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Targeting Gut Microbiota Dysbiosis: Potential Intervention Strategies for Neurological Disorders

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ABSTRACT

It is well known that the gut microbiota plays an extremely important role in modulating host physiological functions such as immunity and metabolic homeostasis. In recent years, accumulated evidence has revealed that the gut microbiota can regulate the functions of the central nervous system (CNS) through the gut–brain axis, which provides a novel insight into the interactions between the gut and brain. This review focuses on the molecular mechanism of the crosstalk between the gut microbiota and the brain via the gut–brain axis, and on the onset and development of neurological disorders triggered by gut microbiota dysbiosis. These topics are followed by a critical analysis of potential intervention strategies targeting gut microbiota dysbiosis, including the use of probiotics, prebiotics, synbiotics, and diets. While research on the microbiota–gut–brain axis is still in its relative infancy, clarifying the molecular mechanism that underlies how the gut microbiota regulates neurological functions not only holds the promise of revealing potentially novel pathogeneses of neurological disorders, but also may lead to the development of potential diagnosis biomarkers and intervention strategies targeting microbiota dysbiosis for neurological disorders.

1. Introduction

It has been estimated that the total number of bacteria in a 70 kg "reference human" is 3.8×10^{13}, which is slightly more than the total number of human cells (approximately 3.0×10^{13}) [1]. The colon and rectum at the end of the gastrointestinal (GI) tract contain the highest microbial density in the human body [2]. The human GI tract is inhabited by trillions of microorganisms, collectively known as the gut microbiota [2]. This complex ecosystem is mainly composed of bacteria; the remainder includes viruses, archae, protozoa, and fungi [2]. It has long been speculated that the symbiotic gut microbiome is a key interface for gene-environment interactions [3], and it is obvious that a mutually connected symbiotic physiology exists between the host and the gut microbiome [4]. Increasing research evidence has demonstrated that the gut microbiome plays important roles in the physiology of the host, including maintenance of the immune function and metabolic homeostasis [5].

The gut microbiome is acquired at birth and undergoes various modifications throughout a person's life (Table 1). At birth, infants acquire their gut microbiome from their mothers. During the first three years of life, gut microbiome diversity is low and variable, and undergoes drastic compositional changes. From the age of three, the microbial composition becomes stable and remains relatively unchanged in healthy adults, who possess mainly Bacteroidetes and Firmicutes. In older adults (≥ 65 years old), the gut microbiota undergoes considerable changes once again [6]. The gut microbiome is also greatly affected by various external conditions that include mode of delivery, dietary habit, lifestyle, drug use, and internal factors such as genetics and health status

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Table 1
Dominant gut microbiome taxa in different life stages.

Life stage	Dominant bacterial taxa
Gestation	Proteobacteria, Actinobacteria (gut), *Lactobacillus* (vaginal)
Birth–1 year	*Bifidobacterium*, *Enterococcus*, *Escherichia/Shigella*, *Streptococcus*, *Bacteroides*, *Rothia*
1–3 years	*Clostridium*, *Ruminococcus*, *Veillonella*, *Roseburia*, *Akkermansia*, *Alistipes*, *Eubacterium*, *Prevotella*
3 years–adulthood	Bacteroidetes, Firmicutes
≥ 65 years	Proteobacteria, *Bacteroides*, *Alistipes*, *Parabacteroides*

[7]. Not all of these determining factors are included in this mini-review, as doing so would be a major undertaking for a comprehensive review.

Accumulated evidence has revealed that gut microbiota dysbiosis contributes to the development of various chronic diseases, such as obesity, type 2 diabetes, and more [8]. These findings indicate that a commensal gut microbiota may impart beneficial health effects, whereas gut microbiota dysbiosis may be associated with various diseases [9].

In recent years, a significant number of studies have highlighted the correlation between the gut microbiota and brain functions [10], with gut microbiota dysbiosis being closely associated with various neurological disorders [11]. Advances in the knowledge of the gut–brain axis not only reveal potentially novel etiologies for various neurological disorders, but also provide potential diagnostic biomarkers and therapeutic strategies targeting gut microbiota dysbiosis for neurological diseases.

This review focuses on the molecular crosstalk between the gut microbiome and mental capacity—namely, the gut–brain axis—and on the association between microbiota dysbiosis and neurological disorders. Building on the current knowledge of the gut–brain axis, potential intervention strategies targeting gut microbiota dysbiosis for neurological and psychiatric disorders are analyzed and evaluated, including the use of probiotics, prebiotics, synbiotics, diets, and nutrition.

2. The gut–brain axis

Increasing evidence has revealed that certain psychiatric and neurological diseases, such as autism, anxiety, depression, and neurodegeneration, are often comorbid with GI dysfunction [10–13]. Furthermore, many studies have indicated that the gut microbiota is closely correlated with the host's neurological functions and corresponding mood and behavior [10]. The precise mechanisms by which gut microbes affect neurological functions are complex and unclear. Recently, the concept of the "microbiota–gut–brain axis" was proposed in order to explore the communication mechanisms between the microbiota, gut, and brain [14]. The microbiota–gut–brain axis is a bi-directional communication network that includes the nervous systems (i.e., the central nervous system (CNS), autonomic nervous system, and enteric nervous system (ENS)), immune systems, endocrine systems, and gut microbiota [14]. The following are some important regulatory pathways for the gut–brain axis.

