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Review Article

Neuroinflammation and depression: An update

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Abstract

Even though depression is usually understood to be explained by the monoamine theory, it is significantly more complicated than that, and treatments that target the disease's pathway have not yet been produced. In this sense, having a better understanding of neuroinflammation and neurovascular dysfunction might make it possible to take a more holistic approach to treating depression. The immune system, endocrine system, and neurological system are all involved in the process of inflammation, which can be thought of as a form of allostatic load. In the pathophysiology of depression, neuroinflammation plays a role by elevating levels of proinflammatory cytokines, activating the hypothalamus–pituitary–adrenal axis, elevating levels of glucocorticoid resistance, and affecting serotonin synthesis and metabolism, neuronal apoptosis and neurogenesis, and neuroplasticity. In the future, the identification of the subtypes of depression that are associated with an increased vulnerability to inflammation and the testing of the effects of inflammatory modulating medications in these patient groups by means of clinical studies will lead to more precise findings regarding the subject matter. Mood disorders are linked to increased inflammation, and the resolution of symptoms following the administration of numerous treatments is frequently accompanied by a return to normal levels of pro-inflammatory. Treatments for refractory mood disorders have included a wide array of neuromodulation procedures, which alter the activities of specific regions of the brain. Their usefulness, on the other hand, varies from person to person and there is no accurate indicator of it. This review provides a summary of human and animal studies on inflammation in brain circuits that are associated with anxiety and depression, as well as the evidence that neuromodulation therapies regulate neuroinflammation in the treatment of neurological illnesses. It has been reported that neuromodulation therapies, such as transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), electroconvulsive therapy (ECT), photobiomodulation (PBM), transcranial ultrasound stimulation (TUS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS), can all attenuate neuroinflammation and reduce the release of pro-inflammatory factors. This may be one of the reasons why patients experience an improvement in their mood. This study gives a better knowledge of the successful mechanism of neuromodulation treatments and reveals that inflammatory biomarkers may serve as a reference for the assessment of pathological states and treatment options in anxiety and depression. Moreover, this research demonstrates that neuromodulation therapies have the potential to be beneficial in the treatment of anxiety and depression.

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1. Introduction

Neurological diseases (NDs) affect an estimated 276 million persons worldwide. This makes them the second leading cause of death worldwide. As the world's population ages, non-communicable illnesses have emerged as a major threat to healthcare systems everywhere [1]. Most NDs still have unexplained mechanisms and origins. Neuroinflammation is characteristic of NDs, even though both genetic and environmental variables have been linked to ND development [2, 3]. The innate immune system of the central nervous system includes the neuroinflammatory response, which helps clear the brain of dangerous infections, cell debris, and misfolded or clumped proteins. When neuroinflammation caused by NDs lasts too long, it might cause permanent damage to neurons. Multiple studies have shown that neuroinflammation can worsen the symptoms of neurological disorders like Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease (AD), and major depressive disorder (MDD). Neurodegenerative diseases (NDs) share several commonalities, including an innate immune response. Neuropathological interactions between microglia (the brain's resident macrophages) and astroglia trigger this reaction, which in turn affects disease severity and progression. The immune system and the brain are intricately connected when it comes to the progression of many diseases [4].

Suicidal ideation and behavior, as well as decreased cognitive and behavioral performance, are hallmarks of major depressive disorder (MDD), a chronic emotional illness. It is not known what causes MDD. Major depressive disorder (MDD) may be caused by more than one factor. Examples of such shifts include alterations in neurotransmission, neurotrophic factors, the hypothalamic-pituitary-adrenal (HPA) axis, inflammation, nutrition, and the brain-gut axis. Recent studies have pointed to oxidative damage and inflammation as potential causes of severe depressive illness. Lack of antioxidants to counteract the effects of reactive oxygen species (ROS) can lead to oxidative stress, which in turn can damage DNA, proteins, and lipids. The result can be an increase in mitochondrial ROS production. Dopamine (DA), serotonin (5-HT), and norepinephrine (NE) are degraded by an enzyme called monoamine oxidase, which can be blocked by reactive oxygen species (ROS). Each of these neurotransmitters is broken down by this enzyme. The brain may only account for 2% of total body weight, yet it uses 20% of the body's oxygen and energy every day. The brain is especially susceptible to injury from ROS due to its high lipid content and high energy demands. The countless mitochondria in neural cells have only one purpose: the generation of ATP [5].

