity to plot the development of biomarkers and correlate them with different types of head injury and PTSD; however, this is only a first step toward fully understanding the relationship of PTSD and TBI to AD. Realization of this goal will require a larger study to collect more subjects, including those with MCI and longitudinal measurements beyond 2 years. Additional studies should be funded to enroll younger subjects to capture early signs of pathology and map the progression to AD. There was broad agreement among participants at the Military Risk Factors for Alzheimer's Disease meeting that coordinated research and data sharing are required to discover relationships among AD, TBI, PTSD, and other military risk factors and to develop effective prevention and treatment strategies.

Additional priorities identified include

- Discovery and validation of additional biomarkers, including markers of inflammation and synaptic dysfunction, as well as other markers that may better predict neurodegeneration after TBI and PTSD.
- Determination of thresholds for exposure to injury in terms of number, timing, and the cumulative effects of exposure as well for TBI and PTSD.
- Development of a validated measure to capture TBI exposure since the point of first injury.

- Continued research on and development of TBI models for basic research.
- Development of standardized assays for biomarkers that will support longitudinal assessments for individuals with injuries. This includes new tests for alterations in olfactory memory and changes in cognition. Development of new radioligands for neuroimaging is also essential.
- Integration of results from standardized assays with electronic medical records or other databases.
- An improved understanding of the frequency of comorbidity of CTE with DAI and/or microhemorrhage.
- Development of tau ligands for imaging tau deposition in the intact brain.
- Support of longitudinal, well-defined studies that focus on the "highest risk" individuals for neurodegenerative disease.
- Creation and dissemination of a study inventory. The inventory would contain new initiatives and those currently funded. This would promote collaboration, avoid unnecessary duplication of efforts, and identify cohorts for longer term evaluation for late-stage disease.

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References

[1] DoD worldwide numbers for TBI. Accessed September 9, 2012 at: http://www.dvbic.org/dod-worldwide-numbers-tbi.
[2] Barth J, Isler W, Helmick K, Wingler I, Jaffee M. Acute battlefield assessment of concussion/mild TBI and return to duty evaluations. In: Kennedy C, Moore J, eds. Military neuropsychology. New York: Springer; 2010. p. 127–74.
[3] Fischer H. U.S. military casualty statistics: Operation New Dawn, Operation Iraqi Freedom, and Operation Enduring Freedom. Washington, DC: Congressional Research Service; 2010.
[4] Seal KH, Metzler TJ, Gima KS, Bertenthal D, Maguen S, Marmar CR. Trends and risk factors for mental health diagnoses among Iraq and Afghanistan veterans using Department of Veterans Affairs health care, 2002-2008. Am J Public Health 2009;99:1651–8.
[5] Invisible wounds: serving service members and veterans with PTSD and TBI Washington, DC: National Council of Disability; 2009.
[6] Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, et al. Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry 2010;67:608–13.
[7] Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000; 55:1158–66.
[8] Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: What is the pathology? Arch Neurol 2012;69:1–7.
[9] Martland H. Dementia pugilistica. JAMA 1928;911:103–7.
[10] McKee AC, Stein TD, Nowinski CJ, Stern RA, Daneshvar DH, Alvarez VE, et al. The Spectrum of Disease in Chronic Traumatic Encephalopathy. Brain 2013;136:43–64.
[11] McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol 2009;68:709–35.
[12] Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. Clin Sports Med 2011;30:179–88. xi.
[13] Terrio H, Brenner LA, Ivins BJ, Cho JM, Helmick K, Schwab K, et al. Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. J Head Trauma Rehabil 2009;24:14–23.
[14] Armonda RA, Bell RS, Vo AH, Ling G, DeGraba TJ, Crandall B, et al. Wartime traumatic cerebral vasospasm: recent review of combat casualties. Neurosurgery 2006;59:1215–25. discussion 1225.
[15] Bell RS, Vo AH, Neal CJ, Tigno J, Roberts R, Mossop C, et al. Military traumatic brain and spinal column injury: a 5-year study of the impact blast and other military grade weaponry on the central nervous system. J Trauma 2009;66:S104–11.
[16] Maas AI, Menon DK. Traumatic brain injury: rethinking ideas and approaches. Lancet Neurol 2012;11:12–3.
[17] Kumar R, Husain M, Gupta RK, Hasan KM, Haris M, Agarwal AK, et al. Serial changes in the white matter diffusion tensor imaging metrics in moderate traumatic brain injury and correlation with neurocognitive function. J Neurotrauma 2009;26:481–95.
[18] Thurmond VA, Hicks R, Gleason T, Miller AC, Szuflita N, Orman J, et al. Advancing integrated research in psychological health and traumatic brain injury: common data elements. Arch Phys Med Rehabil 2010;91:1633–6.
[19] Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. Neuroimaging Clin N Am 2007;17:523–38. ix.
[20] Apfel BA, Ross J, Hlavin J, Meyerhoff DJ, Metzler TJ, Marmar CR, et al. Hippocampal volume differences in Gulf War veterans with current versus lifetime posttraumatic stress disorder symptoms. Biol Psychiatry 2011;69:541–8.
[21] Cardenas VA, Samuelson K, Lenoci M, Studholme C, Neylan TC, Marmar CR, et al. Changes in brain anatomy during the course of posttraumatic stress disorder. Psychiatry Res 2011;193:93–100.
[22] Gilbertson MW, McFarlane AC, Weathers FW, Keane TM, Yehuda R, Shalev AY, et al. Is trauma a causal agent of psychopathologic symptoms in posttraumatic stress disorder? Findings from identical twins discordant for combat exposure. J Clin Psychiatry 2010;71:1324–30.
[23] Yehuda R, Flory JD, Pratchett LC, Buxbaum J, Ising M, Holsboer F. Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. Psychopharmacology (Berl) 2010;212:405–17.
[24] Elder GA, Cristian A. Blast-related mild traumatic brain injury: mechanisms of injury and impact on clinical care. Mt Sinai J Med 2009; 76:111–8.
[25] Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med 2004;351:13–22.
[26] Kennedy JE, Leal FO, Lewis JD, Cullen MA, Amador RR. Posttraumatic stress symptoms in OIF/OEF service members with blast-related and non-blast-related mild TBI. NeuroRehabilitation 2010;26:223–31.
[27] Bryant RA, Harvey AG. Postconcussive symptoms and posttraumatic stress disorder after mild traumatic brain injury. J Nerv Ment Dis 1999; 187:302–5.
[28] McCrea M, Guskiewicz K, Randolph C, Barr WB, Hammeke TA, Marshall SW, et al. Effects of a symptom-free waiting period on clinical outcome and risk of reinjury after sport-related concussion. Neurosurgery 2009;65:876–82.
[29] Bergsneider M, Hovda DA, Lee SM, Kelly DF, McArthur DL, Vespa PM, et al. Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following human traumatic brain injury. J Neurotrauma 2000;17:389–401.
[30] Consolidation of traumatic brain injury initiatives in the Department of Defense. Health Affairs Memorandum dated March 23, 2007. Department of Defense: Washington, DC, 2007.

