REVIEW ARTICLE

CONTENTS

The processing of pro-inflammatory cytokines in post-traumatic stress disorder: Inflammation as a central mechanism in PTSD pathophysiology

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a severe psychiatric condition associated with persistent emotional dysregulation, cognitive impairment, and structural alterations in limbic and prefrontal brain regions. Growing evidence indicates that chronic inflammation and abnormal processing of pro-inflammatory cytokines are central components of PTSD pathophysiology. Activation of the NOD-like receptor family pyrin domain containing 3 inflammasome (NLRP3) and caspase-1 promotes the proteolytic maturation of pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18) into their active forms, amplifying neuroinflammatory signaling. Sustained microglial activation and disrupted neuron–microglia–astrocyte communication contribute to synaptic dysfunction and impaired neuroplasticity. In parallel, dysregulation of the hypothalamic–pituitary–adrenal axis (HPA axis) interacts with inflammatory pathways, leading to altered stress responses and persistent immune activation. Clinical studies have demonstrated associations between circulating inflammatory mediators, including IL-18 and IL-1β, and the severity of emotional inhibition, sleep disturbances, and maladaptive coping strategies in PTSD. Moreover, inflammatory activity has been linked to volumetric and microstructural changes in the hippocampus, amygdala, and prefrontal cortex observed in chronic PTSD. These findings support the concept that the processing of pro-inflammatory cytokines is a central mechanism in PTSD rather than a secondary consequence of stress exposure. Understanding the molecular pathways underlying cytokine maturation and neuroimmune signaling may contribute to improved biomarker-based diagnostics and the development of targeted therapeutic interventions.

KEY WORDS: inflammation; interleukin-1β; interleukin-18; microglia; NLRP3 inflammasome; post-traumatic stress disorder

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is a chronic psychiatric condition that develops after exposure to severe traumatic events and is characterized by intrusive recollections, avoidance, negative changes in cognition and mood, and persistent hyperarousal. In addition to psychological symptoms, PTSD is associated with measurable neurobiological and immunological alterations. Increasing evidence indicates that chronic low-grade inflammation contributes to symptom maintenance and long-term disease progression [1].

Neuroimaging studies have demonstrated structural and functional abnormalities in the hippocampus, amygdala, and prefrontal cortex in individuals with PTSD. These regions are central to fear processing, memory consolidation, and emotional regulation. In parallel, elevated peripheral and central levels of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and interleukin-18 (IL-18), have been reported. These findings support the concept that immune signaling pathways interact with stress-related neural circuits [2].

At the molecular level, activation of the NOD-like receptor family pyrin domain containing 3 inflammasome (NLRP3 inflammasome) has been proposed as a key mechanism linking psychological stress with immune activation. Assembly of this multiprotein complex leads to activation of caspase-1 and proteolytic maturation of pro-interleukin-1β and pro-interleukin-18 into their active forms, thereby amplifying inflammatory signaling. Sustained microglial activation and disturbed neuron–glia communication may impair synaptic plasticity and contribute to persistent symptoms [3, 4].

Furthermore, dysregulation of the hypothalamic–pituitary–adrenal axis (HPA axis) alters the balance between stress hormones and immune responses, potentially promoting glucocorticoid resistance and prolonged inflammation. Clarifying the mechanisms of cytokine processing and neuroimmune interaction is essential for understanding PTSD pathophysiology and for identifying clinically relevant biomarkers and therapeutic targets [5, 6].

AIM

The aim of this review is to critically summarize and integrate current evidence on the role of pro-inflammatory cytokine processing in the pathophysiology of PTSD, with particular emphasis on inflammasome activation, cytokine maturation, neuroimmune interactions, and their clinical relevance. Special attention is given to the NLRP3 inflammasome, caspase-1-dependent processing of interleukin-1β and interleukin-18, neuron–microglia–astrocyte crosstalk, and HPA axis dysregulation as interconnected mechanisms contributing to chronic neuroinflammation in PTSD. In addition, the review discusses the diagnostic and therapeutic implications of inflammatory biomarkers and highlights potential directions for future translational and biomarker-guided research.

MATERIALS AND METHODS

This article is a narrative review based on a structured analysis of the current literature concerning inflammatory mechanisms in post-traumatic stress disorder (PTSD), with particular emphasis on the processing of pro-inflammatory cytokines, inflammasome activation, neuroimmune signaling, and structural brain alterations associated with chronic stress exposure.

