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Invited Review

Microbes and mental health: A review

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ABSTRACT

There is a growing emphasis on the relationship between the microorganisms inhabiting the gut (gastrointestinal microbiota) and human health. The emergence of a microbiota-gut-brain axis to describe the complex networks and relationship between the gastrointestinal microbiota and host reflects the major influence this environment may have in brain health and disorders of the central nervous system (CNS). Bidirectional communication between the microbiota and the CNS occurs through autonomic, neuroendocrine, enteric, and immune system pathways. Potential neurobiological mechanisms through which disruptions in this network may impact health and disease include hypothalamic-pituitary-adrenal (HPA)-axis activation, and altered activity of neurotransmitter and immune systems. Perturbations of the gut microbial community have already been implicated in multiple host diseases such as obesity, diabetes, and inflammation, while recent evidence suggests a potential role of the microbiota-gut-brain axis in neuropsychiatric disorders, such as depression and anxiety. Here, we review the current literature related to the influence of the gut microbial community on central nervous system function, with a specific focus on anxiety and depressive symptoms. The role of stress and stress-mediated changes in autonomic, neuroendocrine, immune, and neurotransmitter systems are examined, followed by a discussion of the role of the microbiota in novel gastrointestinal-based treatment options for the prevention and treatment of brain-based disorders such as anxiety and depression.

Contents

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1. Introduction

The gastrointestinal (GI) tract is home to over 100 trillion microorganisms (bacteria, archaea, yeasts, single-celled eukaryotes, parasites and viruses) that are responsible for multiple host functions and essential for health. This microbiota, the ecological community of commensal, symbiotic, and pathogenic microorganisms, can weigh up to 2 kg and contain at least 1000 different species of known bacteria with more than 3 million genes (Bermon et al., 2015). These microorganisms have been implicated in the development and functioning of a number of basic physiological processes, including digestion, growth, and the maintenance of homeostasis. The GI microbiota may also play a role in multiple chronic diseases, such as obesity, chronic inflammatory diseases, type 2 diabetes, and asthma. Recently, studies have highlighted the influence of the gut microbiota on the gut-brain axis, and its potential role in central nervous system (CNS)-related conditions and neuropsychiatric disorders (Cryan and Dinan, 2012; Foster and McVey Neufeld, 2013). Although the mechanisms of action are not well understood, research suggests bidirectional communication between the gut microbiota and the CNS via autonomic, neuroendocrine, and immune pathways. Key signaling events in this "information highway" likely include the vagus nerve, metabolites and CNS signaling systems, and production and control of neurotransmitters and brain neurotrophins. Accumulating evidence in human and animal studies suggest a role for the gut microbiota in brain function, including for anxiety and mood disorders. Anxiety and depression, two of the most prominent neuropsychiatric disorders that affect millions of people worldwide, may therefore be influenced by this microbiota-gut-brain axis. In this review, we will provide evidence that the gut microbiota influences the development and function of the CNS and, ultimately, behavior. We will specifically highlight evidence supporting the presence of the microbiota-gut-brain axis, biologically plausible pathways through which bidirectional influence occurs, and its relationship with mental health disorders, including anxiety and depression. Finally, emerging treatment and prevention strategies involving the manipulation of microbial communities will be explored, with implication for anxiety and depression. These integrative approaches may provide a novel approach to treat various disorders and chronic diseases.

2. The gut microbiota

An estimated 10^{14} microorganisms inhabit the human GI tract, more than ten times the number of somatic and germ cells in the human body (Gill et al., 2006). Although recent estimates have questioned this ratio and more conservative estimates from the American Academy of Microbiology suggest a ratio of 3:1 for microorganisms to human cells, evidence increasingly points to the potential impact of the microbiota on human health. The majority of the microbiota exists in the large intestine and undergoes change during the host's life cycle, with the most dynamic changes occurring during infancy. It is recognized that approximately one third of our gut microbiota is common among most humans, while the other two-thirds are individually specific (Qin et al., 2010). As a result, the microbiota can provide a personal identity; however, this specificity may result in difficulty in defining and establishing a "healthy" microbiota. Despite this difficulty in establishing microbiota biosignatures, it is generally agreed that the characteristics of a healthy microbiota include the community stability and species diversity. Our understanding of the host-microbiome relationship is rapidly evolving, but it is now thought to be complementary and symbiotic (Backhed et al., 2005). That is, the influence of the microbiota on the development and functioning of multiple host systems, such as innate and adaptive immune responses (Matamoros et al., 2013) and regulation of homeostasis (Round et al., 2010; Olszak et al., 2012), begins early in life during the colonization of the gut, with a continuing influence on metabolism and disease susceptibility throughout the lifespan. Microbes also regulate multiple host metabolic pathways, including gut motility, intestinal barrier homeostasis, nutrient absorption, and fat distribution (Backhed et al., 2004; Bercik et al., 2012). As mentioned, the host and their microbes typically live in symbiosis; however, certain events or circumstances may cause a shift in this relationship leading to dysbiosis (Nicholson et al., 2012), which has been linked to multiple health conditions such as obesity, diabetes, asthma, inflammatory bowel diseases (IBDs), pain, and autism. A deeper understanding of the metabolic, signaling, and immune system axes that physiologically connect the gut, liver, muscle, and brain is prerequisite for optimizing therapeutic strategies to manipulate the gut microbiota to improve human health (Nicholson et al., 2012).

