11 April 2016

DEFENSE AND VETERANS BRAIN INJURY CENTER
RESEARCH REVIEW
ON
MILD TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC STRESS DISORDER

PURPOSE

The purpose of this research review is to provide an overview of the topic of comorbid mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD). This review will focus on symptoms, diagnosis, and treatment of PTSD and mTBI symptoms in patients with mTBI history. While it can be difficult to differentiate symptoms of mTBI from PTSD symptoms, especially months or years after the injury event, this review aims to present information relevant to understanding these often complex cases.

AUDIENCE

This research review is intended for healthcare providers, researchers, and administrators who are interested in the current literature on mTBI and PTSD.

OVERVIEW

While most individuals with mTBI history do not have a comorbid PTSD diagnosis, those who do have such a diagnosis present unique challenges. Symptoms of mTBI and PTSD can be similar, and are often more severe in patients with comorbid PTSD and mTBI history than in patients with only one condition. One third or more of personnel deployed in Operation Enduring Freedom or Operation Iraqi Freedom (OEF/OIF) reporting mTBI history also self-report PTSD symptom levels consistent with probable PTSD. Some patients in this group experience persistent symptoms and demonstrate reduced neuropsychological test performance, even months or years after injury. Tools for differential diagnosis and determining symptom etiology in the clinical setting are lacking. Neuroimaging approaches offer promise for researchers. There is no evidence that standard PTSD treatments are less effective in patients with mTBI history. Treatments for individuals with PTSD and mTBI history should be directed at specific symptoms regardless of etiology. (Department of Defense & Department of Veterans Affairs, 2009)

DEFINITION AND SYMPTOMS OF MTBI

In the U.S., an estimated 2.5 million TBI-related emergency department visits occur annually. (Centers for Disease Control and Prevention, 2014) In the last 15 years (January 2000 to December 2014) over 300,000 service members were diagnosed as having had a TBI; 82.5% of those with mTBI. (Defense and Veterans Brain Injury Center (DVBIC), February 2015) Approximately 20% of individuals deployed in OEF/OIF report at least one deployment-related TBI. (Tanielian et al., 2008; Terrio et al., 2009)

Mild TBI is defined as a brain injury leading to loss of consciousness (LOC) of less than 30 minutes, or a confused or disoriented state persisting for less than 24 hrs, or post-traumatic amnesia for less than 24 hrs, and normal results on structural computed tomography (CT) scans. (Department of Defense & Department of Veterans Affairs, 2009) The acute phase of mTBI recovery is defined as the initial seven days after injury, and the chronic phase of recovery is

defined as 90 days or more after injury. (Department of Defense & Department of Veterans Affairs, 2009) Symptoms typically resolve without treatment within the first two to four weeks, although a minority of patients experience symptoms for a longer period of time. (Department of Defense & Department of Veterans Affairs, 2009) These symptoms can include: headache, sensitivity to light and sound, malaise, fatigue, irritability, depressed feelings, anxiety, emotional lability, memory and cognitive impairment, dizziness, and sleep disturbances. (Stein & McAllister, 2009; Vanderploeg et al., 2007) Although these symptoms are not unique to mTBI, they are often discussed in the literature as post-concussive symptoms.

Mild TBI is commonly comorbid with other conditions. A records review by Lew et al. of 340 TBI survivors seen at a Department of Veterans Affairs (VA) polytrauma center showed that high proportions experienced chronic pain (81.5%), PTSD (68.2%), and post-concussive symptoms (66.8%), with 42.1% of the sample experiencing all three conditions. (Lew et al., 2009) In a series of interviews by Sayer et al., VA clinicians cited sleep problems, pain, substance use disorders, and depression as clinical problems that add complexity to PTSD cases with mTBI history. (Sayer et al., 2009) This research review will focus on mTBI comorbid with PTSD.

DEFINITION AND SYMPTOMS OF PTSD

According to the Institute of Medicine, 13.5% of U.S. Army, 10% of Marines, 4.5% of Navy, and 4% of Air Force service members had PTSD in 2012. Furthermore, over half a million veterans of all conflicts (9.2% of 2012 total VA users) sought VA health services care for PTSD in 2012. (Institute of Medicine of the National Academies, 2014)

PTSD is a psychological condition resulting from exposure to a traumatic event (involving actual or threatened death, serious injury, or sexual violation) characterized by re-experiencing, avoidance, arousal changes, and negative alterations in cognitions and mood, experienced more than one month, and resulting in significant distress or impairment in important area(s) of function. (American Psychiatric Association, 2013b) In 2013, the American Psychiatric Association released the Diagnostics and Statistics Manual, 5th edition (DSM-V). It categorizes PTSD as a disorder related to trauma and stressors, rather than a disorder in the anxiety group, as it was categorized in the 4th edition (DSM-IV). (American Psychiatric Association, 1994) There were several other changes to the diagnostic criteria. The relationship of the patient to the event has been broadened to include repeated exposure or being personally close to a victim of an event. The phrase “physical integrity” was made more specific with the change to “sexual violation” in the DSM-V. The prior requirement that the event evoke “fear, helplessness, or horror” in the patient was removed in the new edition. For the DSM-V, the symptoms were re-categorized into four groups instead of three: one, re-experiencing or intrusion; two, avoidance; three, arousal; and four, negative alterations in cognitions and mood. PTSD symptoms can include nightmares, flashbacks, distress or arousal at reminders of the trauma, avoidance of conversations about the trauma, avoidance of people or places associated with the trauma, incomplete memory of the trauma, diminished interest in activities, social detachment, emotional numbing, sleep disturbances, irritability, difficulty concentrating, hypervigilance, reckless behavior, or exaggerated startle response. (American Psychiatric Association, 2013b; Department of Defense & Department of Veterans Affairs, 2010) Symptoms occurring earlier than one month post-trauma are referred to as acute stress disorder . (American

Psychiatric Association, 1994) The DSM-V recognizes PTSD with delayed expression, in which full diagnosis criteria are not met until six months or more post-trauma. (American Psychiatric Association, 2013a)

PREVALENCE OF COMORBID MTBI AND PTSD

Experiencing a traumatic event that causes TBI may also initiate a constellation of symptoms which secondarily lead to PTSD. However, PTSD can predate injury, arise concurrently or after onset of post-concussive symptoms, or relate to a separate event or series of events. Most literature on comorbid PTSD with military-related mTBI history does not address preexisting trauma or premorbid PTSD symptoms. One prospective, longitudinal study showed that pre-deployment PTSD symptoms were positively correlated with the similar symptoms post-deployment regardless of TBI status. (Yurgil et al., 2014)

Depending on the population under study, the prevalence of comorbid PTSD and TBI can vary greatly. (Carlson et al., 2011) Among military and veteran populations, most studies report the prevalence of PTSD as 10-40% of study participants with probable or diagnosed history of TBI. (Carlson et al., 2011) Three large military and veteran studies of OEF/OIF deployed personnel report probable PTSD in 33-39% of respondents who endorsed having experienced a probable mTBI. (Hoge et al., 2008; Schneiderman et al., 2008; Tanielian et al., 2008) A 2015 systematic review found the range of PTSD prevalence without regard to TBI status in persons (including US and non-US persons) deployed to Iraq and Afghanistan as 0% to 48% in non-treatment-seeking samples, and 2% to 68% in treatment-seeking samples. (Ramchand et al., 2015) In a large retrospective study of Army Special Operations personnel, Kontos et al. found that 28% of those with a diagnosis of mTBI reported clinical levels of PTSD symptoms. (Kontos et al., 2013) In a smaller study of veterans, 35% of those with mTBI diagnosis were also diagnosed with PTSD. (Hill et al., 2009) A recent cross-sectional study of 107 service members or veterans with blast-exposure (97 with at least one mTBI) within 2 years found that PTSD occurred most often with an additional mood or anxiety diagnosis. Only two of the 29 individuals with PTSD had no additional mood or anxiety diagnoses. (Walker et al., 2015)

Risk factors for PTSD after mTBI

Veterans and deployed National Guard and service members with probable mTBI are two to three times more likely to demonstrate clinical levels of PTSD symptoms than those with no brain injury. (Schneiderman et al., 2008; Vanderploeg et al., 2012) Similarly, an increase in PTSD risk associated with history of mTBI has been observed in active duty service members and civilians. The magnitude of increased risk among active duty service members varies from 1.5-fold to 2.7-fold. (Bryant et al., 2010; Miller et al., 2015; Stein et al., 2015; Yurgil et al., 2014) Acute stress symptoms, subsequent PTSD diagnosis and symptoms, and persistent post-concussive symptoms are more common among those reporting mTBI with LOC as compared to those with mTBI without LOC. (Eskridge et al., 2013; Hoge et al., 2008; Norris et al., 2014)

Risk factors for PTSD after trauma have been determined empirically, and fall into three categories: preexisting, trauma-related, and posttraumatic. Preexisting risk factors include low IQ, prior trauma exposure (especially childhood abuse or adversity (Brewin et al., 2000)), and prior psychological disorder. Trauma-related risk factors include perceived fear of death and physical injury. Posttraumatic factors that increase risk of PTSD include low social support, pain

severity, and peritraumatic dissociation (reduced awareness or altered perceptions during and immediately after the trauma). (Ozer et al., 2003; Sareen, 2014)

A recent systematic review of studies on mental health after deployment to Iraq or Afghanistan found several characteristics were associated with increased risk of PTSD, regardless of TBI status. Those include demographic characteristics, military characteristics, deployment-related factors, pre-deployment factors, and post-deployment factors. (Ramchand et al., 2015) Demographic characteristics associated with an increased risk of PTSD were: age under 40 (for males only), lower education, and unmarried status. In civilian studies, women are at increased risk of PTSD (Brewin et al., 2000), but data regarding gender were inconsistent in this systematic review. Military characteristics associated with an increased risk of PTSD were: serving in the US Army or Marines (as compared to serving in other US services); enlisted rank; and health-care occupations, combat specialists, and service and supply personnel (as compared to other occupational specialties). Deployment-related characteristics associated with an increased risk of PTSD were a higher number of deployments and any injury sustained in combat. Pre-deployment factors associated with a higher risk of PTSD diagnosis were: life stress, childhood adversity or vulnerability, poorer perceptions of preparedness, and pre-deployment PTSD symptoms. PTSD was also associated with poor post-deployment social support and post-deployment life stressors.

