Aus der Klinik und Poliklinik für Kinder-, und Jugendpsychiatrie, Psychosomatik und Psychotherapie

Klinikum der Ludwig-Maximilians-Universität München

Post-Traumatic Stress Disorder and Mild Traumatic Brain Injury among Military Veterans: A Diffusion Imaging Analysis of White Matter Microstructure and Sleep Quality

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

vorgelegt von
Philine Rojczyk
aus
Hameln

2023

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

Erster Gutachter:	Prof. Dr. Inga K. Koerte
Zweiter Gutachter:	Prof. Dr. Martha Shenton
Dritter Gutachter:	Prof. Dr. Michael Ingrisch
Weitere Gutachter:	_____
Mitbetreuung durch den promovierten Mitarbeiter:	
Dekan:	Prof. Dr. med. Thomas Gudermann
Tag der mündlichen Prüfung:	21.11.2023

Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

Rojczyk, Philine

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Post-Traumatic Stress Disorder and Mild Traumatic Brain Injury among Military Veterans:

A Diffusion Imaging Analysis of White Matter Microstructure and Sleep Quality

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Hamburg, 16.12.2023	Philine Rojczyk
Ort, Datum	Unterschrift Doktorandin

Disclaimer

Unpublished data from this dissertation is currently being prepared for submission to *Translational Psychiatry* (impact factor 7.989) as a manuscript entitled *"Trauma-related Sleep Disturbances are Associated with White Matter Alterations in Military Veterans"*. All contributing authors and affiliations are listed below.

1. Philine Rojczyk, MSc[a,b]
2. Johanna Seitz-Holland, MD, PhD[a]
3. Elisabeth Kaufmann, MD[a,b,c]
4. Valerie J. Sydnor, BA[a]
5. Cara L. Kim[a,b]
6. Lisa F. Umminger, MD[a,b]
7. Tim L. T. Wiegand[a,b]
8. Jeffrey P. Guenette, MD[a]
9. Fan Zhang, PhD[d]
10. Yogesh Rathi, PhD[a,d]
11. Sylvain Bouix, PhD[a,d]
12. Ofer Pasternak, PhD[a,d]
13. Catherine B. Fortier, PhD[e,f]
14. David Salat, PhD[e,g,h]
15. Sidney R. Hinds, MD[i]
16. Florian Heinen, MD, PhD[j]
17. Lauren J. O'Donnell, PhD[d]
18. William P. Milberg, PhD[e,f,g]
19. Regina E. McGlinchey, PhD[e,f,g]
20. Martha E. Shenton, PhD[a,d]
21. Inga K. Koerte, MD, PhD[a,b,k,l]

a. Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
b. cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany
c. Department of Neurology, Ludwig-Maximilians-University, Munich, Germany

d. Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e. Translational Research Center for TBI and Stress Disorders (TRACTS) and Geriatric Research, Education and Clinical Center (GRECC), VA Boston Healthcare System, Boston, MA, USA
f. Department of Psychiatry, Harvard Medical School, Boston, MA, USA
g. Neuroimaging Research for Veterans (NeRVe) Center, VA Boston Healthcare System, Boston, MA, USA
h. Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital Department of Radiology, Boston, MA, USA
i. Department of Neurology, Uniformed Services University, Bethesda, MD, USA
j. Department of Pediatric Neurology and Developmental Medicine and LMU Center for Children with Medical Complexity, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, Germany
k. Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
l. Graduate School of Systemic Neurosciences, Ludwig-Maximilians-University, Munich, Germany

Content

List of Tables

List of Figures

Abbreviations

ACTH	Adreno-corticotropin hormone
AD	Axial diffusivity
ANCOVA	Analysis of covariance
APOE	Apolipoprotein E
BAT-L	Boston Assessment of TBI-Lifetime
BDNF	Brain-derived neurotrophic factor
CAPS-IV	Clinician-Administered PTSD Scale for DSM-IV
CT	Computed tomography
CRH	Corticotropin-releasing hormone
CSF	Cerebrospinal fluid
DMRI	Diffusion magnetic resonance imaging
DoD	Department of Defense
DRRI-II	Deployment Risk & Resilience Inventory-II
DSM	Diagnostic Statistical Manual for Mental Disorders
EEG	Electroencephalography
FA_T	Fractional anisotropy $_{Tissue}$
FW	Free-water
HPA	Hypothalamic-pituitary-adrenal
IL	Interleukin
MD	Mean diffusivity
MEG	Magnetencephalography
MRI	Magnetic resonance imaging
MTBI	Mild traumatic brain injury
PET	Positron emission tomography
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-traumatic stress disorder
PVN	Paraventricular neurons
RD	Radial diffusivity
REM	Rapid eye movement
SCID-I/NP	Non-patient research version of the Structured Clinical Interview for DSM-IV Axis I Disorders
TNF	Tumor necrosis factor
TRACTS	Translational Research Center for TBI and Stress Disorders

UKF	Unscented Kalman Filter
US	United States
VA	Veterans Affairs
WMA	White Matter Analysis

Abstract

Background: Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are considered the "signature wounds" of military veterans. As one of the most prevalent and debilitating symptoms, poor sleep quality belongs to the hallmarks of PTSD and mTBI. PTSD and mTBI share several pathophysiological features and are impacted by environmental, economic, social, neurophysiological, and genetic factors. Specifically, PTSD and mTBI have been associated with microstructural abnormalities in the brain's white matter. Similarly, poor sleep quality has been linked to white matter microstructural alterations. However, the association between PTSD, mTBI, poor sleep quality, and white matter microstructure is largely unknown. The present work aims at examining the relationship between sleep quality and white matter microstructure in veterans with PTSD and mTBI.

Methods: Diffusion Magnetic Resonance Imaging (dMRI) and clinical data were acquired from 180 male veterans participating in the Translational Research Center for TBI and Stress Disorders (TRACTS) study. Participants were categorized into four groups: 1) PTSD (n = 38), 2) mTBI (n = 25), 3) Comorbid PTSD+mTBI (n = 94), and 4) No history of PTSD or mTBI (n = 23). Sleep quality (Pittsburgh Sleep Quality Index; PSQI) was compared between groups using analyses of covariance (ANCOVAs). Linear regression models were calculated to assess associations between sleep quality and white matter microstructural integrity (whole-brain free-water corrected fractional anisotropy tissue; FA_T). Subsequently, interactions between PTSD, mTBI, sleep quality, and whole-brain FA_T were assessed by applying mediation and moderated mediation models while considering common confounders (i.e., warzone-related stress, neuropsychiatric comorbidities, body mass index (BMI), psychiatric medication use, race, and education).

Results: Veterans with PTSD and comorbid PTSD+mTBI reported poorer sleep quality compared to those with mTBI only or no history of PTSD or mTBI. Poor sleep quality was associated with decreased whole-brain FA_T in veterans with comorbid PTSD+mTBI. Moreover, sleep quality mediated the association between PTSD symptom severity and impaired white matter microstructure, independently of warzone-related stress, neuropsychiatric comorbidities, BMI, psychiatric medication use, race, and education.

Conclusion: Findings from this study suggest that sleep quality plays a vital role in mental and brain health of veterans. Importantly, sleep quality appears to explain the relationship between PTSD symptom severity and alterations in white matter microstructure. Future research is needed to investigate whether sleep-targeted interventions may benefit overall brain health in the veteran population.

Zusammenfassung

Hintergrund: Die posttraumatische Belastungsstörung (PTSD) und das leichte Schädel-Hirn-Trauma (mTBI) sind unter Kriegsveteranen weit verbreitet. Eine gestörte Schlafqualität gehört zu den am häufigsten auftretenden und belastendsten Symptomen von PTSD und mTBI. PTSD und mTBI weisen mehrere gemeinsame pathophysiologische Merkmale auf und werden durch umweltbedingte, wirtschaftliche, soziale, neurophysiologische und genetische Faktoren beeinflusst. Insbesondere wurden PTSD und mTBI mit Veränderungen in der Mikrostruktur der weißen Substanz in Zusammenhang gebracht. Ebenso konnte eine Assoziation zwischen schlechter Schlafqualität und Veränderungen der Mikrostruktur der weißen Substanz gezeigt werden. Die Auswirkungen von PTSD und mTBI auf den Zusammenhang zwischen Schlafqualität und weißer Substanz sind jedoch weitestgehend unbekannt. Die vorliegende Arbeit untersucht die Beziehung zwischen Schlafqualität und Mikrostruktur der weißen Substanz bei Veteranen mit PTSD und mTBI.

Methoden: Diffusions-Magnetresonanztomographie (dMRI) und klinische Daten wurden bei 180 männlichen Veteranen der Translational Research Center for TBI and Stress Disorders (TRACTS) Studie ausgewertet. Die Teilnehmer wurden in vier Gruppen eingeteilt: 1) PTSD (n = 38), 2) mTBI (n = 25), 3) Komorbide PTSD+mTBI (n = 94), und 4) Keine Vorgeschichte von PTSD oder mTBI (n = 23). Schlafqualität (Pittsburgh Sleep Quality Index; PSQI) wurde zwischen den Gruppen mit Hilfe von ANCOVAs verglichen. Lineare Regressionsmodelle wurden berechnet, um die Assoziationen zwischen der Schlafqualität und einem Maß für die Mikrostruktur der weißen Substanz (whole-brain free-water corrected fractional anisotropy tissue, FA_T) zu erfassen. Anschließend wurde die Interaktion zwischen PTSD, mTBI, Schlafqualität, und whole-brain-FA_T mittels Mediations- und Moderationsmodellen unter Berücksichtigung klinischer Störfaktoren (kriegsbedingter Stress, neuropsychiatrische Komorbiditäten, Body mass index (BMI), Einnahme psychiatrischer Medikation, ethnische Herkunft, und Bildungsstatus) untersucht.

Ergebnisse: Veteranen mit PTSD und komorbider PTSD+mTBI berichteten eine schlechtere Schlafqualität im Vergleich zu Veteranen mit mTBI, und Veteranen ohne PTSD oder mTBI. Schlechtere Schlafqualität wurde mit verminderter FA_T der weißen Substanz bei Veteranen mit komorbider PTSD+mTBI in Zusammenhang gebracht. Darüber hinaus erklärte die Schlafqualität die Assoziation zwischen PTSD-Symptomen und der Beeinträchtigung der Mikrostruktur der weißen Substanz, unabhängig von erlebtem kriegsbedingtem Stress, neuropsychiatrischen Komorbiditäten, BMI, Einnahme psychiatrischer Medikation, ethnischer Herkunft, und Bildungsstatus.

Schlussfolgerung: Die Ergebnisse dieser Arbeit deuten darauf hin, dass Schlaf eine wichtige Rolle für die physische und psychische Gesundheit von Veteranen spielt. Als besonders prägnant zeigte sich, dass die Schlafqualität die Beziehung zwischen PTSD-Symptomen und Veränderungen der Mikrostruktur der weißen Substanz zu erklären scheint. Zukünftige Forschungsprojekte sind erforderlich, um zu untersuchen, ob schlafbezogene Interventionen die Gehirngesundheit von Kriegsveteranen verbessern können.

1. Introduction

Since 2001, 2.7 million Unites States (US) service members have been deployed to war zones in Iraq and Afghanistan following the 9/11 terrorist attacks [1]. Operation Enduring Freedom (OEF, Afghanistan, 2001-2014) and Operation Iraqi Freedom (OIF, Iraq, 2003-2011) have been the longest military operations since the Vietnam war and consisted of an all-volunteer force with predominantly male (89%) personnel [2]. The wars cost a total of 6,784 US lives [3], while many more service members were seriously wounded – both physically and mentally. The majority of OEF and OIF military personnel reported being attacked and had personally witnessed or known a fellow combatant who was severely or even fatally injured. Moreover, most were exposed to the traumatic aftermath of war, facing dead bodies or human remains, and injured women or children [4]. Combat stress and other war-related traumatic incidences experienced by military personnel increase the likelihood for developing neuropsychiatric disorders [5–7]. In fact, up to 30% of veterans returning from OEF and OIF are diagnosed with a neuropsychiatric condition [4,6]. Post-traumatic stress disorder (PTSD) is particularly prevalent and comorbidity with other psychiatric conditions, such as anxiety, depressive, and substance use disorders, is common [4,8–11]. Moreover, head trauma resulting in mild traumatic brain injury (mTBI) may lead to the development or exacerbation of psychological symptoms [12–16].

The alarming numbers of neuropsychiatric complaints and associated substantial burdens pose unique challenges to the US Department of Defense (DoD) and Veterans Affairs (VA). Particularly, the "signature wounds" of military veterans – PTSD and mTBI – have been the major focus of attention [17,18]. As one of the most debilitating symptoms, sleep quality disturbances belong to the *hallmarks* of PTSD [19,20]. Moreover, sleep quality disturbances are highly prevalent after mTBI [21–23]. However, until today, understanding the complex underpinnings of sleep quality disturbances following PTSD and mTBI is still in its infancy. Alterations of the brain's white matter – the myelinated nerve fiber bundles that connect different brain regions [24,25] – have been suggested to play a role in sleep quality disturbances. Importantly, initial evidence suggests that sleep quality [26] and white matter health [27–30] are more severely impacted in veterans with greater symptom burden (i.e., veterans with comorbid PTSD+mTBI compared to PTSD or mTBI alone, or no history of PTSD or mTBI). Given that sleep quality disturbances can persist for years after trauma [31,32], have been linked to poor quality of life [33,34], and commonly fail to be alleviated with conventional treatments [35,36], a better understanding of the underlying pathomechanisms is urgently required.

The present work aims at elucidating the relationship between sleep quality disturbances and white matter alterations in the context of PTSD and mTBI. The structure of this dissertation can be summarized as follows. First, the pathogenesis of PTSD and mTBI will be outlined by elaborating on environmental, economic, social, neurophysiological, and genetic factors that contribute to altered brain macrostructure and function. Next, diffusion magnetic resonance imaging (dMRI) will be introduced – an advanced MRI technique for studying tissue microstructure in vivo [37]. Specifically, dMRI studies focusing on subtle microstructural abnormalities in the brain's white matter will be discussed. White matter anatomy is of major importance for optimal brain network functioning [38,39], and disruptions in white matter health have been linked to neuropsychiatric sequelae [40]. In fact, white matter abnormalities have been individually associated with PTSD [41–58], mTBI [59–65], and sleep quality disturbances [66–77]. However, the link between PTSD, mTBI, and sleep quality disturbances in the context of altered white matter is largely unknown. To shed light on the complex interplay between these factors, an automated white matter fiber clustering that uses machine learning to identify fiber tracts [78–81] will be conducted. The magnitude of microstructural white matter alterations in veterans with PTSD, mTBI, comorbid PTSD+mTBI, or no history of PTSD or mTBI will be quantified. Statistical modeling will be applied to uncover the relationship between PTSD, mTBI, and sleep quality disturbances. Moreover, the association between sleep quality and white matter microstructure will be assessed among veterans with and without PTSD and mTBI. Finally, a conclusion on the association between the studied variables will be drawn. An outlook on required future research and potential treatment options for sleep quality disturbances in veterans with PTSD and mTBI will be provided.

2. Post-traumatic Stress Disorder (PTSD)

2.1. Prevalence and Diagnosis

Approximately 23% of military veterans returning from deployment to Iraq and Afghanistan are subsequently diagnosed with post-traumatic stress disorder (PTSD) [82], making it one of the most common psychiatric disorders in veterans [83]. PTSD is a debilitating condition that may develop after personally experiencing or witnessing a traumatic incident that presents as "*exposure to actual or threatened death, serious injury, or sexual violation*" (p.271) [84].

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), PTSD is marked by symptoms that broadly fall into four categories: (A) Re-experiencing symptoms associated with the traumatic incident, such as recurrent distressing recollections, dreams, emotional and physiological reactions to trauma cues, and/or dissociative reactive states (i.e., flashbacks), during which the afflicted individual experiences the traumatic event as actually recurring; (B) avoidance of external reminders concerning the traumatic event and memories that cause distress; (C) altered mood and behavior, presenting as dissociative amnesia, negatively distorted cognitions about self and others, excessive guilt, and anger; and (D) altered arousal and reactivity, including irritability, ruthless or self-destructive conduct, hypervigilance, poor concentration, and sleep quality disturbances [84].

In order to be diagnosed with PTSD, the symptoms need to be present for at least a month, significantly affect daily life, and cannot be attributed to medication and substance use, or any other illness (**Table 1**).

Table 1. Diagnosis of PTSD

Criterion A	A traumatic event	Must be met
Criterion B	Re-experiencing symptoms	At least one Criterion B symptom
Criterion C	Avoidance symptoms	At least one Criterion C symptom
Criterion D	Negative alterations in cognition and mood	At least two Criterion D symptoms
Criterion E	Alterations in arousal and reactivity	At least two Criterion E symptoms
Criterion F	Disturbance lasted for a month	Must be met
Criterion G	Disturbance causing impairment	Must be met
Criterion H	Symptoms not due to medication, substance use, or other illness	Must be met

Note. PTSD, Post-traumatic stress disorder. This table shows the Diagnostic and Statistical Manual for Mental Disorders 5 (DSM-5) criteria for PTSD (p. 271) [84].

2.2. Etiology and Pathophysiology

2.2.1. Social, Economic, and Environmental Factors

The development of PTSD has been linked to various social, economic, and environmental factors. Childhood adverse experiences, pre-existing mental disorder, lack of social support, low socioeconomic status, and migration have all been associated with a

heightened risk of PTSD following exposure to a traumatic event [85–90]. Unfortunately, these risk factors often interact and overlap, thereby enhancing the vulnerability for developing PTSD after trauma. In addition, the perceived severity and nature of the traumatic event play a crucial role in the onset of PTSD. Man-made interpersonal trauma is more likely to elicit PTSD than accidents or natural disasters [91]. For military veterans specifically, more frequent deployments, and greater severity of traumatic combat experiences are linked to an increased risk of PTSD development [87].

2.2.2. Neurophysiological Factors

Endocrine dysregulations of the stress response system constitute an underlying pathology of PTSD. In particular, the hypothalamic-pituitary-adrenal (HPA) axis is a key stress regulatory system that is disturbed in patients with PTSD [92] (**Figure 1**). In response to acute threat, paraventricular neurons (PVN) in the hypothalamus trigger corticotropin-releasing hormone (CRH) production, which in turn stimulates the secretion of adreno-corticotropin hormone (ACTH) from the anterior pituitary. ACTH further stimulates the secretion of the glucocorticoid cortisol from the adrenal cortex. As a negative feedback cycle, cortisol suppresses the production of CRH and ACTH from the hypothalamus and pituitary in an attempt to return to normal states of arousal after a stressor has ceased [93,94].

During acute stress, an increased production of glucocorticoids is beneficial, given that it elevates the availability of glucose to facilitate fighting or fleeing, and preserves the organism's homeostasis [95]. However, as stress becomes chronic, negative feedback inhibition of the HPA axis is triggered by excess cortisol secretion. Thus, increased glucocorticoid receptor binding in the hypothalamus and anterior pituitary results in a surge of CRH secretion [96]. The heightened CRH levels lead to a down-regulation of CRH receptors in the anterior pituitary and consequently suppress ACTH and cortisol release. As a result, *decreased* cortisol levels have repeatedly been demonstrated in patients with PTSD [97,98].

Eventually, these processes fail to restore the HPA activity [99], and ongoing high levels of CRH trigger the sympathetic nervous system and the associated secretion of catecholamines (mainly norepinephrine), which has been linked to symptoms of PTSD [91]. In fact, increased arousal in the presence of diminished available cortisol to regulate the stress response consequently evokes uncontrolled fight or flight reactions – an underlying core feature of PTSD [100,101]. Interestingly, especially cortisol levels that are already low at the time of trauma appear to be particularly likely to facilitate the development of PTSD [102–104]. Basal hypocortisolemia and the associated hyperactive sympathetic nervous system result in an over-consolidation of

traumatic memories and vividness of intrusions [91,105]. It has, thus, been proposed that individuals who develop PTSD after a traumatic experience may already exhibit lower cortisol levels to begin with and therefore lack resilience [106,107].

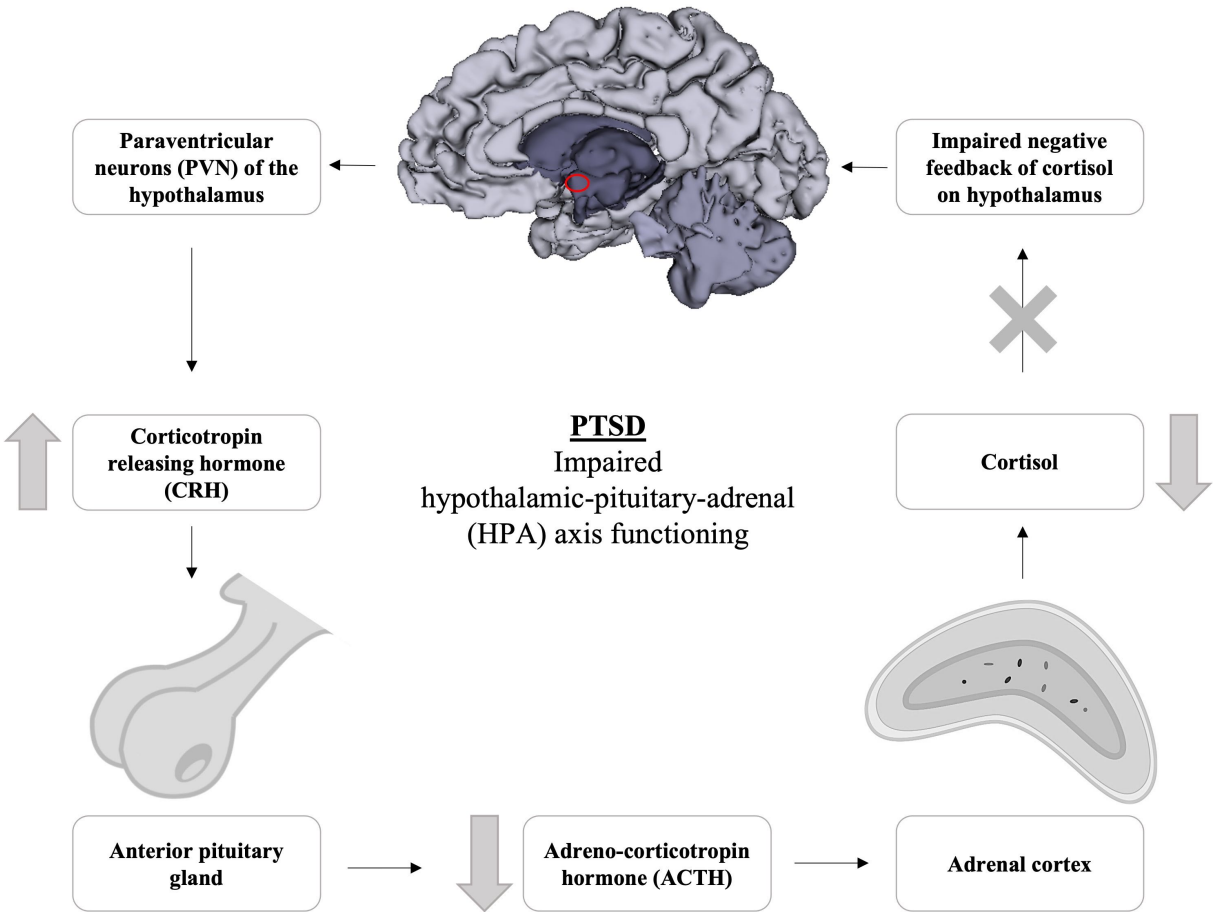

Figure 1. Impaired Hypothalamic-Pituitary-Adrenal (HPA) Axis Functioning in Patients with PTSD

Note. HPA axis, Hypothalamic-pituitary-adrenal axis; PVN, Paraventricular neurons; CRH, Corticotropin releasing hormone; ACTH, Adreno-corticotropin hormone.

This figure visualizes the impaired HPA axis functioning in patients with PTSD. As stress becomes chronic, increased glucocorticoid receptor binding in the hypothalamus and anterior pituitary results in a surge of CRH secretion. The heightened CRH levels lead to a down-regulation of CRH receptors in the anterior pituitary and consequently suppress ACTH and cortisol release. As a result, decreased cortisol levels fail to inhibit CRH production and consequently to restore the HPA activity.

Figure adapted from [101].

Dysregulation of the HPA axis with a blunted cortisol response and simultaneously hyperactivated sympathetic nervous system belong to the core biological underpinnings of PTSD [99,108,109]. The chronically low cortisol levels in patients with PTSD and consequently high

CRH production stimulate increased noradrenergic activity in the locus coeruleus. From here, norepinephrine projects to various brain regions involved in the stress response, such as the prefrontal cortex and limbic structures (i.e., amygdala, hippocampus, hypothalamus) [110]. Excessive noradrenergic activity in the amygdala has been linked to the hyperarousal symptoms of PTSD [111], and the enhanced release of norepinephrine leads to a greater encoding of traumatic memories [112]. With lower cortisol levels, the organism has fewer resources available for shutting down the adrenergic response, enabling damaging effects on brain structure and facilitating the consolidation of traumatic memories [113]. The ongoing hyperarousal has further been associated with an implicit cognitive bias towards potentially threatening stimuli, which is reflected in problems with executive functioning, attention, and concentration [91]. This bias leads to the avoidance of potentially threatening situations, thereby preventing extinction learning [91].

The increased exposition of norepinephrine is followed by an enhanced release of proinflammatory cytokines. This, in turn, stimulates CRH secretion, which further inhibits cortisol release. Cortisol is needed to inhibit not only the sympathetic nervous system but also the proinflammatory cytokine response [99,114]. Thus, a disruption in this mechanism further contributes to the biochemical cascade leading to the manifestation of PTSD [114]. In fact, PTSD patients show elevated levels of inflammatory markers, such as interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and c-reactive protein (CRP), indicating immune dysregulation and inflammation [114].

2.2.3. Genetic Factors

Twin studies have long suggested a genetic contribution to the development of PTSD. A recent meta-analysis proposed a heritability of approximately 5-20% for the likelihood of developing PTSD following a traumatic experience [115]. Interestingly, some studies suggested that patients with PTSD do not only have a genetic risk for developing PTSD after trauma but also to *encounter* traumatic events in general [116,117].

Importantly, environmental factors modify the genetic risk for developing PTSD, and especially childhood traumatic experiences influence the genetic probability [118]. For example, the serotonin transporter gene 5-HTTLPR has not directly been linked to PTSD, but contributes to gene-environment interactions in eliciting PTSD [119]. Individuals with the short allele exhibit greater amygdala activity when facing threatening stimuli, thereby facilitating fear conditioning [120]. Moreover, genes involved in the dysregulation of the stress response system, mainly the HPA axis and noradrenergic system, are altered in patients with PTSD [121]. The FK506 Binding

Protein 51 (FKBP5) gene has been linked to HPA axis dysregulation, particularly of the glucocorticoid receptors [122]. In addition, the Val158Met polymorphism of the Catechol-O-methyltransferase gene has been linked to decreased inactivation of catecholamines [123] and consequently may contribute to stress response system alterations and PTSD development in veterans [124]. Moreover, a genetic variation of the CRP gene has been linked to PTSD symptom severity [125], especially the hyperarousal symptoms [126]. In addition, veterans with PTSD with the apolipoprotein E (APOE) 2 allele demonstrate significantly higher re-experiencing symptoms and worse memory functioning [127].

2.3. Magnetic Resonance Imaging (MRI)

Neuroimaging research contributed greatly to the understanding of PTSD [128] and mTBI [129]. During the last decades, imaging techniques, including magnetic resonance imaging (MRI) [130], positron emission tomography (PET) [131,132], electroencephalography (EEG) [133,134], and magnetencephalography (MEG) [135], allowed for a non-invasive, in-vivo assessment of brain structure and function [136,137].

MRI, in particular, provided some of the most intriguing insights into the pathophysiology of PTSD [138] and mTBI [129]. Medical applications of MRI were introduced in the 1970s [139,140] and offered a more advanced assessment of brain tissue than previous techniques, such as computed tomography (CT). Due to an intense magnetic field, hydrogen protons in tissue (i.e., the brain) are stimulated, while the MRI machine emits radiofrequency pulses [129]. This excites the hydrogen nuclei of water molecules in brain tissue. After each radio wave pulse, the hydrogen nuclei return to their position parallel to the magnetic field. During this so-called relaxation time, the atomic nuclei emit signals that are registered by the MRI device and spatially encoded into images by computer algorithms. Depending on the relaxation time and proton density associated with different types of tissues, differing signals are emitted, which is reflected in the level of brightness in the image. MRI is especially suitable for visualizing the contrast between the brain's gray and white matter and cerebrospinal fluid (CSF), as well as hemorrhages, edema, and contusions [129,141].

2.3.1. Brain Morphology and Function

Among the most consistently observed MRI findings in patients with PTSD are the repeatedly demonstrated smaller hippocampal volumes [142–144], a gray matter brain structure associated with fear conditioning and memory functioning [145–147]. While these findings were initially attributed to the chronicity of the disorder [148,149], twin studies suggested that decreased

hippocampal volumes may actually precede the onset of PTSD, as healthy identical twins of veterans who developed PTSD also showed reduced hippocampal volumes compared to combatants who did not develop PTSD after deployment [150]. Nonetheless, it has been postulated that the manifestation of PTSD leads to a downstream of events causing death of cells and impaired neurogenesis, eventually resulting in volumetric gray matter reductions of the hippocampus [151]. Particularly, glutamate signaling and proinflammatory processes interfere with synaptic connections and lead to atrophy of dendritic spines, thus altering gray matter structure [152–154]. Moreover, individuals with PTSD show decreased levels of brain-derived neurotrophic factor (BDNF), a neurotrophin that is protective against excessive glutamate transmission [155]. It has been suggested that the volumetric reductions of the hippocampus in patients with PTSD prevent extinction learning and the ability to differentiate between potentially threatening and safe environments [96].

Moreover, the amygdala, a brain structure that is anatomically and functionally closely related to the hippocampus [156] and involved in emotional control and fear learning [157–159], shows structural alterations in patients with PTSD [160]. Some studies suggested volumetric reductions of the amygdala in PTSD patients [142,161], however, two recent meta-analyses did not find significant differences between PTSD patients and trauma-exposed controls [142,151], while amygdala volume differed significantly from healthy controls [151]. Structural alterations in the amygdala may, thus, be a marker of extended stress exposure in general, but not necessarily of PTSD symptomatology specifically. **Figure 2** visualizes the bilateral amygdala and hippocampus.

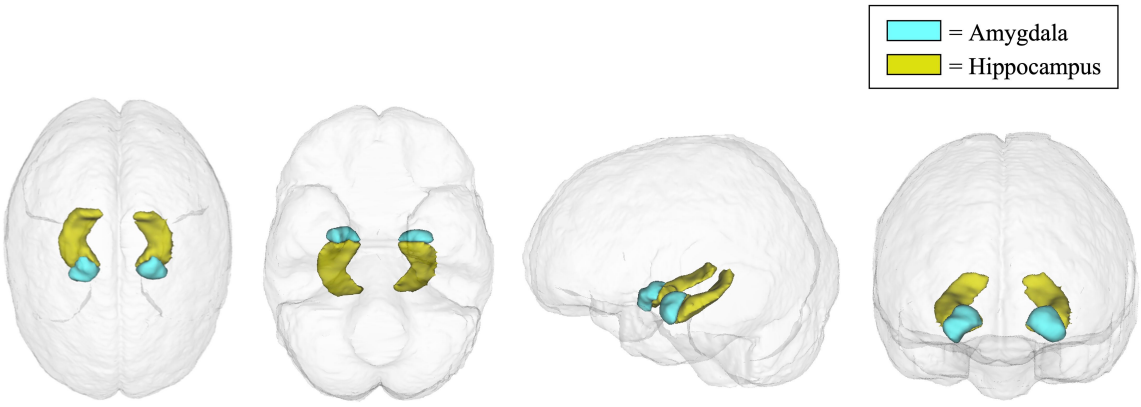

Figure 2. Amygdala and Hippocampus.
Note. Visualization of the amygdala (turquoise) and hippocampus (yellow) in top, bottom, sagittal, and coronal view (from left to right).

2.3.2. Brain Networks

Volumetric alterations in limbic and paralimbic gray matter structures, such as the hippocampus and amygdala [162–166], underlie functional connectivity network abnormalities [167]. Especially altered amygdala-frontal connectivity is one of the core network abnormalities of PTSD [168,169]. The medial prefrontal cortex has long been implicated in playing a major role in regulating emotions by suppressing fear reactions elicited by the amygdala [112]. However, in patients with PTSD the amygdala is overly responsive, while the medial prefrontal cortex is less engaged [170]. This is reflected in an increased blood flow in the amygdala and decreased flow in the medial prefrontal cortex in response to trauma stimuli [171–175]. The heightened amygdala and simultaneously decreased medial prefrontal cortex activity prevents fear extinction learning [176], thereby further imprinting traumatic memories [96]. Particularly PTSD hyperarousal and re-experiencing symptoms have repeatedly been linked to heightened amygdala and decreased medial prefrontal cortex activity [112,167].

2.4. Diffusion Magnetic Resonance Imaging (dMRI)

Network functioning relies on the brain's white matter anatomy [38,39,177]. The white matter fiber tracts compose vast structural and functional connections between different gray matter structures and nodes of brain networks [24,25]. Projection fibers connect sub-cortical with cortical areas. Association fibers link different structures within the same hemisphere. Commissural fibers, such as the corpus callosum, bridge the left and right hemisphere [24]. White matter consists of an accumulation of myelin-coated axons formed into densely packed bundles of fibers. The high concentration of lipids in the axons' insulating sheath lets the fiber tracts appear white, thus the term *white matter* [178]. The electrically insulating myelin sheath enhances the signal transmission to other neurons [25], that is facilitated through a rapid nerve impulse conduction along small gaps in the myelin sheath (nodes of Ranvier) [179]. Action potentials are regenerated at each node and jump along the axons, a process called saltatory conduction [180]. Greater myelination is generally associated with much faster conduction of signals. On the contrary, disrupted myelination has been associated with disturbed stimulus transmission [25]. Impaired signal transmission amongst various brain networks may further impact information processing in adjacent brain structures [181]. This may lead to compromised cognition and mental health, as evidenced in numerous neuropsychiatric conditions [40], including PTSD and mTBI [27–30,41,51–53,182,183].

White matter properties, such as myelinization, axonal diameter and density can be analyzed with diffusion magnetic resonance imaging (dMRI), which is an advanced MRI

technique, specialized in studying tissue microstructure in vivo [37]. DMRI was developed in the 1990s [184] and determines the diffusion of water molecules in tissue [37]. According to Brownian motion rules, water molecules move at random following a 3D Gaussian distribution when free and unrestricted. This is called *isotropic diffusion* and can be found in the CSF, whereas the opposite, *anisotropic diffusion*, refers to water molecule movement restrained by structured tissue, such as the brain's white matter. The cell membranes, myelin sheath, and numerous, densely packed axons force water molecules to diffuse along with the fiber directions [37,185].

DMRI measures the magnitude and directionality of diffusion [37,130] by calculating a diffusion tensor for three perpendicular axes of each brain voxel. This three-dimensional vector is represented as a diffusion ellipsoid (**Figure 3**). The magnitude of diffusion along each axis are the *eigenvectors*, while their length or directionality represents the *eigenvalues* (λ1, λ2, λ3). Diffusion parameters can be determined from the eigenvalues of the diffusion tensor and provide information on tissue microstructure. Fractional anisotropy (FA) is the most frequently reported diffusion metric and represented in a value between 0 (*isotropic diffusion*) and 1 (*anisotropic diffusion*) that provides information on the diffusion directionality [186–189]. Greater restriction of diffusion, e.g., due to greater axonal density and myelin sheath thickness, will thus result in higher FA values [190]. On the contrary, impairments in the myelin sheath [191,192], edema [193], and gliosis [194] may reflect reduced FA values.

Axial diffusivity (AD) represents diffusion parallel to the fiber and equals the largest eigenvalue. Radial diffusivity (RD) reflects the degree of diffusion perpendicularly to the primary direction and is the average of eigenvalue λ2 and λ3. AD has primarily been shown to reflect axonal degeneration, while RD mostly reflects myelination processes [195,196]. Finally, mean diffusivity (MD) provides information on the overall magnitude of diffusivity in a voxel, independent of tissue-restricted direction, and is calculated by summing and averaging all three eigenvalues [197]. MD is typically inversely related to FA [130].

AD, RD, and MD all provide individual information on white matter organization. However, the summary measure (FA) is commonly preferred, given that it provides a proxy for overall white matter microstructural tissue architecture. In addition, in 2009, free-water (FW) imaging was developed [198], a dMRI advancement that is able to measure FW adjacent to cell tissue. FW imaging provides additional information over the conventionally used diffusion measures by separating the MRI signal into two compartments [198]. The isotropic free-water compartment accounts for the proportion of extracellular free-water in each voxel, while the tissue compartment represents free-water-corrected fractional anisotropy $_{\text{Tissue}}$ (FA_{Tissue}, FA_T). In comparison to the conventional FA measure, FA_T is more specific to fiber tract myelination,

axonal density, and fiber orientation, and, thus, a more precise marker for cellular white matter microstructure [199].

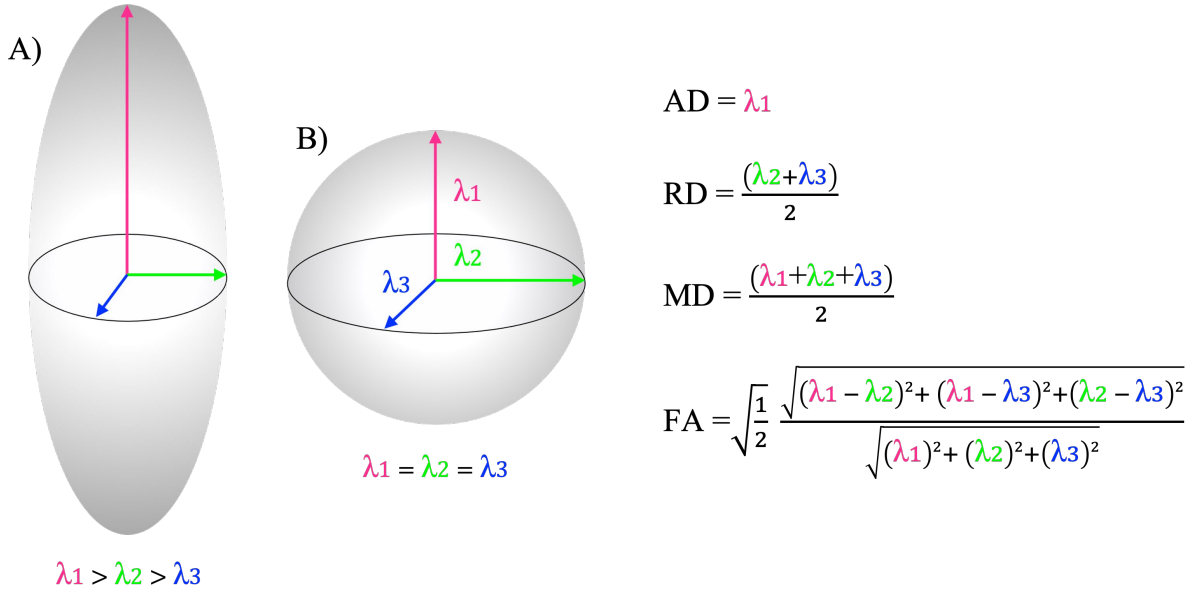

Figure 3. Diffusion Magnetic Resonance Imaging
Note. A) Anisotropic diffusion; B) Isotropic diffusion. AD, Axial diffusivity; RD, Radial diffusivity; MD, Mean diffusivity; FA, Fractional anisotropy. Figure adapted from [37].

2.4.1. White Matter Diffusion

PTSD has been associated with alterations in various white matter fiber tracts throughout the brain, including the major fiber tracts (i.e., arcuate fasciculus, cingulum bundle, inferior longitudinal fasciculus, inferior occipito-frontal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and corpus callosum), and with alterations in global white matter [41,43–58,183]. Importantly, white matter alterations have not only been reported compared to healthy civilians [43,44,50], but also compared to trauma-exposed controls [41,46,47,49,51,52,183]. For example, PTSD patients showed increased MD in the uncinate fasciculus compared to trauma-exposed controls [49]. Moreover, alterations in the uncinate fasciculus showed significant correlations with greater symptom severity, suggesting impaired communication between the amygdala and medial prefrontal cortex [49,200]. Lower FA of the uncinate fasciculus was also negatively associated with re-experiencing symptoms, both acutely and sub-acutely post-trauma, while lower fornix/stria terminalis FA correlated with greater arousal symptoms [201]. While these findings are single observations in small to medium-sized samples, a recent meta-analysis summarized data from different studies and identified lower FA values in PTSD patients compared to trauma-exposed controls in the tapetum of the corpus callosum, a structure

that bridges the left and right hippocampus [51]. Notably, the results persisted even after adjusting for comorbid psychiatric disorders, and medication use [51]. Lower white matter FA_T may reflect an alteration of tissue organization, such as altered myelination processes, membrane thickness, and axon diameter [37]. Indeed, chronic stress incites inflammatory processes [114] (i.e., increased release of inflammatory cytokines [202,203]), and excitotoxic neurotransmitter damage [204,205] (i.e., overly activated glutamate neurotransmission [41,205]) which induce apoptosis and impair myelination [202,203,206].

Even though most of the available studies reported decreased white matter microstructural integrity, some showed an association between PTSD and increased white matter microstructure. For example, decreased MD of the right cingulum bundle was shown in veterans with PTSD compared to those without PTSD, suggesting greater connectivity between the amygdala and anterior cingulate cortex [52]. Moreover, a recent meta-analysis revealed significantly higher inferior occipito-frontal fasciculus and inferior temporal gyrus FA in PTSD patients [43]. Notably, greater white matter FA is not always associated with better functioning [207]. For example, higher FA of the superior fronto-occipital fasciculus has been linked to re-experiencing and dissociative symptoms [183]. The alternations between regional-specific FA increases and decreases in patients with PTSD may suggest that not PTSD per se, but rather distinct symptoms of the disorder may result in different white matter changes [183]. Despite the fact that sleep quality disturbances are a hallmark symptom of PTSD [19,20], research on the association between PTSD-related sleep quality disturbances and white matter alterations is sparse. One study showed an association between the hyperarousal symptoms of PTSD, poor sleep quality, and reduced FA of the right uncinate fasciculus [208]. While requiring further research, the findings may illustrate the increased noradrenergic activity in patients with PTSD [19,209,210], leading to impaired fronto-limbic connectivity [211,212] that is reflected in decreased white matter FA.

3. Mild Traumatic Brain Injury (mTBI)

3.1. Prevalence and Diagnosis

Approximately 12-35% of veterans sustain a mild traumatic brain injury (mTBI) during military deployment [213,214]. According to the American Congress of Rehabilitation Medicine (ACRM) diagnostic criteria, mTBI presents as disturbed brain functioning due to physiological head trauma, that may include immediate loss or alteration of consciousness and/or amnesia before or after the event [215]. Common causes of mTBI in veterans are blunt and blast-related injuries, where the head is struck by an object or exposed to acceleration and deceleration forces

[216]. In order for a traumatic brain injury to be classified as mild, loss of consciousness must not exceed 30 minutes, while posttraumatic amnesia must not last longer than 24 hours. Moreover, the Glasgow Coma Scale score must range between 13 and 15 [215].

