Lead Article

Relationship between the gut microbiome and brain function

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It has become increasingly evident in recent years that the gut microbiome and the brain communicate in a bidirectional manner, with each possibly affecting the other's functions. Substantial research has aimed to understand the mechanisms of this interaction and to outline strategies for preventing or treating nervous system–related disturbances. This review explores the evidence demonstrating how the gut microbiome may affect brain function in adults, thereby having an impact on stress, anxiety, depression, and cognition. In vitro, in vivo, and human studies reporting an association between a change in the gut microbiome and functional changes in the brain are highlighted, as are studies outlining the mechanisms by which the brain affects the microbiome and the gastrointestinal tract. Possible modes of action to explain how the gut microbiome and the brain functionally affect each other are proposed. Supplemental probiotics to combat brain-related dysfunction offer a promising approach, provided future research elucidates their mode of action and possible side effects. Further studies are warranted to establish how pre- and probiotic interventions may help to balance brain function in healthy and diseased individuals.

INTRODUCTION

According to a statement by the World Health Organization, probiotics, when consumed in appropriate amounts, are beneficial to human health and well-being.[1] The benefits of probiotics include, but are not limited to, improved skin health, enhanced resistance to allergens, immune system support, reduction of pathogenic microorganisms, and protection of macromolecules (DNA, proteins, lipids) from oxidative damage.[2–5]

Human health can be both positively and negatively affected by the microorganisms living in the gut, known collectively as the gut microbiota,[6] which consists of bacteria, bacteriophages, viruses, fungi, protozoa, and archaea.[7–9] There is increasing evidence that the intestinal microbiota resembles a remarkably densely populated and diverse microbial community that plays a critical role in both the maintenance of human health and the pathogenesis of disease. The gastrointestinal (GI) tract is home to various microorganisms, whose collective genome is termed the gut microbiome.[10] Advances in DNA sequencing technology combined with novel bioinformatics tools have enabled scientists to describe the gut microbiome with unprecedented precision. It is estimated that the number of bacteria inhabiting the healthy human GI tract reaches up to 50 different phyla, 1000 different bacterial species, and 10^{14} viable bacteria per gram of luminal content.[11,12] The density of the human microbiome is highest in the colon, where Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria[11,13] are the most abundant organisms, constituting approximately 64%, 23%, 8%, and 3% of the population, respectively.[7–9]

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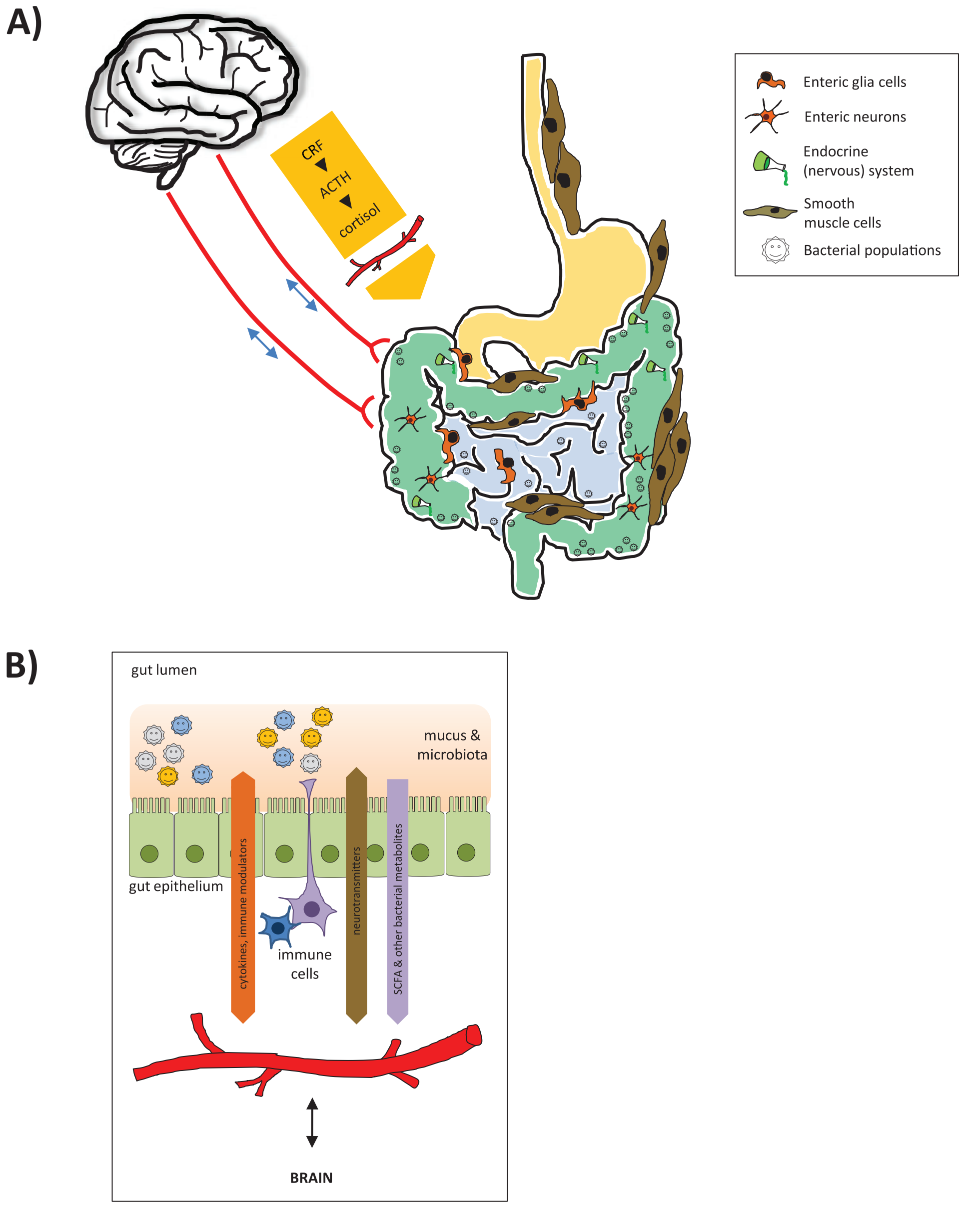

Figure 1 **Schematic presentation of the gut–brain axis.** (**A**) The upper part of the gastrointestinal (GI) tract, shown in yellow, includes the esophagus and the stomach. The small intestine (duodenum, jejunum, ileum) is shown in light blue; the large intestine (cecum and the ascending, transverse, and descending colon) is shown in green. The interactions between the GI tract and the autonomous and central nervous system are indicated by red lines. The short bidirectional blue arrows indicate afferences and efferences. The hypothalamic–pituitary–adrenal (HPA) axis is shown in dark yellow. (**B**) Simplified representation of the crosstalk between the microbiota, the brain, and the immune system. The gut microbiota and the immune system affect each other by releasing immunomodulators and/or cytokines, with potential systemic effects on the host. Short-chain fatty acids and other microbial metabolites are produced by the GI microbiota and may influence brain function, whereas several neurotransmitters are involved in the bidirectional communication between the host and the microbiota (see text for details). *Abbreviations*: ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing hormone; SCFA, short-chain fatty acids.

Diet is an important factor to influence the gut microbiome. For example, short-term consumption of diets composed entirely of animal or plant products rapidly changes structures of the microbial community, overwhelming interindividual differences in microbial gene expression.[14]

Scientific evidence accumulated in recent years suggests that the gut microbiota affects some aspects of brain function and behavior, including emotional behavior and related brain systems.[15] Figure 1 schematically outlines routes of communication between the gut and the brain. This review will examine the mechanisms of action of this communication and explore the implications for human health and daily living.

THE GUT MICROBIOME: ALTERATIONS THROUGHOUT LIFE

In healthy individuals, the gut microbiome is highly variable because the taxonomic variability within the GI tract depends on many factors, including genetic, physiological, psychological, and environmental determinants.[16–18] Despite the notion that each person's microbiota is unique, it is thought that humans might share a core microbiome and have a similar colonization of the GI tract by microbiota throughout life.[19] It has been recently shown that bacteria can be found in amniotic fluid, placenta, and the meconium of newborns,[20] which may help to explain the similarity of the microbiome in infants after a period of adaptation. Notably, developing embryos are exposed to bacteria in utero.[20] While infants born vaginally receive a seed of their microbiota during passage through the birth canal via exposure to maternal vaginal and perhaps fecal microbes, infants born by cesarean delivery receive their first major exposure to bacteria from their mother's skin and the hospital environment.[21] *Bifidobacterium*, *Lactobacillus*, Enterobacteriaceae, and *Staphylococcus* are the most populous organisms in the GI of the healthy, vaginally delivered infant GI tract, followed by *Veillonella* and Lachnospiraceae.[22] The composition of the infant's gut microbiota is unstable until approximately 2 years of age, ie, until the child begins to eat solid food.[21] Breastfed infants have a different microbiome than formula-fed infants, and by age of 3 years, the microbiota of most infants stabilizes and develops toward what becomes the adult microbial composition.[20]

In healthy adults, the gut microbiota is dominated by only a few phyla, as noted above,[7–9] and is characterized by a wide diversity of bacterial species.[17] The human microbiome changes with age, normally becoming less diverse in the elderly as a result of higher numbers of *Bacteroides* species and reduced numbers of *Clostridium* groups.[23] Even if the microbiome of adults is relatively stable when compared with that of infants or elderly, several factors can dramatically influence its composition over a relatively short period of time.[24] Such factors include antibiotic treatment, stress, infection, host genetics, and diet.[19]