EFFECT OF MILD TBI ON PTSD SYMPTOMS

A number of studies have shown that PTSD symptoms are more severe in military and veteran groups with probable or diagnosed mTBI than those with no TBI. A study by Spira et al. of 646 active duty Marines found that PTSD symptoms and other emotional symptoms were worse in those reporting mTBI history as compared to those without mTBI history, and were also more severe in those with recent mTBI and multiple mTBIs as compared to those with a distant past TBI event or a single mTBI, respectively. (Spira et al., 2014) In a sample of 251 OEF/OIF veterans, those diagnosed with PTSD and reporting an event meeting criteria for mTBI had more severe depression, anxiety, and PTSD symptoms than those in the PTSD-only group or the mTBI history only group. Combs et al. (2015) A small, recent study by Mac Donald et al. including 38 service members with blast-related concussion assessed 6 to12 months after injury showed that PTSD symptoms were more severe in the TBI group compared to the uninjured control group. (Mac Donald et al., 2015) One small study of veterans diagnosed with PTSD (including those with and without an mTBI diagnosis) did not find a significant difference in PTSD symptom severity between the two groups. However, the group with mTBI history expressed a decreased ability to cope with PTSD symptoms and increased problems with pain as compared to the no TBI group. (Romesser et al., 2011) In a study by Vanderploeg et al. including Vietnam-era veterans with PTSD history, those with mTBI history were more likely to have delayed resolution or no resolution of PTSD symptoms as compared to those without TBI history. (Vanderploeg et al., 2009) These data demonstrate that mTBI can complicate recovery from PTSD.

EFFECT OF PTSD ON POST-CONCUSSION SYMPTOMS

Post-concussive symptoms are more prevalent in OEF/OIF veterans who report mTBI history and screen positive for PTSD than for those reporting mTBI alone. (Brenner et al., 2010a; Schneiderman et al., 2008) Among VA medical care patients screening positive for mTBI,

cognitive and affective symptoms also appear to be more severe for those who screen positive for PTSD or depression. (Cernich et al., 2012)

Several studies have shown that PTSD is predictive of post-concussive symptoms, and in these studies psychological factors were more predictive of post-concussive symptoms than TBI status or injury characteristics during the chronic phase of injury. A highly cited 2008 study by Hoge et al. of 2525 soldiers found that post-concussive symptoms were not associated with mTBI after adjustment for PTSD and depression. (Hoge et al., 2008) A longitudinal study by Polusny et al. of 953 National Guard members showed that PTSD symptom reports in theater were more potent predictors of post-concussive symptoms at one year follow-up than mTBI reports in theater. (Polusny et al., 2011) In a study of 91 OEF/OIF veterans with blast exposure, who fell into three groups (no TBI, mTBI with LOC, and mTBI without LOC), post-concussive symptom reports were associated with depression and PTSD symptom severity. When the data were adjusted based on these associations, differences in post-concussive symptoms between TBI status groups disappeared. (Verfaellie et al., 2013) A retrospective study of records of 164 mTBI patients at a VA polytrauma/ TBI clinic found that anxiety, depression, and PTSD symptoms were predictive of post-concussive symptoms as measured by the Neurobehavioral Symptom Inventory, but LOC was not. (Waldron-Perrine et al., 2014) A recent study by Dretsch et al. including 458 active-duty soldiers with or without past concussions showed that PTSD symptom scores were partial mediators of post-concussive symptoms as measured by the Neurobehavioral Symptom Inventory (NSI). (Dretsch et al., 2015) Among civilians, post-concussive symptoms were predicted by TBI status in a case-control study at 1 week post-injury, but not 3 months post injury. Instead, at 3 months post injury post-concussive symptoms were predicted by stress, pain, and PTSD and anxiety symptoms. (Ponsford et al., 2012) Taken together, these data suggest that in the chronic phase of mTBI, post-concussive symptoms are more often associated with psychological conditions and symptoms than TBI status or TBI injury characteristics. In the acute phase of injury, one study of service members showed that acute stress reaction may partially mediate post-concussive symptoms. (Norris et al., 2014)

UNCLEAR SYMPTOM ETIOLOGY

Post-concussive symptoms also occur at a high base rate in uninjured civilians, (Wang et al., 2006) and can arise from multiple etiologies. (Vanderploeg et al., 2012; Waldron-Perrine et al., 2014) Indeed, post-concussive symptoms have been associated with psychological conditions independent of TBI among active duty, veteran, deployed Guard, and civilian populations. (Dretsch et al., 2015; Hoge et al., 2008; Iverson & Lange, 2003; Soble et al., 2014; Waldron-Perrine et al., 2014) Post-concussive symptoms are also associated with non-TBI injuries among veterans. (Vanderploeg et al., 2012) To attempt to differentiate symptom patterns between PTSD and mTBI, one study of 1,549 veterans used factor analysis of screen-based symptoms. Dizziness, headaches, memory problems, and photophobia were unique to TBI. Nightmares and avoidance were unique to PTSD. Irritability was shared between PTSD and TBI. (Maguen et al., 2012) However, these assignments of particular symptoms to mTBI or PTSD are not robust between studies. For example, the 2011 study by Polusny et al. of 937 deployed Guard showed dizziness, headaches, memory problems present at a higher rate in the PTSD-only group (no reported mTBI history) than in the mTBI-only group (screened negative for PTSD). (Polusny et al., 2011) In the PTSD-only group, those symptoms may have been caused by blast exposures and vestibular damage that did not meet criteria for mTBI.

There is much discussion in the literature regarding whether persistent symptoms occurring in persons with PTSD and mTBI history are psychogenic or physiogenic. However, the division between the physical and psychological may be more flexible than expected. Functional magnetic resonance imaging (fMRI) data discussed below shows that PTSD symptom changes can be visualized and localized to specific brain anatomy features. (Roy et al., 2010) Some authors argue the discussion of the origin of persistent post-concussive symptoms is unproductive because terms of the debate are framed by the capability of current neuroimaging technology to visualize subtle brain injuries. (Shenton et al., 2012) In addition, both the psychogenic and the physiogenic views neglect important aspects of this patient population.

NEUROPSYCHOLOGICAL FUNCTION

Neuropsychological impairment may not be apparent as symptoms, or they may be absent even with cognitive complaints, as observed in a study of 109 service members with mixed-severity TBI. (French et al., 2014a) Evaluation of neuropsychological function can be achieved with some objectivity using tests of executive and motor function, memory, attention, learning, and other domains. Results from such studies are addressed here.

Comorbid group

Multiple studies in OEF/OIF veteran and service member populations with PTSD and mTBI history have shown that neuropsychological outcomes can be negatively impacted months or years after injury. Studies have shown a correlation between psychological symptoms and reduced neuropsychological test performance in those with mTBI history. For example, a study of 760 active-duty soldiers showed that more severe PTSD and depression symptoms were significantly associated with poorer neuropsychological performance and more functional impairments after adjustment for TBI status. (Vasterling et al., 2012) A smaller case-control study of OEF/OIF veterans with and without mTBI history confirmed the association of PTSD symptom severity with decreased neuropsychological performance. (Amick et al., 2013) Similarly, a recent study by Storzbach et al. of 92 OEF/OIF veterans found differences in neuropsychological test performance between those with and without blast exposure, regardless of mTBI status. However, when the data were adjusted for PTSD symptom severity, most of the associations between blast exposure and neuropsychological performance were eliminated. (Storzbach et al., 2015)

Beyond the association with symptom severity, several studies have shown that those with a PTSD diagnosis in combination with reported mTBI history performed significantly worse on neuropsychological tests as compared to those with PTSD-only, mTBI only, or controls. A recent study by Combs et al. examined a sample of 251 veterans recruited from the community and by referral, and found those diagnosed with PTSD and reporting an event meeting criteria for mTBI performed more poorly than either group with only one of the two conditions on several neuropsychological measures. (Combs et al., 2015) In a study by Nelson et al. of 108 deployed Guard and OEF/OIF veterans, those diagnosed with PTSD and mTBI had poorer cognitive function (learning/memory and processing speed) as compared to deployed controls with neither diagnosis. (Nelson et al., 2012) An earlier study by the same authors compared participant scores to normative values and found impaired performance on processing speed and executive function tasks among OEF/OIF veterans with mild or moderate TBI history who screened positive for PTSD. (Nelson et al., 2009) In a visual attention task, 15 combat

veterans diagnosed with PTSD and mTBI history showed a slower response time as compared to PTSD-only patients or combat controls. (Barlow-Ogden & Poynter, 2012) A small study with civilians similarly showed that patients with PTSD and mTBI diagnoses presented with more cognitive impairment than those with mTBI alone. (Pineau et al., 2014)

In contrast, some studies have found no significant neuropsychological differences between those with mTBI history and PTSD and those with only one condition. (Brenner et al., 2010b; Gordon et al., 2011; Karr et al., 2014; Soble et al., 2014) In an archival records study by Soble et al. of 125 OEF/OIF veterans with a diagnosis of PTSD or comorbid PTSD/mTBI who sought neuropsychological evaluation, mTBI diagnosis had no effect on neuropsychological performance. A norms-based comparison showed that both groups demonstrated normal cognitive performance. (Soble et al., 2013) The authors noted that moderately elevated depression and anxiety symptoms in both groups may have contributed to subjective cognitive complaints. However, anxiety and depression symptoms were elevated in similar groups in Combs et al., who did find neuropsychological impairments and differences between PTSD-only and comorbid group performance. (Combs et al., 2015) The difference in findings may have been due to the participant population characteristics. Another study that did not find the comorbid group to have poorer neuropsychological test performance was Brenner, et al., which studied a convenience sample of 45 returning OEF/OIF soldiers reporting mTBI history and found non-significant differences between those meeting criteria for PTSD and those not. (Brenner et al., 2010b) The failure of the differences to meet statistical significance may have been a function of the study design. In a study by Gordon, et al., 82 older (average age 50 y) veterans with mostly non-combat mTBI were assessed for various neuropsychological outcomes. No group differences were observed between those with and without PTSD diagnosis. (Gordon et al., 2011) Here, participant population factors including age and time since injury (average 20 y as compared to averages of 0-6 y for above-cited studies) may have contributed to the findings. A meta-analysis performed by Karr, et al. examined cognitive outcomes in nine studies, seven of which included information about PTSD status. The analysis did not show a significant difference between PTSD status groups, but was limited in power. (Karr et al., 2014) In a study of learning and memory performance, 103 veterans with mTBI history demonstrated cognitive impairments that were associated with depression symptoms but not PTSD symptoms. (Sozda et al., 2014)

These well-controlled studies have conflicting findings regarding whether mTBI history and PTSD produce an additive effect on neuropsychological outcomes. Participant population, study design, outcomes, and other factors may contribute to the discrepancies.

Mild TBI Only

During the acute phase of mTBI recovery, decreases in neuropsychological test performance have been observed in civilian settings (McCauley et al., 2014; Peterson et al., 2009), and are considered common. (Defense and Veterans Brain Injury Center (DVBIC) & Defense Centers for Psychological Health and Traumatic Brain Injury (DCoE), July 2010) A systematic review of civilian studies showed that most mTBI patients recover from neuropsychological impairments within 1-3 months. (Carroll et al., 2004) Studies of acute mTBI patients in the deployed setting are limited and typically do not involve neuropsychological outcomes.

