Towards a multidimensional model of inflamed depression

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ABSTRACT

Major depressive disorder (MDD) continues to impose a significant burden on individuals and society. Existing data support the important role that inflammatory responses play in its pathophysiology, with new findings continuing to be reported. In this narrative review paper, we focus on three dimensions of inflamed depression: risk factors, clinical symptoms, and neurofunctional changes. We aim to answer the following questions: What characteristics most robustly discriminate between inflamed and non-inflamed depression? How can we leverage on these discriminative characteristics to classify inflamed depressed patients? One important point that has emerged is the heterogeneous nature of the relationship between inflammation and depression. Not all inflamed patients are depressed, and not all depressed patients are inflamed. Some risk factors heighten vulnerability to inflamed depression, including childhood adversity, old age, and being female. The inflamed depression subtype has been associated with distinct clinical phenotypes, most robustly with physical symptoms such as sleep problems, changes in appetite, and fatigue. Neurofunctional changes are found in the dopaminergic reward processing pathways. A better characterization of the inflamed depression subtype by leveraging multidimensional data will help craft a more precise treatment for these patients.

1. Introduction

Major depressive disorder (MDD) is commonly characterized as a long-term psychiatric disorder with recurring depressive episodes. It is a highly prevalent stress-related illness that causes substantial public health costs (Kessler, 2012) and a broad range of long-term functional impairments for afflicted people. Despite the vast research effort spent attempting to understand the pathophysiological and neurobiological mechanisms and risk factors that predispose, precipitate, and maintain depression, it continues to be increasingly prevalent with annually rising morbidity (Liu et al., 2020).

There are striking similarities between MDD symptoms and inflammation-induced sickness behavior. Miller and Raison (2016) proposed that depressive symptoms are essential components of immune-mediated host defense against pathogens. Specifically, depression and pathogen defenses are allegedly supported by the same alleles that are selected from mammalian evolution because of their association with successful host immune responses. They are also selected because in a pathogen-filled world, they provide adaptive benefits that outweigh the costs resulting from any psychological impairment. Highly conserved sickness behavior is critical during times of physical threats or injuries; however, it can also be activated by psychosocial threats, possibly because they can be used to reliably predict subsequent wounding in ancestral environments. This aligns with observations that psychosocial stress is a strong risk factor for MDD and that MDD is highly prevalent in the modern world (Miller and Raison, 2016; Slavich and Irwin, 2014).

Multiple evidence suggests that inflammation is involved in the pathophysiology of MDD (for review, see e.g., Beurel et al., 2020; Leonard, 2018). The association between inflammation and MDD cannot be
fully explained by the common influence of third factor confounds such as physical illness, lifestyle, or sociodemographic factors (Kappelmann et al., 2018; Osimo et al., 2020; Pitharoulis et al., 2021). Furthermore, many studies have revealed temporal precedence that is consistent with a causal relationship. Early interest arose from clinical cases involving interferon-α (IFN-α) treatments for hepatitis C, cancer, and other infectious diseases. The IFN-α molecule induces pro-inflammatory cytokines, including interleukin-6 (IL-6), and some patients developed depression following the treatments (Capuron and Miller, 2004; Chiu et al., 2017; Udina et al., 2012). More evidence comes from multiple longitudinal studies that tracked the relationship between inflammation with the onset of MDD during normal development. Elevated inflammation in childhood has been shown to predict the risk of depression in early adulthood (Khandaker et al., 2014). In older patients, elevated levels of pro-inflammatory molecules (especially IL-6, IL-8, and tumor necrosis factor-α [TNF-α]) preceded the onset of MDD irrespective of baseline scores (Martínez-Cengotitabengoa et al., 2016).

Different aspects of the association between MDD and inflammation have been widely studied and reviewed. Previous reviews have separately covered mechanistic pathways (Beuerl et al., 2020), biomarkers (Malik et al., 2021), brain changes (Han and Ham, 2021), and symptomatology (Majd et al., 2020). In this narrative review paper, we focus on three dimensions of inflamed depression: risk factors, clinical symptoms, and neurofunctional changes. We aim to answer the following questions: What characteristics most robustly discriminate between inflamed and non-inflamed depression? How can we leverage on these discriminative characteristics to classify inflamed depressed patients? We outline the main findings for each dimension and discuss the potentials of combining them towards a multidimensional model for classifying inflamed depression. The evidence presented here adds to the view of inflamed depression as a distinct subtype. The ability to identify this subtype among MDD patients will bring enormous clinical benefits, especially since it is associated with lower responsiveness to conventional treatments, higher suicide risk, and more severe depression. We end by suggesting several directions for future research to advance the field.

