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REVIEW

Neuroimaging Correlates of Post-Traumatic Stress Disorder in Traumatic Brain Injury: A Systematic Review of the Literature

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Abstract

Neuroimaging is widely utilized in studying traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). The risk for PTSD is greater after TBI than after non-TBI trauma, and PTSD is associated with worse outcomes after TBI. Studying the neuroimaging correlates of TBI-related PTSD may provide insights into the etiology of both conditions and help identify those TBI patients most at risk of developing persistent symptoms. The objectives of this systematic review were to examine the current literature on neuroimaging in TBI-related PTSD, summarize key findings, and highlight strengths and limitations to guide future research. A Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) compliant literature search was conducted in PubMed (MEDLINE®), PsycINFO, Embase, and Scopus databases prior to January 2022. The database query yielded 4486 articles, which were narrowed based on specified inclusion criteria to a final cohort of 16 studies, composed of 854 participants with TBI. There was no consensus regarding neuroimaging correlates of TBI-related PTSD among the included articles. A small number of studies suggest that TBI-related PTSD is associated with white matter tract changes, particularly in frontotemporal regions, as well as changes in whole-brain networks of resting-state connectivity. Future studies hoping to identify reliable neuroimaging correlates of TBI-related PTSD would benefit from ensuring consistent case definition, preferably with clinician-diagnosed TBI and PTSD, selection of comparable control groups, and attention to imaging timing post-injury. Prospective studies are needed and should aim to further differentiate predisposing factors from sequelae of TBI-related PTSD.

Keywords: neuroimaging; neuropsychiatric symptoms; post-traumatic stress disorder; traumatic brain injury

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Introduction

Traumatic brain injury (TBI), defined as an alteration of brain function caused by an external physical force, is a common neurological condition affecting 3,200,000–5,300,000 people in the United States.[1] TBI is recognized as a chronic disease process with the potential for both enduring and progressive consequences, rather than as a singular isolated event.[2] The sequelae of TBI encompass a wide variety of neurological, cognitive, and psychological disturbances that may be transient or lead to long-term disability. Cognitive and neurological deficits after TBI are major targets of rehabilitative programs. Less understood are the variety of emotional regulation complications collectively known as neuropsychiatric symptoms (NPS) that can occur after TBI. A wide variety of NPS may be observed transiently after TBI in association with other post-concussive symptoms (PCS). However, there is also an increased rate of syndromal psychiatric disorders in patients with a history of TBI compared with both the general population and non-TBI trauma survivors.[3–5] In particular, patients with a history of TBI are more likely to develop major depressive disorder, anxiety disorders, and post-traumatic stress disorder (PTSD).[4] PTSD is a complex syndrome, which presents as variable combinations of four symptom clusters: intrusion, avoidance, negative alterations of mood or cognition, and alterations in arousal and reactivity. These symptoms must develop in response to a traumatic event and lead to significant impairment of social and occupational function.[6,7] Whereas $\sim$90% of the population will experience a traumatic event in their lifetime, <10% of people go on to develop PTSD.[8]

Historically, there has been controversy over whether TBI could be a precipitant of PTSD, particularly when associated with amnesia concerning the traumatic event. Recently, however, several studies have found that TBI is an independent risk factor for developing PTSD, even if the trauma is not explicitly remembered.[9–11] PTSD is nearly three times more common after TBI than after non-TBI trauma, and TBI may be associated with greater severity and prolongation of PTSD.[5,12] Reciprocally, receiving a PTSD diagnosis after TBI has been associated with a higher likelihood of persistent sensory and cognitive complaints, greater functional impairment, and worse quality of life.[11,13,14] Identification and early treatment of PTSD in TBI patients may mitigate disability and perhaps accelerate recovery.

The vast majority of TBIs are of mild severity and may not come to medical attention immediately, making targeting of post-injury PTSD mitigation efforts and impact quantification challenging. History of TBI and PTSD are therefore dependent on retrospective reports from TBI subjects, who can be prone to poor recall, context dependence, and under-reporting or over-reporting of symptoms.[15–18] Moreover, many of the commonly reported PCS (e.g., depressed mood, poor concentration, insomnia) overlap with symptoms of PTSD or with other psychiatric syndromes linked to TBI (e.g., major depressive disorder, generalized anxiety disorder), causing further diagnostic challenges.[19] Outside the clinic, conducting neuroimaging studies of TBI-related PTSD, for all the reasons discussed, is more complicated than studying either condition in isolation, and there are no objective biomarkers for diagnosis, let alone for monitoring the recovery of higher order brain functions such as cognition and emotion after TBI. Considering these challenges, comorbidity estimates should be interpreted cautiously.

Brain imaging studies of psychiatric conditions secondary to TBI may help clinicians and scientists better understand the neuroanatomical origins of NPS in TBI, highlighting disease processes and potential treatment strategies. Neuroimaging has been a crucial tool in assessing TBI and in investigating psychiatric conditions. Structural imaging studies in TBI suggest that both regional and global brain parenchymal volume change across acute, subacute, and chronic time periods.[20–24] Task-based functional magnetic resonance imaging (fMRI) studies have revealed abnormalities in several brain regions after TBI including the dorsolateral pre-frontal cortex (PFC), ventrolateral PFC, and basal ganglia.[21,25–28] In the case of PTSD, outside of TBI, the most commonly reported structural imaging abnormality is reduced hippocampal volume, though there is debate about whether this is a result of, or a risk factor for, the development of PTSD.[29,30] White matter dysfunction, particularly in the limbic circuits, is similarly posited to be either a risk factor for or a consequence of PTSD.[31–34] Functional neuroimaging studies in PTSD have reported that hyperactivation of the amygdala and insula, as well as hypoactivation in dorsal and rostral anterior cingulate cortices and the medial/ventromedial PFC, are associated with PTSD symptom severity.[29,35] There is also evidence that PTSD is associated with dysfunction in large-scale structural and functional networks.[32,36]

The present study aims to (1) summarize potential neuroimaging correlates of TBI-related PTSD, (2) discuss the clinical significance of trends found in PTSD-related imaging findings, and (3) outline current trends in research practice, identifying potential bias in common study designs, and highlighting the current literature's limitations in order to strengthen future research. The synthesis of high-quality literature will serve to inform preventative efforts, such as post-injury screening and early intervention, help with the identification of neuroimaging correlates to psychiatric symptoms, and, ultimately, guide therapies to improve NPS outcomes.

Methods

Search strategy

A literature search was conducted to extract articles with neuroimaging and NPS components among human TBI patients. PubMed (MEDLINE®), PsycINFO, Embase, and Scopus databases were used to obtain relevant articles. Boolean searches were kept broad in the interest of reflecting all neuroimaging modalities and to capture broad domains of neuropsychiatric symptomatology. TBI literature takes many different approaches to definition, severity, population, and timing of assessment, necessitating a relatively general approach to the literature search. We employed 41 imaging-, 35 NPS-, and 15 TBI-related keywords. Exact search phrases and MeSH search field qualifiers are outlined in Supplementary Appendix SA1.

