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How do Chronic Psychosocial Stressors Induce Inflammation and Alter Brain Function to Shape Mood and Behavioural Adaptation?

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ABSTRACT

Chronic psychosocial stress is unevenly distributed in populations and contributes to health disparities, yet little is known about biological vulnerability to social stressors at an individual level. This narrative review aims to examine the evidence on chronic psychosocial stress as a driver of inflammation and its role in neurobiology, mood, and behaviour.

We reviewed data from primary human studies, human experimental challenge studies, review articles on the topic, and animal studies in which human evidence is lacking. Using these studies, we discussed the mechanisms by which inflammation could drive neurobehavioural abnormalities related to depression and mood. Chronic psychosocial stress has been associated with altered glucocorticoid signalling and inflammatory changes, although the extent to which glucocorticoid resistance mediates the relationship between chronic stress and persistent inflammation remains uncertain.

Pro-inflammatory cytokines may affect multiple components of the central nervous system, including blood-brain barrier function, vagal signalling, microglial activity, and the kynurenine pathway, contributing to depression-related symptoms, anhedonia, fatigue, and motivational deficits. Human experimental challenge studies provide particularly informative evidence on the mechanism by which peripheral inflammation affects the central nervous system, highlighting the dysregulation of reward circuitry. In both animals and humans, there is evidence that individual differences in inflammatory response and baseline pro-inflammatory load contribute to variability in behaviour and response to treatment, highlighting the need to consider interindividual differences when studying the effects of inflammation on the brain.

While individual biological links are empirically supported, connecting chronic social adversity to central neuroinflammation relies on an integrated conceptual framework that explicitly distinguishes mechanisms directly demonstrated in human stress paradigms from those inferred across distinct experimental and clinical domains.

INTRODUCTION

Chronic stress can stem from social, economic, and societal factors. Financial difficulties, prejudice, and pressure to conform to social standards are examples of factors that may negatively influence one's feelings of stress (Pearlin, 1989; Meyer, 2003; Dickerson & Kemeny, 2004). Individuals who face these stressors repeatedly accumulate greater and more prolonged stress than others, and the effects of psychosocial stress are not distributed equally across the population; these inequalities are well documented in the literature (Williams & Mohammed, 2009). Critically, these social experiences do not remain purely psychological. The brain registers them as threats and translates them into physiological signals through the body's stress-response systems, meaning that social disadvantage can leave a measurable biological trace. Tracing that translation, from social and psychological experience to the biological changes it produces, is the focus of this paper.

This paper investigates the question of how chronic psychosocial stressors induce inflammation and alter brain function to shape mood and behavioural adaptation. Answering it requires understanding the HPA axis: under physiological stress, this system is adaptive and helps the body return to baseline once the stressor has ended, but in chronic stress, this return to baseline is thwarted (McEwen, 1998).

The paper is divided into six sections. The first section discusses background information on psychosocial stress and the two stress response systems, namely, the HPA axis and the sympathetic nervous system. The second section discusses the HPA axis in relation to the CRH-ACTH-cortisol pathway as well as the onset of glucocorticoid resistance. The third section looks at glucocorticoid resistance and increased cytokine levels, distinguishing findings from stress-exposed groups from evidence drawn from studies of people with autoimmune diseases or depression. The fourth section explores how peripheral inflammation may affect the brain through changes in the blood–brain barrier, vagal signalling, and microglial activation, noting where the evidence comes from animal studies of stress and where it comes from human observational research. The fifth section explores how these neuroinflammatory mechanisms shape mood and behavioural adaptation. The final section of the paper presents concluding remarks about the implications and limitations of the proposed model between chronic psychosocial stress, inflammation, and brain functioning. Notably, although each of the individual stages has a strong scientific backing, the full chain itself constitutes a conceptual model and not a linear causal link that has been proven.

METHODS

The sources for this narrative literature review were identified through three steps. First, to understand the conceptual framework of the present manuscript and establish the background link between chronic psychosocial stress, HPA axis dysregulation, and upstream immune activation, relevant review articles were evaluated to identify the key biological processes connecting chronic stress, inflammation, and the brain. Second, a PubMed database search was performed on August 3, 2026, to identify relevant primary

literature. The search strategy aimed to identify the most relevant recent studies reporting mechanisms and outcomes related to the topic of this literature review. Thus, the PubMed search was limited to articles published in 2024 and later and restricted to the species category "human." Animal studies were selectively included when human mechanistic data were lacking or ethically unfeasible to obtain. Accordingly, this review used a targeted mechanistic search strategy rather than a comprehensive search of the entire proposed psychosocial stress–inflammation–brain pathway.

The following search terms were used: interventions that could induce or modulate inflammation (lipopolysaccharide/endotoxin, interferon, tumour necrosis factor (TNF) inhibitors, cyclooxygenase-2 (COX-2) inhibitors, typhoid vaccination) and depression, mood, affect, and sickness behaviour. The search strategy excluded articles with the review publication type. After screening the titles and abstracts of 165 results, 12 primary human studies were selected.

The inclusion criteria prioritised articles employing experimental or therapeutic interventions to establish a causal relationship between inflammation and mood, motivation, anhedonia, affect, or sickness behaviour. Additionally, the selection criteria included articles reporting quantitative results and evaluating primary neurobehavioural or biological variables. The sources were identified through backward citation searching, following the references of the included articles and reviews.

While experimental immune challenges establish causal proof-of-mechanism between inflammation and neurobehavioural outcomes, these acute models induce rapid, high-amplitude cytokine surges distinct from the low-grade, persistent inflammation produced by chronic psychosocial stress. Lastly, in addition to the 12 primary studies, sources were identified through specific database searches for particular mechanisms or concepts, resulting in a total of 35 references. The selection of supplementary sources for this narrative literature review was based on conceptual relevance and the strength of evidence rather than strict inclusion-exclusion criteria.