THE MICROBIOTA–GUT–BRAIN AXIS

The commensal bacteria benefit from a nutritionally rich and protected habitat in the human GI tract, while they in turn benefit the host by making indigestible nutrients available to the body. In addition to producing energy, vitamins, and other metabolites, some beneficial bacteria also help restrict the access of pathogenic microorganisms to the gut tissue by building a protective biofilm.[25]

It is now known that the benefits of human–microbe symbiosis can be extended to human mental health, and in recent years evidence has shown that the gut–brain axis, or the bidirectional communication between the resident microbes of the GI tract and the brain,[15] plays a key role in maintaining brain health. The GI microbiota influences human behavior and may affect the pathophysiology of mental illnesses.[26] The knowledge gained in recent years about the function and importance of the microbiome has broadened the concept of the gut–brain axis to the "microbiota–gut–brain axis," emphasizing the importance of the microbiome in the regulation of gut–brain communication.[27–29]

Several systems are at work to ensure the efficient functioning of the microbiota–gut–brain axis, including the central, autonomic, and enteric nervous systems, the immune system, and the endocrine system.[16,26,30,31] The central nervous system (CNS), the enteric nervous system (ENS), the sympathetic and parasympathetic branches of the autonomic nervous system, and neuroendocrine and neuroimmune pathways are all involved in communication with the gut microbes.[16] The neuronal interaction between the GI tract and the brain is facilitated by efferent and afferent nerves.[32] As a consequence, the CNS regulates the secretory and sensory functions as well as the mobility of the GI tract.[33]

The microbiota has the potential to affect neuronal function directly or indirectly through vitamins, neurotransmitters, and neuroactive microbial metabolites such as short-chain fatty acids.[16,33] How these metabolites affect brain function is difficult to ascertain, as the presence of the blood–brain barrier and various feedback mechanisms impede a direct access to the brain. Experimental data suggest that the microbiota may send signals to the brain by activating afferent sensory neurons of the vagus nerve via neuroimmune and neuroendocrine pathways.[19]

The study of germ-free animals shows that brain development is abnormal when the gut microbiome is missing.[21,34] The gut microbiome influences the inflammatory reactions within the brain by modulating the activation of microglial cells[35] and affecting myelination[36] and neurogenesis in adult brains.[37] Fecal transplantation between mouse strains with different levels of anxiety has demonstrated that the microbiota can even change behavioral characteristics of mammals by altering brain chemistry.[38]

Irritable bowel syndrome (IBS) and inflammatory bowel disease in humans are 2 conditions that exemplify the consequences of a faulty gut–brain communication.[39,40] The involvement of the gut microbiota in the pathophysiology of IBS has been shown repeatedly, as symptoms of IBS develop after the disruption of the microbiome due to acute gastroenteritis (ie, postinfectious IBS)[41,42] or following the use of antibiotics.[43] In addition, gastrointestinal dysfunction such as bowel diseases are frequently accompanied by comorbid psychiatric conditions.[44,45]

The ENS, which is part of the automatic nervous system, innervates the wall of the GI tract, covering the entire length from the esophagus to the anus. In addition, the gut also receives input from the vagus nerve and from central spinal and sacral afferent terminals.[32,46] An important feature of the ENS is that it can operate independently of the spinal cord and brain despite being connected to the CNS.[47,48] Apart from the ENS, the vagus nerve is instrumental for the flow of information from the gut to the brain.[32,49] Vagotomy experiments underline the importance of the vagus nerve for microbiota–gut–brain communication,[50–52] even though this connection does not seem to be necessary for all microbes.[27,50] There is great interest in clarifying how probiotic species modulate neuronal pathways, thereby affecting neuronal function and behavior. The neuronal population affected varies, depending on the bacteria used and the experimental paradigm employed. Recent data provide evidence that related bacterial species can interact specifically with a variety of different neuronal populations. For example, *Lactobacillus helveticus* R0052 affects the functioning of CNS neurons in the hippocampus and amygdala,[53] whereas *Lactococcus lactis* subsp *cremoris* H61 modulates the activity of auditory brain stem neurons[54] *and Lactobacillus reuteri* (DSM 17938) is implicated in the function of visceral nociceptive neurons of the gut.[55] This diverse specificity of microorganisms to interact with specific neural circuitries suggests great potential to design dedicated interventions targeted to affect specific neuronal functions. The ability of the ENS system to adapt to altering microbial populations in the GI tract has been known for over 30 years.[56] Indeed, the ENS responds to changing bacterial populations by adapting the neuronal physiology and by changing gene expression. The intracellular recordings of afterhyperpolarization neurons and of sensory neurons residing in the gut wall are different in germ-free mice than in normal mice. Afterhyperpolarization neurons are less excitable in germ-free mice, an abnormality that is normalized after conventionalization with gut microbiota.[55,57,58] In addition, expression of the calcium-binding protein calbindin in the enteric neurons in the gut of conventionalized germ-free mice was similar to that in controls, whereas expression in germ-free animals was significantly less than that in either the conventionalized mice or the controls.[59,60] Calbindin expression is linked to nutritional status because it depends on vitamin D concentrations in the nerve and intestinal cells.[61,62] These findings may indicate that the ENS is plastic, ie, it can sense and react to changes in GI tract microbes. Since the sensory neurons in the ENS are connected to the brain via the vagus nerve, there may be an avenue of communication whereby information about the bacterial contents of the gut can be conveyed to the brain.

The hypothalamic–pituitary–adrenal (HPA) axis, which regulates the body's response to stress, represents another route of gut–brain crosstalk. It is a complex set of involuntary influences and feedback interactions between 3 endocrine glands: the hypothalamus, the pituitary gland, and the adrenal glands. The HPA axis is directly and indirectly controlled by neural activity throughout the forebrain and brainstem.[63] It not only controls the body's reaction to stress but is also implicated in controlling digestion, the immune system, mood and emotional status, sexuality, and energy storage and expenditure. Dysregulation of HPA activity is associated with mental health disorders such as depression and schizophrenia, both of which are known to affect the microbiota composition.[63–65] Stress response by HPA activity involves the secretion of corticotrophin-releasing factor by neurons in the medial parvocellular portion of the hypothalamic paraventricular nucleus, causing the endocrine cells (corticotrophs) in the anterior pituitary to secrete adrenocorticotropic hormone. Adrenocorticotropic hormone, in turn, stimulates the endocrine cells, primarily in the zona fasciculata of the adrenal cortex, to secrete the glucocorticoid hormones cortisol and/or corticosterone (reviewed by Spencer and Deak[66]). Cortisol is released in response to stress, and low blood-glucose concentration affects the response to stress in addition to other metabolic and immune-related functions.[66]

Finally, the role of the immune system in microbiota–gut–brain communication seems to be species-specific. Germ-free mice lacking all gut bacteria exhibit specific abnormalities in immune, neuronal, GI tract, and metabolic function,[67] and infection of mice with a pathogen, *Citrobacter rodentium*, induced anxiety-like behavior.[52] Moreover, the abnormal gut and neuronal function in B- and T-cell–deficient *Rag1* knockout mice was partially normalized by probiotic treatment, providing evidence of a role for the adaptive immune system in maintaining intestinal and brain health.[68]

A number of recent studies provide evidence of the interplay between the microbiome and brain function, which may affect mammalian behavior (Table 1).[27,34,51,52,68–84] Germ-free mice exhibit learning deficits[80] and show anxiolytic-like behavior[85–88] and reduced sociability.[88,89] In addition, they also demonstrate an exaggerated HPA stress response.[69] Importantly, the enhanced HPA response of germ-free mice could be partially corrected by reconstitution with pathogen-free feces of normal animals at an early age, but not at a later age, demonstrating that exposure to microbes at an early developmental stage is required for the HPA system to become fully susceptible to inhibitory neural regulation. These results suggest that commensal microbiota can affect the postnatal development of the HPA stress response in mice.[69]

Recent work in germ-free mice demonstrated hypermyelinated areas in the prefrontal cortex and defective microglial cells with reduced capacity for activation after bacterial or viral challenge.[36] This suggests that germ-free mice have a compromised ability to mount appropriate immune responses in the CNS.[35] The same authors showed that limited diversity in the microbiota composition, achieved by antibiotic treatment, resulted in defective microglia and that recolonization with a complex microbiota partially restored microglial features.[35] In addition, mice deficient for the short-chain fatty acids receptor FFAR2 had the same microglial defects found in germ-free mice.

Taken together, these findings suggest that host bacteria are crucial for regulating microglial maturation and function and that microglial impairment can be ameliorated to some extent by the microbiota.[35] Moreover, the consequences of antibiotic treatment resemble the findings in germ-free animals, such as deficits in social and cognitive behaviors, increased anxiety, and reduced microglial activation and expression of brain-derived neurotrophic factor.[27,34,35]

The role of the microbiome in influencing the crosstalk between periphery and the brain was studied further in a murine model of experimentally induced sickness behavior: mice exhibited elevated levels of inflammatory cytokines such as tumor-necrosis factor-α (TNF-α) and interleukin 6.[72] Sickness behaviors are debilitating symptoms in patients with systemic inflammatory diseases such as irritable bowel disease, rheumatoid arthritis, or chronic liver disease. In a rodent model, an oral gavage of a mixture of 8 bacterial species (VSL#3) was shown to dampen sickness behavior by a mechanism involving reduced activation of microglial cells and reduced infiltration of monocytes into the brain.[72] The authors convincingly showed that the amelioration of behavioral symptoms was related to changes in systemic immune activation, such as lowered TNF-α levels. These data are in agreement with an older report showing that VSL#3 treatment reduced circulating TNF-α levels, which were associated with improved neuropsychiatric outcomes in patients with chronic liver disease.[90] Thus, TNF-α causes sickness behaviors in the murine model by cerebral microglial activation and the recruitment of monocytes into the brain vasculature and brain parenchyma.[72] The mechanisms of organ inflammation in the peripheral organs, leading to alteration of brain functions, are of great importance for the design of clinically acceptable therapeutic agents to prevent peripheral inflammation.