Major depressive disorder (MDD) is characterized by mood swings, a loss of interest in formerly joyful activities, negative thoughts that won't go away, cognitive impairments, and a diminished ability to focus [6]. Patients' loved ones and communities bear the brunt of these characteristics because of the toll they take on the patients' quality of life and their ability to keep a job. Patients with MDD are dealing with a chronic and worsening illness. Some 34%-83% of people with MDD will have another episode of depression within the next six months, and the average person with MDD will have five episodes of depression over the course of a lifetime. Remember that a person's risk of future depression is affected by the frequency with which they have experienced depression in the past [7]. After a first episode of depression, 60% of patients with remitted MDD are at risk for a second episode of depression, 70% after a second, and 90% after a third. People with a diagnosis of recurrent major depressive disorder (rMDD) have a more challenging time returning to normal levels of brain function after experiencing depression [8] (Fig. 1).

This review examines inflammatory alterations in the brain regions involved in anxiety-related threat and fear circuits and depression-related reward circuits. Furthermore, the modulation of inflammation in these key brain areas by various neuromodulation therapies was explored. Also, this review presents a critical synthesis of findings obtained from the growing literature on several aspects of the role of neuroinflammation in the etiology of depressive disorders and how they have upended the trajectory of treatment development and refinement. Herein we review the current literature pertaining to the

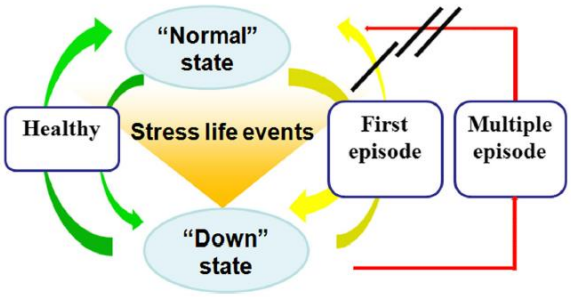

Figure 1. Neural dysfunction becomes increasingly serious in rMDD with increased numbers of depressive episodes. In health, the tendency to enter a "down state" is relatively low, and the ability to return to a "normal state" is relatively rapid and complete (green arrows). In individuals with first episode MDD, the tendency to enter a down state is relatively high, and the ability to return to a normal state is impaired slightly (yellow arrows). This ability becomes impaired more seriously in individuals with rMDD (red arrow). The downstate itself is not abnormal in this model, with the permissions of [8].

common neurological disorders such as depression, Major depressive disorder (MDD) and anxiety in the setting of Inflammation of the Nervus Central. We summarize some of the most relevant literature to provide a better understanding of the mechanistic details regarding these disorders with a goal to help stimulate creative thinking with the supporting references included.

2. Materials and methods

A thorough literature search was conducted in PubMed (https:// www.ncbi.nlm.nih.gov/pubmed/), ScienceDirect (http://www.sci encedirect.com/), and Google Scholar (https://scholar.google.com/) electronic databases during January-May 2023 for this study. The literature search was carried out using the following terms or keywords: "Depression", "Major depressive disorder", "(Neuro)Inflammation", "Cytokines", "HPA axis", "Neurogenesis". We also looked through the reference lists of the articles we picked to see if there were any related published works that could be incorporated into our study.

3. Results and Discussion

3.1 Th17 cells in MDD

Health, social, and economic sectors all face challenges because of the skyrocketing popularity of antidepressants. According to the Global Mental Health Survey's Composite International Diagnostic Interview, MDD is a form of long-term mental disease characterized by persistent depressive symptoms. (Including anxiety, boredom, and a low sense of self-worth). The number of young people with chronic MDD is at an all-time high, making it critical that the condition's genetic roots be discovered and that better treatment methods be created. Although the causes of MDD are not fully understood, it is known that inflammation can exacerbate depressive symptoms and that elevated IL-17A levels have been associated to depression. Depressed people do have more Th17 cells and some proinflammatory cytokines including IL-1b, IL-23, IFN-g, and TNF-a floating around in their blood. Researchers [9,10] found that the circulating population of CD4+ T cells had a stronger potential to evolve into Th17 in adult patients with MDD. Multiple studies have shown that the number of Th17 cells in the brains of animal models of MDD is elevated [11]. Treatment with Th17 cells has been shown to enhance sensitivity to depression in two separate animal models, which is an interesting finding. This discovery bolsters the argument that Th17 cells cause increased susceptibility to depression. Mice deficient in RORgt or given an antibody to neutralize IL-17A were less likely to develop learned helplessness. There is inadequate evidence to support the concept that Th17 cells are responsible for brain damage in MDD, despite the fact that higher levels of IL-17A have been linked with depression in some patients. Results from studies on psoriasis and MS suggest that people with rheumatoid arthritis who have high levels of IL-17A are more likely to experience mental health problems like depression and anxiety [12]. While these results don't prove that Th17 cells are solely responsible for depression, they do show that they play a part in the condition's promotion via other mechanisms. If IL-17A could rapidly modify immune-neurological interactions, it would have enormous implications [13] (Fig. 2).