To distinguish biological processes directly demonstrated in chronic psychosocial stress from those inferred by integrating complementary lines of evidence, reviewed literature was evaluated across four explicit streams: (1) direct human chronic stress studies (e.g., in vitro glucocorticoid insensitivity in parental caregivers); (2) acute experimental immune challenges in humans (e.g., LPS/endotoxin administration, typhoid vaccination, interferon-alpha therapy); (3) clinical population cohorts (e.g., Major Depressive Disorder or systemic lupus erythematosus patients); and (4) preclinical mechanistic models (e.g., chronic unpredictable mild stress, TLR4/NLRP3 knockouts). Throughout this review, mechanisms derived from preclinical models, acute challenge paradigms, or clinical cohorts are explicitly identified as such to differentiate them from direct observations in human chronic social stress.

1. BACKGROUND: STRESS AND THE IMMUNE SYSTEM

A stressor is any environmental, physiological, or psychological event that threatens an individual's homeostasis and requires an adaptive response. The stress reaction refers to how people deal with a challenge in physical and psychological ways. Hans Selye proposed that stress reactions are divided into three stages (Alotiby, 2024), namely alarm, resistance, and exhaustion. In the first stage, the reaction to a challenge occurs instantly; in the second stage, people adapt to persistent pressure. If the pressure lasts for some time, the third stage called exhaustion occurs. Although the alarm and resistance phases are usually transient, the exhaustion phase leads to persistent physiological dysregulation. This paper primarily focuses on the exhaustion phase, examining how allostatic load produces prolonged physiological effects.

There are two types of physiological pathways involved in the stress response, namely the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), which is also known as the sympathetic adrenomedullary (SAM) system. The HPA axis works through a hormonal pathway. The secretion of corticotrophin-releasing hormone (CRH) in the hypothalamus triggers the production of adrenocorticotropic hormone (ACTH) in the pituitary gland, which results in the formation of cortisol in the adrenal cortex. Cortisol is the main glucocorticoid hormone involved in the process of stress. The SNS works through another pathway, via the release of catecholamines, specifically epinephrine (adrenaline) and norepinephrine (noradrenaline). Catecholamines act on the immune cells by binding with the adrenergic cell receptors, reaching them either through the innervations of sympathetic nerves to lymphoid organs or through blood circulation (Alotiby, 2024). While operating differently, both pathways temporarily redistribute immune cells to enhance acute surveillance, whereas chronic activation contributes to systemic immune dysregulation (Alotiby, 2024). These two pathways are illustrated in Figure 1.

To comprehend the process, it is important to look into the workings of the immune system itself. Innate immunity is the first defence mechanism of the body, which is a quick and non-specific response, involving cells like macrophages, neutrophils, dendritic cells, NK cells, and mast cells. The adaptive immune response is slower, although highly efficient. The adaptive immunity system can specifically attack certain pathogens, and it becomes even better at doing so when re-exposed to the same pathogens. The two arms of the immune system rely on immune homeostasis, functioning effectively only when equilibrium is maintained; once this balance is disturbed, normal immune control is lost (Alotiby, 2024).

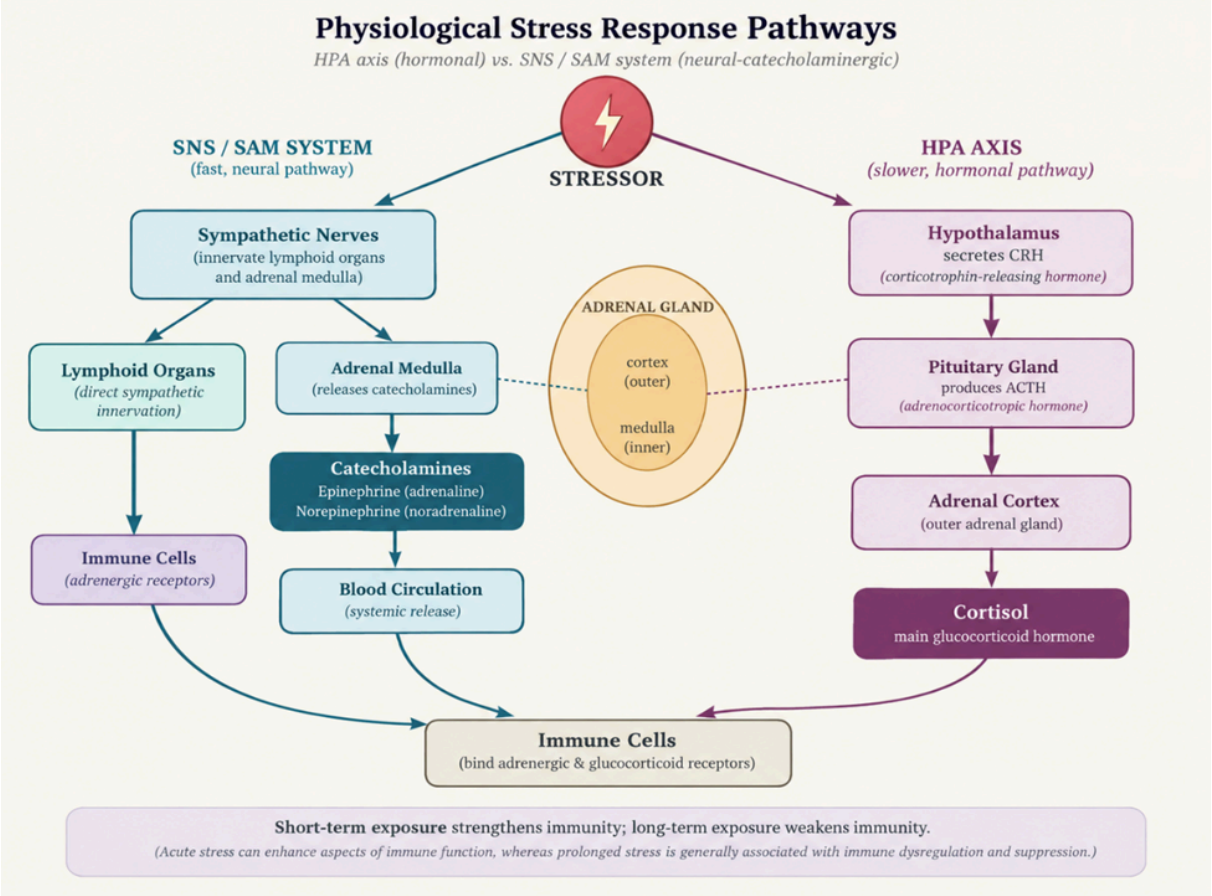


Figure 1: *Physiological Stress Response Pathways: the HPA axis (hormonal) and SNS/SAM system (neural), and their convergence on immune cell signalling. Created by the author using Claude.*

