Chapter

Current Understanding of Biomarkers in Post Traumatic Stress Disorder and Mild Traumatic Brain Injury: A Systematic Review and Implications for Research and Treatment

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Abstract

For nearly 100 years, it was erroneously believed that the loss of consciousness and/or the altered mental status associated with a mild traumatic brain injury (mTBI) offered protection from the development of posttraumatic stress disorder (PTSD). However, it is now accepted that it is possible for PTSD to result from mTBI, and that the co-occurrence of these two conditions creates a more difficult condition to treat and worsens prognosis. In addition, it is known that the symptomology associated with PTSD and mTBI have a great deal of overlap, complicating diagnoses. The objective of this chapter is to review the current state of biomarkers aimed at diagnosing comorbid mTBI and PTSD that are useful on a single-patient basis and are not reliant on self-report or arduous interviews. Further, implications for future research and treatment are discussed.

Keywords: posttraumatic stress disorder, mild traumatic brain injury, biomarker, treatment

1. Introduction

Highlighted by recent world-conflicts, such as the wars in Afghanistan and Iraq, it has become evident that a better and more comprehensive understanding of the relationship between stress-related psychological disorders and traumatic brain injury is much-needed, in both military and civilian populations. For the purposes of this chapter, we will focus on posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI); however, this is not to underplay the crucial need to better understand the wide range of stress-related psychological conditions and

brain injury. The prevalence rates of PTSD and mTBI in American military personnel returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) has been reportedly as high as approximately 14 and 20%, respectively [1]. Despite both PTSD and mTBI conditions being "invisible injuries" (injuries not outwardly observable), they are both capable of creating significant disruptions in normal living for individuals. Further, what little we know about the co-occurrence of these conditions suggests that, when combined, they are more difficult to treat and often result in poorer prognoses [2–4]. This understanding is a significant advancement, as it was once thought that the loss of consciousness or altered mental status that is often observed with brain injury offered protection from the development of stress disorders [5]. Although it is recent military engagements that have highlighted the need for a better understanding of concomitant PTSD and mTBI, these conditions are prevalent in both military and civilian contexts and are therefore issues of broad public health on a global scale.

Approximately 3.5–7.0% of adults within the United States develop PTSD every year. When examining military personnel, this number increases to anywhere between 33 and 65% [6]. On the global scale, approximately 25% of the world's population has been affected by PTSD, making it the most prevalent psychiatric disorder [7]. Traumatic brain injuries are also very commonplace, and well over one-million people within the U.S. seek care annually for brain injury [8], with the majority of these being classified as mild [9, 10]. Worldwide, up to 50-million people annually seek treatment [6]. However, this number is likely an underestimation as many individuals who suffer an mTBI do not seek medical care. Furthermore, those that do seek medical attention oftentimes are misdiagnosed or underdiagnosed, especially if symptoms are mild or transient and loss of consciousness is limited to a short period of time [11]. When examining PTSD comorbid with mTBI, it becomes clear that many of those that have been affected by trauma have also experienced mTBI. Within civilian populations, PTSD following accidents such as falls or automotive collisions in which an mTBI occurs, range from approximately 20–36% [12]. Within a military context, this number increases to roughly 34–44% [13, 14]. However, like the reporting of each condition in isolation, the potential for misdiagnosis or underdiagnosis is large.

The prevalence and impact of both mTBI and PTSD (whether it be together or in isolation) result in a high cost of treatment, increased suicide rates, and lost work, all of which place a substantial burden on healthcare systems. Although the true costs are difficult to quantify, estimates for the health services cost associated with an mTBI alone range from $10,000USD to $100,000+ per patient depending on severity, length of hospital stay, and costs of rehabilitation [15–19], with a mean cost of $96,000USD [20]. The numbers are equally startling for the treatment costs associated with PTSD, with annual costs in excess of 200 million USD in US military personnel alone [21], and civilian costs estimated at even greater levels [22–24]. This estimate does not include the loss of productivity associated with this condition, which easily exceeds billions of dollars at a national level [25]. Although both PTSD and mTBI have substantial costs of care in isolation, when combined, healthcare costs are certainly increased, largely due to the complexity of treating comorbid conditions.

Posttraumatic stress disorder and mild traumatic brain injury have overlapping symptomology yet require different therapeutic approaches. In classical diagnoses, detailed information is collected about the onset and progression of symptoms to arrive at a probable diagnosis, which is then further refined. When dealing with an individual that may meet diagnostic criteria for both conditions, this process becomes much more difficult. In theory, a pattern of symptom overlap and divergence could

help differentiate etiologies when dealing with comorbid PTSD and mTBI, however, recent evidence suggests this is not the case. In a 2009 study, eight symptoms that are related to both PTSD and mTBI (fatigue, irritability, concentration problems, memory problems, depression, anxiety, insomnia, and dizziness) were examined and compared between patients who had experienced a recent mTBI or PTSD, revealing substantial overlap between both clinical groups. Although it was found that patients with PTSD had greater overall symptom severity, the degree of overlap prevented differential diagnoses based on the pattern of symptoms reported [26]. A meta-analysis conducted the same year [27] provided some evidence that there are symptoms unique to each when occurring in isolation (PTSD—shame, guilt, re-experiencing symptoms; mTBI—headache, sensitivity to light, dizziness, memory deficits), however, this information does not assist in the diagnosis of those that experience both mTBI and PTSD. Therefore, it remains unclear which aspects of these disorders play significant roles in disease onset following event exposure (whether it be set individual traits, epigenetic changes, alterations to specific brain area structure and function, or a combination of these and other factors), and ultimately which set of symptoms will manifest that are linked to the genuine presence of PTSD, mTBI, or both.