2.1. The vagus nerve

The ENS is directly connected to the CNS through the vagus nerve, which provides a direct neurocommunication pathway between the gut microbiota and the CNS in order to facilitate regulation of the CNS functions by the gut microbiota [15]. For example, supplementation of the probiotic *Lactobacillus rhamnosus* JB-1 to mice has been shown to alleviate anxiety and depression. However, these beneficial effects were abolished in vagotomized mice [16]. Thus, it was speculated that neurotransmitters or other metabolites produced from the gut microbiota can directly regulate the activity of the vagus nerve by stimulating the vagal afferent sensory neurons [16,17].

2.2. The circulatory system

The circulatory system may be a pathway regulating the effects of various metabolites, induced or produced by the microbiota, on CNS functions. These neuro-regulatory agents include neurotransmitters, hormones, precursors of neurotransmitters and hormones, short-chain fatty acids (SCFAs), and more [10]. Some metabolites can pass through the intestinal barrier and enter into the circulatory system; they subsequently cross the blood–brain barrier (BBB), and finally control neurological functions [18–20].

2.2.1. Microbiota-mediated neurotransmitters

Neurotransmitters are chemical messengers that transmit signals across a chemical synapse from one neuron to another target neuron, muscle cell, or gland cell [8]. Common neurotransmitters include serotonin (5-HT), noradrenaline, dopamine, and gamma-aminobutyric acid (GABA), which have marked effects on the brain and behavior [8].

(1) **The gut microbiota regulates neurotransmitter signals.** It has been demonstrated that the gut microbiota and specific bacterial species can modulate neurotransmitters and related receptors in order to regulate neurotransmitter signals in both the central and peripheral systems.

The gut microbiota can regulate the expression of central neurotransmitters and related receptors. For example, compared with normal mice, germ-free (GF) mice showed different alteration of 5-HT, noradrenaline, dopamine, and related receptors in different areas of the brain [21]. In addition, treatment of normal mice with *Lactobacillus rhamnosus* JB-1 induced changes in the GABA receptor levels in specific brain regions [16].

The gut microbiota can also regulate peripheral neurotransmitter levels. For example, compared with normal mice, GF mice had decreased serotonin in the peripheral nervous system and intestine, which could be restored by colonization with spore-forming bacteria [22]. In addition, compared with normal mice, GF mice had decreased dopamine and GABA levels in serum [23,24].

(2) **The gut microbiota regulates the synthesis of neurotransmitters.** The synthesis of neurotransmitters in the central and peripheral systems can be either directly produced or indirectly induced by the gut microbiota through the following routes.

Route 1. Directly produced by the gut microbiota: It has been shown that gut bacteria can produce a large amount of neurotransmitters. For example, it has been demonstrated *in vitro* that the *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* species can produce 5-HT; the *Bacillus* and *Serratia* species can produce dopamine; the *Escherichia*, *Bacillus*, and *Saccharomyces* species can produce noradrenaline; the *Lactobacillus* species can produce acetylcholine; and *Lactobacillus* and *Bifidobacterium* can secrete GABA [25,26]. It has also been speculated that the tryptamine produced by some gut bacteria may inhibit 5-HT functions in the brain; however, this remains to be further verified [27].

Route 2. Indirectly induced by the gut microbiota: It is remarkable that the total levels of neurotransmitters in the gut could be greater than those in the brain. It has been reported that most of the 5-HT in the body is produced by enterochromaffin cells in the gut [28]. Recent studies have demonstrated that SCFAs produced by gut microbes are necessary for inducing enterochromaffin cells to produce colonic 5-HT [22,29]. It is well known that 5-HT in the gut plays a role in modulating colonic motility [28].

However, it is still unknown whether and how the neurotransmitters produced by the gut microbiota or intestine affect the CNS functions. Although some gut neurotransmitters—such as 5-HT, GABA, and dopamine—cannot cross the BBB, these gut neurotransmitters may act on the vagus nerve or affect periphery signaling, thereby eventually influencing brain functions [26].

In addition, microbial-derived metabolites may act as precursors for the synthesis of neurotransmitters in the brain [18,19]. For example, the tryptophan produced by gut bacteria can cross the intestinal barrier and the BBB and subsequently be used to produce neurotransmitters in the CNS [19].

2.2.2. Microbiota-mediated hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis is a complex bi-directional communication network among the hypothalamus, pituitary, and adrenal glands. The HPA axis acts as a major neuroendocrine system that controls physiological reactions to stress and regulates various body functions, such as digestion and emotions.