Sustaining a mTBI may provoke temporary symptoms that can be classified into three broadly defined categories: (1) Physical symptoms that present as nausea, vomiting, vertigo or dizziness, headache, blurred vision, sensory distortions, and sleep quality disturbances; (2) cognitive distortions, such as attention and concentration problems, forgetfulness and difficulty in decision making; and (3) emotional and behavioral symptoms, including anxiety, depression, irritability, and aggressive behavior [215,217] (**Table 2**). These impairments usually subside after a couple of days or weeks [218]. However, around 15 to 30% of mTBI patients develop long-term post-concussive symptoms [218–220] that can lead to permanent disability [218–220].

Table 2. Diagnosis of mTBI

Cause	1)	The head being struck	
	2)	The head striking an object	
	3)	The brain undergoing an acceleration/deceleration movement (i.e., whiplash) without external head trauma	
Definition	1)	Loss of consciousness < 30 minutes	
	2)	Initial Glasgow Coma Scale score of 13-15	
	3)	Post-traumatic amnesia < 24 hours	
Symptoms	1)	Physical symptoms	Nausea and vomiting
			Vertigo or dizziness and headaches
			Blurred vision and sensory distortions
			Sleep disturbances
	2)	Cognitive symptoms	Attention problems
			Concentration problems
			Forgetfulness
			Difficulty in decision making
	3)	Emotional and behavioral symptoms	Anxiety
			Depression
			Irritability
			Aggressive behavior

Note. mTBI, Mild traumatic brain injury. This table shows the American Congress of Rehabilitation Medicine (ACRM) and Centers for Disease Control and Prevention [221] criteria for diagnosing mTBI.

3.2. Etiology and Pathophysiology

3.2.1. Social, Economic, and Environmental Factors

Low socio-economic status [222], pre-existing psychiatric disorders [223], as well as traumatic combat experiences [224] are among the risk factors for sustaining a mTBI. Alarmingly, sustaining a mTBI has been linked to the development of various mental disorders [225] (most importantly PTSD [12–16]), associated with neuropsychiatric symptoms (e.g., suicidality [226], anger, aggressiveness [227], and sleep quality disturbances [21–23]), and disadvantageous psychosocial outcome (e.g., impaired familial, and other social relationships [227,228], unemployment [229], and homelessness [230]). Moreover, common risk factors for persistent post-

concussive symptoms after mTBI are traumatic stress, history of a psychiatric disorder, additional physical injuries, as well as loss of consciousness and post-traumatic amnesia [231,232]. Importantly, mTBI acquired in a deployed setting is associated with higher incidences of PTSD, depression, substance use, and poor sleep quality [233], indicating that military mTBI requires special attention and customized treatment approaches [232].

3.2.2. Neurophysiological Factors

Sustaining a mTBI may disturb HPA axis functioning in a similar way as observed in patients with PTSD [234–239] (**Figure 1**). In fact, pituitary dysfunction after mTBI is highly common [240–242], and involved in inducing post-concussive symptoms [243]. Mechanical forces can lead to shearing, tearing, contusions, and hemorrhages of brain tissue [244], ischemic injury [245], altered blood flow, and increased intracranial pressure [246]. These processes may cause post-traumatic hypopituitarism [247]. Especially the vulnerable pituitary stalk that connects the anterior pituitary and hypothalamus is affected by mTBI [246].

Similar to PTSD, disturbed pituitary hormone production results in altered glucocorticoid signaling and consequent impaired HPA axis negative feedback control [246,248]. ACTH deficiencies [249], subsequent decreased adrenal gland and cortisol stimulation [246,248], and an accumulation of anti-pituitary anti-bodies that impair the pituitary's functioning [250] have been pointed back to brain trauma. Dysfunction of the HPA axis may further lead to inflammatory dysregulations [248]. After sustaining a mTBI, microglia (central nervous system-specific immune cells) trigger an inflammatory response by releasing proinflammatory cytokines, including IL-6, IL-1, and TNFα [248]. These processes are needed to clear waste products and to re-adjust synapses after injury but become problematic if the inflammatory reaction is constantly activated [248]. MTBI may also affect metabolic functioning [251], and alter lipid and glucose mechanisms [252]. This may further stimulate the genesis of beta-amyloid and tau pathology [253], which are protein aggregates that form pathological plaques and neurofibrillary tangles around cells [254,255]. In fact, beta-amyloid and tau protein may accumulate in the white matter after brain trauma [256]. Alarmingly, mTBI may even show a similar neuropathology (i.e., accumulated tau, disseminated microgliosis, astrocytosis, and neurodegeneration) as seen in patients with chronic traumatic encephalopathy (CTE) – a neurodegenerative condition that has been linked to repetitive head impacts [257].

The endocrine dysregulations following mTBI [239,241] increase the risk for the onset, exacerbation, and recurrence of stress-related conditions, including PTSD, anxiety, and depression [258–265]. Psychiatric symptoms, in turn, perpetuate the endocrine and nervous system

dysregulations, resulting in a greater expression of post-concussive symptoms, including sleep quality disturbances [266].

3.2.3. Genetic Factors

Genetic variations that affect the inflammatory reactions and neurotrophic repairments after injury, and genes that alter mental and cognitive functioning are implicated in the outcome of brain trauma [267]. Genetic polymorphisms controlling inflammatory markers, including TNF-α, IL-1, and IL-6, have been linked to adverse outcomes after mTBI [267]. Moreover, particularly APOE polymorphisms appear to be implicated in mTBI outcome. Carriers of the APOE4 allele with mTBI history have a substantially heightened risk of developing Alzheimer's dementia [268] and CTE [269]. Moreover, they experience longer durations of loss of consciousness when sustaining a head trauma, exhibit worse memory functioning after injury, and suffer from a delayed recovery process [267]. In fact, a recent study showed that mice with the APOE4 genotype compared to those with APOE3 exhibit a greater inflammatory response, tau accumulation, microglia activation, apoptosis, and lower BDNF levels after mTBI, potentially explaining disadvantageous injury outcome [270].

Interestingly, the genetic makeup may not only affect how an individual recovers from a mTBI, but also influences the likelihood of *sustaining* a mTBI in the first place [271]. A systematic review of genetic risk factors for sustaining mTBI identified that the promoter -219 G/T polymorphism of the APOE gene is linked to increased risk for mTBI [271]. Moreover, the BDNF Met/Met genotype (corresponding to decreased BDNF release) was linked to greater incidences of mTBI among military service members [271]. The authors explain the latter by alleging that BDNF polymorphisms have been associated with certain personality characteristics that may incline an individual to engage in risk behaviors potentially leading to mTBI, such as hyperactivity, impulsivity, and aggression [271]. Moreover, the BDNF polymorphism also affects neurochemistry and brain functioning, thereby facilitating that a head impact actually results in a diagnosable mTBI [271].

3.2.4. Brain Morphology and Function

A recent review summarized the current macrostructural brain findings in mTBI and reported alterations in brain volume and cortical thickness after mTBI [272]. Tissue death in gray matter structures may occur particularly in the limbic system [273]. Indeed, smaller hippocampal volumes have not only been shown in patients with PTSD, but also in those with mTBI [274–279]. Damage to white matter tracts connected to the hippocampus may ultimately compromise

hippocampal structure [272], and volumetric reductions of the hippocampus have been associated with poor sleep quality [280–282]. The amygdala is equally vulnerable to the adverse effects of head impacts [63,277,279]. Moreover, lower cingulate gyrus and orbitofrontal cortical volume has been observed [283], the latter particularly in military mTBI [284–286]. Volumetric alterations of the limbic structures after mTBI have been associated with impaired cognitive functioning, such as memory, attention, psychomotor speed [287–289], and with failure to resume employment [290]. Moreover, they pave the way for the emergence of psychiatric disorders, particularly PTSD [291], given the limbic projections to stress response system regulation hubs, e.g., the hypothalamus [292–294].

Importantly, not all studies report changes in cortical thickness [277] and brain volume [288,295] after mTBI. Increases in brain volume one year post-mTBI have been reported in comparison to healthy control subjects [296], which may be interpreted as a compensatory reaction to the injury [297]. Others showed an initial increase and later decrease in cortical thickness [298–300]. Thus, brain structural alterations may vary with the acute, sub-acute and chronic stage of injury and according to specific mTBI symptoms.

3.2.5. Brain Networks

Similar to PTSD, the connectivity of major brain networks is impacted after mTBI [301–305], suggesting that mTBI may lead to widespread intra- and inter-network impairments [306,307]. Specifically, hypoactivity in the default mode network has been observed [308,309], a network that is involved in providing an internal representation of the outer world and is most active at rest when reflecting on personal experiences and memories [310]. These self-referential processes influence social and emotional judgment and decision making [310]. The main hubs of the default mode network are the medial prefrontal cortex, inferior parietal lobule, posterior cingulate cortex, lateral temporal cortex, and the hippocampal formation [310]. Especially alterations in the anterior default mode network have been linked to psychiatric post-concussive symptoms [309], and functional connectivity alterations acutely after mTBI are predictive of persistent post-concussive symptoms [311,312]. Several studies have shown associations between abnormalities of default mode network functioning and military mTBI with comorbid post-traumatic stress [313–316]. Importantly, altered connectivity of the default mode network may further lead to abnormalities in associated networks and, thus, to disruption of information processing, cognitive and emotional control, and adequate adaptation of behavior [317–319]. The findings suggest that mTBI leads to wide-spread impairments in large-scale brain networks [301–305], resulting in neuropsychiatric sequalae [309,311,312].

3.2.6. White Matter Diffusion

Reduced network efficiency results from damages to connecting structures and white matter fiber tracts [320–322]. In fact, traumatic axonal injury is the most common injury type following mTBI [323]. Mechanical forces lead to shearing, tearing, contusions, and hemorrhages of axons [244] (**Figure 4**).

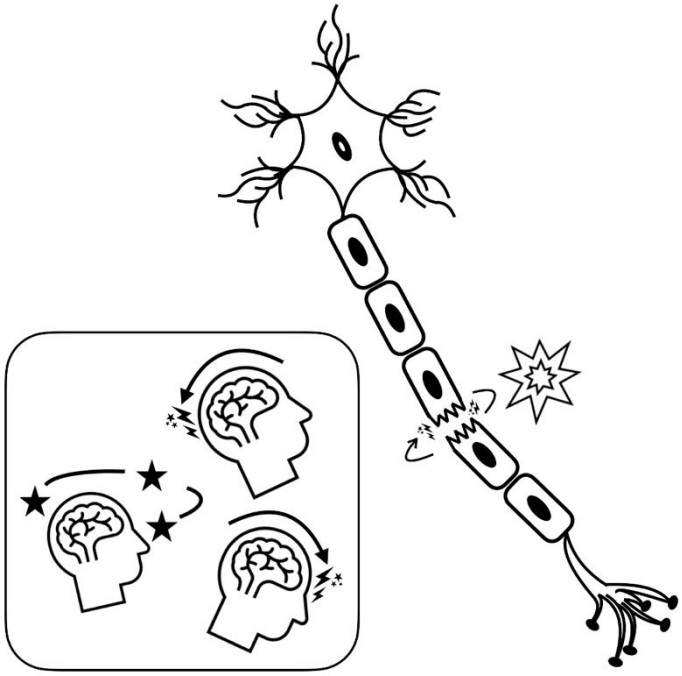

Figure 4. Mild Traumatic Brain Injury Traumatic Axonal Injury
Note. This figure displays the twisting and tearing of an axon due to acceleration, and deceleration forces applied to the brain. Traumatic axonal injury may disrupt communication between brain areas and can lead to a cascade of biological events resulting in adverse neuropsychiatric symptoms.

DMRI studies with mTBI patients report widespread lower white matter FA, particularly for major fiber tracts, such as the corpus callosum [59–63], inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus [63,65]. While numerous white matter tracts are implicated after mTBI [59–65], especially the corpus callosum is affected due to its anatomical susceptibility to mechanical strain [324] and shear lesions [272]. A meta-analysis revealed FA reductions, particularly in the splenium of the corpus callosum [325].

Importantly, it has been stressed that mTBI adversity may be detectable by sensitive imaging methods even years after injury [326,327]. Lower FA in fiber tracts throughout the brain has been reported after two to five years [61,328] or even ten years after mTBI [329]. Interestingly, a recent longitudinal study revealed that while white matter FA levels one year after mTBI were comparable to those of control subjects, FA measures decreased later on, as shown at the five-

year follow-up [330]. The authors suggest that the results are in line with accelerated brain aging in mTBI patients [330,331].

While numerous studies showed white matter degeneration after mTBI, some have found higher white matter FA. A meta-analysis across five military brain injury cohorts identified higher FA in the superior longitudinal fasciculus in comparison to control participants [332]. The finding was interpreted as a rehabilitative process of fiber restructuring after injury [333]. White matter FA may increase especially acutely after injury [334–336] and likely reflects neuroinflammatory processes, such as cytotoxic edema, swelling, or neuropathological gliosis [335,337,338]. However, not all studies reveal initial increases of white matter FA, and the findings are highly variable in general, with some not reporting differences between mTBI patients and controls at all [339]. Further, time since injury appears to play a crucial role in white matter organization after mTBI, as indicated above. In fact, findings vary greatly depending on whether patients have been assessed acutely, sub-acutely, or remotely after mTBI [326]. Importantly, however, white matter alterations at all stages after mTBI have been linked to various post-concussive symptoms, such as impairments in working memory, processing speed, concentration problems, depression, irritability, aggressiveness, and sleep quality disturbances [59,65,67,340–342]. These symptoms are particularly amplified in patients who did not only sustain a mTBI, but also suffer from a psychiatric disorder, particularly PTSD [343].

4. PTSD, mTBI, and White Matter Diffusion

Approximately 33-39% of veterans with mTBI also meet diagnostic criteria for PTSD [344]. PTSD and mTBI do not only share various common symptoms, such as general psychological distress [345], depression [346,347], cognitive impairments [348,349], problems in social life and everyday functioning [228,350], and sleep quality disturbances [351–354], but also influence each other. PTSD worsens the mTBI recovery prognosis [355,356], and mTBI may lead to PTSD development or progression [12–16]. Importantly, it has been postulated that not only does mTBI increase the susceptibility for developing PTSD, but an uncontrolled stress response with associated abnormal limbic-cortical circuitry, as seen in patients with PTSD, enables far more detrimental effects of a head injury [204,357].

The great commonality of neuropsychological impairments in PTSD and mTBI [348,358], and particularly the emergence of PTSD following mTBI may likely be explained by the highly overlapping neural substrates underlying both conditions [204,272,359,360]. Damage to mesial temporal structures, such as the amygdala and hippocampus [361], due to impact or blast-related acceleration and deceleration forces contribute to the emergence of both post-concussive

symptoms and PTSD symptomatology [204,357,362]. Moreover, chronic stress leads to abnormal HPA axis functioning [99,101]. This affects neuronal plasticity due to inflammatory processes [114], and excitotoxic neurotransmitter damage [204], such as overly activated glutamate neurotransmission [41,205]. These processes may ultimately lead to apoptosis and necrosis of brain tissue [206]. Moreover, brain structural abnormalities affect functional connectivity among large scale-brain networks, further reinforcing neuropsychiatric symptom burden [167,363].

The brain's white matter is crucial for optimal network functioning [38,39] and both patients with PTSD [41–58] and mTBI [59–65] exhibit marked, wide-spread alterations of white matter microstructure. However, despite the high co-occurrence and clinical additive effects of PTSD and mTBI [204,348,357,358,362], only a small number of dMRI studies examined both disorders together. These few studies largely suggest that patients with comorbid PTSD and mTBI might have even more severe white matter abnormalities than patients with either disorder alone [27–30]. Specifically, white matter impairments of limbic tracts, e.g., the uncinate fasciculus [29] and cingulum bundle [30], have been reported in veterans with comorbid PTSD+mTBI compared to those with mTBI only. Similarly, a greater number of lower FA clusters was found in veterans with comorbid PTSD+mTBI in comparison to those with mTBI only and healthy controls [341]. However, counterintuitive findings have also been reported. One study showed lower internal capsule FA in patients with PTSD compared to comorbid PTSD+mTBI, mTBI and controls, and therefore indicated no evidence of an additive burden of comorbid PTSD+mTBI [364]. Moreover, other studies revealed higher FA of major white matter tracts in veterans with comorbid PTSD+mTBI [27]. However, it is crucial to consider that higher white matter FA is not always associated with better functioning [207], and may also be interpreted as an attempt of fiber re-organization or battling neuroinflammation [183].

Despite these conflicting results, there is consensus that PTSD and mTBI may lead to impairments in white matter microstructure. Moreover, white matter microstructural alterations correlate with neuropsychiatric symptoms [29,341], particularly sleep quality disturbances [365]. However, knowledge on the impact of PTSD- and mTBI-related sleep quality disturbances on the brain's white matter is still limited.

5. PTSD, mTBI, and Sleep Quality

Sleep quality disturbances are highly prevalent in the veteran population [366,367], with 70% experiencing poor sleep quality after deployment [368]. In particular, sleep quality disturbances are a hallmark symptom of PTSD [19,20]. PTSD-associated sleep quality disturbances encompass difficulties falling asleep, recurrent awakenings during the night, distressing

dreams, and not feeling rested during the day [369–371]. The large majority of PTSD patients experiences difficulties in falling and staying asleep [33]. Moreover, nightmares are particularly indicative of PTSD [372], and constitute a re-enactment of trauma that hinders the affected individual from returning to sleep due to intense anxiety after awakening [372]. Moreover, sleep quality disturbances are common in patients with mTBI [21–23], exacerbate psychiatric symptoms [365], and have been identified as a mediator between TBI and the emergence of PTSD [373]. Importantly, sleep appears to be even more severely impaired in veterans with comorbid PTSD and mTBI compared to those with only one of the conditions [26]. Sleep quality disturbances can persist for years after trauma [31,32], and may not remit even when other PTSD symptoms are [35,36], as sleep is needed for the emotional processing of traumatic events [369]. Indeed, prolonged sleep quality disturbances hinder the recovery from PTSD [374–376] and post-concussive symptoms [377–379], and have been linked to adverse outcomes, including reduced quality of life [365], poor physical and cognitive functioning [33,34], substance use [380], and suicide attempts [381]. In summary, trauma-related sleep quality disturbances may severely affect mental and physical health [382]. However, the underlying pathomechanisms are still poorly understood, impeding the implementation of proper diagnostic and treatment protocols.

5.1. Etiology and Pathophysiology

A healthy human undergoes an entire sleep cycle for four to six times per night, each lasting for an average of approximately 90 minutes [383]. An entire sleep cycle consists of a wake period, three phases of non- rapid eye movement (non-REM) sleep (N1 to N3), and REM sleep. Sleep becomes deeper from non-REM sleep N1 to N3 and is marked by increasingly large-amplitude EEG waves [383], explaining why non-REM sleep is commonly referred to as *slow wave sleep* [384]. During the non-REM sleep stages, arousal is typically decreased, and the body restores its functions [211]. Indeed, slow wave sleep is essential for optimal mental and physical functioning [384]. When the morning approaches, REM sleep covers more time. During REM sleep, muscle tone is inhibited, and only the eyes move under the eyelids, giving REM sleep its name. Breathing and heart rate are more irregular, and most dreaming occurs during this stage [383,385]. Neural activity during REM sleep is comparable to wakefulness, and activity is especially increased in the limbic system and related areas [209,211].

PTSD patients commonly show disruptions in REM sleep [19,386]. Nightmares usually occur during REM sleep [19] and have been suggested to be a failed attempt of incorporating the lived traumatic experience into one's world [210]. In fact, so-called *restless REM sleep* that is marked by especially high arousal and eye movements impairs the overnight resolution of

distress and contributes to chronic hyperarousal symptoms of PTSD [387] by maintaining continued amygdala reactivity [388]. Moreover, in patients with PTSD light sleep is more prominent, while slow-wave deep sleep covers less time [210,389], which has been connected to increased CRH levels and CRH receptor down-regulation – a key pathology of PTSD [97,98,390]. As a consequence, PTSD patients show an abnormally high norepinephrine activity in the brain [19,209], which correlates with the clinical symptoms of hyperarousal [210]. Norepinephrine activity is usually suppressed during sleep [391], however not so in patients with PTSD. PTSD patients lack the overnight drop in norepinephrine levels which correlates with worse sleep quality [392]. Strikingly, analyses of sleep patterns, HPA axis functioning, EEG, and neuroimaging findings suggest that sleep quality disturbances, such as insomnia, reflect a hyperarousal state that persists throughout day *and* night [392,393]. In accordance with the increased norepinephrine tone and hyperarousal, PTSD patients exhibit greater metabolism in the limbic system, brainstem, and cortical regions during REM sleep and while awake [394]. Moreover, PTSD-related sleep quality disturbances have been associated with abnormal functional connectivity in fear-related circuits, particularly between the medial prefrontal cortex and amygdala [211,212], and with gray matter volume loss in limbic and paralimbic areas, such as the amygdala, hippocampus, anterior cingulate, and insula [395]. Disconnection between frontal and limbic areas as a correlate of disturbed sleep quality may further contribute to emotion regulation difficulties [396], and impaired extinction of traumatic distressing memories [397]. Altered sleep patterns and nightmares may, thus, especially emerge due to the disturbed interplay between the amygdala and medial prefrontal cortex seen in patients with PTSD [211,365].

Biological impairments due to mTBI, such as traumatic axonal injury [323,398], may further exacerbate sleep quality disturbances in patients with PTSD. Moreover, mTBI may cause poor sleep quality even without psychiatric comorbidity [399]. Dysregulation of brain circuits involved in circadian rhythmicity [400] (such as the brain stem, reticular activating system, hypothalamus, and retino-hypothalamic tract [401]), damage to arousal neurons, altered glutamate signaling, and reduced melatonin production from the pineal gland after mTBI [402,403] likely play a role. Moreover, hypothalamus-synthesized hypocretin, which is involved in the alteration between wakefulness and sleep, is often decreased in TBI patients [404–406], and may contribute to sleep quality disturbances [407]. Proinflammatory cytokines are elevated both in patients with PTSD [114] and in mTBI [408], and have been linked to sleep quality disturbances [409]. Increased levels of inflammatory cytokines may induce apoptotic processes and may impair myelination [202,203]. Further, it was recently discovered that mTBI leads to impaired glymphatic waste clearance in the limbic system [410]. The glymphatic system is a brain network of perivascular spaces vital for

flushing out accumulated neurotoxins (such as beta-amyloid and tau) that is most active during sleep [411–414]. Impaired waste clearance of the limbic circuits may explain why sleep quality disturbances after TBI fuel the emergence and maintenance of psychiatric symptoms [248].

In summary, PTSD and mTBI have been linked to physiological changes associated with disturbed sleep quality. In turn, sleep quality disturbances have been shown to affect brain structure and function. Sleep is crucial for maintaining the healthy environment the brain needs to perform adequately, and is directly linked to brain homeostasis [415]. As sleep is involved in lipid biosynthesis, myelin deposition, and activates oligodendrocyte precursor proliferation crucial for myelin genesis, it has been argued that sleep may be particularly critical for white matter health [416]. On the opposite, sleep quality disturbances have been linked to brain volume loss, decreased neurogenesis, and decreased cortical activation [417,418]. As a result, poor sleep quality is likely to have an impact on the brain's white matter connections and, vice versa, on neuropsychiatric functioning. However, the complex interplay between PTSD, mTBI, sleep quality, and white matter is largely unknown (**Figure 5**).

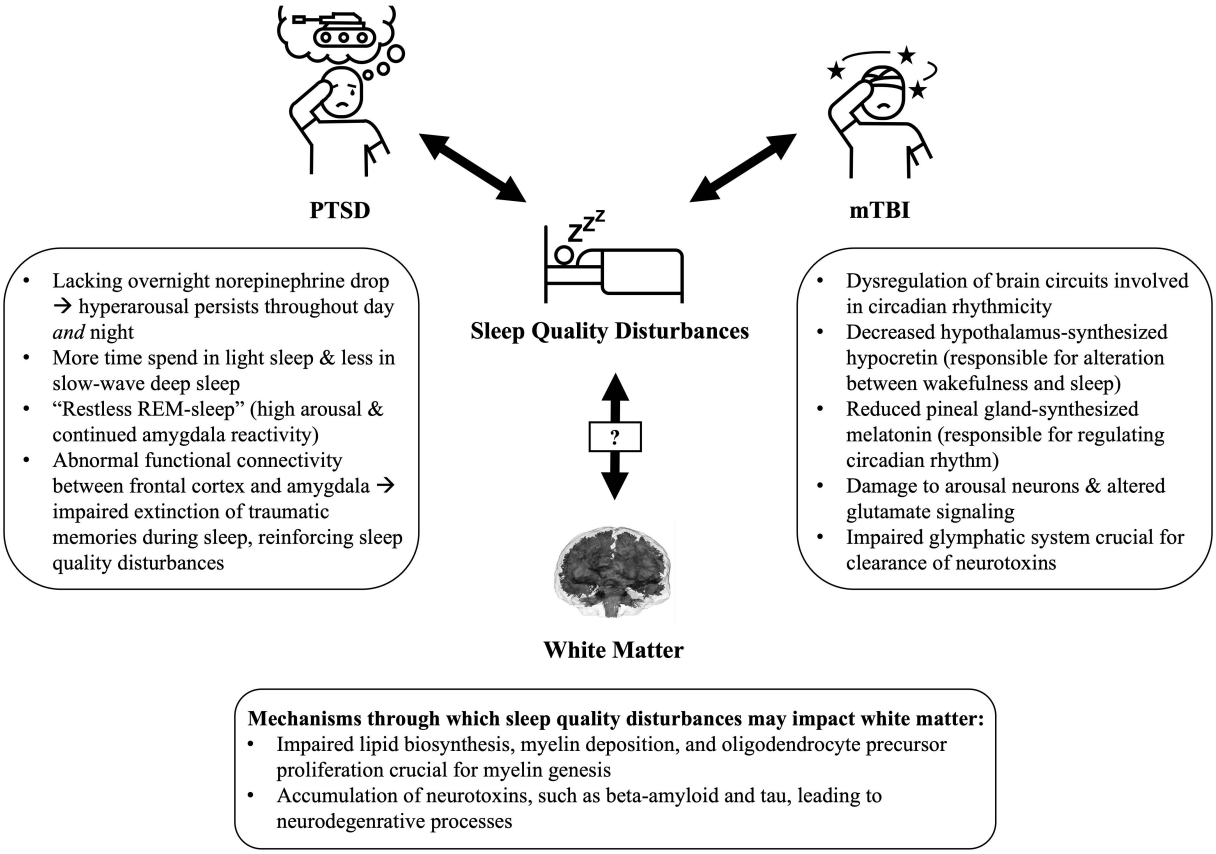

Figure 5. Pathophysiology of Sleep Quality Disturbances in Patients with PTSD and mTBI
Note. PTSD, Post-traumatic stress disorder, mTBI, Mild traumatic brain injury.
This figure outlines the emergence and maintenance of sleep quality disturbances in patients with PTSD and mTBI. Moreover, the potential impact of PTSD- and mTBI-related sleep quality disturbances on white matter microstructure is depicted.

5.2. Sleep Quality and White Matter Diffusion

As outlined above, several dMRI studies revealed microstructural alterations in major fiber tracts and global cortical white matter in patients with PTSD [41,51–53,182,183], mTBI [59–63,65,325,328,419], and comorbid PTSD+mTBI [27–30]. Moreover, a few studies have revealed an association between sleep quality disturbances and alterations in the white matter of patients with PTSD [208], mTBI [66,67], and otherwise healthy individuals [68–77,420]. A significant association between the hyperarousal symptoms of PTSD, poor sleep quality, and reduced FA in the right uncinate fasciculus has been shown [208]. The findings confirm the hypothesized dysregulation of noradrenergic activity in patients with PTSD [19,209,210], leading to impaired fronto-limbic connectivity [211,212]. Moreover, mTBI patients exhibit reduced integrity of the parahippocampal gyri [66], alterations in the internal capsule, corona radiata, fornix and superior fronto-occipital

fasciculus in association with poor sleep quality [67]. The observed low FA in frontal and temporal lobe regions may be responsible for the disturbances in complex cognitive processes, such as attention and memory, commonly associated with sleep quality disturbances [421]. More specifically, it has been suggested that sleep-related reductions in structural connectivity between frontal and temporal regions may impair information processing [77]. In addition, various studies in otherwise healthy individuals [68–77,420] showed both local and widespread alterations of white matter microstructure in association with poor sleep quality, such as lower overall FA and higher MD in frontal, temporal, parietal, and occipital regions [69].

Some studies suggested a link between poor sleep quality and disturbed synchronized neuronal activity, particularly reflected in impaired fronto-subcortical structural pathways [72,73,391,422]. However, across available studies, most of the major white matter tracts were affected by poor sleep quality [68,70–72,75,420,423], thus pointing against region- or pathway-specific patterns of sleep quality disturbances. Rather, disturbed sleep appears to have widespread effects on the brain. Supporting this, it has previously been suggested that region-specific impairments in brain structure associated with poor sleep quality may further affect other connected areas, resulting in widespread pathology [70,424].

While previous research indicates a strong association between sleep quality and white matter health, to date, only very few studies investigated the relationship between PTSD, mTBI, sleep quality and white matter microstructure. These studies commonly failed to assess white matter fiber tracts of the entire brain. Moreover, while sleep quality disturbances have usually been investigated in relation to either PTSD or mTBI individually, the underlying connection between both diagnoses has rarely been explored. This is surprising, given that white matter fiber tracts constitute major connections across various brain networks that affect clinical functioning [38–40] and are commonly impacted in patients with PTSD and mTBI [27–30]. Advanced insights on the association between structural brain health and sleep quality are needed to establish targeted interventions and improve long-term outcomes.

6. Hypotheses

As outlined above, the interplay of social, economic, environmental, genetic, and neurophysiological factors leads to altered brain morphology and function that contribute to the emergence and maintenance of PTSD, mTBI, and associated sleep quality disturbances. Particularly, the brain's white matter anatomy that connects different brain regions is of major importance for optimal brain network functioning and shows abnormalities in association with sleep quality disturbances. However, the complex interactions between PTSD, mTBI, poor sleep quality, and white matter microstructure are largely unknown.

The current work focuses on elucidating the relationship between PTSD, mTBI, sleep quality, and white matter microstructure, leveraging a large and unique sample comprised of veterans returning from deployment to Iraq and Afghanistan ($N = 180$). Self-reported sleep quality is investigated in veterans with PTSD, mTBI, and comorbid PTSD+mTBI. DMRI is utilized to assess the associations between sleep quality and white matter microstructure. Veterans with PTSD, mTBI, or comorbid PTSD+mTBI are hypothesized to experience poorer sleep quality than veterans without a history of PTSD or mTBI [26]. Based on previous studies that suggest a critical role of sleep for white matter microstructure [68,70–72,75,420,423], it is further hypothesized that poorer sleep quality is related to global white matter microstructure abnormalities [68,70–72,75,420,423]. Subsequently, the relationship between PTSD symptom severity, mTBI burden, sleep quality and white matter microstructure will be explored, given that sleep quality disturbances are the hallmark of PTSD [19,20], mTBI may exacerbate PTSD symptomatology [12–16], cumulative mTBIs may increase sleep quality disturbances [425], and PTSD [41,43–58,183], mTBI [59–65] and sleep quality disturbances [68–77,420] have individually been linked to white matter microstructural alterations.

I) Veterans with PTSD, mTBI, or comorbid PTSD+mTBI experience poorer sleep quality than veterans without a history of PTSD or mTBI.

II) Greater PTSD symptom severity and mTBI burden are associated with poorer sleep quality.

III) Poorer sleep quality is associated with abnormalities in white matter microstructure.

IV) There is an association between PTSD symptom severity, mTBI burden, sleep quality, and white matter microstructure.

7. Methods

7.1. Participants

Since 2016, the Translational Research Center for TBI and Stress Disorders (TRACTS) study [426] has been actively recruiting military service members in an effort to understand the consequences of deployment-related physical and psychological trauma (VA Rehabilitation Research and Development National Network Research Center for Traumatic Brain Injury Grant (B9254-C) to Regina E. McGlinchey). OEF and OIF veterans were recruited all over New England and the Boston area. Written informed consent was obtained from all study participants, and the VA Boston Healthcare System Institutional Review Board provided approval for the study protocols.

Out of the first 384 consecutively recruited veterans returning from deployment to Iraq and Afghanistan, 278 participants underwent an MRI assessment and provided consent for sharing their data with researchers of institutions cooperating with TRACTS. Out of these 278, 25 cases failed to persist the visual neuroimaging data quality control for reasons such as exceeding movement during scanning. Additionally, participants with a history of moderate or severe TBI (n = 9), neurological illness unrelated to TBI (n = 1), DSM-IV diagnosis of a cognitive, psychotic or bipolar disorder (n = 1), anoxia (n = 21), meningitis or encephalitis (n = 2), brain surgery (n = 2), exposure to neurotoxic chemicals (n = 9), missing clinical data (n = 10), female sex (n = 5), and participants who had not yet been deployed (n = 13) were excluded, resulting in a final sample of 180 participants. The above stated exclusion criteria were applied to rule out potentially confounding effects on brain structure. The participating veterans were classified into four groups based on lifetime diagnoses of PTSD and mTBI. The groups included veterans with PTSD (n = 38), veterans with mTBI (n = 25), veterans with comorbid PTSD+mTBI (n = 94), and veterans without a history of PTSD or mTBI (n = 23) (**Figure 6**). Lifetime diagnoses were chosen over current PTSD or mTBI diagnoses, since previous studies demonstrate a strong influence on gray matter and white matter structure when considering lifetime diagnoses [27,427], suggesting that neurobiological effects persist or even increase over time.

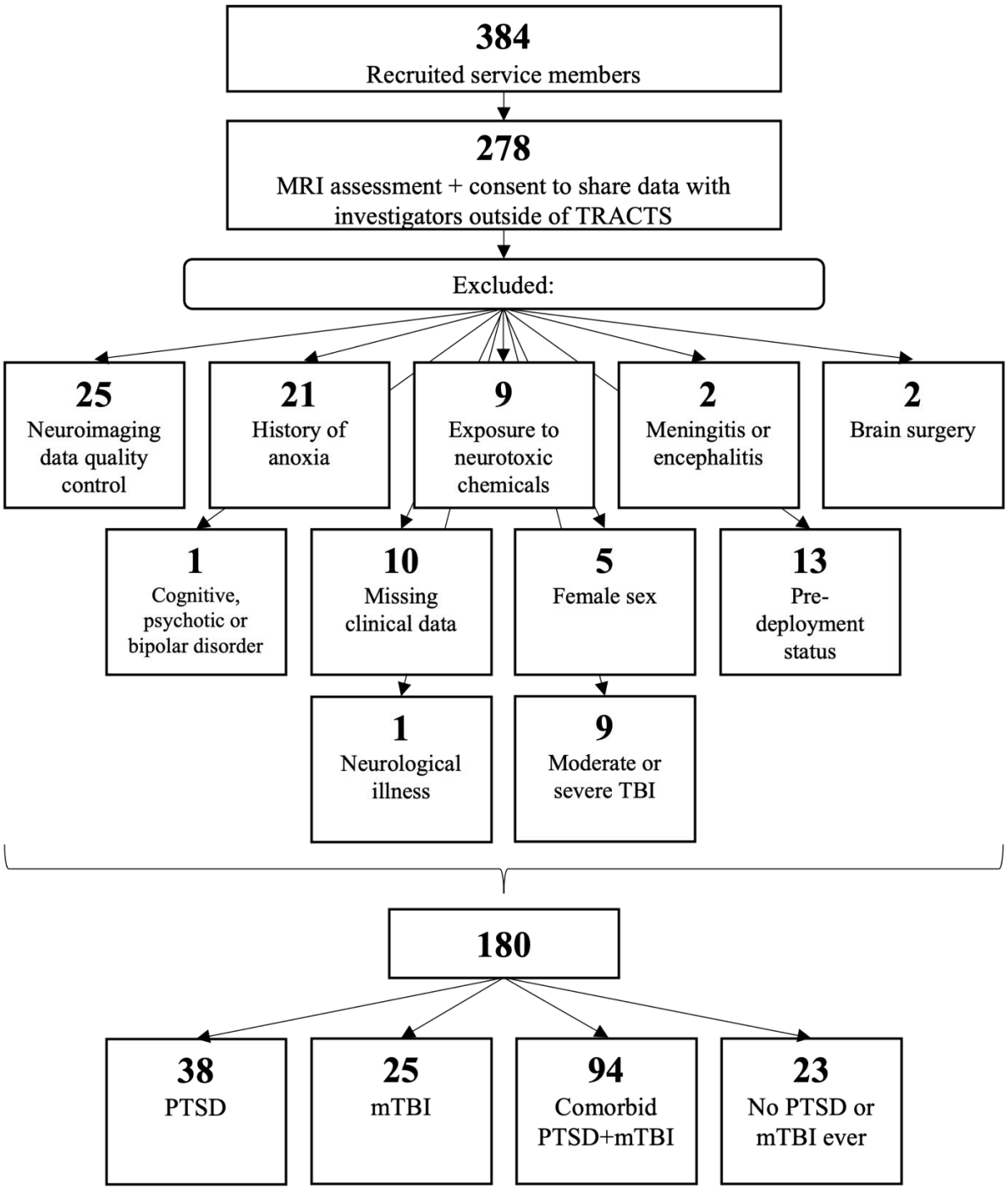

Figure 6. Excluded Participants and Final Sample Size
Note. MRI, Magnetic resonance imaging; TRACTS, Translational Research Center for TBI and Stress Disorders; PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury. This figure shows the number of excluded participants and the number of the total sample (N =180), and groups (PTSD, n = 38; mTBI, n = 25; PTSD+mTBI, n = 94; No history of PTSD or mTBI, n = 23).

7.2. Diagnostic and Clinical Assessment

7.2.1. Assessment of PTSD

Lifetime PTSD diagnosis and current symptom severity was assessed according to the 30-item Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) [428] by trained doctorate level psychologists. The CAPS-IV is a semi-structured interview that includes items that refer to re-experiencing, avoidance, arousal, emotional and cognitive symptoms of the traumatic event (e.g., B3: *"Have you ever suddenly acted or felt as if (EVENT) were happening again? Have you ever had flashbacks about (EVENT)? Tell me more about that."*). Frequency and intensity scores were rated on a scale from 0 = *absent* to 4 = *extreme/incapacitating* and summed into a total PTSD symptom severity score. To assess PTSD symptoms other than sleep quality, two items (i.e., difficulty sleeping, recurrent distressing dreams) were removed from the scale and a sleep-corrected PTSD total score was calculated, in line with prior work [428].

7.2.2. Assessment of mTBI

The Boston Assessment of TBI-Lifetime (BAT-L) [429] was administered to assess mTBI history and to rate the accumulative lifetime mTBI burden. The BAT-L is a semi-structured interview that assesses a history of head injuries across the lifespan, with a particular focus on military TBI. It is sensitive to identifying approximations for altered mental status, post-traumatic amnesia, and loss of consciousness, with a special focus on blast-related injuries that are commonly sustained in the military population. Moreover, the BAT-L is able to differentiate between physiological and psychological symptoms of head trauma [429] and distinguishes between mild, moderate, and severe TBIs. Mild TBI is classified into stages 1-3, where a higher stage refers to a greater mTBI severity. A total mTBI burden score was computed from the number and severity of all mTBIs pre-, during, and post-deployment. Pre-deployment mTBIs included mTBIs before enlistment. MTBIs during deployment referred to all deployments if deployed multiple times.

In the current sample, comorbidity with mTBI was highly prevalent for all psychiatric diagnoses (i.e., PTSD, mood, anxiety, and substance use disorder) (**Figure 7**).

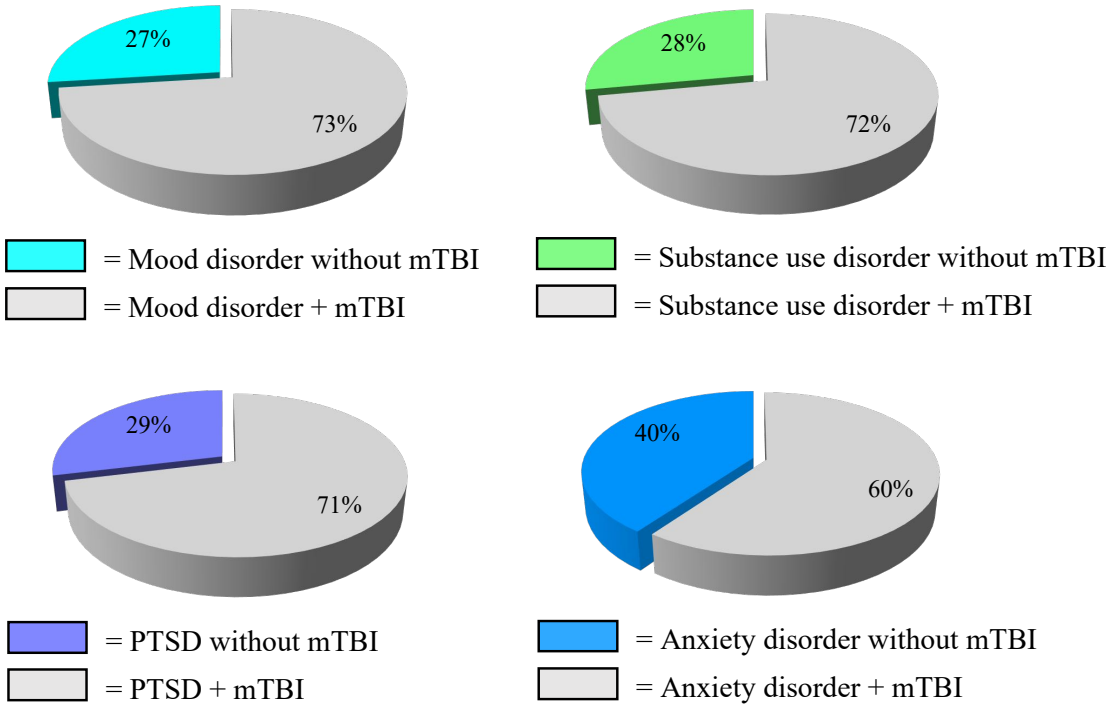

Figure 7. Proportion of mTBI in Psychiatric Diagnoses
Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury.
This figure illustrates the proportion of PTSD, substance use, mood, and anxiety disorder in patients with and without additional mTBI.

7.2.3. Assessment of Sleep Quality

Current sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI) [430], an 18-item self-report questionnaire measuring subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction on seven subscales (**Figure 8**). The PSQI includes a variation between open questions (e.g., *"During the past month, how long (in minutes) has it usually taken you to fall asleep each night?"*), and items that are scored on a 4-point scale, e.g., ranging from 0 = *very good* to 3 = *very bad* (e.g., *"During the past month, how would you rate your sleep quality overall?"*). A previously validated approach suggests that the seven subscales of the PSQI are most adequately characterized by three factors: *sleep efficiency, perceived sleep quality,* and *daily disturbances* [431]. As displayed in **Figure 8,** *sleep efficiency* includes "sleep duration" and "habitual sleep efficiency". *Perceived sleep quality* includes "subjective sleep quality", "sleep latency", and "use of sleep medication". *Daily disturbances* encompasses "sleep disturbances" and "daytime dysfunction". Higher scores on the total scale and all sub-scales refer to lower sleep quality.