The objective of this chapter is to review our current understanding of comorbid mTBI and PTSD, with an emphasis on reviewing the current state of biomarkers used to diagnose comorbid mTBI and PTSD that offer promise on a single-patient basis. To best accomplish these goals, we will begin with providing definitions of what is meant by the terms PTSD and mTBI. Following, we will review the current understanding of the neurological underpinnings of each condition, with a focus on areas of overlap, and examine currently accepted methods of diagnosis and treatment options. Lastly, we will provide an account of the current researchers utilizing biomarkers for either diagnosis or prognosis of PTSD and mTBI, as well as discuss implications for future research and treatment.

2. Definitions

The lack of consistent definitions and assessments of mTBI and PTSD complicates the ability to capture accurate statistics for each condition. We focus on mild traumatic brain injury, as this is both the most common traumatic brain injury in civilian [28] and military populations [29], and is also the most likely to co-occur with PTSD [30]. Additionally, as mTBI is often the hardest to diagnose, the pursuit of biomarkers with clinical utility is of great importance. However, when it comes to describing what constitutes an mTBI, a large amount of ambiguity becomes apparent. What is clear is that for a diagnosis of mTBI, two things need to occur: (1) An external force must be exerted to the head; and (2) there must be a temporary change of mental status and/or other evidence of brain injury. Of course, for a traumatic brain injury to be classified as mild, there also needs to be an upper limit for the severity. This includes: (1) a loss of consciousness that does not exceed 30 minutes; and (2) posttraumatic amnesia that does not exceed 24 hrs. These criteria are largely accepted on a global scale [31–33] and will be used for this chapter as well.

Formal methods for the diagnosis of PTSD currently exist, making the definitions regarding the psychiatric condition somewhat consistent. In general, PTSD is characterized by four symptom clusters that develop in response to a traumatic event. The traumatic event must involve exposure to actual or perceived death, serious injury, or sexual violation. Furthermore, the event must be directly

experienced or witnessed by the individual, or indirectly experienced by subsequently learning about the event after it happened to a close family member or friend. Specific clinical criteria include: (1) intrusive symptoms related to re-experiencing the trauma; (2) avoidance of the traumatic memory or cues; (3) negative mood and thoughts including emotional numbing and anhedonia; and (4) altered arousal including hypervigilance, irritability, aggression, and sleep disturbances [7, 34]. Additionally, symptoms result in significant social, personal, and vocational impairment [7]. PTSD is commonly comorbid with other anxiety or mood disorders, further complicating diagnosis, and is also associated with increased risk for numerous negative behavioral and health conditions, including substance use disorder, type II diabetes, and Alzheimer's disease [35–38], significantly expanding the costs of treatment. Although the criteria for diagnosing PTSD are rather straightforward, this does not mean that PTSD is a static phenomenon without gradation. It is known that PTSD symptoms appear on a continuum and can fluctuate in terms of their functional impact and presence across time. Furthermore, although the precipitating traumatic event is a critical component of PTSD, it is how an individual responds to that trauma that is essential in the diagnosis. An identical traumatic event for one individual may result in PTSD, whereas another person experiencing an identical event may not. Therefore, it is as much about the symptoms and functional impairment as it is about the event itself.

3. Neurobiological underpinnings

Research has shown that both mTBI and PTSD are correlated with both structural and functional changes in the brain, as evidenced by advanced neuroimaging. As can

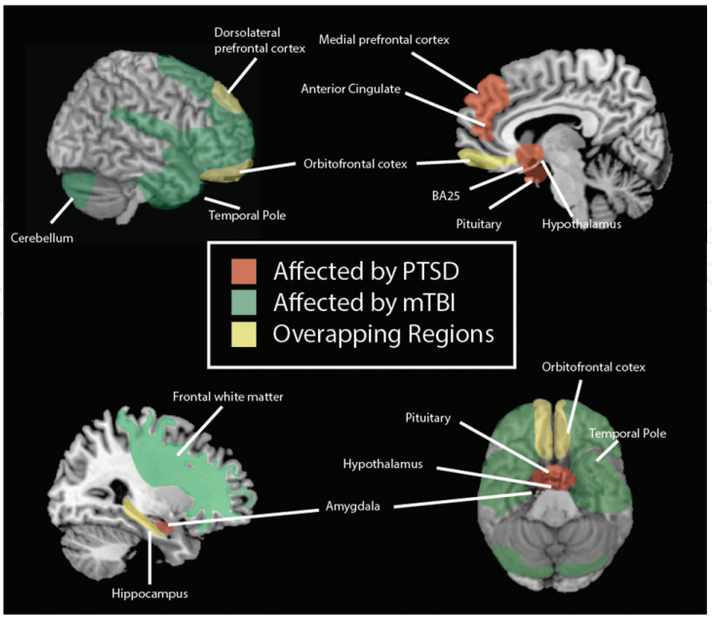

Figure 1.
Multiple brain regions have been suggested as vulnerable to mTBI (green), including the dorsolateral prefrontal cortex, the temporal pole, cerebellum, and frontal white matter tracts connecting the amygdala and medial prefrontal cortex. PTSD has been correlated with numerous brain regions as well (red) including the amygdala, hippocampus, dorsolateral and dorsomedial prefrontal cortex, and orbitofrontal cortex. Areas in common to both PTSD and mTBI are displayed in yellow.

be seen in **Figure 1**, there are many regions of the brain that are known to be particularly susceptible to both mTBI and PTSD.