Mild TBI patients in the chronic phase of recovery without comorbid psychological health conditions do not consistently demonstrate poorer neuropsychological test performance as compared to no TBI controls. Several studies of OEF/OIF veterans assessed 2-5 years after mTBI have found no neuropsychological differences between those with mTBI only and controls without mTBI. (Nelson et al., 2012; Shandera-Ochsner et al., 2013; Verfaellie et al., 2014) A recent study by Dretsch, et al. included 458 active-duty soldiers, 36% of whom screened positive for at least one mTBI, and measured performance on several cognitive processing tasks (e.g., attention, memory, and processing speed). (Dretsch et al., 2015) There were no significant differences between TBI status groups on any cognitive outcomes. These results were consistent with those of a previous study of 108 OEF/OIF veterans with varied combat histories. (Nelson et al., 2012) Similarly, neuropsychological outcomes were evaluated by Verfaellie et al. in 136 OEF/OIF veterans exposed to blast at least 6 months prior to evaluation. Neither TBI status nor LOC at time of injury significantly affected cognitive control, processing speed, or other neuropsychological outcomes. (Verfaellie et al., 2014) A study by Shandera-Ochsner of 81 OEF/OIF veterans found that participants with self-reported mTBI history not meeting criteria for PTSD did not differ on any neurocognitive measures from combat controls. (Shandera-Ochsner et al., 2013) In a study by Amick et al. of 72 OEF/OIF combat veterans including 34 with reported mTBI history, TBI status had no effect on executive function. (Amick et al., 2013)

Similar results have been seen in studies with veterans with more remote injuries. A study by Larson et al. of 205 veterans recruited from the community included 135 participants evaluated an average of 24 years post injury and found that memory impairment was not associated with history of concussion. (Larson et al., 2013)

The finding that mTBI alone has no lasting neuropsychological outcomes is not universal. A study including 53 OEF/OIF veterans with mTBI history not meeting criteria for PTSD showed significantly lower performance on several neuropsychological measures as compared to veteran controls. (Combs et al., 2015) A recent meta-analysis by Karr et al. of nine studies of cognitive function at least 90 days after military-related mTBI in veterans and deployed persons found subtle, chronic cognitive impairments associated with mTBI. (Karr et al., 2014) The meta-analysis may have been able to detect smaller changes than the individual studies. However, a number of these studies had small participant numbers, and several included participants who had sustained a high number of mTBIs. Patients with a history of multiple mTBIs may be at higher risk of chronic cognitive and functional impairment. (Defense and Veterans Brain Injury Center (DVBIC) & Defense Centers for Psychological Health and Traumatic Brain Injury (DCoE), 2014)

PTSD Only

PTSD alone is associated with decreased neurocognitive test performance in several domains, especially verbal learning, speed of information processing, and attention/working memory, according to a recent meta-analysis including data from 1,779 PTSD patients. This meta-analysis included a mixture of studies of military and other trauma survivors. (Scott et al., 2015) These findings are consistent with neuropsychological studies showing reduced performance in veterans with PTSD as compared to controls. The 2013 study by Shandera-Ochsner et al. of OEF/OIF veterans including 19 participants with PTSD and no mTBI history showed that group performed worse than combat controls on several neurocognitive tests. (Shandera-Ochsner et al., 2013) A study including 10 veterans with PTSD without mTBI history

showed poorer executive function as compared to age-matched control veterans. (Swick et al., 2012) The 2012 study by Nelson et al. of OEF/OIF veterans including 58 participants with psychiatric conditions without mTBI history, 35% of whom met criteria for PTSD, showed that cognitive function was lower in the psychiatric condition group than the control group. (Nelson et al., 2012)

In addition to the group-based findings described above, researchers have also found correlations between neuropsychological outcomes and PTSD symptoms (Vasterling et al., 2012; Verfaellie et al., 2014) or diagnosis. (Larson et al., 2013) Taken together, these data suggest that PTSD and subclinical PTSD symptoms may be driving cognitive impairments observed among PTSD patients with mTBI history.

DIAGNOSTIC AND ASSESSMENT TOOLS

Assessment of PTSD and mTBI based on symptoms alone can be difficult due to the significant overlap, and lack of tools for understanding symptom etiology. This section describes common diagnostic and assessment tools relevant to both conditions.

The Department of Defense (DoD) has implemented several policies that enable screening for TBI. In theater, the Military Acute Concussion Evaluation (MACE) is used to evaluate patients immediately following a potentially concussive event. (Defense and Veterans Brain Injury Center, 2007; Defense Brain Injury Center Working Group on the Acute Management of Mild Traumatic Brain Injury in Military Operational Settings, 2006) In the post-deployment health assessment (PDHA), service members answer questions about head injury events, symptoms experienced immediately after the event, and current symptoms. The post-deployment health reassessment (PDHRA) is used to identify service members requiring further evaluation. (Defense and Veterans Brain Injury Center, 2014) A study of PDHA results from 2005 showed that 22.8% of returning soliders were diagnosed with deployment-related TBI. (Terrio et al., 2009) The Veterans Health Administration screens all newly enrolling OEF/OIF veterans for TBI using a four-part interview on possible TBI events, symptoms immediately after the event, new or worsening symptoms following the event, and current symptoms. (Department of Veterans Affairs; Veterans Health Administration, 2010) Among a sample of veterans enrolled in 2007-2008, 17% screened positive for possible TBI. (Sayer et al., 2011) Among all veterans receiving care in the VA health system in 2012 for any indication, 6.8% had a diagnosis of TBI (any severity). (Taylor et al., 2014)

The Neurobehavioral Symptom Inventory (NSI) and the Rivermead Post-concussion Symptoms Questionnaire (RPQ) are patient reporting tools that can be used to determine symptom severity. (Cicerone & Kalmar, 1995; Kaplan, 2014; King et al., 1995) The two instruments are similar in that they provide a list of symptoms (22 on the NSI, 16 on the RPQ) and ask test takers to indicate severity on a five-point scale. The NSI also has two items that invite the test-taker to name a symptom and provide a severity rating. Several factor analysis studies have been performed that seek to group symptoms to improve interpretation of results. (Benge et al., 2009; Caplan et al., 2010; Franke et al., 2015; Vanderploeg et al., 2015) The resulting factor structures vary, but one comparative analysis found that a factor structure including four (vestibular, somatic, cognitive, and affective) provided the best fit for a sample of deployed Guard and veterans. (Vanderploeg et al., 2015)

Neither the NSI nor the RPQ are diagnostic, in part due to the high base rate of these symptoms among uninjured populations (Iverson & Lange, 2003; Wang et al., 2006), and in part because a number of symptoms on these scales also associate with PTSD and other psychological conditions. For PTSD diagnosis, the gold standard is the clinician-administered PTSD scale (CAPS) (Weathers et al., 2001), and tools including the PTSD Checklist (PCL-M and PCL-C) that assess symptom severity. (Forbes et al., 2001) Mild TBI diagnosis is based on injury event criteria, including no more than 30 min of LOC. (Department of Defense & Department of Veterans Affairs, 2009)

The VA/DoD Clinical Practice Guideline for PTSD indicates that "all new patients should be screened for symptoms of PTSD initially and then on an annual basis or more frequently if clinically indicated due to clinical suspicion, recent trauma exposure (e.g., major disaster), or history of PTSD." (Department of Defense & Department of Veterans Affairs, 2010) The DoD includes screening for PTSD in the PDHA and post-deployment health reassessment (PDHRA). (Institute of Medicine of the National Academies, 2014) The most commonly used instrument in the VA and DoD is the Primary Care PTSD Screen (PC-PTSD). (Institute of Medicine of the National Academies et al., 2013) The PC-PTSD is a screen designed for use in primary care and other medical settings. (Prins, 2003) The four questions on the screen relate to avoidance, arousal, vigilance, dissociation, and nightmares. If the patient responds "yes" to any question, that is regarded as a positive screen. (National Center for PTSD, 2015)

Since post-concussive symptoms and PTSD symptoms are mainly subjective, most tools for assessing mTBI and PTSD are limited because of psychological factors and contextual factors; secondary gain such as disability benefits can also influence responses. (Betthauser et al., 2012) A study of veterans recruited from forensic, clinical, and research settings found that those with active disability claims were four times more likely to exaggerate symptoms. (Nelson et al., 2011) A systematic review by Carroll et al. of literature regarding civilian mTBI also noted that litigation and compensation are predictive of poor outcomes in cases with disability or persistent symptoms after mTBI. (Carroll et al., 2004)

Approaches other than self-report scales and interviews can detect differences between mTBI, PTSD, and comorbid groups, but are not currently used to diagnose individual patients. For example, neurocognitive tests are meant to test cognitive performance rather than diagnose mTBI. In addition, they are subject to poor effort and memory malingering. (Nelson et al., 2011; Verfaellie et al., 2014) Promising results have been observed with fluid biomarkers including small nucleolar ribonucleic acids (snoRNAs) found in blood (Ho et al., 2014), although these approaches are not currently available in the clinical setting.

Imaging Approaches

Traditional computed tomography (CT) scans and MRI are not sensitive enough to differentiate TBI history alone from TBI comordbid with PTSD. Instead, researchers have used sophisticated imaging approaches including fMRI (McDonald et al., 2012; Roy et al., 2010) and diffusion tensor imaging (DTI) (Bazarian et al., 2013) to investigate the pathology of mTBI and comorbid PTSD with mTBI history. These approaches are not generally available in the clinical setting, and evidence does not support their widespread use.

