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Role of inflammation in TBI-associated risk for neuropsychiatric disorders: state of the evidence and where do we go from here

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Abstract

In the last decade there has been an increasing awareness that traumatic brain injury (TBI) and concussion substantially increases risk for developing psychiatric disorders. Even mild TBI increases risk for depression and anxiety disorders such as posttraumatic stress disorder (PTSD) by 2-3 fold, predisposing patients to further functional impairment. This strong epidemiological link supports examination of potential mechanisms driving neuropsychiatric symptom development after TBI. One potential mechanism for increased neuropsychiatric symptoms after TBI is via inflammatory processes, as CNS inflammation can last years after initial injury. There is emerging preliminary evidence that TBI patients with PTSD or depression exhibit increased central and peripheral inflammatory markers compared to TBI without these comorbidities. Growing evidence has demonstrated that immune signaling in animals plays an integral role in depressive- and anxiety-like behaviors after severe stress or brain injury. In this review we will (1) discuss current evidence for chronic inflammation after TBI in the development of neuropsychiatric symptoms, (2) highlight potential microglial activation and cytokine signaling contributions and (3) discuss potential promise and pitfalls for immune targeted interventions and biomarker strategies to identify and treat TBI patients with immune-related neuropsychiatric symptoms.

Keywords

Inflammation; traumatic brain injury; depression; PTSD; risk; immune signaling

Introduction

Although well known for associations with neurodegenerative disorders, traumatic brain injury (TBI) has emerged as a significant risk factor for the development of neuropsychiatric disease. A history of TBI and concussion is associated with increased prevalence for depression, post-traumatic stress disorder (PTSD), and suicidal ideation in both military

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and civilian populations (1-10), with prospective studies indicating that mood and anxiety disorders can develop months-years after injury (11). The increased risk for neuropsychiatric disorders associated with TBI is significant; TBI increases the likelihood of a PTSD or major depression diagnosis 2-3 fold (2, 12-17). TBI co-morbidity is common in service members with neuropsychiatric disorders and is associated with greater healthcare utilization than TBI or the disorder alone (18). The emergence of neuropsychiatric symptoms has devastating consequences for long-term recovery, significantly impacting global functioning (19). This consistent and robust epidemiological link suggests that the heightened risk for neuropsychiatric diagnosis after TBI must be considered when developing intervention strategies for TBI (20).

TBI results in a constellation of morphological and molecular changes in the brain, with pathology developing not just from the initial mechanical injury but secondary biochemical/metabolic events (Figure 1; e.g. inflammation, neurodegenerative and excitotoxic processes) that can persist for months to years (21). Chronic/dysregulated inflammatory signaling is one putative mechanism for dysfunction and neural circuit disruption across TBI and mood and anxiety disorders (22-24). There are numerous parallels between neuroinflammation mechanisms in TBI (and other neurological insults such as stroke and spinal cord injury) and those associated with neuropsychiatric disorders, particularly depression and PTSD (25-29). Neuroinflammation induced by TBI could contribute to risk for neuropsychiatric disorders through both direct effects of chronic inflammatory signaling after TBI or indirectly through "priming" the neural-immune system to respond excessively to subsequent homeostatic challenges. Here we review evidence and important gaps in our understanding of the contribution of injury-related immune mechanisms to risk and development for mood and anxiety disorders after TBI, highlighting (1) clinical studies targeting immune signaling measures with psychiatric outcomes and (2) pre-clinical studies probing immune mechanisms associated with anxiety- and depression-like behavior. We discuss considerations in identifying and testing immune-targeted therapies to treat anxiety and mood disorders associated with TBI. Note we will not extensively review studies of inflammation mechanisms of cognitive disruption or predictors of mortality/disability (30), for which there are already a number of excellent reviews (3, 31).

Enduring inflammatory responses after brain injury

TBI is highly heterogenous in severity and thus functional outcome, with milder forms of TBI/concussion difficult to diagnose. Injury severity is typically diagnosed via the Glasgow Coma Scale (GCS) of observations of acute symptoms after injury (e.g. GCS scores of 13-15, 9-12 and ≤ 8 are used to delineate mild, moderate and severe TBI respectively (32)). Computed tomography (CT) scans help rule out false negatives from GCS (33). When GCS is unavailable other retrospective measures of functional effects such as duration of loss of consciousness, duration of post-traumatic amnesia or altered mental state are used to delineate mild-moderate TBI from severe (34, 35). The majority of individuals sustaining moderate-mild injuries show functional recovery within 6-12 months after injury (36, 37). However a significant percentage of mild-moderate TBI cases (~20-50%) endorse long-term cognitive impairment and mood and anxiety symptoms (38-40).