Within PTSD, structural and functional imaging studies have shown a wide range of brain regions that are affected. These regions include the amygdala, hippocampus, dorsolateral and dorsomedial prefrontal cortex, and the orbitofrontal cortex. As should be apparent, many of these regions have functional implications for the onset and maintenance of PTSD symptomology [39, 40]. When examining brain structure, many studies (including two large meta-analyses) have shown reduced volume in the hippocampus, a brain area that is known to mediate declarative memories [41, 42]. Similarly, reduced volume within the anterior cingulate cortex and insula have also been shown to be related to PTSD onset [43]. When examining the functional neuroimaging data related to PTSD, exposure to stimuli related to an individual's trauma is associated with increased PTSD symptoms in concert with decreased activity within the medial prefrontal cortex and anterior cingulate [44–46]. Additional areas of decreased function during exposure to trauma-related stimuli include the inferior frontal gyrus, parietal cortex, visual association cortex, and hippocampus [44, 47, 48]. In contrast, areas of increased activity relative to controls include the amygdala [49, 50], parahippocampal gyrus [44, 51], and posterior cingulate [44, 45, 51]. Taken together, the existing literature provides strong evidence of dysfunction within a network of brain regions that are highly related to PTSD symptoms including the hippocampus and amygdala, cingulate cortex, and medial prefrontal cortex [52].

When examining the neurological correlates of mTBI, brain regions are most often damaged if the shearing forces that the brain undergoes during an mTBI are of sufficient magnitude to deform neural cells beyond normal tolerance levels [53]. If this deformation is of sufficient force to cause axonal tearing, the effects of the mTBI are likely to consist of longer-lasting neurological sequelae resulting from alterations to functional connectivity or difficulty with neuronal processing of information [54]. In comparison, if such forces are of a lesser magnitude, the neurological, cognitive, and behavioral symptoms are more likely to be short lived. In general, these forces particularly affect the longer white-matter tracts of the brain including the hypothalamic-pituitary–adrenal (HPA) axis, frontal, temporal, and limbic areas [55]. Specifically, these include the dorsolateral prefrontal cortex, the temporal pole, cerebellum, and frontal white matter tracts connecting the amygdala and medial prefrontal cortex [39, 40, 55–67]—all aforementioned areas that are also implicated in PTSD.

Although the role each of these regions play in the formation of cognition is beyond the scope of this chapter, it is apparent that many of these regions are involved in both emotional regulation and executive function, especially those that are affected in both PTSD and mTBI, including the prefrontal cortex and hippocampus [58, 68]. Perhaps not surprisingly, with the large amount of overlap in the neural substrates that are affected by both PTSD and mTBI, there is a fair degree of overlapping symptomology that has a significant impact on optimal methods for both diagnosing and treating PTSD concurrent with mTBI.

4. Current methods of diagnosis and treatment options

As stated previously, due to the overlap of symptoms in both PTSD and mTBI (**Table 1**), it is more difficult to both diagnose and treat PTSD when comorbid with mTBI. For example, in a recent study of 630,000+ veterans diagnosed with PTSD,

	PTSD	mTBI	PTSD/mTBI
Behavioral symptoms	Aggression Agitation Avoidance of cues Hostility Hypervigilance Irritability Self-Destructive Behavior	Aggression Impulsivity Irritability	Aggression Impulsivity/Self Destructive Behaviors Irritability
Physical/cognitive symptoms	Inability to concentrate or focus on tasks Insomnia Nightmares Sensitivity to sound	Coordination problems/loss of balance Amnesia Disorientation Dizziness Fatigue Headache Inability to concentrate or focus on tasks Insomnia Sensitivity to sound	Inability to concentrate or focus on tasks Insomnia Sensitivity to sound
Psychological Symptoms	Anhedonia/loss of interest Anxiety Depression Intrusive thoughts/ Unwanted thoughts Reexperiencing the event/ Flashbacks Shame/Guilt Social Isolation/Loneliness	Anxiety Apathy Depression	Anhedonia/Apathy Anxiety Depression

Table 1.
Symptomologies of PTSD and mTBI.

only 30% had PTSD alone, with most suffering from concurrent psychiatric conditions, of which mTBI was a prominent co-condition [69].

Diagnosis of PTSD usually consists of a combination of self-report measures and structured and/or semi-structured interview procedures. These procedures are often based on soliciting the information required to determine whether DSM-5 criteria [34] (or alternatives such as the ICD-10 [70]) have been met and include components of the trauma, symptoms/symptom clusters, and subtypes of the disorder. Common structured interviews, such as the Clinician-Administered PTSD Scale (CAPS), are considered both reliable and valid, however, they are time intensive [71]. Furthermore, due to upwards of 93% of PTSD cases co-reporting another psychiatric disorder, it can become difficult to differentiate between disorders with overlapping symptoms [6].