DTI demonstrates diagnostic and prognostic potential, but is not currently used in routine clinical practice. (Hulkower et al., 2013) For example, in a study by Bazarian et al. of 52 OEF/OIF combat veterans, PTSD severity was associated with higher minimum (1st percentile) values of mean diffusivity on DTI. (Bazarian et al., 2013) Similarly, a recent study by Davenport et al. of 125 OEF/OIF personnel with or without PTSD and mTBI history showed that abnormal mean diffusivity in white matter was associated with a diagnosis of PTSD but not mTBI. (Davenport et al., 2015a) A study by the same group examined DTI data from 133 recently-deployed service members with and without mTBI and PTSD. High fractional anisotropy and low diffusion were associated with PTSD, but mTBI was not associated with DTI abnormalities. (Davenport et al., 2015b) A study of 37 OEF/OIF service members with mixed-severity deployment-related TBI and 14 non-deployed controls showed that PTSD Checklist scores were associated with low fractional anisotropy in several brain regions. (Yeh et al., 2014)

However, a number of DTI studies have failed to find differences between groups with and without PTSD. A DTI study by Matthews et al. of 46 OEF/OIF service members and veterans with blast-related mTBI history, 28 of whom met criteria for PTSD, showed that LOC was associated with lower fractional anisotropy values (indicating more white matter disruption) as compared to alteration of consciousness alone. No differences in white matter integrity were observed between those with and without PTSD. (Matthews et al., 2012) In a study including 34 OEF/OIF veterans with blast mTBI history, several DTI metrics were predictive of TBI status, but no differences were observed between the PTSD and mTBI history group and the mTBI only group. (Petrie et al., 2014) In addition, several studies have found no correlation between DTI metrics and PTSD symptoms. In 30 OEF/OIF veterans with comorbid mTBI history, PTSD, and depression, evaluated by Morey et al. alongside combat controls white matter damage was associated with TBI status, reported AOC, and duration of LOC, but not PTSD or depression symptoms. (Morey et al., 2013) Data from a study by Levin et al. of 37 OEF/OIF service members and veterans with deployment-related mild or moderate TBI history and deployed controls did not show a consistent pattern associating post-concussive or PTSD symptoms with DTI variables, and there was no association between DTI variables and TBI status. (Levin et al., 2010) In a small study of 11 OEF/OIF service members with deployment-related mTBI history, white matter integrity was degraded compared to age-matched combat controls, but no significant associations between PTSD symptoms and DTI variables were observed. (Costanzo et al., 2014) A discussion of DTI methodologies that might shed light on why some studies find unique features in the comorbid PTSD/mTBI population and some do not is beyond the scope of this article, but it is clear that further investigations will be valuable.

Functional MRI biomarkers may also warrant further study. A 2012 meta-analysis of fMRI studies of PTSD and mTBI showed that activation of the middle frontal gyrus may be a marker of interest for distinguishing the two conditions. (Simmons & Matthews, 2012) In a therapeutic intervention trial including eight service members with PTSD, fMRI data showed changes in brain areas associated with PTSD and depression symptoms. (Roy et al., 2010) One of the advantages of fMRI is that it can analyze brain networks, that is, spatially segregated but functionally linked areas. A recent study by Speilberg et al. took advantage of this property. The authors examined 208 veterans of OEF/OIF, 52% of whom met criteria for PTSD, and 63% of whom experienced mTBI, and found two brain networks in which weaker connections were associated with higher PTSD re-experiencing symptoms. (Spielberg et al., 2015)

One research group has recently published two papers on single photon emission computed tomography (SPECT) technology in veterans (Raji et al., 2015) and civilians. (Amen et al., 2015) Amen et al. report high sensitivity and specificity for distinguishing PTSD, TBI, and PTSD/TBI patients using SPECT data. However, in both studies it is unclear what diagnostic instruments were used for PTSD diagnoses. In addition, it is not clear that the imaging-based diagnoses were made independently of clinical data or prior diagnoses.

Brain volume measurements have demonstrated promise for identifying those with comorbid PTSD and mTBI history. Reduced amygdala volume as measured by MRI was observed in 21 OEF/OIF veterans with PTSD and mTBI history. In the same study, certain neuropsychological outcomes and PTSD symptoms were associated with changes in left or right amygdala volume in the comorbid PTSD and mTBI history group, but not in the combat control group. (Depue et al., 2014) An MRI study by Lindemer et al. of 104 OEF/OIF veterans of various ages showed reduced cortical thickness with increasing PTSD symptom severity, and an additive effect in those with comorbid PTSD and mTBI history. (Lindemer et al., 2013)

While imaging approaches are revealing valuable mechanistic and neuroanatomical information, predictive and diagnostic capabilities remain to be demonstrated in larger clinical samples. Imaging studies are not the current clinical standard in diagnosing PTSD or mTBI.

TREATMENT IMPLICATIONS

Clinical practice guidelines

The VA/DoD treatment guidelines for mTBI three months or more post-injury focus on symptom management, education, and return to activity. (Department of Defense & Department of Veterans Affairs, 2009) Regarding persistent symptoms, the guidelines state:

> "Persons who complain about somatic, cognitive or behavioral difficulties after concussion/mTBI should be assessed and treated symptomatically regardless of the elapsed time from injury… The assessment of an individual with persistent concussion /mTBI related symptoms should be directed to the specific nature of the symptoms regardless of their etiology." (Department of Defense & Department of Veterans Affairs, 2009)

Effective treatments for PTSD are in wide dissemination across the VA and DoD. The VA/DoD Clinical Practice Guidelines for PTSD and mTBI emphasize patient education to normalize reactions to trauma, improve self-care, and set realistic expectations of recovery. (Department of Defense & Department of Veterans Affairs, 2010) The VA/DoD Clinical Practice Guideline for PTSD cites selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) as first-line treatments for PTSD. (Department of Defense & Department of Veterans Affairs, 2010)

Evidence regarding non-pharmacological interventions

A recent systematic review by Steenkamp et al. on psychotherapy for military-related PTSD found the treatments with the highest evidence recommendations in clinical guidelines were cognitive processing therapy (CPT), trauma-focused exposure therapies, and eye movement desensitization and reprocessing (EMDR) therapy. (Steenkamp et al., 2015) Randomized

controlled trials of PTSD therapies with veterans and service members from the US and other countries were included in the review, and 36 studies met inclusion criteria. Cognitive processing therapy (CPT) and trauma-focused exposure therapies were supported by more randomized controlled trials than other treatments found in the review, and effect sizes for treatment were large. Despite this, an analysis of six randomized controlled trials of CPT or trauma-focused exposure therapies found that about two-thirds of enrolled patients still met diagnostic criteria for PTSD after treatment, perhaps due to high dropout rates. (Steenkamp et al., 2015) Studies in populations with comorbid PTSD and TBI history show that prolonged exposure therapy is successful in reducing symptoms regardless of their presumed origin. (Sripada et al., 2013; Wolf et al., 2012b)

While PTSD treatments are well-supported by evidence, fewer studies have been performed specifically with comorbid PTSD/ mTBI patients. A retrospective analysis by Davis et al. of CPT for 136 veterans with PTSD showed no difference in treatment completion rates between veterans with or without a history of mTBI. (Davis et al., 2013) A study by Sripada et al. of 73 veterans with PTSD found prolonged exposure therapy to be equally effective at reducing PTSD symptoms in patients with and without a history of TBI. (Sripada et al., 2013) A small study of veterans including some with mTBI found virtual reality exposure therapy and prolonged exposure to be effective at reducing PTSD symptoms, although there were too few participants (N = 15) to detect differences between treatments or TBI status. (Roy et al., 2010) In a comparative study by Walter et al. on 86 veterans with PTSD and mTBI history were randomized to treatment that did or did not include a written account of trauma. Results showed no differences in PTSD-related outcomes, but a non-significant difference in depression symptoms was apparent, with the written account group having a slightly greater improvement after treatment. (Walter et al., 2014) A recent pilot intervention study by Cole et al. involved an 8-week mindfulness group class with one day-long retreat. Nine veterans with PTSD and mTBI history participated and reported high levels of satisfaction with the intervention, which was rated as highly useful. PTSD symptoms measured by the PTSD Checklist were significantly improved after treatment, and gains were maintained at the 3-month follow-up. (Cole et al., 2015)

Janak et al. conducted a multidisciplinary intervention of persistent post-concussive symptoms with a cohort of 257 active duty service members. Participants had mTBI history (median 5 months post-injury) and 34% met criteria for probable PTSD at baseline. The median length of treatment was 2 months, and treatment included cognitive rehabilitation, behavioral health interventions, occupational therapy, vestibular rehabilitation (for some), and medical management. After treatment, both post-concussive symptoms measured by the NSI and PTSD symptoms measured by the PCL-M declined. Among the subset of participants with probable PTSD, post-concussive symptom burden was heavier before and after treatment, and the treatment effect was smaller. (Janak et al., 2015) A recent cognitive rehabilitation study by Walter et al. included 50 OEF/OIF veterans with mild or moderate TBI history and neuropsychological impairment, most of whom met criteria for PTSD. Participants completed a supported employment program and a 12-session Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) intervention. Veterans with PTSD had more severe post-concussive symptoms, but their response to treatment was not different than those without PTSD. (Walter et al., 2015) According to interviewed VA clinicians, PTSD patients with mTBI history require more repetition, attention, and time to complete assignments related to PTSD

treatment. An additional challenge identified in this study of 40 VA providers was that rehabilitation providers may need to work more slowly and incorporate emotion-management into treatment for this population. (Sayer et al., 2009)

A recent systematic review and meta-analysis of hyperbaric oxygen treatment for TBI found two studies with a total of 92 service member participants with mTBI history and mean PCL-M scores indicating significant PTSD symptoms. (Wang et al., 2016) Both were two-arm, randomized, controlled, double-blind trials. (Cifu et al., 2014; Wolf et al., 2012a) Mean PCL-M scores improved in both hyperbaric oxygen and sham treatment groups. Neither study found significant differences between treatment groups on PTSD symptom scores, post-concussion symptom scores, or neuropsychological test scores. Hyperbaric oxygen treatment is discussed in more detail in another research review. (Qashu, 2015)

Evidence regarding pharmacological interventions

Few studies have been performed with pharmacological therapies specifically for patients with comorbid PTSD and mTBI. (Carlson et al., 2009) A 2009 study by Ruff et al. prospectively studied 74 veterans identified at a VA Polytrauma Center who had sustained blast-related mTBI 2.2 years earlier, on average (96% also had a PTSD diagnosis). (Ruff et al., 2009) This uncontrolled pilot study found that prazosin, in combination with sleep hygiene counseling, reduced daytime sleepiness, headache frequency, and headache pain intensity, and improved scores on a cognitive assessment after 9 weeks. After 6 months, those who stayed on prazosin (n = 64) had maintained gains in symptom reduction and showed further improvement on the cognitive assessment. Clinical improvements were correlated with reduced PTSD symptoms. (Ruff et al., 2012) A recent study by McAllister et al. suggested methylphenidate (a central nervous system stimulant) can reduce PTSD, depression, cognitive, and post-concussion symptoms in a mixed military and civilian population with mTBI, PTSD, or comorbid mTBI/PTSD. (McAllister et al., 2015)

Factors protective against PTSD symptoms

Some factors have been identified as providing protective effects for psychological health. A study by Bryant et al. including 459 civilian mTBI patients showed that those with longer duration of post-traumatic amnesia had less severe re-experiencing symptoms when assessed during the acute phase of injury, but overall PTSD symptoms did not differ. (Bryant et al., 2009a) These data indicate that post-traumatic amnesia may be protective against some PTSD symptoms. A study of 46 civilians monitored during the acute phase of mTBI showed that resilience and positive mood as assessed on the day of injury were associated with less severe stress and post-concussive symptoms during the month following injury. (McCauley et al., 2013) Among service members in Afghanistan evaluated for acute concussion, return to duty was associated with the absence of combat stress reaction at the time of injury. (Kennedy et al., 2012) Additionally, two studies have found that comorbid physical injuries, and, perhaps, the associated recovery and rehabilitation, can have a protective effect against post-concussive symptoms and psychological health sequelae in patients with mTBI history. (French et al., 2012; French et al., 2014b) However, patients in these studies were evaluated within about three months of injury, and PTSD can develop later (Grieger et al., 2006) and symptoms may have been dampened at assessment by morphine administration. (Bryant et al., 2009b)