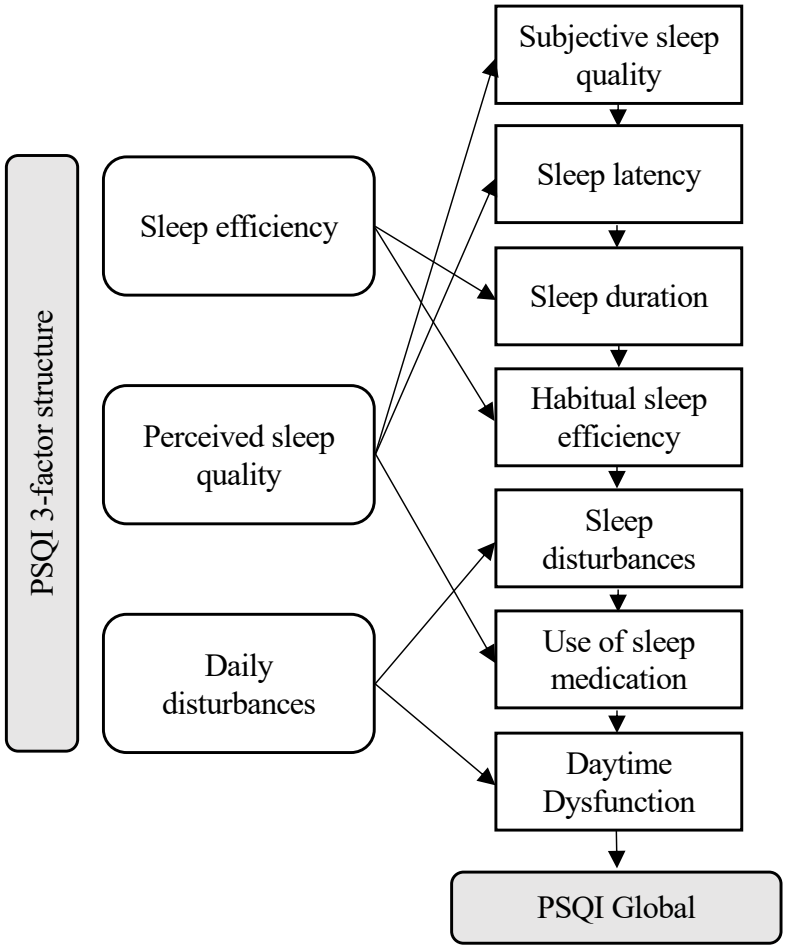

Figure 8. Assessment of Sleep Quality
Note. PSQI, Pittsburgh Sleep Quality Index [430]; PSQI 3-factor structure, The PSQI subscales sleep efficiency, perceived sleep quality and daily disturbances refer to the Pittsburgh Sleep Quality Index 3-Factor Structure [431].
Figure adapted from [431].

7.2.4. Assessment of Comorbid Psychiatric Disorders

The non-patient research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP) [432] (module D: mood disorders; module E: substance use disorders; module F: anxiety disorders) was employed to diagnose comorbid lifetime psychiatric disorders. The SCID-I/NP is a semi-structured clinical interview that was administered by trained doctorate level psychologists. As displayed in **Figure 9**, many veterans presented with psychiatric comorbidities.

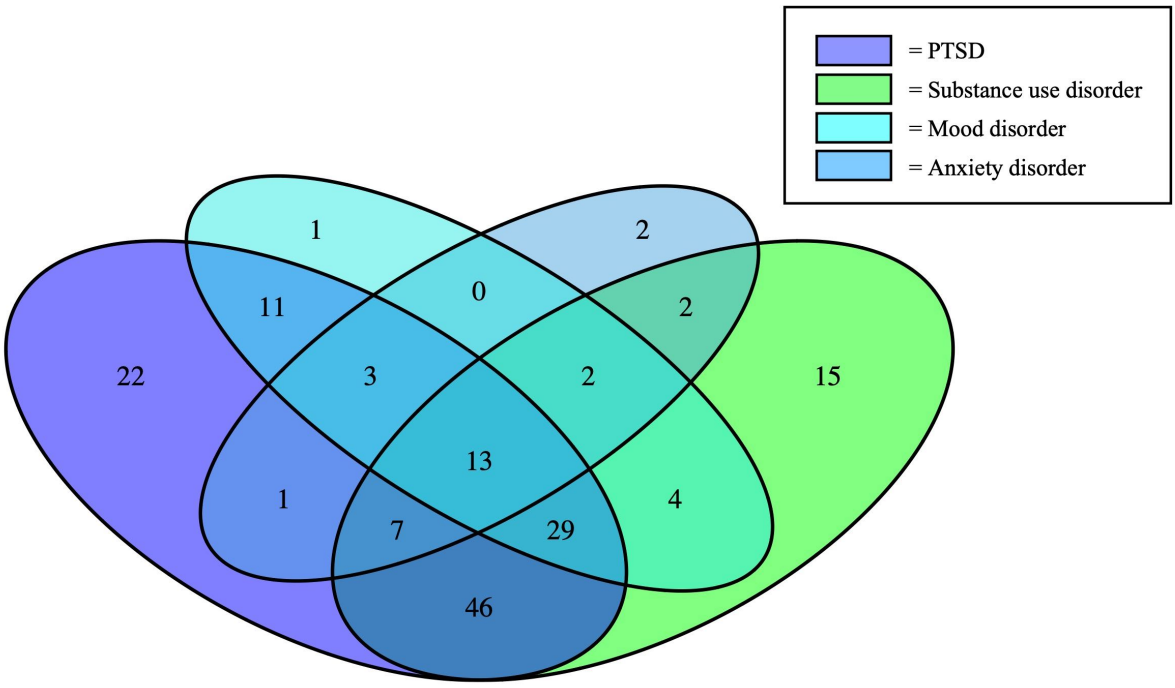

Figure 9. Overlap of Psychiatric Diagnoses
Note. Total sample *N* = 180; PTSD, Post-traumatic stress disorder.

7.2.5. Assessment of Warzone Stress

Warzone-related stress was assessed with the combat experiences and post-battle experiences sub-scales of the Deployment Risk & Resilience Inventory-II (DRRI-II) [433]. The DRRI subscales (DRRI-Combat and DRRI-Other) consist of 16 questions concerning combat or warzone-related events (e.g., DRRI-Combat: *"I personally witnessed someone from my unit or an ally being seriously wounded or killed"*, DRRI-Other: *"I saw civilians after they had been severely wounded or disfigured"*). The DRRI-Combat subscale uses a 5-point scale (0 = *never* to 4 = *daily or almost daily*). The DRRI-Aftermath subscale uses a binary response format (0 = *no* and 1 = *yes*).

7.3. Magnetic Resonance Imaging

7.3.1. Image Acquisition

DMRI data was acquired on a 3-Tesla Siemens TIM Trio scanner (Siemens Healthineers, Erlangen, Germany) at the VA Medical Center in Boston using a single-shot echo-planar sequence with a twice-refocused spin-echo pulse. The following sequence parameters were applied: 64 axial slices with no inter-slice gap, 60 gradient directions with a

b-value of 700 s/mm² and 10 additional scans with $b = 0$ gradients, TR = 10.000 ms, TE = 103 ms, voxel size = 2x2x2 mm^3, FOV = 256 mm^2.

7.3.2. Image Pre-processing

The dMRI data was processed in several steps by employing the image processing pipeline of the Psychiatry Neuroimaging Laboratory (PNL), Brigham and Women's Hospital, Harvard Medical School, USA (https://github.com/pnlbwh/pnlutil/blob/master/pipeline/README.md). First, the images were axis-aligned and centered to a standard position on the x-y-z axis, as well as motion- and eddy current-corrected by registering all gradient volumes to an undistorted $b = 0$ volume with an affine registration (FLIRT) utilizing the FMRIB Software Library (version 5.1, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [434,435]. Image quality was visually checked for artifacts using 3D Slicer (version 4.5, http://www.slicer.org) [436], resulting in the exclusion of 25 participants (e.g., due to severe motion artifact or signal drop). Artifacts are fairly common and can be a result of faulty scanner hardware or patient motion during MRI acquisition [437]. SlicerDMRI [438,439] was employed to create diffusion masks covering the entire brain. Each brain slice was inspected visually in the axial, sagittal, and coronal view and brain masks were manually corrected where necessary. In case the automatically created brain mask failed to cover the entire brain, the mask was manually expanded. In case the skull was mistakenly registered as brain tissue, the mask was narrowed to fit only the brain. Manual correction of brain masks is important to ensure an accurate registration of brain images and to ensure optimal quality of further processing steps.

7.3.3. White Matter Fiber Clustering

As outlined earlier, dMRI offers a non-invasive visualization of white matter fiber tracts in the living brain [184]. A visualization of the white matter microstructure can provide extensive information on brain disease, such as traumatic axonal injury, and may lead to an understanding of abnormal behavioral and cognitive processes [130]. White fiber clustering was conducted by utilizing an openly accessible pipeline, *whitematteranalysis software* (https://github.com/SlicerDMRI/whitematteranalysis), to automatically perform fiber tract parcellation and extraction (**Figure 10**) [81]. White matter fiber tracts were identified for each subject using the White Matter Analysis (WMA) package for tract parcellation. WMA is based on a neuroanatomist-curated white matter atlas and applies machine learning to identify fiber tracts in an individual [78–80]. The white matter fiber clustering approach is capable of extracting

fiber tracts from the entire brain by organizing fiber tracts according to anatomical similarity and location in the brain.

First, a two-tensor whole-brain unscented Kalman Filter (UKF) tractography was conducted (https://github.com/pnlbwh/ukftractography) [440,441]. A two-tensor model was chosen to accommodate for crossing fibers [442,443]. The first tensor is associated with primary fiber tract direction, while the second tensor represents crossing fibers. Qualitative and quantitative quality checks were performed using the *whitematteranalysis software* quality control tool (https://github.com/SlicerDMRI/whitematteranalysis) to ensure correctness of fiber tract anatomy and that the tractography was stored in the same spatial coordinate system as the atlas tractography data. Compared to single single-tensor tractography, the UKF approach is more sensitive [444–446] and exhibits greater consistency [78]. Specifically, UKF tractography has a high ability to identify target fiber tracts correctly, even in the presence of crossing fibers [445,447]. The sensitivity to crossing fibers has both benefits and drawbacks. Increased sensitivity can aid in the detection of more putative true positive fibers while also increasing false positive tracking, which may affect white matter parcellation reproducibility. The subsequently employed white matter fiber clustering can reduce this issue by including a data-driven outlier elimination procedure and utilizing a neuroanatomist-curated atlas of fiber tracts.

This neuroanatomist-curated white matter atlas was trained on 100 healthy community subjects as input data [448]. A joint alignment of the tractography of all atlas subjects was conducted. Based on the joint atlas input tractography, white matter fiber tracts were extracted and used as a reference to identify fiber tracts in the TRACTS study subjects [78–80]. First, each TRACTS subject's tractography was registered into the atlas space. The similarity between the fibers in the atlas and the fibers of the individual TRACTS participants was quantified and used to categorize the fibers into clusters, allotting them to the corresponding tract in the atlas (**Figure 10**). A neuroanatomist identified probable false positive clusters in the atlas (i.e., fibers that were obviously deviating from known anatomical trajectories). As outlined above, this approach enabled to substantially reduce false-positive tracking, which is a common problem with tractography [449]. In further processing and display processes, false positive clusters were excluded and provided a reliable and highly accurate identification of fiber tracts [78]. Thus, it was ensured that the tractography and tract identifications were executed consistently and in the same manner across all subjects. The white matter fiber clustering method has successfully been applied in several studies [450–452], has a high test-retest reproducibility [453], and is robust to individual variation in brain anatomy [454]. By extracting an increased amount of fiber tracts from the entire brain, this approach outperformed previous automated fiber tracking methods, which

were restricted to extracting only major fiber tracts, missing to include all of the brain's white matter [78].

As highlighted in the introduction, a widespread effect of sleep quality on white matter microstructure was expected [68,70–72,77]. Therefore, the entire brain's fiber tracts were merged into one whole-brain white matter variable (**Figure 10**). Additionally, the major white matter fiber tracts (i.e., left/right arcuate fasciculus, cingulum bundle, inferior longitudinal fasciculus, inferior occipito-frontal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and corpus callosum) were extracted. A description of anatomical location, main functions, and associations with sleep quality of the major white matter fiber tracts can be found in **Table 3**. A visualization of the fiber tracts is displayed in **Figure 11**.

7.3.4. Diffusion Parameter Extraction

Free-water (FW) imaging was employed to obtain whole-brain voxel-wise free-water corrected fractional anisotropy (FA_T) values of whole-brain and major fiber tract white matter (i.e., left/right arcuate fasciculus, cingulum bundle, inferior longitudinal fasciculus, inferior occipito-frontal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and corpus callosum). As described earlier, using FW imaging, the MRI signal is divided into two compartments, and is therefore able to eliminate partial volume effects of extracellular FW (e.g., caused by CSF contamination, edema, or atrophy) [198]. The first compartment is the isotropic FW compartment accounting for the relative contribution of extracellular FW in each voxel. The second represents each voxel's tissue compartment from which the FW-corrected fractional anisotropy (FA_{Tissue}, FA_T) can be calculated. Given the correction for FW, FA_T serves as a more precise indicator for cellular WM architecture than the conventional FA measure [199]. Aberrant myelination, degeneration, or atrophy processes can be more accurately depicted when correcting for adjacent FW [199]. This is a significant improvement compared to earlier dMRI analyses of white matter microstructure in relation to PTSD, mTBI, and sleep quality, which largely relied on conventional FA measures.

The streamline quantity in each tract was assessed to ensure that there were no participants with outlier values. Similarly, FA_T-values were inspected for outliers. Moreover, all white matter tracts were subjected to a visual quality assessment to validate anatomical accuracy. The described quality check procedures are in line with best practices employed most recently [455–460]. All data passed the quality checks.

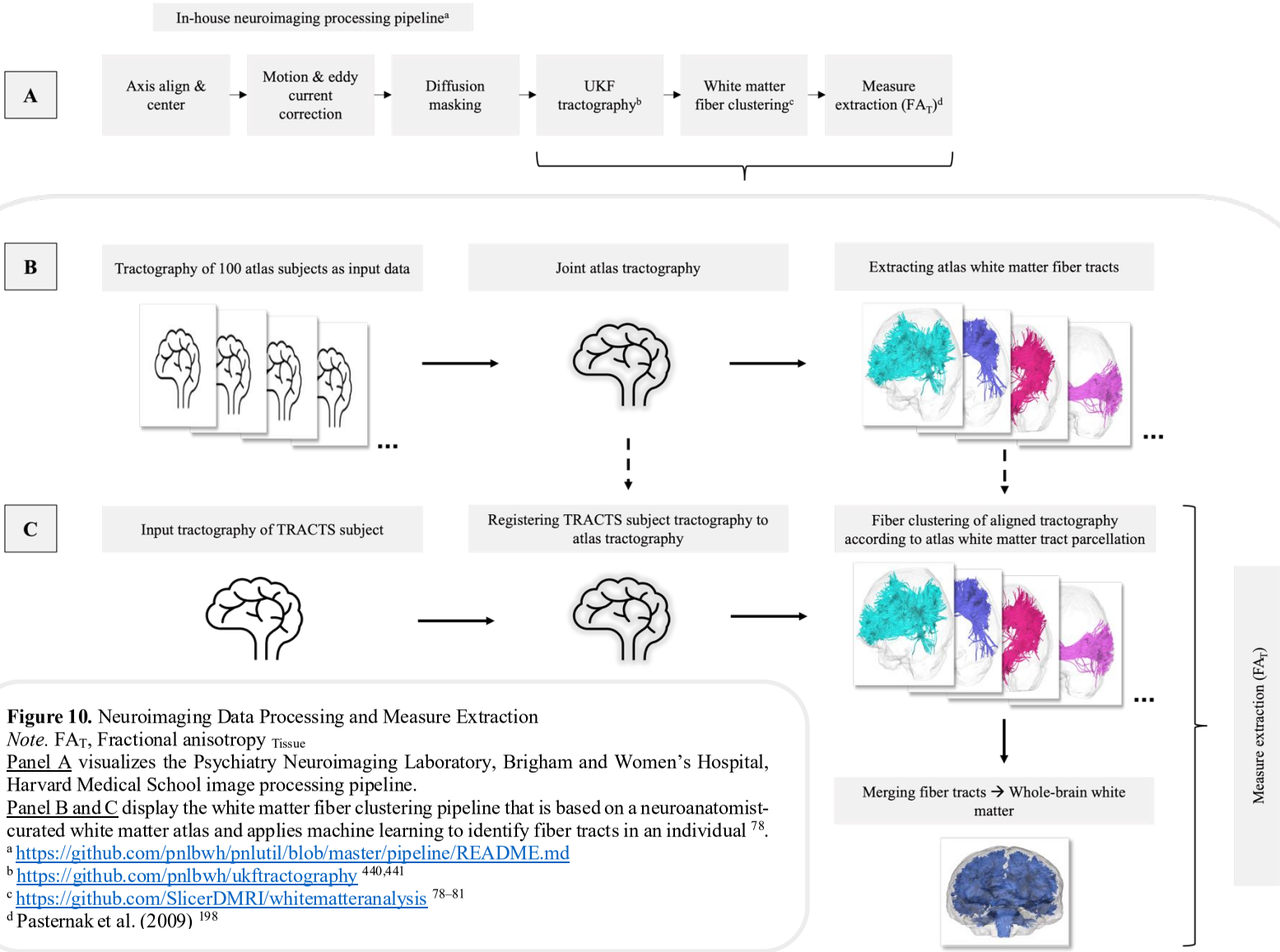

Figure 10. Neuroimaging Data Processing and Measure Extraction

Note. FA_T, Fractional anisotropy $_{Tissue}$

Panel A visualizes the Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School image processing pipeline.

Panel B and C display the white matter fiber clustering pipeline that is based on a neuroanatomist-curated white matter atlas and applies machine learning to identify fiber tracts in an individual [78].

[a] https://github.com/pnlbwh/pnlutil/blob/master/pipeline/README.md

[b] https://github.com/pnlbwh/ukftractography [440,441]

[c] https://github.com/SlicerDMRI/whitematteranalysis [78–81]

[d] Pasternak et al. (2009) [198]

Table 3. Major White Matter Fiber Tracts

White Matter Fiber Tract	Location and Function
Arcuate fasciculus	The arcuate fasciculus connects the peri-sylvian cortex with frontal, parietal, and temporal regions. The left arcuate fasciculus is primarily known for its function in language, while the right arcuate fasciculus is involved in visuospatial processing [461,462]. The arcuate fasciculus has been found to be impacted in patients with self-reported insomnia [75].
Cingulum bundle	The cingulum bundle extends from the orbitofrontal cortices to the temporal pole along the dorsal corpus callosum. It is a major part of the limbic system and responsible for communication between limbic regions [463,464]. Accordingly, the cingulum bundle has been primarily linked to emotional processes, but also to executive control, pain, and memory [463]. The cingulum bundle has been associated with the re-experiencing symptoms of PTSD [465]. Therefore, nightmares (which are considered uncontrolled re-enactments of the traumatic event [372,466]), may similarly be associated with cingulum bundle structure. Reductions in cingulum bundle FA have been associated with overall poor sleep quality [68]. Moreover, an association between better sleep efficiency and lower cingulum bundle MD has been shown [76].
Inferior longitudinal fasciculus	The inferior longitudinal fasciculus links occipital regions with anterior temporal structures [467], and is essential for visual perception, face processing, language, and memory [467,468]. Insomnia has been correlated with lower inferior longitudinal fasciculus MD [420]. Moreover, there are indications of an association between REM sleep behavior disorder (a parasomnia characterized by acting out with abnormal motor behavior and vocalization while dreaming [469]) and reduced inferior longitudinal fasciculus integrity [470].
Inferior occipito-frontal fasciculus	The inferior occipito-frontal fasciculus is a ventral association fiber tract that links the ventral occipital lobe with the orbitofrontal cortex [462]. The inferior occipito-frontal

	fasciculus runs in parallel to the corpus callosum, and in parallel to the inferior longitudinal fasciculus in the occipital lobe [462,471]. The functions of the inferior occipito-frontal fasciculus are not yet entirely understood [462], however, there is evidence of its involvement in language processing, visual perception, and goal-driven behavior [472]. An association between insomnia and lower inferior occipito-frontal fasciculus MD has been shown [420], as well as a link between impaired inferior occipito-frontal fasciculus integrity and obstructive sleep apnea [473], a sleep-related breathing disorder marked by repetitive episodes of upper airway collapse [474]. In fact, obstructive sleep apnea is common among veterans with PTSD and mTBI [475,476], where the repeated episodes of hypoxia may damage the white matter [477–479].
Superior longitudinal fasciculus	The superior longitudinal fasciculus is a major cortical white matter structure (differentiated into three parts) that links the frontal cortex with the superior parietal lobe (superior longitudinal fasciculus I), angular gyrus (superior longitudinal fasciculus II), and supramarginal gyrus (superior longitudinal fasciculus III) [480]. The superior longitudinal fasciculus has been found to be primarily responsible for cognitive processes, including processing speed, executive functioning, and attention [481–485]. There is evidence that the superior longitudinal fasciculus is impacted by poor sleep quality [71], and insomnia specifically [73,75,420].
Uncinate fasciculus	The uncinate fasciculus links the orbitofrontal cortex with the temporal pole [486] and belongs to the limbic system [462,487]. The uncinate fasciculus plays a role in emotion, memory, and language [487–489]. It has been suggested that uncinate fasciculus myelination may be negatively affected by poor sleep quality [490,491]. Supporting this, veterans showed an association between poor

	sleep, reduced uncinate fasciculus FA and increased hyperarousal [208]. Moreover, patients with obstructive sleep apnea similarly exhibit decreased uncinate fasciculus FA [492].
Corpus callosum	The corpus callosum is the brain's largest white matter structure [493], a major commissural fiber tract bridging the left and the right hemisphere [494]. It is primarily responsible for signal transmission between both hemispheres, thereby engaging in sensory and motor processes [494], and integrating cognitive and social-emotional functions [493]. Poor sleep quality has been linked to reduced corpus callosum integrity [71,495,496]. Correspondingly, an association between insomnia and decreased corpus callosum FA [73] and decreased corpus callosum MD [420] has been shown.

Note. PTSD, Post-traumatic stress disorder; mTBI; Mild traumatic brain injury; REM, Rapid eye movement; FA, Fractional anisotropy, MD, Mean diffusivity.

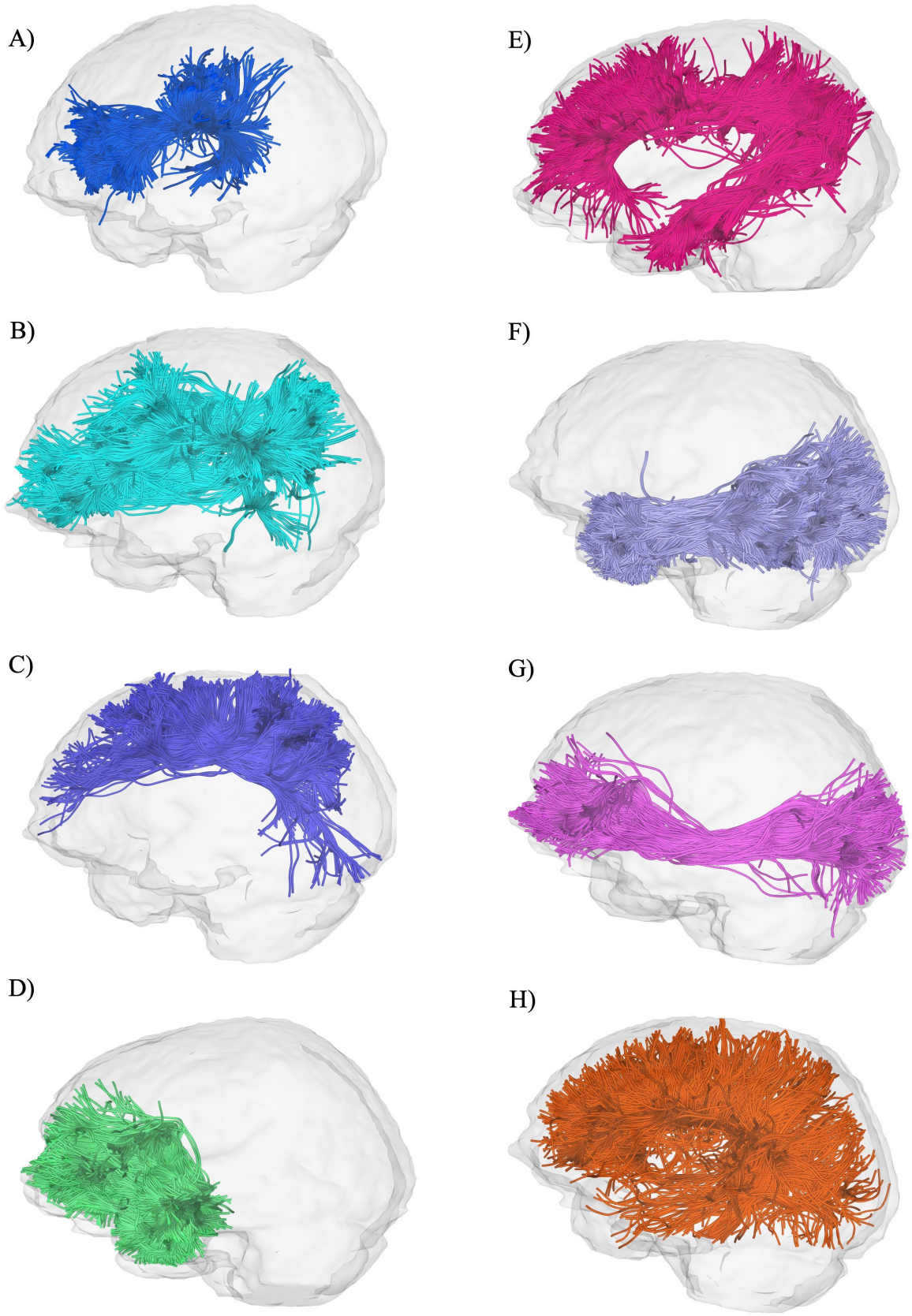

Figure 11. Major White Matter Fiber Tracts
Note. A) Superior longitudinal fasciculus I; B), Superior longitudinal fasciculus II; C) Superior longitudinal fasciculus III; D) Uncinate fasciculus; E) Cingulum bundle; F) Inferior longitudinal fasciculus; G) Inferior occipital frontal fasciculus; H) Corpus callosum.

7.4. Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 27 [497] and R 4.0.3 [498]. Figures were created using R 4.0.3 [498] and GraphPad Prism 9 [499]. A hierarchical statistical approach was applied, conducting all analyses in the total sample and if significant in the four groups (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI; **Figure 12**). All analyses included age as a covariate and were corrected for multiple comparisons, as detailed in **Figure 12**.

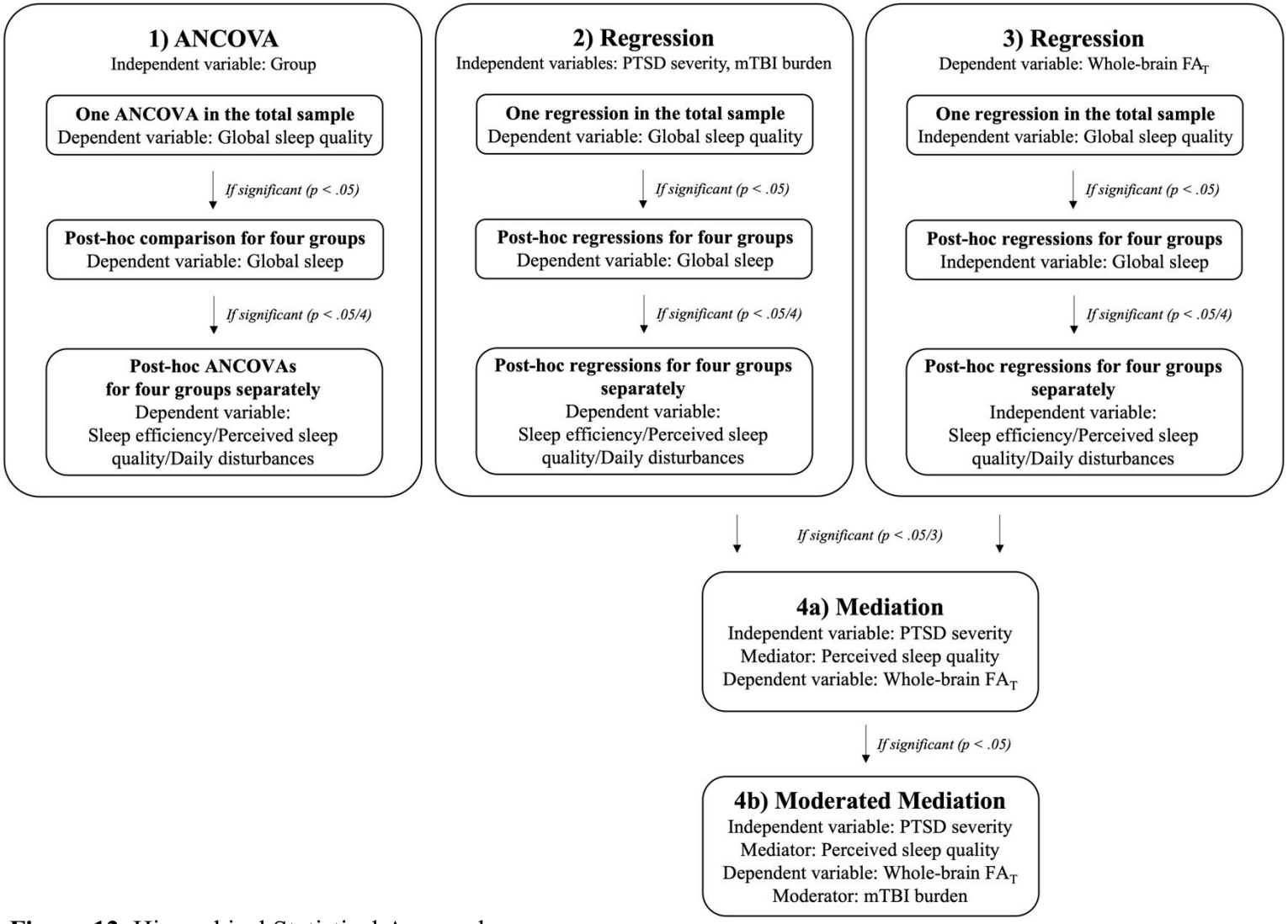

Figure 12. Hierarchical Statistical Approach

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; PSQI, Pittsburgh Sleep Quality Index [430]; FA_T, Fractional anisotropy $_{Tissue}$.

Hypothesis I)

Veterans with PTSD, mTBI, or comorbid PTSD+mTBI experience poorer sleep quality than veterans without a history of PTSD or mTBI.

In line with a previous publication [26], an analysis of covariance (ANCOVA) was conducted to depict differences in global sleep quality across the groups (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI). If the overall ANCOVA was significant ($p < .05$), post-hoc comparisons were performed for the four groups. If the group comparisons for global sleep quality were found significant ($p < .05/4$), post-hoc comparisons between the four groups for sleep efficiency, perceived sleep quality, and daily disturbances (PSQI 3-factor structure [431]) were conducted.

Hypothesis II)

Greater PTSD symptom severity and mTBI burden are associated with poorer sleep quality.

One regression analysis was performed in the total sample, including PTSD symptom severity and mTBI burden as the independent variables and global sleep quality as the dependent variable. In the case of significant associations between PTSD symptom severity, mTBI burden, and global sleep quality ($p < .05$), the regression analysis was repeated within the four groups separately (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI). If a regression model was found significant in one of the groups ($p < .05/4$), three additional regression analyses were conducted, including PTSD symptom severity/mTBI burden as the independent variable and sleep efficiency, perceived sleep quality, and daily disturbances as dependent variables, respectively.

Hypothesis III)

Poorer sleep quality is associated with abnormalities in white matter microstructure.

Next, a regression analysis was conducted in the total sample, including global sleep quality as the independent variable and whole-brain FA_T as the dependent variable. In the case of a significant association ($p < .05$), the regression analysis was repeated within each group (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI). In the case of a significant association between global sleep quality and whole-brain FA_T in a group ($p < .05/4$), additional regression analyses were performed to evaluate the relationship between sleep efficiency, perceived sleep quality, daily disturbances, and whole-brain FA_T in the respective group. Moreover, supplementary analyses were computed to assess the link between sleep quality and white matter microstructure of the major white matter fiber tracts (i.e., left/right

arcuate fasciculus, cingulum bundle, inferior longitudinal fasciculus, inferior occipito-frontal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and corpus callosum) to ensure impairments are widespread as opposed to region-specific, therefore justifying the whole-brain approach.

Hypothesis IV)

There is an association between PTSD symptom severity, mTBI burden, sleep quality, and white matter microstructure.

Given the significant associations between PTSD symptom severity and perceived sleep quality and between perceived sleep quality and white matter microstructure, a post-hoc mediation analysis was performed. It was investigated whether perceived sleep quality (mediator) mediates the association between PTSD symptoms (independent variable) and whole-brain FA_T (dependent variable). The mediation model was calculated using Hayes PROCESS macro [500] for SPSS (model 4), which follows a nonparametric bootstrapping procedure based on n = 5,000 samples and a 95% CI. PROCESS is a tool for mediation and moderation analyses based on the principals of ordinary least squares regression [500]. Direct and indirect effects are estimated in advanced models with single or multiple mediators and/or moderators. PROCESS is suitable for testing mechanisms and contingencies of effects [500]. Mediation and moderation analyses can provide a broader understanding of the impact a variable X has on Y. X may interact with another variable M to impact Y, or a relationship between X and Y may be explained by M entirely [501].

In an additional analysis, lifetime mTBI burden was included as a moderator variable in the above-described mediation model (Hayes PROCESS [500] model 58). Greater lifetime mTBI burden was expected to influence the association between PTSD symptom severity, sleep quality, and whole-brain FA_T. The continuous lifetime mTBI burden score was chosen to be included in the model to account for variations of mTBI severity and symptom burden.

Finally, the mediation and moderation analyses were repeated while controlling for comorbid psychiatric diagnoses (lifetime mood, anxiety, and substance use disorder, **Figure 9**), warzone-related stress, body mass index (BMI), psychiatric medication use (**Figure 13**), race (white, non-white), and completed years of education to ensure that these factors do not confound the primary results. Mood [502–506], anxiety [507–509], and substance use disorders [510,511], warzone-related stress [512–515], BMI [516–521], psychiatric medication use [522–527], race (i.e., racial discrimination) [528], and education [478,529] have repeatedly been associated with alterations in brain structure.

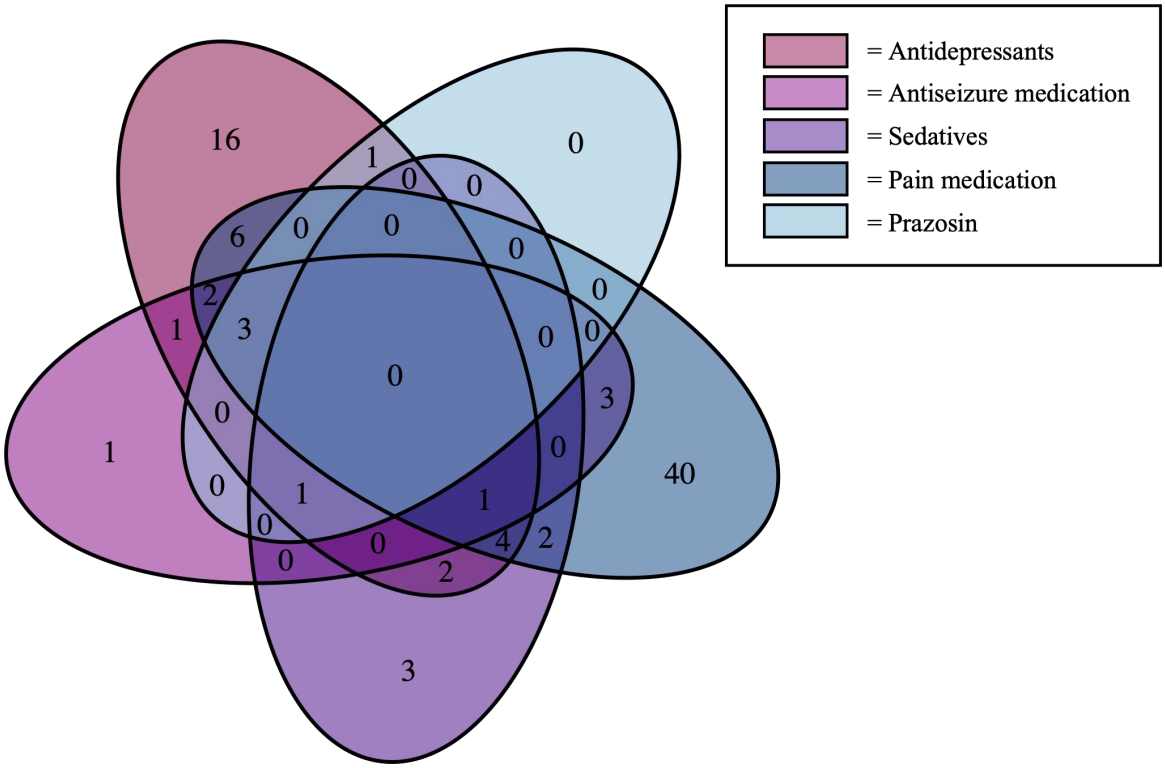

Figure 13. Overlap of Psychiatric Medications
Note. This figure pictures the overlap of psychiatric medication use in the total sample (N = 180).

8. Results

This section contains the results to each hypothesis. A summarizing figure of the results is displayed at the end of this section (**Figure 19**).

Demographic information is displayed in **Table 4** and **5**. The groups (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI) did not differ in age, the number of deployments, and the total duration of deployments. Veterans with comorbid PTSD+mTBI were the most severely clinically burdened group, as indicated by the high number of comorbid psychiatric diagnoses, psychiatric medication use, and the highest rates of mTBI in this group. In fact, veterans with comorbid PTSD+mTBI compared to veterans with mTBI only had higher incidences of military, and military blast-related mTBI. Substance use disorder was significantly more prevalent among veterans with comorbid PTSD+mTBI compared to veterans with mTBI only or no history of PTSD or mTBI. Similarly, more veterans with comorbid PTSD+mTBI were diagnosed with a mood disorder than veterans with mTBI only or no history of PTSD or mTBI. Moreover, mood disorders were more prevalent among veterans with PTSD only compared to veterans without a history of PTSD or mTBI. Importantly, veterans with comorbid PTSD+mTBI showed greater PTSD symptom severity than veterans with PTSD only.

Table 4. Sample Characteristics

		Total sample			PTSD			mTBI			Comorbid PTSD+mTBI			No history of PTSD or mTBI		
		N	mean±SD	range	*n*	mean±SD	range	*n*	mean±SD	range	*n*	mean±SD	range	*n*	mean±SD	range
Age (years)		180	31.49±7.60	20-55	38	31.18±6.79	22-48	25	32.60±9.82	21-55	94	31.22±7.18	20-53	23	31.87±8.24	23-53
Education (years)		180	13.89±1.96	12-20	38	13.34±1.60	12-17	25	14.36±1.78	12-18	94	13.84±2.03	12-20	23	14.48±2.19	12-19
Number of OEF/OIF deployments		180	1.40±.69	1-5	38	1.39±.79	1-4	25	1.40±.65	1-3	94	1.41±.71	1-5	23	1.35±4.87	1-2
Number of other stressful deployments		180	.39±.77	0-5	38	.37±.63	0-3	25	.24±.44	0-3	94	.49±.89	0-5	23	.22±.52	0-2
Total duration of OEF/OIF deployments (months)		180	13.64±8.37	3-53	38	13.84±9.75	5-53	25	14.72±7.89	3-31	94	13.49±8.36	3-52	23	13.87±6.81	4-28
Total duration of other deployments (months)		180	2.84±6.21	0-49	38	3.03±5.22	0-17	25	1.36±3.87	0-16	94	3.41±7.24	0-49	23	1.83±4.93	0-18
Number of lifetime mTBIs		180	1.39±2.18	0-18	38	.00±.00	0-0	25	1.56±.96	1-5	94	2.24±2.62	1-18	23	.00±.00	0-0
Lifetime mTBI burden		180	2.22±3.42	0-31	38	.00±.00	0-0	25	2.40±1.47	1-6	94	3.61±4.10	1-31	23	.00±.00	0-0
Total CAPS		180	45.84±27.14	0-104	38	39.79±21.15	6-88	25	15.84±13.73	0-41	94	51.80±18.65	2-92	23	12.65±10.60	0-39
PSQI Global		178	8.97±4.46	0-20	38	8.71±4.43	0-20	25	6.68±3.61	1-18	92	10.49±4.23	2-18	23	5.78±3.48	0-14
PSQI 3-factor structure	Sleep efficiency	179	1.23±.99	0-3	38	1.13±.98	0-3	25	.86±.99	0-3	93	1.46±.94	0-3	23	.89±1.07	0-3
	Perceived sleep quality	180	1.31±.80	0-3	38	1.30±.73	0-3	25	.99±.64	0-2.67	94	1.54±.82	0-3	23	.72±.52	0-2
	Daily disturbances	179	1.32±.62	0-3	38	1.28±.59	0-2.5	25	1.00±.48	0-2	93	1.53±.61	0-3	23	.91±.47	0-2
					n	**%***		***n***	**%***		***n***	**%***		***n***	**%***	
Ethnicity	American Indian or Alaska Native	1	.56		0	.00		0	.00		1	1.06		0	.00	
	Asian	2	1.11		1	2.63		0	.00		1	1.06		0	.00	
	Black	13	7.22		4	10.53		3	12.00		6	6.38		0	.00	
	Hispanic or Latino	26	14.44		6	15.79		5	20.00		13	13.83		2	8.70	
	Native Hawaiian or Pacific Islander	0	.00		0	.00		0	.00		0	.00		0	.00	
	White	138	76.67		26	68.42		17	68.00		74	78.72		21	91.30	
	Unknown	1	.56		1	2.63		0	.00		0	.00		0	.00	
Service branch	Army	33	18.33		4	10.53		6	24.00		21	22.34		2	8.70	
	Army National Guard	62	34.44		15	39.47		10	40.00		26	27.66		11	47.83	
	Air Force	9	5.00		1	2.63		2	8.00		5	5.32		1	4.35	
	Air Force National Guard	7	3.89		2	5.26		1	4.00		3	3.19		1	4.35	
	Coast Guard	0	.00		0	.00		0	.00		0	.00		0	.00	
	Navy	7	3.89		1	2.63		1	4.00		5	5.32		0	.00	
	Marines	38	21.11		5	13.16		4	16.00		27	28.72		2	8.70	
	Reserves	25	13.89		10	26.32		2	8.00		9	9.57		4	17.39	
	National Guard, branch unknown	6	3.33		1	2.63		0	.00		3	3.19		2	8.70	
Psychiatric diagnoses	Lifetime PTSD	132	73.33		38	100.00		0	.00		94	100.00		0	.00	
	Lifetime substance use disorder	118	65.56		23	60.53		13	52.00		72	76.60		10	43.48	
	Lifetime mood disorder	63	35.00		14	36.84		4	16.00		42	44.68		3	13.04	
	Lifetime anxiety disorder	30	16.67		9	23.68		3	12.00		15	15.96		3	13.04	
Psychiatric medication use		86	47.77		16	42.11		12	48.00		55	58.51		3	13.04	
mTBI	Military mTBI	64	35.56		0	.00		7	28.00		57	60.64		0	.00	
	Blast mTBI	41	22.77		0	.00		1	4.00		40	42.55		0	.00	
	Lifetime mTBI	119	66.11		0	.00		25	100.00		94	100.00		0	.00	

Note. SD, Standard deviation; PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; CAPS, Clinician Administered PTSD Scale [530]; PSQI, Pittsburgh Sleep Quality Index [430]; PSQI 3-factor structure, The PSQI subscales sleep efficiency, perceived sleep quality & daily disturbances refer to the Pittsburgh Sleep Quality Index 3-Factor structure [431]. %* Percentage of total cases per group.

