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Neuroimaging of Traumatic Brain Injury in Military Personnel: An Overview

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Abstract

Background—The incidence of blunt-force traumatic brain injury (TBI) is especially prevalent in the military, where the emergency care admission rate has been reported to be 24.6 to 41.8 per 10,000 soldier-years. Given substantial advancements in modern neuroimaging techniques over the past decade in terms of structural, functional, and connectomic approaches, this mode of exploration can be viewed as best suited for understanding the underlying pathology and for providing proper intervention at effective time-points.

Approach—Here we survey neuroimaging studies of mild-to-severe TBI in military veterans with the intent to aiding the field in the creation of a roadmap for clinicians and researchers whose aim is to understand TBI progression.

Discussion—Recent advancements on the quantification of neurocognitive dysfunction, cellular dysfunction, intracranial pressure, cerebral blood flow, inflammation, post-traumatic neuropathophysiology, on blood serum biomarkers and on their correlation to neuroimaging findings are reviewed to hypothesize how they can be used in conjunction with one another. This may allow clinicians and scientists to comprehensively study TBI in military service members, leading to new treatment strategies for both currently-serving as well as veteran personnel, and to improve the study of TBI more broadly.

Keywords

traumatic brain injury; neuroimaging; biomarkers; military; recovery; metabolism

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Author Contributions

A.B. performed the detailed review of the literature and undertook the writing of the manuscript; J.D.V.H. conceived of the rationale for the article and worked to provide content, to edit, and to refine the manuscript; A.I. provided critical comments, recommendations, and editorial contributions.

Disclosure Statement

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INTRODUCTION

Interest in traumatic brain injury (TBI) has grown considerably both in the public sphere and among bioscientists over the past decade. Across the world, annually, between 64 and 74 million individuals suffer TBIs from all causes, with around 1.4 million cases being recorded in the U.S. alone (1). TBI occurs when a force to the head results in temporary or permanent neurological dysfunction. The demographic affected consists predominantly of males, who are twice as likely as females to experience TBI-eliciting events (2). Aside from primary injuries, TBIs also increase the victims' susceptibility to complications like post-traumatic stress disorder (PTSD), mild cognitive impairment, Alzheimer's disease (AD), Parkinson's disease, chronic traumatic encephalopathy (CTE), and other neurological and psychiatric conditions which can affect mood and fundamental cognitive processes like memory (3, 4).

Cases of head injury are markedly prevalent in the certain branches of military service, where the emergency care admission rate for TBI is 24.6%−41.8% per 10,000 soldier-years, with the hospitalization rate showing an upward trend during deployment (5). According to U.S. Department of Defense (DoD) estimates, by 2010, there had been 379,519 cases of TBI with varying degrees of severity (6). Among modern military service members, chronic exposure to repetitive firing of advanced weapon systems near the head is a frequent cause of sub-concussive forces. More acute sources of injury, such as from explosive devices, have lesser incidence but vary more widely on the scale of TBI severity – from mild to severe to fatal. Out of 7–15% of all reported cases, symptoms of concussion can persist for a year after injury, and such victims are frequently diagnosed with post-concussion syndrome (PCS) (7–9), whose effects can be neurological, affective as well as cognitive (10). Amongst the subclasses of TBI, mild traumatic brain injury (mTBI) is often the most difficult to diagnose, partly due to the potential lack of clinically-measurable outward signs of injury. This has made mTBI pathogenesis a proverbial "black box" where disease progression remains poorly-understood. This, in turn, has resulted in ineffective and/or primarily-palliative approaches to addressing the major neurological and cognitive deficits confronting military veterans, particularly as they age. With the advancement of modern neuroimaging techniques – including structural, functional, and connectomic modalities – assessment using brain imaging can frequently be well suited for discerning TBI pathology and for providing insights which can inform the prescription of effective interventions at the most appropriate time points post-injury.

This survey aims to highlight how the application of neuroimaging examination, when coupled with long-term strategies for pharmaceutical interventions, can be leveraged by clinicians and researchers to better understand the progression and treatment of TBI in both active as well as aging, former military personnel. While a compendium surveying the entirety of current TBI research is beyond the scope of this overview, we seek here to feature recent trends in the field and to propose how the insight which they provide could be used in conjunction with available methods for biomarker characterization. Along with battlefield and clinical assessment strategies, recommendations for the additional integration of neuroimaging and pharmacological interventions are provided.

On the broad spectrum of TBIs, concussions are an increasing medically-critical manifestation of this condition. While they do exhibit not explicit neurological symptoms, these events may still bring about notable psychiatric and neuropsychological deficits. This has been the observed especially in instances of military personnel, where 82.4% of reported TBI cases are reported as concussions. The use of improvised explosive devices during the Iraq and Afghanistan Wars resulted in more concussions as compared to earlier military conflicts like the Vietnam War (11). Moreover, soldiers are as likely to suffer concussions in the line of duty as during training or in the course of military exercises, which is further indicative of military personnel's high susceptibility to this condition. The legendary "toughen up and move forward" sociology in some military circles discourages the reporting these injuries. The repercussions of this can be extremely high because repeat concussions can manifest themselves through serious cognitive or neurological symptoms (11, 12). The potentially-impactful nature of mTBI, both on and off the battlefield, makes its timely identification imperative. When safe to do so, neuroimaging may play an important role in the assessment of brain injury in potentially affected military personnel.

