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Review

The Central Role of Cytokines in PTSD and Major Depressive Disorder: Mechanisms and Clinical Implications

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ABSTRACT: Post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) are debilitating psychiatric conditions that are frequently comorbid and linked to chronic immune dysregulation. Increasing evidence implicates cytokine-mediated inflammation in the pathophysiology of these disorders. Cytokines, key signaling molecules of the immune system, influence central nervous system (CNS) function by crossing the blood-brain barrier or signaling via neural routes, thereby affecting neuronal circuits involved in mood regulation and cognition. Elevated levels of pro-inflammatory cytokines—such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ)—have been observed in both peripheral and central compartments of individuals with PTSD and MDD. These molecules contribute to microglial activation, synaptic remodeling, hippocampal atrophy, and altered neurotransmission. Furthermore, chemokines such as CXCL12 and CCL2 are implicated in stress-induced neuroplasticity impairments. Moderating factors, including genetic polymorphisms (e.g, FKBP5, CRP), early-life adversity, sex differences, and exposure type, influence individual vulnerability to immune-related neuropsychiatric outcomes. This review synthesizes current molecular and clinical evidence, highlighting how cytokine dysregulation bridges peripheral inflammation and CNS pathology. It also explores emerging therapeutic strategies targeting inflammatory pathways and discusses the promise of biomarker-based approaches and machine learning for patient stratification and personalized treatment.

Keywords: Cytokine; Post-traumatic stress disorder; Major depressive disorder; Interleukin; TNF-α; FKBP5



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1. Introduction

Post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) are prevalent and often comorbid psychiatric conditions characterized by emotional, cognitive, and somatic symptoms. Despite differences in etiology—trauma exposure for PTSD and a broader range of psychosocial factors for MDD—both disorders share overlapping pathophysiological features, including dysregulated stress responses, impaired neuroplasticity, and heightened systemic inflammation. In recent years, increasing attention has been directed toward immune dysregulation—particularly cytokine-mediated signaling—as a central contributor to the onset and maintenance of both PTSD and MDD [1,2]. However, the precise mechanisms linking immune alterations to behavioral symptoms remain incompletely understood, representing a critical gap in the literature.

We hypothesize that dysregulation of peripheral and central cytokine signaling is a shared pathophysiological mechanism driving the development and persistence of PTSD and MDD, contributing to structural and functional brain alterations that underlie core affective and cognitive symptoms.

Cytokines are small, secreted proteins that orchestrate immune responses and mediate communication between immune and neural systems. They are broadly categorized into pro-inflammatory (e.g, IL-1β, IL-6, TNF-α) and anti-inflammatory (e.g, IL-10) types. Under chronic stress, sustained production of pro-inflammatory cytokines can disrupt homeostatic brain-immune interactions, contributing to synaptic remodeling, hippocampal atrophy, altered neurotransmission, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. These neurobiological alterations are implicated in core symptoms of PTSD and MDD, such as anhedonia, hyperarousal, and cognitive impairment.

Early studies by Yirmiya and colleagues in the 1990s demonstrated that peripheral administration of IL-1β in rodents could induce behavioral symptoms resembling depression—effects that were reversed by chronic, but not acute, antidepressant treatment [3]. These findings provided initial evidence for a causal role of cytokine signaling in mood regulation. Human studies further supported these observations, showing that experimental immune activation (e.g, through endotoxin or vaccine challenge) could temporarily induce depressive symptoms and cognitive dysfunction, underscoring the translational relevance of cytokine-mediated pathways [4,5].

Subsequent research in PTSD populations has also revealed elevated levels of peripheral pro-inflammatory cytokines, including IL-2, IL-6, IL-1β, and TNF-α, indicating a chronic inflammatory state [6–8]. These immune alterations have been associated with changes in brain structure and function, including reduced hippocampal volume and altered limbic connectivity, potentially contributing to the pathogenesis of PTSD and its frequent overlap with MDD.

In this review, we synthesize current findings on the central role of cytokines in PTSD and MDD, with an emphasis on mechanisms of pathogenesis, clinical correlations, and therapeutic implications. We examine how neuroimmune dysregulation contributes to symptom expression, the moderating effects of genetic and environmental risk factors, and the potential of anti-inflammatory and immunomodulatory treatments. In doing so, we highlight emerging precision medicine approaches—including biomarker-guided stratification and machine learning techniques—that may facilitate more targeted and effective interventions.

2. Literature Synthesis: Cytokine in PTSD

Searched in PubMed using the keywords ‘cytokine and PTSD’ and ‘cytokine and depressive disorder’, we found that there are 440 and 2884 published papers on PTSD and on depressive disorder by 29 April 2025, respectively, showing that cytokines in PTSD and MDD draw more interest over time (Figure 1).