The influence of gut microbiota on neuroinflammation and motor deficits was demonstrated recently in an animal model of Parkinson's disease.[84] Sampson et al.[84] demonstrated that the gut microbiome plays a role in nervous and intestinal dysfunctions specific to Parkinson's disease in a mouse model. Briefly, it was shown that the presence of the normal gut microbiome is required for Parkinson's disease–related motor and brain pathology and that the production of short-chain fatty acids promoted microglial activation and enhanced Parkinson symptoms. When the microbiome was depleted in these mice, reduced activation of microglia and a reduced level of pathology were observed, providing the direct evidence of the contribution of the gut microbiome to Parkinson's disease pathophysiology in this model.[84] In addition, mice that received fecal transplantation from patients with Parkinson's disease, but not mice that received fecal samples from healthy controls, exhibited significant impairment of motor functions, again providing strong evidence of the involvement of the gut microbiome in the pathophysiology of Parkinson's disease. Taken together, these data add to the understanding of how probiotics may influence brain function by modifying immune system signaling to the brain.

MODULATION OF MAMMALIAN BEHAVIOR BY GUT MICROBIOTA

Depression and anxiety

Major depressive disorder, specifically recurrent unipolar depression (normally referred to as depression), is a common, serious, stress-related, debilitating, and, if untreated, life-threatening psychiatric disorder, affecting over 100 million individuals worldwide.[91] The HPA axis is dysregulated in depressive patients, which leads to abnormally high circulating levels of cortiocotropin-releasing factor and cortisol. Often, elevated concentrations of proinflammatory cytokines are also found in the plasma of patients with depression. In recent years, the prospect of using compounds that modulate the gut microbiome, such as probiotics, for treating psychiatric

Table 1 **Animal studies providing evidence of the modulatory role of the microbiota in brain-related pathological conditions**

Reference(s)	Treatment	Animal model	Pathological condition	Outcome	Proposed mechanism of action
Sudo et al. (2004)[69], Desbonnet et al. (2010)[70]	*Bifidobacterium infantis*	Germ-free mice	Anxiety	Antidepressant-like activity	Modulation of HPA response
Bravo et al. (2011)[51]	*Lactobacillus rhamnosus* JB-1	BALB/c mice	Anxiety	Antidepressant-like activity	Modulation of neurotransmission, expression of $GABA_A$ and $GABA_B$ receptors
Bravo et al. (2011)[51], Stilling et al. (2015)[71]	*Lactobacillus rhamnosus*	Germ-free mice	Anxiety	Reduced stress-induced corticosterone levels and anxiety- and depression-related behavior	Higher expression of $GABA_B$ and $GABA_A$ receptors; higher expression of serotonin receptor 1A; involvement of vagus nerve
D'Mello et al. (2015)[72]	Model of liver inflammation and probiotic mixture VSL#3	C57BL/6 mice	Sickness behavior	Reduced symptoms	Monocyte recruitment to the brain in response to systemic TNF-α signaling, leading to microglial activation
Messaoudi et al. (2011)[73]	*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175	Rats	Anxiety	Reduced anxiety-like behavior	Crosstalk between the microbiome and enteric nervous system as well as CNS
Desbonnet et al. (2008)[74]	*Bifidobacterium infantis*	Rats	Anxiety	No effect in naive rats but significantly attenuated IFN-γ, TNF-α, and IL-6 cytokines following mitogen stimulation	Increased plasma concentrations of tryptophan and kynurenic acid; reduced 5-HIAA concentration in the frontal cortex in DOPAC in the amygdaloid cortex
Gareau et al. (2007)[75]	*Lactobacillus rhamnosus* R0011 and *Lactobacillus helveticus* R0052 (5%)	Rat pups	Stress due to maternal separation leading to dysbiosis	Change in gut flora composition observed	Normalization of HPA axis activity
Desbonnet et al. (2015)[34], Frohlich et al. (2016)[76]	Antibiotic treatment	Mice	Depletion of the gut microbiota	Altered gut microbiota, decreased spleen weights in adulthood. Reduced anxiety, induced cognitive deficits, altered dynamics of the tryptophan metabolic pathway	Change in microbial metabolites and in expression of BDNF, NMDA receptor subunit 2B, serotonin transporter, neuropeptide Y, and vasopressin
Li et al. (2009)[77]	Ground beef diet	CF1 mice	None	Increased bacterial diversity in the beef-supplemented diet; improved working and reference memory	TBD

(continued)

Table 1 **Continued**

Reference(s)	Treatment	Animal model	Pathological condition	Outcome	Proposed mechanism of action
Ohland et al. (2013)[78]	Western-style diet and *Lactobacillus helveticus* ROO52	WT and IL-10–deficient 129/SvEv mice	Western diet increased weight gain, changed gut microbiota and cytokine expression, and altered anxiety-like behavior	Probiotics alone decreased anxiety-like behavior in WT mice on a chow diet	Inflammatory pathways
Davari et al. (2013)[79]	*Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Lactobacillus fermentum*	Diabetic rats	Memory impairment related to diabetes mellitus	Improved the impaired spatial memory in diabetic animals	Stimulation of Schaffer collaterals in hippocampus, restoration of long-term potentiation, activation of superoxide dismutase, and increased serum insulin level
Gareau et al. (2011)[80]	*Citrobacter rodentium* in addition to water avoidance stress	C57BL/6 mice and germ-free Swiss-Webster mice	None	Memory impairment observed in C57BL/6 after stress Memory impairment observed in germ-free mice	Modulation of HPA axis and hippocampal plasticity
Lyte et al. (1998)[81]	*Campylobacter jejuni*	CF-1 male mice	Anxiety	Decreased exploratory behaviors and increased nonexploratory behaviors	Activation of immune–neural mechanisms
Lyte et al. (2006)[52]	*Citrobacter rodentium*	CF-1 male mice (model of IBD)	IBD	Increased anxiety-like behavior	Mediated via vagal sensory neurons
Smith et al. (2014)[68]	*Lactobacillus rhamnosus* R0011 and *Lactobacillus helveticus* R0052	B- and T-cell–deficient $Rag1^{-/-}$ mice	Memory deficit, anxiety, dysbiosis	Improved baseline impairments	Modulation of intestinal microbiota, HPA axis, and cFos expression
Bercik et al. (2011)[27]	Microbiota of SPF NIH Swiss and BALB/c mice	Germ-free mice	Baseline behavior of germ-free mice	Altered the composition of the microbiota and increased exploratory behavior	Changes in brain chemistry and in hippocampal expression of BDNF
Gacias et al. (2016)[82]	Microbiota of nonobese diabetic mice	C57BL/6 mice	Social avoidance	Improvement in social avoidance observed	Changes in gene expression and in myelination in frontal cortex
Zheng et al. (2016)[83]	Microbiota of humans with depression	Germ-free mice	Depression	Mice developed depressive symptoms	Neurotransmission, others
Sampson et al. (2016)[84]	Microbiota of patients with PD	α-Synuclein overexpressing germ-free mice	PD pathology	PD-like motor deficits observed in transplanted germ-free mice	Changes in SCFAs modulated neuroinflammation and microglia activation

Abbreviations: BDNF, brain-derived neurotrophic factor; DOPAC, 3,4-dihydroxyphenylacetic acid; HPA, hypothalamic–pituitary–adrenal; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; NIH, National Institutes of Health; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; Rag1, recombination activating gene 1; SCFAs, short-chain fatty acids; SPF, specific pathogen–free; TBD, to be determined; TNF, tumor necrosis factor; WT, wild type; 5-HIAA, 5-hydroxyindoleacetic acid.

disorders has gained great interest among neuroscientists, even though the mechanisms of action of the microbiota on mood in humans remain elusive.

Several lines of evidence in preclinical models that include bacterial infections, probiotic treatment, fecal transplantation, and analysis of germ-free animals suggest that the gut microbiota can influence brain function and, consequently, alter behavior.[16] Anxiety and depression are among the brain-related behavioral changes that are modified by changes in the gut microbiome.[34,51,70,73,87,92–95] Sudo et al.[69] were among the first groups to study the effect of the microbiome on the HPA axis. Their seminal study showed that stressed germ-free mice have an overly responsive HPA axis. The overreaction of the HPA response was reduced by supplementing mice with a single bacterial strain, *Bifidobacterium infantis*.[69] In 2011, Bravo et al.[51] showed that chronic treatment of BALB/c mice with *Lactobacillus rhamnosus* JB-1 moderated anxiety and antidepressant-related behavior, probably by inducing neurochemical changes. The lower anxiety level of *L rhamnosus*–treated animals was concomitant with alterations in the expression of γ-aminobutyric acid (GABA) receptors, both $GABA_A$ and $GABA_B$ receptors, across a variety of brain regions. Importantly, the neurochemical and behavioral effects were not found in vagotomized mice, thus identifying the vagus as a major modulatory pathway between the gut and the brain.[51] This study showed that *L rhamnosus* had antidepressant/anxiolytic activity and demonstrated that, in this animal model, dietary intake of a bacterial strain may alter brain function and behavior. Moreover, the authors identified the vagus nerve as the route of communication between the gut microbiome and the brain. Bercik et al.[27,50] showed that fecal transplantation may result in the transfer of behavioral traits from the donor mouse to the recipient mouse. A recent study confirmed the above findings by showing that the gut microbiome determines behavioral changes in another model, ie, the nonobese diabetic mouse.[82] The transfer of intestinal microbiota from nonobese diabetic mice to C57BL/6 mice was sufficient to induce social avoidance and changes in gene expression and myelination in the prefrontal cortex in the C57BL/6 mice, a phenotype of the nonobese diabetic mouse. In conclusion, these animal data provide evidence that microbes of the GI tract are implicated in the pathophysiology of depression and anxiety and that some strains confer a certain degree of resilience against these conditions.