3.2 NLRP3 inflammasome

The structural domains of their leucine-rich repeat proteins allow NLRs, a class of pattern recognition receptors, to bind nucleotides. Non-specific lectin-like receptors (NLRs) are a type of cytoplasmic sensor that can recognize DAMPs and PAMPs. Based on the findings published by S. Singh (2016). An NLR is composed of three distinct parts: An N-terminal domain, a nucleotide-binding middle region, and a C-

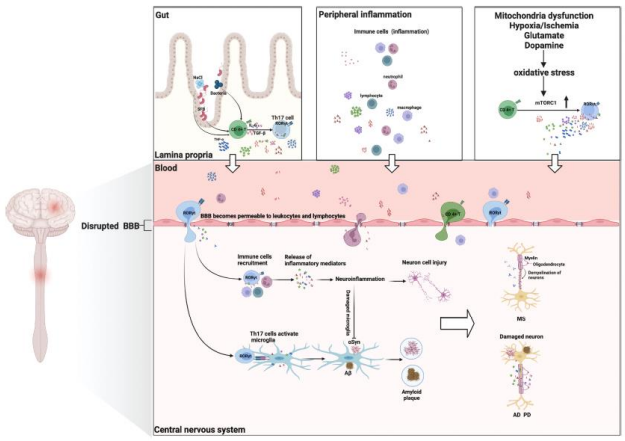

Figure 2. Th17 cells and their cytokines in neurological disorders: possible mechanisms of action. Multiple environmental factors (peripheral inflammation, enhanced oxidative stress, gut–brain axis) induce a pro-inflammatory microenvironment that modifies the CD4+ T-cell phenotype and then differentiates into encephalitogenic Th17 cells, producing inflammatory cytokines (IL-17A, IL-6, IL-21, IFN-g, GM-CSF, and IL-23). These Th17 cells can enter the CNS. They proliferate and produce cytokines that are conducive to BBB disruption and recruitment of other immune cells (lymphocytes, macrophages, and neutrophil cells) into the CNS, ultimately leading to myelin damage (multiple sclerosis). Th17 cells and their cytokines can cause neuronal damage through direct cytotoxic effects or through recruitment of immune cells and induction of neuroinflammation, resulting in deposition of Ab fibrils or the aggregation of aSyn (Alzheimer's disease/Parkinson's disease). Additionally, Th17 cells can activate the microglia and phagocytose amyloid fibrils, but neuroinflammation will induce microglia damage, thereby exacerbating amyloid b deposition or aSyn aggregation (Alzheimer's disease/Parkinson's disease). GM-CSF, granulocyte monocyte-colony stimulating factor; Ab, amyloid b.

terminal segment. NLRs are divided into four groups, based on the structure of their N-terminal domains: NLRA, NLRB, NLRC, and NLRP. Fourteen members of the NLRP family have been identified so far. Inflammasome production, signal transduction, gene transcription, and autophagy are all possible outcomes of NLR activation [14].

The NLRP3 inflammasome is a molecular process that triggers immune system activation in response to stress signals. To paraphrase: Autoimmunity, infection, and inflammation are just a few examples of the multiple roles that NLRP3 plays in the innate immune system [15]. In addition to astrocytes and microglia, neuronal cells also contain the NLRP3 inflammasome [16]. NLRP3 is involved in the onset and perpetuation of neuroinflammation, a key contributor to the emergence of depression. Studies have shown that the central nervous system can undergo pro-inflammatory changes after NLRP3 inflammasome activation. The already negative effects of depression on behavior and thought may be exacerbated by these shifts. Researchers are still scratching their heads over the NLRP3 inflammasome as they try to pin down its function in the onset of depression. Therefore, we may wonder if NLRP3 is a good therapeutic target for treating depression [17].

The NLRP3 inflammasome can be activated by a variety of mediators, including extracellular ATP, potassium ion (K+) or chloride ion (Cl) efflux, lysosomal disruption, mitochondrial failure, and metabolic changes (Fig. 3). The activation of the NLRP3 inflammasome signaling pathway is regulated by a complex regulatory network that includes post-translational and post-transcriptional changes is an illustration [18].