A literature search was conducted using major biomedical databases, including PubMed, Scopus, and Web of Science. The search strategy included combinations of the following keywords: "PTSD", "post-traumatic stress disorder", "inflammation", "neuroinflammation", "cytokines", "interleukin-1β", "interleukin-18", "NLRP3 inflammasome", "caspase-1", "microglia", "astrocytes", "HPA axis", "ER stress", "hippocampus", "amygdala", and "prefrontal cortex". Additional relevant articles were identified through manual screening of reference lists from selected papers.

Priority was given to peer-reviewed original studies, systematic reviews, meta-analyses, and high-quality review articles published in English, with particular focus on papers published between 2016 and 2025. Earlier studies were also included when they were considered fundamental for understanding the molecular and neurobiological basis of cytokine maturation and inflammasome signaling.

The inclusion criteria comprised studies addressing at least one of the following topics: (1) inflammatory and immune mechanisms in PTSD, (2) molecular pathways involved in the maturation of pro-inflammatory cytokines, especially IL-1β and IL-18, (3) activation and regulation of the NLRP3 inflammasome, (4) neuron–microglia–astrocyte interactions in stress-related neuroinflammation, (5) relationships between inflammatory markers and clinical manifestations of PTSD, and (6) structural or microstructural brain changes associated with inflammatory activity in PTSD.

Studies unrelated to PTSD or not directly addressing cytokine processing, neuroinflammation, or stress-related neuroimmune alterations were excluded. Non-peer-reviewed reports, conference abstracts without sufficient methodological detail, and articles lacking clear relevance to the topic were also omitted.

The selected literature was analyzed qualitatively and organized into thematic sections addressing molecular cytokine processing, glial and neuronal interactions, clinical correlates of inflammatory activation, chronicity-related brain alterations, and diagnostic or therapeutic implications. The purpose of this approach was to provide an integrative and clinically relevant overview of evidence supporting inflammation as a central mechanism in PTSD pathology.

REVIEW AND DISCUSSION

MOLECULAR MECHANISMS OF PRO-INFLAMMATORY CYTOKINE PROCESSING IN PTSD

Chronic psychological stress activates innate immune pathways that promote the production and maturation of pro-inflammatory cytokines. In PTSD, increasing evidence indicates that dysregulated cytokine processing contributes to persistent neuroinflammation and symptom maintenance. The maturation of IL-1β and IL-18 is a central event in this process [7].

One of the principal pathways responsible for cytokine maturation involves the NOD-like receptor family pyrin domain containing 3 inflammasome. This multiprotein complex is composed of the sensor molecule NLRP3, the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and pro-caspase-1. Its activation generally requires two sequential signals. The priming signal is initiated by pattern recognition receptors, including Toll-like receptors, and leads to enhanced transcription of NLRP3 and pro-interleukin-1β (pro-IL-1β) through nuclear factor kappa B (NF-κB) signaling. The second signal is triggered by cellular stressors such as mitochondrial dysfunction, generation of reactive oxygen species, potassium efflux, or extracellular adenosine triphosphate release. These stimuli induce assembly of the inflammasome complex and subsequent activation of caspase-1 [8, 9].

Active caspase-1 cleaves pro-IL-1β and pro-IL-18 into their biologically active forms, enabling their secretion. These cytokines amplify inflammatory signaling,

enhance microglial activation, and influence neuronal function. IL-1β modulates synaptic plasticity and long-term potentiation, while IL-18 has been associated with stress reactivity and emotional regulation. Persistent activation of this pathway may therefore contribute to impaired fear extinction, heightened arousal, and cognitive disturbances observed in PTSD [10].

In addition to inflammasome signaling, endoplasmic reticulum stress pathways interact with inflammatory mechanisms. Activation of inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6) may enhance inflammatory gene expression and further promote cytokine production. Crosstalk between cellular stress responses and immune signaling supports a sustained pro-inflammatory state within the central nervous system [3, 11].

Microglia play a central role in this process. Under chronic stress conditions, microglia shift toward a pro-inflammatory phenotype characterized by increased cytokine release and reduced support for synaptic remodeling. Disrupted communication between neurons, microglia, and astrocytes may impair neuroplasticity and structural integrity in stress-sensitive brain regions.

Together, these molecular mechanisms demonstrate how altered processing of pro-inflammatory cytokines can link psychological trauma with sustained neuroinflammation and functional brain changes in PTSD [12].