Several studies in humans (Table 2)[73,96–104] support the data from animal studies and show that the gut microbiota may play a role in modulating depression and anxiety.[73,97,105] Some researchers have reported that the composition of the microbiome was different in patients with major depressive disorder than in their healthy counterparts,[83,106] but others failed to confirm this.[107] Mechanistically fascinating is the result of 1 study (Table 1) in which germ-free mice were inoculated with fecal samples of depressive patients. The transplanted mice developed depressive-like behaviors.[83] This strongly hints for the involvement of the gut microbiome in regulating depressive symptoms in humans. In a randomized, double-blind, placebo-controlled trial, petrochemical workers who consumed a probiotic yogurt or a multispecies probiotic capsule for 6 weeks showed improved mental health as measured by a general health questionnaire and a depression anxiety and stress scale.[96] These data are in line with those from an older study in which supplementation with probiotic yogurt improved the mood status of healthy elderly individuals, especially those with decreased mood scores at baseline.[97] Lastly, probiotic treatment (containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*) for 8 weeks in patients with major depressive disorder was reported to improve clinical signs of depression as assessed by the Beck Depression Inventory in a recent randomized, double-blind, placebo-controlled trial performed in central Iran (Table 2).[103]

Analysis of fecal samples reveals that the microbiome of depressive patients differs from that of healthy controls.[51,106] Indeed, changes in the microbiome of depressive patients can be linked to the severity of depression. These reports revealed a negative correlation between *Faecalibacterium* organisms and the severity of depressive symptoms and an altered composition of the gut microbiota in acutely depressed patients.[106]

Patients with depression show changes in counts of both gram-positive and gram-negative bacteria.[106,107] Increases are reported for *Roseburia*, *Phascolarctobacterium*, *Megamonas*, *Clostridium*, Lachnospiraceae *incertae sedis*, *Blautia*, *Oscillibacter*, *Parasutterella*, *Parabacteroides*, and *Alistipes*, whereas *Ruminococcus*, *Dialister*, *Prevotella*, *Faecalibacterium*, and *Bacteroides* are reduced in people with depression.[108] The genus of *Bifidobacterium* has been studied in detail in relation to depression. *B infantis* was found to normalize the exaggerated HPA axis response and ameliorate depressive symptoms in animal models.[70,109] Another gram-positive bacterium, *Lactobacillus farciminis*, is also able to reverse stress-induced elevation of HPA axis activity and neuroinflammation in vivo.[110] *Lactobacillus rhamnosus* was shown to alter emotional behavior and central GABA receptor expression in vivo via the vagus nerve, thereby decreasing both anxiety and depression-like symptoms in mice.[51] Messaoudi et al.[73] studied probiotic treatment with a combination of *L helveticus* and *Bifidobacterium longum* in rats and

Table 2 **Nonexhaustive list of human studies supplementing probiotics to normal and diseased human populations**

Supplementation	Study population	Behaviors tested	Outcome	Reference(s)
Probiotic yogurt or a multispecies probiotic capsule (*Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12)	Normal population	Depression, anxiety, stress	Improvement in participants supplemented with probiotic yogurt or probiotic capsule	Mohammadi et al. (2016)[96]
Probiotic yogurt (*Lactobacillus casei* Shirota)	Normal elderly individuals with decreased mood	Mood status	Improvement in participants in bottom third of the depressed/elated dimension at baseline	Benton et al. (2007)[97]
Lactobacillus helveticus & *Bifidobacterium longum*	Healthy individuals	Anxiety, stress	Alleviation of psychological distress	Messaoudi et al. (2011)[73]
Bifidobacterium longum 1714	Healthy individuals	Stress response, cognition, brain activity	Change in electroencephalographic activity, dampened stress response, and enhanced cognitive performance	Allen et al. (2016)[98]
Fermented milk product with probiotic containing *Bifidobacterium animalis* subsp *lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus lactis* subsp *lactis*	Healthy women	Emotion, attention	Altered activity of brain regions that control central processing of emotion and sensation by functional MRI	Tillisch et al. (2013)[99]
Lactobacillus helveticus IDCC3801	Healthy elderly individuals	Cognition	Improvement in cognitive functioning during cognitive fatigue tests	Chung et al. (2014)[100]
Bifidobacterium infantis 35624	Patients with IBS	IBS symptoms	Improvement in symptoms	Brenner et al. (2009)[101]
Probiotic milk containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum*	Patients with Alzheimer's disease	Cognitive functions, antioxidative status	Significant improvement in MMSE score (in plasma malondialdehyde, serum hs-CRP, and serum TG	Akbari et al. (2016)[102]
Lactobacillus acidophilus, *Lactobacillus casei*, *Bifidobacterium bifidum*	Patients with major depressive disorder	Depression	Improvement in clinical signs	Akkasheh et al. (2016)[103]
FOS or Bimuno GOS	Healthy individuals	Stress	Significantly lower cortisol awakening response (assessed in saliva) after Bimuno GOS intake	Schmidt et al. (2015)[104]

Abbreviations: FOS, fructooligosaccharides; GOS, galactooligosaccharide; hs-CRP, high-sensitivity C-reactive protein; IBS, irritable bowel syndrome; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; TG, triglycerides.

humans. The treatment was effective in decreasing stress levels, anxiety, and depressive scores in both the animal experiment and the clinical trial, providing the evidence that, in this case, animal models are a reliable model for conditions in humans. Resident gut bacteria can also have negative effects on the host. For example, *Campylobacter jejuni* was shown to induce anxiety-like behavior without inducing immune activation in mice.[81] As noted, in vivo models provide evidence that a heightened HPA axis response and depressive-like symptoms can be reversed by the administration of probiotic bacteria such as *B infantis*.[70] Moreover, probiotics may elevate blood tryptophan concentrations, modulate serotonin levels in the frontal cortex, and modulate cortical dopamine metabolites, thereby ameliorating depressive symptoms.[74] In addition, rat studies showed that the consumption of *L rhamnosus* is associated with improved depressive scores.[51] Together, these studies suggest that probiotics may improve mood status in humans and that (unhealthy) nutrition may be a risk factor for depression. Therefore, a healthy diet could have a preventive effect against depression.[111]

Stress

The gut microbiome and the stress response are interrelated in mammals. Sudo et al.[69] showed that germ-free mice under stress conditions exhibited a strong HPA response when compared with control animals. Their study showed that fecal transfer from specific pathogen-free mice was able to partially normalize the exaggerated stress response in germ-free animals. Most interestingly, the abnormal stress response was age-dependently reversed when animals were treated with the probiotic *B infantis*.[69] Supporting data were provided by a study in which probiotic treatment of rat pups normalized corticosterone release and ameliorated colonic dysfunction induced by stress due to maternal separation.[75] These data are in line with a report in healthy volunteers following prebiotic supplementation. Prebiotic supplementation with fructooligosaccharides or a commercially available powder containing galactooligosaccharides (Bimuno, DSM Nutritional Products, Basel, Switzerland) for 3 weeks revealed that the cortisol awakening response, as assessed by salivary samples, was significantly lower after intake of Bimuno powder than after placebo intake. In addition, participants showed decreased attentional vigilance to negative vs positive information in a dot-probe task after Bimuno powder intake than after placebo intake. No effects were found after the administration of fructooligosaccharides, indicating the specificity of the observed effects.[104] Thus, the above-mentioned studies indicate that the neuroendocrine function of the brain can be affected by the gut microbiome. As outlined in the Introduction, the interaction between the gut and the brain is bidirectional in both rodents and humans. Evidence for the effect of the brain on the gut microbiome can be found in studies documenting that parental stress,[112,113] early-life stress,[114,115] and psychological stress[116–119] change the composition of the gut microbiota.