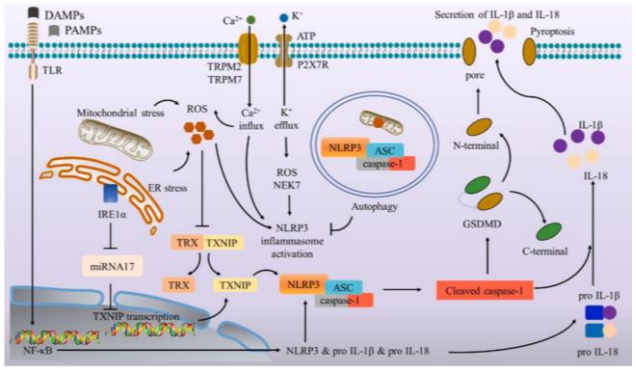

Figure 3. Depression and activation of the NLRP3 inflammasome: potential pathways. The NLRP3 inflammasome requires two signals for activation.

3.3 Evidence of immune dysfunction in MDD

New evidence from the field of neuropsychiatry suggests that the inflammatory response is crucial to the development of major depressive disorder (MDD) and to the success of antidepressant therapy [19, 20]. One of the hallmarks of depression is an altered expression of many inflammatory mediators and their receptors, which may be detected in the peripheral blood and cerebral fluid of depressed patients [21]. Suicidal depressed patients were found to have increased expression of inflammatory genes and proteins such as IL-1, IL-6, and TNF in brain tissue after death. Research shows that depressed persons, compared to healthy people, have higher amounts of immune mediators and pro-inflammatory cytokines in the brain and the rest of the body. Both sexes

experience this reality [22]. Several cytokines are responsible for depressive symptoms in patients after they have been given to them in a therapeutic context. Treatment with anti-inflammatory medicine was found to reduce depressed symptoms in those with depression, while treatment with antidepressant medication was found to have anti-neuroinflammatory effects. This research supports the use of immunomodulatory medicines for the treatment of depression triggered by inflammation [24, 25]. Table 1 shows that there is a correlation between elevated inflammatory responses and clinical depression.

3.4 Inflammation effects on monoamine and glutamate neurotransmitter systems

There is strong support for the idea that inflammatory cytokines can alter the behavior-regulating neurocircuits, specifically those implicated in anhedonia, avoidance, and anxiety. The availability of monoamine neurotransmitters in synapses is influenced by changes in metabolic and molecular pathways. Serotonin (5-HT), norepinephrine (NE), and dopamine (DA) are examples of monoamine neurotransmitters that may be negatively impacted by inflammatory cytokines (Fig. 2). Tryptophan, often known as TRP, is an amino acid necessary for life since it contributes to the production of 5-hydroxytryptophan. The enzyme indoleamine 2,3-dioxygenase (IDO) mediates more than 90% of TRP metabolism via the TRP-KYN pathway [26, 27]. TRP is converted to KYN at a higher rate due to increased IDO activity. Inflammatory mediators include a wide variety of molecules, such as prostaglandin E2, interleukin-1, tumor necrosis factor-alpha, and interferon-gamma. According to this theory, elevated IDO activity promotes an increase in the number of TRP diversions, which leads to decreased brain levels of the neurotransmitter 5-hydroxytryptamine (5-HT). TRP metabolism also promotes the creation of a small number of chemicals with the potential to affect the underlying physiological processes that underlie behavior and mood. Cytokines involved in inflammation can suppress monoamine production by limiting tetrahydrobiopterin breakdown (BH4).

To synthesize monoamine neurotransmitters including 5-hydroxytryptamine (5-HT), dopamine

Table 1. Correlation between elevated inflammatory responses and clinical depression.

Evidence of elevated inflammatory responses in major depression.
Molecular and cellular evidence
•Suicide victims with depression have higher brain levels of various inflammatory genes and proteins, including IL-1, IL-6, and TNF.
Suicide victims with depression have higher levels of protein and mRNA expression of innate immune receptors, including toll-like receptors (TLRs), and inflammasome proteins.
• Microglia and astrocyte activity increased in the thalamus, frontal cortex, and anterior cingulate cortex.
• A higher number of monocytes in the central nervous system, suggesting a faster pace of cell recruitment from the periphery.
Inflammation biomarkers both locally and systemically
Pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-12, IL-15, IL-17, tumor necrosis factor (TNF), and interferon (IFN) are all found in higher concentrations in the blood of people with inflammatory diseases.
• Elevated levels of inflammatory chemokines and reactants in the blood, such as C-reactive protein (CRP) and monocyte chemoattractant protein-1.
• Lower plasma concentrations of chemokines and anti-inflammatory cytokines such interleukin (IL)-10, transforming growth factor (TGF)-1, and interleukin (IL)-4.
• Elevated levels of IL-6, IL-8, and TNF- and other pro-inflammatory cytokines in the cerebrospinal fluid.
Research in practice
• Patients with inflammatory bowel disease, rheumatoid arthritis, or multiple sclerosis have an increased risk of developing depression.
• About 40% of people treated for hepatitis C or cancer with interferon-alpha have depressive symptoms during treatment.
The bacterial endotoxin lipopolysaccharide (LPS) triggers systemic inflammation in otherwise healthy people, which has been linked to the development of illness cognitions and mood disorders.
• When administered alone or in combination with antidepressants, anti-inflammatory drugs including NSAIDs, and anti-cytokine medicines reduced depressive symptoms in patients with MDD.
• In addition to their antidepressant activity, SSRIs and SNRIs have been shown to exert anti-neuroinflammatory actions by decreasing circulating or brain tissue cytokine levels or altering various cytokine production pathways.

