



Neuroinflammation in Major Depressive Disorder: Molecular Mechanisms, Biomarker Signatures, and Emerging Anti-Inflammatory Therapeutic Strategies

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ABSTRACT

Major Depressive Disorder (MDD) is a multifactorial psychiatric disorder and a leading cause of disability worldwide. Although the monoamine hypothesis has guided antidepressant development for decades, its limited therapeutic efficacy has prompted growing interest in the inflammatory hypothesis of depression. This review comprehensively examines the role of neuroinflammation in the pathogenesis and progression of MDD, emphasizing the complex interactions between peripheral immune activation and central nervous system dysfunction. Elevated inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), and C-reactive protein (CRP), are discussed as potential diagnostic and prognostic indicators associated with disease severity and treatment response. The review further explores key neurobiological mechanisms, including blood-brain barrier disruption, microglial activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, alterations in the kynurenine pathway, impaired neurogenesis, and gut-brain axis dysfunction, which collectively contribute to depressive pathology. Emerging neuroimaging biomarkers, particularly translocator protein (TSPO)-based positron emission tomography, are also highlighted for their potential to assess neuroinflammatory activity in vivo. In addition, current evidence supporting anti-inflammatory therapeutic approaches, including non-steroidal anti-inflammatory drugs, cytokine inhibitors, omega-3 polyunsaturated fatty acids, minocycline, ketamine, and lifestyle-based interventions, is critically reviewed. Despite encouraging findings, significant challenges remain regarding biomarker standardization, patient stratification, and clinical translation. Future research integrating multi-omics technologies, advanced neuroimaging, and precision medicine approaches may facilitate biomarker-guided personalized therapies. Overall, this review underscores neuroinflammation as a critical biological contributor to MDD and highlights its potential as a promising target for improving diagnosis, treatment, and long-term clinical outcomes.

Keywords: Major Depressive Disorder (MDD), Neuroinflammation, Inflammatory Biomarkers, Microglial Activation, Precision Medicine.

INTRODUCTION

Depression, therefore, cannot be considered just an emotional state or a passing phase but a chronic illness that affects patients and the entire society significantly. The World Health Organisation consistently reports that there are roughly 350 million people affected by depression worldwide at any time, and nearly 1 million people commit suicide each year due to depression^{1,2}. Clinically, depression involves a depressed mood that is sustained for over 2 weeks; a lack of interest in things that used to be enjoyable for the patient; and other signs and symptoms that involve impaired cognition and disturbed mood that are usually associated with sleep and appetite disturbance and a feeling of worthlessness/suicidal ideation^{3,4}.

For many decades in the 20th century, depression was explained by the monoamine hypothesis. The hypothesis suggested that low-level concentrations of 3 neurotransmitters (serotonin, norepinephrine, and dopamine) cause depression. Following this discovery, the first antidepressant drugs (e.g., SSRIs and SNRIs) were invented and administered. The most significant discovery

from clinical application is, however, that the therapeutic gap between treating patients and full remission of their depression symptoms is enormous⁵. This spurred the search for alternative theories of depression, one of which is the inflammatory hypothesis of depression⁶.

The inflammatory hypothesis proposes that peripheral immune activation, indicated by high levels of peripheral cytokines and acute phase protein concentrations, may impact the brain through several routes: entry of inflammatory molecules across the blood-brain barrier, the activation of glial cells, a detrimental alteration of monoamines via the kynurenine pathway, and a deregulated HPA axis. These effects are not unsubstantiated. In recent years, meta-analyses have consistently found higher peripheral inflammatory marker concentrations in MDD compared to controls^{7,8}.

In this review, I will aim to look at inflammation and depression in terms of (1) peripheral immune activation and consequent central neuroinflammation, (2) peripheral depression-related biomarkers, (3) the effects of inflammation on neurobiology, and finally, (4) treatment strategies available or that could be employed for



depression. It is by bringing these aspects together that the gap will be bridged and the way for specific inflammation-based treatments for depression will be made available.

1. Neuroinflammation: Mechanisms and Pathways in Depression

1.1 Defining Neuroinflammation in a Psychiatric Context

Neuroinflammation is defined as Central Nervous System (CNS) inflammation, including glial activation as well as the recruitment of adaptive immune cells². Some transient neuroinflammation is helpful in the CNS. It helps clear pathogens, repair tissues, and support proper development of the central nervous system⁹. Uncontrolled inflammation in the brain is connected to depression and causes harmful changes in the central nervous system. The blood-brain barrier (BBB) plays a vital role in isolating the CNS from the immune system. In neuroinflammation and systemic inflammation, there is some release of certain pro-inflammatory cytokines that can damage the BBB^{10,11}. And the damage to the BBB may promote neuroinflammation sustained within the CNS.