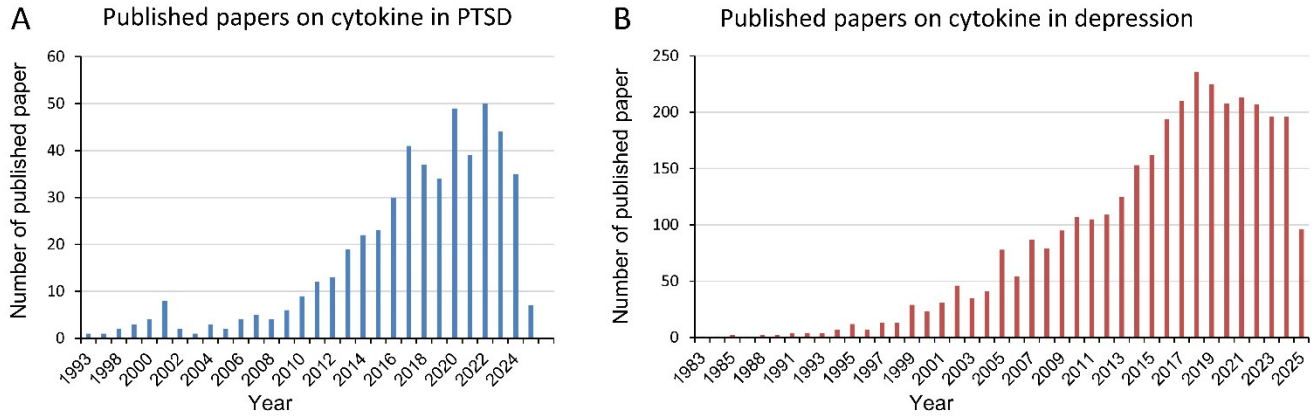


Figure 1. Publications on cytokine in PTSD or MDD. Figure 1 shows the trend of published literatures on cytokine in PTSD (**A**) or MDD (**B**) using PubMed search engine.

2.1. Immune Signatures of Chronic Stress Exposure in PTSD

Trauma can result in a significant psychological and physiological stress response, leading to the release of inflammatory cytokines and subsequent immune cell dysfunction (Figure 2A). This cascade may promote chronic inflammation and cause short- or long-term immune dysregulation, which contributes to the development or exacerbation of PTSD symptoms. For example, veterans of the Gulf War showed a remarkable higher prevalence of immune-related disorders such as rheumatism, sarcoidosis, and multiple sclerosis, suggesting the connection between war-related stress and immune dysfunction [9]. Research has shown significant changes in circulating cytokines and chemokines—key mediators of immune signaling—in individuals with PTSD. These include interferons (IFNs), interleukins (ILs), tumor necrosis factors (TNFs), lymphokines, and chemokines [7,10,11]. Moreover, remarkably elevated peripheral levels of cytokines were observed. IL-2, IL-4, IL-6, IL-8, IL-10, and TNF-α compared were significantly higher in the patients with PTSD compared to age- and sex-matched healthy controls [11]. In addition, cross-sectional and longitudinal studies have demonstrated elevated levels of pro-inflammatory cytokines-particularly IL-6, TNF-α, and IL-1β-in individuals with PTSD [6,7,11–13]. Meta-analyses reveal that PTSD is associated with higher peripheral concentrations of IL-6 and TNF-α, two canonical markers of systemic inflammation [14,15]. Elevated

IL-6 has been linked to increased severity of re-experiencing symptoms and hyperarousal, while TNF-α correlates with impaired cognitive performance and altered sleep architecture in PTSD patients [16].

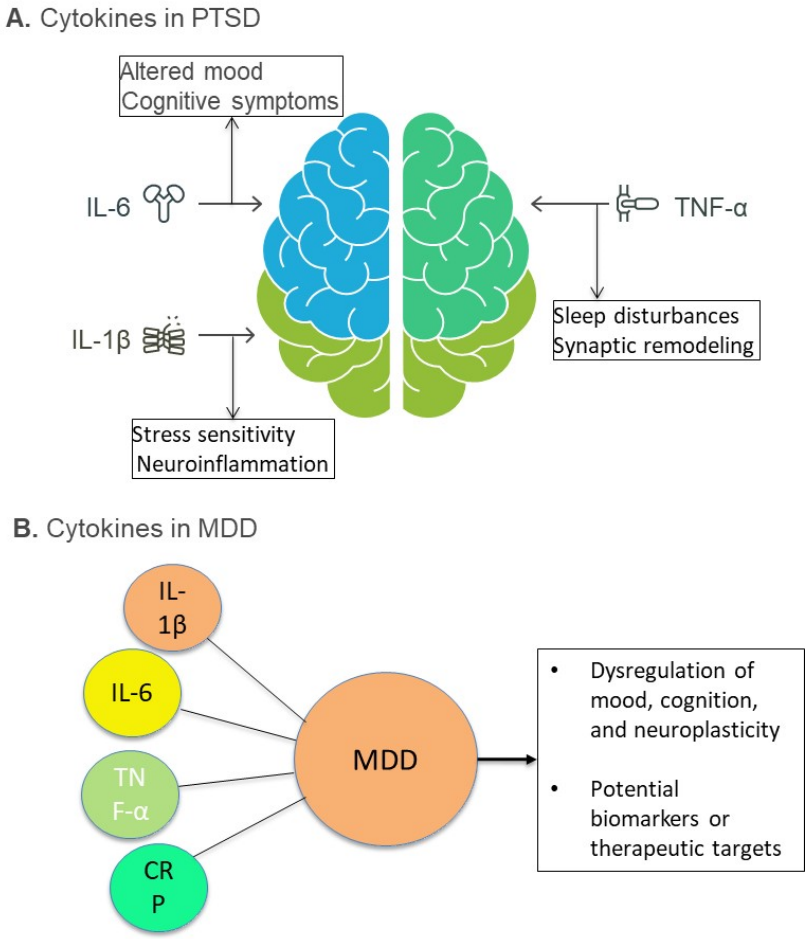


Figure 2. Immune response in PTSD (panel (**A**)). Illustration of key pro-inflammatory cytokines implicated in the pathophysiology of post-traumatic stress disorder (PTSD). Interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) are shown interacting with the brain, reflecting their roles in neuroimmune dysregulation. Elevated IL-6 is associated with altered mood and cognitive symptoms; IL-1β is linked to stress sensitivity and neuroinflammation; TNF-α is implicated in sleep disturbances and synaptic remodeling. These cytokines contribute to the chronic low-grade inflammation observed in individuals with PTSD. Panel (**B**) shows the inflammatory markers associated with MDD. Diagram illustrating key inflammatory markers elevated in individuals with MDD. Interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are consistently found at increased levels in patients with MDD. These pro-inflammatory molecules are implicated in the dysregulation of mood, cognition, and neuroplasticity, and may serve as potential biomarkers or therapeutic targets in the treatment of MDD.

