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REVIEW

Advances in Brain–Gut–Microbiome Interactions: A Comprehensive Update on Signaling Mechanisms, Disorders, and Therapeutic Implications

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SUMMARY

Significant strides have been made in brain–gut–microbiome research over the past 6 years, fueled by technological breakthroughs and the discovery of new mechanistic pathways. This review offers a comprehensive exploration of these advancements since 2018.

The complex, bidirectional interactions between the brain, the gut, and the gut microbes are best referred to as the *brain gut microbiome system*. Animal and clinical studies have identified specific signaling mechanisms within this system, with gut microbes communicating to the brain through neuronal, endocrine, and immune pathways. The brain, in turn, modulates the composition and function of the gut microbiota through the autonomic nervous system, regulating gut motility, secretion, permeability, and the release of hormones impacting microbial gene expression. Perturbations at any level of these interactions can disrupt the intricate balance, potentially contributing to the pathogenesis of intestinal, metabolic, neurologic, and psychiatric disorders. Understanding these interactions and their underlying mechanisms holds promise for identifying biomarkers, as well as novel therapeutic targets, and for developing more effective treatment strategies for these complex disorders. Continued research will advance our knowledge of this system, with the potential for improved understanding and management of a wide range of disorders. This review provides an update on the current state of knowledge regarding this system, with a focus on recent advancements and emerging research areas. *(Cell Mol Gastroenterol Hepatol 2024;18:■–■; https://doi.org/10.1016/j.jcmgh.2024.01.024)*

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The brain–gut–microbiome (BGM) system refers to the bidirectional communication network between the brain, the gut connectome, the gut-associated immune system, and the gut microbiome.[1] This system involves intricate signaling pathways, including neuronal,[2] hormonal,[3] immune,[4] and microbial factors,[5] which play a crucial role in maintaining homeostasis and influencing various physiological processes.

The gut microbiome has a profound impact on host physiology,[1] including digestion,[2] metabolism,[3] immune function,[4] and brain development.[6,7] Based largely on mechanistic studies performed in animal models, and correlational human studies, dysregulation of the system has been implicated in a wide range of disorders, including intestinal disorders, metabolic conditions, psychiatric disorders, and neurologic diseases.[3–5,8] Therefore, gaining comprehensive insights into this system has the potential to develop novel diagnostic tools, therapeutic interventions, and personalized approaches to improve human health.

The previous review article titled "The Brain–Gut–Microbiome Axis" in *Cellular and Molecular Gastroenterology and Hepatology* in 2018[1] provided an overview of the state of the science regarding the BGM system at that time. Since then, significant advancements have been made in the field, necessitating an updated review to encompass the latest research findings, emerging concepts, and therapeutic implications. The insights into the complexity of BGM interactions have resulted in an expanded view of these interactions as a biological system, as opposed to the earlier, linear view as an axis.

Methodological Advances in Studying the BGM System

Over the past several years, the field of microbiome research has advanced exponentially because of the advancements in computing power and sequencing

Abbreviations used in this paper: **AD, Alzheimer disease; ApoE, apolipoprotein E; ASD, autism spectrum disorder; BBB, blood-brain barrier; BGM, brain–gut–microbiome; C/EBPβ/AEP, CCAAT/enhancer binding protein β/asparagine endopeptidase; ECC, enterochromaffin cell; EEC, enteroendocrine cell; FMT, fecal microbiota transplantation; GABA, γ-aminobutyric acid; GEB, gut-epithelial barrier; GF, germ-free; GIP, glucose-dependent insulinotropic polypeptide; IBD, inflammatory bowel disease; PD, Parkinson's disease; PVB, plexus vascular barrier; SCFA, short-chain fatty acid; Trpa1, transient receptor potential ankyrin A1; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5-HT, 5-hydroxytryptamine.**

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technology. Sequencing has become faster, more efficient, and cheaper.[9] This has paved the way for shotgun sequencing to become the gold standard of microbial analysis, replacing previous primer-based 16S sequencing. Furthermore, computational analysis and strategies have advanced considerably and the strategy to combine multiple systems biological processes (ie, multi'omics) has become more common. The integration of metagenomics, metatranscriptomics, and metabolomics with multimodal brain imaging data and clinical parameters has provided comprehensive insights into the BGM system. Metagenomic sequencing and metatranscriptomic analyses allow for the examination of microbial gene expression profiles, revealing the active functions of the gut microbiota in host–microbe interactions. In addition, targeted and untargeted metabolomics techniques enable the identification and quantification of microbial-derived metabolites, such as short-chain fatty acids and neurotransmitter modulators, which play crucial roles in gut–brain communication (Figure 1). For instance, metagenomic studies have identified microbial genes involved in neuroactive metabolites, such as those related to the production of γ-aminobutyric acid (GABA), serotonin, indoles, kynurenine, and others.[10–13] These approaches offer promising avenues for targeted therapeutic interventions, including the development of second-generation probiotics or microbial-derived metabolites, to modulate the system with the potential for improved health outcomes.

