

## RESEARCH REVIEW

### ON

## MILD TRAUMATIC BRAIN INJURY AND POST-TRAUMATIC STRESS DISORDER

### PURPOSE

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

### BACKGROUND

#### **Mild Traumatic Brain Injury**

Traumatic brain injury (TBI) is defined as the alteration of brain function that results from exposure of the head to an external force.<sup>1</sup> For both civilian and military populations, TBI is a prevalent problem. Approximately 2.5 million civilian TBI-related emergency room visits occur each year.<sup>2</sup> In military populations, 17.3% of the individuals deployed in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF) or Operation New Dawn (OND) reported at least one deployment-related TBI.<sup>3</sup> Mild traumatic brain injuries (mTBI) are the most common form of TBI encountered. They account for over 70% of the civilian emergency room visits,<sup>4</sup> and out of the nearly 418,000 service members (SMs) diagnosed with a TBI between January 2000 and March 2020, 82.4% were mTBI.<sup>5</sup> As these data show, mTBI is a serious health concern.

The most common causes of civilian mTBI are unintentional falls, being unintentionally struck by or against an object, and motor vehicle accidents.<sup>6</sup> While SMs are also exposed to these injurious circumstances, the most common source of military mTBI is blast arising from exposure to the detonation of improvised explosive devices (IEDs).<sup>7</sup> Overpressure waves from explosions can cause a blast-related mTBI, which accounts for 33% of mTBIs in SMs.<sup>3</sup> Also capable of eliciting a mechanical mTBI are impact from projectiles created by the explosion, propulsion of an individual into an object after the explosion, or processes not directly attributable to blast but resulting from the effects of blast.<sup>8</sup> Regardless of the origin, experiencing one mTBI increased the risk of sustaining subsequent mTBIs by 1.98 times.<sup>9</sup> This is important for recovery, as the duration of recovery and the severity of deficits increase proportionally with the number of mTBIs sustained.<sup>10</sup>

The diagnostic criteria for mTBI following trauma to the head includes whether the patient experiences a loss of consciousness (LOC) lasting between 0-30 minutes, alteration in consciousness (such as confusion or disorientation) that lasts up to 24 hours, or post-traumatic amnesia that can last up to 24 hours.<sup>11</sup> 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 (CT) scans.<sup>12</sup> The diagnosis of civilian mTBI varies slightly on this requirement. In approximately 10-40% of mTBI cases diagnosed based on Glasgow Coma Scale (GCS) scores, focal intracranial structural

abnormalities can be detected via CT on the day of injury.<sup>13</sup> The civilian diagnosis of mTBI takes this into consideration, and utilizes the presence or absence of abnormalities on CT scans to categorize injuries as complicated or uncomplicated, respectively.<sup>14</sup> 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,<sup>15</sup> the Canadian Head CT rule,<sup>16</sup> or the New Orleans Criteria.<sup>17</sup>

Mild TBI patients may present with somatic, cognitive and/or emotional symptoms early after injury. The somatic symptoms include nausea, dizziness, headache, blurred vision/oculomotor deficits, auditory disturbance, and fatigue. The most common cognitive symptoms that occur are disruption of memory and executive function. Emotional symptoms, such as disinhibition and emotional lability, are also common.<sup>18</sup> For patients with a higher symptom burden acutely following injury, it is recommended that excessive physical and vestibular/balance-dependent activities are returned to gradually to promote recovery and prevent long-term impairment.<sup>19</sup> Post concussive symptoms are thought to occur acutely following injury; however, mTBI may also influence the development of long-term cognitive impairments and psychiatric illnesses.<sup>20</sup>

### Post-Traumatic Stress Disorder

Post-traumatic Stress Disorder (PTSD) is a psychological condition resulting from exposure to a traumatic event often involving actual or threatened death, serious injury, or violation.<sup>21</sup> 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 (DSM-5) recognizes PTSD with delayed expression, in which full diagnostic criteria are not met until one month or more post-trauma.<sup>22</sup> If symptoms occur earlier than one month post-trauma, the resulting condition is referred to as Acute Stress Disorder (ASD).<sup>23</sup>

A diagnosis of PTSD usually occurs when patients experience symptoms from four discrete categories: intrusive thoughts, avoiding reminders, negative thoughts and feelings, and arousal/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.<sup>24</sup>

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%.<sup>25</sup> When examining military populations specifically, the Department of Defense Health Related Behaviors Survey found that 10.5% of U.S. Army, 9.1% of Marines, 9.7% of Navy, and 3.9% of Air Force service members had PTSD in 2015.<sup>26</sup> A total of approximately 500,000 SMs who served in Iraq and Afghanistan over the past 13 years have been diagnosed with PTSD.<sup>27</sup> Those SMs diagnosed with PTSD are highly prone to self-stigmatization about the disorder, or judgments and beliefs that inform their view of seeking treatment for it.<sup>28</sup> This is one of the primary reasons why cases

may be underestimated, as many veterans and SMs suffering from PTSD do not seek treatment.<sup>29,30</sup>