2. Risk factors

Inflammation is not an equipotent inducer of depression. Among patients who received IFN-α treatments, only 50% developed depression (Chiu et al., 2017; Udina et al., 2012). The two-hit model hypothesizes that depression is predicted by the combination of inflammation and select risk factors (Slavich and Irwin, 2014). Some individuals may be more vulnerable to inflamed depression than others due to their age, sex, body mass index (BMI), physical activity, genetic makeup, and childhood experiences.

2.1. Sex

Sex-related differences influence the relationship between inflammation and depression, with females being more vulnerable especially in response to social stress. Compared to males, females exhibited higher depressed mood and feelings of disconnection upon experimentally induced inflammation, and the increase in feelings of social disconnection was positively correlated with increases in pro-inflammatory cytokines only in females (Moieni et al., 2015). These sex-related differences may be mediated by different neural processes that are typically engaged by the two sexes. When female participants were exposed to social exclusion, their IL-6 increase showed a positive relation with the depressed mood that was mediated by activities almost exclusively in the social-pain related brain regions, in contrast to males who showed more widespread neural changes and no mediation effect (Eisenberger et al., 2009).

2.2. Age

The effects of aging on the immune system manifest at multiple levels, leading to less robust responses to immune challenges in the elderly when compared to their younger counterparts (Montecino-Rodriguez et al., 2013) and increased vulnerabilities to depression. Older mice underwent more severe neuroinflammation upon activation of the peripheral innate immune system by lipopolysaccharide injection (Godbout et al., 2005). In humans, older people (age >55 years) treated with IFN-α exhibited a greater increase in glutamate in the left basal ganglia, which was further associated with blood TNF levels and MDD symptoms such as reduced motivation and motor slowing (Haroon et al., 2015).

2.3. BMI and physical activity

Obesity, inflammation, and depression are biochemically interconnected (Plackett, 2022). A higher BMI is consistently correlated with elevated circulating levels of IL-6 and C-reactive protein (CRP) (O’Connor et al., 2009; Rohn et al., 2022). Exercise induces positive neuro-immunological effects which alleviate depression (Eyre and Baune, 2012). The intensity is critical to the outcome. Moderate intensity exercise reduced TNF-α and depressive symptoms while high intensity exercise increased stress levels and IL-6 (Paolucci et al., 2018).

2.4. Genetic

Single nucleotide polymorphisms (SNPs) present in two key genes that support immune function are associated with MDD susceptibility. Individuals with one, two, and three risk alleles were 2.3, 3.2, and 9.8 times more likely to be diagnosed with MDD than others, respectively (Wong et al., 2008). Among MDD patients, SNP variants of the IL-1β gene were associated with different treatment outcomes (Baune et al., 2010). In particular, the GG variant of rs16944 and rs1143643 was associated with an increased risk of non-remission after 6 weeks of anti-depressant treatment. The number of G-alleles in these SNPs was associated with decreased response to emotional stimulation in the amygdala and the anterior cingulate cortex.

2.5. Adverse childhood experiences

Childhood trauma such as abuse or neglect, parental separation, and parental mental illness has long-term physical, psychological, and social consequences (Dubowitz and Bennett, 2007). Vulnerability to depression may be due to the priming and stimulation of the immune system by early adversaries. Adverse experiences during early childhood can predict inflammation later in development (O’Connor et al., 2020). Adult MDD patients who reported to have experienced childhood adversity responded with greater inflammatory responses when exposed to social stress (Pace et al., 2006). They also showed up-regulated monocyte inflammation-related gene expression while those who did not experience childhood adversity showed down-regulation (Schiewek et al., 2020).

