Frontiers in Neuroendocrinology 54 (2019) 100771

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Immune mechanisms of stress susceptibility and resilience: Lessons from animal models

Mariya Tsyglakova[a,b], Dylan McDaniel[a], Georgia E. Hodes[a,*]

[a] School of Neuroscience, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA
[b] Graduate Program in Translational Biology, Medicine and Health, Virginia Tech, Blacksburg, VA, USA

ARTICLE INFO

Keywords:
Innate immune cells
Lymphocytes
Microglia
Blood brain barrier
Astrocytes

ABSTRACT

Stress has an impact on the brain and the body. A growing literature demonstrates that feedback between the peripheral immune system and the brain contributes to individual differences in the behavioral response to stress. Here we examine preclinical literature to demonstrate a holistic vision of risk and resilience to stress. We identify a variety of cellular, cytokine and molecular mechanisms in adult animals that act in concert to produce a stress susceptible individual response. We discuss how cross talk between immune cells in the brain and in the periphery act together to increase permeability across the blood brain barrier or block it, resulting in susceptible or stress resilient phenotype. These preclinical studies have importance for understanding how individual differences in the immune response to stress may be contributing to mood related disorders such as depression, anxiety and posttraumatic stress disorders.

The immune system has evolved as a mechanism to repair injury and defend the body against pathogens (Chaplin, 2010). In addition the immune system regulates the response to stress in both rodent models and humans (Dantzer, 2009; Hodes et al., 2014; Iwata et al., 2013; Pollak and Yirmiya, 2002). Immune cells and their signaling networks influence neural circuitry in the central nervous system (CNS) and result in sickness behaviors which include lethargy and anorexia (Dantzer, 2009). Rodent studies have revealed individual differences in the behavioral response to stress mediated by the activity of the immune system (Hodes et al., 2014; Menard et al., 2017). There are multiple interconnected immune mechanisms that contribute to whether an individual will display behavior indicative of increased negative valence and reduced positive valence following stress (stress susceptible) or behave akin to unstressed controls (stress resilient). These mechanisms include but are not limited to the levels and types of circulating cytokines, chemokines, leukocytes, and immune sensitivity to challenge (Hodes et al., 2014; Niraula et al., 2018). While much of the focus of mechanisms of resilience has been on circuitry within the CNS, there is evidence that the peripheral and central immune system also regulates the stress response (Hodes et al., 2014; Niraula et al., 2018). Here we will review how central and peripheral immune mechanisms interact to generate risk or resilience to stress and its impact on the individual.

1. Peripheral cellular mechanisms of stress susceptibility and resilience

The cells that make up the peripheral immune system primarily consist of leukocytes that originate as pluripotent hematopoietic stem cells in the bone marrow (Zhang, 2012). The process of hematopoiesis eventually gives rise to more limited progenitor cells and includes the common lymphoid and myeloid progenitors (Lai and Kondo, 2008; Zhang, 2012). The common lymphoid progenitor cells differentiate into lymphocytes, which include the B and T cells (Lai and Kondo, 2008). After becoming active plasma cells, the primary role of B cells is to secrete antibodies which recognize and opsonize foreign antigens. T cells, on the other hand, have two main types: cytotoxic and helper T cells, which are involved in viral defense and B cell activation respectively. Together, these lymphocytes make up the cells primarily involved in the adaptive immune response. Monocytes are derived from the myeloid progenitor line during adult hematopoiesis and have been strongly implicated as a mechanism contributing to stress susceptibility and resilience. Monocytes circulate in the blood and are recruited to sites of damage or infection where they become mature macrophages and are largely responsible for the phagocytosis of pathogens and cellular debris (Martin et al., 2014). Depending on their activation state they can also be involved in tissue repair and resolution of inflammation (Mills, 2012). Furthermore, long lived tissue-resident macrophages

* Corresponding author at: Virginia Polytechnic Institute and State University, School of Neuroscience, 1981 Kraft Drive, Blacksburg, VA 24060.
E-mail address: ghodes@vt.edu (G.E. Hodes).

https://doi.org/10.1016/j.yfrne.2019.100771
Received 4 April 2019; Received in revised form 17 June 2019; Accepted 9 July 2019
Available online 17 July 2019
0091-3022/

are derived from a primitive form of hematopoiesis in the yolk sac during embryonic development (Epelman et al., 2014; Hoeffel and Ginhoux, 2018). These cells are thought to be the source of Kupffer cells in the liver or microglia in the brain, the latter will be discussed in more detail later (Epelman et al., 2014; Hoeffel and Ginhoux, 2018).

Altered leukocyte numbers are associated with the response to stress. Mice that become stress susceptible have increased circulating leukocytes four days before being exposed to chronic social defeat stress compared to animals that become resilient (Hodes et al., 2014). These data suggest that individuals prone to developing a social withdrawal response to stress have higher baseline levels of leukocytes compared to resilient individuals and that this primed immune system is a major determining factor of differential behavioral response. Following social stress bone marrow derived hemopoietic progenitor cell production and release are increased and they engraft in the spleen where they proliferate and differentiate into monocytes, neutrophils and erythrocytes creating a persistent cache of myeloid cells (McKim et al., 2018). The spleen is a lymphoid organ split into two main compartments (red and white pulp) and is involved in regulating the defense against blood-borne microorganisms and filtration of cellular debris (Cesta, 2006; Mebius and Kraal, 2005). The white pulp contains lymphocytes, macrophages, plasma cells and dendritic cells (Cesta, 2006; Mebius and Kraal, 2005). When foreign antigens are detected, several mechanisms for defense are in place including phagocytosis by marginal-zone macrophages, migration of circulating dendritic cells into the white pulp and clonal expansion of lymphocytes (Cesta, 2006; Mebius and Kraal, 2005). Stress susceptible mice have increased cellularity in their spleens compared to control mice following chronic social defeat stress (Ambrée et al., 2018). While stress results in changes to the immune cell population in all individuals to some degree, splenic monocytes are specifically increased in stress susceptible individuals (Ambrée et al., 2018). This suggests that monocytes are a major contributing factor in the determination of individual differences in response to stress.

Dendritic cells are myeloid derived cells that specialize in displaying antigens to naïve T cells in secondary lymphoid organs via major histocompatibility complexes (MHC) I and II in order to regulate the activation of the adaptive immune response (Janeway et al., 2005). As such, dendritic cells are often referred to as a bridge between innate (fast-acting) and adaptive (long-term) immunity. Dendritic cells, like other immune cells, are sensitive to stressful stimuli and their numbers are decreased in the spleens of mice following social defeat stress (Ambrée et al., 2018). However, social stress in male mice is also associated with activated splenic dendritic cells (Ambrée et al., 2018; Powell et al., 2009). Specifically, splenic dendritic cells from stress susceptible mice have increased expression of MHC class I, MHC class II, CD80, and secrete higher levels of inflammatory cytokines upon in vitro stimulation compared to resilient or control mice (Ambrée et al., 2018; Powell et al., 2009). While there are fewer dendritic cells in stress susceptible individuals, the ones that are there are more responsive to an immunological insult and are more prepared to present antigens to T cells.

While most of the current research on immune-related differences in stress susceptibility and resilience has focused on the innate immune system, there is some evidence that T cells play a role in the response to stress. Naïve T helper cells can differentiate to various subtypes with distinct functions depending on the type of response needed, which can further complicate their role in stress susceptibility and resilience (Hirahara and Nakayama, 2016). The subsets are typically defined by the cytokines they secrete and include Th1, Th2, and Th17 (Hirahara and Nakayama, 2016). Th1 and Th17 cells are generally considered pro-inflammatory, whereas Th2 cells are considered anti-inflammatory due to their secretion of growth factors and role in tissue repair (Allen and Wynn, 2011). It should be noted that the Th2 response is still an inflammatory response meant to combat and kill parasitic worms and contributes to the symptoms of allergies (Allen and Wynn, 2011). Like innate immune cells, T cells also express glucocorticoid receptors and activation of this receptor promotes apoptosis (Herold et al., 2006; Tuckermann et al., 2005). Increased signaling of the glucocorticoid receptor via a point mutation not only increases T cell susceptibility to apoptosis, but also favors a Th2 subset of T helper cells (Brandt et al., 2007). T cells can be classified as helper or cytotoxic depending on whether they are $CD4^+$ or $CD8^+$ respectively (Laidlaw et al., 2016). Both restraint stress and corticosterone treatment induce a decrease in T cell populations (Ashcraft et al., 2008). Chronic social defeat stress also decreases absolute count of T cells in stress susceptible but not resilient mice (Pfau et al., 2019). Mild chronic stress in mice activates the HPA axis, sympathetic nervous system, and causes a decrease in $CD4^+$ T cells relative to $CD8^+$ cells (Jiang et al., 2017; Silberman et al., 2004). This decrease in the CD4/CD8 ratio is an indication of a weakened or senescent immune response and implicates a mechanism of T helper cell sensitivity to stress (McBride and Striker, 2017). In contrast, blocking NE signaling by β-adrenergic receptors and splenectomy prior to stress can rescue the CD4/CD8 ratio (Jiang et al., 2017). Therefore, T lymphocytes are associated with the physiological response to stress. However, their role in behavior following stress is just beginning to be investigated.

Contributions of lymphocytes to behavioral and physiological stress susceptibility have been studied in *Rag2*$^{-/-}$ mice, which lack mature B and T cells (Brachman et al., 2015). Adoptive transfer of $CD4^+$ T cells from stressed (Brachman et al., 2015) or non-stressed donors (Clark et al., 2016) into *Rag2*$^{-/-}$ mice reduced anxiety- and depressive-like behaviors and promoted the establishment of fear memory. In addition, lymphocytes from stressed donors resulted in increased hippocampal cell proliferation in the dentate gyrus and heightened plasma glucocorticoid levels in hosts receiving cells from a stressed donor, which may act as a compensatory mechanism (Brachman et al., 2015). While hippocampal neurogenesis could not be specifically confirmed in this study due to the time point examined, previous studies have demonstrated that increased glucocorticoids and/or stress generally decrease cell proliferation resulting in reduced neurogenesis (Kim et al., 2015). It should be noted that the donor lymphocytes were produced from animals exposed to chronic social defeat stress. Studies of mice have reported this form of stress produces a transient decrease in cell proliferation that then leads to increased survival of new neurons specifically in socially avoidant (susceptible) subjects (Lagace et al., 2010). Additionally, reductions in neurogenesis during adolescence using targeted irradiation or transgenic methods, promoted resilience by reducing social avoidance (Kirshenbaum et al., 2014; Lagace et al., 2010). Therefore, it is not clear whether the observed increase in cell proliferation in *Rag2*$^{-/-}$ mice (Brachman et al., 2015) would actually contribute to stress resilience.

Increased glucocorticoid signaling favors a Th2 population and could indicate a role for this subset of cells and their cytokine milieu as a contributing factor to the behavioral response to stress. Taken together, it is conceivable that individuals with higher levels of glucocorticoids as a result of psychological stress and HPA axis dysregulation have an altered population of T helper cells, which affects their behavioral response in a currently unknown manner.

2. Molecular mechanisms contributing to stress susceptibility and resilience

A number of recent studies implicate that crosstalk between the hypothalamic pituitary adrenal (HPA) axis and the immune system mediates behavioral responses to stress (Iwata et al., 2013; Malek et al., 2015; Mileva et al., 2017). Immune cells respond to glucocorticoids by entering the circulation and migrating to other tissues during stress, such as the CNS (Fig. 1) (Niraula et al., 2018; Wohleb et al., 2013). Repeated social stress, in addition to causing anxiety and depression-associated behaviors in susceptible individuals, increases plasma corticosterone (CORT), interleukin-6 (IL-6), spleen weight, and circulating monocytes in male C57BL/6 mice (Niraula et al., 2018; Wohleb et al.,

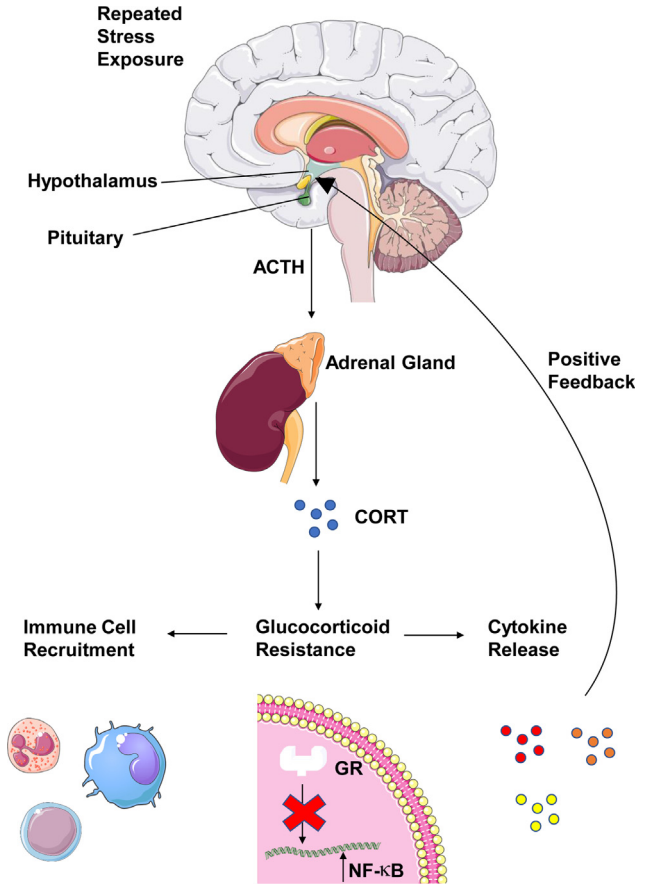

Fig. 1. *Crosstalk between HPA axis and immune system.* Repeated exposure to a stressor activates the HPA axis leading to increased production of CORT. Chronic release of CORT results in decreased sensitivity of immune cells to the anti-inflammatory effects of glucocorticoids. This in turn causes increased recruitment of immune cells and pro-inflammatory cytokine release. Furthermore, pro-inflammatory cytokines such as IL-6, IL-1β and TNF can activate the HPA axis and act as a form of positive feedback on the system.

2013). Activation of these pro-inflammatory outputs is attenuated via adrenalectomy or pharmacological depletion of CORT indicating a causal role in regulating the immune response to stress (Niraula et al., 2018). These data suggest that increased levels of glucocorticoids play a role in stress-mediated immune activation, which may contribute to the primed immune response of susceptible individuals (Fig. 1). While activation of the HPA axis and increased levels of CORT can have various effects on the different components of the immune system, they are traditionally associated with attenuation of the immune system (Franchimont, 2004; Gao et al., 2017). Why then, do stressed individuals have increased pro-inflammatory mediators that are positively correlated with the presence of CORT?

CORT exerts its immune regulatory effects via glucocorticoid receptors expressed on immune cells (Miller et al., 1998). Repeated exposure to a stressor can lead to glucocorticoid resistance via changes in the glucocorticoid receptor (Fig. 1) (Francis et al., 2017; Jung et al., 2015; Li et al., 2018a, 2018b; Quan et al., 2003; Stark et al., 2001; Weber et al., 2017). Splenocytes treated with the endotoxin lipopolysaccharide (LPS) isolated from socially stressed mice are immune to the anti-proliferative effects of CORT (Quan et al., 2003; Stark et al., 2001). Additionally, macrophages of socially stressed mice stimulated with LPS and CORT have reduced nuclear translocation of the glucocorticoid receptor and lack a compensatory attenuation of nuclear factor κB (NF-κB) activation (Quan et al., 2003). Repeated social stress attenuates DNA methylation and expression of glucocorticoid receptor in splenic macrophages (Jung et al., 2015). These data indicate that chronic stress can mediate immune cell responsiveness to glucocorticoids by affecting glucocorticoid receptor expression and function potentially via epigenetic mechanisms. Ultimately, allowing the immune system to become primed in stress susceptible individuals.

The HPA axis is not the only stress regulatory pathway that is involved in susceptibility and resilience. The sympathetic nervous system, along with dopaminergic pathways in the ventral tegmental area (VTA), also regulate stress-related behaviors (Isingrini et al., 2016). Specifically in the CNS, it's been suggested that norepinephrine (NE) signaling to the VTA is critical for the development of a resilient phenotype in response to chronic social defeat (Isingrini et al., 2016). The sympathetic nervous system is involved in priming the peripheral immune system as a result of chronic defeat stress, but the role of this relationship in the behavioral response to stress is just beginning to be realized (Finnell et al., 2017, 2019; Wood et al., 2015). Rats exposed to chronic social defeat stress have significantly elevated levels of NE, IL-1β, IL-13, Tumor necrosis factor (TNF), and IL-10 in the plasma compared with controls (Finnell et al., 2017). The locus coeruleus is the primary brain nucleus responsible for NE synthesis and is disrupted via the selective neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) (Finnell et al., 2019; Ross and Stenfors, 2015). Treatment with DSP-4 reverses the stress-induced immune priming observed following chronic social defeat stress (Finnell et al., 2019). Rats who exhibit a passive coping phenotype have an increased IL-6 to IL-10 ratio in the circulation compared to animals showing an active coping response during chronic social defeat stress (Wood et al., 2015). NE signaling via β-adrenergic receptors is necessary for the increased population of immature inflammatory ($Ly6c^{high}$) monocytes and neutrophils in bone marrow, blood and spleen in mice that underwent repeated unstable social hierarchy exposure and showed anxiety associated behavior (Powell et al., 2013). Chronic social defeat stress in mice also results in increased populations of neutrophils and $Ly6c^{high}$ monocytes along with a suppression of B cells in both susceptible and resilient mice immediately after the cessation of stress (Pfau et al., 2019). The effects of stress on cell populations were only long lasting in susceptible mice. Nine days after the cessation of stress Ly6c high monocytes and neutrophils were elevated and B cells were still decreased in susceptible but not resilient mice. Further studies demonstrated depletion of $Ly6c^{high}$ monocytes to have antidepressant-like effects on social avoidance behavior (Pfau et al., 2019). Taken together, there is an increased innate pro-inflammatory environment in the periphery in association with a stress susceptible phenotype. Direct manipulation of locus coeruleus NE signaling can regulate peripheral immune system priming during stress which in turn contributes to the behavioral response of an individual.

