RESEARCH REVIEW ON MILD TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC STRESS DISORDER

Table of Contents

PURPOSE

The purpose of this research review is to provide an overview of the topic of comorbid mild traumatic brain injury and posttraumatic stress disorder. It will focus on symptoms, anatomy, diagnosis, and treatment of mTBI, PTSD, and the unique circumstances associated with the presentation of both.

BACKGROUND

a. Mild Traumatic Brain Injury

Traumatic brain injury is defined as the alteration of brain function that results from exposure of the head to an external force.[1] For both civilian and military populations, TBI is a prevalent problem. Approximately 2.5 million civilian TBI-related emergency room visits occur each year.[2] In the military population, 5%–35% of service members who deployed to Iraq and Afghanistan sustained a mild TBI, also known as concussion, during their deployment.[3] This is the most common form of TBI, accounting for 82.3% of the nearly 473,000 service members diagnosed with a TBI between 2000 and 2022.[4]

The most common causes of civilian mTBI vary by age and include unintentional falls, being struck by or against an object, motor vehicle accidents, and contact sports.[5,6] While service members are also exposed to these injurious circumstances, the most common source of military mTBI in the past two decades is blast.[3] Overpressure waves from explosions can cause a blast-related mTBI, which accounts for 33% of mTBIs in service members.[7] Other causes include impacts from projectiles created by the explosion, propulsion of an individual into an object after the explosion, processes resulting from the effects of blast rather than the blast itself.[8] Regardless of the origin, experiencing one mTBI nearly doubles the risk of sustaining subsequent mTBIs.[9] This is important for recovery, as the duration of recovery and the severity of deficits increase proportionally with the number of mTBIs sustained.[10]

The diagnostic criteria for mTBI following trauma to the head include loss of consciousness lasting up to 30 minutes and altered consciousness (such as confusion or disorientation) or posttraumatic amnesia that can last up to 24 hours.[11] The VA/DOD clinical guidelines for determining TBI severity stipulate that an injury classified as mTBI should not result in abnormalities detectable via conventional brain imagining, such as computerized tomography scans.[11,12] This contrasts with the diagnosis of civilian mTBI which defines patients with this injury as having a Glasgow Coma Scale score of 13-15, regardless of CT abnormalities. In approximately 10-40% of civilian mTBI cases diagnosed based on the GCS, focal intracranial structural abnormalities can be detected via CT on the day of injury.[13] Mild TBI patients with abnormal CT scans are often described as having complicated mTBI.[14] It should be noted that for both military and civilian mTBI, CT scans are not usually indicated after a concussion. Indications for a CT are typically based on the presence of "red flags" as described in the MACE 2,[15] the Canadian Head CT rule,[16] or the New Orleans Criteria.[17]

Mild TBI patients may present with somatic, cognitive, and/or emotional symptoms soon after injury. Somatic symptoms include nausea, dizziness, headache, blurred vision/oculomotor deficits, auditory disturbances, and fatigue. The most common cognitive symptoms are delayed reaction times and disruption of memory and executive function. Emotional symptoms, such as disinhibition and emotional lability, are also common.[18] For patients with a higher symptom burden acutely following injury, physical and vestibular/balance-dependent activities are not recommended in the

acute period in order to promote recovery and prevent long-term impairment.[19] Mild TBI may also influence the development of long-term cognitive impairments and psychiatric illnesses.[20]

b. Posttraumatic Stress Disorder

Posttraumatic stress disorder is a psychological condition resulting from exposure to a traumatic event often involving actual or threatened death, serious injury, or violation.[21] Exposure can include personal experience of these traumatic events or having a close relationship with a victim of an event. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) recognizes PTSD with delayed expression, in which full diagnostic criteria are not met until one month or more post-trauma.[22] If symptoms occur earlier than one month post-trauma, the resulting condition is referred to as acute stress disorder.[23]

A diagnosis of PTSD usually occurs when patients experience symptoms from four discrete categories: intrusive thoughts; avoiding reminders; negative thoughts and feelings; and arousal and reactive symptoms. Symptoms associated with the intrusive-thoughts category involve experiencing vivid dreams, flashbacks, or involuntary memories. The avoiding-reminders category involves the inclination of patients to actively avoid people, places, activities, or situations that can bring on distressing memories. Avoidance of talking about or thinking about traumatic events is also common. Patients experiencing negative thoughts and feelings display distorted beliefs about themselves and others, as well as chronic fear, horror, guilt, anger, and shame. Finally, arousal and reactive symptoms include irritability, angry outbursts, engaging in reckless activities, proclivity towards being startled, inability to concentrate, and sleep disturbances.[23]

The National Comorbidity Survey Replication reported that in 2017, an estimated 3.6% of U.S. adults had PTSD and the lifetime prevalence of PTSD was 6.8%.[24] The prevalence is higher in the military, and the Department of Defense Health Related Behaviors Survey found that 10.5% of Army, 9.1% of Marines, 9.7% of Navy, and 3.9% of Air Force active duty service members had PTSD in 2015.[25] The prevalence of PTSD in the veteran population is estimated to be between 10% and 15% with a lifetime prevalence ranging from 12% to 30%.[26] Those SMs diagnosed with PTSD are highly prone to self-stigmatization about the disorder, or judgements and beliefs that inform their view of seeking treatment for it.[27] This is one of the primary reasons cases may be underestimated, as many veterans and service members suffering from PTSD do not seek treatment.[28,29]

The prevalence of PTSD is higher after a combat-related mTBI compared to a non-combat mTBI.[30] A systematic review of studies on mental health after deployment to Iraq or Afghanistan found that demographic characteristics, military characteristics, deployment-related factors, pre-deployment factors, and post-deployment factors were associated with an increased risk of PTSD.[31] The demographic characteristics were age under 40 (for males only), lower education, and unmarried status. Military characteristics were serving in the U.S. Army or Marines (as compared to other service branches), having an enlisted rank; and workings as a combat specialists or service and supply personnel (as compared to other occupational specialties). Deployment-related characteristics included a higher number of deployments and any injury sustained in combat. Pre-deployment factors 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. In studies conducted on military populations and

controlling for non-deployment related traumas, the rates of PTSD diagnosis are similar between males and females.[32]

The 11th edition of the International Statistical Classification of Diseases and Related Health Problems manual (developed by the World Health Organization) defined a subtype of PTSD not previously characterized in the DSM-5.[33] This subtype, known as complex PTSD (CPTSD), is thought to differ from PTSD because it is associated with exposure to chronic or prolonged trauma as might be seen with prisoners of war, and can result in higher levels of impairment.[34,35] Diagnosis of CPTSD involves the presence of hallmark PTSD symptoms, as well as additional symptoms that include disturbances in self-organization, affective dysregulation, negative self-concept, and disturbances in relationships.[36,37] When a veteran population was evaluated based on the new guidelines to distinguish PTSD from CPTSD, approximately 25-50% met the criteria for CPTSD.[38] More research and evaluation are needed to determine how CPTSD may affect military populations, and especially how this new classification may impact diagnosis and treatment of PTSD.

COMORBID MTBI AND PTSD

PTSD is one of the most commonly diagnosed psychiatric disorders associated with mTBI. In fact, the risk of PTSD is elevated two-to-threefold after mTBI according to studies of veterans, service members, and civilians.[39-41] The origin of PTSD in groups where mTBI is comorbid is unclear. Experiencing a traumatic event that causes TBI may initiate a constellation of symptoms that secondarily lead to PTSD. However, PTSD can also either predate TBI, arise concurrently or after onset of post-concussive symptoms, or be related to a separate event or series of events.

a. Unclear Symptom Etiology

There is a strong, albeit unclear relationship between PTSD and post-concussive symptoms. Both PTSD and mTBI share some common symptoms, which can complicate PTSD diagnoses in comorbid groups.[42] These common symptoms include insomnia, fatigue, irritability, depression, anxiety, emotional numbing, avoidance, trouble concentrating, memory deficits, and hyperarousal.[43] Biomarkers are being investigated as aids in the differential diagnosis of PTSD and symptoms resulting from mTBI, to determine the presence of any unique protein identifiers of comorbid occurrence.[44]

PTSD symptoms can aid in the prediction of post-concussive symptom onset and severity. In some studies with military or veteran participants, psychological factors were more predictive of post-concussive symptoms than TBI status.[45] PTSD can also influence treatment and recovery time, and can increase post-concussive symptom severity.[46-49] This is particularly true in service members with PTSD who experience mTBI, although misattribution of post-concussive symptoms to PTSD also is common in this group.[50] A number of studies have shown that this relationship is reciprocal, as PTSD symptoms are also more severe in military and veteran groups with probable or diagnosed mTBI than those with no history of mTBI.[51,52]

b. Prevalence

The prevalence rates of PTSD and mTBI can vary depending on the populations assessed. Many studies aimed at determining the prevalence in civilian populations have encountered conflicting results, as it is hard to standardize and compare the mechanisms and circumstances of injury. A 2020 meta-analysis aimed at identifying the prevalence of comorbid PTSD post TBI reported a pooled

prevalence of 15.7% in the civilian population and 36.8% in the military.[53] Mild traumatic brain injury is more frequently associated with PTSD than moderate or severe TBI.[54] Examination of military populations via systematic review found that comorbid mTBI and PTSD are significantly more common in military than civilian subjects. Across all studies included in the systematic review, 11.0–18.6% of the civilians who sustained a TBI developed PTSD within two years of injury compared to 48.2% of service members and veterans.[55]

c. Risk Factors for PTSD and mTBI

Among veterans, risk factors that increase the likelihood of developing PTSD include alcohol and substance abuse, smoking, history of chest pain, and younger age.[56] Other demographic factors associated with an increased PTSD risk include fewer years of education, incidence of pre-trauma psychiatric disorders, and marital status (unmarried)[57], as well as poorer pre-deployment inhibitory control and sustained attention which are also risk factors for post-deployment PTSD in the military.[58] One of the most common risk factors for developing PTSD after mTBI is acute stress disorder which, if diagnosed within 12 months after sustaining a mTBI, doubles the risk of developing PTSD.[59]

While PTSD is associated specifically with mTBI in civilians, the risk of developing PTSD increased with the severity of TBI and blast for those in the military.[41,60,61] However, it is plausible that the loss of consciousness and amnesia endured by a more severe TBI may provide a protective effect.[62] A history of mTBI itself can increase the risk of developing PTSD. It has been shown that, in addition to increasing the likelihood of developing lasting deficits, sustaining multiple mTBIs also increases the risk for developing PTSD.[63] Additionally, those who experience mTBI with extracranial injuries and TBIs resulting from violence had significantly more PTSD than those who did not.[64] As previously mentioned, being a member of the military is also a risk factor for PTSD diagnosis and symptom severity.[65] Combat related mTBI is correlated with increased PTSD symptom severity when compared to non-combat related mTBI.[50] The increased risk could be due to exposure to blast-related mTBI, a more prominent injury mechanism among military populations in recent years. Blast-exposed service members can experience an increase in PTSD symptom severity up to five years post injury, suggesting that an evolving mental health burden is related to this mechanism of mTBI.[66]

The dissonance between civilian and military populations could be attributed to the kinds of trauma to which each group may be exposed. Compared to civilians, military personnel are more likely to be exposed to combat environments during deployment. Combat exposure is associated with an increased likelihood of sustaining multiple lifetime TBIs, and the combination of these two factors yields greater PTSD symptom severity.[63] Morally injurious events are also associated with PTSD and may serve as a risk factor for PCS in veterans with mTBI.[67] These include falling to prevent, witnessing, or committing an action that violates a fundamental moral belief system[68] or an event that produces a sense of betrayal by entrusted authorities.[69] Veterans who screen positive for current PTSD and/or depression are more likely to have experienced a potentially morally injurious event.[70] Specifically, betrayal and perpetration are associated with a two-to-threefold increased odds of a positive PTSD screen, depression, or probable comorbid PTSD and depression.[70] Therefore, characteristics of psychological trauma and factors associated with combat environments may override properties of injury severity that link PTSD prevalence with mTBI.[71]

Genetic risk factors can moderate the relationship between mTBI and PTSD. Expression of the apolipoprotein E4 (APOE) gene, specifically the ε4 allele, is associated with poorer long-term clinical outcomes in all severities of TBI as compared to the ε2 & ε3 alleles.[72] A study examining the relationship between the APOE genotype and PTSD showed that the presence of the APOE ε4 allele was associated with increased PTSD following mTBI in veterans.[73,74] A meta-analysis demonstrated that the APOE ε4 allele can contribute to an increased risk for developing combat-related TBI; however, more research is warranted to gain a comprehensive understanding of APOE gene variants on PTSD outcomes.[75]

PTSD with mTBI history in service members and veterans is often associated with other psychological or physical conditions.[76,77] Individuals with comorbid PTSD and TBI (of all severities) report lower quality of life across all domains of health[78] and worse behavioral functioning.[45] Among recently diagnosed veterans with TBI, those with comorbid PTSD demonstrated lower physical, emotional, and cognitive functioning as well as more depressive symptoms.[78] Additionally, headache, suicidal impulses, substance use disorder, sleep disturbances, cumulative disease burden, and polypharmacy have been documented in this population.[76,77,79-85] Veterans with PTSD report higher pain interference scores compared to those without PTSD.[86-88] Comorbid mTBI and PTSD have also been associated with increased pain disability, impacting satisfaction with quality of life[86,89], and with an increased risk of developing Parkinson's disease.[90] Social outcomes reported in the comorbid PTSD and mTBI population include reduced psychosocial function, driving problems, lower return-to-work rates, and an increased incidence of intimate partner violence.[91-94] Furthermore, comorbid PTSD and mTBI can have a great impact on caregiver quality of life; caregivers report decreased relationship satisfaction and family functioning.[95]

DIAGNOSTIC AND ASSESSMENT TOOLS

Diagnosis of PTSD and mTBI based on symptoms alone can be difficult due to significant symptom overlap[96] and lack of tools for understanding and differentiating symptom etiology. This section describes common diagnostic and assessment tools relevant to both conditions.