Signaling Mechanisms From the Gut Microbiota to the Brain

Enterochromaffin Cell Signaling

Significant advances in research have provided deeper insights into the interactions of gut microbial metabolites with enterochromaffin cells (ECCs) and enteroendocrine cells (EECs) and their crucial role in gut–microbe–brain signaling. Recent studies have shown that these cells, embedded within the gastrointestinal tract lining, act as key intermediaries in the communication between the gut microbiota and the nervous system (Figure 2).[14] These gut-based endocrine cells have been found to detect changes in luminal nutrient levels as well as bacterial metabolites, and respond by releasing various signaling molecules, including

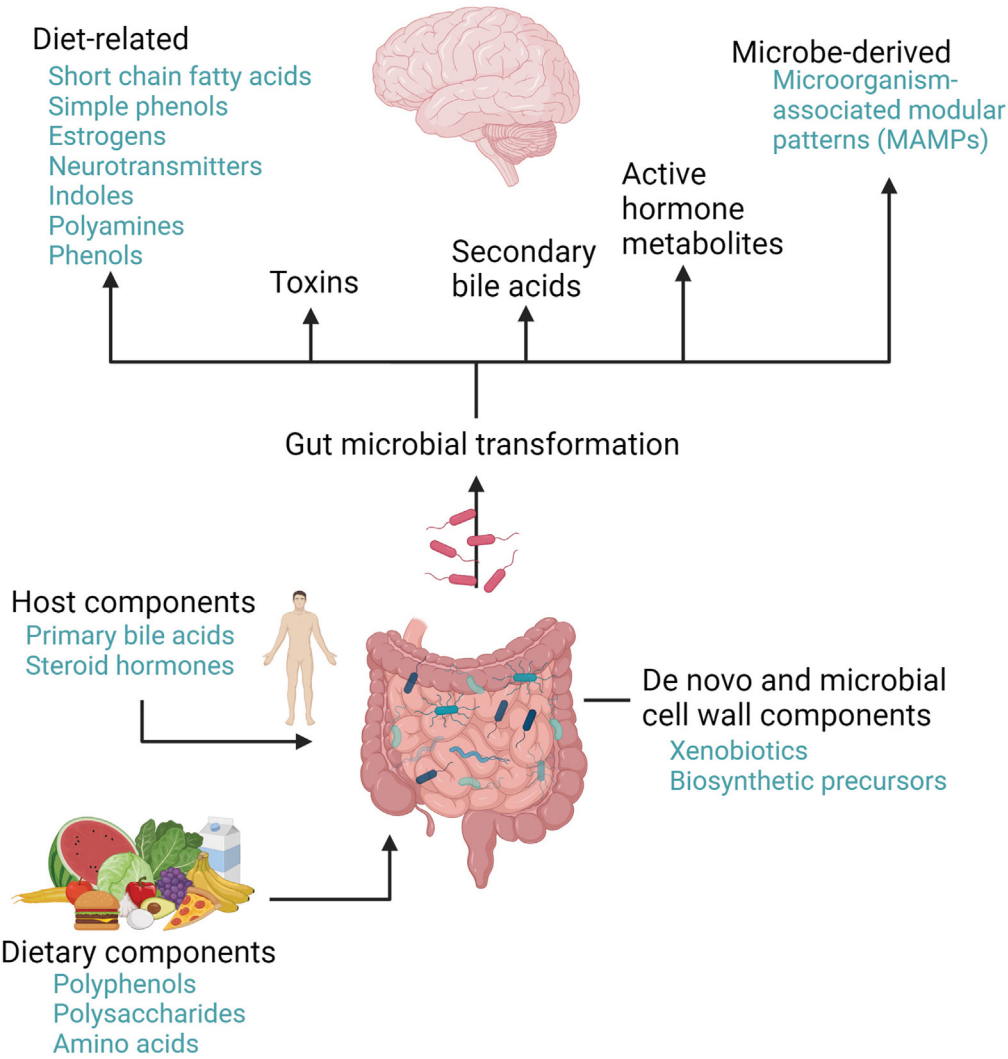

Figure 1. Diagram outlining how host, dietary, and microbial components can be transformed by the gut microbiome to affect brain signaling.

