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Nutritional Modulation of the Intestinal Microbiota; Future Opportunities for the Prevention and Treatment of Neuroimmune and Neuroinflammatory Disease

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Abstract

The gut-brain-axis refers to the bidirectional communication between the enteric nervous system and the central nervous system. Mounting evidence supports the premise that the intestinal microbiota plays a pivotal role in its function and has led to the more common and perhaps more accurate term gut-microbiota-brain axis. Numerous studies have identified associations between an altered microbiome and neuroimmune and neuroinflammatory diseases. In most cases, it is unknown if these associations are cause or effect; notwithstanding, maintaining or restoring homeostasis of the microbiota may represent future opportunities when treating or preventing

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Declarations

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these diseases. In recent years, several studies have identified the diet as a primary contributing factor in shaping the composition of the gut microbiota, and in turn, the mucosal and systemic immune systems. In this review, we will discuss the potential opportunities and challenges with respect to modifying and shaping the microbiota through diet and nutrition in order to treat or prevent neuroimmune and neuroinflammatory disease.

Keywords

Microbiome; neurocognitive; gut-microbiota-brain axis; SCFA; neurotrophic; vitamin; oxidative stress; polyphenols; myalgic encephalomyelitis; Parkinson's disease; Alzheimer's Disease; autism; multiple sclerosis; schizophrenia

1. Introduction

The human body is an ecosystem supporting trillions of microorganisms that live primarily, although not exclusively, within the gastrointestinal track [1]. For many years, it was widely believed the microbiota was mostly comprised of commensal bacteria that do not harm the host nor necessarily impart any significant health benefit. A notable exception to this point of view was based on observations that commensal bacteria compete with pathogenic species for nutrients and sites for colonization and, therefore, a compromised gut microbiota can lead to pathogenic intestinal infection [2]. For instance, the colonization of the gut by the bacteria *Clostridium difficile* can occur as a result of reduced microbiota competition during the course of long-term antibiotic therapy. In fact, the treatment of *C. difficile* infection by fecal transplantation is an excellent example where manipulating the gut microbiota has a direct and verifiable benefit for treating human disease [3].

In contrast to the aforementioned example, a perturbed microbiota may occur as a result of a disease process. For instance, gastrointestinal (GI)-associated CD4 T cells are the primary targets of infection by the human immunodeficiency virus (HIV)[4]. Alterations in mucosal immunity, including bacterial translocation, and subsequent chronic systemic inflammation are common and associate with HIV progression [5, 6]. Furthermore, components of this pathological process persist, despite viral suppression during highly active antiretroviral therapy (HAART) [7–9].

Previous studies have reported significant differences in the gut microbiome of HIV cases when compared to controls. Shifts in bacterial populations toward those with proinflammatory potential, such as *Staphylococcus spp., Pseudomonas spp.*, and *Enterobacteriaceae* family members are commonly reported [10, 11]. In fact, increased *Prevotella* in the stool of HIV-infected individuals has been reported by several groups [12–14]. Vujkovic-Cvijin and coworkers observed that a dysbiotic mucosal-adherent bacterial population, enriched in Proteobacteria and depleted of Bacteroidia members, was associated with markers of mucosal immune disruption, as well as T cell activation, and chronic inflammation in HIV-infected subjects [15]. They additionally reported an upregulation of kynurenine pathway components. The kynurenine pathway, also known as the indoleamine 2,3-dioxygenase (IDO), pathway contributes to metabolic immune regulation by catabolizing the essential amino acid L-tryptophan and has been associated with

inflammation, neurodegenerative diseases, and depression. Importantly, some of products of this pathway, such as quinolinic acid, are neurotoxic and have been associated neurological pathology in HIV infection [16].

With respect to *C. difficile* infection, the benefit of modifying the microbiota through fecal transplantation is fairly straightforward. In the case of HIV-infection, the situation is less obvious, although early studies suggest that altering the microbiota may influence systemic immune responses. Hensley-McBain et al. showed that macaques infected with simian immunodeficiency virus (SIV), the animal model of HIV infection, displayed significant increases in the number of peripheral Th17 and Th22 cells and reduced CD4 T cell activation in GI tissues after receiving antibiotics, followed by fecal transplantation. However, others reported that human subjects with HIV infection showed no significant change, post-fecal transplantation [17]. Albeit, the authors acknowledge that, unlike the macaques in the Hensley-McBain et al. study, the human subjects were not preconditioned with antibiotics, so depleting the previous microbiota may be in important step prior to microbiota transplantation.

At this time, all aspects of altering the microbiota are not fully understood in most cases. However, as our understanding improves with respect to the contributions of specific bacterial groups, rational modification of the microbiota may ultimately become an effective way of modifying diseases associated with an altered microbiota.

2. The gut-microbiota-brain axis

Most neuroimmune diseases are characterized by a spectrum of symptoms and the pathophysiology of these diseases cannot typically be defined by an individual organ or system (such as neurological); instead, a more systemic point of view must be considered. Indeed, it is increasingly evident that the gut microbiota dramatically influences systemic immunity, including the host's neuroimmune status, both beneficially and adversely. The so-called "gut-microbiota-brain" axis dictates that biochemical signaling occurs between the enteric nervous system (ENS) of the GI tract and the central nervous system (CNS) and principally involves the intestinal microbiota [18]. This signaling can occur directly via the vagus nerve or indirectly, through chemical signals that are released into the periphery and act in an endocrine manner (Figure 1) [19–22].

When an imbalance of the gut microbiota occurs and results in an increase in noncommensal microbes (dysbiosis), homeostasis of the gut microbiota is disrupted. Signaling between the gut-brain axis is also impacted, potentially leading to neurological and neuroimmune abnormalities. Indeed, dysbiosis is commonly associated with a compromised gut epithelium and the subsequent bacterial translocation may result in systemic inflammation and innate immune activation such as the upregulation of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) [23, 24]. Furthermore, it is important to appreciate that systemic inflammation can promote neuroinflammation across the blood-brain barrier. In point of fact, it has been shown that a single intraperitoneal injection of TNF-α in mice increased serum and brain levels of the proinflammatory cytokines TNF-α, IL-6, and MCP-1, in a dose- and time-dependent manner [25].

3. Gut microbiota and neurotrophic factors

Biogenic amines such as catecholamines (CA), which include epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine, as well as other neuroactive amines like gamma-aminobutyric acid (GABA) and serotonin (5-hydroxytryptamine, 5-HT) [26–29] interact with several host systems to maintain homeostasis [26, 27]. Strikingly, over 90% of the body's 5-HT is produced in the gut, and through the engagement of at least 14 different receptor subtypes [30], modulates the digestive system [31], the nervous system [32], the immune system [33], and cardiac function [34]. Using an animal model, Yano and coworkers showed that the gut microbiota significantly contributes to the level of colon and blood 5-HT, primarily through elevating its synthesis by host colonic enterochromaffin cells [35]. Furthermore, utilizing specific pathogen-free mice, germ-free mice, and gnotobiotic mice, Asano et al. showed that CA levels in the gut lumen were lower in germ-free mice than in specific pathogen-free mice and, moreover, CA levels correlated with *Clostridium*-associated β-glucuronidase activity [29], directly implicating a specific genus of bacteria. Although it is widely accepted that dopamine levels are primarily synthetized in the CNS, a study in rats showed evidence that the gut lumen also contributes to dopamine production to some extent [29]. Another study showed that administering *Lactobacillus* to germ-free mice not only increased the levels of 5-HT, but significantly increased the level of dopamine in the striatum, raising the possibility of using bacterial transplants for the treatment of Parkinson's disease (PD) [36]. Also, enzymes that regulate dopamine synthesis can be modulated by gut microbiota through the microbiota-gut-brain axis [37].