NEURON–MICROGLIA–ASTROCYTE CROSSTALK IN PTSD - RELATED NEUROINFLAMMATION

Post-traumatic stress disorder (PTSD) is associated with persistent alterations in communication between neurons and glial cells. The interaction between neurons, microglia, and astrocytes is essential for maintaining central nervous system (CNS) homeostasis. Under chronic stress conditions, this balance becomes disrupted, leading to sustained neuroinflammation and impaired synaptic function [13].

Microglia are the principal immune effector cells of the CNS. In response to stress-related signals and increased levels of pro-inflammatory cytokines, microglia shift toward a pro-inflammatory phenotype characterized by enhanced production of IL-1β, IL-18, and tumor necrosis factor-α (TNF-α). Activated microglia also release reactive oxygen species (ROS) and nitric oxide (NO), which may contribute to neuronal damage. Prolonged activation disrupts synaptic remodeling and reduces trophic support for neurons [14, 15].

Astrocytes regulate neurotransmitter clearance, maintain blood–brain barrier (BBB) integrity, and provide metabolic support. During inflammatory activation, astrocytes undergo reactive changes and increase secretion of cytokines and chemokines, which further amplify microglial activation. This process strengthens inflammatory signaling in limbic regions involved in fear processing and emotional regulation.

Neurons actively participate in immune signaling through the release of damage-associated molecular patterns (DAMPs) and neurotransmitters that modulate glial activity. Excessive glutamatergic transmission may enhance microglial activation and promote excitotoxicity, while reduced gamma-aminobutyric acid (GABA) signaling further destabilizes neural networks [16, 17].

Disrupted neuron–glia communication leads to impaired long-term potentiation (LTP), altered dendritic spine density, and reduced neuroplasticity in the hippocampus and prefrontal cortex. Elevated pro-inflammatory cytokines are also associated with decreased hippocampal neurogenesis. These changes contribute to memory disturbances, emotional dysregulation, and impaired fear extinction in PTSD.

Persistent dysregulation of neuron–microglia–astrocyte interactions sustains a self-perpetuating inflammatory environment within the CNS. Restoration of neuroimmune balance may represent an important therapeutic target in PTSD [18, 19].

PRO-INFLAMMATORY CYTOKINES AND CLINICAL MANIFESTATIONS OF PTSD

Pro-inflammatory cytokines play a significant role in linking immune activation with the clinical symptoms of PTSD. Elevated concentrations of IL-1β, IL-18, IL-6, and TNF-α have been reported in individuals with PTSD. These mediators influence neuronal signaling, synaptic plasticity, and neuroendocrine regulation, thereby contributing to emotional and cognitive disturbances [20, 21].

IL-1β is involved in the modulation of synaptic transmission and long-term potentiation. Excessive IL-1β activity impairs hippocampal plasticity and may disrupt memory consolidation and contextual processing. This mechanism may contribute to intrusive recollections and impaired fear extinction. IL-1β also interacts with the HPA axis, influencing cortisol secretion and stress responsiveness [22].

IL-18 has been associated with increased stress sensitivity and emotional dysregulation. Elevated IL-18 levels correlate with the severity of hyperarousal and avoidance symptoms. Through its interaction with inflammatory and stress-related signaling pathways, IL-18 may amplify neuroimmune responses and reinforce persistent symptomatology [23].

IL-6 exerts both pro- and anti-inflammatory effects but is frequently elevated in chronic stress conditions.

Table 1. Inflammatory pathways in PTSD: molecular mechanisms, neurobiological effects, and clinical correlates

Cytokine / pathway	Mechanism of activation	Neurobiological effect	Structural brain changes	Clinical correlates
IL-1β	NLRP3 inflammasome activation; caspase-1 cleavage	Impaired LTP; reduced neurogenesis	Hippocampal volume reduction	Intrusive memories; impaired fear extinction
IL-18	Inflammasome-dependent maturation	Increased stress sensitivity; microglial activation	Amygdala hyperreactivity	Hyperarousal; avoidance
IL-6	NF-κB-mediated transcription	Altered synaptic signaling; fatigue-related mechanisms	Limbic dysconnectivity	Sleep disturbance; cognitive impairment
TNF-α	Modulation of glutamatergic and GABAergic transmission	Increased excitatory tone; endothelial activation	Fronto-limbic imbalance	Emotional instability
HPA axis dysregulation	Glucocorticoid resistance; persistent immune signaling	Sustained inflammatory state	Prefrontal cortical thinning	Chronic symptom persistence
ER stress (IRE1, ATF6)	Amplification of inflammatory gene expression	Enhanced cytokine production	Microstructural alterations	Emotional dysregulation

Source: Compiled by the authors of this study

Increased IL-6 levels have been linked to sleep disturbances, fatigue, and cognitive impairment. Chronic exposure to IL-6 may alter synaptic function and contribute to reduced neuroplasticity in limbic structures [24].

