Brain Research Bulletin 196 (2023) 34–45

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Sex differences in depression: An immunological perspective

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ARTICLE INFO

Keywords:
Stress
Sex
Depression
MDD
Immune

ABSTRACT

Depression is a heterogenous disorder with symptoms that present differently across individuals. In a subset of people depression is associated with alterations of the immune system that may contribute to disorder onset and symptomology. Women are twice as likely to develop depression and on average have a more sensitive adaptive and innate immune system when compared to men. Sex differences in pattern recognition receptors (PRRs), release of damage-associated molecular patterns (DAMPs), cell populations, and circulating cytokines play a critical role in inflammation onset. Sex differences in innate and adaptive immunity change the response of and repair to damage caused by dangerous pathogens or molecules in the body. This article reviews the evidence for sex specific immune responses that contribute to the sex differences in symptoms of depression that may account for the higher rate of depression in women.

1. Introduction

Major depressive disorder (MDD) is a heterogenous illness producing a mixture of different symptoms across individuals. These symptoms can include changes in mood, reduced pleasure, and alterations in energy levels that produce disruptions to daily life. In severe cases this leads to suicidal ideation or attempts. Approximately 3.8% of the world is affected by depression resulting in a disease burden of approximately 48 million disability-adjusted-life-years (GBD, 2019). Depression is associated with changes in both the innate and adaptive immune system that may account for depression etiology in some individuals (Maes, 1995; Leonard and Song, 1996). Genetic, hormonal, and developmental sex impacts the function and properties of the immune system (Klein and Flanagan, 2016).

Women are at a greater risk of developing depression with a prevalence between women and men at 2:1 respectively (Salk et al., 2017). Women also experience first onset of depression at an earlier age and have more cumulative episodes, men have a higher comorbidity with substance use disorders and present with different symptoms including anger (Marcus et al., 2005). There are sex differences in symptomology, especially associated with eating behavior and somatic experience. Many women experience increased appetite, weight increase, fatigue, somatic pain, higher comorbidity with anxiety, gastrointestinal problems, and suicide attempt frequency (Marcus et al., 2008). Many of these symptoms relate to sex differences in the immune responses that occur during MDD (Birur et al., 2017). Here we will explore immune activity that could function as a source of variability in substance use, eating behaviors, pain, anxiety, fatigue, and suicidal ideation.

Many hypotheses have been proposed for the origins of depression. Some indicate serotonergic dysregulation as a probable cause (Coppen, 1967). Some have correlated depression with hormonal alterations and have explored this as a possible avenue for the sex differences in the etiology of depression (Soares and Zitek, 2008). The concept that depression in some individuals has an immune basis developed out of various lines of study, some causal and some correlational. In people treated for hepatitis-c, depression was induced among a large minority (20–40%) when treated with the cytokine interferon alpha (IFN-α) that lasted up to 3 months after cytokine exposure (Bonaccorso et al., 2002; Asnis and De La Garza, 2006; Udina et al., 2012). This finding supports the concept that the heterogeneity of depression is related to a wide range of peripheral and central systems influenced by immune function. Previous theories of depression such as hormonal or monoamine involvement can be integrated into an immune hypothesis of depression. This review addresses how sex differences in immune function

Abbreviations: MDD, Major depressive disorder; DAMPs, Damage/danger associated molecular patterns; LPS, Lipopolysaccharide; TLRs, Toll like receptors; HPA axis, Hypothalamic Pituatary Adrenal axis; CRF, Corticotrophin releasing factor; IL, Interleukins; IFN, Interferons; TNF, Tumor necrosis factor; PRRs, Pattern recognition receptors; ACTH, Adrenocorticotropic hormone; CORT, Corticosterone (rodents)/Cortisol (humans); HMGB1, High mobility group box 1 protein; RAGE, Receptor for advanced glycation end products; SLE, Systemic lupus erythematosus.

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https://doi.org/10.1016/j.brainresbull.2023.02.016
Received 11 November 2022; Received in revised form 5 February 2023; Accepted 27 February 2023
Available online 28 February 2023