Review protocol

This review adhered to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guidelines for implementation and reporting of systematic reviews.[37] A summary of the review protocol, including the number of articles included and excluded in each step, can be found in Figure 1. In the first level of the screening process, titles and abstracts were reviewed in parallel for determination of inclusion or exclusion. Individuals in dyads were blind to each other's determinations, and an identical data extraction sheet was utilized by all reviewers. Discrepancies and cases in which a reviewer was unsure were routed to a third-party reviewer for a final decision. All included articles were then subjected to a full-text review by dyads, again followed by

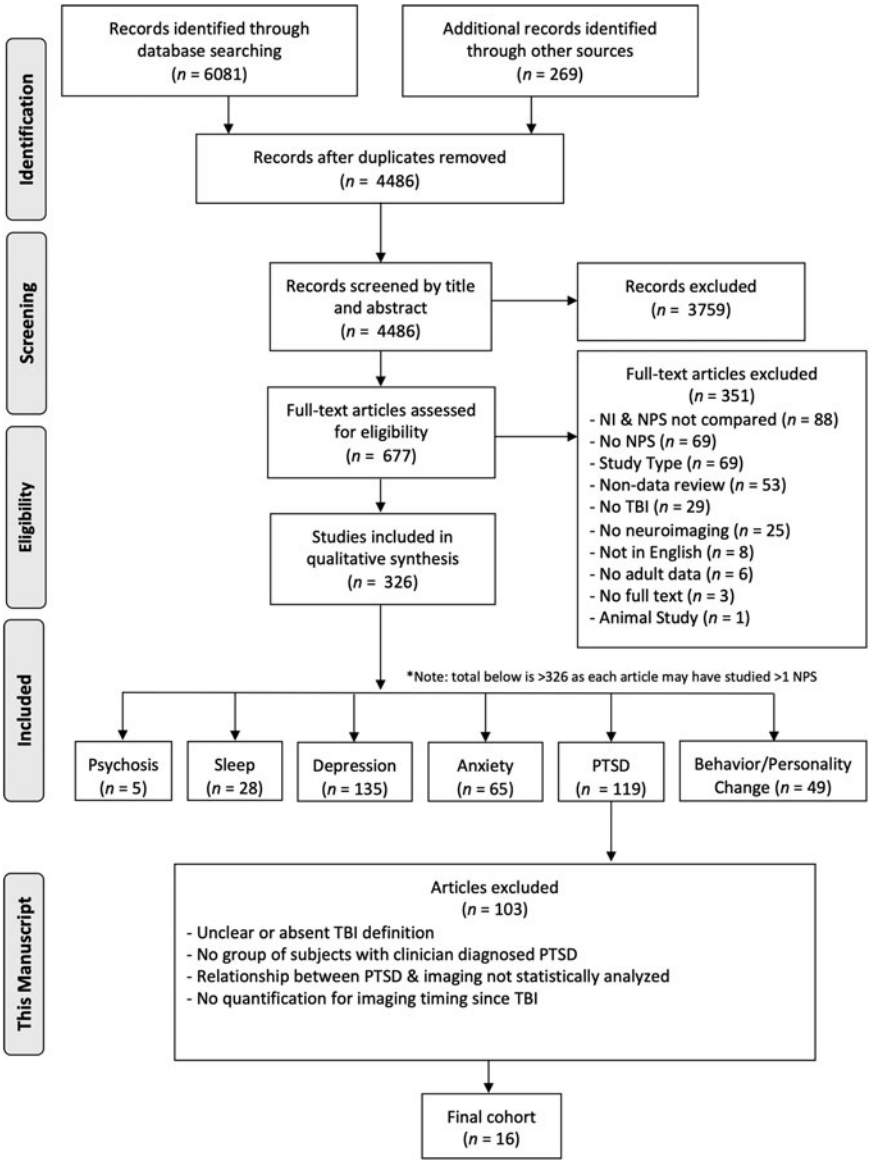

FIG. 1. Article selection process.

a reappraisal if necessary. The resulting article cohort was then divided into six NPS domains: PTSD, depression, anxiety, sleep disturbance, behavior/personality change, and psychosis. The present review focuses on the NPS domain of PTSD. A series of subsequent reviews focused on the other NPS domains will be published from these same efforts.[38,39]

Inclusion and exclusion criteria

For both title/abstract and full-text reviews, a standardized set of inclusion and exclusion criteria were applied. Articles were excluded if they: (1) lacked any one of the three key elements (i.e., neuroimaging, NPS, and TBI), (2) Were of an undesirable study type (i.e., case reports/case series with $n < 5$, editorials, commentary letters, replies to editor, book reviews, non-peer-reviewed articles, conference proceedings, poster abstracts, dissertations), (3) were not written in English, and/or (4) the study population had no human participants or adult (≥18 years) data. Articles were *not* excluded on the basis of TBI severity, singularity, or reoccurrence of TBI, acuity or chronicity of NPS, neuroimaging modality, or whether neuroimaging was conducted in the acute (≤48 h), subacute (2 days – 2 weeks), or chronic (≥6 months) time span post-TBI. This information was, however, collected for all articles for exploratory purposes.

The final articles selected for the present review focusing on PTSD met all of the following additional criteria: they (1) statistically analyzed the relationship between neuroimaging findings and either a diagnosis of PTSD or PTSD symptom severity in individuals with clearly defined TBI, (2) Included a group of participants with clinician-diagnosed PTSD, (3) had a clear TBI definition for participants included in the study (formalized or study-specific criteria with any combination of Glasgow Coma Scale score, loss/alteration in consciousness, and/or post-traumatic amnesia), and (4) quantified the time interval between TBI occurrence and acquisition of neuroimaging. Articles that fulfilled these criteria were then organized based on imaging modality. Originally, we planned to include only studies that conducted neuroimaging in participants with both clinician-diagnosed TBI and clinician-diagnosed PTSD; as no studies met both criteria, clinician-diagnosed TBI was not used as an inclusion criterion for this review.

Article quality

All of the articles included in this study were reviewed for sources of potential bias and methodological quality using the Newcastle–Ottawa Scale.[40] The Newcastle–Ottawa Scale helps evaluate risks associated with selection bias, comparability of comparison groups (e.g., risk of potential confounders), and the validity of outcome/exposure ascertainment for observational, nonrandomized investigation. The scale has distinct evaluation criteria for case-control and cohort studies. In this review, articles were determined to be case-control or cohort studies based on the outcome of interest to the present systematic review, not necessarily the article's primary outcome. Each article was independently scored by a dyad of reviewers (A.I.E. and B.R.B. or D.A.S.) followed by a consensus process to address any differences. For each item scale, bias was scored as high, low, or unclear.