As previously mentioned, mTBI diagnosis requires a clinician's interview and assessment as well as a precipitating injury that results in a loss of consciousness (up to 30 minutes), altered consciousness, or posttraumatic amnesia..[11] Assessment tools include the Neurobehavioral Symptom Inventory (NSI) and the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), both of which are self-reporting tools that can be used to determine post-concussion symptom severity [97,98]. The two instruments are similar in that they provide a list of symptoms (22 on the NSI, 16 on the RPQ) and ask respondents to indicate severity on a five-point Likert-type 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.[99-102] The resulting factor structures vary, but one comparative study that utilized Rasch analysis found that, for the NSI, a three-factor structure including vestibular and somatic, cognitive, and mood and behavioral factors provided the best fit for a sample of OEF and OIF veterans.[101] Normative tables have been created for the NSI which have the potential to be useful in comparing post-deployment NSI questionnaires to peer matched demographics to detect potential medical concerns.[103] Additional studies have determined that, while the NSI is a reliable metric for determining psychological stress, it does not reliably predict or examine changes in functioning.[104]

Neither the NSI nor the RPQ are diagnostic, in part due to the high base rate of these symptoms among uninjured populations[105] and in part because a number of symptoms on these scales are also associated with PTSD and other psychological conditions. The Clinician-administered PTSD Scale is widely used for PTSD diagnosis. The CAPS was updated to reflect revisions to the criteria for PTSD defined in the DSM-5, so the currently preferred version is the CAPS-5.[106] The PTSD checklists for the military (PCL-M) and civilians (PCL-C) have also been updated to the PCL-5 to reflect DSM-5 changes, and are commonly used to assess symptom severity.[107,108]

The VA/DOD Clinical Practice Guideline for PTSD indicates that patients should be screened for PTSD annually during deployment cycles and during the first five years following separation from service.[109] Periodic screening on a five-year basis may then follow. The DOD includes screening for PTSD in the Post-Deployment Health Assessment (DD Form 2796), Post-Deployment Health Reassessment (DD Form 2900),[110] and Deployed Mental Health Assessment (DD Form 2978).[111] But the most commonly used instrument in the VA and DOD is the Primary Care PTSD Screen (PC-PTSD-5), which is specifically designed for use in primary care settings.[112] The five 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[113] and the patient is referred for further evaluation and assessment. The PC-PTSD-5 was found to have good diagnostic utility and can accurately detect PTSD in the VA primary care setting.[114]

Post-concussive and PTSD symptom instruments rely primarily on self-reporting, so most tools for assessing mTBI and PTSD should be used in conjunction with clinician assessment. In a study performed using the Minnesota Multiphasic Personality Inventory (MMPI-2) symptom validity test, it was found that a large portion of treatment-seeking OEF and OIF veterans were prone to exaggeration of cognitive, post concussive and PTSD symptom severity that did not correspond to performance on more objective measures.[115] Exaggeration of PTSD symptoms could arise due to unconscious bias of responses on self-report assessments, or intentional falsification to increase personal or financial gain.[116] To address this problem, many commonly used assessments such as the NSI have modifying additions like the Validity-10 scale that can aid in identifying exaggerated symptom reports in patients with comorbid mTBI and PTSD or other psychological disorders.[117]

To aid with diagnosis, assessment modalities that include structured interviews are being utilized and explored. Structured interviews can support identification of lifetime history of mTBI. The Ohio State University Traumatic Brain Injury Identification Method is an accurate assessment method that can be administered via telephone, in person, or online.[118] The Veterans Health Administration TBI Clinical Reminder is another structured interview developed to support diagnosis of TBI specifically in veterans.[119] In addition to these interviews, there is interest in performing assessments for objective data of vestibular and motor function in persons with PTSD and/or mTBI history.[120,121] Technologies including fluid biomarkers,[122-124] electroencephalography,[125] and magnetoencephalography [126-128] have been used in clinical research studies to characterize subjects with PTSD and/or mTBI, but these approaches have not yet been validated for clinical use.

NEUROPSYCHOLOGICAL MANIFESTATIONS OF MTBI AND PTSD

a. Common Neuropsychological and Neurocognitive Tests

Neuropsychological tests are used to evaluate cognition, mood, social cognition, and motivation.[129] Computerized neurocognitive assessment tests are meant to detect differences in executive function,

memory, attention, processing speed, learning, and other domains of cognition that can be affected by mTBI and/or PTSD.[130] Four computer-based NCATs are commonly administered to evaluate cognitive performance after mTBI: the Automated Neuropsychological Assessment Metric (ANAM), the CNS Vital Signs (CNS-VS), Axon/CogState/CogSport (CogState), and the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT).[131]

- The ANAM was developed by the DOD to measure processing speed, reaction time, memory, and cognitive efficiency. The fourth version, ANAM4 TBI-MIL,[132] is used for military personnel and is required to be performed within 1 year prior to deployment as a baseline.[133] A tablet-based version currently in development will allow for greater portability, particularly among Special Operations Forces. A preliminary study found it to have good-to-excellent test-retest reliability in a cohort of 108 uninjured college students,[134] and additional testing, including psychometric testing, is ongoing in the military population.

- The CNS-VS is used in athletic settings to assess several cognitive domains including visual memory, verbal memory, psychomotor speed, reaction time, complex attention, processing speed, executive function, simple attention, motor speed, and cognitive flexibility.[135]

- The CogState assessment battery is used to evaluate reaction time and processing speed using a playing-card motif.[136]

- ImPACT is the most commonly used NCAT for evaluation of cognitive changes following sports-related concussion, including verbal memory, visual memory, visual motor speed, and reaction time.[137]

For PTSD, an array of neurocognitive tests can be used. The domains most commonly examined with these tests include verbal learning and memory, working memory, visual processing speed, verbal performance IQ, visual attention and task switching, and executive function.[138,139] When assessing comorbid occurrence, a battery of tests is used to provide an objective means of assessing performance in areas affected by both mTBI and PTSD.[140] The battery of tests should include assessments that seek to understand subjective cognitive complaints and objectively measure cognitive performance to better understand the impact of trauma-related psychopathology.[140]

Neurocognitive and neuropsychological changes can greatly affect quality of life for those with PTSD or mTBI. Identifying the cognitive impairment caused by mTBI versus that caused by PTSD is imperative for determining how to target therapeutic interventions to improve performance in comorbid groups. For example, attributing PTSD symptoms to mTBI can reduce adherence to effective treatment protocols.[141] Neuropsychological testing can determine discrete functional changes associated with each condition. This can allow clinicians to prescribe differential cognitive or behavioral therapy that addresses both sets of deficits.

Neuropsychological and neurocognitive tests are not indicated for diagnostic purposes; however, they do provide objective evaluations of neuropsychological manifestations of mTBI, PTSD, and comorbid occurrence. Test performance alone was found to be more robust than neuroimaging measures in differentiating distinct symptom profiles in active duty service members with mTBI and PTSD.[142] This objective information may be important for determining return to duty, benefits, and other decisions.

b. Neuropsychological and Neurocognitive Findings: Mild TBI Only

During the acute phase of mTBI recovery in civilians, decreases in neuropsychological test performance have been observed for attention, language, memory, visual perception, and executive function.[143] Impairments in attention, language, memory, and executive function were found even six months after injury.[144] Reaction time impairments seen with the ANAM appear to be sensitive to mTBI in the active duty military population.[145] For service members who have sustained a blast-related TBI, an acute decline in simple reaction time in ANAM was observed[146,147] and associated with changes in diffusion tensor imaging[148]. Although several studies also report lasting impairments, mTBI patients in the chronic phase of recovery without comorbid psychological health conditions do not consistently demonstrate poorer neuropsychological test performance as compared to non-TBI controls. A study of OEF and OIF veterans assessed several years after mTBI found no neuropsychological differences between those with mTBI only and controls without mTBI,[48] but other studies have found that chronic impairments arise following both blast and non-blast mTBI.[66,149] These variations in the likelihood of chronic deficits may be attributed to the number of mTBIs sustained, as a single mTBI is not generally associated with lasting deficits whereas multiple mTBIs do convey a higher risk.[150]

c. Neuropsychological and Neurocognitive Findings: PTSD Only

PTSD alone is associated with decreased neurocognitive test performance in several domains, especially verbal learning, processing speed, attention, and working memory, according to a recent meta-analysis of data from 1,779 PTSD patients including military and civilian trauma survivors.[151] These findings are consistent with neuropsychological studies showing reduced performance in veterans with PTSD as compared to veteran controls.[152] PTSD also has been shown to cause impairments in multiple domains of neuropsychiatric tests, including episodic memory and executive function.[151,153-155] Increased PTSD symptoms or diagnosis are correlated with higher rates of impaired neuropsychological outcomes.[156,157] Taken together, these data suggest that PTSD and subclinical PTSD symptoms may be bidirectionally related to the cognitive impairments observed among PTSD patients with mTBI history. The origin of impairments cannot be determined from neuropsychological testing, however, so further studies are needed to understand how discrete factors in the constellation of PTSD symptoms can influence cognition.

d. Neuropsychological and Neurocognitive Findings: Comorbid Group

Multiple studies in OEF and OIF veteran and active duty populations with PTSD and mTBI history have shown that neuropsychological outcomes can be negatively impacted months or years after injury. Several studies have shown that those with a PTSD diagnosis or significant PTSD symptoms in combination with mTBI history performed significantly worse on neuropsychological tests as compared to those with PTSD only, mTBI only, or controls. This has been seen with service members,[50,158,159] veterans,[46,51,160] and civilians.[42] Deployment-related TBI was associated with poorer outcomes on several neurocognitive tests compared to non-deployment related TBI.[161] The same is true after blast mTBI wherein the presence of PTSD symptoms is correlated with neuropsychological deficits.[162] Impaired long-term working memory and lower cognitive flexibility has also been associated with probable PTSD in adults with a TBI.[163] In contrast, some studies have found no significant neuropsychological differences between those with mTBI history and PTSD and those with only one condition.[164,165] These inconsistent findings may be due to the characteristics of study participants, study design, outcomes, or other factors.

Additional neuropsychological assessment tools are currently being tested to determine their utility to evaluate comorbid mTBI/PTSD symptoms in military populations. For example, an iPad-based tool in the NIH Toolbox Cognitive Battery has been used for examining mTBI and PTSD symptom severity and resulting cognitive deficits in comorbid groups. This tool was able to detect increased cognitive impairment in the comorbid group as compared to groups with PTSD and mTBI only, and made it possible to accurately assess neuropsychological function in large samples and in conditions that require readily available testing and rapid results.[166] Though the NIH-TB demonstrates potential for usefulness in the military population, further research is needed to determine clinical utility.

CHANGES IN THE BRAIN ASSOCIATED WITH MILD TBI AND PTSD

a. Imaging Approaches

Imaging techniques provide valuable tools to examine the brain and detect alterations resulting from PTSD and mTBI, as well as to identify changes that are unique to their comorbid occurrence. These techniques are not yet routinely used for clinical assessments of patients, as their predictive and diagnostic capabilities remain to be demonstrated in larger clinical samples. They do, however, reveal valuable mechanistic and neuroanatomical information that may prove to have clinical utility.

Various imaging techniques have been used to study the changes in the brain that arise in correlation with PTSD and mTBI. Traditional CT scans and MRI have thus far not been able to differentiate mTBI alone from mTBI comorbid with PTSD. Brain volume measurements have demonstrated promise for identifying those with comorbid PTSD and mTBI history.[167-169] Researchers have used sophisticated imaging approaches including functional MRI to investigate the pathology and changes in brain function unique to mTBI and comorbid PTSD.[170-172] Other imaging approaches that may warrant further study include advanced MRI techniques such as diffusion tensor imaging, diffusion kurtosis imaging, and single photon emission computed tomography (SPECT). Limited evidence shows the potential of SPECT to provide diagnostic information in those with PTSD, mTBI, or both.[173,174] Fluid-attenuated inversion recovery MRI approaches have been used to characterize white matter hyperintensity in these populations.[164,175] DTI demonstrates mixed capabilities for matching white matter integrity to symptom severity in comorbid groups; however, it remains promising in its diagnostic and prognostic potential.[176-179]

Magnetoencephalography (MEG) is a functional imaging technique that detects the magnetic signal in the grey matter produced by neuronal activity.[128,180] This technique has not only shown efficacy in detecting functional changes that occur in specific brain regions after mTBI, but has also demonstrated the ability to identify PTSD-specific influences on these changes in the same brain regions.[180] Imaging with MEG could, therefore, be a powerful tool for use in identifying unique functional changes characteristic of comorbid mTBI and PTSD. While not currently used in routine clinical practice, further research with these imaging techniques will contribute to greater understanding of the brain's activity and response to TBI.

b. Mild TBI Only

Uncomplicated mTBIs are characterized by the presence of diffuse injuries that cannot be detected via CT. They tend to involve areas of damage scattered in various seemingly intact structures throughout the brain. This damage often presents as diffuse neuronal damage, axonal (white matter) perturbation, and changes in vasculature, which are difficult to detect with conventional imaging

modalities.[181] The advent of DTI and similar techniques allow for the detection of diffuse axonal injuries resulting from mTBI.[182] For example, a meta-analysis of DTI studies performed on patients exposed to blast mTBI showed persistent changes in white matter integrity in several prominent white matter tracts throughout the brain, as well as cortical thinning.[183] A separate systematic review and data analysis examining changes in white matter integrity using DTI, found that longitudinal changes in diffusion metrics after mTBI were very heterogeneous.[184] The extent of white matter damage is also correlated with the severity of post-concussive symptoms.[185] Changes in white matter can greatly alter the connectivity between brain regions, resulting in functional impairments.