2.6. Summary and perspective

Other risk factors associated with heightened vulnerability to inflamed depression include adiposity and obesity, unhealthy diet, substance use, higher levels of state anxiety, perceived stress, negative affect, sleep disturbance, and low socioeconomic status (Kiecolt-Glaser et al., 2015; Mac Giollaibhui, 2021; Manigault et al., 2021).

Risk factors may interact with each other to determine individual vulnerability. For example, in response to immunological challenges, females (and not males) with sleep disturbance reported a larger increase in depressed mood and a stronger correlation between depressed mood and cytokine levels, when compared to females with no sleep.
disturbance (Cho et al., 2016). Additionally, genetic factors not only promote inflammation itself but also influence inflammatory status by modulating food intake and smoking habits. One study found that the positive relationship between the polygenic risk scores (PRS) for depression and log CRP levels can be explained by BMI and smoking, supporting the interactions between genetic and lifestyle factors (Pith- arouli et al., 2021).

It is currently unknown whether some risk factors have more significant moderating effect on the relationship between inflammation and depression. Very few studies have directly identified the independent and relative contributions of individual risk factors, and their results are inconclusive. Irwin et al. (2019) reported that only anxiety symptoms remained significant in their multivariate moderation model on healthy participants undergoing endotoxin-induced immunological challenge. However, this was not supported by a prospective study which analyzed anxiety and four other risk factors (perceived stress, negative affect, disturbed sleep, and childhood adversity) among breast cancer survivors and found that none predicted depressive symptoms above and beyond others (Manigault et al., 2021).

3. Clinical symptoms

Not all MDD patients show elevated levels of inflammation. Using a hierarchical clustering technique, Schiweck et al. (2020) reported that only approximately 75% of MDD patients showed upregulation in inflammation-related gene expression, while the remaining 25% showed general downregulation. A meta-analysis of 5166 participants with MDD and 5083 healthy controls found that the population distribution variables of IL-6, IL-3, IL-18, and TNF-α were comparable between the two groups (Osimo et al., 2020).

Among MDD patients, inflammation is associated with and predict worse overall symptom severity (Chiang et al., 2021; Lamers et al., 2019; Köhler-Forsberg et al., 2017). However, this relationship is not uniform across all symptoms. We broadly categorize MDD symptoms into three clusters. Cognitive symptoms include reduced concentration, executive dysfunction, and learning and memory problems. Emotional symptoms are anhedonia, low mood, feeling of hopelessness and guilt, and suicidal thoughts. Physical symptoms consist of sleep disturbances, changes in appetite and weight, and psychomotor agitation or retardation. In the following review of the literature, if there are any discrepancies in the categorization of an individual symptom, we interpret the findings at the level of the individual symptom and recategorize them.

3.1. Cognitive symptoms

In mice model, depressive symptoms are associated with a lower level of anti-inflammatory cytokine IL-10. Administering IL-10 alleviated impairments in spatial working memory and restore hippocampal dendritic spine density (Worthen et al., 2020). In humans, Chu et al. (2019) found longitudinal associations between childhood serum IL-6 and CRP levels and specific depressive symptoms in early adulthood, including concentration difficulties.

3.2. Emotional symptoms

In rodents, levels of peripheral cytokines can predict the development of anhedonic-like behavior (Hodes et al., 2014). Mice who developed the behavior after experiencing social defeat had higher prestress levels of circulating leukocytes and produced more IL-6 when their immune system was stimulated with the injection of bacterial endotoxin, suggesting pre-existing individual differences in the peripheral immune system that predict and promote anhedonia in response to stress.

In humans, cross-sectional data showed that CRP was significantly associated with a group of symptoms including pessimism, loss of interest, and anhedonia (Köhler-Forsberg et al., 2017; Milaneschi et al., 2021). Two other studies found a positive association between depressed mood symptoms and inflammation, including a longitudinal study where baseline inflammation was found to predict increases in depressed mood over 4 years (Niles et al., 2018; White et al., 2017).

Suicide risk differs in MDD patients with up- and down-regulated monocyte inflammation-related gene expression. Analysis of monocyte from blood samples revealed upregulations in genes that encode inflammatory interleukins (i.e., IL-1α, IL-1β, and IL-6) for patients with high suicide risk compared to the healthy controls and the patients without suicide risk; no significant difference was detected between the latter two (Schiweck et al., 2020). Consistently, a genome-wide association study (GWAS) found an association between genetic upregulation of IL-6 signaling and suicidality (Kappelmann et al., 2021).