Unlike the diagnosis of TBI, where CT and MRI structural images readily demonstrate contusions or bleeds verifying their presence, there is a lack of interdisciplinary consensus as to what constitutes an mTBI. Although some criteria have been generally accepted (such as those described within the introduction of this chapter), there are diagnostic criteria available from the American Congress of Rehabilitation Medicine (ACRM), the US Centers for Disease Control and Prevention (CDC), and the World

Health Organization (WHO) [72]. Therefore, the utility of a consistent and universally accepted measure of mTBI presence would be of great benefit when diagnosing a mTBI in isolation, and especially when attempting to diagnose in the presence of the overlapping symptoms commonly reported in PTSD.

As should be apparent from this cursory examination, the current process of diagnosing both PTSD and mTBI is largely reliant on often erroneous self-report techniques and arduous clinical interviews that have an inherent lack of consensus, necessitating improvements in both speed of diagnosis and consistency to best offer care and interventions to patients with PTSD and mTBI. One such avenue of providing this information may be found through the discovery of diagnostic biomarkers, which will be the primary focus of discussion for the remainder of this chapter. Before such a discussion takes place, it is important to further highlight the need for improved methods of diagnosing comorbid mTBI and PTSD by examining the implications such discoveries may have on treatment of each condition.

Although there are recognized "gold-standard" treatments for PTSD, there is still much room for improvement. For PTSD, Cognitive Behavioral Therapy (CBT) [73] and psychopharmacological treatment with selective serotonin reuptake inhibitors (SSRIs) and/or serotonin noradrenaline reuptake inhibitors (SNRIs) are often used for treatment. Similarly, both psychological and pharmacological treatments are recommended for the treatment of mTBI, such as CBT [74] in conjunction with pharmacological treatment of the sequalae associated with mTBI [75]. However, in a recent study of the evaluations of 41 guidelines related to the treatment of mTBI, only three were founded in what was determined to be an evidenced-based fashion [76], highlighting the need for more rigorous and evidence-based treatment regimens. There is even less evidence-based guidance when it comes to the treatment of comorbid mTBI and PTSD, making research on how to best identify multimorbidity in PTSD patients critical to developing effective treatment strategies.

5. Current biomarker research

As should be evident from the previous sections from this chapter, both the ability to diagnose PTSD comorbid with mTBI and the ability to effectively monitor treatment of the concurrent conditions would benefit from the identification of biomarkers. For this discussion we adapt the definition of a biomarker using a conceptual framework that is useful for clinical research and treatment purposes. This may include any information that can be used as an objective indication of a relevant medical state observed from outside the patient. Importantly, these signs must be able to be measured accurately and have high levels of replicability. This is captured in the WHO's definition of a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" [77] and can be expanded to "... almost any measurement reflecting an interaction between a biological system and a potential hazard...[and] may be functional and physiological, biochemical at the cellular level, or a molecular interaction" [78]. In alignment with these requirements, our discussion will focus on the relevance and validity of the suggested biomarkers, allowing for it to be used as a surrogate endpoint [79]. There are a wide range of biomarkers and targets currently being researched for roles in both mTBI and PTSD. A summary of biomarkers currently undergoing research that meet the criteria previously discussed can be seen in **Table 2**, with in-depth discussion of each following.

HPA axis dysregulation	Cortisol	Adrenal glucocorticoid hormone that modulates the HPA axis	PTSD
Monoamine Dysfunction	Norepinephrine (NE)	Endogenous neurotransmitter and stress hormone	PTSD
	Serotonin (5-HT)	Monoamine neurotransmitter	PTSD
Inflammatory and immune function	Interleukin-1ß (IL-1ß) Interleukin-2 (IL-2) Interleukin-6 (IL-6) Interleukin-8 (IL-8) Interleukin-10 (IL-10)	Cytokine protein involved in inflammation Cytokine protein involved in immune function regulation Cytokine protein with pro- and antiinflammatory actions Cytokine protein involved in inflammation Cytokine protein with anti-inflammatory actions	PTSD PTSD PTSD and mTBI mTBI mTBI
	C-reactive protein (CRP)	Circulating protein released in response to inflammation	PTSD
	Tumor Necrosis Factor alpha subunit (TNF-α)	Cytokine protein with pro-inflammatory actions	PTSD
	Interferon gamma (IFN-γ)	Cytokine protein involved in immune function regulation	PTSD
	Marinobufagenin (MBG)	Endogenous steroid related to myocardial infarction, heart failure, and kidney failure	mTBI
Genetic variation	FKBP Prolyl Isomerase 5 (FKBP5) Serotonin transporter gene linked polymorphic region (5-HTTLPR)	Protein coding gene regulating neuroendocrine stress Gene promotor region on the serotonin transporter gene linked to neuropsychiatric disorders	PTSD PTSD
	Nuclear receptor subfamily 3 group C, member 1 (NR3C-1)	Promotor region of the glucocorticoid receptor gene related to metabolism and immune response	PTSD
	Apolipoprotein E (APOE)	Protein coding gene that regulates fat metabolism	mTBI
	brain-derived neurotrophic factor (BDNF)	Protein coding gene that promotes neuronal survival	PTSD and mTBI
Functional and structural neuroimaging	Amygdala Medial Prefrontal Cortex Rostral Anterior Cingulate Cortex Hippocampus	Involved in emotional processing, and conditioned fear Involved in inhibition and goal-directed behaviors Cortical structure involved in mediating emotion and cognitive function Involved in memory and cognition	PTSD PTSD PTSD PTSD
	Diffusion weighted imaging (DWI)	Noninvasive technique using a specific form of Magnetic Resonance Imaging (MRI) to view water diffusion in images	mTBI
	Magnetic resonance spectroscopy (MRS)	Noninvasive technique to analyze metabolic changes in tissue	mTBI