Neuroimaging identification of neural dysfunction

Beyond computed tomography (CT), magnetic resonance imaging (MRI) has proven to be particularly effective in identifying mTBI-compromised brain regions. Additionally, diffusion imaging of white matter (WM) fiber pathways in blast-exposed military veterans who do not show outwardly-visible symptoms of injury sequelae has proven to be an insightful diagnostic tool (13). Aside from structural connectivity changes, studies also point towards functional brain network alterations brought about by concussive injuries. Using resting state functional magnetic resonance imaging (fMRI), findings by Nathan and colleagues (14) highlight alterations in the default mode network (DMN) of military personnel victims, where WM connectivity innervating the anterior cingulate cortex (ACC) is found to be higher in mTBI patients. Since functions like executive control and auditory processing have been associated with ACC, changes in its connectivity could be correlated to cognitive alterations experienced by patients (15, 16). Conversely, posterior cingulate cortex (PCC)—along with other posterior brain structures like the cuneus and the calcarine fissure—tends to exhibit reduced functional connectivity within the DMN (17). This bilateral relationship is also observed in other conditions like epilepsy, with decreased connectivity in medial prefrontal cortex (PFC) and temporal lobe and increased connectivity in patients' PCC (18). This highlights the dynamic nature of the DMN and suggests how changes in one region may elicit compensatory responses in other regions to achieve homeostasis of neural information exchange (19). Together with ACC, the PFC plays a critical role in cognitive control (20). Witt and colleagues (21), using an auditory oddball task, have demonstrated that the right dorsolateral PFC (DLPFC) of mTBI patients exhibits decreased blood oxygenation level dependent (BOLD) effects in the resting state. Similar results have been observed by Lipton *et al.* (22), who found that reduced fractional anisotropy (FA) of WM streamlines innervating this structure significantly correlates with unfavorable executive function performance in mTBI patients.

The PFC also serves as part of the pain modulation system and, in a sample of military veterans, aberrations in PFC connectivity have been associated with the dysfunction of the

endogenous pain modulating system. This was observed in an fMRI study by Strigo and colleagues (23), where participants with a reported history of mTBI showed higher activation in the periaqueductal grey (PAG) matter, right DLPFC and cuneus during pain anticipation. While higher activation of the DLPFC might seem at odds with decreased activity observed under relatively-high cognitive control, Gosselin and colleagues (24) demonstrated that DLPFC shows variable activation levels in working memory vs. pain anticipation tasks. This suggests that connectivity changes in of different regions due to pain rather than to cognitive responses cannot be generalized. Nevertheless, in TBI victims, the likelihood of partial overlap between these functional networks cannot be discounted.

Cognitive disturbances resulting from TBI

Concurrently with cognitive symptoms, chronic TBI presents other mental health comorbidities in military veterans, including affective dysregulation. Damage to PAG matter —which consists of neurons located around the central aqueduct within the tegmentum of the midbrain—is believed to be one of the central contributors to social withdrawal, depressive episodes, inactivity, anxiety and even panic attacks (25). This can be traced to PAG matter receiving projections from the central nucleus of the amydala and to dorsal PAG matter relaying stimuli information to the basolateral amygdalar complex, which directs both innate and learned fear responses (26, 27). A factor contributing to emotional dysregulation may involve reduced FA in the midbrain regions of TBI patients relative to uninjured volunteers, as shown by Newcombe and colleagues (28), and suggesting potential changes in PAG matter volume and/or connectivity.

A commonly-experienced symptom of mTBI involves the disturbance of sleeping patterns. Cross-sectional studies of military personnel—predominantly men—within the first few months after returning from combat report that an overwhelmingly-high number of such individuals are diagnosed with sleep disorders (29). It has also been proposed that the incidence of insomnia increases significantly with the increment in the number of TBIs experienced (30). Although these inferences are based on self-reported information obtained during clinical interviews, the study of sleep neurophysiology using radioisotope tracers has hinted that mTBI-exposed individuals can exhibit reduced cerebral glucose metabolism relative to the general population. In one such study, Stocker and colleagues (31) used [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) to compare wakefulness, rapid eye movement (REM) sleep and non-REM sleep between blast-exposed and otherwise-healthy military veterans. Their findings show significant decreases in the relative cerebral metabolic rate of glucose (CMRglu) during wakefulness and during REM sleep in blast-exposed veterans vs. control participants. Other factors affecting the sleep-wake cycle include low levels of hypocretin-1 (orexin A) in cerebral spinal fluid (CSF) samples collected from acute TBI patients (32). Hypocretin-1 is a wakefulness-promoting neuropeptide produced by hypocretin neurons in the posterolateral nucleus of the hypothalamus (PH). The downregulation of hypocretin-1 in many TBI cases is not permanent and the level of this neuropeptide typically recovers within 6 months after injury. In some patients, however, such recovery may be suboptimal and can additionally result in post-traumatic sleepiness—also known as hypersomnia—defined as sleeping significantly more than prior to TBI (33). In conjunction with PH neurons, cholinergic and glutamatergic