3.3. Physical symptoms

The physical symptoms of MDD (fatigue, sleep disturbance, altered appetite, psychomotor retardation) have been associated with IL-6 and CRP levels in multiple studies with cross-sectional, longitudinal, and cohort design (Chu et al., 2019; Primo de Carvalho Alves & Sica da Rocha, 2020; Milaneschi et al., 2021). Notably, genetically predicted higher expression of IL-6 signalling was associated with increased risk of fatigue and sleep problems, suggesting a potentially causal relationship (Milaneschi et al., 2021).

Lee et al. (2022) found that CRP was only correlated with appetite problems in an Asian elderly sample after adjusting for the sociodemographic, clinical, and lifestyle covariates. Likewise, other researchers detected that there is a strong association between changes in appetite and a composite index of systemic inflammation, and an association between low energy and granulocyte-to-lymphocyte ratio, an indicator of immune system homeostasis (Buonacera et al., 2022), in non-depressed participants.

3.4. Summary and perspective

Overall, there is an association between inflammation and all symptom clusters, however studies that directly compare the strength of evidence for different symptoms suggest that some may be more tightly linked than others. A narrative review of 21 studies (Majd et al., 2020) concluded that there is evidence for an association between physical symptoms of depression and inflammation, independent of emotional symptoms, while the same cannot be said of emotional symptoms and inflammation.

 Quantitative analyses support an association between inflammation and physical symptoms and provide some evidence for an association with anhedonia and cognitive symptoms. One study using the symptom network approach highlighted the central role of concentration difficulty and psychomotor problems on the overall symptom network of a group with high CRP (Moriarity et al., 2021). CRP levels were independently associated with anhedonia as well as multiple physical symptoms that discourage exploratory behaviors, i.e., changes in appetite, feeling everything was an effort, loss of energy, and sleep problems (Frank et al., 2021). These associations remained after adjusting for various covariates and after excluding chronically ill individuals (Frank et al., 2021). Meanwhile, for four emotional symptoms (bothered by things, hopelessness about the future, felt fearful, life had been a failure), the same study found strong evidence against an association with inflammation (Frank et al., 2021). Similarly, in a meta-analysis, CRP was significantly associated only with physical symptoms (i.e., sleep problems, lack of energy and changes in appetite) after adjusting for total scores of remaining symptom items (Jokela et al., 2016).

In summary, existing literature support a robust association between the physical symptoms of MDD and inflammation, especially sleep problems, changes in appetite, and fatigue. Cognitive symptoms such as lack of concentration and emotional symptoms including depressed
mood and anhedonia, have also been widely reported in various studies, although it seems that their links to inflammation may not be independent of the physical symptoms. This probably reflects the vulnerability of physiological processes to inflammatory disturbances, while cognitive-emotional processes might be influenced subsequently via the neurofunctional changes induced by inflammation.

4. Neurofunctional changes

Depression is linked to widespread changes in functional network connectivity. Specific symptoms such as anhedonia, depressed mood, excessive self-focus, and reduced cognitive control are associated primarily with changes in four core networks: the reward network, affective network, default mode network, and cognitive control network, respectively (for review, see Li et al., 2018; Irwin and Piber, 2018). Some cortical and sub-cortical structures within these networks have been identified to be particularly sensitive to changes in peripheral inflammation, including the amygdala, ventral striatum, substantia nigra, insula, sub-genual and dorsal anterior cingulate, orbitofrontal cortex, and hippocampus/parahippocampus (Kraynak et al., 2018; for review, see Harrison, 2017).

4.1. Reward network (RN)

Symptoms such as loss of pleasure, interest, or motivation (anhedonia) may be attributed to diminished interactions in the frontal-striatal RN (Li et al., 2018). This consists of the frontal cortex and striatal regions including the caudate, putamen, and ventral striatum.