Neuronal and axonal injury	Tau Protein Ubiquitin C-terminal hydrolase isozyme L1 (UCHL1) Neuron-specific enolase (NSE)	Protein expressed primarily in neurons, involved in stabilizing microtubules Enzyme involved in axonal transport and integrity Enzyme involved in glycolytic metabolism in the brain	mTBI mTBI mTBI
	Neutrophil gelatinaseassociated lipocalin (NGAL)	Polypeptide released in response to systemic inflammation	mTBI
Blood Brain Barrier Disturbances	CSF/serum albumin ratio Astrocyte-specific SNS protein S100B	Measure of cerebrospinal fluid components in the periphery following injury Binding protein produced by astrocytes involved in intracellular functions	mTBI mTBI
	PrPc-cellular prion protein	Glycoprotein typically anchored to plasma membranes, proposed to be involved in neurodegenerative prion disease	mTBI
Cerebral Blood Flow Changes	Vasoreactivity	MRI measurable changes that could impair smooth muscle and affect cognition	mTBI

Table 2.
Summary of current biomarker research.

5.1 PTSD

Most of the promising biomarkers for the presence of PTSD are related to either dysfunction of the HPA axis, monoamine systems, heightened inflammation, genetic and epigenetic changes thought to be a result of methylation brought about through exposure to prolonged stress, or functional and structural neuroimaging. There has also been growing interest and research in the examination of psychophysical biomarkers of PTSD, such as indicators of hyperarousal (heart rate, blood pressure, skin conductance, etc.). However, examination of these forms of hyperactivity through psychological testing is beyond the scope of this chapter.

HPA Axis Dysregulation. Cortisol, a circulating adrenal glucocorticoid hormone that modulates the HPA axis is known to be involved in anxiety responses and sleep regulation [80]. Research has shown that within a PTSD population, lower salivary cortisol levels were found when compared to control participants, especially when measurements were taken in the morning [80]. Typically, there is a diurnal cycle of salivary cortisol with peak concentration observed shortly after waking, and then drops across the waking hours. In addition to a lower morning level of cortisol, PTSD patients have also demonstrated a blunted cortisol response throughout the day [81]. This blunted cortisol reactivity in response to exposure to acute stress may offer more promise as it removes confounds associated with the measurement of baseline cortisol, such as sex differences and time of day effects. Therefore, although not specific to the presence of PTSD, measurements of circulating cortisol levels may form part of a panel of assays designed to detect the presence of PTSD in a clinical population due to its non-invasive status when measured from a saliva sample.

Monoamine Dysfunction. As PTSD includes increased sympathetic nervous system tone, it is not surprising that levels of norepinephrine (NE) are also heightened [82]. In a prospective study of motor vehicle accident survivors, urinary levels of NE were positively correlated with the likelihood of development of PTSD in the month following trauma, but only in males [83]. Changes in the serotonergic (5-HT) system have also been observed in PTSD. Specifically, 5-HT transporter binding within the amygdala is reduced in PTSD and correlated with both anxiety and depression within PTSD patients [84].

Inflammatory and Immune Function. Stemming from the high comorbidity between PTSD and general physical illnesses [85], there has been extensive examination of the potential role of markers of inflammation as a proxy for PTSD and PTSD symptomology. In all instances examined, there is a positive correlation between inflammatory markers and PTSD symptomology. This includes interleukin (IL) -6 [86], IL-2 [87], IL-1β [88]. Additionally, increased C-reactive protein (CRP) levels are shown to be elevated in individuals with PTSD [89–91], but also has been shown to be predictive of post-deployment PTSD when examined in a prospective study [92]. Continuing this trend, PTSD is also positively correlated with higher levels of TNF-α and IFN-γ when compared to healthy controls, likely as a result of the persistent stress experienced [93]. In general, data concerning the relationship between inflammatory responses and PTSD confirm that PTSD is likely associated with chronic inflammation. Although this may lead to inflammation as a viable therapeutic target to alleviate at least some of the symptoms associated with PTSD, they do not serve well as a general biomarker of PTSD presence or prognosis due to its status as a hallmark finding in many other diseased states, including those that are often comorbid with PTSD [85, 94–97].