neurons in the basal forebrain (BF) are also responsible for regulating the waking cycle, as well as other neurocognitive functions like attention, learning and memory (34, 35). This role of the BF in wakefulness has also been demonstrated in rats, thereby highlighting the influence of the BF on the ACC (36). Neuroimaging studies of TBI patients have indicated that injury to the BF, hippocampus, and to neocortical regions result in globally reduced grey matter (GM), which may cause fatigue and hypersomnia through damage to the reticular activation system (37, 38). As such symptoms persist, their cumulative effects can give rise to complex neuropsychological abnormalities.

Cellular dysfunction

Neurological and cognitive impairments may be elicited by diffuse axonal injury (DAI), which has been a key topic of discussion in the clinical and scientific communities due to insufficient understanding of its effects (39). DAI is induced by the sheer physical force exerted upon neurons during TBI, resulting in the increased permeability of their axolemmas (40). This change in permeability can be demonstrated using horseradish peroxidase as a tracer of axonal processes (41). Increased axolemma permeability triggers abnormal influx of Ca^{2+} ions which activate cysteine pathways that degrade the intra-axonal cytoskeletal framework (42). Contrary to this, however, Wolf and colleagues (43) did not find evidence for increased permeability—but rather dysregulation—in Ca^{2+} membrane transport pathways, where Na^{+} channel activation results in axonal depolarization and in the subsequent opening of Na^{+}/Ca^{2+} channels. While these studies offer complementary—although potentially contradictory—perspectives on the increase of Ca^{2+} uptake, they both appear to suggest a strong correlation between increased Ca^{2+} influx and the imminence of neuronal breakdown. Ca^{2+} influx can modify sub-axolemmal signaling networks via early induction of calpain-mediated spectrin proteolysis or may result in mitochondrion permeabilization through the activation of mitochondrial membrane permeability transition (MPT) pores. This causes increased water intake, reactive oxygen species (ROSs) production and the trans-membrane migration of molecules which contribute to mitochondrial swelling (44, 45). Simultaneously, Ca^{2+} can activate calcinerin, resulting in the alteration of neurofilament phosphorylation followed by neurofilament compaction (NFC). NFC, in particular, has long been associated with TBI and can serve as a precursor to the breakdown of axonal transport, to subsequent cytoskeletal collapse and to the release of amyloid precursor proteins (APPs) in the parenchyma (46).

The potentially wide-ranging effects of DAI make its early detection imperative. Huang and colleagues (47) found that with the joint use of magnetoencephalography (MEG) and diffusion tensor imaging (DTI) can be very useful for studying the functional correlates of DAI (48). Acutely, shear-related injuries in specific brain regions can be followed by increased blood flow due to rising metabolic demands and may also represents intact vaso-reactivity (49). Whereas increased cerebral blood flow (CBF) might represent a neuroprotective measure, persistent CBF increases can result in intracranial hypertension (IH). This can lead to intracranial haematomas, which occur in 5–10% of patients with moderate TBI and in 25–35% patients with severe TBI.

Intracranial pressure and cerebral blood flow

Unregulated intracranial pressure (ICP) can contribute to brain tissue displacement due to pressure gradients across the brain, leading to intraventricular hemorrhage (bleeding into the ventricular system), may lead to acute obstructive hydrocephalus, and subsequent cell death. Decompressive craniotomies, barbiturates and extreme hyperventilation are commonly-utilized procedures to remediate elevated ICP, although these interventions have poor efficacy (50, 51). Where these strategies have been used, studies have found that indomethacin, a non-steroidal anti-inflammatory agent, may reduce CBF substantially (52). Indomethacin's other benefits include the prevention of edema formation and the inhibition of CSF formation, although not without side effects (53, 54). The latter impact 10–50% of patients, are dose-dependent and include dizziness, vertigo, fatigue and impaired renal function, although such symptoms are transient and predominantly affect patients with impaired renal function (55). Hypertonic saline (HTS) is also used for reducing ICP and, in both humans and animal models, has been shown to reduce elevated ICP and cerebral edema, thereby improving cerebral hemodynamics (56, 57). HTS administration *in vitro* has been associated with attenuated astrogliosis post-injury, such that astrocytes may even exert neuroprotective effects to achieve substantial reduction in tissue loss (58). Administering this agent between 30 and 60 minutes post-injury appears to elicit optimal neuroprotective effects (59, 60).