To further validate that preclinical results could be translated to healthy humans, Allen et al.[98] tested whether the consumption of *B longum* strain 1714 affects brain-related functions. They showed that this probiotic modulated electroencephalographic activity, dampened the stress response, and enhanced cognitive performance in healthy volunteers.[98] This study confirmed older data showing that supplementing healthy women with a fermented milk product containing *Bifidobacterium animalis* subsp *lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *L lactis* subsp *lactis* altered activity of brain regions that control central processing of emotion and sensation in a functional magnetic resonance imaging study.[99]

Cognition

The chance of providing cognitive support to humans may be greatest during gestation, infancy, and older age,[120] as these are periods of life with the highest vulnerability and the greatest demand for nutrients. To date, the majority of mechanistic evidence for the involvement of the gut microbiota in cognition is provided by animal experiments of induced infections,[80,121] antibiotic and dietary manipulations,[34,76,77,78] and probiotic interventions.[78,79]

Animal studies suggest that the microbiome may influence neurodevelopment.[87,88,71] Short-chain fatty acids, the major metabolites produced by the microbiome, are implicated in the functionality of the blood–brain barrier and thus have a direct role in determining the accessibility of circulating factors to the brain.[122] Short-chain fatty acids may control gene transcription in the brain via epigenetic mechanisms. Among these, butyrate is shown to be brain active and capable of facilitating long-term potentiation and the formation of long-term memory in rats via an extracellular signal-regulated kinase (ERK)-dependent signaling mechanism.[123] These early reports were confirmed by subsequent studies showing that sodium butyrate facilitates neuronal plasticity and memory formation[124] via a pathway that mimics the beneficial effects of environmental enrichment.[125] These studies have also pointed to butyrate as the most important short-chain fatty acid involved in epigenetic modulation of brain function. The positive effect of butyrate on cognition after systemic and local injections prompted scientists to test it in models of neurodegenerative diseases to counteract cognitive impairment. In animal models of Alzheimer's disease, butyrate showed positive effects on pathology and memory performance.[125,126] In models of other neurodegenerative disorders, including Parkinson's disease,[127] amyotrophic lateral sclerosis,[128] Huntington's disease,[129] and ataxia,[130] butyrate exhibited neuroprotective effects and helped restore, at least partially, neuronal function.

At the cellular level, butyrate's effects are mediated by various receptors, including G protein–coupled receptors, free fatty acid receptors, and transporters,[71] and by the utilization of butyrate as an energy source via the β-oxidation pathway.[71] Butyrate inhibits histone deacetylase, thereby promoting histone acetylation and the epigenetic regulation of gene expression in human cells. Therefore, some have proposed it be tested experimentally to treat cognitive impairment and neurological disorders ranging from depression to neurodegenerative diseases in humans (reviewed by Stilling et al.[71]).

Probiotics were also employed in human studies examining cognitive performance of both healthy and diseased study participants. Probiotic treatment (*L helveticus* IDCC3801) of healthy elderly individuals was shown to improve scores on cognitive fatigue tests.[100] Another study suggests that consumption of a fermented probiotic milk product modulates brain activity during an emotional attention test in healthy women.[99] In addition, prebiotic intake reduced the waking cortisol response and altered emotional bias in healthy volunteers, resulting in improved performance of healthy individuals in an emotional attention task.[104]

Promising results were reported recently by Akbari et al.,[102] who showed that supplementing Alzheimer's disease patients with a probiotic milk containing *L acidophilus*, *L casei*, *B bifidum*, and *Lactobacillus fermentum* (each organism: 2×10^9 CFU/g of milk) for 12 weeks positively affected cognitive function. If these results can be replicated by independent research groups, they would be groundbreaking because they would indicate the potential usefulness of probiotics as a viable and affordable strategy for improving cognitive capacity in both healthy individuals and patients with Alzheimer's disease.

Mechanistic evidence of microbial influence on neuronal signaling

The gut and the brain communicate with each other via central and systemic routes. The major route of central communication between the gut and the brain is the vagus nerve.[16,131] The incoming information from the gut via the vagus nerve to the brain is processed in the nucleus tractus solitarius, which has large projections that include the parabrachial nucleus, which further projects to the prefrontal cortex as well as the amygdala, a region susceptible to microbial transcriptional regulation.[71,132] Moreover, recent findings indicate that gut microbes induce excitability of the intrinsic primary afferent neurons in the intestine after hyperpolarization. This elevated excitability was not observed in germ-free animals, suggesting that colonization restores normal neuronal excitability.[57] Furthermore, neuroactive metabolites of microbiota, such as short-chain fatty acids, constitute a route of information flow between the gut and the brain.[133] Despite the information provided by the above-mentioned research, the role of microorganisms in the regulation of neuronal activity is far from being fully understood. The mechanisms of involvement of the gut microbiota in brain function and disorders, including anxiety and depression, may be related to the ability of the microbiota to synthesize soluble factors (eg, neuromodulators) and modulate their absorption and function.[134] A study by Neufeld et al.[86] showed that the expression of an *N*-methyl-D-aspartate (NMDA) receptor subunit (NMDArec2B) is reduced in the amygdala (a region implicated in the emotional processing of external cues) of germ-free animals. Savignac et al.[93] confirmed the involvement of the microbiome in gene expression by showing that feeding prebiotics elevates levels of brain-derived neurotrophic factor, NMDA receptor subunits, and D-serine in the rat brain. They also showed that prebiotic supplementation normalizes lipopolysaccharide-induced anxiety and cortical levels of serotonin 2 A receptor and interleukin 1β in male mice. Moreover, supplementing germ-free animals with *L rhamnosus* led to higher expression of both the GABA receptor in the amygdala and the serotonin 1 A receptor in the hippocampal formation.[51,71] These data suggest the possibility of treating neuropsychiatric disorders by manipulating the microbiome with specific prebiotics and probiotics.

Gaseous metabolites of bacteria, including carbon monoxide, hydrogen sulfide, nitric oxide, and others, are also implicated in the neuronal control of gut functions by muscarinic cholinergic, vasoactive intestinal peptide.[135,136] The interaction with the nerve cells is indirect and involves enteric glia, a collection of glial cells residing within the walls of the intestinal tract[137,138] and within epithelial and smooth muscle cells,[46] interstitial cells of Cajal,[135] and immune cells.[139] Enteric glia are crucial for the above-mentioned interactions, as they also communicate with various types of non-neuronal cells in the gut wall, such as enterocytes, enteroendocrine cells, and immune cells and are therefore important local regulators of diverse gut functions. Several studies have emphasized the importance of enteric glia as modulators of ENS function, owing to the responsiveness of enteric glia to microbial, luminal, and inflammatory signals.[46,138,140–143] Thus, enteric glial cells regulate intestinal barrier function, immune responses, intestinal secretion, and gut motility and are hypothesized to be moderators of neurotransmission and neuroplasticity in the intestine.[144]

Bile acids are also able to modulate neuronal activity, thus affecting both the host and microbiota, for example, by activating G protein–coupled bile acid receptors on intrinsic primary afferent neurons.[145] This effect, however, depends on the specific bile acid, as some promote bacterial growth, whereas others inhibit it.[146,147]

Quorum sensing, used by bacteria to coordinate gene expression according to the density of their local population, represents a communication route within the gut by which bacteria may react to external (ie, host) factors. The centrally produced neurotransmitter noradrenalin, a major catecholamine neurotransmitter in the sympathetic nervous system, is known to serve as a potent quorum sensing signal in bacteria such as *Escherichia coli*.[148–152] Hence, the host nervous system may regulate bacterial growth, biofilm formation, and virulence mechanisms, including toxin production in the intestine, via noradrenalin-dependent neurotransmission. Catecholamines, on the other hand, have been linked to the virulence of 2 pathogenic bacteria, namely enterohemorrhagic *E coli* and *C jejuni* (reviewed by Savidge[153]). These varying effects of the same neurotransmitter on different microbes demonstrate that much about the optimal utilization of microbes for specific health benefits is still unknown. Nevertheless, it is evident from the above data that microbes in the GI tract interact with the ENS, thereby influencing both host and microbial functions.

There is considerable evidence that the microbiome plays a role in modulating mood disorders, stress, and anxiety, all conditions that are influenced by serotonergic neurotransmission.[33,154] Bravo et al.[51] demonstrated that *L rhamnosus* regulates emotional behavior in mice by modulating central GABA receptor expression via a mechanism that involves the vagus nerve. They also showed that mice are less anxious and exhibit less depressive-like behavior following *L rhamnosus* supplementation. Undoubtedly, nutrition has a major influence on the composition of the gut microbiome. For example, it is known that a Western diet changes the gut microbiome and induces anxiolytic effects in mice.[155] The synthesis of serotonin as well as the availability of its precursor tryptophan is highly regulated during the life span. Metabolism of tryptophan, however, is altered after consumption of a Western diet.[155] Tryptophan is the precursor of serotonin, which therefore links diet, the microbiome, neurotransmission, and effects on behavioral change to each other.[156] This is supported by the findings of Desbonnet et al.,[34] who depleted the gut microbiome in mice by antibiotic treatment, resulting in a dramatic reduction in tryptophan levels in blood as well as a reduction in BDNF levels in the hippocampus. It is worth noting that several bacterial strains, such as *L lactis* subsp *cremoris*, *L lactis* subsp *lactis*, *Lactobacillus plantarum*, and *S thermophilus*, have been shown to produce monogenic amines, including serotonin.[157] Moreover, levodopa, serotonin, dopamine, and noradrenaline were detected during the late growth phase of *E coli* K-12 cultures,[158] and *L plantarum* has been reported to produce acetylcholine.[94] Lastly, several strains of *Lactobacillus brevis*, *Bifidobacterium adolescentis*, *Bifidobacterium dentium*, and *B infantis* have been reported to be GABA producers.[159] In addition, Romano et al.[160] reported that the intestinal microbiota composition modulates the bioavailability of choline. Most efficient in this regard were strains of *Anaerococcus hydrogenalis*, *Clostridium asparagiforme*, *Clostridium hathewayi*, *Clostridium sporogenes*, *Edwardsiella tarda*, and *Escherichia fergusonii* isolated from human samples.[160] It is therefore possible that microbial-derived neurotransmitters can alter the activity of the ENS and, perhaps, the CNS. Lastly, changes in the microbiome composition have a profound effect on the function and responsiveness of the HPA axis.[69] This effect is age dependent, as the abnormal HPA response could be partially normalized after recolonization at an early stage, but not at a late stage, clearly showing that the microbiome modulates the HPA response to stress, an effect that is most prominent during the postnatal period.[69]