Many cells of the innate immune system express germline-encoded receptors known as pattern-recognition receptors (PRRs) (Chen et al., 2018). The best studied of these include the membrane bound toll-like receptors (TLRs) and the cytosolic NOD-like receptors (NLRs) (Chen et al., 2018). Recognition of pathogen associated molecular patterns (PAMPs) or danger associated molecular patterns (DAMPs) via PRRs leads to the induction of intracellular signaling cascades such as the NF-κB pathway (Chen et al., 2018). In fact, components of the NF-κB pathway, such as IκB kinase, have been implicated in the behavioral response to stress, primarily in the nucleus accumbens (NAc) (Christoffel et al., 2011, 2012; LaPlant et al., 2009). The result of these signaling cascades is the production of the chemical messengers of the immune response known as cytokines and chemokines (Zhang and An, 2007). Much of the differentiation, activation, and overall communication of immune cells occurs through cytokines and chemokines. In general, cytokines are primarily involved with the regulation of immune cells, however, non-immune cells such as neurons can both secrete and respond to cytokines (Zhang and An, 2007).

It has been proposed that cytokines also play a role in the activation of the HPA axis and in turn leads to increased glucocorticoid production (Fig. 1) (Malek et al., 2015; Silverman et al., 2005). Ongoing research is examining how HPA crosstalk contributes to stress susceptibility and

resilience in mouse models of depression. The role of cytokines and chemokines as mediators of the immune response is well understood at this point. However, much less is known about the role of these chemical messengers in the response to stress. Cytokine treatment or LPS challenge induces depression-associated behavior in both humans and animals (Iwata et al., 2013; O'Connor et al., 2009; Pollak and Yirmiya, 2002; Yirmiya, 1996). While the mechanism by which cytokines contribute to stress susceptibility is not yet fully understood, overall the hypothesis is that pro-inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor (TNF) are able to act as a positive feedback mechanism and/or trigger activation of the HPA axis (Fig. 1) (Iwata et al., 2013; Malek et al., 2015; Mileva et al., 2017). This is proposed as many of the major pro-inflammatory cytokines are upregulated in response to physiological and/or psychological stress (Fig. 1) (Golovatscka et al., 2012; Maes et al., 1998).

IL-6 is recognized as the most consistently expressed cytokine during pathological stress and major depressive disorder (MDD) (Hodes et al., 2014; Wood et al., 2015; Yang et al., 2015a,b). High serum levels of leukocyte-derived IL-6 were indicative of behavioral susceptibility during social interaction testing following chronic social defeat stress in male C57BL/6 mice (Hodes et al., 2014). The leukocytes largely responsible for elevated IL-6 appear to be monocytes, which were increased at baseline in mice that later become stress susceptible (Hodes et al., 2014). Furthermore, Let7 miRNA clusters associated with IL-6 production were upregulated in susceptible and downregulated in resilient mice following social defeat stress in Ly6c^{high} monocytes. Given the anti-inflammatory properties of the let-7 family this may be a compensatory negative feedback response in these cells (Pfau et al., 2019). Mice treated with an IL-6 antibody, IL-6 knockout (*Il6*$^{-/-}$) mice and IL-6$^{-/-}$ bone marrow chimeras mice expressed a resilient phenotype following chronic social defeat stress (Hodes et al., 2014). Elevated serum levels of IL-6 were also implicated in a rat model of learned helplessness (Yang et al., 2015a,b). Like social defeat stress, only a subpopulation of subjects' express helplessness behavior defined as a passive coping response to inescapable shock. Rats expressing helplessness behavior had increased levels of serum IL-6 compared to controls and animals resilient to stress. Likewise, C57BL/6 mice lacking IL-6 (*Il6*$^{-/-}$) were resistant to learned helplessness following repeated foot shock and showed reduced passive coping behavior in the forced swim and tail suspension tests compared to wild-type (Chourbaji et al., 2006). These studies demonstrate a relationship between circulating levels of IL-6 and stress responsivity. Furthermore, they indicate that IL-6 is necessary for behavioral stress susceptibility.

The cytokine IL-1β, has also been implicated in stress susceptibility in both the periphery and in the CNS (Li et al., 2018a; Mileva et al., 2017; Wood et al., 2015). In the CNS, the primary cells responsible for the secretion of IL-1β are microglia, astrocytes and neurons (Koo and Duman, 2008), while peripherally it is released by monoyctes and macrophages (Zhang and An, 2007). IL-1β interacts with the HPA axis and thus acts as a mediator of the stress response (Koo and Duman, 2009a). Wistar Kyoto rats, which at baseline exhibit many depression associated behaviors, have lower levels of IL-1β in the serum compared to their counterparts both at baseline and following the acute stress of a forced-swim test (Mileva et al., 2017). This is counter-intuitive to other studies in which circulating cytokine levels are higher in susceptible individuals. It is possible that the observed inter-strain differences (i.e. genetic variation) in depressive-behavior between Wistar and Wistar Kyoto rats are not related to higher levels of circulating IL-1β. To our knowledge, IL-1β levels have not been directly compared in the CNS of Wistar Kyoto and Wistar rats in the context of stress susceptibility. It should also be noted that in the same study there was no effect of an acute forced-swim test stress on serum IL-1β levels. Perhaps a more prolonged stressor or more intense stressor would have a larger impact on serum IL-1β levels. For example, male Sprague-Dawley rats exposed to a series of mild stressors over four weeks were shown to have increased plasma IL-1β compared to controls (Grippo et al., 2005). In mice peripheral IL-1β levels were elevated in both susceptible and resilient mice compared to controls within 20 min of their first defeat (Hodes et al., 2014). After 10 days of chronic social defeat stress IL-1β levels were only elevated in the blood of susceptible animals possibly representing a habituation to the stress in resilient mice (Stelzhammer et al., 2015).

It is possible that IL-1β is lower in the periphery of Wister Kyoto rats because it is entering the brain or that central IL-1β and peripheral Il-1β responses are uncoupled in this strain and thus regulate depressive behavior via different mechanisms. A more accurate description of the contribution of IL-1β may be that its levels are dysregulated rather than strictly upregulated like other pro-inflammatory cytokines such as IL-6. This could be explained, in part, by opposing levels of IL-1β in the CNS and the periphery in response to stress. Within the brain increased IL-β seems to be involved in a pro-depressant-like phenotype. Administration of IL-1β via intracerebroventricular injection inhibits hippocampal cell proliferation, which is a common consequence of stress (Koo and Duman, 2008, 2009a). Inhibition of the IL1 receptor, either pharmacologically or genetically, attenuates the reduction of neurogenesis in the hippocampus associated with acute and chronic stress in Sprague-Dawley rats (Koo and Duman, 2008). Furthermore, IL-1 receptor deficiency in animals or central inhibition of IL-1β attenuates anxiety- and depressive-associated behaviors following stress (Koo and Duman, 2008, 2009b, 2009a). The role of IL-1β in the behavioral response to stress is complex and most likely occurs via different mechanisms for the periphery and CNS. Moreover, Il-1β has been found to be elevated in the periphery following prolonged stress, but not acute stress (Mileva et al., 2017) although this may be dependent on the species, strain or intensity of stressor.

In contrast to IL-6, IL-1β requires a cleavage event in order to become active and secreted from the cell (Lopez-Castejon and Brough, 2011). Specifically, the activation of NLR signaling induces the formation of the multi-protein complex known as the inflammasome, which ultimately causes the cleavage and subsequent activation of caspase-1 (Lopez-Castejon and Brough, 2011). Active caspase-1 is then responsible for the cleavage of pro-IL-1β into active IL-1β. Caspase-1 has been shown to be involved in determination of an individual's response to stress as well. Following chronic social defeat stress, circulating monocytes in susceptible C57BL/6 mice had increased gene expression of *Casp1*, while mice lacking *Casp1* were shown to have a resilient phenotype (Li et al., 2018a, 2018b). The fact that NLRs are able to detect a wide range of molecular signals, including DAMPs, presents a possible bridge between psychological stress and the inflammatory response. This response in part may be mediated by the relationship between NLR signaling and autophagy, a homeostatic mechanism involved in cellular waste removal (Zhong et al., 2016). NLRP3 inflammasome assembly is thought to be in part a result of mitochondria damage and is directly counteracted by autophagy of mitochondria (for review see Zhong et al., 2016). In humans, autophagy-associated genes were upregulated in mononuclear cells isolated from the blood of patients with depression compared to controls (Alcocer-Gómez et al., 2017a, 2017b). One possibility is that this is a compensatory mechanism, as upregulated response of autophagy genes in response to ex-vivo application of antidepressants to mononuclear cells isolated from patients with depression also predicted success of clinical treatment (Gassen et al., 2014). In mice exposed to stress or chronic corticosterone, antidepressant treatment was demonstrated to increase upregulation of autophagy genes in the brains (Gassen et al., 2014; Gulbins et al., 2018). However, the possibility also exists that in a subset of patients with depression there is an uncoupling of the autophagy correction of the NLR inflammasome activation. Hyperactivation of the NLRP3 inflammasome has been reported in the peripheral blood mononuclear cells of patients with type 2 diabetes (Lee et al., 2013) and with systemic lupus erythematosus (Yang, 2015) both of which have a high co-morbid rate of occurrence with depression particularly in women (Bachen et al., 2009; Clarke et al., 2017; Simayi and

Mohemaiti, 2019). In the blood mononuclear cells of antidepressant-responding patients NLRP3 inflammasome activation was inhibited along with an increase in expression of autophagy related genes (Alcocer-Gómez et al., 2017a, 2017b). The same decrease in the NLRP3 inflammasome following in vitro antidepressant treatment did not occur in mouse embryonic fibroblast cells from autophagy knockout mice indicating that the autophagy process mediates the response of the NLRP3 inflammasome to antidepressants (Alcocer-Gómez et al., 2017a, 2017b). It would be interesting to test if this response is uncoupled in immune cells from patients with treatment resistant depression.

TNF is another pro-inflammatory cytokine involved in stress susceptibility and resilience. TNF can act through two main receptors known as TNFR1 and TNFR2 and sends survival or death signals depending on which receptor is being activated (Bradley, 2008). TNF levels in the plasma and spleen are positively correlated with greater social withdrawal and other anxiety like behaviors following chronic social defeat stress (Ambrée et al., 2018; Kinsey et al., 2008; Liu et al., 2015). Furthermore, splenocytes from stress susceptible mice stimulated with the TLR4 agonist LPS secreted significantly higher amounts of TNF compared to controls and resilient individuals (Ambrée et al., 2018; Kinsey et al., 2008). Susceptible mice, in this case, were observed to have low social interaction scores and spent a larger amount of time in the corners of the interaction area. Leukocytes isolated from animals four days prior to the start of stress and stimulated with LPS also released higher levels of IL-6 from mice that would later display a susceptible phenotype compared to leukocytes from control and resilient mice (Hodes et al., 2014). Furthermore, the levels of simulated IL-6 were negatively correlated with the social interaction score in these mice, indicating increased IL-6 was related to increased social withdrawal (Hodes et al., 2014). Together these studies suggest that susceptible individuals have overall a more reactive immune response at baseline compared to resilient individuals.

During a normal immune response there is a resolving of release of pro-inflammatory cytokines by anti-inflammatory cytokines, such as IL-4/ IL-10 to allow for negative feedback in order to prevent pathological activation of inflammation and to promote healing. However, in stress susceptible individuals there is a dysregulation of this pro- and anti-inflammatory balance and thus, a shift to a pro-inflammatory profile (Voorhees et al., 2013; Wood et al., 2015). For example, the ratio of IL-6/ IL-10 is significantly higher in the plasma of Sprague Dawley rats with a shorter latency to defeat (susceptible) during chronic social defeat stress compared to controls and rats with longer latency to defeat (resilient) (Wood et al., 2015). Prolonged restraint stress which resulted in increased passive coping during the forced swim test increased circulating IL-6 levels and decreased IL-4 and IL-10 (Voorhees et al., 2013). Injecting mice with recombinant IL-10 during the final week of the restraint stress reduced the expression of depression-associated behavior (Voorhees et al., 2013), thus, supporting a role for anti-inflammatory cytokines as a mechanism of resilience in the periphery.

3. Potential sources of individual differences in inflammation

Women have a much higher incidence of MDD than men (Albert, 2015). In addition, female animals are more susceptible to some forms of stress than males and have differences in their immune state (Hodes et al., 2015; Rainville et al., 2018). As such, estrogen has been implicated as a modulator of inflammation as well as the behavioral response to stress (Finnell et al., 2018; Sharma et al., 2018). Estrogen receptors are present on most immune cells (Keselman and Heller, 2015; Molero et al., 2002; Zierau et al., 2012) and low levels of estrogens stimulate activation of these cells, whereas high levels of estrogen suppress immune function (Rainville et al., 2018). The estrus cycle is a cell death cycle with cornification occurring during estrus and shedding of epithelial cells and leukocytes during diestrus. These cellular effects are accompanied by independently regulated changes of cytokine/ chemokine concentrations in the uterus and vaginal track across the cycle (Hickey et al., 2012). Estrogen receptors directly influence thymus and spleen development as indicated by knockout studies (Erlandsson et al., 2001). Additionally, estrogen can exert effects through non-conical signaling such blocking the effects of LPS on IL-6 levels in monocytes through activation of the splice variant ERα-36 interacting with GPER to produce inhibition of NFkB (Pelekanou et al., 2016). Female mice treated with LPS via i.p. injection have a more persistent increase in peripheral cytokines compared to adult males (Sharma et al., 2018). Ovariectomized rats display significantly less anxiety- and depression-associated behaviors after witnessing a conspecific undergo chronic social defeat stress compared to intact rats (Finnell et al., 2018). Estrogen replacement in ovariectomized rats restores anxiety-associated behavior, but not depression-associated behavior (Finnell et al., 2018). Additionally, intact rats with prior exposure to witnessing chronic social defeat stress show increased levels of circulating pro-inflammatory cytokines such as IL-1β, IL-6 and TNF following re-exposure, while ovariectomized rats had the opposite result (Finnell et al., 2018). While it's clear that females experience higher susceptibility to stress compared to males, the role of estrogen in immune modulation is yet to be clearly defined. Testosterone exerts immunosuppressive effects in both sexes. In gonadectomized mice testosterone is equally effective at blocking LPS induced increases in TNF-α in both sexes whereas only females respond to estrogen replacement (Gaillard and Spinedi, 1998). Testosterone signaling produces apoptosis and contributes to the lower circulating levels of T_H cells in males (McMurray et al., 2001; Trigunaite and Dimo, 2015). We hypothesize that the immune suppression experienced by males due to their higher testosterone levels may result in stress resilience, but at the risk of their survival. The flexibility and stronger response of the female immune system, in particular adaptive immunity, may provide greater protection from pathogens but at the cost of increased autoimmune responses to stress and other danger signals. More studies are needed to test this dichotomy of behavioral and immunological responses to stress in males and females.

Another potential source for individual variation in stress susceptibility of an individual derives from the microorganisms in the digestive tract (along with their genetic material) that make up the gut microbiome. The gut microbiome have been implicated in the normal development of the host's physiology and many diseases including diabetes, obesity, and autoimmune disorders (Shreiner et al., 2015). The mammalian digestive tract is also in direct contact with the CNS via the vagus nerve and the enteric nervous system (ENS), which is often referred to as the gut-brain axis (Evrensel and Ceylan, 2015; Mittal et al., 2017). Recently, research on the gut-brain axis has revealed a possible role for the gut microbiome on depression and stress-related diseases (Evrensel and Ceylan, 2015; Jiang et al., 2015; Liang et al., 2018). Microorganisms in the gut can secrete various neuroactive factors that can affect brain function (Evrensel and Ceylan, 2015) and changes in the homeostatic gut microbiome can lead to pathological consequences. Furthermore, differences in microbiome diversity are present in MDD patients with certain genera being more represented compared to healthy controls (Jiang et al., 2015; Zheng et al., 2016a, 2016b).