The differentiation between acute and chronic stress is an essential component of this argument. In the short term, stress functions in a beneficial manner: it triggers the release of leukocytes into the blood flow, increases the activity of NK cells and macrophages, and causes an increase in inflammatory cytokines IL-6 and TNF-α to get the body ready to fight against any possible challenges. With the end of the threat, the body returns to its baseline state, restoring normal immune function. Chronic stress impairs the body's ability to return to its normal state. The HPA and SNS systems stay active even when the initial trigger for their activity has disappeared, and the result is a constant influence of cortisol and catecholamines. Over time, this process not only negatively impacts the immune function, but also affects the overall regulation of the immune system. Chronic stress may change the number and efficiency of T and NK cells, reduce immune protection and increase the chances of respiratory infections (Cohen et al., 2002). The idea of wear-and-tear, or allostatic load, has been used to explain the effects beyond the immune system (Alotiby, 2024).

2. THE HPA AXIS, CORTISOL, AND GLUCOCORTICOID RESISTANCE

Psychosocial stressors, like economic hardship or discrimination, engage overlapping limbic neural circuits as physical threats, though the magnitude and timing of downstream neuroendocrine responses vary by stressor context (Nunez et al., 2025). Following the perception of either a physical or an emotional threat, the process unfolds in the limbic system where structures like the amygdala and prefrontal cortex send messages to the paraventricular nucleus of the hypothalamus. This area activates the production of corticotrophin-releasing hormone (CRH), which plays a significant role in managing the organism's stress reaction. The release of CRH activates the secretion of adrenocorticotropic hormone (ACTH), which moves to the adrenal gland, where the production and release of cortisol take place. It is important to emphasize that cortisol functions all the time following a circadian rhythm regardless of the presence of stress, but the difference in the case of stress is the rapid surge in secretion. However, psychosocial stressors have the potential to be continuous, repetitive, and difficult to terminate, which means that the neural circuit will get triggered repeatedly without causing direct physical injury or infections, hence providing a biological explanation for the accumulation of social interactions into physiological stress (Nunez et al., 2025).

At the molecular level, cortisol interacts with glucocorticoid receptors by repressing the activity of key pro-inflammatory transcription factors, including nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1). As a result, the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α is downregulated. It should be mentioned, however, that these cytokines also have the potential to act on the brain, triggering the secretion of more stress hormones. Normally, the role of cortisol here is to regulate this loop by inhibiting additional production of stress hormones. Cortisol also inhibits the rapid multiplication of T and B lymphocytes and their migration to sites of inflammation. Moreover, the hormone regulates the sympathetic nervous system, thus potentiating the effects of catecholamines like adrenaline and noradrenaline.

Frequent activation of the axis can interfere with the feedback system and reduce the responsiveness of cells to cortisol. This phenomenon, known as glucocorticoid resistance, stems from an inability to interpret the signal, rather than low hormone concentration. Part of this dysregulation may occur in the brain itself. Prolonged exposure to stress-induced glucocorticoids may affect the functioning of the hippocampus and prefrontal cortex, regions densely packed with glucocorticoid receptors that are responsible for the negative regulation of HPA axis function. Due to the decreased signalling capacity, the negative feedback loop gets disrupted, thus allowing activation of the stress response to continue. Therefore, the issue stems not from high or low levels of cortisol, but from impaired interpretation of the regulatory signal by its target organs (Nunez et al., 2025).

Clinical data confirm this directly. For example, one study observed the parents of children suffering from cancer. This population experiences considerable psychological stress due to their child's illness. In their

immune cells, there was a reduced reaction to dexamethasone in comparison with that observed in parents whose children were healthy. The inability of these immune cells to suppress IL-6 secretion when dexamethasone was applied provides evidence of impaired glucocorticoid signalling (Nunez et al., 2025). Glucocorticoid receptor signalling varies by cell type and hormone levels. Reduced receptor sensitivity weakens normal cytokine suppression, rather than directly triggering an inflammatory shift (Lim et al., 2007; Nunez et al., 2025). It is important to note that although dexamethasone insensitivity in caregivers is a clear indication of glucocorticoid resistance in humans under chronic stress, the assumption that it causes cytokine elevation in the systemic circulation of all individuals exposed to stress is an inferred connection based on similar findings in biomarkers.

3. FROM RESISTANCE TO CHRONIC INFLAMMATION

Glucocorticoid dysregulation is not a uniform switch. It varies widely between individuals, presenting as low cortisol, high cortisol, or tissue-specific resistance depending on stress severity and duration (Nunez et al., 2025). Rather than a single fixed mechanism, blunted glucocorticoid signalling fails to properly suppress NF-κB, allowing IL-6 and TNF-α levels to rise without needing a shift to mineralocorticoid receptors (Lim et al., 2007; Nunez et al., 2025).

