International Journal of Research in Medical Sciences
Sharma S et al. Int J Res Med Sci. 2025 Oct;13(10):4498-4505
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20253213

Review Article

Inflamed and unrewarded: a narrative review exploring neuroinflammation and its impact on the brain's reward mechanisms

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Received: 16 June 2025
Accepted: 01 August 2025

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ABSTRACT

Depression is associated with dysfunction in the brain's reward system, contributing to symptoms like anhedonia. Emerging evidence suggests that neuroinflammation plays a key role in disrupting dopaminergic pathways. This review explores how pro-inflammatory cytokines affect reward circuitry and assesses the potential of anti-inflammatory treatments. A narrative review was conducted using studies from 2000 to 2025. Databases searched included PubMed and Google Scholar. Keywords focused on depression, neuroinflammation, reward systems, cytokines, and treatment strategies. Studies in adults examining neural and behavioural outcomes were included. Pro-inflammatory cytokines (e.g., IL-6, TNF-α) impair dopamine function and alter connectivity in the mesolimbic pathway. These changes are linked to core depressive symptoms. Anti-inflammatory agents—such as TNF inhibitors, NSAIDs, and probiotics—have shown promise in alleviating symptoms, particularly in patients with high inflammation. Neuroinflammation plays a critical role in the pathophysiology of depression through its detrimental impact on dopaminergic reward pathways. Targeting inflammation presents a promising strategy for treating depression, particularly subtypes characterised by elevated immune activation. Future research should aim for biomarker-driven stratification to optimise individualised therapeutic approaches.

Keywords: Depression, Neuroinflammation, Cytokines, Reward system, Dopamine, Inflammation treatment

INTRODUCTION

Depression is a common mood disorder that affects around 350 million people globally. It is a disease of significant mental health importance.[1] Core symptoms include loss of interest in pleasurable activities, sleep disturbances, changes in appetite, excess fatigue, feelings of worthlessness, psychomotor agitation or retardation, poor concentration and recurrent thoughts of dying.

These symptoms highlight that this disease is of significant public health importance as it burdens the population with personal and economic burdens.[2] Many studies have been carried out regarding the aetiology of depressive disorder. While diseases such as bipolar disorder and schizophrenia have a heritability of 70-80%, depression was found to be only 37%. Hence, environmental and neurological mechanisms of depression were also considered.[1]

The reward system of the brain, or the mesolimbic system, is responsible for associating stimuli with a positive or desirable outcome. It requires the coordinated release of neurotransmitters. The reward system is formed by projections of midbrain dopamine neurons of the ventral tegmental area to the striatum, prefrontal cortex, hippocampus, amygdala, and limbic system structures.

Dysfunction of the reward system has been linked to depression in some studies.[6,7] Modalities of treatment of depression include pharmacotherapy, psychotherapy such as cognitive behavioural therapy, and non-pharmacological measures such as electroconvulsive therapy.[3] Recent studies have shown that chronic low-grade inflammation and activation of cell-mediated immunity are associated with depression. The emergence of depressive symptoms was seen when patients were given exogenous cytokine infusions.

Additionally, antidepressants were found to have anti-inflammatory properties by inhibiting pro- inflammatory cytokines. However, the source of this inflammation is yet to be discovered. While some patients were found to have co-existing inflammatory diseases such as multiple sclerosis, these factors were present in a very small percentage of depressed individuals.[4,5]

Among the neural substrates implicated in depression, the brain's reward system, particularly the mesolimbic dopaminergic pathway, has garnered significant interest. This system, critical for motivation and pleasure, is often functionally impaired in depression, particularly in patients experiencing anhedonia. Recent evidence highlights a strong link between chronic low-grade neuroinflammation and alterations in this reward circuitry, mediated by pro-inflammatory cytokines and microglial activation. These inflammatory markers not only affect neurotransmitter dynamics, particularly dopamine, but also disrupt functional connectivity in brain regions such as the ventral striatum, prefrontal cortex, and amygdala.

This narrative review aims to explore the emerging role of neuroinflammation in the pathophysiology of depression through its impact on the reward system. Specifically, it examines the mechanisms through which cytokines disrupt dopaminergic function, the differential inflammatory profiles across depression subtypes, and the potential of anti-inflammatory interventions in restoring normal reward processing and alleviating depressive symptoms.