Acute immune cascade induced by TBI

Immediately after injury, humoral and cellular inflammatory signaling is initiated and typically peaks within seven days of injury, depending on injury severity and presence of secondary injuries (Figure 1)(3). The immune signaling events that immediately follow mechanical injury start with blood-brain barrier disruption and alarmin signaling. These events are followed by microglia activation and inflammasome assembly, complement activation, neutrophil recruitment, subsequent peripheral immune cell (T cell, monocyte, and macrophage) recruitment, adaptive immunity, and finally gliosis (31). Microglia travel to the site of injury where they respond to signals and debris from injured or dying cells (e.g. ATP), initiate cytokine signaling and create a barrier around the injured area. TBI initiates polarization of microglia towards pro-inflammatory and anti-inflammatory phenotypes. Pro inflammatory phenotypes are characterized both by shape (amoeboid) and pro-inflammatory signaling including increased IL-1 β , major histocompatibility complex II [MHCII], CD68, complement receptor [CR]3, and type 1 interferon (Type-I IFN) family gene expression (41). Immune activation induces the release of multiple pro-inflammatory cytokines, including interleukin (IL) 1, 6, and 12, chemokines (chemoattractant cytokines), and tumor necrosis factor-alpha (TNF- α). In contrast, to resolve inflammation, anti-inflammatory microglia release trophic factors to aid regeneration and regulatory cytokines, including IL-10, 13, and 14 (42). Inflammatory signaling is not limited to microglia but is also mediated by astrocytes, endothelial cells, and neurons (43). After responding to primary and secondary injuries sustained during or after the TBI, neutrophils and macrophages are recruited to the CNS vasculature to infiltrate damaged tissue (44-46). These inflammatory signaling factors act at local and potentially more distal receptors to support a number of functions to regain homeostasis, including controlling excitotoxicity, debris removal via macrophages as well as via drainage through the brain glymphatic-meningeal lymphatic system, reparative processes, and neuroplasticity (41, 47, 48). Anti-inflammatory signaling cascades are also initiated, such as IL-10, which directly inhibit the release of pro-inflammatory cytokines from multiple cell types in the brain and initiates endogenous cytokine receptor antagonist release (e.g. IL-1 receptor antagonist)(47). Inflammatory signaling is also limited by relatively unstable RNA and proteins subject to rapid degradation, and receptor downregulation (e.g. internalization and dummy receptors). These regulatory responses confine inflammatory signaling to a limited window after injury. (3). Although inflammation generally resolves, some subpopulations experience chronic inflammation years after injury (49-51). Chronic neuroinflammation exacerbates tissue damage, disrupts synaptic signaling and disrupts white matter integrity.

Chronic inflammation after TBI

Development of chronic inflammation after TBI relates to several factors including injury severity, accumulation of risk genes associated with increased immune response, age at the time of injury, sex, and co-morbidities such as sleep disturbance (49, 52-56). Chronic inflammation is associated with longer recovery and predicts worse long-term outcomes (57). Microglia activation is a significant contributor to long-term inflammation, as it can extend past the focal area of injury and remains activated years after injury (51). In rodents and primates, TBI induces long-term microglial activation, which subserves inflammatory as well as neurotrophic functions (58). Mild-moderate TBI can also "prime" microglia

activation in animals, resulting in amplified and longer-lived inflammatory signaling (see microglia section below) in response to secondary challenge (59-61). TBI may also impair clearance of waste products and debris through glymphatic drainage, resulting in increased distribution and exposure to neurotoxins, cytokines, and chemokines (45), reinforcing continued inflammatory signaling and blood-brain barrier disruption. Finally, there is some evidence for the development of increased prevalence of autoantibodies to neuronal-specific proteins after TBI (e.g., SB100, NMDA receptor), as the peripheral immune system is exposed to CNS-specific proteins after injury (62, for review see 63). These autoantibodies may disrupt neuronal and synaptic function and exacerbate degeneration and cell death (64).

Does inflammation after TBI predict mood and anxiety symptoms?

