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Depression's Unholy Trinity: Dysregulated Stress, Immunity, and the Microbiome

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Abstract

Depression remains one of the most prevalent psychiatric disorders, with many patients not responding adequately to available treatments. Chronic or early-life stress is one of the key risk factors for depression. In addition, a growing body of data implicates chronic inflammation as a major player in depression pathogenesis. More recently, the gut microbiota has emerged as an important regulator of brain and behavior and also has been linked to depression. However, how this holy trinity of risk factors interact to maintain physiological homeostasis in the brain and body is not fully understood. In this review, we integrate the available data from animal and human studies on these three factors in the etiology and progression of depression. We also focus on the processes by which this microbiota-immune-stress matrix may influence centrally mediated events and on possible therapeutic interventions to correct imbalances in this triune.



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1. DEPRESSION

Major depressive disorder (MDD) is a complex debilitating psychiatric disorder that is estimated to account for approximately 10% of worldwide disability; according to the World Health Organization, it is the current leading cause of disability worldwide. Classic symptoms include depressed mood, anxiety, anhedonia, and cognitive impairments that profoundly affect patients' quality of life. Despite major investments over the last decades into understanding the etiology, progression, and biology of this disorder, its molecular and cellular bases remain poorly defined. There is an increasing emphasis on the fact that depression does not affect brain function exclusively, but manifests as a whole-body disorder affecting almost all of the major corporeal systems.

Antidepressant treatments classically involve the manipulation of the serotonergic and noreadrenergic systems. However, these antidepressants are suboptimal, as they have a slow onset of action and adverse side effects that sometimes reduce patient compliance and thus limit their efficacy (O'Leary et al. 2015). Moreover, it is estimated that approximately one third of MDD patients enter remission after first-line antidepressant treatment. Failure to respond to one or more appropriate antidepressant treatments, with appropriate duration of treatment and dosage, is defined as treatment-resistant depression, which contributes significantly to the burden of MDD. Cognitive behavioral therapy is an increasingly prominent intervention that is based on the assertion that maladaptive information processing and inaccurate beliefs that establish the grounds for repetitive negative thinking have a crucial role in depression and, when challenged, can result in the reduction of the acute distress or prevent future symptoms relapse. This strategy is widely used in the clinic, and it has been shown to result in neuroplasticity and modulation of brain connectivity in anxiety and psychosis (Månsson et al. 2016, Mason et al. 2017).

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Figure 1

Depression remains one of the most prevalent psychiatric disorders, with a significant percentage of patients being nonresponsive to treatment. Dysfunction of the balance between the immune system, stress, and gut microbiota can contribute to the development, maintenance, and progression of depression.

Great efforts are ongoing to understand the etiological factors that are responsible for depression in the hope that they can be exploited for therapeutic benefit. Three factors worth noting are stress and the hypothalamic-pituitary-adrenal (HPA) axis, inflammation and aberrant immune system activation, and more recently the gut microbiome. In this review, we integrate data from both animal and human studies on all three of these factors in the etiology and progression of depression (**Figure 1**). We also focus on the processes by which this microbiota-immune-neuroendocrine matrix may regulate and influence centrally mediated events.

1.1. Stress and Depression

Depression is often referred to as a stress-related disorder, and the current dogma is that stress caused by negative life events, including in early life, contributes to the development, manifestation, and neuroprogression of this debilitating disorder (Duman et al. 2016, Larrieu & Sandi 2018). Such adverse life events are perceived by the body as a threat to its homeostasis, leading to physiological responses that promote the adaptation to these challenges—i.e., allostasis. However, such adjustments may represent a great physiological cost to the organism as a result of repeated overactivity or inactivity of the systems, including the HPA axis, leading to an increased allostatic load that has been conceptualized to represent the biological repercussions of the wear and tear of the body after repeated stress exposure (McEwen 1998).

1.2. HPA Axis and Depression

Overall, stress can be viewed as a necessary evolutionary response to a stimulus that results in the activation of the fight-or-flight mechanism in the body that is essential for the survival of any organism (Dhabhar 2014). In mammals, this response is mediated by the HPA axis, a negative feedback system that regulates the physiological responses to stress. In a matter of seconds to minutes, the activation of the HPA axis enables the organism to respond to threats by prioritizing functions essential for defensive behaviors (such as cognition and energy supply) over physiological functions related to sustenance (such as digestion). Activation of the HPA axis activates neurons in the paraventricular nucleus (PVN) of the hypothalamus to secrete arginine vasopressin (AVP) and corticotropin-releasing factor (CRF), which, in turn, prompt the production and secretion of adrenocorticotropic hormone (ACTH) in the anterior pituitary gland. As a consequence, ACTH induces the production and secretion of mineralocorticoids and glucocorticoids (corticosterone in

Gut microbiome: the genetic material of the gut microbiota

rodents, cortisol in humans) from the adrenal cortex into the bloodstream. High levels of cortisol consequently inhibit further release of ACTH and CRF through a negative feedback mechanism that operates through cortisol binding to glucocorticoid receptors (GRs) in the pituitary, the PVN, and the hippocampus. This results in a return to the physiological state after acute activation of the system. Glucocorticoids released by the adrenal cortex interact with GRs that are expressed not only within the HPA axis but also throughout the body, including the gut, in immune cells, and in limbic brain areas such as the hippocampus. Here they act as transcription factors and shape the functional and structural organization of the neural circuitry that controls the behavioral response to stress (de Kloet et al. 2005). In the context of depression, the HPA-axis negative feedback loop is compromised, resulting in prolonged elevation of glucocorticoids (de Kloet et al. 2005). Interestingly, some symptoms of depression such as hopelessness, disrupted sleep, and alterations in appetite and body weight have been associated with HPA-axis impairments, which partially explains the depressive symptoms often observed in patients with Cushing's disease (a medical condition characterized by excessive secretion of cortisol). Furthermore, chronic corticosterone treatment, or chronic stress, induces neuronal hippocampal atrophy (McEwen et al. 2015). It is also worth noting that depression induces an altered HPA response to acute stress, as measured through the Trier social stress test (see Allen et al. 2014 for review).

Moreover, clinical neuroimaging studies have revealed volumetric reductions in the hippocampus in depression (Treadway et al. 2015). Thus, repeated and severe stress exposure, particularly during sensitive periods of neurodevelopment, promotes the reprogramming of the hippocampus, inducing long-lasting alterations that might determine, often in a sex-specific fashion (Bale & Epperson 2015), the response to future stressors (Marečková et al. 2018) that may contribute to some stress-related depressive-like phenotypes.

Prolonged exposure to stress can result in altered gene expression as a direct result of glucocorticoid action (or glucocorticoids acting) on gene transcription along with the induction of epigenetic mechanisms such as methylation, hydroxymethylation, and histone modifications of DNA. These events culminate in the activation or repression of genetic factors in brain regions associated with emotion and cognition, such as the hippocampus and the prefrontal cortex (McEwen et al. 2015). Particularly in the latter structures, it has been shown that stress and the consequent excess of glucocorticoids lead to atrophy of dendritic processes and to the decrease of hippocampal synaptic plasticity (Sapolsky 2015). Therefore, stress-induced structural and functional abnormalities lead to impairments in cognition and affection as a result of the dysregulation of the HPA axis, which is consequently associated with increased risk of disease, particularly depression (Belleau et al. 2019). It is important to note that increased allostatic load as a result of continued stress exposure puts a strain not only on the HPA axis but also on almost every other physiological system, including the cardiovascular and the immune systems.