Results

Application of inclusion and exclusion criteria produced a final cohort of 16 articles published from 2009 to 2022 (Tables 1 and 2). These articles collectively comprised the findings of 854 individuals with TBI. Ten studies had a dedicated experimental group for TBI and co-occurring PTSD ($n = 327$) (all 16 articles studied PTSD in TBI, but not exclusively as a separate experimental group), 10 had a TBI-only group ($n = 233$), 8 included a designated normal or healthy control group ($n = 264$), and 4 utilized a PTSD-only comparison group ($n = 89$). All eight studies with control groups utilized veteran, combat, or physical trauma-exposed control subjects. Across experimental groups, the conglomerate sample size for all 16 articles was 1361.

The 16 articles included the following imaging modalities with accompanying frequencies: nine structure-based magnetic resonance imaging (MRI), seven diffusion tensor imaging (DTI), three resting state functional MRI (rs-fMRI), three magnetoencephalogram (MEG), two 18F-fluorodeoxyglucose positron emission tomography

Table 1. Summary of Article Characteristics ($n = 16$)

Variable	n *(%)*
Study type	
Case-control	10 (62.5)
Observational cohort	6 (37.5)
Population	
Civilian	0
Military	15 (93.75)
Civilian & military	1 (6.25)
Sport	0
TBI Severity	
Mild	14 (87.5)
Any TBI severity	2 (12.5)
TBI occurrence	
Single	1 (6.25)
Single & recurrent	15 (93.75)
Imaging timing post-TBI[a]	
Acute/subacute	-
Intermediate	-
Chronic	16 (100)

[a]Acute/subacute, 0 h−2 weeks; intermediate, 2 weeks −6 months; and chronic, >6 months.

TBI, traumatic brain injury.

Table 2. Articles Comparing Neuroimaging and Post-Traumatic Stress Disorder in Traumatic Brain Injury ($n = 16$)

Article	*Study type*	*Sample size*	*Population*	*TBI diagnostic criteria*	*TBI severity; occurrence*	*Timing of neuroimaging since TBI*	*Neuroimaging modality*	*Neuro-psychiatric outcome measure(s)*	*Pertinent findings*
Bae et al, 2020	Case-control	$n = 82$ (TBI-only = 25, TBI+PTSD = 32, HC = 25)	Military	Ohio State University TBI Identification Method	Mild, moderate, severe; single, recurrent	Average 15.2 (±10.5) years (range 1-39 years); TBI-only = 18.7 (±12.2) years	MRI	SCID-IV	There were no significant differences in bilateral hippocampi volume comparing TBI+PTSD vs. TBI-only. There was a trend toward increased left amygdala volume in TBI+PTSD vs. TBI-only.
Brenner et al, 2009	Case-control	$n = 72$ (TBI-only = 27, PTSD-only = 13, TBI+PTSD = 32)	Military	Study-specific interview based on CDC criterion	Mild, moderate, severe; single, recurrent	Median 23 years (range 1-53)	MRI	SCID-IV	PTSD diagnosis had no impact on TBI-related neuroimaging results. Those with TBI and PTSD were less likely to have trauma-related findings on MRI.
Buchsbaum et al, 2015	Case-control	$n = 48$ (TBI-only = 16, TBI+PTSD = 17, VC = 15)	Military	ACRM, BTBIS	Mild; single, recurrent	mTBI+PTSD = 6.06 (±1.4) years; mTBI-only = 5.00 (±1.6) years	FDG-PET	CAPS	Patients with a history of mTBI + PTSD had lower relative metabolic rates in the left superior amygdala (mean = 0.74; SD = 0.03) than patients with a history of mTBI alone. However, a repeated measures ANOVA was not significant.
Davenport et al, 2016	Case-control	$n = 124$ (Lifetime PTSD = 56, No lifetime PTSD = 68)	Military, civilian	Minnesota Blast Exposure Screening Tool	Mild; single, recurrent	Military+PTSD = median 6.42 (IQR 4.00, 8.58) years; Military-PTSD = 7.25 (4.92, 8.58); Civilian+PTSD = 10.56 (6.00, 15.17); Civilian-PTSD = 12.83 (5.50, 20.59)	MRI, DTI	SCID-IV, CAPS	Civilian mTBI was associated with white matter disruptions; the effect of deployment mTBI on white matter was contingent on PTSD history. The interaction between deployment mTBI and lifetime PTSD had significant effects on the number of voxels with high GFA, mean FA, and mean GFA in the bilateral inferior fronto-occipital fasciculus, bilateral superior and inferior longitudinal fasciculi, right uncinate, and right hippocampal cingulum.

(*continued*)

Table 2. (Continued)

Article	*Study type*	*Sample size*	*Population*	*TBI diagnostic criteria*	*TBI severity; occurrence*	*Timing of neuroimaging since TBI*	*Neuroimaging modality*	*Neuro-psychiatric outcome measure(s)*	*Pertinent findings*
Hayes et al, 2015	Cohort	*n* = 114 (TBI = 59, VC = 55)	Military	Study-specific interview based on BAT-L	Mild; single, recurrent	mTBI+LOC = 4.69 (±1.93) years; mTBI – LOC = 3.65 (±2.27) years; controls = 4.15 (±3.03) years	MRI, DTI	CAPS	Greater PTSD symptom severity was associated with reduced FA in the left retrolenticular internal capsule; PTSD was not associated with spatially heterogeneous white matter abnormalities.
Jak et al, 2020	Case-control	n = 74 (TBI-only = 20, PTSD-only = 16, TBI+PTSD = 22, HC = 16)	Military	VCU rCDI-B, VCU rCDI-G, VA/DoD	Mild; single, recurrent	TBI+PTSD = 12.7 (±8.4) years TBI-only = 7.81 (±6.26) years; TBI+PTSD = 6.69 (±4.65) years	MRI, mc-DESPOT	MINI, PCL-5	PTSD was significantly associated with higher MWF in the genu, body, and splenium of the corpus callosum, anterior, posterior, and retro lenticular limbs of internal capsule, and the cingulum, with no main effect observed for mTBI.
Martindale et al, 2020	Cohort	*n* = 163 (TBI = 67, current PTSD = 43, current PTSD +TBI = 24, lifetime PTSD = 49, lifetime PTSD+TBI = 25)	Military	MMA-TBI, VA/DoD	Mild: single, recurrent	11.19 (±4.18) years (Range 1.87-27.32)	MRI	CAPS-5	Neither current nor lifetime PTSD were significantly correlated with volumetric outcomes. There was a trend toward greater amygdala volumes in the PTSD-only group vs. the TBI+PTSD group, which did not survive FDR correction.
Matthews et al, 2012	Case-control	*n* = 46 TBI (28 with PTSD)	Military	BTBIS	Mild; single, recurrent	3.57 (±1.45) years	MRI, DTI	CAPS	No regions of significant FA difference were identified between individuals with and those without PTSD.
Morey et al, 2013	Cohort	*n* = 100 (TBI = 30, 19 w/ PTSD, VC = 70, 1 w/ PTSD)	Military	Ivins TBI Questionnaire ACRM	Mild; single, recurrent	9.7 (±10.8) years	MRI, DTI	SCID-IV, CAPS	No association was found between PTSD and DTI-based loss of white matter integrity associated with mTBI.
Petrie et al, 2014	Cohort	*n* = 52 (blast-TBI = 34, VC = 18)	Military	ACRM w/o GCS	Mild; single, recurrent	3.8 (±1.5) years	DTI, MPF, FDG-PET	PCL-M, CAPS	Neuroimaging metrics did not differ between participants with and those without PTSD after TBI.