There is a compelling case that neuroinflammation is a mechanism for depression and possibly PTSD in some populations (23). This theory rests on multiple parallel lines of evidence: (1) consistent associations of increased peripheral and central immune markers (e.g., TNF- α , IL-6, IL-1 β) with depression and PTSD symptoms, (2) animal studies indicating peripheral and neuroimmune signaling (e.g., IL-6 and IL-1, microglia activation) induces depression- and anxiety-like behavior, and (3), cytokine treatments in humans (i.e., interferon treatment for Hepatitis C and multiple sclerosis) induce depression symptoms in the majority of patients (23, 24, 65). Longitudinal studies indicate that immune dysregulation can precede mood and anxiety symptom development (66-69). These studies taken together suggest that inflammation is not simply associated with symptom state but may play a causal role in symptom development. Thus, it is reasonable to ask if chronic inflammation related to TBI might contribute to the increased risk for neuropsychiatric symptoms.

Recently studies have begun to directly examine the relationship between inflammation and neuropsychiatric risk after TBI (Table 1 for details). One cross-sectional study in young service members recovered from deployment-related mild-TBI showed that participants with TBI comorbid with depression and PTSD had the highest levels of plasma cytokines IL-6 and TNF- α compared to participants with TBI alone or matched controls (70). This finding was replicated in a study of slightly older service members with repeated TBI (>10 years since TBI), finding plasma IL-6 and IL-10 levels are associated with intrusive and avoidance symptoms of PTSD (71). An association between plasma TNF- α and PTSD symptoms in service members with mild TBI has also been reported (72). A prospective study in individuals with mild TBI found that circulating TNF- α at the acute and chronic phase predicted behavioral disinhibition at six months following the injury, which the authors suggested might contribute to increased risk for suicide after TBI (73). However in a well-controlled prospective study comparing mild-TBI and non-head injury orthopedic surgery controls, plasma cytokine levels within 24 hours of injury were predictive of post-concussive symptoms at one week but did not predict neuropsychiatric symptoms. Because this study focused on markers of acute inflammation after injury, it is unclear if chronic inflammation assessments would have been associated with neuropsychiatric symptoms. This study did find that 6-months post-injury, plasma IL-10 was associated with current depression and PTSD symptoms (74). Thus far, peripheral inflammatory markers are associated with PTSD

and depressive symptoms in individuals with TBI. However, whether peripheral markers of chronic inflammation precede the development of symptoms is unclear.

Studies have also begun to assess putative markers of *central* inflammation associations with mood and anxiety symptoms. Two studies have examined cytokine cargo of extracellular vesicles of neuronal origin that are released into circulation: neuronal-derived exosomes. Circulating exosomes are isolated from plasma and enriched for carrying neuronal- or astrocyte-associated markers, and lysed to examine protein and RNA cargo. Using this technique, Gill et al. examined circulating neuronal-derived exosome samples in Veterans up to 6 years after a TBI injury. Higher levels of IL-10 were positively associated with increased PTSD symptoms in the TBI group (75). Another study found that IL-6 and TNF- α are elevated in neuronal-derived exosomes of TBI patients with cognitive impairment compared to TBI patients without cognitive impairment, although neuropsychiatric symptoms were not assessed (76). Thus central inflammation might be measurable via CNS-derived exosomes, although the preparation does not preclude the possibility that peripheral cytokines from non-CNS sources were attached to the vesicle membrane, confounding a CNS-specific interpretation. Finally, in a small prospective study using CSF, cytokine surface markers (sVCAM-1, sICAM-1, and sFAS) in the acute phase of injury predicted depression symptoms six months after injury (77). Overall these studies support that peripheral cytokines, including IL-6, TNF- α , and IL10, which consistently have been linked to depression and PTSD in non-TBI cohorts, are also linked to these symptoms in populations sustaining a TBI. Preliminary CSF studies also support the possibility that cytokine levels may predict both symptom state and future development of symptoms. However, larger prospective studies assessing chronic phases and acute phases of injury are required to confirm and extend these initial results. Given that excitotoxicity, oxidative stress, and neurodegeneration are also associated with increased psychiatric symptoms in TBI (78, 79), inflammation may be a marker of neurodegenerative mechanisms of symptom development. Thus although biomarkers of inflammation may be associated with, and even in some cases predict, the development of neuropsychiatric symptoms after TBI, we do not know if there is a causal relationship.