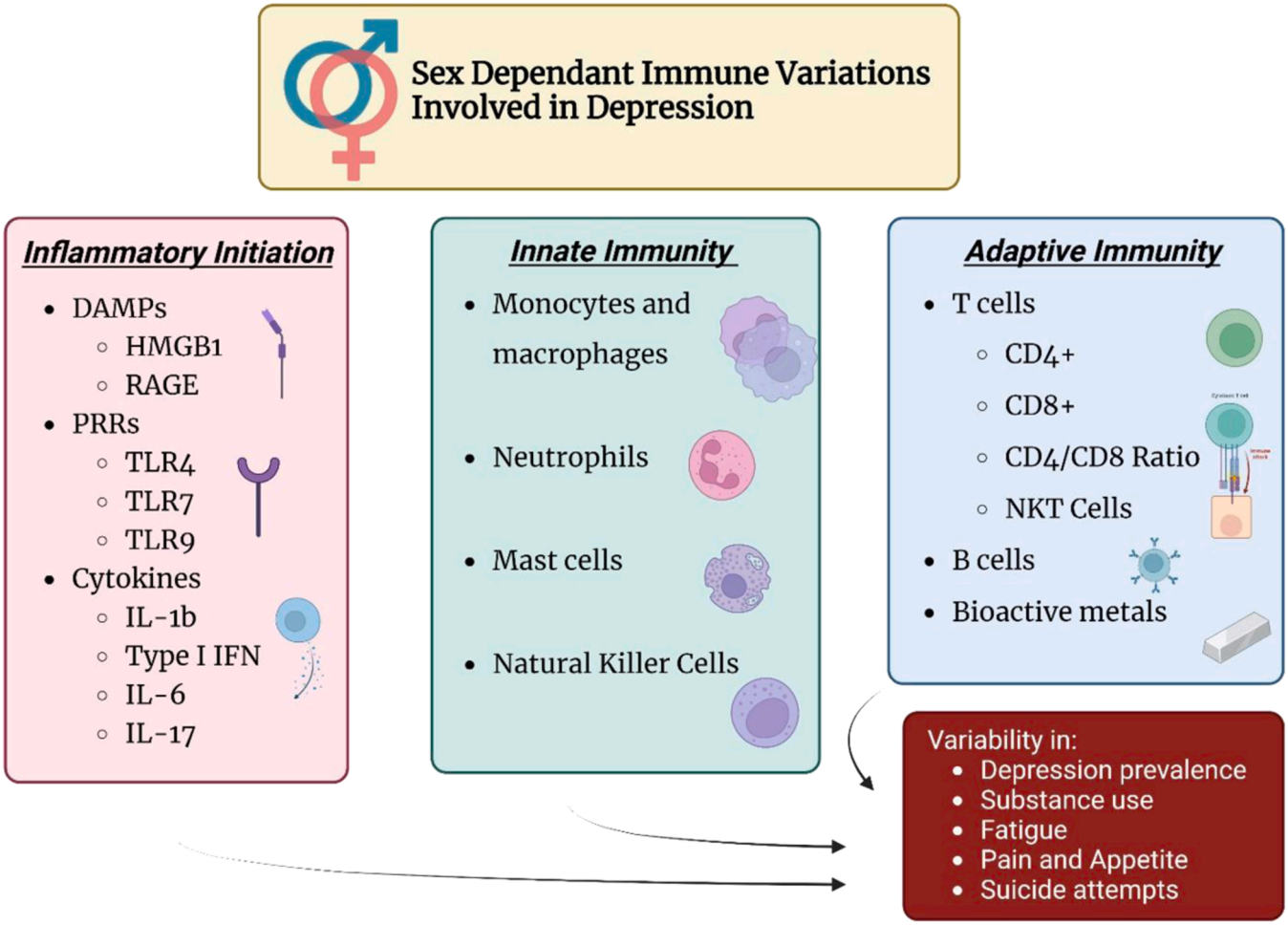

Fig. 1. Variations of the immune system that are affected by genetic, hormonal, and developmental sex. These sex differences can occur during initiation of inflammation, during the innate immune response, or during the adaptive immune response.

contribute to sex differences in the symptoms and etiology of depression.

When inflammation becomes chronic or repetitive there is cellular and/or tissue damage that occurs because of repeated repair and cleanup by immune cells. The immune system has the capacity to activate a proinflammatory response as a result of a nonpathogenic event, often referred to as a sterile event. Although this inflammation can also be generated via pathogens or microbes, psychological stress is a form of sterile inflammation and occurs in the CNS making it a likely candidate for a common cause of immune-related depression. Stress commonly precedes episodes of depression and can act as a potent trigger for its onset (Hammen, 2005). Psychological stress generates molecular patterns that the immune system recognizes and attempts to remove, these molecular patterns are associated with mood disorders (Fleshner et al., 2017). This process in turn engages the HPA axis, which suppresses immune responses. Over activation of the immune system leads to the dysregulation of glucocorticoid responsive genes in immune cells as well as cellular damage leading to dysfunctional regulation of the stress response (Wohleb et al., 2011; Weber et al., 2017; Niraula et al., 2018). Therefore, Stress acts as a potent trigger for depressive symptoms and subsequently repeats cycles of destruction and repair.

The most common model for studying the effect of molecular patterns on mood disorders is through the use of lipopolysaccharide (LPS) which mimics the cell wall of gram-negative bacteria and is thus capable of activating a non-sterile immune response. This model gives insight into depression that is associated with pathogenic inflammation. However, damage/danger associated molecular patterns (DAMPs) and diseases that cause sterile inflammation may represent better models for the neuroinflammation associated with depression.

DAMPs are metabolic products presented on the surface of cells that have undergone physical stress, damage, or destruction (Wohleb et al., 2011; Frank et al., 2013; Picard and McEwen, 2018). Cells present DAMPs to monitoring immune cells such as dendritic cells and macrophages which activates pattern recognition receptors (PRRs) triggering inflammatory cascades that will remove and repair the damage (Rock et al., 2011). DAMPs can be released extracellularly or intracellularly and as a result of the variability of DAMPs (DNA, RNA, Protein, Reactive oxidation species, etc.) there is likewise a wide variety of PRRs to detect them (Roh and Sohn, 2018). Therefore, physical insults to the brain and periphery such as ischemia, autoimmune disease, and noninvasive trauma give insights into sterile immune activity following the release of DAMPs. For example, the proinflammatory response of the central nervous system has been shown to cause myelin and axonal damage in neurons via oxidative stress and proinflammatory cytokines (di Penta et al., 2013). Damage to these systems would make it difficult for an individual to cope with subsequent stressors. There is some evidence of lesions following depression, but it is not conclusive (Leonard, 2000). Excitotoxicity from stress is thought to occur through deficits in GABAergic and glutamatergic neurotransmission (Duman et al., 2019). Some integrative models of depression have implicated specific regions in the etiology of depression (Price and Duman, 2020). If inflammation is initiated by a wide variety of PRRs and a myriad of DAMPs generated in many regions, region-specific inflammation may be generated on a by-individual basis that would make depression heterogeneous and exceedingly difficult to diagnose and treat. However, DAMPs can be

normal metabolic products or released RNAs, therefore DAMPs may be constantly secreted and instead might need to meet a threshold to activate the proinflammatory cascade. To date we do not know how stress or depression causes the release of DAMPS and subsequent activation of PRRs.

Although the central nervous system is thought to be a privileged immune site there are extensive ways that the peripheral immune system can interact with it. Some cytokines are capable of crossing the blood brain barrier. Proinflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α are capable of crossing from the blood into the brain (Banks et al., 1995). All of these cytokines are capable of initiating microglial activity or impacting other cells in the brain (Smith et al., 2012). Therefore, proinflammatory signals circulating in the blood are capable of entering the brain and signaling resident cells. To exacerbate this effect, depression damages the integrity of the blood brain barrier (Menard et al., 2017; Wu et al., 2022). During depression neutrophils can migrate into the brain and can initiate inflammation (Aguliar-Valles et al., 2014). Monocytes are also capable of invading across the blood brain barrier (Fitch and Silver, 1997; Winkler et al., 2021). Natural killer cells, T cells and mast cells exist in the parenchyma of the brain in unstressed conditions (Khalil et al., 2007; Song et al., 2016; Sedgwick et al., 2020). This demonstrates that peripheral immune cells and signaling molecules circulating in the periphery have varied mechanisms to affect signaling in the brain.

The CNS has bidirectional communication with the peripheral immune system. The HPA axis is a communication system that allows for crosstalk between the central and peripheral nervous system. One function of the HPA axis is converting the stimulus of psychological stress into an electrical/chemical/hormonal stress response (Smith and Vale, 2006). Intravenous injection of the cytokine IL-1β can start the secretion of CRF in the hypothalamus activating the HPA axis resulting in increased circulating ACTH and CORT (Sapolsky et al., 1987). Blocking CRF activation during IL-1β injection prevents increases in ACTH and CORT, confirming an indirect mechanism. Intracerebral administration of IL-1β or TNF-α also activates the HPA axis resulting in changes in body temperature, social and eating behavior (Dantzer et al., 2008; Tracey, 2009; Watkins & Maier, 2013). Together these studies support the ability of cytokines to directly activate CRF, resulting in the start of the HPA axis cascade. The glucocorticoids that the HPA axis releases have an effect on a wide array of peripheral immune cells such as macrophages and monocytes, neutrophils, T cells, dendritic cells, and B cells (Bellavance and Rivest, 2014). How an individual perceives stress and how often that stress occurs also plays an important role in immune activation and modulation. These immune cells can then go on to affect the brain once again by releasing molecules that cross the BBB or by crossing it themselves. This leads to a feedback system between stress perception, hormonal release, and immune activation/modulation. Sex differences in these areas leads to different outcomes for cellular repair and cleanup in the brain. Because of these differences, men and women may experience depression differently and therefore by understanding these immune differences a more holistic model of depression can be generated. (Fig. 1).