(*continued*)

Table 2. (Continued)

Article	*Study type*	*Sample size*	*Population*	*TBI diagnostic criteria*	*TBI severity; occurrence*	*Timing of neuroimaging since TBI*	*Neuroimaging modality*	*Neuro-psychiatric outcome measure(s)*	*Pertinent findings*
Rowland et al, 2017	Case-control	$n=28$ (TBI-only = 6, PTSD-only = 6, TBI+PTSD = 6, VC = 10)	Military	ACRM	Mild; single	6.2 (±2.7) years	rs-fMRI, MEG	PCL-M	Participants with PTSD had decreasing order and connectivity, and increased randomness in network topology; networks of participants with PTSD displayed lower levels of small-worldness.
Rowland et al, 2018	Case-control	$n=16$ (TBI-only = 9, TBI+PTSD = 7)	Military	Clinical interview, ACRM, VA/DoD	Mild; single, recurrent	PTSD = 9.07 (±3.66) years; No PTSD = 13.10 years (±7.68)	rs-fMRI, MEG	CAPS-5, PCL-5, NSI	PTSD diagnosis after TBI was associated with increases in small-worldness of the networks, and relatedly clustering within the networks.
Rowland et al, 2021	Cohort	$n=181$ (TBI = 74, PTSD = 51, overlap not reported)	Military	MMA-TBI, VA/DoD	Mild; single, recurrent	11 (±4.1) years	MRI, MEG	CAPS-5	PTSD and blast TBI interaction significantly reduced the number of nodes in connectome, increased the average degree of nodes, and increased the strength of connections; PTSD and non-blast TBI interaction reduced the number of nodes in connectome.
Santhanam, Wilson et al, 2019	Case-control	$n=106$ (TBI-only = 27, TBI+PTSD = 24, HC = 55)	Military	Ohio State University TBI Identification Method	Mild; single, recurrent	TBI-only average = 1.7 years; TBI+PTSD average = 2.2 years	fMRI	SCID-IV, PCL-C	Connectivity within the anterior node of the DMN was decreased in the TBI+PTSD group compared with the TBI-only group. There were no significant differences in DMN connectivity between the TBI+PTSD group and HC.

(*continued*)

Table 2. (Continued)

Article	*Study type*	*Sample size*	*Population*	*TBI diagnostic criteria*	*TBI severity; occurrence*	*Timing of neuroimaging since TBI*	*Neuroimaging modality*	*Neuro-psychiatric outcome measure(s)*	*Pertinent findings*
Santhanam, Teslovich et al, 2019	Case-control	$n=69$ (TBI-only = 35, TBI+PTSD = 34)	Military	Ohio State University TBI Identification Method	Mild; single, recurrent	PTSD = 2.22 (±1.39) years; No PTSD = 2.06 (±1.34) years	MRI, DTI	SCID-IV, PCL-C	Greater FA and lower RD measures in the bilateral uncinate fasciculus correlated with greater PTSD symptoms as well as with avoidance, and re-experiencing sub-scores on the PCL-C.
Sydnor et al, 2020	Cohort	$n=102$ (TBI+PTSD = 48, PTSD-only = 54)	Military	Boston Assessment of TBI-Lifetime	Mild; Single, Recurrent	TBI+PTSD = 4.9 (±3.3) years	MRI, dMRI	CAPS-5	In PTSD+TBI, higher CAPS scores significantly associated with higher FA bilaterally in the amygdala-hippocampus complex and nucleus accumbens, lower FA in the bilateral cingulate, and greater MD in the right amygdala-hippocampus complex.

TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; TBI+PTSD, traumatic brain injury plus post-traumatic stress disorder group; HC, healthy control group; VC, veteran/combat-exposed control; GCS, Glasgow Coma Scale; LOC, loss of consciousness; VA/DoD, Veterans Affairs/Department of Defense; ACRM, American Congress of Rehabilitation Medicine; BTBIS, Brief Traumatic Brain Injury Screen; CDC, Centers for Disease Control; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose-positron emission tomography; DTI, diffusion tensor imaging; rs-fMRI, resting state functional magnetic resonance imaging; mc-DESPOT, multicomponent-driven equilibrium single-pulse observation of T1 and T2; MEG, magnetoencephalography; dMRI, diffusion MRI; MPF, macromolecular proton fraction mapping; FA, fractional anisotropy; RD, radial diffusivity; SCID-IV, Structured Clinical Interview for DSM-4; CAPS-5, clinician administered PTSD scale-5; ANOVA, analysis of variance; IQR, interquartile range; GFA, generalized fractional anisotropy; NSI, Neurobehavioral Symptom Inventory; PCL, PTSD checklist; PCL-M, PTSD checklist military version; PCL-C, PTSD checklist civilian version; PCL-5, PTSD checklist 5th edition; MWF, myelin water fraction; VCU rCDI-B, VCU-rCDI-G, Virginia Commonwealth University Retrospective Concussion Diagnostic Interview blast version, general version respectively; MINI, Mini-International Neuropsychiatric Interview 7.0; FDR, false discovery rate; DMN, default mode network.

Table 3. Limitations Existing Among the Included Studies in the Review and Recommendations for Future Research

Limitations	*Recommendations for future research*
Sample- / Study-related	
Sample heterogeneity (e.g., TBI severity, TBI definition, PTSD definition, time since injury)	In addition to below, more selective inclusion criteria (e.g., mild TBI, subacute TBI).
Insufficient sample sizes	Fully powered and longitudinal cohort studies are missing from the field, and will be needed for causality and directionality determination. Future systematic reviews separated by TBI severity, timing of neuroimaging since injury, and a quantifiable meta-analysis should be considered once the literature base in this area is more developed.
Bias regarding the comparability of cases and controls in case-control studies	Controls must adequately represent cases in case-control studies (e.g., age, education, TBI history), and confounders must be adjusted for in analyses.
Difficulty isolating the direct connections between neuroimaging findings and TBI-associated PTSD	Ensure that studies are properly designed to isolate the neuroimaging findings specific to TBI-related PTSD, such as by including comparison groups with TBI-only and non-TBI-related PTSD-only.
TBI-related	
Inconsistent TBI definitions	Clearly quantify and report on the established National Institute of Neurological Disorders and Stroke common data elements for TBI (e.g., loss of consciousness and post-traumatic amnesia duration, Glasgow Coma Scale score). Utilize established TBI criteria (e.g., Veterans Affairs/Department of Defense, American Congress of Rehabilitation Medicine) rather than study-specific criteria.
Lack of clinician-diagnosed TBI	Include clinician-confirmed TBI diagnosis in future studies.
No severe TBI groups	Future inquiry into the neuroimaging correlates of post-TBI PTSD in patients with severe TBI. Some articles in this review looked at participants with all severities of TBI combined into one sample; however, there were no distinct severe TBI groups.
PTSD-related	
Lack of civilian studies	There is an increased risk of PTSD and TBI in military and veteran populations and therefore a predominance of military studies on this topic. Civilians should be considered separately from military populations and warrant focused study.
Neuroimaging-related	
Neuroanatomical regions of interest on imaging generally broad and not well defined	More in-depth description of the neuroanatomical boundaries of regions of interest.
Variety of time intervals between TBI and neuroimaging, as well as onset of PTSD symptoms and neuroimaging	Quantify timing of TBI, PTSD onset, and neuroimaging collection and adjust analyses accordingly.