A systematic review of studies on mental health after deployment to Iraq or Afghanistan found that several characteristics were associated with an increased risk of PTSD. Those include demographic characteristics, military characteristics, deployment-related factors, pre-deployment factors, and post-deployment factors.<sup>31</sup> The demographic characteristics were age under 40 (for males only), lower education, and unmarried status. Military characteristics were serving in the US Army or Marines (as compared to other US service branches), enlisted rank; and the health-care occupations of combat specialists and 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 the civilian population, women are more likely to be diagnosed with PTSD.<sup>32</sup> In studies conducted on military populations where non-deployment related traumas are controlled for, the rates of PTSD diagnosis are similar between males and females.<sup>33</sup>

The 11<sup>th</sup> edition of the International Statistical Classification of Diseases and Related Health Problems manual (developed by the World Health Organization) has recently defined a subtype of PTSD not previously characterized in the DSM-5.<sup>34</sup> This subtype, known as complex PTSD (CPTSD), is thought to differ from PTSD because it is associated with exposure to chronic or prolonged trauma, and can result in higher levels of impairment.<sup>35,36</sup> 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.<sup>37</sup> When a veteran population was evaluated based on the new guidelines to distinguish PTSD from CPTSD, approximately 25-50% met the criteria for CPTSD.<sup>38</sup> More research and evaluation will need to be done 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-three fold after mTBI, according to studies of veterans, SMs, and civilians.<sup>39-41</sup> The origin of PTSD in groups where mTBI is co-morbid 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.

### **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 co-morbid groups.<sup>42</sup> These common symptoms include insomnia, fatigue, irritability, depression, anxiety, emotional numbing, avoidance, trouble concentrating, memory deficits, and hyperarousal.<sup>43</sup> Biomarker studies currently being performed in patients may eventually aid in the differential diagnosis of PTSD and symptoms resulting from mTBI, as well as determine whether any unique protein identifiers of comorbid occurrence are present.<sup>44</sup>

PTSD symptoms can aid in the prediction of post-concussive symptom onset and severity. In some studies with military or veteran participants after TBI, psychological factors were more predictive of post-concussive symptoms than TBI status.<sup>45</sup> PTSD can also influence treatment and time-to-recovery, as well as symptom severity after mTBI, often leading to greater post-concussive symptoms.<sup>46-49</sup> This is particularly true in SMs with PTSD who experience mTBI, although misattribution of post-concussive symptoms to PTSD is common in this group.<sup>50</sup> 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.<sup>51,52</sup>

## Prevalence

The prevalence 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 recent meta-analysis aimed at identifying the prevalence of comorbid PTSD and TBI determined that among all of the studies assessed, their co-occurrence in civilian samples was approximately 13.5%.<sup>42</sup> It was also shown that mTBI is more commonly associated with PTSD than moderate or severe TBI in civilian populations.<sup>53</sup> Examination of military populations via systematic review has revealed that comorbid mTBI and PTSD are significantly more common in military than civilian subjects. This study determined that, among all of the studies included in the systematic review, 11.0 – 18.6% of the civilians who sustained a TBI (and were included in the review) develop PTSD within two years of injury while 48.2% of SMs and veterans assessed in the study develop PTSD after TBI.<sup>54</sup>

## Risk Factors for PTSD and mTBI

There are several risk factors implicated in increasing the likelihood of developing PTSD. Among them, alcohol and substance abuse, smoking, history of chest pain and younger age were strong risk factors observed in a veteran cohort.<sup>55</sup> Other demographic factors associated with increased risk of developing PTSD include fewer years of education, incidence of pre-trauma psychiatric disorders, and marital status (unmarried).<sup>56</sup> When examining comorbid occurrence, one of the biggest risk factors for developing PTSD after mTBI is ASD. If ASD is diagnosed within 12 months after sustaining a mTBI, the risk of developing subsequent PTSD doubles.<sup>57</sup>

Given the prevalence of comorbid mTBI and PTSD, it is important to identify how mTBI 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 conveys an increased risk for developing PTSD.<sup>58</sup> Specific characteristics of mTBI can also contribute to increasing the risk of PTSD. Those who experience mTBI with LOC may be at higher risk of developing PTSD<sup>59</sup> or having more severe PTSD symptoms<sup>60,61</sup> as compared to those with mTBI without LOC. Additionally, those who experience mTBI with extracranial injuries and TBIs resulting from violence had significantly more PTSD than those who did not.<sup>62</sup>

