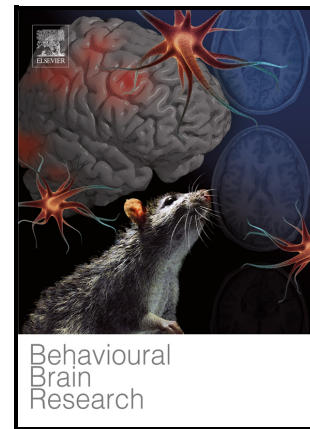


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Psychological stress and immune dysregulation: insights from neuroimmunology and the gut–brain–immune axis

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Abstract

The interplay between mental health, immune function, and gut microbiota has garnered increasing attention in recent years, with mounting evidence indicating that psychological stress and depression are increasingly associated with alterations in immune responses and systemic health. Chronic stress and depression are closely associated with immune dysregulation and have been implicated in the onset and progression of autoimmune diseases, cardiovascular disorders, cancer, and other inflammation-related conditions, although these relationships are complex and not strictly causal. Emerging research highlights the gut–brain–immune axis as a critical mediator of these effects, where alterations in gut microbiota composition, microbial metabolites, and intestinal barrier integrity modulate systemic inflammation, immune cell function, and neural activity. This review examines the intricate relationship between depression, stress, immune dysregulation, and gut microbiota, focusing on

how psychological states are associated with changes in immune markers, inflammatory pathways, and cellular immunity. We discuss the roles of key neural systems, including prefrontal–limbic circuits and brainstem–autonomic pathways, in shaping immune-related processes, the influence of neurotransmitters including serotonin and norepinephrine, and the impact of autonomic nervous system activity on immune modulation. Furthermore, we explore how gut microbial dysbiosis and microbial metabolites contribute to neuroimmune interactions, providing novel insights into the mechanisms linking psychological and immune health. By synthesizing current evidence, this review underscores the potential for integrated therapeutic strategies that simultaneously target mental health, immune function, and gut microbiota, and highlights avenues for future research in psychoneuroimmunology and clinical translation.

Keywords: psychoneuroimmunology, depression and immunity, stress and immune dysregulation, neurobiological mechanisms, gut–brain–immune axis

1. Introduction

Neuroimmunology investigates the bidirectional interactions between the nervous and immune systems, two systems historically studied in isolation[1-2]. While the immune system is primarily responsible for defending against pathogens, the nervous system governs cognition, behavior, and emotion[3]. However, emerging evidence reveals a profound interconnection between these systems, influencing each other in both health and disease. The brain and immune system communicate through neural, hormonal, and cytokine signaling pathways, a cross-talk that is particularly relevant in understanding how psychological factors such as stress and depression modulate immune function[4-5].

Psychological stress, whether acute or chronic, is a ubiquitous feature of modern life and has been shown to significantly impact immune function[6]. The body's stress response is primarily mediated by the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), particularly the sympathetic nervous system (SNS)[7-8]. In response to stress, the brain activates these pathways, resulting in the

release of cortisol and other stress hormones that influence immune cell behavior. While acute stress may transiently enhance immune function as part of the "fight or flight" response, chronic stress is associated with immune dysregulation, and prolonged activation of stress-related pathways has been linked to increased inflammatory signaling, impaired immune cell function, and reduced resistance to infections. Moreover, chronic stress has been implicated in the development of various diseases, including autoimmune disorders, cardiovascular disease, and cancer[9].

Depression, a prevalent mental health condition, also exerts significant effects on immune function[10]. Depression is characterized by alterations in brain chemistry, particularly in the regulation of neurotransmitters such as serotonin, norepinephrine, and dopamine[11]. These neurotransmitters not only regulate mood and cognition but also play critical roles in immune system modulation[12]. Recent studies have demonstrated that depression is associated with chronic low-grade inflammation, marked by elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α)[13-14]. This inflammatory state has been linked to numerous health problems, including cardiovascular disease, diabetes, and neurodegenerative disorders. Furthermore, chronic inflammation in the brain is thought to contribute to the behavioral symptoms of depression, creating a vicious cycle that exacerbates both psychological and physical health issues[15].

The mechanisms underlying the neuroimmunological connection between stress, depression, and immune function are complex. One critical aspect is the role of the ANS, which regulates involuntary bodily functions, including immune responses. The SNS promotes inflammation by stimulating the production of pro-inflammatory cytokines, while the parasympathetic nervous system (PNS) typically exerts anti-inflammatory effects[16]. The balance between these two branches of the ANS significantly influences the immune system's ability to respond to stressors. Additionally, the central nervous system (CNS) communicates with immune cells through neuropeptides such as corticotropin-releasing hormone (CRH) and substance P, which modulate cytokine production and immune activity[17-18]. In addition, key brain regions such as the prefrontal cortex, amygdala, and hippocampus have been implicated in immune modulation, likely through distributed neural circuits involving hypothalamic–pituitary–adrenal (HPA) axis signaling and autonomic (particularly vagal) pathways, although much of this evidence remains indirect or correlative. These regions not only process emotional and cognitive responses to stress but may also influence immune function through neural and neuroendocrine pathways. For example, the prefrontal cortex, which regulates higher-order cognitive functions, may influence

immune-related processes through modulation of stress hormone signaling[19]. The amygdala, involved in emotional processing, activates the HPA axis in response to stress, leading to increased cortisol release and subsequent immune modulation[20-21]. Similarly, the hippocampus, critical for memory and learning, has been shown to regulate inflammation and immune responses in both the CNS and peripheral tissues[22-23].

Despite advances in understanding these mechanisms, many questions remain. For instance, it is still unclear how neuroimmune interactions contribute to the pathogenesis of chronic diseases or how they influence disease progression in individual patients. This review aims to explore the neuroimmunological mechanisms linking psychological stress, depression, and immune responses. By examining how stress and depression influence immune function through neural pathways, we can better understand the bidirectional relationship between mental health and immune regulation. Furthermore, we will discuss how these interactions contribute to disease outcomes, with a focus on chronic inflammatory diseases, autoimmune disorders, and conditions such as cardiovascular disease and cancer. Recent research has highlighted the critical role of the gut–brain–immune axis in mediating the effects of psychological stress on immune function. The gut microbiota, comprising trillions of bacteria, viruses, and fungi, interacts bidirectionally with the central nervous system through neural, endocrine, and immune pathways. Alterations in gut microbial composition, known as dysbiosis, have been linked to heightened inflammation, changes in cytokine profiles, and modulation of immune cell activity. In addition, gut-derived metabolites such as short-chain fatty acids (SCFAs), tryptophan metabolites, and bile acids can influence both brain function and peripheral immunity. Psychological stress has been shown to disrupt microbial balance, leading to increased intestinal permeability ("leaky gut"), systemic inflammation, and altered HPA axis activity. Conversely, certain probiotics or dietary interventions can restore microbial homeostasis and ameliorate stress-induced immune dysregulation, suggesting a therapeutic potential for targeting the gut–brain–immune axis. This emerging perspective underscores the importance of considering not only neural and hormonal pathways but also microbial and intestinal mechanisms when exploring the neuroimmunological effects of stress and mood disorders. Ultimately, this review seeks to provide insights into how understanding the neuroimmune axis may lead to innovative therapeutic strategies for improving both psychological and physical health outcomes. Given the complexity of neuroimmune interactions, many of the

relationships described in this review likely reflect indirect and context-dependent mechanisms rather than direct causal effects.

2. Neuroimmune pathways: stress, depression and immunity

The connection between psychological stress, depression, and immune function is an area of growing interest in neuroimmunology. Both psychological stress and depression are associated with measurable changes in immune function, often accompanied by features of a chronic inflammatory state that affects the body's ability to fight infections, repair tissue, and regulate immune responses. We will discuss stress and depression influence immune function, focusing on CNS, ANS, and the role of key molecules such as cytokines, neuropeptides, and neurotransmitters.