Physical health and medication use among those with PTSD and mTBI history

Hoge et al. found that mTBI in combination with PTSD or depression is associated with poor overall health, missed work, and medical visits. In that study, PTSD and depression were found to mediate the relationship between mTBI and poor health outcomes. (Hoge et al., 2008) A recent retrospective cohort study of OEF/OIF veterans examined headache comorbidities. Participants were those treated in the VA healthcare system for the first time in 2008. Participants treated for headache in 2008 (n = 5264) were more likely than those without headache (n = 33162) to have a TBI diagnosis, as would be expected. The risk of TBI plus PTSD (odds ratio 10.16; 95%; confidence interval 8.96 to 11.53) among those with headache was significantly greater than the risk of TBI alone (odds ratio 6.75 95%; confidence interval 5.79 to 7.86). A similar pattern was also true for TBI plus depression and TBI plus depression plus PTSD. These data show that psychiatric comorbidities including PTSD increase risk of headache among those with TBI. (Jaramillo et al., 2016)

Evidence shows that veterans with persistent symptoms after mTBI have greater healthcare and medication use. In a sample of 421 OEF/OIF veterans with persistent post-concussive symptoms compared with age-matched control veterans, King et al. observed greater utilization in medication records and in almost every category of health service. (King et al., 2014) A retrospective study by Morgan et al. on pharmacotherapy in 707 veterans with PTSD or PTSD and mTBI history veterans showed that patients with both conditions were more likely to be prescribed psychotropic medications including antidepressants, sedative-hypnotic medications, and antipsychotics compared to patients with PTSD without mTBI history. (Morgan et al., 2012) The mTBI and PTSD group also had a higher chance of being prescribed more than one psychotropic medication compared to the PTSD only group, suggesting comorbid PTSD and mTBI patients may respond differently to medication. Interviews conducted by Sayer et al. with VA clinicians revealed a treatment challenge in this comorbid population in that providers treating PTSD can prescribe medications contraindicated in patients with mTBI history, or vice versa. (Sayer et al., 2009) These data emphasize the importance of integrated care.

DISCUSSION

Comorbid PTSD and mTBI history cases are often challenging and complex, with some patients presenting more severe or persistent symptoms than individuals without mTBI or with mTBI alone. Current data regarding long-term neuropsychological function in comorbid PTSD and mTBI patients are not consistent.

Since mTBI and PTSD symptoms are similar, differential diagnosis will likely continue to be a challenge, although neuroimaging techniques and other biomarkers may provide new diagnostic tools. Evidence shows that standard PTSD treatments can be effective in this population despite challenges cited by clinicians. Further research on mTBI may reveal more effective treatment options and diagnostic tools that benefit PTSD patients with mTBI history.

REFERENCES

Amen, D. G., Raji, C. A., Willeumier, K., Taylor, D., Tarzwell, R., Newberg, A., & Henderson, T. A. (2015). Functional Neuroimaging Distinguishes Posttraumatic Stress Disorder from Traumatic Brain Injury in Focused and Large Community Datasets. *PLoS One, 10*(7), e0129659. doi: 10.1371/journal.pone.0129659

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV*. (4th ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013a). *Diagnostic and statistical manual of mental disorders: DSM-V* (5th ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013b). Posttraumatic Stress Disorder. Retrieved from http://www.dsm5.org/Documents/PTSD%20Fact%20Sheet.pdf

Amick, M. M., Clark, A., Fortier, C. B., Esterman, M., Rasmusson, A. M., Kenna, A., . . . McGlinchey, R. (2013). PTSD modifies performance on a task of affective executive control among deployed OEF/OIF veterans with mild traumatic brain injury. *J Int Neuropsychol Soc, 19*(7), 792-801. doi: 10.1017/S1355617713000544

Barlow-Ogden, K., & Poynter, W. (2012). Mild traumatic brain injury and posttraumatic stress disorder: investigation of visual attention in Operation Iraqi Freedom/Operation Enduring Freedom veterans. *J Rehabil Res Dev, 49*(7), 1101-1114.

Bazarian, J. J., Donnelly, K., Peterson, D. R., Warner, G. C., Zhu, T., & Zhong, J. (2013). The relation between posttraumatic stress disorder and mild traumatic brain injury acquired during Operations Enduring Freedom and Iraqi Freedom. *J Head Trauma Rehabil, 28*(1), 1-12. doi: 10.1097/HTR.0b013e318256d3d3

Benge, J. F., Pastorek, N. J., & Thornton, G. M. (2009). Postconcussive symptoms in OEF-OIF veterans: factor structure and impact of posttraumatic stress. *Rehabil Psychol, 54*(3), 270-278. doi: 10.1037/a0016736

Betthauser, L. M., Bahraini, N., Krengel, M. H., & Brenner, L. A. (2012). Self-report measures to identify post traumatic stress disorder and/or mild traumatic brain injury and associated symptoms in military veterans of Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF). *Neuropsychol Rev, 22*(1), 35-53. doi: 10.1007/s11065-012-9191-4

Brenner, L. A., Ivins, B. J., Schwab, K., Warden, D., Nelson, L. A., Jaffee, M., & Terrio, H. (2010a). Traumatic brain injury, posttraumatic stress disorder, and postconcussive symptom reporting among troops returning from iraq. *J Head Trauma Rehabil, 25*(5), 307-312. doi: 10.1097/HTR.0b013e3181cada03

Brenner, L. A., Terrio, H., Homaifar, B. Y., Gutierrez, P. M., Staves, P. J., Harwood, J. E., . . . Warden, D. (2010b). Neuropsychological test performance in soldiers with blast-related mild TBI. *Neuropsychology, 24*(2), 160-167. doi: 10.1037/a0017966

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol, 68*(5), 748-766.

Bryant, R. A., Creamer, M., O'Donnell, M., Silove, D., Clark, C. R., & McFarlane, A. C. (2009a). Post-traumatic amnesia and the nature of post-traumatic stress disorder after mild traumatic brain injury. *J Int Neuropsychol Soc, 15*(6), 862-867. doi: 10.1017/S1355617709990671

Bryant, R. A., Creamer, M., O'Donnell, M., Silove, D., & McFarlane, A. C. (2009b). A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. *Biol Psychiatry, 65*(5), 438-440. doi: 10.1016/j.biopsych.2008.10.032

Bryant, R. A., O'Donnell, M. L., Creamer, M., McFarlane, A. C., Clark, C. R., & Silove, D. (2010). The psychiatric sequelae of traumatic injury. *Am J Psychiatry, 167*(3), 312-320. doi: 10.1176/appi.ajp.2009.09050617

Caplan, L. J., Ivins, B., Poole, J. H., Vanderploeg, R. D., Jaffee, M. S., & Schwab, K. (2010). The Structure of Postconcussive Symptoms in 3 US Military Samples. *J Head Trauma Rehabil, 25*(6), 447-458.

Carlson, K., Kehle, S., Meis, L., Greer, N., MacDonald, R., Rutks, I., & Wilt, T. J. (2009) *The Assessment and Treatment of Individuals with History of Traumatic Brain Injury and Post-Traumatic Stress Disorder: A Systematic Review of the Evidence*. Washington (DC).

Carlson, K. F., Kehle, S. M., Meis, L. A., Greer, N., Macdonald, R., Rutks, I., . . . Wilt, T. J. (2011). Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. *J Head Trauma Rehabil, 26*(2), 103-115. doi: 10.1097/HTR.0b013e3181e50ef1

Carroll, L. J., Cassidy, J. D., Peloso, P. M., Borg, J., von Holst, H., Holm, L., . . . Injury, W. H. O. C. C. T. F. o. M. T. B. (2004). Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*(43 Suppl), 84-105.

Centers for Disease Control and Prevention. (2014). *Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation.* Atlanta, GA.

Cernich, A. N., Chandler, L., Scherdell, T., & Kurtz, S. (2012). Assessment of co-occurring disorders in veterans diagnosed with traumatic brain injury. *J Head Trauma Rehabil, 27*(4), 253-260. doi: 10.1097/HTR.0b013e3182585cd5

Cicerone, K., & Kalmar, K. (1995). Persistent postconcussion syndrome: the structure of subjective complaints after mild traumatic brain injury. *Journal of Head Trauma Rehabilitation, 10*(3), 1-17.

Cifu, D. X., Hart, B. B., West, S. L., Walker, W., & Carne, W. (2014). The effect of hyperbaric oxygen on persistent postconcussion symptoms. *J Head Trauma Rehabil, 29*(1), 11-20. doi: 10.1097/HTR.0b013e3182a6aaf0

Cole, M. A., Muir, J. J., Gans, J. J., Shin, L. M., D'Esposito, M., Harel, B. T., & Schembri, A. (2015). Simultaneous Treatment of Neurocognitive and Psychiatric Symptoms in Veterans with Post-Traumatic Stress Disorder and History of Mild Traumatic Brain Injury: A Pilot Study of Mindfulness-Based Stress Reduction. *Mil Med, 180*(9), 956-963. doi: 10.7205/MILMED-D-14-00581

Combs, H. L., Berry, D. T., Pape, T., Babcock-Parziale, J., Smith, B., Schleenbaker, R., . . . High, W. M., Jr. (2015). The Effects of Mild Traumatic Brain Injury, Post-Traumatic Stress Disorder, and Combined Mild Traumatic Brain Injury/Post-Traumatic Stress Disorder on Returning Veterans. *J Neurotrauma*. doi: 10.1089/neu.2014.3585

Costanzo, M. E., Chou, Y. Y., Leaman, S., Pham, D. L., Keyser, D., Nathan, D. E., . . . Roy, M. J. (2014). Connecting combat-related mild traumatic brain injury with posttraumatic stress disorder symptoms through brain imaging. *Neurosci Lett, 577*, 11-15. doi: 10.1016/j.neulet.2014.05.054

Davenport, N. D., Lim, K. O., & Sponheim, S. R. (2015a). Personality and neuroimaging measures differentiate PTSD from mTBI in veterans. *Brain Imaging Behav*. doi: 10.1007/s11682-015-9371-y

Davenport, N. D., Lim, K. O., & Sponheim, S. R. (2015b). White matter abnormalities associated with military PTSD in the context of blast TBI. *Hum Brain Mapp, 36*(3), 1053-1064. doi: 10.1002/hbm.22685

Davis, J. J., Walter, K. H., Chard, K. M., Parkinson, R. B., & Houston, W. S. (2013). Treatment adherence in cognitive processing therapy for combat-related PTSD with history of mild TBI. *Rehabil Psychol, 58*(1), 36-42. doi: 10.1037/a0031525

Defense and Veterans Brain Injury Center. (2007). Military Acute Concussion Evaluation (MACE).