Chemokines, a subclass of cytokines involved in immune cell trafficking and neuroimmune communication, also show altered profiles in PTSD. Studies report increased levels of CCL2 (MCP-1), CXCL8 (IL-8), and CXCL10 (IP-10) in both blood and cerebrospinal fluid (CSF) samples [17–19]. Our previous study using both the before-and-after and the case-control design revealed that CCL2, CCL15, CCL22, CCL25, CXCL2, and CXCL12 are associated with PTSD onset; CCL3, CXCL11, and CXCL16 are related to stress response. CCL13, CCL20, and CXCL6 were possible PTSD risk markers; CX3CL1 is a potential resilience marker [20]. While CCL11, CCL13, CCL20, and CCL25 are correlated to PTSD symptom severity [20], elevated pre-deployment levels of IL-6 and CCL2 could predict post-deployment PTSD symptoms [21]. More interestingly, tenacious elevations of CRP and IL-10 were associated with delayed-onset PTSD in the post-deployment individuals, indicating the potential utility of immune markers for PTSD [22]. However, the literature has presented inconsistent findings. For instance, while studies reported elevated levels of IL-1β [6,12], IL-6 [13], and TNF-α [7] in the plasma of PTSD patients [11], others have found no statistically significant differences in IL-1β [7], IL-6 [6,7], or IL-8 [6] levels between the cases and controls. These discrepancies may be attributed to several confounding variables, including differences in the type and timing of trauma (e.g, childhood *vs.* adulthood), the chronicity or immediacy of trauma exposure, civilian *vs.* military populations, geographical variations, the use of

psychotropic medications, and methodological differences in biomarker detection (e.g, ELISA *vs.* Western blot, single versus multiplex assays, saliva- *vs.* blood-based sampling).

2.2. Cytokine in MDD

Alterations in cytokine levels have been observed in MDD, a commonly comorbid condition with PTSD. Cytokines may be associated with depressive symptoms [23]. An animal study showed that injecting rats with endotoxin, which stimulates the immune system, leads to depression-like behavior [3]. Similarly, immune challenges in humans using endotoxin administration have resulted in emotional and cognitive disturbances, indicating a role for cytokines in regulating mood and cognitive function [24] (Figure 2B).

Patients with MDD exhibit elevated inflammatory markers. IL-1β, IL-6, TNF-α, and C-reactive protein (CRP) are consistently upregulated in individuals with MDD compared to healthy controls [4,25–27]. Moreover, cytokine elevation is correlated with MDD severity and treatment resistance [28]. Notably, longitudinal studies have shown that baseline elevations in IL-6 and CRP could predict future onset of depressive symptoms, suggesting a causal role in disease development [29,30]. Following acute trauma exposure, IL-6 and IL-1RA (IL-1 receptor antagonist) levels were significantly increased and associated with increased risk of developing MDD [31]. These findings underscore the prognostic value of inflammatory markers and support their inclusion in early screening protocols for stress-related psychopathology.

Growing data point to increased levels of CCL2, CCL11, and CXCL10, particularly in individuals with treatment-resistant MDD [32–34]. These chemokines are known to promote leukocyte infiltration into the central nervous system (CNS), supporting the hypothesis that MDD is, at least in part, an inflammatory disorder of the brain.

CRP is correlated with [35] and a risk factor for MDD [36]. However, it is present only in a subset of individuals with MDD [37]. The inconsistency is probably related to many factors, e.g, the size of samples and symptom heterogeneity. In a large sample size ($n = 4157$), Moriarity et al. report that the elevated CRP group has greater symptom connectivity (stronger total associations between symptoms). Difficult concentrating and psychomotor difficulties have higher expected influence (concordance with other symptoms) in the elevated CRP group. In addition, several symptoms are moderated by CRP [38]. Also, a meta-analysis in 5166 patients and 5083 controls out of 107 studies demonstrates that levels of CRP, IL-3, IL-6, IL-12, IL-18, sIL-2R, and TNFα are significantly higher in patients with MDD. Furthermore, Moriarity et al. report CRP is simultaneously associated with latent depression, appetite, and fatigue after analyzing a 27,730 adults [39].

2.3. Shared Immune Profiles by Both PTSD and MDD

PTSD and MDD frequently co-occur, with comorbidity rates as high as 50% in some populations [40]. They often share inflammatory profiles with each other. Both disorders show elevations in IL-6, TNF-α, IL-1β, and chemokines like CXCL10. Therefore, this convergence suggests common upstream drivers, such as chronic stress, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and altered glucocorticoid sensitivity, which are known to modulate immune function [41,42]. Trauma-exposed individuals who developed either PTSD, depression, or both demonstrated that the magnitude and duration of cytokine dysregulation may differ depending on the clinical outcome. While elevated IL-6 and TNF-α were observed in all trauma-exposed individuals, those with comorbid PTSD and MDD exhibited the highest cytokine levels [43], showing a possible additive or synergistic inflammatory burden in dual-diagnosis cases (Figure 3).