The ENS is a unique division of the peripheral nervous system that controls the functions of the gastrointestinal tract independent of direction from the CNS and plays a role in both sensory and motor functions in the gut (Mittal et al., 2017; Rao and Gershon, 2016). However, there are connections between the ENS and CNS that allow the two systems to communicate and influence one another. Thus, it is likely that communication between the ENS and CNS is involved in the behavioral response to stress and the development of neurological disorders such as MDD. For example, social stress increases gene expression of neuropeptide Y receptor 1 (NPY1R) in the locus coeruleus, a receptor generally associated with immune system activation in the gut (Chandrasekharan et al., 2013; Hassani et al., 2005; Wood et al., 2015). Neuropeptide Y (NPY) is involved in NE signaling and inhibits firing in the locus coeruleus via inhibition of tyrosine hydroxylase (TH) (Finta

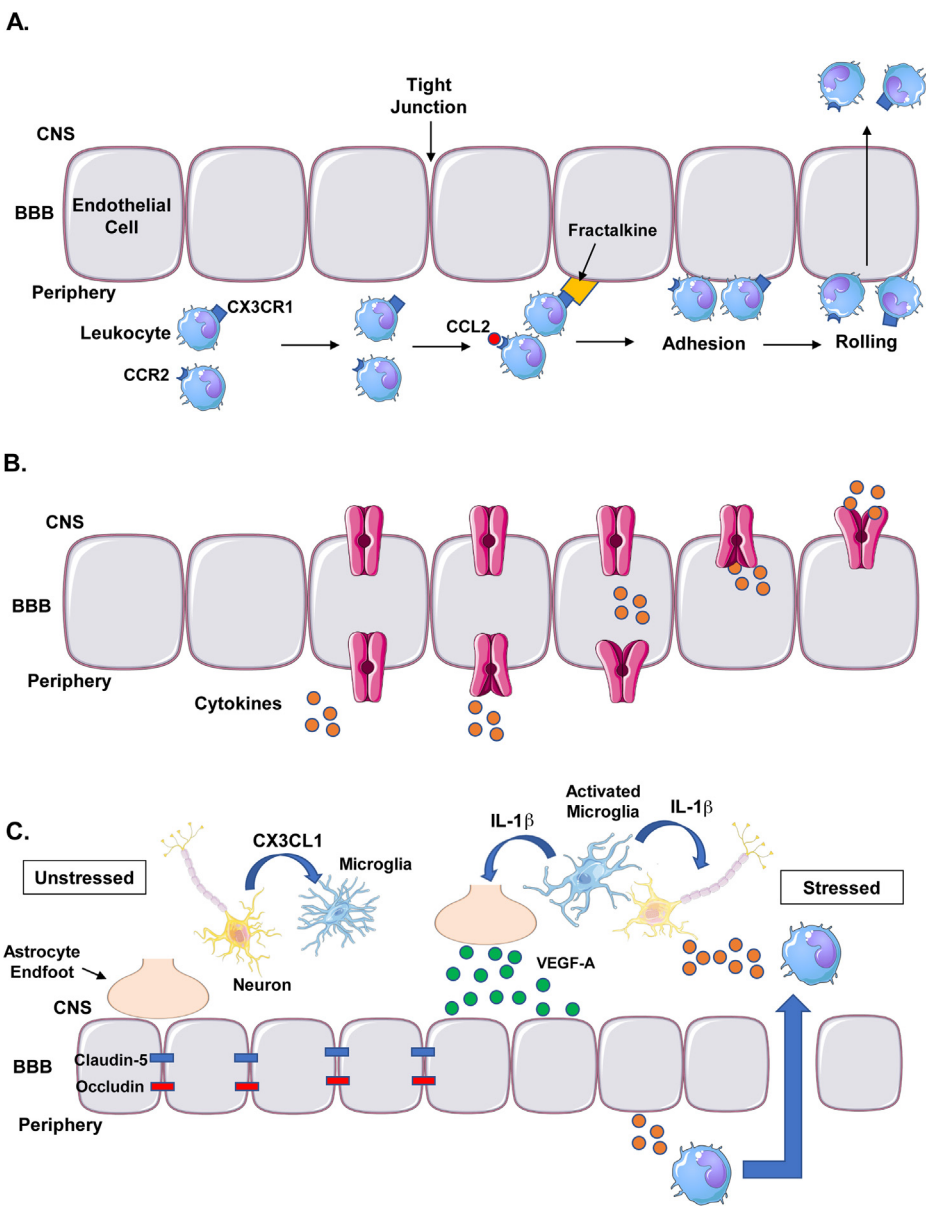

Fig. 2. *Mechanisms for peripheral immune components to cross the blood-brain barrier*. There are multiple ways in which immune components can cross the blood–brain barrier (BBB) and include (A) diapedesis, (B) saturable transport and (C) neuron-microglia-astrocyte crosstalk. (A) Diapedesis involves binding and activation of chemokine receptors on leukocytes such as CCR2 and CX3CR1, leading to an increase in integrin adhesiveness and binding of the leukocyte to the endothelial cells in the BBB. This slows the flow of the leukocyte and causes it to roll along the luminal wall of the vessel allowing it to move through the endothelium. (B) Alternatively, cytokines move through the BBB using the selective carrier-mediated transport known as saturable transport. These carriers are oriented in such a way to allow the flow of cytokines through the endothelial cell into the brain. (C) Finally, neurons and microglia communicate via the CX3CL1/CX3CR1 under normal healthy conditions. This communication keeps the microglia in a non-inflammatory state. During stress, microglia become activated and secrete IL-1β, binding and activating astrocytes and neurons potentially producing eventual atrophy. Activated astrocytes then release VEGF-A leading to decreased expression of the tight junction proteins claudin-5 and occludin, resulting in breakdown of the BBB, leukocyte migration and cytokine passage from the periphery into the CNS.

et al., 1992; Mittal et al., 2017). Furthermore, NPY secreted by the ENS is implicated in the activation of immune cells such as macrophages, neutrophils and lymphocytes (Chandrasekharan et al., 2013). Taken together, this suggests a role in regulating peripheral cytokine responses driving susceptibility and resilience via changes in the activation of the sympathetic nervous system.

Psychological stress in mice results in increased expression of pro-inflammatory cytokines (iNOS, TNF, and IL-1β) and dysregulation of the microbiome in the gut (Bailey et al., 2011, 2010; Maltz et al., 2018). Short chain fatty acids (SCFAs) are produced via fermentation of carbohydrates by the microorganisms in the gut and are affected by stress. For example, the SCFAs acetic and butyric acid are reduced while propionic acid is increased during stress compared to unstressed mice (Maltz et al., 2018). The microbiome can affect gene expression in the brain as well as circulating cytokine levels, which in turn can have effects on depression- and anxiety-associated behavior. Administration of an antibiotic cocktail prior to stress exposure can reduce the stress-mediated increases in circulating IL-6 that are typically observed (Bailey et al., 2011). Germ free mice have decreased 5HT1A gene expression in the dentate gyrus and display less anxiety- and depression-associated behaviors compared to specific pathogen free (SPF) mice (Neufeld et al., 2011; Zheng et al., 2016a, 2016b).

Microbiota transplantation from patients with MDD into germ free mice results in increased depression-associated behaviors compared to mice transplanted with microbiota from healthy controls (Zheng et al., 2016a, 2016b). Maternal separation of rats at a young age results in depression-associated behavior, which can be reversed with chronic treatment of the probiotic *Bifidobacterium infantis* (*B. infantis*) in adult animals (Desbonnet et al., 2010). Furthermore, chronic treatment with probiotics such as *B. infantis* and *Lactobacillus rhamnosus* (*L. rhamnosus*) affect the levels of GABA and NE in the CNS, in addition to their ability to reduce anxiety- and depression-associated behaviors (Bravo et al., 2011; Desbonnet et al., 2010). However, vagotomy attenuates the anxiolytic effects of *L. rhamnosus*, indicating a possible pathway through which the gut microbiota communicates with the CNS to regulate the stress response (Bravo et al., 2011). These findings implicate a role for probiotics to affect neurotransmitter levels in the brain and opens an avenue for microbiome-based therapeutic intervention for MDD. Taken together, the gut microbiome clearly plays a role in regulating the CNS and the behavioral response to stress.

4. How do peripheral immune signals cross into the brain?

The brain was initially thought to be immune privileged as the CNS is protected by the blood brain barrier (BBB) from systemic pathogens, immune cells and other factors circulating in the blood, such as cytokines. The BBB, being both a physical and selective exchange barrier, is able to effectively control the brain microenvironment (Lampron et al., 2013). The BBB is formed by endothelial cells closely connected to each other by tight junctions and adherens junctions. These are intracellular bridges made up of multiple transmembrane protein complexes, including claudins, occludin, junctional adhesion molecules and glycoprotein cadherins (Lampron et al., 2013). There are only a few mechanisms through which substances can enter the brain, including diapedesis and saturable transport (Banks et al., 1995). Peripheral leukocytes cross the BBB through the process of diapedesis, which involves invagination of the endothelial cell and podocytosis of the peripheral leukocyte, enabling the leukocyte to tunnel through the endothelial cell (Banks et al., 1995). Leukocyte trafficking across the BBB depends on phenotype and expression of the chemokine receptor 2 (CCR2) or fractalkine receptor CX3CR (Auffray et al., 2007; Geissmann et al., 2003). Diapedesis of CCR2-expressing leukocytes is directed by selectins and integrin. Initial contact of leukocytes and rolling on the endothelium is mediated by selectins. Subsequent activation of G protein-coupled receptors by chemoattractants leads to activation of integrin adhesiveness and stable arrest of leukocytes, ultimately allowing leukocytes to move through endothelium via diapedesis (Fig. 2A) (Campbell et al., 1998; Fong et al., 1998; Springer, 1994). Diapedesis of CX3CR1-expressing leukocytes is mediated by fractalkine CX3CL1, transmembrane chemokine expressed on the activated endothelium. CX3CL1 has been shown to mediate rapid capture and firm adhesion of leukocytes both through integrin-independent and integrin-dependent mechanisms (Fong et al., 1998; Goda et al., 2000).

Cytokines usually cross the BBB via the process of saturable transport, which has the advantage of being sensitive to physiological and pathological stimuli (Fig. 2B) (Banks et al., 1995; Kastin and Pan, 2008). Saturable transport is a selective carrier-mediated transport, with the membrane carriers being oftentimes polarized for the optimal transport of the substances into the brain (Brasnjevic et al., 2009). Cytokines implicated in stress susceptibility and resilience, such as IL-1β, IL-6, and TNF, have been shown to cross BBB by the means of distinct saturable transport systems (Banks et al., 2001a, 2001b, 1994, 1995; Pan and Kastin, 2008) and rates of saturable transport of cytokines can vary regionally. For example, the hypothalamus absorbs TNF-α much faster than the rest of the brain (Banks et al., 2001a, 2001b). Saturable transport systems are sensitive to systemic inflammation, including upregulation of influx transport carriers for TNF (Osburg et al., 2002; Varatharaj and Galea, 2017). However, this transport system has some limitations. The rate of cytokine transport through the BBB is slow and accounts for only 0.08% of systemically injected cytokines (Banks et al., 1991). Additionally, not all cytokines are able to cross the BBB via saturable transport, as in the case with IL-2 (Banks et al., 2004).

Another way by which cytokines can interact with the brain is through the circumventricular organs (CVOs). CVOs are specialized structures with permeable capillaries located around the third and fourth ventricles that allow for greater exchange between the body and peripheral blood. These structures are usually divided into sensory CVOs: subfornical organ, organum vasculosum of the lamina terminalis and area postrema and secretory CVOs: neurohypophysis, median eminence and pineal gland (Erickson and Banks, 2018). Because of their highly permeable status, CVOs allow passage of sevenfold more cytokines compared to the adjacent areas (Erickson and Banks, 2018). Apart from allowing direct entry of cytokines, CVOs are involved in the immune signaling by transducing inflammatory signals from the periphery to the brain. Furthermore, cells in these areas express cytokine receptors such as CD14 and various TLRs (Ericsson et al., 1995; Lacroix et al., 1998; Laflamme and Rivest, 2001; Vallières and Rivest, 1997), which, once activated, result in secretion and release of pro-inflammatory cytokines, including IL-1β, Il-6 and TNF (Goehler et al., 2006; Langgartner et al. 2019; Nadeau and Rivest, 1999). Interestingly, there are bidirectional neuronal projections between the CVOs and the major brain areas implicated in depression, such as the hippocampus, hypothalamus and amygdala (Quan, 2008). These physiological properties and location in the brain make CVOs important in the neuroimmune communication and future research is needed to shed light on the potential involvement of CVOs in stress resilience and susceptibility.

Under pathological conditions, the BBB can lose its integrity leading to the passage of peripheral cytokines into the brain. Pathological conditions in this context can include infection, inflammation and physiological/psychological stress. Even a single exposure to restraint stress was sufficient to significantly increase BBB permeability in the cerebellum and the diencephalon in male Sprague-Dawley rats (Esposito et al., 2001). Increased BBB permeability to peripheral pro-inflammatory cytokines is thought to be a mechanism involved in stress susceptibility and resilience (Esposito et al., 2001; Sántha et al., 2016).

Studies have reported infiltration of monocytes into the mouse brain following stress (Fig. 2C). Repeated social stress promotes infiltration of peripheral macrophages specifically in stress-responsive regions, including the prefrontal cortex (PFC), amygdala and hippocampus in stress susceptible mice (Wohleb et al., 2013). This migration was dependent on the presence of CX3CR1 and CCR2, as stress resilient mice were deficient in these receptors and as a result didn't exhibit monocyte infiltration into the brain (Wohleb et al., 2013). Furthermore, psychological stress was also able to induce BBB permeability. Psychological stress induced by a C57BL/6 mice witnessing a conspecific undergoing foot shock, resulted in the recruitment of bone marrow derived-monocytes into the paraventricular nucleus in stress susceptible mice (Ataka et al., 2013).

Individual differences in molecular mechanisms of BBB permeability mediate the behavioral response to chronic social defeat stress (Menard et al., 2017). Chronic social stress significantly downregulated claudin-5, an integral component of tight junctions, in the NAc of stress susceptible mice, but not resilient mice (Fig. 2 C). Moreover, social defeat stress resulted in ultrastructural abnormalities of blood vessels in the NAc in stress susceptible, but not resilient mice. Increased BBB permeability in stress susceptible mice led to passage of peripherally-injected biotin-labeled IL-6 into NAc and hippocampus, and this does not occur in stress resilient or control mice (Menard et al., 2017). To confirm IL-6 involvement in depression-associated behavior, IL-6 was directly administered into the NAc of the cannulated mice. Following subthreshold defeat stress, these mice displayed social avoidance (Menard et al., 2017). Depression-like behaviors have also been demonstrated in mice injected with IL-6 intracerebroventricularly (Sukoff Rizzo et al., 2012). Specifically, there were significant increases of IL-6 levels in the hippocampus, hypothalamus and frontal cortex in addition to increased immobility times in forced swim and tail suspension tests along with reduced social interaction with a female stimulus mouse (Sukoff Rizzo et al., 2012). Restoring BBB integrity and preventing peripheral cytokines from entering the brain blocks the effects of chronic stress (Hodes et al., 2014; Menard et al., 2017). Viral-mediated restoration of claudin-5 reversed anhedonia, one of the key symptoms of clinical depression. Thus, repairing endothelial damage in the stress-related brain regions might be a new target for therapeutics treating depression and anxiety. Further, these data indicate that individual differences in BBB permeability controlled by the molecular make up of endothelial cells directly contribute to whether an individual will be behaviorally susceptible to stress.

5. Cellular and molecular mechanisms of individual differences in the central immune response to stress

Microglia are resident immune cells of the brain and comprise about 10% of the total glial population of the central nervous system (Rosen et al., 2017). These cells are derived from the embryonic yolk sac and migrate to the brain during early development before the BBB is formed (Ginhoux et al., 2010; Nikodemova et al., 2015). Under non-pathological conditions, microglia perform a range of functions, including surveillance of the surrounding environment (Nimmerjahn et al., 2005), and synaptic pruning, which is especially crucial during neuronal development (Schafer et al., 2012; Schafer and Stevens, 2013). Using microscopy, microglial states can be identified according to morphology. In the healthy adult brain, microglia are mostly in a ramified state, characterized by small cell bodies and numerous long processes, which help to survey the environment (Hanisch and Kettenmann, 2007). Following infection or injury, microglia act as the first line of defense by moving to the site of injury and becoming activated. This activated state is characterized by morphological changes including thickening and shortening of processes along with an increased soma size and can result in increased secretion of the pro-inflammatory cytokines Il-1β, IL-6 and TNF (Hanisch and Kettenmann, 2007; Nelson et al., 2017).

Microglia become activated not only in response to injury or infection, but also in response to stress (Bollinger et al., 2016; Hellwig et al., 2016). Specifically, microglia became activated in response to stress in brain regions implicated in depression and the stress response. Both functional and structural abnormalities in the prefrontal cortex and limbic regions, such as hippocampus, NAc, amygdala and thalamus, have been reported in patients with MDD (Pandya et al., 2013; Pizzagalli et al., 2009). Region-specific microglia activation indicates a potential for microglial involvement in stress resilience and susceptibility. In the event of injury, microglia respond by moving to the site of the insult, however following stress it is unclear whether microglia move to the brain regions involved in the stress response from other brain areas. To our knowledge, no studies have addressed this question and further work is needed to elucidate microglia region specific recruitment in response to stress.