Converging immune signaling pathways linked to chronic inflammation after TBI and effects on anxiety- and mood-relevant behavior

Animal models of TBI have identified several converging immune signaling pathways linked to chronic inflammation and increased anxiety- and depressive-like behavior (Supplemental Table 1)(80). Animal models of TBI include: (1) focal injury models e.g. controlled cortical impact (CCI) injury and lateral fluid percussion injury, (2) weight drop models (focal or diffuse) and (3) shock tube models that produce diffuse injuries to model non-penetrative blast injuries. Immune signaling mechanisms can differ across models, in particular between models with minimal vs. significant exposure of the CNS to peripheral immune system signaling through bleeding and BBB disruption (for review see (80)). Common mechanisms of long-term dysfunction across models however include microglial activation and pro-inflammatory cytokine and chemokine signaling (Supplemental Table 1) (81).

Microglial activation: As indicated in the introduction, pro-inflammatory microglia activation is one of the potential long-term drivers of chronic inflammation after TBI, and could contribute to neuropsychiatric symptom development. In humans, imaging markers of microglia activation (PET ligands to measure translocator protein binding, TSPO) are detectable 17 years after a TBI (51). Microglial activation is also implicated in depression and suicide (82, 83), with TSPO occupancy increased in depressed patients compared to controls (84, 85) and reduced after treatment (86). Post-mortem tissue from depressed patients shows increased microglial activation and localization of macrophages in CNS vasculature (87-89). These studies indicate that microglial dynamics may contribute to depressive symptoms after TBI, however preclinical studies are needed to test causality.

Similar to humans, TBI induces long-term microglial activation in rodents and non-human primates (58). Microglia require tonic signaling of the macrophage colony stimulating factor 1 receptor (CSF1R) to survive, and pharmacological or genetic blockade of CSF1R depletes CNS microglia, with repopulation occurring ~2 weeks after CSF1R inhibition is removed (90). Depletion enables direct interrogation of the necessity of microglia in TBI-induced inflammation and subsequent behavioral dysfunction. In CCI models, *temporary* microglia depletion after injury reduces pro-inflammatory cytokine protein and mRNA expression as well as reactive microglia numbers, reduces neuronal death and prevents long-term cognitive deficits (91). *Chronic* depletion does not improve outcome after CCI however, suggesting that not only is removal of reactive microglia important, but repopulation of microglia in a homeostatic, non-reactive state, may be necessary for recovery (92, 93). These studies focused on cognitive deficits however, and did not interrogate microglia depletion effects on anxiety or depressive like behaviors. Delayed microglia depletion using CSF1R inhibition as far as 1-3 months after CCI, reduces both cognitive disruption and depressive-like behaviors in mice, suggesting continued microglia activation is a necessary component for long-term effects of TBI on depression-related phenotypes (94, 95). In parallel with microglia depletion studies, pharmacological or genetic inhibition of pathways involved in microglial polarization to proinflammatory function such as Type-1 interferon signaling also implicate pro-inflammatory microglia activation in neurodegeneration (e.g. white matter loss) and development of anxiety- and depressive-like behavior or cognitive disruption after TBI (96-98).

Microglia are adaptive to past immune challenges, reflecting “immune memory” (99). Rodent models suggest that TBI “primes” microglia to mount rapid and robust responses to subsequent immune challenges. After midline fluid percussion injury, de-ramified and MHCII positive microglia are observed, suggestive of microglia in a primed state (59). A secondary immune challenge then increases depression- and anhedonia-like behaviors (59). Secondary immune challenge after TBI also increases numbers of pro-inflammatory microglia and pro-inflammatory cytokine levels in hippocampus, a circuit critical for cognitive and emotional functions (60). Thus taken together there is reasonable evidence that microglia activation, either via chronic activation that is not resolved after injury, or via priming of microglia pro-inflammatory response to subsequent immune challenges may mediate increased risk for depression and anxiety symptoms long after initial injury.