2. THE IMMUNE SYSTEM AND DEPRESSION

Almost a century ago, Nobel Prize winner Julius Wagner-Jauregg observed that activation of the immune system (due to inoculation with malaria) could affect psychiatric functioning. However, it took many decades for the field of psychoneuroimmunology to emerge in the context of depression and psychosomatic medicine. The importance of this field in the context of depression was bolstered by studies noting that changes in various psychological parameters that accompany the onset and duration of infection in humans are similar to those seen in depression (Dantzer 2018). In addition, there was a growing realization that individuals suffering from autoimmune disorders showed a high incidence of depressive disorders. By the early 1990s it became clear that hypersecretion of immunomodulatory signaling molecules, and in particular

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proinflammatory cytokines, may play a role in the onset and maintenance of depressive illness (Maes et al. 1995). Increased plasma concentrations of interleukin-6 (IL-6), interferon-gamma (IFN- γ), and acute-phase proteins were initially reported, and it is now well established that these and other cytokines, including tumor necrosis factor (TNF) in particular, are elevated in depressed patients (Dowlati et al. 2010). This inflammatory phenotype is also believed to be a significant contributor to treatment resistance in depression. The theory has led researchers to investigate the antidepressant actions of anti-inflammatory compounds, and results have shown that TNF antagonism in particular improves depressive symptoms in patients with high baseline inflammatory biomarkers (Kappelmann et al. 2018). Furthermore, treatment of hepatitis C virus with proinflammatory agents such as interferon-alpha (IFN- α) has led to the development of depressive symptoms in one out of four patients (Udina et al. 2012). Given the anti-inflammatory effects of many antidepressant medications (Hashioka et al. 2007), neuroimmune mechanisms are now viewed as central to the development of depressive symptoms.

In recent years, a growing interest has been drawn to the cellular mechanisms underlying immune trafficking to the brain in the context of overall brain health. It was initially thought that the central nervous system (CNS) was somewhat isolated from the peripheral immune system, because during initial observations it was observed that engraftment of tumors or fetal tissue in the brain were successful, and this lack of rejection of donor tissue suggested that the immune system was unable to act. As these observations differed from what was reported in the peripheral immune system, it was believed that the CNS failed to prompt an immune response (Engelhardt et al. 2017). However, in the wake of the evidence indicating that circulating cytokines can indeed influence brain and behavior, research has shown that despite the tight regulation of immune cell migration into the CNS by the blood-brain barrier (BBB), peripheral leukocytes can infiltrate the cerebral spinal fluid (CSF), meninges, choroid plexus, perivascular spaces, and ultimately the brain parenchyma (Engelhardt et al. 2017). Subsequently, specialized innate immune sentinel cells—choroid plexus macrophages, perivascular macrophages, mast cells, meningeal macrophages, and microglia (the CNS resident macrophages)—surveil the CNS under steady-state conditions and are the first responders to potential danger, detect pathogens or tissue damage, and trigger an immunological response (Rua & McGavern 2018). Lymphocytes also accumulate in perivascular spaces upon recruitment to the CNS in response to altered levels of chemokines in order to combat pathogens (Rua & McGavern 2018). Despite the constitutive presence of cytokines in the CNS under normal homeostasis and their role in synaptic plasticity, an increase in monocyte trafficking and/or an alteration to pro/anti-inflammatory cytokine balance may contribute to the etiology or progression of neuroinflammatory events (Dantzer 2018). Furthermore, recent provocative studies have shown that the CNS is in fact directly connected to secondary cervical lymph nodes by a lymphatic drainage system that can evoke peripheral immune responses (Louveau et al. 2015).

2.1. Activation of the Peripheral Innate and Adaptive Immune System in Stress and Depression

The innate immune system serves as the first line of defense against infection and stressors, and it is inherent from birth. Of primary importance with regard to the pathophysiology of depression is the role of the innate immune system in recruiting immune cells through the production of cytokines, activation of the complement cascade, and subsequent activation of the adaptive immune system through antigen presentation.

Researchers have reported elevated levels of circulating immune cells such as monocytes and granulocytes in MDD patients (for review, see Medina-Rodriguez et al. 2018). Many studies have

Cytokine: signaling peptide that regulates immune communication and function

Mast cell: innate immune cell that resides in specific tissues capable of eliciting inflammation

Microglia: immune cells residing in the central nervous system, capable of pruning synapses and responding to inflammatory stimuli

Monocyte: bone marrow-derived circulating cell that can differentiate into tissue macrophages in inflammatory sites

Neutrophil: immune cell responsible for mediating acute inflammatory responses to pathogens

T cell: adaptive immune cell responsible for cell-mediated immune responses; it expresses specific receptors capable of recognizing antigens

B cell: adaptive immune cell that mediates humoral responses by releasing antibodies specific to the antigens recognized on their cell surfaces

also demonstrated increased concentrations of immune signaling molecules—chemokines and adhesion molecules such as human macrophage chemoattractant protein-1 (MCP-1), soluble intracellular adhesion molecule-1 (sICAM-1), and E-selectin—as well as acute-phase proteins and proinflammatory cytokines such as IL-6 or proinflammatory factors as prostaglandins in the serum of depressed patients, suggesting an involvement of the peripheral immune system in depression (Miller & Raison 2015). Likewise, in animals exposed to social defeat stress, there is an increase in neutrophils and macrophages (Hodes et al. 2014, Wohleb et al. 2015). Dampening of peripheral monocytes resulted in the amelioration of the depressive-like effects caused by chronic exposure to stress (X. Zheng et al. 2016). Moreover, deletion of proinflammatory cytokines such as IL-6 (Chourbaji et al. 2006) and TNF- α (Simen et al. 2006) resulted in the reduction of depressive-like behavior in mice.

Mast cells are innate immune cells involved in immune response regulation and homeostasis support, and they play a key role in allergy and cancer, HIV, and colitis. Moreover, mast cells have been found in the brain, where they have been shown to play a role in neuroinflammation (Dong et al. 2014), anxiety (Nautiyal et al. 2008), and in shaping neurodevelopmental pathways relevant to sexual behavior (Lenz et al. 2018). They have also been shown to be involved in depression by a process dependent on tryptophan metabolism (Georgin-Lavialle et al. 2016). However, further studies are required to uncover the mechanisms underlying the relationship between peripheral innate immune activity and the development of depression.

Adaptive immunity involves the phenomenon of immunological memory, whereby a particular lymphocyte (T cell or B cell) specifically recognizes unique determinants (antigens) to mount a more effective response on second and subsequent encounters with a pathogen. It is thus a highly specific defense mechanism for the body to respond to a particular pathogen.

A role for the adaptive immune system in the etiology of depression was initially proposed when studies revealed that depressed patients had increased numbers of circulating T helper (Th) cells (CD4+), cytotoxic T cells (CD8+), and B cells (Maes et al. 1992). Impaired maturation of Th2 and Th17 cells (Grosse et al. 2016), a reduction in diverse CD4+ T cell repertoire (Patas et al. 2018), and a reduction in B regulatory cells (Ahmetpasic et al. 2018) in depressed individuals have been more recently reported. Likewise, studies in animal models have also shown that glucocorticoid and stress exposure modulate T and B cell response (Clark et al. 2019, Roque et al. 2011).

Given that some of the cytokines involved in these processes are associated with the development of sickness behavior—which in the context of infection represents an important coping mechanism—the prolonged imbalance of these molecules can explain the development of symptoms such as nausea, loss of appetite, sleep disturbances, fatigue, and anhedonia (Dantzer 2018). Moreover, cytokines have also been associated to the bioavailability of monoamines in the CNS, particularly in limbic regions that are very relevant in depression (Dantzer 2018).

At a mechanistic level, increasing evidence points to a role for the adaptive immune system in gating stress responses. Studies in lymphopenic mice, which lack a functional mature adaptive immune system, have shown that the transfer of lymphocytes from stressed to stress-naïve animals led to the improvement of social behavior, reduced anxiety-like behavior, and increased proliferation of hippocampal cells (Brachman et al. 2015). Adoptive transfer of lymphocytes not only improved the deleterious effects of stress in animals, but these cells also engrafted the choroid plexus and the meninges of the recipient mice exposed to stress (Scheinert et al. 2016). Furthermore, a recent study reported that even though CD4+ T cells seem not to be directly involved in the response to stress, CD8+ cytotoxic T cells respond to stress not only by modulating the corticosterone and behavior response but also by inducing the production of proinflammatory cytokines, possibly through the induction of monocytes and macrophages (Clark et al. 2019). Additionally, it has been suggested that immunological memory to self-antigens, in a process dependent on

memory T cells, might contribute to the development of stress-coping mechanisms (Lewitus et al. 2009).

In accordance with the nature and intensity of the stressful insult, an increase in immunomodulators in the circulation may result in the indirect trigger of neuroinflammation via the release of cytokines from endothelial cells of peripheral capillaries at the BBB (Spranger et al. 2006), or alternatively through vagal nerve stimulation in response to peripheral inflammatory mediators (Eskandari et al. 2003).