(DA), and norepinephrine (NE), the enzymes tryptophan hydroxylase, tyrosine hydroxylase, and phenylalanine hydroxylase need the cofactor BH4. The enzyme's cofactor, however, is particularly susceptible to oxidative damage due to its position. (OS). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated by inflammatory cytokines, leading to oxidative stress. For instance, microglia and astrocytes' production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in response to IL-1 and TNF- may exacerbate OS. BH4, which is extremely vulnerable to the actions of OS, can be irreversibly broken down by large quantities of OS. Nitric oxide synthase (NOS) is an enzyme that uses L-arginine as a substrate and the cofactor BH4 to create nitric oxide. As stated in the report [28]. Activation of iNOS by inflammatory mediators is well known to increase iNOS's requirement for BH4 for optimal enzymatic function and drive the release of many oxygen free radicals. Because of the oxidation, the BH4 molecule is destroyed. Mood disorders may have a common etiology with the increased consumption and loss of BH4 caused by chronic inflammation, which in turn alters the function of BH4-dependent enzymes. Pro-inflammatory mediators can change the expression and function of monoamine reuptake transporters, which in turn changes the reabsorption of monoamine neurotransmitters, in depressive diseases. Potential activators of the crucial signaling pathway p38 MAPK include pro-inflammatory cytokines like IL-1 and TNF-. This decreases the quantity of 5-HT accessible in the synaptic cleft [19-21] and increases the expression and activity of 5-HT transporters. It has been demonstrated that MAPK signaling pathways can modify DA transporter function. This was done to establish DA reuptake. Cytokines involved in inflammation can inhibit the neurotransmitter monoamine synthesis, reducing the neurotransmitter's effectiveness. The vesicular monoamine transporter 2 (VMAT2) protein regulates the loading of cytosolic DA into vesicles and their subsequent release into the synapse, hence determining the total amount of DA present in the synaptic area. Inflammatory cytokines like interleukin-1 and tumor necrosis factor-alpha suppress the expression and function of the protein VMAT2, which blocks DA release [25].

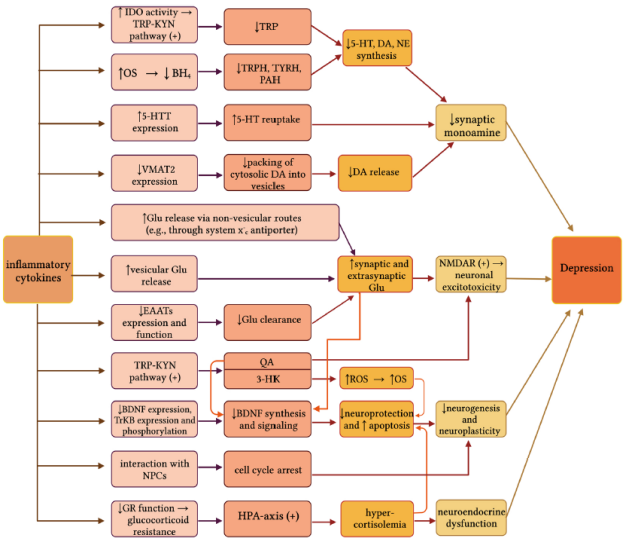

Figure 4. Inflammatory mechanisms in the pathophysiology of depression: a mechanistic review.