Interestingly, some research has showed that the HPA axis' response to stress is also regulated by the gut microbiota [30]. In comparison with specific-pathogen-free (SPF) mice, GF mice showed substantially higher HPA axis activity under restraint stress [30]. However, supplementing GF mice with *Bifidobacterium infantis* was shown to alleviate the increased HPA axis activity [30]. Furthermore, the enhanced HPA response in GF mice was decreased by the fecal microbiota transplantation (FMT) of SPF mice at an earlier stage, which indicated that normal gut microbiota composition at an earlier developmental stage was necessary to the development of a normal HPA stress response [30].

Prebiotic and probiotic interventions were also shown to normalize the HPA axis function and show beneficial psychological effects in healthy human volunteers [31,32]. As a next step, it is necessary to investigate whether microbiota interventions can normalize the HPA axis function in psychiatric populations.

2.2.3. Microbiota-produced SCFAs

SCFAs, which mainly contain acetate, propionate, and butyrate, are produced by the gut microbiota in the fermentation process of complex carbohydrates. SCFAs have various effects on the physiological functions of the host's brain.

A recent study demonstrated the closed linkage between microglia maturation and SCFAs in the brain. Microglia are the resident macrophages and major immune defense cells in the CNS [33]. The number, morphology, and function of microglia in GF mice were abnormal and defective compared with those in SPF mice [33]. However, the administration of SCFAs to GF mice normalized the number, morphology, and function of microglia in GF mice [33]. Furthermore, these effects were dependent upon the activation of G-protein coupled receptor (GPR) 43 by SCFAs [33]. Therefore, it was revealed that the gut bacteria modulated microglia maturation through microbial SCFAs.

In addition, it was reported that SCFAs regulate the permeability of the BBB [34]. GF mice showed more severe permeability of the BBB than SPF mice, as a result of the decreased expression of endothelial tight junction proteins in the BBB [34]. Interestingly, colonization with either *Clostridium tyrobutyricum* or *Bacteroides thetaiotaomicron* was shown to rescue the BBB integrity by promoting the expression of tight junction proteins [34]. Subsequent research revealed that butyrate produced by these gut bacteria was responsible for restoring the BBB integrity [34].

2.3. Microbiota-mediated neuro-immune signaling

It is well established that the immune system acts as an important regulator of the microbiota–gut–brain axis. The gut microbiota not only modulates the maturation and function of resident immune cells in the CNS (such as microglia) [33], but also influences the activation of peripheral immune cells to subsequently regulate CNS immune reactions [21,35]. As neuroinflammation is one of the major pathological mechanisms of psychiatric and neurological diseases, it is speculated that the gut microbiota may be implicated in neurological disorders through its regulation of the immune system [35].

In general, the metabolites or components of the microbiota mediate immune system activities. For example, microbiota-produced SCFAs modulate the maturation and function of microglia, which is important for the development of the CNS immune system [33]. In addition, it was demonstrated that microbiota-derived microbial-associated molecular patterns (MAMPs), such as lipopolysaccharide (LPS), bacterial lipoprotein (BLP), flagellin, and cytosine-phosphate-guanosine (CpG) DNA, could activate immune cells of the peripheral immune system and subsequently release a considerable amount of pro-inflammatory cytokines, such as interleukin (IL)-1α and tumor necrosis factor (TNF)-α [10]. These pro-inflammatory cytokines can work on the vagus nerve to transfer signals to the CNS [35–37]. Furthermore, these pro-inflammatory cytokines, when released systemically, can enter the brain by crossing the BBB; the cytokines then act on neurons and glial cells, and eventually alter the neurological functions in the CNS [35–37].

3. The gut microbiota modulates neurological disorders in different life stages

3.1. The gut microbiota modulates neurodevelopmental disorders

Recent research publications have reported that the gut microbiota modulates some basic neurodevelopmental processes, including BBB formation and integrity [34], neurogenesis [38], microglia maturation [33], and myelination [39], as well as the expression of neurotrophins [40], neurotransmitters, and their respective receptors in mice [11]. These findings indicate that the gut microbiota is of great importance in modulating normal human neurodevelopment.

Gut microbiota dysbiosis in early life stages before three years of age—such as in the perinatal and postnatal periods—can result in neurodevelopmental diseases such as autism spectrum disorder (ASD) [41]. Therefore, it is meaningful to study the effects of the gut microbiota on neurodevelopment and intervention methods targeting microbiota dysbiosis.

ASD is a neurodevelopmental disease that arises before three years of age, which involves a complex set of neurodevelopmental disorders including social interaction and communication disorder, and repetitive behaviors and interests [41]. The most typical characteristic of autism is social communication disorder, which is the biggest problem for children with autism [41]. However, the pathophysiology of autism is not fully clear; most studies involve genetic, maternal, and perinatal adverse factors, immunodeficiency, brain imaging, neurobiochemistry, and so on [41]. In recent years, many studies have found that children with ASD often have GI problems, such as indigestion, poor absorption, overgrowth of intestinal pathogenic bacteria (fungi, bacteria, and viruses), and abnormal GI fistula [42].

