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(REVIEW ARTICLE)

Neuroinflammation in major depressive disorder: Mechanisms, biomarkers, and emerging therapeutic targets

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Abstract

Major depressive disorder (MDD) affects an estimated 280 million people worldwide and remains a leading cause of disability. The monoamine hypothesis, and later the neuroplasticity hypothesis, transformed treatment but leave a substantial share of patients with delayed response, partial remission, or outright treatment resistance. Over the past two decades, evidence has accumulated that a subset of MDD is driven by chronic, low-grade neuroinflammation rather than, or in addition to, monoaminergic deficits.

This review synthesizes current evidence on the neuroimmune mechanisms involved in MDD microglial activation, pro-inflammatory cytokine signaling, blood–brain barrier disruption, oxidative stress, kynurenine pathway dysregulation, and impaired neuroplasticity and examines how these mechanisms are captured by peripheral, central, neuroimaging, and emerging molecular biomarkers. It then reviews therapeutic strategies that target inflammation directly (minocycline, celecoxib, TNF-α antagonists), indirectly (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), ketamine), or through lifestyle modification (exercise, diet, sleep), with attention to why inflammation-stratified trials have outperformed unstratified ones.

Across mechanisms, biomarkers, and treatment response, a consistent pattern emerges: neuroinflammation does not simply co-occur with depression, it may mark a biologically distinct, identifiable subtype roughly a quarter to a third of patients with elevated high-sensitivity C-reactive protein (hsCRP) or IL-6 for whom anti-inflammatory or immune-modulating strategies produce disproportionate benefit. Overall, the findings suggest that neuroinflammation represents a promising and increasingly actionable target for biomarker-guided, personalized psychiatric care.

Keywords: Major depressive disorder; Neuroinflammation; Microglia; Inflammatory biomarkers; Kynurenine pathway; Precision psychiatry.

1. Introduction

Depression is one of the most common and disabling psychiatric conditions worldwide, affecting an estimated 280 million people and ranking among the leading causes of years lived with disability[1]. Beyond its personal toll, MDD carries substantial economic and public health burden through lost productivity, medical comorbidity, and elevated suicide risk.

For decades, treatment has been guided mainly by the monoamine hypothesis, which attributes depressive symptoms to deficient serotonergic, noradrenergic, or dopaminergic transmission, and by the newer neuroplasticity hypothesis, which emphasizes impaired synaptic connectivity and reduced hippocampal neurogenesis as the deeper substrate beneath monoamine changes.

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The neuroplasticity framework, most visibly validated by the rapid, synapse-restoring effects of ketamine, has reframed depression as a disorder of structural and functional brain connectivity rather than a simple chemical deficiency[2]. Yet neither framework fully explains why roughly a third of patients fail to achieve remission after multiple medication trials, why antidepressant response is often delayed by weeks despite immediate receptor occupancy, or why depression is biologically heterogeneous.

Although neuroinflammation has become an increasingly recognized contributor to the pathophysiology of major depressive disorder (MDD), existing reviews often focus on individual aspects of the inflammatory response, such as cytokine signaling, microglial activation, or specific therapeutic interventions, rather than integrating these findings into a unified mechanistic framework. In addition, rapid advances in biomarker discovery, neuroimaging, precision psychiatric and immune-targeted therapies have significantly expanded the field over the past few years. This review synthesizes current evidence on the neuroinflammatory mechanisms underlying MDD, examines established and emerging biomarkers and discussed evolving therapeutic strategies, with particular emphasis on how these advances may facilitate biomarker-guided, personalized approaches to diagnosis and treatment.

2. Methods

This narrative review was informed by a targeted literature search of PubMed, Google Scholar, and major scientific publisher databases, including Nature Portfolio, Frontiers, Elsevier (ScienceDirect), Wiley, and Springer, to identify publications examining neuroinflammation in major depressive disorder (MDD). The search primarily covered literature published between January 2023 and March 2026, while incorporating landmark studies that established foundational concepts in the field, including the work of Dantzer et al. (2008), Raison et al. (2013), Yirmiya et al. (2015), Duman et al. (2016), and Miller and Raison (2016).