3. Microbiota-gut-brain axis

Reciprocal communication between the gut and brain is now well recognized (Cryan and Dinan, 2012). Multiple overlapping pathways including neuroendocrine, immune, and autonomic (ANS) and enteric nervous (ENS) systems (Banks, 2008; Mayer, 2011; Aziz and Thompson, 1998) allow for two-way exchange of afferent and efferent information across disparate bodily areas (Mayer, 2011). For instance, interactions within these systems often co-occur within the GI tract, which is home to approximately 500 million nerve endings and the largest concentration of immune cells in the body (Furness et al., 1999). These nerves comprise the ENS and approximately 20% have been classified as intrinsic primary afferent neurons. These afferent neurons within the ENS communicate subtle changes within the GI tract to the brain via the vagus nerve (Furness et al., 1999). Immune cells release cytokines that are important in host responses to inflammation and infection, while neuroendocrine hormones (e.g., cortisol) alter gut permeability, barrier function, and communicate with immune cells regarding cytokine secretion (Cryan and Dinan, 2012). This neuronal and biochemical signaling process occurs throughout the body, including through pathways established between the GI tract and the CNS. Researchers have referred to this dynamic signaling pathway as the 'gut-brain axis,' which includes the tissues and organs (brain, glands, gut, immune cells and GI microbiota). To date, components of this axis have received extensive study due to their role in digestive function and satiety (Tache et al., 1980; Konturek et al., 2004). Dysfunction of this gut-brain axis may have broad pathophysiological consequences and is associated with inflammation, chronic abdominal pain, eating disorders,

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nausea, and stress (Mayer, 2011; Drossman, 1998). Furthermore, the gut also contains millions of bacteria, which may also play an important role in the gut-brain axis and exert a substantial influence on human health. Elucidating the pathways through which the gut and brain interact and the biological mechanisms involved may help to advance integrative approaches to both GI and CNS disorders.

4. Key communication pathways and neurobiological mechanisms

Evidence from across the fields of neuroscience, gastroenterology, and microbiology have supported a modulatory role of gut microorganisms in various metabolic, GI, and neurological diseases (Sherwin et al., 2016). Given the complex network of communication between the gut microbiota and brain and the exchange of information across the gut-brain axis, these microorganisms may also influence brain chemistry and behavior. There are multiple mechanisms and pathways through which the CNS and microbes interact with each other and influence host behavior, including through the sympathetic and parasympathetic branches of the ANS, and neuroendocrine and neuroimmune systems implicated in stress and stress-related disorders (Grenham et al., 2011). Our discussion below highlights several of these key communication and neurobiological pathways, including through the vagus nerve, cell wall, metabolites, and neurotransmitters and brain neurotrophic factors, which collectively may help to elucidate the effects of the microbiota on homeostasis and complex CNS disorders.

4.1. Vagus nerve

The vagus or tenth (X) cranial nerve, which conveys efferent and afferent sensory information between the periphery and the CNS, constitutes a direct link from the gut to the brain (Moriss, 2013). Findings from multiple studies have indicated that primary afferent pathways through the vagus mediate communications between gut microbes and the CNS (Goehler et al., 2008; Lyte et al., 2006). These studies have identified the induction of c-FOS in vagal sensory neurons and post vagotomies as a possible neural mechanism of these interactions. The expression of c-FOS and upregulation of neuronal c-FOS mRNA have been proposed as indicators of recent neuronal activity. Interestingly, animals infected with pathogenic *Citrobacter rodentium* and *Campylobacter jejuni* evidence increased levels of c-FOS in vagal sensory ganglia and visceral sensory nuclei in autonomic and select brain regions (paraventricular nuclei, basolateral nuclei of the amygdala, bed nucleus of the stria terminalis, medial prefrontal and anterior cingulate cortices) compared to non-infected animals, suggesting links between GI pathogenic challenges and brain regions implicated in anxiety (Goehler et al., 2008; Lyte et al., 2006). Vagotomy studies in rats infected with *Salmonella typhimurium* to mimic the condition of natural bacterial infection further confirmed a role of the vagal nerve pathway in the transmission of gut immune signals to the CNS; once the vagal pathway was severed, c-FOS expression in those neurons was attenuated and there were a decreased percentage of immune cells (Wang et al., 2002). Thus, exploring the role of vagal afferent pathways in mediating cross-talk between the gut microbiota and brain may prove useful in developing therapeutic interventions for behavioral disorders.

4.2. Cell wall components and immune responses

Bacteria have a peptidoglycan cell wall that activates both the innate and adaptive arms of the host mucosal immune system. The innate immune response is primarily stimulated by the recognition of these pro-inflammatory microbial constituents generally known as pathogen-associated molecular patterns (PAMPs). PAMPs bind to pattern-recognition receptors (PRRs) on defense cells, triggering the production of inflammatory cytokines which can influence the brain either indirectly through peripheral vagal pathways or directly through permeable regions of the blood-brain-barrier (Sherwin et al., 2016). For example, pro-inflammatory cytokines, such as interleukin 6 (IL-6) and chemokine ligand 2 (CCL2) can act on the brain via two pathways: 1) a humoral pathway in which PAMPs act on toll-like receptors (TLRs) in specific brain areas; and 2) a neural pathway through afferent nerves. PAMPs associated with the Gram-negative cell wall include peptidoglycan monomers, lipopolysaccharide (LPS), porins, and mannose-rich sugar chains. PAMPs associated with Gram-positive bacteria include peptidoglycan monomers and lipoteichoic acids. Many of these cell wall components may stimulate the production of additional molecules involved with neural signaling from intestinal epithelial cells (Forsythe and Kunze, 2013). More studies are necessary to confirm these findings; however, the potent immunomodulatory effects of the gut microbiota on both the mucosal and systemic immune system highlights potential mechanisms through which the gut microbiota may influence brain function and behavior.