In fact, cognitive behavioral therapy has been shown to effectively modulate the levels of proinflammatory cytokines such as IL-6 and TNF- α while reducing depressive symptoms, therefore indicating that the reduction of the imbalanced proinflammatory signal is linked to better clinical outcomes (Del Grande da Silva et al. 2016).

2.2. Inflammasome and Depression.

There is an increasing interest in the role of the inflammasome in both stress sensitivity and depression (Fleshner et al. 2017). Inflammasomes are protein complexes that are generated in cells from the bone marrow lineage as a response to pathogenic microorganisms or to so-called sterile stressors, such as psychological stress (Miller & Raison 2015). Assembly of the inflammasome results in the activation of caspase-1, which in turn cleaves the precursor forms of IL-1 β and IL-18, resulting in the activation of these proinflammatory cytokines (Strowig et al. 2012) and leading to pyroptosis, a form of programmed cell death distinct from apoptosis. During an infection, one of the first forms of defense enforced by specific innate immune cells is the presentation of a group of pattern recognition receptors (PRRs) encoded in the germline to recognize molecular patterns expressed by invading pathogens. These may be either on the membrane surface, such as Toll-like receptors (TLRs), or inside the cytoplasm, such as Nod-like receptors (NLRs) (Kaufmann et al. 2017).

NLRs are cytosolic receptors that are able to recognize nonself-molecules and associated cell damage and are triggered by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (Kaufmann et al. 2017).

NLRP3 is a subset of NLR and the most studied inflammasome involved in the activation of caspase-1; it is expressed in the CNS in microglia and undifferentiated neurons (Fleshner et al. 2017). Rodent studies have shown that chronic stress resulted in the overexpression of NLRP3 in microglia (Pan et al. 2014, Y. Zhang et al. 2015, Zhu et al. 2017), which can be reversed by selective serotonin reuptake inhibitor (SSRI) antidepressants (Pan et al. 2014). Furthermore, in other stress models, targeting specific glial and neuronal modulators ameliorated depressive-like behavior, while concurrently modulating NLRP3 inflammasome (Z.-Q. Li et al. 2018, Yue et al. 2017). Additionally, genetically modified NLRP3 knockout mice administered lipopolysaccharides (LPS) (Jeon et al. 2017) or exposed to chronic unpredictable mild stress (Su et al. 2017) showed a reduction in depressive-like behavior, further reinforcing the involvement of NLRP3 in this stress-induced behavior.

In humans, overexpression of NLRP3 was observed in peripheral blood cells of nontreated MDD patients, along with increased serum levels of IL-1 β and IL-18, which was reversed by antidepressant treatment (Alcocer-Gómez et al. 2017). The inflammasome therefore is poised to be a crucial modulator of the inflammatory response, even though the mechanisms underlying this sophisticated response remain relatively unexplored. Nevertheless, a feedback loop initiated by cytotoxic T cells triggers the NLRP3 inflammasome in antigen-presenting cells to enhance IL-1 β maturation, suggesting that the feedback loop generated by adaptive immune cells contributes to the stimulation of innate immune cells in order to boost innate immunity (Yao et al. 2017).

Inflammasome:
pro-inflammatory signaling cascade activated upon sensing of pathogenic microorganisms and sterile stressors, such as psychological stress



Astrocyte: the most common glial cell in the central nervous system, responsible for several key physiological functions

2.3. Neuroimmunity, Stress, and Depression

Growing evidence suggest that there is a neuroimmune basis for depression (Bekhbat & Neigh 2018). As stated earlier, microglia are key innate sentinel immune cells that are restricted to the CNS and monitor the environment with motile protrusions to determine changes in the physiological environment. In addition to their crucial role as responders to infection and injury, microglia are also involved in neuronal events at different stages throughout neurodevelopment and adulthood, including synaptic remodeling to shape neuronal network signaling (Norris & Kipnis 2019). These cells are involved in a dynamic system—the neurovascular unit—that includes the cells that surround the BBB and relay the interaction between CNS cells and the periphery (Banks 2016). Recent studies have determined that microglia are maintained in the brain through self-renewal and maintain long-term interactions with the neurons. Moreover, microglia can release inflammatory cytokines to influence neuronal activity and trafficking of neurotransmitter receptors as well as gene expression. In addition, neurons regulate microglia function through soluble factors including chemokines, cytokines, and neurotransmitters (CX3CL1, TGF β , CSF1, UDP, ATP, glutamate, GABA, norepinephrine) to promote microglial function and cellular adaption, to direct motility and phagocytosis, and to initiate and propagate an appropriate inflammatory response (Wohleb 2016). The reciprocal communication between microglia and the neurons likely facilitates neuroplasticity, neurogenesis, proliferation, pruning, and neurodegeneration throughout the life span, and it likely plays a key role in stress and neuroinflammatory response (Li & Barres 2018).

Glucocorticoid receptors are widely expressed on microglia throughout the brain (Sierra et al. 2008), and integration of stress-induced signaling is mediated in the CNS by neuroinflammatory signaling through modulated microglia (Wohleb et al. 2014). In response to stress, microglia undergo dynamic alterations in morphology and function within corticolimbic regions implicated in depressive-like symptoms. Under stressful conditions, neuroendocrine pathways fine-tune central and peripheral immune responses, resulting in monocyte trafficking and priming, subsequent changes in microglia phenotype, and, ultimately, neuroinflammation, which in turn can contribute to the development of several stress-related disorders, including depression (Hodes et al. 2015). The exposure to cytokines released upon microglia activation has been linked to the development of aberrant behavioral phenotypes in stress models. As a result, cumulative evidence reveals a clear link between the release of cytokines and the activity of the HPA axis. A recent study showed that immunization with *Mycobacterium vaccae*, a bacterium with immunoregulatory and anti-inflammatory properties, resulted in the improvement of anxiety-like behavior caused by exposure to stress, through attenuation of the microglial priming of the proinflammatory response (Frank et al. 2018). An immunological challenge can also stimulate HPA-axis activity by the translocation of immunomodulators through the choroid plexus (Kunis et al. 2013) and the BBB (Capuron & Miller 2011, Turrin & Rivest 2004). In fact, under physiological conditions lymphocytes are present in the brain parenchyma in low numbers, accumulating mainly in the choroid plexus, the meningeal spaces, and the cerebrospinal fluid. Curiously, evidence suggests that T cells accumulate in these areas in response to signals triggered by the CNS, namely in the meninges upon performance of cognitive tasks (Derecki et al. 2010) or, strikingly, in the choroid plexus after stress exposure (Lewitus et al. 2008).

It should be noted that the most common glial cell types in the CNS are astrocytes, which are a key player in maintaining brain function regulating neurotransmission, metabolism, and energy supply (Q. Wang et al. 2017). Astrocytes have also been reported to be reduced in terms of density and number in depression (Rajkowska & Miguel-Hidalgo 2007). Recent human brain imaging studies using translocator protein 18 kDa (TSPO) as a marker of reactive astrocytes and microglia

have shown increased neuroinflammation in MDD patients, which is reduced by antidepressant treatment (Richards et al. 2018).

Taken together, these findings clearly show that depression is a complex psychiatric disorder that is intrinsically linked to maladaptation to stress, which results in a dysregulated HPA axis and immune system. Over the past number of years it has become clear that this altered stress and inflammatory response converge on brain function to disrupt normal neuroimmune homeostasis. Thus, in the field of immunopsychiatry, much enthusiasm has accompanied the idea that targeting this altered stress-immune axis may yield novel therapeutic approaches for depression (Pape et al. 2019). However, recently a new player has emerged—the gut microbiota—which is also a key regulator of both stress and inflammation, and thus its role in depression is also being investigated.

Gut microbiota:
collective name
for the trillions of
microorganisms that
inhabit the intestine

3. MICROBIOME-IMMUNE COMMUNICATION

The mammalian gut plays host to a myriad of microorganisms collectively referred to as the gut microbiota (Gilbert et al. 2018). Emerging evidence supports a role for the bidirectional communication of the gastrointestinal microbiota with the endocrine and immune systems to mediate key brain processes including neuroinflammation, activation of the stress axes, neurotransmission, and neurogenesis (Cryan & Dinan 2015b, Rhee et al. 2009). Moreover, in psychology there is a growing appreciation of the role of the microbiota-gut-brain axis in psychopathology (Allen et al. 2017, Cryan 2019, Sarkar et al. 2018).