Acute stress increases microglial activation in the hypothalamus, thalamus and hippocampus (Sugama et al., 2007). However, the activation is not associated with changes in inflammatory indicators such as IL-1β, IL-6 or inducible nitric oxide synthase. The cytokine IL-18 was implicated in microglia activation in response to acute stress, as *Il18*$^{-/-}$ mice displayed significant reduction of activated microglia following stress exposure (Sugama et al., 2007). In contrast, another study that reported acute foot shock resulted in microglia activation found increased levels of IL-1β in the hypothalamus (Blandino et al., 2006a, 2006b). The microglia activation inhibitor minocycline blocked the increase of IL-1β, suggesting that activated microglia were a possible source of stress-induced IL-1β production in the brain (Blandino et al., 2006a, 2006b). Chronic stress studies also support region specific activation of microglia. Chronic restraint stress for 14 days resulted in increased microglia activation in the medial PFC, NAc, and CA3 region of hippocampus in stress susceptible rats (Tynan et al., 2010). Repeated social stress increased the number of activated microglia in the hippocampus, PFC, amygdala and paraventricular nucleus of the hypothalamus (Wohleb et al., 2012). Moreover, mRNA levels of Il-1β and Tnf were elevated in microglia isolated from stress susceptible mice, confirming an earlier finding that stress primes an inflammatory state in microglia, as microglia from the hippocampus of stress susceptible Sprague-Dawley rats had elevated levels of mRNA after *ex vivo* stimulation with LPS (Frank et al., 2007). These changes in microglia activation may contribute to susceptibility and resilience of the effects of stress on cognition. Chronic restraint stress induced working memory deficits in rats. These behavioral changes were accompanied by microglia activation in the medial PFC and inhibition of microglia activation with minocycline improved working memory (Hinwood et al., 2012).

Microglia activation following stress may be modulated by glucocorticoids. An examination of two different chronic stress paradigms, repeated restraint stress and variable stress, both lasting for 14 days, found that microglia activation in the PFC increased following repeated restraint stress, but not chronic variable stress. The authors proposed the difference was due to the non-habituating nature of chronic variable stress, which causes significant HPA axis sensitization and increased glucocorticoids which inhibit microglia activation. Conversely, repeated restraint stress, being repetitive and predictable in nature, results in HPA axis habituation and low glucocorticoid levels therefore without the anti-inflammatory effects of elevated glucocorticoids, microglia become activated (Kopp et al., 2013). Supporting this concept, adrenalectomy increased microglia activation following acute stress in the hypothalamus and hippocampus and treatment with exogenous CORT blocked the increase in activation (Sugama et al., 2013). Stressed adrenalectomized rats with activated microglia had increased OX-6 (major histocompatibility complex class II marker) immunoreactivity in the dentate gyrus which was also attenuated by glucocorticoid treatment, indicating that glucocorticoids act as anti-inflammatory signal in the brain during stress (Sugama et al., 2013).

Contrary to anti-inflammatory effects of glucocorticoids, norepinephrine is likely producing pro-inflammatory effects in most areas of the brain. Treatment with propranolol, a non-selective β-blocker, completely blocked increases in IL-1β in the hypothalamus and hippocampus following acute stress. (Blandino et al., 2006a, 2006b; Johnson et al., 2005). At the same time, increasing synaptic norepinephrine via the norepinephrine reuptake inhibitor desipramine caused increased levels of IL-1β in the hypothalamus following stress (Blandino et al., 2006a, 2006b; Porterfield et al., 2011). Similarly, direct activation of β-adrenergic receptors with isoproterenol, a β-adrenergic receptor agonist, produced induction of IL-1β in the hypothalamus and hippocampus (Johnson et al., 2005). Another study using isoproterenol, demonstrated that pretreatment with isoproterenol significantly increased IL-1β and IL-6 production by cultured microglia following LPS stimulation (Johnson et al., 2013). In the context of repeated social stress, propranolol blocked microglial activation and anxiety associated behavior when administered during stress (Wohleb et al., 2011). Microglia derived mRNA revealed increased levels of IL-1β and reduced levels of GC responsive genes (GILZ and FKBP51), pretreatment with propranolol restored IL-1β to baseline and prevented the down-regulation of the GC responsive genes in stress susceptible mice, demonstrating that repeated stress might be desensitizing microglia to glucocorticoid anti-inflammatory effects (Wohleb et al., 2011).

The effects of stress on microglia activation are likely sex specific. Female rats have a higher ratio of primed to ramified microglia compared to male rats at baseline in the PFC, indicating a more activated state in females (Bollinger et al., 2016). Following both acute and chronic restraint stress in females, the number of primed to ramified microglia decreased whereas no significant changes were found in males (Bollinger et al., 2016). In contrast, a different study found that males exhibited microglial activation in the same region following chronic stress (Hinwood et al., 2012). The differences may be due to the time course and duration of the stress exposure as longer exposure to stress may be required to activate microglia in males. More work is needed to determine if sex-dependent microglial activation may be contributing to higher rates of susceptibility to stress and depression in females, as they are already more primed prior to stress.

The effects of stress on microglia activation may also be age-dependent. A study of young adult and aged Mongolian gerbils exposed to chronic restraint stress only found activation of microglia in the hippocampus of adult, but not aged animals (Park et al., 2011). This effect was accompanied by a greater decrease in glucocorticoid receptor immunoreactivity in the young adult group. In contrast to the effects in

aged animals, early life exposure results in lasting priming effects on microglia (Diz-Chaves et al., 2013; Roque et al., 2016; Takatsuru et al., 2015). Prenatally stressed mice displayed a higher percentage of activated microglia and had higher levels of IL-1β and TNF in the hippocampus at 4 months of age compared to control mice (Diz-Chaves et al., 2013). Furthermore, prenatally stressed mice had an exacerbated response to LPS, resulting in increased TNF immunoreactivity and number of immunoreactive microglia, whereas the response was not found in prenatal control subjects (Diz-Chaves et al., 2013). Early life maternal separation also led to microglia activation, accompanied by higher levels of IL-1β in the hippocampus in 15 day old male rats (Roque et al., 2016). During adolescence, exposure to repeated social stress resulted in changes in microglia number and morphology when examined subsequently in adulthood (Rodriguez-Arias et al., 2018). Stress decreased the number of Iba1 + cells in the prelimbic cortex and at the same time increased the proportion of activated microglia in both prelimbic cortex and NAc (Rodriguez-Arias et al., 2018).

One of the potential mechanisms involved in stress susceptibility and resilience is the CX3CL1/CX3CR1 interaction. Neurons and microglia bidirectionally communicate via the CX3C axis. The chemokine receptor CX3CR1 is exclusively expressed on microglia in the CNS and its ligand CX3CL1 is secreted by neurons and can regulate microglial activation (Cardona et al., 2006). Following i.p. injections of LPS, CX3CR1 deficient mice showed increased microglial activation as well as neural damage (Cardona et al., 2006). Furthermore, CX3CR1 deficient mice had higher levels of microglial expression of IL-1β in the hippocampus and the cortex compared to control mice after i.p. injections of LPS (Cardona et al., 2006; Corona et al., 2010). In a microglial culture, CXCL1 dose-dependently attenuated the production of Il-6, TNF, and nitric oxide by LPS-activated microglia (Mizuno et al., 2003). CX3CR1 deficiency also led to behavioral changes, such as social withdrawal and extended depression associated behavior following LPS administration (Corona et al., 2010).

CX3CR1 deficiency leads to impediment in normal microglia–neuron cross talk, preventing microglia from responding to both environmental enrichment and negative environmental challenge in the form of stress (Hellwig et al., 2016; Milior et al., 2016; Winkler et al., 2017). The effects of CX3CL1/CX3CR1 interaction is dependent on the nature and duration of the stimulus. CX3CR1 deficiency leads to increased microglial activation and depression associated behavior following acute immune activation by LPS. However, in the context of chronic stress and in the absence of acute immune activation, CX3CR1 deficiency prevents microglial response to environmental stimuli, including stress, resulting in stress resilience. Stress did not change microglial morphology in the hippocampus of CX3CR1 deficient mice compared to wild-type (Hellwig et al., 2016; Milior et al., 2016), but it reduced microglia activation in the paraventricular hypothalamic area (Winkler et al., 2017). Behaviorally, CX3CR1 deficient mice displayed a resilient phenotype. They engaged in an active escape strategy and did not express anxiety associated or depression associated behaviors following acute stress (Winkler et al., 2017). Following chronic stress, they did not develop anhedonia or express a memory decline (Milior et al., 2016; Rimmerman et al., 2017; Winkler et al., 2017). Stress resilience in CX3CR1 deficient male mice results from both basal and stress-induced changes in hippocampal transcription (Rimmerman et al., 2017). Hippocampal whole transcriptome analysis found basal differences in CX3CR1 deficient mice compared to wild-type. CX3CR1 deficient mice had lower expression of interferon regulated and MHC1 gene transcripts along with increased activation of downstream targets of the anti-inflammatory IL-10 receptor (Rimmerman et al., 2017). After chronic stress, CX3CR1 deficient mice showed activation of targets involved in 17β-estradiol signaling, in particular *Igf2* and *Igfbp2*, both being ESR1-regulated genes (Rimmerman et al., 2017). These reported differences in estrogen signaling might be a contributing factor in stress resilience. Estrogen in the brain produces anti-inflammatory effects in microglia (Bruce-Keller et al., 2000; Dimayuga et al., 2005), thus playing a neuroprotective role. In particular, 17β-estradiol in a dose dependent manner attenuates microglial phagocytic activity and release of superoxide (Bruce-Keller et al., 2000). Following LPS application, estrogen decreased microglial secretion of TNF-α and IFN-γ (Dimayuga et al., 2005). Furthermore, estradiol has been shown to reduce depression-like and anxiety-like behaviors in ovariectomized female rats (Bastos et al., 2015; Walf et al., 2009; Xu et al., 2015). In females, estrogen potentiates excitatory synaptic activation, suppresses inhibition, and increases spine density in the hippocampus (Huang and Woolley, 2012; Jain et al., 2019; Woolley et al., 1997) and has similar effects on spine density on pyramidal neurons in the prefrontal cortex (Tuscher et al., 2016) all of which are thought to be important for generating antidepressant-like behavioral effects. In the hippocampus these effects are thought to be mediated by locally synthesized neurosteroids as aromatization blocks this process in rodents and humans (Bayer et al., 2015). Research is needed in both male and female rodents to further examine the role of locally synthesized neurosteroids on cross talk between microglia and neurons in the same subjects following stress.

Microglia engage in bidirectional communication not only with neurons, but also with astrocytes. Astrocytes are another type of glial cells, but unlike microglia, they are derived from neural stem cells. They are the most abundant glial cells in the CNS and are spread throughout the brain. Astrocytes respond to inflammation or other pathological conditions through a process called astrogliosis, which includes changes in gene expression, proliferation and upregulation of the astrocyte marker glial fibrillary acidic protein (GFAP) (John et al., 2005; Sofroniew, 2015). Astrocytes interact with brain blood vessels, which is crucial in the function of BBB and the maintenance of homeostasis (Lampron et al., 2013). They also form borders that isolate neural parenchyma and non-neural cells along the blood vessels, blocking circulating leukocytes from accessing the brain, thus restricting inflammation (Sofroniew, 2015). Astrocytes also directly interact with neurons through the tripartite synapse, where astrocytic end-feet wrap around presynaptic and postsynaptic nerve terminals (Araque et al., 1999).

One of the mechanisms through which astrocytes and neurons are able to influence microglia is via the regulated release of adenosine triphosphate (ATP) shaping microglia response to injury (Rodrigues et al., 2015). ATP exerts its effect on microglia though P2X7R, a nonselective cation channel. P2X7R has also been implicated in resilience to the behavioral response to stress (Basso et al., 2009). P2X7R knock out mice expressed active coping responses to the tail suspension and forced swim tests compared to wild-type mice. Additionally, these mice demonstrated an amplified response to the administration of imipramine, a tricyclic antidepressant (Basso et al., 2009). ATP activation stimulates microglia secretion of pro-inflammatory cytokines IL-1β and TNF (Bianco et al., 2005; Ferrari et al., 2006; Monif et al., 2009). Overexpression of P2X7R alone was sufficient to induce activation and proliferation of microglia, along with secretion of TNF in hippocampal culture, whereas treatment with oxidized ATP, a P2X7R antagonist, resulted in dampened microgliosis (Monif et al., 2009). In hippocampal astrocyte–microglia cultures, ATP derived from astrocytes has been shown to stimulate IL-1β release through the shedding of vesicles from the plasma membrane from neighboring microglia (Bianco et al., 2005). Microglia also react to ATP by rapidly moving their processes to the site of injury (Davalos et al., 2005). Connexin channels are highly expressed on astrocytes and are involved in the astrocytic release of ATP (Stout et al., 2002). Blocking connexin channels prevented microglial response (Davalos et al., 2005), suggesting that microglia react to ATP specifically released from astrocytes. Catalytic activation of AKT also initiates autophagy during periods of energy depletion through its effects on the mTOR pathway (for review see Kroemer et al., 2010) and also may be a mechanism involved in the response to stress particularly in response to increased glucocorticoids. In the prefrontal cortex, but not the hippocampus, autophagy contributed to the degradation of connexin 43 in

astrocytes following exposure to corticosterone which in turn impaired gap junctions (Xia et al., 2018). A type 2 diabetes treatment, Rosiglitazone, which activates AKT through insulin receptors was found to have antidepressant behavioral properties (Zhao et al., 2017). Rosiglitazone promoted astrocyte proliferation and neuronal axon plasticity in the prefrontal cortex following unpredictable chronic mild stress by increased autophagy in neurons and acting as an anti-apoptotic agent in astrocytes (Zhao et al., 2017). In the hippocampus, unpredictable chronic mild stress decreased level of mTOR and AKT in hippocampus along with autophagy related genes, effects that were attenuated with chronic antidepressant treatment (Yang Yang et al., 2017). Therefore, AKT may have a multifaceted role in stress sensitivity acting on different mechanisms in a region and cell type specific manner.

Microglia can engage in a feedback loop with astrocytes via ATP activation. IL-1β secreted by microglia in response to astrocytic ATP binds to receptors on astrocytes, leading to astrocytic secretion of vascular endothelial growth factor A (VEGF-A), disruption of BBB and ultimately entry of leukocytes from the periphery (Fig. 2C). Astrocytic release of VEGF-A results in decreased expression of claudin-5 and occludin, leading to BBB breakdown (Fig. 2C) (Argaw et al., 2009). Therefore, microglia and astrocytes might be involved in inducing stress susceptibility not only in isolation from each other, but through working in tandem via crosstalk. During CNS injury, microglia react first to the insult and start secreting pro-inflammatory cytokines, which activate astrocytes. Reactive astrocytes, in turn, may contribute to the sustained activation of microglia (Gao et al., 2013). Further studies are needed to elucidate synergetic role of microglia and astrocytes in the response to acute and chronic stress.

Another mechanism by which astrocytes affect BBB permeability is apolipoprotein E (APOE), produced primarily by astrocytes (Kim et al., 2009; Xu et al., 2006). Specifically, the E4 isoform of this apolipoprotein leads to BBB breakdown through activation of a proinflammatory NF-κB-matrix metallopeptidase-9 (MMP9) pathway in pericytes (Bell et al., 2012; Teng et al., 2017). Transgenic mice expressing humanized APOE4 displayed increased expression of MMP-9 and reduced levels of claudin-5 and occludin following traumatic brain injury (Main et al., 2018). Given the previously discussed role of claudin-5 in BBB stress susceptibility (Main et al., 2018), these data support the notion that both peripheral and central mechanisms are acting on both sides, contributing to increased BBB permeability.

Furthermore, astrocytes are actively involved in recruitment of peripheral leukocytes into the brain though the release of CC-chemokine ligand 2 (CCL2) and CXC-chemokine ligand 10 (CXCL10) (Sofroniew, 2015). CCL2 can activate chemokine receptor CCR2 expressed on peripheral monocytes, promoting their migration into the brain (Fig. 2A) (Ransohoff and Tani, 1998). Conditional deletion of astroglial CCL2 results in reduced trafficking of peripheral leukocytes into the CNS (Moreno et al., 2014). Moreover, deletion of CCL2 in astrocytes results not only in less recruitment of macrophages and T cells, but also in reduced microglial activation (Kim et al., 2014), again supporting the idea of cross-talk between microglia and astrocytes. Consistent with these findings, suppressing peripheral Ly6C^{hi} monocyte migration to the brain results in decreased activation of astrocytes suggesting a bidirectional relationship as the ensuing lower CCL2 release by astrocytes, in turn leading to reduced recruitment of peripheral leukocytes. This astrocyte-involved inhibition of leukocyte infiltration improved depression-like symptoms in mice following chronic social defeat stress (Zheng et al., 2016a, 2016b).