TBI, traumatic brain injury; PTSD, post-traumatic stress disorder.

(FDG-PET), and one multicomponent-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT). Five of the 16 studies reported at least one statistically significant neuroimaging correlate of PTSD in TBI. For details regarding article percentages by study design, population, TBI severity, TBI occurrence, and timing of imaging post-TBI, refer to Table 1. For limitations of the included articles and recommendations based on these limitations, refer to Table 3.

Findings by imaging modality

Structural findings visualized by neuroanatomical region of interest via brain mapping are displayed in Figures 2 and 3.

Cortical structure (MRI)

Eight of the 16 included articles utilized MRI for structural imaging analysis. None of these articles identified specific cortical structure changes that were associated with TBI-related PTSD. Brenner and coworkers imaged 59 veterans with a history of chronic TBI (of all severities), 32 of whom had PTSD, and found that participants with TBI and PTSD were significantly less likely to have ''trauma-related'' MRI abnormalities than those with TBI only.[41] A study by Bae and coworkers imaging 57 veterans with a history of TBI, 32 of whom had comorbid PTSD, found no statistically significant differences between the groups, but did note a trend toward increased left amygdala volume in those with comorbid PTSD.[42] The six remaining articles found no significant structural changes associated with PTSD.[43–48]

White matter (DTI, mcDESPOT, dMRI with free-water imaging)

Eight of the included articles studied the integrity of white matter in TBI-related PTSD, and four identified

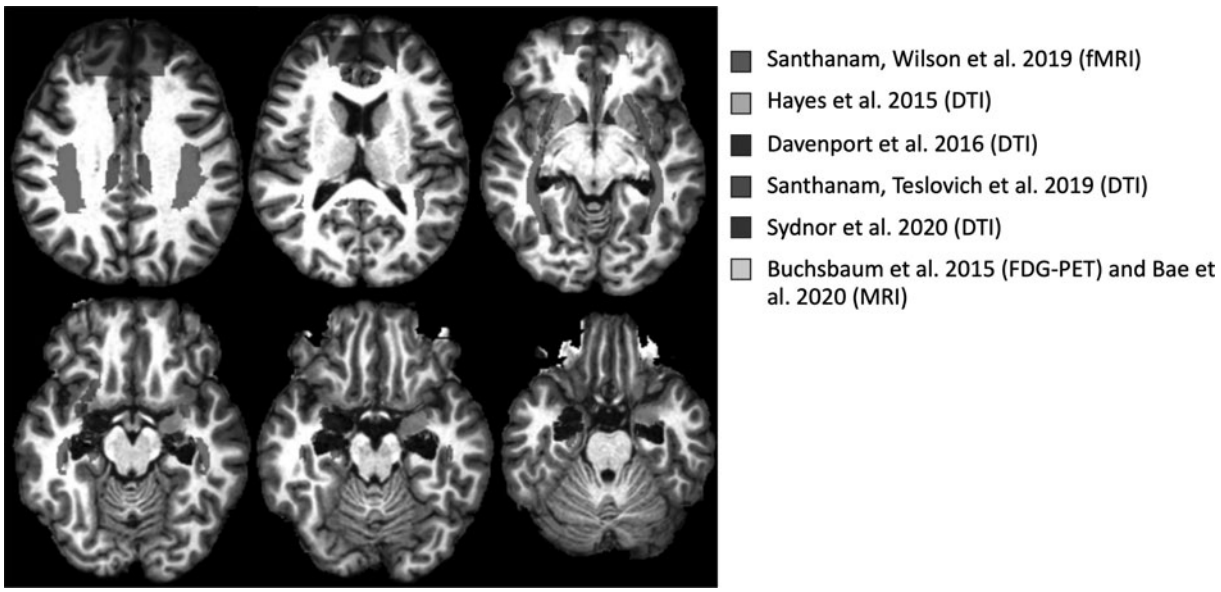

FIG. 2. Brain mapping by article of approximate structural (diffusion tensor imaging [DTI], magnetic resonance imaging [MRI]) and metabolic (positron emission tomography [PET]) region of interest (ROI) overlays implicated in traumatic brain injury (TBI)-related post-traumatic stress disorder (PTSD)

potential neuroimaging correlates specific to PTSD in TBI.[43,44,49,50] A study of 124 Operation Iraqi Freedom (OIF) / Operation Enduring Freedom (OEF) veterans found deployment-related mild TBI (mTBI) and lifetime PTSD to be significantly correlated with DTI-based greater fractional anisotropy (FA), generalized fractional anisotropy (GFA), and the number of voxels with high GFA in 10 regions of interest (ROIs) including: the bilateral inferior fronto-occipital fasciculus (IFOF), bilateral superior longitudinal fasciculus (SLF), bilateral temporal portion of the SLF, bilateral inferior longitudinal fasciculus (ILF), right uncinate, and right hippocampal cingulum.[44] They observed a similar interaction of lifetime PTSD with blast TBI, a subset of those with deployment TBI. Notably, they did not observe any correlation between current PTSD and measures of white matter integrity.

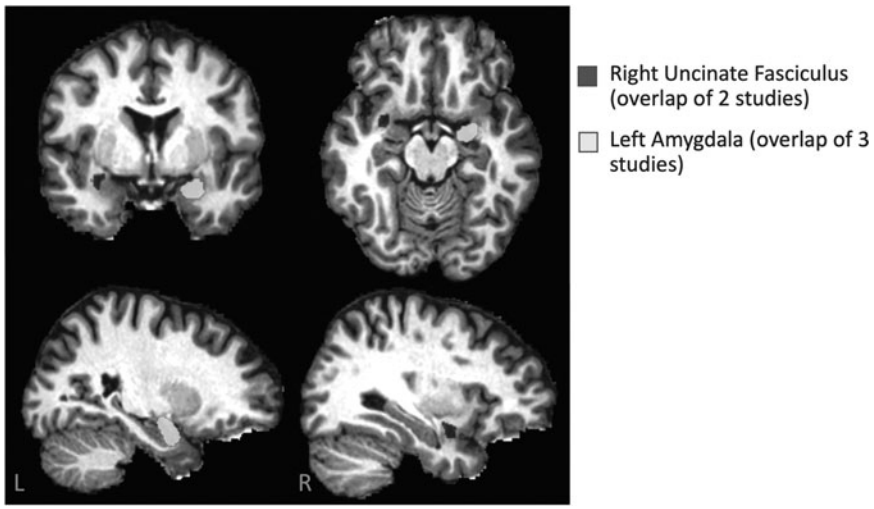

FIG. 3. Brain map representing the approximate location of replicated structural neuroimaging findings in traumatic brain injury (TBI)-related post-traumatic stress disorder (PTSD): right uncinate fasciculus and left amygdala.