Gut microbiota influence the relative populations, migration, and phenotype of various subsets of immune cells (Dorrestein et al. 2014), and several different studies have illustrated how the gut microbial populations can influence innate and adaptive immune responses at mucosal surfaces upon inflammation, infection, and autoimmunity (El Aidy et al. 2015). Additionally, there is an increasing understanding of the importance of alterations in the cross talk between gut microbes, the intestinal epithelium, and the intestinal immune system, which in turn has been linked to the modulation of systemic immunity (Belkaid & Hand 2014). In fact, it has been shown that the intestinal immune system is a sophisticated structure that has developed specific mechanisms to ensure that commensal bacteria load is maintained, and if bacteria cross the intestinal barrier, these will be targeted and eliminated by the immune system, preventing their possible invasion to the periphery (Hooper & Macpherson 2010). On the other hand, commensal bacteria also shape immune response by triggering the activation of regulatory T cells through direct recognition of microbial metabolites or products, such as short-chain fatty acids (SCFAs), by T cells or dendritic cells. Furthermore, commensals stimulate the induction of Th17 cells that in turn modulate the function and homeostasis of epithelial cells (Belkaid & Hand 2014).

4. MICROBIOME-IMMUNE BRAIN SIGNALING

Thus, the microbiota contribute to the priming, education, and activation of the immune response; in turn, the immune system plays a role in the maintenance and regulation of the number and diversity of gut bacteria. Current evidence suggests that in homeostatic conditions, a healthy and dynamic low-grade inflammatory tone is maintained to continually communicate across the gut immune and enteric nervous systems with the brain (**Figure 2**). In addition to influencing the immune system at the level of the gut, the microbiota have also been linked with the tight regulation of microglia (Erny et al. 2015, Thion et al. 2018). In fact, the microbiome has been implicated in the regulation of neuroinflammatory processes through the modulation of SCFAs, which are microbially derived by-products of fiber metabolism, particularly in an animal model of Parkinson's



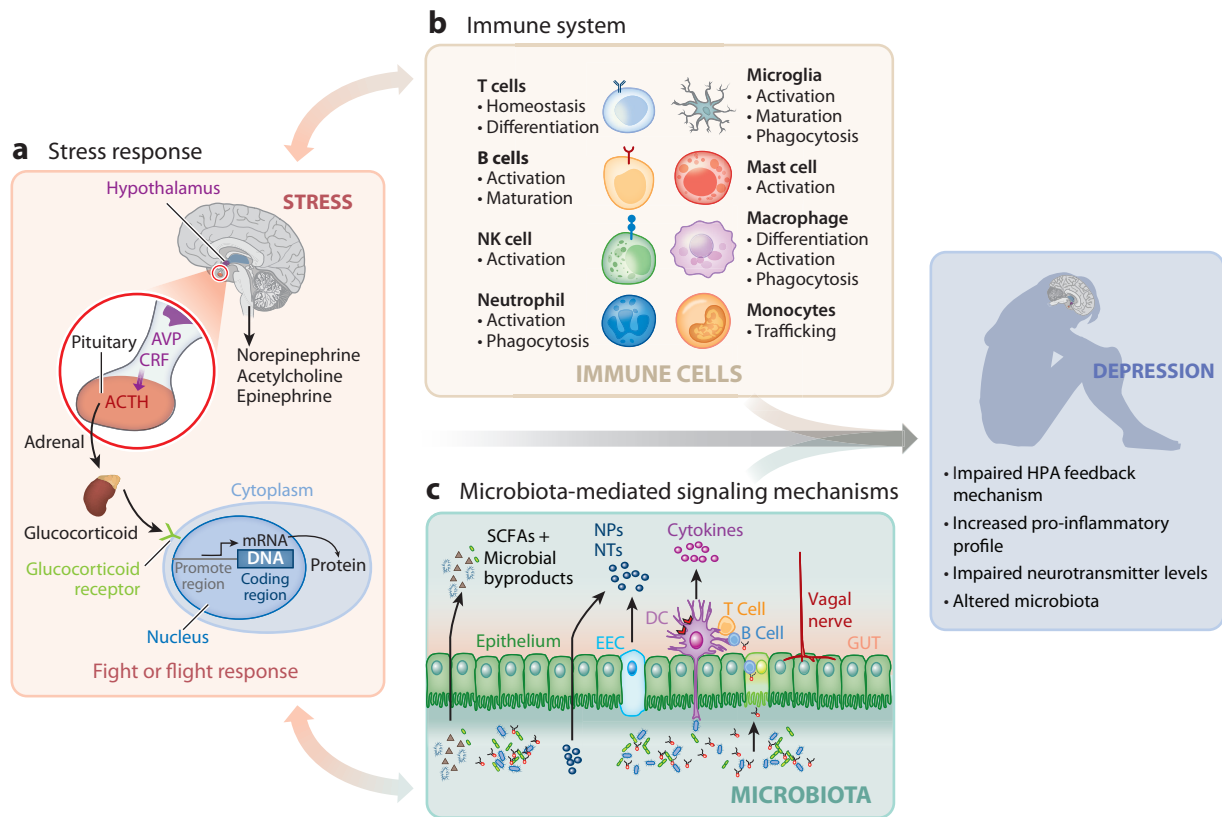


Figure 2

The interconnecting contribution of (a) the stress response via hypothalamic-pituitary-adrenal (HPA) axis activation, (b) the immune system via multiple effector cell types, and (c) the microbiota-mediated signaling mechanisms to centrally mediated events that may lead to depression. Abbreviations: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRF, corticotropin-releasing factor; DC, dendritic cell; EEC, enteroendocrine cell; NK, natural killer; NP, neuropeptide; NT, neurotransmitter; SCFA, short-chain fatty acid.

Germ-free animal: animal raised completely in the absence of bacteria

disease (Sampson et al. 2016). It is worth noting that monocytes display free fatty acid receptors (FFARs), which are one of the endogenous molecular targets for SCFAs.

A growing body of evidence has highlighted a compelling role for the gut microbiome in the mediation of neuroinflammation processes. In a fascinating study, cerebral cavernous malformations—vascular defects that potentiate the risk of seizure and hemorrhagic stroke—were found to be stimulated by activation of endothelial Toll-like receptor 4 (TLR4), which is involved in the activation of innate immunity, by gram-negative bacteria and LPS (Tang et al. 2017). Conversely, pharmacological blockade of TLR4 signaling prevented the development of the referred malformations. More importantly, these malformations failed to develop in germ-free mice, and antibiotic exposure significantly decreased the susceptibility to the referred malformations (Tang et al. 2017). Taken together, these results suggest that the gut microbiome is undoubtedly involved in innate immune signaling pathways that impact brain morphology and function.

Multiple sclerosis (MS) is a CNS autoimmune disorder, mainly linked to impairments in T cell function. Specific bacteria have been found altered in MS patients, and recolonization of germ-free mice with microbiota from MS patients not only alters the immune profile of the mice but also

increases their susceptibility to the development of clinical scores (Cekanaviciute et al. 2017). Also, in a study on gut microbiota from MS discordant twins, microbiota transplantation of MS patients increased the development of spontaneous CNS autoimmunity in comparison to the animals that received a fecal transplantation from the healthy twins (Berer et al. 2017). Therefore, it seems that the gut microbiome might be relaying the impaired T cell response, possibly potentiating malfunctioning adaptive immune signaling by contributing to the development of defective anti-inflammatory or regulatory responses.

Impairments in regulatory and inflammatory adaptive immune responses have also been implicated in the development of ischemic stroke. Antibiotic exposure has been found to alter immune gut function while reducing ischemic brain injury in mice (Benakis et al. 2016). In this model, intestinal T cells migrate to the meninges after a stroke, which is reversed by the depletion of particular groups of gut bacteria (Benakis et al. 2016). The relevance of bacterial colonization in stroke outcome is further strengthened by the observation that germ-free mice are protected from the development of ischemic lesions in a lymphocyte-dependent manner (Singh et al. 2018), further reinforcing a role for the gut microbiome in immune outcomes that impact the brain.