In many individuals, this manifests as low-grade systemic inflammation marked by elevated IL-6, TNF-α, or IL-1β, though individual cytokine profiles vary by stressor duration and biology (Beurel et al., 2020). Macrophages, which are normally responsible for maintaining tissue health and removing dead cells, instead develop heightened reactivity and continuously release these cytokines into the bloodstream in a manner best described as a steady stream of inflammatory signalling. Such a process is supported by observational data in clinical cohorts. For example, women with systemic autoimmune disorders, such as lupus, Sjögren's syndrome, and systemic sclerosis, present with coexisting cortisol dysregulation and systemic inflammation (Nunez et al., 2025). A meta-analysis of nearly 3,200 patients with major depressive disorder (representing a distinct clinical pathology rather than general stress adaptation) also demonstrated persistently elevated IL-6, TNF-α, and C-reactive protein (Beurel et al., 2020). These clinical cohorts do demonstrate the co-existence of systemic inflammation and endocrine dysregulation in established disease states, but the inference of these biomarker profiles to healthy individuals under chronic psychosocial adversity is an inference rather than a directly observed causal sequence. IL-6 and TNF-α have been found to be the most consistently replicated markers in this line of research (Beurel et al., 2020). More specifically, IL-6 has been shown to be related to acute exacerbations and chronicity of the disorder, whereas TNF-α was associated with severity and resistance to treatment.

An understanding of the impact of chronic stress on immunity is of paramount importance. Describing chronic stress as immune suppression is a simplification of the biological mechanisms of its effects. Chronic stress does not just suppress immunity but also may lead to the disorganisation of the immune response resulting in the simultaneous weakening of some immune functions and perpetuation of inflammation. On one hand, chronic stress compromises host protective mechanisms. Specifically, the

regulatory capacity of T-cells declines, IL-10 secretion is suppressed, and natural killer cell cytotoxicity is reduced. Consequently, the organism loses its ability to regulate inflammatory pathways, rendering it highly susceptible to infection (Nunez et al., 2025). Inflammatory mechanisms, on the other hand, might become enhanced. There can be an increased activity of Th17 cells; increased secretion of IL-17; increased pathological immunity; increased level of pro-inflammatory cytokines. Preclinical animal models provide a key cellular mechanism for this shift through bone marrow haematopoiesis. In rodent chronic stress paradigms, prolonged stress triggers a shift in haematopoiesis toward enhanced production of pro-inflammatory myeloid cells (monocytes and granulocytes) over lymphocytes (Nunez et al., 2025). Extension of this stress-induced myelopoiesis model to human social adversity remains inferred from parallel peripheral monocyte and cytokine profiles in humans.

A similar paradox also holds true for depression, where the markers of both immunological activation and suppression can be observed simultaneously. Increased cytokines are associated with decreased proliferation of lymphocytes, depressed function of natural killer cells, and limited T-cell receptor diversity characteristic of the state of an exhausted immune response typical of chronic viral infection. The practical implications of this process have been demonstrated through data collected by longitudinal studies; people who have experienced episodes of depression are at increased risk of developing common infections, and the risk of such infections increases in line with the frequency of depressive episodes from 64 percent after one episode to 84 percent after four or more (Beurel et al., 2020). In combination, integrating these distinct lines of evidence suggests a conceptual framework in which chronic stress disrupts the balance between protective immune defence and inflammatory signalling. However, establishing whether low-grade systemic inflammation in social adversity arises through glucocorticoid resistance, bone marrow myelopoiesis, or co-occurring health behaviours requires synthesizing direct human caregiver data with preclinical stress paradigms and clinical depression cohorts.

4. HOW INFLAMMATION REACHES THE BRAIN

Traditionally, central and peripheral inflammatory processes were regarded as relatively distinct. However, recent studies have established that there is a connection between the processes of peripheral inflammation and the brain because inflammatory mediators from the periphery may influence the central nervous system via numerous pathways which include neuronal, humoral, and cellular routes (Dantzer et al., 2008). The mechanism of the influence of peripheral cytokines includes three pathways: through a damaged or permeable blood-brain barrier, nerve impulses from peripheral nerves (primarily vagus nerve), and penetration of activated immune cells into the brain. Each pathway might result in the development of neuroinflammation in the brain and distinct localised disturbances. These parallel routes are summarised in Figure 2.

4.1 BLOOD-BRAIN BARRIER DISRUPTION

The blood-brain barrier is one of the barriers that has been studied extensively. When intact, the blood-brain barrier prevents almost all circulating antibodies and molecules from penetrating brain parenchyma due to the highly adherent connections between endothelial cells (Beurel et al., 2020). However, the protection is not fully provided, as some sites, such as circumventricular organs and the choroid plexus, have a higher permeability and facilitate the immune surveillance in cerebrospinal fluid (Beurel et al., 2020). Changes in blood–brain barrier integrity have been associated with chronic stress and systemic inflammatory conditions, although the evidence comes from different experimental models and clinical populations. Pro-inflammatory cytokines such as IL-6 and TNF-α may contribute to this dysfunction, but their specific role in mediating the effects of chronic psychosocial stress in humans remains incompletely established.

In rodent models, inflammatory signalling directly degrades the BBB to cause depressive behaviours; in human chronic stress, this central breach remains an inferred mechanism (Beurel et al., 2020). In chronically stressed animals with learned helplessness, increased levels of TNF-α and other cytokines were associated with the increased permeability of the blood-brain barrier and decreased expression of tight-junction proteins. Pharmacological inhibition of TNF-α or activation of sphingosine-1-phosphate receptors restores BBB function and reverses behavioural impairment (Cheng et al., 2018). Barrier stability therefore appears to be an important contributor to several of the other pathways discussed below, though, as the next section shows, at least one of them (vagal signalling) can operate independently of it.

For example, there is one particular antibody that causes an opening of the blood-brain barrier in neuropsychiatric disease associated with lupus, which makes it different from other circulating antibodies not possessing this property (Beurel et al., 2020). When the barrier becomes more permeable, certain peripheral immune cells may enter the brain. For instance, in studies on animal models, Th17 cells that migrate into the hippocampus and prefrontal cortex can induce depression-like conditions independently, while the penetration of monocytes into the brain is associated with anxiety-like conditions (Beurel et al., 2020). Thus, this cellular migration is seen by scientists as a possible source of biomarkers for mood disorders.