Santhanam and coworkers conducted a case-control study of 69 active military and veteran participants who had sustained at least one mTBI, finding that impaired DTI-based white matter integrity in the limbic regions was associated with the presence and severity of current PTSD. Specifically, the mTBI+PTSD group had significantly higher mean diffusivity (MD) and radial diffusivity (RD) in both the right and left uncinate fasciculi, and lower FA in the right uncinate than the mTBI-only group. Further, PTSD severity, as measured by the Post-Traumatic Stress Disorder Checklist, Civilian Version (PCL-C), positively correlated with RD values and inversely correlated with FA values for both the left and right uncinate fasciculi.[43]

Jak and coworkers employed mcDESPOT in a case-control study of 74 veterans. In the PTSD and mTBI cohort, more severe PTSD symptoms were associated with higher myelin water fraction (MWF) in the genu, body, and splenium of corpus callosum; anterior, posterior, and retro lenticular limbs of internal capsule; and the cingulum.[49]

Sydnor and coworkers, in a 2020 cohort study, conducted diffusion MRI (dMRI) with free-water imaging in 102 male combat veterans with a current diagnosis of PTSD. They observed that in the PTSD+TBI group, higher Clinician-Administered PTSD Scale (CAPS) scores were significantly associated with higher FA bilaterally in the amygdala–hippocampus complex and nucleus accumbens, but with lower FA in the bilateral cingulate.[50]

Hayes and coworkers also conducted DTI in 114 veterans, 59 with TBI. They found a trend toward reduced FA with increasing PTSD symptom severity in the left retrolenticular aspect of the internal capsule.[45] The three remaining studies analyzing white matter found no significant differences associated with TBI-related PTSD.[47,51,52]

Networks (functional imaging: rs-fMRI, MEG, FDG-PET)

Six articles reported on functional imaging analyses, utilizing measures of glucose metabolism, rs-fMRI, and/or MEG, with five identifying potential neuroimaging correlates specific to PTSD in TBI.[46,53–56] Two studies measured cerebral glucose metabolism. Buchsbaum and coworkers measured 18-FDG uptake in a sample of 33 veterans with TBI, 17 with comorbid PTSD, and 15 combat-exposed controls. An *a-priori* region of interest (ROI) analysis of FDG uptake in the amygdala found participants with a history of mTBI and PTSD to have significantly lower relative metabolic rates in the left superior amygdala than participants with mTBI alone. It should be noted, however, that neither TBI group showed statistically significant differences from controls, and a repeated measures analysis of variance (ANOVA) inclusive of diagnostic group, hemisphere, and inferior/superior dimensions was not significant.[46] A second study by Petrie and coworkers showed no significant PTSD-related changes in cerebral glucose metabolism in analyzed regions.[52]

Santhanam and coworkers employed a data-driven analysis of rs-fMRI data in a sample of 51 active-duty soldiers or veterans with a history of TBI, 24 of whom had a comorbid PTSD diagnosis, and identified significant changes in connectivity within the default mode network (DMN), which correlated PTSD symptoms as assessed by the PCL-C.[53]

Rowland and coworkers, in a series of rs-fMRI and MEG studies published in 2017, used graph theory-based network analyses to identify PTSD-associated changes in patterns of whole-brain resting state connectivity. In a study of 28 veterans (6 with mTBI, 6 with PTSD, 6 with PTSD+TBI, and 10 controls), they found that PTSD, particularly in the absence of mTBI history, was associated with reductions in clustering coefficient, modularity, and small-worldness.[54] In a subsequent study from 2018 using a similar approach, Rowland and coworkers evaluated a sample of 16 combat veterans and observed that the development of PTSD after deployment-acquired TBI was associated with increased small-worldness and clustering.[55] Finally, in 2021, Rowland and coworkers employed MEG to investigate the network characteristics of a larger sample of 181 combat-exposed veterans (including the 16 from the previous study). They did not identify any network characteristics that correlated with either current PTSD or lifetime PTSD. They did however observe an interaction between PTSD and blast TBI that significantly ($p < 0.05$, false discovery rate [FDR] corrected) reduced the number of nodes present in the connectome (probable error [PE] = -12.47), increased the average degree of nodes that were present (PE = 0.054), and increased the strength of connections within the connectome (PE = 0.048). PTSD also interacted with non-blast mTBI, reducing the number of nodes present in the connectome (PE = -18.03).[56]

Article quality

Among the 16 articles included in this review, all 16 were rated to have a high level of potential bias for the representativeness of cases/cohorts and for ascertainment of exposure. All the studies were conducted in military populations, most recruited very few female subjects (or excluded females entirely), and most excluded moderate or severe TBI, limiting the generalizability of the results. Ascertainment of exposure was also scored high in potential bias, as no articles required witnessed, documented, or clinician diagnosed TBI, and studies used a variety of screening measures. Four case-control studies were scored to have a high level of potential bias for comparability of cases and controls, because of significant differences in either demographic characteristics and/or TBI history.[41,43,53,55] All 10 of the case-control studies had an unclear bias related to non-response rate,