Despite increased *global* CBF, brain *regions* affected by primary TBI frequently experience reduced blood flow leading to cellular organelle damage, including mitochondrial damage (61). These modifications to the cellular machinery can alter the metabolic state of the neuron from aerobic to anaerobic, resulting in an uptick of reactive oxygen species (ROS) production (62). ROSs—or free radicals—oxidize the cellular membrane through different pathways, including the lipoxygenase pathway, to create inflammatory precursors while also contributing to a reduction in the pH of the brain known as acidosis (63). Changes in pH levels and subsequent acidosis can be measured via cerebral microdialysis, in which a probe is inserted into the brain at injury locations (64). However, emerging contrast-enhanced methods such as CEST MRI, initially applied in mapping pH-related change in cancer patients (65), are providing means for non-invasive imaging of pH in TBI patients (65, 66).

Early-stage clinical interventions like normobaric and hyperbaric hyperoxia can counter sudden loss in regional CBF while meeting increased global CBF demands. This impact is brought about by increases in adenosine triphosphate (ATP) synthesis and in the cerebral metabolic rate of oxygen, or $CMRO_2$ (67). Increasing cerebral oxygen levels can, in turn, result in a global increase in aerobic metabolism and in a deceleration of ROS production, although there is a fixed window for this intervention to have a neuroprotective effect. In a cerebral microdialysis study by Magnoni and colleagues (68), the induction of hyperoxia post-injury resulted in a 40% reduction of lactate (Lac) levels in the cerebral extracellular fluid (CEF). Increases in Lac levels are generally accompanied by increases in the lactate/pyruvate ratio (LPR) in the CEF, as frequently observed under conditions of hypoxia or mitochondrial dysfunction (69, 70). This increase in Lac is also thought to be one of the early markers of brain injury (71) and can be measured using magnetic resonance

spectroscopy (MRS) (72). This allows Lac levels to be utilized as a metrics to gauge the efficacy of early-stage interventions post-injury.

Inflammation

Following brain injury, inflammation is one of the first physiological responses to limit the impact of neural damage. The immune system deploys leukocytes which attempt to contribute to the restoration of homeostasis by killing damaged cells, facilitating CBF increases and reducing infection severity (73). These leukocytes exert their impact via a class of molecules known as leukotrienes. Leukotrienes upregulation after TBI is brought about by the binding of arachidonic acid to 5-lipoxygenase binding protein and then by the interaction of this complex with 5-lypoxygenase to produce leukotriene A4 (LTA4) (74). LTA4 further interacts with various synthases and hydrolases to produce other leukotrienes which contribute to cerebral edema (75). An MRI modality called fluid-attenuated inversion recovery (FLAIR) allows imaging of such edema, which appears hyper-intense in FLAIR images (76). Brain injury also causes cells to release danger-associated molecular patterns (DAMPs) such as ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and heat shock proteins (HSPs) to sustain non-infectious inflammatory responses (77). Some DAMPs bind to toll-like receptors, activating pathways for nuclear-factor κB (NFκB) and mitogen-activated protein kinase (MAPK) to release Interleukin-1ß (IL-1ß), Interleukin-6 and other chemokines (78). The levels of these cytokines are higher in the early stages of injury—early as within a few minutes post-trauma—and typically subside over time (79). This phenomenon, termed a *cytokine storm*, is specifically observed in CSF and cannot typically be traced to blood samples. A cytokine storm in the brain's blood stream has both beneficial and detrimental effects, bringing about positive changes like astrogliosis stimulation and neurovascularization, but also negative ones like axonal dysfunction (80). This dichotomous response to injury is also exhibited by other immune cells and neurotransmitters, as in the case of microglia.

In the healthy brain, microglia serve as highly-active cells scanning the central nervous system (CNS) for various signals which are indicative of homeostasis disruption (81). From the early stages of brain development, these cells play a critical role in regulating cell death, contributing to neuronal plasticity and refining neuronal circuitry (82). Such behavior assists in clearing out accumulated metabolites and cellular debris while maintaining normal phenotypic function (83). During embryonic stages, cerebral microglial formation precedes blood brain barrier (BBB) endothelial cell formation. Certain studies suggests that these macrophages may also play a role in imparting tight junction properties to the cerebral vasculature (84). This is critical, as any compromise in the BBB can result in the influx of harmful metabolites, especially after TBI. This phenomenon was shown in a study by Sumi and colleagues (85) where microglial activation in microvascular endothelial tissue of the rat brain — when mediated by lipo-polysaccharides—leads to BBB dysfunction by activating NADPH oxidase — the reduced form of nicotinamide adenine dinucleotide phosphate (NADP)—which results in the production of ROSs or superoxides (O_2^-) to increase BBB permeability (86). This allows the discharge of plasma proteins, like fibrinogen, into the brain. Fibrinogen deposition promotes further neuroinflammation via the activation of the tumor growth factor-ß (TGF-ß) pathway (87, 88). Cumulatively, fibrinogen deposition in the

brain's vascular space and the permeabilization of the BBB makes the brain more susceptible to neurological diseases like AD.