1.2 Microglial Activation and Glial Dysregulation

Microglia are uniquely positioned, being the primary immunological sentinels in the central nervous system. Microglia continuously monitor the neuronal environment in their resting state. Peripheral and central inflammatory cues prompt a transition, both morphologically and functionally, leading to a cascade of pro-inflammatory mediators, including tumour necrosis factor-alpha (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6) and reactive oxygen species. Chronic activation of the microglia has been linked to synaptic stripping, impairment of neurogenesis, and ultimately the chronic neuroinflammatory condition thought to underlie some presentations of depression, while acute activation is beneficial⁶.

It is also important to note the role of the astrocyte. Astrocytes are essential to both the neuroinflammatory response and tryptophan kynurenine metabolism, which has a direct bearing on both serotonin levels and mood¹². As well as the standard role in synaptic support and clearance of neurotransmitters. Thus, in the context of a chronic inflammatory response, failure of the astrocyte can contribute to the structural and neurochemical effects of peripheral immune activation.

1.3 The Blood–Brain Barrier as a Critical Interface

The most important anatomophysiological separation between the CNS and peripheral blood flow is the BBB. It is widely reported that inflammation associated with depression causes clinical disruption to the BBB¹³. In particular, TNF and IL-6 attack junction proteins and cause leakage through paracellular pathways¹⁴.

Once this boundary has been breached, then monocytes, macrophages and soluble pro-inflammatory substances can penetrate into the brain, inducing neuroinflammation and microglial activation, which can form a positive feedback loop.

This hypothesis is also backed up by data derived from post-mortem analyses on individuals suffering from depression. Research has found that people who are depressed often have higher levels of inflammatory substances in their cerebrospinal fluid, more active macrophages and microglia in areas of the brain like the frontal cortex and hippocampus, and more genes related to inflammation being expressed in the brain tissue compared to people who are not depressed¹⁴. This would suggest that peripheral inflammation has an active role in the neuropathophysiology of depression and is not simply an epiphenomenon.

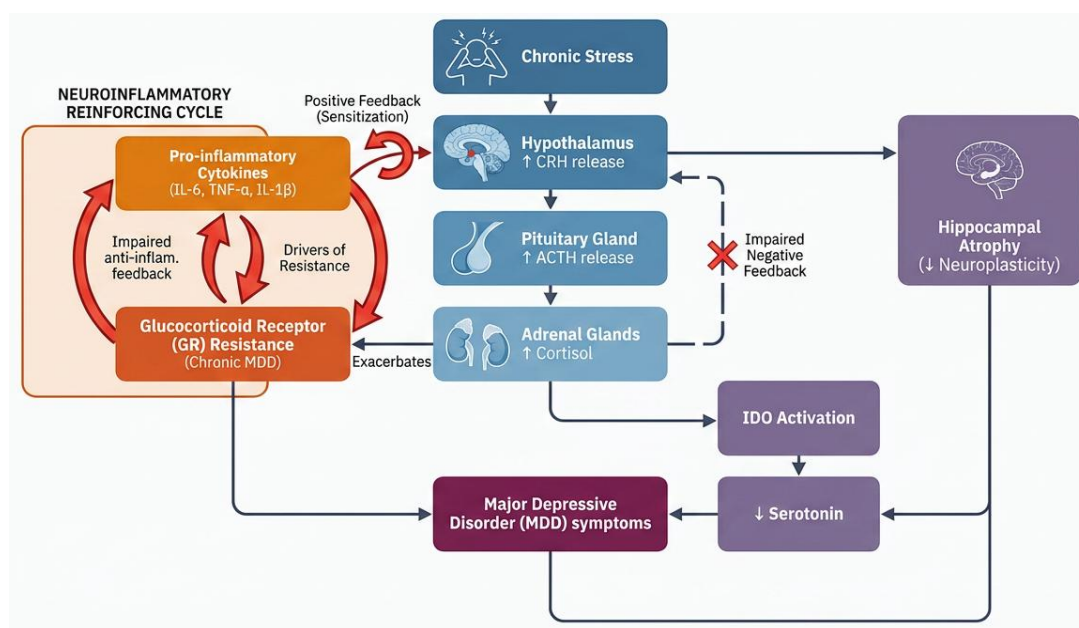


Figure 1: Chronic stress activates the HPA axis, increasing cortisol and inflammatory cytokines. Impaired GR feedback maintains this imbalance, contributing to the development of MDD.

1.4 The HPA Axis, Stress, and Inflammatory Dysregulation

The HPA axis is of central importance to neuroinflammation in depression. Psychological and physiological stressors lead to activation of the hypothalamus, release of corticotropin-releasing hormone (CRH), stimulation of the pituitary to release adrenocorticotrophic hormone (ACTH), and, subsequently, stimulation of the adrenal glands to release cortisol. Ordinarily, cortisol inhibits the axis through negative feedback mechanisms; it also has potent anti-inflammatory actions. With chronic stress or major depressive disorder (MDD), however, glucocorticoid receptor (GR) resistance occurs, which interferes with both the negative feedback inhibition and the anti-inflammatory action of cortisol¹⁵.