4.2 VAGUS NERVE SIGNALLING

There also exists a second significant pathway which operates through direct neural signalling independent of the physical breach of the barrier. The vagus nerve provides another route through which peripheral inflammation can signal the brain, independently of the blood-brain barrier. Immune cells found in the outer layer of the vagus nerve recognise the levels of important cytokines, including interleukin-6, tumour necrosis factor and interleukin-1 beta. These send signals to the central nervous system which causes sickness behaviour. This pathway works in another direction and it performs the

function of regulation in addition to signalling. The activation of the vagal pathway stimulates cholinergic signalling which operates as an anti-inflammatory process through suppressing the production of pro-inflammatory cytokines (Tracey, 2002). Chronic stress has also been linked to changes in cholinergic signalling, which may contribute to increased inflammation (Zhao et al., 2017).

4.3 LOCAL TOLL-LIKE RECEPTOR AND INFLAMMASOME ACTIVATION

Thirdly, this signalling pathway works directly in the brain tissue itself, and not through agents that get to the brain tissue via the bloodstream. The stress response in the brain causes a release of alarmins which are danger signals, including high-mobility group box 1 protein (HMGB1) and ATP. Alarmins are normally found in cells only, and the appearance of these molecules in extracellular space is seen as a signal of damage, and therefore triggers an immune response.

Alarmins activate Toll-like receptor 4 (TLR4) that would normally detect threats such as bacteria. Activation of TLR4, thus, uses the detection system of threat as a signal of danger in the absence of any infections. When activated, TLR4 starts a cascade involving the enzyme GSK3 that activates nuclear factor kappa B (NF-κB), the transcription factor responsible for inflammatory cytokines. Studies using knockout mice support a causal role for this pathway. Specifically, TLR4-knockout mice were largely resistant to learned helplessness after stress exposure (Cheng et al., 2016). TLR4 gene expression was higher in humans suffering from major depressive disorder, and decreased with antidepressants.

TLR4 signalling also engages the inflammasome, which functions differently from the standard cytokine signalling process by converting precursors of cytokines into cytokine molecules rather than activating more genes. The inflammasome consists of a sensor protein, an adaptor protein, and the enzyme caspase-1, which performs the process of conversion. Among the inflammasomes, the NLRP3 type seems to play a significant role in developing depression under stress, as demonstrated by the fact that its inhibition in mice reduces both inflammatory signals and depression (Zhang et al., 2015).

The effects of chronic stress may cause the brain to become insensitive to the action of cortisol. The active form of caspase-1 is able to cleave the glucocorticoid receptors, effectively disabling the way cortisol acts to calm inflammation. While TLR4/NLRP3 knockouts prove molecular causality in mice, human evidence relies on correlational gene expression in depression cohorts

4.4 MICROGLIAL DYSREGULATION

Microglia occupy the position where all these pathways meet. They constitute five to ten percent of the overall brain volume and have the ability to self-renew without involvement of any periphery-derived immune cells. In addition, these cells are responsible for neural homeostasis, synaptic pruning, and neurogenesis. During depression and chronic inflammation, microglial activity gets disturbed. Imaging

studies using positron emission tomography and translocator protein, which is upregulated during pathologic activation, reveal an increased signal in regions that regulate mood, like the prefrontal cortex, insula, and anterior cingulate cortex, and the intensity of the signal correlates with the severity and duration of illness (Beurel et al., 2020).

However, the recent findings add to the complexity of the situation because the increase in the signal also shows the proliferation of local myeloid cells and the migration of peripheral monocytes instead of pathologic microglial activation and, thus, has a direct connection to blood-brain barrier breach (Beurel et al., 2020). There is a similar paradox that emerges from post-mortem and structural research. On one hand, there are indications of an excessive level of microglial activation, and on the other, there is evidence of an overall decrease in the number of glial cells, such as astrocytes and oligodendrocytes, which are necessary for the proper functioning of the nervous system. These discoveries have suggested a completely different theory – it is possible that the brains of people with depression do not have enough protective microglial subtypes but maintain excessive ones (Beurel et al., 2020). This may explain the paradox. It is not that microglia overall become more active, but that the protective subtypes are lost while the harmful ones remain.

Drugs that suppress COX-1 – the enzyme mostly present in microglia – exacerbate the state of depression, whereas COX-2 blockers, affecting neurons and astrocytes, have shown antidepressant effects in some studies because they eliminate pathological over-inflammation without destroying all protective microglia (Beurel et al., 2020). In a study conducted by Chen et al. (2025) using the chronic unpredictable mild stress paradigm, it was discovered that changes in the microglial count, their morphology, as well as their reaction to another acute stressor occurred during two, four, and six weeks of chronic stress. Although rodent models demonstrate progressive microglial priming under stress, human PET TSPO signals cannot differentiate intrinsic microglial activation from infiltrating peripheral monocytes.

4.5 THE KYNURENINE PATHWAY

Lastly, pro-inflammatory signals from the periphery can be transduced into the brain and affect the CNS through the kynurenine pathway. Pro-inflammatory cytokines, psychological stress, and glucocorticoid signalling can cause indoleamine 2,3-dioxygenase (IDO), an enzyme that initiates the kynurenine pathway by converting tryptophan into kynurenine, though the broader serotonin-deficiency theory of depression itself remains debated. The kynurenine pathway has two branches which have opposite effects on the CNS; microglia produce the neurotoxic quinolinic acid, while astrocytes produce the neuroprotective kynurenic acid. Thus, the total amount of kynurenine is not informative about the balance between the two pathways. Accumulating evidence supports the involvement of the kynurenine pathway in depression, as shown in the study by O'Connor et al. (2009). The study demonstrated that L-kynurenine dose-dependently induced behavioural despair in mice, while the blockade of IDO prevented the development of depressive-like behaviour in mice after endotoxin injection. Similar results

were found in patients who received interferon-alpha treatment for hepatitis C; the higher the levels of kynurenine in blood and CSF, the more severe the depression was (Raison et al., 2010).