Clinical and translational studies have shown that the hippocampus is vulnerable to changes in function, volume, and connectivity following one or multiple mTBIs.[186-189] A history of deployment-related TBI has been associated with lower volumes in the right medial orbitofrontal cortex as well as bilateral hippocampal volume.[189] White matter changes[190] as well as changes in function and electrographic activity [191] in the dorsomedial and dorsolateral prefrontal cortex have also been found. These changes are thought to contribute to the impairments in executive function commonly observed in patients who sustain mTBIs. Given the importance of the dorsomedial and dorsolateral prefrontal cortex in facilitating learning and memory, it is not surprising that many patients who experience mTBI develop learning and memory deficits. Thalamic functional connectivity is additionally thought to be disrupted after mTBI, and that disruption is correlated with worse symptoms and poor recovery in neuropsychological assessments.[192] Given the role of the thalamus in functions such as gating pain, mediating sleep and fatigue, and regulating certain elements of cognition, it also is not surprising that posttraumatic headache and disturbances in sleep and cognition are observed following mTBI. [193]

c. PTSD Only

Imaging studies have identified brain regions that are altered structurally and functionally in PTSD. Three primary brain regions have frequently been investigated: the amygdala, hippocampus, and medial prefrontal cortex. [194]

The amygdala is thought to play a role in behavioral and physiological responses to fear, and many studies have indicated that changes in its activity and structure are a hallmark of PTSD. Amygdala volume is decreased in combat veterans with PTSD, which has been linked to hyper-responsiveness, and subsequent anxious arousal (a common symptom of PTSD).[195] Increased or decreased activation of the amygdala does not seem to be uniform across all PTSD patients.[196] In fact, it has been suggested that increased or decreased amygdala activity can be associated with specific PTSD symptoms.[197]

The hippocampus is primarily responsible for orchestrating normal learning and memory. In PTSD, increased hippocampal activity is associated with reliving symptoms and impaired episodic memory.[196] Structural imaging studies have shown that decreased hippocampal volume may also be associated with PTSD.[198,199] Structural connectivity between the left and right hippocampus may also be impacted by PTSD.[200]

The medial prefrontal cortex is responsible for processing and encoding emotional information and using that information to add valence and context to memories. Reduced activity of the ventromedial prefrontal cortex, which is linked to the experience and regulation of motion, is also

observed in PTSD.[201] This decrease in activity seems to be an acquired characteristic caused by PTSD.[202] Smaller mPFC volumes are also a hallmark of PTSD.[203]

d. Comorbid Group

Many studies have aimed to examine the amygdala, hippocampus, and medical prefrontal cortex to determine if key pathological features of the individual groups are made worse by comorbid occurrence. A study exploring the impact of PTSD on cortical structural integrity in a group of veterans showed a potential dose-response relationship with individuals with comorbid severe PTSD and deployment-related mTBI, with a stronger association between age and cortical changes compared to PTSD alone.[204] Decreased cortical thickness has been seen in individuals diagnosed with PTSD with a history of mTBI.[205] When the volume of the amygdala and hippocampus were analyzed in veteran populations, the comorbid group exhibited an increase in amygdala volume and a decrease in left hippocampal volume that was not apparent in the TBI only group.[206] Increased amygdala volume specific to the comorbid mTBI and PTSD group was also observed in veterans from OEF and OIF using different techniques to normalize and account for variable head size.[167] Several PTSD studies have shown that amygdala volume decreases, which could indicate that the mTBI and PTSD comorbid group may have a distinct phenotype detectable through brain imaging. To further delineate between mTBI and PTSD conditions, differences in imaging studies that correspond to brain regions associated with the cognitive capabilities assessed in neurocognitive tests can also aid in identifying differences unique to participants in the comorbid group.[207]

The current view of how changes in brain structure and function can uniquely underlie symptom manifestation in comorbid groups is that both PTSD and mTBI alter the ability of networks of brain structures to communicate. A recent systematic review including 16 articles involving service members and veterans found no consensus among neuroimaging correlates of TBI-related PTSD.[208] Trends did emerge that suggested TBI-related PTSD may be associated with disruption of white matter tracts as well as changes in whole-brain networks or resting-state MEG connectivity.[208] Pivotal are white matter integrity changes observed in mTBI, as they alter the connectivity between structures, resulting in a higher likelihood of developing behavioral and cognitive symptoms.[209] These changes occur in white matter tracts that connect regions important for PTSD symptom generation, including the corpus callosum and tracts connecting limbic system structures, such as the hippocampus and amygdala.[210] Symptom severity for PTSD is also positively correlated with the extent of reduction in white matter integrity in mTBI patients in these tracts.[211,212] There are more regions with changes in white matter integrity in the mTBI and PTSD comorbid group as compared to PTSD and mTBI groups alone.[177] These findings suggest that while PTSD is associated with overt structural differences, the white matter changes associated with mTBI are an insidious contributor to increased PTSD symptom manifestation. Similar overlapping patterns of reduced resting-state functional connectivity have also been seen in working memory regions in mTBI and PTSD, supporting the idea of shared neural substrates of working memory in individuals with mTBI or PTSD.[213] Furthermore, positron emission tomography scans suggest altered metabolic interrelationships in the cortico-limbic circuity in mTBI patients with persistent and significant comorbid PTSD. PET scans seem to indicate that the temporo-limbic system is associated with hyperarousal and post-concussive symptoms.[214]

TREATMENT IMPLICATIONS

a. Clinical Practice Guidelines

The VA/DOD treatment guidelines for post-acute mTBI focus on symptom management, education, and evidence-based diagnosis and treatment of possible comorbid conditions.[11] The VA/DOD Clinical Practice Guidelines for PTSD emphasizes a collaborative treatment approach, manualized trauma-focused psychotherapy, and recognition of possible comorbid conditions.[109] Prescribing medication for patients with comorbid TBI and PTSD is challenging, as some medications can exacerbate the symptoms of one condition while effectively treating the other.[71] Because of this, special attention must be paid to pharmacology for integrated mTBI and PTSD care.

Patient retention can also be a treatment challenge.[215,216] It is widely suggested in the literature that one of the most common barriers to treatment compliance is the deficit in executive function that may exist in patients with comorbid mTBI and PTSD.[160] Therefore, greater executive functioning at baseline has also been associated with improvements in quality of life following participation in cognitive processing therapy.[217] In addition, problems with emotional regulation, impulse control, and symptom severity from PTSD as well as the stigma related to seeking treatment can limit the patient's ability to engage in treatment, or incite drop-out.[218,219] These cognitive and psychological barriers can result in poor treatment outcomes. Therefore, the efficacy of PTSD/mTBI treatments should also be evaluated with consideration given to the likelihood of compliance with treatment recommendations.

A systematic review of studies performed on treatments for comorbid mTBI and PTSD was conducted to evaluate the efficacy of different treatment paradigms used between 1980 and 2019. From the 26 studies included in the review,[218] it was determined that CPT or other kinds of cognitive behavioral therapy reduced PTSD symptoms in patients when combined with other treatment types. Pharmacological agents showed some promise in treating chronic PTSD. Novel treatments like vestibular rehabilitation are promising, but require further study.[218] The efficacy of many of these treatments has not been adequately evaluated with comorbid PTSD/mTBI, and most of the studies focus on one of the two conditions. Given the unique circumstances generated by comorbid occurrence, they may not adequately address the overall symptom burden. These treatment modalities are discussed further below.

b. Evidence Regarding Non-Pharmacological Interventions

A 2015 systematic review on psychotherapy for military-related PTSD found that the treatments supported by the most evidence were CPT, trauma-focused exposure therapies, and eye movement desensitization and reprocessing therapy.[215]

While PTSD treatments are well-supported by evidence, fewer studies have been performed with comorbid PTSD and mTBI patients. Studies in populations with comorbid PTSD and TBI history show that prolonged exposure therapy is successful in reducing symptoms regardless of their presumed origin.[220] Studies of PE therapy,[80,141,221,222] CPT,[223] and mindfulness intervention [224] have had positive results. Cognitive rehabilitation interventions have reduced psychiatric symptoms according to several studies.[225-229] Combined strategies for administering therapies to better address comorbid TBI and PTSD are currently being explored. One such therapy is the SMART-CPT approach, which integrates the compensatory cognitive training aspects of Cognitive Symptom

Management and Rehabilitation Therapy into CPT. A randomized, controlled trial found that while both CPT and SMART-CPT saw nearly equivalent reductions in PTSD and post-concussive symptoms, SMART-CPT was better able to improve learning and memory, attention, and problem solving.[230] Additionally, SMART-CPT demonstrated similar improvements in life satisfaction, family and health outcomes, and daily activities compared to those receiving CPT. It can be administered in less time than both treatments separately.[230] A form of cognitive behavioral therapy known as stress inoculation training has also shown efficacy in treating comorbid mTBI and PTSD symptoms. A study that implemented SIT in a group of veterans with comorbid mTBI and PTSD found that it could effectively reduce PTSD symptoms and produce self-reported improvements in their ability to concentrate and engage in valued/functional activities in their daily life.[231] SIT is not recommended as a replacement for primary treatments but a paradigm of care to augment CPT and PE.[231] Improvement in cognition and emotional disturbances has also been seen in the goal-oriented attentional self-regulation cognitive rehabilitation training program.[232,233] A randomized controlled trial in veterans compared GOALS to brain-health education training and found that participants who completed GOALS showed a decrease in PTSD symptoms and significant improvements in attention, executive functioning, mood disturbances, and complex functional task performance.[233] As the primary target of GOALS training is to focus on improving self-regulation and cognitive control to achieve personalized goals, the application and generalization of the skills learned in this training can have a significant positive impact on quality of life.[233]

Repetitive transcranial magnetic stimulation, a non-invasive brain stimulation technique, is also being explored as a potential treatment for comorbid mTBI and PTSD.[234] A review of all of the rTMS studies completed between 2002 and 2018 showed that, in combination with psychotherapy, high-frequency rTMS over the dorsolateral prefrontal cortex or other frontal regions was effective for alleviating depressive symptoms associated with PTSD or core PTSD symptoms (respectively).[235] When rTMS was applied at low frequency to the dorsolateral prefrontal cortex, it alleviated hyperarousal resulting from comorbid anxiety. More testing is required to determine whether this will be an efficacious treatment option leading to lasting clinically relevant outcomes.[236]

c. Evidence Regarding Pharmacological Interventions

Though psychotherapy is the first-line treatment for PTSD, a study among 207,354 adults with TBI observed low psychotherapy participation, and psychotropic medication was more commonly used for individuals diagnosed with anxiety or PTSD post TBI.[237] Antidepressants have been widely studied as a potential treatment for PTSD. Selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors such as sertraline and venlafaxine, respectively, are the first line of prescribed medications for PTSD. They have been shown to effectively reduce symptoms in multiple clinical trials.[238] Tricyclic antidepressants and monoamine oxidase inhibitors have also been tested for alleviation of PTSD symptoms and have shown some efficacy, although the side effects of these medications make them less desirable candidates for therapeutic interventions at this time.[239]

Anti-adrenergic agents such as prazosin, have yielded both negative and positive results in clinical trials. While some studies have shown that prazosin can effectively reduce posttraumatic nightmares, avoidance, and hypervigilance, others have found no difference between prazosin and placebo treated groups in symptom severity.[240-243] Propranolol, another anti-adrenergic agent, has also been explored as a potential treatment for PTSD symptoms; overall, the data do not provide support for its efficacy as a stand-alone treatment.[244,245] A randomized control trial 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 both,[246] but larger randomized control trials, that include multiple sites, are needed to confirm these findings.[246] Other classes of drugs, such as anticonvulsants or mood stabilizers, antipsychotics, and benzodiazepines, have also been considered as potential therapies. However, these drugs have either not been effectively evaluated in randomized clinical trials, or have shown serious side effects and/or minimal efficacy, making them undesirable candidates for the current treatment of mTBI/PTSD.[239]

d. Factors Protective Against PTSD Symptoms

A 2021 study of factors that are protective against self-harm found patients who reported having personal protective factors (such as social competency and positive temperament), social protective factors (such as social support in the form of family, colleague, and community connection),[247] and other factors (including pets and hobbies) were less likely to be diagnosed with PTSD.[248] A study of veterans showed that higher dispositional optimism and higher levels of community integration also protected against PTSD.[249] Resilience is another important factor associated with better outcomes and reduced PTSD symptoms after injury.[71] When specifically assessing characteristics of TBI that could be protective, longer durations of posttraumatic amnesia are associated with a reduction in the development of PTSD.[42,250] This explains why those with moderate or severe TBI associated with prolonged loss of consciousness are much less likely to develop PTSD than those with mTBI.

SUMMARY

Substantial evidence demonstrates that comorbid TBI and PTSD can have a considerable impact on the function and psychological well-being of service members and veterans. Military providers treating service members and veterans with PTSD and comorbid mTBI are often faced with complex decision making as these patients present with more severe or persistent symptoms compared to individuals diagnosed with only one of these conditions. Evidence shows that standard PTSD treatments can be effective for treating the more salient PTSD symptoms in this population; however, combinatorial approaches that address negative outcomes from both conditions are required. Promising research with imaging, blood, and other fluid biomarkers continues to be ongoing with the potential to guide management and clinical decision making in the future. However, at this time, further research is needed to identify more effective diagnostic and assessment tools, treatment options, and prognostic tools to benefit patients with PTSD and with history of mTBI.

CONCLUSIONS & RECOMMENDATIONS

- Service members and veterans are at increased risk for developing comorbid mTBI and PTSD.

- Due to overlapping symptomology and reliance on self-report, distinguishing between PTSD and mTBI can be difficult. Patients should be screened for PTS when presenting for evaluation following mTBI.

- The environment in which the mTBI was sustained can impact clinical outcomes.

- When compared to non-combat related mTBI, the risk of developing of PTSD and increased PTSD symptom severity is more highly correlated with combat-related mTBI.