METHODS

The primary objective was to synthesise current evidence on the impact of neuroinflammatory markers (e.g., microglial activation, pro-inflammatory cytokines such as IL-6 and TNF-α) on structures and functions of the brain's reward system, the correlation between inflammation and functional changes in mesolimbic dopaminergic pathways and the efficacy of anti-inflammatory treatments in modulating the reward system and alleviating depressive symptoms.

Search strategy

A comprehensive literature search was conducted using PubMed and Google Scholar. The search covered publications from 2000 to 2025 to ensure inclusion of contemporary research.

Key search terms included combinations of depression, major depressive disorder, neuroinflammation, cytokines, microglia, reward system, mesolimbic pathway, anhedonia, IL-6, TNF-alpha, neuroimaging, fMRI, PET, anti-inflammatory treatment and Boolean operators (AND, OR) were applied to enhance search sensitivity and specificity. Reference lists of included articles and relevant reviews were also manually screened for additional studies.

Inclusion criteria

Inclusion criteria included peer-reviewed original research articles, reviews, and meta-analyses, studies conducted in adult human populations (≥18 years) diagnosed with depressive disorders, research addressing the interaction between neuroinflammation and the brain's reward system, articles reporting functional, structural, or behavioural outcomes relevant to reward processing, studies examining the impact of pro-inflammatory cytokines or neuroinflammation-modulating interventions, and research employing neuroimaging modalities (e.g., fMRI, PET) to assess changes in reward circuitry.

Exclusion criteria

Exclusive criteria studies focused on non-depressive psychiatric conditions (e.g., schizophrenia, bipolar disorder), research involving paediatric or adolescent populations (<18 years), articles lacking focus on neuroinflammation or the reward system, studies on peripheral inflammation without direct neural relevance, publications that do not investigate depressive symptoms or reward-related outcomes, interventions unrelated to inflammation or the reward system (e.g., psychotherapy alone), non-peer-reviewed articles, opinion pieces, editorials, letters, and case studies and non-English language publications or those with inaccessible full texts.

Data synthesis and reporting

Included studies were narratively synthesized by identifying common findings and divergences related to the effect of neuroinflammation on reward processing in depression.

Particular emphasis was placed on findings from neuroimaging studies, cytokine assays, and intervention trials using anti-inflammatory agents.

PRO-INFLAMMATORY CYTOKINES AND REWARD CIRCUITRY IN DEPRESSION

Inflammatory cytokines influence the reward circuitry in two primary ways: by altering the function of neurotransmitters in the reward system, particularly dopamine (DA), and by disrupting functional connectivity in brain regions involved in reward processing. Many studies on how inflammation affects the functional dynamics of reward circuitry come from preclinical studies using animal models or experimental clinical trials, in which the effects of pro-inflammatory cytokines in depression can be best understood by analyzing the changes seen in structures of the limbic system on various imaging modalities, particularly functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).[8]

The current hypothesis suggests that inflammation and cytokines directly and indirectly disrupt dopamine function, while also impairing the reward circuitry in the central nervous system. Inflammation has been implicated in the pathophysiology of mood disorders, including depression, through its effects on dopaminergic (DA) neurotransmission. Proinflammatory cytokines can disrupt dopamine availability and function through multiple mechanisms, impairing reward processing and motor function in the basal ganglia.[8] A primary mechanism by which inflammation reduces DA availability is by impairing its synthesis. Inflammatory cytokines deplete tetrahydrobiopterin (BH4), an essential cofactor for tyrosine hydroxylase (TH), the rate-limiting enzyme responsible for converting tyrosine to L-DOPA, the precursor of dopamine. Additionally, inflammation induces nitric oxide synthase (iNOS) activity, which competes for BH4, leading to oxidative stress and further DA synthesis reduction.[9] Inflammatory cytokines, particularly interferon-alpha (IFN-α), also affect dopamine and serotonin transport via activation of the p38 mitogen-activated protein kinase (MAPK) signalling pathway. This pathway increases the expression and function of serotonin (5-HT) and dopamine transporters (5-HTT and DAT), leading to increased monoamine reuptake and reduced synaptic dopamine availability.[8] The combined effects of decreased DA synthesis, impaired packaging and release, and increased DA reuptake contribute to impaired dopaminergic signalling in brain regions associated with reward and motor control and have been linked to critical features of depression, including anhedonia, fatigue, and psychomotor slowing.[9]