As previously mentioned, being a member of the military is also a risk factor for PTSD diagnosis and symptom severity.<sup>63</sup> Combat related mTBI is correlated with increased PTSD symptom severity when compared to non-combat related mTBI.<sup>50</sup> The increased risk could be due to exposure to blast-related mTBI, a more prominent injury mechanism among military populations in recent years. There is an increase in PTSD diagnosis and symptom severity after

exposure to blast-related mTBI compared to non-blast mTBI.<sup>64</sup> Blast exposed SMs 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.<sup>65</sup> While PTSD is associated specifically with mTBI and not more severe forms of TBI in civilian populations, the risk of PTSD development increases with the severity of TBI endured in military populations.<sup>41</sup> This dissonance between civilian and military populations could be attributed to the kinds of trauma to which each group may be exposed. For civilians, mTBI most likely occurs in the context of a traumatic event. Military personnel are more likely to experience chronic psychological trauma based on deployment to active-combat environments where many of their TBIs are sustained. Combat exposure is also associated with an increased likelihood of sustaining multiple lifetime TBIs, and the combination of these two factors yields greater PTSD symptom severity.<sup>58</sup> Therefore, characteristics of psychological trauma and factors associated with combat environments may override properties of injury severity that link PTSD prevalence with mTBI, specifically in civilians.<sup>66</sup>

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.<sup>67</sup> In a study conducted to examine the relationship between the APOE genotype and PTSD, it was shown that the presence of the APOE-  $\epsilon$ 4 allele was associated with increased PTSD diagnosis following mTBI in veterans.<sup>68,69</sup>

### **Population Characteristics**

PTSD with mTBI history in SMs and veterans is often associated with other psychological or physical conditions.<sup>70,71</sup> Specifically, depression, headache, suicidal impulses, substance use disorder, pain, sleep disturbances, cumulative disease burden, and polypharmacy have been documented in this population.<sup>70-77</sup> Social outcomes reported in the comorbid PTSD and mTBI population include reduced psychosocial function, driving problems, missed work, and intimate partner violence.<sup>78-80</sup> Comorbid PTSD and mTBI has also been correlated with an increased risk of developing Parkinson's disease.<sup>81</sup>

### **DIAGNOSTIC AND ASSESSMENT TOOLS**

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

The Neurobehavioral Symptom Inventory (NSI) and the Rivermead Post-concussion Symptoms Questionnaire (RPQ) are patient reporting tools that can be used to determine symptom severity<sup>45,82</sup> for symptoms commonly observed following mTBI. 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.<sup>83-86</sup> The resulting factor structures vary, but one comparative study that utilized Rasch analysis found that, for the NSI, a three factor structure including vestibular/somatic, cognitive, and mood/behavioral factors provided the best fit for a sample of OEF/OIF veterans.<sup>85</sup> Subsequent

studies have gone on to determine that, while the NSI is a reliable metric for determining psychological stress, it is not reliable for use to predict or examine changes in functioning.<sup>87</sup>

Neither the NSI nor the RPQ are diagnostic, in part due to the high base rate of these symptoms among uninjured populations,<sup>88</sup> and in part because a number of symptoms on these scales are also associated with PTSD and other psychological conditions. For PTSD diagnosis, one of the gold standards is the clinician-administered PTSD scale (CAPS). The CAPS was updated to reflect revisions to the criteria for PTSD defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), so the currently preferred CAPS is the CAPS-5.<sup>89</sup> 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.<sup>90,91</sup>

Mild TBI diagnosis is based on an injury event resulting in no more than 30 min of LOC, and associated with alterations of consciousness and/or post-traumatic amnesia.<sup>92</sup>

The VA/DoD Clinical Practice Guideline for PTSD indicates that “all new patients should be screened for symptoms of PTSD initially and then on an annual basis or more frequently if clinically indicated due to clinical suspicion, recent trauma exposure (e.g., major disaster), or history of PTSD.”<sup>93</sup> The DoD includes screening for PTSD in the Post Deployment Health Assessment (PDHA; DD Form 2796) and post-deployment health reassessment (PDHRA).<sup>94</sup> The most commonly used instrument in the VA and DoD is the Primary Care PTSD Screen (PC-PTSD). As the name implies, the PC-PTSD is a screen designed for use in primary care and other medical settings.<sup>95</sup> 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.<sup>96</sup>

Post-concussive and PTSD symptom instruments are primarily self-report, 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/OIF veterans were prone to exaggeration of cognitive, post concussive and PTSD symptom severity that did not correspond to performance on more objective measures.<sup>97</sup> 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.<sup>98</sup> To address this problem, many commonly used assessments such as the NSI have modifying additions like the Validity 10 that can aid in identifying exaggerated symptom reports in patients with comorbid mTBI and PTSD or other psychological disorders.<sup>99</sup>

To aid with diagnosis, new assessment modalities that do not involve self-report are being utilized and explored. Structured interviews can aid in identifying 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 via the internet.<sup>100</sup> The Veterans Health Administration TBI Clinical Reminder is another structured interview developed to aid in TBI diagnosis, specifically in veterans.<sup>101</sup> In addition to structured interviews, there is currently an interest in performing assessments of vestibular and motor function in persons with PTSD and/or mTBI history.<sup>102,103</sup> Technologies including fluid biomarkers,<sup>104-106</sup> electroencephalography,<sup>107</sup> and magnetoencephalography<sup>108</sup> have been used to characterize subjects with PTSD and/or mTBI, but these approaches are not currently used as diagnostics in the clinical setting.