- Blast-related mTBI may be associated with more severe PTSD symptoms compared to non-blast-related mTBI.

- Exposure to combat conveys an increased risk of multiple lifetime TBIs, which can also influence PTSD symptom severity.

- Advanced imaging techniques (DTI, MRI, MEG, fMRI) may eventually help clinicians better identify and understand the structural and functional brain changes and origins of neuropsychiatric symptoms in traumatic brain injury and PTSD. At this time, these techniques are not widely available for clinical use.

- Chronic neuropsychological impairments in domains like learning, memory, and executive function have been linked to PTSD and mTBI individually. Results are inconclusive as to whether the presence of both increases the incidence and severity of these impairments.

- A holistic treatment plan that includes integrated behavioral health and rehabilitation interventions is recommended when managing service members and veterans with mTBI and PTSD.

  - Consider patient-centered treatment strategies and multidisciplinary coordinated care when treating patients with co-occurring mTBI and PTSD.

  - Effectively treating PTSD can lead to less severe neurobehavioral outcomes, improved sleep, and decreased pain.

  - Engaging in cognitive rehabilitation may also have a positive impact on other domains including emotional regulation and functional performance. Several cognitive processing/behavioral therapies including SMART-CPT and SIT show promise for treating comorbid mTBI and PTSD.

  - Newer treatments like rTMS are also being explored to treat comorbid symptoms.

  - Retention and compliance are necessary factors to consider when designing successful therapies. It is important for military providers to address barriers, provide psychoeducation, and consider family or significant others' involvement in planning and treatment.

- Non-pharmacological management of mTBI and PTSD should always be the first choice for treatment.

  - Pharmacological treatment with SSRIs and SNRIs may be used in some cases for alleviating PTSD symptoms.

Disclaimer

TABLES

Table 1: Clinical Tools

PTSD			
Tool	Tool Type	Domain Explained	VA/DOD Specific (Y/N)
Minnesota Multiphasic Personality Inventory (MMPI-2)	Self-Report	Personality	N
Clinician-Administered PTSD Scale (CAPS)	Assessment	Symptoms	N
Post-Deployment Health Assessment (PDHA)	Assessment	Symptoms	Y
Post-Deployment Health Reassessment (PDHRA)	Assessment	Symptoms	Y
Deployed Mental Health Assessment (DMHA)	Assessment	Symptoms	Y
Primary Care PTSD Screen (PC-PTSD-5)	Screening	Symptoms	N
Rivermead Post-Concussion Symptoms Questionnaire (RPQ)	Self-Report	Symptoms	N
PTSD Checklist — Military Version (PCL-M)	Self-Report	Symptoms	Y
PTSD Checklist — Civilian Version (PCL-C)	Self-Report	Symptoms	Y
Mild TBI			
Tool	Tool Type	Domain Explained	VA/DOD Specific (Y/N)
The Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)	Screening	Semi-structured Interview	N
Veterans Health Administration TBI Clinical Reminder	Screening	Semi-structured Interview	Y

Automated Neuropsychological Assessment Metric (ANAM 4 TBI-MIL)	NCAT	Cognitive Function	Y
CNS Vital Signs (CNS-VS)	NCAT	Cognitive Function	N
Axon/CogState/CogSport (CogState)	NCAT	Cognitive Function	N
Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)	NCAT	Cognitive Function	N
Military Acute Concussion Evaluation-2 (MACE 2)	Screening	Multiple Domains	Y
Canadian Head CT Rule	Screening	Multiple Domains	N
New Orleans Criteria	Screening	Multiple Domains	N
Neurobehavioral Symptom Inventory (NSI)	Self-Report	Symptoms	N

Table 2: Military Relevant CRs/CPGs

Name of CR/CPGs	Website Address	Last Revised
Military Acute Concussion Evaluation-2 (MACE 2)	https://health.mil/MACE2	2021
VA/DOD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury	https://www.healthquality.va.gov/guidelines/Rehab/mtbi/index.asp	2021
VA/DoD Clinical Practice Guideline for Posttraumatic Stress Disorder	https://www.healthquality.va.gov/guidelines/MH/ptsd/	2023

REFERENCES

1.   Peterson AB, Kegler, S.R. Deaths from fall-related traumatic brain injury- United States, 2008-2017. Centers for Disease Control and Prevention. 27 July, 2020. Accessed 27 July, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6909a2.htm?s_cid=mm6909a2_w
2.   Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. (2014).
3.   Lindberg MA, Moy Martin EM, Marion DW. Military Traumatic Brain Injury: The History, Impact, and Future. *J Neurotrauma*. Sep 2022;39(17-18):1133-1145. doi:10.1089/neu.2022.0103
4.   Department of Defense. DOD TBI Worldwide Numbers https://health.mil/Military-Health-Topics/Centers-of-Excellence/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers
5.   Centers for Disease Control and Prevention. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. 2020. https://www.cdc.gov/traumaticbraininjury/pdf/TBI-Surveillance-report-final_508.pdf
6.   Reid DBC, Shah KN, Baum EJ, Daniels AH. Concussion: Mechanisms of Injury and Trends from 1997 to 2019. *Rhode Island medical journal (2013)*. Sep 1 2020;103(7):71-75.

7.   Lindquist LK, Love HC, Elbogen EB. Traumatic brain injury in Iraq and Afghanistan veterans: new results from a national random sample study. *The Journal of neuropsychiatry and clinical neurosciences*. 2017;29(3):254-259.

8.   Kinch K, Fullerton JL, Stewart W. One hundred years (and counting) of blast-associated traumatic brain injury. British Medical Journal Publishing Group; 2019.

9.   Van Pelt KL, Allred D, Cameron KL, et al. A cohort study to identify and evaluate concussion risk factors across multiple injury settings: findings from the CARE Consortium. *Injury epidemiology*. 2019;6(1):1-11.

10.   Greco T, Ferguson L, Giza C, Prins M. Mechanisms underlying vulnerabilities after repeat mild traumatic brain injuries. *Experimental neurology*. 2019;

11.   Management and Rehabilitation of Post-Acute of mild Traumatic Brain Injury (mTBI) (Veterans Affairs Office of Quality, Safety and Value & U.S. Army Medical Command Office of Evidence Based Practice) (2021).

12.   Department of Defense. *Department of Defense Instruction: DoD Policy Guidance for Management of Traumatic Injury/ Concussion in the Deployed Setting*. 2012. 6490.11. Accessed January 12 2023. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/649011p.pdf

13.   Isokuortti H, Iverson GL, Silverberg ND, et al. Characterizing the type and location of intracranial abnormalities in mild traumatic brain injury. *Journal of neurosurgery*. Dec 1 2018;129(6):1588-1597. doi:10.3171/2017.7.JNS17615

14.   Karr JE, Iverson GL, Berghem K, Kotilainen A-K, Terry DP, Luoto TM. Complicated mild traumatic brain injury in older adults: Post-concussion symptoms and functional outcome at one week post injury. *Brain injury*. 2020;34(1):26-33.

15.   Traumatic Brain Injury Center of Excellence. Military Acute Concussion Evaluation 2 (MACE 2). Updated March 2021. https://health.mil/Reference-Center/Publications/2020/07/30/Military-Acute-Concussion-Evaluation-MACE-2

16.   Sharp AL, Huang BZ, Tang T, et al. Implementation of the Canadian CT Head Rule and its association with use of computed tomography among patients with head injury. *Annals of emergency medicine*. 2018;71(1):54-63. e2.

17.   Yarlagadda J, Joshi S, Cerasale MT, Rana S, Heidemann D. The Applicability of New Orleans Criteria for Head Computed Tomography in Inpatient Falls With Injury. *Neurohospitalist*. Oct 2019;9(4):197-202. doi:10.1177/1941874419832441

18.   Polinder S, Cnossen MC, Real RGL, et al. A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury. *Front Neurol*. 2018;9:1113. doi:10.3389/fneur.2018.01113

19.   Remigio-Baker RA, Bailie JM, Gregory E, et al. Activity Level During Acute Concussion May Predict Symptom Recovery Within an Active Duty Military Population. *J Head Trauma Rehabil*. Mar/Apr 2020;35(2):92-103. doi:10.1097/HTR.0000000000000498

20.   Rao V, Syeda A, Roy D, Peters ME, Vaishnavi S. Neuropsychiatric aspects of concussion: acute and chronic sequelae. *Concussion*. 2017;2(1):CNC29.

21.   Yehuda R, Hoge CW, McFarlane AC, et al. Posttraumatic stress disorder. *Nature Reviews Disease Primers*. 2015;1(1):1-22.

22.   Bryant RA. The Current Evidence for Acute Stress Disorder. *Curr Psychiatry Rep*. Oct 13 2018;20(12):111. doi:10.1007/s11920-018-0976-x

23.   American Psychiatric Association. What Is Posttraumatic Stress Disorder? Accessed May 8, 2018. https://www.psychiatry.org/patients-families/ptsd/what-is-ptsd

24.   National Institute of Mental Health. Posttraumatic Stress Disorder (PTSD). https://www.nimh.nih.gov/health/statistics/posttraumatic-stress-disorder-ptsd.shtml#part_155471

25.   Meadows SO, Engel CC, Collins RL, et al. 2015 Department of Defense Health Related Behaviors Survey (HRBS). *Rand health quarterly*. 2018;8(2)

26.   Stefanovics EA, Potenza MN, Pietrzak RH. PTSD and obesity in U.S. military veterans: Prevalence, health burden, and suicidality. *Psychiatry research*. Sep 2020;291:113242. doi:10.1016/j.psychres.2020.113242

27.   Straud CL, Siev J, Messer S, Zalta AK. Examining military population and trauma type as moderators of treatment outcome for first-line psychotherapies for PTSD: a meta-analysis. *Journal of anxiety disorders*. 2019;67:102133.

28.   Barr N, Davis JP, Diguiseppi G, Keeling M, Castro C. Direct and indirect effects of mindfulness, PTSD, and depression on self-stigma of mental illness in OEF/OIF veterans. *Psychological Trauma: Theory, Research, Practice, and Policy*. 2019;

29.   Sharp M-L, Fear NT, Rona RJ, et al. Stigma as a barrier to seeking health care among military personnel with mental health problems. *Epidemiologic reviews*. 2015;37(1):144-162.

30.   Hardy M, Kennedy J, Reid M, Cooper D. Differences in Posttraumatic Stress Disorder, Depression, and Attribution of Symptoms in Service Members With Combat Versus Noncombat Mild Traumatic Brain Injury. *J Head Trauma Rehabil*. Jan/Feb 2020;35(1):37-45. doi:10.1097/htr.0000000000000486

31.   Ramchand R, Rudavsky R, Grant S, Tanielian T, Jaycox L. 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*. May 2015;17(5):37. doi:10.1007/s11920-015-0575-z

32.   Frank C, Zamorski MA, Lee JE, Colman I. Deployment-related trauma and posttraumatic stress disorder: does gender matter? *European journal of psychotraumatology*. 2018;9(1):1486123.

33.   World Health Organization. ICD-11 for Mortality and Morbidity Statistics. Updated 04/2019. Accessed 07/13, 2020. https://icd.who.int/browse11/l-m/en#http%3a%2f%2fid.who.int%2ficd%2fentity%2f585833559

34.   Rosenfield PJ, Stratyner A, Tufekcioglu S, Karabell S, McKelvey J, Litt L. Complex PTSD in ICD-11: A Case Report on a New Diagnosis. *J Psychiatr Pract*. Sep 2018;24(5):364-370. doi:10.1097/PRA.0000000000000327

35.   Affairs USDoV. Complex PTSD. 27 July, 2020. Accessed 27 July, 2020. https://www.ptsd.va.gov/professional/treat/essentials/complex_ptsd.asp

36.   Gilbar O. Examining the boundaries between ICD-11 PTSD/CPTSD and depression and anxiety symptoms: A network analysis perspective. *Journal of affective disorders*. 2020;262:429-439.

37.   Nestgaard Rød Å, Schmidt C. Complex PTSD: what is the clinical utility of the diagnosis? *Eur J Psychotraumatol*. 2021;12(1):2002028. doi:10.1080/20008198.2021.2002028

38.   Wolf EJ, Miller MW, Kilpatrick D, et al. ICD-11 Complex PTSD in US National and Veteran Samples: Prevalence and Structural Associations with PTSD. *Clin Psychol Sci*. Mar 2015;3(2):215-229. doi:10.1177/2167702614545480

39.   Brassil HE, Salvatore AP. The frequency of posttraumatic stress disorder symptoms in athletes with and without sports related concussion. *Clinical and translational medicine*. 2018;7(1):25.

40.   Miller SC, Whitehead CR, Otte CN, et al. Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of US Air Force personnel. *Occup Environ Med*. Aug 2015;72(8):560-6. doi:10.1136/oemed-2014-102646

41.   Stein MB, Kessler RC, Heeringa SG, et al. 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). *The American journal of psychiatry*. Sep 4 2015:appiajp201514121572. doi:10.1176/appi.ajp.2015.14121572

42.   Van Praag DL, Cnossen MC, Polinder S, Wilson L, Maas AI. Posttraumatic stress disorder after civilian traumatic brain injury: a systematic review and meta-analysis of prevalence rates. *Journal of neurotrauma*. 2019;36(23):3220-3232.

43.   Dieter JN, Engel SD. Traumatic Brain Injury and Posttraumatic Stress Disorder: Comorbid Consequences of War. *Neuroscience Insights*. 2019;14:1179069519892933.

44.   Huguenard CJ, Cseresznye A, Evans JE, et al. Plasma lipidomic analyses in cohorts with mTBI and/or PTSD reveal lipids differentially associated with diagnosis and APOE ε4 carrier status. *Frontiers in physiology*. 2020;11:12.