4.3. Metabolites

Metabolites derived from both the digestion and microbial fermentation of dietary and nutritional components may have a significant effect on brain processes and immune responses. For instance, manipulating the composition of the gut microbiota has been shown to influence the availability and regulation of fatty acids and tryptophan. In turn, fatty acids and tryptophan can interact with the immune system, thus regulating cellular immune responses. Considering the essential role of these metabolites to human health, they are important mediators of the gut-brain axis and may serve as effective targets for clinical intervention (Fig. 1).

4.3.1. Fatty acids

The brain is enriched with fatty acids that help regulate several processes such as neurotransmission, cell survival, and neuroinflammation (Bazinet and Laye, 2014). Further, dietary fatty acids are involved in the production of eicosanoids, a class of chemical messengers involved in immune and inflammatory responses through gene regulation, cytokine biosynthesis, and membrane composition and function alterations (Fritsche, 2006). Fatty acids can also regulate gene transcription by binding to and activating a family of nuclear receptors known as peroxisome proliferator-activated receptors (PPARs), which affect cellular differentiation and functional properties. Fatty acids may also bind to specific immune cells (e.g., T-cells, B-cells, macrophages) to promote inflammation. In contrast, microbial-derived short-chain fatty acids possess potent anti-inflammatory properties and are the primary metabolites of gut bacteria. Specifically, species of *Eubacterium, Roseburia, Faecalibacterium, Bifidobacterium, Lactobacillus and Enterobacter*, all found within the microbiota, produce acetate, butyrate, isobutyrate, hexonate, and propionate (Nicholson et al., 2012). These fatty acids have been shown to impact intestinal permeability, enhance immune system functioning, alter lipoprotein profiles, and decrease colonic pH. In addition, short-chain fatty acids have a particular role in enteroendocrine signaling by binding to a cognate receptor (e.g. GPR43 or GPR41) to stimulate the release of neuropeptides, such as peptide YY (PYY) and glucagon-like peptide (GLP-1) (Kuwahara, 2014). Once released, these peptides influence the regulation of energy homeostasis through the activation of both enteric and primary afferent vagal pathways

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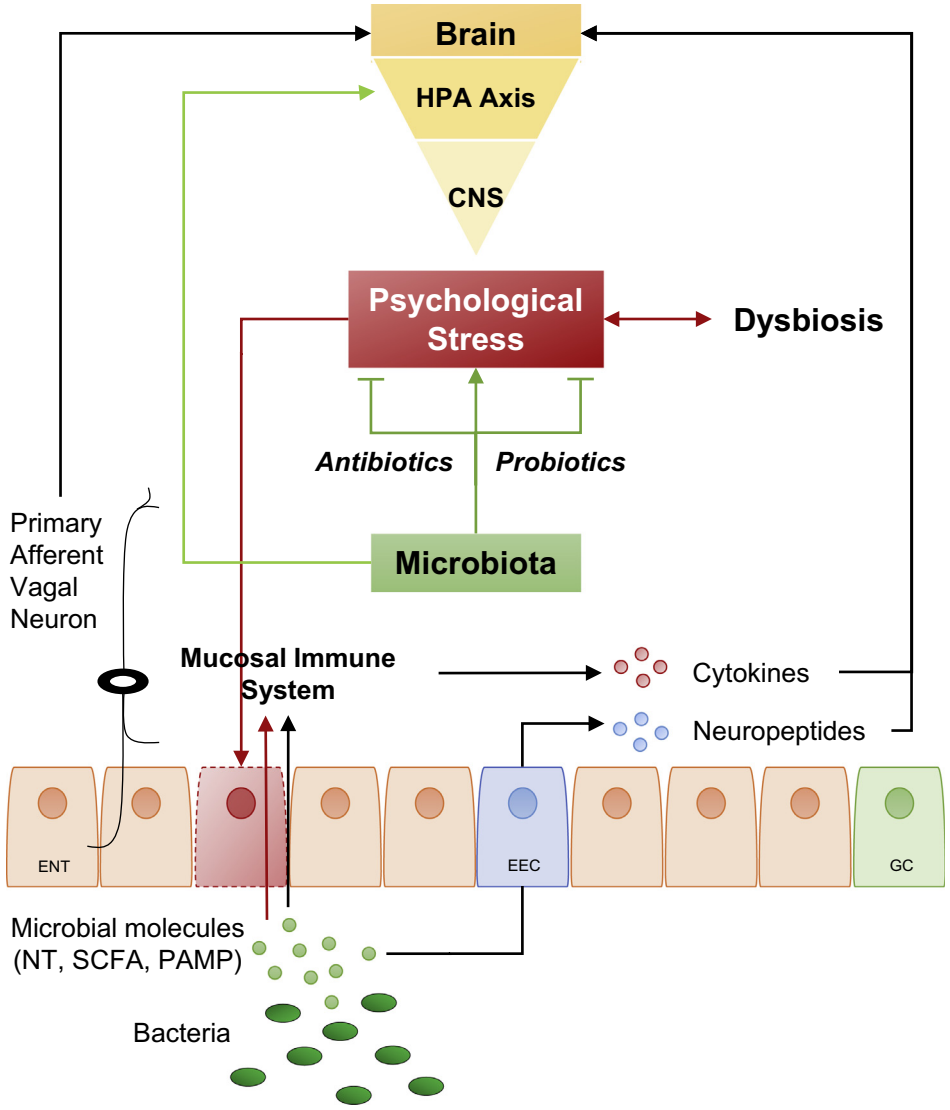