2. How does the innate immune response contribute to sex differences in depression?

2.1. Sex differences in the initiation of inflammation

The innate immune system becomes activated in response to a threat to the host organism. It is capable of responding to a vast number of immune insults through nonspecific innate immune activity. Inflammation is multifaceted, it can be a response to foreign invaders or to cellular events such as heat shock, excitotoxicity, and stretching which require an immune response and involve only native cells. Toll-Like Receptors (TLRs) are a class of PRRs responsible for sensing molecular patterns in the environment that pose a potential threat to the host. There are sex differences in TLR4 expression in innate immune cells dependent upon the presence of steroid hormones. For example, exposure of androgen naïve cultured macrophages to testosterone resulted in a decrease of TLR4 expression (Rettew et al., 2008). TLR4 is a receptor capable of triggering proinflammatory activity in response to DAMPs, therefore its testosterone dependent decrease results in a diminished sensitivity of the immune response in males. TLR4 activity also contributes to inflammatory responses within the central nervous system. The functional removal of TLR4 in mice significantly attenuated the proinflammatory response in the spinal cord as mediated by microglia (Bell et al., 2013). However, this experiment was performed exclusively in male mice leaving a gap in the literature regarding the effects of TLR4 removal in female mice. Ablation of TLR4 receptors in male mice only, led to protection from chronic pain induced by the DAMP high mobility group box 1 (HMGB1), this did not occur in female mice undergoing the same procedure (Agalave et al., 2021). Male and female mice both express decreases in pain presentation when TLR4 is systemically ablated, however females required central TLR4 ablation along with the peripheral for pain cessation whereas males only required ablation of TLR4 receptors on spinal microglia (Huck et al., 2021a, 2021b). Female mice have supernumerary systems involved in pain activation and therefore are more difficult to target for pain relief. If this translates to humans, it may contribute to the increase in somatic pain perception in MDD for women, when TLR4 receptors are activated (Marcus et al., 2008). Additionally, non-sterile activation of TLR4 with LPS, was sufficient to produce pain behaviors in male mice, but not in female mice (Sorge et al., 2011). These data support convergent sex differences in immune induced pain indicating different mechanisms are responsible for the same experience of immune related pain in males and females.

HMGB1 is a well-studied DAMP that is associated with stress and depression (B. Wang et al., 2018; J. Wang et al., 2018; Zhang et al., 2019). Differences in TLR4 activation due to sex specific HMGB1 is one area where sex differences in immune activation between men and women could occur. Less HMGB1 was released by male mouse cultured pulmonary endothelial cells in response to hypoxia than female cells, however a different stimulus, mitochondrial damage triggered a greater release of HMGB1 in male cells compared to female cells (Zemskova et al., 2020). In addition to activating TLR4, HMGB1 is also capable of activating the receptor for advanced glycation end products (RAGE). Increased levels of advanced glycation end products in the skin are associated with more severe symptoms of depression and higher depression prevalence (van Dooren et al., 2017). RAGE becomes upregulated when it is persistently activated in male rats due to chronic unpredictable stress, whereas TLR4 regulation is not altered. Male RAGE knockout mice were behaviorally resistant to the effects of chronic unpredictable stress but females were not tested (Franklin et al., 2018). The vast variety of PRR types and differences in their regulatory properties could contribute to heterogeneity of symptoms in people experiencing depression.

TLR7 and TLR9 are other PRRs that have been associated with depression. Depressed patients had increased expression of TLR7 and TLR9 that was attenuated after 4 weeks of antidepressant use (Hung et al., 2016a., 2016b). TLR7 can be activated by antiphospholipid antibodies or single strand RNAs (ssRNAs) (Piccinini and Midwood, 2010). Antiphospholipid antibodies are increased in depressed patients when compared to controls (Maes et al., 1993a, 1993b). There is currently a gap in the literature on whether or not there is a link between depression and the ssRNAs that activate TLR7. COVID-19 is an ssRNA and approximately ~15% of people develop depression within 6 months of COVID-19 infection with ~6% reporting it as their first episode of depression (Taquet et al., 2021). Sex differences in rates of COVID infection and mortality were reported early in the pandemic, with males showing a greater sensitivity to COVID 19 and a worse outcome (Alwani et al., 2021). One study found that the rates of depression following COVID 19 were not significantly different in men and women whereas the experience of anxiety following COVID was higher in women (Xiao

et al., 2022). Additionally, women are more likely than men to develop long COVID, with symptoms that include changes in smell and taste, throat pain, heart palpitations and sleep disturbance (Pelà et al., 2022). The results from clinical trials suggest that the antidepressant fluvoxamine is a potential treatment for COVID 19 as it blocks disease related deterioration, although it should be noted, the participants skew female (~70% women) (Wen et al., 2022).

TLR9 is activated by IgG-Chromatin complexes and by unmethylated CpG sites. While more data is needed to understand if TLR9 could be used as biomarker for depression, there is some indication that in the periphery TLR9, along with other TLRs are altered by depression and sensitive to antidepressant treatment. TLR9 expression was elevated in the peripheral blood mononuclear cells of patients with depression along with a number of other TLRs (3,4,5,7,8) and 4 weeks of antidepressant treatment normalized TLR9 levels along with TLRs 3,5,7, and 8 (Hung et al., 2016a., 2016b). Participants in this study skewed female (~ 70%) and sex was not examined as a co-variate. In a study that skewed male (~30% female) TLR9 was not altered post-mortem in the prefrontal cortex taken from depressed and/or suicidal people even though protein levels of other TLRs were (TLR 2,3,4,6,10) (Pandey et al., 2019). A study better controlled for sex could identify whether this is a male/female difference or a difference between the brain/periphery.