2.1 The hypothalamic-pituitary-adrenal axis and stress-induced immune dysfunction

The HPA axis plays a central role in the body's response to stress. When an individual encounters a stressor, whether physical or psychological, the brain signals the hypothalamus to release CRH, which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH)[24]. ACTH, in turn, stimulates the adrenal glands to release cortisol, the primary stress hormone[25-26]. Cortisol has widespread effects on many bodily systems, including the immune system[27]. Cortisol is generally considered to be immunosuppressive because it dampens the activation of immune cells and reduces the production of pro-inflammatory cytokines. This is part of the body's adaptive response to stress, as chronic inflammation can be harmful[9]. However, when stress is chronic or prolonged, this feedback system becomes dysregulated. Although cortisol is classically immunosuppressive, sustained exposure to elevated glucocorticoid levels can lead to the development of glucocorticoid resistance, characterized by reduced sensitivity of glucocorticoid receptors in immune cells. As a result, the anti-inflammatory effects of cortisol are diminished, allowing pro-inflammatory signaling pathways to persist despite high circulating cortisol levels. This paradoxical state may provide a mechanistic explanation for the coexistence of impaired immune regulation and chronic low-grade inflammation observed in individuals with prolonged stress or depression. Consequently, HPA axis dysregulation reflects not only hypercortisolemia, but also altered receptor responsiveness and downstream signaling dynamics.[14-28]. Chronic inflammation is linked to the development of various diseases, including autoimmune disorders, cardiovascular disease, and cancer[29-30]. The immune system becomes less efficient at distinguishing between harmful invaders and the body's own tissues, leading to

autoimmune reactions. In such cases, stress-induced dysregulation of the immune response may contribute to disease progression.

2.2 The autonomic nervous system in stress and immune modulation

The ANS is another critical component of the body's response to stress. The ANS is composed of two branches: the SNS and PNS. These two branches work in concert to regulate involuntary physiological functions such as heart rate, digestion, and immune function. The SNS is the "fight or flight" branch of the ANS, activated during times of stress. Upon activation, The SNS can modulate immune responses through the release of catecholamines, and its effects on inflammation are context-dependent and receptor-specific. While sympathetic activation is often associated with pro-inflammatory cytokine production, activation of β 2-adrenergic receptors on immune cells can also exert anti-inflammatory effects depending on the cellular context and duration of stimulation[31]. This process is adaptive in acute situations, as inflammation is necessary to fight infections and repair damaged tissues. However, chronic SNS activation, as seen in prolonged stress, has been associated with sustained inflammation, which has been linked to a variety of chronic conditions, including cardiovascular disease, depression, and cancer[32]. In contrast, the PNS, particularly via vagal signaling, is generally associated with anti-inflammatory effects through mechanisms such as the cholinergic anti-inflammatory pathway; however, its immunomodulatory role is also influenced by context, target cell types, and signaling dynamics.[33]. This anti-inflammatory effect is crucial for maintaining immune homeostasis and preventing the harmful consequences of chronic inflammation. Dysfunction of the PNS, or an imbalance between the SNS and PNS, may contribute to immune dysregulation and the development of various stress-related diseases.

The interplay between the SNS and PNS is particularly evident in the regulation of inflammation. Recent studies have also highlighted the role of the vagus nerve in regulating immune responses through a mechanism known as the "cholinergic anti-inflammatory pathway." This pathway involves the activation of acetylcholine receptors on immune cells, such as macrophages, leading to the suppression of pro-inflammatory cytokine production[34]. Dysregulation of this pathway may contribute to the chronic inflammatory states observed in stress and depression, highlighting the importance of balancing the activity of the SNS and PNS in maintaining immune health[35].

2.3 Neurotransmitters and cytokines: bridging the nervous and immune systems

Neurotransmitters and cytokines serve as key mediators in communication between the brain and the immune system, but their interactions occur across distinct central and peripheral compartments. Neurotransmitters such as serotonin, dopamine, and norepinephrine, which are involved in regulating mood, cognition, and behavior, have been implicated in immune modulation. However, current evidence suggests that their effects on peripheral immune function are often indirect, context-dependent, and mediated through complex neuroendocrine and cellular signaling pathways rather than direct causal regulation[36-37]. Imbalances in neurotransmitter systems are a hallmark of depression and have been shown to affect immune function. For example, serotonin, often referred to as the “feel-good” neurotransmitter, is implicated in immune-related processes, primarily through indirect and context-dependent mechanisms. Serotonin receptors are present on immune cells such as lymphocytes and macrophages, and their activation has been associated with changes in the production of pro-inflammatory cytokines [38]. In depression, where serotonin levels are often dysregulated, this leads to increased inflammation and immune dysfunction. Moreover, serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have been shown to modulate immune cell activity[39]. Specifically, 5-HIAA promotes neutrophil recruitment through the G-protein-coupled receptor GPR35, highlighting the intricate link between serotonin metabolism and immune regulation[39]. Additionally, serotonin itself modulates the function of the HPA axis, further connecting it to the stress response and immune regulation[40]. Norepinephrine, another neurotransmitter that plays a critical role in the stress response, is produced by neurons in the sympathetic nervous system. Norepinephrine interacts with adrenergic receptors on immune cells and promotes the production of pro-inflammatory cytokines[41]. Dysregulation of norepinephrine signaling, which occurs in both chronic stress and depression, can lead to a hyper-inflammatory state, exacerbating immune-related conditions. In addition to central neurotransmission, peripheral neurotransmitter systems also contribute to immune regulation. For example, serotonin is stored in platelets and released upon activation, while immune cells themselves can synthesize and respond to monoamines, indicating that neurotransmitter-immune interactions occur at both central and peripheral levels.

Cytokines are signaling molecules that mediate communication between immune cells and are central to the regulation of immune responses. Under normal conditions, cytokines help orchestrate the body's defense mechanisms against infection and tissue injury. However, in chronic stress and depression, the production of pro-

inflammatory cytokines such as TNF- α , interleukin-1 β (IL-1 β), and IL-6 becomes dysregulated. Elevated levels of these cytokines are often found in individuals with depression and chronic stress and are thought to contribute to the low-grade inflammation seen in these conditions. For example, elevated levels of IL-6 are commonly observed in patients with major depressive disorder (MDD). Dysregulation of IL-6, both peripherally and in the brain, contributes to depression symptomatology by promoting inflammatory responses, and targeting IL-6 may offer new therapeutic avenues for diagnosing, treating, and preventing depression[42]. The "cytokine hypothesis" of depression suggests that chronic inflammation, as indicated by increased levels of pro-inflammatory cytokines, plays a central role in the pathogenesis of depression[43]. This theory is supported by studies showing that cytokines can influence brain function through peripheral-to-central signaling pathways as well as through central neuroinflammatory processes mediated by resident CNS cells, thereby affecting neurotransmitter metabolism, neurogenesis, and the integrity of brain regions involved in mood regulation, such as the prefrontal cortex and hippocampus [44]. However, clinical studies indicate that elevated inflammatory markers are present only in a subset of patients with depression, highlighting substantial heterogeneity in immune profiles and suggesting that the cytokine hypothesis may not be universally applicable. Furthermore, chronic inflammation is thought to contribute to the behavioral symptoms of depression, such as anhedonia, fatigue, and cognitive dysfunction.

Beyond its role in immune modulation, dopamine is a central component of the mesolimbic reward pathway, particularly involving projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), which are critically implicated in motivation and reward processing. In depression, reduced dopaminergic signaling within this circuit contributes to anhedonia, a core clinical feature of the disorder. Emerging evidence suggests that gut-derived signals, including microbial metabolites such as short-chain fatty acids and tryptophan metabolites, as well as vagus nerve-mediated pathways, can influence dopaminergic tone in the mesolimbic system. These signals may modulate neurotransmitter release, neuroinflammation, and synaptic plasticity within the NAc, thereby linking gut microbiota composition to reward-related behaviors and emotional regulation.

2.4 Neural regulation of immune function in depression

The neural regulation of immune function in depression is a key area of research in neuroimmunology. Rather than acting as isolated structures, these brain regions are increasingly understood as components of distributed neuroimmune circuits that

interact with endocrine and autonomic pathways. In particular, hypothalamic–pituitary–adrenal (HPA) axis signaling, sympathetic–parasympathetic balance, and vagus nerve–mediated pathways provide key routes through which neural activity is linked to peripheral immune modulation. Depression is characterized by alterations in brain structure and function, particularly in regions involved in emotion regulation, stress response, and cognition. Brain regions such as the prefrontal cortex, hippocampus, and amygdala are implicated in immune-related processes, likely through distributed neural circuits involving HPA axis signaling and autonomic pathways (Table 1), although much of the supporting evidence is indirect. Each of these regions plays a unique role in regulating emotional and physiological responses, and their dysfunction contributes to both depression and immune dysregulation.