Fig. 1. The influence of the microbiota-gut-brain axis on stress-related disorder and mental health. Multiple mechanisms are involved by which the microbiota influences the brain and host behavior. Bacteria and their components are sampled and removed from the mucosa by both the innate and adaptive arms of the mucosal immune system, releasing cytokines and other CNS signaling molecules. Microbial metabolites, such as short-chain fatty acids (SCFA), can stimulate the release of neuropeptides and other gut hormones from enteroendocrine cells. Intrinsic primary afferent neurons (IPAN) monitor the mucosa and communicate mucosal status to the brain mainly through vagal afferent neurons. Chronic stress-related disorders, including anxiety and depression, may be influenced by the gastrointestinal microbiota and microbiota-gut-brain axis. Further, the disruption of homeostasis in the HPA axis contributes to the pathophysiology of these disorders. Increasing evidence suggests that the microbiota significantly influences the development and hypersensitivity of the HPA axis in response to stressors. Psychological stress has also been shown to promote intestinal inflammation, thereby disrupting the intestinal barrier and promoting the influx of microorganisms and their components into the mucosa and contributing to an enhanced immune response. Dysbiosis of the microbiota may exacerbate the degree of psychological stress as well. Conversely, chronic psychological stress may compound the degree of dysbiosis. Both antibiotics and probiotics have shown to attenuate psychological stress responses, suggesting that the microbiota may have a more putative role in mediating the effects of stressors on psychological outcomes. ENT, enterocyte; EEC, enteroendocrine cell; GC, goblet cell; NT, neurotransmitters; PAMP, pathogen associated molecular patterns.

(Kuwahara, 2014). Interestingly, N-butyrate and propionate have been shown to have neuroactive properties as well (den Besten et al., 2013). Given the influence of microbial-derived short-chain fatty acids on energy metabolism and the production of secondary peptides, this represents another plausible mechanism through which the gut microbiota influences human behavior.

4.3.2. Tryptophan

Tryptophan is an essential amino acid and is a precursor to many biologically active agents, including in the synthesis of serotonin in the CNS. Serotonin, which has been implicated in depression, is predominantly located in the gut where it is synthesized from tryptophan in enterochromaffin cells of the GI tract. Synthesis of serotonin relies heavily on the availability of tryptophan and the rate-limiting enzyme tryptophan hydroxylase. Low levels of plasma tryptophan have been associated with alterations in immune function (Song et al., 1998; Schrocksnadel et al., 2006). This co-influence of tryptophan and immune system function may have marked effects on CNS function and the development of mood disorders. To evaluate the potential antidepressant properties of probiotics, Desbonnet et al. demonstrated that rats fed the probiotic bacterium *Bifidobacterium infantis* (*B. infantis*) had an attenuation in several proinflammatory cytokines, increased plasma concentrations of tryptophan, and exhibited a reduction in depressive-like behaviors following a forced swim test (Desbonnet et al., 2008). Importantly, probiotic treatment also

resulted in a reduced concentration of serotonin and dopamine metabolites in the frontal cortex and amygdala.

The dominant physiological pathway for tryptophan metabolism is the kynurenine pathway, whose dysregulation has also been implicated in many disorders of the brain and GI tract. Kynurenine can be further metabolized into two different products, one which produces a number of neurotoxic metabolites (e.g., quinolinic acid) and the other being the neuroprotective kynurenic acid. Indeed, the increased conversion of plasma kynurenine to kynurenic acid has been proposed to be neuroprotective and attenuate stress-induced depression (Agudelo et al., 2014). Findings from the Desbonnet et al. study indicated a preferential metabolism of kynurenine to kynurenic acid (Desbonnet et al., 2008); as tryptophan levels increased in animals treated with *B. infantis*, kynurenic acid also increased. These findings suggest that certain probiotics may have the ability to influence tryptophan metabolism and attenuate the extent of stress-induced depression through an increased conversion of peripheral kynurenine to kynurenic acid.

5. Neurotransmitters and neuropeptides

It has been shown that multiple bacteria (*Lactobacillus, Bifidobacterium, Escherichia, Enterococcus* and *Truchuris*) produce neurotransmitters and neuropeptides (Cryan and Dinan, 2012; Bercik et al., 2010; Barrett et al., 2012; Higuchi et al., 1997). Some of these include gamma-aminobutyric acid (GABA), serotonin and brain-derived neurotrophic factor (BDNF). Neurotransmitters are chemical messengers that transmit signals across a chemical synapse from one neuron to another target neuron, muscle cell, or gland cell. Neuropeptides are small proteins that can be released in the brain to activate different receptors allowing neurons to communicate with each other. Neuropeptides serve many functions and differ from neurotransmitters in several ways, including that many neuropeptides appear to be associated with specific behaviors (e.g., role of oxytocin in maternal behavior and pair bonding). Both are considered neuronal signaling messengers, and imbalances can have marked effects on brain and behavior.