Defense and Veterans Brain Injury Center. (2014). Concussion/mTBI Screening. Retrieved from http://dvbic.dcoe.mil/diagnosis-assessment/article/concussionmtbi-screening

Defense and Veterans Brain Injury Center (DVBIC). (February 2015). *DoD Numbers for Traumatic Brain Injury Worldwide: 2000-2014*. Retrieved from http://dvbic.dcoe.mil/sites/default/files/DoD-TBI-Worldwide-Totals-2000-2014-Q1-Q4-Feb23-2015.pdf.

Defense and Veterans Brain Injury Center (DVBIC), & Defense Centers for Psychological Health and Traumatic Brain Injury (DCoE). (2014). *Multiple Traumatic Brain Injury / Multiple Concussion*. Retrieved

from http://dvbic.dcoe.mil/sites/default/files/DVBIC_Research-IP_Multiple-TBI_v1.0_December_2014.pdf.

Defense and Veterans Brain Injury Center (DVBIC), & Defense Centers for Psychological Health and Traumatic Brain Injury (DCoE). (July 2010). *Cognitive Rehabilitation for Mild Traumatic Brain Injury Consensus Conference – 2009*. Retrieved from http://www.dcoe.mil/content/navigation/documents/Cognitive%20Rehabilitation%20Clinical%20Guidance%20Fact%20Sheet.pdf.

Defense Brain Injury Center Working Group on the Acute Management of Mild Traumatic Brain Injury in Military Operational Settings. (2006). Joint Theater Trauma System: Clinical Practice Guideline Theatre Screening and Management of Mild Traumatic Brain Injury (Concussion). Retrieved from http://www.dmrti.army.mil/documents/mTBI%20Screening%20and%20Management%20with%20Alternative%20MACE%20Scores.pdf

Department of Defense, & Department of Veterans Affairs. (2009). VA/DoD Clinical Practice Guideline for Management of Concussion/mild Traumatic Brain Injury. Retrieved from http://www.healthquality.va.gov/guidelines/Rehab/mtbi/concussion_mtbi_full_1_0.pdf

Department of Defense, & Department of Veterans Affairs. (2010). VA/DoD Clinical Practice Guideline for Management of Post-traumatic Stress. Retrieved from http://www.healthquality.va.gov/guidelines/MH/ptsd/cpg_PTSD-FULL-201011612.pdf

Department of Veterans Affairs; Veterans Health Administration. (2010). VHA Directive 2010-012: Screening And Evaluation Of Possible Traumatic Brain Injury In Operation Enduring Freedom (OEf) And Operation Iraqi Freedom (OIF) Veterans Retrieved from http://www.va.gov/optometry/docs/vha_directive_2010-012_screening_and_evaluation_of_possible_tbi_in_oef-oif_veterans.pdf

Depue, B. E., Olson-Madden, J. H., Smolker, H. R., Rajamani, M., Brenner, L. A., & Banich, M. T. (2014). Reduced amygdala volume is associated with deficits in inhibitory control: a voxel- and surface-based morphometric analysis of comorbid PTSD/mild TBI. *Biomed Res Int, 2014*, 691505. doi: 10.1155/2014/691505

Dretsch, M. N., Silverberg, N. D., & Iverson, G. L. (2015). Multiple Past Concussions Are Associated with Ongoing Post-Concussive Symptoms but Not Cognitive Impairment in Active-Duty Army Soldiers. *J Neurotrauma*. doi: 10.1089/neu.2014.3810

Eskridge, S. L., Macera, C. A., Galarneau, M. R., Holbrook, T. L., Woodruff, S. I., MacGregor, A. J., . . . Shaffer, R. A. (2013). Influence of combat blast-related mild traumatic brain injury acute symptoms on mental health and service discharge outcomes. *J Neurotrauma, 30*(16), 1391-1397. doi: 10.1089/neu.2012.2537

Forbes, D., Creamer, M., & Biddle, D. (2001). The validity of the PTSD checklist as a measure of symptomatic change in combat-related PTSD. *Behav Res Ther, 39*(8), 977-986.

Franke, L. M., Czarnota, J. N., Ketchum, J. M., & Walker, W. C. (2015). Factor analysis of persistent postconcussive symptoms within a military sample with blast exposure. *J Head Trauma Rehabil, 30*(1), E34-46. doi: 10.1097/HTR.0000000000000042

French, L. M., Lange, R. T., & Brickell, T. (2014a). Subjective cognitive complaints and neuropsychological test performance following military-related traumatic brain injury. *J Rehabil Res Dev, 51*(6), 933-950. doi: 10.1682/JRRD.2013.10.0226

French, L. M., Lange, R. T., Iverson, G. L., Ivins, B., Marshall, K., & Schwab, K. (2012). Influence of bodily injuries on symptom reporting following uncomplicated mild traumatic brain injury in US military service members. *J Head Trauma Rehabil, 27*(1), 63-74. doi: 10.1097/HTR.0b013e3182248344

French, L. M., Lange, R. T., Marshall, K., Prokhorenko, O., Brickell, T. A., Bailie, J. M., . . . Kennedy, J. E. (2014b). Influence of the severity and location of bodily injuries on post-concussive and combat stress

symptom reporting after military-related concurrent mild traumatic brain injuries and polytrauma. *J Neurotrauma, 31*(19), 1607-1616. doi: 10.1089/neu.2014.3401

Gordon, S. N., Fitzpatrick, P. J., & Hilsabeck, R. C. (2011). No effect of PTSD and other psychiatric disorders on cognitive functioning in veterans with mild TBI. *Clin Neuropsychol, 25*(3), 337-347. doi: 10.1080/13854046.2010.550634

Grieger, T. A., Cozza, S. J., Ursano, R. J., Hoge, C., Martinez, P. E., Engel, C. C., & Wain, H. J. (2006). Posttraumatic stress disorder and depression in battle-injured soldiers. *Am J Psychiatry, 163*(10), 1777-1783; quiz 1860. doi: 10.1176/ajp.2006.163.10.1777

Hill, J. J., 3rd, Mobo, B. H., Jr., & Cullen, M. R. (2009). Separating deployment-related traumatic brain injury and posttraumatic stress disorder in veterans: preliminary findings from the Veterans Affairs traumatic brain injury screening program. *Am J Phys Med Rehabil, 88*(8), 605-614. doi: 10.1097/PHM.0b013e3181ae0f83

Ho, L., Lange, G., Zhao, W., Wang, J., Rooney, R., Patel, D. H., . . . Pasinetti, G. M. (2014). Select small nucleolar RNAs in blood components as novel biomarkers for improved identification of comorbid traumatic brain injury and post-traumatic stress disorder in veterans of the conflicts in Afghanistan and Iraq. *Am J Neurodegener Dis, 3*(3), 170-181.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med, 358*(5), 453-463. doi: 10.1056/NEJMoa072972

Hulkower, M. B., Poliak, D. B., Rosenbaum, S. B., Zimmerman, M. E., & Lipton, M. L. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *AJNR Am J Neuroradiol, 34*(11), 2064-2074. doi: 10.3174/ajnr.A3395

Institute of Medicine of the National Academies. (2014). Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment. The National Academies Press, Washington, DC. Retrieved from http://www.iom.edu/Reports/2014/Treatment-for-Posttraumatic-Stress-Disorder-in-Military-and-Veteran-Populations-Final-Assessment.aspx

Institute of Medicine of the National Academies, Committee on the Assessment of the Readjustment Needs of Military Personnel Veterans and Their Families, & Board on the Health of Select Populations. (2013). Returning Home from Iraq and Afghanistan: Assessment of Readjustment Needs of Veterans, Service Members, and Their Families. The National Academies Press, Washington, DC. Retrieved from http://www.nap.edu/catalog/13499/returning-home-from-iraq-and-afghanistan-assessment-of-readjustment-needs

Iverson, G. L., & Lange, R. T. (2003). Examination of "postconcussion-like" symptoms in a healthy sample. *Appl Neuropsychol, 10*(3), 137-144. doi: 10.1207/S15324826AN1003_02

Janak, J. C., Cooper, D. B., Bowles, A. O., Alamgir, A. H., Cooper, S. P., Gabriel, K. P., . . . Orman, J. A. (2015). Completion of Multidisciplinary Treatment for Persistent Postconcussive Symptoms Is Associated With Reduced Symptom Burden. *J Head Trauma Rehabil*. doi: 10.1097/HTR.0000000000000202

Jaramillo, C. A., Eapen, B. C., McGeary, C. A., McGeary, D. D., Robinson, J., Amuan, M., & Jo Pugh, M. (2016). A cohort study examining headaches among veterans of Iraq and Afghanistan wars: Associations with traumatic brain injury, PTSD, and depression. *Headache, 56*(3), 528-539. doi: 10.1111/head.12726

Kaplan, D. (2014). Neurobehavioral Symptom Inventory (NSI): Recommendations for Scoring and Serial Administration for Concussion Health Care Outcomes Standardization. Defense and Veterans Brain Injury Center (DVBIC), Defense Centers for Psychological Health and Traumatic Brain Injury (DCoE). Retrieved from http://dvbic.dcoe.mil/sites/default/files/DVBIC_-_NSI_Information_Paper_Final.pdf

Karr, J. E., Areshenkoff, C. N., Duggan, E. C., & Garcia-Barrera, M. A. (2014). Blast-related mild traumatic brain injury: a Bayesian random-effects meta-analysis on the cognitive outcomes of concussion among military personnel. *Neuropsychol Rev, 24*(4), 428-444. doi: 10.1007/s11065-014-9271-8

Kennedy, C. H., Porter Evans, J., Chee, S., Moore, J. L., Barth, J. T., & Stuessi, K. A. (2012). Return to combat duty after concussive blast injury. *Arch Clin Neuropsychol, 27*(8), 817-827. doi: 10.1093/arclin/acs092

King, N. S., Crawford, S., Wenden, F. J., Moss, N. E., & Wade, D. T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol, 242*(9), 587-592.