Excess/chronic inflammatory cytokine release: IL-1 cytokines (e.g. IL-1 β , IL-1 α) and IL-1 receptors (IL-1R) are key regulators of the immune response, particularly immune signaling from the periphery to the brain. After severe stress, microglia recruit IL-1 β producing monocytes to CNS endothelium to induce anxiety and depressive like-behaviors (100). Endothelial IL-1R α initiates the release of microglial activating factors to trigger pro-inflammatory microglia polarization and other pro-inflammatory signaling cascades (101). IL-1Rs are expressed by neurons, and their selective ablation prevents social withdrawal, depression-like behaviors and cognitive disruption after chronic stress (102). Studies in animals suggest that IL-1R signaling disrupts contextual fear conditioning and fear extinction, fear learning processes that are disrupted in PTSD patients and are critical mechanisms for trauma recovery (for review see 24). After TBI, IL-1R signaling induces tissue damage and long-term behavioral disruption. IL-1 neutralization through antibodies, pharmacological or genetic approaches reduces tissue loss and motor and cognitive dysfunction in animal models of TBI (103-106). Blockade of CCL2 signaling, a chemokine required for monocyte infiltration also reduces IL-1 β levels and prevents development of anxiety-like behaviors and cognitive deficits after blast-induced TBI (107). Thus, IL-1R signaling may contribute to enduring effects on depression and anxiety-related behaviors after chronic stress or TBI. However, study design of these models predominantly manipulated IL-1 genetically, before or immediately after injury. IL-1 may have temporally specific effects over the time course of inflammation, having toxic effects acutely but potentially regenerative effects at later time points; thus, the timing of IL-1 neutralization may be critical. IL-1 has dual functions via signaling through extracellular receptors and intranuclear effects on gene expression in various cell types (108). Beneficial effects of IL-1 neutralization may also be specific to injury type, with efficacy in preventing chronic cognitive dysfunction in closed head injury models while making cognition worse in the CCI model (109). Injury-specific effects are likely due to different inflammatory patterns/temporal gradients that follow diffuse vs. penetrative head injuries, in part due to differential exposure to peripheral inflammatory responses associated with bleeding, and secondary infection (110).

Interventions targeting inflammation for TBI-associated neuropsychiatric symptoms

Clinical trials for TBI pharmacotherapy have been relatively limited to interventions at the acute stage and in moderate-severe patients; thus, there is little clinical information for or against targeting immune signaling for chronic TBI. Thus far, treatments with anti-inflammatory properties have had limited efficacy in improving long-term outcome in TBI as measured by mortality, cognitive function, and psychological symptoms (111). However, these treatments (1) have been given primarily at the acute phase of injury only (2) were applied primarily in severe TBI populations, and (3) have non-specific anti-inflammatory functions (e.g., steroids) (111). The acute treatment time and non-specificity could result in non-specific inhibition of both toxic and restorative functions of immune signaling (112).

Preclinical models of chronic TBI indicate modulation of microglial activation and other cytokine signaling pathways at chronic phases of inflammation could prevent/reverse long term cognitive changes after brain injury, including (1) inhibition of inflammasome activity and its cytokine products like IL-1 for some injury types, (2) targeting BBB and glymphatic

system restoration and function (3) selectively inhibiting microglial pro-inflammatory functions or promoting activation of anti-inflammatory functional phenotypes (113-118). Other potential non-pharmacologic treatments for chronic inflammation are stem cell and stem cell-associated exosome treatments (119-121), exogenous miRNA treatments (117) and behavioral interventions such as exercise (122). Some of these treatments are also being targeted for depression and PTSD (123-128). Similar to depression, interventions targeting immune signaling will likely require the development of biomarkers to identify patients with chronic inflammation.

Because of the substantial heterogeneity of TBI types, severity, and individual risk factors that will affect inflammation course and chronicity, a one size fits all approach to immune targeting for TBI-associated neuropsychiatric symptoms is unlikely to succeed. Targeting immune signaling will require the ability to identify sub-populations with chronic inflammation (129-131) to understand when, and in whom, to target immune interventions. How to accurately categorize neuropsychiatric patient groups with increased inflammation, however, is not clear cut, with peripheral biomarkers such as C-reactive protein showing inconsistent utility as predictors of anti-depressive response to anti-inflammatory treatments (132, 133). One small study suggests cytokine content from putative CNS sources (CNS-derived extracellular vesicles) may provide a biomarker for central anti-inflammatory response (134). Other biomarker strategies include transcriptomic and proteomic profiling (31), use of *ex vivo* immune challenge assays to measure changes in dynamic immune response to challenge rather than baseline immune markers (135), or imaging markers of microglial activation (e.g. TSPO) (136).

Considerations for future research of immune mechanisms and treatments for TBI-associated neuropsychiatric disorders

The review shows that currently there is circumstantial evidence that immune mechanisms may contribute to the increased risk for neuropsychiatric disorders, particularly mood and anxiety disorders after TBI, with a number of remaining questions of the causal role for immune signaling in TBI-associated neuropsychiatric disorders, as well as identifying when and in whom immune interventions would be most effective.