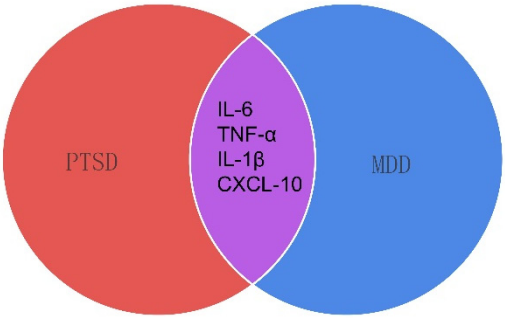


Figure 3. Shared and distinct inflammatory profiles in PTSD and MDD. Venn diagram illustrating the overlap in immune dysregulation between post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Both disorders exhibit shared

immune signatures, including elevated pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. These overlapping inflammatory markers suggest a common pathophysiological mechanism underlying stress-related psychiatric conditions. Disorder-specific immune patterns may also exist, but are not depicted here.

3. Mechanistic Pathways Linking Immune Dysregulation to PTSD

A complex network of neuroimmune interactions underpins the relationship between immune system dysfunction and PTSD. Cytokines may link peripheral immune activation to CNS alterations that led to the onset of psychiatric symptoms. Here, we summarize the major mechanistic pathways through which immune dysregulation contributes to PTSD (Figure 4).

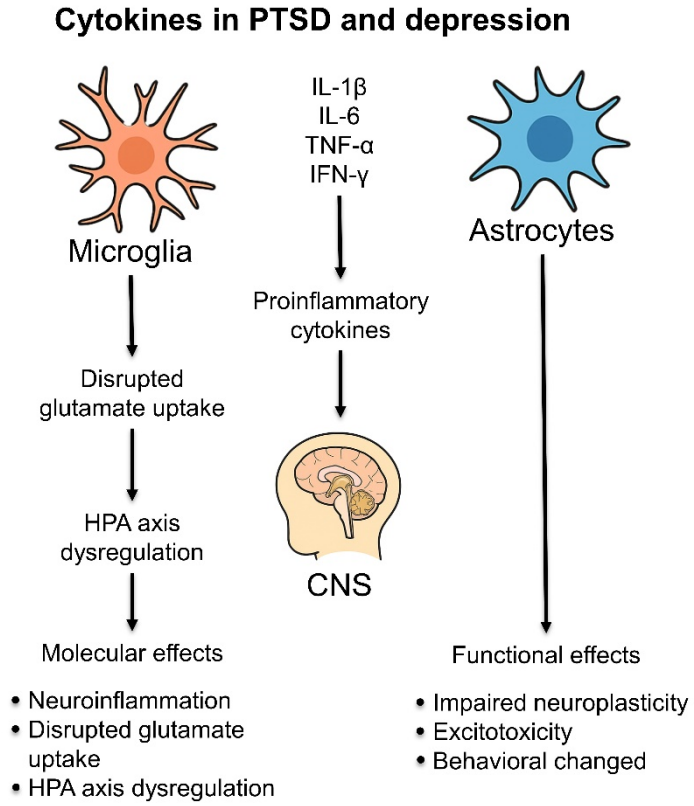


Figure 4. Neuroimmune mechanisms linking cytokine dysregulation to depression and PTSD pathology. This schematic illustrates how peripheral and central pro-inflammatory cytokines (e.g, IL-1β, IL-6, TNF-α, IFN-γ) influence central nervous system (CNS) function in the context of post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Stress and trauma activate the immune system, leading to increased peripheral cytokine release and blood-brain barrier (BBB) permeability. Cytokines access the brain via humoral routes or activating afferent nerves (e.g, vagus nerve), subsequently activating glial cells—particularly astrocytes and microglia. Activated astrocytes release further cytokines and reduce glutamate clearance by downregulating excitatory amino acid transporters (EAAT1/2), contributing to excitotoxicity, synaptic dysfunction, and impaired neurogenesis, especially in the hippocampus and prefrontal cortex. These changes are associated with core symptoms of depression and PTSD, including cognitive deficits, anhedonia, and hyperarousal. Cytokine signaling modulates HPA axis activity by altering corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoid receptor sensitivity, thereby sustaining maladaptive stress responses. Chronic neuroinflammation reinforces behavioral pathology and may define a biological subtype of inflammatory-driven mood and trauma-related disorders.

3.1. Stress-Induced Activation of the Immune System

Psychological stress activates the HPA axis and the sympathetic nervous system, leading to the release of glucocorticoids and catecholamines. Acute stress typically suppresses immune activity *via* glucocorticoid-mediated anti-inflammatory effects. However, chronic or repeated stress can result in glucocorticoid receptor resistance in immune cells, impairing the resolution of inflammation and promoting a sustained pro-inflammatory state [44–46].

This paradoxical activation of the immune system may increase production of pro-inflammatory cytokines (e.g, IL-1β, IL-6, TNF-α) and chemokines (e.g, CXCL8, CCL2), which can then influence brain function through both humoral and neural pathways [47].

3.2. Cytokine Signaling Across the Blood-Brain Barrier

Pro-inflammatory cytokines may affect CNS processes through several mechanisms: (1) passive diffusion *via* regions with reduced blood-brain barrier (BBB) integrity (e.g, circumventricular organs), (2) active transport mechanisms, (3) signaling through vagal afferent neurons, and (4) activation of endothelial cells to release secondary messengers into the brain parenchyma [48–50]. Once in the brain, cytokines can directly interact with neurons and glial cells to modulate neurobiological processes relevant to mood and stress responses, including neurotransmitter metabolism, neuroendocrine regulation, and synaptic plasticity.