DISCUSSION

Elucidating the mechanisms by which microbes affect brain function constitutes an exciting field of research. In vivo data have been instrumental in showing that the excitability of enteric and vagal afferent neurons may be modulated by the microbiota[131] and that the brain modulates intestinal motility, intestinal secretion, and immune function.[161] Research in preclinical models suggests that the effect of the microbiome on behavior may be related to changes in the amygdala and hippocampus.[67,162] A significant difference in the volume and dendritic morphology of the amygdala and hippocampus was observed between conventionally colonized mice and germ-free mice, including shorter neurites, a smaller degree of branching, and thinner spines in germ-free mice,[162] suggesting that the microbiota is required for the normal morphology and ultrastructure of brain neurons. The authors argue that dysbiosis and the consequent neural remodeling may contribute to the maladaptive stress responsivity and behavioral profile observed in germ-free mice.[162] On the other hand, the nervous system controls the intestinal physiology. The involvement of neural circuits, neurotransmitters, and receptors in the sympathetic regulation of intestinal function is well established. Dysregulated neurotransmission, altered HPA response, and damage of enteric neurons result in an abnormal microbiome. For example, stress conditions can cause abdominal pain and constipation.[148,152,163] In addition, psychological stress has been shown to shift the microbial colonization on the mucosal surface and alter the susceptibility of the host to infection.[152] Moreover, the ENS and the immune system both play important roles in the development of irritable bowel disease. Both the ENS and the CNS can modulate intestinal inflammation through secretion of neuropeptides or other soluble molecules.[164] In addition, the innervation of the GI tract by the sympathetic nervous system controls the motility, fluid exchange, and blood flow in the gut of healthy individuals.[165] Lastly, human studies show that the HPA axis is dysregulated in depression; however, this can be reversed after the resolution of depression.[26] The stress response is immature at birth. Its maturation is governed by genetic factors of the host, as different mouse strains have been shown to exhibit different stress and behavior responses to environmental stimuli.[26]

CONCLUSION

Many of the state-of-the art therapies for brain disorders aim to restore dysregulated neurotransmission in affected brain areas. As noted in this review, data are increasingly showing that bacteria can produce important neurotransmitters such as GABA, acetylcholine, and serotonin. Research aiming to understand the communication between the intestinal microbiota and the brain peaked in recent years but revealed multiple mechanisms by which the human host responds to commensal and pathogenic bacteria.[16] Communication between the brain and the microbiota involves epithelial receptor–mediated signaling, immune modulation, and stimulation of enteric neurons by bacterial metabolites. Important for this crosstalk is the ability of the microbiota to regulate the availability of circulating tryptophan, which affects serotonin synthesis, and to alter the expression of some CNS receptors, thereby enabling them to directly influence brain excitability and function as well as to exert epigenetic control of gene expression.

Industry has undertaken enormous effort to tackle diseases of old age, such as Parkinson's disease and Alzheimer's disease, as well as diseases that affect younger persons, such as attention-deficit/hyperactivity disorder and autism, but results have been disappointing at times. Future research will show whether microbes can be used to produce therapeutic neurotransmitters for treating psychiatric disorders. For therapy to be successful, any potential adverse effects must be studied, such as those caused by the presence of receptors or epigenetic processes in tissues other than the brain. In conclusion, regulation or modification of the GI microbiome through diet may provide critical benefits for preventing and treating brain-related disorders, which has prompted several experts to propose specific developments of the microbiota for use as potential psychotropic therapies.[109] Since there are seemingly endless possibilities to combine pre- and probiotics with other nutritional compounds, future mechanistic studies are needed to determine the true potential of such psychotropic therapies to produce the envisaged benefits in the targeted populations.

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REFERENCES

1. Kennedy RJ, Kirk SJ, Gardiner KR. Probiotics [comment on *Br J Surg* 2001;88:161–162]. Br J Surg. 2001;88:1018–1019.
2. Gruner D, Paris S, Schwendicke F. Probiotics for managing caries and periodontitis: systematic review and meta-analysis. J Dent. 2016;48:16–25.
3. Jafarnejad S, Shab-Bidar S, Speakman JR, et al. Probiotics reduce the risk of antibiotic-associated diarrhea in adults (18–64 years) but not the elderly (>65 years): a meta-analysis. Nutr Clin Pract. 2016;31:502–513.
4. Martin-Cabezas R, Davideau JL, Tenenbaum H, et al. Clinical efficacy of probiotics as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis: a systematic review and meta-analysis. J Clin Periodontol. 2016;43:520–530.
5. Zhang Q, Wu Y, Fei X. Effect of probiotics on body weight and body-mass index: a systematic review and meta-analysis of randomized, controlled trials. Int J Food Sci Nutr. 2015;67:571–580.
6. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444:1027–1031.
7. Backhed F, Ley RE, Sonnenburg JL, P, et al. Host-bacterial mutualism in the human intestine. Science. 2005;307:1915–1920.
8. Jumpstart Consortium Human Microbiome Project Data Generation Working Group. Evaluation of 16S rDNA-based community profiling for human microbiome research. PLoS One. 2012;7:e39315. doi:10.1371/journal.pone.0039315
9. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486:222–227.
10. Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. Nature. 2007;449:804–810.
11. Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312:1355–1359.
12. Saito YA, Schoenfeld P, Locke GR, 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol. 2002;97:1910–1915.
13. Backhed F, Fraser CM, Ringel Y, et al. Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe. 2012;12:611–622.
14. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505:559–563.
15. Mayer EA, Knight R, Mazmanian SK, et al. Gut microbes and the brain: paradigm shift in neuroscience. J Neurosci. 2014;34:15490–15496.
16. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13:701–712.
17. Lozupone CA, Stombaugh JI, Gordon JI, et al. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489:220–230.
18. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006;118:511–521.
19. Kennedy PJ, Cryan JF, Dinan TG, et al. Kynurenine pathway metabolism and the microbiota-gut-brain axis. Neuropharmacology. 2017;112(pt B):399–412.
20. Rodriguez JM, Murphy K, Stanton C, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. Microb Ecol Health Dis. 2015;26:26050. doi:10.3402/mehd.v26.26050
21. Borre YE, O'Keeffe GW, Clarke G, et al. Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol Med. 2014;20:509–518.
22. Palmer C, Bik EM, DiGiulio DB, et al. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5:e177. doi:10.1371/journal.pbio.0050177
23. Claesson MJ, Cusack S, O'Sullivan O, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci USA. 2011;108(suppl 1):4586–4591.