Astrocytes residing in the hippocampus may be modulating stress susceptibility in a glucocorticoid receptor-dependent manner through their involvement in fear learning and aversive memory formations. Fearful and aversive memory formation is thought to be involved in depression and post-traumatic stress disorder (Goosens, 2011). Astrocytes express glucocorticoid receptors and activation produces an increase of intracellular calcium concentrations and metabolic changes (Carter et al., 2013; Piechota et al., 2017; Simard et al., 1999; Tertil et al., 2018). Astrocyte specific glucocorticoid receptor knock-out mice have impaired contextual fear memory and do not form aversive memories compared to controls (Tertil et al., 2018). Additionally, astrocytes also modulate stress-enhanced fear learning in an IL-1β–dependent manner. Dorsal hippocampus astrocytes have been shown to be the source of stress-induced IL-1β (Jones et al., 2018a, 2018b). Using a stress-enhanced fear learning paradigm, Jones et al. (2015) showed that foot shocks increased IL-1β immunoreactivity in the dentate gyrus of the dorsal hippocampus. Administration of an IL-1 receptor antagonist following foot shock led to stress resilience and prevented stress-enhanced fear learning (Jones et al., 2015).

Building on their previous work, Jones et al. (2018a, 2018b) used glial-expressing designer receptors exclusively activated by designer drugs (DREADDs) to manipulate astroglial G_i and to further elucidate the role of astrocytes in stress-enhanced fear learning. They showed that activation of astroglial G_i signaling in the dorsal hippocampus attenuated stress-enhanced fear learning. The authors propose that IL-1β signaling might be one of the potential mechanisms through which astroglial G_i prevents stress-enhanced fear learning (Jones et al., 2018a, 2018b).

In addition to increasing BBB permeability and recruitment of leukocytes from the periphery, astrocytes also contribute to stress susceptibility through direct interaction with neurons. Kir4.1, an inwardly rectifying K^+ channel, is expressed on astrocytic end-feet wrapping synapses and is involved in buffering extra extracellular K^+ in synapses. Upregulation of astrocytic Kir4.1 in the lateral habenula causes excessive clearance of extracellular K^+ from synapses. Low levels of extracellular K^+ leads to hyperpolarization and increased bursting activity of neurons. Both congenitally learned helpless Sprague-Dawley rats and Wistar rats with LPS-induced depression-like symptoms have significantly increased Kir4.1 in the lateral habenula (Cui et al., 2018). Loss of function of Kir4.1 eliminated neuronal bursting activity and rescued depression associated behavior of congenitally learned helpless rats (Cui et al., 2018). Ketamine, the N-methyl-D-aspartate receptor antagonist, rapidly relieved depression associated behavior by blocking NMDAR-dependent neuronal bursting activity in the lateral habenula (Yang et al., 2018). Ketamine also exerted its antidepressant effects through activation of astrocytes in the hippocampus (Wang et al., 2018). Recent approval of esketamine, enantiomer S-ketamine, for treatment-resistant depression is a major advancement in depression treatment. Future research should consider elucidating the antidepressant mechanisms of ketamine exerted on astrocytes as well as neurons.

6. Conclusion

Differences in the peripheral and central immune system have a profound effect on the susceptibility or resilience of an individual to stress. Various immune-related markers are changed in susceptible individuals compared to resilient. More work needs to be done to understand how these changes in the immune system function together and contribute to the risk of experiencing an adverse response to stress. The studies presented in this review describe greater activation of an inflammatory feed forward loop in which the stress acts on both the peripheral and central immune system to open up the BBB resulting in a stress susceptible individual. Additional research is needed to determine the important molecular cascades that confer protection and prevent the activated inflammatory state. Finally, much of the work on stress susceptibility to this point has been conducted on males. However, female mice have different hormonal factors that influence their immune system and show a higher incidence of MDD in humans (Albert, 2015; Hodes et al., 2015). There are studies indicating similarities and differences in the female immune response. In particular, many studies in the periphery indicate that females show an earlier or more intense activation of the immune system, although this may be countered by sex and region-specific changes in microglia or astrocytes.

Future work on this subject should include both males and females in order to fully appreciate the mechanisms involved in individual differences in response to stress.

Acknowledgments

This work was supported by a young investigator NARSAD award from the Brain and Behavior Research Foundation to GEH. We would also like to thank Dr. Jennifer Rainville for her assistance and support. We would also like to acknowledge Servier Medical Art for their stock images, some of which have been adapted for use in the figures of this manuscript.

Disclosures

The authors have nothing to disclose and no conflicts of interest to report.

References

Albert, P.R., 2015. Why is depression more prevalent in women? J. Psychiat. Neurosci.: JPN 40 (4), 219–221.

Alcocer-Gómez, E., Casas-Barquero, N., Núñez-Vasco, J., Navarro-Pando, J.M., Bullón, P., 2017a. Psychological status in depressive patients correlates with metabolic gene expression. CNS Neurosci. Ther. 23 (10), 843–845. https://doi.org/10.1111/cns.12755.

Alcocer-Gómez, E., Casas-Barquero, N., Williams, M.R., Romero-Guillena, S.L., Cañadas-Lozano, D., Bullón, P., et al., 2017b. Antidepressants induce autophagy dependent-NLRP3-inflammasome inhibition in Major depressive disorder. Pharmacol. Res. 121, 114–121. https://doi.org/10.1016/J.PHRS.2017.04.028.

Allen, J.E., Wynn, T.A., 2011. Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. PLoS Pathog. 7 (5), e1002003. https://doi.org/10.1371/journal.ppat.1002003.

Ambrée, O., Ruland, C., Scheu, S., Arolt, V., Alferink, J., 2018. Alterations of the innate immune system in susceptibility and resilience after social defeat stress. Front. Behav. Neurosci. 12, 141. https://doi.org/10.3389/fnbeh.2018.00141.

Araque, A., Parpura, V., Sanzgiri, R.P., Haydon, P.G., 1999. Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. 22 (5), 208–215. https://doi.org/10.1016/S0166-2236(98)01349-6.

Argaw, A.T., Gurfein, B.T., Zhang, Y., Zameer, A., John, G.R., 2009. VEGF-mediated disruption of endothelial CLN-5 promotes blood-brain barrier breakdown. Proc. National Acad. Sci. 106 (6), 1977–1982.

Ashcraft, K.A., Hunzeker, J., Bonneau, R.H., 2008. Psychological stress impairs the local CD8+ T cell response to mucosal HSV-1 infection and allows for increased pathogenicity via a glucocorticoid receptor-mediated mechanism. Psychoneuroendocrinology 33 (7), 951–963. https://doi.org/10.1016/j.psyneuen.2008.04.010.

Ataka, K., Asakawa, A., Nagaishi, K., Kaimoto, K., Sawada, A., Hayakawa, Y., et al., 2013. Bone marrow-derived microglia in ltrate into the paraventricular nucleus of chronic psychological stress- loaded mice. PLoS ONE 1–13.

Auffray, C., Fogg, D., Garfa, M., Elain, G., Join-Lambert, O., Kayal, S., et al., 2007. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. Science 317 (5838), 666–670. https://doi.org/10.1126/SCIENCE.1142883.

Bachen, E.A., Chesney, M.A., Criswell, L.A., 2009. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. Arthritis Rheum. 61 (6), 822–829. https://doi.org/10.1002/art.24519.

Bailey, M.T., Dowd, S.E., Galley, J.D., Hufnagle, A.R., Allen, R.G., Lyte, M., 2011. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. Brain Behav. Immun. 25 (3), 397–407. https://doi.org/10.1016/j.bbi.2010.10.023.

Bailey, M.T., Dowd, S.E., Parry, N.M.A., Galley, J.D., Schauer, D.B., Lyte, M., 2010. Stressor exposure disrupts commensal microbial populations in the intestines and leads to increased colonization by Citrobacter rodentium. Infect. Immun. 78 (4), 1509–1519. https://doi.org/10.1128/IAI.00862-09.

Banks, A., Ortiz, L., Plotkin, S.A., Kastin, A.J., 1991. Human interleukin (IL)la, Murine IL-la and Murine IL-lfl Are transported from blood to brain in the mouse by a shared saturable mechanism. J. Pharmacol. Exp. Therapeut. 259 (3), 988–996.

Banks, W.A., Farr, S.A., Scola, M.E.L.A., Morley, J.E., 2001a. Intravenous human interleukin-1 impairs memory processing in mice: dependence on blood-brain barrier transport into posterior division of the. Septum 299 (2), 536–541.

Banks, W.A., Kastin, A.J., Gutierrez, E.G., 1994. Penetration of interleukin-6 across the murine blood-brain barrier. Neurosci. Lett. 179 (1–2), 53–56. https://doi.org/10.1016/0304-3940(94)90933-4.

Banks, W.A., Moinuddin, A., Morley, J.E., 2001b. Regional transport of TNF-α across the blood-brain barrier in young ICR and young and aged SAMP8 mice. Neurobiol. Aging 22 (4), 671–676. https://doi.org/10.1016/S0197-4580(01)00220-2.

Banks, W.A., Niehoff, M.L., Zalcman, S.S., 2004. Permeability of the mouse blood–brain barrier to murine interleukin-2: predominance of a saturable efflux system. Brain Behav. Immun. 18 (5), 434–442. https://doi.org/10.1016/J.BBI.2003.09.013.

Banks, W., Kastin, A., Broadwell, R., 1995. Passage of cytokines across the blood-brain barrier. Recent Progr. Neuroimmunomodulat. 241–248.

Basso, A.M., Bratcher, N.A., Harris, R.R., Jarvis, M.F., Decker, M.W., Rueter, L.E., 2009. Behavioral profile of P2X7 receptor knockout mice in animal models of depression and anxiety: relevance for neuropsychiatric disorders. Behav. Brain Res. 198 (1), 83–90. https://doi.org/10.1016/J.BBR.2008.10.018.

Bastos, C.P., Pereira, L.M., Ferreira-Vieira, T.H., Drumond, L.E., Massensini, A.R., Moraes, M.F.D., Pereira, G.S., 2015. Object recognition memory deficit and depressive-like behavior caused by chronic ovariectomy can be transitorialy recovered by the acute activation of hippocampal estrogen receptors. Psychoneuroendocrinology 57, 14–25. https://doi.org/10.1016/J.PSYNEUEN.2015.03.020.

Bayer, J., Rune, G., Schultz, H., Tobia, M.J., Mebes, I., Katzler, O., Sommer, T., 2015. The effect of estrogen synthesis inhibition on hippocampal memory. Psychoneuroendocrinology 56, 213–225. https://doi.org/10.1016/J.PSYNEUEN.2015.03.011.

Bell, R.D., Winkler, E.A., Singh, I., Sagare, A.P., Deane, R., Wu, Z., et al., 2012. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature 485 (7399), 512–516. https://doi.org/10.1038/nature11087.

Bianco, F., Pravettoni, E., Colombo, A., Schenk, U., Möller, T., Matteoli, M., Verderio, C., 2005. Astrocyte-derived ATP induces vesicle shedding and IL-1β release from microglia. J. Immunol. 174 (11), 7268–7277. https://doi.org/10.4049/JIMMUNOL.174.11.7268.

Blandino, P., Barnum, C.J., Deak, T., 2006a. The involvement of norepinephrine and microglia in hypothalamic and splenic IL-1 h responses to stress. J. Neuroimmunol. 173, 87–95. https://doi.org/10.1016/j.jneuroim.2005.11.021.

Blandino, Peter, Barnum, C.J., Deak, T., 2006b. The involvement of norepinephrine and microglia in hypothalamic and splenic IL-1β responses to stress. J. Neuroimmunol. 173 (1–2), 87–95. https://doi.org/10.1016/J.JNEUROIM.2005.11.021.

Bollinger, J.L., Bergeon Burns, C.M., Wellman, C.L., 2016. Differential effects of stress on microglial cell activation in male and female medial prefrontal cortex. Brain Behav. Immun. 52, 88–97. https://doi.org/10.1016/j.bbi.2015.10.003.

Brachman, R.A., Lehmann, M.L., Maric, D., Herkenham, M., 2015. Lymphocytes from chronically stressed mice confer antidepressant-like effects to naive mice. J. Neurosci.: Off. J. Soc. Neurosci. 35 (4), 1530–1538. https://doi.org/10.1523/JNEUROSCI.2278-14.2015.

Bradley, J.R., 2008. TNF-mediated inflammatory disease. J. Pathol. 214 (2), 149–160. https://doi.org/10.1002/path.2287.

van den Brandt, J., Lühder, F., McPherson, K.G., de Graaf, K.L., Tischner, D., Wiehr, S., et al., 2007. Enhanced glucocorticoid receptor signaling in T cells impacts thymocyte apoptosis and adaptive immune responses. Am. J. Pathol. 170 (3), 1041–1053. https://doi.org/10.2353/AJPATH.2007.060804.

Brasnjevic, I., Steinbusch, H.W.M., Schmitz, C., Martinez-Martinez, P., 2009. Delivery of peptide and protein drugs over the blood–brain barrier. Prog. Neurobiol. 87 (4), 212–251. https://doi.org/10.1016/J.PNEUROBIO.2008.12.002.

Bravo, J.A., Forsythe, P., Chew, M.V., Escaravage, E., Savignac, H.M., Dinan, T.G., et al., 2011. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. PNAS 108 (38), 16050–16055. https://doi.org/10.1073/pnas.1102999108.

Bruce-Keller, A.J., Keeling, J.L., Keller, J.N., Huang, F.F., Camondola, S., Mattson, M.P., 2000. Antiinflammatory effects of estrogen on microglial activation. Endocrinology 141 (10), 3646–3656. https://doi.org/10.1210/endo.141.10.7693.

Campbell, J., Hedrick, J., Zlotnik, A., Siani, M., Thompson, D., Butcher, E., 1998. Chemokines and the arrest of lymphocytes rolling under flow conditions. Science 5349, 381–384. https://doi.org/10.1126/science.7973629.

Cardona, A.E., Pioro, E.P., Sasse, M.E., Kostenko, V., Cardona, S.M., Dijkstra, I.M., et al., 2006. Control of microglial neurotoxicity by the fractalkine receptor. Nat. Neurosci. 9 (7), 917–924. https://doi.org/10.1038/nn1715.

Carter, B.S., Hamilton, D.E., Thompson, R.C., 2013. Acute and chronic glucocorticoid treatments regulate astrocyte-enriched mRNAs in multiple brain regions in vivo. Front. Neurosci. 7, 139. https://doi.org/10.3389/fnins.2013.00139.

Cesta, M.F., 2006. Normal structure, function, and histology of the spleen. Toxicol. Pathol. 34 (5), 455–465. https://doi.org/10.1080/01926230600867743.

Chandrasekharan, B., Nezami, B.G., Srinivasan, S., 2013. Emerging neuropeptide targets in inflammation: NPY and VIP. Am. J. Physiol.-Gastrointestinal Liver Physiol. 304 (11), G949–G957. https://doi.org/10.1152/ajpgi.00493.2012.

Chaplin, D.D., 2010. Overview of the immune response. J. Allergy Clin. Immunol. 125 (2), S3–S23. https://doi.org/10.1016/J.JACI.2009.12.980.

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., et al., 2018. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 9 (6), 7204–7218. https://doi.org/10.18632/oncotarget.23208.

Chourbaji, S., Urani, A., Inta, I., Sanchis-Segura, C., Brandwein, C., Zink, M., et al., 2006. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. Neurobiol. Disease 23 (3), 587–594. https://doi.org/10.1016/j.nbd.2006.05.001.

Christoffel, D.J., Golden, S.A., Dumitriu, D., Robison, A.J., Janssen, W.G., Ahn, H.F., et al., 2011. IκB kinase regulates social defeat stress-induced synaptic and behavioral plasticity. J. Neurosci.: Off. J. Soc. Neurosci. 31 (1), 314–321. https://doi.org/10.1523/JNEUROSCI.4763-10.2011.

Christoffel, D.J., Golden, S.A., Heshmati, M., Graham, A., Birnbaum, S., Neve, R.L., et al., 2012. Effects of inhibitor of κB kinase activity in the nucleus accumbens on emotional behavior. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 37 (12), 2615–2623. https://doi.org/10.1038/npp.2012.121.

Clark, S.M., Soroka, J.A., Song, C., Li, X., Tonelli, L.H., 2016. CD4(+) T cells confer anxiolytic and antidepressant-like effects, but enhance fear memory processes in Rag2(-/-) mice. Stress (Amsterdam, Netherlands) 19 (3), 303–311. https://doi.org/10.1080/10253890.2016.1191466.

Clarke, T.-K., Obsteter, J., Hall, L.S., Hayward, C., Thomson, P.A., Smith, B.H., et al., 2017. Investigating shared aetiology between type 2 diabetes and major depressive disorder in a population based cohort. Am. J. Med. Genet. Part B: Neuropsychiatr. Genet. 174 (3), 227–234. https://doi.org/10.1002/ajmg.b.32478.

Corona, A.W., Huang, Y., O'Connor, J.C., Dantzer, R., Popovich, P.G., Kelley, K.W., Godbout, J.P., 2010. Fractalkine receptor (CX3CR1) deficiency sensitizes mice to the behavioral changes induced by lipopolysaccharide. J. Neuroinflamm. 7 (1), 1–14. https://doi.org/10.1186/1742-2094-7-93.