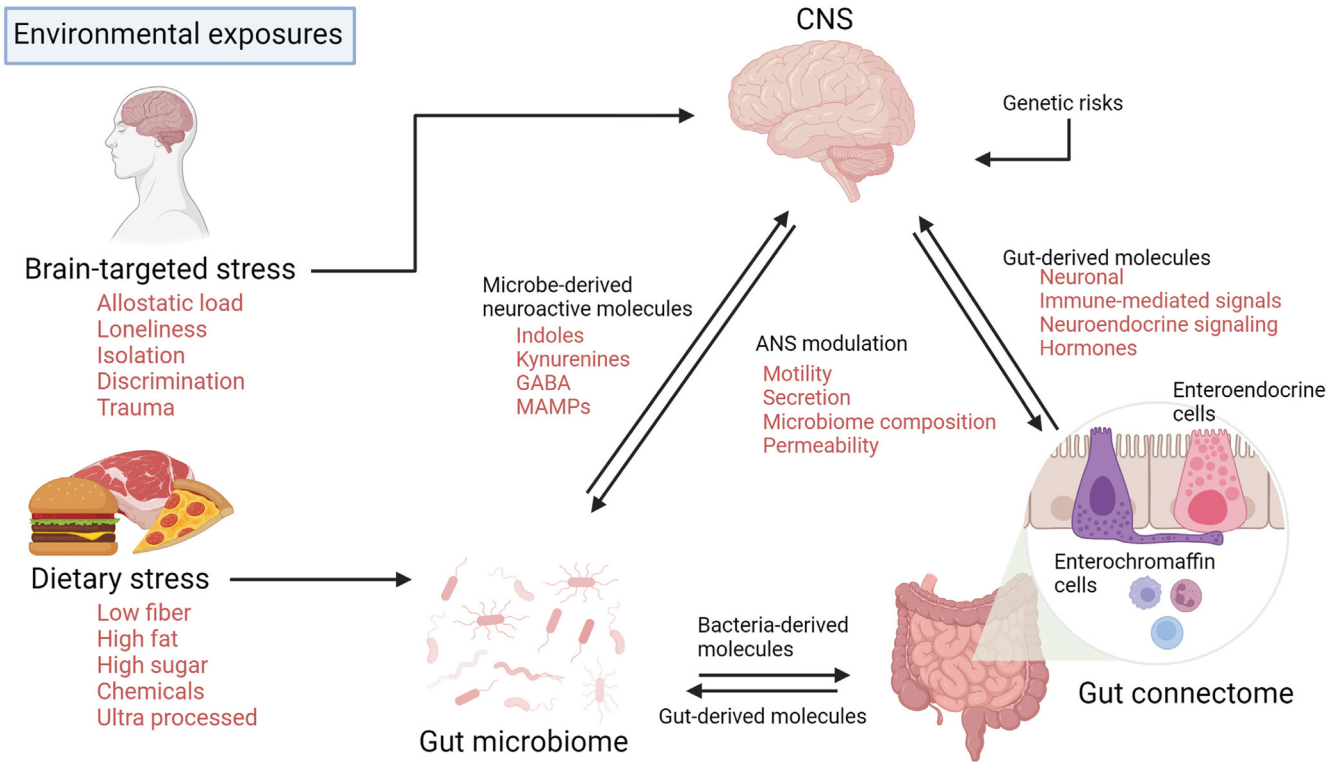

Figure 2. Schematic of the brain–gut–microbiome (BGM) system as interactions between the environment, gut microbiome, host enteric and immune system, autonomic nervous system, and brain. ANS, autonomic nervous system CNS, central nervous system; MAMP, microbial-associated molecular patterns.

serotonin, and the satiety hormones cholecystokinin, peptide YY, and glucose-dependent insulinotropic polypeptide (GIP).[14] For instance, ECCs can sense high-fat or high-sugar diets and release serotonin, which can influence both the enteric nervous system as well as gut to brain signaling via the vagus nerve, and impact brain regions involved in mood, behavior, and gastrointestinal function.[15]

ECCs produce and release a range of neurotransmitters and signaling molecules that participate actively in gut–brain communication. Serotonin, synthesized and secreted by ECCs and modulated by gut microbial metabolites, plays a crucial role in regulating gut motility and secretion, intestinal permeability, and immune responses in the gut.[16] Serotonin released from these cells into the gut lumen during stress can alter gut microbial gene expression, microbial behavior, and interactions with the host. In addition, certain EECs release cholecystokinin, glucagon-like peptide, and peptide YY, which are involved in the regulation of satiety, appetite, and gastrointestinal motility.[14] The release of these signaling molecules from extensions of the EECs and probably EECs (so-called *neuropods*) onto vagal afferent nerve endings or into the systemic circulation can modulate neural circuits and affect brain regions involved in emotion regulation, cognition, and feeding behavior.[14]

Although the effect of EECs on the gut and vagus nerve have long been established, more recent evidence has emerged regarding how certain gut microbes interact directly with EECs. For example, it has been shown how the short-chain fatty acid (SCFA) isovalerate, a specific bacterial metabolites, can activate EECs via the G-protein–coupled receptor Olfactory Receptor 558, causing the production of serotonin and sensitization of primary afferents in an ex vivo nerve–gut model.[17] In another study Ye et al,[18] using real-time in vivo analysis in zebrafish, established a molecular pathway on how EEC cells can respond to microbial signals. The researchers found that the bacterium *Edwardsiella tarda* activates EECs via the transient receptor potential ankyrin A1 (Trpa1) receptor, leading to increased intestinal motility. Activation of Trpa1+EECs, whether by microbes, pharmacologic means, or optogenetics, directly stimulates vagal sensory ganglia and triggers cholinergic enteric neurons by releasing the neurotransmitter 5-hydroxytryptamine (5-HT).[18] Furthermore, a specific subset of indole derivatives generated from tryptophan catabolism by *E tarda* and other gut microbes activates Trpa1 signaling in EECs. These catabolites also have a direct stimulatory effect on human and mouse Trpa1, leading to increased intestinal 5-HT secretion. These findings elucidate a pathway through which EECs respond to microbial signals, regulating enteric and vagal neuronal pathways in the process.[18]

The important role of EECs in gut–brain interactions was highlighted by a report showing that sustained activation of EECs led to persistent visceral hypersensitivity even without an initial inflammatory trigger. In addition, alterations in EEC function were linked to anxiety-like behaviors, which was normalized upon blocking serotonergic signaling.

These findings were more significant in female mice compared with male mice, which potentially could explain some the sex-based differences seen in disorders of the brain–gut such as irritable bowel syndrome.[19]

Gut Microbiota as a Source of Neuroactive Signaling Molecules

Emerging research has highlighted the capacity of the gut microbiota to produce and release neuroactive metabolites with significant homology to host neurotransmitters, which can interact with other microbes, epithelial and immune cells, with vagal afferent nerve endings, and directly with the brain. Various microbial species within the gut have been found to synthesize neurotransmitters such as GABA,[20] dopamine,[21] norepinephrine,[22] and serotonin.[14] For example, specific strains of *Bifidobacterium* can produce GABA,[20] an inhibitory neurotransmitter involved in regulating neuronal excitability and anxiety. These microbial-derived neurotransmitters can interact with the host's nervous system, influencing brain function, behavior, and mental health.[14,20,21] Yet, it remains to be determined whether the levels of these neuroactive substances produced in the gut reach sufficiently high levels in the brain to impact behavior by affecting brain circuits.[23] In addition, the role of subsets of vagal afferent neurons with different receptor profiles in gut-to-brain signaling requires further investigation.[24]

Neuroimmune Signaling

The immune system plays a vital role in the dynamic communication between the gut microbiota and the brain. Recent studies have explored the crosstalk between cells of the gut-associated immune system and the gut microbiota, mediated by microbial-associated molecular patterns interacting with Toll-like receptors on dendritic cells and other gut-based immune cells, and immunomodulatory molecules derived from gut bacteria.[25,26]