2.4.1 Prefrontal Cortex

The prefrontal cortex (PFC) is responsible for higher-order cognitive functions such as decision-making, emotional regulation, and stress response. In depression, reduced activity in the PFC is thought to impair its ability to regulate emotional responses and stress. This hypofunctionality of the PFC may be associated with heightened sensitivity to stressors and an exaggerated inflammatory response[45]. The PFC is also involved in regulating the HPA axis, which controls the body's stress response[46]. This influence is likely mediated through integrated neuroendocrine and autonomic pathways, particularly via modulation of HPA axis activity and downstream immune signaling. When the PFC is less active, it is less able to inhibit the HPA axis, potentially contributing to prolonged activation of the stress response, which can contribute to chronic inflammation. As a result, immune cells may become chronically activated, promoting a persistent inflammatory state in individuals with depression.

2.4.2 Hippocampus

The hippocampus, a critical brain region for memory consolidation and stress regulation, plays a vital role in modulating immune function[47]. Chronic stress, a key factor in depression, has been shown to have a particularly detrimental effect on the hippocampus, leading to structural changes and reduced neurogenesis. In individuals with depression, these changes impair the hippocampus' ability to regulate the body's inflammatory response, contributing to sustained inflammation[48-49]. The hippocampus is closely connected to both the HPA axis and the immune system, and is therefore implicated in the regulation of inflammatory signaling, potentially through integrated neuroendocrine and immune pathways[50]. These interactions are thought to occur through circuit-level integration of stress-related neuroendocrine signaling and

immune feedback mechanisms. Under normal conditions, the hippocampus helps regulate the stress response by inhibiting the activation of the HPA axis once a stressor has passed. However, in depression, reduced hippocampal volume and activity disrupt this feedback loop, resulting in prolonged activation of the HPA axis and continuous production of pro-inflammatory cytokines[31]. This chronic inflammation contributes to immune system dysfunction, reinforcing the cycle of depression[51]. Furthermore, the hippocampus plays a crucial role in maintaining the balance between pro-inflammatory and anti-inflammatory signals in the body. When this regulatory function is impaired, as seen in depression, it leads to a chronic low-grade inflammatory state, which has been linked to both the behavioral symptoms of depression and increased susceptibility to various physical health conditions[52]. Thus, the hippocampus' dysfunction in depression significantly contributes to immune dysregulation, highlighting its central role in the neuroimmune axis.

2.4.3 Amygdala

The amygdala, a key brain region involved in emotional processing, particularly fear and anxiety, plays a critical role in the body's stress response. Under normal conditions, the amygdala is activated during stress, triggering the release of stress hormones like cortisol and adrenaline, which prepare the body for a "fight or flight" response. However, in depression, the amygdala becomes hyperactive, which contributes to heightened anxiety, emotional dysregulation, and exaggerated stress responses[53]. This overactivity in the amygdala is linked to a disruption in immune function. Studies have shown that the amygdala can influence immune responses through its interactions with the hypothalamus and other brain regions involved in the autonomic nervous system[54]. This effect is likely mediated through its connections with hypothalamic and brainstem circuits that regulate autonomic and endocrine outputs. Specifically, chronic activation of the amygdala in depression may promote sustained immune activation, leading to a pro-inflammatory state. This prolonged inflammation can exacerbate depressive symptoms and contribute to the heightened vulnerability of individuals with depression to stress-related diseases. Thus, the amygdala's role in both emotional regulation and immune modulation highlights its central involvement in the neuroimmune interactions that underpin depression. Together, these findings support a model in which neuroimmune regulation emerges from coordinated interactions across distributed neural circuits, rather than isolated brain regions.

Table 1 Brain regions, key functions, and immune system interactions

Brain Region	Key Functions	Immune System Interaction
Prefrontal Cortex	Decision-Making, Executive Function, Emotional Regulation	Modulates stress response, influences HPA axis activity
Amygdala	Fear, Emotional Processing, Stress Response	Activates HPA axis, promotes inflammation under chronic stress
Hippocampus	Memory, Learning, Spatial Navigation	Regulates glucocorticoid feedback, modulates inflammation
Substantia Nigra	Motor Control, Dopamine Production	Dopamine modulates immune cell activity (e.g., T cells)
Serotonin	Mood Regulation, Sleep, Appetite	Regulates immune cell function, impacts cytokine production
Dopamine	Reward, Motivation, Mesolimbic signaling (VTA–NAc pathway)	Influences T cell proliferation and cytokine release
Norepinephrine	Alertness, Arousal, Stress Response	Enhances pro-inflammatory responses via sympathetic activation
Cortisol	Stress Response, Metabolism	Suppresses immune activation, anti-inflammatory effects

The relationship between the brain and the immune system is bidirectional. Just as psychological stress and depression affect immune function, immune dysfunction can also impact brain health. Chronic inflammation, as seen in autoimmune disorders or chronic infections, have direct effects on the brain, leading to changes in mood, cognition, and behavior[14]. This bidirectional communication underscores the importance of understanding the complex interplay between the nervous system and the immune system in maintaining overall health. In depression, inflammation contribute to changes in brain structure and function, which, in turn, exacerbate depressive symptoms[55]. This feedback loop creates a vicious cycle that can be difficult to break without intervention. Moreover, the same immune dysregulation that contributes to depression may also increase the risk of other health conditions, including cardiovascular disease, diabetes, and cancer[13]. Thus, understanding how the neuroimmune axis operates in depression and other stress-related conditions may help identify novel therapeutic targets for treating both mental and physical health disorders.

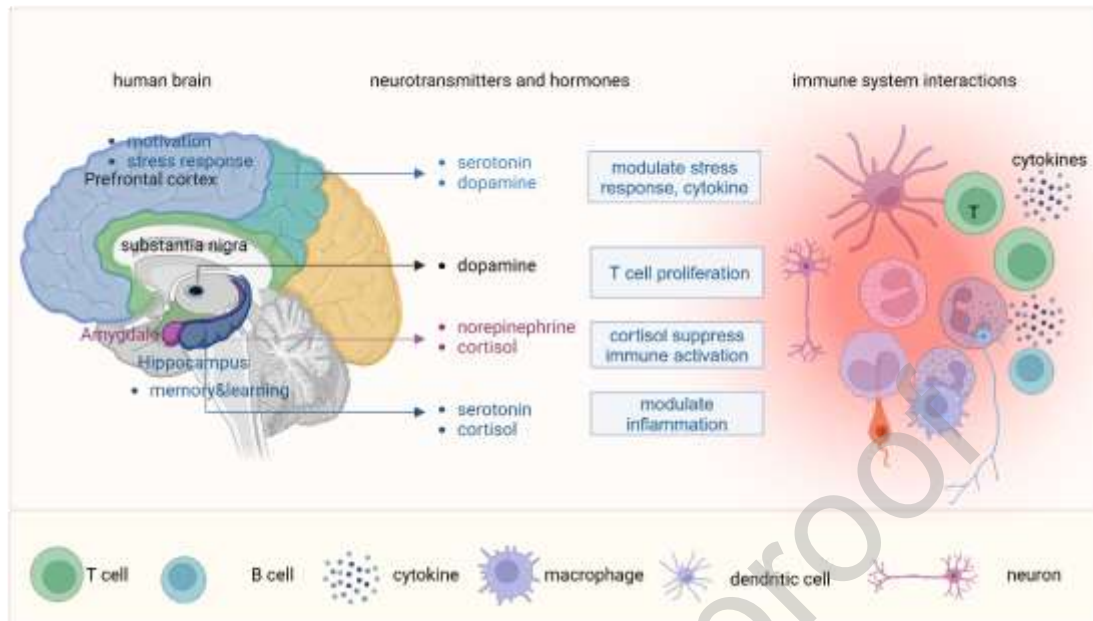


Figure 1. Neuroimmune interactions: brain, neurotransmitters, and immune function

This figure illustrates the bidirectional communication between key brain regions (prefrontal cortex, amygdala, hippocampus, substantia nigra), neurotransmitters (serotonin, dopamine, norepinephrine), cortisol, and the immune system. Dopaminergic signaling within mesolimbic pathways (e.g., ventral tegmental area–nucleus accumbens circuit) is particularly relevant for reward processing and anhedonia in depression. Brain regions modulate stress responses, cytokine production, and inflammation. Neurotransmitters influence immune cell activity, including T and B cells, macrophages, and dendritic cells. Cortisol released during stress regulates immune activation. This diagram highlights how psychological states, such as stress and motivation, impact immune function and contribute to disease outcomes. Key signaling pathways involved in neuroimmune communication, including cytokine-mediated signaling and receptor-specific interactions (e.g., dopamine and serotonin receptors on immune cells), are illustrated to highlight the mechanistic basis of these interactions.