With regard to inflammasome interactions with the microbiota-gut-brain axis, NLPR6 has been shown to respond to gut microbial metabolite signaling, leading to the activation of the host immune response (Levy et al. 2015). Genetic deletion of caspase-1, a key component of this signaling cascade, reduces depressive-like behavior in mice while resulting in gut microbiome alterations (Wong et al. 2016). Antibiotic treatment of stressed mice promoted a rebalance of the gut microbiome in a similar fashion to that found in caspase-1 knockout mice, further implying a role for the gut microbiome in the regulation of inflammasome pathways that affect brain function (Wong et al. 2016).

Taken together, these results have challenged the pre-established concept that the relationship between gut microbiota, the immune system, and neurodevelopment is immutable in adulthood. In fact, a healthy and diverse gastrointestinal microbiota is deemed vital for the maintenance of a balanced immune system and appropriate brain function throughout the life span (Cryan & Dinan 2015a).

Another mechanism by which the microbiota and the immune system may be interacting with gut-brain signaling is via the vagus nerve (Fülling et al. 2019). The endings of the vagus nerve are sensitive to neural communication from the enteric nervous system and to the release of inflammatory factors from the gut, and they relay this sensory information through the brainstem to higher centers in the brain. Recent studies using vagotomy report a key role for gut microbiota in regulating neurogenesis, possibly through mechanisms involving brain-derived neurotrophic factor (BDNF) (O'Leary et al. 2018). These findings support earlier work where the positive effects of the probiotic *Lactobacillus rhamnosus* JB-1 on stress-induced depressive- and anxiety-like behavior were ablated with vagotomy (Bravo et al. 2011). The precise mechanisms underlying these effects remain to be disentangled, but given the role of vagal nerve stimulation as a treatment in some cases of depression, a role for vagal stimulation in the mechanism of action of certain probiotics seems evident.

In addition to playing a role in the positive effects on neurogenesis, communication from higher centers in the brain through efferent vagal impulses suppresses peripheral inflammatory cytokines, such as TNF- α and IL-1 β in the spleen (Rosas-Ballina & Tracey 2009), to influence local events in the adrenals (Pavlov & Tracey 2017); thus, such communication plays a role in regulating the stress response. Although research has not clearly identified a direct link involving the gut microbiota in regulating immune and stress-related events through the vagus nerve, the existing data suggest that the vagus nerve may in some part be responsible for some of the effects of gut microbiota in depression.

Probiotic: live microorganism strain that confers health benefits to the host



Prebiotic:

nondigestible food element that favors the growth of particular groups of bacteria, promoting health benefits to the host

5. MICROBIOTA, THE STRESS RESPONSE, AND DEPRESSION

Mechanistic, longitudinal clinical studies investigating the role of the gut microbiome on the host mental health are lacking. There is evidence for an altered microbiota composition in depressed individuals (Huang et al. 2018, Kelly et al. 2016, Naseribafrouei et al. 2014, P. Zheng et al. 2016), with the abundance of *Faecalibacterium* negatively correlated with symptom severity (Jiang et al. 2015). An observational study reported that challenging the microbiota with single and recurrent antibiotic treatment augmented the risk of depression and anxiety (Lurie et al. 2015). Recently, a large population study showed that *Coprococcus* and *Dialister* strains not only were predictors of a better quality of life but were also consistently depleted in untreated depressed patients, while *Butyrivococcus* was associated to antidepressant treatment (Valles-Colomer et al. 2019). Interestingly, recent studies demonstrated that fecal matter transplantation from MDD patients affected depressive-like behavior in recipient animals (Kelly et al. 2016, P. Zheng et al. 2016), thus suggesting further involvement of the gut microbiome in depression.

5.1. Microbiome Manipulations in Preclinical Models of Stress and Depression

Many different stress paradigms—including chronic social defeat, restraint stress, maternal separation, crowding, heat stress, and acoustic stress—can impact the composition of the microbes in the gut, as determined in preclinical models (Bailey et al. 2011; Bharwani et al. 2016; De Palma et al. 2014, 2015; O'Mahony et al. 2009). Accordingly, multiple studies have focused on understanding the role of the gut microbiota in exposure to stress following positive or negative manipulation of the gut microbiota with antibiotic administration, prebiotic and probiotic intervention, fecal transplantation, and in response to stress in specific pathogen-free and germ-free animals (**Table 1**).

Preclinical studies have demonstrated that germ-free animals—raised in a sterile environment from birth, and therefore lacking gastrointestinal bacteria—show behavioral and phenotypical outcomes that can be reversed by colonization with bacteria and have increased sensitivity to acute stress (Clarke et al. 2013, Crumeyrolle-Arias et al. 2014, Sudo 2012). Another approach to dissect the involvement of gut microbiota on stress physiology is to ablate stable core bacterial populations by exposure to antibiotics. Increasingly, studies are demonstrating a modulation of behavior after antibiotic treatment, suggesting that particular populations of gut bacteria might positively or negatively influence neurobehavioral outcomes (Desbonnet et al. 2015, Hao et al. 2013, Hoban et al. 2016, Majidi et al. 2016, O'Mahony et al. 2014, H.T. Wang et al. 2017).

However, further preclinical studies examining the outcomes of antibiotic administration on alterations in neuroendocrine levels in response to stress exposure are still lacking. Given that gut bacteria might influence stress response and emotional behavior, multiple studies have explored the effect of prebiotic and probiotic administration in stress models. In fact, both prebiotic and probiotic interventions have been shown to protect against the deleterious effects of stress, possibly by modulation of the immune system, while improving behavior (Ait-Belgnaoui et al. 2012, Bravo et al. 2011, Desbonnet et al. 2010, Palomar et al. 2014, Savignac et al. 2014) (see **Table 1**).

Moreover, in a chronic psychosocial stress paradigm, transplantation of feces from nonstressed animals partially attenuated some of the deleterious effects of stress, and likewise, fecal transplantation from stressed to naïve mice was sufficient to induce stress effects on recipient mice (Langgartner et al. 2018). Moreover, fecal transplantation from stressed mice to naïve recipients led to anxiety-like behavior and to the accumulation of monocytes and activated microglia in the hippocampus, while treatment with beneficial microbes from unstressed animals improved anxiety-like behavior by amelioration of inflammation in the gut (Jang et al. 2018). These studies are in line with earlier studies from Bercik and colleagues (2011) that showed that the phenotype

Table 1 Preclinical studies of microbiota manipulations relevant to microbiota-immune-stress responses

Microbiome manipulation	Details	Species	Stress exposure	Physiological/behavioral outcome	References
Germ-free	Recolonization	Mice	Novel-environment stress	Hyperactivity of the HPA axis ↑ Corticosterone ↑ ACTH ↓ Anxiety-like behavior (reversed by colonization)	Clarke et al. 2013, Sudo 2012
	NA	Rats	Open-field	↑ HPA-axis response ↑ Anxiety-like behavior	Crumeyrolle-Arias et al. 2014
	Recolonization	Mice	No	↓ Anxiety-like behavior	Nishino et al. 2013
Antibiotic treatment	Ampicillin, vancomycin, ciprofloxacin hydrochloride, imipenem, metronidazole, pimaricin, bacitracin, neomycin	Rats	No	↑ Visceral sensitivity ↑ Depressive-like behavior ↔ Anxiety-like behavior	Hoban et al. 2016, O'Mahony et al. 2014
	Ampicillin, vancomycin, neomycin, metronidazole	Mice	Acute restraint	↓ Anxiety-like behavior Cognitive impairments	Desbonnet et al. 2015
	Ampicillin, cefoperazone	Mice	No	↑ Depressive-like behavior ↑ Anxiety-like behavior	Ceylani et al. 2018
	Azithromycin	Mice	LPS	↓ Depressive-like behavior ↓ Pro-inflammatory cytokines	Hao et al. 2013
	Dapsone	Mice	Surgical stress	↓ Depressive-like behavior ↓ Anxiety-like behavior	T. Zhang et al. 2015
	Minocycline	Mice	LPS Early-life social isolation	↓ Depressive-like behavior	Majidi et al. 2016, Wang et al. 2017a
	Minocycline	Mice	No	↔ Depressive-like behavior ↔ Anxiety-like behavior	Vogt et al. 2016
Fecal transplantation	Feces from nonstressed to stressed animals Feces from stressed animals to nonstressed animals	Mice	Chronic subordinate colony housing	↓ Anxiety-like behavior ↓ Systemic low-grade inflammation ↓ Thymus atrophy	Langgartner et al. 2018
	Feces from animals exposed to stress or treated with <i>Escherichia coli</i>	Mice	Restraint stress	↓ Anxiety-like behavior	Jang et al. 2018
Probiotic administration	<i>Bifidobacterium infantis</i> 35624	Rats	Maternal separation	Immune response normalization ↓ Depressive-like behavior	Desbonnet et al. 2010
	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BB-12, <i>Propionibacterium jensenii</i>	Rats	Maternal separation Restraint stress	↑ Corticosterone ↑ ACTH ↑ IgA Improved immune phenotype	Barouei et al. 2012