The ventral striatum (VS) was found to be functionally altered by inflammation. Exposure to bacterial endotoxin led to changes in peripheral immunological markers which were positively related to blunted activations during reward anticipation in the VS in both healthy adults and MDD patients (Costi et al., 2021; Eisenberger et al., 2010). A large-scale network including the VS, ventromedial PFC (vmPFC), as well as parahippocampal gyrus/amygdala, orbitofrontal, insular, and posterior cingulate cortices showed reduced resting-state functional connectivity in relation to increased CRP levels and increased anhedonia (Felger et al., 2016; Mehta et al., 2020; Yin et al., 2019).

Notably, the relationship between CRP levels and poor VS-vmPFC connectivity was still significant even after controlling for overall depression severity and poor VS-vmPFC connectivity mediated a significant relationship between CRP and anhedonia (Felger et al., 2016). Taken together, the evidence highlights a key role for the VS and vmPFC in mediating the effect of inflammation on anhedonia, with the latter hypothesized as a key hub for the effects of inflammation on the network’s functioning (Yin et al., 2019).

4.2. Affective network (AN)

Depressed mood in MDD is linked to elevated connectivity of the ventral limbic AN comprising the orbitofrontal cortex (OFC), insula, amygdala, hippocampus, and anterior cingulate cortex (ACC) (Li et al., 2018; Irwin and Piber, 2018).

When considering total depressive symptoms, amygdala, OFC, and hippocampus showed heightened activities in relation to both inflammation and depressive severity (for review, see Byrne et al., 2016). For example, inflammation is associated with hyperactivation of the amygdala. Compared to healthy control, MDD patients exhibited increased threat-related activation of the amygdala, which was positively correlated with the immune score yield from peripheral blood after immunological challenge (Boskoczi et al., 2022). Hepatitis C patients receiving IFN-α treatment showed significantly enhanced right amygdala response to sad (compared with neutral) faces, while patients receiving anti-TNF therapy for inflammatory arthritis, showed a reduction in amygdala response. In both groups, these changes predicted the subsequent changes in the overall depressive symptoms (Davies et al., 2021).

In healthy participants, available evidence does not consistently support the link between inflammation and enhanced AN connectivity. Across two studies in non-clinical sample, Nusslock et al. (2019) observed no statistically significant relationship between the resting-state functional connectivity of a network anchored in anterior insula and dorsal ACC with inflammatory signaling (as indexed by a composite measure of CRP, IL-6, IL-10, TNF-α). However, a different conclusion was offered by a study which applied inflammatory challenge and measured depressed mood using Profile of Mood States (Harrison et al., 2009). Participants received typhoid or placebo injection, where the former produced inflammatory responses as indexed by increased levels of IL-6. A significant mood deterioration was observed at 3 h post-injection, which correlated with enhanced activity within the subgenual ACC during emotional face processing. Inflammation-associated mood changes also decreased the connectivity between subgenual ACC with amygdala, which was mediated by IL-6 (Harrison et al., 2009).

4.3. Default mode network (DMN)

The DMN mainly encompasses the precuneus, posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC) which includes subgenual ACC, as well as the inferior parietal cortex. Enhanced connectivity within the DMN and reduced connectivity between DMN and other networks are tentatively linked to rumination and negative self-referential thoughts, two important components of MDD (Li et al., 2018).

Existing evidence are equivocal with respect to the existence and direction of correlation between inflammation and DMN connectivity. Within-DMN connectivity was not significantly associated with circulating inflammatory biomarkers including CRP and IL-6 in healthy adults and MDD patients (Nusslock et al., 2019; Beckmann et al., 2022). However, Marsland et al. (2017) reported that IL-6 covaried positively with connectivity of the subgenual ACC and negatively with the dmPFC of the DMN, although they did not find any correlation either between IL-6 level and depressive symptoms or within-DMN connectivity and depressive symptoms among their healthy participants.

Decreased connectivity between the DMN and attention-related regions was found in MDD patient with high CRP when compared to healthy controls, which scaled with levels of CRP, IL-6, and neutrophils (Aruldass et al., 2021). This is in line with prior findings from the same sample showing that CRP-related changes in functional connectivity colocalized in nodes within the DMN that also significantly displayed reduced global connectivity in MDD (Kitzbichler et al., 2021). Among COVID-19 survivors, immune cell count was associated with a reduction of connectivity between DMN and the salience network and between DMN and the dorsal attentional network (Benedetti et al., 2021). The latter study measured depressive symptoms but did not report whether they were associated with these functional connectivity changes. In contrast, another study reported that elevated CRP level was associated with an increased functional connectivity between DMN and attention network, a pattern which did not overlap with the functional changes when contrasting healthy controls and MDD patients (Beckmann et al., 2022).

