

RESEARCH REVIEW ON MILD TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC STRESS DISORDER

Table of Contents

PURPOSE	2
BACKGROUND	2
a. Mild Traumatic Brain Injury.....	2
b. Posttraumatic Stress Disorder.....	3
COMORBID mTBI and PTSD.....	4
a. Unclear Symptom Etiology	4
b. Prevalence.....	4
c. Risk Factors for PTSD and mTBI	5
DIAGNOSTIC AND ASSESSMENT TOOLS.....	6
NEUROPSYCHOLOGICAL MANIFESTATIONS OF MTBI AND PTSD.....	7
a. Common Neuropsychological and Neurocognitive Tests	7
b. Neuropsychological and Neurocognitive Findings: Mild TBI Only.....	9
c. Neuropsychological and Neurocognitive Findings: PTSD Only	9
d. Neuropsychological and Neurocognitive Findings: Comorbid Group.....	9
CHANGES IN THE BRAIN ASSOCIATED WITH MILD TBI AND PTSD	10
a. Imaging Approaches.....	10
b. Mild TBI Only	10
c. PTSD Only.....	11
d. Comorbid Group	12
TREATMENT IMPLICATIONS.....	13
a. Clinical Practice Guidelines	13
b. Evidence Regarding Non-Pharmacological Interventions	13
c. Evidence Regarding Pharmacological Interventions.....	14
d. Factors Protective Against PTSD Symptoms.....	15
SUMMARY	15
CONCLUSIONS & RECOMMENDATIONS	15
TABLES.....	17
Table 1: Clinical Tools	17
Table 2: Military Relevant CRs/CPGs.....	18
REFERENCES.....	18

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 imaging, 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 system⁶⁸ 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 $\epsilon 4$ allele, is associated with poorer long-term clinical outcomes in all severities of TBI as compared to the $\epsilon 2$ & $\epsilon 3$ alleles.⁷² A study examining the relationship between the APOE genotype and PTSD showed that the presence of the APOE $\epsilon 4$ allele was associated with increased PTSD following mTBI in veterans.^{73,74} A meta-analysis demonstrated that the APOE $\epsilon 4$ 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 health⁷⁸ 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 overlap⁹⁶ 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 populations¹⁰⁵ 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 screen¹¹³ 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 magnetoencephalography¹²⁶⁻¹²⁸ 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 imaging¹⁴⁸. 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 changes¹⁹⁰ as well as changes in function and electrographic activity¹⁹¹ 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 emotion, 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 medial 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 circuitry 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 intervention²²⁴ 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.

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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

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