This chronic hypercortisolaemia results in non-suppression of inflammation but rather concomitant high pro-inflammatory cytokines, atrophy of the hippocampus, lack of neuroplasticity, and worse depressive symptoms. Cortisol additionally induces IDO, which shunts tryptophan from serotonin metabolism¹⁶.

2. Peripheral Inflammatory Biomarkers in Depression

2.1 Cytokines: IL-6, TNF- α , IL-1 β , and Beyond

Inflammatory cytokines IL-6, TNF-alpha, and IL-1, and the acute-phase protein CRP (C-reactive protein) are the most reliably replicated peripheral inflammatory markers of depression. In a series of meta-analyses of single studies, they are all significantly elevated in the peripheral blood of depressed subjects compared to normal, with IL-6 and CRP having the strongest and most consistent correlation¹⁷. Even after factors such as age, sex, body mass index, and smoking habits were controlled for, the effect still proved to be significant, suggesting that these cytokines were linked to depression itself, and not merely associated with lifestyle characteristics⁷.

IL-6 is another target that has attracted scientific attention both clinically and scientifically; a study that evaluated the activity of IL-6 by measuring a ratio including sIL-6 R and s glycoprotein 130 as well as serum IL-6, found a significant relationship between an increased ratio (which represents activity) and the presence of physical symptoms of depression, tiredness, overall depression, diminished quality of life and reduced movement and thought processes in depressed patients¹⁸. Further systematic review and meta-analysis by Elgellaie⁸ demonstrated that psychological symptoms of depression are related to pro-inflammatory cytokines, such as IL-1, IL-6, and TNF- α , and that the association may be different depending on the individual. Therefore, it may be of significant interest to realise that there may be biological variation in the relation between inflammation and depression. TNF- α plays a role beyond its functions as a pro-inflammatory signal; it can also be involved in altering the stability of the blood-brain barrier, promoting microglia activation, facilitating a shift in kynurenine metabolism and resulting in lower serotonin levels¹⁶.

Patients who were treated with a TNF- α inhibitor for inflammatory conditions such as rheumatoid arthritis also showed a greater improvement in mood than was expected from pain reduction alone, demonstrating the causal effect of TNF- α in depression. IL-1 is poorly studied as it circulates in very low levels in peripheral blood. Nevertheless, it has been studied in at least 14 meta-analytic research studies with inconsistent results, which may be related to different measurement techniques¹⁴.

However, it has a known effect within the nervous system as it has been implicated in the impairment of neurogenesis within the hippocampus, in reduced synaptogenesis, and in an increase in the degradation of Tryptophan by Indoleamine 2,3-dioxygenase (IDO).

In the more recent literature, additional cytokines, including IL-8, IL-2, IL-4, IL-17A, and TGF- β 1, have been reported to show significantly elevated levels in depression¹⁹.

IL-17A, which is produced by T helper 17 (Th17) cells, is an increasingly important target of interest in the context of brain inflammation²⁰.

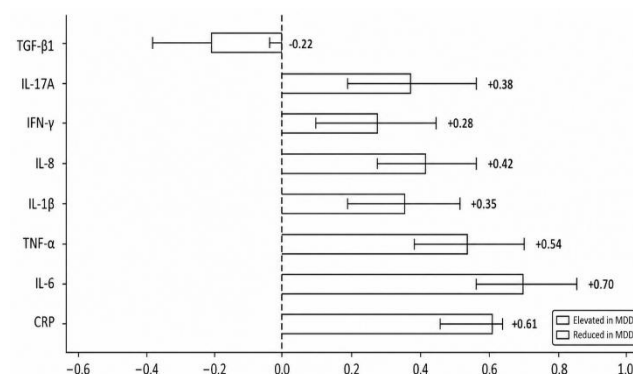


Figure 2: Compares inflammatory biomarkers between individuals with MDD and healthy controls. Positive SMD values indicate higher biomarker levels in patients with depression, while error bars show the 95% confidence intervals.

2.2 C-Reactive Protein (CRP) as a Clinical Biomarker

C-reactive protein is among all inflammatory markers that are available in the human body; it has gained most prominence as a useful marker in research into depression, partly due to being already included in standard laboratory test batteries, being cost-effective and well-tested. Several studies indicated a positive correlation between high levels of hs-CRP and a subgroup of depressed patients who report increased symptoms and impairments in thinking, as well as a worse outcome after treatment with antidepressant medication²¹.

Demonstrated that changes in inflammatory markers, including C-Reactive Protein Tracking, correlated with antidepressant response and long-term prognosis, suggesting that CRP tracking over the course of treatment might serve as a guide to therapeutic optimisation. This aligns with the notion that at least a subgroup of depressed patients, sometimes termed the inflammatory biotype, may

respond preferentially to treatments targeting inflammatory pathways rather than monoamine systems^{6,14}.