Genetic Variation. Most genetic and epigenetic findings have clustered around modulators of HPA axis function either before or following trauma. Perhaps the most cited modulator is FKBP5, a protein encoding gene involved in immunoregulation [98]. Polymorphisms on FKBP5, specifically Val66Met, have been associated PTSD [99]. Met-allele carriers are also reported to have greater severity in PTSD symptoms amongst veterans compared to Val/Val genotypes [100]. However, FKBP5 is also associated with depression [101], a condition known to often co-occur with PTSD therefore making its use as a solitary differential marker of PTSD unlikely. The serotonin transporter gene linked polymorphic region (5-HTTLPR short and long) has also been linked to trauma exposure and depression. Individuals with the LL genotype exhibit lower intrusion and avoidance symptoms compared to those with the S-allele, though no differences were found in other PTSD symptoms [102]. Increased methylation levels at 4 promotor sites on BDNF were found in PTSD patients that experienced high combat exposure compared to those without PTSD [103]. Reduced glucocorticoid receptor NR3C1-1F promotor methylation was found in combat veterans that developed PTSD when compared to those that did not [104]. Hypermethylation at NR3C1 gene promoters were associated with lower risk of PTSD in male genocide survivors, but not female [105].

As has become apparent, many (if not all) of these genetic regions have been associated with other psychiatric conditions and may therefore be a better marker of stress-induced psychopathology in general rather than PTSD specifically, and there has yet to be a single genetic or epigenetic factor that reliably predicts the presence or severity of PTSD in isolation of other psychiatric conditions.

Functional and Structural Neuroimaging. One of the most consistent findings regarding neuroimaging of PTSD is the presence of increased amygdala activation when compared to controls when patients have been exposed to fear inducing

stimuli [106]. For example, there have now been a number of studies that demonstrate hyperactivity of the amygdala when PTSD participants have been exposed to trauma-relevant words when compared to amygdala activity of control participants [107–110]. Further studies have shown that this increased activity may be a result of weakened inhibitory control of the amygdala by the medial prefrontal cortex [106, 108, 110]. Furthering these findings, a recent meta-analysis of imaging studies during emotional tasks for individuals with PTSD, anxiety, and phobia revealed that only the PTSD patients demonstrated decreased activity within the rostral anterior cingulate cortex, offering a potential mechanism to distinguish between aberrant functional activity observed in PTSD and not in other anxiety disorders [111].

In addition to functional studies, a number of structural examinations of PTSD have taken place using neuroimaging techniques. Early studies examining structural differences between PTSD and non-PTSD patients demonstrated that smaller hippocampal volume may be associated with an increased risk of developing PTSD [112], though this finding has more recently been questioned with hippocampal volume reductions being acquired with trauma exposure [113]. When examining specific regions of the hippocampus using structural MRI, it appears as though reductions in specific subregions can be associated with PTSD symptoms. Specifically, reductions within the cornu ammonis 3 (CA3) layer of the hippocampus and the dentate gyrus are related to PTSD symptomology [114].

5.2 mTBI

Currently, mTBI is typically diagnosed based solely on clinical presentation, in comparison to TBI which has prominent and objective neuroimaging findings. This has several implications as to the utility of biomarkers of mTBI. Perhaps of primary concern is the fact that any biomarker that would offer clinical benefits must be correlated with clinical symptom presentation. For example, a marker that elevates with impacts to the head without observable changes in clinical presentation in the patient would be of little clinical use. Potential biomarkers for mTBI are most often related to, or spawned, by the axonal injury that occurs following the much smaller forces related to a mTBI. These can be broadly categorized as those that are related to neuronal and axonal injury, blood brain barrier disturbances, neuroinflammation, cerebral blood flow changes, and genetic variation.

Neuronal and Axonal Injury. Disturbances of the cellular environment often occur following the shearing forces that often accompany mTBI [115], and while this usually is not to the extend to the point of axonal disconnection, it can indirectly affect membrane homeostasis which ultimately results in cell damage [53, 116]. There are several potential biomarkers associated with neuronal damage. Tau protein is known to be changed in response to injury [117] including mTBI, at least in animal models [118]. In one of the larger human studies (196 patients), the ratio of phosphorylated-tau to total tau had both a good diagnostic and prognostic marker for acute TBI, including those with a mild severity [119]. Other biomarkers of neuronal and axonal injury that have been explored as potentials include ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL1), [120–122], neuron-specific enolase (NSE) [123–125], and neutrophil gelatinase-associated lipocalin (NGAL) [126]. However, current research into their utility has not demonstrated sufficient levels of specificity and/or replicability to be discussed in detail, but likely warrant further examination.

Blood Brain Barrier Disturbances. Although it has been well demonstrated that blood brain barrier (BBB) disruptions are associated with TBI [127], there is growing