As measured by inflammatory cytokines, high levels of inflammation are associated with reduced functional connectivity within the ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC) circuit, a key pathway in the brain's reward system linked to depression. Felger used resting-state fMRI to measure the connectivity between the VS and vmPFC in patients with major depressive disorder (MDD) and found that increased plasma levels of IL-6, IL-1β, and IL-1 receptor antagonists were negatively correlated with connectivity between the VS and vmPFC, providing evidence for the link between inflammation, mesolimbic system dysfunction, and anhedonia, a key symptom of depression.[11] Similar findings were shown in another study about the effects of systemic IFN-α on whole-brain functional connectivity architecture and its relationship to mood changes in patients with Hepatitis C treated with IFN-α therapy.

The study demonstrated that IFN-α disrupted the functional connectivity of brain regions involved in motivation and motor regulation, including the VS-vmPFC pathway, through inflammation-induced structural and neurotransmitter alterations. IFN-α rapidly impaired global network efficiency and mean node degree, directly associated with impairments in mood and cognition.[12] Another study examined VS-vmPFC resting-state functional connectivity, along with plasma IL-6 and TNF-α, in patients with treatment-resistant depression (TRD) and a history of childhood trauma. Results showed higher plasma levels of IL-6 and TNF-α in TRD patients compared to healthy controls. IL-6 was negatively associated with left VS-vmPFC connectivity, while childhood trauma moderated the relationship between TNF-α and right VS-vmPFC connectivity, with stronger connectivity as trauma severity increased. This study highlights the role of inflammation and early-life trauma in brain function changes, contributing to the pathophysiology of TRD and depression overall.[13]

Another brain structure associated with the reward system is the amygdala, the central structure of emotion processing, which is closely linked to psychiatric disorders.[14] A study in which patients receiving IFN-α treatment for conditions like Hepatitis C showed the heightened reactivity of the right amygdala to emotional and threat-related stimuli, which was associated with depressive symptoms and social disconnection induced by IFN-α.[15] Similarly, endogenous inflammatory markers, plasma C- reactive protein (CRP) and inflammatory cytokines and their soluble receptors, and right amygdala–vmPFC rsFC were studied in medically stable, unmedicated patients with a primary diagnosis of depression. The result revealed that elevated CRP levels and anxiety symptoms were associated with decreased functional connectivity between the right amygdala and vmPFC, particularly in patients with comorbid PTSD or anxiety disorders.[16] Amygdala activation in response to stressors was also found in healthy females with greater increases in IL-6 and TNF-α levels measured before and after the stress task, suggesting a crucial role of the amygdala in regulating the body's inflammatory response. Stronger functional connectivity between the amygdala and the dorsomedial prefrontal cortex (dmPFC) was also associated with elevated inflammatory responses. This indicates that not only the activity within these regions but also their interaction contributes to how the body responds to stress at the inflammatory level. Findings from this study contribute to neural mechanisms that might link

stress with increased risk for inflammation-related disorders such as depression.[17]

While previously discussed brain regions play a critical role in reward processing, the impact of inflammation on other brain structures and the interactions between them reveal additional complexities in neural function and behaviour. One such structure is the nucleus accumbens (NAc), a key component of the reward system, which interacts closely with the ventral tegmental area (VTA). In patients with MDD, increased IL-6 and CRP correlated with stronger VTA-NAc connectivity, which was associated with anhedonia.[18]

Another crucial structure within the reward circuit is the anterior cingulate cortex (ACC), which regulates emotions and motivation involved in effort-based decision-making and reinforcement learning.[19] Magnetic resonance imaging (MRI) studies in patients with depression have consistently reported volume loss and atrophy in the hippocampus, ACC, and amygdala.[20]

Among these, hippocampal atrophy has been linked to increased levels of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and IL-6.[21] fMRI studies further demonstrate the triggered activation of amygdala, hippocampus, hypothalamus, striatum, brainstem, dorsal ACC, and dorsomedial prefrontal cortex (dmPFC) in depression, particularly in response to elevated cytokines like interleukin-1 (IL-1), IL-6, interleukin-1 receptor antagonist (IL-1RA), and TNF receptor 2 (TNF-R2).[22]