5.1. GABA

GABA, the main inhibitory neurotransmitter of the CNS, acts as a principal chemical regulating neuronal excitability and is produced from glutamate metabolism. Dysfunction of the GABA system has been implicated in the pathophysiology of several chronic diseases, including anxiety and depression. Microbes, such as species of *Lactobacillus* and *Bifidobacterium,* are able to produce GABA from glutamate in culture (Barrett et al., 2012; Higuchi et al., 1997). Further, *L. rhamnosus* is able to modulate the central expression of GABA receptors in key CNS brain regions in mice and therefore may have beneficial effects in the treatment of depression and anxiety. In addition, the vagus nerve has been shown to be necessary for some of the behavioral and molecular changes induced by *L. rhamnosus*, further demonstrating a functional communication pathway between bacteria, the gut, and the brain (Bravo et al., 2011). Thus, one proposed mechanism through which bacteria may be influencing brain chemistry is through regulation of the GABA system.

5.2. Serotonin

Serotonin is also a monoamine neurotransmitter implicated in the regulation of virtually all brain functions and modulates a number of physiological processes such as mood, sleep, pain, aggression and sexual behavior. Dysregulation of the serotonergic system has been implicated in the pathogenesis of many neuropsychiatric disorders, including anxiety and depression. Reduced production of serotonin, lack of receptor sites for serotonin, or inability of serotonin to reach the receptor sites all are potential problems that could contribute to dysfunction. Noteworthy, approximately 90% of serotonin is produced in the enterochromaffin cells in the GI tract. Species of *Escherichia* and *Enterococcus*, commonly found in the gut, can also produce serotonin (Cryan and Dinan, 2012). Further, gut microbes can promote serotonin production through the activities of short chain fatty acids on enterochromaffin cells (Reigstad et al., 2015). By controlling production of serotonin, gut microbes could be directly influencing CNS function. For instance, Clarke et al. reported increases in hippocampal concentrations of serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in male germ-free (GF) animals compared with conventionally colonized control animals (Clarke et al., 2013). Plasma concentrations of tryptophan were also increased in the male GF animals, suggesting a possible humoral route through which the gut microbiota may influence CNS serotonergic neurotransmission. Furthermore, once the GF mice reached adulthood, they were unable to reverse the levels of serotonin and 5-HIAA with colonization of microbiota from conventionally colonized mice. While GF animals are providing insight to development of these host systems in the absence of microbiota, caution should be taken when interpreting the results or making comparisons to humans.

5.3. Brain derived neurotrophic factor (BDNF)

BDNF is a neurotrophin (protein) widely expressed in the CNS that supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses. Substantial evidence supports the neuroprotective functions of BDNF and its role in the growth and plasticity of synapses and the survival and differentiation of neurons. Decreased levels of BDNF have been associated with chronic depression and various treatments for depression (e.g., antidepressants) have been shown to increase the expression of BDNF in the brain. Interestingly, BDNF mRNA and protein levels have been associated with the gut-brain axis. Specifically, intestinal microbiota have been noted to increase levels of hippocampal BDNF in specific pathogen free mice after being treated with antimicrobials and fecal transplants (Bercik et al., 2011). In mice infected with *Truchuris muris*, a decreased level of hippocampal BDNF mRNA was observed, but after treatment with *B. longum,* levels of BDNF were normalized (Bercik et al., 2010). Oral antibiotics given to specific pathogen free mice and colonization of GF BALB/c mice with NIH Swiss mice have been shown to increase exploratory behavior with increased BDNF expression as well (Esworthy et al., 2010). Yet, studies using GF mice have shown conflicting results relative to BDNF, and associations between levels of BDNF with anxiety-like behaviors. Swiss Webster, NMRI, and BALB/c male mice were found to have decreases in BDNF levels correlating with reduced anxiety (Clarke et al., 2013; Diaz Heijtz et al., 2011; Sudo et al., 2004). However, two additional studies involving Swiss Webster female mice reported decreases (Gareau et al., 2011) and increases in BDNF (Neufeld et al., 2011). It is possible that the influence of the gut microbiota on BDNF is moderated by not only strain and sex, but also by other hormonal and/or experimental factors. For instance, estrous cycles can influence stress-related behaviors, and this may have resulted in differences in BDNF expression that have been reported between male and female mice. Also, housing conditions of GF mice and the order and timing of behavioral testing may have impact BDNF outcomes. Considering the role BDNF in neuroplasticity and neurological disorders, future research is warranted to examine associations with BDNF and other neurotrophins, and under what conditions these growth factors are influenced by the microbiota.