4.4. Cognitive control network (CCN)

The cognitive control network comprises the dorsolateral prefrontal cortex (dlPFC), the cognitive (dorsal) subdivision of anterior cingulate cortex (dACC), and the parietal cortex. Cognitive impairments in sustained attention, memory, and executive functions frequently occur in MDD, although there are conflicting findings on their neural mechanisms, with some studies reporting an increase in functional connectivity of the CCN and others reporting a decrease (e.g., Vasic et al., 2009; Stange et al., 2017). Additionally, ineffective top-down control of...
negative thoughts and emotion is also a prominent feature of MDD which has largely been linked to attenuated fronto-limbic connectivity, including the dmPFC and OFC (Conjeevo et al., 2019).

Inflammation is associated with increased activation of regions in CCN in cognitive tasks. Typhoid vaccination led to a greater recruitment of the dIPFC during the attentionally demanding incongruent trials of the color-word Stroop task (Harrison et al., 2009). IFN-α treatment in hepatitis C patients caused significantly greater activity in dACC, which was highly correlated with the number of errors in a visuospatial attention task (Capuron et al., 2005). In the latter study, a group comparison between patients treated with IFN-α and the waitlist control did not reveal any difference in task performance, however the IFN-α group exhibited higher depressive symptom severity scores, especially on items assessing fatigue and loss of concentration.

Social stressors are one of the strongest risk factors for MDD, possibly related to a deficit in regulation of negative emotions after experiencing stressful life events (Li et al., 2018; Slavich and Irwin 2014; Irwin and Piber, 2018). Laboratory-based social stressors are linked to changes in peripheral inflammatory markers, which also in turn linked to changes in the activation of top-down emotional regulatory regions. In Trier Social Stress Test where participants are asked to perform tasks in front a nonresponsive and socially rejecting panel of evaluators, greater dACC activity was associated with greater increases in a soluble receptor for TNF-α (Slavich et al., 2010). When comparing experimental social exclusion versus social inclusion, IL-1β was found to be negatively associated with right OFC activation while IL-2 was positively associated with activation of the right ACC and OFC (Conjeevo et al., 2019). The sample consisted of euthymic patients with or without history of suicide attempts and healthy controls, however the group effect did not moderate the relationship between inflammatory markers and brain activities, so it remains to be seen whether and how the inflammation-related neural changes are related to depressive symptoms.

Increased levels of peripheral inflammatory markers due to social stressor task were associated with increased functional connectivity of AN and CCN (Muscattell et al., 2015). In contrast, in Labrenz et al. (2016), application of low dose lipopolysaccharide (LPS) led to a widespread reduction in the functional coupling of the amygdala, insula, and cingulate cortices to multiple brain networks, notably LPS was associated with reduced connectivity between amygdala and cognitive-regulatory prefrontal structures. The latter is more in line with studies on non-clinically depressed sample, which showed that peripheral inflammation was linked to reduced resting-state connectivity (Nusslock et al., 2019; Benedetti et al., 2021). Labrenz et al. (2016) measured mood at baseline, 3- and 6-h post-injection. Positive mood significantly declined after LPS injection. However, resting-state connectivity was not associated with either inflammatory responses or mood.

4.5. Summary and perspective

The above review points to alterations in affective, reward, cognitive control, and default mode network in inflamed depression. To the best of our knowledge, there is currently no quantitative analysis on the consistency of findings across these networks and which one most robustly mediates the relationship between inflammation and depression. However, there are theoretical and empirical reasons to expect that different networks are differently vulnerable to the effect of inflammation. The reallocation of energy resources to fight infection is facilitated by inhibition of reward-motivated behavior to prioritize clearing the infecting pathogen (Miller and Raison, 2015). This overlaps with impairments that are underpinned by changes in the reward circuitry of MDD patients, particularly the diminished interactions between the frontal cortex and striatal regions. In this regard, the vmPFC has been identified as the hub for the effect of inflammation on broadly distributed changes of functional connectivity across multiple networks (Yin et al., 2019). In this study, the identified multivariate network features were able to predict anhedonia and motor slowing with high accuracy. This is in line with behavioral works showing that inflammation is associated most robustly with physical symptoms, including psychomotor slowing and anhedonia (Frank et al., 2021).