Acute immune challenges (e.g., typhoid vaccination) prove that peripheral cytokines drive human neuroinflammation and fatigue, yet extrapolating these high-amplitude surges to low-grade chronic social stress remains an inference (Plank et al., 2024). Complementary results were found by Colle et al. (2025) who showed that during six months of antidepressant treatment, 173 patients with depression had increases in several kynurenine pathway metabolites. Increases in kynurenine and the ratio of kynurenine to tryptophan were linked to decreases in depression severity. However, since the ratios of quinolinic acid to kynurenic acid were not assessed, it is possible that patients exhibited an increase in the neuroprotective branch of the kynurenine pathway, rather than a decrease in the neurotoxic one.

The discussed preclinical and clinical findings highlight several mechanisms by which peripheral inflammation can affect the brain. The blood-brain barrier, vagal nerve projections, Toll-like receptors, inflammasomes, microglia, and the kynurenine pathway are involved in the inflammatory response. These mechanisms are interconnected and can interact with one another, as was shown by Haroon et al. (2012) and Miller and Raison (2016). In turn, this knowledge can help in developing new treatments for depression, which target inflammatory pathways, but the role of these mediators in different diseases and in different people can vary (Hong & Banks, 2015; Miller & Raison, 2016).

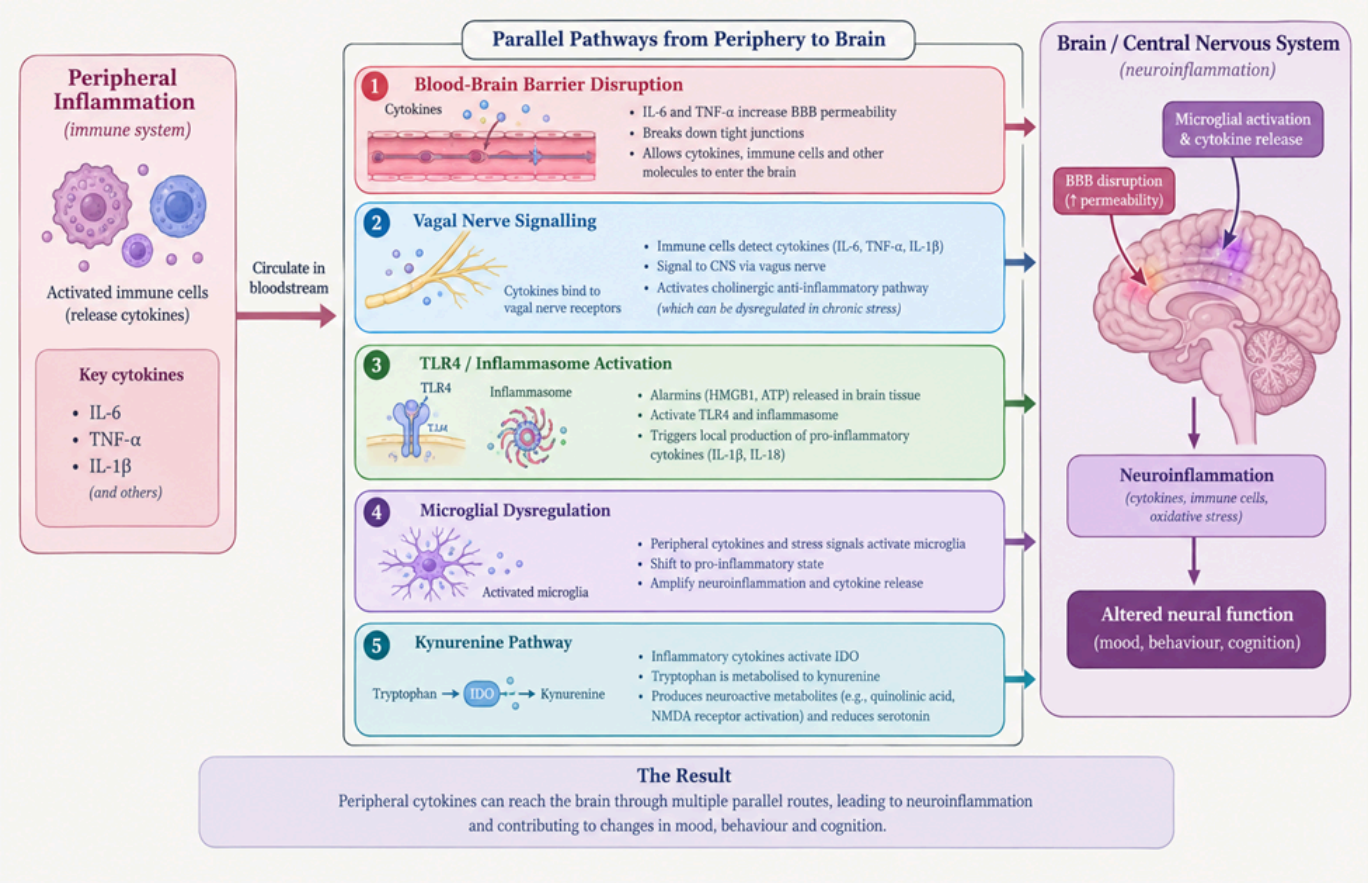


Figure 2
Peripheral-to-Central Inflammation Bridge. Created by the author using Claude.

5. INFLAMMATION, MOOD, AND BEHAVIOR

Inflammatory processes can affect mood, motivation, and behaviour. Peripheral cytokines alter corticostriatal reward circuits, though evidence is drawn from acute challenge models (e.g., endotoxin, vaccines) and clinical depression cohorts rather than direct social adversity paradigms. Individual vulnerability factors like existing levels of inflammation, age, quality of sleep, and social circumstances may influence these behavioural outcomes.

As discussed in Section 4, some microglial subpopulations may perform protective functions, which means that their inhibition may lack efficacy in treating clinical depression or general stress-induced behavioural changes.