First, there are still relatively few studies specifically measuring neuropsychiatric symptoms and inflammation in TBI, especially that assess whether inflammation predicts development of symptoms or arises at the same time as symptoms develop. Second, there are as yet no clear biomarkers of chronic inflammation associated with neuropsychiatric symptoms, with or without TBI, although there are some potentially promising tools (e.g. extracellular vesicle cargo, TSPO imaging). Such studies would ideally include markers of neurodegeneration, to compare the relative utility of inflammation and neurodegeneration in predicting symptom development. Longitudinal studies of development of neuropsychiatric symptoms after TBI will be critical in identifying future accessible biomarkers to target who and when to treat (137). Third, such studies will need to carefully consider additional comorbidities that can affect immune function, including physical health, lifestyle, sleep and substance use. Finally, clinical studies directly manipulating neuroinflammation in TBI patients with neuropsychiatric assessments will be one of the most important future

research avenues. There are currently trials with interventions targeted at inhibiting neuroinflammatory systems (e.g. www.clinicaltrials.gov, C-1 inhibition, IL-1R signaling) however stated outcomes do not include psychiatric symptom measures.

Human studies provide primarily correlational evidence, and do not address mechanistic contribution. Preclinical studies using gene deletion and pharmacological tools suggest that microglial activation and cytokine signaling are necessary for long-term effects of TBI on mood and anxiety-like behavior (Supplemental Table 1), and preclinical studies also indicate that these signaling systems are also sufficient at least in part to increase mood and anxiety-like behaviors. Most studies of TBI-related immune effects on anxiety/depression-related behaviors are relatively limited assessment of these behaviors; expansion past simple locomotor-based approach/avoidance and despair-based tests will be important to understand specific domains (e.g. reward system, threat responding) affected and improve translation to humans (138). Some preclinical models of TBI (e.g. CCI) are also not consistent in producing depression-like or anxiety-like behaviors, despite having robust effects on memory (108). These differing effects across models may provide clues as to what immune signaling mechanisms are most robustly associated with anxiety- and depression-like phenotypes. Finally, preclinical studies are needed to dissect the trajectory of pro and anti-inflammatory immune response after different injury types, enabling identification of potential optimal intervention points after TBI to dampen excess (maladaptive) inflammation and promote healing. For example, a recent study suggests that *enhancement* of immune signaling immediately after injury may help prevent long-term cognitive deficits and anxiety/depression-like behaviors, while immune challenge 5-30 days will exacerbate mild TBI effects, especially on mood/anxiety-like behaviors (139).

It is also unclear what circuits may be most important for putative immune effects of TBI on neuropsychiatric symptom development. Inflammation resulting from severe stress can modify striatal circuits (e.g. nucleus accumbens) to affect reward processes and anhedonia, as well as modify synaptic mechanisms of emotional memory such as learned fear (for review see (24)). These mechanisms may be relevant to putative TBI-induced inflammation effects on these functions. For example, mild closed-head injury TBI is associated with increased fear learning and poor extinction in humans and animals (140, 141). In both preclinical and clinical studies, examination of reward processing and fear learning circuit abnormalities in conjunction with CNS-associated inflammatory biomarkers may aid mechanistic understanding of symptom domains most affected by chronic inflammation after TBI.

Conclusions: Taken together there is considerable circumstantial evidence that chronic inflammation after TBI likely contributes to increased risk for mood and anxiety. The challenge is in moving from circumstantial evidence to understanding identifying the putative causal role inflammation may play in psychiatric symptom development after TBI. Certainly there is good evidence that certain kinds of immune challenges, such as interferon treatment, can drive depression in individuals without neural injury. In TBI however, there are multiple factors at play that can mediate development of psychiatric symptoms, including neurodegeneration, cell death, axonal injury, maladaptive neuroplasticity and long lasting disruption in blood-brain-barrier as well as lymphatic systems. Whether