3.3. Microglial Activation and Neuroinflammation

Microglia, the resident immune cells of the CNS, play a central role in mediating the neuroinflammatory effects of peripheral cytokine signaling. Chronic peripheral inflammation primes microglia, making them hyperresponsive to subsequent stimuli. This leads to exaggerated production of pro-inflammatory mediators such as IL-1β, TNF-α, and reactive oxygen species (ROS) within the brain [47,51,52]. Sustained microglial activation has been implicated in hippocampal atrophy, reduced neurogenesis, and impaired synaptic function in patients with PTSD and MDD [53]. Neuroinflammation also disrupts the balance between excitatory and inhibitory neurotransmission, contributing to anxiety, anhedonia, and cognitive deficits commonly seen in these disorders. Chronic stress activates microglial P2Y12 receptors, leading to synaptic loss in the prefrontal cortex; this synaptic remodeling is associated with behavioral deficits relevant to depression [54]. Moreover, stress may cause microglia to deviate from their finely tuned homeostasis, as both clinical and preclinical studies show. Triggering factors include dysregulation of the neuroendocrine system, the noradrenergic system, the gut-brain axis, and an imbalance between pro- and anti-inflammatory milieus composed of diverse cytokines and neurotransmitters. Therefore, functional changes in microglia may strongly influence neuronal network activity through dysregulated cytokine secretion, ultimately contributing to pathological outcomes under stress conditions [55].

3.4. Impact on Monoaminergic Systems

Inflammatory cytokines impact monoaminergic neurotransmission by altering the synthesis, reuptake, and metabolism of key neurotransmitters such as serotonin, dopamine, and norepinephrine. For instance, IL-1β and IFN-α upregulate the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan—the precursor to serotonin—into kynurenine [56,57]. This shift not only reduces serotonin availability but also leads to the accumulation of neurotoxic kynurenine metabolites (e.g, quinolinic acid), which can impair glutamatergic signaling and promote neurotoxicity [58]. These processes contribute to the development of symptoms such as low mood, fatigue, and impaired cognition, which are often seen in PTSD or MDD.

3.5. Disruption of Neuroendocrine Feedback Loops

Inflammatory cytokines interfere with HPA axis regulation by influencing the release and receptor sensitivity of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. For example, IL-6 and TNF-α can increase CRH expression in the hypothalamus, leading to elevated cortisol levels [59–61]. Over time, chronic cortisol exposure and cytokine-induced glucocorticoid receptor resistance contribute to impaired feedback inhibition of the HPA axis—a hallmark feature in PTSD and MDD [62–64]. IL-6 can directly stimulate the HPA axis independently of CRH. IL-6 administration significantly increased plasma ACTH levels in both wild-type and CRH knockout mice. The findings suggest that IL-6 can act directly on pituitary corticotrophs and adrenal cells, influencing ACTH and corticosterone release, thereby modulating the HPA axis during immune activation [65]. Compared to IL6, IL-1 was a more potent activator of the HPA axis [66].

3.6. Chemokine-Mediated Neuroplasticity and Neural Circuit Remodeling

In addition to their roles in immune cell trafficking, chemokines directly influence neurodevelopment, synaptic plasticity, and neurogenesis. Dysregulated expression of chemokines such as CXCL12 and CCL2 in response to chronic stress is associated with impaired adult hippocampal neurogenesis and altered neuronal connectivity in limbic regions [67,68].

Altered chemokine signaling may contribute to the structural and functional brain changes observed in PTSD and MDD, including reduced hippocampal and prefrontal cortex volumes and altered amygdala reactivity. These brain alterations correlate with symptom domains such as emotional dysregulation, impaired memory, and heightened threat sensitivity.

4. Clinical Implications: Diagnostic and Prognostic Value

Understanding the clinical implications of immune dysregulation in PTSD and MDD has opened new avenues for biomarker discovery, personalized treatment approaches, and improved prediction of disease trajectory. Cytokines and chemokines, due to their dynamic responsiveness to stress and neurobiological effects, are emerging as potential tools for diagnostic classification, prognostic evaluation, and therapeutic monitoring (Figure 5).

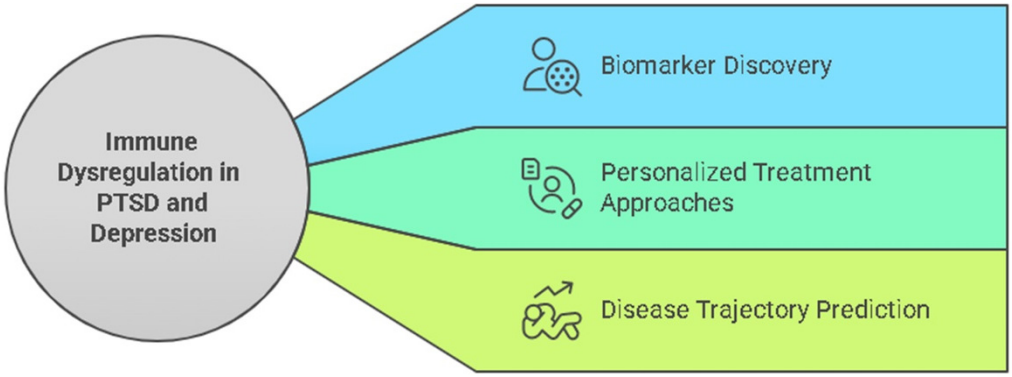


Figure 5. Exploring cytokines and chemokines in mental health. Conceptual model illustrating the implications of immune dysregulation in post-traumatic stress disorder (PTSD) and depression. Chronic alterations in immune signaling, particularly involving cytokines and chemokines, may contribute to disease pathophysiology and serve as a foundation for translational applications. These include: (1) biomarker discovery to aid in diagnosis and monitoring, (2) personalized treatment approaches guided by individual immune profiles, and (3) prediction of disease trajectory and treatment response. This framework supports the development of precision psychiatry strategies targeting immune-related mechanisms.