Moreover, inflammatory signals could lead to a more specific set of behavioural symptoms rather than generalized mood changes. One hypothesis states that fatigue could be caused by cellular processes happening even before the disease itself is manifested in its full clinical picture. During an exploratory longitudinal study, in which patients were given interferon-alpha treatment for hepatitis C, the researchers observed changes in blood-cell gene expression 4.5 hours after interferon-alpha was administered. The activation of a protein network consisting of ribosomal and ubiquitin proteins involved in the mTOR signalling pathway predicted higher levels of fatigue 4 weeks later (Periche-Tomas et al., 2025). While pharmacological interferon-alpha therapy proves that acute, high-dose cytokine surges induce cellular changes driving fatigue, this represents an acute pharmacological challenge rather than chronic, low-grade psychosocial stress. Clinical observations support this phenomenon. Around 40 percent of patients being treated with interferon-alpha for hepatitis C or some types of cancer suffer from depression after starting treatment (Beurel et al., 2020).

There is evidence that individual differences might mediate susceptibility to inflammation-induced mood changes. In a study on adults suffering from major depressive disorder, individuals with elevated levels of C-reactive protein had higher rates of anhedonia and IL-6 elevation compared to individuals with low baseline CRP following an endotoxin challenge. The responses to TNF and IL-10 were not statistically different (Savitz et al., 2025). Hence, inflammation that exists prior to the intervention might lead to increased sensitivity of reward-related symptoms to inflammation challenge. There is also evidence of such moderation in healthy samples. Specifically, low enjoyment of close social relationships was associated with an elevated increase in depressed mood following inflammation challenge, but general social and non-social experience was not linked to this result (Boyle et al., 2026). This relationship was moderated by age: younger women (aged 25-44) experienced increased depressed mood and reward sensitivity reduction following endotoxin injection while older women (aged 60-80) did not experience these changes. Reward learning was equally reduced for both age groups (Boyle et al., 2025). In addition, older individuals who suffered from insomnia appeared to be more vulnerable to inflammation as endotoxin was associated with an increase in depressed mood and depressive symptoms in the presence of insomnia compared to healthy controls, and cytokines were not different between the two groups. The association between inflammatory response and worsening mood was present only in the insomnia group (Irwin et al., 2025). Taken together, these studies suggest that inflammation does not affect mood uniformly. Its psychological consequences depend partly on pre-existing inflammatory status, age, social reward sensitivity, and sleep quality as summarised in Figure 3.

There can be psychological components affecting the way one experiences inflammation and, hence, creating another dimension of how inflammation interacts with moods. For instance, in a randomized controlled trial investigating endotoxemia, positive expectations of treatment reduced the experience of

affective sickness symptoms even when the subjects were treated with a placebo and enhanced the effects of ibuprofen on these symptoms (Schmidt et al., 2025). The levels of physiological inflammation were not affected. It implies that the relationship between systemic inflammation and mood is not purely linear, demonstrating that psychological context influences the degree to which physiological inflammatory signals alter mood.

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One of the ways through which inflammation impacts behaviour is by disrupting the circuits involved in reward and decision-making. These findings provide evidence as to why patients with depression suffer from anhedonia and lack of motivation. As a proof-of-concept for causal pathways, acute typhoid vaccination in healthy males decreased dorsomedial prefrontal cortex activation during decision-making (Queirazza et al., 2024), confirming that acute immune challenges alter corticostriatal circuitry. Inflammation also led to reduced reward prediction errors in the ventral striatum and amygdala (Queirazza et al., 2024). The findings show how inflammation can impact not only decisions but also the way people use past experience of rewards. Consistent with the above observation, in a randomized proof-of-mechanism trial conducted among patients with major depressive disorder and high levels of C-reactive protein, blocking of TNF signalling through the use of infliximab was seen to increase the willingness of patients to make efforts to earn rewards. The above behaviours were associated with changes in the dorsomedial prefrontal cortex, ventral striatum, putamen, and the connections between the regions (Treadway et al., 2025). Overall, the observations go further than the link between inflammation and reduced motivation and provide evidence as to how inflammation impacts the corticostriatal circuits behind reward-based behaviours.

The overall evidence shows that inflammation does not simply cause depression on its own. Instead, it targets specific neural circuits, leading to distinct symptoms like anhedonia, cognitive fatigue, and altered social behaviour. This process is affected by individual vulnerability, thus explaining why not all people develop depression under the influence of chronic stress and why anti-inflammatory trials have yielded inconsistent clinical efficacy in the treatment of depression. It means that depression should be seen as a biopsychosocial disorder characterised by interactions between stress, dysregulation of the immune system, vulnerability of neural circuits, and psychological factors.