## **NEUROPSYCHOLOGICAL MANIFESTATIONS OF COMORBID MTBI AND PTSD**

### **Common Neuropsychological and Neurocognitive Tests**

Neuropsychological tests are employed to evaluate many domains, including cognition, mood, social cognition, and motivation.<sup>109</sup> Neurocognitive assessment tests (NCATs) are meant to detect differences in executive function, memory, attention, processing speed, learning, and other domains of cognition specifically that can be altered by mTBI and/or PTSD.<sup>110</sup> There are four computer-based NCATs that 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).<sup>111</sup> The ANAM was developed by the DoD to measure processing speed, reaction time, memory, and cognitive efficiency. The fourth version, specifically designed for military personnel, is required to be performed on SMs within 1 year prior to deployment as a baseline.<sup>112</sup> The CNS-VS is commonly 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.<sup>113</sup> The CogState assessment battery is used in military and sports settings to evaluate reaction time and processing speed using a playing-card motif.<sup>114</sup> ImPACT is used to evaluate cognitive changes following sports-related concussion, including verbal memory, visual memory, visual motor speed, and reaction time.<sup>115</sup> 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.<sup>116,117</sup> When assessing comorbid occurrence, a battery of tests is used to provide an objective means of assessing performance in areas affected by the presence of both mTBI and PTSD.<sup>118</sup> To further delineate the two conditions, differences in imaging studies that correspond to brain regions associated with the cognitive capabilities assessed in these neurocognitive tests can also aid in identifying differences unique to participants in the comorbid group.<sup>119</sup>

Neurocognitive/ neuropsychological changes can greatly affect quality of life for those with PTSD and/or mTBI. Identifying the cognitive impairment elicited by mTBI and PTSD individually is imperative for determining how to target therapeutic interventions to improve performance in comorbid groups. Those with PTSD and mTBI can attribute their cognitive symptoms to the injury instead of the presence of a psychological condition, which can reduce their adherence to treatment protocols.<sup>120</sup> Through neuropsychological testing, discrete functional changes associated with each condition can be determined. This can allow for caregivers to prescribe differential cognitive or behavioral therapy that addresses both sets of deficits.

Currently, neuropsychological/ neurocognitive tests are not indicated for diagnostic purposes in comorbid groups, as the results for PTSD related symptoms can be ambiguous. Symptom severity inferences in related tasks can be occluded by attention, memory, interpretation and cognitive biases that seem counterintuitive to the conventional behaviors associated with PTSD. This can make the results of these assessments hard to interpret for diagnosis.<sup>121</sup> These tests do provide objective evaluations of neuropsychological manifestations of mTBI, PTSD, and comorbid occurrence, which is important for determining return-to-duty, benefits, and other decisions.

**Neuropsychological/Neurocognitive Findings: Mild TBI Only**

During the acute phase of mTBI recovery, decreases in neuropsychological test performance have been observed in civilian settings for attention, language, memory, visuospatial and executive function.<sup>122</sup> Impairments in attention, language, memory, and executive function were found even six months after injury.<sup>123</sup> 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/OIF veterans assessed several years after mTBI found no neuropsychological differences between those with mTBI only and controls without mTBI.<sup>48</sup> These findings are contradicted by studies showing that chronic impairments arise following both blast and non-blast mTBI.<sup>65,124</sup> These variations in the likelihood of chronic deficit development may be attributed to the number of mTBIs sustained, as a single mTBI is not generally associated with lasting deficits whereas multiple mTBIs convey a higher risk of developing lasting deficits.<sup>125</sup>

**Neuropsychological/Neurocognitive Findings: PTSD Only**

PTSD alone is associated with decreased neurocognitive test performance in several domains, especially verbal learning, speed of information processing, and attention/working memory, according to a recent meta-analysis including data from 1,779 PTSD patients including a mixture of studies of military and other trauma survivors.<sup>126</sup> These findings are consistent with neuropsychological studies showing reduced performance in veterans with PTSD as compared to veteran controls.<sup>127</sup> PTSD has been shown to cause impairments in multiple domains of neuropsychiatric tests, including episodic memory and executive function.<sup>128-131</sup> Researchers have also found correlations between increased PTSD symptoms or diagnosis and higher rates of impaired neuropsychological outcomes.<sup>132,133</sup> Taken together, these data suggest that PTSD and subclinical PTSD symptoms may be bi-directionally 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 must be performed to understand how discrete factors in the constellation of PTSD symptoms can influence cognition.