4.1. Cytokines and Chemokines as Diagnostic Biomarkers

The identification of reliable biomarkers for PTSD and MDD has long been a challenge due to the heterogeneity of these disorders. Recent findings suggest that specific inflammatory profiles may help differentiate patients with psychiatric conditions from healthy individuals and even distinguish subtypes within disorders.

In PTSD, elevated peripheral levels of IL-6, TNF-α, and CRP have been consistently reported, with some studies proposing thresholds that differentiate PTSD patients from trauma-exposed but resilient individuals [69–72]. Similarly, in MDD, meta-analyses have shown that elevated IL-1β, IL-6, and CRP levels are associated with the presence of MDD [73]. The integration of inflammatory markers with clinical interviews and neuroimaging may improve diagnostic accuracy, especially in ambiguous or comorbid presentations.

Importantly, chemokines such as CCL2, CXCL10, and CX3CL1 are gaining attention due to their specificity for neuroimmune pathways. For example, elevated CXCL10 levels are associated with intrusive re-experiencing symptoms in PTSD, while CCL11 elevation has been linked to cognitive dysfunction in MDD [74,75].

4.2. Prognostic Utility and Risk Prediction

Longitudinal studies have highlighted the prognostic potential of cytokines and chemokines in predicting the onset and course of stress-related disorders. Elevated baseline levels of IL-6, IL-10, or CRP have been associated with an increased risk of developing PTSD or MDD following trauma exposure, suggesting that immune activation precedes symptom emergence in vulnerable individuals [21,22,39,76,77].

Additionally, persistently elevated inflammatory markers are associated with chronicity and poorer outcomes. For instance, PTSD patients with sustained elevations in IL-6 and CRP are more likely to exhibit treatment resistance and comorbid conditions such as cardiovascular disease [78]. In MDD, high IL-1β and IL-6 levels have been linked to poor response to standard antidepressant therapies, reinforcing the need for inflammation-informed treatment selection [79].

4.3. Stratification and Personalized Medicine

Cytokine and chemokine profiles may aid in stratifying patients into biologically distinct subgroups, thereby facilitating personalized interventions. Several studies have identified a subset of patients with high inflammation

("inflammatory biotype") who may benefit from adjunctive anti-inflammatory therapies or specific antidepressants with immunomodulatory effects [80–82].

Trauma and its associated PTSD have been linked to elevated inflammation in numerous studies. Systemic inflammation, in turn, has been implicated in the pathophysiology of several common chronic physical diseases that are more prevalent following trauma. Moreover, inflammation may contribute to the development of PTSD and depression symptoms. In PTSD, immune profiling may help distinguish individuals more likely to benefit from exposure-based therapies versus those who might respond better to interventions targeting systemic inflammation, such as aerobic exercise, mindfulness-based stress reduction, or pharmacological agents like minocycline or ketamine [83–85]. Research suggests that adjunctive anti-inflammatory therapies and certain antidepressants with immunomodulatory effects may offer benefits in treating PTSD [86].

This precision psychiatry approach has been explored through the use of anti-cytokine therapies. The anti-cytokine drug infliximab, a TNF-α inhibitor, has been shown to reduce depressive symptoms, particularly in patients with elevated baseline C-reactive protein (CRP) levels. Clinical trials have demonstrated significant reductions in anhedonia and depressive symptoms. However, the efficacy of infliximab is not generalized across all patients; studies indicate that its effectiveness is largely limited to individuals with higher baseline inflammatory biomarkers, including high-sensitivity CRP (hs-CRP) [87]. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors have been found to exhibit antidepressant effects. Anti-inflammatory agents have been examined in the treatment of depression and have yielded positive results [87–91]. Meta-analysis studies showed that anti-inflammatory agents reduced depressive symptoms, with higher response and remission rates when used alongside antidepressants. A meta-analysis of 14 RCTs on various non-steroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors suggested that these interventions reduced depressive symptoms compared with placebo, in both patients with depression and those with primary inflammatory disorders and comorbid depressive symptoms [92]. However, there was a significant heterogeneity among included studies. Another meta-analysis of 30 RCTs suggested that anti-inflammatory agents, including NSAIDs, omega 3 fatty acids, statins, and minocyclines, reduced depressive symptoms and resulted in higher response and remission rates compared with placebo, an effect that was more pronounced when the anti-inflammatory agents were used as adjunctive treatments to antidepressants, rather than monotherapies [93] This finding illustrates the value of cytokine-based stratification in enhancing treatment efficacy and minimizing unnecessary exposure to ineffective therapies.

4.4. Integration into Multimodal Assessment Tools

As stand-alone markers, cytokines and chemokines may have limited specificity. However, their integration into multimodal diagnostic models—including neuroimaging, genetic, epigenetic, and behavioral data—could enhance clinical utility. Machine learning approaches have begun to identify immune-related biosignatures that predict PTSD and MDD onset, symptom clusters, and treatment responses with greater accuracy than clinical assessments alone [94–96].