Simultaneously, PET studies highlight increased elevated 18 kDa translocator protein (TSPO) binding in depressive patients, which preferentially binds in the ACC and the prefrontal cortex. Studies examining surrogate markers for TSPO distribution volume, such as ln (prostaglandin E2/CRP) and ln (TNF /CRP), have been shown to correlate positively in patients with depression. In addition, the administration of celecoxib, a non-steroidal anti-inflammatory agent, has been shown to reduce TSPO distribution volumes in patients experiencing a major depressive episode.[23] Beyond regional structural changes, pro-inflammatory cytokines have also been implicated in functional disruptions within the default mode network (DMN). Elevated IL-6 levels have been shown to increase ACC connectivity within the DMN, reduce dorsomedial prefrontal cortex connectivity, and enhance connectivity between the right posterior cingulate cortex and the left thalamus.[24,25] These findings underline the importance of considering inflammatory processes affecting the mesolimbic dopaminergic circuit in the pathophysiology of depression.

Differences in neuroinflammation reward systems in depression subtypes

Given the evidence of a link between neuro-inflammatory processes and depression, there has been research into a possible explanation of the basis of varying clinical symptoms and behavioural patterns in different subtypes of depression and resultant differences in inflammatory marker and neurotransmitter levels between these subtypes. For instance, studies have shown that patients with atypical depression tend to have a higher body mass index (BMI) compared to those with melancholic depression. Since adipose tissue stores adipo-cytokines, analyses accounting for BMI revealed higher levels of pro-inflammatory cytokines, such as CRP, IL-6, and TNF-α, in atypical depression. Kaestner et al found that non-melancholic patients had higher levels of IL-1β and a lower IL-1 receptor antagonist/IL-1β ratio than melancholic patients.[44] Yoon et al observed an imbalance in Th cell cytokines, with decreased IL-4 (Th2) and increased IL-2 (Th1) levels in atypical compared to melancholic depression, suggesting a key role of Th cell imbalance.[43] However, some studies found no significant cytokine differences between melancholic and non-melancholic subtypes, possibly due to variations in subtype definitions.[39] Glucocorticoids like cortisol regulate inflammation through pro-inflammatory gene programs. In melancholic depression, a hyperactive HPA axis leads to elevated cortisol, associated with sleep and appetite disturbances. In contrast, atypical depression is marked by lower cortisol levels and higher inflammation markers, with reduced cortisol potentially worsening inflammation.

Non-melancholic patients show no elevated ACTH or cortisol but higher inflammation levels. Inflammation activates microglia, increasing glutamate and NMDA receptor activity in the dACC, leading to its hyperactivation. This hyperactivation, linked to heightened sensitivity to negative events, is observed in atypical depression, suggesting a link between inflammation and dACC hyperactivity that requires further investigation.[39]

The biological profiles of atypical and melancholic depression show overlapping features, complicating their categorisation. For instance, mood impairment following acute inflammation correlates with increased sgACC activity, and microglia-related QUIN expression is elevated in both the dACC and sgACC. While the sgACC is linked to neuroinflammation, it has also been associated with melancholic depression, suggesting that neuroinflammation may play a role in multiple depression subtypes.[39]

In an individual under chronic psychological stress, microglia, the brain's immune cells, are activated, thus releasing interleukin-6 (IL-6), tumour necrosis factor (TNF-α), and C-reactive protein, proinflammatory cytokines which disrupt neural transmission, cause neurotransmitter imbalance and exert neurotoxic effects.[40] The proinflammatory cytokines secreted by the microglia cells affect the brain via the kynurenine pathway by increasing the activity of the enzyme indoleamine 2,3 dioxygenase, which metabolises tryptophan to kynurenine.

This increase in kynurenine pathway metabolites depletes serotonin in the CNS by reducing serotonin synthesis, which is closely involved with depression.[40]

With different subtypes of depression, the neuroinflammatory profiles differ significantly. In atypical or treatment-resistant subtypes of depression, it is reported that peripheral inflammatory markers are consistently elevated, while patients suffering from melancholic depression exhibit a less reactive inflammatory profile. A meta-analysis study suggests that interleukin-6 (IL6) and tumour necrosis factor (TNF-α) are more elevated in chronic or atypical forms than the melancholic subtype, which can show reduced immune activation or immune suppression.[41]

Dysfunction of the brain's reward system is a common neurological substrate of depression, particularly in the mesolimbic and frontostriatal pathways. The reward system includes brain structures such as the nucleus accumbens, ventral tegmental area (VTA), prefrontal cortex, and hippocampus. All these structures are important for the regulation of motivation, pleasure, and reinforcement behaviour.