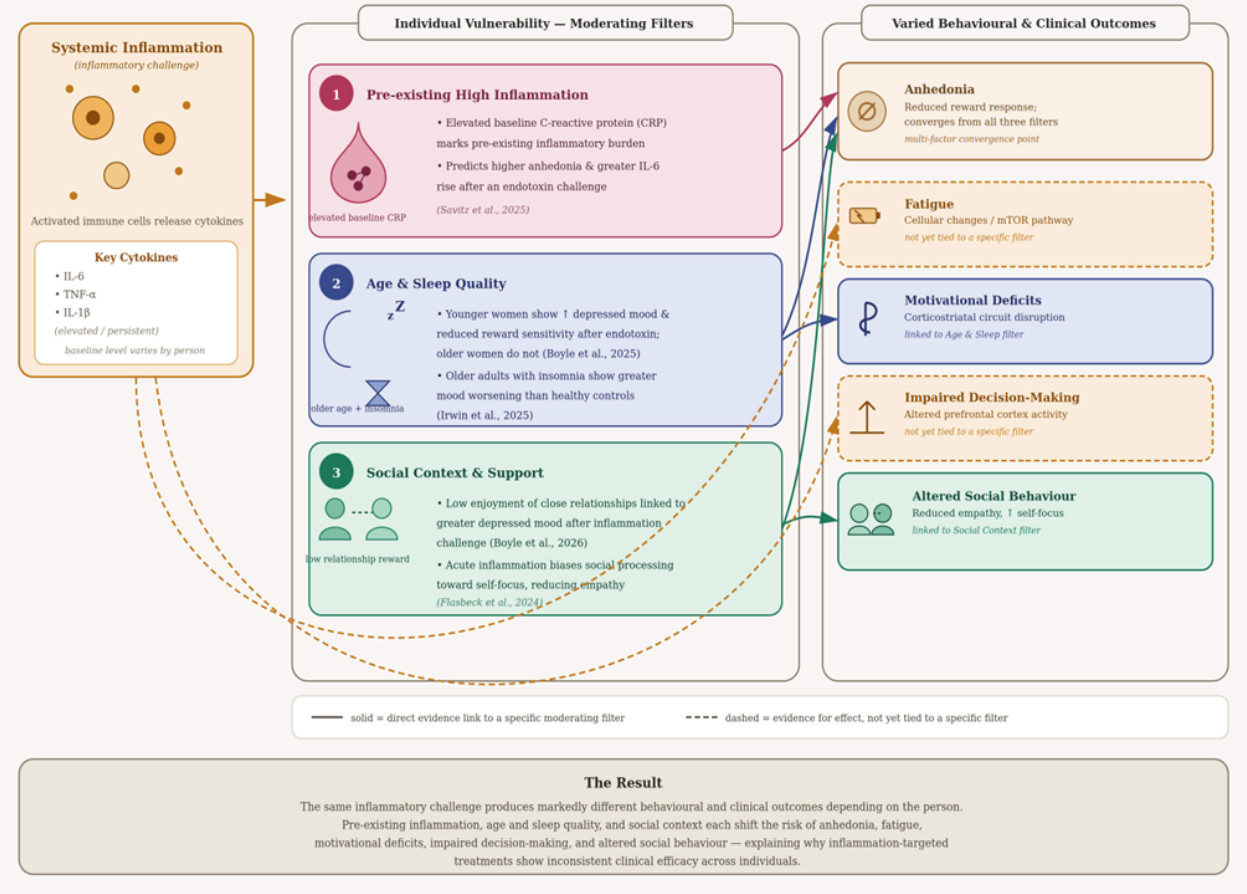


Figure 3

Individual Vulnerability and Moderation. Created by the author using Claude.

Though mechanistic findings have provided strong evidence, implementation of these findings in the clinic proves difficult. Therapeutic evidence highlights that one should not consider elevated inflammation as an identifier of patients who could potentially benefit from anti-inflammatory therapy. In a placebo-controlled, randomized, double-blind study conducted among depressed patients being treated with vortioxetine, elevated hsCRP at baseline did not correlate with a greater response to concomitant celecoxib, and no differences between subjects with elevated versus low inflammation were observed in response to the therapy (Kavakbasi et al., 2024). This dissociation agrees with the pathway-specific model described in Section 4, where hsCRP is indicative of the burden of systemic inflammation but not of the pathway involved, whether it is due to blood-brain barrier dysfunction, vagus nerve signalling, TLR4 or inflammasome activation, microglia dysregulation, or kynurenine pathway changes. It follows that a general marker indicating peripheral inflammation will not be able to predict the effect of a general

anti-inflammatory drug even when inflammation plays a role in the pathogenesis of a condition affecting a patient.

6. CONCLUSION

Though mechanistic findings have provided strong evidence, implementation of these findings in the clinic proves difficult. Therapeutic evidence highlights that one should not consider elevated inflammation as an identifier of patients who could potentially benefit from anti-inflammatory therapy. In a placebo-controlled, randomized, double-blind study conducted among depressed patients being treated with vortioxetine, elevated hsCRP at baseline did not correlate with a greater response to concomitant celecoxib, and no differences between subjects with elevated versus low inflammation were observed in response to the therapy (Kavakbasi et al., 2024). This dissociation agrees with the pathway-specific model described in Section 4, where hsCRP is indicative of the burden of systemic inflammation but not of the pathway involved, whether it is due to blood-brain barrier dysfunction, vagus nerve signalling, TLR4 or inflammasome activation, microglia dysregulation, or kynurenine pathway changes. It follows that a general marker indicating peripheral inflammation will not be able to predict the effect of a general anti-inflammatory drug even when inflammation plays a role in the pathogenesis of a condition affecting a patient.

Connecting social adversity to these central pathways relies on an integrated conceptual framework that explicitly distinguishes direct human stress findings from preclinical models, acute challenges, and clinical cohorts. Once the process of central inflammatory signalling becomes active, neurotransmitter systems and neural circuitry responsible for mood, motivation, reward, executive functioning, and behaviour are affected. Data obtained from inflammatory challenge experiments indicate the presence of such connections. Thus, such mechanisms can explain the development of symptoms like anhedonia, fatigue, lack of motivation, and cognitive impairment.

Therefore, the response to the research question is that chronic psychosocial stress can affect mood and behavioural adaptation by translating psychological stress into sustained biological dysregulation: repeated exposure to stress may lead to HPA axis dysfunction; dysregulation in glucocorticoid signalling can allow inflammation to become sustained, and inflammation can modify neural systems associated with mood and behaviour through its signalling. However, this chain is not linear or deterministic – the presence of initial inflammation, age, sleep quality, social environment, and individual predisposition can affect the impact of inflammation on behaviour, and inflammatory signalling does not necessarily lead to depression.

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Future work needs to clarify which patients respond best to targeted anti-inflammatory interventions through longitudinal studies stratified according to inflammation biomarkers and specific symptoms like anhedonia and fatigue. Work on resilience to stress might help explain the differences in biological and behavioural responses of people subjected to the same stressful events.

While this review focuses on neurobehavioural outcomes, chronic stress and inflammation similarly contribute to cardiovascular, autoimmune, and metabolic conditions. Because psychosocial stressors such as poverty and discrimination are unequally distributed, their biological consequences may also be unequally distributed. A biopsychosocial framework therefore provides a more complete understanding of how social adversity is translated through psychological, immunological, neuroendocrine, and neural mechanisms into differences in health.

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