Immune-mediated signaling pathways have been implicated in the bidirectional communication between the gut microbiota and the brain.[27] For instance, proinflammatory cytokines released by immune cells in response to gut dysbiosis can activate vagal afferent pathways and impact brain regions associated with mood and behavior.[4] In conditions such as inflammatory bowel disease (IBD) or systemic infections, the immune response triggered by the gut microbiota can lead to altered neurotransmitter metabolism, neuronal excitability, and changes in neuroinflammatory processes.[28] These immune-mediated signaling cascades can have implications for conditions such as chronic fatigue syndrome and long coronavirus disease, as well as some forms of depression.[29]

Recent research has provided several examples of how priming of the immune system by bacterial signaling in the gut can have protective effects in the brain. Polysaccharide A, a key component of the bacterial cell surface, produced from *Bacteroides fragilis*, has been shown to reduce autoimmune encephalitis and alter T-cell function in animal models of multiple sclerosis.[30,31] Specifically, mice exposed to polysaccharide A have higher levels of regulatory T-cell production of interleukin 10, which controls innate inflammatory responses relating to viral encephalitis.[31] The priming effect of the gut microbiome on the neuroimmune system recently was shown by Fitzpatrick et al.[32] Under normal conditions, both mouse and human meninges harbor IgA-secreting plasma cells. These cells strategically position themselves adjacent to dural venous sinuses, areas characterized by slow blood flow and fenestrations that potentially could allow blood-borne pathogens access to the brain. It was found that the population of peri-sinus IgA plasma cells increases with age and in response to breaches in the gut-epithelial barrier (GEB).[32] Conversely, they are scarce in germ-free mice but can be restored through gut recolonization.[32] B-cell receptor analysis confirms that meningeal IgA+ cells originate in the intestine.[32] Notably, the specific depletion of meningeal plasma cells or IgA deficiency results in decreased entrapment of fungi in the peri-sinus region and increased spread into the brain after intravenous challenge, highlighting the indispensable role of meningeal IgA in safeguarding the central nervous system at this vulnerable venous barrier interface.[32]

Microbial Metabolites and Their Influence on the Brain

Recent studies in animals have highlighted the profound influence of microbial metabolites on brain function and behavior.[33] Microbes in the gut produce a diverse array of metabolites, including SCFAs, tryptophan metabolites, secondary bile acids, and neurotransmitter homologues, which can act as signaling molecules with neuroactive properties. SCFAs, such as butyrate, acetate, and propionate, can modulate neuronal activity, neuroinflammation, and neurotransmitter synthesis and release.[33] For example, butyrate has been shown to promote neuronal growth,[34] enhance synaptic plasticity,[35] and inhibit immune responses in the gut and brain.[36] Tryptophan metabolites, such as indoles and kynurenin, have been implicated in neurodegenerative and neuroimmune processes by impacting mood regulation and mental health via changes in catecholamine biosynthesis.[37] A novel metabolite, known as 4-ethylphenyl sulfate, recently was found to reduce myelination of neuronal axons, leading to anxiety-like behaviors in mice.[38] Seo et al[39] explored the effect of SCFAs on tau pathology and neurodegeneration in a mouse model of tauopathy expressing different human apolipoprotein E (ApoE) isoforms. They found that manipulating the gut microbiota through germ-free conditions and antibiotic treatment significantly reduced tau pathology and neurodegeneration, with these effects varying based on the ApoE isoform and sex. Notably, SCFAs were identified as mediators of this process. When SCFAs were supplemented in mice expressing ApoE4, there was an increase in glial reactivity and phosphorylated tau pathology. The direct effect of SCFAs on glial cells remains uncertain owing to the absence of SCFA-receptor genes in these cells. However, it is theorized that SCFAs may influence other components of the immune system, such as meningeal natural killer and

plasmacytoid dendritic cells, as well as $\gamma\delta$ T, and plasmacytoid dendritic cells are known to produce cytokines such as interleukin 17 and interferon type-I.[40]

Barriers to Bottom-Up Signaling

There are several barriers that regulate brain–gut–microbiome interactions. These barriers are specialized cellular interfaces that maintain strict homeostasis of different compartments within the BGM system. They include the GEB, the blood-brain barrier (BBB), and the blood–cerebrospinal barrier.

Gut Epithelial Barrier

Intestinal permeability plays a pivotal role in brain–gut communication by controlling the passage of molecules and microbial membrane components from the gut lumen into the bloodstream, depending on the state of the organism. Disruptions in the GEB, such as thinning of the mucus layer, can lead to activation of Toll-like receptors on dendritic cell luminal extensions, interacting with microbial microbial-associated molecular patterns (including lipopolysaccharides), and, ultimately, to the translocation of microbial-derived cell-wall components into the systemic circulation, a situation referred to as *metabolic endotoxemia*.[41] This systemic immune activation can compromise the BBB, trigger activation of glial cells, fostering neurotoxicity, resulting in neuroinflammation, ultimately, impacting brain function and contributing to the pathogenesis of neurologic and psychiatric disorders.[42]

The mucus layer, an essential component of the GEB, has gained attention for its crucial role in brain–gut communication.[43] Recent studies have shown the interplay between the gut microbiota, mucus layer, and the host immune system.[44] The layer harbors antimicrobial peptides and other immune-related molecules, contributing to host defense and shaping the gut microbial community.[45] Multiple studies have indicated that the mucus layer's glycans have direct immunologic impacts because they can bind directly to immune cells through lectin-like proteins present on the immune cells themselves.[46] There are different mechanisms by which certain gut microbes can influence the mucus layer. For example, the gram-negative *Akkermansia muciniphila*, which normally colonizes the outer layer of the mucus layer, feeds on the mucins making up the layer, a process that is increased during fasting and in the absence of complex carbohydrates in the diet. At the same time, *Akkermansia* up-regulates the synthesis of Mucin 2 (MUC2) by goblet cells through metabolites, preventing a degradation of the mucus layer. The combined effects on degradation and synthesis are thought to result in strengthening the gut barrier. Another potential mechanism underlying the microbial effects on the mucus layer is the alteration of glycosyltransferases. Certain bacteria possess the ability to trigger the host's expression of fucosyltransferases, enzymes responsible for adding L-fucose at the $\alpha-1,2$ position, and sialyltransferases.[47] In addition, the host's bacterial communities have the capacity to influence both MUC2 glycosylation and the glycosylation of transmembrane mucins.[48] Disruptions in the mucus layer, such as alterations in its thickness or composition, can impact the gut microbiota–host interactions and subsequent brain–gut signaling.