45.   Lange RT, French LM, Lippa SM, Bailie JM, Brickell TA. Posttraumatic Stress Disorder is a Stronger Predictor of Long-Term Neurobehavioral Outcomes Than Traumatic Brain Injury Severity. *Journal of traumatic stress*. Jun 2020;33(3):318-329. doi:10.1002/jts.22480

46.   Aase DM, Babione JM, Proescher E, et al. Impact of PTSD on post-concussive symptoms, neuropsychological functioning, and pain in post-9/11 veterans with mild traumatic brain injury. *Psychiatry research*. 2018;268:460-466.

47.   Cnossen MC, van der Naalt J, Spikman JM, et al. Prediction of persistent post-concussion symptoms after mild traumatic brain injury. *Journal of neurotrauma*. 2018;35(22):2691-2698.
48.   Dretsch MN, Silverberg ND, Iverson GL. Multiple Past Concussions Are Associated with Ongoing Post-Concussive Symptoms but Not Cognitive Impairment in Active-Duty Army Soldiers. *J Neurotrauma*. May 14 2015;doi:10.1089/neu.2014.3810
49.   Garcia K, Moore B, Kim G, Dsurney J, Chan L. The Impact of Affective States on Postconcussive Symptoms in a TBI Population. *Military medicine*. 2019;184(Supplement_1):168-173.
50.   Hardy M, Kennedy J, Reid M, Cooper D. Differences in posttraumatic stress disorder, depression, and attribution of symptoms in service members with combat versus noncombat mild traumatic brain injury. *The Journal of head trauma rehabilitation*. 2020;35(1):37-45.
51.   Combs HL, Berry DT, Pape T, et al. The Effects of Mild Traumatic Brain Injury, Posttraumatic Stress Disorder, and Combined Mild Traumatic Brain Injury/Posttraumatic Stress Disorder on Returning Veterans. *J Neurotrauma*. Feb 26 2015;doi:10.1089/neu.2014.3585
52.   Mac Donald CL, Adam OR, Johnson AM, et al. Acute posttraumatic stress symptoms and age predict outcome in military blast concussion. *Brain*. Mar 4 2015;doi:10.1093/brain/awv038
53.   Loignon A, Ouellet MC, Belleville G. A Systematic Review and Meta-analysis on PTSD Following TBI Among Military/Veteran and Civilian Populations. *J Head Trauma Rehabil*. Jan/Feb 2020;35(1):E21-e35. doi:10.1097/htr.0000000000000514
54.   Qureshi KL, Upthegrove R, Toman E, Sawlani V, Davies DJ, Belli A. Posttraumatic stress disorder in UK civilians with traumatic brain injury: an observational study of TBI clinic attendees to estimate PTSD prevalence and its relationship with radiological markers of brain injury severity. *BMJ Open*. Feb 19 2019;9(2):e021675. doi:10.1136/bmjopen-2018-021675
55.   Iljazi A, Ashina H, Al-Khazali HM, et al. Posttraumatic stress disorder after traumatic brain injury-a systematic review and meta-analysis. *Neurological sciences*. 2020;
56.   Müller J, Ganeshamoorthy S, Myers J. Risk factors associated with posttraumatic stress disorder in US veterans: A cohort study. *PloS one*. 2017;12(7)
57.   Haarbauer-Krupa J, Taylor CA, Yue JK, et al. Screening for posttraumatic stress disorder in a civilian emergency department population with traumatic brain injury. *Journal of neurotrauma*. 2017;34(1):50-58.
58.   Samuelson KW, Newman J, Abu Amara D, et al. Predeployment neurocognitive functioning predicts postdeployment posttraumatic stress in Army personnel. *Neuropsychology*. Mar 2020;34(3):276-287. doi:10.1037/neu0000603
59.   Scofield DE, Proctor SP, Kardouni JR, Hill OT, McKinnon CJ. Risk factors for mild traumatic brain injury and subsequent posttraumatic stress disorder and mental health disorders among United States Army Soldiers. *Journal of neurotrauma*. 2017;34(23):3249-3255.
60.   Martindale SL, Shura RD, Rostami R, Taber KH, Rowland JA. Research Letter: Blast Exposure and Brain Volume. *J Head Trauma Rehabil*. Nov-Dec 01 2021;36(6):424-428. doi:10.1097/htr.0000000000000660
61.   Ord AS, Epstein EL, Shull ER, Taber KH, Martindale SL, Rowland JA. Factors associated with recovery from posttraumatic stress disorder in combat veterans: The role of deployment mild traumatic brain injury (mTBI). *Rehabil Psychol*. Aug 2022;67(3):356-368. doi:10.1037/rep0000400
62.   Howlett JR, Nelson LD, Stein MB. Mental Health Consequences of Traumatic Brain Injury. *Biological psychiatry*. Mar 1 2022;91(5):413-420. doi:10.1016/j.biopsych.2021.09.024
63.   Albanese BJ, Macatee RJ, Stentz LA, Schmidt NB, Bryan CJ. Interactive effects of cumulative lifetime traumatic brain injuries and combat exposure on posttraumatic stress among deployed military personnel. *Cognitive behaviour therapy*. 2019;48(1):77-88.
64.   Stein MB, Jain S, Giacino JT, et al. Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury: a TRACK-TBI study. *JAMA psychiatry*. 2019;76(3):249-258.
65.   Loignon A, Ouellet M-C, Belleville G. A systematic review and meta-analysis on PTSD following TBI among military/veteran and civilian populations. *The Journal of Head Trauma Rehabilitation*. 2020;35(1):E21-E35.
66.   Mac Donald CL, Barber J, Patterson J, et al. Association between 5-year clinical outcome in patients with nonmedically evacuated mild blast traumatic brain injury and clinical measures collected within 7 days postinjury in combat. *JAMA network open*. 2019;2(1):e186676-e186676.

67.   Kinney AR, Gerber HR, Hostetter TA, Brenner LA, Forster JE, Stephenson RO. Morally injurious combat events as an indirect risk factor for postconcussive symptoms among veterans: The mediating role of posttraumatic stress. *Psychological trauma : theory, research, practice and policy*. Jan 27 2022;doi:10.1037/tra0001213

68.   Litz BT, Stein N, Delaney E, et al. Moral injury and moral repair in war veterans: a preliminary model and intervention strategy. *Clin Psychol Rev*. Dec 2009;29(8):695-706. doi:10.1016/j.cpr.2009.07.003

69.   Shay. Moral injury *Psychoanalytic Psychology* 2014;31(2):182-191. doi:https://doi.org/10.1037/a0036090

70.   Norman SB, Nichter B, Maguen S, Na PJ, Schnurr PP, Pietrzak RH. Moral injury among U.S. combat veterans with and without PTSD and depression. *J Psychiatr Res*. Oct 2022;154:190-197. doi:10.1016/j.jpsychires.2022.07.033

71.   Vasterling JJ, Jacob SN, Rasmusson A. Traumatic Brain Injury and Posttraumatic Stress Disorder: Conceptual, Diagnostic, and Therapeutic Considerations in the Context of Co-Occurrence. *The Journal of neuropsychiatry and clinical neurosciences*. Spring 2018;30(2):91-100. doi:10.1176/appi.neuropsych.17090180

72.   Li L, Bao Y, He S, et al. The association between apolipoprotein E and functional outcome after traumatic brain injury: a meta-analysis. *Medicine*. 2015;94(46)

73.   Nielsen DA, Spellicy CJ, Harding MJ, Graham DP. Apolipoprotein E DNA methylation and posttraumatic stress disorder are associated with plasma ApoE level: A preliminary study. *Behavioural brain research*. 2019;356:415-422.

74.   Merritt VC, Lapira KM, Clark AL, et al. APOE-ε4 genotype is associated with elevated post-concussion symptoms in military veterans with a remote history of mild traumatic brain injury. *Archives of clinical neuropsychology*. 2019;34(5):706-712.

75.   Roby Y. Apolipoprotein E variants and genetic susceptibility to combat-related posttraumatic stress disorder: a meta-analysis. *Psychiatric genetics*. Aug 2017;27(4):121-130. doi:10.1097/ypg.0000000000000174

76.   Blakey SM, Wagner HR, Naylor J, et al. Chronic Pain, TBI, and PTSD in Military Veterans: A Link to Suicidal Ideation and Violent Impulses? *J Pain*. Mar 8 2018;doi:10.1016/j.jpain.2018.02.012

77.   Jaramillo CA, Eapen BC, McGeary CA, et al. A cohort study examining headaches among veterans of Iraq and Afghanistan wars: Associations with traumatic brain injury, PTSD, and depression. *Headache*. Mar 2016;56(3):528-39. doi:10.1111/head.12726

78.   Moriarty H, Robinson KM, Winter L. The additional burden of PTSD on functioning and depression in veterans with traumatic brain injury. *Nursing outlook*. Mar-Apr 2021;69(2):167-181. doi:10.1016/j.outlook.2020.11.003

79.   Balba NM, Elliott JE, Weymann KB, et al. Increased sleep disturbances and pain in veterans with comorbid traumatic brain injury and posttraumatic stress disorder. *Journal of clinical sleep medicine*. 2018;14(11):1865-1878.

80.   Gros DF, Lancaster CL, Horner MD, Szafranski DD, Back SE. The influence of traumatic brain injury on treatment outcomes of Concurrent Treatment for PTSD and Substance Use Disorders Using Prolonged Exposure (COPE) in veterans. *Compr Psychiatry*. Oct 2017;78:48-53. doi:10.1016/j.comppsych.2017.07.004

81.   Isaac L, Main KL, Soman S, et al. The impact of depression on Veterans with PTSD and traumatic brain injury: a diffusion tensor imaging study. *Biol Psychol*. Feb 2015;105:20-8. doi:10.1016/j.biopsycho.2014.12.011

82.   Kennedy JE, Lu LH, Reid MW, Leal FO, Cooper DB. Correlates of Depression in U.S. Military Service Members With a History of Mild Traumatic Brain Injury. *Mil Med*. Mar 1 2019;184(Suppl 1):148-154. doi:10.1093/milmed/usy321

83.   Stojanovic MP, Fonda J, Fortier CB, et al. Influence of Mild Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD) on Pain Intensity Levels in OEF/OIF/OND Veterans. *Pain Med*. Nov 2016;17(11):2017-2025. doi:10.1093/pm/pnw042

84.   Williams JL, McDevitt-Murphy ME, Murphy JG, Crouse EM. Postconcussive Symptoms, PTSD, and Medical Disease Burden in Treatment-Seeking OEF/OIF/OND Veterans. *Mil Med*. Mar 2017;182(3):e1645-e1650. doi:10.7205/MILMED-D-16-00221

85.   O'Neil ME, Agyemang A, Walker WC, et al. Demographic, military, and health comorbidity variables by mild TBI and PTSD status in the LIMBIC-CENC cohort. *Brain Inj*. Apr 16 2022;36(5):598-606. doi:10.1080/02699052.2022.2033847

86.   Ord AS, Lad SS, Shura RD, Rowland JA, Taber KH, Martindale SL. Pain interference and quality of life in combat veterans: Examining the roles of posttraumatic stress disorder, traumatic brain injury, and sleep quality. *Rehabil Psychol.* Feb 2021;66(1):31-38. doi:10.1037/rep0000333
87.   Morasco BJ, Lovejoy TI, Lu M, Turk DC, Lewis L, Dobscha SK. The relationship between PTSD and chronic pain: mediating role of coping strategies and depression. *Pain.* Apr 2013;154(4):609-616. doi:10.1016/j.pain.2013.01.001
88.   Asmundson GJ, Wright KD, Stein MB. Pain and PTSD symptoms in female veterans. *Eur J Pain.* Aug 2004;8(4):345-50. doi:10.1016/j.ejpain.2003.10.008
89.   Seal KH, Bertenthal D, Barnes DE, Byers AL, Strigo I, Yaffe K. Association of Traumatic Brain Injury With Chronic Pain in Iraq and Afghanistan Veterans: Effect of Comorbid Mental Health Conditions. *Arch Phys Med Rehabil.* Aug 2017;98(8):1636-1645. doi:10.1016/j.apmr.2017.03.026
90.   White DL, Kunik ME, Yu H, et al. Post-traumatic stress disorder is associated with further increased Parkinson's disease risk in veterans with traumatic brain injury. *Annals of neurology.* 2020;
91.   Iverson KM, Dardis CM, Pogoda TK. Traumatic brain injury and PTSD symptoms as a consequence of intimate partner violence. *Compr Psychiatry.* Apr 2017;74:80-87. doi:10.1016/j.comppsych.2017.01.007
92.   Jackson CE, Green JD, Bovin MJ, et al. Mild Traumatic Brain Injury, PTSD, and Psychosocial Functioning Among Male and Female U.S. OEF/OIF Veterans. *Journal of traumatic stress.* Aug 2016;29(4):309-16. doi:10.1002/jts.22110
93.   Van Voorhees EE, Moore DA, Kimbrel NA, et al. Association of posttraumatic stress disorder and traumatic brain injury with aggressive driving in Iraq and Afghanistan combat veterans. *Rehabil Psychol.* Feb 2018;63(1):160-166. doi:10.1037/rep0000178
94.   van der Vlegel M, Polinder S, Mikolic A, et al. The Association of Post-Concussion and Posttraumatic Stress Disorder Symptoms with Health-Related Quality of Life, Health Care Use and Return-to-Work after Mild Traumatic Brain Injury. *J Clin Med.* Jun 2 2021;10(11)doi:10.3390/jcm10112473
95.   Brickell TA, French LM, Varbedian NV, et al. Relationship satisfaction among spouse caregivers of service members and veterans with comorbid mild traumatic brain injury and posttraumatic stress disorder. *Family process.* Dec 2 2021;doi:10.1111/famp.12731
96.   O'Neil ME, Klyce DW, Pogoda TK, et al. Associations Among PTSD and Postconcussive Symptoms in the Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium Prospective, Longitudinal Study Cohort. *J Head Trauma Rehabil.* Nov-Dec 01 2021;36(6):E363-e372. doi:10.1097/htr.0000000000000665
97.   Porter KE, Stein MB, Martis B, et al. Postconcussive symptoms (PCS) following combat-related traumatic brain injury (TBI) in Veterans with posttraumatic stress disorder (PTSD): Influence of TBI, PTSD, and depression on symptoms measured by the Neurobehavioral Symptom Inventory (NSI). *J Psychiatr Res.* Mar 10 2018;102:8-13. doi:10.1016/j.jpsychires.2018.03.004
98.   Vos L, Whiteneck GG, Ngan E, Leon Novelo L, Harik LM, Sherer M. Comparison of the Neurobehavioral Symptom Inventory and the Rivermead Postconcussion Symptoms Questionnaire. *Brain injury.* 2019;33(9):1165-1172.
99.   Franke LM, Czarnota JN, Ketchum JM, Walker WC. Factor analysis of persistent postconcussive symptoms within a military sample with blast exposure. *J Head Trauma Rehabil.* Jan-Feb 2015;30(1):E34-46. doi:10.1097/HTR.0000000000000042
100.   Vanderploeg RD, Silva MA, Soble JR, et al. The structure of postconcussion symptoms on the Neurobehavioral Symptom Inventory: a comparison of alternative models. *J Head Trauma Rehabil.* Jan-Feb 2015;30(1):1-11. doi:10.1097/HTR.0000000000000009
101.   Bahraini NH, Hostetter TA, Forster JE, Schneider AL, Brenner LA. A Rasch analysis of the Neurobehavioral Symptom Inventory in a national cohort of Operation Enduring and Iraqi Freedom veterans with mild traumatic brain injury. *Psychological assessment.* 2018;30(8):1013.
102.   Dretsch M, Bleiberg J, Williams K, et al. Three scoring approaches to the neurobehavioral symptom inventory for measuring clinical change in service members receiving intensive treatment for combat-related mTBI. *The Journal of head trauma rehabilitation.* 2016;31(1):23-29.