In addition to the host's production of biogenic amines, which may occur as a result of host-bacterial interactions, it has been reported that a number of gut-associated bacteria have the capacity to directly produce these signaling molecules. For example, Pessione et al. reported that *Lactobacillus spp.* and *Enterococcus* produce and release histamine and tyramine into the intestinal lumen [38]. Also, *Escherichia coli* and *Pseudomonas* have been reported to produce endogenous GABA [39] and *Bifidobacteria* has been reported to produce melatonin [40].

4. The gut microbiota, mucosal immunity, and neuroinflammation

Our current understanding supports the premise that the microbiota plays a pivotal role in maintaining mucosal immune competence and GI integrity. Indeed, previous studies show that animals who develop under germ-free conditions display extensive deficits in the development of the gut-associated lymphoid tissues (GALT), suggesting that commensal bacteria are important, not only for maintaining gastrointestinal health, but are also critical for the proper development of mucosal immunity. Several observations support the premise that the microbiota can influence the inflammatory state of intestinal epithelium and, in turn, its integrity. For instance, *Bacteroides fragilis* as well as some members of the genus *Clostridia* promote an antiinflammatory state through the production of antiinflammatory cytokines, such as IL-10 and IL-13, while some pathogenic bacteria, including *Salmonella typhimurium* and *C. difficile*, drive the production of inflammatory cytokines [41, 42].

The innate immune system senses microorganisms of the gut, primarily through their interaction with pattern recognition receptors, and their engagement by bacterial products is essential for maintaining intestinal homeostasis [43–45]. The structural constituents of bacterial cell walls persistently stimulate the innate immune system to produce inflammatory cytokines, thus generating a basal state of low-level immune activation that originates at the intestinal mucosal surface and affects the entire body [46]. To this end, a compromised gut epithelium and the subsequent bacterial translocation exacerbates this process, resulting in greater systemic inflammation and innate immune activation including the upregulation of inflammatory cytokines [23, 24]. The upregulation of these inflammatory mediators can promote pathological responses including sickness behavior, neurocognitive dysfunction, sleep abnormalities, and chronic fatigue [47, 48].

In addition to the previous examples that largely rely on innate immune responses, cell-mediated immunity is also influenced by the gut microbiota. Notably, the majority of Th1 and Th17 cells reside in the small intestine and differentiate as a result of signals associated with the gut microbiota [49, 50]. Failure to maintain the proper balance of these T cells leads to increased bacterial translocation and innate immune activation [51, 52]. Importantly, current estimates suggest that more than 60% of all T-cells reside within the small intestine [53] underscoring the potential contribution of the gut to systemic immunity. Therefore, a compromised gut may have a profound and complex influence on the host's neuroimmune system.

Alterations in gut microbiota can also indirectly affect mucosal immunity by adversely dysregulating energy homeostasis and promoting oxidative stress. For instance, hydrogen sulfide (H_2S), which is produced during the course of anaerobic respiration by bacteria such as *Prevotella*, is associated with mitochondrial dysfunction, epithelial damage, and increased intestinal inflammation [54, 55]. Furthermore, elevated lactic acid production from bacteria such as *Enterococcus* and *Streptococcus spp.* can also contribute to GI pathology by promoting mitochondrial dysfunction and enhance oxidative stress. These examples are but a few of the putative mechanisms whereby the microbiota impacts neuroimmune and neuroinflammatory processes.

It is important to bear in mind that the composition of the gut microbiota is influenced by a combination of factors including genetics, diet, antibiotic use, and disease, all of which may act in concert and these factors will need to be considered [56, 57]. Additionally, most investigations into the composition of disease-associated microbiomes have relied on 16S ribosomal analysis, which primarily identify families of bacteria, but few studies have conducted a comprehensive survey at the species level. In one of the few instances, Li and coworkers conducted a comprehensive survey by combining 249 newly sequenced samples from the Metagenomics of the Human Intestinal Tract project with 1,018 previously sequenced samples to create a cohort from three continents and concluded that almost 10 million unique bacterial genes are potentially represented [58]. These data emphasize the potential diversity of the human microbiota and challenges that lay ahead with respect to understanding the contributions of specific bacterial species. However, as our knowledge increases as to the contributions of each species, with respect to neuroimmune and

neuroinflammatory diseases, the rational modulation of the intestinal microbiota will ultimately be within our grasp.

5. Neuroimmune and neuroinflammatory diseases associated with alterations of the gut microbiota

5.1 Parkinson's disease

Parkinson’s disease (PD) is a devastating, neurodegenerative disorder characterized by the progressive degeneration of axons that project from midbrain dopamine neurons to the striatum. Pathologically, PD is characterized by an accumulation of intracellular, protein aggregates termed “Lewy bodies” in midbrain dopamine neurons. The progressive loss of midbrain dopamine neurons leads to the onset of clinical symptoms, including the presence of tremors and bradykinesia. Additionally, the loss of posture/balance and the onset of dementia are observed in late-stage PD.

PD is also characterized by the presence of non-motor symptoms. In fact, it is generally accepted that the majority of individuals who suffer with PD also suffer from gastrointestinal comorbidities, of which constipation is considered the most prominent [59]. Specifically, PD cases show signs of gastrointestinal dysmotility including delayed gastric emptying and constipation. Indeed, approximately 50% of PD cases suffer from severe constipation and show comorbidity with bowel-related disorders including Crohn’s disease and inflammatory bowel syndrome. Additionally, constipation can occur 20 years before the onset of motor symptoms in PD. These observations suggest that constipation represent an early pathological event that precedes the onset of neurological and motor symptoms in PD by 10–15 years. As previously mentioned, the gut lumen can contribute to the production of dopamine [29]. Therefore, given the observation that the ENS produces some level of dopamine and that PD symptoms are caused by a reduction in dopamine, it is conceivable that gut pathology observed in the majority of PD cases is a major risk factor that can exacerbate the depletion of dopamine and worsen PD neuropathology.

PD cases show altered gut homeostasis including increased oxidative stress which contributes to barrier and intestinal permeability, leading to a leaky gut and systemic low-grade inflammation [60–62]. While the pathophysiological mechanisms that contribute to altered gut homeostasis in PD are not known, mounting evidence suggest that early alterations in the microbiome are associated with constipation and gut-related disorders. Consistent with this model, Lai et al. reported that a diagnosis of IBS is associated with an increase in risk of PD [63, 64]. Other studies have shown that PD cases present with altered microbiomes including an over-abundance of a number of bacterial groups, including Bacteroidetes, Lactobacillaceae, *Faecalibacterium prausnitzii, Enterococcaceae*, [65] *Prevotella*, [65, 66] and *Clostridium spp.* [67]. Moreover, there is strong evidence that the microbiota is altered early during the course of disease. One recent study showed that the prevalence of *Bifidobacterium* and *Bacteroides fragilis* is decreased, along with an increase in *Lactobacilli gasseri* and Enterobacteriaceae [66, 67]. Notably, alterations in the gut microbiome in PD cases are significantly associated with worsened PD-associated symptoms [68].

Although it is not known if an altered microbiota is the initiating factor of PD, a major drive of etiology or consequence of disease progression, there is some evidence that suggests an altered gut microbiome contributes to PD pathophysiology. Importantly, there is convincing evidence of strong interactions between the ENS and the CNS via a braingut/enteric axis in PD. Like the brain, significant accumulation of Lewy bodies has been observed in the ENS of PD cases suggesting that the aberrant accumulation of protein aggregates contributes to neurodegeneration of the ENS and gut pathology [69] which predates the PD symptoms by 10 to 20 years [70]. Furthermore, fecal transplantation studies have compellingly shown that an altered microbiota contributes to PD symptoms. Strikingly, transplanting microbiota from six PD cases worsened the motor symptoms in α-synuclein expressing mice [71]. Conversely, depleting the gut microbiota in this transgenic PD mouse model ameliorated the symptoms of PD, reduced the aggregation of Lewy bodies in the CNS, and reversed constipation. Finally, an altered microbiome in PD may contribute to an increase in oxidative stress caused by overactive macrophages, which lead to increase wall permeability and enhances the aggregation of α-synuclein and in an *in vivo* chemical model of PD [69, 72, 73]. Overall, this data suggests causation between altered gut microbiome and PD symptoms.