3 Gut–Brain–Immune axis: neuroimmune modulation by microbiota and microbial metabolites

The gut–brain–immune axis represents a complex bidirectional communication network in which gut microbiota influence central nervous system CNS function and immunity through neural, metabolic, and immune-mediated pathways[56]. Increasing evidence indicates that microbial communities modulate microglial maturation, astrocyte activity, T cell differentiation, and cytokine profiles, ultimately shaping brain development, stress responses, and behavior[57]. Microbial metabolites such as short-chain fatty acids

(SCFAs), tryptophan derivatives, and secondary bile acids act as key mediators in this axis, linking diet, microbial composition, and host neuroimmune function[58]. Conversely, gut dysbiosis can disrupt these interactions, leading to neuroinflammatory disorders including multiple sclerosis, Parkinson's disease, autism spectrum disorder, and depression.

3.1 Gut Microbiota composition and immune modulation

The human gastrointestinal tract harbors a complex microbial ecosystem consisting of bacteria archaea viruses and fungi which collectively contribute to the maintenance of host homeostasis and immune function. Recent advances in high throughput sequencing and metagenomics have elucidated the specific roles of gut microbiota in regulating both innate and adaptive immunity[59].

Firmicutes and *Bacteroidetes* represent the predominant bacterial phyla in the human gut, with specific genera such as *Lactobacillus*, *Faecalibacterium*, *Bifidobacterium*, *Clostridium*, and *Prevotella* containing strains that have been shown to exert immunomodulatory effects; however, these effects are highly strain-specific and should not be generalized across species or genera.[60]. For instance *Faecalibacterium prausnitzii* has been shown to produce butyrate a short chain fatty acid SCFA that promotes regulatory T cell Treg differentiation through histone deacetylase inhibition and upregulation of Foxp3 expression in CD4 positive T cells[61]. In mouse models, colonization with *F. prausnitzii* or supplementation with butyrate increased the frequency of IL-10–producing Tregs in the lamina propria, leading to suppression of intestinal inflammation[62]. The anti-inflammatory effects of *F. prausnitzii* in intestinal epithelial cells are mediated, at least in part, by butyrate through Dact3 signaling[63].

Recent studies have highlighted the immunomodulatory effects of *Bifidobacterium longum*. In the intestinal lamina propria, *B. longum* promotes dendritic cells (DCs) to secrete anti-inflammatory cytokines, including IL-10, TGF- β 1, and GM-CSF, while suppressing pro-inflammatory cytokines such as IL-6 and TNF- α , thereby regulating immune responses[64]. Mechanistically, these effects involve inhibition of JAK and NF- κ B signaling and the subsequent promotion of naïve CD4⁺ T cell differentiation into Foxp3⁺ regulatory T cells (Tregs), enhancing systemic immune tolerance[65]. In mouse models, exosomes derived from *B. longum* NSP001 or colonization with *B. longum* BL-10 similarly increased Treg-associated cytokines (IL-10, TGF- β) and modulated Th1/Th2 balance, leading to reduced intestinal inflammation and improved immune homeostasis[66].

Moreover, specific bacterial components such as polysaccharide A (PSA) from *Bacteroides fragilis* can interact with Toll like receptor 2 (TLR2) on DCs to induce Treg proliferation and IL-10 secretion thereby modulating systemic immune responses[67]. In contrast certain

pathobionts such as *Enterococcus faecalis*, *Escherichia coli* and *Ruminococcus gnavus* have been associated with pro inflammatory states characterized by increased Th17 cell differentiation elevated IL-17a production and activation of NF- κ B signaling which may contribute to the pathogenesis of autoimmune diseases including multiple sclerosis rheumatoid arthritis and inflammatory bowel disease[68]. In addition metabolites produced by gut bacteria such as secondary bile acids including lithocholic acid and deoxycholic acid can influence the balance between pro inflammatory Th17 cells and anti inflammatory Tregs by activating the vitamin D receptor and farnesoid X receptor pathways[69].

Gut microbiota diversity itself has been correlated with immune resilience. Low diversity states often characterized by expansion of Proteobacteria and reduction of Firmicutes are associated with heightened susceptibility to infections impaired vaccine responses and increased systemic inflammation. Importantly, the gut microbiota also interacts with innate lymphoid cells ILCs in the intestinal mucosa ILC3 cells expressing ROR gamma t respond to microbial cues and SCFAs by secreting IL-22 which enhances epithelial barrier integrity and antimicrobial peptide production[70]. These interactions underscore the bidirectional relationship between the gut microbiota and host immune system which extends beyond local intestinal immunity to influence systemic immune responses. In germ free mice absence of microbiota results in impaired development of lymphoid tissues reduced IgA production decreased Th17 cell numbers and diminished NK cell cytotoxicity highlighting the necessity of commensal microbes in shaping the immune repertoire[71]. Collectively these findings demonstrate that specific gut bacterial taxa their metabolites and microbial associated molecular patterns orchestrate immune cell differentiation cytokine profiles and signaling pathways thereby modulating systemic immune responses and influencing susceptibility to inflammatory autoimmune and infectious diseases. Collectively, these findings demonstrate that gut microbiota influence immune function primarily through shared mechanisms, including microbial metabolite production, immune cell modulation, and microbial-associated molecular pattern signaling, thereby shaping systemic immune responses and susceptibility to inflammatory, autoimmune, and infectious diseases. However, these effects are often dependent on specific microbial strains and host context, highlighting the limitations of generalizing findings at the taxonomic level and underscoring the need to prioritize functional mechanisms over descriptive classification.

3.2 Neuroimmune communication mediated by the gut

The gut microbiota communicates with the central nervous system CNS through multiple neuroimmune pathways influencing brain development function and behavior (Figure 2). These effects involve both peripheral immune and metabolic signaling and central neuroinflammatory responses, which should be distinguished because they operate under

different regulatory constraints. This communication occurs via the modulation of immune cells cytokine profiles microbial metabolites and direct neural signaling primarily through the vagus nerve[72]. Recent studies have begun to identify more defined neuroimmune circuits, including vagal pathways and brainstem–immune interfaces, which provide more direct mechanistic links between neural activity and immune regulation[73]. However, much of the mechanistic evidence supporting these interactions is derived from preclinical models, and their direct translation to human systems remains to be fully established. Microbial dysbiosis alters microglial maturation and function in the brain leading to changes in synaptic pruning neuroinflammation and cognitive function[74]. In particular, germ free mice exhibit defects in microglial development characterized by reduced expression of CD11b Iba1 and MHC-II molecules which can be partially rescued by colonization with a complex microbiota[75-76]. However, it should be noted that germ-free models exhibit an underdeveloped immune repertoire and altered neuroanatomy, and therefore may not fully recapitulate microbiota-mediated modulation in an established adult host. Microglia in these models show impaired responses to immune challenges with LPS demonstrating that microbial signals are critical for innate immune training in the CNS.