3.5 Relationship between pro-inflammatory cytokines and the brain in MDD

The inflammatory theory of depression was developed in the early 1990s when studies indicated that peripheral cytokines interacted with major depressive disorder (MDD). Pro-inflammatory cytokines, such as interleukin (IL)-1, interleukin (IL)-6, tumor necrosis factor (TNF-), and the acute phase reactant C-reactive protein (CRP), have been linked to MDD in both clinical and experimental studies. These cytokines may be present in high concentrations, but they are still significantly lower than those seen in autoimmune diseases or viral infections. Patients with rMDD showed considerably higher rates of raised CRP and IL-6 compared to healthy controls, and depression was associated with elevated CRP levels, especially in persons who had experienced repeated bouts of depression. Inflammation begins early on in MDD, as higher CRP and IL-6 levels at baseline both predict and are linked with cognitive symptoms at a mean follow-up of 11.8 years. This is since increased levels of CRP and IL-6 at baseline are predictive of cognitive symptoms. Keep in mind that the immune system relies on peripheral cytokines to help coordinate its responses to infections and inflammation. Countless cell types, such as macrophages, B lymphocytes, T lymphocytes, mast cells, endothelial cells, fibroblasts, and stromal cells, release these cytokines. It is believed that the brain is

able to communicate with the rest of the body through mechanisms such as the immunological effect, which includes activated microphages and micro-glial cells, the transport of cytokines across the blood-brain barrier, and the interaction of the HPA with stress and neurotransmitters [29].

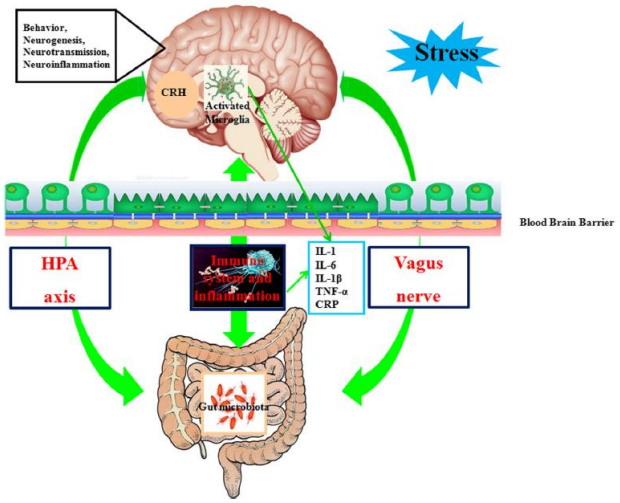

Figure 5. Relationship between inflammation and rMDD. Stress is an important factor in the occurrence of depression relapse. Neuroendocrine- and inflammation-related signals generated by gut microbiota and specialized cells within the gut can, in principle, affect the brain and may lead to release of neurotransmitters, excessive activation of microglial cells, increased levels of inflammatory factors from the peripheral nervous system and the central nervous system, release of inflammatory cytokines by immune macrophages, and depressive-like behaviors. CRH corticotropin releasing hormone, CRP C-reactive protein, HPA hypothalamic–pituitary–adrenal, IL interleukin, TNF-α tumor necrosis factor-α.

Subgroups of people with MDD often share the physiological effects of increased inflammation and hyperactivity of the HPA axis. There is a mountain of evidence from many studies that backs this up. Bhagwagar et al. observed that HPA dysregulation is linked to a poor clinical outcome in remitted MDD patients who are at high risk for recurrence. Chronic exposure to cytokines may alter the HPA axis' reliance on the glucocorticoid receptor. Activation of the glucocorticoid receptor is affected by cytokine signaling molecules such as cyclooxygenase-2 (COX-2), nuclear factor kappa-light-chain-enhancer of activated B cells, and p38 mitogen-activated protein kinase. Then Immune activation may occur in response to glucocorticoid resistance, which is characterized by hyperactivity of the HPA axis. One mechanism by which cytokines can stimulate the HPA axis is by the upregulation of glucocorticoid receptors. Monoamine neurotransmitter production, reuptake, and release are all affected by the cytokine and glucocorticoid receptor signaling pathways. Tryptophan, a precursor to serotonin, is converted to kynurenine by the enzyme indoleamine 2,3 dioxygenases (IDO), which can be activated by certain proinflammatory cytokines. The next step is for kynurenine to become serotonin. Decreased serotonin synthesis has been linked to the breakdown of tryptophan, which in turn has been linked to the development of depression. Inflammatory cytokines stimulate the development and activity of reuptake pumps (transporters) for the neurotransmitters serotonin, norepinephrine, and dopamine via activating mitogen-activated protein kinase (MAPK) pathways. When inflammation levels are high, antidepressants may not be as effective in treating chronic types of MDD due to these cytokine-driven changes in neurotransmitter biochemistry. Patients with rMDD who have elevated inflammatory markers may be at increased risk for health complications [29].