Moreover, dynamic changes in inflammatory markers may serve as early indicators of therapeutic response. A decrease in IL-6 or CRP following psychotherapy or pharmacotherapy has been associated with symptomatic improvement, suggesting their utility in monitoring treatment efficacy [97]. Elevated levels of CRP, IL-6, and TNF-α were more pronounced in female versus male MDD patients, while one meta-analysis found that the three cytokines were significantly elevated at baseline in MDD patients, but their treatment trajectories differed [98,99].

5. Therapeutic Targeting of Cytokine and Chemokine Pathways

As the role of inflammation in the pathophysiology of PTSD and MDD becomes increasingly evident, there is growing interest in immunomodulatory therapies that specifically target cytokine, including chemokine, signaling. These strategies include repurposing anti-inflammatory agents, developing biologics targeting key immune mediators, and lifestyle interventions known to impact immune health. This section highlights current and experimental approaches to restore immune balance in stress-related psychiatric disorders.

5.1. Anti-Inflammatory Pharmacological Agents

Several conventional anti-inflammatory drugs have been evaluated for their antidepressant and anxiolytic properties, particularly in individuals with elevated inflammatory markers. Minocycline, a tetracycline antibiotic with anti-inflammatory and neuroprotective properties, has also shown promise. A 12-week RCT of minocycline augmentation in MDD found significant improvement in depressive symptoms, particularly in patients with high

inflammatory profiles [100]. Although limited data exist in PTSD populations, a small RCT of the COX-2 inhibitor rofecoxib in PTSD showed improved symptom scores, and several preclinical studies support the efficacy of cytokine-modulating strategies in stress-exposed rodents [101].

5.1.1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs such as celecoxib, a COX-2 inhibitor, have shown promise as adjunctive treatments in major depressive disorder (MDD), particularly in patients with high baseline levels of CRP or IL-6 [89,92]. Although less explored in PTSD, some preliminary studies suggest that COX-2 inhibitors may reduce re-experiencing symptoms and irritability by dampening systemic inflammation.

5.1.2. Cytokine Antagonists

Recognition of immune dysregulation—particularly involving pro-inflammatory cytokines—as a key mechanism in PTSD and MDD has fueled growing interest in anti-inflammatory therapies as adjunctive treatments. We hypothesize that pro-inflammatory cytokine dysregulation contributes to a distinct immune-biological subtype of PTSD and MDD that is associated with treatment resistance and can be effectively targeted through immunomodulatory interventions, including anti-cytokine agents, repurposed anti-inflammatory drugs, and behavioral interventions that reduce systemic inflammation. Traditional antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are only partially effective for many individuals, particularly those with elevated peripheral inflammatory markers. Meta-analyses suggest that inflammation contributes to treatment resistance, underscoring the rationale for targeting immune pathways in specific subgroups.

Monoclonal antibodies targeting pro-inflammatory cytokines have shown mixed results in the treatment of PTSD or MDD. The TNF-α blocker infliximab demonstrated antidepressant effects in a subset of MDD patients with elevated CRP (>5 mg/L), but not in the broader population [81]. Similarly, IL-6 receptor antagonists (e.g, tocilizumab) are under investigation for mood and cognitive symptoms associated with chronic inflammation and autoimmune disease, with emerging relevance to PTSD. Unfortunately, it seems that the IL-6 receptor antagonist tocilizumab does not improve and may actually worsen depression and related symptoms—including anxiety, pain, and sleep—among medically ill individuals undergoing allogeneic cell transplantation [102]. The immunosuppressive nature of these biologics raises concerns regarding infection risk, cost, and long-term safety, limiting their widespread use in psychiatric populations without co-occurring inflammatory disease. However, the evidence for tocilizumab directly affecting PTSD symptoms is limited. More research is needed to determine if tocilizumab or other anti-inflammatory treatments could be beneficial in managing PTSD.

5.2. Glucocorticoid and HPA Axis Modulation

Given the interaction between immune dysregulation and the HPA axis, pharmacologic agents that restore glucocorticoid sensitivity have been explored. Agents such as mifepristone (a glucocorticoid receptor antagonist) have demonstrated symptom reduction in subsets of patients with psychotic depression and trauma-related disorders, possibly via normalization of feedback inhibition and immune modulation. It is being investigated as a potential treatment for PTSD, particularly in individuals who haven't responded well to standard therapies like SSRIs or psychotherapy [103].

Hydrocortisone administration immediately following trauma exposure has also been investigated as a preventive measure against PTSD, with some evidence suggesting reduced inflammation and symptom severity when administered early [104]. Recently, it has been reported that hydrocortisone promotes an accelerated degradation of sensory-perceptual representations underlying traumatic intrusive memories in PTSD treatment [105].

5.3. Immunomodulatory Properties of Psychotropics

Several conventional psychotropic medications exert immunomodulatory effects independent of their neurotransmitter actions. For example:

- Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline reduce peripheral levels of IL-1β and TNF-α, which may contribute to their efficacy in both MDD and PTSD [106,107]. Several clinical trials have evaluated anti-cytokine therapies in mood disorders. Notably, a randomized controlled trial (RCT) of the TNF-α antagonist infliximab in patients with treatment-resistant depression (TRD) found that although infliximab was not effective overall. However, infliximab was not effective overall, it significantly improved depressive symptoms in

patients with elevated baseline C-reactive protein (CRP ≥ 5 mg/L) [29]. Similarly, the COX-2 inhibitor celecoxib has demonstrated antidepressant efficacy in combination with SSRIs, particularly in patients with major depression and elevated inflammatory markers [87,89]. A meta-analysis of 10 RCTs found that celecoxib augmentation significantly reduced depressive symptoms compared to placebo [92]. Ketamine, an NMDA receptor antagonist with rapid antidepressant effects, has been shown to reduce IL-6 and TNF-α levels post-administration in treatment-resistant depression, and may influence microglial activation states [108].