Furthermore, specific gut bacteria influence neuroimmune interactions through the production of metabolites including short chain fatty acids SCFAs such as acetate propionate and butyrate. These SCFAs can cross the blood brain barrier BBB and act on microglia to modulate histone acetylation and the expression of anti inflammatory genes including IL-10 and arginase 1[77]. Additionally, SCFAs activate G protein coupled receptors including GPR41 and GPR43 on enteric neurons and immune cells leading to downstream modulation of CNS immune function[78]. Beyond SCFAs, microbial derived tryptophan metabolites including indole 3 propionic acid indole 3 acetic acid and kynurenine have been shown to regulate astrocyte activity microglial maturation and T cell trafficking to the CNS[79]. Kynurenine, produced through gut microbial metabolism and host indoleamine 2,3-dioxygenase (IDO) activity, can be further metabolized into both neuroactive kynurenic acid (KYNA) and quinolinic acid (QUIN), which exert opposing effects on neuronal function. KYNA acts as a neuroprotective metabolite by antagonizing NMDA receptors, whereas QUIN functions as a neurotoxic agonist that promotes excitotoxicity and neuroinflammation. Importantly, the balance between KYNA and QUIN production, rather than the absolute level of kynurenine alone, is increasingly recognized as a critical determinant of neuroimmune outcomes[80]. Studies in multiple sclerosis MS models have demonstrated that colonization with segmented filamentous bacteria SFB promotes Th17 differentiation in the gut which subsequently migrates to the CNS contributing to neuroinflammation while colonization with *Bacteroides fragilis* producing polysaccharide A can increase Treg numbers and IL-10 secretion leading to attenuation of

CNS autoimmunity[81].

In addition, microbial modulation of systemic cytokines such as $\text{TNF}\alpha$, IL-6 and IL-1- β affect BBB integrity and facilitate immune cell trafficking into the CNS thereby influencing neuroinflammatory processes[82]. Moreover, the vagus nerve provides a direct neural route for gut to brain signaling wherein microbial products such as LPS peptidoglycans and SCFAs activate enteroendocrine cells and afferent vagal fibers resulting in modulation of hypothalamic and brainstem circuits involved in stress responses mood regulation and autonomic function[83]. Importantly, microbial interventions including probiotics prebiotics and fecal microbiota transplantation FMT alter neuroimmune communication leading to changes in microglial activation cytokine profiles and behavioral outcomes in both animal models and clinical populations[84]. For example, administration of *Lactobacillus rhamnosus* JB-1 in mice resulted in increased GABA receptor expression in the brain, reduced anxiety-like behavior, and altered vagal-mediated cytokine expression; however, these findings are strain-specific and do not necessarily extend to other strains within the same species[85-86]. Collectively these findings provide compelling evidence that the gut microbiota communicates with the CNS through both immune mediated and neural pathways influencing microglial development astrocyte function T cell trafficking cytokine expression and behavioral outcomes and underscore the therapeutic potential of targeting gut microbiota for neuroimmune disorders.

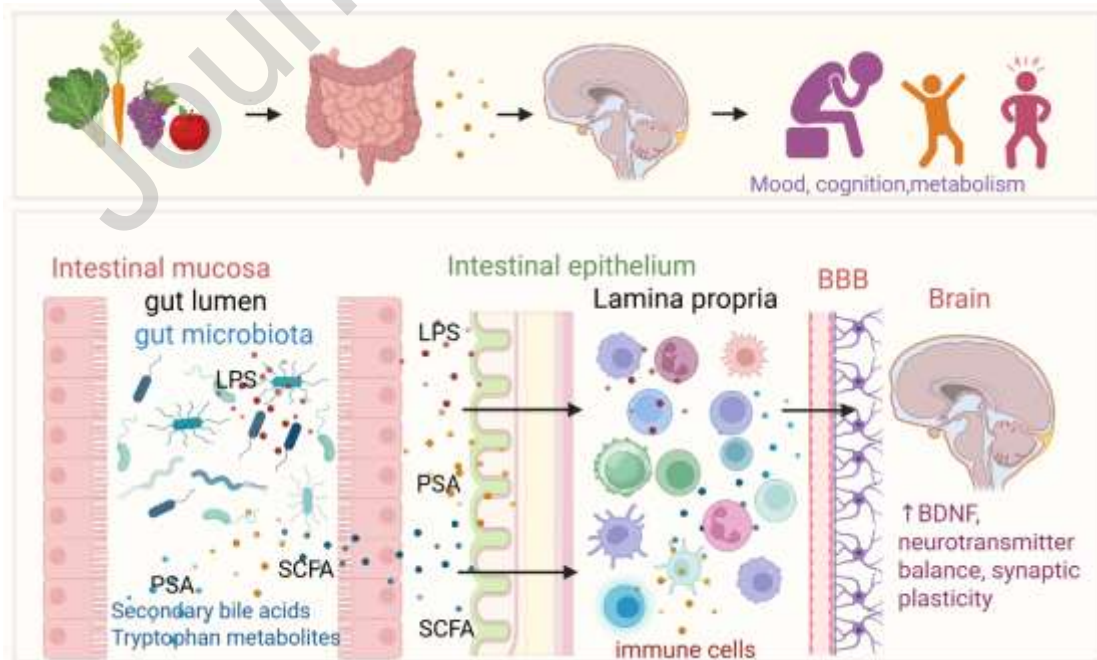


Figure 2. Microbial metabolites modulate neuroimmune function. SCFAs, tryptophan derivatives, and secondary bile acids produced by gut microbiota regulate immune cell differentiation and cytokine production in the gut (Tregs, Th17, DC, ILC3). These metabolites and systemic cytokines cross the BBB or act via neural pathways to influence microglial and astrocyte activity, impacting synaptic plasticity, neuroinflammation, and behavior. Pathobionts and LPS promote pro-inflammatory responses, demonstrating the balance between protective and pathogenic microbial influences on neuroimmune homeostasis. Mechanistic pathways, including vagal signaling, microbial metabolite-mediated effects, and immune cell activation, are highlighted to provide a more detailed representation of gut–brain–immune communication.

3.3 Impact of gut dysbiosis on neuroimmune disorders

Gut dysbiosis characterized by reduced microbial diversity and overgrowth of pathobionts has been implicated in the pathogenesis of multiple neuroimmune disorders including multiple sclerosis (MS), Parkinsons disease (PD), autism spectrum disorder (ASD), and major depressive disorder (MDD)[87]. Dysbiosis leads to alterations in microbial metabolites immune cell function and neuroinflammatory signaling which collectively disrupt the gut brain immune axis[88]. In MS patients decreased abundance of *F. prausnitzii* and *Bacteroides fragilis* has been associated with reduced SCFA levels impaired Treg differentiation and increased pro inflammatory Th17 responses contributing to CNS autoimmunity[89]. Similarly, in PD patients reduced *Prevotella* and increased *Enterobacteriaceae* correlate with decreased production of SCFAs and increased systemic inflammation including elevated TNF α , IL-6 and IL-1 β which may exacerbate neurodegeneration through microglial activation and oxidative stress[90-91]. Furthermore, in ASD children decreased *Bifidobacterium* and increased *Clostridium* species have been linked to elevated gut permeability altered tryptophan metabolism increased kynurenine pathway activation and neuroinflammation affecting social behavior and cognitive function[92]. Clinical trials in MDD and ASD patients using *Lactobacillus rhamnosus* *Bifidobacterium longum* and multi strain probiotics have demonstrated improvements in depressive symptoms anxiety social behavior and inflammatory markers highlighting translational potential[93]. In addition, Dysbiosis induced by high-fat diet or chronic stress has been associated with increased intestinal permeability and the translocation of microbial products such as lipopolysaccharide (LPS) into systemic circulation. However, this process is tightly regulated by host defense mechanisms. Notably, the liver functions as a critical “first-pass” filter, where Kupffer cells clear circulating LPS through phagocytosis and receptor-mediated uptake[94]. In parallel, intestinal alkaline phosphatase (IAP) detoxifies LPS by dephosphorylating its lipid A moiety, thereby reducing its immunostimulatory activity[95].

Therefore, systemic inflammation may not solely arise from increased epithelial

permeability, but also from impaired clearance and detoxification pathways. Disruption of these regulatory systems may amplify the inflammatory consequences of microbial translocation, leading to activation of TLR4 signaling in immune cells and microglia, and subsequent pro-inflammatory cytokine production and neuroinflammation.