To date, little is known about the molecular causes of altered gut homeostasis in PD. A reduction in the level of neurotrophins, including brain-derived neurotrophic factor (BDNF), may contribute to deregulated gut homeostasis and constipation in PD based on the following evidence. BDNF is one of the most abundant neurotrophins produced in the gut to support normal brain development, neuronal survival and the differentiation of midbrain dopamine neurons [74]. Furthermore, BDNF can exert strong antiinflammatory processes in models of immune-graft rejection, allergy and experimental meningitis models suggesting that BDNF can regulate the immune system. [75–77]. Based on studies performed in postmortem brain tissue, midbrain dopamine neurons in PD show a significant reduction in neurotrophic factors such as BDNF and of the BDNF receptor TrkB [78–80] suggesting that a decrease in BDNF reduces neuronal survival and increases the susceptibility of dopamine neurons to oxidative stress.

A proper level of BDNF is critical for the expression and proper function of the N-methyl-D-aspartate (NMDA) receptor in the CNS and ENS [81]. Given that a low level of BDNF in the CNS and the ENS in PD has been well-documented, it has been postulated that a reduction in the level of membrane-bound NMDA receptor may contribute to alterations in gut homeostasis and changes in CNS function, via affecting the kynurenine pathway [81]. Furthermore, as the gut microbiome produces a significant level of BDNF to support normal gut function [81], these data suggest that a low BDNF level plays a pivotal role in neurodegeneration of dopamine neurons in the CNS and ENS, gut pathology and inflammation in PD.

Finally, there is experimental evidence that suggest that supplementation of exogenous recombinant human BDNF, or of compounds that increase BDNF levels, may ameliorate constipation, oxidative stress and clinical symptoms in PD. For instance, Vidal-Martinez et al. showed that transgenic mice that overexpress mutant α-synuclein (A53T), a genetic model of PD, shows decreased gut motility compared to wild-type mice whereas treating

mice with AN121, an antagonist of the BDNF receptor, reversed the ameliorative effects of BDNF on constipation [82]. Overall, these data suggest that low levels of BDNF and a decline in BDNF-mediated signaling contributes to gut pathology and subsequent neurodegeneration of dopamine neurons in PD.

5.2 Myalgic encephalomyelitis

Many chronic diseases are characterized by systemic immune activation, gastrointestinal issues and neurocognitive abnormalities. One such example, myalgic encephalomyelitis (ME), is a heterogeneous disorder often identified by incapacitating post-exertional fatigue, not relieved by rest, accompanied by neurological symptoms (e.g. brain fog, modest brain atrophy, and gradual decline in cognitive function), and inflammatory sequelae [83]. GI abnormalities are also commonly reported by those with ME, and, in fact, are so prevalent and their symptoms overlap with irritable bowel syndrome (IBS) to such an extent that many individuals diagnosed with ME report that they received a previous diagnosis of IBS [84]. This assertion is supported by studies conducted by Maes and coworkers, who reported that a majority of subjects with ME (59.6% vs. 17.7%) experienced GI symptoms and that these symptoms strongly associated with a diagnosis of IBS [85].

Consistent with a GI involvement in the pathophysiology of ME, several studies have reported alterations of the ME microbiota and microbiome. For instance, using culture- and metabolomic-based analyses, Sheedy and colleagues reported significantly increased proportions of D-lactic acid-producing *Enterococcus* and *Streptococcus* spp. in fecal samples of subjects with ME [86]. Recently, Wallis et al. conducted a systematic literature review to examine similarities between ME and acute D-Lactic acidosis and concluded that high levels of D-lactate may play a role in the neurological comorbidity in ME [87]. However, as there have not been any robust clinical studies to evaluate the circulating levels of D-lactate in ME subjects, the contribution of D-lactate in the neurological comorbidity of ME remains to be established.

In the first published metagenomics analysis of an ME cohort, Fremont et al. observed that subjects with ME displayed an overall gut microbiome that is different from non-ME subjects when geographically controlled [88]. In this study, stool from ME cases and controls from Belgium and Norway were analyzed by pyrosequencing, which revealed that Belgian cases and controls differed, as did Norwegian cases and controls. Interestingly, Belgian and Norwegian ME cases differed from each other, as did Belgian and Norwegian controls. Not only does this study articulate an association between ME and alterations in the gut microbiome, these data emphasize the potential for geographic differences as well as disease differences when investigating disease associations with an altered microbiome. Variations in the gut microbiota of ME cases were later confirmed by Giloteaux and colleagues, who showed that ME is characterized by dysbiosis, bacterial translocation and an altered microbiome, and additionally reported that overall bacterial diversity was lower in the ME cases when compared to controls. In particular, they observed large reduction in the relative abundance and diversity of members of the Firmicute phylum.

In a later study, it was revealed by Nagy-Szakal and coworkers that ME cases without IBS can be differentiated from those with IBS based on their microbiome profile [89].

Specifically, ME cases with IBS were identified by an increase of unclassified *Alistipes* and decreased *Faecalibacterium* whereas increased unclassified *Bacteroides* abundance and decreased *Bacteroides vulgatus* were more prevalent in ME cases without IBS. It was also revealed that the severity of symptoms such as pain, fatigue, and reduced motivation were correlated with the abundance of specific bacterial taxa [89]. When taken together, these studies strongly imply that an altered microbiome profile is common among those with ME and, additionally, may differentiate specific subgroups.

Although not all individual with ME report GI comorbidity, previous research suggests that gut pathology may not be a requisite for alterations in the microbiota. For example, Shaukla and colleagues observed differences in gut and plasma microbiome following an exercise challenge that was not recapitulated in controls subjects [90]. Interestingly, as previously indicated, on average, the composition of microbiome of those with ME is reported to be less diverse; however, following exercise challenge, an increase in relative abundance of six of the nine major bacterial phyla/genera was observed in ME cases compared to only two of the nine in controls. Previous studies in animal models [91, 92] as well as humans [93], suggest that exercise is associated with increased microbiota diversity, as well as an expansion of beneficial bacteria, such as butyrate-producing species. However, the increased microbiota diversity observed in ME subjects was observed concurrently with an increase in bacterial products in the blood, suggesting bacterial translocation is associated with strenuous exercise in ME. Although, it is yet to be determined whether or not the increased bacterial diversity induced by exercise is beneficial or pathological for those with ME [94]. Further studies will be required to determine if the bacterial translocation and potentially associated systemic inflammation observed during strenuous exercise in ME contributes to the manifestation of exercise intolerance; however, this study does introduce the intriguing possibility of a connection between the gut microbiota, intestinal integrity and systemic inflammation observed in ME.

5.3 Schizophrenia

The role of the human microbiome in schizophrenia is largely undiscovered, but many argue that it’s an endeavor worth pursuing [95]. Currently there are limited published studies involving the fecal and orophyngeal microbiome in those with schizophrenia. One such oropharyngeal investigation using metagenomic analysis (16 adults with schizophrenia, 16 non-psychiatric controls) found differences at both the phylum and the genus levels. Samples from subjects with schizophrenia had less overall diversity of species compared to controls, and an increased number of metabolic pathways representing metabolite transport systems, including siderophores (iron-chelating compounds secreted by microorganisms such as bacteria and fungi), glutamate and vitamin B12; this is in contrast to carbohydrate, lipid pathways and energy metabolism which were abundant in controls [96]. Another study of the oropharyngeal microbiome (41 adults with schizophrenia, 33 non-psychiatric controls) assessed bacteriophages (viruses that infect bacteria and alter their metabolism) and found that the *Lactobacillus* phage phi adh was significantly more abundant in schizophrenia cases than in controls [97].