evidence that there are BBB disruptions following mTBI during both the chronic and the acute phase [128]. There are a number of non-invasive indirect measures of BBB dysfunction that rely on the detection of cerebrospinal fluid (CSF) components within peripheral serum, however, there has been little convincing evidence that suggests it will be a suitable biomarker of mTBI if used in isolation. The CSF/serum albumin ratio is the standard biomarker for BBB integrity [129] but is not sensitive enough to detect the presence of BBB disruption as a result of mTBI [130]. Perhaps the most studied is the astrocyte-specific SNS protein S100B. Research has shown that the detection of this marker approaches the same levels of sensitivity as the CSF/serum albumin ratio [127], and has been used to rule out mTBI in emergency medicine already, where S100B levels have a high (99 + %) predictive value [131]. However, there is relative non-specificity of elevated S100B (as there are extracerebral sources of S100B in peripheral blood), and it has also shown to be elevated in clinical cases without head trauma [132]. Further dampening enthusiasm, there is still conflicting evidence as to whether S100B levels are positively correlated with mTBI [133]. A less explored, though perhaps more promising marker is the glycoprotein PrPc—cellular prion protein. Since this plasma-soluble prion protein is located within the plasma membrane, is has been suggested that it may be released following an mTBI as a result of BBB dysfunction [134], with animal models showing increased serum levels following blast exposure induced mTBI [135, 136]. Within humans, a small (N = 6) study amongst athletes demonstrated PrPc levels increased and remained elevated following mTBI [134]. More recently, a slightly larger study conducted within a hospital setting (N = 20) confirmed this effect with elevated PrPc levels following TBI, with 8 of the 20 being classified as mild injuries. However, PrPc did levels did not correlate with severity of trauma [137]. A third study confirmed the ability for PrPc levels to differentiate TBI with cognitive symptoms versus TBI in which no cognitive symptoms were present [138]. Although additional study is required, these specific features of PrPc make it a particularly attractive candidate biomarker for mTBI. Specifically, its relative specificity with regard to cognitive dysfunction, and ability to be detected years following trauma, are likely of great utility.

Neuroinflammation. Following TBI, including mTBI, there is a cascade of events that ultimately results in the presence of inflammation [139–142], offering an opportunity to examine markers of the neuroinflammatory response as a marker of brain injury. Two promising classes of markers of neuroinflammation are the inflammatory interleukin proteins and the cardiotonic steroid marinobufagenin. There have been many studies demonstrating elevated levels of interleukins including IL-6, IL-8 and IL-10 following brain injury [143–148], as well as studies showing these levels are related to clinical outcome in mTBI [149, 150]. In a small (N = 6) study, marinobufagenin (MBG) levels were initially increased following mTBI, along with symptomology [151]. As MBG levels decreased, symptom scores also decreased, suggesting there may be a relationship between symptoms and MBG. A larger study (N = 110) found MBG levels were elevated following mTBI, and were also correlated with reported symptoms [151] adding further evidence for the potential utility of MBG.

A further drawback to most biofluid based biomarkers of mTBI is the timescale at which they can be detected, necessitating their examination within the acute stage of the injury as they return to baseline levels rather quickly (though PrPc is an exception to this). As an alternative, potentially longer-lasting biomarker, advanced neuroimaging techniques such as diffusion weighted imagery (DWI) and magnetic resonance spectroscopy (MRS) for diagnosing the presence of an mTBI at a timescale that extends beyond the acute stage. Genetic information may offer additional

information not available through the other methods discussed, such as the susceptibility to mTBI following head trauma, reflected in the likelihood of developing symptoms based on genetic variation.

Cerebral Blood Flow Changes. Recent research has shown that following mTBI, there are changes in vasoreactivity that impair smooth muscle response [152], ultimately affecting cerebral blood flow that animal models have shown can persist up to a year after initial damage [153]. Due to the extended period of blood flow changes, this may be an ideal candidate for evaluating whether long-term changes in cognition are a result of a previously acquired mTBI [154]. These changes in blood flow can be detected using modern magnetic resonance imaging techniques as hypoperfusion in many of the anatomical regions previously described as particularly susceptible to mTBI injury including the prefrontal, frontal, and temporal regions of the brain [118].

Genetic Variation. The two leading genetic candidates are the genetic mutations in the genes encoding for apolipoprotein E (APOE) and brain-derived neurotrophic factor (BDNF). It is important to note that both of these genes are already being explored as they pertain to the risk of generating various types of neurodegeneration disorders, such as Alzheimer's disease [155]. This finding is not all that unexpected considering the building link between mTBI and subsequent neurodegenerative conditions [156–159]. The APOE ε4 allele has been shown to be a significant risk factor for the development of Alzheimer's disease, but systematic review [160] has shown it is unrelated to mTBI diagnosis. Interestingly, this same allele confers increased risk to some of the cognitive impairment associated with the longer-term symptoms of mTBI [161]. When it comes to studies examining the role of BDNF, a small sample (at least on the scale of genetic studies; N = 110) showed a link between carriers of the minor allele of rs115769 and the memory impairments often associated with mTBI [162], as well as the BDNF Val66Met allele being linked to a higher risk of experiencing an mTBI [163], and increased experience of emotional symptoms following the occurrence of an mTBI [164]. Further, it was been shown that mutations of BDNF rs6265 Val66Met polymorphisms affect neurocognitive performance in patients following mTBI, offering the potential for predicting which patients will go on to develop neurocognitive symptoms following mTBI [165].