**Neuropsychological/Neurocognitive Findings: Comorbid Group**

Multiple studies in OEF/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 reported mTBI history performed significantly worse on neuropsychological tests as compared to those with PTSD only, mTBI only, or controls. This has been seen in different populations, including SMs,<sup>50,134,135</sup> veterans,<sup>46,51,136</sup> and civilians.<sup>42</sup> The same is true after blast mTBI wherein the presence of PTSD symptoms is correlated with the presentation of neuropsychological deficits.<sup>137</sup> In contrast, some studies have found no significant neuropsychological differences between those with mTBI history and PTSD and those with only one condition.<sup>138,139</sup> The inconsistency in findings between these and the above-cited works may be due to participant population, study design, outcomes, or other factors.

New neuropsychological assessment tools are currently being tested to determine their utility to evaluate comorbid mTBI/PTSD symptoms in military populations. An iPad-based tool with the NIH Toolbox Cognitive Battery (NIH-TB) was 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.<sup>140</sup>

## **CHANGES IN THE BRAIN ASSOCIATED WITH MILD TBI AND PTSD**

### **Imaging Approaches**

Imaging techniques provide valuable tools with which 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 relevant predictive and diagnostic capabilities remain to be demonstrated in larger clinical samples. They do, however, reveal valuable mechanistic and neuroanatomical information that may soon be translated into clinical utility.

To study the changes in the brain that arise in correlation with PTSD and mTBI, various imaging techniques have been employed. Traditional computed tomography (CT) scans and magnetic resonance imaging (MRI) has thus far not been able to differentiate mTBI history alone from mTBI comorbid with PTSD. Brain volume measurements have demonstrated promise for identifying those with comorbid PTSD and mTBI history.<sup>141-143</sup> Researchers have used sophisticated imaging approaches including functional magnetic resonance imaging (fMRI) to investigate the pathology and changes in brain function unique to mTBI and comorbid PTSD.<sup>144-146</sup> Other imaging approaches that may warrant further study include advanced MRI-approaches and single photon emission computed tomography (SPECT). Limited evidence shows the potential of SPECT to provide diagnostic information in those with PTSD, mTBI history, or both.<sup>147,148</sup> Fluid-attenuated inversion recovery (FLAIR) MRI approaches have been used to characterize white matter hyper-intensity and default mode network activity in these populations.<sup>138,149</sup> Diffusion tensor imaging (DTI), which is also utilized to examine white matter integrity in major tracts throughout the brain, demonstrates mixed capabilities for matching white matter integrity changes to symptom severity in comorbid groups; however, it remains promising in its diagnostic and prognostic potential.<sup>150-153</sup> Magnetoencephalogram (MEG) is a functional imaging technique that detects the magnetic signal in the grey matter produced by neuronal activity.<sup>154</sup> 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 in comorbid occurrence.<sup>154</sup> 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 both mTBI and TBI.

### **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 throughout 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 the current imaging modalities.<sup>155</sup> The advent of DTI and similar techniques allows for the

detection of diffuse axonal injuries (changes in white matter) resulting from mTBI.<sup>156</sup> For example, a meta-analysis of various imaging 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.<sup>157</sup> The extent of white matter damage is also correlated with the severity of post-concussive symptoms.<sup>158</sup> Changes in white matter can greatly alter the connectivity between brain regions, resulting in functional impairments.

Although gross structural damage is uncommon, functional alterations can occur in specific brain regions after mTBI that contribute to deficit development. Clinical and translational studies have shown that the hippocampus is vulnerable to changes in function and connectivity following mTBI.<sup>159,160</sup> White matter changes,<sup>161</sup> as well as changes in function and electrographic activity<sup>162</sup> in the dorsomedial and dorsolateral prefrontal cortex have also been found. These changes are thought to contribute to the impairments in executive function commonly recorded in patients that sustain mTBIs. Given the importance of these two structures in facilitating learning and memory, it is not surprising that many patients who experience mTBI develop learning and memory deficits. Thalamic functional connectivity is also thought to be disrupted after mTBI, and that disruption is correlated with worse symptoms and poor recovery in neuropsychological assessments.<sup>163</sup> Given the role of the thalamus in functions such as gating pain, mediating sleep/fatigue, and regulating certain elements of cognition, it is not surprising that post traumatic headache and disturbances in sleep and cognition are observed following mTBI.<sup>164</sup>