One small study that used fecal samples to investigate the role of the gut microbiome in first episode psychosis (FEP) (28 cases, 16 controls) reported an elevation of the *Lactobacillus* group and a positive correlation with the severity of psychotic symptoms in multiple domains. Differences in the microbiota were also associated with poorer treatment response in one FEP subgroup [98]. Another case-control study looked at exposures to fungal members of the gut microbiome, including the yeast species, *Candida albicans*. Severance et al. investigated antifungal IgG antibody responses of participants with bipolar disorder (n=270) and schizophrenia (n=261) revealing sex-specific differences; *C. albicans* seropositivity conferred increased odds for a schizophrenia diagnosis in males, while *C. albicans* seropositivity in females was associated with higher odds of cognitive impairment (lower cognitive scores) [99]. In a follow-up, 56 of the outpatients with schizophrenia were enrolled in a longitudinal, double-blind, placebo-controlled study, showing sex-specific effects; probiotic treatment significantly reduced levels of *C. albicans* antibodies over the 14-week study period in males, but not in females [100].

The maternal immune activation (MIA) mouse model mimics neurodevelopmental disorders such as autism or schizophrenia by administering immune stimulants [such as the endotoxin lipopolysaccharide (LPS), mimicking a bacterial infection, or the double-stranded RNA molecule, polyinosinic:polycytidylic acid (poly I:C), mimicking a viral infection] to the pregnant mouse to induce behavior change in the offspring. This model is based on the theory that it is not the infectious agent, but rather the maternal immune activation that causes the behavior change in the offspring. The gut microbiome likely plays a pivotal role in the MIA model, as offspring have gastrointestinal abnormalities and altered microbiota, similar to humans with autism and schizophrenia [101]. Additionally, one promising MIA study gave the probiotic *Bacteriodes fragilis* to MIA offspring, and by doing so, corrected their intestinal permeability deficits and reversed some of their behaviors (communicative, stereotypic, anxiety-like and sensorimotor); however, social deficits persisted. After *B. fragilis* treatment, two serum metabolites normalized, 4-ethylphenylsulfate (4EPS) and indolepyruvate; notably, 4EPS is structurally similar to p-cresol, the putative autism spectrum disorders (ASD) biomarker, and indolepyruvate is theorized to be a metabolic byproduct of gut bacteria [101]. A recent MIA mouse study demonstrated that IL-6 in the placenta activates inflammatory signals to influence fetal brain development and behavior [102].

5.4 Autism spectrum disorders

As with other neurological disorders, such as PD and Alzheimer's disease (AD), ASD are exceedingly comorbid with GI symptoms such as constipation, bloating and diarrhea, and several previous studies have reported that ASD often associate with an altered intestinal microbiome [103]. For instance, Finedgold et al. reported that the number of *Clostridial* species found in the stool samples of children with ASD was greater than in the stool samples of control children [104]. Also, Tomova and coworkers reported that microbiomes of children with ASD exhibit a significant decrease in the *Bacteroidetes/Firmicutes* ratio and an elevation in the amount of *Lactobacillus* species as well as the *Desulfovibrio* species when compared to siblings and healthy controls [105].

Although the precise mechanism connecting the microbiota to the neuropathology of ASD is not fully elucidated, recent studies by Golubeva et al. support that social behavior deficits in the BTBR *T*$^{+}$*Itpr3*^{tf}/J mouse model of ASD are associated with microbiota-related alterations in bile acid and tryptophan metabolism [106]. Particularly, they observed that tissue levels of 5-HT were decreased in the small and large intestine of BTBR mice by 50% when compared to control mice. Furthermore, this decrease coincided with decreased tryptophan hydroxylase 1 (*Tph1*) transcription and increased transporter (*Sert*) transcription. These observations were associated with GI distress, intestinal permeability, and changes in ENS morphology.

A recent clinical trial was conducted by Kang and coworkers to investigate the potential benefits of fecal transplantation in autistic children [107]. After a two-week pretreatment with antibiotics to deplete the existing microbiota, subjects were treated with an initial bolus of transplant bacteria, followed by a lower daily maintenance dose for seven to eight weeks. Upon completion of the treatment, a significant improvement in gastrointestinal symptoms was observed, including constipation, diarrhea, indigestion, and abdominal pain. They additionally reported that behavioral symptoms, as indicated using the PGI-II assessment, showed significant improvements which were maintained at eight-weeks post-treatment. Finally, microbiome pyrosequencing confirmed that the donor transplant was partially maintained as well as beneficial changes in the gut environment.

In order to explore the possibility that microbiome-driven behavioral changes are accompanied by corresponding changes in neurological tissue, Ong et al. utilized diffusion tensor imaging to show that over-all changes in white matter structural integrity occurred in a diet-dependent manner [108]. They further reported that the changes in diet were accompanied by changed in the microbiome. These studies provide compelling evidence that modifying the microbiota through diet, may represent an effective strategy to treat neurological pathology; however, it should be pointed out that other investigators have reported subjects with AD are also characterized by alterations in their oral microbiome, raising the possibility that more than just the gut microbiota may be involved in these observations [109].

5.5 Multiple sclerosis

Multiple sclerosis (MS) is a severely debilitating autoimmune disease, characterized by chronic inflammation of the CNS, leading to demyelination. Although the etiology of MS is presently unknown, genetics and environmental factors are thought to play an important role [110, 111]. In addition to a host of neurological symptoms, individuals with MS commonly experience GI aberrations [112]. In fact, a survey-based study revealed that approximately two thirds of individuals with MS reported GI complaints that persist for at least six months, which include diarrhea, constipation, and fecal incontinence [113].

Several previous studies have reported that subjects with MS have an altered microbiome when compared to age- and gender-matched controls [114–116]. For instance, Miyake and coworkers conducted a longitudinal study to compare the gut microbiota of Japanese subject with relapsing-remitting MS (RRMS) to that of healthy controls and observed that 21 species of bacteria exhibited significant changes in relative abundance in addition to

observing an overall moderate dysbiosis in the RRMS cohort. However, in contrast to other disease, such as inflammatory bowel disorders, which show reduced diversity [117, 118], they reported that RRMS cases displayed similar bacterial diversity to that of controls.

Perhaps the most compelling evidence for a microbiota-MS connection arise from observations conducted using the classical MS mouse model, experimental autoimmune encephalomyelitis (EAE). Lee and colleagues reported that intestinal microbiota significantly influence the balance between proinflammatory and antiinflammatory and immune responses during the induction of EAE [119]. Specifically, they observed that mice, reared under germ-free conditions developed an attenuated form of EAE characterized by decreased levels of the proinflammatory cytokines IL-17A and IFN-γ in the intestine and spinal cord with an concomitant increase in CD4+CD25+Foxp3+ regulatory T cells (Tregs). The authors of this study additionally showed that specific pathogen-free mice that harbor segmented filamentous bacteria fully developed EAE, thus providing compelling evidence that the bacterial composition of the gut can influence neurologic inflammation in MS.

Subsequent to this study, Haghikia and coworkers showed that long-chain fatty acids (LCFAs) promote polarization of naive T cells toward a Th1 and Th17 differentiation and impaired their intestinal sequestration via the p38-MAPK signaling pathway. In contrast, EAE mice treated with short-chain fatty acids (SCFAs) displayed increased differentiation and proliferation of Tregs, and an accompanying resolution of EAE pathology. It is noteworthy that microbiome survey studies of other neuroimmune disease such as ME [120] and autoimmune diseases, such as Crohn's disease [121], are characterized by reduced levels of butyrate-producing bacteria. These data suggest that rationally modifying the gut microbiota through diet, in order to promote the growth and maintenance of SCFAproducing bacterial, represents a potential strategy for treating neuroinflammatory disease.