103.   Llop JZ, Hoover PJ, Nix CA, Lu LH, Bowles AO, Caban JJ. NSI and PCL-5 Normative Tables for Active Duty Service Members Affected by Traumatic Brain Injury. *Mil Med*. Jul 7 2022;doi:10.1093/milmed/usac189

104.   Caplan B, Bogner J, Brenner L, et al. Utility of the neurobehavioral symptom inventory as an outcome measure: a VA TBI model systems study. *Journal of Head Trauma Rehabilitation*. 2017;32(1):46-54.

105.   Andrews RJ, Fonda JR, Levin LK, McGlinchey RE, Milberg WP. Comprehensive analysis of the predictors of neurobehavioral symptom reporting in veterans. *Neurology*. 2018;91(8):e732-e745.

106.   Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychol Assess*. Mar 2018;30(3):383-395. doi:10.1037/pas0000486

107.   Bovin MJ, Marx BP, Weathers FW, et al. Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental disorders–fifth edition (PCL-5) in veterans. *Psychological assessment*. 2016;28(11):1379.

108.   Franklin CL, Raines AM, Cuccurullo L-AJ, et al. 27 ways to meet PTSD: Using the PTSD-checklist for DSM-5 to examine PTSD core criteria. *Psychiatry research*. 2018;261:504-507.

109.   VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder (2023).

110.   Mustillo SA, Kysar-Moon A, Douglas SR, et al. Overview of depression, posttraumatic stress disorder, and alcohol misuse among active duty service members returning from Iraq and Afghanistan, self-report and diagnosis. *Military medicine*. 2015;180(4):419-427.

111.   Deployment Health Assessments Accessed December 27 2022. https://www.med.navy.mil/Navy-Marine-Corps-Public-Health-Center/Population-Health/Epi-Data-Center/Deployment-Health-Assessments/

112.   Prins A, Bovin MJ, Smolenski DJ, et al. The primary care PTSD screen for DSM-5 (PC-PTSD-5): development and evaluation within a veteran primary care sample. *Journal of General Internal Medicine*. 2016;31(10):1206-1211.

113.   National Center for PTSD. Primary Care PTSD Screen (PC-PTSD). 2015.

114.   Bovin MJ, Kimerling R, Weathers FW, et al. Diagnostic Accuracy and Acceptability of the Primary Care Posttraumatic Stress Disorder Screen for the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) Among US Veterans. *JAMA network open*. Feb 1 2021;4(2):e2036733. doi:10.1001/jamanetworkopen.2020.36733

115.   Jurick S, Crocker L, Keller A, et al. The Minnesota Multiphasic Personality Inventory-2-RF in treatment-seeking Veterans with history of mild traumatic brain injury. *Archives of Clinical Neuropsychology*. 2019;34(3):366-380.

116.   Butler O, Herr K, Willmund G, Gallinat J, Zimmermann P, Kühn S. Neural correlates of response bias: Larger hippocampal volume correlates with symptom aggravation in combat-related posttraumatic stress disorder. *Psychiatry Research: Neuroimaging*. 2018;279:1-7.

117.   Dretsch MN, Williams K, Staver T, et al. Evaluating the clinical utility of the Validity-10 for detecting amplified symptom reporting for patients with mild traumatic brain injury and comorbid psychological health conditions. *Applied Neuropsychology: Adult*. 2017;24(4):376-380.

118.   Lequerica AH, Lucca C, Chiaravalloti ND, Ward I, Corrigan JD. Feasibility and preliminary validation of an online version of the ohio state university traumatic brain injury identification method. *Archives of physical medicine and rehabilitation*. 2018;99(9):1811-1817.

119.   Vanderploeg RD, Belanger HG. Stability and validity of the veterans health administration's traumatic brain injury clinical reminder screen. *Journal of Head Trauma Rehabilitation*. 2015;30(5):E29-E39.

120.   Haber YO, Chandler HK, Serrador JM. Symptoms Associated with Vestibular Impairment in Veterans with Posttraumatic Stress Disorder. *PLoS One*. 2016;11(12):e0168803. doi:10.1371/journal.pone.0168803

121.   Kontos AP, Van Cott AC, Roberts J, et al. Clinical and Magnetic Resonance Spectroscopic Imaging Findings in Veterans With Blast Mild Traumatic Brain Injury and Posttraumatic Stress Disorder. *Mil Med*. Mar 2017;182(S1):99-104. doi:10.7205/MILMED-D-16-00177

122.   Nielson JL, Cooper SR, Yue JK, et al. Uncovering precision phenotype-biomarker associations in traumatic brain injury using topological data analysis. *PloS one*. 2017;12(3)

123.   Emmerich T, Abdullah L, Crynen G, et al. Plasma Lipidomic profiling in a military population of mild traumatic brain injury and posttraumatic stress disorder with apolipoprotein E ε4–dependent effect. *Journal of neurotrauma*. 2016;33(14):1331-1348.

124.   Kulbe JR, Geddes JW. Current status of fluid biomarkers in mild traumatic brain injury. *Experimental neurology*. 2016;275:334-352.

125.   Franke LM, Walker WC, Hoke KW, Wares JR. Distinction in EEG slow oscillations between chronic mild traumatic brain injury and PTSD. *Int J Psychophysiol*. Aug 2016;106:21-9. doi:10.1016/j.ijpsycho.2016.05.010

126.   Rowland JA, Stapleton-Kotloski JR, Dobbins DL, Rogers E, Godwin DW, Taber KH. Increased Small-World Network Topology Following Deployment-Acquired Traumatic Brain Injury Associated with the Development of Posttraumatic Stress Disorder. *Brain Connect*. Apr 20 2018;doi:10.1089/brain.2017.0556

127.   Zhang J, Emami Z, Safar K, et al. Teasing apart trauma: neural oscillations differentiate individual cases of mild traumatic brain injury from posttraumatic stress disorder even when symptoms overlap. *Transl Psychiatry*. Jun 4 2021;11(1):345. doi:10.1038/s41398-021-01467-8

128.   Huang M, Lewine JD, Lee RR. Magnetoencephalography for Mild Traumatic Brain Injury and Posttraumatic Stress Disorder. *Neuroimaging clinics of North America*. May 2020;30(2):175-192. doi:10.1016/j.nic.2020.02.003

129.   Bland AR, Roiser JP, Mehta MA, et al. EMOTICOM: a neuropsychological test battery to evaluate emotion, motivation, impulsivity, and social cognition. *Frontiers in Behavioral Neuroscience*. 2016;10:25.

130.   MacDonald J, Duerson D. Reliability of a computerized neurocognitive test in baseline concussion testing of high school athletes. *Clinical Journal of Sport Medicine*. 2015;25(4):367-372.

131.   Arrieux JP, Cole WR, Ahrens AP. A review of the validity of computerized neurocognitive assessment tools in mild traumatic brain injury assessment. *Concussion*. 2017;2(1):CNC31.

132.   Iverson GL, Ivins BJ, Karr JE, et al. Comparing Composite Scores for the ANAM4 TBI-MIL for Research in Mild Traumatic Brain Injury. *Arch Clin Neuropsychol*. Jan 24 2019;35(1):56-69. doi:10.1093/arclin/acz021

133.   Meyers JE, Vincent AS. Automated Neuropsychological Assessment Metrics (v4) Military Battery: Military Normative Data. *Military Medicine*. 2020;

134.   Vincent AS, Fuenzalida E, Beneda-Bender M, Bryant DJ, Peters E. Neurocognitive assessment on a tablet device: Test-retest reliability and practice effects of ANAM Mobile. *Appl Neuropsychol Adult*. May-Jun 2021;28(3):363-371. doi:10.1080/23279095.2019.1640698

135.   Anderson M, Lempke L, Bell D, Lynall R, Schmidt J. The ability of CNS vital signs to detect coached sandbagging performance during concussion baseline testing: a randomized control trial. *Brain Injury*. 2020;34(3):369-374.

136.   Cole WR, Arrieux JP, Ivins BJ, Schwab KA, Qashu FM. A comparison of four computerized neurocognitive assessment tools to a traditional neuropsychological test battery in service members with and without mild traumatic brain injury. *Archives of clinical neuropsychology*. 2018;33(1):102-119.

137.   Masterson CJ, Tuttle J, Maerlender A. Confirmatory factor analysis of two computerized neuropsychological test batteries: Immediate post-concussion assessment and cognitive test (ImPACT) and C3 logix. *Journal of clinical and experimental neuropsychology*. 2019;41(9):925-932.

138.   Mueser KT, McGurk SR, Xie H, et al. Neuropsychological predictors of response to cognitive behavioral therapy for posttraumatic stress disorder in persons with severe mental illness. *Psychiatry research*. 2018;259:110-116.

139.   Vasterling JJ, Grande L, Graefe AC, Alvarez JA. Neuropsychological assessment of posttraumatic stress disorder (PTSD). *Handbook of Medical Neuropsychology*. Springer; 2019:599-619.

140.   Mattson EK, Nelson NW, Sponheim SR, Disner SG. The impact of PTSD and mTBI on the relationship between subjective and objective cognitive deficits in combat-exposed veterans. *Neuropsychology*. 2019;

141.   Wolf GK, Mauntel GJ, Kretzmer T, et al. Comorbid Posttraumatic Stress Disorder and Traumatic Brain Injury: Generalization of Prolonged-Exposure PTSD Treatment Outcomes to Postconcussive

Symptoms, Cognition, and Self-Efficacy in Veterans and Active Duty Service Members. *J Head Trauma Rehabil*. Mar/Apr 2018;33(2):E53-E63. doi:10.1097/HTR.0000000000000344

142.   de Souza NL, Esopenko C, Jia Y, et al. Discriminating Mild Traumatic Brain Injury and Posttraumatic Stress Disorder Using Latent Neuroimaging and Neuropsychological Profiles in Active-Duty Military Service Members. *J Head Trauma Rehabil*. Dec 30 2022;doi:10.1097/htr.0000000000000848

143.   de Freitas Cardoso MG, Faleiro RM, de Paula JJ, et al. Cognitive Impairment Following Acute Mild Traumatic Brain Injury. *Front Neurol*. 2019;10:198. doi:10.3389/fneur.2019.00198

144.   Veeramuthu V, Narayanan V, Kuo TL, et al. Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study. *J Neurotrauma*. Oct 1 2015;32(19):1497-509. doi:10.1089/neu.2014.3750

145.   Rice VJ, Schroeder PJ, Cassenti DN, Boykin GL. The Effect of Traumatic Brain Injury (TBI) on Cognitive Performance in a Sample of Active Duty U.S. Military Service Members. *Mil Med*. Jan 7 2020;185(Suppl 1):184-189. doi:10.1093/milmed/usz202

146.   Baker MT, Moring JC, Hale WJ, et al. Acute Assessment of Traumatic Brain Injury and Posttraumatic Stress After Exposure to a Deployment-Related Explosive Blast. *Mil Med*. Nov 1 2018;183(11-12):e555-e563. doi:10.1093/milmed/usy100

147.   Carr W, Stone JR, Walilko T, et al. Repeated Low-Level Blast Exposure: A Descriptive Human Subjects Study. *Mil Med*. May 2016;181(5 Suppl):28-39. doi:10.7205/milmed-d-15-00137

148.   Adam O, Mac Donald CL, Rivet D, et al. Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan. *Neurology*. Jul 21 2015;85(3):219-27. doi:10.1212/wnl.0000000000001758

149.   Mac Donald CL, Barber J, Jordan M, et al. Early Clinical Predictors of 5-Year Outcome After Concussive Blast Traumatic Brain Injury. *JAMA Neurol*. Jul 1 2017;74(7):821-829. doi:10.1001/jamaneurol.2017.0143

150.   Manley G, Gardner AJ, Schneider KJ, et al. A systematic review of potential long-term effects of sport-related concussion. *Br J Sports Med*. Jun 2017;51(12):969-977. doi:10.1136/bjsports-2017-097791