Once immune cells are activated by DAMPs they coordinate an immune response with cytokines, immune signaling molecules. Interferon alpha (IFN-α) is a proinflammatory type 1 interferon that triggered depression following treatment for hepatitis in ~40% of people (Bonaccorso et al., 2002; Hoyo-Becerra et al., 2014). High levels of type 1 interferons are secreted by plasmocytoid dendritic cells, specialized dendritic cells located in primary and secondary lymph organs (Segura et al., 2012; Chistiakov et al., 2014; Ye et al., 2020). These cells are also involved in systemic lupus erythematosus (SLE), an autoimmune disease characterized by self-attacking antibodies that cause damage to cellular structures because of improper cellular repair and cleanup (Mok, Lau, 2003). The immune changes associated with this disease may also help us understand immune regulation of depression since the pathogenesis of the disorder is sterile and it is predominantly diagnosed in females. It is estimated that ~30% of people affected by SLE will also present with depression (Zhang et al., 2017). Plasmacytoid dendritic cells derived from women produced more IFN-α than cells from men mediated by levels of IFN regulatory factor 5 (Griesbeck et al., 2015). Furthermore, the binding of ligands to TLR7 in cells derived from women caused increased release of IFN-α when activated compared to men, this subsequently produced stronger activation of cytotoxic T cells (CD8 + t cells) implicating innate to adaptive immune cross talk as a potential mechanism (Meier et al., 2009). IFN-α production was reduced in plasmacytoid predendritic cells of patients with SLE when TLR7 and/or TLR9 were inhibited (Barrat et al., 2005). Together these results suggest that females produce more IFN-α compared to males because of differences in TLR7, representing yet another area where the increased sensitivity of the immune system leads to a stronger inflammatory response in depressed females. Interestingly, polymorphisms in TLR7 also provide protection against hepatitis C infection in men but not in women (Schott et al., 2007). In addition to the sex specific properties of its TLRs, dendritic cells have steroid hormone driven immune properties that may also contribute to sex differences in MDD through innate to adaptive immune system cross talk. For example, treatment of dendritic cells with 17β-estradiol produced a stronger anti-inflammatory T-helper (Th_2) cell response than occurred in cells in the absence of estradiol (Masuda et al., 2018).

Another cytokine, interleukin 6 (IL-6) has repeatedly been reported as elevated in people with depression (Dowlati et al., 2010). There is evidence that IL-6 is implicated in the etiology of depression or stress susceptibility in some individuals. In humans, a longitudinal study demonstrated that participants with higher circulating IL-6 during childhood were more likely to develop depression or psychosis in late adolescence (Khandaker et al., 2014). In male mice, higher levels monocytes or peripheral IL-6 were a predictor of higher stress susceptibility during late adolescence/early adulthood, Blocking IL-6 with a neutralizing IL-6 antibody prevented the onset of stress susceptibility (Hodes et al., 2014). Furthermore, knockout of IL-6 in the periphery only, through adaptive transfer from IL-6 knockout mice, promoted behavioral resiliency. Bone marrow transplants from stress susceptible mice made naïve hosts more susceptible to subthreshold stress (Hodes et al., 2014). Later studies used biotin labeled IL-6 to confirm that peripheral IL-6 was getting into the brain of stress susceptible but not stress resilient mice (Menard et al., 2017). IL-6 infusion directly into the nucleus accumbens was also sufficient to induce susceptibility to subthreshold levels of stress (Menard et al., 2017). With IL-6 being capable of crossing the blood brain barrier and the BBB being made more permeable by stress, these studies demonstrate a way for peripheral immune elements to enact central immune changes involving stress perception.

Higher levels of IL-6 predicting depression vulnerability reinforces the notion that depression occurs as a result of previous proinflammatory insults in the brain. While social stress increases peripheral IL-6 in female mice (Menard et al., 2017) it does not determine whether or not a female will be stress resilient or susceptible and may not impact the brain through the same mechanisms (B. Wang et al., 2018; J. Wang et al., 2018). Social defeat stress altered broader array of peripheral cytokines in females compared to males. Dihydrocaffeic acid (DHCA) and malvin-3 O-glucoside (Mal-gluc), a combination of phytochemicals that blocks the effects of stress on peripheral cytokines and detrimental changes in brain plasticity was protective in both males and females but through different changes in transcriptional pathways and through different cytokines (B. Wang et al., 2018; J. Wang et al., 2018). In male mice, DHCA/Mal-gluc blocked the effects of stress on peripheral IL-6 but did not significantly decrease the cytokine in females. Instead DHCA/Mal-gluc treatment significantly impacted IL-12p70 and regulated on activation normal T cell expressed and secreted Rantes/CCL5, both of which act on T cells. Together these studies support the concept of convergent sex differences for cytokine dynamics in depression and stress susceptibility. These data suggest that women and men would need different immune based therapies to treat depression.

2.2. *Monocytes and macrophages*

While both men and women with depression have increased white blood cell counts, men had increased circulating levels of monocytes compared to women (Maes et al., 1992a, 1992b, 1992c). In depressed patient's, a longitudinal study of white blood cell counts and their correlation with self-reported symptom severity revealed monocytes to be an indicator of disease severity and treatment outcomes, with decreased amounts indicating less severe symptoms (Seidel et al., 1996). Monocytes from the spleen migrate to the CNS when activated by stress in mice of both sexes, demonstrating a way for peripheral immune activation to lead to CNS dysfunction (Wohleb et al., 2014; Yin et al., 2019). Strokes are a cause of a sterile inflammation with ~33% of patients experiencing post stroke depression (Hackett et al., 2005) and therefore provides relevant information on how the immune system responds to DAMP release from cells in the CNS. Commonly reported symptoms include apathy as well as alterations in weight and sleep behavior (Arcadi et al., 2021). In male rats, splenectomy preceding a stroke reduced the area of damage induced by the infarction. Following stroke, the spleen intact males had significantly more peripheral monocytes than males and females without spleens and spleen intact females. The pattern was also identified in the CNS, with spleen intact males having higher monocyte to microglia ratios than that of the other groups (Dotson et al., 2015). Additional studies support that females may have greater protection from monocyte induced activation because females have a higher resting state baseline inflammatory profile. Monocytes from females typically produce 1.8 times more leukotrienes than males (Pergola et al., 2011). Leukotrienes are a pro-inflammatory mediator

biosynthesized by monocytes. Circulating steroid hormones likely mediate this effect as the increased female production of leukotrienes was ameliorated by resuspending the cells in male plasma with higher circulating testosterone (Pergola et al., 2011).