### **PTSD Only**

An array of imaging studies have been performed in order to identify brain regions that are altered structurally and functionally in PTSD. Three primary brain regions have been heavily implicated: the amygdala, hippocampus, and medial prefrontal cortex.<sup>165</sup>

The amygdala is a part of the fear circuitry in the brain, and many studies have indicated that changes in its activity and structure are a hallmark of PTSD. It has been shown that 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).<sup>166</sup> However, this increased activation of the amygdala does not seem to be uniform across all PTSD patients.<sup>167</sup> In fact, it has been suggested that either increased or decreased amygdala activity are associated with specific PTSD symptoms.<sup>168</sup>

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.<sup>167</sup> Structural imaging studies have shown that decreased hippocampal volume may also be associated with PTSD.<sup>169,170</sup>

The medial prefrontal cortex (mPFC) 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, was also observed in PTSD.<sup>171</sup> This decrease in activity seems to be an acquired characteristic caused by PTSD.<sup>172</sup> Smaller mPFC volumes are also a hallmark of PTSD.<sup>173</sup>

## Comorbid Group

Many studies have aimed to examine the aforementioned structures, in order to determine if key pathological features of the individual groups are made worse by comorbid occurrence. 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.<sup>174</sup> Increased amygdala volume specific to the comorbid mTBI and PTSD group was also observed in veterans from OEF/OIF using different techniques to normalize and account for variable head size.<sup>141</sup> Several studies of PTSD only 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.

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. 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.<sup>175</sup> 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.<sup>176</sup> Symptom severity for PTSD is also positively correlated with the extent of reduction in white matter integrity in mTBI patients in these tracts.<sup>177,178</sup> 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.<sup>151</sup> 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.

## TREATMENT IMPLICATIONS

### Clinical Practice Guidelines

The VA/DoD treatment guidelines for mTBI three months or more post-injury focus on symptom management, education, and evidence-based diagnosis and treatment of possible comorbid conditions.<sup>92</sup> Effective treatments for PTSD are in wide dissemination across the VA and DoD. The VA/DoD Clinical Practice Guideline for PTSD emphasizes a collaborative treatment approach, manualized trauma-focused psychotherapy, and recognition of possible comorbid conditions.<sup>93</sup> Prescribing medication for patients with comorbid TBI and PTSD is challenging, as some medications can exacerbate the symptoms of one condition while treating the other.<sup>66</sup> Because of this, special attention must be paid to pharmacology for integrated mTBI and PTSD care. Patient retention can also be a treatment challenge.<sup>179,180</sup> It is widely suggested in the literature that one of the most common barriers to treatment completion is the deficit in executive function that is present in patients with comorbid mTBI and PTSD.<sup>136</sup> In addition, problems with emotional regulation, impulse control, and symptom severity from PTSD, as well as stigma for treatment seeking can limit the patient's ability to engage in treatment or incite drop-out.<sup>181,182</sup> 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,<sup>181</sup> it was determined that cognitive processing therapy or other kinds of cognitive behavioral therapy produced a reduction of PTSD symptoms in patients when combined with other treatment types. Pharmacological agents showed some promise in treating chronic PTSD. Novel treatments like brain and vestibular rehabilitation may be promising, but require further scientific exploration.<sup>181</sup> The efficacy of many of these treatments must be evaluated further for use in the comorbid PTSD/mTBI population, as they mostly 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.

### **Evidence Regarding Non-Pharmacological Interventions**

A systematic review by Steenkamp et al. on psychotherapy for military-related PTSD found that the treatments supported by the most evidence were cognitive processing therapy (CPT), trauma-focused exposure therapies, and eye movement desensitization and reprocessing (EMDR) therapy.<sup>179</sup>

While PTSD treatments are well-supported by evidence, fewer studies have been performed with comorbid PTSD/ 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.<sup>183</sup> Studies of exposure therapy,<sup>73,120,184,185</sup> cognitive processing therapy (CPT),<sup>186</sup> and a mindfulness intervention<sup>187</sup> have had positive results. Cognitive rehabilitation interventions have reduced psychiatric symptoms in several studies.<sup>188-192</sup> Combined strategies for administering therapies to better address comorbid TBI and PTSD are currently being explored. One such therapy is the novel SMART-CPT approach, which integrates the compensatory cognitive training aspects of Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) 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.<sup>193</sup> A form of cognitive behavioral therapy known as stress inoculation training (SIT) 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.<sup>194</sup> Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, is also being explored as a potential treatment for comorbid mTBI and PTSD. 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).<sup>195</sup> When rTMS was applied at low frequency to the dorsolateral prefrontal cortex, it alleviated PTSD with hyperarousal resulting from comorbid anxiety. More testing is required in order to determine whether this will be an efficacious treatment option in the future.