Finegold et al. [43] reported that in patients with severe autism, Bacteroidetes and Actinobacteria phyla were at a higher level, while Firmicutes and Proteobacteria phyla were more abundant in the healthy. *Desulfovibrio* species and *Bacteroides vulgatus* in the feces of autistic children were significantly higher than the healthy controls. Moreover, Wang et al. [44] confirmed that *Bifidobacteria* species and *Akkermansia muciniphila* in autistic

children were at lower relative abundances when compared with the control. The decrease of the mucolytic bacterium *Akkermansia muciniphila* suggests that the mucus barrier changes in autism. Kang et al. [45,46] demonstrated that there was lower diversity in the feces microbiome of autistic patients, with lower abundances of *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae*, and that these low abundances were closely related to the presence of autism rather than to the GI symptoms. Kang et al. [47] also confirmed lower gut microbial diversity and reduced relative abundances of the phylotypes most closely related to *Prevotella copri* in children with ASD, along with lower abundances of *Faecalibacterium prausnitzii* and *Haemophilus parainfluenzae*. In another study, GI disturbances were observed to be caused by high levels of *Clostridium* and *Sutterella* species in children with autism [48]. More detailed studies on the gut microbiota of autistic children in comparison with healthy controls are summarized in recent reviews [49–51].

The microbiological imbalance occurs not only in the colon and ileum, which are mainly dominated by Gram-negative species, but also in the duodenum, which is mainly dominated by Gram-positive microorganisms from the oropharynx [52,53].

Recently, Yim et al. [54] and Kim et al. [55] verified that the gut microbiota was the main culprit in the birth of autistic children by infected mothers during pregnancy, and confirmed that segmented filamentous bacteria (SFB) were associated with autism in the offspring. Thus, a promising strategy to reduce the risk of offspring autistic traits may be through the direct manipulation of the mothers' gut microbiota.

In addition, some preclinical research has indicated that probiotic supplementation can alleviate ASD symptoms. Tabouy et al. [56] revealed that *Lactobacillus reuteri* treatment could relieve microbiota dysbiosis and ASD behavior in the *Shank3* knock-out (KO) mice model. In addition, it has been reported that the use of *Bacteroides fragilis* can help to improve ASD-like behavioral performance in mice, for example by lowering anxiety, increasing interaction with other mice, and significantly decreasing repetitive behaviors. These studies lay a foundation for the development of a probiotics intervention method to treat human neurodevelopmental disorders.

3.2. The gut microbiota modulates psychological disorders

Anxiety, a psychological state characterized by apprehension or fear, is one of the most commonly experienced psychiatric disorders [57]. Depression is a psychological state characterized by sadness or irritability and accompanied by several psychophysiological changes, such as disturbances in sleep, appetite, or sexual desire; constipation; and loss of the ability to experience pleasure in work [58]. An increasing number of people around the world suffer from anxiety and depression [59]. These mental health disorders cause significant impairment and contribute to a loss of productivity and increased annual healthcare costs; thus, they represent an economic burden on the public healthcare system [8].

It has been reported that anxiety and depression are highly comorbid with functional bowel disorders, which indicates that the gut–brain axis may be implicated in the pathological mechanisms of these psychological dysfunctions [16,60]. Anxiety and depression patients always exhibit HPA axis dysfunction, increased inflammatory levels, neurotransmitter signaling dysfunction, and so on. Given that the gut microbiota can regulate these events [30,37], the gut microbiota may hold potent potential for regulating depressive and anxiety disorders [61].

3.2.1. The gut microbiota modulates anxiety

It has been indicated that the gut microbiota could regulate anxiety in mice. For example, GF Swiss Webster, National Institutes of Health (NIH) Swiss, and Naval Medical Research Institute (NMRI) mice showed decreased anxiety-like behavior compared with the SPF control [10]. Conversely, GF BALB/c and C57BL/6 mice showed increased anxiety-like behavior compared with the SPF control [10]. Although different GF mouse strains had different anxiety-like behavior, all of these results indicated that anxiety-like behavior was highly correlated with the gut microbiota in mice. Furthermore, it was shown that anxiety-like behavior in GF mice could be normalized by recolonizing the fecal microbiota of SPF mice prior to critical neurodevelopmental time windows—although this did not work in the adult stage—which confirmed that the gut microbiota can modulate anxiety in mice [62].

Recently, a great deal of evidence has demonstrated the potential anxiolytic-like activity of probiotics. Sudo et al. [30] reported that supplementing GF mice with *Bifidobacterium infantis* could alleviate the enhanced HPA stress response, including reversing the elevation of plasma adrenocorticotropic hormone (ACTH) and corticosterone. Moreover, treating mice with *Lactobacillus rhamnosus* JB-1 induced different changes in the GABA receptor level in specific brain regions, reducing the stress-induced HPA response and anxiety-like behavior [16]. Recently, it was observed that the administration of *Lactobacillus helveticus* to adult SPF rats improved the anxiety and depression induced by restraint stress. Moreover, *Lactobacillus helveticus* treatment decreased the exaggerated HPA and inflammation stress response, and restored serotonin and norepinephrine levels in stress rats [63]. Furthermore, Messaoudi et al. [32] demonstrated that a combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 exhibited potential anxiolytic-like activity in rats, and provided the benefits of promoting psychological properties in healthy humans. Savignac et al. [64] demonstrated that supplementing daily with *Bifidobacterium longum* 1714 or *Bifidobacterium breve* 1205 could reduce stress-related behavior (anxiety or depression) in innately anxious BALB/c mice.