Cui, Y., Yang, Y., Ni, Z., Dong, Y., Cai, G., Foncelle, A., et al., 2018. Astroglial Kir4.1 in the lateral habenula drives neuronal bursts in depression. Nature 554, 323–327. https://doi.org/10.1038/nature25752.

Dantzer, R., 2009. Cytokine, sickness behavior, and depression. Immunol. Allergy Clin. North Am. 29 (2), 247–264. https://doi.org/10.1016/j.iac.2009.02.002.

Davalos, D., Grutzendler, J., Yang, G., Kim, J.V., Zuo, Y., Jung, S., Littman, D.R., Dustin, M.L., et al., 2005. ATP mediates rapid microglial response to local brain injury in vivo. Nature 8 (6). https://doi.org/10.1038/nn1472.

Desbonnet, L., Garrett, L., Clarke, G., Kiely, B., Cryan, J.F., Dinan, T.G., 2010. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. Neuroscience 170 (4), 1179–1188. https://doi.org/10.1016/j.neuroscience.2010.08.005.

Dimayuga, F.O., Reed, J.L., Carnero, G.A., Wang, C., Dimayuga, E.R., Dimayuga, V.M., et al., 2005. Estrogen and brain inflammation: effects on microglial expression of MHC, costimulatory molecules and cytokines. J. Neuroimmunol. 161 (1–2), 123–136. https://doi.org/10.1016/j.jneuroim.2004.12.016.

Diz-Chaves, Y., Astiz, M., Bellini, M.J., Garcia-Segura, L.M., 2013. Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice. Brain Behav. Immun. 28, 196–206. https://doi.org/10.1016/j.bbi.2012.11.013.

Epelman, S., Lavine, K.J., Randolph, G.J., 2014. Origin and functions of tissue macrophages. Immunity 41 (1), 21–35. https://doi.org/10.1016/J.IMMUNI.2014.06.013.

Erickson, M.A., Banks, W.A., 2018. Neuroimmune axes of the blood – brain barriers and blood – brain interfaces: bases for physiological regulation, disease states, and pharmacological interventions. Pharmacol. Rev. 70, 278–314. https://doi.org/10.1124/pr.117.014647.

Ericsson, A., Liu, C., Hart, R.P., Sawchenko, P.E., 1995. Type 1 interleukin-1 receptor in the rat brain: Distribution, regulation, and relationship to sites of IL-1–induced cellular activation. J. Compara. Neurol. 361 (4), 681–698. https://doi.org/10.1002/cne.903610410.

Erlandsson, M.C., Ohlsson, C., Gustafsson, J.A., Carlsten, H., 2001. Role of oestrogen receptors alpha and beta in immune organ development and in oestrogen-mediated effects on thymus. Immunology 103 (1), 17–25. https://doi.org/10.1046/j.1365-2567.2001.01212.x.

Esposito, P., Gheorghe, D., Kandere, K., Pang, X., Connolly, R., Jacobson, S., Theoharides, T.C., 2001. Acute stress increases permeability of the blood – brain-barrier through activation of brain mast cells. Brain Res. 888, 117–127.

Evrensel, A., Ceylan, M.E., 2015. The gut-brain axis: the missing link in depression. Clin. Psychopharmacol. Neurosci.: Off. Sci. J. Korean Coll. Neuropsychopharmacol. 13 (3), 239–244. https://doi.org/10.9758/cpn.2015.13.3.239.

Ferrari, D., Pizzirani, C., Adinolfi, E., Lemoli, R.M., Curti, A., Idzko, M., et al., 2006. The P2X7 receptor: a key player in IL-1 processing and release. J. Immunol. (Baltimore, Md.: 1950) 176 (7), 3877–3883. https://doi.org/10.4049/JIMMUNOL.176.7.3877.

Finnell, J.E., Lombard, C.M., Padi, A.R., Moffitt, C.M., Wilson, L.B., Wood, C.S., Wood, S.K., 2017. Physical versus psychological social stress in male rats reveals distinct cardiovascular, inflammatory and behavioral consequences. PLoS ONE 12 (2), e0172868. https://doi.org/10.1371/journal.pone.0172868.

Finnell, J.E., Moffitt, C.M., Ande Hesser, L., Harrington, E., Melson, M.N., Wood, C.S., Wood, S.K., 2019. The contribution of the locus coeruleus-norepinephrine system in the emergence of defeat-induced inflammatory priming. Brain Behav. Immun. https://doi.org/10.1016/j.bbi.2019.01.021.

Finnell, J.E., Muniz, B.L., Padi, A.R., Lombard, C.M., Moffitt, C.M., Wood, C.S., et al., 2018. Essential role of ovarian hormones in susceptibility to the consequences of witnessing social defeat in female rats. Biol. Psychiatry 84 (5), 372–382. https://doi.org/10.1016/j.biopsych.2018.01.013.

Finta, E.P., Regenold, J.T., Illes, P., 1992. Depression by neuropeptide Y of noradrenergic inhibitory postsynaptic potentials of locus coeruleus neurones. Naunyn-Schmiedeberg's Arch. Pharmacol. 346 (4), 472–474. http://www.ncbi.nlm.nih.gov/pubmed/1436133.

Fong, A.M., Robinson, L.A., Steeber, D.A., Tedder, T.F., Yoshie, O., Imai, T., Patel, D.D., 1998. Fractalkine and CX3CR1 mediate a novel mechanism of leukocyte capture, firm adhesion, and activation under physiologic flow. J. Exp. Med. 188 (8), 1413–1419. https://doi.org/10.1084/jem.188.8.1413.

Franchimont, D., 2004. Overview of the actions of glucocorticoids on the immune response: a good model to characterize new pathways of immunosuppression for new treatment strategies. Ann. N. Y. Acad. Sci. 1024 (1), 124–137. https://doi.org/10.1196/annals.1321.009.

Francis, T.C., Chandra, R., Gaynor, A., Konkalmatt, P., Metzbower, S.R., Evans, B., et al., 2017. Molecular basis of dendritic atrophy and activity in stress susceptibility. Mol. Psychiatry 22 (11), 1512–1519. https://doi.org/10.1038/mp.2017.178.

Frank, M.G., Baratta, M.V., Sprunger, D.B., Watkins, L.R., Maier, S.F., 2007. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-in X ammatory cytokine responses. Brain Behav. Immun. 21, 47–59. https://doi.org/10.1016/j.bbi.2006.03.005.

Gaillard, R.C., Spinedi, E., 1998. Sex- and stress-steroids interactions and the immune system: evidence for a neuroendocrine-immunological sexual dimorphism. Domest. Anim. Endocrinol. 15 (5), 345–352. https://doi.org/10.1016/S0739-7240(98)00028-9.

Gao, S., Sanchez, C., Deviche, P.J., 2017. Corticosterone rapidly suppresses innate immune activity in the house sparrow (Passer domesticus). J. Exp. Biol. 220 (Pt 2), 322–327. https://doi.org/10.1242/jeb.144378.

Gao, Z., Zhu, Q., Zhang, Y., Zhao, Y., Cai, L., Shields, C.B., Cai, J., 2013. Reciprocal modulation between microglia and astrocyte in reactive gliosis following the CNS injury. Mol. Neurobiol. 48 (3), 690–701. https://doi.org/10.1007/s12035-013-8460-4.

Gassen, N.C., Hartmann, J., Zschocke, J., Stepan, J., Hafner, K., Zellner, A., et al., 2014. Association of FKBP51 with priming of autophagy pathways and mediation of antidepressant treatment response: evidence in cells, mice, and humans. PLoS Med. 11 (11), e1001755. https://doi.org/10.1371/journal.pmed.1001755.

Geissmann, F., Jung, S., Littman, D.R., 2003. Blood monocytes consist of two principal subsets with distinct migratory properties. Immunity 19 (1), 71–82. http://www.ncbi.nlm.nih.gov/pubmed/12871640.

Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., et al., 2010. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 330 (6005), 841–845.

Goda, S., Imai, T., Yoshie, O., Yoneda, O., Inoue, H., Nagano, Y., et al., 2000. CX3C-chemokine, fractalkine-enhanced adhesion of THP-1 cells to endothelial cells through integrin-dependent and -independent mechanisms. J. Immunol. 164 (8), 4313–4320. https://doi.org/10.4049/jimmunol.164.8.4313.

Goehler, L.E., Erisir, A., Gaykema, R.P.A., 2006. Neural–immune interface in the rat area postrema. Neuroscience 140 (4), 1415–1434. https://doi.org/10.1016/J.NEUROSCIENCE.2006.03.048.

Golovatscka, V., Ennes, H., Mayer, E.A., Bradesi, S., 2012. Chronic stress-induced changes in pro-inflammatory cytokines and spinal glia markers in the rat: a time course study. NeuroImmunoModulation 19 (6), 367–376. https://doi.org/10.1159/000342092.

Goosens, K.A., 2011. Hippocampal regulation of aversive memories. Curr. Opin. Neurobiol. 21 (3), 460–466. https://doi.org/10.1016/j.conb.2011.04.003.

Grippo, A.J., Francis, J., Beltz, T.G., Felder, R.B., Johnson, A.K., 2005. Neuroendocrine and cytokine profile of chronic mild stress-induced anhedonia. Physiol. Behav. 84 (5), 697–706. https://doi.org/10.1016/J.PHYSBEH.2005.02.011.

Gulbins, A., Schumacher, F., Becker, K.A., Wilker, B., Soddemann, M., Boldrin, F., et al., 2018. Antidepressants act by inducing autophagy controlled by sphingomyelin–ceramide. Mol. Psychiatry 23 (12), 2324–2346. https://doi.org/10.1038/s41380-018-0090-9.

Hanisch, U.-K., Kettenmann, H., 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. 10 (11). https://doi.org/10.1038/nn1997.

Hassani, H., Lucas, G., Rozell, B., Ernfors, P., 2005. Attenuation of acute experimental colitis by preventing NPY Y1 receptor signaling. Am. J. Physiol.-Gastrointestinal Liver Physiol. 288 (3), G550–G556. https://doi.org/10.1152/ajpgi.00182.2004.

Hellwig, S., Brioschi, S., Dieni, S., Frings, L., Masuch, A., Blank, T., Biber, K., 2016. Altered microglia morphology and higher resilience to stress-induced depression-like behavior in CX3CR1-deficient mice. Brain Behav. Immun. 55, 126–137. https://doi.org/10.1016/j.bbi.2015.11.008.

Herold, M.J., McPherson, K.G., Reichardt, H.M., 2006. Glucocorticoids in T cell apoptosis and function. Cell. Mol. Life Sci. 63 (1), 60–72. https://doi.org/10.1007/s00018-005-5390-y.

Hickey, D.K., Fahey, J.V., Wira, C.R., 2012. Mouse estrous cycle regulation of vaginal versus uterine cytokines, chemokines, α-/β-defensins and TLRs. Innate Immun. 19 (2), 121–131. https://doi.org/10.1177/1753425912454026.

Hinwood, M., Morandini, J., Day, T.A., Walker, F.R., 2012. Evidence that microglia mediate the neurobiological effects of chronic psychological stress on the medial prefrontal cortex. Cereb. Cortex 22 (6), 1443–1454. https://doi.org/10.1093/cercor/bhr229.

Hirahara, K., Nakayama, T., 2016. CD4 $^{+}$ T-cell subsets in inflammatory diseases: beyond the T_h1/T_h2 paradigm. Int. Immunol. 28 (4), 163–171. https://doi.org/10.1093/intimm/dxw006.

Hodes, G.E., Pfau, M.L., Leboeuf, M., Golden, S.A., Christoffel, D.J., Bregman, D., et al., 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc. Natl. Acad. Sci. 111 (52), 18799. https://doi.org/10.1073/pnas.1423575112.

Hodes, G.E., Pfau, M.L., Purushothaman, I., Ahn, H.F., Golden, S.A., Christoffel, D.J., et al., 2015. Sex differences in nucleus accumbens transcriptome profiles associated with susceptibility versus resilience to subchronic variable stress. J. Neurosci.: Off. J. Soc. Neurosci. 35 (50), 16362–16376. https://doi.org/10.1523/JNEUROSCI.1392-15.2015.

Hoeffel, G., Ginhoux, F., 2018. Fetal monocytes and the origins of tissue-resident macrophages. Cell. Immunol. 330, 5–15. https://doi.org/10.1016/J.CELLIMM.2018.01.001.

Huang, G.Z., Woolley, C.S., 2012. Estradiol acutely suppresses inhibition in the hippocampus through a sex-specific endocannabinoid and mGluR-dependent mechanism. Neuron 74 (5), 801–808. https://doi.org/10.1016/j.neuron.2012.03.035.

Isingrini, E., Perret, L., Rainer, Q., Amilhon, B., Guma, E., Tanti, A., et al., 2016. Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. Nat. Neurosci. 19 (4), 560–563. https://doi.org/10.1038/nn.4245.

Iwata, M., Ota, K.T., Duman, R.S., 2013. Brain, Behavior, and Immunity The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav. Immun. 31, 105–114. https://doi.org/10.1016/j.bbi.2012.12.008.

Jain, A., Huang, G.Z., Woolley, C.S., 2019. Latent sex differences in molecular signaling that underlies excitatory synaptic potentiation in the hippocampus. J. Neurosci.: Off. J. Soc. Neurosci. 39 (9), 1552–1565. https://doi.org/10.1523/JNEUROSCI.1897-18.2018.

Janeway, C.A., Travers, P., Walport, M., Shlomchik, M.J., 2005. The components of the immune system. Immunobiol.: Immune Syst. Health Disease 1–35. https://doi.org/