Accumulating evidence suggests that some factors may contribute to the differential vulnerability across brain regions. First is the disparate distribution of microglia across the brain. As an important player that drives immune response, microglia are widely distributed in the brain. However, the number, gene expression patterns, and morphology of microglia are different among different brain regions. They are 5 times richer in gray matter than in white matter (Sun et al., 2022) and they are most concentrated in the hippocampus and basal ganglia (Lawson et al., 1990; Sun et al., 2022). Second is the region-specific cytokine gene expressions. For example, an immunohistochemical study revealed that the C-X3-C motif chemokine receptor 1 (CX3CR1) was expressed at a higher level in the cortex, hippocampus, and basal ganglia (Tarozzo et al., 2002). Lastly, dopamine and dopamine receptors also play a role in modulating inflammation and inflammation-induced depressive behavior at the molecular level. Dopamine has been found to inhibit NLRP3 inflammasome activation by activating the dopamine D1 receptor (DRD1) downstream signaling (Yan et al., 2015) and suppressing neuroinflammation and systemic inflammation. Similarly, the dopamine D3 receptor, which is expressed by astrocytes or microglia in the medial PFC, nucleus accumbens, and VS also played a role in regulating inflammatory responses. Dopamine D3 receptor knock-out mice exhibited depressive-like behaviors and extensive microglia specifically in meso-limbic dopaminergic brain areas (Wang et al., 2020). The latter has been especially highlighted for its importance in mediating the relationship between inflammation and anhedonia (Bekkhat et al., 2022).

5. Multi-dimensional models of inflamed depression

Among depressed individuals, variability in immune markers is linked to treatment outcomes, with inflamed depressed patients being less likely to respond to conventional treatment (Chamberlain et al., 2019; Strawbridge et al., 2015). The use of anti-inflammatory drugs (e.g., nonsteroidal anti-inflammatory add-on therapy) has shown some promising antidepressant effects, independent of the improvement in physical illnesses (Kappelmann et al., 2018). This strategy may especially benefit inflamed depressed patients. For example, patients with treatment-resistant depression with higher baseline levels of CRP (>5 mg/L) showed more improvement in the Hamilton Depression Rating Scale (HAM-D) scores after 12-week treatment with the TNF inhibitor infliximab (Raison et al., 2013). However, liberally prescribing anti-inflammatory treatments to all depressed patients may cause negative side effects for non-inflamed depressed patients.

To date, most works in classifying MDD patients with inflammation have focused on peripheral immunological markers. Existing results highlight IL-6 and CRP as two particularly promising candidates. Although CRP has been already used in a routine blood test that checks for infection or inflammation in the body, the common cut-off (CRP >3 mg/L) likely will lead to underestimation in identifying inflamed depression cases (Lynall et al., 2020). Efforts are currently underway to stratify patients based on their levels of CRP at baseline to test the efficacy of a monoclonal antibody that inhibits IL-6 signalling in reducing symptom severity (Khandaker et al., 2018).