Higher baseline monocyte activation in females may also result in a stronger or faster monocyte response to chemokine signaling. Monocytes from females expressed more fractalkine receptors (CX3CR1) on the surface compared to male cells, a receptor for the chemokine fractalkine/CX3CL1 involved in macrophage recruitment (Becerra-Díaz et al., 2021). This increase in receptor expression produces increased sensitivity of the monocytes to traffic to the source of the ligand. Additionally, stimulation with LPS, a non-sterile TLR4 agonist, caused female monocytes to produce more of the cytokine IL-6 than monocytes derived from males (O'Connor et al., 2007). Increased release of IL-6 from female monocytes could be a mechanism for the increased prevalence of depression in women. Together these studies suggest that the involvement of monocytes in stress susceptibility and depression may result in different downstream activation in males and females.

Macrophages, tissue resident mature monocytes, have been commonly associated with depression symptoms and severity, even spawning the term "The macrophage theory of depression", whereby increased activation of macrophages results in increased proinflammatory activity leading to depressive outcomes (Smith, 1991). Steroid hormones including estrogens, androgens, and progesterones have been strongly linked to macrophage function in immune response (Miller and Hunt, 1996). Stimulation of female cells with the anti-inflammatory cytokine IL-4 produced greater activation of genes that promote tissue repair in females compared to males (Keselman et al., 2017; Becerra-Díaz et al., 2021). Macrophages were originally thought to be polarized between a pro-inflammatory M1 state and an anti-inflammatory M2 state, however recent data suggest that the same cells may transition from one to another across time (Martinez and Gordon, 2014; Alhamdi et al., 2019). Increased anti-inflammatory M2 activation is protective against parasitic worms and has been associated with conditions such as asthma and allergies (Girodet et al., 2016). Cultured human monocytic/macrophage cells activated by the anti-viral cytokine IFN- γ had cell growth inhibition and apoptosis when cultured in testosterone. Whereas activation with IFN-γ in cells cultured in 17β-estradiol caused the transcription factor NF-kB to bind more efficiently (Cutolo et al., 2005). NF-kB transcription activates a pro-inflammatory molecular cascade. Mechanistic studies suggest regulation of NF-kB has opposite effects on stress related behavioral responses in male and female mice and is mediated in females by estrogens (LaPlant et al., 2009; Christoffel et al., 2011, 2012). In female mice, ovariectomy increased IkB kinase, part of the NF-kB signaling cascade, and blocked the effects of 6 days of variable stress on increased immobility in the forced swim test (LaPlant et al., 2009). Using a constitutively active version of IkB kinase to overexpress transcription protects against stress in intact females mimicking the effects of ovariectomy whereas a virally expressed dominant negative to IkB kinase blocked the protective effects of ovariectomy and increased immobility (LaPlant et al., 2009). In males, blocking NF-kB expression with the same dominant negative IkB kinase was protective against social defeat stress and the constitutively active expression of IkB kinase promoted stress susceptibility to subthreshold social defeat stress and increased the time spent immobile in the forced swim test (Christoffel et al., 2011, 2012). Together these studies support that testosterone and estrogens are interreacting differently with NF-kB activity as simply removing estrogens did not induce a male like behavioral response to decreased IkB kinase in females. The relationship between gonadal hormones and NF-kB signaling supports this is an important mechanism for sex differences in immune related behavioral outcomes.

2.3. Neutrophils

Neutrophils are another innate immune cell that is altered in people suffering from depression. Neutrophils are the most abundant leukocyte in the peripheral immune system and act to destroy invading pathogens as well as mediate the ongoing immune response (Rosales, 2018). Higher neutrophil to lymphocyte ratios are implicated in depression and also correlate with the symptom severity (Demir et al., 2015; Aydin Sunbul et al., 2016). Women have on average 0.66 times higher levels of neutrophils than men (Bain and England, 1975). Neutrophils play a key role in conveying inflammatory signals between the central nervous system and immune system. A recent study demonstrated that acute stress results in neutrophilia caused by release from bone marrow (Poller et al., 2022). This effect was independent of the sympathetic nervous system. Rather the authors determined that the chemokine CXCL1 released from muscle tissue was responsible for the neutrophil exodus. The signaling that produced the chemokine release came from motor centers in the medulla and neutrophilia could be induced by optogenetic stimulation. It should be noted that this is an acute response to stress and as such is not indicative of a pathological response (Poller et al., 2022).

Another unexpected mechanism of neutrophil brain communication involves the metabolic hormone leptin. Increases in leptin concentration in obese mice positively correlated with sickness behavior and the migration of IL-1β expressing neutrophils to the brain. Neutralization of serum leptin concentration attenuated sickness behaviors and blocked the transmigration neutrophils to the brain (Aguliar-Valles et al., 2014). In humans, higher levels of leptin also correlate with depression (Morris et al., 2012). Women on average have higher levels of circulating leptin due to higher levels of adipose tissue, where leptin is produced, and a faster rate of leptin production (Hellström et al., 2000). These data show that neutrophils in women are more likely to migrate from the periphery to the CNS in order to activate immune circuitry due to a higher number of neutrophils at baseline and higher levels of circulating leptin that mediate the migration. With leptin also correlating with sickness behaviors this may explain differences in fatigue symptomology reporting between men and women.

Like monocytes, neutrophils have increased ability to biosynthesize leukotrienes in females when compared to males (Pace et al., 2017). Females have more mature neutrophils at baseline that release more neutrophil extracellular traps (NETs), a marker for neutrophil activation, in response to LPS as well as to sera from SLE patients (Blazkova et al., 2017). This means that neutrophils from females are more sensitive to both sterile and non-sterile causes of inflammation. Sex hormones likely drive the sex differences in neutrophilic activity between men and women. Estradiol treatment in female mice increased the number of activated neutrophils compared to placebo (Robinson et al., 2014). Testosterone has been shown to increase phagocytic activity while reducing the anti-microbial activity of neutrophils in vivo, it also has antioxidant properties (Marin et al., 2010). These studies together demonstrate that females are more sensitive to pro-inflammatory signaling from neutrophils both in their greater abundance at baseline and increased sensitivity to activation.