Blood-Brain Barrier

The BBB is a dynamic interface between the periphery and the brain. Emerging evidence suggests that the gut microbiota can influence the integrity and function of the BBB.[49] In prior investigations, mice exposed to antibiotic-induced intestinal dysbiosis showed reduced expression of tight junction proteins specifically in the hippocampus, although no such reduction occurred in the prefrontal cortex and hypothalamus.[50] Gut dysbiosis and the subsequent release of microbial metabolites and immune mediators into the systemic circulation can trigger systemic inflammation (metabolic endotoxemia) and affect BBB permeability.[51] For instance, gut microbiota–derived lipopolysaccharides can activate immune responses and promote the release of proinflammatory cytokines, leading to BBB disruption.[52] Moreover, microbial metabolites, such as SCFAs and secondary bile acids, can exert direct or indirect effects on BBB integrity through modulating tight junction proteins or immune responses.[53]

Although previous studies have shown how the intestinal environment can alter BBB integrity, a recent study provided evidence for a part of the BBB that responds independently to intestinal inflammation.[54] The study showed the existence of a brain choroid plexus vascular barrier (PVB) that responds to intestinal inflammation triggered by bacterial lipopolysaccharide. During inflammation, the PVB closes after the initial opening of the gut vascular barrier, primarily through the activation of the Wnt/β-catenin signaling pathway.[54] This closure restricts the passage of large molecules into the brain. Using a model in which choroid plexus endothelial cells were induced genetically to close, researchers observed impairments in short-term memory and anxiety-like behavior, suggesting a potential correlation between PVB closure and cognitive deficits.[54]

The BGM System in Gastrointestinal and Metabolic Disorders

Obesity/Food Addiction/Metabolic-Associated Steatotic Liver Disease

Evidence suggests that dysregulation of the BGM system also plays a significant role in the development of metabolic diseases. Dysbiosis of the gut microbiota, characterized by reduced microbial diversity and an imbalance in microbial composition, has been associated with metabolic disturbances and an increased risk of obesity.[55] Over the years, a reduction in *A muciniphila* has been the most well-cited bacterial alteration associated with metabolic syndrome.[56] A recent randomized control trial in 40 obese subjects with metabolic syndrome showed that *Akkermansia* supplementation was linked to a reduction of markers of fatty liver disease, inflammation, and a trend toward weight

loss.[57] *Akkermansia* abundance in bariatric surgery patients has been associated with improved gut barrier function as well as altered gut hormones such as GIP.[58] Moreover, both mechanistic studies in mice and association studies in human beings have shown that the gut microbiota can influence appetite regulation and food cravings.[59] In a recent study, a distinct brain–gut microbiome signature was found in females with food addiction that was independent of weight.[60] Disruptions in the gut–brain signaling pathways involved in satiety and reward can lead to overeating and contribute to the development of food addiction.[60] Human studies have identified alterations in the gut microbial composition, such as an increase in potentially harmful bacteria such as *Enterobacteriaceae* and a decrease in beneficial species such as *A muciniphila*, in individuals with metabolic-associated steatotic liver disease.[61] Dysbiosis of the gut microbiota has been associated with liver inflammation, oxidative stress, and the development of nonalcoholic steatohepatitis.[62] In a recent study, microbial transplant from patients from patients who underwent sleeve gastrectomy for weight loss was able to prevent nonalcoholic fatty liver disease development in a nonalcoholic fatty liver disease mouse model, and these changes were associated positively with small-bowel *Akkermansia* levels and GIP serum changes.[58]

The BGM System in IBD

IBDs, including Crohn's disease and ulcerative colitis, are characterized by chronic inflammation in the gastrointestinal tract. The BGM system plays a crucial role in the pathogenesis and progression of these disorders.[63] Chronic psychologic stress through activation of the sympathetic nervous system (SNS) can lead to increased intestinal permeability, triggering an inflammatory response in the intestine, to alterations in regional motility and to the development of visceral hypersensitivity.[64] SNS activation can lead to the activation of mast cells and macrophages through the nuclear factor-κB signaling pathway, resulting in cytokine secretion.[65,66] Only 3 observational studies have been conducted to investigate the bidirectional relationship of the brain–gut system in individuals with IBD.[67–69] Gracie et al[68] found an association of heightened baseline clinical disease activity and abnormal anxiety scores, although no such association was observed with depression scores. The second observational study showed a mutual relationship between perceived stress and symptoms.[67] In a longitudinal study, Sauk et al[69] found that increased perceived stress and associated increased tonic sympathetic nervous system activity was an independent risk factor for clinical IBD flares. As previously mentioned, recent research also showed that during states of inflammation in the gut, the PVB closes as a protective barrier, but in doing so increases the risk of anxiety-like behavior and cognitive deficits.[54] These research findings highlight the significance of brain–gut interactions in clinical manifestations of IBD. They emphasize potential implications for novel management strategies, taking into account both gut inflammation and psychological factors such as stress perception.

Disorders of Gut–Brain Interactions/Functional Gastrointestinal Disorders

Alterations in brain–gut interactions have long been proposed as a key pathophysiological mechanism in IBS and other functional gastrointestinal disorders,[70] and more recently have resulted in renaming these common syndromes as disorders of gut–brain interactions.[71] Numerous reports have reported alterations in gut microbial composition in subsets of IBS, even though a causal role in IBS symptoms has not been established.[72–74] For instance, reduced abundance of beneficial bacteria, such as *Bifidobacterium* and *Faecalibacterium prausnitzii*, and an increased abundance of potentially pathogenic species, such as *Enterobacteriaceae*, have been reported in individuals with IBS compared with healthy control subjects.