[31] French L, McCrea M, Baggett M. The Military Acute Concussion Evaluation (MACE). J Special Operations Med 2008;8:68–77.
[32] Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. Brain Pathol 2012;22:142–9.
[33] Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci U S A 1986;83:4913–7.
[34] Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med 2012;4:134ra60.
[35] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.
[36] Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of *APOE*4 allele and outcome after traumatic brain injury. J Neurotrauma 2008;25:279–90.
[37] Freeman T, Roca V, Guggenheim F, Kimbrell T, Griffin WS. Neuropsychiatric associations of apolipoprotein E alleles in subjects with combat-related posttraumatic stress disorder. J Neuropsychiatry Clin Neurosci 2005;17:541–3.
[38] Scarmeas N, Stern Y. Cognitive reserve and lifestyle. J Clin Exp Neuropsychol 2003;25:625–33.
[39] Kremen WS, Koenen KC, Boake C, Purcell S, Eisen SA, Franz CE, et al. Pretrauma cognitive ability and risk for posttraumatic stress disorder: a twin study. Arch Gen Psychiatry 2007;64:361–8.
[40] Fay TB, Yeates KO, Taylor HG, Bangert B, Dietrich A, Nuss KE, et al. Cognitive reserve as a moderator of postconcussive symptoms in children with complicated and uncomplicated mild traumatic brain injury. J Int Neuropsychol Soc 2010;16:94–105.
[41] Zetterberg H, Hietala MA, Jonsson M, Andreasen N, Styrud E, Karlsson I, et al. Neurochemical aftermath of amateur boxing. Arch Neurol 2006;63:1277–80.
[42] Neselius S, Brisby H, Theodorsson A, Blennow K, Zetterberg H, Marcusson J. CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. PLoS One 2012;7:e33606.
[43] Blennow K, Jonsson M, Andreasen N, Rosengren L, Wallin A, Hellstrom PA, et al. No neurochemical evidence of brain injury after blast overpressure by repeated explosions or firing heavy weapons. Acta Neurol Scand 2011;123:245–51.
[44] Mac Donald CL, Johnson AM, Cooper D, Nelson EC, Werner NJ, Shimony JS, et al. Detection of blast-related traumatic brain injury in U.S. military personnel. N Engl J Med 2011;364:2091–100.
[45] Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement 2012;8:S1–68.
[46] Rowe CC, Villemagne VL. Brain amyloid imaging. J Nucl Med 2011;52:1733–40.
[47] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.
[48] Stomrud E, Hansson O, Zetterberg H, Blennow K, Minthon L, Londos E. Correlation of longitudinal cerebrospinal fluid biomarkers with cognitive decline in healthy older adults. Arch Neurol 2010;67:217–23.
[49] Carrillo MC, Bain LJ, Frisoni GB, Weiner MW. Worldwide Alzheimer's disease neuroimaging initiative. Alzheimers Dement 2012;8:337–42.