2.3 Translocator Protein (TSPO) and Neuroinflammatory Imaging Biomarkers

Neuroimaging in living patients with depression has further corroborated the role of neuroinflammation in CNS-level processes with studies of Positron Emission Tomography (PET) tracers targeting translocator protein (TSPO), a mitochondrial membrane protein present on activated microglia. Higher density of TSPO has been observed during the acute phase of depression, and its magnitude was positively related to depressive symptoms. A relatively high level of microglial activation was seen in the hippocampus, prefrontal cortex, and anterior cingulate cortex in patients suffering from depression. However, it should be noted that TSPO-PET is a research tool now, but the outcome proves the plausibility that neuroinflammation could be a CNS-level process in depression²².

3. Neurobiological Consequences of Inflammatory Dysregulation

3.1 The Kynurenine Pathway: Linking Inflammation to Serotonin Depletion

The kynurenine pathway of tryptophan catabolism is one of the most important and applicable inflammatory bridges connecting to depression. Since Trp, which is an essential amino acid and has to be obtained from the diet, is catabolized via two major metabolic pathways: the serotonin pathway and the kynurenine pathway. Normally, a large portion of Trp can be converted into serotonin, which is the neurotransmitter for the control of emotions, feelings and thoughts. However, in the context of inflammation, pro-inflammatory cytokines such as IFN-, IL-6 and TNF- greatly activate the enzyme Indoleamine 2,3-Dioxygenase (IDO). It is the enzyme that starts the kynurenine pathway, and it is the first and major step in the kynurenine pathway¹⁵.

It is the ever-increasing activation of the IDO that transports tryptophan ever more from serotonin to the kynurenine pathway. If only that were the case, as it decreases the amount of tryptophan for serotonin by far too much, that is, however, not all, after that the tryptophan degradation products enter microglial cells (immune cells found in the brain), where kynurenine monooxygenase (KMO) will further convert kynurenine into 3-hydroxykynurenine (3-HK) and ultimately to quinolinic acid (QUIN). According to Pharmacological Reports in 2025, it is a harmful substance that can make NMDA receptors overactive, leading to the damage or death of brain cells. However, tryptophan can also be produced in support cells, known as astrocytes, via a process involving kynurenine aminotransferases (KATs). This molecule is a blocker for N-methyl-D-aspartate (NMDA) receptors and may protect the brain from damage.

It is ultimately the competition of the KMO in the microglial cell (damaging) vs. kynurenine aminotransferases (KATs) in the astrocytes (protecting) that decides whether inflammation-mediated tryptophan breakdown has an adverse or beneficial effect in the brain²³.

In depression and particularly in treatment-resistant depression (TRD), the microglial neurotoxic branch appears to predominate, resulting in elevated quinolinic acid (QUIN), reduced kynurenic acid (KYNA), and increased QUIN/KYNA ratios, a profile associated with impaired neuroplasticity, synaptic dysfunction, and treatment resistance²⁴. The HPA axis further compounds this picture: elevated cortisol activates tryptophan 2,3-dioxygenase (TDO) in the liver, a parallel enzyme to IDO, which also promotes kynurenine production and amplifies the serotonin-depleting effect of chronic stress¹⁶.

3.2 Neurotrophic Factors, Neurogenesis, and Synaptic Dysfunction

Both the effects of inflammation on BDNF signalling and on neurogenesis are relevant, as these mechanisms are important for synaptic plasticity and emotional resilience⁷.

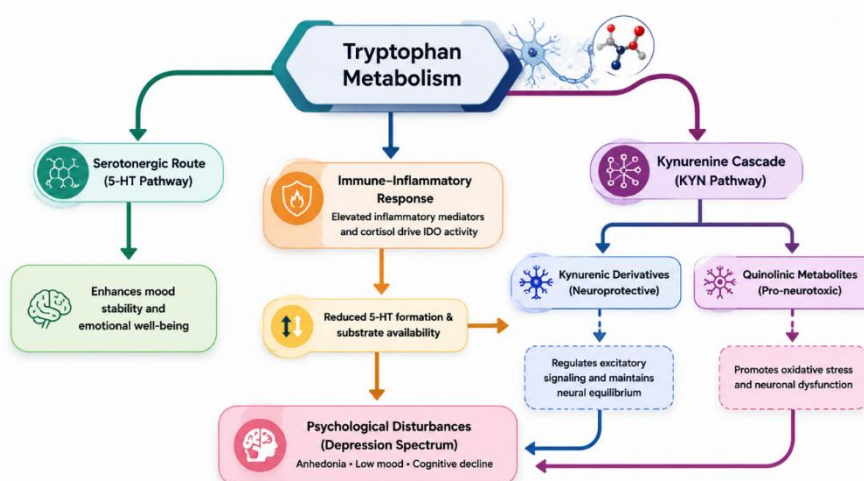


Figure 3: Inflammation activates the kynurenine pathway, diverting tryptophan metabolism from serotonin synthesis toward kynurenine metabolites, including neurotoxic QUIN and neuroprotective KYNA, which influence depression-related neurobiology.