Prebiotics treatment also showed the beneficial effects of improving anxious and depressive disorders. A recent study demonstrated that a supplement of galacto-oligosaccharides (GOS) and a combination of GOS and fructo-oligosaccharides (FOS) could improve anxious and depressant behavior in rodents [65]. In addition, prebiotic administration resulted in increased concentrations of *Bifidobacterium* and *Lactobacillus*, increased SCFA levels (acetate and propionate), and decreased HPA activity and pro-inflammatory cytokine levels in stressed animals [65].

3.2.2. The gut microbiota modulates depression

Recently, an increasing number of studies have indicated that the constitution of the gut microbiome is altered in major depressive disorder (MDD) patients in comparison with healthy controls. Zheng et al. [66] reported that MDD patients showed increased Actinobacteria and decreased Bacteroidetes compared with healthy controls. However, Jiang et al. [67] reported that at the phylum level, MDD patients showed strongly increased Bacteroidetes, Proteobacteria, and Actinobacteria, but significantly reduced Firmicutes compared with healthy controls. In addition, Lin et al. [68] revealed that at the phylum level, MDD patients had more Firmicutes and less Bacteroidetes than healthy controls. Although these results were not exactly the same, they all confirmed that the constitution of the gut microbiome in MDD patients was altered.

Interestingly, some studies have shown that gut microbiota dysbiosis induces depression-like behaviors in GF mice. For example, Zheng et al. [66] reported that GF mice transplanted with fecal microbiota from MDD patients exhibited depression-like behaviors and disturbances of the host metabolism compared with colonization with microbiota from healthy controls. In line with Zheng's finding, Kelly et al. [69] confirmed that transplantation of GF mice

with fecal microbiota from depressed patients could induce depression-related behaviors. The results of these studies suggest that gut microbiota dysbiosis plays a causal role in MDD.

Furthermore, some studies have reported that gut microbiota dysbiosis is associated with MDD. Jiang et al. [67] reported that MDD patients had increased *Enterobacteriaceae* and *Alistipes*, but reduced *Faecalibacterium*, which was negatively correlated with the severity of depression. Aizawa et al. [70] reported that MDD patients had lower *Bifidobacterium* and *Lactobacillus* than healthy controls, which might be associated with the development of MDD. Lin et al. [68] revealed that at the genus level, MDD patients had more *Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium* XI. Furthermore, *Prevotella* and *Klebsiella* levels were consistent with the Hamilton depression rating scale during the diagnoses of MDD patients. Kelly et al. [69] also pointed out that *Prevotellaceae* was decreased but *Thermoanaerobacteriaceae* was increased in depressed patients, compared with healthy controls. Yu et al. [71] revealed that gut microbiota dysbiosis is significantly associated with the altered metabolism of tryptophan and bile acids in depressive rat.

Strikingly, it has been reported that probiotics—such as *Lactobacillus rhamnosus* [16], *Lactobacillus helveticus* [32], *Bifidobacterium longum* [64], and *Bifidobacterium infantis* [72]—and prebiotics including FOS + GOS could attenuate depression-related behavior [65]. Moreover, probiotics treatment could reduce self-reported depression, increase self-reported happiness, and decrease ruminative thinking in humans [21].

3.3. The gut microbiota modulates neurodegenerative disorders

Throughout the aging process, mammals undergo physiological changes that increase their susceptibility to neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) [11]. Interestingly, the incidence of some GI diseases increases with age [73], and the prevalence of diagnosed GI disorders is about 24% in people over 65 [74]. Evidence has shown that a high percentage of GI disturbances are comorbid with neurodegenerative disease, which suggests that gut microbiota dysbiosis can influence the onset and development of neurological diseases [75,76].

3.3.1. The gut microbiota modulates AD

AD is a chronic, rapidly progressive neurodegenerative disease that is characterized by memory loss, inability to carry out normal daily life activities, and behavioral changes [77]. At present, AD is considered to be the most common form of dementia in the elderly [77]. The incidence of AD increases with age; it has been estimated that 5.5 million Americans are affected by AD, including 5.3 million people aged 65 years or over [77]. AD is characterized by two main hallmarks: cerebral deposits of neuritic plaques (NPs), consisting of assembled and insoluble forms of amyloid-beta (Aβ)-peptide, and neurofibrillary tangles (NFTs), composed of hyperphosphorylated microtubule-associated tau protein [77].

Some preclinical and epidemiological studies have indicated that gut microbiota dysbiosis is associated with the onset and development of AD [78]. For example, one epidemiological study showed that patients with irritable bowel syndrome (IBS) showed a high risk for the onset of AD [79].