Table 5. Sample Characteristics: Group Comparisons

		PTSD vs. mTBI vs. Comorbid PTSD+mTBI vs. No history of PTSD or mTBI		Post-hoc **PTSD vs. mTBI**	Post-hoc **PTSD vs. Comorbid PTSD+mTBI**	Post-hoc **mTBI vs. Comorbid PTSD+mTBI**	Post-hoc **PTSD vs. No history of PTSD or mTBI**	Post-hoc **mTBI vs. No history of PTSD or mTBI**	Post-hoc **Comorbid PTSD+mTBI vs. No history of PTSD or mTBI**
		ANCOVA							
		F*(df), *p		***p***	***p***	***p***	***p***	***p***	***p***
Age (years)		.25(3, 176), .859		.473	.979	.425	.735	.741	.717
Education (years)		2.07(3, 175), .106		.058	.171	.311	**.029**	.761	.175
Number of OEF/OIF deployments		.09(3,175), .968		.920	.883	.809	.749	.839	.627
Number of other stressful deployments		1.59(3, 175), .195		.387	.404	.090	.390	.990	.097
Total duration of OEF/OIF deployments (months)		.03(3, 175), .995		.820	.819	.948	.946	.888	.911
Total duration of other deployments (months)		1.30(3, 175), .275		.205	.742	.084	.397	.720	.218
Number of lifetime mTBIs		16.51(3, 175), **<.001**		-	-	.123	-	-	-
Lifetime mTBI burden		17.47(3,175), **<.001**		-	-	.075	-	-	-
Total CAPS		47.40(3, 175), **<.001**		**<.001**	**.001**	**<.001**	**<.001**	.555	**<.001**
		F*(df), *p	η^2	***p****	***p****	***p****	***p****	***p****	***p****
PSQI Global		11.430(3, 173), **<.001**	.17	.055	.026	**<.001**	**.008**	.457	**<.001**
PSQI 3-factor structure	Sleep efficiency	4.16(3, 174), **.007**	.07	.259	.078	**.006**	.339	.894	**.012**
	Perceived sleep quality	9.20(3, 175), **<.001**	.14	.112	.091	**.001**	**.004**	.224	**<.001**
	Daily disturbances	10.66(3, 174), **<.001**	.16	.057	.025	**<.001**	.017	.618	**<.001**
		Chi-square or Fisher's exact test							
		χ^2**(df), *p***		***p***	***p***	***p***	***p***	***p***	***p***
Ethnicity	American Indian or Alaska Native	2.04(3), 1.000		-	1.000	1.000	-	-	1.000
	Asian	1.69(3), .729		1.000	.494	1.000	1.000	-	1.000
	Black	3.34(3), .318		1.000	.373	.395	.287	.235	.596
	Hispanic or Latino	1.36(3), .713		.741	.772	.530	.698	.419	.732
	Native Hawaiian or Pacific Islander	-		-	-	-	-	-	-
	White	5.71(3), .137		.972	.211	.261	**.039**	.075	.237
	Unknown	3.85(3), .478		1.000	.288	-	1.000	-	-
Service branch	Army	4.33(3), .226		.176	.117	.860	1.000	.249	.240
	Army National Guard	4.51(3), .212		.967	.184	.233	.523	.585	.062
	Air Force	1.15(3), .844		.557	.673	.637	1.000	1.000	1.000
	Air Force National Guard	.99(3), .938		1.000	.625	1.000	1.000	1.000	1.000
	Coast Guard	-		-	-	-	-	-	-
	Navy	1.06(3), .838		1.000	.673	1.000	1.000	1.000	.581
	Marines	6.69(3), .080		1.000	.059	.198	.700	.668	**.046**
	Reserves	6.74(3), .070		.103	**.013**	1.000	.422	.407	.282
	National Guard, branch unknown	5.44(3), .080		1.000	1.000	1.000	.146	.102	.051
Psychiatric diagnoses	Lifetime substance use disorder	12.50(3), **.005**		.503	.063	**.016**	.195	.555	**.002**
	Lifetime mood disorder	12.77(3), **.005**		.073	.409	**.009**	**.045**	1.000	**.005**
	Lifetime anxiety disorder	1.81(3), .638		.334	.297	.761	.508	1.000	1.000
Psychiatric medication use		16.70(3), **<.001**		.796	.122	.372	**.023**	**.013**	**<.001**
mTBI	Military mTBI	60.09(3), **<.001**		-	-	**.004**	-	-	-
	Blast mTBI	43.90(3), **<.001**		-	-	**<.001**	-	-	-

Note. SD, Standard deviation; PTSD, Post-traumatic stress disorder; mTBI, mild traumatic brain injury; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; CAPS, Clinician Administered PTSD Scale [530]; PSQI, Pittsburgh Sleep Quality Index [430]; PSQI 3-factor structure, The PSQI subscales sleep efficiency, perceived sleep quality & daily disturbances refer to the Pittsburgh Sleep Quality Index 3-Factor structure [431]. All ANCOVA's were corrected for age. *p** corrected for multiple comparisons as outlined in **Figure 12**.

8.1. Sleep Quality, PTSD, and mTBI

Hypothesis I)

Veterans with PTSD, mTBI, or comorbid PTSD+mTBI experience poorer sleep quality than veterans without a history of PTSD or mTBI.

First, the influence of a diagnosis of PTSD and mTBI on sleep quality was examined by employing ANCOVAS. **Table 5** and **Figure 14** display the differences in sleep quality between the groups. The PTSD and comorbid PTSD+mTBI groups demonstrated more significant impairments on the PSQI global sleep quality, sleep efficiency, perceived sleep quality, and daily disturbances scales than those with mTBI or no history of PTSD or mTBI. There were no significant differences in sleep quality between the PTSD and comorbid PTSD+mTBI groups.

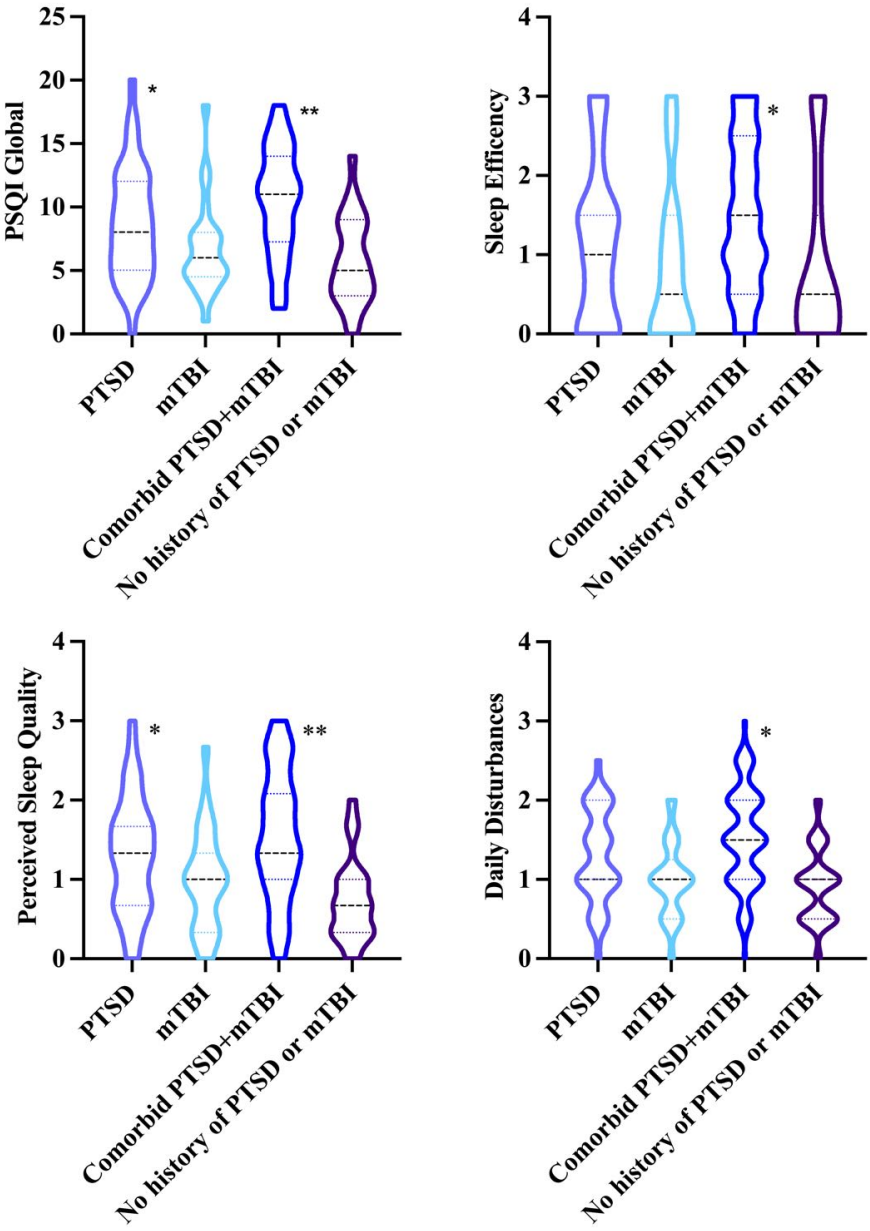

Figure 14. Sleep Quality Group Comparisons

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; PSQI, Pittsburgh Sleep Quality Index [430]; The PSQI subscales sleep efficiency, perceived sleep quality & daily disturbances refer to the Pittsburgh Sleep Quality Index 3-Factor structure [431].

This figure illustrates the significant differences in sleep quality between groups (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI). Lower scores on the PSQI scales represent better sleep quality.

PSQI Global: * Significantly higher than no history of PTSD or mTBI. ** Significantly higher than mTBI and no history of PTSD or mTBI.

PSQI Sleep efficiency: * Significantly higher than mTBI and no history of PTSD or mTBI.

PSQI Perceived sleep quality: * Significantly higher than no history of PTSD or mTBI. ** Significantly higher than mTBI and no history of PTSD or mTBI.

PSQI Daily disturbances: * Significantly higher than mTBI and no history of PTSD or mTBI.

All analyses are corrected for multiple comparisons as outlined in **Figure 12**.

Hypothesis II)

Greater PTSD symptom severity and mTBI burden are associated with poorer sleep quality.

The regression analyses revealed a significant association between PTSD symptom severity and poorer global sleep quality in the total sample ($\beta = .58$, $t = 9.15$, $p <$ **.001**), whereas there was no significant association between mTBI burden and global sleep quality ($\beta = .07$, $t = 1.07$, $p = .288$). Post-hoc analyses demonstrated that more severe PTSD symptoms were associated with poorer global sleep quality in the PTSD, mTBI, and comorbid PTSD+mTBI groups. Moreover, more severe PTSD symptoms were associated with poorer perceived sleep quality and greater daily disturbances in the PTSD and comorbid PTSD+mTBI groups. In the mTBI group, more severe PTSD symptoms were associated with poorer sleep efficiency (**Table 6**).

8.2. Sleep Quality and White Matter Microstructure

Hypothesis III)

Poorer sleep quality is associated with abnormalities in white matter microstructure.

Next, the association between sleep quality and white microstructure was explored. The regression analyses investigating the association between global sleep quality and whole-brain FA_T in the total sample was significant ($\beta = -.24$, $t = -3.35$, $p =$ **.001**). Moreover, post-hoc analyses revealed a significant association between global sleep quality and whole-brain FA_T in the comorbid PTSD+mTBI group ($\beta = -.39$, $t = -4.04$, $f^2 = .18$, $p <$ **.001**, **Table 7**). Supplementary analyses of the major white fiber tracts similarly showed significant associations between global sleep quality and white matter FA_T of the major fiber tracts in the comorbid PTSD+mTBI group (**Table 8**). No region-specific pattern was observed, supporting the hypothesis that poor sleep quality may lead to widespread white matter alterations. Subsequently, the relationship between the three PSQI sub-scales (sleep efficiency, subjective sleep quality, and daily disturbances) and whole-brain FA_T was examined in the comorbid PTSD+mTBI group. Only perceived sleep quality was significantly associated with whole-brain FA_T ($\beta = -.43$, $t = -3.86$, $f^2 = .21$, $p <$ **.001**, **Table 7**, **Figure 15**).

Table 6. Association between PTSD Symptom Severity and Sleep Quality

			PTSD				mTBI				Comorbid PTSD+mTBI				No history of PTSD or mTBI			
			Regression				Regression				Regression				Regression			
DV		**IV**	***β***	***t***	***f²***	***p****	***β***	***t***	***f²***	***p****	***β***	***t***	***f²***	***p****	***β***	***t***	***f²***	***p****
PSQI Global		Total CAPS	.49	3.40	.32	**.002**	.62	3.68	.61	**.001**	.53	5.82	.38	**<.001**	-.15	-.64	.02	.531
PSQI 3-factor structure	Sleep efficiency	Total CAPS	.32	2.07	.11	.046	.51	2.79	.36	**.011**	.22	2.17	.05	.033				
	Perceived sleep quality	Total CAPS	.45	2.99	.25	**.005**	.40	2.03	.18	.055	.51	5.55	.34	**<.001**				
	Daily disturbances	Total CAPS	-48	3.25	.30	**.003**	.47	2.57	.29	.018	.55	6.16	.42	**<.001**				

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; DV, Dependent variable; IV, Independent variable; *β*, Standardized beta coefficient; f^2, effect size; CAPS, Clinician Administered PTSD Scale [530]; PSQI, Pittsburgh Sleep Quality Index [430]; The PSQI subscales sleep efficiency, perceived sleep quality & daily disturbances refer to the Pittsburgh Sleep Quality Index 3-Factor Structure [431]. p^* corrected for multiple comparisons as outlined in **Figure 12**.

Table 7. Association between Sleep Quality and Whole-brain FA_T

		PTSD				mTBI				Comorbid PTSD+mTBI				No history of PTSD or mTBI			
		Regression				Regression				Regression				Regression			
DV	**IV**	***β***	***t***	***f²***	***p****	***β***	***t***	***f²***	***p****	***β***	***t***	***f²***	***p****	***β***	***t***	***f²***	***p****
Whole-Brain FA_T	PSQI Global	.06	.35	.00	.727	-.15	-.80	.02	.434	-.39	-4.04	.18	**<.001**	-.25	-1.21	.07	.241
	PSQI Sleep efficiency									.10	1.02	.01	.309				
	PSQI Perceived sleep quality									-.43	-3.86	.21	**<.001**				
	PSQI Daily disturbances									-.15	-1.46	.09	.149				

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; DV, Dependent variable; IV, Independent variable; *β*, Standardized beta coefficient; f^2, effect size; FA_T, Fractional anisotropy $_{Tissue}$; PSQI, Pittsburgh Sleep Quality Index [430]; The PSQI subscales sleep efficiency, perceived sleep quality & daily disturbances refer to the Pittsburgh Sleep Quality Index 3-Factor Structure [431]. p^* corrected for multiple comparisons as outlined in **Figure 12**.

Table 8. Association between Sleep Quality and Major White Matter Fiber Tracts FA_T

		PTSD		mTBI		Comorbid PTSD+mTBI		No history of PTSD or mTBI	
DV	**IV**	**Regression**		**Regression**		**Regression**		**Regression**	
Right FA_T	**PSQI Global**	***t***	***p***	***t***	***p***	***t***	***p***	***t***	***p***
Arcuate fasciculus		.09	.926	-.26	.797	-.25	.803	-.43	.669
Cingulum bundle		.845	.404	-.70	.491	-3.56	**<.001**	-1.35	1.92
Inferior longitudinal fasciculus		.984	.332	-2.51	**.020**	-2.04	**.044**	-.62	.542
Inferior occipito-frontal fasciculus		.543	.590	.65	.525	-2.87	**.005**	-.75	.465
Superior longitudinal fasciculus-I		1.33	.192	-1.23	.230	-2.49	**.015**	-.25	.806
Superior longitudinal fasciculus-II		.284	.805	-.72	.481	-1.31	.195	-1.25	.277
Superior longitudinal fasciculus-III		.034	.973	-1.39	.178	-1.01	.318	-.15	.884
Uncinate fasciculus		.126	.900	-.83	.418	-1.33	.188	-.43	.674
Left FA_T	**PSQI Global**								
Arcuate fasciculus		1.00	.323	-.04	.968	-1.03	.307	-1.77	.092
Cingulum bundle		-.25	.806	.59	.561	-1.963	.053	-1.46	.160
Inferior longitudinal fasciculus		.678	.502	.77	.446	-2.72	**.008**	-2.56	**.019**
Inferior occipito-frontal fasciculus		.816	.420	-.94	.355	-3.53	**<.001**	-1.16	.260
Superior longitudinal fasciculus-I		-.21	.832	-.47	.644	-2.42	**.017**	-1.49	.151
Superior longitudinal fasciculus-II		.21	.835	1.03	.315	-2.35	**.021**	-.812	.426
Superior longitudinal fasciculus-III		.61	.545	-.02	.984	-2.55	**.012**	-1.00	.336
Uncinate fasciculus		.43	.674	-.838	.411	-2.15	**.035**	-.138	.892
Commissural FA_T	**PSQI Global**								
Corpus callosum-I		-1.12	.272	-.25	.028	-3.61	**<.001**	-.97	.343
Corpus callosum-II		-.67	.506	-190	.071	-2.41	**.018**	-1.03	.314
Corpus callosum-III		-.44	.661	-.97	.344	-2.14	**.035**	-1.77	.092
Corpus callosum-IV		1.52	.139	-.86	.399	-2.52	**.013**	-.42	.680
Corpus callosum-V		1.38	.176	-.16	.871	-2.09	**.040**	-.64	.531
Corpus callosum-VI		.10	.918	-.225	8.24	-1.33	.189	-.48	.635
Corpus callosum-VII		-.07	.944	-.75	.461	.23	.819	-.62	.543

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; DV, Dependent variable; IV, Independent variable; FA_T, Fractional anisotropy $_{Tissue}$; PSQI, Pittsburgh Sleep Quality Index [430].

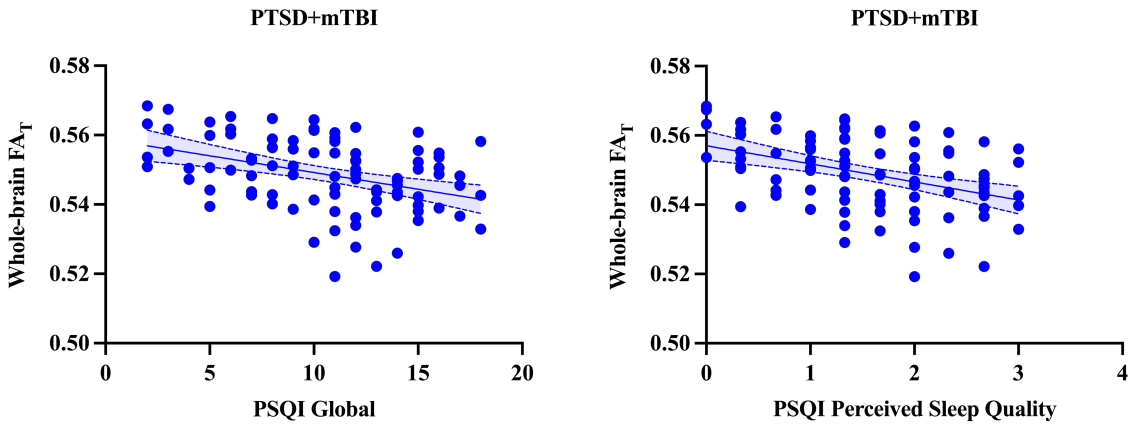

Figure 15. Association between Sleep Quality and Whole-brain FA_T

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; PSQI, Pittsburgh Sleep Quality Index [430]; FA_T, Fractional anisotropy $_{Tissue}$.

This figure illustrates the significant association between global sleep quality and whole-brain FA_T ($p <$ **.001**) and between perceived sleep quality and whole-brain FA_T ($p <$ **.001**). Lower scores on the PSQI scales represent better sleep quality.

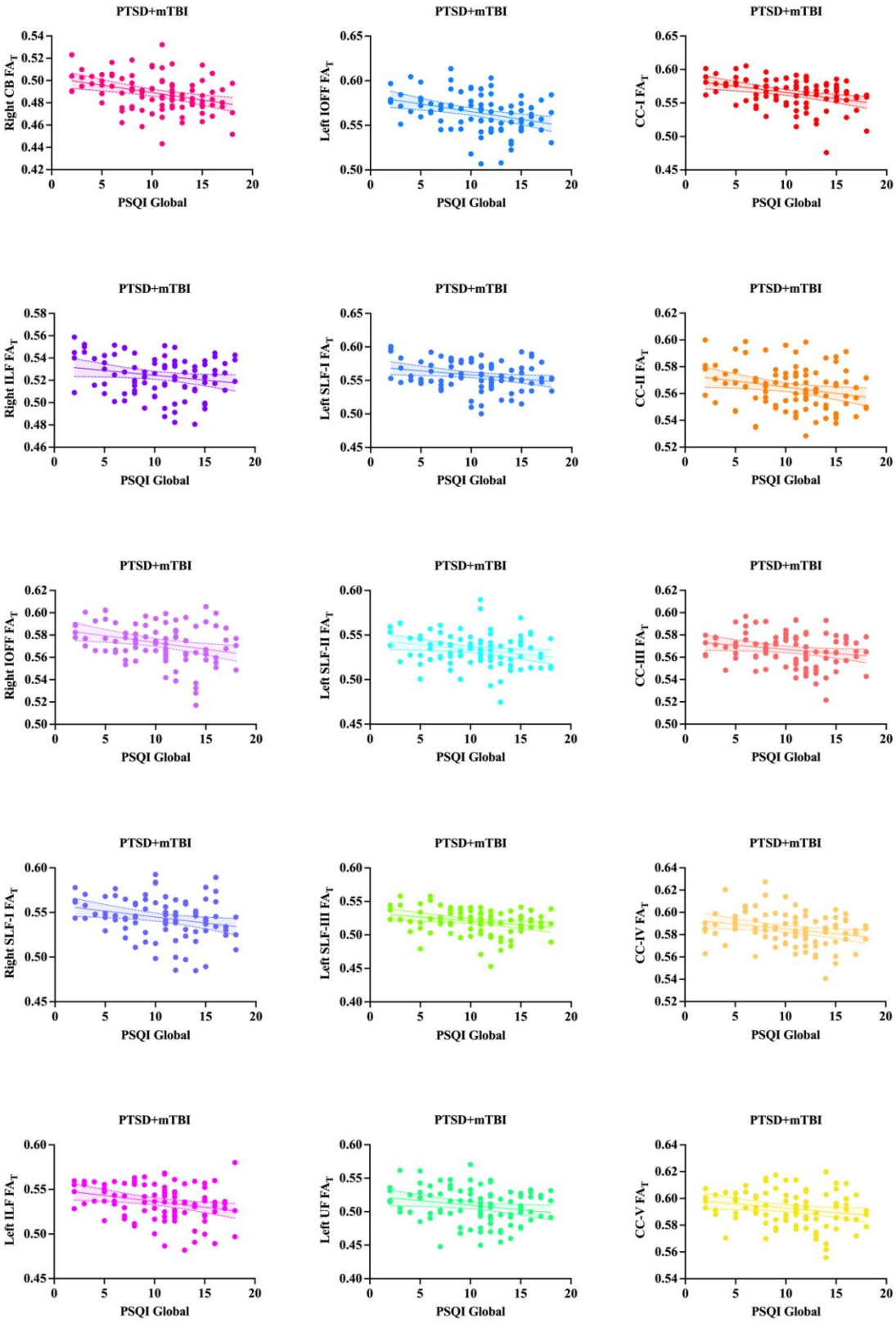

Figure 16. Association between Sleep Quality and Major White Matter Fiber Tracts FA_T

Note. Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; FA_T, Fractional anisotropy $_{Tissue}$; PSQI, Pittsburgh Sleep Quality Index [430]; AF, Arcuate fasciculus, CB, Cingulum bundle; ILF; Inferior longitudinal fasciculus; IOFF, Inferior occipito-frontal fasciculus; SLF, Superior longitudinal fasciculus; UF, Uncinate fasciculus; CC, Corpus callosum.

8.3. Sleep Quality, PTSD, mTBI, and White Matter Microstructure

Hypothesis IV)

There is an association between PTSD symptom severity, mTBI burden, sleep quality, and white matter microstructure.

Given the significant association between PTSD symptom severity and perceived sleep quality as well as between perceived sleep quality and white matter microstructure in the comorbid PTSD+mTBI group, additional mediation analyses were performed to assess whether perceived sleep quality mediates the association between PTSD symptom severity (independent variable) and whole-brain FA_T (dependent variable). PTSD symptom severity was significantly associated with whole-brain FA_T (b = -.00, SE = .00, $t(91)$ = -2.88, p = **.005**, **Figure 17 path c**) when not including perceived sleep quality in the model. When inserting perceived sleep quality as a mediator, the relationships between PTSD symptom severity and perceived sleep quality (b = .02, SE = .00, $t(91)$ = 5.55, p < **.001**, **Figure 17 path a**), perceived sleep quality and whole-brain FA_T (b = -.00, SE = .00, $t(90)$ = -3.26, p = **.002**, **Figure 17 path b**), and the model's total effect ($F(3, 90)$ = 6.81, R^2 = .19, p < **.001**) were significant. However, the direct effect of PTSD symptom severity on whole-brain FA_T was not significant (b = -.00, SE = .00, $t(90)$ = -.97, p = .331, **Figure 17 path c'**). Therefore, the findings indicate that the association between PTSD symptom severity and whole-brain FA_T is fully statistically mediated by perceived sleep quality (completely standardized β = -.18, *bootSE* = .06, *bootCI* [-.29, -.07]).

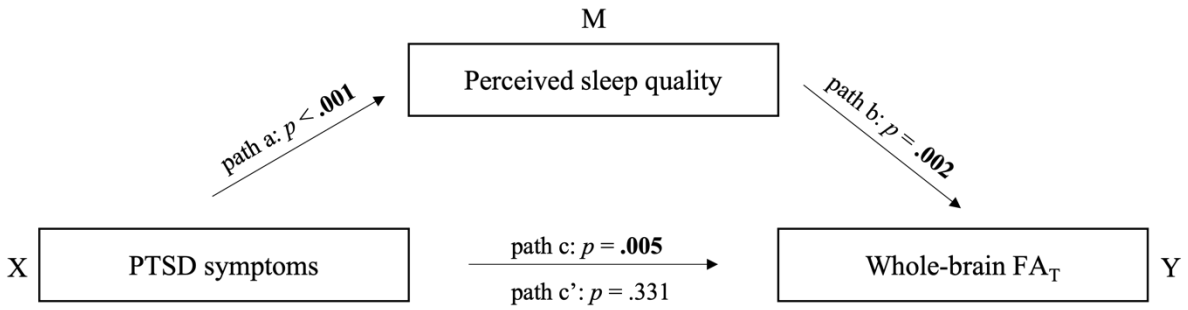

Figure 17. Mediation Model

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; FA_T, Fractional anisotropy $_{Tissue}$.

This figure illustrates the fully mediating effect of perceived sleep quality between PTSD symptoms and whole-brain FA_T. Path a refers to the association between X and M. Path b refers to the association between M and Y when taking X into account. Path c represents the total effect of X on Y, including the axb path. Path c' shows the direct effect of X on Y when M is omitted.

In an additional analysis, mTBI burden was included as a moderator variable in the mediation model to assess whether lifetime mTBI burden significantly influences the relationship between PTSD symptom severity, perceived sleep quality, and whole-brain FA_T. There was no significant effect of mTBI burden on the associations between PTSD symptom severity and perceived sleep quality (b = -.00, SE = .00, $t(89)$ = -.66, p = .509) or the associations between perceived sleep quality and whole-brain FA_T (b = -.00, SE = .01, $t(88)$ = .08, p = .936, **Figure 18**) as revealed by non-significant moderator effects.

All analyses were controlled for age. Of note, when including psychiatric comorbidities (anxiety, depression, substance use disorder), warzone-related stress, BMI, and psychiatric medication use, race, and education as additional covariates in the mediation and moderated mediation model, results did not change significantly.

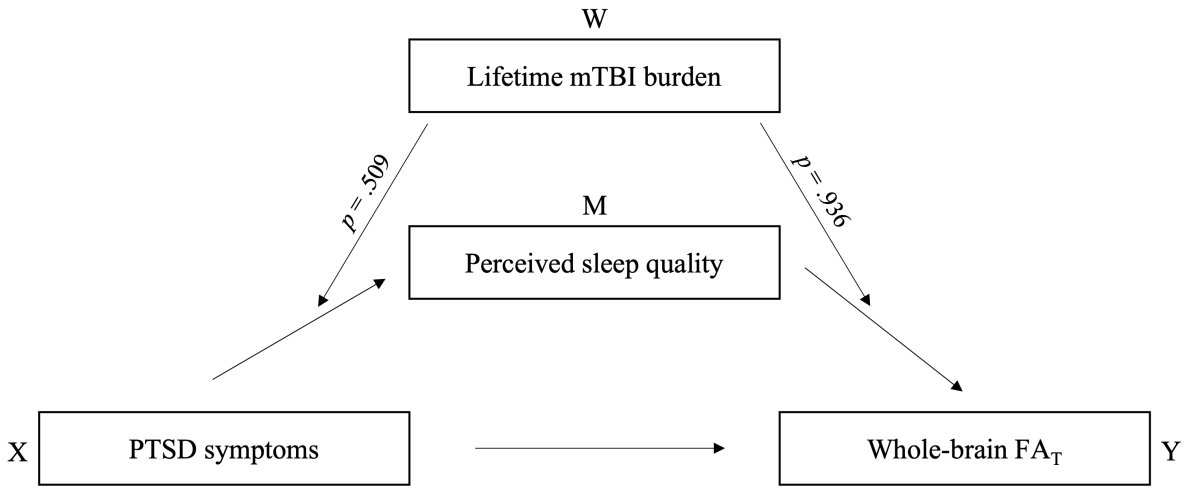

Figure 18. Moderated Mediation Model
Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; FA_T, Fractional anisotropy $_{Tissue}$.
This figure illustrates the non-significant effects of moderator W on the mediated association between X and Y via M. Both the association between X and M and the association between M and Y were not significantly moderated by W.

8.4. Summary of Results

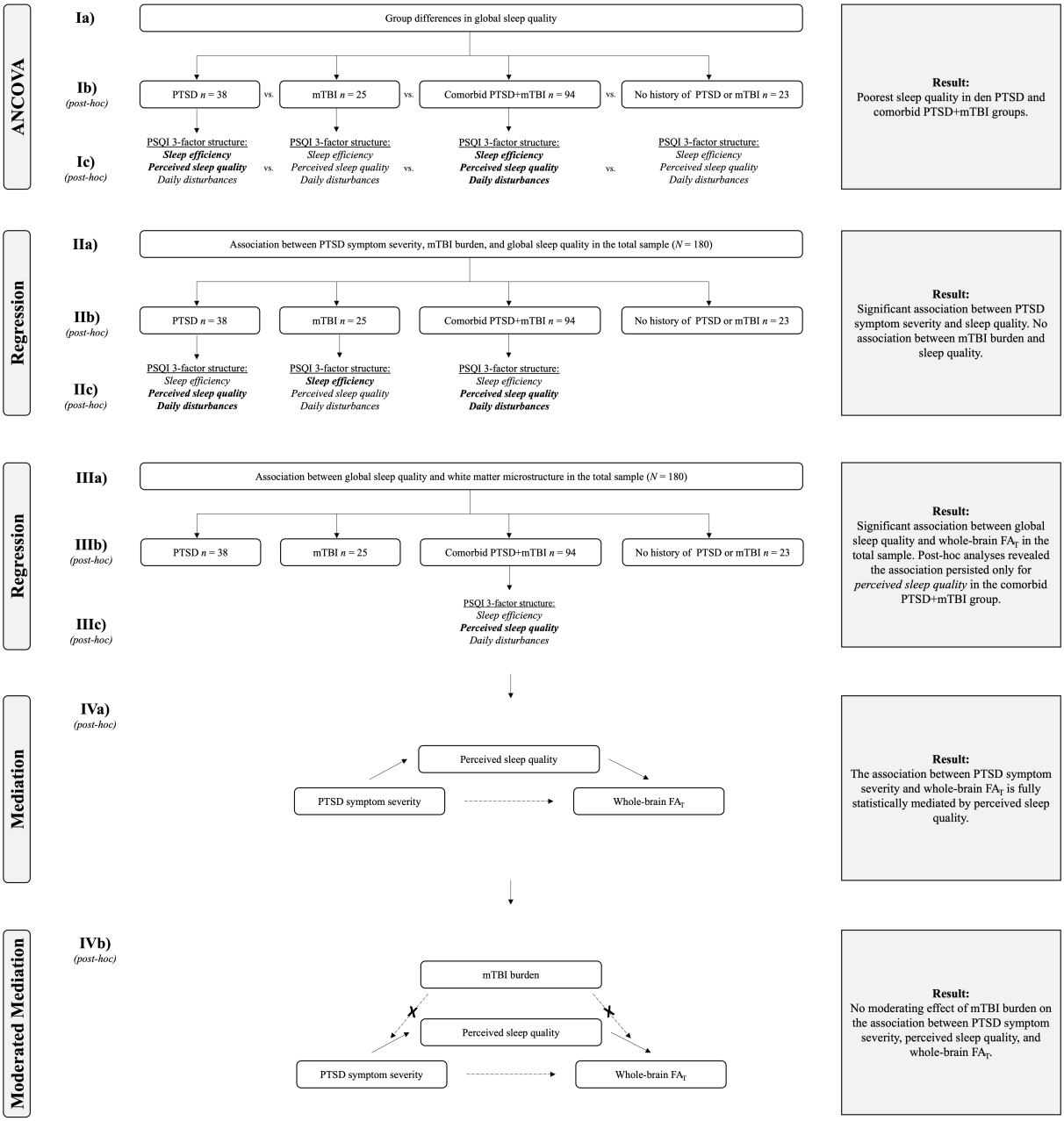

Figure 19. Summary of Results

Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury; PSQI, Pittsburgh Sleep Quality Index [430], FA_T, Fractional anisotropy $_{Tissue}$.

This figure displays the statistical approach and summary of results.

9. Discussion

The current work investigated the relationship between PTSD, mTBI, sleep quality, and white matter microstructure in veterans. Poorer sleep quality was observed in veterans with PTSD and comorbid PTSD+mTBI compared to those with mTBI only or no history of PTSD or mTBI. Additionally, global and perceived sleep quality was associated with characteristics of white matter microstructure in veterans with comorbid PTSD+mTBI. Most importantly, perceived sleep quality fully accounted for the association between PTSD symptoms and white matter microstructure. This finding was independent of the mTBI burden, psychiatric comorbidities, warzone-related stress, BMI, psychiatric medication use, race and education. The findings suggest a crucial role of sleep in understanding the association between trauma-related neuropsychiatric diagnoses and brain health.

9.1. Sleep Quality, PTSD, and mTBI

Hypothesis I)

Veterans with PTSD, mTBI, or comorbid PTSD+mTBI experience poorer sleep quality than veterans without a history of PTSD or mTBI.

In line with previous studies [26,531], veterans with PTSD or comorbid PTSD+mTBI experienced poorer sleep quality than veterans with mTBI only or no history of PTSD or mTBI. The findings underline the profound effect of post-deployment PTSD on sleep quality, that appears to outweigh the effects induced by head trauma alone. Indeed, sleep quality disturbances are a hallmark symptom of PTSD specifically [19,20], and usually range from insomnia, to difficulties falling asleep, and recurrent awakenings during the night due to nightmares [369–371]. While it has been suggested that sleep quality is most impaired in those who suffer from comorbid PTSD+mTBI [26] the present work did not observe an additive burden of sleep quality disturbances in veterans with PTSD+mTBI compared to those with PTSD only. In fact, it is notable that – contrary to previous findings [21,532] – there was no difference in sleep quality between veterans with mTBI only and those without a history of mTBI. An explanation for this finding may be that sleep quality disturbances resolved after time, given that some veterans in the present study may have sustained their head trauma many years in the past. In fact, while many mTBI patients experience sleep quality disturbances acutely and sub-acutely after mTBI [533], only a small proportion of individuals with mTBI suffers from persistent post-concussive symptoms (including sleep quality disturbances) [218–220], while residual sleep quality disturbances are still highly prevalent in remitted PTSD patients [35,36]. Therefore, it can be

concluded that PTSD is a powerful indicator of poor sleep quality, even in the absence of comorbid mTBI.

Hypothesis II)

Greater PTSD symptom severity and mTBI burden are associated with poorer sleep quality.

As expected, a significant association between greater PTSD symptom severity and poorer global sleep quality, sleep efficiency, perceived sleep quality, and more daily disturbances were observed across the PTSD, mTBI, and comorbid PTSD+mTBI groups. The findings align with previous studies, highlighting an integral role of impaired sleep quality in PTSD [19,20], and suggesting that veterans' poor sleep quality originates in traumatic stress [286,531]. The interplay of several factors may account for the association between PTSD symptom severity and sleep quality disturbances. Especially the re-experiencing and hyperarousal symptoms of PTSD contribute to poor sleep quality [210,534]. HPA axis disturbances commonly observed in PTSD lead to alterations in sleep [535]. Heightened CRH levels and a down-regulation of CRH receptors are core features of PTSD-related HPA axis abnormalities [97,98,390] and result in abnormally high norepinephrine activity in the brain [19,209]. While in healthy individuals norepinephrine activity is suppressed during sleep [391], PTSD patients lack the overnight drop of norepinephrine [392] and exhibit heightened levels that persist throughout the night [392,393]. Moreover, brain networks that are implicated in PTSD likewise impact sleep quality. For example, the disturbed relationship between the limbic system and the medial prefrontal cortex gives rise to sleep quality disturbances, including insomnia and distressing dreams [211,365]. In fact, PTSD-typical *restless REM sleep* that is marked by especially high arousal and eye movements impairs the overnight resolution of distress, leads to continued amygdala reactivity [388], and therefore perpetuates the chronic hyperarousal symptoms of PTSD [387]. Moreover, the disconnection between frontal and limbic areas leads to insufficient extinction of traumatic memories [397] and difficulties with emotion regulation [396], resulting in a vicious cycle that perpetuates poor sleep quality.

Interestingly, there was no significant association between mTBI burden and sleep quality. The results highlight an integral role of poor sleep quality in PTSD severity [19,20], underscoring that traumatic experiences might be the driving force behind sleep quality disturbances in veterans [286,531].

9.2. Sleep Quality and White Matter Microstructure

Hypothesis II)

Poorer sleep quality is associated with abnormalities in white matter microstructure.

As hypothesized [66–77], a significant relationship between impaired sleep quality and characteristics of white matter microstructure was observed. It can be speculated that the observed white matter microstructural alterations can be traced back to impaired myelin repair and genesis processes. Previous research has demonstrated that sleep is crucial for sustaining white matter health, as sleep initiates myelin deposition and repair processes by fueling lipid biosynthesis, and activating oligodendrocyte precursor proliferation crucial for myelin genesis [416]. Myelin genesis and repair processes rely on the sufficient clearance of brain waste products [414]. The glymphatic system is an innate brain clearance system, which consists of perivascular spaces vital for flushing out accumulated neurotoxins, such as beta-amyloid and tau [411,413]. Critically, the glymphatic system is most active during sleep [414], and deprivation of sleep for as little as one night can lead to an accumulation of brain waste products, such as beta-amyloid [536]. Therefore, it can be anticipated that poor sleep quality is linked to reduced neurotoxic clearance, which, in turn, leads to neurodegenerative processes including impaired myelination. Incomplete clearance of brain waste products has been suggested by previous research, which showed an association between white matter damage and increased amyloid and tau deposition in military veterans with comorbid PTSD+mTBI [537,538].

The present work revealed that the association between impaired sleep quality and abnormal white matter microstructure pertained solely to veterans with comorbid PTSD+mTBI – the most clinically burdened group. Veterans with comorbid PTSD+mTBI presented with the highest PTSD symptom severity, a high number of comorbid psychiatric diagnoses (**Figure 20**), medication use, and the highest mTBI and blast exposure rates. Deployed military personnel commonly experience blast-related injuries resulting from military artillery explosions that may cause even greater adversity than blunt injuries [539] (including swelling of the brain and traumatic axonal injury [216]). In fact, brain structural alterations [284] and neuropsychological sequelae [539] appear to be more profound after blast exposures, and military mTBI in general may be associated with greater adversity than civilian mTBI [540]. The combination of these factors may increase brain vulnerability [27–30,284], potentially creating a neural environment that leaves the brain unprotected from the harmful effects of impaired sleep quality. Similarly, poor sleep quality negatively impacts brain structure and function [68–77,420,541,542], thus fueling the onset or progression of neuropsychiatric disorders and related brain abnormalities [365].

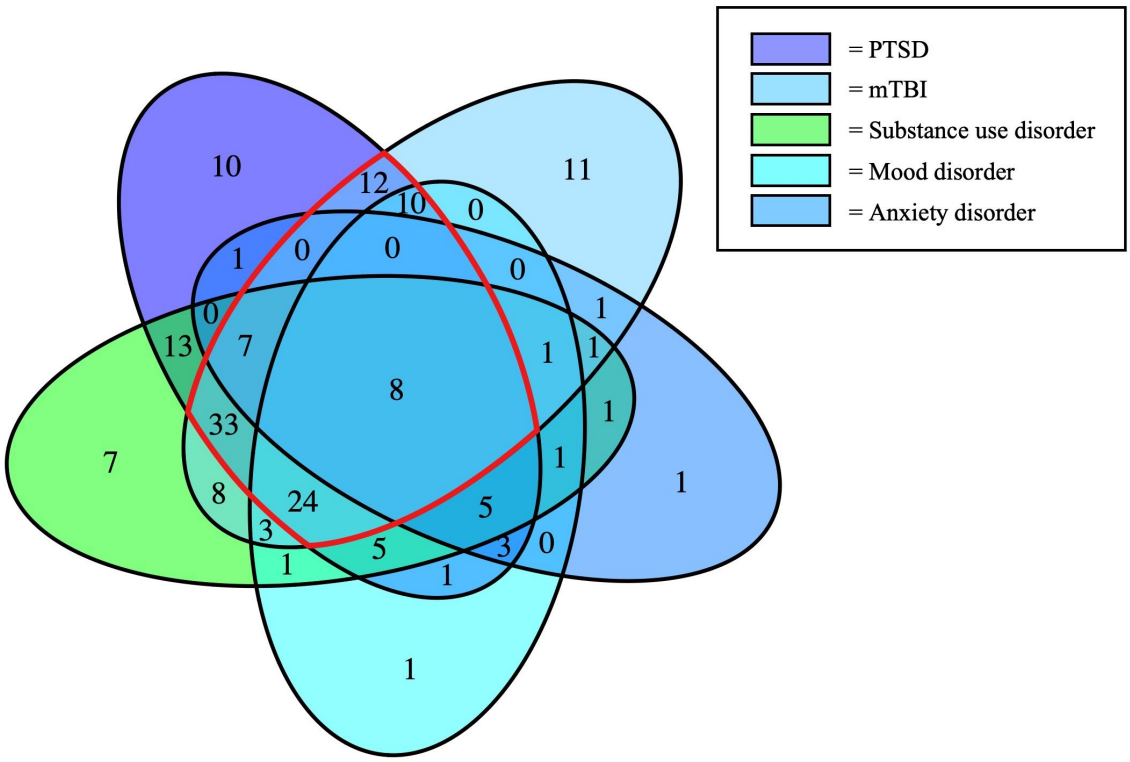

Figure 20. Overlap of Diagnoses
Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury. The red-lined area pictures the comorbid PTSD+mTBI sample (n = 94) with overlapping substance use, mood, and anxiety disorder.

Lower perceived sleep quality was the only significant indicator of alterations in white matter microstructure when all aspects of sleep quality (sleep efficiency, perceived sleep quality, and daily disturbances) were considered. This finding is consistent with a prior study revealing that perceived sleep quality was the driving factor between overall poor sleep quality and reduced cortical gray matter. [542]. Supporting this, it has previously been demonstrated that the personal perception of sleep quality is most essential for functional outcome and mental health in patients with PTSD [34].