King, P. R., Wade, M. J., & Beehler, G. P. (2014). Health service and medication use among veterans with persistent postconcussive symptoms. *J Nerv Ment Dis, 202*(3), 231-238. doi: 10.1097/NMD.0000000000000103

Kontos, A. P., Kotwal, R. S., Elbin, R. J., Lutz, R. H., Forsten, R. D., Benson, P. J., & Guskiewicz, K. M. (2013). Residual effects of combat-related mild traumatic brain injury. *J Neurotrauma, 30*(8), 680-686. doi: 10.1089/neu.2012.2506

Larson, E., Zollman, F., Kondiles, B., & Starr, C. (2013). Memory deficits, postconcussive complaints, and posttraumatic stress disorder in a volunteer sample of veterans. *Rehabil Psychol, 58*(3), 245-252. doi: 10.1037/a0032953

Levin, H. S., Wilde, E., Troyanskaya, M., Petersen, N. J., Scheibel, R., Newsome, M., . . . Li, X. (2010). Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. *J Neurotrauma, 27*(4), 683-694. doi: 10.1089/neu.2009.1073

Lew, H. L., Otis, J. D., Tun, C., Kerns, R. D., Clark, M. E., & Cifu, D. X. (2009). Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. *J Rehabil Res Dev, 46*(6), 697-702.

Lindemer, E. R., Salat, D. H., Leritz, E. C., McGlinchey, R. E., & Milberg, W. P. (2013). Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF Veterans and the impact of comorbid TBI. *Neuroimage Clin, 2*, 601-611. doi: 10.1016/j.nicl.2013.04.009

Mac Donald, C. L., Adam, O. R., Johnson, A. M., Nelson, E. C., Werner, N. J., Rivet, D. J., & Brody, D. L. (2015). Acute post-traumatic stress symptoms and age predict outcome in military blast concussion. *Brain*. doi: 10.1093/brain/awv038

Maguen, S., Lau, K. M., Madden, E., & Seal, K. (2012). Relationship of screen-based symptoms for mild traumatic brain injury and mental health problems in Iraq and Afghanistan veterans: Distinct or overlapping symptoms? *J Rehabil Res Dev, 49*(7), 1115-1126.

Matthews, S. C., Spadoni, A. D., Lohr, J. B., Strigo, I. A., & Simmons, A. N. (2012). Diffusion tensor imaging evidence of white matter disruption associated with loss versus alteration of consciousness in warfighters exposed to combat in Operations Enduring and Iraqi Freedom. *Psychiatry Res, 204*(2-3), 149-154. doi: 10.1016/j.pscychresns.2012.04.018

McAllister, T. W., Zafonte, R., Jain, S., Flashman, L. A., George, M. S., Grant, G. A., . . . Stein, M. B. (2015). Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury. *Neuropsychopharmacology*. doi: 10.1038/npp.2015.282

McCauley, S. R., Wilde, E. A., Barnes, A., Hanten, G., Hunter, J. V., Levin, H. S., & Smith, D. H. (2014). Patterns of early emotional and neuropsychological sequelae after mild traumatic brain injury. *J Neurotrauma, 31*(10), 914-925. doi: 10.1089/neu.2012.2826

McCauley, S. R., Wilde, E. A., Miller, E. R., Frisby, M. L., Garza, H. M., Varghese, R., . . . McCarthy, J. J. (2013). Preinjury resilience and mood as predictors of early outcome following mild traumatic brain injury. *J Neurotrauma, 30*(8), 642-652. doi: 10.1089/neu.2012.2393

McDonald, B. C., Saykin, A. J., & McAllister, T. W. (2012). Functional MRI of mild traumatic brain injury (mTBI): progress and perspectives from the first decade of studies. *Brain Imaging Behav, 6*(2), 193-207. doi: 10.1007/s11682-012-9173-4

Miller, S. C., Whitehead, C. R., Otte, C. N., Wells, T. S., Webb, T. S., Gore, R. K., & Maynard, C. (2015). Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of US Air Force personnel. *Occup Environ Med, 72*(8), 560-566. doi: 10.1136/oemed-2014-102646

Morey, R. A., Haswell, C. C., Selgrade, E. S., Massoglia, D., Liu, C., Weiner, J., . . . McCarthy, G. (2013). Effects of chronic mild traumatic brain injury on white matter integrity in Iraq and Afghanistan war veterans. *Hum Brain Mapp, 34*(11), 2986-2999. doi: 10.1002/hbm.22117

Morgan, M., Lockwood, A., Steinke, D., Schleenbaker, R., & Botts, S. (2012). Pharmacotherapy regimens among patients with posttraumatic stress disorder and mild traumatic brain injury. *Psychiatr Serv, 63*(2), 182-185. doi: 10.1176/appi.ps.201000531

National Center for PTSD. (2015). Primary Care PTSD Screen (PC-PTSD). Retrieved from http://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp

Nelson, L. A., Yoash-Gantz, R. E., Pickett, T. C., & Campbell, T. A. (2009). Relationship between processing speed and executive functioning performance among OEF/OIF veterans: implications for postdeployment rehabilitation. *J Head Trauma Rehabil, 24*(1), 32-40. doi: 10.1097/HTR.0b013e3181957016

Nelson, N. W., Hoelzle, J. B., Doane, B. M., McGuire, K. A., Ferrier-Auerbach, A. G., Charlesworth, M. J., . . . Sponheim, S. R. (2012). Neuropsychological outcomes of U.S. Veterans with report of remote blast-related concussion and current psychopathology. *J Int Neuropsychol Soc, 18*(5), 845-855. doi: 10.1017/S1355617712000616

Nelson, N. W., Hoelzle, J. B., McGuire, K. A., Sim, A. H., Goldman, D. J., Ferrier-Auerbach, A. G., . . . Sponheim, S. R. (2011). Self-report of psychological function among OEF/OIF personnel who also report combat-related concussion. *Clin Neuropsychol, 25*(5), 716-740. doi: 10.1080/13854046.2011.579174

Norris, J. N., Sams, R., Lundblad, P., Frantz, E., & Harris, E. (2014). Blast-related mild traumatic brain injury in the acute phase: acute stress reactions partially mediate the relationship between loss of consciousness and symptoms. *Brain Inj, 28*(8), 1052-1062. doi: 10.3109/02699052.2014.891761

Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. *Psychol Bull, 129*(1), 52-73.

Peterson, S. E., Stull, M. J., Collins, M. W., & Wang, H. E. (2009). Neurocognitive function of emergency department patients with mild traumatic brain injury. *Ann Emerg Med, 53*(6), 796-803 e791. doi: 10.1016/j.annemergmed.2008.10.015

Petrie, E. C., Cross, D. J., Yarnykh, V. L., Richards, T., Martin, N. M., Pagulayan, K., . . . Peskind, E. R. (2014). Neuroimaging, behavioral, and psychological sequelae of repetitive combined blast/impact mild traumatic brain injury in Iraq and Afghanistan war veterans. *J Neurotrauma, 31*(5), 425-436. doi: 10.1089/neu.2013.2952

Pineau, H., Marchand, A., & Guay, S. (2014). Objective neuropsychological deficits in post-traumatic stress disorder and mild traumatic brain injury: what remains beyond symptom similarity? *Behav Sci (Basel), 4*(4), 471-486. doi: 10.3390/bs4040471

Polusny, M. A., Kehle, S. M., Nelson, N. W., Erbes, C. R., Arbisi, P. A., & Thuras, P. (2011). Longitudinal effects of mild traumatic brain injury and posttraumatic stress disorder comorbidity on postdeployment outcomes in national guard soldiers deployed to Iraq. *Arch Gen Psychiatry, 68*(1), 79-89. doi: 10.1001/archgenpsychiatry.2010.172

Ponsford, J., Cameron, P., Fitzgerald, M., Grant, M., Mikocka-Walus, A., & Schonberger, M. (2012). Predictors of postconcussive symptoms 3 months after mild traumatic brain injury. *Neuropsychology, 26*(3), 304-313. doi: 10.1037/a0027888

Prins, A. O., P.; Kimerling, R.; Cameron, R. P.; Hugelshofer, D. S.; Shaw-Hegwer, J.; Thrailkill, A.; Gusman, F.D.; Sheikh, J. I. (2003). The Primary Care PTSD Screen (PC-PTSD): Development and operating characteristics. *Primary Care Psychiatry, 9*, 9-14. doi: 10.1185/13552570312500236

Qashu, F. (2015). Hyperbaric Oxygen for Traumatic Brain Injury (TBI): State of the Science. Defense and Veterans Brain Injury Center (DVBIC), Defense Centers for Psychological Health and Traumatic Brain Injury (DCoE). Retrieved from http://dvbic.dcoe.mil/sites/default/files/DVBIC_Research_Information-Paper_HBO2-State-of-the-Science_v1.0_2015-06-02.pdf

Raji, C. A., Willeumier, K., Taylor, D., Tarzwell, R., Newberg, A., Henderson, T. A., & Amen, D. G. (2015). Functional neuroimaging with default mode network regions distinguishes PTSD from TBI in a military veteran population. *Brain Imaging Behav*. doi: 10.1007/s11682-015-9385-5

Ramchand, R., Rudavsky, R., Grant, S., Tanielian, T., & Jaycox, L. (2015). Prevalence of, risk factors for, and consequences of posttraumatic stress disorder and other mental health problems in military populations deployed to Iraq and Afghanistan. *Curr Psychiatry Rep, 17*(5), 37. doi: 10.1007/s11920-015-0575-z

Romesser, J., Shen, S., Reblin, M., Kircher, J., Allen, S., Roberts, T., & Marchand, W. R. (2011). A preliminary study of the effect of a diagnosis of concussion on PTSD symptoms and other psychiatric variables at the time of treatment seeking among veterans. *Mil Med, 176*(3), 246-252.

Roy, M. J., Francis, J., Friedlander, J., Banks-Williams, L., Lande, R. G., Taylor, P., . . . Rothbaum, B. (2010). Improvement in cerebral function with treatment of posttraumatic stress disorder. *Ann N Y Acad Sci, 1208*, 142-149. doi: 10.1111/j.1749-6632.2010.05689.x

Ruff, R. L., Riechers, R. G., 2nd, Wang, X. F., Piero, T., & Ruff, S. S. (2012). For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. *J Rehabil Res Dev, 49*(9), 1305-1320.

Ruff, R. L., Ruff, S. S., & Wang, X. F. (2009). Improving sleep: initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury. *J Rehabil Res Dev, 46*(9), 1071-1084.

Sareen, J. (2014). Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. *Can J Psychiatry, 59*(9), 460-467.

Sayer, N. A., Nelson, D., & Nugent, S. (2011). Evaluation of the Veterans Health Administration traumatic brain injury screening program in the upper Midwest. *J Head Trauma Rehabil, 26*(6), 454-467. doi: 10.1097/HTR.0b013e3181ff393c

Sayer, N. A., Rettmann, N. A., Carlson, K. F., Bernardy, N., Sigford, B. J., Hamblen, J. L., & Friedman, M. J. (2009). Veterans with history of mild traumatic brain injury and posttraumatic stress disorder: challenges from provider perspective. *J Rehabil Res Dev, 46*(6), 703-716.