24. Knights D, Ward TL, McKinlay CE, et al. Rethinking "enterotypes." Cell Host Microbe. 2014;16:433–437.
25. McVey Neufeld KA, Luczynski P, Seira Oriach C, et al. What's bugging your teen?—The microbiota and adolescent mental health. Neurosci Biobehav Rev. 2016;70:300–312.
26. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. 2013;36:305–312.
27. Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology. 2011;141:599–609. 609 e591–593.
28. Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011;23:187–192.
29. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain–gut–enteric microbiota axis. Nat Rev Gastroenterol Hepatol. 2009;6:306–314.
30. El Aidy S, Dinan TG, Cryan JF. Gut microbiota: the conductor in the orchestra of immune–neuroendocrine communication. Clin Ther. 2015;37:954–967.
31. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest. 2015;125:926–938.
32. Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9:286–294.
33. Badawy AA. Tryptophan availability for kynurenine pathway metabolism across the life span: control mechanisms and focus on aging, exercise, diet and nutritional supplements. Neuropharmacology. 2017;112(pt B):248–263.
34. Desbonnet L, Clarke G, Traplin A, et al. Gut microbiota depletion from early adolescence in mice: implications for brain and behaviour. Brain Behav Immun. 2015;48:165–173.
35. Erny D, Hrabe de Angelis AL, Jaitin D, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18:965–977.
36. Hoban AE, Stilling RM, Ryan FJ, et al. Regulation of prefrontal cortex myelination by the microbiota. Transl Psychiatry. 2016;6:e774.
37. Ogbonnaya ES, Clarke G, Shanahan F, et al. Adult hippocampal neurogenesis is regulated by the microbiome. Biol Psychiatry. 2015;78:e7–e9.
38. Collins SM, Kassam Z, Bercik P. The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications. Curr Opin Microbiol. 2013;16:240–245.
39. Mayer EA, Aziz Q, Coen S, et al. Brain imaging approaches to the study of functional GI disorders: a Rome Working Team report. Neurogastroenterol Motil. 2009;21:579–596.
40. Mayer EA, Tillisch K, Bradesi S. Review article: modulation of the brain–gut axis as a therapeutic approach in gastrointestinal disease. Aliment Pharmacol Ther. 2006;24:919–933.
41. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome—a meta-analysis. Am J Gastroenterol. 2006;101:1894–1899.
42. Schwille-Kiuntke J, Enck P, Zendler C, et al. Postinfectious irritable bowel syndrome: follow-up of a patient cohort of confirmed cases of bacterial infection with *Salmonella* or *Campylobacter*. Neurogastroenterol Motil. 2011;23:e479–e488.
43. Maxwell PR, Rink E, Kumar D, et al. Antibiotics increase functional abdominal symptoms. Am J Gastroenterol. 2002;97:104–108.
44. Mayer EA. The neurobiology of stress and gastrointestinal disease. Gut. 2000;47:861–869.
45. Mayer EA. Psychological stress and colitis. Gut. 2000;46:595–596.
46. Sharkey KA, Savidge TC. Role of enteric neurotransmission in host defense and protection of the gastrointestinal tract. Auton Neurosci. 2014;181:94–106.
47. Costa M, Brookes SJ, Hennig GW. Anatomy and physiology of the enteric nervous system. Gut. 2000;47(suppl 4):iv15–iv19; discussion iv26.
48. Costa M, Glise H, Sjodahl R. The enteric nervous system in health and disease. Gut. 2000;47(suppl 4):iv1. doi:10.1136/gut.47.suppl_4.iv1
49. Furness JB. The organisation of the autonomic nervous system: peripheral connections. Auton Neurosci. 2006;130:1–5.
50. Bercik P, Verdu EF, Foster JA, et al. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. Gastroenterology. 2010;139:2102.e1–2112.e1.
51. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA. 2011;108:16050–16055.
52. Lyte M, Li W, Opitz N, et al. Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia *Citrobacter rodentium*. Physiol Behav. 2006;89:350–357.
53. Gilbert K, Arseneault-Breard J, Flores Monaco F, et al. Attenuation of post-myocardial infarction depression in rats by n-3 fatty acids or probiotics starting after the onset of reperfusion. Br J Nutr. 2013;109:50–56.
54. Oike H, Aoki-Yoshida A, Kimoto-Nira H, et al. Dietary intake of heat-killed *Lactococcus lactis* H61 delays age-related hearing loss in C57BL/6J mice. Sci Rep. 2016;6:23556. doi:10.1038/srep23556
55. Perez-Burgos A, Wang B, Mao YK, et al. Psychoactive bacteria *Lactobacillus rhamnosus* (JB-1) elicits rapid frequency facilitation in vagal afferents. Am J Physiol Gastrointest Liver Physiol. 2013;304:G211–G220.
56. Galligan JJ, Furness JB, Costa M. Migration of the myoelectric complex after interruption of the myenteric plexus: intestinal transection and regeneration of enteric nerves in the guinea pig. Gastroenterology. 1989;97:1135–1146.
57. McVey Neufeld KA, Mao YK, Bienenstock J, et al. The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. Neurogastroenterol Motil. 2013;25:183–e88.
58. Wu RY, Pasyk M, Wang B, et al. Spatiotemporal maps reveal regional differences in the effects on gut motility for *Lactobacillus reuteri* and *rhamnosus* strains. Neurogastroenterol Motil. 2013;25:e205–e214.
59. McVey Neufeld KA, Perez-Burgos A, Mao YK, et al. The gut microbiome restores intrinsic and extrinsic nerve function in germ-free mice accompanied by changes in calbindin. Neurogastroenterol Motil. 2015;27:627–636.
60. Perez-Burgos A, Wang L, McVey Neufeld KA, et al. The TRPV1 channel in rodents is a major target for antinociceptive effect of the probiotic *Lactobacillus reuteri* DSM 17938. J Physiol (Lond). 2015;593:3943–3957.
61. Lee YS, Taylor AN, Reimers TJ, et al. Calbindin-D in peripheral nerve cells is vitamin D and calcium dependent. Proc Natl Acad Sci USA. 1987;84:7344–7348.
62. Meyer J, Fullmer CS, Wasserman RH, et al. Dietary restriction of calcium, phosphorus, and vitamin D elicits differential regulation of the mRNAs for avian intestinal calbindin-D28k and the 1,25-dihydroxyvitamin D3 receptor. J Bone Miner Res. 1992;7:441–448.
63. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology. 2000;23:477–501.
64. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. CNS Spectr. 2009;14(1 suppl 1):13–24.
65. Walker EF, Trotman HD, Pearce BD, et al. Cortisol levels and risk for psychosis: initial findings from the North American Prodrome Longitudinal Study. Biol Psychiatry. 2013;74:410–417.
66. Spencer RL, Deak T. A users guide to HPA axis research. Physiol Behav. 2017;178:43–65.
67. Luczynski P, McVey Neufeld KA, et al. Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior. Int J Neuropsychopharmacol. 2016;19. doi:10.1093/ijnp/pyw020
68. Smith CJ, Emge JR, Berzins K, et al. Probiotics normalize the gut-brain-microbiota axis in immunodeficient mice. Am J Physiol Gastrointest Liver Physiol. 2014;307:G793–G802.
69. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. J Physiol. 2004;558:263–275.
70. Desbonnet L, Garrett L, Clarke G, et al. Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. Neuroscience. 2010;170:1179–1188.
71. Stilling RM, Ryan FJ, Hoban AE, et al. Microbes & neurodevelopment—absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala. Brain Behav Immun. 2015;50:209–220.
72. D'Mello C, Ronaghan N, Zaheer R, et al. Probiotics improve inflammation-associated sickness behavior by altering communication between the peripheral immune system and the brain. J Neurosci. 2015;35:10821–10830.
73. Messaoudi M, Lalonde R, Violle N, et al. Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. Br J Nutr. 2011;105:755–764.
74. Desbonnet L, Garrett L, Clarke G, et al. The probiotic *Bifidobacteria infantis*: an assessment of potential antidepressant properties in the rat. J Psychiatr Res. 2008;43:164–174.
75. Gareau MG, Jury J, MacQueen G, et al. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. Gut. 2007;56:1522–1528.
76. Frohlich EE, Farzi A, Mayerhofer R, et al. Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. Brain Behav Immun. 2016;56:140–155.
77. Li W, Dowd SE, Scurlock B, et al. Memory and learning behavior in mice is temporally associated with diet-induced alterations in gut bacteria. Physiol Behav. 2009;96:557–567.
78. Ohland CL, Kish L, Bell H, et al. Effects of *Lactobacillus helveticus* on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. Psychoneuroendocrinology. 2013;38:1738–1747.
79. Davari S, Talaei SA, Alaei H, et al. Probiotics treatment improves diabetes-induced impairment of synaptic activity and cognitive function: behavioral and electrophysiological proofs for microbiome–gut–brain axis. Neuroscience. 2013;240:287–296.
80. Gareau MG, Wine E, Rodrigues DM, et al. Bacterial infection causes stress-induced memory dysfunction in mice. Gut. 2011;60:307–317.
81. Lyte M, Varcoe JJ, Bailey MT. Anxiogenic effect of subclinical bacterial infection in mice in the absence of overt immune activation. Physiol Behav. 1998;65:63–68.
82. Gacias M, Gaspari S, Santos PM, et al. Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. eLife. 2016;5. doi:10.7554/eLife.13442