Brain-Derived Neurotrophic Factor (BDNF) is vital for neuronal survival and dendritic arborisation, and for long-term potentiation; it is downregulated by pro-inflammatory cytokines. A deficit in the signalling by its receptor, Tropomyosin receptor kinase B (TrkB), is thought to underlie volume reduction and synaptic dysfunction in the hippocampus, two of the most prominent findings in MDD^{13,14}. The hippocampus appears particularly susceptible to inflammatory insult, with chronic inflammation, HPA axis hyperactivity and a decrease in BDNF interacting synergistically to decrease neurogenesis and grey matter volume in the hippocampus¹⁴, and impaired dentate gyrus neurogenesis is considered to be a cellular basis linking inflammation with memory loss, anhedonia and emotional blunting in depression.

3.3 Gut Microbiota, the Gut–Brain Axis, and Systemic Inflammation

The gut microbiome and its dialogue with the brain, the gut-brain axis, is a plausible mediator in this loop between inflammation and depression. The imbalance of healthy gut species in dysbiosis allegedly leads to an increase in permeability of the intestine, which subsequently leads to the passage of bacterial elements such as lipopolysaccharides (LPS) into the systemic circulation. Toll-Like Receptor 4 (TLR4) receptors are present on the cells in the immune system, and binding of LPS to TLR4 on these cells leads to very strong pro-inflammatory signalling pathways which raise the levels of circulating cytokines, thus initiating systemic low-grade inflammation. This is an intriguing correlation between such an unhealthy diet, antibiotics, early stress and possibly other gut-damaging influences and inflammatory propensity to depression.

4. Therapeutic Implications: Anti-Inflammatory Strategies in Depression

4.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The theory that inflammation is involved in depression has led to a vast amount of clinical trials using anti-inflammatory drugs as both adjuvant and primary treatments of the disorder. NSAIDs operate via inhibiting Cyclooxygenase enzymes (COX), thus blocking Prostaglandin E₂ (PGE₂) synthesis, and indirectly reducing IDO activation and tryptophan to kynurenine. This is the rationale for the use of NSAIDs in the treatment of depression, as supported by efficacy meta-analyses^{24,25}.

Celecoxib, the selective COX-2 inhibitor, has been the most investigated NSAID in this respect. The results of a meta-analysis of 4 RCTs showed a statistically significant increase in remission rate in MDD patients receiving celecoxib as an adjunct compared with placebo. Another large trial, in adults with osteoarthritis, demonstrated statistically significant improvement in depression score over placebo for both ibuprofen and naproxen. Long-term cardiovascular and gastrointestinal risk profile of NSAIDs, however, remains a cause of concern in their widespread clinical use and needs proper patient selection²⁶.

4.2 Cytokine Inhibitors and Targeted Biologics

There is a limited number of scientific research results indicating the efficacy of using certain biological agents aimed at reducing the impact of particular cytokines in alleviating the symptoms of depression in those patients who have inflammatory disorders along with their mental state disorder. One such biological substance, infliximab, which functions as a monoclonal antibody to TNF- α , is known to have an antidepressant effect in only those people who have depression in combination with an initially increased level of CRP. This fact is crucial to note, as it proves that inhibition of cytokines is the most effective strategy in the case of inflammatory depression²⁷. Other methods that act on cytokines, including inhibition of IL-6 receptors and IL-1 receptors, have also been explored. These drugs have demonstrated better moods among patients with autoimmune disorders and may provide some therapeutic value to individuals suffering from MDD due to inflammation⁷.

4.3 Omega-3 Fatty Acids

The anti-inflammatory nutraceutical agents that have been investigated thus far that show the most promise are the Omega-3 Polyunsaturated Fatty Acids (PUFAs), EPA (Eicosapentaenoic Acid) and DHA (Docosahexaenoic Acid). The role of NF- κ B (Nuclear Factor- κ B) as a primary controller of inflammation was also explored, with findings indicating that omega-3 PUFAs blocked NF- κ B²⁸. Meta-analysis has shown that omega-3 PUFA supplementation had a small but consistent effect on the improvement of depression symptoms, with Eicosapentaenoic Acid (EPA) being more effective at mood state improvement compared to Docosahexaenoic Acid (DHA)²⁹. Further support for the role of omega-3 in reducing inflammation has been reported, with diets high in omega-3 showing a correlation with a reduced prevalence of depression²⁵.