TNF-α modulates glutamatergic and GABAergic neurotransmission. Elevated TNF-α levels may enhance excitatory signaling and reduce inhibitory control, leading to increased arousal and emotional instability. TNF-α also promotes endothelial activation and may affect blood–brain barrier integrity, further facilitating neuroinflammatory processes [25].

Inflammatory cytokines are not only peripheral markers but also active modulators of brain function. Their sustained elevation may contribute to structural changes observed in the hippocampus, amygdala, and prefrontal cortex. Chronic inflammatory signaling may therefore represent a biological substrate underlying symptom persistence and disease chronicity [26].

Associations between cytokine levels and clinical features such as emotional inhibition, maladaptive coping strategies, and sleep quality suggest that immune markers may have diagnostic and prognostic value. Understanding the relationship between pro-inflammatory cytokines and clinical manifestations may support the development of targeted interventions aimed at reducing inflammation and improving functional outcomes in PTSD [27].

The relationship between cytokine maturation, neurobiological alterations, and clinical manifestations in PTSD is summarized in Table 1.

CHRONICITY OF PTSD AND STRUCTURAL BRAIN ALTERATIONS

The duration of PTSD is associated with progressive neurobiological changes that may reflect sustained inflammatory and stress-related mechanisms. Chronic exposure to elevated pro-inflammatory cytokines and persistent dysregulation of the HPA axis can influence brain structure and microarchitecture, particularly in regions involved in memory, emotional regulation, and executive control [28].

Neuroimaging studies have consistently demonstrated volumetric reductions in the hippocampus in individuals with long-standing PTSD. The hippocampus is highly sensitive to stress hormones and inflammatory mediators. Prolonged exposure to IL-1β, IL-6, and IL-18 may impair neurogenesis and synaptic plasticity, leading to decreased dendritic complexity and neuronal loss. These changes are associated with deficits in contextual memory processing and impaired fear extinction [29, 30].

The amygdala, a key structure in threat detection and emotional reactivity, may show altered functional connectivity and, in some cases, volumetric changes depending on illness duration. Chronic inflammatory signaling can enhance excitatory neurotransmission and reinforce hyperresponsiveness within amygdala circuits, contributing to persistent hyperarousal and exaggerated stress responses [31].

The prefrontal cortex, particularly the medial and dorsolateral regions, plays a central role in top-down regulation of emotional responses. Structural and microstructural alterations in this region have been linked to impaired inhibitory control over limbic structures. Sustained neuroinflammation, microglial activation, and oxidative stress may disrupt white matter integrity and synaptic organization, further weakening regulatory circuits [32, 33].

Diffusion tensor imaging studies suggest that chronic PTSD is associated with reduced white matter coherence

Table 2. Potential therapeutic targets and intervention strategies related to neuroinflammation in PTSD

Therapeutic target	Proposed intervention	Expected biological effect	Current limitations
NLRP3 inflammasome	Direct or indirect inhibition of NLRP3 signalling	Reduced maturation of IL-1β and IL-18 and attenuation of downstream inflammatory responses	Limited evidence from PTSD-specific clinical studies
Oxidative stress and mitochondrial dysfunction	Antioxidant strategies and interventions supporting mitochondrial function	Reduced generation of reactive oxygen species and decreased inflammasome activation	Variable efficacy and limited biomarker-guided evidence
HPA-axis dysregulation	Interventions aimed at restoring glucocorticoid sensitivity and neuroendocrine balance	Improved regulation of stress responses and reduced immune activation	Considerable heterogeneity in endocrine profiles among patients with PTSD
Microglial activation	Modulation of pro-inflammatory microglial activity	Reduced neuroinflammatory signalling and improved synaptic support	Lack of selective, microglia-specific therapeutic approaches
Sleep disturbance	Behavioural and pharmacological interventions aimed at improving sleep quality	Reduced inflammatory burden and improved neuroplasticity	Bidirectional relationship between sleep disturbance and PTSD severity
Physical inactivity	Structured physical activity and exercise-based programmes	Improved inflammatory regulation, neuroplasticity, and stress resilience	Differences in adherence, intensity, and treatment response
Glutamatergic and GABAergic imbalance	Restoration of excitatory–inhibitory neurotransmitter balance	Reduced excitotoxicity and secondary inflammatory amplification	Underlying mechanisms remain incompletely understood
ER stress pathways	Modulation of IRE1- and ATF6-dependent signalling	Reduced expression of inflammatory genes and cytokine production	Predominantly preclinical evidence and limited treatment specificity

Source: Compiled by the authors of this study

in fronto-limbic pathways. These microstructural abnormalities may reflect long-term inflammatory effects on axonal integrity and myelination. The interaction between inflammatory mediators and stress hormones likely accelerates these structural changes over time.