83. Zheng P, Zeng B, Zhou C, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry. 2016;21:786–796.
84. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016;167:1469.e12–1480.e12.
85. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA. 2011;108:3047–3052.
86. Neufeld KM, Kang N, Bienenstock J, et al. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterol Motil. 2011;23:255–e119.
87. Clarke G, Grenham S, Scully P, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Mol Psychiatry. 2013;18:666–673.
88. Desbonnet L, Clarke G, Shanahan F, et al. Microbiota is essential for social development in the mouse. Mol Psychiatry. 2014;19:146–148.
89. Arentsen T, Raith H, Qian Y, et al. Host microbiota modulates development of social preference in mice. Microb Ecol Health Dis. 2015;26:29719. doi:10.3402/mehd.v26.29719
90. Dhiman RK, Rana B, Agrawal S, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology. 2014;147:1327.e3–1337.e3.
91. World Health Organization. Depression: let's talk. WHO website. http://www.who.int/mental_health/management/depression/en/. Accessed March 21, 2018.
92. Midtvedt T. Society for microbial ecology, microbial ecology in health and disease, and the future. Microb Ecol Health Dis. 2013;24. doi:10.3402/mehd.v24i0.23315
93. Savignac HM, Corona G, Mills H, et al. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. Neurochem Int. 2013;63:756–764.
94. Savignac HM, Kiely B, Dinan TG, et al. *Bifidobacteria* exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. Neurogastroenterol Motil. 2014;26:1615–1627.
95. Wong ML, Inserra A, Lewis MD, et al. Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition. Mol Psychiatry. 2016;21:797–805.
96. Mohammadi AA, Jazayeri S, Khosravi-Darani K, et al. The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: a randomized, double-blind, placebo-controlled trial in petrochemical workers. Nutr Neurosci. 2016;19:387–395.
97. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. Eur J Clin Nutr. 2007;61:355–361.
98. Allen AP, Hutch W, Borre YE, et al. *Bifidobacterium longum* 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. Transl Psychiatry. 2016;6:e939. doi:10.1038/tp.2016.191
99. Tillisch K, Labus J, Kilpatrick L, et al. Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology. 2013;144:1394.e4–1401.e4.
100. Chung Y-C, Jin H-M, Cui Y, et al. Fermented milk of *Lactobacillus helveticus* IDCC3801 improves cognitive functioning during cognitive fatigue tests in healthy older adults. J Funct Foods. 2014;10:465–474.
101. Brenner DM, Moeller MJ, Chey WD, et al. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. Am J Gastroenterol. 2009;104:1033–1049.
102. Akbari E, Asemi Z, Daneshvar Kakhaki R, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front Aging Neurosci. 2016;8:256. doi:10.3389/fnagi.2016.00256
103. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. Nutrition. 2016;32:315–320.
104. Schmidt K, Cowen PJ, Harmer CJ, et al. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology (Berl). 2015;232:1793–1801.
105. Steenbergen L, Sellaro R, van Hemert S, et al. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. Brain Behav Immun. 2015;48:258–264.
106. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun. 2015;48:186–194.
107. Naseribafrouei A, Hestad K, Avershina E, et al. Correlation between the human fecal microbiota and depression. Neurogastroenterol Motil. 2014;26:1155–1162.
108. Jagmag SA, Tripathi N, Jha MP, et al. Exploring the relationship between gut microbiome and depression. Trends Gastroenterol. 2016;1:1–5.
109. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. Biol Psychiatry. 2013;74:720–726.
110. Ait-Belgnaoui A, Durand H, Cartier C, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. Psychoneuroendocrinology. 2012;37:1885–1895.
111. Evrensel A, Ceylan ME. The gut-brain axis: the missing link in depression. Clin Psychopharmacol Neurosci. 2015;13:239–244.
112. Golubeva AV, Crampton S, Desbonnet L, et al. Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in adulthood. Psychoneuroendocrinology. 2015;60:58–74.
113. Jasarevic E, Howerton CL, Howard CD, et al. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. Endocrinology. 2015;156:3265–3276.
114. Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev Psychobiol. 1999;35:146–155.
115. O'Mahony SM, Marchesi JR, Scully P, et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. Biol Psychiatry. 2009;65:263–267.
116. Bailey MT, Dowd SE, Galley JD, et al. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. Brain Behav Immun. 2011;25:397–407.
117. Bharwani A, Mian MF, Foster JA, et al. Structural & functional consequences of chronic psychosocial stress on the microbiome & host. Psychoneuroendocrinology. 2016;63:217–227.
118. Galley JD, Nelson MC, Yu Z, et al. Exposure to a social stressor disrupts the community structure of the colonic mucosa-associated microbiota. BMC Microbiol. 2014;14:189. doi:10.1186/1471-2180-14-189.
119. Reber SO, Siebler PH, Donner NC, et al. Immunization with a heat-killed preparation of the environmental bacterium *Mycobacterium vaccae* promotes stress resilience in mice. Proc Natl Acad Sci USA. 2016;113:E3130–E3139.
120. Prenderville JA, Kennedy PJ, Dinan TG, et al. Adding fuel to the fire: the impact of stress on the ageing brain. Trends Neurosci. 2015;38:13–25.
121. Gareau MG. Microbiota-gut-brain axis and cognitive function. Adv Exp Med Biol. 2014;817:357–371.
122. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. 2015;17:565–576.
123. Levenson JM, O'Riordan KJ, Brown KD, et al. Regulation of histone acetylation during memory formation in the hippocampus. J Biol Chem. 2004;279:40545–40559.
124. Lattal KM, Barrett RM, Wood MA. Systemic or intrahippocampal delivery of histone deacetylase inhibitors facilitates fear extinction. Behav Neurosci. 2007;121:1125–1131.
125. Fischer A, Sananbenesi F, Wang X, et al. Recovery of learning and memory is associated with chromatin remodelling. Nature. 2007;447:178–182.
126. Govindarajan N, Agis-Balboa RC, Walter J, et al. Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. J Alzheimers Dis. 2011;26:187–197.
127. Sharma S, Taliyan R, Singh S. Beneficial effects of sodium butyrate in 6-OHDA induced neurotoxicity and behavioral abnormalities: modulation of histone deacetylase activity. Behav Brain Res. 2015;291:306–314.
128. Ryu H, Smith K, Camelo SI, et al. Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. J Neurochem. 2005;93:1087–1098.
129. Ferrante RJ, Kubilus JK, Lee J, et al. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci. 2003;23:9418–9427.
130. Chou AH, Chen SY, Yeh TH, et al. HDAC inhibitor sodium butyrate reverses transcriptional downregulation and ameliorates ataxic symptoms in a transgenic mouse model of SCA3. Neurobiol Dis. 2011;41:481–488.
131. Bravo JA, Julio-Pieper M, Forsythe P, et al. Communication between gastrointestinal bacteria and the nervous system. Curr Opin Pharmacol. 2012;12:667–672.
132. Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett. 1993;163:109–113.
133. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. Science. 2012;336:1262–1267.
134. Stilling RM, van de Wouw M, Clarke G, et al. The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochem Int. 2016;99:110–132.
135. Farrugia G, Szurszewski JH. Carbon monoxide, hydrogen sulfide, and nitric oxide as signaling molecules in the gastrointestinal tract. Gastroenterology. 2014;147:303–313.
136. Savidge TC. S-nitrosothiol signals in the enteric nervous system: lessons learnt from big brother. Front Neurosci. 2011;5:31. doi:10.3389/fnins.2011.00031
137. Gulbransen BD, Bashashati M, Hirota SA, et al. Activation of neuronal P2X7 receptor-pannexin-1 mediates death of enteric neurons during colitis. Nat Med. 2012;18:600–604.
138. Gulbransen BD, Sharkey KA. Novel functional roles for enteric glia in the gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2012;9:625–632.
139. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014;38:1–12.
140. Kabouridis PS, Lasrado R, McCallum S, et al. Microbiota controls the homeostasis of glial cells in the gut lamina propria. Neuron. 2015;85:289–295.

141. MacEachern SJ, Patel BA, Keenan CM, et al. Inhibiting inducible nitric oxide synthase in enteric glia restores electrogenic ion transport in mice with colitis. Gastroenterology. 2015;149:445.e3–455.e3.
142. MacEachern SJ, Patel BA, McKay DM, et al. Nitric oxide regulation of colonic epithelial ion transport: a novel role for enteric glia in the myenteric plexus. J Physiol. 2011;589:3333–3348.
143. Savidge TC, Newman P, Pothoulakis C, et al. Enteric glia regulate intestinal barrier function and inflammation via release of *S*-nitrosoglutathione. Gastroenterology. 2007;132:1344–1358.
144. Grubišić V, Gulbransen BD. Enteric glia: the most alimentary of all glia. J Physiol. 2017;595:557–570.
145. Alemi F, Poole DP, Chiu J, et al. The receptor TGR5 mediates the prokinetic actions of intestinal bile acids and is required for normal defecation in mice. Gastroenterology. 2013;144:145–154.
146. Sorg JA, Sonenshein AL. Chenodeoxycholate is an inhibitor of *Clostridium difficile* spore germination. J Bacteriol. 2009;191:1115–1117.
147. Sorg JA, Sonenshein AL. Inhibiting the initiation of *Clostridium difficile* spore germination using analogs of chenodeoxycholic acid, a bile acid. J Bacteriol. 2010;192:4983–4990.
148. Chen C, Brown DR, Xie Y, et al. Catecholamines modulate *Escherichia coli* O157:H7 adherence to murine cecal mucosa. Shock. 2003;20:183–188.
149. Chen C, Lyte M, Stevens MP, et al. Mucosally-directed adrenergic nerves and sympathomimetic drugs enhance non-intimate adherence of *Escherichia coli* O157:H7 to porcine cecum and colon. Eur J Pharmacol. 2006;539:116–124.
150. Freestone PP, Sandrini SM, Haigh RD, et al. Microbial endocrinology: how stress influences susceptibility to infection. Trends Microbiol. 2008;16:55–64.
151. Hughes DT, Clarke MB, Yamamoto K, et al. The QseC adrenergic signaling cascade in enterohemorrhagic E. coli (EHEC). PLoS Pathog. 2009;5:e1000553. doi:10.1371/journal.ppat.1000553
152. Lyte M, Vulchanova L, Brown DR. Stress at the intestinal surface: catecholamines and mucosa–bacteria interactions. Cell Tissue Res. 2011;343:23–32.
153. Savidge TC. Epigenetic regulation of enteric neurotransmission by gut bacteria. Front Cell Neurosci. 2015;9:503. doi:10.3389/fncel.2015.00503
154. Ruddick JP, Evans AK, Nutt DJ, et al. Tryptophan metabolism in the central nervous system: medical implications. Expert Rev Mol Med. 2006;8:1–27.
155. Ohland CL, Pankiv E, Baker G, et al. Western diet-induced anxiolytic effects in mice are associated with alterations in tryptophan metabolism. Nutr Neurosci. 2016;19:337–345.
156. Reigstad CS, Salmonson CE, Rainey JF III, et al. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB J. 2015;29:1395–1403.
157. Özoğul F. Production of biogenic amines by *Morganella morganii*, *Klebsiella pneumoniae* and *Hafnia alvei* using a rapid HPLC method. Eur Food Res Technol. 2004;219:465–469. 219(5): 465–469.
158. Shishov VA, Kirovskaia TA, Kudrin VS, et al. Amine neuromediators, their precursors, and oxidation products in the culture of *Escherichia coli* K-12 [in Russian]. Appl Biochem Microbiol. 2009;45:550–554.
159. Barrett E, Ross RP, O'Toole PW, et al. γ-Aminobutyric acid production by culturable bacteria from the human intestine. J Appl Microbiol. 2012;113:411–417.
160. Romano KA, Vivas EI, Amador-Noguez D, et al. Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-*N*-oxide. MBio. 2015;6:e02481. doi:10.1128/mBio.02481-14
161. Kelly JR, Kennedy PJ, Cryan JF, et al. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci. 2015;9:392. doi:10.3389/fncel.2015.00392
162. Luczynski P, Whelan SO, O'Sullivan C, et al. Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. Eur J Neurosci. 2016;44:2654–2666.
163. Simren M, Barbara G, Flint HJ, et al. Intestinal microbiota in functional bowel disorders: a Rome Foundation report. Gut. 2013;62:159–176.
164. Margolis KG, Gershon MD. Neuropeptides and inflammatory bowel disease. Curr Opin Gastroenterol. 2009;25:503–511.
165. Lomax AE, Sharkey KA, Furness JB. The participation of the sympathetic innervation of the gastrointestinal tract in disease states. Neurogastroenterol Motil. 2010;22:7–18.