Another manner in which microglia have been shown to respond to injury is via macrophage polarization, where the phenotype and functions of the latter are altered via two groups of mechanisms referred to M1-like and M2-like polarization, respectively (89). Activation of M1-like (classical) microglia generally has a protective effect upon the injured brain, and their response to injury is downregulated once damage has been contained. In some cases, however, M1-like microglia may become unregulated, which brings about neurotoxicity and neurodegeneration via the uncontrolled release of pro-inflammatory factors such as IL-1ß, IL-12 and ROSs (90). In military veterans, a higher concentration of these inflammatory markers is observed in patients with PTSD compared to PTSD-free subjects, and there is a correlation between neuroinflammation, on the one hand, and chronic behavioral and affective symptoms, on the other hand (91). Maladaptive microglial activations may last for years after injury and their impact can be compounded through thinning of the corpus callosum (90, 92, 93).

M1-like macrophages upregulate chondroitin sulphate proteoglycans, which act as axonal regrowth inhibitors (94). Whereas most research on M1-like, M2-like microglia and macrophages involves focal cortical injury models, the activity of macrophages observed in diffuse injuries exhibits characteristics which are like those of M1-like macrophages. These similarities involve the elevation of IL-1ß and TNF-alpha levels as early as 4 hours post-injury and a return to baseline within 72 hours (95). By contrast, microglial activation in the presence of IL-4 also elicits neurogenesis in adult stem cells by recruiting M2-like microglia (96). Similar neuronal proliferation is mediated by downstream effects of activated mitogen-activated protein kinases (MAPKs) and of other neurotrophic factors via microglia-released activators (97).

Post-traumatic neuropathophysiology

Military personnel's protective equipment may protect them from flesh wounds but does not eliminate the likelihood of TBI and soldiers' subsequent susceptibility to post-traumatic epilepsy (PTE). Injury severity modulates the extent of disruptions in neurotransmitter and neurometabolite pathways, leading to PTE which is partially due to the disruption of γ-aminobutyric acid (GABA) signaling pathways (98). GABA serves as the main inhibitory neurotransmitter of the CNS and via the activation of $GABA_A$ receptors. Aberrations in GABAergic signaling can result in epileptogenesis, which may chronically transforms into PTE (99). A head injury study in Vietnam War veterans showed that 53% of enrolled veterans who had suffered penetrating head injuries had had at least one seizure, and that, in 50% of veterans, seizures occurred in the first year post-injury (100). PTE seizures differ from those observed in non-traumatic epilepsy because they vary in symptoms and mortality (101). PTE can be classified into immediate, early, and late, based on the time lag between the primary injury and the incidence of the first seizure. In each of the three categories, seizures may constitute a single episode within (A) the first 24 hours, (B) the first week or (C) the period after the first week post-injury, respectively (102). The likelihood that patients fall into any of these categories is dependent on the severity of the injury. The relative risk of

epilepsy increases by factors of 2.22 and 7.40 after mild vs. severe injury, respectively (103). Furthermore, the risk of seizures is found to be highest immediately after TBI and may remain high for more than ten years after injury.

To treat PTE, clinicians employ a range of pharmacological interventions. Seizure medications like magnesium, valproate, carbamazepine and phenytoin (PHT) are most commonly administered. Amongst these, phenytoin (PHT) is among the most commonly-used prophylactic agents and is typically administrated within the first seven days after injury (104). When compared to placebo, PHT has been shown to reduce early PTE seizure incidence from 14.2% to 3.6% - although this result should not be interpreted as implying that PHT can reduced PTE risk (105, 106). The risk in question is modulated by changes in brain neurochemistry over several weeks, by effective dosage and interaction between drugs administered acutely. Despite its effectiveness in reducing early-stage post-traumatic seizures, PHT elicits multiple side effects, which arise from its pharmacokinetic interactions with other drugs during the first few days after injury. Studies have shown that, in some forms of brain injury, PHT administration may have a negative impact upon cognitive recovery. One such study by Bhullar and colleagues (107) found that PHT prophylaxis results in lower functional outcome as measured using the Glasgow outcome scale (GOS) and the modified Rankin scale. Vespa and colleagues (108) showed that the incidence of seizures is closely linked to ICP increase, and proposed ICP as a metric for monitoring the effects of therapeutic interventions.

Modern neuroimaging allows the study of PTE both at the macro- and at the micro-scale. Epileptic seizures can be measured using electroencephalography (EEG), MEG, fMRI, as well as simultaneous EEG/fMRI (109). Aberrant electrical rhythms due to interictal brain activity can be localized using EEG and MEG to identify epileptogenic foci (110). At the molecular scale, GABA signaling cannot be directly measured due to its intercoupling with glutamate (Glu) pathways, but its downstream products can be measured to identify disruptions in its metabolism. This can be accomplished using a spectroscopy method termed MEGA-PRESS (111), which combines MEGA (a frequency-selective editing technique) and PRESS (point-resolved spectroscopy sequence). $GABA_A$ can also be imaged using PET tracers like [^{11}C]-Flumazenil or [^{11}C]-Ro 15–4513, which is a partial inverse agonist of the benzodiazepine receptor (111, 112). Furthermore, MRS can also be utilized to measure relative changes in GABA levels compared to N-acetyl aspartate (NAA) or to other neurometabolites (113).