151.   Scott JC, Matt GE, Wrocklage KM, et al. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull*. Jan 2015;141(1):105-40. doi:10.1037/a0038039

152.   Samuelson KW, Abadjian L, Jordan JT, Bartel A, Vasterling J, Seal K. The Association Between PTSD and Functional Outcome Is Mediated by Perception of Cognitive Problems Rather Than Objective Neuropsychological Test Performance. *Journal of traumatic stress*. Oct 2017;30(5):521-530. doi:10.1002/jts.22223

153.   Alzoubi KH, Al-Ibbini AM, Nuseir KQ. Prevention of memory impairment induced by posttraumatic stress disorder by cerebrolysin. *Psychiatry research*. Dec 2018;270:430-437. doi:10.1016/j.psychres.2018.10.008

154.   Zlomuzica A, Woud ML, Machulska A, et al. Deficits in episodic memory and mental time travel in patients with posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. Apr 20 2018;83:42-54. doi:10.1016/j.pnpbp.2017.12.014

155.   Woon FL, Farrer TJ, Braman CR, Mabey JK, Hedges DW. A meta-analysis of the relationship between symptom severity of Posttraumatic Stress Disorder and executive function. *Cogn Neuropsychiatry*. Jan 2017;22(1):1-16. doi:10.1080/13546805.2016.1255603

156.   McFarland CP, Clark JB, Lee LO, Grande LJ, Marx BP, Vasterling JJ. Event-based prospective memory among veterans: The role of posttraumatic stress disorder symptom severity in executing intentions. *J Clin Exp Neuropsychol*. 2016;38(2):251-60. doi:10.1080/13803395.2015.1102203

157.   Jacob SN, Dodge CP, Vasterling JJ. Posttraumatic stress disorder and neurocognition: A bidirectional relationship? *Clin Psychol Rev*. Aug 2019;72:101747. doi:10.1016/j.cpr.2019.101747

158.   Boyd B, Rodgers C, Aupperle R, Jak A. Case report on the effects of cognitive processing therapy on psychological, neuropsychological, and speech symptoms in comorbid PTSD and TBI. *Cognitive and Behavioral Practice*. 2016;23(2):173-183.

159.   Crocker LD, Keller AV, Jurick SM, et al. Mild traumatic brain injury burden moderates the relationship between cognitive functioning and suicidality in Iraq/Afghanistan-era veterans. *Journal of the International Neuropsychological Society*. 2019;25(1):79-89.

160.   Crocker LD, Jurick SM, Thomas KR, et al. Worse baseline executive functioning is associated with dropout and poorer response to trauma-focused treatment for veterans with PTSD and comorbid traumatic brain injury. *Behaviour research and therapy*. 2018;108:68-77.

161.   Martindale SL, Ord AS, Lad SS, Miskey HM, Taber KH, Rowland JA. Differential effects of deployment and nondeployment mild TBI on neuropsychological outcomes. *Rehabil Psychol*. May 2021;66(2):128-138. doi:10.1037/rep0000374

162.   Nelson NW, Disner SG, Anderson CR, et al. Blast concussion and posttraumatic stress as predictors of postcombat neuropsychological functioning in OEF/OIF/OND veterans. *Neuropsychology*. 2019;

163.   Van Praag DLG, Van Den Eede F, Wouters K, et al. The Impact of Neurocognitive Functioning on the Course of Posttraumatic Stress Symptoms following Civilian Traumatic Brain Injury. *J Clin Med*. Oct 30 2021;10(21)doi:10.3390/jcm10215109

164.   Clark AL, Sorg SF, Schiehser DM, et al. Deep white matter hyperintensities affect verbal memory independent of PTSD symptoms in veterans with mild traumatic brain injury. *Brain Inj*. 2016;30(7):864-71. doi:10.3109/02699052.2016.1144894

165.   Hale AC, Bohnert KM, Grekin R, Sripada RK. Traumatic Brain Injury in the General Population: Incidence, Mental Health Comorbidity, and Functional Impact. *The Journal of nervous and mental disease*. Jan 2019;207(1):38-42. doi:10.1097/NMD.0000000000000915

166.   Dunbar KE, Raboy AL, Kirby ZM, Taylor PL, Roy MJ. Distinguishing the Relative Impact of Posttraumatic Stress Disorder and Traumatic Brain Injury on iPad-Measured Cognitive Function. *Cyberpsychol Behav Soc Netw*. Dec 2019;22(12):761-765. doi:10.1089/cyber.2019.0296

167.   Pieper J, Chang DG, Mahasin SZ, et al. Brain Amygdala Volume Increases in Veterans and Active-Duty Military Personnel With Combat-Related Posttraumatic Stress Disorder and Mild Traumatic Brain Injury. *J Head Trauma Rehabil*. Jan/Feb 2020;35(1):E1-e9. doi:10.1097/htr.0000000000000492

168.   Tate DF, Wade BS, Velez CS, et al. Volumetric and shape analyses of subcortical structures in United States service members with mild traumatic brain injury. *Journal of neurology*. 2016;263(10):2065-2079.

169.   Hayes JP, Reagan A, Logue MW, et al. BDNF genotype is associated with hippocampal volume in mild traumatic brain injury. *Genes, Brain and Behavior*. 2018;17(2):107-117.

170.   Rangaprakash D, Deshpande G, Daniel TA, et al. Compromised hippocampus-striatum pathway as a potential imaging biomarker of mild-traumatic brain injury and posttraumatic stress disorder. *Human brain mapping*. 2017;38(6):2843-2864.

171.   Gordon EM, Scheibel RS, Zambrano-Vazquez L, et al. High-fidelity measures of whole-brain functional connectivity and white matter integrity mediate relationships between traumatic brain injury and posttraumatic stress disorder symptoms. *Journal of neurotrauma*. 2018;35(5):767-779.

172.   McCurry KL, Frueh BC, Chiu PH, King-Casas B. Opponent effects of hyperarousal and re-experiencing on affective habituation in posttraumatic stress disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2020;5(2):203-212.

173.   Raji CA, Willeumier K, Taylor D, et al. Functional neuroimaging with default mode network regions distinguishes PTSD from TBI in a military veteran population. *Brain Imaging Behav*. Apr 23 2015;doi:10.1007/s11682-015-9385-5

174.   Amen DG, Raji CA, Willeumier K, et al. Functional Neuroimaging Distinguishes Posttraumatic Stress Disorder from Traumatic Brain Injury in Focused and Large Community Datasets. *PLoS One*. 2015;10(7):e0129659. doi:10.1371/journal.pone.0129659

175.   Santhanam P, Wilson SH, Oakes TR, Weaver LK. Effects of mild traumatic brain injury and posttraumatic stress disorder on resting-state default mode network connectivity. *Brain research*. 2019;1711:77-82.

176.   Dretsch MN, Lange RT, Katz JS, et al. Examining microstructural white matter in active duty soldiers with a history of mild traumatic brain injury and traumatic stress. *The open neuroimaging journal*. 2017;11:46.

177.   Lepage C, de Pierrefeu A, Koerte IK, et al. White matter abnormalities in mild traumatic brain injury with and without posttraumatic stress disorder: a subject-specific diffusion tensor imaging study. *Brain Imaging Behav*. Jun 2018;12(3):870-881. doi:10.1007/s11682-017-9744-5

178.   Bolzenius JD, Velez CS, Lewis JD, et al. Diffusion imaging findings in US service members with mild traumatic brain injury and posttraumatic stress disorder. *The Journal of head trauma rehabilitation*. 2018;33(6):393-402.

179.   Sydnor VJ, Bouix S, Pasternak O, et al. Mild traumatic brain injury impacts associations between limbic system microstructure and posttraumatic stress disorder symptomatology. *Neuroimage: clinical*. 2020;26:102190.

180.   Huang M, Risling M, Baker DG. The role of biomarkers and MEG-based imaging markers in the diagnosis of posttraumatic stress disorder and blast-induced mild traumatic brain injury. *Psychoneuroendocrinology*. 2016;63:398-409.

181.   McGinn MJ, Povlishock JT. Pathophysiology of Traumatic Brain Injury. *Neurosurg Clin N Am*. Oct 2016;27(4):397-407. doi:10.1016/j.nec.2016.06.002

182.   Davitz MS, Gonen O, Tal A, Babb JS, Lui YW, Kirov, II. Quantitative multivoxel proton MR spectroscopy for the identification of white matter abnormalities in mild traumatic brain injury: Comparison between regional and global analysis. *J Magn Reson Imaging*. Nov 2019;50(5):1424-1432. doi:10.1002/jmri.26718

183.   Mu W, Catenaccio E, Lipton ML. Neuroimaging in Blast-Related Mild Traumatic Brain Injury. *J Head Trauma Rehabil*. Jan/Feb 2017;32(1):55-69. doi:10.1097/HTR.0000000000000213

184.   Kim E, Yoo RE, Seong MY, Oh BM. A systematic review and data synthesis of longitudinal changes in white matter integrity after mild traumatic brain injury assessed by diffusion tensor imaging in adults. *European journal of radiology*. Feb 2022;147:110117. doi:10.1016/j.ejrad.2021.110117

185.   Miller DR, Hayes JP, Lafleche G, Salat DH, Verfaellie M. White matter abnormalities are associated with chronic postconcussion symptoms in blast-related mild traumatic brain injury. *Hum Brain Mapp*. Jan 2016;37(1):220-9. doi:10.1002/hbm.23022

186.   Leh SE, Schroeder C, Chen JK, et al. Microstructural Integrity of Hippocampal Subregions Is Impaired after Mild Traumatic Brain Injury. *J Neurotrauma*. Apr 1 2017;34(7):1402-1411. doi:10.1089/neu.2016.4591

187.   Girgis F, Pace J, Sweet J, Miller JP. Hippocampal Neurophysiologic Changes after Mild Traumatic Brain Injury and Potential Neuromodulation Treatment Approaches. *Front Syst Neurosci*. 2016;10:8. doi:10.3389/fnsys.2016.00008

188.   Meier TB, España LY, Kirk AJ, et al. Association of Previous Concussion with Hippocampal Volume and Symptoms in Collegiate-Aged Athletes. *J Neurotrauma*. May 15 2021;38(10):1358-1367. doi:10.1089/neu.2020.7143

189.   Martindale SL, Rostami R, Shura RD, Taber KH, Rowland JA. Brain Volume in Veterans: Relationship to Posttraumatic Stress Disorder and Mild Traumatic Brain Injury. *J Head Trauma Rehabil*. Jul/Aug 2020;35(4):E330-e341. doi:10.1097/htr.0000000000000559

190.   Sullivan DR, Hayes JP, Lafleche G, Salat DH, Verfaellie M. Functional Brain Alterations Associated With Cognitive Control in Blast-Related Mild Traumatic Brain Injury. *J Int Neuropsychol Soc*. Aug 2018;24(7):662-672. doi:10.1017/S1355617718000279

191.   Kaltiainen H, Liljestrom M, Helle L, et al. Mild Traumatic Brain Injury Affects Cognitive Processing and Modifies Oscillatory Brain Activity during Attentional Tasks. *J Neurotrauma*. Jul 15 2019;36(14):2222-2232. doi:10.1089/neu.2018.6306

192.   Banks SD, Coronado RA, Clemons LR, et al. Thalamic Functional Connectivity in Mild Traumatic Brain Injury: Longitudinal Associations With Patient-Reported Outcomes and Neuropsychological Tests. *Arch Phys Med Rehabil*. Aug 2016;97(8):1254-61. doi:10.1016/j.apmr.2016.03.013

193.   Grossman EJ, Inglese M. The Role of Thalamic Damage in Mild Traumatic Brain Injury. *J Neurotrauma*. Jan 15 2016;33(2):163-7. doi:10.1089/neu.2015.3965

194.   Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences*. 2006;1071(1):67-79.

195.   Pietrzak RH, Averill LA, Abdallah CG, et al. Amygdala-hippocampal volume and the phenotypic heterogeneity of posttraumatic stress disorder: a cross-sectional study. *JAMA psychiatry*. 2015;72(4):396-398.

196.   Henigsberg N, Kalember P, Petrović ZK, Šečić A. Neuroimaging research in posttraumatic stress disorder–focus on amygdala, hippocampus and prefrontal cortex. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2019;90:37-42.

197.   Brashers-Krug T, Jorge R. Bi-Directional Tuning of Amygdala Sensitivity in Combat Veterans Investigated with fMRI. *PLoS One*. 2015;10(6):e0130246. doi:10.1371/journal.pone.0130246

198.   O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry research*. Apr 30 2015;232(1):1-33. doi:10.1016/j.pscychresns.2015.01.002

199.   Logue MW, van Rooij SJH, Dennis EL, et al. Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. *Biological psychiatry*. Feb 1 2018;83(3):244-253. doi:10.1016/j.biopsych.2017.09.006

200.   Dennis EL, Disner SG, Fani N, et al. Altered white matter microstructural organization in posttraumatic stress disorder across 3047 adults: results from the PGC-ENIGMA PTSD consortium. *Mol Psychiatry*. Aug 2021;26(8):4315-4330. doi:10.1038/s41380-019-0631-x

201.   Butler O, Adolf J, Gleich T, et al. Military deployment correlates with smaller prefrontal gray matter volume and psychological symptoms in a subclinical population. *Transl Psychiatry*. Feb 14 2017;7(2):e1031. doi:10.1038/tp.2016.288

202.   Dahlgren MK, Laifer LM, VanElzakker MB, et al. Diminished medial prefrontal cortex activation during the recollection of stressful events is an acquired characteristic of PTSD. *Psychol Med*. May 2018;48(7):1128-1138. doi:10.1017/S003329171700263X

203.   Morey RA, Haswell CC, Hooper SR, De Bellis MD. Amygdala, Hippocampus, and Ventral Medial Prefrontal Cortex Volumes Differ in Maltreated Youth with and without Chronic Posttraumatic Stress Disorder. *Neuropsychopharmacology*. Feb 2016;41(3):791-801. doi:10.1038/npp.2015.205

204.   Brown EM, Salat DH, Milberg WP, Fortier CB, McGlinchey RE. Accelerated longitudinal cortical atrophy in OEF/OIF/OND veterans with severe PTSD and the impact of comorbid TBI. *Hum Brain Mapp*. Aug 15 2022;43(12):3694-3705. doi:10.1002/hbm.25877

205.   Kinzel P, Marx CE, Sollmann N, et al. Serum Neurosteroid Levels Are Associated With Cortical Thickness in Individuals Diagnosed With Posttraumatic Stress Disorder and History of Mild Traumatic Brain Injury. *Clinical EEG and neuroscience*. Jul 2020;51(4):285-299. doi:10.1177/1550059420909676

206.   Bae S, Sheth C, Legarreta M, McGlade E, Lyoo IK, Yurgelun-Todd DA. Volume and shape analysis of the Hippocampus and amygdala in veterans with traumatic brain injury and posttraumatic stress disorder. *Brain imaging and behavior*. 2019:1-15.