(Continued)



Table 1 (Continued)

Microbiome manipulation	Details	Species	Stress exposure	Physiological/behavioral outcome	References
	<i>Lactobacillus casei</i> CRL 431	Mice	Restraint stress Food deprivation	↑ IgA ↑ T helper cells ↓ IFN- γ	Palomar et al. 2014
	<i>Bifidobacterium longum</i> 1714, <i>Bifidobacterium breve</i> 1205	Mice	No	↓ Depressive-like behavior ↓ Anxiety-like behavior	Savignac et al. 2014
	<i>Lactobacillus rhamnosus</i> JB-1	Mice	No	↓ Depressive-like behavior ↓ Anxiety-like behavior ↓ Corticosterone	Bravo et al. 2011
	<i>Lactobacillus farciminis</i>	Rats	Partial restraint stress	↓ HPA-axis response Improved immune phenotype	Ait-Belgnaoui et al. 2012
	<i>Lactobacillus helveticus</i> NS8	Rats	Chronic restraint stress	↓ HPA-axis response ↓ Depressive-like behavior ↓ Anxiety-like behavior	Liang et al. 2015
	<i>Bifidobacterium pseudocatenulatum</i> CECT 7765	Mice	Maternal separation	↓ Intestinal inflammation ↓ Anxiety-like behavior	Moya-Perez et al. 2017
	<i>Lactobacillus rhamnosus</i> R0011, <i>Lactobacillus helveticus</i> R0052	Mice	Water avoidance	↑ Non-spatial memory ↓ Anxiety-like behavior	Smith et al. 2014
	<i>Lactobacillus helveticus</i> R0052, <i>Lactobacillus plantarum</i> R1012, <i>Bifidobacterium longum</i> R0175	Mice	Chronic mild stress	↓ Depressive-like behavior ↓ Anxiety-like behavior ↓ TNF- α and IFN- γ	N. Li et al. 2018
Prebiotic administration	Fructo-oligosaccharides, galacto-oligosaccharides	Mice	Chronic unpredictable social stress	↓ Corticosterone ↓ Pro-inflammatory cytokines ↓ Depressive-like behavior ↓ Anxiety-like behavior	Burokas et al. 2017
	Galacto-oligosaccharides	Mice	LPS	↓ Anxiety-like behavior ↓ Cortical IL-1 β	Savignac et al. 2016
Prebiotic + probiotic (synbiotic) administration	Polydextrose, galacto-oligosaccharides, <i>Lactobacillus rhamnosus</i> GG	Rats	Maternal separation	↓ Anxiety-like behavior ↑ Spatial learning	McVey Neufeld et al. 2019

↑ = increase, ↓ = decrease, ↔ = no change in behavioral or immune outputs. Abbreviations: ACTH, adrenocorticotropic hormone; HPA, hypothalamic pituitary adrenal; IFN- γ , interferon-gamma; IgA, immunoglobulin A; IL-1 β , interleukin-1 beta; LPS, lipopolysaccharides; NA, not available; TNF α , tumor necrosis factor-alpha.

of a stress-sensitive strain of mouse could be transferred via the microbiome to a strain that had a normal stress response, and vice versa.

Taken together, a growing body of evidence suggests that the gut microbiome is undoubtedly involved in the mechanisms underlying the stress response, and shaping the gut microbial communities might shed some light on the development of more targeted stress-signaling manipulations.

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5.2. Toward Psychobiotics

The concept of psychobiotics was recently coined (Anderson et al. 2017) to indicate live bacteria that confer mental health benefits. Its definition has been expanded to refer to any targeted intervention of the microbiome that facilitates brain health (Cryan et al. 2019, Sarkar et al. 2016). Although research is still in its early days, there is a growing body of data, especially in healthy volunteers, supporting the concept. For example, treatment with the probiotics *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 (Messaoudi et al. 2011) and galacto-oligosaccharide prebiotic (Schmidt et al. 2015) resulted in the reduction of cortisol, thus promoting the subject's resilience to stress and ameliorating emotional responses in healthy subjects. Additionally, ingestion of a probiotic cocktail resulted in altered brain activity and processing of emotional information in a functional magnetic resonance imaging study (Tillisch et al. 2013) and in the attenuation of negative thoughts associated with a negative mood (Steenbergen et al. 2015), supporting the importance of gut microbiota in stress and emotional responses. Consumption of *Bifidobacterium longum* 1714 was associated with a reduction in stress and cognitive improvements in healthy subjects (Allen et al. 2016). Notwithstanding these findings, the exact mechanisms that compose the communication between the microbiota and the stress response remain to be elucidated. More recently, treatment with probiotics was shown to improve stress response (Nishida et al. 2017, Papalini et al. 2019) and depression scores in MDD (Kazemi et al. 2019) and irritable bowel syndrome patients (Pinto-Sanchez et al. 2017) and in postpartum depression (Slykerman et al. 2017). In a separate study, eight weeks of probiotic adjuvant treatment, in combination with antidepressants in treatment-resistant depressive patients, led to significant improvements in depression, thus improving response to treatment (Miyaoaka et al. 2018). Likewise, probiotic augmentation with *Lactobacillus plantarum* 299v ameliorated cognitive function and decreased kynurenine concentration in MDD patients undergoing SSRI treatment (Rudzki et al. 2019).

However, there is not a clear consensus on the overall efficacy of probiotics as a preventive measure for MDD. Over the last decade, an important discussion has started in the scientific community, particularly in the field of social psychology, regarding reproducibility and replication in science (Baker 2016). Despite the great potential presented by psychobiotics and their huge popularity, not only within the science community, but also within the general public, caution is needed when drawing conclusions from what is still a limited amount of evidence. Hence, it is clear that strain selection and more longitudinal large-scale studies are required to prove a specific role of any potential psychobiotic intervention (Dinan & Cryan 2019).

6. ADULT HIPPOCAMPAL NEUROGENESIS: HEART OF THE UNHOLY TRINITY?

Given that stress, inflammation, and microbiome all are risk factors for depression, there is a growing interest in understanding the neurobiological circuits and cellular mechanisms that each can impinge on to affect MDD symptomatology. Adult hippocampal neurogenesis is emerging as one such process. Pioneering studies from the 1960s first provided evidence that new neurons are generated in the adult rat and guinea pig hippocampus (Altman & Das 1965), ending the long-standing dogma that neurons are no longer generated in the CNS after birth. It is now widely accepted that adult neurogenesis is primarily restricted to the subventricular zone lining the lateral ventricles and in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus in several species including rats, mice, and humans (Spalding et al. 2013). In the SGZ of the DG of the hippocampus, neural progenitor cells (NPCs) proliferate and differentiate into astroglia, oligodendrocytes, or neurons, which then migrate into the granule cell layer (GCL) of the DG

Psychobiotic:

beneficial microorganism or food element that targets the gut microbiome to promote mental well-being

Adult neurogenesis:

the process of generation of new neural cells from a pool of neural stem cells



and ultimately project to the CA3 region of the hippocampus, where they become fully functional neurons that are integrated into the brain circuitry. While there has been some recent controversy over the maintenance of hippocampal neurogenesis across the life span in humans, it is generally accepted that neurogenesis occurs in the hippocampus and has functional relevance (Boldrini et al. 2018, Lee & Thuret 2018, Lucassen et al. 2019, Snyder 2018, Sorrells et al. 2018). However, until advances in clinical neuroimaging technologies are made, it will be difficult to fully determine the exact role neurogenesis plays in these clinical conditions (Lee & Thuret 2018).