Glutamate (Glu) is an important excitatory neurotransmitter which suffers from disruption of brain biochemistry following TBI (114). Glu activates different classes of receptors such as AMPA, NMDA and metabotropic Glu receptors, leading to alterations in cognitive function, including learning and memory. Following TBI, there may be abnormal O_2/ATP metabolism causing Glu imbalance and the malfunction of Glu reuptake transporters. Neuroimaging methods like ^{1}H MRS, along with cerebral microdialysis, can be used to measure dwindling Glu levels, although microdialysis offers relatively-poor specificity compared to MRS (115). Other neurotransmitters like acetylcholine (Ach) and nitric oxide (NO) serve as signal-relaying and vasodilating neurotransmitters under normal physiological circumstances, while also playing a role in sleep regulation to bring about REM sleep and REM-related

changes in regional blood flow (116). The vasodilatory effect of NO and, by association, changes in its levels can be measured using fMRI, whereas Ach levels can be imaged using 123I-3-[2(S)-2-azetidinylmethoxy]pyridine (^{123}I-5-IA) single-photon emission computed tomography (SPECT) (117, 118).

Neurotransmitter signaling pathways may be markedly damaged in military veterans who have suffered TBI. For this reason, clinicians routinely prescribe benzodiazepines (BDZs), prazosin and/or cognitive behavioral therapy (CBT) in such patients to partially relieve symptoms of PTSD-related sleep disruption. BDZs act by non-selective activation of BDZ-subtype receptors in the GABA receptor complex. These drugs are very useful for reducing sleep latency but tend to have side-effects like dizziness, nausea, headache, as well as visual memory impairment (119). In some patients, side effects are reversible post-treatment secession, whereas in others they may not (120). These side effects and other cognitive deficits can often be successfully alleviated via administration of pregabalin, which has been suggested as a viable option in the treatment of patients who have been administered BDZs for more than a decade (121).

Prazosin, on the other hand, is a pharmacological agent which acts as an α−1 receptor antagonist. This drug has been found to be effective in military veterans with mTBI, where its administration can relieve trauma, reduce nightmare frequency and improve sleep quality (122). The effects of prazosin extend to other disorders beyond insomnia, and may assist with alleviating daytime PTSD symptoms even at high daily doses like 45 mg, although potentially with side effects (123, 124). Thus, current TBI treatment may involve a wide array of narcotic analgesics, antidepressants, anti-convulsants and other psychotropic medications but not without side effects(125). For this reason, tailoring pharmacological treatments to different patients may be difficult without underlying neuroimaging evidence, as well as the availability of key biomarkers which can accompany the alleviation of side effects.

Blood biomarkers

TBI disrupts the pharmacological homeostasis of the brain, resulting in dysregulation of biochemical compounds which can be detected in CSF and blood serum. Tracking these biomolecules could, thus, complement other prognostic tools to better gauge injury extent, but also to offer clinicians more options for identifying biochemical pathways whose disruption can have substantially-deleterious downstream effects. Common blood biomarkers which have been proposed to detect and gauge mTBI severity include serum ubiquitin C-terminal hydrolase L1 (UCH-L1), glial fibrillary acidic protein (GFAP) and monocyte protein-1 (MCP-1) (126–128). UCH-L1 is a relatively promising biomarker since it is a protein whose presence and activity are specific to the brain, where it comprises as much as 1%−5% of soluble brain proteins (129). UCH-L1 shows high serum concentrations in TBI patients compared to normal control subjects, indicating its value as a potential biomarker of brain damage (128). A dangerous increase in UCH-L1 levels has also been implicated as a risk factor for serious brain damage, including intracerebral hemorrhage (130). The normal function of UCH-L1 is currently enigmatic, with researchers linking it to proteasomal, lysosomal or to pro-ubiquitination functions in the cell (131). No definitive

link to a specific mechanistic pathway has been established, and often times UCH-L1 deficient mice do not exhibit a detectable lack of neural function (132). Despite the uncertainty surrounding its mechanistic pathway, the role of UCH-L1 in maintaining axonal health and stability has been well documented (133). For example, UCH-L1-deficient mice show marked impairment of synaptic transmission at the neuromuscular junction (134). Due to its critical role in neuronal integrity, abnormal concentrations of UCH-L1 in blood serum could suggest several pathways through which TBI impacts the brain (135).

One such pathway involves the correlation of UCH-L1 with abnormal blood brain barrier (BBB) integrity as observed in patients with TBI or with non-traumatic headaches (136). BBB function after TBI can be assessed using the CSF-serum albumin quotient (Q_A), where higher Q_A indicates decreased BBB integrity (137). Studies indicate that Q_A and UCH-L1 are significantly elevated in TBI compared to headache patients, especially at the 12-hour mark after injury; Q_A and UCH-L1 levels are also strongly correlated. Furthermore, elevated serum levels of S100 calcium-binding protein B (S100B) are related to levels of Q_A, suggesting BBB damage (138).