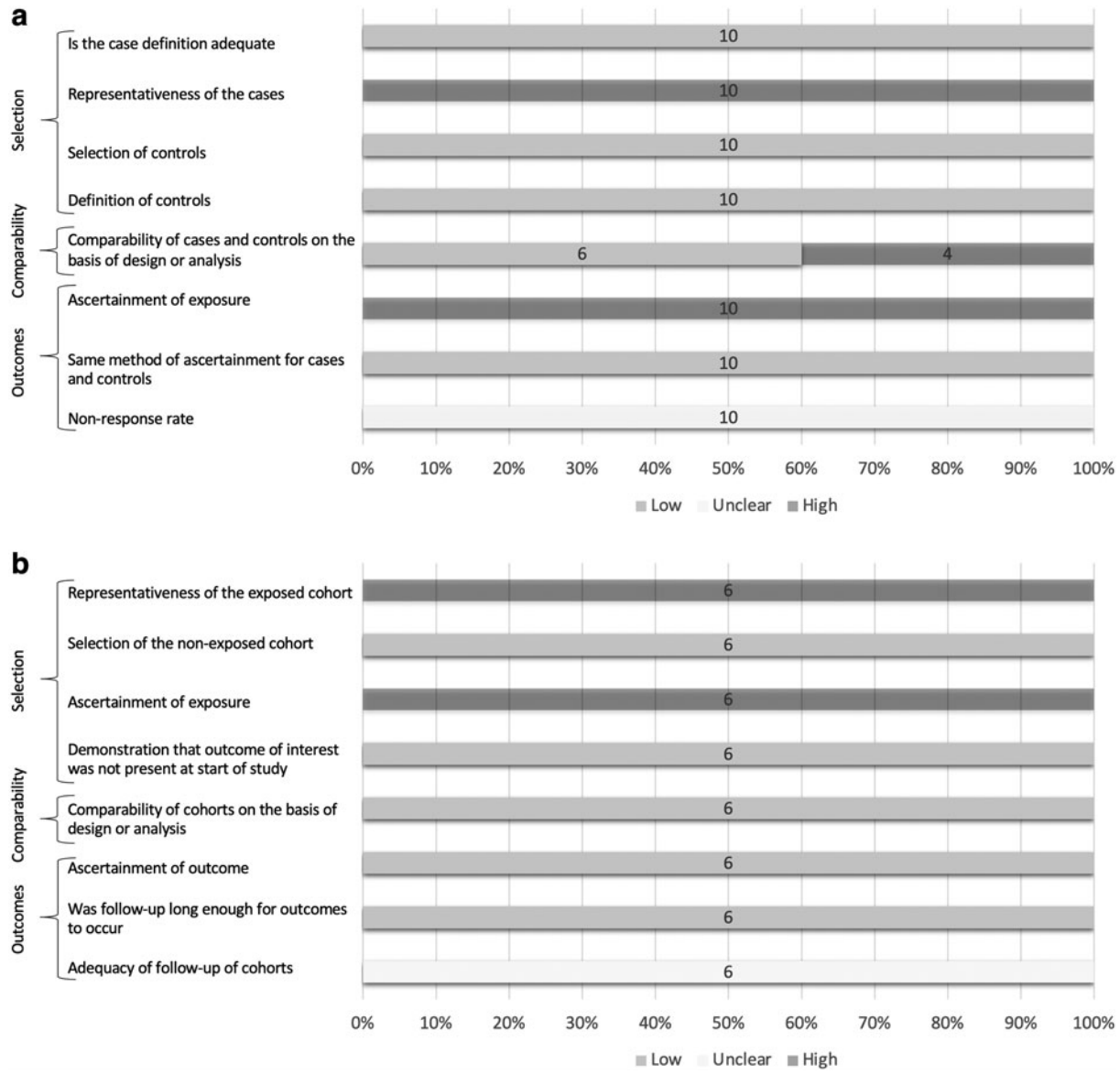

FIG. 4. **(a)** Sources of potential bias in case-control studies ($n = 10$). **(b)** Sources of potential bias in cohort studies ($n = 6$).

as this information was not provided (Fig. 4a). Moreover, all six cohort studies had an unclear level of bias in terms of adequacy of follow-up, as this information was also not provided (Fig. 4b).

Discussion

We conducted a systematic review of the literature for neuroimaging correlates of PTSD in TBI. Among the 16 articles meeting inclusion criteria, 9 reported significant neuroimaging findings associated with TBI-related PTSD, with 4 being studies of white matter integrity and 5 being studies of brain functional activity. We found no consensus among these studies regarding neuroimaging correlates of PTSD in TBI. Trends among the included articles suggest that TBI-related PTSD may be associated with disruption of white matter tracts as well as changes in whole-brain networks of resting state/MEG connectivity. White matter tracts found to exhibit significant changes in TBI-related PTSD were diffuse and included the uncinate fasciculus and cingulum as well as the corpus collosum and internal capsule.

Two studies provided evidence of microstructural white matter differences in the right uncinate fasciculus in TBI-related PTSD (Fig. 3).[43,44] The uncinate fasciculus is a major fronto-limbic connection, connecting the amygdala with the orbitofrontal cortex. Alterations of this tract have been observed in studies of trait anxiety as well as in anxiety-related disorders.[57] Damage to the

uncinate fasciculus may also be linked to cognitive changes (language and memory), aberrant social and emotional processing, depression, and apathy.[58] Thus, changes in the uncinate fasciculus offer a plausible mechanism or risk factor for the development of several PTSD symptoms. Previous DTI studies in TBI (with or without PTSD) suggest that changes to the uncinate fasciculus are more often associated with moderate to severe TBI.[59,60] Given that the included studies were primarily of mild severity TBI, changes in the uncinate fasciculus may be specific for PTSD. Alternatively, observation of changes in the uncinate fasciculus could reflect differences in recollection and reporting of mTBI.[17,18,44]

Interestingly, the two studies observing correlations of PTSD with differences in the uncinate fasciculi appear to report conflicting findings. Santhanam and coworkers observed a correlation between PTSD and greater FA in the uncinate fasciculus, implying overall better microstructural integrity. Meanwhile, Davenport and coworkers observed lower FA in the uncinate fasciculus, which was correlated with PTSD in subjects with a history of TBI during a combat employment, as opposed to those incurring a TBI outside of combat.[43,44] Differences in study population and study design may account for some of this disparity. First, it is difficult to compare these studies, because Davenport and coworkers focused on the interaction of retrospectively diagnosed lifetime PTSD with subsets of the TBI subjects (deployment, civilian). This study did not observe any primary effects for PTSD. Meanwhile, Santhanam and coworkers reported that there was a primary effect of current PTSD (diagnosis and symptom severity) on FA in the uncinate fasciculi without statistical consideration of the number, context, or nature of the TBIs. Another consideration is that the average time between TBI and neuroimaging in the study by Santhanam and coworkers was $\sim$2 years, whereas the average time since TBI in the study by Davenport and coworkers was >6 years for the deployment-TBI group and 10–13 years for the civilian-TBI group.[43,44]

In addition to the uncinate fasciculi, structural alterations were observed in other major white matter tracts, such as the bilateral IFOF and SLF. These findings align with previous DTI studies on adult-onset PTSD in non-military populations.[33,61–63] Moreover, a recent meta-analysis of adult-onset PTSD showed that dysregulated white matter in the SLF and diffuse frontal cortex changes were consistent across studies.[34] Evidence of disruption of fronto-limbic tracts could be considered consistent with the many observed structural and functional changes in limbic regions associated with PTSD.[29,30,35]

Two studies included in this review found that TBI-related PTSD was associated with differences in small-worldness and clustering coefficient, a finding that may be consistent with theories of hyperconnectivity as a compensatory mechanism after TBI. Small-worldness and clustering coefficient are measures of interconnectedness between local nodes in a network. Here again, we find disparate findings across studies. In a 2017 study, Rowland and coworkers found that PTSD was associated with lower small-worldness and clustering coefficient, suggesting that PTSD is associated with reduced resting-state network structure (more randomness) with less regional and hierarchical connectivity and more diffuse patterns of connectivity. Meanwhile, in their 2018 study, PTSD was found to be associated with greater small-worldness and clustering coefficient.[54,55] The primary difference between these studies was the inclusion of a PTSD-only group in the 2017 study. The authors note that the finding of low small-worldness and clustering coefficient were particularly strong in the PTSD-only group and less pronounced in the TBI+PTSD group.