Of particular interest here, perceived sleep quality may not necessarily mirror objectively measured sleep quality. A recent meta-analysis did not find a difference in actigraphy-measured total sleep time, wake after sleep onset, sleep latency, or sleep efficiency between patients with versus without PTSD [543]. Actigraphy is a convenient way of assessing sleep quality objectively by employing a small device that is worn on the wrist [544]. The actigraph can be used over a period of time in the home environment, and measures sleep parameters, such as sleep latency, total sleep time, wake after onset, and sleep efficiency [544]. Moreover, studies that included both objective measures of sleep and self-report tools, such as the PSQI, reported large discrepancies, indicating that veterans may rate their sleep as poorer than actually

assessed by actigraphy [543]. However, contrary to findings on actigraphically-measured sleep quality, a meta-analysis on polysomnographically-assessed sleep reported a decrease in total sleep time, slow-wave sleep, sleep efficiency, and greater waking periods following sleep onset in patients with PTSD compared to healthy controls. Polysomnography is usually conducted in a sleep laboratory and gathers physiological parameters during sleep, utilizing EEG, electrooculography, electromyography, and electrocardiography, among others [545]. Unlike actigraphy, polysomnography can discern between different sleep cycles and evaluate the nature of REM- and non-REM sleep [546]. This feature may be of particular importance, considering the high prevalence of nightmares in PTSD [33].

While polysomnography is widely recognized as the gold standard for objectively assessing sleep quality [19,547,548], concerns regarding its usefulness in evaluating PTSD-related sleep quality disturbances have been voiced. Patients with PTSD might either feel safer or more threatened when sleeping in a laboratory setting, which may reflect itself in altered sleep duration, intensity, and in the frequency of trauma-related dreams [23,543]. Moreover, sleep is usually assessed only during one or two nights in a laboratory setting. This may miss intermittently occurring PTSD-related sleep quality disturbances [549] or falsely imply sleep quality disturbances are frequent, even if they actually only occur occasionally. Keeping these potentially confounding effects in mind and considering the aforementioned findings from actigraphy studies [543], it is questionable whether differences in sleep quality between PTSD patients and healthy controls truly exist, or at least to which extent. Indeed, the phenomenon of paradoxical insomnia – the discrepancy between subjective and objective assessments of sleep [550] – is common among veterans with sleep disorders [551] and PTSD [552]. Similarly, patients with mTBI report worse sleep quality disturbances than actually picked up by polysomnographic measures [553]. General distress, continuous hyperarousal states, and a negative cognitive bias that impacts sleep perception are among the factors linked to paradoxical insomnia [543,551,554–557].

Importantly, perceived sleep quality (rather than the objective assessment of sleep) appears to be an adequate indicator of overall well-being. [393,557–559]. This is supported by a recent study, showing that self-reported sleep quality is a more powerful predictor of mental and physical health than objectively measured sleep duration [560]. Moreover, it has been revealed that the association between objectively measured sleep quality and quality of life appears to be partially mediated by perceived sleep quality [561]. Perceived sleep quality is, thus, a crucial diagnostic assessment tool that should be employed in clinical care and future research. Nonetheless, future longitudinal studies are needed to further illuminate the relationship

between subjective and objective measures of sleep quality and their relation to brain structure in veterans.

9.3. Sleep Quality, PTSD, mTBI, and White Matter Microstructure

Hypothesis IV)

There is an association between PTSD symptom severity, mTBI burden, sleep quality, and white matter microstructure.

Strikingly, perceived sleep quality fully mediated the association between PTSD symptom severity and white matter microstructure (**Figure 21**). Several previous studies reported white matter microstructure alterations in patients with PTSD [41,51–53,182,183], and lower FA has been observed for several major white matter fiber tracts [41,43,151]. A chronically activated stress response and overly activated glutamate neurotransmission affects neuronal plasticity [41,205] and has been suggested as the link between PTSD and impaired white matter. However, it is notable that none of the previously conducted studies that investigated the association between PTSD and white matter microstructure adjusted for sleep quality disturbances or assessed sleep quality disturbances as an influential factor. This is striking, given that disturbed sleep is not only the hallmark symptom of PTSD [19,20], but also has a profound impact on brain structure and function [211,212,395,542]. In fact, studies assessing the link between sleep and gray matter volume in trauma-exposed veterans previously observed that sleep quality disturbances may affect neural structure even independently of other psychiatric symptoms. Greater self-reported insomnia severity has been associated with smaller hippocampal volumes in veterans whilst controlling for other PTSD symptoms [541]. Similarly, lower self-reported sleep quality was linked to reduced total cortical and frontal gray matter volume in veterans, even when correcting for comorbid psychiatric conditions [542].

Notably, when including PTSD symptom severity, sleep quality, and white matter in the same statistical model, sleep quality fully accounted for the relationship between PTSD symptoms and white matter microstructure. This finding suggests that poor sleep might be the most damaging symptom for the brain's white matter microstructure. Moreover, the finding questions the interpretability of previous studies on the relationship between PTSD and white matter that did not consider the individual effect of sleep quality on brain structure [41,43–58,183]. Alterations in white matter that have previously been ascribed to PTSD as a disorder *per se* may instead be attributable to *one symptom* (disturbed sleep quality) of the disorder. This is critical information for future diagnostic and treatment approaches and warrants a thorough assessment of sleep quality in the veteran population.

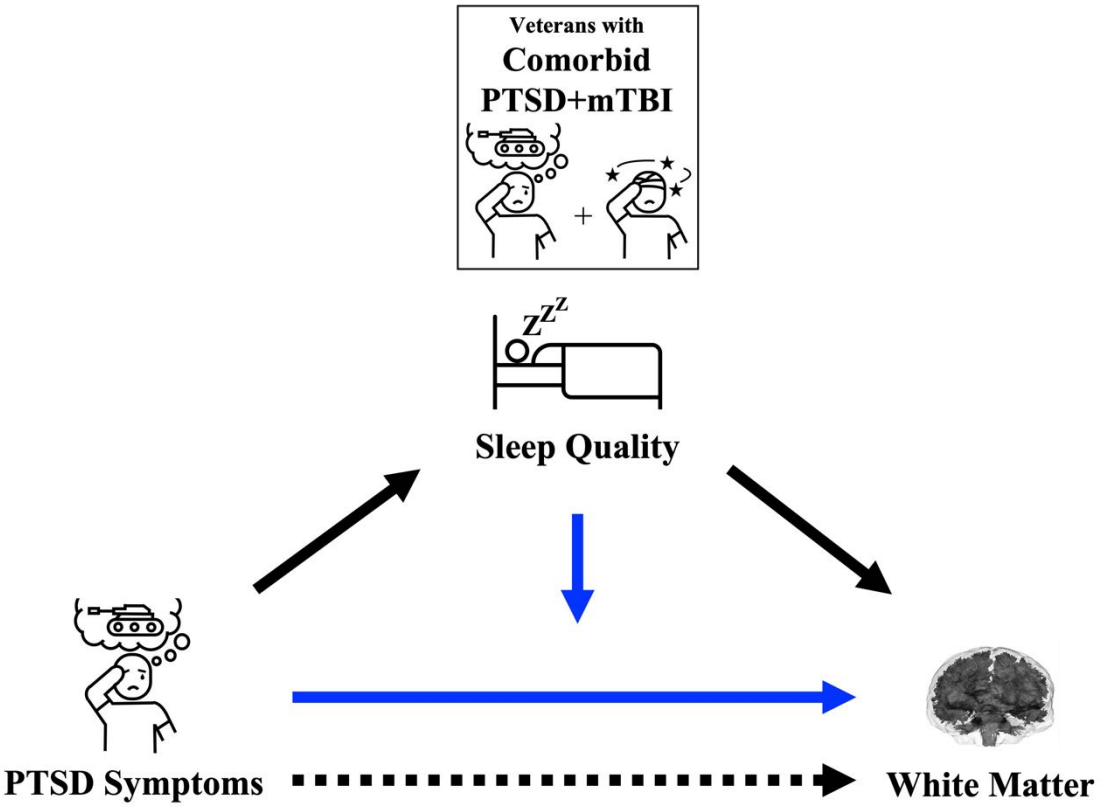

Figure 21. Mediating Effect of Sleep Quality
Note. PTSD, Post-traumatic stress disorder; mTBI, Mild traumatic brain injury.
This figure depicts the fully mediating effect of sleep quality between PTSD symptom severity and white matter microstructure.

There was no statistically significant influence of the mTBI burden (indicated by the number and severity of lifetime mTBIs) on the association between PTSD symptoms, sleep quality, and white matter microstructure. This is surprising, given that cumulative TBIs exacerbate PTSD symptomatology [12–16], and may increase sleep quality disturbances [425]. Mild traumatic brain injury alters glutamate signaling, melatonin production [402,403], and circadian rhythmicity [400], thereby contributing to the development of sleep quality disturbances. Moreover, adverse inflammatory processes can be elicited both by psychological [114] and head trauma [408], contribute to sleep quality disturbances [409], and alter brain structure [202,203]. As outlined earlier, mTBI in particular may lead to impaired glymphatic clearance of brain toxins during sleep [411–413]. Especially impeded waste removal in the limbic system after mTBI [410] may fuel the emergence and maintenance of psychiatric symptoms [248] and could explain how sleep quality disturbances after TBI contribute to neuropsychiatric sequelae.

While there is evidence that mTBI alters biological processes related to sleep quality and psychological functioning, studies focusing on the impact of increasing mTBI severity on sleep quality and brain structure are limited. Other than hypothesized, the current findings

suggest that sleep quality mediates the association between PTSD symptom severity and white matter microstructure independently of increased mTBI burden. While some previous studies report an adverse effect of more significant mTBI burden on neuropsychological functioning and brain structure and function [562–567], others did not [568–571]. Differences in the assessment of mTBI burden may account for the lack of consistency in previous findings. For example, some studies assessed only the severity or number of mTBIs, compared to both. Moreover, the present study focused on mild TBI exclusively, however, it is possible that TBI burden of greater severity (i.e., moderate or severe TBI) would have impacted the findings. Sleep quality disturbances increase with TBI severity [572], and greater white matter abnormalities have been reported with moderate to severe compared to mild TBI [419]. Future research is needed to explore whether mTBI of increasing severity impacts trauma-related sleep quality disturbances and associated brain structural alterations.

9.4. Limitations and Future Directions

Several study limitations are acknowledged. First, an entirely male sample of military veterans was enrolled, which may not be generalizable to the entire population of OEF/OIF veterans that includes women. Indeed, sleep and white matter microstructure may be affected by sex [573,574] and the present findings may, therefore, only pertain to a limited sample. Next, the varying sample sizes across the groups (PTSD, mTBI, comorbid PTSD+mTBI, no history of PTSD or mTBI) may have impacted statistical power and type I error rates [575,576], necessitating replications with balanced designs and larger samples. Further, while potentially confounding factors, such as psychiatric comorbidity, warzone-related stress, BMI, psychiatric medication use, race, and education were considered, additional stressors associated with transitioning from combat duty to a non-deployed setting have not been captured. Moreover, medical records for verifying mTBI diagnoses were not available. Instead, information on head trauma relied on retrospective self-recall, potentially distorting accurate reports of mTBI occurrence and severity [577]. However, the current study employed the BAT-L for identification of mTBI [429], which is considered the current gold standard for assessing combat-related mTBI retrospectively. Similarly, sleep quality was assessed with the most commonly utilized self-report tool to measure sleep quality (the PSQI [430]) which has proven high psychometric validity and reliability [578,579]. Nevertheless, sleep quality was determined entirely based on self-report, which may not accurately reflect objective sleep quality [543]. However, it is significant to note that perceived sleep quality is a valuable diagnostic tool for assessing mental and brain health [393,557–561].

The mediation and moderation analyses allowed for an advanced statistical assessment of complex interactions between the target variables. However, the cross-sectional design restricts the interpretability of causal relationships. It is possible that sleep quality disturbances were present in some veterans even before deployment and predisposed a minority group to develop more severe neuropsychiatric symptoms and brain structural impairments [177,580–583]. Moreover, future studies may benefit from the inclusion of a general population control group to understand whether the present findings exclusively pertain to the veteran population, given that some civilian studies did not show an association between self-reported sleep quality and white matter microstructural integrity [423,584,585]. Thus, future longitudinal studies, including an increased number of participants and a non-veteran control group, are required to elucidate the underlying pathomechanisms of impaired sleep quality.

In addition, the relationship between self-reported sleep quality, objective sleep quality, and brain structure should be assessed. Polysomnography may serve as an important tool for objective sleep quality assessment [546], especially considering the high prevalence of PTSD-related nightmares [33]. The implementation of polysomnography in an ambulatory setting may mitigate the confounding effects attributed to a sleep laboratory environment [586] and should thus be pursued. An analysis of the relationship between subjective and objective measures of sleep and their associations with brain structure may contribute to the understanding of possible paradoxical insomnia in the veteran population. Future studies should also differentiate between sleep disorders (e.g., insomnia, nightmare disorder, obstructive sleep apnea), given that different aspects of sleep or distinct sleep disorders may be associated with alterations in specific white matter tracts. For example, nightmares, which are considered uncontrolled re-enactments of the traumatic event [372,466], may especially affect tracts of the limbic system, such as the uncinate fasciculus and cingulum bundle [465]. Objective measures of REM sleep should be supplemented with self-report questionnaires and clinical interviews specifically tailored to dreaming. Similarly, assessment tools primarily focusing on insomnia may assist with classifying behavioral and brain abnormalities specific to insomnia.

Brain imaging analyses would benefit from a combination between structural MRI and fMRI to identify an association between structural brain changes and brain networks related to sleep quality, PTSD, and mTBI. Moreover, measuring volumetric changes and diffusivity along the brain's perivascular spaces (i.e., the glymphatic system) may be a powerful way to complement the present findings. While changes in the glymphatic system have currently only been linked to military mTBI and consequent poor sleep quality [413], PTSD likely also harms glymphatic clearance. In healthy individuals, norepinephrine levels decline during the night and

the perivascular spaces of the glymphatic system enlarge to enable the removal of waste products from the brain [587]. In fact, norepinephrine antagonists have been shown to fuel glymphatic clearance [588]. This mechanism is likely impaired in patients with PTSD, as PTSD patients lack the normal drop in norepinephrine levels during the night [392]. As discussed above, the unsuccessful clearance of neurotoxins may lead to neurodegenerative processes, including impaired myelination. These processes should be evaluated in association with objectively and subjectively measured sleep quality disturbances among military veterans.

There is a vast array of possibilities for future research on sleep quality disturbances in the context of PTSD and mTBI. Concluding, a combined assessment of objective and subjective sleep quality, an analysis of the brain's glymphatic system that is most active during sleep [411–414], and a longitudinal study design belong to the core components required for future research on sleep in the context of PTSD and mTBI.

9.5. Clinical Implications

The insights that arise from the present findings may be of high importance for the clinical care of veterans with PTSD and mTBI. Service members should be evaluated for mental health problems and sleep quality disturbances even before deployment to assess the individual risk status and to implement preventive efforts. Moreover, returning veterans should be carefully monitored for emerging sleep quality disturbances and associated brain structural alterations. Novel treatment options may assist standard care procedures in alleviating sleep disturbances.

9.5.1. Early Identification of At-Risk Patients

The current findings suggest a close monitoring and early treatment interventions regarding sleep quality complaints in veterans. Identifying at-risk patients even before deployment may be a powerful way to prevent patient and health-care burden. As outlined earlier, several environmental, social, economic, genetic, and neurophysiological factors influence the likelihood of developing PTSD, mTBI, and poor sleep quality. Individuals from a low socio-economic background [87,222], who struggle with pre-existing mental health conditions [87,223], including sleep quality disturbances [353,589], are more prone to developing PTSD and mTBI after a traumatic life experience. Indeed, poor sleep quality is not only a resulting symptom of deployment-related traumatic experiences, but also a risk factor for the development of PTSD [353,580,581,589,590], post-concussive symptoms [265,591], and associated brain structural impairments [177,580–583]. In fact, pre-deployment sleep quality disturbances are

predictive of PTSD re-experiencing symptoms three- and six-months post-deployment, even independently of combat-stress severity [581]. In line with the diathesis-stress model of PTSD [592], pre-existing sleep quality disturbances interact with social, environmental and biophysiological diatheses to elicit PTSD symptoms after a traumatic event [581,592]. Individuals with a greater variety of premorbid factors (including sleep quality disturbances) are more vulnerable to show aversive reactions to even less severe stressors [592]. Sleep quality disturbances are considered a diathesis that facilitates the development of mental health problems when encountering a traumatic life experience [353,580,581,589,590]. Especially impairments of specific sleep stages have been thought to predispose veterans to exhibit mental health symptoms post-deployment [590]. While REM sleep disturbances are a characteristic following both PTSD [19,386] and mTBI [593], REM sleep impairments most likely also facilitate the development of mental disorders, as it has been shown that impaired REM sleep is associated with lack of fear extinction and safety learning [594]. In fact, *restless REM sleep* is marked by high arousal and eye movements that impair the overnight resolution of distress and lead to continuous amygdala reactivity [388], and chronic hyperarousal [387], facilitating the emergence and maintenance of psychiatric symptoms.

Just like several environmental, social, economic, genetic, and neurophysiological factors influence the likelihood of developing PTSD and mTBI, disrupted sleep emerges due to the interplay of various etiological factors. Genetic studies suggest a heritability for PTSD [115], mTBI [267], and sleep quality complaints [595–597]. Genes that are involved in alterations of the HPA axis, such as the FKBP5 gene [122], Val158Met polymorphism of the Catechol-O-methyltransferase gene [123], and a genetic variation of the CRP gene [125] contribute to the development of PTSD [124], most importantly the hyperarousal symptoms [126] that have repeatedly been linked to sleep quality disturbances [210,534]. Indeed, substantial genetic overlap has been identified between PTSD and sleep quality impairments, such as insomnia [598], providing an explanation for the common co-occurrence of the conditions and bi-directional relationship [599]. Similarly, genetic polymorphisms that control inflammatory markers, such as TNF-α, IL-1, and IL-6 and those that regulate the circadian rhythm influence mTBI outcome and associated sleep quality disturbances [267,600–603]. Indeed, insomnia symptoms that improve after standard treatment correlate with altered expression of inflammatory genes in military personnel [604]. Shared genetic etiology suggests that genetic testing may be highly informative for identifying at-risk patients even before deployment. However, the interest in genetic testing to evaluate risk status for poor mental health outcome is still relatively low among veterans, calling for educative interventions that outline potential benefits [605].

Neuroimaging markers may additionally assist in identifying service members prone to developing poor neuropsychiatric outcome, including sleep quality disturbances. While it is assumed that trauma-related sleep quality disturbances affect white matter health through impaired glymphatic brain waste clearance [411–414], and compromised myelin deposition and genesis processes [416], it is similarly possible that white matter microstructural architecture that is already compromised before deployment predisposes for the development of sleep quality disturbances. In fact, while several studies have shown white matter alterations in patients with PTSD [41,43–58,183], it has not been evaluated whether white matter alterations before encountering a traumatic life event predict the development of PTSD and associated sleep quality disturbances. A recent study revealed that white matter alterations of fronto-limbic fiber tracts one month following trauma predicted PTSD symptoms after three months [606]. It is conceivable that at-risk individuals with a genetic predisposition to developing sleep quality disturbances, PTSD, and persistent post-concussive symptoms exhibit structural brain alterations that render the brain vulnerable for poor mental outcome after trauma. As outlined earlier, smaller hippocampal volumes [142–144] have been suggested as a genetic predisposition to PTSD [150]. Similarly, smaller hippocampal volumes were shown in individuals with mTBI [274–279] and have further been associated with poor sleep quality [280–282]. Moreover, abnormalities in several functional connectivity networks have been linked to both PTSD [167] and mTBI [301–305]. Especially the hyperarousal and re-experiencing symptoms of PTSD that are closely linked to sleep quality disturbances [210,534] have repeatedly been associated with altered amygdala-frontal connectivity [112,167]. Similarly, mTBI has been linked to wide-spread disruptions in large-scale brain networks [301–305], leading to neuropsychiatric sequalae [363]. In fact, disruptions in major networks, such as the default mode network, have been shown to mediate the association between sleep disturbances and mental health problems [607]. Pre-existing alterations in brain structure and function may, thus, increase the likelihood of developing sleep quality disturbances (both pre- and post-deployment) that further translate into poor mental health outcome and compromised brain health.

In summary, research to date suggests bi-directional relationships between sleep quality disturbances, brain alterations, and mental health outcome. Unfortunately, the cross-sectional nature of the present work precludes the inference of causal conclusions. While it has been suggested that sleep quality disturbances account for the relationship between PTSD symptoms and global white matter alterations, altered brain structure may have been present even before deployment and predisposed to poor outcome. Indeed, previous research suggests that various social, economic, environmental, genetic, and neurophysiological factors contribute to an

individual's disposition for the development of PTSD and associated sleep quality disturbances. Future research will reveal whether neuropsychiatric screening, genetic testing, and brain imaging can pinpoint reliable markers to identify individuals at risk for poor outcome after deployment.

9.5.2. Treatment of Sleep Quality Disturbances in Veterans

The present work identified a strong relationship between PTSD symptoms and sleep quality disturbances. However, it is crucial to highlight that while PTSD has been shown to illicit sleep quality disturbances [370], sleep quality disturbances also perpetuate PTSD symptomatology [608]. First-line treatments for PTSD frequently fail to alleviate sleep problems, even when other PTSD symptoms subside [35,36]. Persistent disruptions in sleep quality may, in turn, increase the risk to maintain PTSD symptoms, resulting in a vicious cycle [36,609]. On the contrary, treatment strategies aimed at improving sleep quality may also help with overall PTSD symptom resolution [20,36,610,611], given that restorative sleep is required for the remission of anxiety [612,613] and thus aids with the emotional processing of traumatic experiences [369]. In fact, addressing poor sleep quality is often an essential initial treatment target when commencing a trauma therapy in order to strengthen the required emotional coping mechanisms and cognitive resources [614]. Moreover, since sleep-targeted interventions are less stigmatized than mental health therapies, they may result in improved acceptability and compliance rates, encouraging more veterans to seek the necessary professional support [615].

Cognitive behavioral therapy for insomnia (CBTi) is a widely accepted intervention for treating sleep quality disturbances that combines cognitive therapy and education on sleep hygiene and bedtime relaxation and was rated beneficial for veterans [616]. As a multiple approach treatment that combines several different strategies, CBTi relies on cognitive therapy but also includes strategies for reducing hyperarousal, and promoting circadian rhythm regulation by following a sleep schedule [617]. Maladaptive associations with bedtime or the sleeping environment are targeted over six to eight weeks. Patients are encouraged to set fixed sleeping and waking times, and to keep sleep diaries. Cognitive therapy changes distorted negative thoughts and believes around sleep and nighttime, while relaxation techniques are practiced to reduce the hyperarousal symptoms [617]. Positive changes are not only seen in subjective but also objective measures of sleep quality, such as significant increases in REM sleep [618]. Especially CBTi with adjunctive psychotherapy appears to be of value [616]. Accompanying psychotherapy may include image rehearsal, rescripting, exposure, or relaxation therapy [616]. The treatments aim at alleviating PTSD symptoms and may be especially important for patients who primarily

struggle with nightmares. Nightmares have been described as “uncontrolled re-exposure” of the traumatic event that fuel the maintenance of PTSD [466]. In image rehearsal therapy, the patient is instructed to change the narrative and storyline of a recurrent nightmare and to rehearse the new positive version multiple times. Successes from practicing the new pleasant dreams have been observed already after a couple of weeks [619,620]. Moreover, exposure therapy, a treatment option that is generally applied for alleviating post-traumatic memories [621], has been adapted to serve nightmare cessation. Exposure consists of a gradual approach to trauma-related content until habituation is achieved. The patient may be instructed to focus on nightmare content that gradually increases in intensity [376]. In addition, audio recordings of imaginal exposures are used to practice between sessions [622]. Other exposure treatments may additionally incorporate psychoeducation and sleep hygiene, nightmare image rehearsal therapy, and relaxation techniques [376]. CBTi and adjunctive exposure therapy have been found to reduce both PTSD and insomnia symptoms and enhance quality of life [623]. Moreover, it is important to note that in some cases CBTi is applied to stabilize a patient before even starting exposure therapy. Exposure therapy for PTSD can be highly challenging, and establishing adaptive coping mechanisms before commencing the treatment can be a great source of support [624]. Sleep therapies may thus not only be beneficial for treating sleep quality disturbances but also prepare for trauma therapy.

In addition to psychotherapy, pharmacotherapy is often used to complement other methods when treating sleep quality disturbances related to trauma [625]. Antidepressants and antipsychotics exert sedative effects, but only antipsychotics have been found moderately effective in treating PTSD-related sleep quality disturbances [626]. While benzodiazepines are sometimes used in the treatment of nightmares, their highly addictive nature [627] and rather disappointing treatment outcome do not support their appliance as a first-line treatment for sleep quality disturbances [626]. Instead, the anti-hypertensive drug prazosin has surprisingly been found to reduce symptoms of insomnia, nightmares, and overall PTSD symptomatology [626,628]. Prazosin blocks abnormally high noradrenergic activity in PTSD patients [19,209], decreases hyperarousal symptoms [210], and has been shown to be particularly effective against nightmares [19,629].

9.5.3. Treatment Impact on Brain Structure and Function

While several approaches to treat sleep quality disturbances in the veteran population exist, their effect on brain structure and function has rarely been assessed. There is evidence that pharmacotherapy and psychological interventions for PTSD can exert beneficial effects on

brain structure and function, such as increases in hippocampal volume, a reduction in amygdala activity, and a concurrent increase in dorsolateral prefrontal cortex activity [522,630]. However, research on the effect of treatment for sleep quality disturbances on brain structure and function is scarce. A small study with insomnia patients showed decreased activity in the precentral, prefrontal, fusiform, and posterior cingulate cortices in response to sleep-related stimuli after CBTi treatment [631]. Clinical improvements in sleep quality correlated with brain activity [631]. While this is promising, no reports on a potential history of psychological or physical trauma have been made in this sample. Moreover, the effect of treatment on trauma-related sleep quality disturbances and gray or white matter structure has not yet been explored. A few studies reviewed treatment effects for obstructive sleep apnea on neuropsychological outcome, and brain structure. Increased hippocampal and frontal gray matter volume that correlated with improvements in neuropsychological functioning was observed after treatment [479]. Moreover, white matter diffusion measures that were lower than those of control participants at baseline approximated control levels after treatment [632]. Interventions for obstructive sleep apnea, such as continuous positive airway pressure [587], are obviously different from the psychological and pharmacological interventions applied to treat trauma-related sleep quality disturbances. However, obstructive sleep apnea is fairly common among veterans [633] and strongly associated with PTSD and mTBI [475]. In fact, sleep apnea is often accompanied by other sleep disturbances, such as insomnia [476], and should thus be considered in future diagnostic and treatment efforts in the veteran population.

Further research is required to elucidate the effects of different treatment methods for sleep quality disturbances on brain structure and function. Besides sleep-targeted psychological interventions and current pharmacotherapies, newer approaches, such as neurofeedback [634,635], may constitute a promising therapeutic tool for improving sleep quality and brain health. Neurofeedback involves the conditioned learning of self-regulating brain activity [636]. Specifically, a positive stimulus is presented together with desired EEG activity, supporting certain brain states over others. In the case of sleep quality disturbances, a patient may be conditioned to produce more large-amplitude delta waves to decrease arousal and induce tranquility [637]. Initial studies suggest that neurofeedback is effective in treating sleep quality disturbances [637,638] and PTSD symptoms [639], although future research needs to confirm the findings. Interestingly, neurofeedback may directly improve white matter health by increasing myelinization [634,635]. Together with the above-mentioned psychotherapeutic and pharmacological interventions, neurofeedback may, thus, assist with battling trauma-related sleep quality disturbances and compromised brain health.

10. Conclusion

Findings from the present work suggest that sleep quality plays a vital role in mental and brain health of veterans. Veterans with PTSD and comorbid PTSD+mTBI experienced poorer sleep quality than veterans with mTBI only or no history of PTSD or mTBI, underscoring the profound association between deployment-related PTSD and poor sleep quality. HPA axis disturbances and abnormally high norepinephrine activity in the brain that persists throughout day and night have been suggested to account for the strong relationship between traumatic stress and poor sleep quality. Importantly, poor sleep quality mediated the relationship between PTSD symptom severity and white matter microstructural alterations among veterans with comorbid PTSD+mTBI, independently of neuropsychiatric comorbidities, warzone-related stress, BMI, psychiatric medication use, race, and education. Various social, economic, environmental, genetic, and neurophysiological factors that impact PTSD and mTBI ultimately contribute to biological processes that enable and maintain sleep quality disturbances and brain abnormalities. It is possible that the observed white matter microstructural alterations emerge due to impaired myelin repair processes, given that sleep is necessary for lipid biosynthesis, and oligodendrocyte precursor proliferation that are crucial for myelin genesis and deposition. Moreover, poor sleep quality has been associated with insufficient brain waste clearance through the perivascular glymphatic system, which is vital for flushing out accumulated neurotoxins. An accumulation of brain waste products, such as beta-amyloid and tau, has been linked to neurodegenerative processes, including impaired myelination. Notably, the current work employed self-report assessments of sleep quality, precluding inferences to objectively assessed sleep quality. Discrepancies between self-reported and device-assessed sleep quality have been noted, indicating that veterans may rate their sleep as poorer than depicted by actigraphy or polysomnography. Future studies are needed to assess the level of consensus between subjective and objective measures of sleep quality. Nevertheless, self-reported sleep quality has proven as a valuable indicator of mental and brain health that should be considered when investigating the impact of trauma-related sleep disturbances on white matter structure. Given the importance of white matter health for successful signal transmission amongst various brain networks and neuropsychiatric functioning, effective preventive and treatment strategies are urgently required. Future research is needed to examine whether novel sleep-targeted interventions can complement treatment-as-usual in supporting overall brain health of veterans suffering from PTSD and mTBI.

References

1. Costs of war – US veterans and military families. Watson Institute of International and Public Affairs. https://watson.brown.edu/costsofwar/costs/human/veterans. Published 2015.
2. Committee on the initial assessment of readjustment needs of military personnel veterans and their families. Returning home from Iraq and Afghanistan: Preliminary assessment of readjustment needs of veterans, service members, and their families. In: Washington, D.C.: The National Academies Press; 2010.
3. Casualty status. U.S. Department of Defense. https://www.defense.gov/Newsroom/Casualty-Status//. Published 2019.
4. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004;351(1):13-22. doi:10.1056/NEJMoa040603
5. Lippa SM, Fonda JR, Fortier CB, et al. Deployment-Related psychiatric and behavioral conditions and their association with functional disability in OEF/OIF/OND veterans. *J Trauma Stress*. 2015;28(1):25-33. doi:10.1002/jts.21979
6. Ramchand R, Rudavsky R, Grant S, Tanielian T, Jaycox L. Prevalence of, risk factors for, and consequences of posttraumatic stress disorder and other mental health problems in military populations deployed to Iraq and Afghanistan. *Curr Psychiatry Rep*. 2015;17(5):37. doi:10.1007/s11920-015-0575-z
7. Callahan DJ. Combat-related mental health disorders: The case for resiliency in the long war. *J Am Osteopath Assoc*. 2010;110(9):520-527. doi:20876837
8. Simon NM, Hoeppner SS, Lubin RE, et al. Understanding the impact of complicated grief on combat related posttraumatic stress disorder, guilt, suicide, and functional impairment in a clinical trial of post-9/11 service members and veterans. *Depress Anxiety*. 2020;37(1):63-72. doi:10.1002/da.22911
9. Brady KT, Tuerk P, Back SE, Saladin ME, Waldrop AE, Myrick H. Combat posttraumatic stress disorder, substance use disorders, and traumatic brain injury. *J Addict Med*. 2009;3(4):179-188. doi:10.1097/ADM.0b013e3181aa244f
10. Larson MJ, Wooten NR, Adams RS, Merrick EL. Military combat deployments and substance use: Review and future directions. *J Soc Work Pract Addict*. 2012;12(1):6-27. doi:10.1080/1533256X.2012.647586
11. Sipos ML, Bar-Haim Y, Abend R, Adler AB, Bliese PD. Postdeployment threat-related attention bias interacts with combat exposure to account for PTSD and anxiety symptoms

in soldiers. *Depress Anxiety*. 2014;31(2):124-129. doi:10.1002/da.22157

12. Lagarde E, Salmi L-R, Holm LW, et al. Association of symptoms following mild traumatic brain injury with posttraumatic stress disorder vs. postconcussion syndrome. *JAMA Psychiatry*. 2014;71(9):1032-1040. doi:10.1001/jamapsychiatry.2014.666
13. Miller SC, Whitehead CR, Otte CN, et al. Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of US Air Force personnel. *Occup Environ Med*. 2015;72(8):560-566. doi:10.1136/oemed-2014-102646
14. Vanderploeg RD, Belanger HG, Curtiss G. Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. *Arch Phys Med Rehabil*. 2009;90(7):1084-1093. doi:10.1016/j.apmr.2009.01.023
15. Vasterling JJ, Aslan M, Lee LO, et al. Longitudinal associations among posttraumatic stress disorder symptoms, traumatic brain injury, and neurocognitive functioning in Army soldiers deployed to the Iraq war. *J Int Neuropsychol Soc*. 2018;24(4):311-323. doi:10.1017/S1355617717001059
16. Warren AM, Boals A, Elliott TR, et al. Mild traumatic brain injury increases risk for the development of posttraumatic stress disorder. *J Trauma Acute Care Surg*. 2015;79(6):1062-1066. doi:10.1097/TA.0000000000000875
17. Scurfield RM. *War Trauma and Its Wake*. New York: Routledge; 2012. doi:10.4324/9780203126707
18. Tanev KS, Pentel KZ, Kredlow MA, Charney ME. PTSD and TBI co-morbidity: Scope, clinical presentation and treatment options. *Brain Inj*. 2014;28(3):261-270. doi:10.3109/02699052.2013.873821
19. Germain A. Sleep disturbances as the hallmark of PTSD: Where are we now? *Am J Psychiatry*. 2013;170(4):372-382. doi:10.1176/appi.ajp.2012.12040432
20. Khazaie H. Sleep disturbances in veterans with chronic war-induced PTSD. *J Inj Violence Res*. 2016;8(2):99-107. doi:10.5249/jivr.v8i2.808
21. Grima N, Ponsford J, Rajaratnam SM, Mansfield D, Pase MP. Sleep disturbances in traumatic brain injury: A meta-analysis. *J Clin Sleep Med*. 2016;12(3):419-428. doi:10.5664/jcsm.5598
22. Mathias JL, Alvaro PK. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: A meta-analysis. *Sleep Med*. 2012;13(7):898-905. doi:10.1016/j.sleep.2012.04.006
23. Gilbert KS, Kark SM, Gehrman P, Bogdanova Y. Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clin Psychol Rev*. 2015;40(3):195-212.

doi:10.1016/j.cpr.2015.05.008

24. Wycoco V, Shroff M, Sudhakar S, Lee W. White matter anatomy. What the radiologist needs to know. *Neuroimaging Clin N Am*. 2013;23(2):197-216. doi:10.1016/j.nic.2012.12.002
25. Fields RD. Change in the brain's white matter. *Science*. 2010;330(6005):768-769. doi:10.1126/science.1199139
26. DeGutis J, Chiu C, Thai M, Esterman M, Milberg W, McGlinchey R. Trauma sequelae are uniquely associated with components of self-reported sleep dysfunction in OEF/OIF/OND veterans. *Behav Sleep Med*. 2018;16(1):38-63. doi:10.1080/15402002.2016.1173550
27. Davenport ND, Lamberty GJ, Nelson NW, Lim KO, Armstrong MT, Sponheim SR. PTSD confounds detection of compromised cerebral white matter integrity in military veterans reporting a history of mild traumatic brain injury. *Brain Inj*. 2016;30(12):1491-1500. doi:10.1080/02699052.2016.1219057
28. Lepage C, Pasternak O, Bouix S, et al. White matter abnormalities in mild traumatic brain injury with and without post-traumatic stress disorder: a subject-specific diffusion tensor imaging study. *Brain Imaging Behav*. 2017;12(3):870-881. doi:10.1007/s11682-017-9744-5
29. Santhanam P, Teslovich T, Wilson SH, Yeh P-H, Oakes TR, Weaver LK. Decreases in white matter integrity of ventro-limbic pathway linked to post-traumatic stress disorder in mild traumatic brain injury. *J Neurotrauma*. 2019;36(7):1093-1098. doi:10.1089/neu.2017.5541
30. Lopez KC, Leary JB, Pham DL, Chou Y-Y, Dsurney J, Chan L. Brain volume, connectivity, and neuropsychological performance in mild traumatic brain injury: The impact of post-traumatic stress disorder symptoms. *J Neurotrauma*. 2017;34(1):16-22. doi:10.1089/neu.2015.4323
31. Rosen J, Reynolds CF, Yeager AL, Houck PR, Hurwitz LF. Sleep disturbances in survivors of the Nazi Holocaust. *Am J Psychiatry*. 1991;148(1):62-66. doi:10.1176/ajp.148.1.62
32. Lavie P, Hefez A, Halperin G, Enoch D. Long-term effects of traumatic war-related events on sleep. *Am J Psychiatry*. 1979;136(2):175-178. doi:10.1176/ajp.136.2.175
33. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: Epidemiology, impact and approaches to management. *CNS Drugs*. 2006;20(7):567-590. doi:10.2165/00023210-200620070-00003

34. McCarthy E, DeViva JC, Norman SB, Southwick SM, Pietrzak RH. Self-assessed sleep quality partially mediates the relationship between PTSD symptoms and functioning and quality of life in U.S. veterans: Results from the National Health and Resilience in Veterans Study. *Psychol Trauma Theory, Res Pract Policy*. 2019;11(8):869-876. doi:10.1037/tra0000436

35. Colvonen PJ, Ellison J, Haller M, Norman SB. Examining insomnia and PTSD over time in veterans in residential treatment for substance use disorders and PTSD. *Behav Sleep Med*. 2019;17(4):524-535. doi:10.1080/15402002.2018.1425869

36. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? *Sleep Med Rev*. 2008;12(3):169-184. doi:10.1016/j.smrv.2007.08.008

37. Koerte IK, Muehlmann M. Diffusion Tensor Imaging. In: *MRI in Psychiatry*. Berlin, Heidelberg: Springer; 2014:77-86. doi:10.1007/978-3-642-54542-9

38. McDonough IM, Siegel JT. The relation between white matter microstructure and network complexity: Implications for processing efficiency. *Front Integr Neurosci*. 2018;12:1-15. doi:10.3389/fnint.2018.00043

39. Teipel SJ, Bokde ALW, Meindl T, et al. White matter microstructure underlying default mode network connectivity in the human brain. *Neuroimage*. 2010;49(3):2021-2032. doi:10.1016/j.neuroimage.2009.10.067

40. Fields RD. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci*. 2008;31(7):361-370. doi:10.1016/j.tins.2008.04.001

41. Schuff N, Zhang Y, Zhan W, et al. Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: An MRI study. *Neuroimage*. 2011;54(Suppl1):S62-S68. doi:10.1016/j.neuroimage.2010.05.024

42. Aschbacher K, Mellon SH, Wolkowitz OM, et al. Posttraumatic stress disorder, symptoms, and white matter abnormalities among combat-exposed veterans. *Brain Imaging Behav*. 2018;12(4):989-999. doi:10.1007/s11682-017-9759-y

43. Ju Y, Ou W, Su J, et al. White matter microstructural alterations in posttraumatic stress disorder: An ROI and whole-brain based meta-analysis. *J Affect Disord*. 2020;266:655-670. doi:10.1016/j.jad.2020.01.047

44. O'Doherty DCM, Ryder W, Paquola C, et al. White matter integrity alterations in post-traumatic stress disorder. *Hum Brain Mapp*. 2018;39(3):1327-1338. doi:10.1002/hbm.23920

45. Siehl S, King JA, Burgess N, Flor H, Nees F. Structural white matter changes in adults

and children with posttraumatic stress disorder: A systematic review and meta-analysis. *NeuroImage Clin*. 2018;19:581-598. doi:10.1016/j.nicl.2018.05.013

46. Graziano R, Bruce S, Paul R. The Corpus Callosum and PTSD Severity. *J Interpers Violence*. 2021;36(15-16):7480-7494. doi:10.1177/0886260519835007
47. Olson EA, Cui J, Fukunaga R, Nickerson LD, Rauch SL, Rosso IM. Disruption of white matter structural integrity and connectivity in posttraumatic stress disorder: A TBSS and tractography study. *Depress Anxiety*. 2017;34(5):437-445. doi:10.1002/da.22615
48. Averill CL, Averill LA, Wrocklage KM, et al. Altered white matter diffusivity of the cingulum angular bundle in posttraumatic stress disorder. *Complex Psychiatry*. 2018;4(2):75-82. doi:10.1159/000490464
49. Koch SBJ, Van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. Decreased uncinate fasciculus tract integrity in male and female patients with PTSD: A diffusion tensor imaging study. *J Psychiatry Neurosci*. 2017;42(5):331-342. doi:10.1503/jpn.160129
50. McCunn P, Richardson JD, Jetly R, Dunkley B. Diffusion tensor imaging reveals white matter differences in military personnel exposed to trauma with and without post-traumatic stress disorder. *Psychiatry Res*. 2021;298:113797. doi:10.1016/j.psychres.2021.113797
51. Dennis EL, Disner SG, Fani N, et al. Altered white matter microstructural organization in posttraumatic stress disorder across 3047 adults: Results from the PGC-ENIGMA PTSD consortium. *Mol Psychiatry*. 2021;26(8):4315-4330. doi:10.1038/s41380-019-0631-x
52. Bierer LM, Ivanov I, Carpenter DM, et al. White matter abnormalities in Gulf War veterans with posttraumatic stress disorder: A pilot study. *Psychoneuroendocrinology*. 2015;51:567-576. doi:10.1016/j.psyneuen.2014.11.007
53. Sanjuan PM, Thoma R, Claus ED, Mays N, Caprihan A. Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: A diffusion tensor imaging study. *Psychiatry Res Neuroimaging*. 2013;214(3):260-268. doi:10.1016/j.pscychresns.2013.09.002
54. Kennis M, van Rooij SJH, Tromp DPM, et al. Treatment outcome-related white matter differences in veterans with posttraumatic stress disorder. *Neuropsychopharmacology*. 2015;40(10):2434-2442. doi:10.1038/npp.2015.94
55. Hedges DW, Thatcher GW, Bennett PJ, et al. Brain integrity and cerebral atrophy in Vietnam combat veterans with and without posttraumatic stress disorder. *Neurocase*.