- Atypical antipsychotics (e.g, quetiapine, risperidone) can reduce CRP and other pro-inflammatory cytokines and have been used off-label in PTSD, particularly for managing hyperarousal and psychotic symptoms [109].

The immune-modulating properties of these agents may partly explain differential treatment responses among individuals with varying levels of inflammation.

5.4. Lifestyle Interventions Targeting Inflammation

In addition to pharmacological interventions, non-pharmacological lifestyle modifications known to reduce systemic inflammation—such as aerobic exercise, mindfulness-based stress reduction (MBSR), and anti-inflammatory diets—are increasingly being integrated into treatment plans. Exercise has been shown to reduce IL-6 and TNF-α levels and improve depressive symptoms [110]. Similarly, dietary interventions such as the Mediterranean diet have been associated with lower systemic inflammation and lower depression risk [111].

5.4.1. Physical Activity

Regular aerobic exercise has well-documented anti-inflammatory effects, including reduced IL-6 and TNF-α levels and improved immune cell function. Exercise also enhances hippocampal neurogenesis and is associated with symptom improvement in PTSD [112] and MDD [113,114].

5.4.2. Dietary Interventions

Anti-inflammatory diets rich in omega-3 fatty acids, antioxidants, and polyphenols (e.g, Mediterranean diet) are associated with lower rates of depression and anxiety. Omega-3 supplementation, particularly eicosapentaenoic acid (EPA), has demonstrated mood-stabilizing effects, possibly suppressing IL-1β and TNF-α [115,116].

5.4.3. Mind-Body Practices

Mindfulness-based stress reduction (MBSR), yoga, and meditation have been shown to decrease pro-inflammatory cytokines and normalize immune cell function in individuals with PTSD and MDD. These practices may work by downregulating SNS and HPA axis activity and promoting parasympathetic tone [117,118].

5.5. Emerging and Experimental Approaches

5.5.1. Chemokine Receptor Antagonists

Novel agents targeting chemokine receptors (e.g, CCR2, CXCR3) are under investigation for their neuroimmune regulatory roles. Preclinical studies suggest blocking CCL2-CCR2 signaling may reduce microglial activation and behavioral symptoms in stress-exposed rodents [119]. While human studies remain limited, this represents a promising area of therapeutic development.

5.5.2. Microbiome-Based Interventions

The gut microbiota significantly influences systemic inflammation and neuroimmune signaling. Dysbiosis has been linked to both increased gut permeability and elevated cytokine production. Probiotics, prebiotics, and dietary fiber can promote a favorable microbial environment, potentially reducing IL-6 and TNF-α levels and improving psychiatric symptoms [120,121].

5.5.3. Neuromodulation Techniques

Transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS) have demonstrated anti-inflammatory effects via central modulation of autonomic and immune networks. VNS, in particular, enhances

cholinergic anti-inflammatory pathways and may lower peripheral TNF-α and IL-1β, showing promise in treatment-resistant depression and PTSD [122–124].

As the field moves toward precision psychiatry, peripheral inflammatory markers such as IL-6, TNF-α, and CRP are increasingly evaluated for treatment stratification. These markers may help identify inflammation-related subtypes of depression or PTSD that respond preferentially to immunomodulatory strategies [125]. Despite growing interest, challenges remain. Anti-inflammatory agents may have limited efficacy in unselected populations, and long-term safety—especially in psychiatric use—requires further study. Future trials should incorporate biomarker-guided stratification, focus on reproducible inflammatory subtypes, and include PTSD cohorts to better characterize therapeutic targets in trauma-related disorders.

6. Future Directions and Conclusions

Despite considerable progress, research gaps remain in understanding the role of cytokines and chemokines in PTSD and MDD. Longitudinal and mechanistic studies are needed to clarify whether immune dysregulation precedes, coincides with, or follows the onset of these disorders. Research using both in vitro and in vivo models is essential to identify specific immune mechanisms underlying psychopathology. A major challenge ahead is establishing standardized protocols for biomarker sampling, assay techniques, and statistical adjustments for confounding factors such as medication use, circadian rhythms, BMI, and smoking, which are necessary to improve reproducibility and comparability across studies. Additionally, immune signatures may vary among individuals; therefore, identifying stable inflammatory biotypes that span PTSD and MDD could promote the development of personalized, immune-targeted treatments. Integration of cytokine and chemokine profiles with machine learning algorithms and digital health technologies may provide new avenues for dynamic, individualized treatment strategies. Translational research that stratifies participants by immune status could facilitate testing immunomodulatory therapies. Combining biological and psychological treatments may offer greater benefits for both patients and clinicians. Ultimately, precision psychiatry frameworks that incorporate endocrine and immune profiles could optimize early interventions and improve the prediction of clinical outcomes. In conclusion, targeting the immune system in stress-related psychiatric disorders holds great promise. Cytokines and chemokines, long studied as downstream correlates of stress and trauma, are now emerging as active contributors to disease mechanisms and clinical trajectories. By advancing biomarker-guided treatment and personalized medicine, the immune-based approach may pave the way for more effective, tailored interventions for individuals suffering from PTSD and MDD.

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