2.4. Mast cells

Mast cells, which engage in the parasitic worm/allergic response, are also implicated in the immunological cascade that occurs before and during depression. Depression rates and suicidal ideation increase during spring months and have been linked to seasonal allergies (Plemmons et al., 2018). One report found that ~70% of patients diagnosed with depression also suffered from allergies (Bell et al., 1991). Patients with an overaccumulation of mast cells in their tissue present with lower levels of tryptophan and serotonin, and these tryptophan levels are correlated with higher levels of reported stress in patients (Georgin-Lavialle et al., 2016). This could provide an additional mechanism by which increased serotonin alleviates depression symptoms in some patients. Sex differences in mast cells occur early with perinatal androgens providing males more protection against mast-cell related diseases than females (Mackey et al., 2020). Elegant work by the McCarthy

lab and Lenz lab have shown that mast cells play an important role in masculinizing the medial pre-optic area, a nucleus in the brain important for male sexual behavior. During a critical period of development high levels of testosterone are aromatized into estrogens which trigger mast cell degranulation (Lenz et al., 2018). Histamines released by the mast cells trigger a feed forward mechanism of prostaglandins from microglia and permanently increase dendritic spines on neurons. This can be triggered in females by activating any step in the pathway, and if these brain-masculinized females are given testosterone in adulthood they will engage in male sexual behavior when presented with a sexually receptive female (Lenz et al., 2013). Stress during gestation increases mast cells in the hypothalamus of female offspring. Postnatal stress caused a reduction in degranulated cells in hippocampus and granulated cells in hypothalamus in females but not males. Both males and females saw a reduction in total mast cells in hypothalamus following postnatal stress (Joshi et al., 2019). In adulthood, depletion of mast cells triggers anxiety-like behavior in male mice (Nautiyal et al., 2008). Mast cells are increased in the brains of males across species when repeatedly exposed to a receptive female (Silverman et al., 2002). Together, these studies frame mast cells as positioned to shape the effects of stress on social and sexual behavior.

2.5. Natural Killer cells

Natural Killer cells are lymphocytes that act to stop the advance of viruses and tumors in the body (Vivier et al., 2008). Natural killer cells also provide insights into sex differences in depression. Diminished natural killer cell activity is associated with increased incidence of MDD (Evans et al., 1992; Maes et al., 1994; Pike and Irwin, 2006). This effect was found mainly to occur in men, who had an inverse relationship between measures of natural killer activity and depression severity (Evans et al., 1992). Diminished natural killer activity has also been observed in studies of cells from multiple sclerosis patients, with men having more reduced activity than women (Benczur et al., 1980). Patients with multiple sclerosis are two to five times more likely to develop depression than someone without (Feinstein et al., 2014). Individuals suffering from chronic fatigue syndrome are also more likely to have a low natural killer cell count (Whiteside and Friberg, 1998) and may contribute to increased depression associated lethargy. Inversely, high natural killer cell counts have been correlated with healthier lifestyles including more nutritious eating, lower levels of stress, and lower levels of drug use (Kusaka et al., 1992). Low natural killer cell counts preceded lesions in multiple sclerosis patients (Kastrukoff et al., 1998). Interestingly, the use of drugs such as alcohol and morphine are capable of lowering natural killer cell levels (Irwin et al., 1990; Yeager et al., 1995). This represents one area where males are at higher risk due to their increased vulnerability to substance use disorder. This would cause that subset of individuals suffering from depression and a substance use disorder to enter a compounded depression-prone immune state.

3. Sex differences of depression in adaptive immunity

3.1. Role of adaptive immunity in depression

Sex differences in adaptive immunity are an essential area in depression research. The bulk of recent immune work related to depression has focused on the innate immune system. Studies prior to the ability to detect innate immune cells explored the relationship between the adaptive immune system and depression, the adaptive immune system is made up of T cells and B cells. T cells act to combat specific antigens using a vast series of receptors, they also help maintain memory for the immune system and regulate how strongly the immune system responds to molecular patterns from the host (Kumar et al., 2018). B cells engage in antibody production and release, act as antigen presenting cells, and support other immune cells during proinflammatory action (Carter, 2006). Depression was initially thought to be due to a suppressed immune system because of the effects on adaptive immunity where bereaved people were found to have significantly lower levels of B and T cells immediately following the loss of a loved one (Bartrop et al., 1977; Schleifer et al., 1983). Around this same time depression was also associated with decreased levels of B and T cells compared to controls (Kronfol et al., 1983). Transfer of adaptive immune cells between mice have shown a transfer in susceptibility to stress (Brachman et al., 2015). Like innate immune cells, T & B cells are also sensitive to the effects of steroid hormones. Testosterone suppresses immune activation for T and B cells resulting in reduced efficacy of vaccines (Furman et al., 2014). Cell phenotyping of patients with depression indicated that both males and females with depression had elevated white blood cell counts. In men these were due to increases in neutrophil and monocyte populations, whereas for women it was leukocytes (Maes et al., 1992a., 1992b., 1992c). However, little research has gone on to identify which specific leukocyte populations are altered in female depression.

3.2. T cells

T cells exist in different forms which can be identified in part by their cell surface markers. CD4 + cells are helper T (T_h) cells. These cells further differentiate into different subsets depending upon cytokine exposure and direct the subsequent immune response. T_h cells are activated when they interact with antigens that are presented on the major histocompatibility complex, they serve to facilitate the immune response by further activating innate and adaptive immune cells (Luckheeram et al., 2012). CD4 + cells can develop into T_h1 & T_h17 which are generally pro-inflammatory or T_h2 & T_h9 which are anti-inflammatory. CD4 + cells are also capable of becoming regulatory T (T_{regs}) or T_h follicular cells (Luckheeram et al., 2012). As a result of different cytokine exposure, they produce cytokines, help with the maturation of B cells and/or activation of cytotoxic T cells (CD8 +) or macrophages. CD8 + T cells are cytotoxic and evolved to kill virally infected cells. They produce granzymes, perforin, cathepsin C and granulysin in order to bore holes into virally infected cells and destroy them (Raskov et al., 2021). Depressed patients have significantly higher CD4/CD8 ratios than that of control patients (Maes et al., 1992a., 1992b., 1992c). CD4/CD8 T cell ratios have a strong genetic component, possibly presenting one mechanism for heritability of stress resilience (Amadori et al., 1995). There are regional differences when it comes to population T-cell data. Data from studies in Malaysia and Singapore showed little to no sex differences in CD4 + and CD4/CD8 ratios of healthy participants (Lee et al., 1996; Abdullah et al., 2012). However, studies out of India and West Africa have shown that females often have higher levels of CD4 + cells and CD4/CD8 ratios, whereas males often have higher levels of CD8 + cells (Lisse et al., 1997; Uppal et al., 2003). Another study out of Scandinavia had the same findings among healthy schoolchildren (Afoke et al., 1993). These data show how an increased baseline level of CD4 + cells in females may skew the CD4/CD8 ratio into dysfunctional levels more frequently than it does for males. This would increase the prevalence and likely the severity of depressive episodes.