Importantly, the severity and duration of PTSD symptoms appear to correlate with both biomarker levels and neuroimaging findings. This relationship supports the hypothesis that chronic immune activation contributes to progressive brain alterations rather than representing a transient response to trauma [34].

Understanding the link between inflammatory processes and structural brain changes may provide clinically relevant information regarding prognosis and therapeutic timing. Early modulation of inflammatory pathways may reduce the risk of long-term neurobiological consequences in PTSD.

DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS OF NEUROINFLAMMATION IN PTSD

Recognition of neuroinflammation as a central component of PTSD has important diagnostic and therapeutic implications. Elevated levels of pro-inflammatory cytokines, including IL-1β, IL-18, IL-6, and TNF-α, may serve as measurable biological indicators of immune activation. When interpreted alongside clinical assessment, these biomarkers may improve risk stratification and support a more precise characterization of disease subtypes [35].

Peripheral inflammatory markers may reflect central immune processes, particularly when associated with microglial activation and BBB alterations. Combined evaluation of cytokine profiles, stress-related hormones, and markers of oxidative stress may provide a more comprehensive understanding of the neuroimmune state in individual patients. Such an approach may help identify patients at risk of chronicity, cognitive decline, or poor response to conventional therapy [36].

Therapeutically, modulation of inflammatory pathways represents a potential strategy in PTSD management. Targeting the NLRP3 and related signaling cascades may reduce maturation of IL-1β and IL-18 and attenuate downstream inflammatory effects. Although specific inflammasome inhibitors are still under investigation, indirect strategies such as reducing oxidative stress and stabilizing mitochondrial function may decrease inflammasome activation [37, 38].

Regulation of the HPA axis is also relevant. Interventions aimed at restoring glucocorticoid sensitivity may limit excessive immune activation. In addition, non-pharmacological strategies, including structured physical activity and sleep normalization, have been shown to influence inflammatory markers and improve neuroplasticity.

Understanding the interaction between inflammatory signaling and neurotransmitter systems, including glutamatergic and GABA pathways, may further refine treatment approaches. Reducing excessive excitatory activity and supporting inhibitory balance may indirectly limit neuroinflammatory amplification.

A biomarker-guided approach could facilitate personalized treatment planning, integrating psychotherapeutic, pharmacological, and lifestyle interventions. Continued investigation of neuroimmune mechanisms is necessary to clarify which patients may benefit most from anti-inflammatory strategies and to determine optimal timing of intervention in the course of PTSD [39, 40].

Potential therapeutic targets related to inflammatory signaling pathways in PTSD are presented in Table 2.

CONCLUSIONS

Current evidence indicates that the processing of pro-inflammatory cytokines is a central mechanism in the pathophysiology of PTSD. Activation of the NOD-like receptor NLRP3 and subsequent maturation of IL-1β and IL-18 contribute to sustained neuroinflammatory signaling. This process interacts with dysregulation of the HPA axis, microglial activation, and impaired neuron–glia communication.

Persistent inflammatory activity influences synaptic plasticity, neurogenesis, and structural integrity in the hippocampus, amygdala, and prefrontal cortex. These alterations provide a biological substrate for emotional dysregulation, intrusive memories, hyperarousal, and cognitive impairment. The association between cytokine levels and clinical features supports the relevance of immune markers in understanding disease heterogeneity and chronicity.

Neuroinflammation in PTSD should not be considered a secondary epiphenomenon but rather an integral component of disease mechanisms. The interaction between cellular stress pathways, inflammatory mediators, and neuroendocrine regulation forms a complex network that sustains symptom persistence.

Integration of inflammatory biomarkers with clinical and neuroimaging findings may improve diagnostic precision and facilitate individualized treatment strategies. Targeting inflammatory signaling pathways, restoring neuroimmune balance, and modulating stress-related mechanisms may represent promising directions for future therapeutic development.

Further translational and longitudinal studies are necessary to clarify causal relationships, identify reliable biomarkers, and determine whether early intervention in inflammatory pathways can prevent long-term structural and functional brain changes in PTSD.

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CONFLICT OF INTEREST

The Author declares no conflict of interest

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