Search terms included combinations of major depressive disorder, depression, neuroinflammation, microglia, cytokines, blood-brain barrier, kynurenine pathway, oxidative stress, TSPO-PET, biomarkers, and therapeutic keywords such as minocycline, celecoxib, infliximab, ketamine, exercise, and precision psychiatry.

Priority was given to systematic reviews, meta-analyses, randomized controlled trials, and high-quality mechanistic studies, while landmark investigations were retained where they provided seminal evidence or established concepts that continue to inform contemporary research. Studies were selected based on their relevance to the review's primary themes, including neuroinflammatory mechanisms, inflammatory biomarkers, neuroimaging, and emerging therapeutic strategies in major depressive disorder (MDD).

3. The Neuroimmune System and Depression

The brain maintains a specialized, regulated immune system. Microglia, the brain's resident macrophages, continuously survey the parenchyma and shift from a surveillant resting state to an activated, pro-inflammatory state in response to injury, infection, or psychological stress[5,6]. Astrocytes, typically viewed as purely supportive glia, also participate directly in immune signaling and, together with microglia, can propagate inflammatory cascades throughout brain circuits implicated in mood regulation.

The blood–brain barrier (BBB) normally restricts the entry of peripheral immune cells and inflammatory mediators into the central nervous system. Chronic psychological stress and systemic inflammation, however, can compromise BBB integrity, allowing peripheral cytokines and, in some cases, monocytes to enter brain parenchyma and interact directly with neurons and glia. This mechanism has emerged as a bridge between peripheral systemic inflammation and central neuroinflammation in MDD.

The principal signaling molecules in this system are pro-inflammatory cytokines, most consistently interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ). These cytokines act on brain regions governing mood, motivation, and cognition the prefrontal cortex, hippocampus, and basal ganglia altering neurotransmitter metabolism, synaptic plasticity, and neuroendocrine (HPA axis) regulation[7,8]. This convergence of systemic and central immune signaling forms the biological basis for the neuroinflammatory hypothesis of depression developed in the sections that follow.

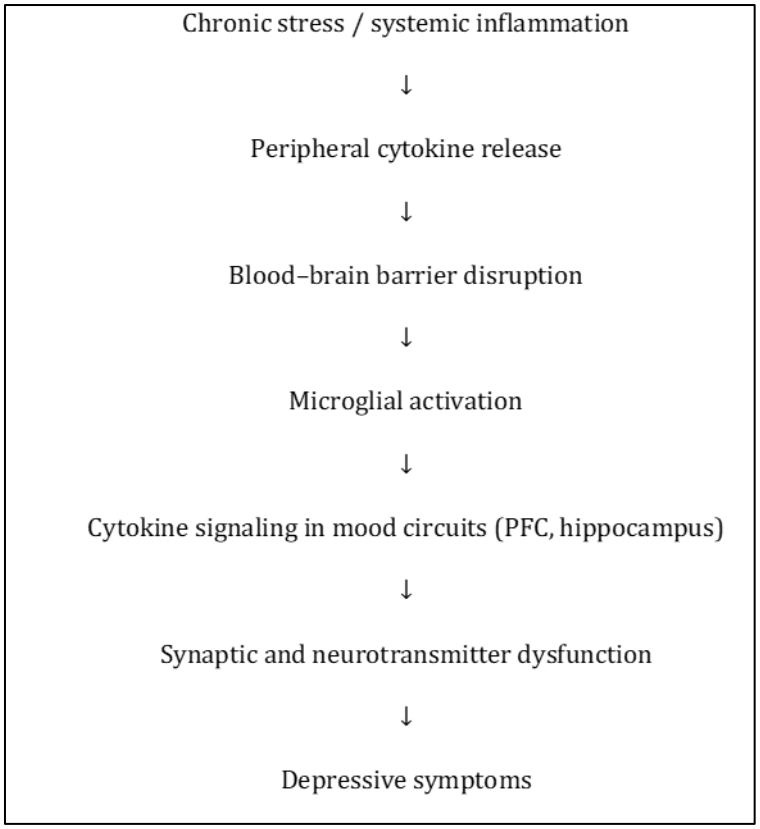

Figure 1 The neuroinflammatory cascade proposed to link systemic stress and inflammation to depressive symptoms.