Sex hormones are not only implicated in innate immune regulation but in adaptive immune regulation as well. Steroid hormones can regulate T cell activity. Estrogen receptor alpha (ERα) knockout mice have reductions in IFN-γ production from T_h cells (Maret et al., 2003). T_h17 cells have been shown to promote depressive symptomology in rodents and are increased in the blood of patients suffering from depression (Dantzer et al., 2008; Beurel and Lowell, 2018). T_h17 cells express IL-17, an interleukin that activates neutrophils and promotes their movement. IL-17 mediates diseases involving inflammation such as rheumatoid arthritis and psoriasis (Zenobia and Hajishengallis, 2015). Increased expression of IL-17 from T_h17 cells would further exacerbate the proinflammatory activity of neutrophils leading to increased depression prevalence and symptomology. CD4 + T cells of male mice

produce more IL-17 than cells from female mice and is thought to be driven by peroxisome proliferator-activated receptor (PPAR) alpha and gamma (Zhang et al., 2012). T_h17 cells of mice released less IL-17 in response to estradiol exposure (Wang et al., 2009). These studies indicate that estrogens provide protective benefits against the proinflammatory effects of IL-17 and females are also less likely to experience IL-17 activated neutrophilic activity. This may be an area of interest for the differences that are seen in male symptomology and experience of depression. Blocking IL-17 signaling was sufficient to curb excess drinking in male mice (Xu et al., 2020). Chronic mild stress during development was sufficient to cause depressive-like symptoms promoted by IL-17 (Kim et al., 2021). These indicate a mechanism for differences in male symptom experience and increase prevalence of substance use disorder. More research needs to be performed with females included to confirm these sex-specific effects.

Alterations in T cell dynamics gives insight into what immune mechanisms may be underlying depression in women through the study of preeclampsia induced postpartum depression. Symptoms of preeclampsia include the sudden onset of hypertension during pregnancy (Wallace et al., 2014). Preeclampsia during pregnancy provides a model of sterile inflammation contributing to depression postpartum, as stress is also capable of causing hypertension. Preeclampsia severity during pregnancy predicts prevalence of postpartum depression with 44% of severe preeclampsia cases resulting in depression (Hoedjes et al., 2011). A subsequent meta-analysis confirmed the severity of preeclampsia correlates with prevalence of depression (Caropreso et al., 2020). CD4 + T cells from women suffering from preeclampsia induced preeclampsia like symptoms when transplanted into rats (Harmon et al., 2019). Pregnant women with preeclampsia had significantly more IL-17 producing CD4 + cells than control women (Santner-Nanan et al., 2009). Sterile inflammation during pregnancy increases CD4 +, thereby increasing CD4/CD8 ratios, as well as increasing IL-17 activity through increased CD4 + IL-17 release. Many cytokine changes have been observed in the CSF and serum of postpartum mothers in clinical studies. TNF-α and IL-6 in CSF and serum were correlated with depressive symptoms after four days, IL-6 in CSF was still significantly correlated with symptoms after six weeks (Boufidou et al., 2009). Levels of IL-6 and IL-10 were increased in the hippocampus following pregnancy in rats (Haim et al., 2017). These data provide support for the integration of female postpartum depression into the immune hypothesis of depression. The topic of immunity during pregnancy is vast and going into a full account of postpartum immunity is beyond the scope of this review. A thorough review was performed on the nutrition and psychoneuroimmunology of postpartum depression that covers the topic well (Ellsworth-Bowers and Corwin, 2012). Another noteworthy review covers how central and peripheral immune system dynamics change during and after pregnancy by studying available clinical research data (Dye et al., 2022). Postpartum depression occurs in 15–20% of women as well as 8 − 10% of men (Scarff, 2019). Men whose partners experience postpartum depression are more likely to experience it as well. Male postpartum depression is very understudied and identifying differences in the immune mechanisms of postpartum depression may provide insight for other forms such as MDD.

Natural killer T (NKT) cells which differ from innate natural killer cells and can be identified with the cell surface marker CD56 +, are activated by presented antigens during an immune response. NKT cells act to combat pathogens, tumors, allergens as well as general damage through the release large numbers of cytokines (Van Kaer et al., 2011). Natural killer T cells are negatively correlated with depression symptoms as reported with a depression survey (Park et al., 2006; Suzuki et al., 2017). Healthy men already had lower numbers of circulating NKT cells than women (Sandberg et al., 2003; Kee et al., 2012; Bernin et al., 2016). Interestingly, stimulation of NKT cells from women with αGalCer increased IFN-γ production, a proinflammatory cytokine, but also increased IL-4 production, an anti-inflammatory cytokine, compared to men (Bernin et al., 2016). These results indicate that men may be more prone to depressive outcomes due to their lower baseline NKT cells. However, this conclusion is complicated by the cytokine dynamics of NKT cells between men and women. With NKT cells from healthy females producing more IFN-γ and IL-4 (which may cancel each other out) it is unclear how these dynamics will impact depression outcomes without a study using participants during a depressive episode.

3.3. B cells

B cells play an important role in adaptive immunity where they release antibodies and regulate immune homeostasis. B cells have been implicated in the etiology and pathogenesis of depression although many specific cells and molecular mechanisms are still unknown. Naïve B cells responsible for immunoglobulin D were reduced in patients suffering from severe depression. Depressed patients had decreased expression of regulatory (CD5 +) B cells (Ahmetspahic et al., 2018). CD5 + B cells of healthy mice produce more autoantibodies when exposed to estrogen than that of cells exposed to testosterone (S Ansar Ahmed et al., 1989). This indicates another area of the immune system where female-associated hormones are leading to a stronger adaptive immune response. Other cell surface markers are more common in depression, particularly in participants with melancholic depression (Maes et al., 1992a, 1992b, 1992c). The cell surface markers CD19 +, CD21 +, and HLA-DR+ were increased on B cells from depressed patients but no sex differences were identified, although the subject group skewed female (Maes et al., 1992a, 1992b, 1992c). CD19 and 21 can form part of a complex to reduce the threshold for B cell signaling (Wang et al., 2012) whereas HLA-DR is used to identify activated B cells (Forestier et al., 2018). In a healthy elderly population, women had higher levels of CD19 + cells compared to men (Huppert et al., 1998). One study found that after a stroke, female mice had significantly more CD19 + cells in their spleen compared to males (Seifert et al., 2017). These studies suggest that CD19 + cells are increased in females at baseline and are also increased following sterile inflammation. Polymorphism of the − 499 T allele that codes for CD19 leads to significant increase in the prevalence of systemic sclerosis, an autoimmune disorder (Tsuchiya et al., 2004). Together these studies suggest that B cell activation and signaling contribute to depression and response in females following sterile inflammation. However, given previous data supporting decreased B cells in depression, more research needs to be performed both on specific subtypes of B cells as well as sex differences in basal levels during healthy and diseased states in order to make stronger conclusions about their role in depression.