2007;13(5-6):402-410. doi:10.1080/13554790701851551

56. Daniels JK, Lamke JP, Gaebler M, Walter H, Scheel M. White matter integrity and its relationship to PTSD and childhood trauma - A systematic review and meta-analysis. *Depress Anxiety*. 2013;30(3):207-216. doi:10.1002/da.22044
57. Abe O, Yamasue H, Kasai K, et al. Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism. *Psychiatry Res - Neuroimaging*. 2006;146(3):231-242. doi:10.1016/j.pscychresns.2006.01.004
58. Harnett NG, Goodman AM, Knight DC. PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. *Exp Neurol*. 2020;330:113331. doi:10.1016/j.expneurol.2020.113331
59. Dailey NS, Smith R, Bajaj S, et al. Elevated aggression and reduced white matter integrity in mild traumatic brain injury: A DTI study. *Front Behav Neurosci*. 2018;12:118. doi:10.3389/fnbeh.2018.00118
60. Nakayama N, Okumura A, Shinoda J, Yasokawa Y-T, Miwa K, Yoshimura S-I. Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. *J Neurol Neurosurg Psychiatry*. 2006;77:850-855. doi:10.1136/jnnp.2005.077875
61. Petrie EC, Cross DJ, Yarnykh VL, et al. Neuroimaging, behavioral, and psychological sequelae of repetitive combined blast/impact mild traumatic brain injury in Iraq and Afghanistan war veterans. *J Neurotrauma*. 2014;31(5):425-436. doi:10.1089/neu.2013.2952
62. Rutgers DR, Fillard P, Paradot G, Tadié M, Lasjaunias P, Ducreux D. Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *Am J Neuroradiol*. 2008;29(9):1730-1735. doi:10.3174/ajnr.A1213
63. Mu W, Catenaccio E, Lipton ML. Neuroimaging in blast-related mild traumatic brain injury. *J Head Trauma Rehabil*. 2017;32(1):55-69. doi:10.1097/HTR.0000000000000213
64. Wallace EJ, Mathias JL, Ward L. Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: A meta-analysis. *Brain Imaging Behav*. 2018;12(6):1607-1621. doi:10.1007/s11682-018-9823-2
65. Xiong K, Zhu Y, Zhang Y, et al. White matter integrity and cognition in mild traumatic brain injury following motor vehicle accident. *Brain Res*. 2014;1591(1):86-92. doi:10.1016/j.brainres.2014.10.030

66. Fakhran S, Yaeger K, Alhilali L. Symptomatic white matter changes in mild traumatic brain injury resemble pathologic features of early Alzheimer dementia. *Radiology*. 2013;269(1):249-257. doi:10.1148/radiol.13122343

67. Raikes AC, Bajaj S, Dailey NS, et al. Diffusion Tensor Imaging (DTI) correlates of self-reported sleep quality and depression following mild traumatic brain injury. *Front Neurol*. 2018;9:468. doi:10.3389/fneur.2018.00468

68. Khalsa S, Hale JR, Goldstone A, et al. Habitual sleep durations and subjective sleep quality predict white matter differences in the human brain. *Neurobiol Sleep Circadian Rhythm*. 2017;3:17-25. doi:10.1016/j.nbscr.2017.03.001

69. Yaffe K, Nasrallah I, Hoang TD, et al. Sleep duration and white matter quality in middle-aged adults. *Sleep*. 2016;39(9):1743-1747. doi:10.5665/sleep.6104

70. Bresser T, Foster-Dingley JC, Wassing R, et al. Consistent altered internal capsule white matter microstructure in insomnia disorder. *Sleep*. 2020;43(8):1-8. doi:10.1093/sleep/zsaa031

71. Sexton CE, Zsoldos E, Filippini N, et al. Associations between self-reported sleep quality and white matter in community-dwelling older adults: A prospective cohort study. *Hum Brain Mapp*. 2017;38(11):5465-5473. doi:10.1002/hbm.23739

72. Spiegelhalder K, Regen W, Prem M, et al. Reduced anterior internal capsule white matter integrity in primary insomnia. *Hum Brain Mapp*. 2014;35(7):3431-3438. doi:10.1002/hbm.22412

73. Li S, Tian J, Bauer A, et al. Reduced integrity of right lateralized white matter in patients with primary insomnia: A diffusion-tensor imaging study. *Radiology*. 2016;280(2):520-528. doi:10.1148/radiol.2016152038

74. Kang JM, Joo SW, Son YD, et al. Low white-matter integrity between the left thalamus and inferior frontal gyrus in patients with insomnia disorder. *J Psychiatry Neurosci*. 2018;43(6):366-374. doi:10.1503/jpn.170195

75. Cai W, Zhao M, Liu J, Liu B, Yu D, Yuan K. Right arcuate fasciculus and superior longitudinal fasciculus abnormalities in primary insomnia. *Brain Imaging Behav*. 2019;13(6):1746-1755. doi:10.1007/s11682-019-00160-1

76. Kocevska D, Tiemeier H, Lysen TS, et al. The prospective association of objectively measured sleep and cerebral white matter microstructure in middle-aged and older persons. *Sleep*. 2019;42(10):1-8. doi:10.1093/sleep/zsz140

77. Lu F-M, Dai J, Couto TA, et al. Diffusion tensor imaging tractography reveals disrupted white matter structural connectivity network in healthy adults with insomnia symptoms.

Front Hum Neurosci. 2017;11:1-11. doi:10.3389/fnhum.2017.00583

78. Zhang F, Wu Y, Norton I, et al. An anatomically curated fiber clustering white matter atlas for consistent white matter tract parcellation across the lifespan. *Neuroimage*. 2018;179:429-447. doi:10.1016/j.neuroimage.2018.06.027
79. O'Donnell LJ, Wells WM, Golby AJ, Westin C-F. Unbiased groupwise registration of white matter tractography. *Med Image Comput Comput Assist Interv*. 2012;15:123-130. doi:10.1007/978-3-642-33454-2_16
80. O'Donnell LJ, Westin CF. Automatic tractography segmentation using a high-dimensional white matter atlas. *IEEE Trans Med Imaging*. 2007;26(11):1562-1575. doi:10.1109/TMI.2007.906785
81. O'Donnell LJ, Kubicki M, Shenton ME, Dreusicke MH, Grimson WEL, Westin CF. A method for clustering white matter fiber tracts. *Am J Neuroradiol*. 2006;27(5):1032-1036.
82. Fulton JJ, Calhoun PS, Wagner HR, et al. The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans: A meta-analysis. *J Anxiety Disord*. 2015;31:98-107. doi:10.1016/j.janxdis.2015.02.003
83. Trivedi RB, Post EP, Sun H, et al. Prevalence, comorbidity, and prognosis of mental health among US veterans. *Am J Public Health*. 2015;105(12):2564-2569. doi:10.2105/AJPH.2015.302836
84. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. In: Washington, DC: Arlington, VA; 2013.
85. McGuinness TM, Waldrop JR. Adverse childhood experiences and the mental health of veterans. *J Psychosoc Nurs Ment Health Serv*. 2015;53(6):23-26. doi:10.3928/02793695-20150527-55
86. Aronson KR, Perkins DF, Morgan NR, et al. The impact of adverse childhood experiences (ACEs) and combat exposure on mental health conditions among new post-9/11 veterans. *Psychol Trauma Theory, Res Pract Policy*. 2020;12(7):698-706. doi:10.1037/tra0000614
87. Xue C, Ge Y, Tang B, et al. A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans. *PLoS One*. 2015;10(3):1-21. doi:10.1371/journal.pone.0120270
88. Boscarino JA. Post-traumatic stress and associated disorders among Vietnam veterans: The significance of combat exposure and social support. *J Trauma Stress*. 1995;8(2):317-336. doi:10.1007/BF02109567

89. Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychol Bull*. 2006;132(6):959-992. doi:10.1037/0033-2909.132.6.959

90. Bustamante LHU, Cerqueira RO, Leclerc E, Brietzke E. Stress, trauma, and posttraumatic stress disorder in migrants: A comprehensive review. *Rev Bras Psiquiatr*. 2018;40(2):220-225. doi:10.1590/1516-4446-2017-2290

91. Bryant RA. Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. *World Psychiatry*. 2019;18(3):259-269. doi:10.1002/wps.20656

92. Daskalakis NP, Lehrner A, Yehuda R. Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. *Endocrinol Metab Clin North Am*. 2013;42(3):503-513. doi:10.1016/j.ecl.2013.05.004

93. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin Neurosci*. 2006;8(4):383-395. doi:10.31887/DCNS.2006.8.4/ssmith

94. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol*. 2016;8(4):603-621. doi:10.1002/cphy.c150015

95. Myers B, McKlveen JM, Herman JP. Glucocorticoid actions on synapses, circuits, and behavior: Implications for the energetics of stress. *Front Neuroendocrinol*. 2014;35(2):180-196. doi:10.1016/j.yfrne.2013.12.003

96. Sherin J, Nemeroff C. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. *Dialogues Clin Neurosci*. 2011;13(3):263-278. doi:10.31887/DCNS.2011.13.2/jsherin

97. Meewisse ML, Reitsma JB, De Vries GJ, Gersons BPR, Olff M. Cortisol and post-traumatic stress disorder in adults: Systematic review and meta-analysis. *Br J Psychiatry*. 2007;191:387-392. doi:10.1192/bjp.bp.106.024877

98. Morris MC, Compas BE, Garber J. Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: A systematic review and meta-analysis. *Clin Psychol Rev*. 2012;32(4):301-315. doi:10.1016/j.cpr.2012.02.002

99. Daskalakis NP, Mcgill MA, Lehrner A, Yehuda R. *Comprehensive Guide to Post-Traumatic Stress Disorder*. Cham: Springer; 2014. doi:10.1007/978-3-319-08613-2

100. Van der Kolk B. Posttraumatic stress disorder and the nature of trauma. *Dialogues Clin Neurosci*. 2000;2(1):7-22. doi:10.31887/DCNS.2000.2.1/bvdkolk

101. Yehuda R, Hoge CW, McFarlane AC, et al. Post-traumatic stress disorder. *Nat Rev Dis*

Prim. 2015;1:1-22. doi:10.1038/nrdp.2015.57

102. McFarlane AC, Barton CA, Yehuda R, Wittert G. Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology*. 2011;36(5):720-727. doi:10.1016/j.psyneuen.2010.10.007
103. Mouthaan J, Sijbrandij M, Luitse JSK, Goslings JC, Gersons BPR, Olff M. The role of acute cortisol and DHEAS in predicting acute and chronic PTSD symptoms. *Psychoneuroendocrinology*. 2014;45:179-186. doi:10.1016/j.psyneuen.2014.04.001
104. Yehuda R, McFarlane AC, Shalev AY. Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biol Psychiatry*. 1998;44(12):1305-1313. doi:10.1016/S0006-3223(98)00276-5
105. Chou CY, La Marca R, Steptoe A, Brewin CR. Biological responses to trauma and the development of intrusive memories: An analog study with the trauma film paradigm. *Biol Psychol*. 2014;103:135-143. doi:10.1016/j.biopsycho.2014.08.002
106. Galatzer-Levy IR, Steenkamp MM, Brown AD, et al. Cortisol response to an experimental stress paradigm prospectively predicts long-term distress and resilience trajectories in response to active police service. *J Psychiatr Res*. 2014;56(5):36-42. doi:10.1016/j.jpsychires.2014.04.020
107. Kobayashi I, Delahanty DL. Awake/sleep cortisol levels and the development of posttraumatic stress disorder in injury patients with peritraumatic dissociation. *Psychol Trauma Theory, Res Pract Policy*. 2014;6(5):449-456. doi:10.1037/a0033013
108. Hendrickson RC, Raskind MA. Noradrenergic dysregulation in the pathophysiology of PTSD. *Exp Neurol*. 2016;284:181-195. doi:10.1016/j.expneurol.2016.05.014
109. Daskalakis NP, Cohen H, Nievergelt CM, et al. New translational perspectives for blood-based biomarkers of PTSD: From glucocorticoid to immune mediators of stress susceptibility. *Exp Neurol*. 2016;284(3):133-140. doi:10.1016/j.expneurol.2016.07.024
110. Bailey CR, Cordell E, Sobin SM, Neumeister A. Recent progress in understanding the pathophysiology of post-traumatic stress disorder. *CNS Drugs*. 2013;27(3):221-232. doi:10.1007/s40263-013-0051-4
111. Ronzoni G, del Arco A, Mora F, Segovia G. Enhanced noradrenergic activity in the amygdala contributes to hyperarousal in an animal model of PTSD. *Psychoneuroendocrinology*. 2016;70:1-9. doi:10.1016/j.psyneuen.2016.04.018
112. Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog Brain Res*. 2008;167(1):171-186. doi:10.1016/S0079-6123(07)67012-5

113. Pitman RK, Delahanty DL. Conceptually driven pharmacologic approaches to acute trauma. *CNS Spectr*. 2005;10(2):99-106. doi:10.1017/S109285290001943X

114. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. *Psychiatry Clin Neurosci*. 2019;73(4):143-153. doi:10.1111/pcn.12820

115. Nievergelt CM, Maihofer AX, Klengel T, et al. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat Commun*. 2019;10(1):4558. doi:10.1038/s41467-019-12576-w

116. Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: A twin study. *Am J Psychiatry*. 2002;159(10):1675-1681. doi:10.1176/appi.ajp.159.10.1675

117. Sartor CE, Grant JD, Lynskey MT, et al. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. *Arch Gen Psychiatry*. 2012;69(3):293-299. doi:10.1001/archgenpsychiatry.2011.1385

118. Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*. 2008;299(11):1291-1305. doi:10.1001/jama.299.11.1291

119. Sheerin CM, Lind MJ, Bountress KE, Nugent NR, Amstadter AB. The genetics and epigenetics of PTSD: Overview, recent advances, and future directions. *Curr Opin Psychol*. 2017;14(3):5-11. doi:10.1016/j.copsyc.2016.09.003

120. Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297(5580):400-403. doi:10.1126/science.1071829

121. Cornelis MC, Nugent NR, Amstadter AB, Koenen KC. Genetics of post-traumatic stress disorder: Review and recommendations for genome-wide association studies. *Curr Psychiatry Rep*. 2010;12(4):313-326. doi:10.1007/s11920-010-0126-6

122. Daskalakis NP, Rijal CM, King C, Huckins LM, Ressler KJ. Recent genetics and epigenetics approaches to PTSD. *Curr Psychiatry Rep*. 2018;20(5):30. doi:10.1007/s11920-018-0898-7

123. Chen J, Lipska BK, Halim N, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet*. 2004;75(5):807-821. doi:10.1086/425589

124. Clark R, DeYoung CG, Sponheim SR, et al. Predicting post-traumatic stress disorder in veterans: Interaction of traumatic load with COMT gene variation. *J Psychiatr Res*. 2013;47(12):1849-1856. doi:10.1016/j.jpsychires.2013.08.013

125. Miller MW, Maniates H, Wolf EJ, et al. CRP polymorphisms and DNA methylation of the AIM2 gene influence associations between trauma exposure, PTSD, and C-reactive protein. *Brain Behav Immun*. 2018;67(3):194-202. doi:10.1016/j.bbi.2017.08.022

126. Michopoulos V, Rothbaum AO, Jovanovic T, et al. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *Am J Psychiatry*. 2015;172(4):353-362. doi:10.1176/appi.ajp.2014.14020263

127. Freeman T, Roca V, Guggenheim F, Kimbrell T, Griffin WST. Neuropsychiatric associations of apolipoprotein E alleles in subjects with combat-related posttraumatic stress disorder. *J Neuropsychiatry Clin Neurosci*. 2005;17(4):541-543. doi:10.1176/jnp.17.4.541

128. Harnett NG, Goodman AM, Knight DC. PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. *Exp Neurol*. 2020;330(October 2019). doi:10.1016/j.expneurol.2020.113331

129. Shenton ME, Hamoda HM, Schneiderman JS, et al. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav*. 2012;6(2):137-192. doi:10.1007/s11682-012-9156-5

130. Shenton ME, Hamoda HM, Schneiderman JS, et al. A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav*. 2012;6(2):137-192. doi:10.1007/s11682-012-9156-5

131. Im JJ, Namgung E, Choi Y, Kim JY, Rhie SJ, Yoon S. Molecular neuroimaging in posttraumatic stress disorder. *Exp Neurobiol*. 2016;25(6):277-295. doi:10.5607/en.2016.25.6.277

132. Byrnes KR, Wilson CM, Brabazon F, et al. FDG-PET imaging in mild traumatic brain injury: a critical review. *Front Neuroenergetics*. 2014;5:13. doi:10.3389/fnene.2013.00013

133. Lobo I, Portugal LC, Figueira I, et al. EEG correlates of the severity of posttraumatic stress symptoms: A systematic review of the dimensional PTSD literature. *J Affect Disord*. 2015;183:210-220. doi:10.1016/j.jad.2015.05.015

134. Haneef Z, Levin HS, Frost JD, Mizrahi EM. Electroencephalography and quantitative electroencephalography in mild traumatic brain injury. *J Neurotrauma*. 2013;30(8):653-656. doi:10.1089/neu.2012.2585

135. Huang M, Lewine JD, Lee RR. Magnetoencephalography for mild traumatic brain injury and posttraumatic stress disorder. *Neuroimaging Clin N Am*. 2020;30(2):175-192.

doi:10.1016/j.nic.2020.02.003

136. Zhang J, Chen K, Wang D, Gao F, Zheng Y, Yang M. Editorial: Advances of neuroimaging and data analysis. *Front Neurol*. 2020;11:10-12. doi:10.3389/fneur.2020.00257
137. Morita T, Asada M, Naito E. Contribution of neuroimaging studies to understanding development of human cognitive brain functions. *Front Hum Neurosci*. 2016;10:464. doi:10.3389/fnhum.2016.00464
138. Kunimatsu A, Yasaka K, Akai H, Kunimatsu N, Abe O. MRI findings in posttraumatic stress disorder. *J Magn Reson Imaging*. 2020;52(2):380-396. doi:10.1002/jmri.26929
139. Lauterbur PC. Image formation by induced local interactions: Examples employing nuclear magnetic resonance. *Nature*. 1973;242:190-191. doi:10.1038/242190a0
140. Rinck PA. An excursion into the history of magnetic resonance imaging. In: *Magnetic Resonance in Medicine - A Critical Introduction*. ; 2018:374-416.
141. Berger A. Magnetic resonance imaging. *BMJ*. 2002;324(7328):35-35. doi:10.1136/bmj.324.7328.35
142. Logue MW, van Rooij SJH, Dennis EL, et al. Smaller hippocampal volume in posttraumatic stress disorder: A multisite ENIGMA-PGC study: Subcortical volumetry results from posttraumatic stress disorder consortia. *Biol Psychiatry*. 2018;83(3):244-253. doi:10.1016/j.biopsych.2017.09.006
143. Gurvits T V., Shenton ME, Hokama H, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry*. 1996;40(11):1091-1099. doi:10.1016/S0006-3223(96)00229-6
144. Nelson MD, Tumpap AM. Posttraumatic stress disorder symptom severity is associated with left hippocampal volume reduction: A meta-analytic study. *CNS Spectr*. 2017;22(4):363-372. doi:10.1017/S1092852916000833
145. Opitz B. Memory function and the hippocampus. *Hippocampus Clin Neurosci*. 2014;34:51-59. doi:10.1159/000356422
146. Voss JL, Bridge DJ, Cohen NJ, Walker JA. A closer look at the hippocampus and memory. *Trends Cogn Sci*. 2017;21(8):577-588. doi:10.1016/j.tics.2017.05.008
147. Ji J, Maren S. Hippocampal involvement in contextual modulation of fear extinction. *Hippocampus*. 2007;17(9):749-758. doi:10.1002/hipo.20331
148. Bremner JD, Randall P, Scott TM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry*. 1995;152(7):973-981. doi:10.1176/ajp.152.7.973

149. Bremner JD, Randall P, Vermetten E, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – A preliminary report. *Biol Psychiatry*. 1997;41(1):23-32. doi:10.1016/S0006-3223(96)00162-X

150. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci*. 2002;5(11):1242-1247. doi:10.1038/nn958.Smaller

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

152. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. *Neurosci Lett*. 2017;649(203):147-155. doi:10.1016/j.neulet.2016.11.064

153. Smith KL, Kassem MS, Clarke DJ, et al. Microglial cell hyper-ramification and neuronal dendritic spine loss in the hippocampus and medial prefrontal cortex in a mouse model of PTSD. *Brain Behav Immun*. 2019;80:889-899. doi:10.1016/j.bbi.2019.05.042

154. Kassem MS, Lagopoulos J, Stait-Gardner T, et al. Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses. *Mol Neurobiol*. 2013;47(2):645-661. doi:10.1007/s12035-012-8365-7

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

156. McDonald AJ, Mott DD. Functional neuroanatomy of amygdalohippocampal interconnections and their role in learning and memory. *J Neurosci Res*. 2017;95(3):797-820. doi:10.1002/jnr.23709

157. Janak PH, Tye KM. From circuits to behaviour in the amygdala. *Nature*. 2015;517(7534):284-292. doi:10.1038/nature14188

158. Duvarci S, Pare D. Amygdala microcircuits controlling learned fear. *Neuron*. 2014;82(5):966-980. doi:10.1016/j.neuron.2014.04.042

159. Yang Y, Wang JZ. From structure to behavior in basolateral amygdala-hippocampus circuits. *Front Neural Circuits*. 2017;11:86. doi:10.3389/fncir.2017.00086

160. Henigsberg N, Kalember P, Petrović ZK, Šečić A. Neuroimaging research in

posttraumatic stress disorder – Focus on amygdala, hippocampus and prefrontal cortex. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2019;90:37-42. doi:10.1016/j.pnpbp.2018.11.003

161. Morey RA, Gold AL, LaBar KS, et al. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Arch Gen Psychiatry*. 2012;69(11):1169. doi:10.1001/archgenpsychiatry.2012.50
162. Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, Pitman RK. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biol Psychiatry*. 2008;63(6):550-556. doi:10.1016/j.biopsych.2007.06.022
163. Yamasue H, Kasai K, Iwanami A, et al. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci U S A*. 2003;100(15):9039-9043. doi:10.1073/pnas.1530467100
164. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry*. 2006;59(7):582-587. doi:10.1016/j.biopsych.2005.07.033
165. Rauch SL, Shin LM, Segal E, et al. Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport*. 2003;14(7):913-916. doi:10.1097/00001756-200305230-00002
166. Kitayama N, Quinn S, Bremner JD. Smaller volume of anterior cingulate cortex in abuse-related posttraumatic stress disorder. *J Affect Disord*. 2006;90(2-3):171-174. doi:10.1016/j.jad.2005.11.006
167. Akiki TJ, Averill CL, Abdallah CG. A network-based neurobiological model of PTSD: Evidence from structural and functional neuroimaging studies. *Curr Psychiatry Rep*. 2017;19(11):81. doi:10.1007/s11920-017-0840-4
168. Selemon LD, Young KA, Cruz DA, Williamson DE. Frontal lobe circuitry in posttraumatic stress disorder. *Chronic Stress*. 2019;3:1-17. doi:10.1177/2470547019850166
169. Stevens JS, Jovanovic T, Fani N, et al. Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. *J Psychiatr Res*. 2013;47(10):1469-1478. doi:10.1016/j.jpsychires.2013.05.031
170. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci*. 2006;1071:67-79. doi:10.1196/annals.1364.007
171. Shin LM, Orr SP, Carson MA, et al. Regional cerebral blood flow in the amygdala and

medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry*. 2004;61(2):168-176. doi:10.1001/archpsyc.61.2.168

172. Britton JC, Phan KL, Taylor SF, Fig LM, Liberzon I. Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. *Biol Psychiatry*. 2005;57(8):832-840. doi:10.1016/j.biopsych.2004.12.025
173. Lanius R a, Williamson PC, Hopper J, et al. Recall of emotional states in posttraumatic stress disorder: An fMRI investigation. *Biol Psychiatry*. 2003;53(3):204-210. doi:10.1016/S0006-3223(02)01466-X
174. Shin LM, Wright CI, Cannistraro PA, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry*. 2005;62(3):273-281. doi:10.1001/archpsyc.62.3.273
175. Bremner JD, Vermetten E, Vythilingam M, et al. Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. *Biol Psychiatry*. 2004;55(6):612-620. doi:10.1016/j.biopsych.2003.10.001
176. Bremner JD, Vermetten E, Schmahl C, et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med*. 2005;35(6):791-806. doi:10.1017/s0033291704003290
177. van den Heuvel MP, Mandl RCW, Kahn RS, Hulshoff Pol HE. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum Brain Mapp*. 2009;30(10):3127-3141. doi:10.1002/hbm.20737
178. Douglas Fields R. White matter matters. *Sci Am*. 2008;298(3):54-61. doi:10.1038/scientificamerican0308-54
179. Brivio V, Faivre-Sarrailh C, Peles E, Sherman DL, Brophy PJ. Assembly of CNS nodes of ranvier in myelinated nerves is promoted by the axon cytoskeleton. *Curr Biol*. 2017;27(7):1068-1073. doi:10.1016/j.cub.2017.01.025
180. Kalat JW. The myelin sheath and saltatory conduction. In: *Biological Psychology*. 11th ed. Cengage Learning; 2012.
181. van den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci*. 2013;17(12):683-696. doi:10.1016/j.tics.2013.09.012
182. Davenport ND, Lim KO, Sponheim SR. White matter abnormalities associated with military PTSD in the context of blast TBI. *Hum Brain Mapp*. 2015;36(3):1053-1064. doi:10.1002/hbm.22685

183. Aschbacher K, Mellon SH, Wolkowitz OM, et al. Posttraumatic stress disorder, symptoms, and white matter abnormalities among combat-exposed veterans. *Brain Imaging Behav*. 2018;12(4):989-999. doi:10.1007/s11682-017-9759-y

184. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J*. 1994;66(1):259-267. doi:10.1016/S0006-3495(94)80775-1

185. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology*. 1996;201(3):637-648. doi:10.1148/radiology.201.3.8939209

186. Soares JM, Marques P, Alves V, Sousa N, Klein A. A hitchhiker's guide to diffusion tensor imaging. 2013. doi:10.3389/fnins.2013.00031

187. Delouche A, Attyé A, Heck O, et al. Diffusion MRI: Pitfalls, literature review and future directions of research in mild traumatic brain injury. *Eur J Radiol*. 2016;85(1):25-30. doi:10.1016/j.ejrad.2015.11.004

188. Basser PJ, Jones DK. Diffusion-tensor MRI: Theory, experimental design and data analysis - A technical review. *NMR Biomed*. 2002;15(7-8):456-467. doi:10.1002/nbm.783

189. Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *J Mol Neurosci*. 2008;34(1):51-61. doi:10.1007/s12031-007-0029-0

190. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR Biomed*. 2002;15(7-8):435-455. doi:10.1002/nbm.782

191. Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH. Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. *Neurology*. 1999;52(8):1626-1632. doi:10.1212/WNL.52.8.1626

192. Aung WY, Mar S, Benzinger TL. Diffusion tensor MRI as a biomarker in axonal and myelin damage. *Imaging Med*. 2013;5(5):427-440. doi:10.2217/iim.13.49

193. Wang H, Wang X, Guo Q. The correlation between DTI parameters and levels of AQP-4 in the early phases of cerebral edema after hypoxic-ischemic/reperfusion injury in piglets. *Pediatr Radiol*. 2012;42(8):992-999. doi:10.1007/s00247-012-2373-7

194. Budde MD, Janes L, Gold E, Turtzo LC, Frank JA. The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: Validation in the rat using Fourier analysis of stained tissue sections. *Brain*. 2011;134:2248-2260. doi:10.1093/brain/awr161

195. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion Tensor Imaging of the Brain.

Neurotherapeutics. 2007;4(3):316-329. doi:10.1016/j.nurt.2007.05.011

196. Feldman HM, Yeatman JD, Lee ES, Barde LHF, Gaman-Bean S. Diffusion tensor imaging: A review for pediatric researchers and clinicians. *J Dev Behav Pediatr*. 2010;31(4):346-356. doi:10.1097/DBP.0b013e3181dcaa8b
197. Trivedi R, Rathore R, Gupta R. Review: Clinical application of diffusion tensor imaging. *Indian J Radiol Imaging*. 2008;18(1):45. doi:10.4103/0971-3026.38505
198. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. *Magn Reson Med*. 2009;62(3):717-730. doi:10.1002/mrm.22055
199. Metzler-Baddeley C, O'Sullivan MJ, Bells S, Pasternak O, Jones DK. How and how not to correct for CSF-contamination in diffusion MRI. *Neuroimage*. 2012;59(2):1394-1403. doi:10.1016/j.neuroimage.2011.08.043
200. Etkin A, Wager TD. Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476-1488. doi:10.1176/appi.ajp.2007.07030504
201. Harnett NG, Ference EW, Knight AJ, Knight DC. White matter microstructure varies with post-traumatic stress severity following medical trauma. *Brain Imaging Behav*. 2020;14(4):1012-1024. doi:10.1007/s11682-018-9995-9
202. Merson TD, Binder MD, Kilpatrick TJ. Role of cytokines as mediators and regulators of microglial activity in inflammatory demyelination of the CNS. *NeuroMolecular Med*. 2010;12(2):99-132. doi:10.1007/s12017-010-8112-z
203. McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism*. 2006;55:20-23. doi:10.1016/j.metabol.2006.07.008
204. McAllister TW, Stein MB. Effects of psychological and biomechanical trauma on brain and behavior. *Ann N Y Acad Sci*. 2010;1208(1):46-57. doi:10.1111/j.1749-6632.2010.05720.x
205. Moghaddam B. Stress activation of glutamate neurotransmission in the prefrontal cortex: Implications for dopamine-associated psychiatric disorders. *Biol Psychiatry*. 2002;51(10):775-787. doi:10.1016/S0006-3223(01)01362-2
206. Mayer AR, Quinn DK. Neuroimaging biomarkers of new-onset psychiatric disorders following traumatic brain injury. *Biol Psychiatry*. 2022;91(5):459-469. doi:10.1016/j.biopsych.2021.06.005
207. Hoeft F, Barnea-Goraly N, Haas BW, et al. More is not always better: Increased fractional anisotropy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams syndrome. *J Neurosci*. 2007;27(44):11960-11965.

doi:10.1523/JNEUROSCI.3591-07.2007

208. Bottari SA, Lamb DG, Murphy AJ, et al. Hyperarousal symptoms and decreased right hemispheric frontolimbic white matter integrity predict poorer sleep quality in combat-exposed veterans. *Brain Inj*. 2021;35(8):922-933. doi:10.1080/02699052.2021.1927186
209. Goldstein AN, Walker MP. The role of sleep in emotional brain function. *Annu Rev Clin Psychol*. 2014;10:679-708. doi:10.1146/annurev-clinpsy-032813-153716
210. Van Wyk M, Thomas KGF, Solms M, Lipinska G. Prominence of hyperarousal symptoms explains variability of sleep disruption in posttraumatic stress disorder. *Psychol Trauma Theory, Res Pract Policy*. 2016;8(6):688-696. doi:10.1037/tra0000115
211. Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses. *Sleep Med Rev*. 2008;12(3):185-195. doi:10.1016/j.smrv.2007.09.003
212. Wang Z, Zhu H, Yuan M, et al. The resting-state functional connectivity of amygdala subregions associated with post-traumatic stress symptom and sleep quality in trauma survivors. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(6):1053-1064. doi:10.1007/s00406-020-01104-3
213. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: Persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol*. 2008;167(12):1446-1452. doi:10.1093/aje/kwn068
214. Lindquist LK, Love HC, Elbogen EB. Traumatic brain injury in Iraq and Afghanistan veterans: New results from a national random sample study. *J Neuropsychiatry Clin Neurosci*. 2017;29(3):254-259. doi:10.1176/appi.neuropsych.16050100
215. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 1993;8:86-87.
216. DePalma RG, Kobeissy FH. Combat TBI: History, epidemiology, and injury modes. In: *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*. Boca Raton (FL): CRC Press/Taylor & Francis; 2015.
217. Centers for Disease Control and Prevention. *Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation*.; 2015.
218. Gonschorek AS, Schwenkreis P, Guthke T. Psychische Störungen nach leichtem Schädel-Hirn-Trauma. *Nervenarzt*. 2016;87(5):567-579. doi:10.1007/s00115-016-0119-8
219. Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-

term disability following traumatic brain injury hospitalization, United States, 2003. *J Head Trauma Rehabil*. 2008;23(2):123-131. doi:10.1097/01.HTR.0000314531.30401.39

220. Cassidy JD, Cancelliere C, Carroll LJ, et al. Systematic review of self-reported prognosis in adults after mild traumatic brain injury: Results of the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil*. 2014;95(3):132-151. doi:10.1016/j.apmr.2013.08.299
221. Frieden TR, Houry D, Baldwin G. Traumatic brain injury in the United States: Epidemiology and rehabilitation. *CDC NIH Rep to Congr*. 2015:1-74.
222. Nordström A, Edin BB, Lindström S, Nordström P. Cognitive function and other risk factors for mild traumatic brain injury in young men: Nationwide cohort study. *BMJ*. 2013;346(7899):1-9. doi:10.1136/bmj.f723
223. Vassallo JL, Proctor-Weber Z, Lebowitz BK, Curtiss G, Vanderploeg RD. Psychiatric risk factors for traumatic brain injury. *Brain Inj*. 2007;21(6):567-573. doi:10.1080/02699050701426832
224. Williams JL, McDevitt-Murphy ME, Murphy JG, Crouse EM. Deployment risk factors and postdeployment health profiles associated with traumatic brain injury in heavy drinking veterans. *Mil Med*. 2012;177(7):789-796. doi:10.7205/MILMED-D-12-00019
225. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med*. 2008;358(5):453-463. doi:10.1056/NEJMoa072972
226. Bryan CJ, Clemans TA. Repetitive traumatic brain injury, psychological symptoms, and suicide risk in a clinical sample of deployed military personnel. *JAMA Psychiatry*. 2013;70(7):686-691. doi:10.1001/jamapsychiatry.2013.1093
227. Wojtowicz M, Silverberg ND, Bui E, Zafonte R, Simon N, Iverson GL. Psychiatric comorbidity and psychosocial problems among treatment-seeking veterans with a history of mild traumatic brain injury. *Focus*. 2017;15(4):384-389. doi:10.1176/appi.focus.20170028
228. Temkin NR, Corrigan JD, Dikmen SS, MacHamer J. Social functioning after traumatic brain injury. *J Head Trauma Rehabil*. 2009;24(6):460-467. doi:10.1097/HTR.0b013e3181c13413
229. Doctor JN, Castro J, Temkin NR, Fraser RT, Machamer JE, Dikmen SS. Workers's risk of unemployment after traumatic brain injury: A normed comparison. *J Int Neuropsychol Soc*. 2005;11(6):747-752. doi:10.1017/S1355617705050836

230. Stubbs JL, Thornton AE, Sevick JM, et al. Traumatic brain injury in homeless and marginally housed individuals: A systematic review and meta-analysis. *Lancet Public Heal*. 2020;5(1):e19-e32. doi:10.1016/S2468-2667(19)30188-4

231. Lange RT, Brickell T, French LM, et al. Risk factors for postconcussion symptom reporting after traumatic brain injury in U.S. military service members. *J Neurotrauma*. 2013;30(4):237-246. doi:10.1089/neu.2012.2685

232. Stein MB, Ursano RJ, Campbell-Sills L, et al. Prognostic indicators of persistent post-concussive symptoms after deployment-related mild traumatic brain injury: A prospective longitudinal study in U.S. Army Soldiers. *J Neurotrauma*. 2016;33(23):2125-2132. doi:10.1089/neu.2015.4320

233. Martindale SL, Epstein EL, Taber KH, et al. Behavioral and health outcomes associated with deployment and nondeployment acquisition of traumatic brain injury in Iraq and Afghanistan veterans. *Arch Phys Med Rehabil*. 2018;99(12):2485-2495. doi:10.1016/j.apmr.2018.04.029

234. Undurti A, Colasurdo EA, Sikkema CL, et al. Chronic hypopituitarism associated with increased postconcussive symptoms is prevalent after blast-induced mild traumatic brain injury. *Front Neurol*. 2018;9:72. doi:10.3389/fneur.2018.00072

235. Bondanelli M, Ambrosio MR, Cavazzini L, et al. Anterior pituitary function may predict functional and cognitive outcome in patients with traumatic brain injury undergoing rehabilitation. *J Neurotrauma*. 2007;24(11):1687-1697. doi:10.1089/neu.2007.0343

236. West TA, Sharp S. Neuroendocrine dysfunction following mild TBI: When to screen for it. *J Fam Pract*. 2014;63(1):11-16. http://www.ncbi.nlm.nih.gov/pubmed/24475461.

237. Wilkinson CW, Pagulayan KF, Petrie EC, et al. High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. *Front Neurol*. 2012;3:11. doi:10.3389/fneur.2012.00011

238. Llompart-Pou JA, Raurich JM, Pérez-Bárcena J, Barceló A, Ibáñez J, Ayestarán JI. Acute hypothalamic-pituitary-adrenal response in traumatic brain injury with and without extracerebral trauma. *Neurocrit Care*. 2008;9(2):230-236. doi:10.1007/s12028-008-9115-6

239. Agha A, Phillips J, Thompson CJ. Hypopituitarism following traumatic brain injury (TBI). *Br J Neurosurg*. 2007;21(2):210-216. doi:10.1080/02688690701253331

240. Kleindienst A, Brabant G, Bock C, Maser-Gluth C, Buchfelder M. Neuroendocrine function following traumatic brain injury and subsequent intensive care treatment: A prospective longitudinal evaluation. *J Neurotrauma*. 2009;26(9):1435-1446.

doi:10.1089/neu.2008.0601

241. Lieberman SA, Oberoi AL, Gilkison CR, Masel BE, Urban RJ. Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. *J Clin Endocrinol Metab*. 2001;86(6):2752-2756. doi:10.1210/jc.86.6.2752
242. Fernandez-Rodriguez E, Bernabeu I, Castro AI, Kelestimur F, Casanueva FF. Hypopituitarism following traumatic brain injury: Determining factors for diagnosis. *Front Endocrinol*. 2010;2:1-6. doi:10.3389/fendo.2011.00025
243. Molaie AM, Maguire J. Neuroendocrine abnormalities following traumatic brain injury: An important contributor to neuropsychiatric sequelae. *Front Endocrinol*. 2018;9:1-10. doi:10.3389/fendo.2018.00176
244. Pearn ML, Niesman IR, Egawa J, et al. Pathophysiology associated with traumatic brain injury: Current treatments and potential novel therapeutics. *Cell Mol Neurobiol*. 2017;37(4):571-585. doi:10.1007/s10571-016-0400-1
245. Bavisetty S, McArthur DL, Dusick JR, et al. Chronic hypopituitarism after traumatic brain injury: Risk assessment and relationship to outcome. *Neurosurgery*. 2008;62(5):1080-1093. doi:10.1227/01.neu.0000325870.60129.6a
246. Sav A, Rotondo F, Syro L V., Serna CA, Kovacs K. Pituitary pathology in traumatic brain injury: A review. *Pituitary*. 2019;22(3):201-211. doi:10.1007/s11102-019-00958-8
247. Schneider M, Schneider HJ, Yassouridis A, Saller B, Von Rosen F, Stalla GK. Predictors of anterior pituitary insufficiency after traumatic brain injury. *Clin Endocrinol*. 2008;68(2):206-212. doi:10.1111/j.1365-2265.2007.03020.x
248. Tapp ZM, Godbout JP, Kokiko-Cochran ON. A tilted axis: Maladaptive inflammation and HPA axis dysfunction contribute to consequences of TBI. *Front Neurol*. 2019;10:345. doi:10.3389/fneur.2019.00345
249. Tanriverdi F, Unluhizarci K, Kocyigit I, et al. Brief communication: Pituitary volume and function in competing and retired male boxers. *Ann Intern Med*. 2008;148(11):827. doi:10.7326/0003-4819-148-11-200806030-00005
250. Tanriverdi F, De Bellis A, Bizzarro A, et al. Antipituitary antibodies after traumatic brain injury: Is head trauma-induced pituitary dysfunction associated with autoimmunity? *Eur J Endocrinol*. 2008;159(1):7-13. doi:10.1530/EJE-08-0050
251. Prodam F, Gasco V, Caputo M, et al. Metabolic alterations in patients who develop traumatic brain injury (TBI)-induced hypopituitarism. *Growth Horm IGF Res*. 2013;23(4):109-113. doi:10.1016/j.ghir.2013.04.001

252. Rege SD, Royes L, Tsai B, Zhang G, Yang X, Gomez-Pinilla F. Brain trauma disrupts hepatic lipid metabolism: Blame it on fructose? *Mol Nutr Food Res*. 2019;63(15):1801054. doi:10.1002/mnfr.201801054

253. Xu XJ, Yang MS, Zhang B, Niu F, Dong JQ, Liu BY. Glucose metabolism: A link between traumatic brain injury and Alzheimer's disease. *Chinese J Traumatol - English Ed*. 2021;24(1):5-10. doi:10.1016/j.cjtee.2020.10.001

254. Bloom GS. Amyloid-β and tau: The trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol*. 2014;71(4):505-508. doi:10.1001/jamaneurol.2013.5847

255. Deture MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*. 2019;14(1):1-18. doi:10.1186/s13024-019-0333-5

256. Uryu K, Chen XH, Martinez D, et al. Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. *Exp Neurol*. 2007;208(2):185-192. doi:10.1016/j.expneurol.2007.06.018

257. McKee AC, Robinson ME. Military-related traumatic brain injury and neurodegeneration. *Alzheimer's Dement*. 2014;10(1):S242-S253. doi:10.1016/j.jalz.2014.04.003

258. Juengst SB, Kumar RG, Wagner AK. A narrative literature review of depression following traumatic brain injury: Prevalence, impact, and management challenges. *Psychol Res Behav Manag*. 2017;10:175-186. doi:10.2147/PRBM.S113264

259. Singh R, Mason S, Lecky F, Dawson J. Prevalence of depression after TBI in a prospective cohort: The SHEFBIT study. *Brain Inj*. 2018;32(1):84-90. doi:10.1080/02699052.2017.1376756

260. Albrecht JS, Barbour L, Abariga SA, Rao V, Perfetto EM. Risk of depression after traumatic brain injury in a large national sample. *J Neurotrauma*. 2019;36(2):300-307. doi:10.1089/neu.2017.5608

261. Stein MB, Jain S, Giacino JT, et al. Risk of posttraumatic stress disorder and major depression in civilian patients after mild traumatic brain injury: A TRACK-TBI study. *JAMA Psychiatry*. 2019;76(3):249-258. doi:10.1001/jamapsychiatry.2018.4288

262. Zaninotto AL, Vicentini JE, Fregni F, et al. Updates and current perspectives of psychiatric assessments after traumatic brain injury: A systematic review. *Front Psychiatry*. 2016;7:95. doi:10.3389/fpsyt.2016.00095

263. Bombardier CH, Hoekstra T, Dikmen S, Fann JR. Depression trajectories during the first year after traumatic brain injury. *J Neurotrauma*. 2016;33(23):2115-2124. doi:10.1089/neu.2015.4349

264. Kumar RG, Bracken MB, Clark AN, Nick TG, Melguizo MS, Sander AM. Relationship of preinjury depressive symptoms to outcomes 3 mos after complicated and uncomplicated mild traumatic brain injury. *Am J Phys Med Rehabil*. 2014;93(8):687-702. doi:10.1097/PHM.0000000000000077

265. Yue JK, Cnossen MC, Winkler EA, et al. Pre-injury comorbidities are associated with functional impairment and post-concussive symptoms at 3- and 6-months after mild traumatic brain injury: A TRACK-TBI study. *Front Neurol*. 2019;10:343. doi:10.3389/fneur.2019.00343

266. Hou R, Moss-Morris R, Peveler R, Mogg K, Bradley BP, Belli A. When a minor head injury results in enduring symptoms: A prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2012;83(2):217-223. doi:10.1136/jnnp-2011-300767

267. Bennett ER, Reuter-Rice K, Laskowitz DT, Laskowitz D, Grant G. Genetic Influences in Traumatic Brain Injury. In: *Translational Research in Traumatic Brain Injury*. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016.

268. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon4 in patients with Alzheimer's disease. *Neurology*. 1995;45(3):555-557. doi:10.1212/WNL.45.3.555

269. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: Progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709-735. doi:10.1097/NEN.0b013e3181a9d503

270. Giarratana AO, Zheng C, Reddi S, et al. APOE4 genetic polymorphism results in impaired recovery in a repeated mild traumatic brain injury model and treatment with Bryostatin-1 improves outcomes. *Sci Rep*. 2020;10(1):19919. doi:10.1038/s41598-020-76849-x

271. Panenka WJ, Gardner AJ, Dretsch MN, Crynen GC, Crawford FC, Iverson GL. Systematic review of genetic risk factors for sustaining a mild traumatic brain injury. *J Neurotrauma*. 2017;34(13):2093-2099. doi:10.1089/neu.2016.4833

272. Bigler ED. Volumetric MRI findings in mild traumatic brain injury (mTBI) and neuropsychological outcome. *Neuropsychol Rev*. 2021. doi:10.1007/s11065-020-09474-0

273. Meyer DL, Davies DR, Barr JL, Manzerra P, Forster GL. Mild traumatic brain injury in the rat alters neuronal number in the limbic system and increases conditioned fear and anxiety-like behaviors. *Exp Neurol*. 2012;235(2):574-587.

doi:10.1016/j.expneurol.2012.03.012

274. Singh R, Meier TB, Kuplicki R, et al. Relationship of collegiate football experience and concussion with hippocampal volume and cognitive outcomes. *JAMA*. 2014;311(18):1883. doi:10.1001/jama.2014.3313
275. Bigler ED, Blatter DD, Anderson C V., et al. Hippocampal volume in normal aging and traumatic brain injury. *Am J Neuroradiol*. 1997;18(1):11-28.
276. Martindale SL, Rostami R, Shura RD, Taber KH, Rowland JA. Brain volume in veterans: Relationship to posttraumatic stress disorder and mild traumatic brain injury. *J Head Trauma Rehabil*. 2020;35(4):E330-E341. doi:10.1097/HTR.0000000000000559
277. Wojtowicz M, Gardner AJ, Stanwell P, Zafonte R, Dickerson BC, Iverson GL. Cortical thickness and subcortical brain volumes in professional rugby league players. *NeuroImage Clin*. 2018;18:377-381. doi:10.1016/j.nicl.2018.01.005
278. Misquitta K, Dadar M, Tarazi A, et al. The relationship between brain atrophy and cognitive-behavioural symptoms in retired Canadian football players with multiple concussions. *NeuroImage Clin*. 2018;19:551-558. doi:10.1016/j.nicl.2018.05.014
279. Zagorchev L, Meyer C, Stehle T, et al. Differences in regional brain volumes two months and one year after mild traumatic brain injury. *J Neurotrauma*. 2016;33(1):29-34. doi:10.1089/neu.2014.3831
280. Fjell AM, Sørensen Ø, Amlien IK, et al. Self-reported sleep relates to hippocampal atrophy across the adult lifespan: Results from the lifebrain consortium. *Sleep*. 2020;43(5):1-15. doi:10.1093/sleep/zsz280
281. Liu C, Lee SH, Loewenstein DA, Galvin JE, Camargo CJ, Alperin N. Poor sleep accelerates hippocampal and posterior cingulate volume loss in cognitively normal healthy older adults. *J Sleep Res*. 2022;31(4):1-14. doi:10.1111/jsr.13538
282. Liu C, Lee SH, Hernandez-Cardenache R, Loewenstein D, Kather J, Alperin N. Poor sleep is associated with small hippocampal subfields in cognitively normal elderly individuals. *J Sleep Res*. 2021;30(5):1-11. doi:10.1111/jsr.13362
283. Zhou Y, Kierans A, Kenul D, et al. Mild traumatic brain injury: longitudinal regional brain volume changes. *Radiology*. 2013;267(3):880-890. doi:10.1148/radiol.13122542
284. Eierud C, Nathan DE, Bonavia GH, Ollinger J, Riedy G. Cortical thinning in military blast compared to non-blast persistent mild traumatic brain injuries. *NeuroImage Clin*. 2019;22:101793. doi:10.1016/j.nicl.2019.101793
285. Patel JB, Wilson SH, Oakes TR, Santhanam P, Weaver LK. Structural and volumetric brain MRI findings in mild traumatic brain injury. *Am J Neuroradiol*. 2020;41(1):92-99.

doi:10.3174/ajnr.A6346

286. Martindale SL, Konst MJ, Bateman JR, Arena A, Rowland JA. The role of PTSD and TBI in post-deployment sleep outcomes. *Mil Psychol*. 2020;32(2):212-221. doi:10.1080/08995605.2020.1724595
287. Lepage C, Muehlmann M, Tripodis Y, et al. Limbic system structure volumes and associated neurocognitive functioning in former NFL players. *Brain Imaging Behav*. 2019;13(3):725-734. doi:10.1007/s11682-018-9895-z
288. España LY, Lee RM, Ling JM, Jeromin A, Mayer AR, Meier TB. Serial assessment of gray matter abnormalities after sport-related concussion. *J Neurotrauma*. 2017;34(22):3143-3152. doi:10.1089/neu.2017.5002
289. Monti JM, Voss MW, Pence A, McAuley E, Kramer AF, Cohen NJ. History of mild traumatic brain injury is associated with deficits in relational memory, reduced hippocampal volume, and less neural activity later in life. *Front Aging Neurosci*. 2013;5:41. doi:10.3389/fnagi.2013.00041
290. Ross DE, Ochs AL, Seabaugh JM, et al. Progressive brain atrophy in patients with chronic neuropsychiatric symptoms after mild traumatic brain injury: A preliminary study. *Brain Inj*. 2012;26(12):1500-1509. doi:10.3109/02699052.2012.694570
291. Williamson JB, Heilman KM, Porges EC, Lamb DG, Porges SW. A possible mechanism for PTSD symptoms in patients with traumatic brain injury: Central autonomic network disruption. *Front Neuroeng*. 2013;6:13. doi:10.3389/fneng.2013.00013
292. Russell AL, Tasker JG, Lucion AB, et al. Factors promoting vulnerability to dysregulated stress reactivity and stress-related disease. *J Neuroendocrinol*. 2018;30(10):139-148. doi:10.1111/jne.12641
293. Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Ann N Y Acad Sci*. 2008;1148(1):64-73. doi:10.1196/annals.1410.012
294. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol*. 2016;6(2):603-621. doi:10.1002/cphy.c150015
295. Davenport ND, Gullickson JT, Grey SF, Hirsch S, Sponheim SR. Longitudinal evaluation of ventricular volume changes associated with mild traumatic brain injury in military service members. *Brain Inj*. 2018;32(10):1245-1255. doi:10.1080/02699052.2018.1494854
296. Ross DE, Seabaugh JD, Seabaugh JM, et al. Patients with chronic mild or moderate

traumatic brain injury have abnormal brain enlargement. *Brain Inj*. 2020;34(1):11-19. doi:10.1080/02699052.2019.1669074

297. Killgore WDS, Singh P, Kipman M, Pisner D, Fridman A, Weber M. Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury. *Neurosci Lett*. 2016;612:238-244. doi:10.1016/j.neulet.2015.12.033
298. Wiegand TLT, Sollmann N, Bonke EM, et al. Translational neuroimaging in mild traumatic brain injury. *J Neurosci Res*. 2022;100(5):1201-1217. doi:10.1002/jnr.24840
299. Clark AL, Merritt VC, Bigler ED, et al. Blast-exposed veterans with mild traumatic brain injury show greater frontal cortical thinning and poorer executive functioning. *Front Neurol*. 2018;9:1-11. doi:10.3389/fneur.2018.00873
300. Tate DF, York GE, Reid MW, et al. Preliminary findings of cortical thickness abnormalities in blast injured service members and their relationship to clinical findings. *Brain Imaging Behav*. 2014;8(1):102-109. doi:10.1007/s11682-013-9257-9
301. Xiao H, Yang Y, Xi J, Chen Z. Structural and functional connectivity in traumatic brain injury. *Neural Regen Res*. 2015;10(12):2062. doi:10.4103/1673-5374.172328
302. Vakhtin AA, Calhoun VD, Jung RE, Prestopnik JL, Taylor PA, Ford CC. Changes in intrinsic functional brain networks following blast-induced mild traumatic brain injury. *Brain Inj*. 2013;27(11):1304-1310. doi:10.3109/02699052.2013.823561
303. Li F, Lu L, Shang S, et al. Disrupted functional network connectivity predicts cognitive impairment after acute mild traumatic brain injury. *CNS Neurosci Ther*. 2020;26(10):1083-1091. doi:10.1111/cns.13430
304. Nathan DE, Oakes TR, Yeh PH, et al. Exploring variations in functional connectivity of the resting state default mode network in mild traumatic brain injury. *Brain Connect*. 2015;5(2):102-114. doi:10.1089/brain.2014.0273
305. Koerte IK, Hufschmidt J, Muehlmann M, et al. Advanced Neuroimaging of Mild Traumatic Brain Injury. In: *Translational Research in Traumatic Brain Injury*. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016.
306. Stevens MC, Lovejoy D, Kim J, Oakes H, Kureshi I, Witt ST. Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain Imaging Behav*. 2012;6(2):293-318. doi:10.1007/s11682-012-9157-4
307. Shumskaya E, Andriessen TMJC, Norris DG, Vos PE. Abnormal whole-brain functional networks in homogeneous acute mild traumatic brain injury. *Neurology*. 2012;79(2):175-182. doi:10.1212/WNL.0b013e31825f04fb

308. Mayer AR, Mannell M V., Ling J, Gasparovic C, Yeo RA. Functional connectivity in mild traumatic brain injury. *Hum Brain Mapp*. 2011;32(11):1825-1835. doi:10.1002/hbm.21151

309. Zhou Y, Milham MP, Lui YW, et al. Default-mode network disruption in mild traumatic brain injury. *Radiology*. 2012;265(3):882-892. doi:10.1148/radiol.12120748

310. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: Anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1-38. doi:10.1196/annals.1440.011

311. Hou W, Sours Rhodes C, Jiang L, et al. Dynamic functional network analysis in mild traumatic brain injury. *Brain Connect*. 2019;9(6):475-487. doi:10.1089/brain.2018.0629

312. Van Der Horn HJ, Scheenen ME, De Koning ME, Liemburg EJ, Spikman JM, Van Der Naalt J. The Default Mode Network as a Biomarker of Persistent Complaints after Mild Traumatic Brain Injury: A Longitudinal Functional Magnetic Resonance Imaging Study. *J Neurotrauma*. 2017;34(23):3262-3269. doi:10.1089/neu.2017.5185

313. Dretsch MN, Rangaprakash D, Katz JS, et al. Strength and Temporal Variance of the Default Mode Network to Investigate Chronic Mild Traumatic Brain Injury in Service Members with Psychological Trauma. *J Exp Neurosci*. 2019;13:117906951983396. doi:10.1177/1179069519833966

314. Nathan DE, Bellgowan JAF, French LM, et al. Assessing the Impact of Post-Traumatic Stress Symptoms on the Resting-State Default Mode Network in a Military Chronic Mild Traumatic Brain Injury Sample. *Brain Connect*. 2017;7(4):236-249. doi:10.1089/brain.2016.0433

315. Santhanam P, Wilson SH, Oakes TR, Weaver LK. Effects of mild traumatic brain injury and post-traumatic stress disorder on resting-state default mode network connectivity. *Brain Res*. 2019;1711(May 2018):77-82. doi:10.1016/j.brainres.2019.01.015

316. Costanzo ME, Chou Y-Y, Leaman S, et al. Connecting combat-related mild traumatic brain injury with posttraumatic stress disorder symptoms through brain imaging. *Neurosci Lett*. 2014;577(22):11-15. doi:10.1016/j.neulet.2014.05.054

317. Menon V. Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn Sci*. 2011;15(10):483-506. doi:10.1016/j.tics.2011.08.003

318. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349-2356. doi:10.1523/JNEUROSCI.5587-06.2007

319. Schneider F, Fink GR. *Funktionelle MRT in Psychiatrie Und Neurologie*. Berlin,

Heidelberg: Springer; 2013. doi:10.1007/978-3-642-29800-4

320. Bigler ED. Neuropathology of mild traumatic brain injury. In: *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects.* Boca Raton (FL): CRC Press/Taylor & Francis; 2015.
321. Alves PN, Foulon C, Karolis V, et al. An improved neuroanatomical model of the default-mode network reconciles previous neuroimaging and neuropathological findings. *Commun Biol*. 2019;2(1):1-14. doi:10.1038/s42003-019-0611-3
322. Sharp DJ, Scott G, Leech R. Network dysfunction after traumatic brain injury. *Nat Rev Neurol*. 2014;10(3):156-166. doi:10.1038/nrneurol.2014.15
323. Koerte IK, Lin AP, Willems A, et al. A review of neuroimaging findings in repetitive brain trauma. *Brain Pathol*. 2015;25(3):318-349. doi:10.1111/bpa.12249
324. Ghajari M, Hellyer PJ, Sharp DJ. Computational modelling of traumatic brain injury predicts the location of chronic traumatic encephalopathy pathology. *Brain*. 2017;140(2):333-343. doi:10.1093/brain/aww317
325. Aoki Y, Inokuchi R, Gunshin M, Yahagi N, Suwa H. Diffusion tensor imaging studies of mild traumatic brain injury: A meta-analysis. *J Neurol Neurosurg Psychiatry*. 2012;83(9):870-876. doi:10.1136/jnnp-2012-302742
326. Asken BM, DeKosky ST, Clugston JR, Jaffee MS, Bauer RM. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. *Brain Imaging Behav*. 2018;12(2):585-612. doi:10.1007/s11682-017-9708-9
327. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol*. 2013;246(1):35-43. doi:10.1016/j.expneurol.2012.01.013
328. Davenport ND, Lim KO, Armstrong MT, Sponheim SR. Diffuse and spatially variable white matter disruptions are associated with blast-related mild traumatic brain injury. *Neuroimage*. 2012;59(3):2017-2024. doi:10.1016/j.neuroimage.2011.10.050
329. Morey RA, Haswell CC, Selgrade ES, et al. Effects of chronic mild traumatic brain injury on white matter integrity in Iraq and Afghanistan war veterans. *Hum Brain Mapp*. 2013;34(11):2986-2999. doi:10.1002/hbm.22117
330. Mac Donald CL, Barber J, Andre J, Panks C, Zalewski K, Temkin N. Longitudinal neuroimaging following combat concussion: Sub-acute, 1 year and 5 years post-injury. *Brain Commun*. 2019;1(1):1-13. doi:10.1093/braincomms/fcz031
331. Trotter BB, Robinson ME, Milberg WP, McGlinchey RE, Salat DH. Military blast exposure, ageing and white matter integrity. *Brain*. 2015;138(8):2278-2292.

doi:10.1093/brain/awv139

332. Dennis EL, Wilde EA, Newsome MR, et al. ENIGMA military brain injury: A coordinated meta-analysis of diffusion MRI from multiple cohorts. *IEEE Int Symp Biomed Imaging*. 2018:1386-1389. doi:10.1109/ISBI.2018.8363830
333. Dennis EL, Baron D, Bartnik-Olson B, et al. ENIGMA brain injury: Framework, challenges, and opportunities. *Hum Brain Mapp*. 2022;43(1):149-166. doi:10.1002/hbm.25046
334. Kikinis Z, Muehlmann M, Pasternak O, et al. Diffusion imaging of mild traumatic brain injury in the impact accelerated rodent model: A pilot study. *Brain Inj*. 2017;31(10):1376-1381. doi:10.1080/02699052.2017.1318450
335. Wilde EA, McCauley SR, Hunter J V., et al. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*. 2008;70(12):948-955. doi:10.1212/01.wnl.0000305961.68029.54
336. Mayer AR, Ling J, Mannell M V, et al. A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology*. 2010;74(8):643-650. doi:10.1212/WNL.0b013e3181d0ccdd
337. Pasternak O, Koerte IK, Bouix S, et al. Hockey Concussion Education Project, Part 2. Microstructural white matter alterations in acutely concussed ice hockey players: a longitudinal free-water MRI study. *J Neurosurg*. 2014;120(4):873-881. doi:10.3171/2013.12.JNS132090
338. Sasaki T, Pasternak O, Mayinger M, et al. Changes in white matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study. *J Neurosurg*. 2014;120(4):882-890. doi:10.3171/2013.12.JNS132092
339. Levin HS, Wilde E, Troyanskaya M, et al. Diffusion tensor imaging of mild to moderate blast-related traumatic brain injury and its sequelae. *J Neurotrauma*. 2010;27(4):683-694. doi:10.1089/neu.2009.1073
340. Hellstrøm T, Westlye LT, Kaufmann T, et al. White matter microstructure is associated with functional, cognitive and emotional symptoms 12 months after mild traumatic brain injury. *Sci Rep*. 2017;7(1):1-14. doi:10.1038/s41598-017-13628-1
341. Lepage C, de Pierrefeu A, Koerte IK, et al. White matter abnormalities in mild traumatic brain injury with and without post-traumatic stress disorder: a subject-specific diffusion tensor imaging study. *Brain Imaging Behav*. 2018;12(3):870-881. doi:10.1007/s11682-017-9744-5
342. Sanchez E, El-Khatib H, Arbour C, et al. Brain white matter damage and its association

with neuronal synchrony during sleep. *Brain*. 2019;142(3):674-687. doi:10.1093/brain/awy348

343. Brenner LA, Ivins BJ, Schwab K, et al. Traumatic brain injury, posttraumatic stress disorder, and postconcussive symptom reporting among troops returning from Iraq. *J Head Trauma Rehabil*. 2010;25(5):307-312. doi:10.1097/HTR.0b013e3181cada03
344. Carlson KF, Kehle SM, Meis LA, et al. Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: A systematic review of the evidence. *J Head Trauma Rehabil*. 2011;26(2):103-115. doi:10.1097/HTR.0b013e3181e50ef1
345. Shafiei E, Fakharian E, Omidi A, Akbari H, Delpisheh A. Effect of mild traumatic brain injury and demographic factors on psychological outcome. *Arch Trauma Res*. 2016;5(2):e29729. doi:10.5812/atr.29729
346. Contractor AA, Greene T, Dolan M, Elhai JD. Relations between PTSD and depression symptom clusters in samples differentiated by PTSD diagnostic status. *J Anxiety Disord*. 2018;59:17-26. doi:10.1016/j.janxdis.2018.08.004
347. Ma H, Chen P-S, Wong C, et al. Psychometric evaluation of anxiety, depression, and sleep quality after a mild traumatic brain injury: A longitudinal study. *Behav Neurol*. 2019;2019:4364592. doi:10.1155/2019/4364592
348. Combs HL, Berry DTR, Pape T, et al. The effects of mild traumatic brain injury, post-traumatic stress disorder, and combined mild traumatic brain injury/post-traumatic stress disorder on returning veterans. *J Neurotrauma*. 2015;32(13):956-966. doi:10.1089/neu.2014.3585
349. Seal KH, Bertenthal D, Samuelson K, Maguen S, Kumar S, Vasterling JJ. Association between mild traumatic brain injury and mental health problems and self-reported cognitive dysfunction in Iraq and Afghanistan veterans. *J Rehabil Res Dev*. 2016;53(2):185-198. doi:10.1682/JRRD.2014.12.0301
350. Kaye JL, Dunlop BW, Iosifescu D V., Mathew SJ, Kelley ME, Harvey PD. Cognition, functional capacity, and self-reported disability in women with posttraumatic stress disorder: Examining the convergence of performance-based measures and self-reports. *J Psychiatr Res*. 2014;57(1):51-57. doi:10.1016/j.jpsychires.2014.06.002
351. Koffel E, Khawaja IS, Germain A. Sleep disturbances in posttraumatic stress disorder: Updated review and implications for treatment. *Psychiatr Ann*. 2016;46(3):173-176. doi:10.3928/00485713-20160125-01
352. Leskin GA, Woodward SH, Young HE, Sheikh JI. Effects of comorbid diagnoses on

sleep disturbance in PTSD. *J Psychiatr Res*. 2002;36(6):449-452. doi:10.1016/S0022-3956(02)00025-0

353. Rosen RC, Cikesh B, Fang S, et al. Posttraumatic stress disorder severity and insomnia-related sleep disturbances: Longitudinal associations in a large, gender-balanced cohort of combat-exposed veterans. *J Trauma Stress*. 2019;32(6):936-945. doi:10.1002/jts.22462
354. Zhou Y, Greenwald B. Update on insomnia after mild traumatic brain injury. *Brain Sci*. 2018;8(12):223. doi:10.3390/brainsci8120223
355. Mac Donald CL, Adam OR, Johnson AM, et al. Acute post-traumatic stress symptoms and age predict outcome in military blast concussion. *Brain*. 2015;138(5):1314-1326. doi:10.1093/brain/awv038
356. Vasterling JJ, Jacob SN, Rasmusson A. Traumatic brain injury and posttraumatic stress disorder: Conceptual, diagnostic, and therapeutic considerations in the context of co-occurrence. *J Neuropsychiatry Clin Neurosci*. 2018;30(2):91-100. doi:10.1176/appi.neuropsych.17090180
357. Dieter JN, Engel SD. Traumatic brain injury and posttraumatic stress disorder: Comorbid consequences of war. *Neurosci Insights*. 2019;14:1-17. doi:10.1177/1179069519892933
358. Dolan S, Martindale S, Robinson J, et al. Neuropsychological sequelae of PTSD and TBI following war deployment among OEF/OIF veterans. *Neuropsychol Rev*. 2012;22(1):21-34. doi:10.1007/s11065-012-9190-5
359. Stein MB, McAllister TW. Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. *Am J Psychiatry*. 2009;166(7):768-776. doi:10.1176/appi.ajp.2009.08101604
360. Bremner JD. Traumatic stress: Effects on the brain. *Dialogues Clin Neurosci*. 2006;8(4):445-461. doi:10.31887/DCNS.2006.8.4/jbremner
361. Sydnor VJ, Bouix S, Pasternak O, et al. Mild traumatic brain injury impacts associations between limbic system microstructure and post-traumatic stress disorder symptomatology. *NeuroImage Clin*. 2020;26:102190. doi:10.1016/j.nicl.2020.102190
362. McAllister TW. Neurobiological consequences of traumatic brain injury. *Dialogues Clin Neurosci*. 2011;13(3):287-300. doi:10.31887/DCNS.2011.13.2/tmcallister
363. Dunkley BT, Da Costa L, Bethune A, et al. Low-frequency connectivity is associated with mild traumatic brain injury. *NeuroImage Clin*. 2015;7:611-621. doi:10.1016/j.nicl.2015.02.020
364. Bolzenius JD, Velez CS, Lewis JD, et al. Diffusion imaging findings in US service

members with mild traumatic brain injury and posttraumatic stress disorder. *J Head Trauma Rehabil*. 2018;33(6):393-402. doi:10.1097/HTR.0000000000000378

365. Gilbert KS, Kark SM, Gehrman P, Bogdanova Y. Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clin Psychol Rev*. 2015;40(5):195-212. doi:10.1016/j.cpr.2015.05.008
366. McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. *Mil Med*. 2010;175(10):759-762. doi:10.7205/MILMED-D-10-00193
367. Seelig AD, Jacobson IG, Smith B, et al. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. *Sleep*. 2010;33(12):1615-1622. doi:10.1093/sleep/33.12.1615
368. Germain A, Richardson R, Stocker R, et al. Treatment for insomnia in combat-exposed OEF/OIF/OND military veterans: Preliminary randomized controlled trial. *Behav Res Ther*. 2014;61:78-88. doi:10.1016/j.brat.2014.07.016
369. Mellman TA, David D, Bustamante V, Torres J, Fins A. Dreams in the acute aftermath of trauma and their relationship to PTSD. *J Trauma Stress*. 2001;14(1):241-247. doi:10.1023/A:1007812321136
370. Mellman TA, Hipolito MMS. Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. *CNS Spectr*. 2006;11(8):611-615. doi:10.1017/S1092852900013663
371. Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep - What a nightmare! *Sleep Med Rev*. 2000;4(2):183-200. doi:10.1053/smrv.1999.0095
372. El-Solh AA. Management of nightmares in patients with posttraumatic stress disorder: Current perspectives. *Nat Sci Sleep*. 2018;10:409-420. doi:10.2147/NSS.S166089
373. Macera CA, Aralis HJ, Rauh MJ, MacGregor AJ. Do sleep problems mediate the relationship between traumatic brain injury and development of mental health symptoms after deployment? *Sleep*. 2013;36(1):83-90. doi:10.5665/sleep.2306
374. Babson KA, Feldner MT. Temporal relations between sleep problems and both traumatic event exposure and PTSD: A critical review of the empirical literature. *J Anxiety Disord*. 2010;24(1):1-15. doi:10.1016/j.janxdis.2009.08.002
375. Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: A review. *Clin Psychol Rev*. 2003;23(3):377-407. doi:10.1016/S0272-7358(03)00032-1
376. Nappi CM, Drummond SPA, Hall JMH. Treating nightmares and insomnia in

posttraumatic stress disorder: A review of current evidence. *Neuropharmacology*. 2012;62(2):576-585. doi:10.1016/j.neuropharm.2011.02.029

377. Hinds A, Jungquist CR, Leddy JJ, Seemant F, Baker JG, Willer B. Sleep disturbance in patients with chronic concussive effects. *Concussion*. 2016;1(3):CNC15. doi:10.2217/cnc-2016-0002
378. Kalmbach DA, Conroy DA, Falk H, et al. Poor sleep is linked to impeded recovery from traumatic brain injury. *Sleep*. 2018;41(10):1-9. doi:10.1093/sleep/zsy147
379. Lu LH, Reid MW, Cooper DB, Kennedy JE. Sleep problems contribute to post-concussive symptoms in service members with a history of mild traumatic brain injury without posttraumatic stress disorder or major depressive disorder. *NeuroRehabilitation*. 2019;44(4):511-521. doi:10.3233/NRE-192702
380. Saladin ME, Brady KT, Dansky BS, Kilpatrick DG. Understanding comorbidity between PTSD and substance use disorders: Two preliminary investigations. *Addict Behav*. 1995;20(5):643-655. doi:10.1016/0306-4603(95)00024-7
381. Bishop TM, Walsh PG, Ashrafioun L, Lavigne JE, Pigeon WR. Sleep, suicide behaviors, and the protective role of sleep medicine. *Sleep Med*. 2020;66:264-270. doi:10.1016/j.sleep.2019.07.016
382. Mollayeva T, D'Souza A, Mollayeva S. Sleep and psychiatric disorders in persons with mild traumatic brain injury. *Curr Psychiatry Rep*. 2017;19(8):47. doi:10.1007/s11920-017-0800-z
383. Patel AK, Reddy V, Shumway KR, Araujo JF. *Physiology, Sleep Stages*. Treasure Island (FL): StatPearls; 2022.
384. de Andrés I, Garzón M, Reinoso-Suárez F. Functional anatomy of non-REM sleep. *Front Neurol*. 2011;NOV(November):1-14. doi:10.3389/fneur.2011.00070
385. Carley DW, Farabi SS. Physiology of sleep. *Diabetes Spectr*. 2016;29(1):5-9. doi:10.2337/diaspect.29.1.5
386. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry*. 2002;159(10):1696-1701. doi:10.1176/appi.ajp.159.10.1696
387. Wassing R, Benjamins JS, Dekker K, et al. Slow dissolving of emotional distress contributes to hyperarousal. *Proc Natl Acad Sci U S A*. 2016;113(9):2538-2543. doi:10.1073/pnas.1522520113
388. Wassing R, Lakbila-Kamal O, Ramautar JR, Stoffers D, Schalkwijk F, Van Someren EJW. Restless REM sleep impedes overnight amygdala adaptation. *Curr Biol*.

2019;29(14):2351-2358. doi:10.1016/j.cub.2019.06.034

389. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. *Psychophysiology*. 2007;44(4):660-669. doi:10.1111/j.1469-8986.2007.537.x
390. Neylan TC, Otte C, Yehuda R, Marmar CR. Neuroendocrine regulation of sleep disturbances in PTSD. *Ann N Y Acad Sci*. 2006;1071(1):203-215. doi:10.1196/annals.1364.015
391. Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of sleep and wakefulness. *Physiol Rev*. 2012;92(3):1087-1187. doi:10.1152/physrev.00032.2011
392. Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. *Biol Psychiatry*. 1995;38(3):174-179. doi:10.1016/0006-3223(94)00238-X
393. Fernandez-Mendoza J, Calhoun SL, Bixler EO, et al. Sleep misperception and chronic insomnia in the general population: Role of objective sleep duration and psychological profiles. *Psychosom Med*. 2011;73(1):88-97. doi:10.1097/PSY.0b013e3181fe365a
394. Germain A, James J, Insana S, et al. A window into the invisible wound of war: Functional neuroimaging of REM sleep in returning combat veterans with PTSD. *Psychiatry Res Neuroimaging*. 2013;211(2):176-179. doi:10.1016/j.pscychresns.2012.05.007
395. Nardo D, Högberg G, Jonsson C, Jacobsson H, Hällström T, Pagani M. Neurobiology of sleep disturbances in PTSD patients and traumatized controls: MRI and SPECT findings. *Front Psychiatry*. 2015;6:134. doi:10.3389/fpsyt.2015.00134
396. Vandekerckhove M, Wang YL. Emotion, emotion regulation and sleep: An intimate relationship. *AIMS Neurosci*. 2018;5(1):1-17. doi:10.3934/Neuroscience.2018.1.1
397. Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: The role of extinction memory. *Biol Mood Anxiety Disord*. 2015;5:3. doi:10.1186/s13587-015-0018-9
398. Narayana PA. White matter changes in patients with mild traumatic brain injury: MRI perspective. *Concussion*. 2017;2(2):CNC35. doi:10.2217/cnc-2016-0028
399. Leng Y, Byers AL, Barnes DE, Peltz CB, Li Y, Yaffe K. Traumatic brain injury and incidence risk of sleep disorders in nearly 200,000 US veterans. *Neurology*. 2021;96(13):e1792-e1799. doi:10.1212/WNL.0000000000011656
400. Boone DR, Sell SL, Micci M-A, et al. Traumatic brain injury-induced dysregulation of the circadian clock. *PLoS One*. 2012;7(10):e46204. doi:10.1371/journal.pone.0046204

401. Aoun R, Rawal H, Attarian H, Sahni A. Impact of traumatic brain injury on sleep: An overview. *Nat Sci Sleep*. 2019;11:131-140. doi:10.2147/NSS.S182158
402. Sandsmark DK, Elliott JE, Lim MM. Sleep-wake disturbances after traumatic brain injury: Synthesis of human and animal studies. *Sleep*. 2017;40(5):zsx044. doi:10.1093/sleep/zsx044
403. Viola-Saltzman M, Watson NF. Traumatic brain injury and sleep disorders. *Neurol Clin*. 2012;30(4):1299-1312. doi:10.1016/j.ncl.2012.08.008
404. Baumann CR, Bassetti CL, Valko PO, et al. Loss of hypocretin (orexin) neurons with traumatic brain injury. *Ann Neurol*. 2009;66(4):555-559. doi:10.1002/ana.21836
405. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain*. 2007;130(7):1873-1883. doi:10.1093/brain/awm109
406. Thomasy HE, Opp MR. Hypocretin mediates sleep and wake disturbances in a mouse model of traumatic brain injury. *J Neurotrauma*. 2019;36(5):802-814. doi:10.1089/neu.2018.5810
407. Baumann CR, Khatami R, Werth E, Bassetti CL. Hypocretin (orexin) deficiency predicts severe objective excessive daytime sleepiness in narcolepsy with cataplexy. *J Neurol Neurosurg Psychiatry*. 2006;77(3):402-404. doi:10.1136/jnnp.2005.067207
408. Sun Y, Bai L, Niu X, et al. Elevated serum levels of inflammation-related cytokines in mild traumatic brain injury are associated with cognitive performance. *Front Neurol*. 2019;10:1120. doi:10.3389/fneur.2019.01120
409. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. 2016;80(1):40-52. doi:10.1016/j.biopsych.2015.05.014
410. Christensen J, Wright DK, Yamakawa GR, Shultz SR, Mychasiuk R. Repetitive mild traumatic brain injury alters glymphatic clearance rates in limbic structures of adolescent female rats. *Sci Rep*. 2020;10(1):6254. doi:10.1038/s41598-020-63022-7
411. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373-377. doi:10.1126/science.1241224
412. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4(147):147ra111. doi:10.1126/scitranslmed.3003748
413. Piantino J, Schwartz DL, Luther M, et al. Link between mild traumatic brain injury, poor sleep, and magnetic resonance imaging: Visible perivascular spaces in veterans. *J*

Neurotrauma. 2021;38(17):2391-2399. doi:10.1089/neu.2020.7447

414. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The glymphatic system: A beginner's guide. *Neurochem Res*. 2015;40(12):2583-2599. doi:10.1007/s11064-015-1581-6
415. Eugene AR, Masiak J. The neuroprotective aspects of sleep. *MEDtube Sci*. 2015;3(1):35-40.
416. de Vivo L, Bellesi M. The role of sleep and wakefulness in myelin plasticity. *Glia*. 2019;67(11):2142-2152. doi:10.1002/glia.23667
417. He Y, Cornelissen-Guillaume GG, He J, Kastin AJ, Harrison LM, Pan W. Circadian rhythm of autophagy proteins in hippocampus is blunted by sleep fragmentation. *Chronobiol Int*. 2016;33(5):553-560. doi:10.3109/07420528.2015.1137581
418. Wu JC, Gillin JC, Buchsbaum MS, et al. The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. *Sleep*. 1991;14(2):155-162. doi:10.1093/sleep/14.2.155
419. Wallace EJ, Mathias JL, Ward L. Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: A meta-analysis. *Brain Imaging Behav*. 2018;12(6):1607-1621. doi:10.1007/s11682-018-9823-2
420. Grau-Rivera O, Operto G, Falcón C, et al. Association between insomnia and cognitive performance, gray matter volume, and white matter microstructure in cognitively unimpaired adults. *Alzheimer's Res Ther*. 2020;12(1):4. doi:10.1186/s13195-019-0547-3
421. Fortier-Brochu É, Beaulieu-Bonneau S, Ivers H, Morin CM. Insomnia and daytime cognitive performance: A meta-analysis. *Sleep Med Rev*. 2012;16(1):83-94. doi:10.1016/j.smrv.2011.03.008
422. Jespersen K V., Stevner A, Fernandes H, et al. Reduced structural connectivity in insomnia disorder. *J Sleep Res*. 2020;29(1):e12901. doi:10.1111/jsr.12901
423. Altendahl M, Cotter DL, Staffaroni AM, et al. REM sleep is associated with white matter integrity in cognitively healthy, older adults. *PLoS One*. 2020;15(7):e0235395. doi:10.1371/journal.pone.0235395
424. Van Someren EJW. Brain mechanisms of insomnia: New perspectives on causes and consequences. *Physiol Rev*. 2021;101(3):995-1046. doi:10.1152/physrev.00046.2019
425. Bryan CJ. Repetitive traumatic brain injury (or concussion) increases severity of sleep disturbance among deployed military personnel. *Sleep*. 2013;36(6):941-946. doi:10.5665/sleep.2730

426. McGlinchey RE, Milberg WP, Fonda JR, Fortier CB. A methodology for assessing deployment trauma and its consequences in OEF/OIF/OND veterans: The TRACTS longitudinal prospective cohort study. *Int J Methods Psychiatr Res*. 2017;26(3). doi:10.1002/mpr.1556

427. Lindemer ER, Salat DH, Leritz EC, McGlinchey RE, Milberg WP. Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF veterans and the impact of comorbid TBI. *NeuroImage Clin*. 2013;2(1):601-611. doi:10.1016/j.nicl.2013.04.009

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

429. Fortier CB, Amick MM, Grande L, et al. The Boston Assessment of Traumatic Brain Injury–Lifetime (BAT-L) semistructured Interview: Evidence of research utility and validity. *J Head Trauma Rehabil*. 2014;29(1):89-98. doi:10.1097/HTR.0b013e3182865859

430. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4

431. Cole JC, Motivala SJ, Buysse DJ, Oxman MN, Levin MJ, Irwin MR. Validation of a 3-factor scoring model for the Pittsburgh Sleep Quality Index in older adults. *Sleep*. 2006;29(1):112-116. doi:10.1093/sleep/29.1.112

432. First MB, Gibbon M, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*. Washington, DC: American Psychiatric Press; 1997.

433. Vogt DS, Smith BN, King LA, King DW, Knight JA, Vasterling JJ. Deployment Risk and Resilience Inventory-2 (DRRI-2): An updated tool for assessing psychosocial risk and resilience factors among service members and veterans. *J Trauma Stress*. 2013;26:710-717. doi:10.1002.jts.21868

434. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*. 2009;48(1):63-72. doi:10.1016/j.neuroimage.2009.06.060

435. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825-841. doi:10.1016/S1053-8119(02)91132-8

436. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. 2012;30(9):1323-1341. doi:10.1016/j.mri.2012.05.001

437. Bekiesińska-Figatowska M. Artifacts in Magnetic Resonance Imaging. *Polish J Radiol*. 2015;80:93-106. doi:10.12659/PJR.892628

438. Zhang F, Noh T, Juvekar P, et al. SlicerDMRI: Diffusion MRI and tractography research software for brain cancer surgery planning and visualization. *JCO Clin Cancer Informatics*. 2020;(4):299-309. doi:10.1200/cci.19.00141

439. Norton I, Essayed WI, Zhang F, et al. SlicerDMRI: Open source diffusion MRI software for brain cancer research. *Cancer Res*. 2017;77(21):e101-e103. doi:10.1158/0008-5472.CAN-17-0332

440. Lienhard S, Malcolm JG, Westin C-F, Rathi Y. A full bi-tensor neural tractography algorithm using the unscented Kalman filter. *EURASIP J Adv Signal Process*. 2011;2011:77. doi:10.1186/1687-6180-2011-77

441. Malcolm JG, Shenton ME, Rathi Y. Filtered multitensor tractography. *IEEE Trans Med Imaging*. 2010;29(9):1664-1675. doi:10.1109/TMI.2010.2048121

442. Vos SB, Viergever MA, Leemans A. Multi-fiber tractography visualizations for diffusion MRI data. *PLoS One*. 2013;8(11):e81453. doi:10.1371/journal.pone.0081453

443. Farquharson S, Tournier J-D, Calamante F, et al. White matter fiber tractography: Why we need to move beyond DTI. *J Neurosurg*. 2013;118(6):1367-1377. doi:10.3171/2013.2.JNS121294

444. Baumgartner C, Michailovich O, Levitt J, et al. A unified tractography framework for comparing diffusion models on clinical scans. In: *International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'12) - Computational Diffusion MRI Workshop*. ; 2012:27-32.

445. Chen Z, Tie Y, Olubiyi O, et al. Reconstruction of the arcuate fasciculus for surgical planning in the setting of peritumoral edema using two-tensor unscented Kalman filter tractography. *NeuroImage Clin*. 2015;7:815-822. doi:10.1016/j.nicl.2015.03.009

446. Liao R, Ning L, Chen Z, et al. Performance of unscented Kalman filter tractography in edema: Analysis of the two-tensor model. *NeuroImage Clin*. 2017;15:819-831. doi:10.1016/j.nicl.2017.06.027

447. Chen Z, Tie Y, Olubiyi O, et al. Corticospinal tract modeling for neurosurgical planning by tracking through regions of peritumoral edema and crossing fibers using two-tensor unscented Kalman filter tractography. *Int J Comput Assist Radiol Surg*. 2016;11(8):1475-1486. doi:10.1007/s11548-015-1344-5

448. Zhang F, Wu Y, Norton I, et al. An anatomically curated fiber clustering white matter atlas for consistent white matter tract parcellation across the lifespan. *Neuroimage*.