[96]. In rodent models, depletion or absence of the gut microbiota—through broad-spectrum antibiotics or germ-free conditions—disrupts neuroimmune development. Germ-free animals display defective microglial maturation, impaired myelination, and altered synaptic pruning, resulting in behavioral abnormalities. Importantly, colonization with a complex microbiota or fecal microbiota transplantation (FMT) from healthy donors can restore microglial function and behavioral phenotypes, supporting a causal role for the microbiota in brain–immune axis regulation[97-98], although these findings are largely derived from germ-free or microbiota-depleted animal models and may not fully reflect modulation of an already established adult human microbiome, with human evidence remaining largely correlational and variable. These studies collectively indicate that gut dysbiosis exerts profound effects on neuroimmune homeostasis through specific microbial taxa alterations metabolic changes immune cell modulation and neural signaling disruptions providing a mechanistic framework for microbiota targeted therapeutic strategies.

4. Depression and immune dysregulation: cytokine alterations and immune cell dysfunction

Depression is a multifaceted psychiatric disorder with profound effects on both mental and physical health. Individuals with depression frequently exhibit immune dysregulation, which contributes to a chronic inflammatory state. This section explores the psychological mechanisms underlying depression, the relationship between depression and immune system markers, and the role of chronic low-grade inflammation in the pathogenesis of depression, as well as the neural pathways that link depression, stress, and immune dysfunction.

4.1 Neurotransmitter imbalances and their impact on immune function

Depression is commonly associated with disruptions in neurotransmitter systems, particularly serotonin, dopamine, and norepinephrine. These imbalances not only affect mood and cognition but also influence immune function, creating a complex interplay between the CNS and the immune system.

4.1.1 Serotonin

Serotonin, often referred to as the "feel-good" neurotransmitter, plays a crucial role in mood regulation, appetite control, and sleep. In depression, serotonin levels are frequently dysregulated, leading to alterations in mood, behavior, and cognitive processes[99]. Serotonin receptors are expressed on various immune cells, including lymphocytes and macrophages, and serotonin has been shown to modulate the production of pro-inflammatory cytokines[100]. However, much of this evidence is derived from experimental or peripheral systems, and direct causal links between central serotonin signaling and systemic immune regulation remain incompletely understood. Individuals with depression exhibit reduced serotonin levels, which lead to immune system changes that favor inflammation. In particular, lower serotonin levels are associated with higher circulating levels of inflammatory cytokines, such as TNF- α , IL-6, and C-reactive protein (CRP). These cytokines, which are typically produced during inflammatory responses, create a feedback loop in which inflammation exacerbates depression, leading to a vicious cycle[4].

The mechanisms underlying serotonin's role in immune modulation are multifaceted. First, serotonin receptors on immune cells (e.g., 5-HT_{1A} on T cells and 5-HT_{2A} on macrophages) regulate immune cell activity. Reduced serotonin levels impair receptor signaling, leading to increased production of pro-inflammatory cytokines and decreased anti-inflammatory responses[101]. Second, serotonin deficiency disrupts the HPA axis, resulting in elevated cortisol levels. Chronic cortisol exposure induces glucocorticoid resistance in immune cells, further promoting inflammation[102]. Third, Serotonin dysregulation shifts tryptophan metabolism toward the kynurenine pathway, leading to the generation of downstream metabolites with divergent effects, including neuroprotective kynurenic acid (KYNA) and neurotoxic quinolinic acid (QUIN). An imbalance favoring QUIN over KYNA has been associated with neuroinflammation and neuronal dysfunction[103-104].

These inflammatory cytokines, in turn, create a feedback loop that exacerbates depression. For example, IL-6 and TNF- α cross the blood-brain barrier and activate microglia, leading to neuroinflammation and further serotonin depletion[105]. This vicious cycle of serotonin deficiency, immune dysregulation, and chronic inflammation contributes to the persistence of depressive symptoms and increases the risk of comorbid physical health conditions, such as cardiovascular disease and diabetes.

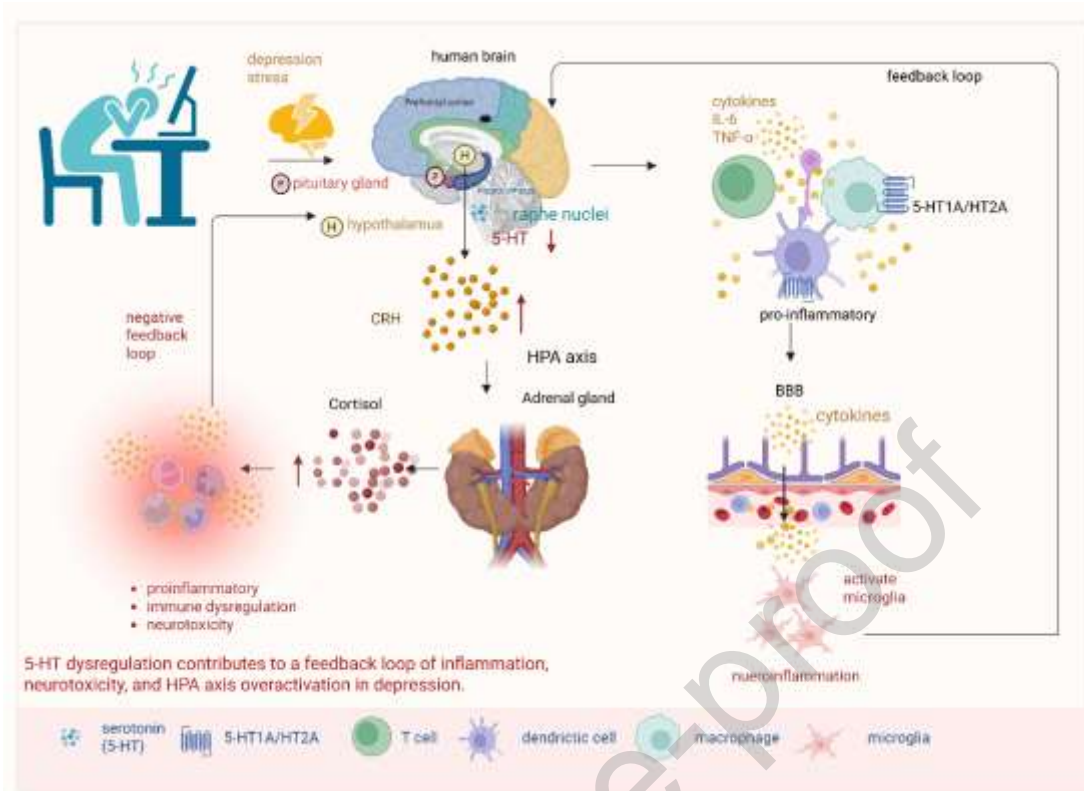


Figure 3 Mechanistic role of serotonin in immune dysregulation and HPA axis activation in depression

This diagram illustrates the multifaceted role of serotonin (5-HT) dysregulation in the pathophysiology of depression, highlighting its effects on the immune system and the hypothalamic-pituitary-adrenal (HPA) axis. Reduced serotonin levels, originating primarily from the raphe nuclei in the brainstem, lead to impaired signaling through serotonin receptors (5-HT1A, 5-HT2A) on immune cells such as T cells and macrophages. This disruption contributes to increased production of pro-inflammatory cytokines including TNF- α , IL-6, and CRP. These cytokines cross the blood-brain barrier and activate microglia in the central nervous system, promoting neuroinflammation and further reducing serotonin availability—thus establishing a vicious cycle. Additionally, elevated cytokine levels stimulate the HPA axis, beginning with the hypothalamus releasing CRH, followed by pituitary secretion of ACTH, and culminating in cortisol release from the adrenal glands. Chronic elevation of cortisol leads to glucocorticoid resistance in immune cells and contributes to immune dysregulation and neurotoxicity, including hippocampal damage and impaired neurogenesis. Negative feedback from cortisol to the hypothalamus and pituitary is indicated but may become dysregulated in chronic stress or depressive states. Together, this pathway illustrates the bidirectional interaction between neurotransmitter imbalance, immune activation, and stress hormone regulation in major depressive

disorder.