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6. Influence of the microbiota-gut-brain axis on anxiety and depression

Anxiety, a psychological state characterized by apprehension or fear, is among the most commonly experienced psychiatric disorders (Baxter et al., 2013) and globally, more than 350 million people suffer from depression (Kessler and Bromet, 2013). These mental health disorders cause significant impairment and contribute to loss of productivity, increased annual health care costs, and represent an economic burden to the public health care system (Center for Disease Control, 2013). Alarmingly, many individuals who suffer from these mental health disorders either fail to seek or fail to respond to traditional forms of treatment (i.e., antidepressants, cognitive behavioral therapy). While the precise etiology of these disorders remains unknown, several proposed neurobiological mechanisms have been proposed and range from chemical imbalances in the brain to illnesses, inflammation, and stress. For instance, reductions in key neurotransmitters (serotonin, norepinephrine, dopamine), changes in neuroendocrine pathways and hormones (e.g., cortisol), increased inflammatory cytokines (e.g., IL-6), and circulating leukocytes in response to illness and inflammation have all been implicated in anxiety and depression. One way to conceptualize these dynamic and interrelated physiological changes is through stress. Key biological responses involved in stress include not only the hypothalamic-pituitary-adrenal (HPA)-axis and the autonomic nervous system, but also their complex interactions with metabolism and the pro- and anti-inflammatory components of the immune system (McEwen et al., 2015). Of importance to the current review, a growing body of evidence supports a bidirectional relationship between commensal organisms within the gut and programming and responsivity of the stress system (Cryan and Dinan, 2012). The gut microbiota may play an important role in the treatment and prevention of anxiety and depression through stress-related neuroendocrine, autonomic, and immune pathways.

6.1. Microbes and stress

Psychological stress is an inherent part of life, yet perturbations in stress responses have widespread psychobiological implications for brain and behavior. Research from disparate fields such as neurobiology and microbiology has demonstrated that natural barrier defenses, such as those provided by commensal microbes, can be disrupted by exposure to psychological stressors. For instance, an early study by Tannock and Savage (1974) demonstrated that moving mice into a cage lacking bedding, food, and water reduced the number of *Lactobacilli* that could be cultured from the gastrointestinal tract. While this study had several methodological limitations (e.g., the lack of provision of food and water), the adverse consequences of novel housing was suggested as a potential cause. Nonetheless, this study prompted further investigation into the influence of psychological stressors on microbial health. For instance, infant rhesus monkeys who received *ad libitum* access to food and water were exposed to a maternal separation stressor and showed a substantial decrease in overall cultured *Lactobacilli* (Tannock and Savage, 1974). Interestingly, those monkeys who showed the greatest signs of behavioral stress had the lowest number of cultured *Lactobacilli*.

Chronic stress in adulthood has also been shown to affect the composition of gut microbiota. Bailey et al. (2011) exposed mice to a social disruption stressor, which results in an increase in circulating cytokines and enhanced innate immune reactivity. They found that the microbiome in mice exposed to the stressor differed from that of non-stressed control mice, with significant decreases in the abundance of *Bacteroides* spp. and *Clostridium* spp. Moreover, mice exposed to the social stressor demonstrated enhanced immune and inflammatory responses indicated by increased circulating levels of IL-6 and reactivity of splenic macrophages to microbial stimulation. In contrast, mice treated with antibiotics or who were GF and exposed to the social disruption stressor showed no increase in circulating IL-6 and splenic reactivity, indicating a potential necessary link of microbiota for stressor-induced immune activation.

A landmark study by Sudo et al. (2004) demonstrated that GF mice have an overactive HPA-axis response to stress whereby exposure to a mild restraint stressor induced an exaggerated release of adrenocorticotropic hormone and corticosterone. This response was partially reversed by colonization with microbes from control mice, and it was fully reversible through colonization with *B. infantis* (Sudo et al., 2004). Interestingly, it was noted that the reversal of the exaggerated stress hormone response may require re-colonization during a "critical window" of time (Sudo et al., 2004). This suggestion was supported by the inability to reverse the exaggerated HPA-axis response in adult mice (9 weeks of age). Similar studies involving GF mice and behavior have pointed to this critical time period and suggest that reconstitution of microbiota should occur early in life (Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011). Indeed, Swiss Webster GF female mice conventionalized with specific pathogen free microbiota after week 10 were unable to reverse anxiety-like behaviors (Diaz Heijtz et al., 2011; Neufeld et al., 2011), whereas introduction of specific bacterial strains at birth and 3 weeks were normalized (Clarke et al., 2013; Diaz Heijtz et al., 2011). Furthermore, Sudo et al. observed complete reversal of the stress response in adult offspring when GF mothers were inoculated prior to giving birth (Sudo et al., 2004). Similarly, a study on asthma showed reversal of symptoms when mice were colonized with a unique mixture of bacteria within the first 100 days of life (Arrieta et al., 2015). These critical windows of inoculation warrant future investigation and may serve as novel approaches to address stress-related diseases.

6.2. Microbes and behavior

In addition to the influence of microbiota on physiology, emerging evidence indicates that behavior is also impacted through manipulations of gut bacterial composition. For instance, gut microbiota has been examined in relation to eating behavior (Alcock et al., 2014) and alterations in gut microbial composition has been associated with marked changes in behaviors relevant to mood, pain and cognition (Borre et al., 2014). Bercik et al. used GF animals to examine alterations in gut microbial communities in contributing to IBDs and neuropsychiatric disorders (Bercik et al., 2011). BALB/c and NIH Swiss mice raised in GF conditions were colonized with microbial profiles from either their own or an opposite strain. Notably, the behavioral traits specific to one strain transmitted along with the microbiota. For example, when BALB/c mice were inoculated from NIH Swiss mice, they increased exploratory behavior, whereas NIH Swiss mice inoculated with BALB/c microbes had reduced exploratory behavior (Bercik et al., 2011). It was suggested that BDNF might play a role in the induction of these behaviors during the transfer period, but not during the maintenance period (Bercik et al., 2011). Reversal of anxiety-like behaviors was also observed in Swiss Webster male mice colonized with conventionally colonized counterparts (Clarke et al., 2013). In sum, these studies point to a meaningful influence of gut microbes on behavior.