Furthermore, it has been reported that gut microbiota dysbiosis is associated with the amyloid formation and neuroinflammation pathologies in AD. It is notable that some gut bacteria, such as *Escherichia coli*, can produce amyloid in the gut. The amyloid can then easily enter the systemic circulation and accumulate in the brain, which could trigger the activation of a pro-inflammatory reaction to subsequently promote Aβ pathology in AD [78,80]. In another study, amyloid-positive patients exhibited decreased *Eubacterium rectale* and *Bacteroides fragilis* and increased *Escherichia/Shigella* in feces, compared with healthy controls [81]. Moreover, it was found that *Escherichia/Shigella* was positively correlated with pro-inflammatory cytokines, whereas *Eubacterium rectale* was negatively correlated with pro-inflammatory cytokines [81]. In addition, at the phylum levels, pro-inflammatory bacteria of Proteobacteria were increased, whereas anti-inflammatory bacteria of Firmicutes and Bacteroidetes were decreased in amyloid-positive patients [81]. These results confirmed that gut microbiota dysbiosis is associated with the amyloid formation and neuroinflammation pathologies in AD.

Some research has also suggested that gut microbiota dysbiosis contributes to AD by affecting the production of neurotoxins (e.g., β-*N*-methylamino-*L*-alanine, anatoxin-α, and saxitoxin) and neurotransmitters (e.g., GABA) [78].

Akbari et al. [82] demonstrated that probiotics treatment could improve AD. Akbari et al. [82] reported that the treatment of AD patients with milk enriched with *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* for 12 weeks significantly elevated learning and memory capacity in the mini-mental-state examination (MMSE) test. In addition, some researchers reported that supplementing with polyphenols could reduce the Firmicutes-to-Bacteroidetes ratio in the gut, which is associated with reduced inflammation and may be beneficial in lowering the risk of AD [78].

3.3.2. The gut microbiota modulates PD

PD is the second most common neurodegenerative disorder in the world, with a prevalence of 1%–2% in the population over 65 years [83]. The major features of PD are motor function symptoms that include resting tremor, rigidity, bradykinesia, and postural instability [84]. PD is also associated with a significant number of non-motor symptoms—particularly GI dysfunction [85].

Interestingly, constipation is the most common premotor symptom in PD, and constipation appears earlier than the motor symptoms by ten or more years [85]. In addition, abnormally aggregated α-synuclein (Lewy bodies)—the pathohistological hallmark of PD—is observed in the ENS of the GI tract prior to its appearance in the CNS [86]. Animal experiments have demonstrated that α-synuclein can spread from the intestinal wall to the vagus nerve and the CNS [87]. Furthermore, Danish and Swedish cohort studies reported that truncal vagotomy is associated with a decreased incident rate of PD, suggesting that the vagus nerve is critical to the pathogenesis of PD [88,89]. All of these studies provide evidence to support Braak's hypothesis that in PD, the Lewy bodies pathology may start in the ENS and later spread to the CNS through the vagus nerve in a prion-like way [89]. Therefore, PD pathology may start in the gut, and the gut may act as a potential early-intervention site for PD.

In animal experiments, it has been reported that gut microbiota dysbiosis is closely associated with PD pathology. In an α-synuclein overexpression model of PD, GF mice generated fewer motor deficits, microglia activation, and α-synuclein pathology than SPF mice [90]. Moreover, FMT of GF mice with gut microbiota from PD patients induced PD pathologic changes compared with the gut microbiota of healthy people [90]. These findings indicate that the gut microbiota regulates the pathological process of PD, and that alterations of the gut microbiome in humans represent a risk factor for PD [90]. Another study also confirmed that colonization of normal mice with fecal microbiota from PD mice induced gut microbiota dysbiosis and PD pathologic changes, which was consistent with former reports [91]. Furthermore, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced model of PD, FMT with normal control mice could reduce gut microbial dysbiosis, alleviate physical impairment, suppress neuroinflammation, and increase striatal neurotransmitters

dopamine and 5-HT contents in PD mice [91]. These results suggest that modulating the microbiota dysbiosis is a potential intervention strategy for PD [91].

Therefore, it is meaningful to explore the relationships between microbiota dysbiosis and the pathophysiology processing of PD. By now, many studies have reported the intestinal microbiota dysbiosis in PD patients and the potential correlation with the progression of PD [92–98]. Detailed information is provided in Table 2.

Further in-depth study of the microbiota–gut–brain axis interactions could bring new insight into the pathological mechanisms of PD and provide an earlier diagnosis biomarker for PD in the ENS. Existing research already indicates the great potential of modulating gut microbiota dysbiosis as an intervention strategy for PD through, for example, supplementing with probiotics, prebiotics, and synbiotics, or regulation of dietary habits.