207.   Lopez KC, Leary JB, Pham DL, Chou Y-Y, Dsurney J, Chan L. Brain volume, connectivity, and neuropsychological performance in mild traumatic brain injury: The impact of posttraumatic stress disorder symptoms. *Journal of neurotrauma*. 2017;34(1):16-22.

208.   Esagoff AI, Stevens DA, Kosyakova N, et al. Neuroimaging Correlates of Posttraumatic Stress Disorder in Traumatic Brain Injury: A Systematic Review of the Literature. *J Neurotrauma*. Oct 19 2022;doi:10.1089/neu.2021.0453

209.   Kaplan GB, Leite-Morris KA, Wang L, et al. Pathophysiological bases of comorbidity: Traumatic brain injury and posttraumatic stress disorder. *Journal of neurotrauma*. 2018;35(2):210-225.

210.   Klimova A, Korgaonkar MS, Whitford T, Bryant RA. Diffusion tensor imaging analysis of mild traumatic brain injury and posttraumatic stress disorder. *Biological psychiatry: cognitive neuroscience and neuroimaging*. 2019;4(1):81-90.

211.   Santhanam P, Teslovich T, Wilson SH, Yeh PH, Oakes TR, Weaver LK. Decreases in White Matter Integrity of Ventro-Limbic Pathway Linked to Posttraumatic Stress Disorder in Mild Traumatic Brain Injury. *J Neurotrauma*. Apr 1 2019;36(7):1093-1098. doi:10.1089/neu.2017.5541

212.   Yeh PH, Guan Koay C, Wang B, et al. Compromised Neurocircuitry in Chronic Blast-Related Mild Traumatic Brain Injury. *Hum Brain Mapp*. Jan 2017;38(1):352-369. doi:10.1002/hbm.23365

213.   Runyan A, Philippi CL, Pessin S, et al. Comparing resting-state connectivity of working memory networks in U.S. Service members with mild traumatic brain injury and posttraumatic stress disorder. *Brain Res*. Dec 1 2022;1796:148099. doi:10.1016/j.brainres.2022.148099

214.   Song C, Yeh PH, Ollinger J, et al. Altered Metabolic Interrelationships in the Cortico-Limbic Circuitry in Military Service Members with Persistent Posttraumatic Stress Disorder Symptoms Following Mild Traumatic Brain Injury. *Brain Connect*. Sep 2022;12(7):602-616. doi:10.1089/brain.2021.0036
215.   Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for Military-Related PTSD: A Review of Randomized Clinical Trials. *JAMA*. Aug 4 2015;314(5):489-500. doi:10.1001/jama.2015.8370
216.   Fleming CE, Kholodkov T, Dillon KH, Belvet B, Crawford EF. Actuarial prediction of psychotherapy retention among Iraq-Afghanistan veterans with posttraumatic stress disorder. *Psychol Serv*. May 2018;15(2):172-180. doi:10.1037/ser0000139
217.   Crocker LD, Sullan MJ, Jurick SM, et al. Baseline executive functioning moderates treatment-related changes in quality of life in veterans with posttraumatic stress disorder and comorbid traumatic brain injury. *Journal of traumatic stress*. Oct 6 2022;doi:10.1002/jts.22883
218.   Mikolic A, Polinder S, Retel Helmrich IRA, Haagsma JA, Cnossen MC. Treatment for posttraumatic stress disorder in patients with a history of traumatic brain injury: A systematic review. *Clin Psychol Rev*. Nov 2019;73:101776. doi:10.1016/j.cpr.2019.101776
219.   Berke DS, Kline NK, Wachen JS, et al. Predictors of attendance and dropout in three randomized controlled trials of PTSD treatment for active duty service members. *Behaviour research and therapy*. 2019;118:7-17.
220.   Foa EB, McLean CP, Zang Y, et al. Effect of Prolonged Exposure Therapy Delivered Over 2 Weeks vs 8 Weeks vs Present-Centered Therapy on PTSD Symptom Severity in Military Personnel: A Randomized Clinical Trial. *JAMA*. Jan 23 2018;319(4):354-364. doi:10.1001/jama.2017.21242
221.   Roy MJ, Francis J, Friedlander J, et al. Improvement in cerebral function with treatment of posttraumatic stress disorder. *Ann N Y Acad Sci*. Oct 2010;1208:142-9. doi:10.1111/j.1749-6632.2010.05689.x
222.   Wolf GK, Kretzmer T, Crawford E, et al. Prolonged Exposure Therapy With Veterans and Active Duty Personnel Diagnosed With PTSD and Traumatic Brain Injury. *Journal of traumatic stress*. Aug 2015;28(4):339-47. doi:10.1002/jts.22029
223.   Walter KH, Dickstein BD, Barnes SM, Chard KM. Comparing effectiveness of CPT to CPT-C among U.S. Veterans in an interdisciplinary residential PTSD/TBI treatment program. *Journal of traumatic stress*. Aug 2014;27(4):438-45. doi:10.1002/jts.21934
224.   Cole MA, Muir JJ, Gans JJ, et al. Simultaneous Treatment of Neurocognitive and Psychiatric Symptoms in Veterans with Posttraumatic Stress Disorder and History of Mild Traumatic Brain Injury: A Pilot Study of Mindfulness-Based Stress Reduction. *Mil Med*. Sep 2015;180(9):956-63. doi:10.7205/MILMED-D-14-00581
225.   Janak JC, Cooper DB, Bowles AO, et al. Completion of Multidisciplinary Treatment for Persistent Postconcussive Symptoms Is Associated With Reduced Symptom Burden. *J Head Trauma Rehabil*. Dec 24 2015;doi:10.1097/HTR.0000000000000202
226.   Walter KH, Jak AJ, Twamley EW. Psychiatric Comorbidity Effects on Compensatory Cognitive Training Outcomes for Veterans With Traumatic Brain Injuries. *Rehabil Psychol*. Jul 6 2015;doi:10.1037/rep0000049
227.   Cooper DB, Bunner AE, Kennedy JE, et al. Treatment of persistent post-concussive symptoms after mild traumatic brain injury: a systematic review of cognitive rehabilitation and behavioral health interventions in military service members and veterans. *Brain Imaging Behav*. Sep 2015;9(3):403-20. doi:10.1007/s11682-015-9440-2
228.   Cooper DB, Curtiss G, Armistead-Jehle P, et al. Neuropsychological Performance and Subjective Symptom Reporting in Military Service Members With a History of Multiple Concussions: Comparison With a Single Concussion, Posttraumatic Stress Disorder, and Orthopedic Trauma. *J Head Trauma Rehabil*. Mar/Apr 2018;33(2):81-90. doi:10.1097/HTR.0000000000000375
229.   Cooper DB, Bowles AO, Kennedy JE, et al. Cognitive Rehabilitation for Military Service Members With Mild Traumatic Brain Injury: A Randomized Clinical Trial. *J Head Trauma Rehabil*. May/Jun 2017;32(3):E1-E15. doi:10.1097/HTR.0000000000000254
230.   Jak AJ, Jurick S, Crocker LD, et al. SMART-CPT for veterans with comorbid posttraumatic stress disorder and history of traumatic brain injury: a randomised controlled trial. *J Neurol Neurosurg Psychiatry*. Mar 2019;90(3):333-341. doi:10.1136/jnnp-2018-319315

231.   Jackson S, Baity MR, Bobb K, Swick D, Giorgio J. Stress inoculation training outcomes among veterans with PTSD and TBI. *Psychological trauma: theory, research, practice, and policy*. 2019;11(8):842.
232.   Maruyama BA, Abrams G, Kornblith E, et al. Improvement in executive functioning after Goal-Oriented Attentional Self-Regulation training is associated with reduction in PTSD hyperarousal symptoms among veterans with comorbid PTSD and mild TBI. *Appl Neuropsychol Adult*. Aug 19 2021:1-9. doi:10.1080/23279095.2021.1960531
233.   Novakovic-Agopian T, Posecion L, Kornblith E, et al. Goal-Oriented Attention Self-Regulation Training Improves Executive Functioning in Veterans with Posttraumatic Stress Disorder and Mild Traumatic Brain Injury. *J Neurotrauma*. Mar 2021;38(5):582-592. doi:10.1089/neu.2019.6806
234.   Huntley JH, Rezvani Habibabadi R, Vaishnavi S, Khoshpouri P, Kraut MA, Yousem DM. Transcranial Magnetic Stimulation and its Imaging Features in Patients With Depression, Posttraumatic Stress Disorder, and Traumatic Brain Injury. *Academic radiology*. Apr 15 2022;doi:10.1016/j.acra.2022.03.016
235.   Namgung E, Kim M, Yoon S. Repetitive transcranial magnetic stimulation in trauma-related conditions. *Neuropsychiatr Dis Treat*. 2019;15:701-712. doi:10.2147/NDT.S189498
236.   Petrosino NJ, Cosmo C, Berlow YA, Zandvakili A, van 't Wout-Frank M, Philip NS. Transcranial magnetic stimulation for posttraumatic stress disorder. *Therapeutic advances in psychopharmacology*. 2021;11:20451253211049921. doi:10.1177/20451253211049921
237.   Marks MR, Dux MC, Rao V, Albrecht JS. Treatment Patterns of Anxiety and Posttraumatic Stress Disorder Following Traumatic Brain Injury. *The Journal of neuropsychiatry and clinical neurosciences*. Summer 2022;34(3):247-253. doi:10.1176/appi.neuropsych.21040104
238.   Hoskins M, Pearce J, Bethell A, et al. Pharmacotherapy for posttraumatic stress disorder: systematic review and meta-analysis. *Br J Psychiatry*. Feb 2015;206(2):93-100. doi:10.1192/bjp.bp.114.148551
239.   Friedman MJ. Pharmacological Treatments for PTSD. *Posttraumatic and Acute Stress Disorders*. Springer International Publishing; 2015:93-114.
240.   Raskind MA, Peskind ER, Chow B, et al. Trial of Prazosin for Posttraumatic Stress Disorder in Military Veterans. *N Engl J Med*. Feb 8 2018;378(6):507-517. doi:10.1056/NEJMoa1507598
241.   Singh B, Hughes AJ, Mehta G, Erwin PJ, Parsaik AK. Efficacy of Prazosin in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. *Prim Care Companion CNS Disord*. Jul 28 2016;18(4)doi:10.4088/PCC.16r01943
242.   Simon PY, Rousseau PF. Treatment of Posttraumatic Stress Disorders with the Alpha-1 Adrenergic Antagonist Prazosin. *Can J Psychiatry*. Mar 2017;62(3):186-198. doi:10.1177/0706743716659275
243.   Reist C, Streja E, Tang CC, Shapiro B, Mintz J, Hollifield M. Prazosin for treatment of posttraumatic stress disorder: a systematic review and meta-analysis. *CNS Spectr*. Aug 2021;26(4):338-344. doi:10.1017/s1092852920001121
244.   Johnson JM, Capehart BP. Psychiatric care of the post-September 11 combat veteran: a review. *Psychosomatics*. 2019;60(2):121-128.
245.   Raut SB, Canales JJ, Ravindran M, et al. Effects of propranolol on the modification of trauma memory reconsolidation in PTSD patients: A systematic review and meta-analysis. *J Psychiatr Res*. Jun 2022;150:246-256. doi:10.1016/j.jpsychires.2022.03.045
246.   McAllister TW, Zafonte R, Jain S, et al. Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury. *Neuropsychopharmacology*. Apr 2016;41(5):1191-8. doi:10.1038/npp.2015.282
247.   Zalta AK, Tirone V, Orlowska D, et al. Examining moderators of the relationship between social support and self-reported PTSD symptoms: A meta-analysis. *Psychol Bull*. Jan 2021;147(1):33-54. doi:10.1037/bul0000316
248.   Williamson AK, Riendeau RP, Stolzmann K, et al. An Exploratory Analysis of Self-Reported Protective Factors against Self-Harm in an Enrolled Veteran General Mental Health Population. *Mil Med*. Dec 1 2019;184(11-12):e738-e744. doi:10.1093/milmed/usz111
249.   Nichter B, Haller M, Norman S, Pietrzak RH. Risk and protective factors associated with comorbid PTSD and depression in U.S. military veterans: Results from the National Health and Resilience in Veterans Study. *J Psychiatr Res*. Feb 2020;121:56-61. doi:10.1016/j.jpsychires.2019.11.008

250.   Al-Ozairi A, McCullagh S, Feinstein A. Predicting Posttraumatic Stress Symptoms Following Mild, Moderate, and Severe Traumatic Brain Injury: The Role of Posttraumatic Amnesia. *J Head Trauma Rehabil.* Jul-Aug 2015;30(4):283-9. doi:10.1097/HTR.0000000000000043