6.1. Neurogenesis, Stress, and Depression

One of the main drivers for interrogating the potential role of adult hippocampal neurogenesis in depression is that chronic stress, a risk and precipitating factor for depression, has been consistently reported to decrease adult hippocampal neurogenesis, which is reversed by antidepressant treatment (Levone et al. 2015, Morais et al. 2014, Sapolsky 2004, Snyder et al. 2011, Surget et al. 2011). Since the hippocampus participates in the modulation of the negative feedback of the HPA axis, it has been speculated that impairments in adult hippocampal neurogenesis may be involved in the disruption of the HPA-axis feedback loop, thus potentiating its dysregulation, as observed in a large proportion of MDD patients. Indeed, there is some preclinical evidence to suggest that adult hippocampal neurogenesis buffers the corticosterone and behavioral response to stress (Snyder et al. 2011). However, neurogenesis-ablation in the absence of stress does not seem to induce a depressive phenotype. On the other hand, chronic treatment with different types of antidepressant drugs (Malberg et al. 2000) and other manipulations that induce antidepressant-like effects, such as electroconvulsive therapy (Madsen et al. 2000) and exercise (van Praag et al. 1999), have been shown to increase adult hippocampal neurogenesis in rodents. There is also some evidence from human postmortem brain tissue that hippocampal progenitor cell proliferation is increased with antidepressant medication in depression (Boldrini et al. 2012). Preclinical models have also provided evidence that intact adult hippocampal neurogenesis is required for at least some of the behavioral effects of some antidepressants (Perera et al. 2011, Santarelli et al. 2003, Surget et al. 2011). Interestingly, and very much relevant to the HPA-axis hyperactivity observed in depression, it has been demonstrated that adult hippocampal neurogenesis is required for normalization of HPA-axis functioning by antidepressant treatment (Surget et al. 2011). The time it takes for antidepressants to exert their therapeutic benefits matches the time necessary for the newly generated hippocampal cells to mature and integrate into the neuronal network (Esposito et al. 2005, Ngwenya et al. 2006), which fits the observation that adult hippocampal neurogenesis is required for antidepressant activity (Santarelli et al. 2003). Moreover, stress induces a deleterious effect on adult neurogenesis by inducing depressive-like behaviors, and this effect is reversed by treatment with antidepressants (Morais et al. 2014, Snyder et al. 2011, Surget et al. 2011).

6.2. Neuroinflammation and Hippocampal Neurogenesis

The first evidence of the impact of inflammation on adult hippocampal neurogenesis came when peripheral or central injection of LPS to rodents decreased neurogenesis and concurrently increased the number of microglia in the DG of the hippocampus (Ekdahl et al. 2003, Monje et al. 2003). Since then it has become clear that the classic proinflammatory cytokines IL-1 β , IL-6, and TNF- α are the primary negative inflammatory modulators of hippocampal neurogenesis (Borsini et al. 2015, Green et al. 2012, Keohane et al. 2010, O'Leime et al. 2017).

Due to the fact that chronically elevated levels of hippocampal IL-1 β have detrimental effects on memory and cognition and also promote behavioral depression in animal studies (Goshen et al. 2008, Hueston et al. 2018), that there is heightened receptor expression of the

cognate IL-1 type I receptor (IL-1R1) in the hippocampus (Farrar et al. 1987), and that antidepressant treatment reduces IL-1 β levels in the hippocampus (Molteni et al. 2013, Sitges et al. 2014), it is not surprising that this proinflammatory cytokine is now established as a significant contributor to hippocampal dysfunction in depression. As well as influencing the function of mature neurons, IL-1 β can directly interact with newly born neurons as a result of the expression of IL-1R1 on neural progenitor cells in the hippocampus (Koo & Duman 2008, Ryan et al. 2013). Several groups have now published key studies demonstrating that IL-1 β negatively affects hippocampal neurogenesis and that there are associated behavioral consequences (Goshen et al. 2008, Green et al. 2012, Hueston et al. 2018, O'Leime et al. 2018). Indeed, IL-1 β is suggested to be important for chronic stress-induced depression through its negative impact on hippocampal neurogenesis (Goshen et al. 2008). Moreover, studies have reported that IL-1 β -induced reductions in hippocampal neurogenesis are reversed by antidepressant treatment in vitro and in vivo (Koo & Duman 2008). IL-1 β is produced predominantly by microglia in the hippocampus, and so this dynamic cell, which has an important role to play in shaping the development of neurons, has been investigated for its contribution to stress-induced depressive-like behavior through changes in hippocampal neurogenesis. Interestingly, blockade of stress-induced microglial activation and the antidepressant drug imipramine independently rescued the stress-induced depressive-like behavior and suppressed neurogenesis (Kreisel et al. 2014). In addition to proinflammatory cytokines and microglia, there is evidence to suggest that T cells are also required to sustain hippocampal neurogenesis (Wolf et al. 2009, Ziv et al. 2006).

6.3. Microbiome and Hippocampal Neurogenesis

Growing evidence suggests that the gut microbiome is also a critical modulator of the immune system in the context of adult hippocampal neurogenesis (**Figure 3**). Indeed, germ-free mice presented increased levels of adult hippocampal cell proliferation and neurogenesis, which were not prevented by microbial recolonization from three weeks of age (Ogbonnaya et al. 2015). Interestingly, these effects were predominantly observed in the dorsal hippocampus rather than the ventral hippocampus, which may have interesting implications for cognitive functions that predominantly engage the dorsal hippocampus such as spatial learning and memory (O'Leary & Cryan 2014). On the other hand, a recent study showed that antibiotic treatment reduced adult hippocampal neurogenesis, which was reversed by probiotic treatment and voluntary exercise, not through fecal transplantation but by modulating Ly6Chi monocyte trafficking (Möhle et al. 2016). Therefore, the gut microbiome seems to be involved in the modulation of adult hippocampal neurogenesis, possibly through its interaction with the immune system. However, communication from the vagus nerve might also have a role to play, because we have found that vagotomy itself decreased hippocampal cell proliferation and neurogenesis, as measured using the marker for immature neurons, doublecortin (O'Leary et al. 2018). Moreover, vagus nerve stimulation is a treatment used in treatment-resistant depression and has also been shown to facilitate the maturation of immature newly born neurons in the hippocampus (Biggio et al. 2009) and to increase hippocampal cytogenesis (Revesz et al. 2008). There are limited data on whether probiotics can affect adult hippocampal neurogenesis, but one study has reported that treatment with a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 combination) could prevent stress-induced decreases in the number of cells expressing doublecortin, a marker of neurogenesis (Ait-Belgnaoui et al. 2014).

It is clear from animal studies that adult hippocampal neurogenesis is pivotal for antidepressant action and has been consistently proven to be dampened by stress and in depression. The recent re-appreciation of the importance of adult neurogenesis in the human hippocampus



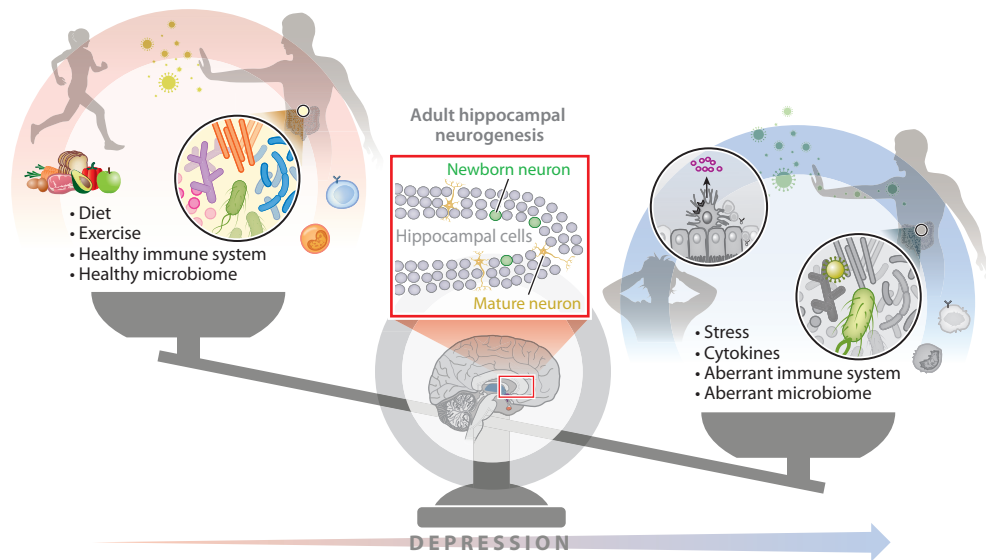


Figure 3

Adult hippocampal neurogenesis is an important modulator in the orchestrated pathways involved in depression. This process is positively influenced by diet and exercise along with a healthy immune system and gut microbiome, while being negatively affected by factors such as stress and an aberrant immune system and gut microbiome. A role for adult hippocampal neurogenesis at the heart of this unholy trinity seems likely, as this crucial process is regulated by this triune.