4. The role of diets and nutrition in shaping the gut microbiota

Recently, molecular pathological epidemiology (MPE) has been widely used to study the effects of external and internal factors on the phenotypes of disease outcome such as cancer and neurological disorders through molecular pathologic analyses [99,100]. In research on the gut microbiome and neurological disorders, MPE permits analyses of external and internal factors in relation to the gut microbiome and neurological disorders. MPE analyses can not only provide new insights into the interactions between the gut microbiome and neurological disorders, but also reveal potentially novel pathogenesis and intervention strategies for neurological disorders targeting microbiota dysbiosis. Therefore, studying the interactions between the gut microbiome and neurological disorders by means of MPE analyses has great value.

The gut microbiome is greatly affected by various external conditions including mode of delivery, dietary habit, lifestyle, and drug use, and by internal factors such as genetics and health status [7]. Not all of these determining factors are included in this mini-review, as doing so would be a major undertaking for a comprehensive review.

It has been demonstrated that diets are one of the most important factors affecting gut microbiota establishment and composition throughout the lifespan [101,102], and that major changes in diet during adulthood can modify the microbiota in a matter of days [103]. Therefore, we selected diet as one representative factor determining the gut microbiota, and will discuss how diet and nutrition can influence the gut microbiota and phenotypes of disease outcome in this mini-review.

4.1. Dietary patterns influence the gut microbiota

The human gut microbiota contains thousands of species of microorganisms [104]; hence, it requires a wide array of nutrients and energy sources to support the growth, function, and diversity of the normal gut microbiota [105]. Reduced dietary diversity and insufficient essential nutrients may influence the growth of specific microorganisms, and may even lead to gut microbiota dysbiosis [105]. We now discuss how several different dietary patterns can influence the gut microbiota.

4.1.1. Western diet

The Western diet is characterized by an increased intake of red meat, high-fat foods, and refined sugars, which always leads to obesity, cardiovascular disease, diabetes, and depression [105]. Consumption of a Western diet showed a decrease in Bacteroidetes and an increase in Firmicutes, which might be associated with increased gut permeability, a higher capacity for energy harvesting and storage, and inflammation [106].

4.1.2. Mediterranean diet

The Mediterranean diet consists mainly of cereals (whole grains), legumes, nuts, vegetables, and fruits, with moderate consumption of fish and poultry and low consumption of meat; it has long been regarded as a healthy dietary habit [107].

Table 2
Potential correlation between altered gut microbiota and the pathophysiology processing of PD.

Patients and samples	Altered gut microbiota and metabolites	Potential correlation with progression of PD	Ref.
Fecal samples of 72 PD patients vs. 72 controls	*Prevotellaceae* ↓ *Enterobacteriaceae* ↑	Low *Prevotellaceae* was associated with increased gut permeability and reduced SCFA High *Enterobacteriaceae* was positively associated with the severity of postural instability and gait difficulty	[92]
Sigmoid mucosal biopsies and fecal samples of 38 PD patients vs. 34 healthy controls	"Anti-inflammatory" butyrate-producing bacteria: (*Blautia*, *Coprococcus*, and *Roseburia* in feces) ↓ (*Faecalibacterium* in the mucosa) ↓ "Pro-inflammatory" Proteobacteria: (*Ralstonia* in mucosa) ↑	Genes involved in metabolism were significantly lower in the PD fecal microbiome Pro-inflammatory dysbiosis in fecal microbiome was positively associated with PD	[93]
Fecal samples of 52 PD patients vs. 36 healthy cohabitants	*Lactobacillus* ↑ *Clostridium coccoides*, *Bacteroides fragilis* ↓ Hydrogen-producing bacteria↓ Serum LPS-binding protein levels ↓	PD disease duration was negatively correlated with *Clostridium coccoides*, but positively correlated with *Lactobacillus gasseri*	[94]
Fecal samples of 34 PD patients vs. 34 age-matched controls	Bacteroidetes ↓ *Prevotellaceae* ↓ *Enterobacteriaceae* ↑ SCFA ↓	The decrease in SCFA might induce ENS dysfunction and GI dysmotility in PD	[95]
Fecal samples of 31 early stage PD patients vs. 28 age-matched controls	*Verrucomicrobiaceae* (*Akkermansia muciniphila*) and unclassified Firmicutes ↑ *Prevotellaceae* (*Prevotella copri*) and *Erysipelotrichaceae* (*Eubacterium biforme*) ↓	Alteration of β-glucuronate and tryptophan metabolism in PD	[96]
Fecal samples of 24 PD patients vs. 14 healthy volunteers	The putative cellulose degrading bacteria: (*Blautia*, *Faecalibacterium*, *Ruminococcus*) ↓ The putative pathobionts: (*Escherichia/Shigella*, *Streptococcus*, *Proteus*, *Enterococcus*) ↑	PD severity and duration was negatively correlated with the putative cellulose degraders, whereas positively correlated with the putative pathobionts	[97]
Fecal samples and demographic features in 2 years in 36 PD patients (0 year vs. 2 year)	The deteriorated PD group had lower *Bifidobacterium*, *Bacteroides fragilis*, and *Clostridium leptium* than the stable group at year 0 but not at year 2	Lower *Bifidobacterium* and *Bacteroides fragilis* at year 0 were positively associated with the worsening of PD in 2 years	[98]

↓: decrease; ↑: increase.