### **Evidence Regarding Pharmacological Interventions**

Antidepressants have been widely studied as a potential treatment for PTSD. Selective serotonin reuptake inhibitors (SSRI), and selective serotonin-norepinephrine reuptake inhibitors

(SSNRI), 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.<sup>196</sup> 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.<sup>197</sup>

Other drug classes investigated as therapeutic agents to mitigate PTSD symptoms include anti-adrenergic agents, such as prazosin, which has yielded both negative and positive results in clinical trials. While some studies have shown that prazosin can effectively reduce trauma nightmares, avoidance, and hypervigilance, others have found no difference between prazosin and placebo treated groups in symptom severity.<sup>198-200</sup> Propranolol, a similar 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.<sup>201</sup> A study by McAllister et al. suggested methylphenidate (a central nervous system stimulant) can reduce PTSD, depression, cognitive, and post-concussion symptoms in a mixed military and civilian population with mTBI, PTSD, or comorbid mTBI/PTSD.<sup>202</sup> Other classes of drugs, such as anticonvulsants/ mood stabilizers, antipsychotics and benzodiazepines, have also been considered as potential therapies. These compounds 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.<sup>197</sup>

### **Factors Protective Against PTSD Symptoms**

A recent 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), and other factors (including pets and hobbies) were less likely to be diagnosed with PTSD.<sup>203</sup> A study of veterans showed that higher dispositional optimism and higher levels of community integration also protected against PTSD.<sup>204</sup> Resilience is another important factor associated with better outcomes and reduced PTSD symptoms after injury.<sup>66</sup> When specifically assessing characteristics of TBI that could be protective, longer durations of post traumatic amnesia are associated with a reduction in the development of PTSD.<sup>42,205</sup>

### **SUMMARY**

Mild TBI results in acute symptoms that usually resolve spontaneously, but in some cases can lead to chronic impairments. The likelihood of developing lasting neuropsychological deficits from a single mTBI is still unclear, but sustaining multiple mTBIs is associated with a greater propensity towards long-term impairment. Military populations have additional mTBI risk due to exposure to blasts that can cause overpressure or mechanical injury. In the majority of cases of both military and civilian mTBI, structural deficits are not present on CT scans. Despite this, microstructural white matter damage may be detected with imaging techniques, such as DTI, in several major tracts throughout the brain that can reduce connectivity after injury, and may contribute to deficit development. The findings from DTI studies are still being researched to determine how they align with clinical abnormalities. Functional changes in brain regions like the thalamus and hippocampus could also serve as mechanisms for the symptoms that arise after a concussion, including sleep disruptions and memory deficits (respectively). Most therapeutic

interventions aimed at addressing these deficits involve a protocol for progressive return to activity, setting expectations for recovery, and providing medical management of symptoms (e.g. sleep disturbances) and secondary sequelae (e.g. post-traumatic epilepsy) that may arise.

A diagnosis of PTSD is made when key symptoms are present for no less than one month after exposure to a traumatic event. These symptoms include intrusive thoughts, avoiding reminders, negative thoughts and feelings, and arousal/reactive symptoms. Multiple studies have shown that, in addition to the hallmark symptoms of PTSD, chronic neurocognitive deficits are also common and can influence PTSD symptom severity. The prevalence of PTSD is higher among SMs and veterans than it is in the civilian population, making it a significant health concern for military populations. Imaging studies have identified structural and functional changes in the amygdala, hippocampus, and medial prefrontal cortex as hallmarks of PTSD. The function of each of these regions in maintaining physiological arousal, memory, and emotional processing provides a reasonable explanation as to how their dysfunction could be related to certain PTSD symptoms.

PTSD and mTBI are each prominent health concerns for many SMs and veterans, and they have the highest incidence of comorbidity in these populations. When they are comorbid, they present a unique set of challenges for diagnosis, treatment and prevention of chronic neuropsychological deficit development. Their co-occurrence increases risk of developing depression, headache, suicidal impulses, substance use disorder, pain, and sleep disturbances. Most of the currently used pharmacological treatments target the PTSD symptoms. Specifically, SSRIs and SSNRIs have provided substantial PTSD symptom alleviation, but may not adequately address post-concussive symptoms. The comorbid occurrence of mTBI and PTSD are also related by symptom severity, meaning that the presence of PTSD symptoms has been shown to exacerbate post-concussive symptoms. This can greatly impact quality of life for patients with both conditions and make treatment difficult. Currently, diagnosis of comorbid PTSD and mTBI relies on primarily self-report assessment methods. Because of this, the similarity between some post-concussive symptoms and PTSD symptoms can complicate the identification of each one separately. Identification and treatment of PTSD and mTBI is important because the likelihood of developing long-term neuropsychological deficits, such as learning and memory impairment, is increased with comorbid mTBI and PTSD occurrence.