3.6 Microglia in depression Clinical evidence

Multiple studies have found that abnormalities in the development and shape and function of adult brain microglia lay at the root of depressive illnesses. Microglial changes in the amygdala, insula, anterior cingulate cortex, and prefrontal cortex have all been linked to the onset of depression. Microglia are brain cells that can be activated during severe episodes of MDD, and recent investigations have indicated that this activation occurs mostly in the prefrontal cortex and the anterior cingulate cortex. The severity of a depressive episode is also related to the level of microglial activation in the anterior cingulate cortex (ACC). This is in accordance with the findings of Setiawan E., et al. [30]. A rise in microglia in the ACC has been linked to MDD episodes using PET imaging. The levels of TSPO also increased in MDD patients at the same time that microglial activation did. An 18F-FEPPA PET cross-sectional investigation found that the total volume of TSPO distribution was significantly correlated with the duration of untreated MDD, the duration of the overall illness, and the use of antidepressants. This was proven to be true very lately [30, 31].

Suicide victims with major depressive illness had more of the chemical quinolinic acid (QUIN), produced by microglia, in their subgenual anterior cingulate cortex and anterior midcingulate brain regions, according to an analysis of autopsies. There were similarities and discrepancies in the findings of various studies on the prefrontal white matter. Overexpression of ionized calcium binding adapter molecule 1 (Iba-1), CD45, and monocyte chemoattractant protein-1 indicated an increase in microglial density in the dorsal anterior cingulate cortex (ACC) white matter of suicidal individuals. The ACC is short for anterior cingulate cortex and is found in the brain's upper regions. Whether or not microglia-caused inflammation has a role in the development of depression is still debated. Researchers have found that depressed people have fewer microglia than the general population. Patients with a familial form of MDD have a similar number of neuronal cells, but a much smaller number of glial cells. Cortical atrophy was observed in the subgenual region of the brain, namely in Brodmann area 24. Reductions in glial density were identified after laminar analysis in the same regions of the brain: the orbital cortex, the anterior cingulate cortex, and the dorsolateral prefrontal cortex. Using stereology, researchers discovered fewer glial cells in the amygdala and hippocampus of patients with MDD.

There was no overall loss of glia in the somatosensory cortex area 3b in depressed patients, suggesting that the glial cell loss linked with mood disorders is regional. Microglial activity has been linked to a few psychological disorders [32], including depression, anxiety, schizophrenia, and autism spectrum disorder. Anxiety problems are common in adolescents and have been connected to a variety of physical ailments. Some investigations into the connection between microglia and anxiety disorders have been conducted only in animal models. A higher susceptibility to psychosis was linked to greater microglial activation in a PET imaging investigation of people with schizophrenia. The amount of microglia in the visual cortex and anterior insula is often elevated in autistic people. Despite this, numerous studies of people with schizophrenia or autism have failed to find any signs of microgliosis or other abnormalities in the expression of glial cell markers. The activation of microglia has been linked to the onset of numerous mental diseases; however, opinions diverge on the role that microglial activation plays in the development of disease and the manifestation of symptoms. Due to the intricacy of their illness, patients with severe depression and varied degrees of microglial activation will require a wide range of treatment options. The prevalence of suicide attempts among those with severe mental illness should also be considered. Increased microglial density is associated with suicidality in patients with schizophrenia and major depression [33], suggesting a possible role for microglial activity changes in mental illnesses. make use of 4 as a numerical example.

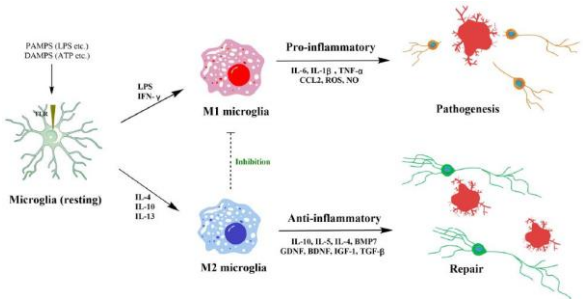

Figure 6. The roles that M1/M2 polarized microglia play in the regulation of processes inside the central nervous system.

3.7 Th17 cells in MDD

Major depressive disorder (MDD) is the most common mental illness. The rising demand for antidepressants poses serious challenges for healthcare systems, communities, and economies. According to the Global Mental Health Survey's Composite International Diagnostic Interview, MDD is a form of long-term mental disease characterized by persistent depressive symptoms. (Including anxiety, boredom, and a low sense of self-worth). There is a pressing need to develop more effective treatment options and better understand the genetic basis of MDD considering the rising prevalence of the disorder in young people. Although the precise origins of MDD remain unknown, mounting data suggest that elevated IL-17A levels are associated with sadness and that inflammation exacerbates depressive symptoms. True, people with depression often have higher than average levels of Th17 cells, IL-1b, IL-23, IFN-g, and TNF-a in their blood [9, 34]. Researchers Alvarez-Mon et al. found that persons with MDD are more likely to have a higher frequency of Th17 in their peripheral CD4+ T cell population.