The Mediterranean diet has shown potent protective effects against cancer, neurodegenerative, neuropsychiatric, and autoimmune diseases [108]. It is notable that a Mediterranean-inspired diet can reduce inflammation in Crohn's disease [109], along with a small reduction of C-reactive protein (CRP), an increase in Bacteroidetes and *Clostridium* clusters, and a decrease in Proteobacteria and *Bacillaceae* [109].

4.1.3. Vegetarian/vegan diets

Vegan diets may have protective effects against metabolic and inflammatory diseases [105]. Vegan diets induce a unique gut microbiota profile that is characterized by a reduced abundance of pathobionts and a greater abundance of protective species [110]. Reduced levels of inflammation may be the key feature linking the vegan gut microbiota with protective health effects [110]. In comparison with an omnivore diet, vegetarian and vegan diets induce an increase in *Bacteroides Prevotella*, *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme*, and *Faecalibacterium prausnitzii*, but a decrease in *Clostridium* cluster XIVa [111].

4.1.4. High-fiber diets

Consumption of high-fiber diets promotes hydrolytic bacteria and stimulates the production of SCFAs [112]. High-fiber diets have been positively associated with the abundance of Actinobacteria and Bacteroidetes [113].

4.1.5. High-protein diets

High-protein diets show a higher ratio of bile-tolerant microorganisms including *Alistipes, Bilophila*, and *Bacteroides*, but a lower ratio of Firmicutes, such as *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*, which metabolize dietary plant polysaccharides [103].

4.2. Nutrition composition influences the gut microbiota

The effects of diets that influence the gut microbiota and regulate neurologic or psychiatric functions depend on the bioactivity of the nutrition composition in the diets [107]. Many studies have suggested that the nutrition composition in diets interacts with the host microbiota and modulates the host neurologic or psychiatric functions through the gut–brain axis pathway [107]. Detailed information on various nutrition compositions that influence the gut microbiota and regulate neurologic or psychiatric functions is provided in Sandhu's review [107], which includes the effects of carbohydrates (e.g., resistant carbohydrates, fiber, FOS, GOS, inulins, beta-glucans), proteins, bile acids, omega-3 and omega-6 polyunsaturated fatty acids, vitamins, and polyphenols.

In conclusion, the studies described above indicate that dietary interventions targeting gut microbiota dysbiosis and treating dysfunction of the gut–brain axis may hold potential as therapeutic strategies for neurologic and psychiatric disorders.

5. Future directions and conclusions

Accumulated evidence has revealed that the gut microbiota plays an extremely important role in modulating neurological functions throughout the whole human lifespan. It has been increasingly demonstrated that the gut microbiota regulates CNS functions through direct or indirect pathways in the gut–brain axis, and that this regulation involves the immune, nervous, or endocrine systems.

Research on the regulation of CNS functions by the gut microbiota has attracted attention worldwide in different disciplines, including microbiology, immunology, neuroscience, and bioinformatics. High correlations between gut microbiota dysbiosis and neurological dysfunctions have led to a focus on the gut microbiota as a promising prospect for revealing novel pathogeneses and providing potential intervention strategies for various neurological disorders in different life stages—especially for neurodevelopmental, psychiatric, and neurodegenerative disorders, whose etiologies remain unknown and whose therapies are undesirable to date. At present, it is encouraging that some intervention strategies for neurological disorders targeting microbiota dysbiosis have acquired exciting positive results in preclinical studies.

Although this field of research has been growing rapidly in recent years, it is still in its infancy. Research largely remains on the association between alteration of the gut microbiota and certain clinical conditions, and it is unclear whether alteration of the gut microbiota is the cause or the consequence of some neurological disorders. Therefore, future research should tackle these challenging questions in order to clarify the intricate interaction between the host and its associated gut microbiota, and to clarify the molecular mechanism that underlies the beneficial or pathogenic effects of different microbial populations on host health and diseases. A combination of multi-omics, including genomics, proteomics, and metabolomics analyses, could be applied to identify critical products or compounds from the gut microbiota along with related signal pathways in order to regulate host neurophysiology. Furthermore, as most data to date is preclinical and few of these promising studies have been translated into humans, there is a growing urgency for more clinical trials in this field.

Tackling these challenging questions will be helpful not only to verify the novel etiologies of neurological disorders mediated by the gut microbiota and gut–brain axis, but also to explore potential diagnostic biomarkers and promising therapeutic approaches targeting microbiota dysbiosis in neurological disorders.

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Compliance with ethics guidelines

Wanqiang Wu, Qingmin Kong, Peijun Tian, Qixiao Zhai, Gang Wang, Xiaoming Liu, Jianxin Zhao, Hao Zhang, Yuan Kun Lee, and Wei Chen declare that they have no conflict of interest or financial conflicts to disclose.

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