4.1.2 Dopamine

Dopamine is another key neurotransmitter involved in mood regulation, motivation, and reward processing. In depression, dopaminergic dysfunction leads to anhedonia (the inability to experience pleasure), one of the core symptoms of depression[106]. Dopamine also plays a role in modulating immune responses. Dopamine receptors are found on immune cells such as T-cells and macrophages, and dopamine has been shown to influence the production of cytokines like IL-10, an anti-inflammatory cytokine. Dopamine influences Treg function by modulating their proliferation and suppressive activity, and through dopamine receptors expressed on immune cells, it may influence Treg-mediated immune suppression and the balance between pro-inflammatory and anti-inflammatory signals[107]. A lack of dopamine activity, as seen in depression, may disrupt this balance and promote a pro-inflammatory immune response. The altered dopamine signaling in depression may lead to an increased susceptibility to chronic inflammation and immune dysfunction, further contributing to the immune dysregulation observed in depressed individuals.

However, immune alterations in depression are highly heterogeneous, and findings across studies are variable. Changes in T cell subsets, including Th17 and Treg populations, may differ depending on factors such as sex, age, comorbidities, and treatment status, and therefore a uniform pattern of immune dysregulation cannot be assumed.

4.1.3 Norepinephrine

Norepinephrine, produced primarily in the brainstem and adrenal glands, is involved in regulating the body's "fight or flight" response to stress[108]. In depression, norepinephrine levels are often low, which can impair the body's ability to mount an appropriate immune response to stressors. Additionally, norepinephrine activates adrenergic receptors on immune cells, leading to the release of pro-inflammatory cytokines. This contributes to a pro-inflammatory state, which, in turn, may exacerbate the symptoms of depression and create a cycle of immune dysregulation[109]. Low norepinephrine levels in depression also affect the HPA axis, further compounding immune dysfunction and contributing to chronic low-grade inflammation. These neurotransmitter imbalances contribute to the neurobiological underpinnings of depression and influence immune function by altering the signaling pathways that regulate immune cell activity.

4.2 Crosstalk between immune markers and depression

One of the most significant physiological changes observed in depression is the alteration of cytokine profiles. Cytokines are small signaling molecules that mediate communication between immune cells and are crucial in the regulation of immune responses. In healthy individuals, cytokine production is tightly regulated to ensure an appropriate immune response. However, in depressed individuals, there is often an imbalance in cytokine production, leading to a chronic inflammatory state.

4.2.1 Pro-inflammatory cytokines

Depression is consistently associated with increased levels of pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6. These cytokines play a central role in immune responses by promoting inflammation and facilitating the immune system's response to infection or injury. In individuals with depression, the elevated production of these cytokines is thought to contribute to the inflammatory environment that exacerbates depressive symptoms. Studies have found that individuals with MDD exhibit significantly higher levels of IL-6 and CRP, which are biomarkers of inflammation. Chronic exposure to these pro-inflammatory cytokines can affect brain function by altering neurotransmitter metabolism, reducing neurogenesis, and impairing the functioning of brain regions involved in mood regulation, such as the hippocampus and prefrontal cortex.

4.2.2 Immune cell dysfunction

Depression is also associated with alterations in the function of various immune cells. For example, depressed individuals often exhibit increased numbers of activated monocytes and macrophages, which are key producers of pro-inflammatory cytokines[10-110]. These cells play an essential role in the immune response to infection and tissue damage, but when chronically activated, they contribute to persistent inflammation. T-cells, which are involved in adaptive immunity, also show altered function in depression[111]. In particular, T-helper 1 (Th1) cells, which promote cellular immune responses, are often upregulated in depressed individuals, further enhancing the inflammatory response[112]. Moreover, the function of natural killer (NK) cells, which are responsible for recognizing and killing infected or tumor cells, is impaired in depression[113]. This impaired immune surveillance can make individuals more susceptible to infections and diseases, including cancer. Reduced NK cell activity is often observed in depressed patients, highlighting the impact of mood disorders on immune cell function and overall immune competence. The dysregulated immune response in depression not only increases susceptibility to illness but also plays a role

in the pathogenesis of other comorbid conditions, such as cardiovascular disease, autoimmune disorders, and cancer. As chronic inflammation becomes a persistent feature in depression, the immune system's ability to resolve inflammation and maintain homeostasis becomes compromised, leading to a maladaptive immune response that contributes to disease development.

Table 2. Summary of immune markers and cytokine profiles in depression.

Immune marker/cytokine	Increased/decreased in depression	Associated immune cell	Functional implications
C-reactive protein (CRP)	Increased	Macrophages, endothelial cells	Marker of systemic inflammation, associated with chronic inflammatory state.
Interleukin-6 (IL-6)	Increased	Monocytes, T-cells, macrophages	Pro-inflammatory cytokine, linked to mood disorders and inflammation in depression.
Tumor Necrosis Factor-alpha (TNF- α)	Increased	Macrophages, T-cells	Major pro-inflammatory cytokine, involved in depression-induced immune dysregulation.
Interleukin-10 (IL-10)	Decreased	Regulatory T-cells, macrophages	Anti-inflammatory cytokine, reduced levels observed in depression, contributing to immune imbalance.
Interleukin-1 β (IL-1 β)	Increased	Monocytes, macrophages	Key mediator in inflammation, elevated in depression and linked to "sickness behavior." Involved in inflammatory response, their increased numbers in depression contribute to chronic inflammation.
T-helper 17 (Th17) cells	Increased	T-cells	Reduced Treg activity observed in depression, leading to impaired immune regulation.
Regulatory T-cells (Tregs)	Decreased	T-cells	

Interferon-gamma (IFN- γ)	Increased	T-cells, NK cells	Cytokine involved in inflammation, increased in depression, exacerbating immune dysfunction.
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5. Clinical implications

The intricate relationship between psychological states, particularly depression and stress, and immune responses has significant implications for understanding and treating chronic diseases. Psychoneuroimmunology (PNI) research highlights how emotional and mental well-being influence physical health, offering insights for improving patient care across conditions such as autoimmune disorders, cardiovascular disease (CVD), and cancer[114-115]. Chronic stress and depression are associated with immune dysregulation and have been linked to worse outcomes in autoimmune diseases such as rheumatoid arthritis and lupus, although these relationships are complex and not strictly causal[50]. In CVD, depression and stress are associated with immune dysregulation and may contribute to atherosclerosis and increased cardiovascular risk, including heart attacks and strokes, partly through elevated pro-inflammatory cytokines.[116]. Similarly, in cancer, depression has been associated with poorer prognosis, potentially through mechanisms involving altered immune surveillance and increased inflammation, potentially weakening the body's ability to combat tumor growth. Therapeutic approaches that target both mental health and immune function, such as cognitive-behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), and pharmacological interventions, may improve outcomes by reducing inflammation and enhancing immune regulation. However, current clinical trials of microbiota-based interventions, including probiotics and prebiotics, are limited by small sample sizes, strain specificity, and inconsistent outcomes, which constrain their translational applicability. These findings underscore the importance of integrating mental health care into the treatment of chronic diseases, offering a holistic approach to improving both psychological and physical health. However, clinical responses to anti-inflammatory therapies in depression have been inconsistent, underscoring the heterogeneity of immune involvement and the need for patient stratification in future therapeutic approaches.

Additionally, emerging research on the gut–brain–immune axis provides further insight into the mechanisms linking psychological states to immune function. Alterations in gut microbiota composition, often induced by chronic stress or depression, can lead to

dysbiosis, affecting both local gastrointestinal immunity and systemic immune responses. Specific bacterial genera such as *Bifidobacterium*, *Lactobacillus*, *Prevotella*, and *Akkermansia* have been implicated in modulating the production of short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate, which influence regulatory T cell (Treg) activity and reduce systemic inflammation. Moreover, microbial metabolites such as tryptophan-derived kynurenine and serotonin precursors can cross the blood–brain barrier, affecting neuroinflammation, microglial activation, and HPA axis function. Dysbiosis-induced increases in lipopolysaccharide (LPS) levels may trigger Toll-like receptor 4 (TLR4) signaling, amplifying NF- κ B–mediated pro-inflammatory cytokine production, which has been linked to depression severity and cognitive dysfunction. Understanding the gut–brain–immune crosstalk not only elucidates the bidirectional influence of mood disorders on immune responses but also highlights potential intervention points, including probiotics, prebiotics, dietary modifications, and microbiota-targeted therapies to restore immune homeostasis and improve clinical outcomes.

5.1 Treatment approaches

The implications of the mind-immune connection extend to various treatment approaches. Understanding how depression and stress modulate immune responses has important ramifications for therapeutic strategies that target both psychological well-being and immune health.