To improve the diagnosis and treatment of comorbid mTBI and PTSD, several promising lines of research should be pursued. Importantly, further research in the field of fluid biomarkers may aid in differential diagnosis capabilities. Preclinical and clinical studies have identified targets, such as microRNA/non-coding mRNA sequences,<sup>206</sup> phospholipids,<sup>44,105</sup> and inflammatory cytokines,<sup>175,207</sup> that are uniquely altered by comorbid mTBI and PTSD. These biomarkers could provide a more definitive method of diagnosis, unlike conventional self-report methods, allowing clinicians to better identify these conditions to implement the proper treatments. Second, imaging techniques, such as functional and structural MRI and DTL, have provided valuable information about the changes in the brain that are associated with comorbid mTBI and PTSD. Although not currently used in the clinic as diagnostic or assessment tools, the development of imaging biomarkers for PTSD and mTBI is a promising research avenue. Changes in white matter,<sup>151</sup> structure and function of specific brain regions,<sup>141,144</sup> and the aggregation of proteins such as amyloid  $\beta$  in discrete regions of the brain,<sup>208</sup> have been observed in the brains of patients with PTSD and/or mTBI. These changes, if further investigated clinically, could provide a non-invasive evaluation to aid in diagnosis of either or both

conditions. The use of both fluid and imaging biomarkers could provide a quicker, more objective diagnostic tool to allow for a more focused implementation of treatment.

Treatments for comorbid mTBI and PTSD are also a prominent research interest, as the presentation of both conditions poses a challenge for addressing the symptom burden of the patient population. There is an increased prevalence of lasting neurocognitive deficits that develop as a result of PTSD and/or mTBI. A directly proportional relationship is also observed between PTSD and TBI symptoms and neurocognitive deficits, wherein increased symptom severity is associated with increased neurocognitive impairment.<sup>209</sup> Therefore, developing accessible neuropsychological assessment tools is paramount to identify deficits that can be addressed with cognitive/behavioral therapies while treating symptoms. Interventions such as CogSMART show promise for not only PTSD symptom mitigation, but improving learning and memory performance over time. Combinatorial interventions like CogSMART could aid in improving chronic outcomes for patients with comorbid PTSD and mTBI. Special considerations must be made to facilitate treatment by promoting adherence and retention. Since executive function deficits are one of the biggest obstacles for treatment completion, identifying strategies to treat this impairment may foster adherence. Implementation of cognitive training prior to engaging in psychotherapy has been shown to increase mental health treatment completion rates.<sup>210</sup> Psychological factors and social stigma also reduce retention in treatment programs; thus, supportive measures that address these barriers to treatment will be instrumental in ensuring appropriate care for this patient group. The co-occurrence of mTBI and PTSD creates unique structural and functional changes in the brain, which results in symptoms that may be more resistant to treatment.<sup>211</sup> Objective diagnostic tools, combinatorial treatment strategies that supersede treatments for each condition individually, and supportive measures to encourage patient retention must therefore be developed to better address the needs of this population.

PTSD co-occurring in patients with a history of mTBI is often challenging and complex with some patients presenting more severe or persistent symptoms than 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. Further research is needed to identify more effective diagnostic tools, treatment options and prognostic tools to benefit patients with a history of PTSD and mTBI.

### **KEY POINTS**

- PTSD is often associated with mTBI, and the presence of one condition can increase the symptom severity of the other.
- Service members and veterans have the highest risk for developing comorbid mTBI and PTSD.
  - When compared to non-combat related mTBI, the risk of developing of PTSD and increased symptom severity are more highly correlated with combat-related mTBI.
  - Blast mTBI has been shown to increase symptom severity and PTSD diagnosis compared to non-blast mechanisms of injury.

- Exposure to combat conveys an increased incidence of multiple lifetime TBIs, which can also influence PTSD symptom severity.
- Stigma of treatment seeking in military and civilian populations can adversely affect outcomes by reducing adherence to treatment programs. Retention is a necessary factor to consider when designing successful therapies.
- Chronic neuropsychological impairments in domains like learning, memory, and executive function have been linked to PTSD and mTBI individually. Results are inconclusive when trying to determine whether the presence of both increases the incidence and severity of these impairments.
- Imaging techniques like DTI and MRI, as well as MEG and fMRI, are used to understand structural and functional brain changes, respectively, that occur in mTBI and PTSD.
- Commonly used pharmacological treatments like SSRIs and SSNRIs focus primarily on alleviating PTSD symptoms; investigators continue to try to pinpoint compounds that can treat symptoms of both mTBI and PTSD.
- Several cognitive processing/behavioral therapies show promise for treating comorbid mTBI and PTSD, including SMART-CPT and SIT. Newer treatments like rTMS are also being explored to treat comorbid symptoms.

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