4.4 Minocycline as a Glial-Targeting Agent

The most potential re-purposed anti-inflammatory compound suggested to be used as an antidepressant is Minocycline. The second-generation tetracycline penetrating the central nervous system has powerful effects on inflammatory cells due to its easy passing through the BBB and having very good anti-inflammatory actions, such as the suppression of microglia, which are key effectors of neuroinflammation, inhibition of COX-2, caspase-1 and Matrix Metalloproteinases (MMPs)³⁰. In animal models for depression, the use of minocycline has revealed effective results consistently, which has resulted in reversal of depressive like behaviors, and some human trials show the presence of medium or high antidepressant effect in MDD patients³¹. Further clinical trials like NCT02456948 are being conducted on treatment-resistant depression patients and are likely to respond well to its mechanism of action²⁵.

4.5 Ketamine and Glutamate-Targeting Strategies

This has led to ketamine, a NMDA receptor antagonist that has revolutionised the management of Treatment-Resistant



Depression (TRD) to be identified as a rapid-acting antidepressant, and may, in part, work via anti-inflammatory mechanisms as well. QUIN, produced by the kynurene pathway described above, will overactivate the N-methyl-D-aspartate (NMDA) receptors and promote excitotoxicity and blocking this receptor by ketamine will break the cascade of neurotoxicity³². Systematic reviews have shown that ketamine can decrease the dysregulation of pro-inflammatory cytokines in adults with Treatment-Resistant Depression. (TRD)³³. And this simultaneous blockage of glutamatergic excitotoxicity and inflammation explains part of its novel, rapid-acting nature compared to typical antidepressants³².

4.6 Non-Pharmacological Approaches

Besides medication, several non-pharmacological treatments have proved to possess anti-inflammatory as well as antidepressant effects. Among those, exercise has

been best documented, with aerobic exercise decreasing systemic levels of CRP, IL-6 and TNF (all being inflammatory mediators) and increasing the levels of Brain-Derived Neurotrophic Factor (BDNF) and hippocampal neurogenesis²⁶. The most effective treatment available for patients with severe or treatment-resistant depression, electroconvulsive therapy (ECT), also seems to affect some immune markers, with certain pro-inflammatory cytokines being lowered after a treatment course.

The effects on inflammatory mediators associated with evidence-based psychotherapies, such as Cognitive Behavioural Therapy (CBT), appear to be less significant, although IL-6 and C-Reactive Protein have been observed to decrease after successful psychological treatment, implying that inflammation found in depression may be at least partly susceptible to psychotherapeutic interventions³⁴.

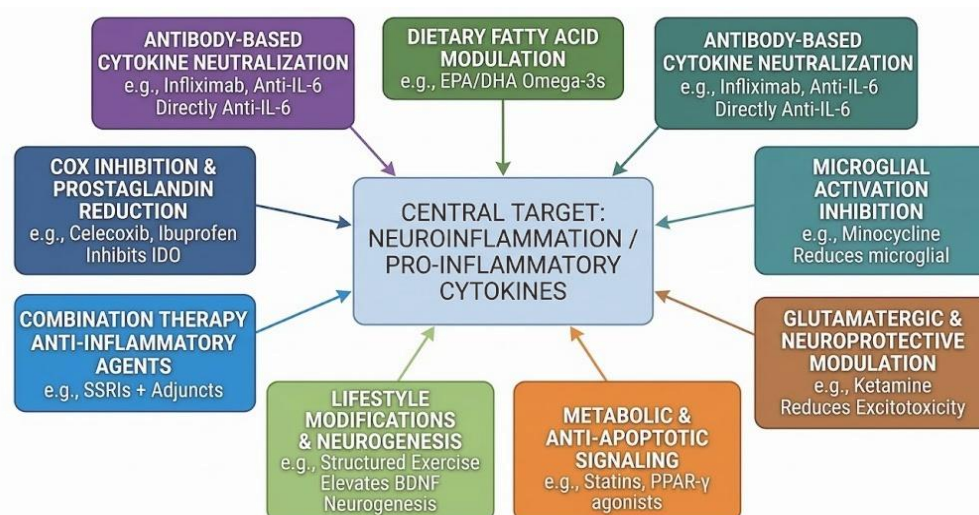


Figure 4: Anti-inflammatory therapies target key neuroinflammatory pathways in depression, with treatment selection guided by inflammatory biomarkers such as CRP and IL-6.

5. Challenges, Limitations, and Future Directions

While a substantial body of research already exists and is expanding quickly, there are several limitations that constrain translating this hypothesis into actual clinical practice. Firstly, while a clear connection has been proven to exist between neuroinflammation and major depression, whether neuroinflammation causes depression or depression, by virtue of the changes to one's behaviour caused by depression (such as increased stress, disturbed sleep pattern, unhealthy diet), remains uncertain¹⁴.

A second challenge in this field is the considerable methodological heterogeneity across studies, including differences in patient selection criteria, approaches used to identify neuroinflammation, methods for assessing depression severity, and treatment strategies. Consequently, there is limited consensus to support robust recommendations for clinical application. Furthermore, although the inflammatory hypothesis of depression provides a compelling theoretical framework, it has not yet

been fully integrated into clinical diagnostic practice. Not all individuals with depression exhibit inflammation-related abnormalities, and among those who do, substantial variability exists in both the extent of these abnormalities and their cytokine profiles⁶.