An important serum biomarker thought to be an indicator of TBI is GFAP (139). GFAP is a key component of glial filaments in differentiated astrocytes of the CNS (140). It is responsible for the stable formation of astrocytic processes in response to neurons and hence imparts astrocytes their structural phenotype (141). Given its role in astrocytic structural organization, changes in the serum levels of GFAP could be an indicator of astrocytic damage extent brought about by TBI. In samples collected from trauma patients over a period of three days after injury, serum GFAP levels showed trends like those of UCH-L1 (142). Levels of serum GFAP, S100B, and neuron-specific enolase are elevated in TBI compared to non-TBI patients; the serum GFAP level one day after injury appears to have highest sensitivity and specificity for TBI (143).

Although biomarkers can assist in discriminating non-traumatic head injury from TBI by themselves, these compounds are typically more robust when used together, and one blood test measuring the serum levels of GFAP and UCH-L1 has in fact been approved by the Food and Drug Administration (FDA) (144). Due to the diffusion of injury-relevant proteins in the blood within the first few hours post-injury, these tests can be administered in circumstances where CT/MRI are not readily available and/or to reduce the number of diagnostic steps required to quickly ascertain the extent of brain damage. Such diagnostic measures can thus be useful in military field hospital situations, especially when there is no sterile environment or appropriate tools to extract CSF.

Proteins like tau are particularly useful for diagnostic purposes because not only can their levels be measured, but their spatial distribution can also be imaged (145–147). In healthy individuals, tau proteins form a part of the microtubular architecture. In eukaryotic cells, microtubules carry out the process of transporting membrane organelles bi-directionally, thereby promoting fast axonal transport. Along with this, microtubules also contribute to the maintenance of cellular infrastructure. Microtubules are abundant in neurons, where inter-axonal, intra-axonal and dendritic microtubules link to provide cytoskeletal shape and stability. The tau protein is one of several microtubule-associated proteins (MAPs) which

serve this function (148). Microtubules degrade in degenerative diseases like Alzheimer's Disease (149).

In TBI, WM fibers are frequent sheared or otherwise damaged, which slowly results in a breakdown of neuronal structure, accompanied by the cleavage of tau proteins from microtubules and by their transportation into CSF. In samples extracted from head trauma patients' CSF about 3–8 hours after post-injury resuscitation, cleaved-tau (C-tau) levels are found to be elevated by a factor in excess of 1000 compared to control subjects (150). Furthermore, hypo-phosphorylated tau protein (P-tau), total tau levels and the P-tau-total-tau ratios in plasma samples of acute and chronic TBI patients are typically higher than in healthy control subjects (151). There is also evidence of elevated peripheral blood tau levels in military personnel with a deployment history, where tau levels have been significantly associated with their TBI-related outcome prognosis (152). In addition to being a promising indicator of TBI, tau protein levels also provide insight into how long a patient might take to recover for active duty. Results from studies of acute blast exposure suggest transient changes in cell membrane integrity in multiple organs leading to abnormal migration of proteins from the tissues to the plasma and vice versa, possibly contributing to the pathophysiology of TBI and polytrauma after blast exposure (153). Moreover, elevated exosomal tau and p-tau correlate with post-traumatic and post-concussive symptoms, with exosomal tau also relating specifically to cognitive, affective, and somatic post-concussive symptoms (154). It might be surmised that these metrics could be used in conjunction with conventional neuroimaging methods, where specific radioisotopes used as tracers allow one to visualize the extent of tau accumulation. For example, [^{18}F]AV-1451, [^{18}F]THK5351 and [^{11}C]Pittsburgh compound-B are commonly-used PET ligands in clinical settings, with [^{18}F]AV-1451-PET being particularly useful for visualizing tau accumulation in CTE patients (155, 156).

CONCLUSION

TBI is a severe condition having causes ranging from repetitive sub-concussive and/or object-related impact to the brain to blast-induced forces - these events are not uncommon for active duty military personnel during combat and/or tour duties. In particular, the current body of research suggests that military veterans notably experience emotional dysregulation, abnormal pain perception and insomnia, along with a variety of cognitive symptoms subsequent to TBI. A culmination of these symptoms can accelerate psychiatric diagnosis and, for instance, may result in a high likelihood of suicide attempts (157). Suffering individuals often develop substance dependencies, including alcohol consumption, and studies have shown an association between TBI-induced loss of consciousness and a four-fold increase in negative, drinking-related daily-life outcomes (158). The consequences of TBI can be debilitating over the sufferer's lifetime. While the U.S. Department of Veterans Affairs does not currently recommend using neuroimaging, blood biomarkers, or EEG for the assessment and/or diagnosis of mTBI, a growing and quantifiable body of research results provides mixed evidence in favor of using such assessments for TBI assessment and characterization. Based on current knowledge, it appears that a combination of multimodal neuroimaging techniques and serum biomarkers could offer a more systematic picture of the existence and progression of TBI in military service members. Task-based fMRI

methodologies and analyses may be important for the long-term monitoring of TBI, its prognosis, as well as efficacy of prescribed drugs. Additionally, the accessibility of various radioactive tracers for use with PET imaging may further enable precise tracking of specific biomarkers which can be measured and manipulated to improve functional outcomes.