5.6 Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder and is typically associated with a toxic buildup of β-amyloid plaques and hyperphosphorylated and misfolded tau protein in the brain [122]. As with PD cases, recent evidence suggest that alterations in the microbiome of those with AD may be associated with or contribute to the pathophysiology of AD [123]. Recently, Minter et al. reported that antibiotic treatment of a murine model of AD lead to reduced amyloidosis [124]. Subsequent to this study, Kobayashi and colleagues reported that oral administration of *Bifidobacterium breve* strain A1 to a mouse model of AD (intracerebroventricularly administered Aβ25–35) resulted in reversal of cognitive impairment [125]. This study raises the possibility that an altered microbiome contributes to the neuropathological progression in AD. The authors of this study additionally reported that transcriptional profiling of the hippocampus revealed that a total of 305 genes (247 upregulated, 58 downregulated) were differentially expressed in the AD animal model when compared to non-AD mice and that most of the differentially expressed genes were involved in immune response. Strikingly, upon treatment with *B. breve* A, the transcriptional profiles AD mice differed from non-AD mice by only two genes, suggesting that *B. breve* A could modulate excessive AD-associated immune responses and underscores the relevance of the altered microbiome the progression of AD pathology.

Recently, an association between an altered microbiome and the presentation of AD was demonstrated in human subjects by Vogt and coworkers [126]. In this report, it was showed that the gut microbiome of AD cases contains less microbial diversity and was compositionally distinct from age- and sex-matched controls. It has also been shown that a significant reduction in BDNF and of neuroprotective signaling is observed in postmortem brain tissue as well as *in vivo* models of AD and this has been suggested to contribute to the overt and progressive neurodegeneration of hippocampal neurons [127]. In light of recent evidence showing that BDNF levels are regulated by the gut microbiome and the neuroprotective role of BDNF, it would be relevant to understand whether the altered microbiota in AD cases can contribute to a reduction of BDNF, and thereby, exacerbate AD neuropathology. As mentioned in the PD section, a reduction in BDNF can also exacerbate oxidative stress and alter gut homeostasis in AD cases. In addition to supporting a role for the microbiota in the pathophysiology of AD, these murine and human studies suggest that the progression and presentation of AD may be modified through the modification of the microbiota. Nonetheless, it has been suggested that pathology of AD commences as early as 20 years prior to the manifestation of overt symptoms [128]; therefore, in light of this protracted prodromal phase, modifying AD progression after symptoms are manifest may prove to be impractical. It is possible that the greatest opportunities in modifying the microbiota will be in the proactive prevention of AD for those with a hereditary predisposition.

6. Modifying the Microbiota through the use of prebiotics and probiotics

6.1 Prebiotics

Modulation of the microbiota is an evolving strategy as a part of comprehensive approach to lifestyle wellness [129]. The diverse ecosystem that the microbial organisms inhabit in the gut allow for potential targets to maintain or improve health as well as treat disease. Advances in microbiome research utilizing high-throughput RNA sequencing has improved our knowledge of the composition of the microbiota and the substances that influence their colonizing abilities. Therefore, these methods can be used as a prognostic tool to follow the effects of dietary interventions on the composition of these microbial populations in a longitudinal manner [130, 131]. Prebiotics, are a class of compounds that has been recognized for their ability to manipulate the host's microbiota. Whereas probiotics are live microorganisms, prebiotics are nonviable substrates that serve as nutrients for beneficial microorganisms harbored by the host. It is important to note that prebiotics differ from most dietary fibers such as pectins, cellulose and xylans, which encourage growth of a wide variety of gut microorganisms. A prebiotic is more specific in that it is not broadly metabolized, but elicits a metabolism biased towards health-promoting microorganisms within the indigenous ecosystem. Simpson and Campbell provide a comprehensive review of microbiota interaction and compare studies on fiber and prebiotics [130].

The first prebiotics assessed in humans and used commercially stimulated *Lactobacillus* and *Bifidobacterium* but not pathogens such as *Clostridium* or *Escherichia* [132]. In 2004, the definition of prebiotics was altered to "selectively fermented ingredients that allow specific changes, both in composition and/or activity in the gastrointestinal microflora that confers

benefits upon host well-being and health" [131]. It is important to note that the prebiotic is selectively utilized by microorganisms and can lead to an overall health benefit for the host. However, if additional microorganisms that have pathogenic effects have enhanced function or growth and lead to a negative consequence for the host then this substrate can no longer be called a prebiotic. This distinction makes it important to determine both function and composition of the gut microbiota involved. Furthermore, prebiotics should not cause gas formation, unfavorable changes in bowel habits, or any type of negative symptom for the human host [133].

There are many fermentable carbohydrates that have a prebiotic effect, but the dietary prebiotics most extensively documented to have health benefits in humans are the non-digestible oligosaccharides fructans and galactans, which are preferentially utilized by *Bifidobacteria* [133, 134]. In contrast to many other genera of bacteria, *Bifidobacteria* have the β-fructanosidase and β-galactosidase enzymes necessary to digest the linkage bonds in fructan and galactan oligosaccharides as well as the transport machinery to necessary capture and deliver the substrates into their cytoplasm.

Interestingly, the first oligosaccharides identified to have prebiotic effects and positively impact gastrointestinal health are present in human milk. Human milk oligosaccharides are particularly important for the development of the newborn baby's intestinal microbiota and metabolic and immunologic systems, which have consequences for health in early development as well as later in life. Human milk oligosaccharides, after fucosylation and sialylation, prevents adhesion of pathogens to the neonate's intestinal epithelium by a competitive mechanism which infers protection from infection [129, 135, 136].

Ultimately, utilizing prebiotics as an intervention to improve health and reduce risk of disease is the goal. The approach that is the most effective are those that rely on prevention and recognition that life strategies adopted in early in life, which, when maintained, will promote a viably diverse and durable microbiota that will promote greatest potential to benefit the health of the host.

6.2 Probiotics

Probiotics are preparations of live or attenuated microorganisms, such as bacteria or yeast, which may afford certain health benefits when consumed. Several different probiotic preparations are commercially available and differ from one manufacturer to another in a number of ways, including bacterial composition, number of organisms, and biological activity. Many health benefits are attributed to probiotics, such as improving or supporting immunity, competitively inhibiting noncommensal bacteria growth and providing many of the essential vitamins and cofactors necessary for human health, that are not endogenously produced by the host [137–140].

Various food preparations, such as yogurt and some fermented foods, are natural sources of probiotics. Pu et al. conducted a clinical trial to evaluate the efficacy of yogurt containing *Lactobacillus paracasei* strain N1115, to prevent acute infection in elderly subjects and observed a significant benefit, potentially through an enhancement of the T-cell-mediated natural immune defense [141]. Indeed, N1115 is reported to exhibit substantial resistance to

acid and bile stresses and also stimulates macrophages to produce IL-10, IL-6, and TNF-α [142]. Bercik and coworkers reported that mice infected with the nematode parasite *Trichuris muris*, displayed anxiety-like behavior which correlated with decreased level of BDNF. However, upon treatment with the common probiotic *Bifidobacterium longum*, the anxiety-like behavior was reversed and BDNF levels were normalized [21]. Also, Messaoudi et al. evaluated the efficacy of a probiotic formulation containing *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175, to reduce anxiety in rats and also its possible effects on anxiety, depression, stress and coping strategies in healthy human volunteers [143]. The authors of that study concluded that the probiotic formulation exhibited anxiolytic-like activity in rats and provided beneficial psychological effects in healthy human subjects.