6. Summary and conclusions

Biomarkers for PTSD. At this time, there are a number of biomarkers that are associated with PTSD risk, symptoms, and symptom progression. Despite this association, due to the common comorbidity with both other psychiatric conditions and general health status, there is currently little chance of using any single marker as a diagnostic characterization. Future studies must do a more thorough examination of biological and psychological states within PTSD to be able to characterize a combination of biomarkers that may cluster around symptoms and symptom progression in a meaningful way. One way that this may be accomplished is through the use of biomarkers to identify features associated with PTSD, rather than with markers that are consistent with the DSM criteria [166]. For example, it may be that reduced hippocampal volume is associated both with PTSD and comorbid depressive state and can serve as a biomarker of the cluster of symptoms associated with both. This approach would necessitate a panel of biomarkers to increase the specificity, sensitivity, and replicability of any proposed tool. In fact, such an approach utilizing signals from multiple biological domains totaling in excess of one million unique markers was used

to define 343 candidate biomarkers via a combination of data-driven and hypothesis driven approaches. These features were further reduced to 28 based on performance and ability to track phenotype, resulting in a final panel which obtained impressive levels of accuracy, sensitivity, and specificity (81, 85, and 77%, respectively) [167].

Biomarkers for mTBI. Currently, there is insufficient evidence to support a relationship between biomarkers of mTBI and clinical outcomes, though many offer promise of acting in this capacity. For this relationship to be drawn, it is imperative that future research includes clinical outcome measures and that a standardized study design is utilized. From the non-exhaustive work cited here, it is clear that differences in methodology, especially related to the timing of sample collection, the length of follow-up, the clinical measurements performed, and the clinical population studied all could be leading to the sometimes-conflicting results reported and the relatively small, unconvincing effect sizes. Further, it is also apparent that although many of the reported biomarkers are sensitive to the presence of head impact, unless the candidate biomarker scales with symptoms reported, it will be of little clinical utility. In fact, there is often little disagreement as to whether an impact to the head has occurred, but rather, the intent of the biomarker is to assess whether that impact is going to result (or is the cause) of symptoms being reported.

7. Summary of differential features

Differential features of biomarkers specific to PTSD

- HPA Axis Dysregulation (cortisol)
- Monoamine Dysfunction (norepinephrine and serotonin)
- Inflammatory and Immune Function (interleukins 2 and 1ß, C-reactive protein)
- Genetic Variation (polymorphisms and methylation on genes FKBP5, 5-HTTLPR, and NR3C1)
- Functional and Structural Neuroimaging (differential activation in amygdala, prefrontal cortex, hippocampus and rostral anterior cingulate cortex)

Differential features of biomarkers specific to mTBI

- Neuronal and Axonal Injury (Tau protein, ubiquitin carboxyl-terminal hydrolase, neuron-specific enolase, neutrophil gelatinase-associated lipocalin)
- Blood Brain Barrier Disturbances (CSF/serum albumin ratio, S100B, PrPC levels)
- Neuroinflammation (interleukins 8 and 10, marinobufagenin)
- Cerebral Blood Flow Changes (magnetic resonance imaging techniques to detect hypoperfusion)

Biomarkers for PTSD comorbid with mTBI. It should be apparent from the lack of conclusive biomarkers for PTSD and mTBI when occurring in isolation that there

is currently little prospect for a single biomarker that will be able to diagnose PTSD concurrent with mTBI versus detecting the presence of each condition in isolation. Part of this difficulty directly stems from the current method of diagnoses for each of these conditions. As previously discussed, although mTBI is most certainly a neurological event, it is diagnosed in a manner consistent with a psychiatric condition—based on the collection of symptoms reported. With the overlap of symptoms between both mTBI and PTSD, many of the identified biomarker candidates would be expected to be present in both PTSD and mTBI, ultimately hindering a differential diagnosis. In essence, the same conditions that necessitate the identification of a biomarker of these conditions also prevents its discovery. In addition to the necessity for larger and better designed studies, it is clear that examining the potential of any biomarker in isolation is ultimately a futile event. What may be possible in the near future is the union of several different biomarkers that are selected based on their specificity and replicability in differentially identifying PTSD and mTBI. This will require larger scale studies that collect a wide range of neuropsychological and biological samples, as well as neuroimaging, and combine them to truly accomplish these goals. In recent years there has been some progress in this regard [168, 169], at least signifying that within the field there is a recognized need and attempt to combine biomarkers not only from separate conditions, but indeed separate disciplines to discover ways to diagnose PTSD concurrent with mTBI in a more rigorous and efficient manner. This use of a collective intelligence approach, common in other fields such as finance [170], would allow for domain area expertise to identify successful candidates from what is a current, and continually growing, set of candidate biomarkers.

In summary, posttraumatic stress disorder and mTBI are both significant problems that lead to reduced quality of life for a wide range of people. Due to the nature of symptoms, diagnosis and treatment is inefficient and often delayed, resulting in additional complications in patient outcomes. Determining consistent and accurate biomarkers to improve diagnostic measures of both PTSD and mTBI as well as to differentiate between the two would improve outcomes for both disorders. In the near future, the combination of a selection of the individual biomarkers discussed could be used to design a comprehensive screening tool for individuals following a traumatic event. Additionally, identification of biomarkers involved in the transition post-injury to long-term post-concussive symptoms could allow for early intervention and prevent development of PTSD following trauma. Further, the monitoring and classification of individual responses to screening arrays could dictate the best treatment options, and inform recommendations of medication, therapies, neuromodulation techniques and various combinations from those currently available. Ultimately, this could allow patients and physicians to better direct treatment and response measures based on the individual's biological makeup.

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