4. Neuroinflammatory Mechanisms in Depression

4.1. Microglial Activation

In the healthy brain, microglia exist in a ramified, surveillant state, continuously sampling their environment without releasing inflammatory mediators. Under chronic stress or peripheral inflammatory challenge, microglia shift toward an activated, amoeboid morphology characterized by increased pro-inflammatory cytokine production and altered phagocytic activity[5,6]. Sustained activation is of particular concern because activated microglia mediate excessive synaptic pruning via the complement system, a process that, when dysregulated, may contribute to the reduced synaptic density observed in depression. Positron emission tomography (PET) studies using translocator protein (TSPO) radioligands have repeatedly found elevated microglial marker binding in the prefrontal cortex, anterior cingulate cortex, hippocampus, and insula of individuals with MDD, particularly those with greater symptom severity or suicidal ideation[13,14,15], providing direct in vivo evidence that this cellular process occurs in living patients rather than only in animal models.

4.2. Cytokine Signaling

IL-6, TNF-α, and IL-1β act on neurons through well-characterized receptor pathways that alter monoamine synthesis, reuptake, and receptor sensitivity. Chronically elevated cytokine signaling activates indoleamine 2,3-dioxygenase (IDO), shifting tryptophan metabolism away from serotonin synthesis (discussed further below), and activates the kynurenine pathway toward neurotoxic metabolites. Cytokines also act on the hypothalamic-pituitary-adrenal (HPA) axis, often producing the glucocorticoid resistance and cortisol dysregulation seen in many patients with depression, further compounding neuroinflammatory signaling in a feed-forward loop.

4.3. Oxidative Stress

Activated microglia and infiltrating immune cells generate reactive oxygen species (ROS) as part of the inflammatory response. In the CNS, this oxidative burden is compounded by the brain's high metabolic rate, high lipid content, and comparatively limited antioxidant reserves, making neurons particularly vulnerable to oxidative damage[5,9]. Chronic oxidative stress impairs mitochondrial function, promotes lipid peroxidation of neuronal membranes, and can produce

oxidative DNA damage each of which further compromises neuroplasticity and cellular resilience, and each of which has been reported at elevated levels in depressed patients relative to controls.

4.4. The Kynurenine Pathway

The kynurenine pathway is the principal route of tryptophan catabolism outside of serotonin synthesis, and it is one of the most direct mechanistic links between inflammation and depressive neurobiology. Under inflammatory conditions, cytokine-driven activation of indoleamine 2,3-dioxygenase (IDO) with concurrent suppression of tryptophan 2,3-dioxygenase (TDO) diverts tryptophan away from serotonin production and toward kynurenine[10,11]. Kynurenine is then metabolized along two competing branches: in astrocytes, kynurenine aminotransferase produces kynurenic acid, an NMDA receptor antagonist with neuroprotective properties; in microglia, kynurenine 3-monooxygenase instead produces 3-hydroxykynurenine and, downstream, quinolinic acid, a potent NMDA receptor agonist with excitotoxic and pro-oxidant effects.

Meta-analytic evidence indicates that depressed patients show a shift toward this neurotoxic branch reduced kynurenic acid and, in unmedicated patients, elevated quinolinic acid relative to controls producing an imbalanced kynurenic acid-to-quinolinic acid ratio that favors NMDA receptor overactivation and excitotoxicity[12]. Peripheral kynurenine metabolites also correlate with structural brain measures, including hippocampal and amygdalar volume, as well as suicide risk, further supporting Kynurenine pathway as both a mechanistic driver and a measurable biomarker of neuroinflammatory depression.

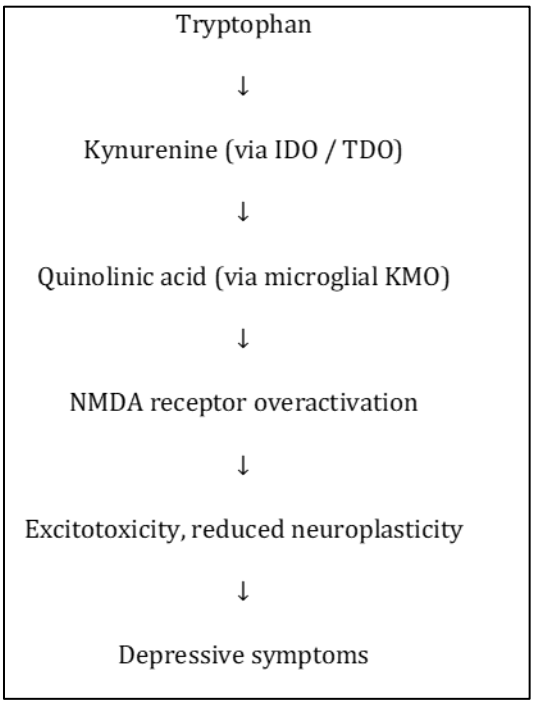

Figure 2 The kynurenine pathway as a mechanistic bridge between inflammation and glutamatergic excitotoxicity in depression.