An increasing number of studies support the notion that probiotics have significant benefit in maintaining homeostasis of the CNS. However, most of these studies are based on indirect evidence. In an effort to reveal the biological underpinnings of the gut-brain axis, researchers in the laboratory of John Cryan, show that protracted treatment of mice with the lactic acid bacteria *Lactobacillus rhamnosus* induced alterations in the mRNA which codes for the GABA B1b subunit in specific regions in the brain [20]. They additionally showed that the probiotic reduced stress-induced corticosterone and anxiety- and depression-related behavior. Importantly, the neurochemical and behavioral effects were not observed in mice upon vagotomy, unequivocally showing a role for bacteria in the bidirectional communication between the gut and the brain via the vagus nerve.

The term psychobiotics, initially coined by Dinan et al. is typically defined as any live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness [144]. Accordingly, psychobiotics are, by definition, a subgroup of probiotics with the added emphasis on mental illness. Most psychobiotics are capable of producing or promoting the endogenous synthesis of neurotransmitters such GABA, catecholamines, and 5-HT, all of which influence the brain-gut axis and mental health. A list of biogenic amines implicated in neuroimmune disease pathology as well as the microbes that associate with changes in the respective neurotransmitter are given in Table 1.

As early as 2005, Logan and Katzman proposed the use of probiotics for the treatment of major depressive disorders [197]. Later studies, using animal models, supported the notion that certain psychobiotics possess antidepressant or anxiolytic properties. For instance, Barrett et al. reported that specific strains of *Lactobacillus* and *Bifidobacterium* produce GABA [167], the principal inhibitory neurotransmitter in the brain and which plays an essential role in anxiety and depression [198, 199]. In addition to producing and promoting the production of neuroactive substance, psychobiotics also can act on the brain through epigenetic modulation [26], by reducing inflammation [200, 201], and by influencing the body's stress response via the hypothalamic-pituitary-adrenal (HPA) axis [202]. It should be noted that some prebiotics support the growth of psychobiotics and for this reason, some researchers have suggested that these prebiotics be classified as psychobiotics [203].

7. Fatty acids and polyphenols

7.1 Short chain and omega-3 fatty acids

Short-chain fatty acids are the end-products of fermentation of nondigestible carbohydrates by intestinal microbiota and have antiinflammatory and histone deacetylase-inhibiting properties [204]. As they are critical for homeostasis of the GI tract, they also represent important players in the gut-microbiota-brain axis. The three principal SCFAs produced by the intestinal microbiota, acetate, propionate, and butyrate are important for colonic health and have been implicated in protection against colitis and colorectal cancer [205–208]. Although all three are taken up by the colonic mucosa, previous studies suggest that butyrate is transported preferentially and appears to be the preferred energy source for colonocytes [209, 210]. The production of propionate is primarily restricted to anaerobic bacteria family of *Clostridiales*; however, the bacteria responsible for the production of the other principal SCFAs are more broadly distributed [211]. In addition to the production of SCFAs through anaerobic formation in the gut, a significant amount is found in dairy products such as whole milk and cheese [212].

Given that SCFAs are necessary for proper intestinal function and are primarily made by intestinal bacteria, perturbations in the gut microbiota may have profound effects on the gut-microbiota-brain axis. As previously articulated, several neurological disorders are characterized by intestinal comorbidity. An altered mucosal immune environment may lead to changes in the microbiota, therefore, it is reasonable to assume that restoring homeostasis of the mucosal immune system may be a first step in establishing and maintaining a healthy microbiota profile. Accordingly, introduction of SCFAs may represent one method of indirectly modifying the microbiota, and in turn the gut-microbiota-brain axis. To the best of our knowledge, no previous human clinical trials have been conducted to assess the benefit of SCFA supplementation in the treatment of neurodegenerative or neuroimmune disorders. Albeit, because of their histone deacetylase-inhibiting properties, it has been suggested that they may be of benefit in treating disease such as Huntington's disease, Parkinson's disease and amyotrophic lateral sclerosis [213].

In addition to the benefits imparted by SCFAs, several studies have reported that omega-3 polyunsaturated fatty acids (n-3-PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may improve or prevent some neurological and neuroimmune disorders. For instance, Jiang et al. reported that supplementation with DHA enhanced serotoninergic and dopaminergic neurotransmission, and decreases the levels of several hypothalamic–pituitary adrenal hormones in mice, suggesting that DHA may be efficacious in treating depression [214]. Also, a number of clinical studies have shown n-3-PUFA treatments to benefit subjects with AD [215–218]. While the exact mechanisms underlying such effects are a matter of ongoing investigations, previous studies show that n-3-PUFAs are required for normal neuronal function. In fact, postmortem AD brain biopsies have been shown to exhibit lower DHA levels. Yassine and coworkers reported that the AD risk allele apolipoprotein ε4 (APOE ε4) and lower CSF Aβ42 levels were associated with decreased transport of DHA to cerebrospinal fluid and concluded that brain amyloid pathology may limit the transport of DHA to the brain [219].

Recently, Watson et al. conducted a randomized trial to investigate the effect of n-3-PUFA supplements on the human intestinal microbiota and observed that supplementation induces a reversible increase in several SCFA-producing bacteria, including *Bifidobacterium, Roseburia* and *Lactobacillus* [220]. These observations suggest that n-3-PUFA supplementation may represent an effective way to modify the productions of SCFAs, and in turn, improve GI homeostasis. Consistent with this, Ramos-Romero et al. reported that supplementation with n-3-PUFA modified the populations of *Lactobacillus, Bifidobacterium* and SCFAs in rats [221]; and Pusceddu and colleagues showed EPA and DHA supplementation alters the gut microbiota composition of both neurodevelopmentally normal and early-life stressed Sprague-Dawley female rats [222]. Although DHA and EPA are available commercially as purified supplements, they are present in high quantities in fish, especially cold-water fatty fish, such as salmon, mackerel, tuna, herring, and sardines

7.2 Polyphenols

Polyphenols are large organic molecules that contain at least one hydroxyl group attached to the carbon atom of an aromatic ring. They are naturally occurring in many plants and fruit and are largely responsible for their brilliant color. Seasonings are probably the highest sources of polyphenols, followed by seeds, vegetables, and fruits. Polyphenols are classified according to their structure as either flavonoids or non-flavonoids with the non-flavonoids being further subclassified as either phenolic acids, stilbenes, and lignans. They have been the focus of a significant body of research for their protective effects against cancer, cardiovascular disease, diabetes, and Alzheimer's disease, as well as for their antiaging properties [223–226].

Several polyphenolics are found in green and black tea, and many excellent reviews are available that address the putative health benefits of tea-derived polyphenolics [227–230]. Although research that addresses their influence on the microbiome is less developed than that for other health benefits, previous studies do support the premise that these molecules have the capacity to influence the microbiota. For instance, Ankolekar et al. investigated nine tea extracts and concluded that gallic acid, quercetin, and tea catechins (including catechin, epicatechin, and epigallocatechin) have the capacity to inhibit *H. pylori* without affecting the beneficial lactic acid bacteria [231]. Additionally, Wang et al. reported that mice infected with *E. coli* O157:H7, displayed improve immune function and increased microbiota diversity upon treatment of mice with fuzhuan brick-tea extract [232]. However, Janssens and colleagues reported that long-term green tea supplementation does not change the human gut microbiome profile [233]. These studies suggest that tea-derived polyphenolics may impact pathogenic bacteria without altering the normal gut flora; however, further studies will be required with purified polyphenolics in order to make definitive determinations.