In addition to summarizing potential neuroimaging correlates of PTSD in TBI, we sought to highlight key limitations of the current TBI-related PTSD literature in order to propose recommendations for future research (summarized in Table 3). A key limitation of the current literature is that no studies were found that conducted neuroimaging in participants with both clinician-diagnosed TBI and clinician-diagnosed PTSD. In the case of PTSD, self-report and screening measures for PTSD are widely used in research. Most studies in the field rely on various forms of the PCL for determining both diagnosis and severity of PTSD, sometimes employing arbitrary cutoffs and subscale or symptom cluster analyses, which are difficult to interpret. There has been significant discourse in the literature of the limitations of the PCL. The PCL is heavily affected by pre-test probability and has been shown to have widely varied sensitivity and specificity.[64] Moreover, there are several factors specific to the TBI population that may undermine the specificity of such self-report measures, most significantly, the degree of overlapping symptoms between TBI and PTSD. Other factors such as memory deficits or personality characteristics of populations at risk for TBI may lead to under-reporting of symptoms of either PCS or PTSD.

In the case of TBI, organizations such as the Department of Veterans Affairs (VA) and the American Congress of Rehabilitation Medicine (ACRM) have defined criteria for assessing the presence and severity of TBI.[2,65] All the included studies used inclusion criteria and severity ratings based on one of these two guidelines. Some used study specific interviews, but most made use of one of several validated instruments available to collect information about possible TBI events. One such screening instrument, the VA TBI screen, has been assessed against clinician-diagnosed TBI in large studies of OIF/OEF veterans. The Ohio State University TBI Identification Method, Boston Assessment of TBI-Lifetime (BAT-L), and the Mid-Atlantic Mental Illness-

Research, Education, and Clinical Center (MIRECC) Assessment of TBI (MMA-TBI), compare favorably with the VA TBI screen.[66–68] However, the BAT-L shows poor correspondence with the VA Comprehensive TBI Evaluation (CTBIE) even when considering symptom validity testing. In addition to the criteria used for defining TBI and TBI severity, we list the screening instrument used by each study in Table 2. Regardless of the screening instrument used, few studies refer to collateral information from either witnesses or medical records. The validity of these screening tools, whether self-report or structured interview, are therefore reliant on a subject's recall of events and reported symptoms, which can be influenced by the study population, subject specific factors, and the context of the interview.[15–18]

All studies meeting inclusion criteria for this review were conducted in military or veteran populations. Civilian studies were excluded for a variety of reasons, but reliance on the PCL without confirmatory diagnosis was the primary reason for exclusion of most of the articles passing initial screening. The predominance of military studies is consistent with the increased risk for both TBI and PTSD in this population. Factors unique to the experiences of veterans sustaining TBI in combat, such as a higher proportion of blast exposure, chronic threat/stress exposure, multiple deployments, history of TBI or PTSD, separation from support systems, and sleep deprivation, may contribute to increased risk of both TBI and PTSD. Accordingly, a recent meta-analysis suggests that military context is a major modifier of PTSD risk after TBI.[5] Given differences in predisposition, risk factors, nature of the trauma, and follow-up care, it is possible that results of studies in military populations may not be generalizable to civilian TBI. There is also some evidence of sex differences in the brain's response to trauma, but to date most studies in military populations recruit relatively few female subjects.[69,70]

We were also unable to reach any conclusion about the role of TBI severity in neuroimaging correlates of PTSD. All but two studies restricted participation to mild severity TBI. It is estimated that 70–90% of documented TBI cases are rated mild in severity, bolstering the included articles as representative of the distribution of TBI.[71] Lack of well-controlled studies in moderate or severe TBI may be the result of there being a lower number of available subjects, greater difficulties in confirming PTSD, and other challenges related to studying individuals with more severe injury.

Beyond meeting criteria for TBI and PTSD, exclusion criteria varied by study. Some studies excluded participants with certain psychiatric conditions (e.g., major depressive disorder) or those taking certain medications (e.g., selective serotonin reuptake inhibitors), whereas others did not. Further, as publication dates for the studies included in this review range from 2009 to 2022, studies varied in use of the *Diagnostic and Statistical Manual for Mental Disorders, Fourth and Fifth Edition* criteria in clinical interviews.

Another key limitation of the available literature is that the timing of imaging data acquisition as it relates to TBI and PTSD varies greatly among articles. Additionally, nearly half of the articles that passed abstract screening were excluded at least in part because of a failure to report the timing of neuroimaging relative to the TBI or failure to compare this variable between experimental groups. Although all the articles that met inclusion criteria for this review conducted imaging in participants with chronic TBI, the mean time since TBI for the included studies ranged from 2 to 23 years, with some studies scanning participants as soon as 1 year after TBI and others scanning participants >50 years after TBI. This is of concern in both PTSD and TBI. TBI has been associated with accelerated brain atrophy, particularly of white matter.[72] PTSD has been associated with chronic progressive changes in brain structure and circuit-level dysfunction, thought to be in part mediated by chronic neuroinflammation and hypothalamic-pituitary-adrenal (HPA) axis changes.[73,74]

Authors' Contributions

Aaron I. Esagoff was responsible for the conceptualization, methodology, validation, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, and project administration. Daniel A. Stevens was responsible for the conceptualization, methodology, validation, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, and project administration. Natalia Kosyakova was responsible for the formal analysis, investigation, writing – review and editing, and visualization. Kaylee Woodard was responsible for the formal analysis, investigation, writing – review and editing, and visualization. Diane Jung was responsible for formal analysis, investigation, writing – review and editing, and visualization. Lisa N. Richey was responsible for conceptualization, methodology, validation, formal analysis, and writing – original draft. Nicolas O. Daneshvari was responsible for formal analysis, investigation, writing – review and editing. Licia P. Luna was responsible for conceptualization, methodology, formal analysis, writing – review and editing, and visualization. Michael J.C. Bray was responsible for conceptualization, methodology and investigation. Barry R. Bryant was responsible for conceptualization, methodology, and investigation. Carla P. Rodriguez was responsible for conceptualization, methodology, and investigation. Akshay Krieg was responsible for conceptualization, methodology and investigation. Nicholas T. Trapp was responsible for conceptualization, methodology, and investigation. Melissa B. Jones was responsible for conceptualization, methodology, and investigation. Carrie Roper was responsible

for conceptualization, methodology and investigation. Eric L. Goldwaser was responsible for conceptualization, methodology, and investigation. Emily Berich-Anastasio was responsible for conceptualization, methodology, and investigation. Alexandra Pletnikova was responsible for conceptualization, methodology, and investigation. Katie Lobner was responsible for conceptualization, methodology, and investigation. Margo Lauterbach was responsible for conceptualization, methodology, and investigation. Haris I. Sair was responsible for conceptualization, methodology, and visualization. Matthew E. Peters was responsible for conceptualization, methodology, validation, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, and project administration.

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Supplementary Material
Supplementary Appendix SA1

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