Injury prognosis might also benefit from neuroimaging measurement of the glymphatic system and exploring how it is affected during these neuronal homeostatic disruptions (159). Responsible for clearing the harmful metabolites, this system could play an important role in maintaining neuronal health during acute stages of the injury and could also serve as a potential drug target to minimize further damage (160). Radiolabeled tracers using PET could provide opportunities to understand these systems via labeling receptors like Aquaporin-4 (161) that show selective permeability to water across the perivascular space (162).

Because pharmacological treatments and other therapies have been suggested for palliative care (163, 164), more research should be dedicated to (A) identifying neurological changes which take place in the human brain post-injury and (B) determining how palliative solutions affect the brain's neurochemistry, if at all. Because symptom amelioration alone is likely to be insufficient for the full treatment of TBI in military service members, prescribed medications should be carefully researched against neuroimaging evidence on their effects on brain structure, function, and connectomics to inform the recovery process.

Finally, closer collaborative efforts between military-affiliated and academic research institutions should be undertaken using neuroimaging methods to understand how brain injuries progress, the role of blood biomarkers, and how best to attend to the needs of active and former military service members (165, 166). Doing so will necessitate greater sharing of data, consideration of how study participation might affect service member VA benefits, accounting for variables unique to each military experience such as duration of a tour, length of active combat scenarios, etc. However, greater cooperation between military service agency and university researchers is the likely best path forward in the identification of blood and neuroimaging biomarkers having the greatest predictive power concerning clinical outcome and recovery from TBI in active and former military service members.

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Highlights

- TBI affects military service members at 24.6–41.8% per 10,000 soldier-years
- MRI, CT, PET, etc are suited for quantifying battlefield and training-related TBI
- TBI neuroimaging studies, while promising, tend to be under-represented
- Neuroimaging approaches have potential for pharmacological treatment validation
- Neuroimaging with other biomarkers may offer new strategies for military TBI

Table 1:

Pharmacological agents used to treat TBI, their provider, and their potential side-effects

Stages of brain injury in military personnel and pharmacological interventions thought to be effective against TBI-related comorbidities. Outlined are the benefits of current interventions, their side effects and how TBI polypharmacy, particularly at high dosages, may prevent the recovery of cognitive capacities.

Condition	Drug	Manufacturer	Side effects
elevated ICP	indomethacin	Merck & Co.	dizziness, fatigue, vertigo, negative renal function (Harrigan, Tuteja et al. 1997)
insomnia	benzodiazepine	Roche	dizziness, nausea, headache, non-verbal visual memory impairment (Barker, Greenwood et al. 2004)
	prazosin	Pfizer	dizziness, weakness, nausea (Koola, Varghese et al. 2014)
hypersomnia	modafinil	Teva Pharmaceutical	headache, nausea (167)
PTE	phenytoin	Pfizer	poor cognitive recovery (Bhullar, Johnson et al. 2014)
emotional dysregulation	fluoxetine	Eli Lily	delusions, aggression and suicidal ideation (168)
	methylphenidate	Novartis	insomnia, decreased appetite, headache (169)

Table 2:
Blood biomarkers and neuroimaging modalities

Blood biomarkers which can be imaged ***in vivo***. Some measures require the use of imaging tracers to isolate their location and concentration. The molecules listed typically have a downstream neurological impact and imaging can be useful for the formulation of adequate therapeutic interventions.

sequela	biomarker	imaging modality	references
wakefulness/insomnia	glucose	[^{18}F]-FDG-PET	Stocker, Cieply et al. 2014
neuronal integrity	NAA	MRS	Gujar, Maheshwari et al. 2005
oxidative stress	pH	cerebral microdialysis	Landolt, Langemann et al. 1994
hypoxia	Lac	MRS cerebral microdialysis	Makoroff, Cecil et al. 2005 Magnoni, Ghisoni et al. 2003
edema	LTA4	FLAIR	Irimia, Chambers et al. 2011
PTE/seizures	GABA	MEGA-PRESS [^{11}C] flumazenil/ [^{11}C] Ro 15–4513-PET	Edden and Barker 2007; Edden and Barker 2007, Asahina, Shiga et al. 2008
memory impairment	Glu	MRS	Benveniste, Drejer et al. 1984
sleep dysregulation	NO	fMRI/DWI	Attwell and Iadecola 2002
	Ach	^{123}I-5-IA SPECT	Esterlis, Hannestad et al. 2013
microtubule disintegration	tau	[^{18}F] AV-1451-PET	Maruyama, Shimada et al. 2013; Dickstein, Pullman et al. 2016