Red wine, is also a significant source of polyphenols that have been shown to influence the intestinal microflora, as well as oxidative damage and gene expression profiles of colonic mucosa. For instance, Rodrıguez Vaquero and coworkers showed that polyphenols of different wines have antibacterial properties with *E. coli* being most sensitive bacterium and *Flavobacterium sp*. showing the most resistance [234]. Also, Dolara et al. reported that

polyphenols from red wine (50 mg/kg) inhibited colon cancer in a rat model [235]. They further reported that the microbiome profile was shifted in polyphenol-treated rats when compared to the control rats and that the rats not treated with carcinogens, produced a significant decrease in the basal level of DNA oxidative damage of the colon mucosa. Finally, they observed that the transcription of genes involved in inflammatory response and steroid metabolism were downregulated in colon mucosa of polyphenols-treated rats. While these studies clearly underscore the potential benefits of polyphenols in modifying and modulating the gut microbiota, most of these studies have been carried out using animal models. Therefore, more human subject studies will be required to fully appreciate their benefit.

8. Vitamins

7.2 Vitamin A

The microbiota utilizes dietary vitamins and minerals and, accordingly, these micronutrients represents potential mechanisms to modify the gut microbiota. For instance, vitamin A (vA) plays an important role in neurological function as well as regulating the central nervous system development [236, 237]. Additionally, vA, through its metabolite retinoic acid, is an important factor that promotes intestinal immunity [238] and maintains mucosal epithelial integrity [239]. vA supplementation has been shown to be efficacious for a number of disease characterized by altered microbiome profiles and neuroimmune abnormalities. For instance, Liu et al. reported that autistic children who received vA intervention displayed a significant increase in Bacteroidetes/Bacteroidales and a decrease in *Bifidobacterium* [240]. Additionally, they reported that vA intervention results in significant changes in autism-related biomarkers. Indeed, vA has been shown to influence commensal GI bacterial profiles. For instance, Lee and Ko reported that vA supplementation significantly increased the GI levels of *Lactobacillus s*p. during norovirus infection, and was associated with decreased viral load [241]. Finally, in a recent report, Hibberd and coworkers utilized a humanized microbiota mouse model to evaluate the effects of micronutrient deficiencies in humans showed that acute vA deficiency led to the largest impact [242].

7.3 Vitamin D

Several neuroimmune and neuroinflammatory diseases characterized by putative microbiome alterations, such as multiple sclerosis, autism and Alzheimer's disease, have been associated with Vitamin D (vD) deficiency [243–245]. For instance, Shen and Ji conducted a meta-analysis of the existing literature and reported that subjects deficient for 25-hydroxyvitamin D (< 50 nmol/L) were at increased risk of developing AD by 21 % compared with those with vD levels greater than 50 nmol/L [245]. As an additional example, Mostafa and AL-Ayadhi evaluated serum 25-hydroxyvitamin D levels in 50 autistic children and 30 healthy-matched controls and determined that the autistic children had significantly lower levels than healthy children ($P < 0.001$) with 40% and 48% being vitamin D deficient and insufficient, respectively [246]. While direct evidence for the efficacy of vD in altering the microbiota in neuroimmune and neuroinflammatory diseases is limited, a substantial body of evidence supports its role in maintaining GI homeostasis, and potentially the

microbiota, by regulating mucosal inflammatory responses [247], modulating pattern recognition receptors [248] and maintaining intestinal barrier function [249, 250].

The potential benefits of using vD to modulate the microbiota in the context of neuroimmune and neuroinflammatory disease is supported by indirect evidence. For instance, NOD2 (nucleotide-binding oligomerization domain 2), which recognizes bacterial-derived LPS, has been reported as susceptibility gene contributing to the development of Crohn's disease (CD) [251]. Dionne and coworkers showed that when monocyte-derived dendritic cells isolated from subjects with CD are treated with the hormonal form of vD, 1,25-dihydroxy vitamin D (1,25D) a decrease in Toll-like receptor (TLR)-induced cytokine production is observed as well as NOD2-associated NF-kappa-B activation [248]. Additionally, previous studies have shown that 1,25D induces the transcription of genes that encode antimicrobial peptides [252]. Earlier studies showed that the promoters of the human cathelicidin antimicrobial peptide and defensin beta2 genes contain consensus vD response elements that mediate 1,25D-dependent gene expression [253].

Recently, Wang et al. conducted genome-wide association study (GWAS) to investigate potential genetic contributions to variations in the gut microbiota and identified polymorphisms in the vD receptor (VDR) as a significant contributing factor [254]. Although these observations may suggest that vD may play a role in disease characterized by alterations in the microbiota, future studies will be required to determine if supplementing vD as a means to treat these diseases is efficacious.

Although vD is typically supplemented as 25-hydroxyvitamin D, 1,25D is primarily the biologically active form [255]. It is largely formed in the kidneys but is also generated locally by many other body tissues. It is noteworthy that Bora et al. recently shown that germ-free mice are deficient 1,25-hydroxyvitamin D [256], suggesting that not only can vD modulate the gut microbiota, a healthy microbiome is likely necessary for vD homeostasis.

7.4 B Vitamins

In humans, B vitamins are acquired through diet or from the gut microbiota and their deficiencies are often found in patients with intestinal malabsorption [257–259]. Additionally, B vitamin deficiencies lead to deleterious neurological effects including polyneuropathy, diabetic polyneuropathy, optic atrophy, myelopathy and cerebellar ataxia [260, 261]. Recent studies have shown that the ability of the microbiota to synthesize B vitamins increases as the microbial community of the gut matures early in life [262].

Vitamin B12 is made in significant quantities by commensal bacteria in the large intestine; however, the necessary transport receptors in humans are primarily in the small intestine suggesting that the B12 produced by the microbiota are primarily consumed by the microbiota [263]. Accordingly, B12 supplementation may represent an effective way to modulate the gut microbiota, particularly in the small intestine [264].

8. Conclusions

Over the last decade, it has become evident that the GI microbiota is a key regulator of the gut-brain axis and several lines of well-accepted evidence support the premise that it influences human health and disease. Stress-related behaviors, including those relevant to anxiety and depression as well as neuroinflammatory and neuroimmune disease have all been implicated in dysregulation of the GI microbiota. Additionally, if we acknowledge that an altered microbiota may contribute the development of disease, we must also acknowledge that some dietary factors may change the microbiota in a way that negatively impacts human health. Indeed, previous studies have shown that artificial sweeteners, when given to laboratory animals, raise blood sugar levels potentially leading to insulin resistance [265–267]. Moreover, this observation is directly linked to changes in the microbiota in that non-absorbable antibiotics can reverse this observation. Additionally, several studies have shown that a high fat diet is associated with a decrease in butyrate-producing bacteria, and increased gastrointestinal inflammation [268, 269].

Numerous studies have now identified alterations in the gut microbiota in a wide range of neuroimmune diseases, although, in most instances, it has yet to be determined if the aberrant microbiota contributes to the disease or is a result of the disease [88, 270–273]. As evidence mounts connecting the gut microbiota to neuroimmune and neuroinflammatory disease, the possibility for altering the microbiota as a treatment strategy is a logical progression in an age of translational medicine.