10.1017/CBO9780511575266.001.
Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., et al., 2015. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav. Immun. 48, 186–194. https://doi.org/10.1016/j.bbi.2015.03.016.
Jiang, W., Li, Y., Sun, J., Li, L., Li, J.-W., Zhang, C., et al., 2017. Spleen contributes to restraint stress induced changes in blood leukocytes distribution. Sci. Rep. 7 (1), 6501. https://doi.org/10.1038/s41598-017-06956-9.
John, G.R., Lee, S.C., Song, X., Rivieccio, M., 2005. IL-1-regulated responses in astrocytes: relevance to injury and recovery. Glia 176 (June 2004), 161–176. https://doi.org/10.1002/glia.20109.
Johnson, J.D., Campisi, J., Sharkey, C.M., Kennedy, S.L., Nickerson, M., Greenwood, B.N., Fleshner, M., 2005. Catecholamines mediate stress-induced increases in peripheral and central inflammatory cytokines. Neuroscience 135 (4), 1295–1307. https://doi.org/10.1016/J.NEUROSCIENCE.2005.06.090.
Johnson, John D., Zimomra, Z.R., Stewart, L.T., 2013. Beta-adrenergic receptor activation primes microglia cytokine production. J. Neuroimmunol. 254 (1–2), 161–164. https://doi.org/10.1016/J.JNEUROIM.2012.08.007.
Jones, M.E., Lebonville, C.L., Barrus, D., Lysle, D.T., 2015. The role of brain interleukin-1 in stress-enhanced fear learning. Neuropsychopharmacology 40 (5), 1289–1296. https://doi.org/10.1038/npp.2014.317.
Jones, M.E., Lebonville, C.L., Paniccia, J.E., Balentine, M.E., Reissner, K.J., Lysle, D.T., 2018a. Hippocampal interleukin-1 mediates stress-enhanced fear learning: a potential role for astrocyte-derived interleukin-1β. Brain Behav. Immun. 67, 355–363. https://doi.org/10.1016/j.bbi.2017.09.016.
Jones, M.E., Paniccia, J.E., Lebonville, C.L., Reissner, K.J., Lysle, D.T., 2018b. Chemogenetic manipulation of dorsal hippocampal astrocytes protects against the development of stress-enhanced fear learning. Neuroscience 388, 45–56. https://doi.org/10.1016/J.NEUROSCIENCE.2018.07.015.
Jung, S.H., Wang, Y., Kim, T., Tarr, A., Reader, B., Powell, N., Sheridan, J.F., 2015. Molecular mechanisms of repeated social defeat-induced glucocorticoid resistance: role of microRNA. Brain Behav. Immun. 44, 195–206. https://doi.org/10.1016/j.bbi.2014.09.015.
Kastin, A., Pan, W., 2008. Blood-brain barrier and feeding: regulatory roles of saturable transport systems for ingestive peptides. Curr. Pharm. Des. 14 (16), 1615–1619. https://doi.org/10.2174/138161208784705423.
Kim, E.J., Pellman, B., Kim, J.J., 2015. Stress effects on the hippocampus: a critical review. Learn. Mem. (Cold Spring Harbor, N.Y.) 22 (9), 411–416. https://doi.org/10.1101/lm.037291.114.
Keselman, A., Heller, N., 2015. Estrogen signaling modulates allergic inflammation and contributes to sex differences in Asthma. Front. Immunol. 6 (568), 1–14 (in press).
Kim, J., Basak, J.M., Holtzman, D.M., 2009. Review the role of apolipoprotein E in Alzheimer's disease. Neuron 63 (3), 287–303. https://doi.org/10.1016/j.neuron.2009.06.026.
Kim, R.Y., Hoffman, A.S., Itoh, N., Ao, Y., Spence, R., Sofroniew, M.V., Voskuhl, R.R., 2014. Astrocyte CCL2 sustains immune cell in fi ltration in chronic experimental autoimmune encephalomyelitis. J. Neuroimmunol. 274 (1–2), 53–61. https://doi.org/10.1016/j.jneuroim.2014.06.009.
Kinsey, S.G., Bailey, M.T., Sheridan, J.F., Padgett, D.A., 2008. The inflammatory response to social defeat is increased in older mice. Physiol. Behav. 93 (3), 628–636. https://doi.org/10.1016/j.physbeh.2007.11.003.
Kirshenbaum, G.S., Lieberman, S.R., Briner, T.J., Leonardo, E.D., Dranovsky, A., 2014. Adolescent but not adult-born neurons are critical for susceptibility to chronic social defeat. Front. Behav. Neurosci. 8, 289. https://doi.org/10.3389/fnbeh.2014.00289.
Koo, J.W., Duman, R.S., 2008. IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. PNAS 105 (2), 751–756. https://doi.org/10.1073/pnas.0708092105.
Koo, J.W., Duman, R.S., 2009a. Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression. Curr. Opin. Investig. Drugs (Lond., Engl.: 2000) 10 (7), 664–671.
Koo, J.W., Duman, R.S., 2009b. Interleukin-1 receptor null mutant mice show decreased anxiety-like behavior and enhanced fear memory. Neurosci. Lett. 456 (1), 39–43. https://doi.org/10.1016/j.neulet.2009.03.068.
Kopp, B.L., Wick, D., Herman, J.P., 2013. Differential effects of homotypic vs. heterotypic chronic stress regimens on microglial activation in the prefrontal cortex. Physiol. Behav. 2, 1–17. https://doi.org/10.1016/j.physbeh.2013.05.030.Differential.
Kroemer, G., Mariño, G., Levine, B., 2010. Autophagy and the integrated stress response. Mol. Cell 40 (2), 280–293. https://doi.org/10.1016/j.molcel.2010.09.023.
Lacroix, S., Feinstein, D., Rivest, S., 1998. The bacterial endotoxin lipopolysaccharide has the ability to target the brain in upregulating its membrane CD14 receptor within specific cellular populations. Brain Pathol. 8 (4), 625–640. https://doi.org/10.1111/j.1750-3639.1998.tb00189.x.
Laflamme, N., Rivest, S., 2001. Toll-like receptor 4: the missing link of the cerebral innate immune response triggered by circulating gram-negative bacterial cell wall components. FASEB J. 15 (1), 155–163. https://doi.org/10.1096/fj.00-0339com.
Lagace, D.C., Donovan, M.H., DeCarolis, N.A., Farnbauch, L.A., Malhotra, S., Berton, O., et al., 2010. Adult hippocampal neurogenesis is functionally important for stress-induced social avoidance. PNAS 107 (9), 4436–4441. https://doi.org/10.1073/pnas.0910072107.
Lai, A.Y., Kondo, M., 2008. T and B lymphocyte differentiation from hematopoietic stem cell. Semin. Immunol. 20 (4), 207–212. https://doi.org/10.1016/J.SMIM.2008.05.002.
Laidlaw, B.J., Craft, J.E., Kaech, S.M., 2016. The multifaceted role of CD4+ T cells in CD8+ T cell memory. Nat. Rev. Immunol. 16 (2), 102–111. https://doi.org/10.1038/nri.2015.10.
Lampron, A., ElAli, A., Rivest, S., 2013. Innate immunity in the CNS: redefining the relationship between the CNS and its environment. Neuron 78 (2), 214–232. https://doi.org/10.1016/j.neuron.2013.04.005.
Langgartner, D., Lowry, C.A., Reber, S.O., 2019. Old friends, immunoregulation, and stress resilience. Eur. J. Physiol. 471, 237–269. https://doi.org/10.1007/s00424-018-2228-7.
LaPlant, Q., Chakravarty, S., Vialou, V., Mukherjee, S., Koo, J.W., Kalahasti, G., et al., 2009. Role of nuclear factor κB in ovarian hormone-mediated stress hypersensitivity in female mice. Biol. Psychiatry 65 (10), 874–880. https://doi.org/10.1016/j.biopsych.2009.01.024.
Lee, H.-M., Kim, J.-J., Kim, H.J., Shong, M., Ku, B.J., Jo, E.-K., 2013. Upregulated NLRP3 inflammasome activation in patients with type 2 diabetes. Diabetes 62 (1), 194–204. https://doi.org/10.2337/db12-0420.
Li, M.-X., Zheng, H.-L., Luo, Y., He, J.-G., Wang, W., Han, J., et al., 2018a. Gene deficiency and pharmacological inhibition of caspase-1 confers resilience to chronic social defeat stress via regulating the stability of surface AMPARs. Mol. Psychiatry 23 (3), 556–568. https://doi.org/10.1038/mp.2017.76.
Li, Y., Jiang, W., Li, Z.-Z., Zhang, C., Huang, C., Yang, J., et al., 2018b. Repetitive restraint stress changes spleen immune cell subsets through glucocorticoid receptor or β-adrenergic receptor in a stage dependent manner. Biochem. Biophys. Res. Commun. 495 (1), 1108–1114. https://doi.org/10.1016/j.bbrc.2017.11.148.
Liang, S., Wu, X., Hu, X., Wang, T., Jin, F., 2018. Recognizing depression from the microbiota–gut–brain axis. Int. J. Mol. Sci. 19 (6). https://doi.org/10.3390/ijms19061592.
Liu, Y.N., Peng, Y.L., Wu, T.Y., Zhang, Y., Lian, Y.J., Yang, Y.Y., Kelley, K.W., Jiang, C.L., et al., 2015;al., n.d.. TNFα mediates stress-induced depression by upregulating indoleamine 2,3-dioxygenase in a mouse model of unpredictable chronic mild stress. Eur. Cytokine Netw. 26 (1), 15–25. https://doi.org/10.1684/ecn.2015.0362.
Lopez-Castejon, G., Brough, D., 2011. Understanding the mechanism of IL-1β secretion. Cytokine Growth Factor Rev. 22 (4), 189–195. https://doi.org/10.1016/j.cytogfr.2011.10.001.
Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., et al., 1998. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10 (4), 313–318.
Main, B.S., Villapol, S., Sloley, S.S., Barton, D.J., Parsadanian, M., Agbaegbu, C., et al., 2018. Apolipoprotein E4 impairs spontaneous blood brain barrier repair following traumatic brain injury. Mol. Neurodegenerat. 1–18.
Malek, H., Ebadzadeh, M.M., Safabakhsh, R., Razavi, A., Zaringhalam, J., 2015. Dynamics of the HPA axis and inflammatory cytokines: insights from mathematical modeling. Comput. Biol. Med. 67, 1–12. https://doi.org/10.1016/j.compbiomed.2015.09.018.
Maltz, R.M., Keirsey, J., Kim, S.C., Mackos, A.R., Gharaibeh, R.Z., Moore, C.C., et al., 2018. Social stress affects colonic inflammation, the gut microbiome, and short chain fatty acid levels and receptors. J. Pediatr. Gastroenterol. Nutr. https://doi.org/10.1097/MPG.0000000000002226.
Martin, C.J., Peters, K.N., Behar, S.M., 2014. Macrophages clean up: efferocytosis and microbial control. Curr. Opin. Microbiol. 17, 17–23. https://doi.org/10.1016/j.mib.2013.10.007.
McBride, J.A., Striker, R., 2017. Imbalance in the game of T cells: what can the CD4/CD8 T-cell ratio tell us about HIV and health? PLoS Pathog. 13 (11), e1006624. https://doi.org/10.1371/journal.ppat.1006624.
McKim, D.B., Yin, W., Wang, Y., Cole, S.W., Godbout, J.P., Sheridan, J.F., 2018. Social stress mobilizes hematopoietic stem cells to establish persistent splenic myelopoiesis. Cell Rep. 25 (9), 2552–2562.e3. https://doi.org/10.1016/j.celrep.2018.10.102.
McMurray, R.W., Suwannaroj, S., Ndebele, K., Jenkins, J.K., 2001. Differential effects of sex steroids on T and B cells: modulation of cell cycle phase distribution, apoptosis and bcl-2 protein levels. Pathobiology 69 (1), 44–58 https://doi.org/48757.
Mebius, R.E., Kraal, G., 2005. Structure and function of the spleen. Nat. Rev. Immunol. 5 (8), 606–616. https://doi.org/10.1038/nri1669.
Menard, C., Pfau, M.L., Hodes, G.E., Kana, V., Victoria, X., Bouchard, S., et al., 2017. Social stress induces neurovascular pathology promoting depression. Nat. Neurosci. 20 (12), 1752–1760. https://doi.org/10.1038/s41593-017-0010-3.Social.
Mileva, G.R., Rooke, J., Ismail, N., Bielajew, C., 2017. Corticosterone and immune cytokine characterization following environmental manipulation in female WKY rats. Behav. Brain Res. 316, 197–204. https://doi.org/10.1016/j.bbr.2016.09.004.
Milior, G., Lecours, C., Samson, L., Bisht, K., Poggini, S., Pagani, F., et al., 2016. Fractalkine receptor deficiency impairs microglial and neuronal responsiveness to chronic stress. Brain Behav. Immun. 55, 114–125. https://doi.org/10.1016/j.bbi.2015.07.024.
Miller, A.H., Spencer, R.L., Pearce, B.D., Pisell, T.L., Azrieli, Y., Tanapat, P., et al., 1998. Glucocorticoid receptors are differentially expressed in the cells and tissues of the immune system. Cell. Immunol. 186 (1), 45–54. https://doi.org/10.1006/cimm.1998.1293.
Mills, C.D., 2012. M1 and M2 macrophages: oracles of health and disease. Crit. Rev. Immunol. 32 (6), 463–488.
Mittal, R., Debs, L.H., Patel, A.P., Nguyen, D., Patel, K., O'Connor, G., et al., 2017. Neurotransmitters: the critical modulators regulating gut-brain axis. J. Cell. Physiol. 232 (9), 2359–2372. https://doi.org/10.1002/jcp.25518.
Mizuno, T., Kawanokuchi, J., Numata, K., Suzumura, A., 2003. Production and neuroprotective functions of fractalkine in the central nervous system. Brain Res. 979 (1–2), 65–70. https://doi.org/10.1016/S0006-8993(03)02867-1.
Molero, L., et al., 2002. Expression of estrogen receptor subtypes and neuronal nitric oxide synthase in neutrophils from women and men: regulation by estroge. Cardiovasc. Res. 56, 43–51 (in press).
Monif, M., Reid, C.A., Powell, K.L., Smart, M.L., Williams, D.A., 2009. The P2X7 receptor drives microglial activation and proliferation: a trophic role for P2X7R pore. J. Neurosci.: Off. J. Soc. Neurosci. 29 (12), 3781–3791 https://doi.org/20026618.
Moreno, M., Bannerman, P., Ma, J., Guo, F., Miers, X.L., Soulika, A.M., Pleasure, D., 2014. Conditional ablation of astroglial CCL2 suppresses CNS accumulation of M1