GF mice exhibit consistently reduced anxiety symptoms across different laboratories and published studies (Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011). Three independent laboratories have now shown that GF animals (of different strains

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and sex) show reduced anxiety-like behaviors in the elevated plus maze or light–dark box tests (Diaz Heijtz et al., 2011; Neufeld et al., 2011; Clarke, 2012). One study also reported changes in hippocampal BDNF mRNA and serotonin receptor 1A receptor mRNA expression in the dentate granule layer of the hippocampus in GF mice (Neufeld et al., 2011). However, the direction of these changes is not in agreement with other data reported (Bailey and Coe, 1999). The reasons for these discrepancies are currently unclear and further studies are required to establish how these changes at the molecular level contribute to the reductions seen anxiety-like behavior observed in GF animals.

Animal studies have demonstrated increased anxiety and stress-induced memory dysfunction related to alterations in the pathogenic bacteria *T. muris*, *C. rodentium*, and *C. jejuni* (Goehler et al., 2008; Lyte et al., 1998, 2006; Bercik et al., 2010). For instance, *C. rodentium* infection in C57BL/6 mice did not impact anxiety-like behavior either at the height of infection (10 days) or following bacterial clearance (30 days). However, following the exposure to acute stress, impairments in non-spatial memory were apparent after infection (10 days and 30 days), which was prevented by daily treatment of probiotics (Gareau, 2011). *C. jejuni* has also been shown to induce anxiety-like behavior eight-hours post-infection and multiple brain regions associated with anxiety-like behavior were activated, including the amygdala (Gareau, 2011). While *C. rodentium* and *C. jejuni* may have different effects on anxiety-like behaviors, these findings suggest that infection/inflammation may trigger bacteria to be pathogenic. From a clinical perspective, this may in part account for the relationship between abdominal pain/illnesses and stress-related psychiatric symptoms (Reber, 2012).

7. Gut microbiota treatments

7.1. Probiotics

The dynamic relationship between the gut microbiota and various health conditions have led to increasing interest in using probiotics to positively influence the gut microbiota. Probiotics are defined as living microorganisms that are believed to provide health benefits when consumed (Butel, 2014) and numerous preclinical and animal studies have demonstrated the potential of probiotics for the treatment and prevention of many diseases. The main bacterial genera used to alter the composition and diversity of the gut microbiota are the lactic acid-producing bacteria *Lactobacillus* and *Bifidobacterium* (Sherwin et al., 2016). There is also evidence supporting these probiotics in relation to anxiety, stress, and depressive-like behaviors in both animal and human studies. For instance, 55 participants were randomly assigned to either a probiotic mixture composed of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 or a placebo for 30 days. The participants were examined and those individuals who took probiotics displayed decreased scores on the global severity index of the Hopkins symptoms (HSCL-90) checklist and improved symptoms of anxiety and depression based on the hospital anxiety and depression (HAD) scale (Messaoudi et al., 2011a). A follow-up study among participants with the lowest urinary free cortisol levels at baseline suggested that daily intake of a probiotic could prevent symptoms of these mood disorders in those with low to mild stress levels (Messaoudi et al., 2011b).

Bifidobacterium longum subsp. *Infantis* 35624 (*B. infantis*) has recently been studied for treating gastrointestinal disorders among 275 non-patients with symptoms of abdominal discomfort and bloating. *B. infantis* has previously been shown to reverse the exaggerated stress response exhibited by GF animals (Sudo et al., 2004) and observed to reduce depressive-like symptoms in adult rats exposed to maternal separation during the neonatal period (Desbonnet et al., 2008, 2010). Although the mechanisms of action are unknown, *B. infantis* also has been shown to normalize peripheral pro-inflammatory cytokine and tryptophan concentrations implicated with depression (Maes et al., 2012). However, unlike the effect of *B. infantis* on abdominal pain and discomfort in patients with irritable bowel syndrome (IBS) Ringel and Ringel-Kulka, 2015, no effects were observed in non-patients in a large, multi-center clinical trial (Ringel-Kulka et al., 2016).

A similar double-blind trial was conducted to examine mood (assessed by the Profile of Mood States, POMS) and cognition (memory and verbal fluency) among 124 participants after 3 weeks of consuming either a probiotic milk mixture containing *Lactobacillus* or a placebo. The consumption of the probiotic-containing yoghurt improved the mood of those whose mood was initially poor, although no effects on cognition were found (Benton et al., 2007). Another recent clinical study was performed to determine whether consumption of a probiotic fermented dairy product alters emotional and visceral afferent brain responses during an emotional reactivity task (Tillisch et al., 2012). Otherwise healthy women were randomly assigned to three intervention groups: a no product, a control consisting of a milk-based non-fermented dairy product, or a probiotic dairy product containing *Bifidobacterium lactis* CNCM I-2494, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, and *Lactobacillus lactis*. Functional magnetic resonance imaging (fMRI) conducted at the end of the four-week intervention period showed that women in the probiotic group had less blood oxygen level dependent (BOLD) responses in the mid/posterior insula during the emotional reactivity task compared to the other groups. Perhaps related to emotional reactivity, women in the probiotic group also showed decreased connectivity of an amygdala-centered network with the insula, dorsal striatum and lateral prefrontal cortex. This pioneering study suggests that consumption of a probiotic fermented dairy product may be associated with modulations of brain regions concerned with the central processing of afferent signals from the gut and brain regions involved in emotional reactivity.