Systematic review and meta-analyses have shown that certain probiotics containing *Bifidobacterium* and *Lactobacillus* may be helpful in managing IBS symptoms,[75] even though no general recommendations about the use of probiotics in IBS can be made based on available evidence.[76] Multiple studies have reported higher gastrointestinal permeability in subsets of IBS subjects, suggesting that therapies enhancing barrier function may be able to alleviate symptoms, however, clinical trials that show such an effect are lacking. Our understanding of the specific mechanisms of probiotic microbes and the subgroups of patients benefiting from such treatments remains limited, and these effects often are strain- or species-specific.

The BGM System in Psychiatric and Neurologic Disorders With Gastrointestinal Comorbidities

Depression and Anxiety

Several studies in animals and transfer studies from human beings to animals have shown that there is a mechanistic relationship between the gut microbiome and depression and anxiety. For instance, in several studies, fecal microbiota from human patients diagnosed with major depressive disorder was transplanted into germ-free mice, resulting in behavioral changes indicative of increased depression-like responses.[77,78] Even though definitive evidence for a causal relationship between gut microbiota and human brain disorders has not been established, these microbial human to mouse transfer experiments provide compelling evidence of bidirectional communication within the BGM system.

For example, germ-free mouse models have shown a reduction of emotion-like behaviors, highlighting the role of gut microbiota in modulating the brain's emotional and cognitive networks.[79] In a mouse model of depression, phenotypic depression could be transferred from human patients to mice via fecal microbial transplant that was associated with a reduction in endocannabinoid signaling.[80] A recent study showed that increasing intestinal luminal 5-HT levels through oral supplementation or genetic deficiency in the host 5-HT serotonin transporter (SERT) lead to an increase in the relative abundance of spore-forming

members of the gut microbiota.[81] These taxa were associated previously with promoting host 5-HT biosynthesis.[82] Furthermore, among these gut microbes, *Turicibacter sanguinis* was identified as a bacterium expressing a neurotransmitter sodium symporter-related protein showing both sequence and structural similarities to mammalian SERT.[81]

Metagenomic analyses of 1054 healthy and depressed participants with external validation in a group of 1070 participants showed *Faecalibacterium* and *Coprococcus* bacteria that produce butyrate showed a consistent link with improved quality of life, whereas *Coprococcus* species, along with *Dialister*, remained diminished in depression, even after accounting for the potential influence of antidepressants.[83] In addition, longitudinal studies investigating the effects of dietary interventions, such as prebiotics or probiotics, have shown changes in gut microbial composition and some improvements in mood-related symptoms in individuals with major depressive disorder and anxiety.[84,85]

In mice, *Bifidobacterium breve* reversed chronic stress-induced depression-like behavior.[86] Supplementation showed the potential to alleviate the hyperactive hypothalamic–pituitary–adrenal response and inflammation, potentially by modulating the expression of glucocorticoid receptors.[86] In addition, supplementation down-regulated the phosyphorylation cyclic adenosine monophosphate (cAMP) response element binding c-Fos (pCREB-c-Fos) pathway while enhancing the expression of brain-derived neurotrophic factor.[86] Furthermore, it successfully restored gut microbial abnormalities induced by chronic stress, leading to increased levels of SCFAs and 5-hydroxytryptophan. Notably, intestinal 5-hydroxytryptophan biosynthesis showed a positive correlation with fecal SCFA and *B breve* levels.[86]

Although previous studies have focused on serotonin pathways, recent research has shown the effects of the BGM axis on depression via estrogen metabolism. In a recent study, Li et al[87] investigated the potential link between estradiol decline and depressive disorders in premenopausal females. They isolated a strain of *Klebsiella aerogenes* from the feces of depressed premenopausal females, which was found to degrade estradiol. In mouse experiments, administering this strain resulted in estradiol decline and depression-like behaviors. The specific enzyme responsible for estradiol degradation, 3β-hydroxysteroid dehydrogenase (3β-HSD), was identified in *K aerogenes*. 3β-HSD converts estradiol to estrone in the gut.[87] Expressing 3β-HSD in *Escherichia coli* conferred estradiol-degrading abilities to the bacteria. When mice were gavaged with 3β-HSD expressing *E coli*, their serum estradiol levels decreased, leading to depression-like behaviors. The prevalence of *K aerogenes* and 3β-HSD was higher in premenopausal women with depression compared with those without depression. These findings suggest that targeting estradiol-degrading bacteria and 3β-HSD enzymes could be potential interventions for treating depression in premenopausal women.[87]

Parkinson Disease

Advancements in research have unraveled the close relationship between the gut and Parkinson disease (PD). Studies have shown alterations in the gut microbiota composition in individuals with PD, characterized by reduced abundance of certain bacterial taxa, such as Prevotellaceae and Lachnospiraceae, and increased levels of potentially proinflammatory species.[88] Furthermore, the deposition of misfolded α-synuclein, a hallmark of PD, can initiate in the enteric nervous system and travel to the brain through neural pathways, suggesting a bidirectional gut–brain involvement in PD pathogenesis.[89]

The BGM system in PD extends beyond the gastrointestinal symptoms commonly experienced by patients. Emerging evidence suggests that alterations in the gut microbiota can influence motor symptoms, disease progression, and treatment response in PD.[90,91] Different *Prevotella* strains have been associated with clinical features of PD. *Prevotella*, identified as a prodromal marker of PD, has shown associations with rapid eye movement sleep behavior disorder (a major early risk factor for PD) and progressive PD motor symptoms over a 2-year period.[92] On the other hand, individuals with a *Prevotella*-enriched enterotype showed lower levels of constipation and less-frequent subthreshold parkinsonism.[93] Modulation of the gut microbiota through interventions such as probiotics, prebiotics, and fecal microbial transfer has shown promise in animal models and some human studies, highlighting a potential avenue for early therapeutic strategies in PD.[94] Targeting the BGM system in PD not only may alleviate common gastrointestinal symptoms in PD, but such a therapeutic approach also may impact neuroinflammation, α-synuclein pathology, and motor dysfunction in these patients, and delay the onset of neurologic symptoms if initiated early in individuals with new-onset constipation and rapid eye movement sleep abnormality.