Schneiderman, A. I., Braver, E. R., & Kang, H. K. (2008). Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol, 167*(12), 1446-1452. doi: 10.1093/aje/kwn068

Scott, J. C., Matt, G. E., Wrocklage, K. M., Crnich, C., Jordan, J., Southwick, S. M., . . . Schweinsburg, B. C. (2015). A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull, 141*(1), 105-140. doi: 10.1037/a0038039

Shandera-Ochsner, A. L., Berry, D. T., Harp, J. P., Edmundson, M., Graue, L. O., Roach, A., & High, W. M., Jr. (2013). Neuropsychological effects of self-reported deployment-related mild TBI and current PTSD in OIF/OEF veterans. *Clin Neuropsychol, 27*(6), 881-907. doi: 10.1080/13854046.2013.802017

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y., . . . Zafonte, R. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav, 6*(2), 137-192. doi: 10.1007/s11682-012-9156-5

Simmons, A. N., & Matthews, S. C. (2012). Neural circuitry of PTSD with or without mild traumatic brain injury: a meta-analysis. *Neuropharmacology, 62*(2), 598-606. doi: 10.1016/j.neuropharm.2011.03.016

Soble, J. R., Silva, M. A., Vanderploeg, R. D., Curtiss, G., Belanger, H. G., Donnell, A. J., & Scott, S. G. (2014). Normative Data for the Neurobehavioral Symptom Inventory (NSI) and post-concussion symptom profiles among TBI, PTSD, and nonclinical samples. *Clin Neuropsychol, 28*(4), 614-632. doi: 10.1080/13854046.2014.894576

Soble, J. R., Spanierman, L. B., & Fitzgerald Smith, J. (2013). Neuropsychological functioning of combat veterans with posttraumatic stress disorder and mild traumatic brain injury. *J Clin Exp Neuropsychol, 35*(5), 551-561. doi: 10.1080/13803395.2013.798398

Sozda, C. N., Muir, J. J., Springer, U. S., Partovi, D., & Cole, M. A. (2014). Differential learning and memory performance in OEF/OIF veterans for verbal and visual material. *Neuropsychology, 28*(3), 347-352. doi: 10.1037/neu0000043

Spielberg, J. M., McGlinchey, R. E., Milberg, W. P., & Salat, D. H. (2015). Brain network disturbance related to posttraumatic stress and traumatic brain injury in veterans. *Biol Psychiatry, 78*(3), 210-216. doi: 10.1016/j.biopsych.2015.02.013

Spira, J. L., Lathan, C. E., Bleiberg, J., & Tsao, J. W. (2014). The impact of multiple concussions on emotional distress, post-concussive symptoms, and neurocognitive functioning in active duty United States marines independent of combat exposure or emotional distress. *J Neurotrauma, 31*(22), 1823-1834. doi: 10.1089/neu.2014.3363

Sripada, R. K., Rauch, S. A., Tuerk, P. W., Smith, E., Defever, A. M., Mayer, R. A., . . . Venners, M. (2013). Mild traumatic brain injury and treatment response in prolonged exposure for PTSD. *J Trauma Stress, 26*(3), 369-375. doi: 10.1002/jts.21813

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA, 314*(5), 489-500. doi: 10.1001/jama.2015.8370

Stein, M. B., Kessler, R. C., Heeringa, S. G., Jain, S., Campbell-Sills, L., Colpe, L. J., . . . Army Starrs collaborators. (2015). Prospective Longitudinal Evaluation of the Effect of Deployment-Acquired Traumatic Brain Injury on Posttraumatic Stress and Related Disorders: Results From the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *Am J Psychiatry*, appiajp201514121572. doi: 10.1176/appi.ajp.2015.14121572

Stein, M. B., & McAllister, T. W. (2009). Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry, 166*(7), 768-776. doi: 10.1176/appi.ajp.2009.08101604

Storzbach, D., O'Neil, M. E., Roost, S. M., Kowalski, H., Iverson, G. L., Binder, L. M., . . . Huckans, M. (2015). Comparing the Neuropsychological Test Performance of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans with and without Blast Exposure, Mild Traumatic Brain Injury, and Posttraumatic Stress Symptoms. *J Int Neuropsychol Soc, 21*(5), 353-363. doi: 10.1017/S1355617715000326

Swick, D., Honzel, N., Larsen, J., Ashley, V., & Justus, T. (2012). Impaired response inhibition in veterans with post-traumatic stress disorder and mild traumatic brain injury. *J Int Neuropsychol Soc, 18*(5), 917-926. doi: 10.1017/S1355617712000458

Tanielian, T., Jaycox, L., & Eds. (2008). Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery. RAND Corporation, Santa Monica, CA

Taylor, B. C., Campbell, E., Nugent, S., Cutting, A., Bidelspach, D. E., Carlson, K. F., & Sayer, N. A. (2014). Fiscal Year 2012 VA Utilization Report for Iraq and Afghanistan War Veterans Diagnosed with TBI. Prepared for the VA Polytrauma and Blast-Related Injuries QUERI #PLY 05-2010-2. Retrieved from http://www.queri.research.va.gov/ptbri/docs/FY12-TBI-Diagnosis-HCU-Report.pdf

Terrio, H., Brenner, L. A., Ivins, B. J., Cho, J. M., Helmick, K., Schwab, K., . . . Warden, D. (2009). Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. *J Head Trauma Rehabil, 24*(1), 14-23. doi: 10.1097/HTR.0b013e31819581d8

Vanderploeg, R. D., Belanger, H. G., & Curtiss, G. (2009). Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. *Arch Phys Med Rehabil, 90*(7), 1084-1093. doi: 10.1016/j.apmr.2009.01.023

Vanderploeg, R. D., Belanger, H. G., Horner, R. D., Spehar, A. M., Powell-Cope, G., Luther, S. L., & Scott, S. G. (2012). Health outcomes associated with military deployment: mild traumatic brain injury, blast, trauma, and combat associations in the Florida National Guard. *Arch Phys Med Rehabil, 93*(11), 1887-1895. doi: 10.1016/j.apmr.2012.05.024

Vanderploeg, R. D., Curtiss, G., Luis, C. A., & Salazar, A. M. (2007). Long-term morbidities following self-reported mild traumatic brain injury. *J Clin Exp Neuropsychol, 29*(6), 585-598. doi: 10.1080/13803390600826587

Vanderploeg, R. D., Silva, M. A., Soble, J. R., Curtiss, G., Belanger, H. G., Donnell, A. J., & Scott, S. G. (2015). The structure of postconcussion symptoms on the Neurobehavioral Symptom Inventory: a comparison of alternative models. *J Head Trauma Rehabil, 30*(1), 1-11. doi: 10.1097/HTR.0000000000000009

Vasterling, J. J., Brailey, K., Proctor, S. P., Kane, R., Heeren, T., & Franz, M. (2012). Neuropsychological outcomes of mild traumatic brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. *Br J Psychiatry, 201*(3), 186-192. doi: 10.1192/bjp.bp.111.096461

Verfaellie, M., Lafleche, G., Spiro, A., 3rd, Tun, C., & Bousquet, K. (2013). Chronic postconcussion symptoms and functional outcomes in OEF/OIF veterans with self-report of blast exposure. *J Int Neuropsychol Soc, 19*(1), 1-10. doi: 10.1017/S1355617712000902

Verfaellie, M., Lafleche, G., Spiro, A., & Bousquet, K. (2014). Neuropsychological outcomes in OEF/OIF veterans with self-report of blast exposure: associations with mental health, but not MTBI. *Neuropsychology, 28*(3), 337-346. doi: 10.1037/neu0000027

Waldron-Perrine, B., Hennrick, H., Spencer, R. J., Pangilinan, P. H., & Bieliauskas, L. A. (2014). Postconcussive symptom report in polytrauma: influence of mild traumatic brain injury and psychiatric distress. *Mil Med, 179*(8), 856-864. doi: 10.7205/MILMED-D-13-00282

Walker, W. C., Franke, L. M., McDonald, S. D., Sima, A. P., & Keyser-Marcus, L. (2015). Prevalence of mental health conditions after military blast exposure, their co-occurrence, and their relation to mild traumatic brain injury. *Brain Inj, 29*(13-14), 1581-1588. doi: 10.3109/02699052.2015.1075151

Walter, K. H., Dickstein, B. D., Barnes, S. M., & Chard, K. M. (2014). Comparing effectiveness of CPT to CPT-C among U.S. Veterans in an interdisciplinary residential PTSD/TBI treatment program. *J Trauma Stress, 27*(4), 438-445. doi: 10.1002/jts.21934

Walter, K. H., Jak, A. J., & Twamley, E. W. (2015). Psychiatric Comorbidity Effects on Compensatory Cognitive Training Outcomes for Veterans With Traumatic Brain Injuries. *Rehabil Psychol*. doi: 10.1037/rep0000049

Wang, F., Wang, Y., Sun, T., & Yu, H. L. (2016). Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis. *Neurol Sci*. doi: 10.1007/s10072-015-2460-2

Wang, Y., Chan, R. C., & Deng, Y. (2006). Examination of postconcussion-like symptoms in healthy university students: relationships to subjective and objective neuropsychological function performance. *Arch Clin Neuropsychol, 21*(4), 339-347. doi: 10.1016/j.acn.2006.03.006

Weathers, F. W., Keane, T. M., & Davidson, J. R. (2001). Clinician-administered PTSD scale: a review of the first ten years of research. *Depress Anxiety, 13*(3), 132-156.

Wolf, G., Cifu, D., Baugh, L., Carne, W., & Profenna, L. (2012a). The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. *J Neurotrauma, 29*(17), 2606-2612. doi: 10.1089/neu.2012.2549

Wolf, G. K., Strom, T. Q., Kehle, S. M., & Eftekhari, A. (2012b). A preliminary examination of prolonged exposure therapy with Iraq and Afghanistan veterans with a diagnosis of posttraumatic stress disorder and mild to

moderate traumatic brain injury. *J Head Trauma Rehabil, 27*(1), 26-32. doi: 10.1097/HTR.0b013e31823cd01f

Yeh, P. H., Wang, B., Oakes, T. R., French, L. M., Pan, H., Graner, J., . . . Riedy, G. (2014). Postconcussional disorder and PTSD symptoms of military-related traumatic brain injury associated with compromised neurocircuitry. *Hum Brain Mapp, 35*(6), 2652-2673. doi: 10.1002/hbm.22358

Yurgil, K. A., Barkauskas, D. A., Vasterling, J. J., Nievergelt, C. M., Larson, G. E., Schork, N. J., . . . Marine Resiliency Study, T. (2014). Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines. *JAMA Psychiatry, 71*(2), 149-157. doi: 10.1001/jamapsychiatry.2013.3080