Although the precise mechanisms-of-action remain unknown, considerable data supports the possibility that probiotics confer health benefits (Ouwehand et al., 2002). Probiotics have also been shown to qualitatively alter the composition of bacterial species in the gut, leading to changes in the intestinal microbiota. Thus, the microbiota may serve as a mediator of the health benefits of probiotics. Future research in this area is promising and may help to advance our understanding of for whom and under what conditions probiotics may be used to treat and possibly prevent neuropsychiatric disorders.

7.2. Antibiotics

Antibiotics, also called antibacterials, are used in the treatment and prevention of bacterial infections and are an essential component of our microbial defenses (Keren et al., 2013). Given their significant impact on the GI microbiota, antibiotics are likely to affect the microbiota-gut-brain axis. Indeed, Bercik et al. (2011) showed that oral administration of neomycin and bacitracin combined with the antifungal agent primaricin to perturb the microbiota for seven days increased exploratory behavior. Specifically, adult male mice that were given antibiotic treatment for seven days showed reduced anxiety-like and increased exploratory behavior in the step-down and light/dark tests (Bercik et al., 2011). These findings indicate that alteration of the GI microbiota in adult mice results in measurable changes in anxiety-like behaviors. Interestingly, the authors reported that neither vagotomy nor sympathectomy affected the ability of the antimicrobials to impact anxiety-like behavior. These data point to other unidentified mechanisms

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as future candidates of study to understand the effects of this antibiotic regimen on physiology and behavior.

Although the manipulation of the microbiota for treating anxiety and depression-like behaviors has received little study, these findings highlight the potential for GI microbiota-based strategies using antibiotics as a potential treatment strategy for a variety of neuropsychiatric disorders. Caution, however, should be exercised due to antibiotic resistant bacteria or the potential to develop other antibiotic resistant bacteria.

7.3. Transplants

Recently, the idea of fecal microbiota transplantation (FMT) for a variety of health disorders has emerged. FMT has received the most scientific attention and seems to be a highly effective as a treatment for *Clostridium difficile* (Drekonja et al., 2015). For instance, Bercik et al. (2011) reported a reduction in anxiety-like behaviors among BALB/c mice after receiving a transplanted microbiome from NIH Swiss mice (Bercik et al., 2011). Several recent preclinical studies have used GF mice that have not been naturally colonized by microorganisms as a way to investigate the development and pathways through which gut microbiota can affect brain development and behavior. Germ free mice display increased motor activity and reduced anxiety, as well as alterations in CNS neurochemistry, compared with specific pathogen free mice with a normal gut microbiota (Diaz Heijtz et al., 2011). GF animals with transplanted bacteria from specific pathogen free mice demonstrated a reversal of the reduced anxiety, although these effects may be limited to sensitive periods across development (Clarke et al., 2013; Diaz Heijtz et al., 2011). In a clinical trial of patients with metabolic syndrome, half received a transplant from a lean donor while half received an auto-fecal transplant (Vrieze et al., 2012). Transplant from the lean donors resulted in improved insulin sensitivity and butyrate-producing intestinal microbiota, suggesting that intestinal microbiota might be a potential therapeutic agent to improve insulin sensitivity in humans. Although there is currently insufficient research involving the potential efficacy of FMT in depression, emerging evidence supports its use in patients with Parkinson's disease, multiple sclerosis, and autism (Xu et al., 2015). Overall, there is a marked lack of *in vivo* translational studies assessing the role of metabolite-producing bacteria and FMT approaches on key biological pathways and, ultimately, on brain and behavior. Successful preclinical and mechanistic studies are needed to determine if and how microbes are affecting brain and behavior before innovative treatment options can be tested in human clinical trials, and made available to individuals suffering from these illnesses.

8. Conclusions and future directions

Although we are still at a very early stage of understanding, bacteria and microbes within the human gut appear to play a fundamental role in immune function, adaptive stress responding, and ultimately, in brain function and behavior. Stress impacts the composition of gut microbiota and recent findings suggest that gut microbes can affect the stress-related HPA-axis, autonomic, and neurobiological functioning, thereby constituting fundamental mechanisms through which the microbiota may influence the CNS. Although a number of transmission routes for this complex network of communication are possible, recent findings point to the vagus nerve, neuroendocrine systems, and CNS neurotransmitters and growth factors. Preclinical studies and human clinical trials are early, but point to a potential role of various treatments (e.g., probiotics, antibiotics, FMT) in altering the composition of the gut microbiota, with accompanying changes in biobehavioral health outcomes. These studies represent an innovative approach to the prevention and treatment of various psychiatric disorders, such as depression and anxiety. Future work in this area may help to elucidate key interoceptive connections in human physiology and may also result in the advancement of state-of-the-art approaches for CNS and brain-based disorders. Noteworthy, there have been recent investigations of the influence of sleep (or lack thereof) and circadian rhythms on neurodegenerative diseases, such as Alzheimer's disease (Musiek and Holtzman, 2016; Cedernaes et al., 2016). Considering that short-term sleep deprivation has also been shown to induce slight changes in gut microbial communities (Benedict et al., 2016), this may suggest unique behavioral pathways through which alterations in the gut microbiota may influence human health.

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