4.5. Neuroplasticity: BDNF, Hippocampus, and Neurogenesis

Brain-derived neurotrophic factor (BDNF) supports synaptic growth, dendritic spine density, and hippocampal neurogenesis. Chronic inflammation suppresses BDNF signaling both directly, via cytokine effects on translation, and indirectly, via glucocorticoid dysregulation and excitotoxic kynurenine metabolites[2,22]. The resulting loss of synaptic density and impaired hippocampal neurogenesis is now considered a convergence point for monoaminergic, inflammatory, and stress-related models of depression alike one reason rapid restoration of BDNF/mTOR signaling, as seen with ketamine, produces such distinctive clinical effects.

5. Neuroinflammatory Biomarkers

5.1. Peripheral Biomarkers

Blood-based markers remain the most accessible and widely studied biomarkers in MDD. High-sensitivity C-reactive protein (hsCRP), IL-6, TNF-α, and IL-1β are consistently elevated, on average, in depressed cohorts relative to controls, and elevated hsCRP in particular has been used to define an "immune-mediated" or "inflammatory" subtype of depression estimated at up to 30% of patients that is disproportionately marked by atypical symptoms such as fatigue, hypersomnia, and increased appetite, and disproportionately unresponsive to first-line antidepressants[17,18]. This subtype framing, rather than treating inflammation as a uniform feature of MDD, is central to current clinical trial design.

5.2. Central Biomarkers

Cerebrospinal fluid studies allow more direct sampling of central inflammatory and kynurenine pathway metabolites, though they are invasive and less feasible for large studies. In vivo, TSPO-PET imaging has become the principal tool for visualizing microglial activation in living patients, with the majority of studies reporting elevated TSPO binding in MDD, particularly in prefrontal, cingulate, and hippocampal regions[13,14,15], though findings are not fully consistent across radioligands and patient populations, underscoring the need for standardized imaging protocols.

5.3. Neuroimaging and Emerging Biomarkers

Structural and functional MRI studies link inflammatory markers to reduced hippocampal volume, altered white matter integrity, and disrupted connectivity within reward and salience networks, demonstrating an intermediate phenotype between molecular inflammation and clinical symptoms. Beyond established markers, extracellular vesicles, circulating microRNAs, and multi-omic (proteomic and metabolomic) profiling are emerging as higher-resolution tools for characterizing inflammatory subtypes of depression.

MicroRNAs have drawn attention as regulators that sit directly upstream of microglial polarization, cytokine release, and blood-brain barrier integrity, positioning them as both mechanistic actors and candidate biomarkers, although discordance between peripheral and central microRNA profiles and a lack of standardized reference ranges currently limit clinical translation[16].

Table 1 Major inflammatory biomarkers implicated in major depressive disorder.

Biomarker	Role	Clinical significance
IL-6	Pro-inflammatory cytokine	Elevated in MDD; predicts poorer antidepressant response
TNF-α	Pro-inflammatory cytokine; neurotoxic signaling	Associated with symptom severity and treatment resistance
hsCRP	Acute-phase systemic inflammation marker	Used to stratify "inflammatory" MDD subtype (commonly >3 mg/L)
IL-1β	Pro-inflammatory cytokine	Linked to synaptic dysfunction and HPA axis dysregulation
TSPO (PET)	Marker of activated microglia	Elevated binding in PFC, cingulate, hippocampus in MDD

Table 2 Core neuroinflammatory mechanisms in depression by implicated brain region and downstream effect.