Alzheimer Disease

Several recent studies have shown the mechanistic relationship between the gut microbiome and Alzheimer disease (AD). In 2020, gut dysbiosis was observed in 5xFAD mice, an established animal model of AD, in an age-dependent manner, characterized by a reduction in phylogenetic richness and an increase in specific microbial taxa, including *Helicobacter* and *Prevotella*.[95] Although it is important to note that there are several potentially beneficial as well as harmful *Prevotella* subspecies, this study showed certain *Prevotella* subspecies to be increased significantly in 5xFAD mice.[95] Importantly, this gut dysbiosis was linked to the activation of the CCAAT/enhancer binding protein β/asparagine endopeptidase (C/EBPβ/AEP) pathway, a key player in AD pathologies in the brain. The microbiota from aged 3xTg mice, another established genetic mouse model for AD, accelerated AD pathology in young 3xTg mice, with active C/EBPβ/AEP signaling in the brain. Antibiotic treatment reduced this signaling and improved cognitive function in 5xFAD mice. In addition, the prebiotic R13 suppressed the C/EBPβ/AEP axis and amyloid aggregates in the gut, mediated by *Lactobacillus salivarius*. These findings suggest that gut dysbiosis can activate the C/EBPβ/AEP signaling pathway, implicating it in AD

pathogenesis, and provide insights into potential therapeutic interventions targeting the BGM system in AD.[95]

Seo et al[39] recently reported studies on the possible role of the gut microbiota in tau pathology and neurodegeneration in the context of AD and primary tauopathies. They used a mouse model of tauopathy expressing different human ApoE isoforms (ApoE3 and ApoE4) and manipulated the gut microbiota through germ-free (GF) conditions and antibiotic treatment early in life. The study showed that, in mice, alterations in the gut microbiota had a significant impact on tau pathology and neurodegeneration, and this effect was dependent on the ApoE isoform. Male GF mice expressing ApoE4 showed reduced brain atrophy compared with conventionally raised mice. Similarly, male antibiotic-treated mice expressing ApoE3 showed milder hippocampal atrophy. These changes were associated with lower levels of phosphorylated tau in the hippocampus.

Further investigations into the mechanisms behind these effects showed that the gut microbiota influenced the state of glial cells in the brain, shifting them toward a more homeostatic-like state. This modulation of neuroinflammation and tau-mediated neurodegeneration was linked to microbiota-produced SCFAs. Supplementing SCFAs to GF mice expressing ApoE4 resulted in increased glial reactivity and phosphorylated tau pathology.[39] However, it is important to note that although this study showed potentially negative effects of SCFA in AD, there are several other studies that have shown positive effects in AD and cognitive decline.[96,97]

These findings highlight the intricate interplay between the gut microbiota, the immune response, and tau-mediated neurodegeneration, providing valuable insights into potential avenues for the prevention and treatment of AD and primary tauopathies by targeting ApoE-associated gut microbiota. This study underscores the role of SCFAs as mediators in the neuroinflammation-neurodegeneration axis and emphasizes the importance of considering the BGM system in neurodegenerative diseases.[39] For instance, colonization of germ-free mice with specific microbial strains, such as *Lactobacillus* and *Bifidobacterium*, has been shown to improve cognitive performance in tasks related to memory and learning through modulation of interleukin 1β and the suppression of inflammation and immune-reactive genes.[98,99]

Autism Spectrum Disorder

Research exploring the BGM system has shed light on the possible involvement of gut dysbiosis in the pathogenesis of autism spectrum disorder (ASD). Studies have shown alterations in the gut microbiota composition in individuals with ASD compared with neurotypical controls, characterized by reduced microbial diversity, imbalances in specific bacterial taxa, and altered metabolic pathways.[100,101] Numerous studies conducted over the past 2 decades consistently have found that individuals with ASD have distinct clostridial species in their stool compared with neurotypical individuals.[101,102] Specifically, *Clostridium bolteae* notably has been linked to ASD patients with gastrointestinal issues.[103] Despite these observed differences in proportions, the specific impact of Clostridiales on host physiology in individuals with ASD remains unknown. Correlational studies of the gut microbiome in ASD have to be interpreted with caution owing to the dramatic dietary restrictions that many patients undergo, and because of the limited validity of dietary reports by patients or their parents. In addition, the significant impact of chronic psychosocial stress in affected patients on gastrointestinal function and the microbial ecosystem has to be taken into account when interpreting observed microbiome alterations.