3.4. Bioactive metals

Certain bioactive metals in the body can also play a role in immune activity. Zinc and copper have been identified as bioactive metals that are altered in depressed individuals. Low levels of zinc have been associated with treatment resistant depression (TRD) (Maes et al., 1997). Zinc levels may represent a basis for the higher rate in TRD in women. Women on average have a lower level of zinc and higher levels of copper compared to men (Buxaderas and Farré-Rovira, 1985, 1986; Hennigar et al., 2018; Mattern et al., 2021). Lower levels of circulating zinc are associated with TRD whereas higher levels of serum copper were associated with non-TRD. Antidepressants significantly reduce serum Cu but had no effect on zinc. Zinc levels were negatively correlated with CD4/CD8 T-cell ratio suggesting a link between the zinc levels and adaptive immune activity (Maes et al., 1997). These studies suggest a mechanism by which women have more incidence of TRD and depression at large because zinc and copper serum levels in women are more prone to dysfunctional outcomes. Copper and zinc are both closely related to the stomach and intestines with nutrients coming in through food and being converted by biological mechanisms into zinc and copper (Cousins, 1985). Because of this it would be useful to further investigate

Table 1
Overview of immune mechanisms that drive sex differences and are associated with symptoms of depression.

Immune Mechanism	Sex	Model	Location	Outcome	Reference
CNS TLR4 ablation	Male	Rodent	CNS	Attenuated pain response	Huck et al. (2021a, 2021b)
Systemic TLR4 ablation	Female	Rodent	CNS and PNS	Attenuated pain response	Huck et al. (2021a, 2021b)
Increased TLR7 activity post-activation	Female	Human Cell Culture	PNS	Higher type I interferon release	Meier et al. (2009)
IL-6 crossing Blood Brain Barrier	Male	Rodent	PNS to CNS	Promotes stress susceptibility	Menard et al. (2017)
Increased Monocyte activation	Female	Human Blood	PNS	Higher IL-6 and leukotriene release	O'Connor et al. (2007); Pergola et al. (2011)
Increased Macrophage activation	Female	Human Cell Culture	PNS	Worsened depression symptom severity	Smith (1991); Becerra-Díaz et al. (2021)
Increased baseline neutrophils	Female	Human Blood	CNS and PNS	Higher proinflammatory activity in PNS and CNS	Bain and England (1975)
Increased baseline leptin levels	Female	Human Blood	PNS to CNS	Higher neutrophil trafficking to CNS, increased lethargy	Hellström et al. (2000)
Mastocytosis	Male/ Female	Human	CNS and PNS	Lowered serotonin production/worsened symptom severity	Georgin-Lavialle et al. (2016)
Mast cell depletion	Male	Rodent	CNS and PNS	Increased anxiety-like behavior	Nautiyal et al. (2008)
Decreased Natural Killer Cell counts	Male	Human	CNS and PNS	Increased lethargy, association with substance abuse	Benczur et al. (1980); Irwin et al. (1990)
Increased baseline CD4 + levels	Female	Human	PNS	Increased prevalence of depression	Lisse et al. (1997); Uppal et al. (2003)
Increased Th17 activity/IL-17 release	Male	Rodent	PNS	Increased symptom severity/SUD susceptibility	Xu et al., 2020; Kim et al. (2021)
Estrogen exposed CD5 + B cells more active	Female	Human Cell Culture	PNS	Increased autoantibodies/host damage	Ahmed et al. (1989)
Increased CD19 + B cells at baseline and after insult	Female	Rodent/Cell Culture	PNS	Altered B cell activation threshold	Wang et al. (2012)
Higher baseline Copper, lower baseline Zinc	Female	Human	PNS	Increased depression prevalence, increased CD4 + levels	Buxaderas and Farré-Rovira, 1985, 1986

the microbiome and how it may work towards dysfunction of zinc and copper levels as well as how the biological pathways that process the zinc and copper are affected during various treatments.

4. Conclusion

The immune hypothesis of depression would be aided by both improving current methodological practices as well as committing to future immunological studies that examine the body and brain. Researchers should aim to be as descriptive as possible with demographic information provided in the methods sections of their articles. The simple act of reporting whether males and/or females were included in a study helps future researchers to parse out sex differences without any extra experimentation on the part of the author. Inclusion of females in sufficient numbers to determine sex differences in the experimental design of both human and animal studies would allow for a wealth of insights into sex differences occurring in both depression as well as other conditions. There is also much work to be done on the side of adaptive immunity. Having a greater understanding of the subtypes of B and T cells in depression, and whether or not they display sex differences, would go a long way in completing a holistic immune representation of symptoms of depression.

The immune hypothesis of depression has expanded rapidly over time and there has been a wealth of information indicating that depression is a heterogenous, whole-body disease. To date, a lot of studies have focused on single immune mechanisms of depression however, the data suggests there is no single cytokine or immune cell to "rule them all". We suggest the following refinements to improve how we study the relationship between inflammation and mood disorders.

1. Take a systems approach; examining the patterns of shifts in multiple cell types and cytokines in depressed individuals may provide a better framework for developing treatments.
2. Integrate dynamic cycles of sterile as well as nonsterile inflammation into the research. Depression is the result of chronic inflammation as initiated by both sterile and nonsterile means. It may be that only after repeated cycles of activation, repair and cleanup by the hosts immune system do we see the damage that produces subsequent depressive symptoms.
3. Given that men and women have diverse immune responses because of genetics, hormones, and developmental factors it is imperative that sex is taken into account and is considered a factor. These differences are capable of modulating immune response and protection of cells from immune repair and cleanup, therefore a difference in disease severity and symptomology occurs.
4. Take an RDOC approach to understanding the relationship between symptoms and immune function. Immune function relates to specific sypmtoms such as fatigue, appetite changes, pain sensation, substance use, and suicidal ideation (Table 1). These symptoms and the changes in immune signaling and function cross diseases. As a result, the same cytokines or immune cells are altered across different forms of "mental" illness. Instead of looking for immune signatures of diseases such as depression a focus on symptom-immune signatures may have a better chance at improving patient care.
5. Immune alterations associated with symptoms of depression should be screened for early in life to limit the neuroinflammatory damage that can occur following repeated cycles of activation and repair. Management of the triggers of inflammation prior to chronic inflammation may help prevent future depressive symptoms. Unhealthy modern diets, pollution, pathogenic illnesses, chronic stress, substance use, and sterile inflammation all present possible triggers for inflammatory immune activation in the brain and body. By screening for and treating inflammation in early life, and by understanding the heterogeneity of depression through its symptoms and immune properties, there will be significant improvement in the prevalence and prognosis of mood disorders.

Author contributions

Manuscript was written by DRK and GEH.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by NIMH R56MH124930 (GEH). Figure was created using biorender.com.

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