Mechanism	**Brain region(s) most implicated**	**Principal effect**
Microglial activation	Prefrontal cortex, hippocampus, cingulate cortex	Excessive synaptic pruning, sustained cytokine release
Cytokine signaling (IL-6, TNF-α, IL-1β)	HPA axis, hippocampus, prefrontal cortex	Altered monoamine metabolism, glucocorticoid resistance

Kynurenine pathway / quinolinic acid	Hippocampus, anterior cingulate cortex	NMDA receptor overactivation, excitotoxicity
Oxidative stress	Mitochondria-rich regions (hippocampus, PFC)	Lipid peroxidation, DNA damage, impaired plasticity
Blood–brain barrier disruption	Cerebral microvasculature	Peripheral immune cell and cytokine infiltration

6. Therapeutic Targets

6.1. Conventional Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were not designed as anti-inflammatory agents, but a portion of their clinical benefit may derive from secondary immunomodulatory effects; for example, the multimodal antidepressant vortioxetine has been shown to inhibit NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome signaling, contributing to both antidepressant and cognitive benefits[6]. More broadly, meta-analyses find that successful antidepressant treatment is associated with modest reductions in circulating IL-1β and IL-6, suggesting a bidirectional relationship between mood improvement and peripheral inflammation.

6.2. Ketamine and Rapid-Acting Agents

Ketamine's rapid antidepressant effect is mediated primarily through N-methyl-D-aspartate (NMDA) receptor blockade on gamma-aminobutyric acid (GABA)-ergic interneurons, producing a glutamate surge, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation, and downstream brain-derived neurotrophic factor (BDNF) release and mechanistic target of rapamycin (mTOR)-dependent synaptic protein synthesis a mechanism that directly restores the synaptic connectivity eroded by chronic inflammation and excitotoxic kynurenine signaling[22,23]. This mechanistic overlap ketamine acting on the same NMDA receptor system that quinolinic acid pathologically overactivates is one reason the drug is of particular interest in inflammation-associated depression, although direct anti-inflammatory stratification trials for ketamine remain limited relative to those for nonsteroidal anti-inflammatory drugs (NSAIDs) and minocycline.

6.3. Anti-Inflammatory Agents

Directly targeting inflammation has produced instructive, albeit mixed, clinical trial results. In an early randomized trial of the TNF-α antagonist infliximab, the drug showed no overall benefit over placebo in treatment-resistant depression. However, in a post-hoc analysis, patients with baseline C-reactive protein (CRP) above 5 mg/L improved significantly more with infliximab than with placebo, while lower-inflammation patients did worse on active drug than placebo[19]. This single finding reshaped the field's approach: rather than treating "depression" as a uniform target, subsequent trials have prospectively stratified patients by baseline high-sensitivity C-reactive protein (hsCRP) before randomizing to minocycline or celecoxib, an approach exemplified by the MINDEP and INSTA-MD trials[17,18]. A 2025 systematic review and meta-analysis of anti-inflammatory augmentation trials found that benefits on depressive symptoms and anhedonia were concentrated in patients with elevated baseline inflammation, reinforcing that immune-targeted treatment is a subtype-specific rather than universal strategy[20]. Low-dose interleukin-2, which expands regulatory T-cell populations rather than blocking inflammation outright, has also shown early promise as an immune-modulating antidepressant augmentation strategy[21].

6.4. Lifestyle Interventions

Exercise is among the best-studied non-pharmacological anti-inflammatory interventions in depression. Meta-analyses of exercise trials in depressed populations report reductions in CRP, IL-1β, and TNF-α alongside increases in the anti-inflammatory cytokine IL-10 following sustained training, with reductions in inflammatory markers statistically predicting improvement in depressive symptoms[24,25,26]. Mediterranean-style dietary patterns, adequate sleep, and stress-reduction practices are similarly associated with lower systemic inflammation, though trial evidence specific to depression outcomes is less mature than for exercise.

6.5. Novel and Emerging Therapies

Stem cell-based and regenerative approaches remain preclinical for MDD. Psychedelic-assisted therapies (e.g., psilocybin) show rapid, sustained antidepressant effects thought to converge on the same synaptic plasticity pathways engaged by ketamine, with immunomodulatory effects an active area of investigation. Neuromodulation techniques including transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) have documented effects on peripheral and central inflammatory markers, though their primary mechanism is understood to be circuit-level rather than immunological.