2018;179:429-447. doi:10.1016/j.neuroimage.2018.06.027

449. Maier-Hein KH, Neher PF, Houde J-C, et al. The challenge of mapping the human connectome based on diffusion tractography. *Nat Commun*. 2017;8(1):1349. doi:10.1038/s41467-017-01285-x
450. Sydnor VJ, Rivas-Grajales AM, Lyall AE, et al. A comparison of three fiber tract delineation methods and their impact on white matter analysis. *Neuroimage*. 2018;178:318-331. doi:10.1016/j.neuroimage.2018.05.044
451. Wu Y, Zhang F, Makris N, et al. Investigation into local white matter abnormality in emotional processing and sensorimotor areas using an automatically annotated fiber clustering in major depressive disorder. *Neuroimage*. 2018;181:16-29. doi:10.1016/j.neuroimage.2018.06.019
452. Wang J, Zhang F, Zhao C, et al. Investigation of local white matter abnormality in Parkinson's disease by using an automatic fiber tract parcellation. *Behav Brain Res*. 2020;394:112805. doi:10.1016/j.bbr.2020.112805
453. Zhang F, Wu Y, Norton I, Rathi Y, Golby AJ, O'Donnell LJ. Test–retest reproducibility of white matter parcellation using diffusion MRI tractography fiber clustering. *Hum Brain Mapp*. 2019;40(10):3041-3057. doi:10.1002/hbm.24579
454. O'Donnell LJ, Suter Y, Rigolo L, et al. Automated white matter fiber tract identification in patients with brain tumors. *NeuroImage Clin*. 2017;13:138-153. doi:10.1016/j.nicl.2016.11.023
455. Xue T, Zhang F, Zhang C, et al. Supwma: Consistent and efficient tractography parcellation of superficial white matter with deep learning. In: *2022 IEEE 19th International Symposium on Biomedical Imaging (ISBI)*. IEEE; 2022:1-5. doi:10.1109/ISBI52829.2022.9761541
456. Steinmann S, Lyall AE, Langhein M, et al. Sex-Related differences in white matter asymmetry and its implications for verbal working memory in psychosis high-risk state. *Front Psychiatry*. 2021;12:686967. doi:10.3389/fpsyt.2021.686967
457. Zhang F, Cetin Karayumak S, Hoffmann N, Rathi Y, Golby AJ, O'Donnell LJ. Deep white matter analysis (DeepWMA): Fast and consistent tractography segmentation. *Med Image Anal*. 2020;65:101761. doi:10.1016/j.media.2020.101761
458. Hong Y, O'Donnell LJ, Savadjiev P, et al. Genetic load determines atrophy in hand cortico-striatal pathways in presymptomatic Huntington's disease. *Hum Brain Mapp*. 2018;39(10):3871-3883. doi:10.1002/hbm.24217
459. Zekelman LR, Zhang F, Makris N, et al. White matter association tracts underlying

language and theory of mind: An investigation of 809 brains from the Human Connectome Project. *Neuroimage*. 2022;246:118739. doi:10.1016/j.neuroimage.2021.118739

460. Levitt JJ, Zhang F, Vangel M, et al. The organization of frontostriatal brain wiring in healthy subjects using a novel diffusion imaging fiber cluster analysis. *Cereb cortex*. 2021;31(12):5308-5318. doi:10.1093/cercor/bhab159
461. Ivanova M V., Zhong A, Turken A, Baldo J V., Dronkers NF. Functional contributions of the arcuate fasciculus to language processing. *Front Hum Neurosci*. 2021;15:672665. doi:10.3389/fnhum.2021.672665
462. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44(8):1105-1132. doi:10.1016/j.cortex.2008.05.004
463. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. *Neurosci Biobehav Rev*. 2018;92:104-127. doi:10.1016/j.neubiorev.2018.05.008
464. Jones DK, Christiansen KF, Chapman RJ, Aggleton JP. Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking: Implications for neuropsychological investigations. *Neuropsychologia*. 2013;51(1):67-78. doi:10.1016/j.neuropsychologia.2012.11.018
465. Weis CN, Belleau EL, Pedersen WS, Miskovich TA, Larson CL. Structural connectivity of the posterior cingulum is related to reexperiencing symptoms in posttraumatic stress disorder. *Chronic Stress*. 2018;2:1-9. doi:10.1177/2470547018807134
466. Schoenfeld FB, DeViva JC, Manber R. Treatment of sleep disturbances in posttraumatic stress disorder: A review. *J Rehabil Res Dev*. 2012;49(5):729-742. doi:10.1682/JRRD.2011.09.0164
467. Zemmoura I, Burkhardt E, Herbet G. The inferior longitudinal fasciculus: anatomy, function and surgical considerations. *J Neurosurg Sci*. 2021;6:590-604. doi:10.23736/S0390-5616.21.05391-1
468. Herbet G, Zemmoura I, Duffau H. Functional anatomy of the inferior longitudinal fasciculus: From historical reports to current hypotheses. *Front Neuroanat*. 2018;12. doi:10.3389/fnana.2018.00077
469. Khawaja I, Spurling BC, Singh S. *REM Sleep Behavior Disorder*. Treasure Island (FL): StatPearls; 2022.
470. Lim J-S, Shin SA, Lee J-Y, Nam H, Lee J-Y, Kim YK. Neural substrates of rapid eye

movement sleep behavior disorder in Parkinson's disease. *Parkinsonism Relat Disord*. 2016;23:31-36. doi:10.1016/j.parkreldis.2015.11.027

471. Makris N, Papadimitriou GM, Sorg S, Kennedy DN, Caviness VS, Pandya DN. The occipitofrontal fascicle in humans: A quantitative, in vivo, DT-MRI study. *Neuroimage*. 2007;37(4):1100-1111. doi:10.1016/j.neuroimage.2007.05.042
472. Conner AK, Briggs RG, Sali G, et al. A connectomic atlas of the human cerebrum — Chapter 13: Tractographic description of the inferior fronto-occipital fasciculus. *Oper Neurosurg*. 2018;15:S436-S443. doi:10.1093/ons/opy267
473. Mei L, Li X, Wang S, et al. The impacts of obstructive sleep apnea severity on brain white matter integrity and cognitive functions in children: A diffusion tensor imaging study. *Nat Sci Sleep*. 2021;13:2125-2135. doi:10.2147/NSS.S329408
474. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. 2014;383(9918):736-747. doi:10.1016/S0140-6736(13)60734-5
475. Haynes ZA, Stewart IJ, Poltavskiy EA, et al. Obstructive sleep apnea among survivors of combat-related traumatic injury: a retrospective cohort study. *J Clin Sleep Med*. 2022;18(1):171-179. doi:10.5664/jcsm.9530
476. Mysliwiec V, Gill J, Lee H, et al. Sleep disorders in US military personnel: A high rate of comorbid insomnia and obstructive sleep apnea. *Chest*. 2013;144(2):549-557. doi:10.1378/chest.13-0088
477. Macey PM. Structural brain neuroimaging changes in obstructive sleep apnea. *Neuroimaging Sleep Sleep Disord*. 2010:248-255. doi:10.1017/CBO9781139088268
478. Tummala S, Roy B, Park B, et al. Associations between brain white matter integrity and disease severity in obstructive sleep apnea. *J Neurosci Res*. 2016;94(10):915-923. doi:10.1002/jnr.23788
479. Canessa N, Castronovo V, Cappa SF, et al. Obstructive sleep apnea: Brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med*. 2011;183(10):1419-1426. doi:10.1164/rccm.201005-0693OC
480. Makris N, Kennedy DN, McInerney S, et al. Segmentation of subcomponents within the superior longitudinal fascicle in humans: A quantitative, in vivo, DT-MRI study. *Cereb Cortex*. 2005;15(6):854-869. doi:10.1093/cercor/bhh186
481. Genova HM, Deluca J, Chiaravalloti N, Wylie G. The relationship between executive functioning, processing speed, and white matter integrity in multiple sclerosis. *J Clin Exp Neuropsychol*. 2013;35(6):631-641. doi:10.1080/13803395.2013.806649
482. Kerchner GA, Racine CA, Hale S, et al. Cognitive processing speed in older adults:

Relationship with white matter integrity. *PLoS One*. 2012;7(11):e50425. doi:10.1371/journal.pone.0050425

483. Santiago C, Herrmann N, Swardfager W, et al. White matter microstructural integrity is associated with executive function and processing speed in older adults with coronary artery disease. *Am J Geriatr Psychiatry*. 2015;23(7):754-763. doi:10.1016/j.jagp.2014.09.008
484. Nakajima R, Kinoshita M, Shinohara H, Nakada M. The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. *Brain Imaging Behav*. 2020;14(6):2817-2830. doi:10.1007/s11682-019-00187-4
485. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Front Neurosci*. 2013;7:32. doi:10.3389/fnins.2013.00032
486. Papagno C. Naming and the role of the uncinate fasciculus in language function. *Curr Neurol Neurosci Rep*. 2011;11(6):553-559. doi:10.1007/s11910-011-0219-6
487. Papagno C, Miracapillo C, Casarotti A, et al. What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. *Brain*. 2011;134(2):405-414. doi:10.1093/brain/awq283
488. Olson IR, Heide RJ Von Der, Alm KH, Vyas G. Development of the uncinate fasciculus: Implications for theory and developmental disorders. *Dev Cogn Neurosci*. 2015;14:50-61. doi:10.1016/j.dcn.2015.06.003
489. Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain*. 2013;136(6):1692-1707. doi:10.1093/brain/awt094
490. Jamieson D, Schwenn P, Beaudequin DA, et al. Short strides to important findings: A short interval longitudinal study of sleep quality, psychological distress and microstructure changes to the uncinate fasciculus in early adolescents. *Int J Dev Neurosci*. 2021;81(1):82-90. doi:10.1002/jdn.10077
491. Jamieson D, Shan Z, Lagopoulos J, Hermens DF. The role of adolescent sleep quality in the development of anxiety disorders: A neurobiologically-informed model. *Sleep Med Rev*. 2021;59:101450. doi:10.1016/j.smrv.2021.101450
492. Koo DL, Kim HR, Kim H, Seong J-K, Joo EY. White matter tract-specific alterations in male patients with untreated obstructive sleep apnea are associated with worse cognitive function. *Sleep*. 2020;43(3):zsz247. doi:10.1093/sleep/zsz247
493. Hinkley LBN, Marco EJ, Findlay AM, et al. The role of corpus callosum development

in functional connectivity and cognitive processing. *PLoS One*. 2012;7(8):e39804. doi:10.1371/journal.pone.0039804

494. Goldstein A, Covington BP, Mahabadi N, Mesfin FB. *Neuroanatomy, Corpus Callosum*. Treasure Island (FL): StatPearls; 2022.
495. Bruce HA, Kochunov P, Kvarta MD, et al. Frontal white matter association with sleep quality and the role of stress. *J Sleep Res*. 2022:e13669. doi:10.1111/jsr.13669
496. Baillet M, Dilharreguy B, Pérès K, Dartigues JF, Mayo W, Catheline G. Activity/rest cycle and disturbances of structural backbone of cerebral networks in aging. *Neuroimage*. 2017;146:814-820. doi:10.1016/j.neuroimage.2016.09.051
497. IBM Corp. IBM SPSS Statistics for Mac. In: Armonk, NY: IBM Corp; 2020.
498. R Core Team. R: A Language and Environment for Statistical Computing. https://www.r-project.org. Published 2020.
499. GraphPad Prism for Mac. In: San Diego, USA: GraphPad Software. www.graphpad.com.
500. Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis - A Regression-Based Approach.* New York, NY: Guilford Press; 2013.
501. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behav Res Ther*. 2017;98:39-57. doi:10.1016/j.brat.2016.11.001
502. Isaac L, Main KL, Soman S, et al. The impact of depression on veterans with PTSD and traumatic brain injury: A diffusion tensor imaging study. *Biol Psychol*. 2015;105:20-28. doi:10.1016/j.biopsycho.2014.12.011
503. Espinoza Oyarce DA, Shaw ME, Alateeq K, Cherbuin N. Volumetric brain differences in clinical depression in association with anxiety: A systematic review with meta-analysis. *J Psychiatry Neurosci*. 2020;45(6):406-429. doi:10.1503/jpn.190156
504. Davey DK, Jurick SM, Crocker LD, et al. White matter integrity, suicidal ideation, and cognitive dysfunction in combat-exposed Iraq and Afghanistan veterans. *Psychiatry Res - Neuroimaging*. 2021;317:111389. doi:10.1016/j.pscychresns.2021.111389
505. Zhang FF, Peng W, Sweeney JA, Jia ZY, Gong QY. Brain structure alterations in depression: Psychoradiological evidence. *CNS Neurosci Ther*. 2018;24(11):994-1003. doi:10.1111/cns.12835
506. van Velzen LS, Kelly S, Isaev D, et al. White matter disturbances in major depressive disorder: a coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. *Mol Psychiatry*. 2020;25(7):1511-1525. doi:10.1038/s41380-019-0477-

2

507. Lee KS, Lee SH. White matter-based structural brain network of anxiety. *Adv Exp Med Biol*. 2020;1191:61-70. doi:10.1007/978-981-32-9705-0_4
508. Wu Y, Zhong Y, Ma Z, et al. Gray matter changes in panic disorder: A voxel-based meta-analysis and meta-analytic connectivity modeling. *Psychiatry Res - Neuroimaging*. 2018;282(264):82-89. doi:10.1016/j.pscychresns.2018.09.009
509. Harrewijn A, Cardinale EM, Groenewold NA, et al. Cortical and subcortical brain structure in generalized anxiety disorder: findings from 28 research sites in the ENIGMA-Anxiety Working Group. *Transl Psychiatry*. 2021;11(1):502. doi:10.1038/s41398-021-01622-1
510. Pando-Naude V, Toxto S, Fernandez-Lozano S, Parsons CE, Alcauter S, Garza-Villarreal EA. Gray and white matter morphology in substance use disorders: A neuroimaging systematic review and meta-analysis. *Transl Psychiatry*. 2021;11(1):29. doi:10.1038/s41398-020-01128-2
511. Navarri X, Afzali MH, Lavoie J, et al. How do substance use disorders compare to other psychiatric conditions on structural brain abnormalities? A cross-disorder meta-analytic comparison using the ENIGMA consortium findings. *Hum Brain Mapp*. 2022;43(1):399-413. doi:10.1002/hbm.25114
512. Kuo JR, Kaloupek DG, Woodward SH. Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: A cross-sectional study. *Arch Gen Psychiatry*. 2012;69(10):1080-1086. doi:10.1001/archgenpsychiatry.2012.73
513. Aupperle RL, Connolly CG, Stillman AN, May AC, Paulus MP. Deployment and post-deployment experiences in OEF/OIF veterans: Relationship to gray matter volume. *PLoS One*. 2013;8(9):e75880. doi:10.1371/journal.pone.0075880
514. Clausen AN, Billinger SA, Sisante J-F V., Suzuki H, Aupperle RL. Preliminary evidence for the impact of combat experiences on gray matter volume of the posterior insula. *Front Psychol*. 2017;8:2151. doi:10.3389/fpsyg.2017.02151
515. Butler O, Adolf J, Gleich T, et al. Military deployment correlates with smaller prefrontal gray matter volume and psychological symptoms in a subclinical population. *Transl Psychiatry*. 2017;7:e1031. doi:10.1038/tp.2016.288
516. McWhinney SR, Abé C, Alda M, et al. Association between body mass index and subcortical brain volumes in bipolar disorders–ENIGMA study in 2735 individuals. *Mol Psychiatry*. 2021;26(11):6806-6819. doi:10.1038/s41380-021-01098-x
517. Medic N, Ziauddeen H, Ersche KD, et al. Increased body mass index is associated with

specific regional alterations in brain structure. *Int J Obes*. 2016;40(7):1177-1182. doi:10.1038/ijo.2016.42

518. Steegers C, Blok E, Lamballais S, et al. The association between body mass index and brain morphology in children: a population-based study. *Brain Struct Funct*. 2021;226(3):787-800. doi:10.1007/s00429-020-02209-0
519. Bolzenius JD, Laidlaw DH, Cabeen RP, et al. Brain structure and cognitive correlates of body mass index in healthy older adults. *Behav Brain Res*. 2015;278:342-347. doi:10.1016/j.bbr.2014.10.010
520. Gunstad J, Paul RH, Cohen RA, et al. Relationship between body mass index and brain volume in healthy adults. *Int J Neurosci*. 2008;118(11):1582-1593. doi:10.1080/00207450701392282
521. Alosco ML, Stanek KM, Galioto R, et al. Body mass index and brain structure in healthy children and adolescents. *Int J Neurosci*. 2014;124(1):49-55. doi:10.3109/00207454.2013.817408
522. Thomaes K, Dorrepaal E, Draijer N, Jansma EP, Veltman DJ, van Balkom AJ. Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. *J Psychiatr Res*. 2014;50(1):1-15. doi:10.1016/j.jpsychires.2013.11.002
523. Scherk H, Falkai P. Changes in brain structure caused by neuroleptic medication. *Nervenarzt*. 2004;75(11):1112-1117. doi:10.1007/s00115-004-1793-5
524. Seiger R, Gryglewski G, Klöbl M, et al. The influence of acute SSRI administration on white matter microstructure in patients suffering from major depressive disorder and healthy controls. *Int J Neuropsychopharmacol*. 2021;24(7):542-550. doi:10.1093/ijnp/pyab008
525. Dusi N, Barlati S, Vita A, Brambilla P. Brain structural effects of antidepressant treatment in major depression. *Curr Neuropharmacol*. 2015;13(4):458-465. doi:10.2174/1570159X1304150831121909
526. Vieira R, Coelho A, Reis J, et al. White matter microstructure alterations associated with paroxetine treatment response in major depression. *Front Behav Neurosci*. 2021;15:693109. doi:10.3389/fnbeh.2021.693109
527. Liu J, Xu X, Luo Q, et al. Brain grey matter volume alterations associated with antidepressant response in major depressive disorder. *Sci Rep*. 2017;7(1):10464. doi:10.1038/s41598-017-10676-5
528. Fani N, Harnett NG, Bradley B, et al. Racial discrimination and white matter

microstructure in trauma-exposed black women. *Biol Psychiatry*. 2022;91(3):254-261. doi:10.1016/j.biopsych.2021.08.011

529. Noble KG, Korgaonkar MS, Grieve SM, Brickman AM. Higher education is an age-independent predictor of white matter integrity and cognitive control in late adolescence. *Dev Sci*. 2013;16(5):653-664. doi:10.1111/desc.12077
530. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75-90.
531. Balba NM, Elliott JE, Weymann KB, et al. Increased sleep disturbances and pain in veterans with comorbid traumatic brain injury and posttraumatic stress disorder. *J Clin Sleep Med*. 2018;14(11):1865-1878. doi:10.5664/jcsm.7482
532. Martindale SL, Farrell-Carnahan L V., Ulmer CS, Kimbrel NA, McDonald SD, Rowland JA. Sleep quality in returning veterans: The influence of mild traumatic brain injury. *Rehabil Psychol*. 2017;62(4):563-570. doi:10.1037/rep0000159
533. Wickwire EM, Williams SG, Roth T, et al. Sleep, sleep disorders, and mild traumatic brain injury. What we know and what we need to know: Findings from a national working group. *Neurotherapeutics*. 2016;13(2):403-417. doi:10.1007/s13311-016-0429-3
534. Babson K, Feldner M, Badour C, et al. Posttraumatic stress and sleep: differential relations across types of symptoms and sleep problems. *J Anxiety Disord*. 2011;25(5):706-713. doi:10.1016/j.janxdis.2011.03.007
535. Inslicht SS, Rao MN, Richards A, et al. Sleep and hypothalamic pituitary adrenal axis responses to metyrapone in posttraumatic stress disorder. *Psychoneuroendocrinology*. 2018;88(415):136-143. doi:10.1016/j.psyneuen.2017.12.002
536. Shokri-Kojori E, Wang G-J, Wiers CE, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci*. 2018;115(17):4483-4488. doi:10.1073/pnas.1721694115
537. Mohamed AZ, Cumming P, Nasrallah FA, Department of Defense Alzheimer's Disease Neuroimaging Initiative. White matter alterations are associated with cognitive dysfunction decades after moderate-to-severe traumatic brain injury and/or posttraumatic stress disorder. *Biol psychiatry Cogn Neurosci neuroimaging*. 2021;6(11):1100-1109. doi:10.1016/j.bpsc.2021.04.014
538. Wooten DW, Ortiz-Terán L, Zubcevik N, et al. Multi-modal signatures of tau pathology, neuronal fiber integrity, and functional connectivity in traumatic brain injury. *J Neurotrauma*. 2019;36(23):3233-3243. doi:10.1089/neu.2018.6178

539. Mendez MF, Owens EM, Reza Berenji G, Peppers DC, Liang L-J, Licht EA. Mild traumatic brain injury from primary blast vs. blunt forces: Post-concussion consequences and functional neuroimaging. *NeuroRehabilitation*. 2013;32(2):397-407. doi:10.3233/NRE-130861

540. Chapman JC, Diaz-Arrastia R. Military traumatic brain injury: A review. *Alzheimer's Dement*. 2014;10(3S):S97-104. doi:10.1016/j.jalz.2014.04.012

541. Neylan TC, Mueller SG, Wang Z, et al. Insomnia severity is associated with a decreased volume of the CA3/dentate gyrus hippocampal subfield. *Biol Psychiatry*. 2010;68(5):494-496. doi:10.1016/j.biopsych.2010.04.035

542. Chao LL, Mohlenhoff BS, Weiner MW, Neylan TC. Associations between subjective sleep quality and brain volume in Gulf War veterans. *Sleep*. 2014;37(3):445-452. doi:10.5665/sleep.3472

543. Lewis C, Lewis K, Kitchiner N, Isaac S, Jones I, Bisson JI. Sleep disturbance in post-traumatic stress disorder (PTSD): A systematic review and meta-analysis of actigraphy studies. *Eur J Psychotraumatol*. 2020;11(1):1767349. doi:10.1080/20008198.2020.1767349

544. Smith MT, McCrae CS, Cheung J, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: An American academy of sleep medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2018;14(7):1209-1230. doi:10.5664/jcsm.7228

545. Rundo JV, Downey R. Polysomnography. In: *Handbook of Clinical Neurology*. Vol 160. Elsevier; 2019:381-392. doi:10.1016/B978-0-444-64032-1.00025-4

546. Zhang Y, Ren R, Sanford LD, et al. Sleep in posttraumatic stress disorder: A systematic review and meta-analysis of polysomnographic findings. *Sleep Med Rev*. 2019;48:101210. doi:10.1016/j.smrv.2019.08.004

547. Ibáñez V, Silva J, Cauli O. A survey on sleep assessment methods. *PeerJ*. 2018;6:e4849. doi:10.7717/peerj.4849

548. Kim E-J, Dimsdale JE. The effect of psychosocial stress on sleep: A review of polysomnographic evidence. *Behav Sleep Med*. 2007;5(4):256-278. doi:10.1080/15402000701557383

549. Straus LD, Drummond SPA, Nappi CM, Jenkins MM, Norman SB. Sleep variability in military-related PTSD: A comparison to primary insomnia and healthy controls. *J Trauma Stress*. 2015;28(1):8-16. doi:10.1002/jts.21982

550. Rezaie L, Fobian AD, McCall WV, Khazaie H. Paradoxical insomnia and subjective–

objective sleep discrepancy: A review. *Sleep Med Rev*. 2018;40:196-202. doi:10.1016/j.smrv.2018.01.002

551. Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. *Sleep*. 2013;36(2):167-174. doi:10.5665/sleep.2364
552. Ghadami MR, Khaledi-Paveh B, Nasoori M, Khazaie H. PTSD-related paradoxical insomnia: an actigraphic study among veterans with chronic PTSD. *J Inj Violence Res*. 2015;7(2):54-58. doi:10.5249/jivr.v7i2.607
553. Ouellet M-C, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: A preliminary study. *Sleep Med*. 2006;7(6):486-497. doi:10.1016/j.sleep.2006.03.017
554. Werner KB, Griffin MG, Galovski TE. Objective and subjective measurement of sleep disturbance in female trauma survivors with posttraumatic stress disorder. *Psychiatry Res*. 2016;240(1):234-240. doi:10.1016/j.psychres.2016.04.039
555. Kram Mendelsohn A, Daffre C, Oliver KI, Seo J, Lasko NB, Pace-Schott EF. 1071 subjective measures of hyperarousal predict subjective longitudinal And retrospective measures of sleep quality in individuals exposed to trauma. *Sleep*. 2020;43(Supplement_1):A408. doi:10.1093/sleep/zsaa056.1067
556. Parrino L, Milioli G, De Paolis F, Grassi A, Terzano MG. Paradoxical insomnia: The role of CAP and arousals in sleep misperception. *Sleep Med*. 2009;10:1139-1145. doi:10.1016/j.sleep.2008.12.014
557. Johnson DA, Javaheri S, Guo N, et al. Objective measures of sleep apnea and actigraphy-based sleep characteristics as correlates of subjective sleep quality in an epidemiologic study: The Jackson Heart Sleep Study. *Psychosom Med*. 2020;82(3):324-330. doi:10.1097/PSY.0000000000000778
558. Moshkani Farahani D, Tavallaie A, Vahedi E, Rezaiemaram P, Naderi Z, Talaie A. The relationship between perceived sleep quality, polysomnographic measures and depressive symptoms in chemically-injured veterans: A pilot study. *Iran J Psychiatry*. 2014;9(3):169-174.
559. Strasshofer DR, Pacella ML, Irish LA, Palmieri PA, Johnson DM, Delahanty DL. The role of perceived sleep quality in the relationship between PTSD symptoms and general mental health. *Ment Heal Prev*. 2017;5:27-32. doi:10.1016/j.mhp.2017.01.001
560. Muzni K, Groeger JA, Dijk D, Lazar AS. Self-reported sleep quality is more closely associated with mental and physical health than chronotype and sleep duration in young

adults: A multi-instrument analysis. *J Sleep Res*. 2021;30(1):1-15. doi:10.1111/jsr.13152

561. Lemola S, Ledermann T, Friedman EM. Variability of sleep duration is related to subjective sleep quality and subjective well-being: An actigraphy study. *PLoS One*. 2013;8(8):e71292. doi:10.1371/journal.pone.0071292
562. Crocker LD, Keller A V., Jurick SM, et al. Mild traumatic brain injury burden moderates the relationship between cognitive functioning and suicidality in Iraq/Afghanistan-era veterans. *J Int Neuropsychol Soc*. 2019;25(1):79-89. doi:10.1017/S1355617718000851
563. Valera EM, Cao A, Pasternak O, et al. White matter correlates of mild traumatic brain injuries in women subjected to intimate-partner violence: A preliminary study. *J Neurotrauma*. 2019;36(5):661-668. doi:10.1089/neu.2018.5734
564. Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. *The Lancet Psychiatry*. 2018;5(5):424-431. doi:10.1016/S2215-0366(18)30065-8
565. Gordon EM, May GJ, Nelson SM. MRI-based measures of intracortical myelin are sensitive to a history of TBI and are associated with functional connectivity. *Neuroimage*. 2019;200:199-209. doi:10.1016/j.neuroimage.2019.06.026
566. Gilmore CS, Lim KO, Garvin MK, et al. Association of optical coherence tomography with longitudinal neurodegeneration in veterans with chronic mild traumatic brain injury. *JAMA Netw Open*. 2020;3(12):e2030824. doi:10.1001/jamanetworkopen.2020.30824
567. Elliott TR, Hsiao Y-Y, Kimbrel NA, et al. Resilience facilitates adjustment through greater psychological flexibility among Iraq/Afghanistan war veterans with and without mild traumatic brain injury. *Rehabil Psychol*. 2019;64(4):383-397. doi:10.1037/rep0000282
568. Panenka WJ, Lange RT, Bouix S, et al. Neuropsychological outcome and diffusion tensor imaging in complicated versus uncomplicated mild traumatic brain injury. *PLoS One*. 2015;10(4):1-27. doi:10.1371/journal.pone.0122746
569. Lange RT, Iverson G, Franzen MD. Neuropsychological functioning following complicated vs. uncomplicated mild traumatic brain injury. *Brain Inj*. 2009;23(2):83-91. doi:10.1080/02699050802635281
570. Lange RT, Brickel TA, French LM, et al. Neuropsychological outcome from uncomplicated mild, complicated mild, and moderate traumatic brain injury in us military personnel. *Arch Clin Neuropsychol*. 2012;27(5):480-494. doi:10.1093/arclin/acs059

571. Merritt VC, Jurick SM, Crocker LD, et al. Associations between multiple remote mild TBIs and objective neuropsychological functioning and subjective symptoms in combat-exposed veterans. *Arch Clin Neuropsychol*. 2020;35(5):491-505. doi:10.1093/arclin/acaa006

572. Al-Ameri LT, Mohsin TS, Wahid ATA. Sleep disorders following mild and moderate traumatic brain injury. *Brain Sci*. 2019;9(1):10. doi:10.3390/brainsci9010010

573. Foster SN, Hansen SL, Capener DC, Matsangas P, Mysliwiec V. Gender differences in sleep disorders in the US military. *Sleep Heal*. 2017;3(5):336-341. doi:10.1016/j.sleh.2017.07.015

574. Seitz J, Cetin-Karayumak S, Lyall A, et al. Investigating sexual dimorphism of human white matter in a harmonized, multisite diffusion magnetic resonance imaging study. *Cereb Cortex*. 2021;31(1):201-212. doi:10.1093/cercor/bhaa220

575. Rusticus SA, Lovato CY. Impact of sample size and variability on the power and type I error rates of equivalence tests: A simulation study. *Pract Assessment, Res Eval*. 2014;19(11):1-10.

576. Faber J, Fonseca LM. How sample size influences research outcomes. *Dental Press J Orthod*. 2014;19(4):27-29. doi:10.1590/2176-9451.19.4.027-029.ebo

577. Bailie J, Babakhanyan I, Jolly M, et al. Accuracy of self-reported questions for assessment of TBI history. *Arch Clin Neuropsychol*. 2017;32(6):656-666. doi:10.1093/arclin/acx075.14

578. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test–retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res*. 2002;53(3):737-740. doi:10.1016/S0022-3999(02)00330-6

579. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Med Rev*. 2016;25:52-73. doi:10.1016/j.smrv.2015.01.009

580. Koffel E, Polusny MA, Arbisi PA, Erbes CR. Pre-deployment daytime and nighttime sleep complaints as predictors of post-deployment PTSD and depression in National Guard troops. *J Anxiety Disord*. 2013;27(5):512-519. doi:10.1016/j.janxdis.2013.07.003

581. Acheson DT, Kwan B, Maihofer AX, et al. Sleep disturbance at pre-deployment is a significant predictor of post-deployment re-experiencing symptoms. *Eur J Psychotraumatol*. 2019;10(1):1679964. doi:10.1080/20008198.2019.1679964

582. Van Liempt S, Van Zuiden M, Westenberg H, Super A, Vermetten E. Impact of impaired

sleep on the development of PTSD symptoms in combat veterans: A prospective longitudinal cohort study. *Depress Anxiety*. 2013;30(5):469-474. doi:10.1002/da.22054

583. Wang HE, Campbell-Sills L, Kessler RC, et al. Pre-deployment insomnia is associated with post-deployment post-traumatic stress disorder and suicidal ideation in US Army soldiers. *Sleep*. 2019;42(2):1-9. doi:10.1093/sleep/zsy229
584. Gadie A, Shafto M, Leng Y, Kievit RA. How are age-related differences in sleep quality associated with health outcomes? An epidemiological investigation in a UK cohort of 2406 adults. *BMJ Open*. 2017;7:e014920. doi:10.1136/bmjopen-2016-014920
585. Zitser J, Anatürk M, Zsoldos E, et al. Sleep duration over 28 years, cognition, gray matter volume, and white matter microstructure: A prospective cohort study. *Sleep*. 2020;43(5):1-7. doi:10.1093/sleep/zsz290
586. Phelps AJ, Kanaan RAA, Worsnop C, Redston S, Ralph N, Forbes D. An ambulatory polysomnography study of the post-traumatic nightmares of post-traumatic stress disorder. *Sleep*. 2018;41(1). doi:10.1093/sleep/zsx188
587. Calik MW. Treatments for obstructive sleep apnea. *J Clin Outcomes Manag*. 2016;23(4):181-192. doi:10.1146/annurev-pathol-051217-111018.The
588. Lilius TO, Blomqvist K, Hauglund NL, et al. Dexmedetomidine enhances glymphatic brain delivery of intrathecally administered drugs. *J Control Release*. 2019;304:29-38. doi:10.1016/j.jconrel.2019.05.005
589. DeViva JC, McCarthy E, Southwick SM, Tsai J, Pietrzak RH. The impact of sleep quality on the incidence of PTSD: Results from a 7-Year, nationally representative, prospective cohort of U.S. military veterans. *J Anxiety Disord*. 2021;81:102413. doi:10.1016/j.janxdis.2021.102413
590. Gehrman P, Seelig AD, Jacobson IG, et al. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. *Sleep*. 2013;36(7):1009-1018. doi:10.5665/sleep.2798
591. Sufrinko A, Pearce K, Elbin RJ, et al. The effect of preinjury sleep difficulties on neurocognitive impairment and symptoms after sport-related concussion. *Am J Sports Med*. 2015;43(4):830-838. doi:10.1177/0363546514566193
592. McKeever VM, Huff ME. A diathesis-stress model of posttraumatic stress disorder: Ecological, biological, and residual stress pathways. *Rev Gen Psychol*. 2003;7(3):237-250. doi:10.1037/1089-2680.7.3.237
593. Mantua J, Henry OS, Garskovas NF, Spencer RMC. Mild traumatic brain injury chronically impairs sleep- and wake-dependent emotional processing. *Sleep*.

2017;40(6):1-11. doi:10.1093/sleep/zsx062

594. Marshall AJ, Acheson DT, Risbrough VB, Straus LD, Drummond SPA. Fear conditioning, safety learning, and sleep in humans. *J Neurosci*. 2014;34(35):11754-11760. doi:10.1523/JNEUROSCI.0478-14.2014

595. Genderson MR, Rana BK, Panizzon MS, et al. Genetic and environmental influences on sleep quality in middle-aged men: a twin study. *J Sleep Res*. 2013;22(5):519-526. doi:10.1111/jsr.12048

596. Kocevska D, Barclay NL, Bramer WM, Gehrman PR, Van Someren EJW. Heritability of sleep duration and quality: A systematic review and meta-analysis. *Sleep Med Rev*. 2021;59:101448. doi:10.1016/j.smrv.2021.101448

597. Madrid-Valero JJ, Rubio-Aparicio M, Gregory AM, Sánchez-Meca J, Ordoñana JR. Twin studies of subjective sleep quality and sleep duration, and their behavioral correlates: Systematic review and meta-analysis of heritability estimates. *Neurosci Biobehav Rev*. 2020;109(5):78-89. doi:10.1016/j.neubiorev.2019.12.028

598. Lind MJ, Brick LA, Gehrman PR, et al. Molecular genetic overlap between posttraumatic stress disorder and sleep phenotypes. *Sleep*. 2020;43(4):zsz257. doi:10.1093/sleep/zsz257

599. Richards A, Kanady JC, Neylan TC. Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. *Neuropsychopharmacology*. 2020;45(1):55-73. doi:10.1038/s41386-019-0486-5

600. Castriotta RJ, Murthy JN. Sleep disorders in patients with traumatic brain injury: a review. *CNS Drugs*. 2011;25(3):175-185. doi:10.2165/11584870-000000000-00000

601. Mollayeva T, Mollayeva S, Colantonio A. The risk of sleep disorder among persons with mild traumatic brain injury. *Curr Neurol Neurosci Rep*. 2016;16(6):55. doi:10.1007/s11910-016-0657-2

602. Zhanfeng N, Hechun X, Zhijun Z, Hongyu X, Zhou F. Regulation of circadian clock genes on sleep disorders in traumatic brain injury patients. *World Neurosurg*. 2019;130:e475-e486. doi:10.1016/j.wneu.2019.06.122

603. Popko K, Gorska E, Potapinska O, et al. Frequency of distribution of inflammatory cytokines IL-1, IL-6 and TNF-alpha gene polymorphism in patients with obstructive sleep apnea. *J Physiol Pharmacol*. 2008;59 Suppl 6:607-614. http://www.ncbi.nlm.nih.gov/pubmed/19218687.

604. Livingston WS, Rusch HL, Nersesian P V, Baxter T, Mysliwiec V, Gill JM. Improved

sleep in military personnel is associated with changes in the expression of inflammatory genes and improvement in depression symptoms. *Front Psychiatry*. 2015;6:59. doi:10.3389/fpsyt.2015.00059

605. Lent MR, Hoffman SN, Kirchner HL, Urosevich TG, Boscarino JJ, Boscarino JA. Attitudes about future genetic testing for posttraumatic stress disorder and addiction among community-based veterans. *Front Psychiatry*. 2017;8:76. doi:10.3389/fpsyt.2017.00076
606. Harnett NG, Ference EW, Knight AJ, Knight DC. White matter microstructure varies with post-traumatic stress severity following medical trauma. *Brain Imaging Behav*. 2020;14(4):1012-1024. doi:10.1007/s11682-018-9995-9
607. Yang FN, Liu TT, Wang Z. Functional connectome mediates the association between sleep disturbance and mental health in preadolescence: A longitudinal mediation study. *Hum Brain Mapp*. 2022;43(6):2041-2050. doi:10.1002/hbm.25772
608. Germain A, Buysse DJ, Shear MK, Fayyad R, Austin C. Clinical correlates of poor sleep quality in posttraumatic stress disorder. *J Trauma Stress*. 2004;17(6):477-484. doi:10.1007/s10960-004-5796-6
609. Cox RC, Tuck BM, Olatunji BO. Sleep disturbance in posttraumatic stress disorder: Epiphenomenon or causal factor? *Curr Psychiatry Rep*. 2017;19(4):22. doi:10.1007/s11920-017-0773-y
610. Gillin JC, Smith-Vaniz A, Schnierow B, et al. An open-label, 12-week clinical and sleep EEG study of nefazodone in chronic combat-related posttraumatic stress disorder. *J Clin Psychiatry*. 2001;62(10):789-796. doi:10.4088/JCP.v62n1007
611. Neylan TC, Lenoci M, Maglione ML, et al. The effect of nefazodone on subjective and objective sleep quality in posttraumatic stress disorder. *J Clin Psychiatry*. 2003;64(4):445-450. doi:10.4088/JCP.v64n0415
612. Pace-Schott EF, Milad MR, Orr SP, Rauch SL, Stickgold R, Pitman RK. Sleep promotes generalization of extinction of conditioned fear. *Sleep*. 2009;32(1):19-26. doi:10.5665/sleep/32.1.19
613. Pace-Schott EF, Verga PW, Bennett TS, Spencer RMC. Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. *J Psychiatr Res*. 2012;46(8):1036-1044. doi:10.1016/j.jpsychires.2012.04.015
614. Merritt VC, Jurick SM, Crocker LD, et al. Associations between multiple remote mild TBIs and objective neuropsychological functioning and subjective symptoms in combat-exposed veterans. *Arch Clin Neuropsychol*. 2020;35(5):491-505.

doi:10.1093/arclin/acaa006

615. Epstein DR, Babcock-Parziale JL, Herb CA, Goren K, Bushnell ML. Feasibility test of preference-based insomnia treatment for Iraq and Afghanistan war veterans. *Rehabil Nurs*. 2013;38(3):120-132. doi:10.1002/rnj.67
616. Phelps AJ, Varker T, Metcalf O, Dell L. What are effective psychological interventions for veterans with sleep disturbances? A rapid evidence assessment. *Mil Med*. 2017;182(1):e1541-e1550. doi:10.7205/MILMED-D-16-00010
617. Pigeon WR. Treatment of adult insomnia with cognitive-behavioral therapy. *J Clin Psychol*. 2010;66(11):1148-1160. doi:10.1002/jclp.20737
618. Cervena K, Dauvilliers Y, Espa F, et al. Effect of cognitive behavioural therapy for insomnia on sleep architecture and sleep EEG power spectra in psychophysiological insomnia. *J Sleep Res*. 2004;13(4):385-393. doi:10.1111/j.1365-2869.2004.00431.x
619. Germain A, Nielsen T. Impact of imagery rehearsal treatment on distressing reams, psychological distress, and sleep parameters in nightmare patients. *Behav Sleep Med*. 2003;1(3):140-154. doi:10.1207/S15402010BSM0103_2
620. Swanson LM, Favorite TK, Horin E, Arnedt JT. A combined group treatment for nightmares and insomnia in combat veterans: A pilot study. *J Trauma Stress*. 2009;22(6):639-642. doi:10.1002/jts.20468
621. Rauch SAM, Eftekhari A, Ruzek JI. Review of exposure therapy: a gold standard for PTSD treatment. *J Rehabil Res Dev*. 2012;49(5):679-687. doi:10.1682/jrrd.2011.08.0152
622. Paunovic N, Öst LG. Cognitive-behavior therapy vs exposure therapy in the treatment of PTSD in refugees. *Behav Res Ther*. 2001;39(10):1183-1197. doi:10.1016/S0005-7967(00)00093-0
623. Colvonen PJ, Drummond SPA, Angkaw AC, Norman SB. Piloting cognitive-behavioral therapy for insomnia integrated with prolonged exposure. *Psychol Trauma Theory, Res Pract Policy*. 2019;11(1):107-113. doi:10.1037/tra0000402
624. Baddeley JL, Gros DF. Cognitive behavioral therapy for insomnia as a preparatory treatment for exposure therapy for posttraumatic stress disorder. *Am J Psychother*. 2013;67(2):199-210. doi:10.1176/appi.psychotherapy.2013.67.2.203
625. El-Solh AA, Riaz U, Roberts J. Sleep disorders in patients with posttraumatic stress disorder. *Chest*. 2018;154(2):427-439. doi:10.1016/j.chest.2018.04.007
626. Lipinska G, Baldwin DS, Thomas KGF. Pharmacology for sleep disturbance in PTSD. *Hum Psychopharmacol*. 2016;31(2):156-163. doi:10.1002/hup.2522

627. Gutierrez L, Ghadimi S, Krall A, et al. Posttraumatic stress disorder risk and benzodiazepine dependence in older veterans with insomnia symptoms. *Clin Gerontol*. 2022;45(2):414-418. doi:10.1080/07317115.2021.1954123

628. Yücel DE, van Emmerik AAP, Souama C, Lancee J. Comparative efficacy of imagery rehearsal therapy and prazosin in the treatment of trauma-related nightmares in adults: A meta-analysis of randomized controlled trials. *Sleep Med Rev*. 2020;50:101248. doi:10.1016/j.smrv.2019.101248

629. Detweiler M, Pagadala B, Candelario J, Boyle J, Detweiler J, Lutgens B. Treatment of Post-Traumatic Stress Disorder Nightmares at a Veterans Affairs Medical Center. *J Clin Med*. 2016;5(12):117. doi:10.3390/jcm5120117

630. Malejko K, Abler B, Plener PL, Straub J. Neural correlates of psychotherapeutic treatment of post-traumatic stress disorder: A systematic literature review. *Front Psychiatry*. 2017;8:85. doi:10.3389/fpsyt.2017.00085

631. Kim SJ, Lee YJ, Kim N, et al. Exploration of changes in the brain response to sleep-related pictures after cognitive–behavioral therapy for psychophysiological insomnia. *Sci Rep*. 2017;7(1):12528. doi:10.1038/s41598-017-13065-0

632. Baril AA, Martineau-Dussault MÈ, Sanchez E, et al. Obstructive sleep apnea and the brain: A focus on gray and white matter structure. *Curr Neurol Neurosci Rep*. 2021;21(3):11. doi:10.1007/s11910-021-01094-2

633. Alexander M, Ray MA, Hébert JR, et al. The national veteran sleep disorder study: Descriptive epidemiology and secular trends, 2000-2010. *Sleep*. 2016;39(7):1399-1410. doi:10.5665/sleep.5972

634. Ghaziri J, Tucholka A, Larue V, et al. Neurofeedback training induces changes in white and gray matter. *Clin EEG Neurosci*. 2013;44(4):265-272. doi:10.1177/1550059413476031

635. Loriette C, Ziane C, Ben Hamed S. Neurofeedback for cognitive enhancement and intervention and brain plasticity. *Rev Neurol*. 2021;177(9):1133-1144. doi:10.1016/j.neurol.2021.08.004

636. Marzbani H, Marateb H, Mansourian M. Neurofeedback: A comprehensive review on system design, methodology and clinical applications. *Basic Clin Neurosci J*. 2016;7(2):143-158. doi:10.15412/J.BCN.03070208

637. Lambert-Beaudet F, Journault W-G, Rudziavic Provençal A, Bastien CH. Neurofeedback for insomnia: Current state of research. *World J Psychiatry*. 2021;11(10):897-914. doi:10.5498/wjp.v11.i10.897

638. Kwan Y, Yoon S, Suh S, Choi S. A randomized controlled trial comparing neurofeedback and cognitive-behavioral therapy for insomnia patients: Pilot study. *Appl Psychophysiol Biofeedback*. 2022;47(2):95-106. doi:10.1007/s10484-022-09534-6

639. Steingrimsson S, Bilonic G, Ekelund A-C, et al. Electroencephalography-based neurofeedback as treatment for post-traumatic stress disorder: A systematic review and meta-analysis. *Eur Psychiatry*. 2020;63(1):e7. doi:10.1192/j.eurpsy.2019.7

Acknowledgements

First and foremost, I want to express special gratitude to the veterans participating in the TRACTS study, who were willing to share their experiences after deployment to contribute to this research.

I am beyond thankful for my first supervisor, Professor Inga K. Koerte. Thank you for your guidance, academic, and emotional support. Thank you for reminding me that every obstacle can be overcome with passion and perseverance. Thank you for giving me endless scientific opportunities and encouraging me to pursue what I feel most passionate about. Navigating through the intriguing and fascinating world of research would not have been possible without you. I am incredibly grateful for being a part of your scientific community and consider myself most fortunate for everything I was able to learn from you.

I am indebted to Professor Martha E. Shenton, for giving me the opportunity to work on projects involving post-traumatic stress disorder and mild traumatic brain injury. I am beyond grateful for the possibility of spending time at the Psychiatry Neuroimaging Laboratory at Harvard Medical School. I gained invaluable knowledge on neuroimaging techniques and traumatic stress that paved the way for a successful scientific career. I will always cherish the memories and never forget this special time of my life.

I would further like to thank Professor Florian Heinen for his guidance and input to challenging scientific questions and his commitment to supervising me. Thank you, for providing help with answering challenging methodological questions and invaluable knowledge on sleep quality in association with post-traumatic stress disorder and mild traumatic brain injury.

Dr. Johanna Seitz-Holland deserves a very special thank you. Thank you for always being there for me and helping me navigate in the research world. There's no doubt in saying I could not have done it without you! You were always there – whether it was research-related or of personal matter. I am grateful for everything you taught me, and I continue to be amazed by everything you achieve.

I would like to thank Elena, my friend and cBRAIN companion from day one. Thank you for the amazing time we had at cBRAIN, your scientific and emotional support. I am

amazed by your conscientiousness and dedication, but mostly by your kindness. You never fail to look out for others and offer your help. There's so much I learned from you and I'm looking forward to what the future holds for us.

Moreover, I want to thank my friend and fellow PhD student, Lisa, for mastering the ups and downs with me, for endless nights working on our manuscripts, and re-running statistical analyses, but most of all for your unbreakable optimism that we will succeed.

Carina, when we first met in Boston, you made me feel so welcome. I am beyond thankful that we've grown to be so close and for the time we spent together at the PNL. You supported me whenever I felt discouraged, and you never failed to take hours of your time to discuss challenging research questions and run complex analyses. There's so much I learned from you, and I am amazed by how passionate you are about improving women's health through research. It is an honor to work with you, but more so, to be your friend.

Last, I want to thank the entire cBRAIN, PNL, and TRACTS team, as well as my friends and family for supporting me throughout the process. It would not have been possible without you!

Thank you,
Philine