inflammation is a primary mediator (thus warranting treatment development) or is a correlational marker of the underlying pathology requires further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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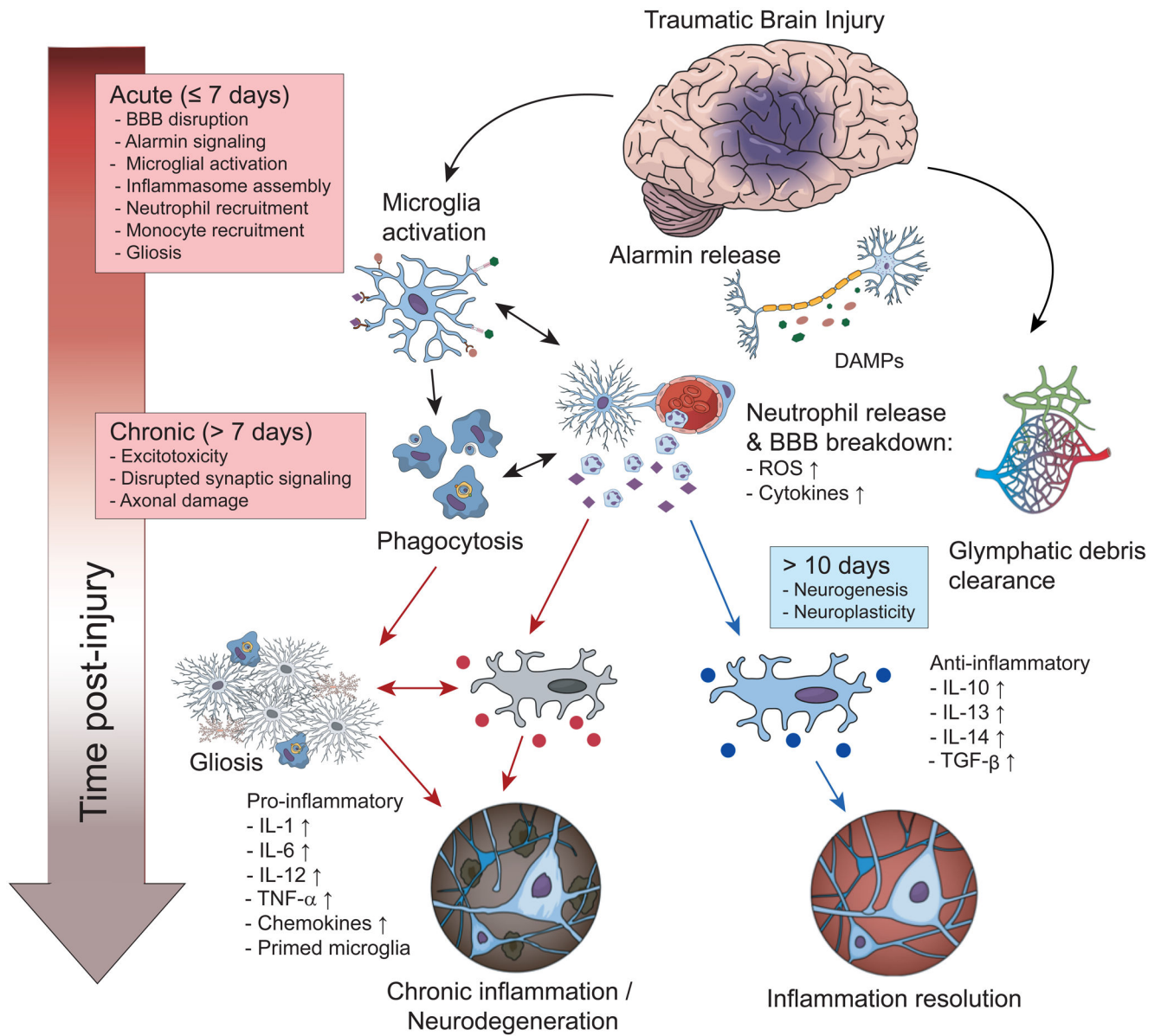


Figure 1. Schematic of immune signaling cascade and functional changes after TBI.
Image created using Biorender.

Table 1. Clinical studies of associations between inflammation and mood and anxiety symptoms after TBI.

↑=increased compared to TBI alone or positive association with neuropsychiatric symptoms, ↓= decreased compared to TBI alone or negative association with neuropsychiatric symptoms, ↔ = no change compared to TBI alone or no relationship with psychiatric symptoms.