Some studies have shown that in MDD, numerous fMRI studies demonstrated hypoactivation of the brain's reward system during reward-related tasks, especially in patients with high levels of inflammation. It is because of this hypoactivation of the brain's reward system, which causes anhedonia and motivational deficits, that are the clinical features of depressive episodes.[40] Furthermore, in these reward systems, inflammatory cytokines like IL-1β and IL-6 have been directly linked to reducing dopamine signalling.[41]

ANTI-INFLAMMATORY INTERVENTIONS IN RESTORING REWARD SYSTEM FUNCTIONALITIES

As demonstrated, neuroinflammation has been implicated in depressive disorders and symptoms and hence traditional and non-traditional anti-inflammatory agents have emerged as a potential new therapy for the same. Multiple studies have demonstrated the efficacy of traditional anti-inflammatory agents. Treadway et al performed a double-blind, placebo-controlled, single-dose RCT with 5 mg/kg infliximab (a potent tumour necrosis factor antagonist) versus placebo in a sample of 42 patients who were medically stable and unmedicated for their major depression, who had a C-reactive protein >3 mg/l. Their results found that the single use of this anti-inflammatory treatment improved the willingness towards effort- based decision-making for rewards via associated brain circuitry and TNF signalling in depressed patients with high inflammation.[26]

Another significant study involving the administration of a cytokine modulator agent Etanercept, in a rat model provides evidence that peripheral administration of an anti-inflammatory agent can mitigate depressive behaviours and restore neural pathways involving the hippocampus, underscoring the interplay between neuroinflammation and neural systems involved in mood regulation. Inhibitors of pro- inflammatory cytokines such as IL-6, IL-12 and IL-23 have also shown antidepressant effects in clinical trials.[27,28]

In a review published in 2022, some of the newer and alternative antidepressant treatments, especially used for treatment resistance, like ketamine/NMDA receptor antagonists, cannabis/cannabinoid and psychedelics, have also been shown to have anti-inflammatory properties via different mechanisms. Ketamine's anti-inflammatory effect was hypothesised via decreasing pro-inflammatory cytokines (i.e TNF-α, which was correlated with decreased depression). Conversely, for cannabis/cannabinoid, it was mediated via decreased inflammatory cytokines (e.g., IL-6, TNF-α, IFN-ß) and decreased PGE2, COX activity, oxygen-derived free radicals, and nitric oxide. Psychedelics' effect on attenuating depression was correlated with decreased CRP. Additionally, 5-MeO-DsMT increased cortisol and decreased IL-6.[29]

Hassamal found extensive literature supporting the use of NSAIDs, statins, omega-3 fatty acids, N- acetylcysteine, and COX-2 inhibitors having small to moderate antidepressant effect sizes throughout 4 to 12 weeks. Compared to monotherapy, adjunctive treatment has a larger antidepressant effect size due to the synergistic effects of monoamine-based treatments and anti-inflammatory agents, and the augmentation was 52% more effective compared to placebo.[30] Du et al had similar findings and demonstrated that anti-inflammatory agents had a significant antidepressant effect as well as acceptability, and adjunctive treatment was more efficacious than monotherapy. However, they also found that even though NSAIDs exhibited the highest acceptability, their efficacy was only comparable to placebo.[31]

Other interventions with secondary anti-inflammatory actions have also been explored. Probiotics are currently being suggested as a potential adjuvant therapy for MDD due to the "gut-brain axis", a concept of growing importance.[32]

Among others, a randomised, double-blind, placebo-controlled clinical trial including 40 patients with MDD conducted by Akkasheh et al showed that after 8-week supplementation with probiotics, Beck depression inventory total scores were significantly decreased (−5.7±6.4 versus −1.5±4.8, p=0.001) compared with the placebo. The effect of probiotics is linked with the reduction in concentrations of inflammatory markers, including CRP, TNF-α, IFN-γ, IL-6, IL-12 and IL-4.[33]