Another area of research is establishing cutoff values for inflammatory markers that correlate with differential treatment response. Research that looks more broadly at the field of inflammatory biomarkers associated with treatment response in depression is warranted. However, at least three broad areas of research seem most promising moving forward. The integration of multiple omics analysis, including genomics, metabolomics, proteomics, and microbiomics, along with inflammatory marker measurement, can provide insight into the biological subtypes of depression and thus allow for a personalised treatment approach. Novel imaging-based biomarkers such as TSPO-PET allow for the non-invasive monitoring of neuroinflammation throughout the course of treatment, and a promising pipeline of pharmacological targets for

inflammatory pathways is being developed that could benefit patients with resistant depression, such as NLRP3 inflammasome inhibitors, JAK/STAT pathway modulators and gut microbiome manipulation²².

CONCLUSION

Neuroinflammation has emerged as a fundamental biological mechanism underlying the pathogenesis and progression of Major Depressive Disorder (MDD), extending beyond the traditional monoamine hypothesis. Accumulating evidence demonstrates that peripheral inflammatory mediators, including IL-6, TNF- α , IL-1 β , and C-reactive protein (CRP), contribute to central nervous system dysfunction through blood-brain barrier disruption, microglial activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and alterations in the kynurenine pathway. These interconnected mechanisms impair neuroplasticity, reduce neurogenesis, and promote synaptic dysfunction, ultimately contributing to the onset and persistence of depressive symptoms.

Recent advances in neuroimaging, inflammatory biomarker profiling, and precision medicine have strengthened the understanding of neuroimmune interactions in depression and have identified novel therapeutic opportunities. Anti-inflammatory interventions, including non-steroidal anti-inflammatory drugs, cytokine-targeting biologics, omega-3 fatty acids, minocycline, ketamine, and lifestyle-based strategies, have shown encouraging outcomes, particularly in patients with elevated inflammatory markers. However, the heterogeneity of MDD and the lack of standardized biomarker-guided treatment algorithms remain significant challenges for clinical implementation.

Overall, the evidence reviewed supports neuroinflammation as a clinically relevant therapeutic target and highlights the importance of integrating inflammatory biomarkers with molecular, imaging, and multi-omics approaches to improve patient stratification and treatment selection. Future research should focus on validating reliable biomarker panels and developing personalized anti-inflammatory therapies to enhance treatment efficacy and long-term outcomes for individuals with Major Depressive Disorder.

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REFERENCES

1. Ara A. Global burden of depression: epidemiology, risk factors, and treatment trends. *J Glob Health Perspect.* 2022; 12:1–15.
2. Zeng Q, Liu T, Liang J. Neuroinflammation and stress-induced pathophysiology in major depressive disorder: mechanisms and therapeutic implications. *Front Cell Neurosci.* 2024; 19:1538026. doi:10.3389/fncel.2025.1538026
3. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. *Nat Rev Dis Primers.* 2016; 2:16065. doi:10.1038/nrdp.2016.65
4. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron.* 2002;34(1):13–25. doi:10.1016/S0896-6273(02)00653-0
5. Kofod J, Elfving B, Nielsen EH, Mors O, Köhler-Forsberg O. Depression and inflammation: correlation between changes in inflammatory markers with antidepressant response and long-term prognosis. *Eur Neuropsychopharmacol* 2022;54: 116-125. doi: 10.1016/j.euroneuro. 2021.10.003
6. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol.* 2016;16(1):22–34. doi:10.1038/nri.2015.5
7. Paganin W, Signorini S. Inflammatory biomarkers in depression: scoping review. *BJPsych Open.* 2024;10(5):e165. doi:10.1192/bjo.2024.787
8. Elgellaie A, Thomas SJ, Kaelle J, Bartschi J, Larkin T. Pro-inflammatory cytokines IL-1 α , IL-6 and TNF- α in major depressive disorder: sex-specific associations with psychological symptoms. *Eur J Neurosci.* 2023;57(11):1913–1928. doi:10.1111/ejn.15952
9. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5
10. Hu X, Pang H, Liu J, Wang Y, Lou Y, Zhao Y. A network medicine-based approach to explore the relationship between depression and inflammation. *Front Psychiatry.* 2023; 14:1184188. doi:10.3389/fpsy.2023.1184188
11. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. *Neurobiol Dis.* 2010;37(1):13–25. doi: 10.1016/j.nbd.2009.07.030
12. Hassamal S. Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. *Front Psychiatry.* 2023; 14:1130989. doi:10.3389/fpsy.2023.1130989
13. Benros ME, Toftdahl NG, Mortensen PB. Inflammatory and immune biomarkers in mood disorders: from mechanistic pathways to clinical translation [Internet]. 2025 [cited 2025 Jun]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12524191/>
14. Miller AH, Bhalla IP. Advancing an inflammatory subtype of major depression [Internet]. 2025 [cited 2025 Jun]. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12282100/>
15. Józwiak-Bebenista M, Sokolowska P, Wiktorowska-Owczarek A, Kowalczyk E, Sienkiewicz M. The HPA axis and kynurenine pathway: exploring the role of stress and neuroinflammation in treatment-resistant depression. *Pharmacol Rep.* 2025. doi:10.1007/s43440-025-00806-6
16. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces IDO, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites. *Prog Neuro psychopharmacol Biol Psychiatry.* 2011;35(3):702–721. doi: 10.1016/j.pnpbp.2010.12.017
17. Köhler CA, Freitas TH, Maes M, De Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations



- in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand.* 2017;135(5):373–387. doi:10.1111/acps.12698
18. Mondelli V, Vernon AC, Turkheimer F, Dazzan P, Pariante CM. A novel biomarker of interleukin 6 activity and clinical and cognitive outcomes in depression. *Brain Behav Immun.* 2020; 89:617–624. doi: 10.1016/j.bbi.2020.05.011
19. Elovainio M, Aalto AM, Kivimäki M, Pirkola S, Sundvall J, Lönnqvist J, et al. Depression and C-reactive protein: population-based Health 2000 Study. *Psychosom Med.* 2009;71(4):423–430. doi:10.1097/PSY.0b013e31819e333a
20. Körschgen AJ, Schlagenhauf F, Otte C. Selected biomarkers of depression: what are the effects of cytokines and inflammation? *Int J Mol Sci.* 2023;24(1):578. doi:10.3390/ijms24010578
21. Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73 131 individuals. *JAMA Psychiatry.* 2013;70(2):176–184. doi: 10.1001/2013.jamapsychiatry.102
22. Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miler L, Rajkowska G, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry.* 2015;72(3):268–275. doi:10.1001/jamapsychiatry.2014.2427
23. Savitz J. The kynurenine pathway: a finger in every pie. *Mol Psychiatry.* 2020;25(1):131–147. doi:10.1038/s41380-018-0361-2
24. Liu JJ, Wei YB, Strawbridge R, Bao Y, Chang S, Shi L, et al. Comparative efficacy and acceptability of anti-inflammatory agents on major depressive disorder: a network meta-analysis. *J Neuroinflammation.* 2021; 18:1–12. doi:10.1186/s12974-021-02197-1
25. Köhler-Forsberg O, Lydholm CN, Hjorthøj C, Nordentoft M, Mors O, Benros ME. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatrica Scand.* 2019;139(5):404–419. doi:10.1111/acps.13016
26. Dogaru IA, Puiu MG, Manea M, Dionisie V. Current perspectives on pharmacological and non-pharmacological interventions for the inflammatory mechanism of unipolar depression. *Brain Sci.* 2022;12(10):1403. doi:10.3390/brainsci12101403
27. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomised controlled trial of the tumour necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry.* 2013;70(1):31–41. doi: 10.1001/2013.jamapsychiatry.4
28. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans.* 2017;45(5):1105–1115. doi:10.1042/BST20160474
29. Liu JJ, Galfalvy HC, Cooper TB, Oquendo MA, Grunebaum MF, Mann JJ, et al. Omega-3 polyunsaturated fatty acid (PUFA) status in major depressive disorder with comorbid anxiety disorders. *J Clin Psychiatry.* 2013;74(7):732–738. doi:10.4088/JCP.12m08122
30. Amin N, Ali S, Islam F, Akram R, Anwar H, Fatima M, et al. A comprehensive review of minocycline as a repurposed drug for neuropsychiatric conditions. *Drug Des Devel Ther.* 2023; 17:2979–2995. doi:10.2147/DDDT.S428858
31. Dean OM, Kanchanatawan B, Ashton M, Mohebbi M, Ng CH, Maes M, et al. Adjunctive minocycline treatment for major depressive disorder: a proof-of-concept trial. *Aust N Z J Psychiatry.* 2017;51(8):829–840. doi:10.1177/0004867416651295
32. Jozwiak-Bebenista M, Sokolowska P, Wiktorowska-Owczarek A, Kowalczyk E, Sienkiewicz M. Ketamine: a new antidepressant drug with anti-inflammatory properties. *J Pharmacol Exp Ther.* 2024;388(1):134–144. doi:10.1124/jpet.123.001817
33. Sukhram SD, Yilmaz G, Gu J. Antidepressant effect of ketamine on inflammation-mediated cytokine dysregulation in adults with treatment-resistant depression: rapid systematic review. *Oxid Med Cell Longev.* 2022; 2022:1061274. doi:10.1155/2022/1061274
34. Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R. Novel and emerging treatments for major depression. *Lancet.* 2023;401(10371):141–153. doi:10.1016/S0140-6736(22)02080-3

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