Study	N	Inflammatory markers assessed	Marker source	Time after injury sample collected	Type of injury (measure)	Symptoms assessed (measure)	Time of symptom assessment
Devoto et al., 2017	63 +TBI, 20 -TBI	↑TNF-α, ↑IL-6, ↔IL-10	Plasma	≤16 months	+/-AOC (WARCAT)	Depression (QIDS), PTSD (PCL-M), quality of life (SF-36)	≤16 months
Rodney et al., 2020	44 ≥3 TBI, 29 <3 TBI, 33 - TBI	↔TNF-α, ↑IL-6, ↔IL-10	Serum	Mean=8.3 years	+AOC or +LOC (OSU TBI-ID)	Depression (PHQ-9), PTSD (PCL-C)	Mean=8.3 years
Kanefsky et al., 2019	25 TBI -LOC, 36 TBI +LOC, 82 -TBI	↔TNF-α, ↑IL-6, ↔IL-10	Plasma	3-18 months	Mild (LOC 20 ≤min) (WARCAT)	Depression (QIDS), PTSD (PCL-M), quality of life (SF-36)	3-18 months
Juengst et al., 2014	74 +TBI, 15 -TBI	↑TNF-α (both CSF and Serum)	CSF, Serum	≤6 days	Moderate to severe TBI (GCS ≤12)	Depression and suicidality (PHQ-9), disinhibition (FrSBe)	6-, 12-months post injury
Vedantam et al., 2021	53 +TBI, 24 -TBI	↓IL-1β, ↓IL-2, ↓IL-4, ↓IL-6, ↔IL-10, ↔IL12p70, ↔IL-17a, ↓IFNγ, and ↔TNF-α	Plasma	~1 day	Mild (LOC 20 ≤min) (WARCAT)	post-concussive symptoms (RPCSQ), PTSD (PCL-C), depression (CES-D)	1 week, 1-, 3-, and 6-months post injury
Gill et al., 2018	42 +TBI, 22 -TBI	↑Tau, ↔Aβ40, ↑Aβ42, ↔TNF-α, ↔IL-6, ↑IL-10	Neuronal-derived exosomes (plasma source)	≤18 months	Mild (LOC 20 ≤min) (WARCAT)	Post-concussive symptoms (NSI), PTSD (PCL-M), depression (QIDS)	≤18 months
Juengst et al., 2015	41 +TBI (CSF), 50 +TBI (serum), 15 -TBI	↑IL-1β, ↑IL-4, ↔IL-5, ↑IL-6, ↑IL-7, ↑IL-8, ↑IL-10, ↔IL12, ↑TNF-α, ↑sVCAM-1, ↑sICAM-1, ↑sFAS	CSF, Serum	≤6 days	Moderate to severe TBI (GCS ≤12)	Depression (PHQ-9),	6-, 12-months post injury
Pattinson et al., 2019	84 +TBI, 18 -TBI	↑Tau, ↔Aβ42,	Plasma	3-121 months	Mild +AOC, +LOC, or +PTA (Chart review and OSU TBI-ID)	PTSD (PCL-C), post-concussive symptoms (NSI), , depression (QIDS), quality of life (TBI-QOL)	3-121 months
Merritt et al., 2018	79 +TBI, 54 -TBI	↑APOE ε4 allele	Buccal saliva	Mean~6 years (76.3 months)	Mild to moderate TBI +AOC, +LOC, or +PTA (VA semi-structured clinical interview)	Depression (BDI-II), anxiety (BDA), PTSD (PCL-M)	Mean~6 years (76.3 months)

* Additional Abbreviations: Warrior Administered Retrospective Casualty Assessment Tool (WARCAT); Alteration of consciousness (AOC); Loss of consciousness (LOC); Ohio State University TBI identification method (OSU TBI-ID); Quick Inventory of Depressive Symptomatology (QIDS); PTSD Checklist Military Version (PCL-M); PTSD Checklist Civilian Form (PCL-C); Short Form 36 (SF-36); Frontal Systems Behavior Scale (FrSBe); Verbal Selective Reminding Test (VSRT); Symbol-Digit Modalities Test (SDMT); Rivermead Post-Concussion Symptoms Questionnaire

(RPCSQ); Post-traumatic Stress Checklist-Civilian Form (PCL-C); Center for Epidemiologic Studies Depression Scale (CES-D) depression; Brief Visuospatial Memory Test-Revised (BVM-T-R) visuospatial learning and memory; Delis-Kaplan Executive Functioning System Verbal Fluency Test (D-KEFS VFT); The Neurobehavioural Symptom Inventory (NSI); Post-traumatic Amnesia (PTA); Traumatic Brain Injury-Quality of Life Scale (TBI-QOL); Beck Depression Inventory-II (BDI-II); Beck Anxiety Inventory (BDA)