5.1.1 Mental health interventions

The integration of mental health interventions into clinical practice is crucial for improving both mental and immune health. Cognitive-behavioral therapy (CBT), a common and effective treatment for depression and anxiety, helps patients learn to manage stress and negative thought patterns, leading to improved psychological well-being[117-118]. Furthermore, CBT reduces levels of inflammatory cytokines, highlighting its potential to influence immune function[119]. Recent studies have shown that CBT not only reduces symptoms of depression but also normalizes immune biomarkers such as IL-6 and CRP[120]. For example, in patients with rheumatoid arthritis, CBT has been linked to lower disease activity and fewer flare-ups, likely due to its ability to suppress stress-related immune activation[121]. In cancer patients, CBT has been shown to improve natural killer (NK) cell activity, which plays a crucial role in tumor surveillance and immune defense. Recent studies also suggest that CBT and other behavioral interventions may indirectly modulate gut microbiota composition and its metabolite production, contributing to improved gut–brain–immune homeostasis

and further reducing systemic inflammation. These findings suggest that mental health therapies can have direct physiological impacts beyond mood stabilization. By addressing the root psychological causes of immune dysregulation, such interventions may enhance the body's ability to respond to illness, reduce inflammation, and promote healing.

5.1.2 Antidepressants and immune function

Antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are commonly used to treat depression and anxiety[122]. These medications work by increasing the levels of serotonin and norepinephrine in the brain, which in turn improve mood and emotional regulation. Beyond their psychological effects, SSRIs and SNRIs may have immunomodulatory properties as well[123]. For instance, SSRIs have been shown to reduce pro-inflammatory cytokines in patients with depression, suggesting that these medications can help mitigate the immune dysfunction associated with the disorder[124-125]. However, the full range of antidepressant effects on immune function remains an area of active research, and there is a need for further studies to understand how different classes of antidepressants influence the immune system. Emerging evidence indicates that certain SSRIs, such as fluoxetine and sertraline, can inhibit microglial activation and suppress the production of neurotoxic metabolites in the kynurenine pathway, suggesting neuroprotective and anti-inflammatory roles[126]. Additionally, a 2022 meta-analysis found that SSRI treatment was associated with lower peripheral levels of TNF- α and IL-1 β , particularly in patients with treatment-responsive depression[127-128]. Interestingly, some preclinical studies indicate that SSRIs may also influence gut microbiota composition and metabolite signaling, suggesting a possible dual effect on both central and peripheral immune regulation via the gut-brain-immune axis. Novel antidepressants such as ketamine and esketamine, though primarily investigated for rapid mood relief, are also being studied for their effects on neuroinflammation and synaptic plasticity[129]. This growing body of research opens the door to dual-purpose psychiatric medications that address both mood and immune dysfunction.

5.1.3 Mindfulness and stress reduction practices

Mindfulness-based practices such as meditation, yoga, and MBSR have been shown to be effective in reducing stress and improving emotional well-being[130]. These practices also influence immune function by reducing cortisol levels and enhancing parasympathetic nervous system activity[131]. Mindfulness has been found to reduce

the production of pro-inflammatory cytokines and enhance immune cell function, offering a holistic approach to improving both mental and immune health[132-133]. Incorporating such practices into treatment regimens for depression and chronic disease management may provide additional benefits by not only alleviating psychological symptoms but also improving the body's ability to regulate immune responses. For example, an 8-week MBSR program was found to significantly reduce levels of IL-6 and increase anti-inflammatory cytokines such as IL-10 in patients with generalized anxiety disorder[134]. In breast cancer survivors, regular yoga practice led to decreased NF- κ B expression and improved immune recovery post-chemotherapy[135]. Recent research further suggests that mindfulness and stress reduction practices can positively influence gut microbiota diversity, enhance SCFA production, and reduce LPS-mediated inflammation, thereby supporting systemic immune regulation via the gut–brain–immune axis. Neuroimaging studies have further shown that long-term meditators exhibit decreased amygdala reactivity and increased prefrontal cortex activity—brain regions closely linked to both emotional regulation and HPA axis control. These physiological shifts underscore the biological plausibility of mindfulness as a therapeutic tool for psychoneuroimmune regulation.

6. Conclusions and perspectives

In this review, we have explored the complex and bidirectional relationship between depression, stress, and immune dysregulation. Depression is associated with changes in immune cell function, chronic low-grade inflammation, and altered cytokine profiles. The underlying neural pathways—spanning brain regions like the prefrontal cortex, amygdala, and hippocampus—play a critical role in modulating these immune responses. Neurotransmitters such as serotonin and norepinephrine also significantly influence immune function, adding another layer of complexity to the interplay between the brain and the immune system. Furthermore, the autonomic nervous system regulates immune responses during periods of stress and depression, with imbalances between the sympathetic and parasympathetic branches contributing to chronic inflammation. In addition, the emerging evidence on the gut–brain–immune axis emphasizes that mental health, immune regulation, and gut microbiota are tightly interconnected. Dysbiosis in the gut microbiome, characterized by reduced beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* and increased opportunistic pathogens, can exacerbate systemic inflammation through mechanisms including increased intestinal permeability, lipopolysaccharide (LPS)-induced TLR4 signaling, and altered short-chain fatty acid (SCFA) production. Microbial metabolites such as butyrate and tryptophan-derived kynurenine further modulate Treg differentiation,

microglial activation, and HPA axis function, providing a mechanistic link between psychological stress and immune dysregulation. These findings underscore that mental health interventions may exert systemic benefits not only through central nervous system pathways but also by restoring gut microbial balance and associated immune homeostasis.

The implications of understanding the relationship between mental health and immune function are profound for public health. As depression and stress are highly prevalent, with millions of people affected worldwide, addressing the psychological causes of immune dysregulation could significantly improve both mental and physical health. Chronic diseases, particularly those associated with inflammation could benefit from integrated treatment approaches that target both the immune system and mental health. Public health policies should emphasize the importance of mental health care, particularly in the context of chronic disease prevention and management.

Despite the significant progress made in understanding the psychoneuroimmunological pathways linking stress, depression, and immune dysfunction, much remains to be learned. Future research should focus on elucidating the precise molecular mechanisms involved in this relationship, identifying biomarkers for immune dysfunction in depression, and developing integrated treatment models that address both mental and physical health. By advancing our understanding of how psychological and immune systems interact, we can develop more effective strategies for preventing and treating chronic diseases, ultimately improving overall public health outcomes. Importantly, many of the interactions described here are likely to reflect indirect, context-dependent mechanisms, and further circuit-level and mechanistic studies will be required to establish causal relationships.

Abbreviations

5-HT1A: 5-Hydroxytryptamine 1A receptor

5-HT2A: 5-Hydroxytryptamine 2A receptor

5-HIAA: 5-hydroxyindoleacetic acid

ACTH: adrenocorticotrophic hormone

ANS: autonomic nervous system

BBB: *blood–brain barrier*

BDNF: *brain-derived neurotrophic factor*

CBT: Cognitive-behavioral therapy

CNS: central nervous system

CRH: corticotropin-releasing hormone
CRP: C-reactive protein
CVD: cardiovascular disease
DC: *dendritic cell*
HPA: hypothalamic-pituitary-adrenal
IL-6: interleukin-6
IL-10: Interleukin-10
ILC3: *type 3 innate lymphoid cell*
IFN- γ : Interferon-gamma
IL-1 β : interleukin-1 β
LPS: *lipopolysaccharide*
MBSR: mindfulness-based stress reduction
MDD: major depressive disorder
NK: natural killer
PNI: Psychoneuroimmunology
PNS: parasympathetic nervous system
PSA: *polysaccharide A*
SCFA: *short-chain fatty acids*
SNS: sympathetic nervous system
SNRIs: serotonin-norepinephrine reuptake inhibitors
SSRIs: selective serotonin reuptake inhibitors
TNF- α : tumor necrosis factor-alpha
Th1: T-helper 1
Th17: T-helper 17
Tregs: Regulatory T-cells

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Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

K.Z and Y.L organized the article writing and critically modified the manuscript. J.Z wrote the manuscript. All authors read and approved the manuscript.

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