macrophages and preserves axons in mice with MOG. Peptide EAE 34 (012886), 8175–8185. https://doi.org/10.1523/JNEUROSCI.1137-14.2014.
Nadeau, S., Rivest, S., 1999. Regulation of the gene encoding tumor necrosis factor alpha (TNF-α) in the rat brain and pituitary in response to different models of systemic immune challenge. J. Neuropathol. Exp. Neurol. 58 (1), 61–77. https://doi.org/10.1097/00005072-199901000-00008.
Nelson, L.H., Warden, S., Lenz, K.M., 2017. Sex differences in microglial phagocytosis in the neonatal hippocampus. Brain Behav. Immun. 64, 11–22. https://doi.org/10.1016/j.bbi.2017.03.010.
Neufeld, K.M., Kang, N., Bienenstock, J., Foster, J.A., 2011. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterol. Motil.: Off. J. Eur. Gastrointest. Motil. Soc. 23 (3). https://doi.org/10.1111/j.1365-2982.2010.01620.x. 255–264, e119.
Nikodemova, M., Kimyon, R.S., De, I., Small, A.L., Collier, L.S., Watters, J.J., 2015. Microglial numbers attain adult levels after undergoing a rapid decrease in cell number in the third postnatal week. J. Neuroimmunol. 278, 280–288. https://doi.org/10.1016/j.jneuroim.2014.11.018.
Nimmerjahn, A., Kirchhoff, F., Helmchen, F., 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308 (5726), 1314–1318.
Niraula, A., Wang, Y., Godbout, J.P., Sheridan, J.F., 2018. Corticosterone production during repeated social defeat causes monocyte mobilization from the bone marrow, glucocorticoid resistance and neurovascular adhesion molecule expression. The Journal of Neuroscience 38 (9), 2568–2617. https://doi.org/10.1523/JNEUROSCI.2568-17.2018.
O'Connor, J.C., Lawson, M.A., André, C., Moreau, M., Lestage, J., Castanon, N., et al., 2009. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol. Psychiatry 14 (5), 511–522. https://doi.org/10.1038/sj.mp.4002148.
Osburg, B., Peiser, C., Dömling, D., Schomburg, L., Ko, Y.T., Voigt, K., Bickel, U., 2002. Effect of endotoxin on expression of TNF receptors and transport of TNF-α at the blood-brain barrier of the rat. Am. J. Physiol.-Endocrinol. Metabol. 283 (5), E899–E908. https://doi.org/10.1152/ajpendo.00436.2001.
Pan, W., Kastin, A.J., 2008. Cytokine transport across the injured blood-spinal cord barrier. Curr. Pharm. Des. 14 (16), 1620–1624. http://www.ncbi.nlm.nih.gov/pubmed/18673204.
Pandya, M., Altinay, M., Malone, D., Anand, A., 2013. Where is the brain in depression? Curr Psychiatry Rep 14 (6), 634–642. https://doi.org/10.1007/s11920-012-0322-7. Where.
Park, J.H., Yoo, K.-Y., Lee, C.H., Kim, I.H., Shin, B.N., Choi, J.H., et al., 2011. Comparison of glucocorticoid receptor and ionized calcium-binding adapter molecule 1 immunoreactivity in the adult and aged gerbil hippocampus following repeated restraint stress. Neurochem. Res. 36 (6), 1037–1045. https://doi.org/10.1007/s11064-011-0444-z.
Pelekanou, V., Kampa, M., Kiagiadaki, F., Deli, A., Theodoropoulos, P., Agrogiannis, G., et al., 2016. Estrogen anti-inflammatory activity on human monocytes is mediated through cross-talk between estrogen receptor ERα36 and GPR30/GPER1. J. Leukoc. Biol. 99 (2), 333–347. https://doi.org/10.1189/jlb.3A0914-430RR.
Pfau, M.L., Menard, C., Cathomas, F., Desland, F., Kana, V., Chan, K.L., et al., 2019. Role of monocyte-derived microRNA106b~25 in resilience to social stress. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2019.02.023.
Piechota, M., Korostynski, M., Golda, S., Ficek, J., Jantas, D., Barbara, Z., Przewlocki, R., 2017. Transcriptional signatures of steroid hormones in the striatal neurons and astrocytes. BMC Neurosci. 18 (1), 37. https://doi.org/10.1186/s12868-017-0352-5.
Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., et al., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am. J. Psychiatry 166 (6), 702–710. https://doi.org/10.1176/appi.ajp.2008.08081201.
Pollak, Y., Yirmiya, R., 2002. Cytokine-induced changes in mood and behaviour: implications for "depression due to a general medical condition", immunotherapy and antidepressive treatment. Int. J. Neuropsychopharmacol. 5 (4), 389–399. https://doi.org/10.1017/S1461145702003152.
Porterfield, V.M., Zimomra, Z.R., Caldwell, E.A., Camp, R.M., Gabella, K.M., Johnson, J.D., 2011. Rat strain differences in restraint stress-induced brain cytokines. Neuroscience 188, 48–54. https://doi.org/10.1016/J.NEUROSCIENCE.2011.05.023.
Powell, N.D., Sloan, E.K., Bailey, M.T., Arevalo, J.M.G., Miller, G.E., Chen, E., et al., 2013. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via -adrenergic induction of myelopoiesis. Proc. Natl. Acad. Sci. 110 (41), 16574–16579. https://doi.org/10.1073/pnas.1310655110.
Powell, Nicole D., Bailey, M.T., Mays, J.W., Stiner-jones, L.M., Hanke, M.L., Padgett, D.A., Sheridan, J.F., 2009. Brain, Behavior, and Immunity Repeated social defeat activates dendritic cells and enhances Toll-like receptor dependent cytokine secretion. Brain Behav. Immun. 23 (2), 225–231. https://doi.org/10.1016/j.bbi.2008.09.010.
Quan, N., 2008. Immune-to-brain signaling: how important are the blood-brain barrier-independent pathways? Mol. Neurobiol. 37 (2–3), 142–152. https://doi.org/10.1007/s12035-008-8026-z.
Quan, N., Avitsur, R., Stark, J.L., He, L., Lai, W., Dhabhar, F., Sheridan, J.F., 2003. Molecular mechanisms of glucocorticoid resistance in splenocytes of socially stressed male mice. J. Neuroimmunol. 137 (1–2), 51–58.
Rainville, J., Tsyglakova, M., Hodes, G., 2018. Deciphering sex differences in the immune system and depression. Front. Neuroendocrinol. 50, 67–90. https://doi.org/10.1016/j.yfrne.2017.12.004.
Ransohoff, R.M., Tani, M., 1998. Do chemokines mediate leukocyte recruitment in post-traumatic CNS inflammation? Trends Neurosci. 2236 (97).
Rao, M., Gershon, M.D., 2016. The bowel and beyond: the enteric nervous system in neurological disorders. Nat. Rev. Gastroenterol. Hepatol. 13 (9), 517–528. https://doi.org/10.1038/nrgastro.2016.107.
Rimmerman, N., Schottlender, N., Reshef, R., Dan-Goor, N., Yirmiya, R., 2017. The hippocampal transcriptomic signature of stress resilience in mice with microglial fractalkine receptor (CX3CR1) deficiency. Brain Behav. Immun. 61, 184–196. https://doi.org/10.1016/J.BBI.2016.11.023.
Rodrigues, R.J., Tomé, A.R., Cunha, R.A., 2015. ATP as a multi-target danger signal in the brain. Front. Neurosci. 9, 148. https://doi.org/10.3389/FNINS.2015.00148.
Rodríguez-Arias, M., Montagud-Romero, S., Carrion, A.M.G., Ferrer-Perez, C., Pérez-Villalba, A., Marco, E., et al., 2018. Social stress during adolescence activates long-term microglia inflammation insult in reward processing nuclei. PloS One 1–19.
Roque, A., Ochoa-zarzosa, A., Torner, L., 2016. Maternal separation activates microglial cells and induces an inflammatory response in the hippocampus of male rat pups, independently of hypothalamic and peripheral cytokine levels. Brain Behav. Immun. 55, 39–48. https://doi.org/10.1016/j.bbi.2015.09.017.
Rosen, S., Ham, B., Mogil, J.S., 2017. Sex differences in neuroimmunity and pain. J. Neurosci. Res. 95 (1–2), 500–508. https://doi.org/10.1002/jnr.23831.
Ross, S.B., Stenfors, C., 2015. DSP4, a selective neurotoxin for the locus coeruleus noradrenergic system. A review of its mode of action. Neurotox. Res. 27 (1), 15–30. https://doi.org/10.1007/s12640-014-9482-z.
Sántha, P., Veszelka, S., Hoyk, Z., Mészáros, M., Walter, F.R., 2016. Restraint stress-induced morphological changes at the blood-brain barrier in adult rats. Front. Mol. Neurosci. 8 (January), 1–15. https://doi.org/10.3389/fnmol.2015.00088.
Schafer, D.P., Lehrman, E.K., Kautzman, A.G., Koyama, R., Mardinly, A.R., Yamasaki, R., et al., 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74 (4), 691–705. https://doi.org/10.1016/j.neuron.2012.03.026.
Schafer, D.P., Stevens, B., 2013. Phagocytic glial cells: sculpting synaptic circuits in the developing nervous system. Curr. Opin. Neurobiol. 23 (6), 1034–1040. https://doi.org/10.1016/j.conb.2013.09.012.
Sharma, R., Rooke, J., Kolmogorova, D., Melanson, B., Mallet, J.-F., Matar, C., et al., 2018. Sex differences in the peripheral and central immune responses following lipopolysaccharide treatment in pubertal and adult CD-1 mice. Int. J. Dev. Neurosci.: Off. J. Int. Soc. Dev. Neurosci. 71, 94–104. https://doi.org/10.1016/j.ijdevneu.2018.07.012.
Shreiner, A.B., Kao, J.Y., Young, V.B., 2015. The gut microbiome in health and in disease. Curr. Opin. Gastroenterol. 31 (1), 69–75. https://doi.org/10.1097/MOG.0000000000000139.
Silberman, D.M., Ayelli-Edgar, V., Zorrilla-Zubilete, M., Zieher, L.M., Genaro, A.M., 2004. Impaired T-cell dependent humoral response and its relationship with T lymphocyte sensitivity to stress hormones in a chronic mild stress model of depression. Brain Behav. Immun. 18 (1), 81–90.
Silverman, M.N., Pearce, B.D., Biron, C.A., Miller, A.H., 2005. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. Viral Immunol. 18 (1), 41–78. https://doi.org/10.1089/vim.2005.18.41.
Simard, M., Couldwell, W.T., Zhang, W., Song, H., Liu, S., Cotrina, M.L., et al., 1999. Glucocorticoids-potent modulators of astrocytic calcium signaling. Glia 28 (1), 1–12. https://doi.org/10.1002/(SICI)1098-1136(199910)28:1<1::AID-GLIA1>3.0.CO;2-4.
Simayi, A., Mohemaiti, P., 2019. Risk and protective factors of co-morbid depression in patients with type 2 diabetes mellitus: a meta analysis. Endocr. J. https://doi.org/10.1507/endocrj.EJ18-0579.
Sofroniew, M.V., 2015. Astrocyte barriers to neurotoxic inflammation. Nat. Rev. Neurosci. 16 (5), 249–263. https://doi.org/10.1038/nrn3898.
Springer, T.A., 1994. Traffic signals for lymphocyte review recirculation and leukocyteemigration: the multistep paradigm. Cell 76, 301–314 https://doi.org/papers2://publication/uuid/BF267575-2D14-4291-9E26-025360D4A4BF.
Stark, J.L., Avitsur, R., Padgett, D.A., Campbell, K.A., Beck, F.M., Sheridan, J.F., 2001. Social stress induces glucocorticoid resistance in macrophages. Am. J. Physiol.-Regulat. Integrat. Compara. Physiol. 280 (6), R1799–R1805. https://doi.org/10.1152/ajpregu.2001.280.6.R1799.
Stelzhammer, V., Ozcan, S., Gottschalk, M.G., Steeb, H., Hodes, G.E., Guest, P.C., et al., 2015. Central and peripheral changes underlying susceptibility and resistance to social defeat stress – a proteomic profiling study. Diagnost. Neuropsychiatry 1 (1–4), 1–7. https://doi.org/10.1016/j.dineu.2015.08.001.
Stout, C.E., Costantin, J.L., Naus, C.C.G., Charles, A.C., 2002. Intercellular calcium signaling in astrocytes via ATP release through connexin hemichannels. J. Biol. Chem. 277 (12), 10482–10488. https://doi.org/10.1074/jbc.M109902200.
Sugama, S., Fujita, M., Hashimoto, M., Conti, B., 2007. Stress induced morphological microglial activation in the rodent brain: involvement of interleukin-18. Neuroscience 146 (3), 1388–1399. https://doi.org/10.1016/j.neuroscience.2007.02.043.
Sugama, S., Takenouchi, T., Fujita, M., Kitani, H., Conti, B., Hashimoto, M., 2013. Corticosteroids limit microglial activation occurring during acute stress. Neuroscience 232, 13–20. https://doi.org/10.1016/j.neuroscience.2012.12.012.
Sukoff Rizzo, S.J., Neal, S.J., Hughes, Z.A., Beyna, M., Rosenzweig-Lipson, S., Moss, S.J., Brandon, N.J., 2012. Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. Transl. Psychiatry 2 (12), e199. https://doi.org/10.1038/tp.2012.120.
Takatsuru, Y., Nabekura, J., Ishikawa, T., Kohsaka, S.ichi, Koibuchi, N., 2015. Early-life stress increases the motility of microglia in adulthood. J. Physiol. Sci. 65 (2), 187–194. https://doi.org/10.1007/s12576-015-0361-z.
Teng, Z., Guo, Z., Zhong, J., Cheng, C., Huang, Z., Wu, Y., 2017. ApoE influences the blood-brain barrier through the NF-κB/MMP-9 pathway after traumatic brain injury. Sci. Rep. 3–10. https://doi.org/10.1038/s41598-017-06932-3.
Tertil, M., Skupio, U., Barut, J., Dubovyk, V., Wawrzczak-bargiela, A., Soltys, Z., et al., 2018. Glucocorticoid receptor signaling in astrocytes is required for aversive memory formation. Transl. Psychiatry. https://doi.org/10.1038/s41398-018-0300-x.

Trigunaite, A., Dimo, J., 2015. Suppressive effects of androgens on the immune system. Cell. Immunol. 294 (2), 87–94. https://doi.org/10.1016/J.CELLIMM.2015.02.004.
Tuckermann, J.P., Kleiman, A., McPherson, K.G., Reichardt, H.M., 2005. Molecular mechanisms of glucocorticoids in the control of inflammation and lymphocyte apoptosis. Crit. Rev. Clin. Lab. Sci. 42 (1), 71–104.
Tuscher, J.J., Luine, V., Frankfurt, M., Frick, K.M., 2016. Estradiol-Mediated Spine Changes in the dorsal hippocampus and medial prefrontal cortex of ovariectomized female mice depend on ERK and mTOR activation in the dorsal hippocampus. J. Neurosci. 36 (5), 1483–1489. https://doi.org/10.1523/JNEUROSCI.3135-15.2016.
Tynan, R.J., Naicker, S., Hinwood, M., Nalivaiko, E., Buller, K.M., Pow, D.V., et al., 2010. Brain, behavior, and immunity chronic stress alters the density and morphology of microglia in a subset of stress-responsive brain regions. Brain Behav. Immun. 24 (7), 1058–1068. https://doi.org/10.1016/j.bbi.2010.02.001.
Vallières, L., Rivest, S., 1997. Regulation of the genes encoding interleukin-6, its receptor, and gp130 in the rat brain in response to the immune activator lipopolysaccharide and the proinflammatory cytokine interleukin-1β. J. Neurochem. 69 (4), 1668–1683. https://doi.org/10.1046/j.1471-4159.1997.69041668.x.
Varatharaj, A., Galea, I., 2017. The blood-brain barrier in systemic inflammation. Brain Behav. Immun. 60, 1–12. https://doi.org/10.1016/J.BBI.2016.03.010.
Voorhees, J.L., Tarr, A.J., Wohleb, E.S., Godbout, J.P., Mo, X., Sheridan, J.F., et al., 2013. Prolonged restraint stress increases IL-6, reduces IL-10, and causes persistent depressive-like behavior that is reversed by recombinant IL-10. PLoS ONE 8 (3), e58488. https://doi.org/10.1371/journal.pone.0058488.
Walf, A.A., Paris, J.J., Frye, C.A., 2009. Chronic estradiol replacement to aged female rats reduces anxiety-like and depression-like behavior and enhances cognitive performance. Psychoneuroendocrinology 34 (6), 909–916. https://doi.org/10.1016/J.PSYNEUEN.2009.01.004.
Wang, Y., Xie, L., Gao, C., Zhai, L., Zhang, N., Guo, L., 2018. Astrocytes activation contributes to the antidepressant-like effect of ketamine but not scopolamine. Pharmacol. Biochem. Behav. 170, 1–8. https://doi.org/10.1016/J.PBB.2018.05.001.
Weber, M.D., Godbout, J.P., Sheridan, J.F., 2017. Repeated social defeat, neuroinflammation, and behavior: monocytes carry the signal. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 42 (1), 46–61. https://doi.org/10.1038/npp.2016.102.
Winkler, Z., Kuti, D., Ferenczi, S., Gulyás, K., Polyák, Á., Kovács, K.J., 2017. Impaired microglia fractalkine signaling affects stress reaction and coping style in mice. Behav. Brain Res. 334 (July), 119–128. https://doi.org/10.1016/j.bbr.2017.07.023.
Wohleb, E.S., Fenn, A.M., Pacenta, A.M., Powell, N.D., John, F., Godbout, J.P., 2012. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social withdrawal in socially defeated mice. Psychoneuroendocrinology 37 (9), 1491–1505. https://doi.org/10.1016/j.psyneuen.2012.02.003.Peripheral.
Wohleb, E.S., Hanke, M.L., Corona, A.W., Powell, N.D., Stiner, L.M., Bailey, M.T., et al., 2011. β-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J. Neurosci.: Off. J. Soc. Neurosci. 31 (17), 6277–6288. https://doi.org/10.1523/JNEUROSCI.0450-11.2011.
Wohleb, E.S., Powell, N.D., Godbout, J.P., Sheridan, J.F., 2013. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behaviour. J. Neurosci. 33 (34), 13820–13833. https://doi.org/10.1523/JNEUROSCI.1671-13.2013.
Wood, S.K., Wood, C.S., Lombard, C.M., Lee, C.S., Zhang, X.-Y., Finnell, J.E., Valentino, R.J., 2015. Inflammatory factors mediate vulnerability to a social stress-induced depressive-like phenotype in passive coping rats. Biol. Psychiatry 78 (1), 38–48. https://doi.org/10.1016/j.biopsych.2014.10.026.
Woolley, C.S., Weiland, N.G., McEwen, B.S., Schwartzkroin, P.A., 1997. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. J. Neurosci.: Off. J. Soc. Neurosci. 17 (5), 1848–1859. https://doi.org/10.1523/JNEUROSCI.17-05-01848.1997.
Xia, C.-Y., Wang, Z.-Z., Zhang, Z., Chen, J., Wang, Y.-Y., Lou, Y.-X., et al., 2018. Corticosterone impairs gap junctions in the prefrontal cortical and hippocampal astrocytes via different mechanisms. Neuropharmacology 131, 20–30. https://doi.org/10.1016/J.NEUROPHARM.2017.12.003.
Xu, Q., Bernardo, A., Walker, D., Kanegawa, T., Mahley, R.W., Huang, Y., 2006. Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus. J. Neurosci. 26 (19), 4985–4994. https://doi.org/10.1523/JNEUROSCI.5476-05.2006.
Xu, Y., Sheng, H., Tang, Z., Lu, J., Ni, X., 2015. Inflammation and increased IDO in hippocampus contribute to depression-like behavior induced by estrogen deficiency. Behav. Brain Res. 288, 71–78. https://doi.org/10.1016/J.BBR.2015.04.017.
Yang, C.-A., Huang, S.-T., Chiang, B.-L., 2015a. Sex-dependent differential activation of NLRP3 and AIM2 inflammasomes in SLE macrophages. Rheumatology 54 (2), 324–331. https://doi.org/10.1093/rheumatology/keu318.
Yang, C., Shirayama, Y., Zhang, J.-C., Ren, Q., Hashimoto, K., 2015b. Peripheral interleukin-6 promotes resilience versus susceptibility to inescapable electric stress. Acta Neuropsychiatrica 27 (5), 312–316. https://doi.org/10.1017/neu.2015.36.
Yang, Yan, Cui, Y., Sang, K., Dong, Y., Ni, Z., Ma, S., Hu, H., 2018. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature 554 (7692), 317–322. https://doi.org/10.1038/nature25509.
Yang, Yang, Hu, Z., Du, X., Davies, H., Huo, X., Fang, M., 2017. miR-16 and fluoxetine both reverse autophagic and apoptotic change in chronic unpredictable mild stress model rats. Front. Neurosci. 11, 428. https://doi.org/10.3389/fnins.2017.00428.
Yirmiya, R., 1996. Endotoxin produces a depressive-like episode in rats. Brain Res. 711 (1–2), 163–174.
Zhang, C.C., 2012. Hematopoietic stem cells: interplay with immunity. Am. J. Blood Res. 2 (4), 219–227. http://www.ncbi.nlm.nih.gov/pubmed/23226622.
Zhang, J., An, J., 2007. Cytokines, inflammation, and pain. Int. Anesthesiol. Clin. 45 (2), 27–37.
Zhao, Z., Zhang, L., Guo, X.-D., Cao, L.-L., Xue, T.-F., Zhao, X.-J., et al., 2017. Rosiglitazone exerts an anti-depressive effect in unpredictable chronic mild-stress-induced depressive mice by maintaining essential neuron autophagy and inhibiting excessive astrocytic apoptosis. Front. Mol. Neurosci. 10, 293. https://doi.org/10.3389/fnmol.2017.00293.
Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., et al., 2016a. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol. Psychiatry 21 (6), 786–796. https://doi.org/10.1038/mp.2016.44.
Zheng, X., Ma, S., Kang, A., Wu, M., Wang, L., Wang, Q., 2016b. Chemical dampening of Ly6C hi monocytes in the periphery produces anti-depressant effects in mice. Nature Publ. Group 1–14. https://doi.org/10.1038/srep19406.
Zhong, Z., Sanchez-Lopez, E., Karin, M., 2016. Autophagy, NLRP3 inflammasome and auto-inflammatory/immune diseases. Clin. Exp. Rheumatol. 34 (4 Suppl 98), 12–16. http://www.ncbi.nlm.nih.gov/pubmed/27586797.
Zierau, O., Zenclussen, A., Jensen, F., 2012. Role of female sex hormones, estradiol and progesterone, in mast cell behavior Oliver. Front. Immunol. 3 (169), 1–4. https://doi.org/10.3389/fimmu.2012.00169.