(Moreno-Jiménez et al. 2019) gives further impetus to discover strategies that target it in order to maintain normal hippocampal function. Given the potential modulation of gut microbiome on this central process, future studies should tackle the potential mechanistic pathways that might connect the gut microbiome to the brain and the correct integration of adult neurogenesis, particularly in the context of stress, inflammation, and subsequent depression.

7. DIET AND THE MICROBIOTA-GUT-BRAIN AXIS

In recent decades a massive shift in lifestyle, and in particular in diet, has occurred. Essentially, a great proportion of the human population adopted Western-style diets, which are high in processed foods, sugar, and fat, which are linked to the growing prevalence of obesity, diabetes, and cardiovascular disease (Pavillard et al. 2018). On the other hand, healthy diets such as the Mediterranean diet provide essential macronutrients such as flavonoids, omega-3 fatty acids, and omega-6 polyunsaturated fatty acids (Willett et al. 1995) that are associated with better life expectancy and health (Sofi et al. 2013). However, reports have also linked the consumption of Western diets with cognitive and mood disorders (Jacka et al. 2010, Kanoski & Davidson 2011), while the Mediterranean diet has been associated with better cognitive function (Feart et al. 2010, Firth et al. 2019, Lassale et al. 2019). Moreover, a recent systematic review concluded that adhering to a healthy diet, in particular a traditional Mediterranean diet, or avoiding a proinflammatory diet, appears to confer some protection against depression in observational studies (Feart et al. 2010, Firth et al. 2019, Lassale et al. 2019). Such studies provide clear evidence for a nutritional approach to preventing depression. Understanding the mechanisms underpinning such effects will be important moving forward, especially at the microbiota-immune-stress level.

Indeed, recent studies showed that higher intakes of unhealthy foods and lower consumption of nutrient-dense foods were associated with decreased hippocampal volume (Jacka et al. 2015), and

inversely, that healthier diets were linked with larger hippocampal volume in humans (Akbaraly et al. 2018). In fact, in preclinical models different dietary interventions have been implicated in neuronal plasticity in the hippocampus, which further highlights the paramount importance of a healthy diet in the promotion of the homeostasis and function of the brain. Moreover, it has recently been shown that the addition of a modified Mediterranean diet to normal antidepressant or psychotherapy can have a marked positive effect on depression (Jacka et al. 2017). Given that the Mediterranean diet markedly affects the microbiota composition, it is tempting to speculate that the microbiota may play a role in the beneficial effects of such dietary interventions.

Dietary changes seem therefore, an interesting intervention to promote general health. In fact, there is growing interest in lifestyle changes, particularly in adopting distinct diets—such as the Paleolithic, ketogenic, and plant-based diets, among others—that are thought to promote health benefits, which in turn might be related to the modulation of inflammation and/or the gut microbiome (Dinu et al. 2017, Whalen et al. 2016, Williams & Cervenka 2017, Zopf et al. 2018). Moreover, given that the early-life environment deeply shapes neurodevelopment and that diet has been linked to neuroplasticity, it would be extremely important to assess the relevance of diet in early life. Further studies should tackle the potential brain health benefits of these diets and their underlying mechanisms.

8. CONCLUSION

The fine balance between gut microbiome, immunity and the stress response is crucial for nervous system health. Ultimately, disruption of one or more factors in this matrix (for example, by negative life events) can result in the dysregulation of brain physiology and behavior, contributing to the development of mood disorders such as MDD. Although the components of this unholy trinity are being studied individually in the context of depression, much work is needed at a mechanistic level in preclinical and human studies to tease apart the relative contribution of each of them and how they interact with each other.

As stated in the introduction, there is a large population of patients who do not respond to conventional treatments for depression, and understanding how this triune may play a role in treatment-resistant depression is an important avenue for further research. We now appreciate that imbalanced stress and inflammatory responses are undoubtedly involved in the development and maintenance of depression, but recent evidence suggests that the gut microbiome, too, may play a role in the imbalance of these pathways and in neuropsychology, indicating that therapeutics that target these factors might be more effective. The role of the microbiota in disease is only now emerging, particularly in the field of neuropsychology. Studies are pointing to a role for gut microbial alteration in depressive patients and following antidepressant medications (Cusotto et al. 2019); however, further studies should examine the changes in the microbiome following psychological therapies such as cognitive behavioral therapy.

Therefore, psychobiotic interventions may potentiate the beneficial effect of the existing therapeutics, likely resulting in better outcomes. However, there is a real need for large-scale, double-blind, placebo-controlled trials with specific strains of bacteria, or combinations thereof, to validate such approaches. Furthermore, a healthy lifestyle that includes a nourishing, balanced diet and regular exercise may contribute to the balance of the gut microbiome and to adult neurogenesis, which in turn feed the mutual exchange with the immune system and the stress response, potentially preventing conditions such as depression.

In conclusion, the ideal treatment for depression is maybe one that resets the imbalance in immunity, stress physiology, and microbiota. We await this elusive four-leaf clover (**Figure 4**), but current research suggests that it is a viable strategy to elucidate.





Figure 4

The underlying contribution of stress, the immune system, and the gut microbiome to depression. Understanding the complex communication among these factors, and their consequent effects on key processes such as adult hippocampal neurogenesis, may lead to better, more targeted treatment to the patients that do not respond to conventional antidepressant treatment.

SUMMARY POINTS

1. Negative life events may be perceived by the body as an imminent threat, and the body's response to stress can lead to long-term negative impacts after repeated exposure, affecting not only the HPA axis but also the immune system.
2. Stress exposure may also promote inflammatory states that lead to detrimental clinical features of depression.
3. In the intestinal environment, gut bacteria and the host's immune system act synergistically controlling/promoting each other's activity, which influences brain-gut communication.
4. Psychobiotic interventions may protect against the harmful physiological impacts caused by stress exposure; however, further large-scale, longitudinal, placebo-controlled studies are warranted.
5. Adult hippocampal neurogenesis is a crucial brain process regulated by neuroinflammation, stress, and microbiome composition that plays a key role in the etiology of depression.
6. Balanced diets have been shown not only to promote brain function in preclinical models but also to have a markedly positive effect in depression when added to conventional psychotherapeutic treatment in humans.
7. Overall, depression is an unholy trinity of alterations at the level of stress, inflammation, and microbiome; thus, any successful treatment should tackle all these aspects.

FUTURE ISSUES

1. Growing evidence shows that peripheral inflammation along with neuroinflammation seem to be crucial in the development of depression; however, future studies should target specifically how inflammation develops in response to stress and how novel therapeutics might target these processes.

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2. Large-scale, longitudinal clinical studies are needed to further dissect the involvement of the gut microbiome in the host's response to repeated stress exposure and to investigate whether this factors into the individual's susceptibility to develop depression.
3. Preclinical studies are required to understand the involvement of the gut microbiome in adult hippocampal neurogenesis and how this potentially relates to antidepressant efficacy, given the relevance of the latter process in the action of these therapeutics.
4. Early-life insults deeply impact neurodevelopment, resulting in long-lasting susceptibility to neuropsychiatric disorders; therefore, future studies should tackle the importance of diet in early life.

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