Data-driven profiling of gene expression and immune markers from peripheral blood have been found to differentiate the inflammation profile of MDD cases and correlate with suicide risk and symptom severity (Kokkeler et al., 2022; Lynall et al., 2020; Schiweck et al., 2020). In Lynall et al. (2020), a within-group analysis showed that the inflamed depression group comprised 39% of the sample and exhibited increased monocyte, CD4$$^+$$, and neutrophil counts as well as increased CRP and IL-6. Similarly, Kokkeler et al. (2022) reported a group characterized by increased levels of CRP and IL-6 among older MDD patients, although they comprised a much smaller percentage of their sample.
Inflamed depression is characterized by a group of risk factors, presentation of specific symptom clusters, and circumscribed neurofunctional changes. A multidimensional approach that utilizes objective measurement at multiple levels, such as behavioral, neural circuit, and physiological will be useful to differentiate this subtype from other MDD patients and assist in designing more precise mechanism-based interventions. CRP measurement has been used to classify patients in combination with basal ganglia glutamate (Glu) measurement obtained from magnetic resonance spectroscopy (Haroon et al., 2018). High CRP-Glu group status was associated with greater severity of anhedonia and cognitive and motor slowing. More broadly, the multidimensional approach has been used to predict risk and treatment outcomes for MDD, for example by integrating risk factor profiling and genetic analysis for MDD risk categorization (Meng et al., 2022) and combining genetic, cognitive, neuroendocrine and personalistic markers to predict antidepressant responses (Bi et al., 2021). Notably, one study has integrated markers for mitochondrial metabolism, cellular aging, metabolic function, and childhood trauma to predict anti-depressant responses of diabetic medication (Nasca et al., 2021). The authors reported that MDD patients with shorter leukocyte telomere length show decreased levels of a mitochondrial mediator of epigenetic function, increased BMI, and a history of particular types of childhood trauma. Compared to individual factors, a combination of all these markers was a better predictor of longitudinal changes in depression severity in response to diabetic medication (Nasca et al., 2021).

6. Future directions

The present review has revealed several future directions. First, some evidence above was drawn from studies that calculated indices from a mix of inflammatory markers, whereas most were drawn from studies that investigated a single marker or multiple markers but separately. Future researchers could consider bigger networks of cytokines holistically, which means they need to take into account the fact that cytokines interact with one another and do not have exclusively pro-inflammatory or anti-inflammatory roles. For example, IL-6 can serve both roles via two separate signaling pathways (Scheller et al., 2011). In the short term, this will provide a fuller picture of immune function in MDD, while in the long term it may lead to the development of a valid and reliable “inflammation index”. Pursuing this research direction may also reveal more information to the possibility that there may be more than one inflamed depression subtype. In a data-driven analysis without constraints on the number of categories, Lynall et al. (2020) found 4 subtypes of MDD patients, two of which (67% in total) were associated with increased inflammatory proteins but differed by their distinctively myeloid- versus lymphoid-biased immune cell profiles, suggesting that there may be more than one mechanism to the same manifestation of high depressive symptoms and increased inflammatory proteins.

Second, classification using functional neuroimaging data such as resting-state functional connectivity is a potential avenue to explore. For example, Drysdale et al. (2017) found 4 subtypes of MDD that are defined by distinct patterns of dysfunctional connectivity in the limbic and frontostriatal networks. These subtypes were associated with distinct profiles of clinical symptoms and showed promising potential as diagnostic classifiers with high sensitivity and specificity. Combining risk factor profile, symptom clusters, peripheral blood markers, and functional neuroimaging data may lead to the development of valid and reliable biomarkers that can aid in the diagnosis, prognosis, and treatment of MDD. Measures of functional connectivity in networks centered on vmPFC seems particularly promising. The evidence reviewed here suggest that a combination of aberrant functional connectivity, heightened peripheral inflammation markers (CRP or IL-6), and presentation of physical symptoms of depression may categorize MDD patients who are likely to benefit from anti-inflammatory treatment intervention.

7. Conclusions

Inflamed depression is associated with specific clinical symptoms and neurofunctional changes and is moderated by several individual risk factors (Fig. 1). Depression and inflammation-induced sickness behavior are hypothesized to share genetic determinants and serve an adaptive function by saving energy and preventing further infections. Some populations may be more vulnerable to inflamed depression, including the elderly and females. Disruption of brain functions, particularly in the reward processing network may give rise to changes in motivated behavior that characterize inflamed depression. Taken together, the evidence outlined above paint MDD as a heterogeneous disorder. This is in line with the view that MDD is not a unitary construct. According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013), a major depressive episode is diagnosed when an individual reports 5 or more of 9 symptoms, which means there are more than 250 unique combinations of symptom presentations. This is most likely the result of disruptions in different aspects of normal neural functions that can range from the molecular level up to the neural circuit, only some of which are directly linked to inflammation (Filatova et al., 2021). A better understanding of the inflammatory pathways must be considered in the context of its interactions with other pathways to allow neurobiologically based subtyping of depression to inform clinical decision making.

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Disclosure

The authors have no competing interest to declare.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence...
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