Minocycline, a commonly used tetracycline antibiotic, has demonstrated an exceptional ability to cross the BBB and block microglial activation and subsequent cytokine

release.[34] Additionally, some preclinical studies show that Minocycline can inactivate the KYN pathway involved in neuroinflammation by inhibiting the rate-limiting enzyme IDO.[35] Agmatine, a polyamine, has been shown to have antidepressant effects in various animal models. It acted on the NLRP3 inflammasome pathway in the prefrontal and frontal cortex and hippocampus of mice, affecting the reward pathway.[36]

A second-line antidiabetic, Pioglitazone, has also experimentally shown anti-inflammatory, neuroprotective, and anti-excitotoxic properties. A randomised control trial investigated 37 individuals suffering from depression and found that 12 weeks of pioglitazone as an adjuvant to a standard psychiatric regimen significantly improved the antidepressant effect in patients with insulin resistance as well as in younger patients.[37] Apart from pharmacological modalities, certain neuromodulation techniques like transcranial magnetic stimulation, transcranial electrical stimulation, photo biomodulation, electroconvulsive therapy, transcranial ultrasound stimulation, Deep brain stimulation, vagus nerve stimulation have also been shown to affect the inflammatory response of the body during their application, hence working on depression.[38]

DISCUSSION

The accumulated evidence underscores the central role of neuroinflammation in modulating the brain's reward circuitry and contributing to the development and persistence of depressive symptoms. Inflammatory cytokines such as IL-6, TNF-α, and IFN-α interfere with dopamine synthesis and reuptake, impairing reward signalling, particularly in mesolimbic structures such as the ventral striatum, ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC).

Functional neuroimaging studies consistently demonstrate disrupted connectivity in these regions in depressed patients with elevated inflammatory markers. The relationship between inflammation and reward processing appears bidirectional and complex. Cytokines not only reduce dopamine availability through enzymatic competition and transporter regulation but also alter the structural and functional architecture of key brain regions. These disruptions correlate strongly with clinical features such as anhedonia, psychomotor slowing, and fatigue. Furthermore, the heterogeneity in inflammatory responses among depression subtypes, such as melancholic versus atypical, adds another layer of complexity. Atypical and treatment-resistant depression often show higher systemic inflammatory markers and different cortisol dynamics compared to melancholic depression.

These findings support a model of depression that is not monolithic but biologically stratified, suggesting that targeted anti-inflammatory interventions could be more effective in certain subgroups. Therapeutically, anti-inflammatory agents from TNF antagonists like infliximab to repurposed medications such as minocycline and pioglitazone have shown promise in modulating inflammation- linked neural dysfunction. Adjunctive therapies combining traditional antidepressants with anti-inflammatory agents appear particularly effective in treatment-resistant populations. Novel approaches like probiotics, cannabinoids, and psychedelics, which exert immunomodulatory effects, further broaden the therapeutic landscape.

However, while the preliminary findings are encouraging, limitations persist. Many studies are constrained by small sample sizes, short follow-up durations, and heterogeneity in outcome measures. Additionally, not all patients with elevated inflammatory markers respond to anti-inflammatory treatments, indicating that further biomarker-driven stratification is necessary.

CONCLUSION

The integration of neuroinflammatory mechanisms into our understanding of depression marks a significant shift from traditional monoamine-based theories.

This review highlights the intricate interplay between immune signalling and the brain's reward system, shedding light on how chronic inflammation contributes to anhedonia and motivational deficits in depression. It also reveals how these insights may pave the way for more precise, biologically informed interventions.

As research progresses, future studies must aim to standardize measurement tools, stratify patient populations based on inflammatory profiles, and explore long-term efficacy and safety of immunomodulatory treatments. Understanding individual differences in neuro-inflammatory responses could lead to personalized therapeutic strategies, offering new hope to patients with depression, particularly those unresponsive to conventional treatments.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sharma S, Kaur H, Kumar AJ, Gandhi D, Malhotra V, Srinivasan S, et al. Inflamed and unrewarded: a narrative review exploring neuroinflammation and its impact on the brain's reward mechanisms. Int J Res Med Sci 2025;13:4498-505.