Table 3 Current and emerging therapeutic strategies targeting neuroinflammation in depression**.**

Treatment	Primary mechanism	Evidence base
SSRIs/SNRIs	Monoamine reuptake inhibition; secondary anti-inflammatory effects	Modest reduction in IL-6/IL-1β with treatment response
Ketamine	NMDA blockade → BDNF/mTOR-driven synaptogenesis	Rapid, robust effect in treatment-resistant depression
Minocycline / celecoxib	Microglial inhibition / COX-2 inhibition	Benefit concentrated in hsCRP-elevated subgroups
Infliximab (TNF-α antagonist)	Direct cytokine blockade	No overall effect; benefit only above CRP >5 mg/L
Exercise	Reduced CRP/TNF-α, increased IL-10, BDNF upregulation	Consistent modest anti-inflammatory and mood benefit

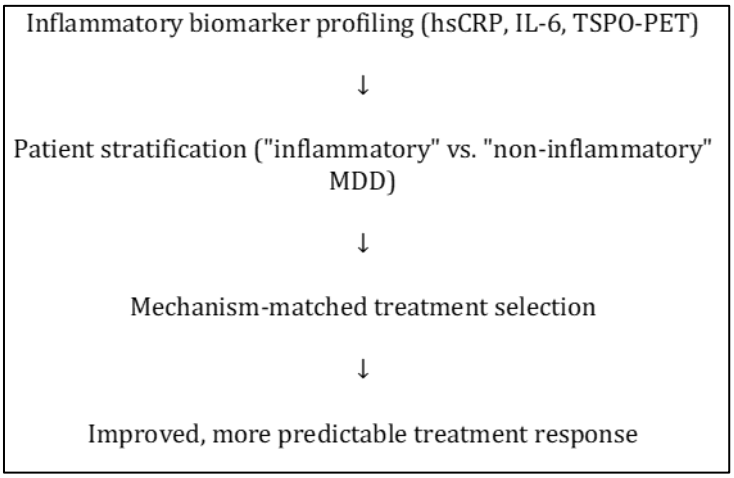

Figure 3 A biomarker-guided treatment selection pathway for inflammation-associated depression.

7. Future Directions

The clearest lesson from two decades of anti-inflammatory depression trials is that inflammation marks a subtype, not the whole disorder which reframes the central task ahead as one of stratification rather than blanket treatment. Precision psychiatry initiatives are increasingly combining genomic, transcriptomic, proteomic, and metabolomic data with neuroimaging and digital phenotyping (wearable-derived sleep, activity, and heart-rate variability data) to build more complete, individualized biological profiles of depression[27,28,29,30]. Machine learning models trained on these multi-omic datasets are being explored as tools to predict, before treatment begins, which patients are likely to respond to immune-targeted versus monoaminergic versus neuroplasticity-targeted interventions.

Practical barriers remain substantial: multi-omic biomarker platforms are expensive and not yet standardized across laboratories, prospective biomarker-guided trials are still relatively few, and clinical workflows for interpreting composite inflammatory-genomic risk scores do not yet exist in routine psychiatric practice. Combination therapies for

example, pairing an anti-inflammatory agent with a rapid-acting glutamatergic drug in inflammation-positive, treatment-resistant patients represent a promising but still largely untested direction warranting dedicated trial design.

8. Conclusion

The evidence reviewed here traces a coherent path: chronic stress and systemic inflammation compromise the blood-brain barrier and activate microglia; activated microglia and circulating cytokines drive oxidative stress and divert tryptophan metabolism toward neurotoxic kynurenine pathway products; the resulting excitotoxicity and impaired neuroplasticity produce and sustain depressive symptoms; and each of these steps is measurable, and in some cases treatable, with existing or emerging clinical tools.

Neuroinflammation is not simply associated with depression accumulating biomarker and treatment-response data suggest it may define a biologically distinct subtype of the disorder, identifiable through peripheral and central biomarkers and disproportionately responsive to immune-targeted intervention. Neuroinflammation therefore represents one of the most promising avenues for understanding the biological heterogeneity of depression and developing more personalized, biomarker-guided therapeutic strategies.

Compliance with ethical standards

Disclosure of Conflict of Interest

The author declares that there are no conflicts of interest related to this work.

Statement of Ethical approval

Ethical approval was not required for this study, as it is a narrative literature review based exclusively on previously published research and did not involve human participants, animals, or the collection of primary data.

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