The findings confirmed our suspicions. It has also been shown that there is an uptick in Th17 cells in the brains of animal models with MDD. However, other studies have shown that Th17 cells administered to mice increased their susceptibility to depression in two different mouse models, establishing a causal link between Th17 cells and depression, seeing that RORgt deficiency and IL-17A neutralization protected mice from learned helplessness intriguing. The association between Th17 cells and depression strengthens the case that the former contributes to the latter. Increased levels of IL-17A are not necessarily associated with depression, and there is insufficient evidence to show that Th17 cells are responsible for the neuronal damage found in MDD. Results from studies on psoriasis and MS suggest that people with rheumatoid arthritis who have high levels of IL-17A are more likely to experience mental health problems like depression and anxiety [35, 36]. Considering these findings, it appears that Th17 cells may contribute to the promotion of sorrow but may not be sufficient to produce depression on their own. More study is needed to see if IL-17A immediately affects how the immune system communicates with the neurological system [13] (See Fig. 7).

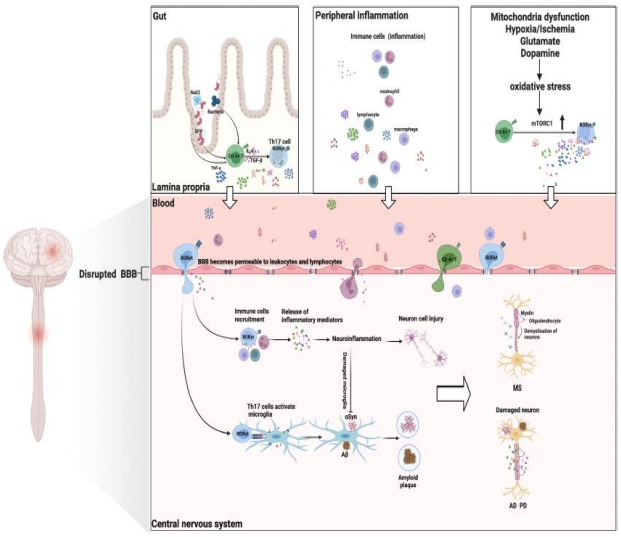

Figure 7. Possible mechanisms of action in neurological illnesses that are caused by Th17 cells and the cytokines they produce.

4. Conclusion

In the published research, there is abundant data that strongly links MDD to inflammatory pathways. Inflammation can influence the functioning of brain circuitry in a variety of different ways, including those involving neuronal, immunological, and neuro endocrine-mediated communication.

Surprisingly, high levels of pro-inflammatory cytokines are related to regions in the DMN, SN, and CEN that have been identified as "hotspots" in many imaging investigations of MDD. These regions include the central executive network (CEN) and the default mode network (DMN). To have a complete understanding of the connection that exists between neuroimaging markers, inflammation, and rMDD, additional study is required. Neuroimaging in this field is still in its infancy. More research is required to achieve a deeper comprehension of how inflammtion controls brain function in MDD. Despite this, several of the conclusions that were given do have some restrictions. First and foremost, a significant number of the findings are based on correlations. As a result of this, causality and generalizability are still able to be improved through the conduct of further research, through the application of preclinical experimental models. Because of the nature of the subject matter, sample sizes are frequently low, and both the controllability and validity of the measures are occasionally lacking. Despite this, it appears that there is at least some degree of replicability. As a result of the fact that this line of inquiry is still in its infant stage, most of the hypothesized correlations are theoretical. Animal models continue to supply extremely significant information even though there are problems with their ability to be translated. In the future, clinical investigations on early diagnoses of MDD and prodromal markers that are in line with preclinical models would enrich and improve longitudinal and experimental designs. Researchers would therefore be able to monitor inflammatory processes, neurological alterations, and the MDD phenotype throughout time thanks to this ability. Alternately, additional research is required on each of the medication treatment approaches that were presented, particularly in the context of the functioning of the DMN and the HPA axis. Clinical research should be carried out on related and/or comorbid conditions (such as anxiety and TBI) that may be associated with inflammation to further validate the inflammation hypothesis of major

depressive disorder (MDD). Increased inflammatory processes are a fundamental contributor to the development of major depressive disorder and/or to its exacerbation. These processes can be regulated and treated by a variety of therapeutic options that have both antidepressant and anti-inflammatory qualities.

Authors' contributions

Conceptualization, investigation, data curation, writing–original draft, visualization, L.D.H.; Formal analysis, writing–original draft, writing – review & editing, formal analysis, visualization, M.F.D.R.

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Conflicts of interest

All authors declare that they have no financial or commercial conflicts of interest.

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