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Abbreviations

4EPS	4-ethylphenylsulfate
5-HT	5-hydroxytryptamine
AD	Alzheimer’s disease
ASD	Autism spectrum disorders
BDNF	Brain-derived neurotrophic factor
CA	Catecholamines
CD	Crohn's disease
CNS	Central nervous system
DHA	Docosahexaenoic acid
EAE	Experimental autoimmune encephalomyelitis
ENS	Enteric nervous system
EPA	Eicosapentaenoic acid
FEP	First episode psychosis
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissues
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HAART	Highly active antiretroviral therapy
IBS	Irritable bowel syndrome
IDO	Indoleamine 2,3-dioxygenase
IL	Interleukin
LCFAs	Long-chain fatty acids
ME	Myalgic encephalomyelitis
MIA	Maternal immune activation
MS	Multiple sclerosis
NMDA	N-methyl-D-aspartate
PD	Parkinson’s disease
poly I:C	Polyinosinic:polycytidylic

RRMS	Relapsing-remitting MS
SCFAs	Short-chain fatty acids
SIV	Simian immunodeficiency virus
TLF	Toll-like receptor
TNF-α	Tumor necrosis factor-alpha
Tregs	Regulatory T cells
vA	Vitamin A
vD	Vitamin D
VDR	Vitamin D receptor

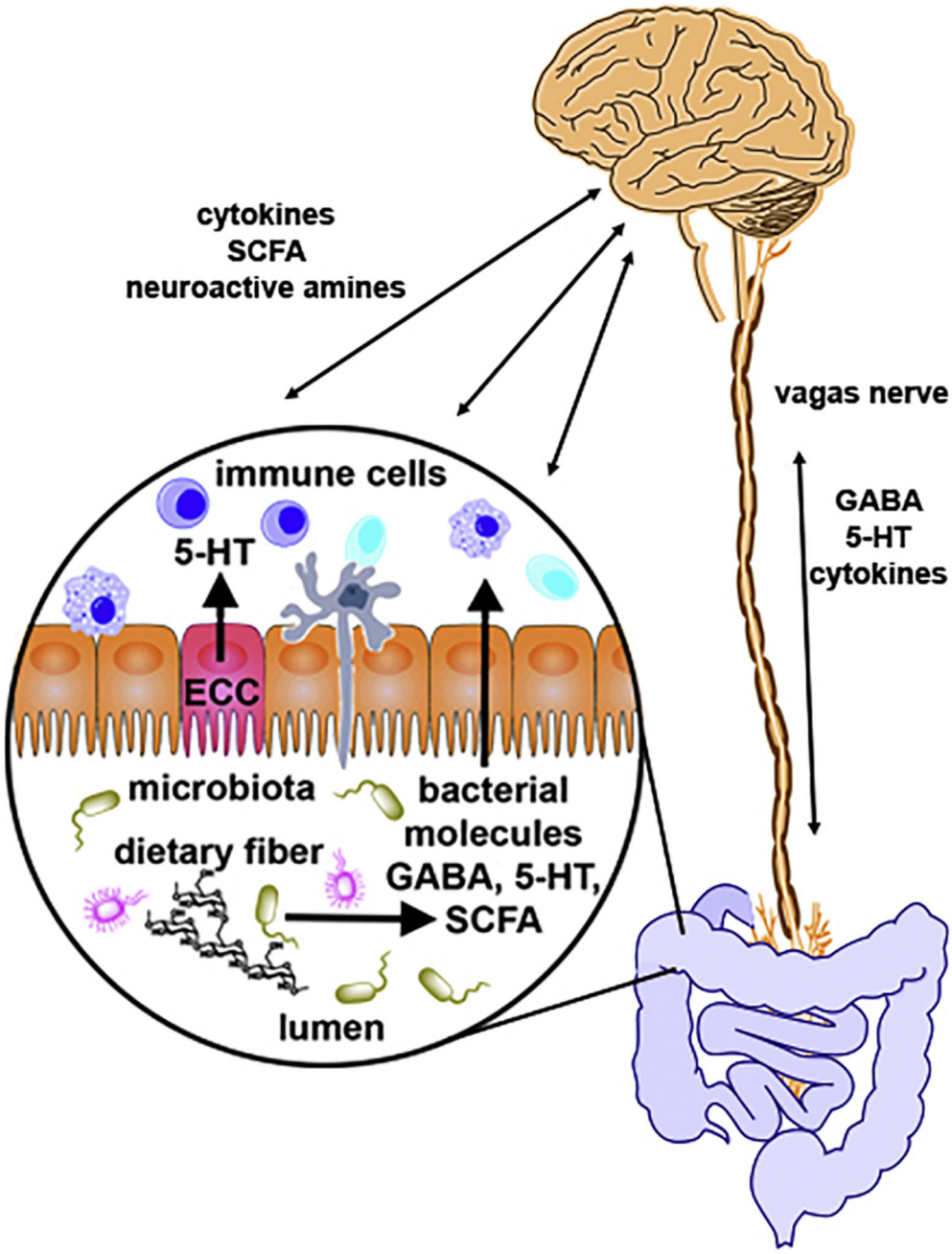

Figure 1. Representation of the bidirectional communication between the gut-microbiota-brain axis

Signaling can occur directly via the vagus nerve, through signaling molecules such as GABA (γ-Aminobutyric acid), serotonin (5-hydroxytryptamine, 5-HT) and antiinflammatory cytokines. Conversely, signaling can occur indirectly, through chemical messengers that are released into the periphery and act in an endocrine manner including GABA, 5-HT, produced by enterochromaffin cells (ECC) and short chain fatty acids (SCFA), such as butyrate and propionate, produced through bacterial fermentation of nondigestible fiber.

Table 1

Biogenic amines implicated in neuroimmune disease pathology and microbes that associate with changes in the respective biogenic amines.

Neurotransmitter	Function	Neuroimmune Disease Association	Microbe family or genus implicated*	Reference
Brain-derived neurotrophic factor (BDNF)	Neurotrophin	Alzheimer's Disease Autism Multiple Sclerosis Myalgic Encephalomyelitis Parkinson's Disease Schizophrenia	*Bifidobacterium breve, Bifidobacterium longum*	[21, 145–152]
Dopamine	Neurotransmitter, precursor of epinephrine and norepinephrine	Alzheimer's Disease Autism Multiple Sclerosis Myalgic Encephalomyelitis Parkinson's Disease Schizophrenia	*Bacillus cereus* and *Serratia*	[153–161]
Gamma-aminobutyric acid (GABA)	Inhibitory neurotransmitter	Alzheimer's Disease Autism Multiple Sclerosis Schizophrenia	*Bifidobacterium dentium, Lactobacillus rhamnosus,* Escherichia *coli, Pseudomonas*	[162–167]
Glutamate	Excitatory neurotransmitter	Alzheimer's Disease Autism Myalgic Encephalomyelitis Schizophrenia	*Lactobacillus plantarum, Bifidobacteria, Lactobacilli*	[147, 166, 168–171]
Histamine	Neurotransmitter, regulates physiologic function in the gut	Alzheimer's Disease Parkinson's Disease Schizophrenia	*Lactobacillus vaginalis, Morganella morganii*	[172]
Melatonin	Hormone, regulates synchronization of the circadian rhythm	Alzheimer's Disease Autism Myalgic Encephalomyelitis Multiple Sclerosis Parkinson's Disease Schizophrenia	*Bifidobacteria Firmicutes Verrucomicrobia Enterobacter aerogenes, Escherichia coli*	[40, 173–181]
Norepinephrine	Hormone and neurotransmitter	Alzheimer's Disease Autism Myalgic Encephalomyelitis Multiple Sclerosis Parkinson's Disease	*Escherichia, Bacillus, Saccharomyces*	[182–187]

Neurotransmitter	Function	Neuroimmune Disease Association	Microbe family or genus implicated*	Reference
		Schizophrenia		
Serotonin (5-HT)	Monoamine neurotransmitter	Alzheimer's Disease Autism Multiple Sclerosis Myalgic Encephalomyelitis Parkinson's Disease Schizophrenia	*Candida, Streptococcus, Escherichia coli, Enterococcus, L. bolteae, L. hathewayi, F. plautii, Lactobacillus Plantarum, Lactococcus lactis subsp. Cremoris, L. lactis subsp. Lactis, Streptococcus thermophiles, Morganella morganii, Hafnia alvei*	[188–196]

Note

*The listed microbes are reported to influence the production of the respective neurotransmitters implicated in neuroimmune disease but are not necessary implicated in the referenced neuroimmune disease directly.