Those limitations were highlighted recently in a study exploring the potential link between the gut microbiome and ASD using a large data set of 247 participants.[104] Contrary to previous findings, the study did not find direct associations between an ASD diagnosis and the gut microbiome. Instead, it proposed a different model, suggesting that the severity of restricted interests in individuals with ASD may be linked to specific dietary preferences. These dietary preferences, in turn, were associated with reduced microbial diversity and differences in stool consistency. Although the study identified microbiome associations with factors such as age, diet, and stool consistency, it concluded that microbiome differences in ASD primarily may reflect dietary choices related to diagnostic features, cautioning against claims of a causal role for the microbiome in patients with ASD.[104]

Modulation of the BGM System

Dietary Interventions and Nutritional Strategies

Emerging evidence has suggested that certain dietary patterns and components can influence the gut microbial composition and activity, as well as impact brain function and mental health.[105]

The traditional Mediterranean diet, the most well-studied diet in the field of BGM disorders, is characterized by high consumption of fruits, vegetables, whole grains, legumes, and healthy fats, and variations of this diet include the reduced intake of ultraprocessed foods, the reduction or elimination of sugar, and red meat. This dietary pattern is rich in fiber, polyphenols, and omega-3 fatty acids, which can promote the growth of beneficial gut bacteria and contribute to a balanced gut microbial ecosystem.[106] Studies have shown that adherence to a Mediterranean diet is associated with a lower risk of depression, anxiety, and cognitive decline.[107]

Other dietary components, such as polyphenols found in fruits, seeds, berries, and tea, have been shown to exert beneficial effects on the BGM system.[108] Even though polyphenols exhibit antioxidant effects in vitro, little if any of their beneficial effects in human beings can be attributed to such antioxidant effects. Rather, it is metabolism by the gut microbiota that generates bioactive metabolites that can modulate brain function and neuroinflammation.[109]

Even though current evidence strongly suggests universal health benefits of a Mediterranean-type diet for human beings, it is worth noting that personalized dietary approaches, tailored to an individual's specific gut microbial

profile, hold promise for optimizing therapeutic outcomes in patients with food sensitivities, allergies, celiac disease, and IBS.[110] The concept of precision nutrition aims to identify an individual's unique gut microbial composition and develop personalized dietary interventions that target specific microbial functions or imbalances.[111] This approach recognizes the interindividual variability in gut microbiota composition and response to dietary interventions. However, evidence from controlled clinical trials confirming the therapeutic potential for personalized strategies in patients other than those with celiac disease or food allergies is currently not available.

Probiotics and Prebiotics

Probiotics and prebiotics have gained considerable attention as potential therapeutic tools for modulating the BGM system. For example, certain strains of *Bifidobacterium* and *Lactobacillus* have been shown to improve anxiety- and depression-like behaviors in animal models through modulation of neurotransmitter signaling, reduction of systemic inflammation, and enhancement of the GEB function.[112,113] Extensive research has shown how probiotic bacteria influence immune system functions within the human gastrointestinal mucosa.[114] In mice, *Lactobacillus acidophilus* enhances the expression of m-opioid and cannabinoid receptors in colonic epithelial cell lines,[115] and in human beings the same probiotic has been reported to reduce self-reported stomach pain in patients with functional abdominal pain.[116] However, evidence for clinically meaningful benefits of probiotics in patients with brain disorders still is lacking.

In contrast to traditional probiotics, second-generation probiotics are microorganisms that have been genetically engineered, also known as genetically modified microorganisms.[117] This class of probiotics represent a cutting-edge approach in the field of microbiome research, offering a platform for precise manipulation of the gut microbial ecosystem. Through targeted genetic engineering, these probiotics are tailored to exert specific effects on host physiology and health.[118] By introducing or modifying genes within the probiotic strains, researchers can enhance the production of bioactive molecules, metabolites, or therapeutic proteins that have potential implications for human well-being.[118] However, the field also demands rigorous consideration of safety and ethical implications, ensuring that the benefits of genetically modified probiotics are accompanied by a thorough understanding of their potential risks and unintended effects on the microbial ecosystem.

Prebiotics, on the other hand, are dietary fibers that selectively promote the growth and activity of beneficial gut microorganisms. Recent research has explored the effects of various prebiotic fibers, such as inulin, fructooligosaccharides, and galactooligosaccharides, on the BGM system.[119,120] Several studies have shown that prebiotic supplementation can modulate the gut microbial composition positively, increase the production of SCFAs, and improve gut barrier function.[121] These effects have been associated with improved cognitive function, reduced anxiety-like behavior, and enhanced stress resilience in animal models, but clinically meaningful effects need to be confirmed in well-controlled human studies.[122,123] These findings suggest caution with the long-term use of elimination diets, such as the low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, which are devoid of such prebiotics.

Other Therapeutic Approaches

In addition to probiotics, prebiotics, and dietary interventions, other microbiome-targeted therapeutic approaches include fecal microbiota transplantation (FMT) and microbial-derived bioactive compounds.

FMT is being investigated for its potential in modulating the BGM system in psychiatric and neurologic disorders.[124] Some evidence suggests that FMT may be beneficial in reducing both behavioral and gastrointestinal symptoms in ASD patients.[125] However, more research is needed to understand the long-term effects, safety, and optimal protocols for FMT and to develop strategies to overcome colonization resistance.

Furthermore, ongoing research is focused on identifying microbial-derived bioactive compounds that can modulate the BGM system. These compounds, produced exclusively by gut bacteria, have the potential to interact with the host nervous system, immune system, and other physiological processes. The most well-studied bioactive compounds are indoles. When tryptophan reaches the gut, it can be acted upon by specific gut bacteria, particularly those belonging to the genus *Clostridium* and other indole-producing bacteria. These bacteria have the ability to convert tryptophan into indole and other indole derivatives through a series of enzymatic reactions.[126] Although certain indoles have negative effects on the BGM system,[126] others can have beneficial effects.[127] Understanding the mechanisms of action and therapeutic potential of these bioactive compounds is an exciting area of investigation.

Future Directions and Implications

Emerging Research Areas and Unanswered Questions

The study of the BGM system is a dynamic and rapidly evolving field, with several emerging research areas and unanswered questions, and a paucity of successful translation into human disease populations. These areas include the investigation of microbial metabolites and their specific effects on the host, the role of viral and fungal components within the gut microbial ecosystem, and the influence of environmental factors (exposome) on the system. Furthermore, exploring the role of the BGM system in different phases of the life span, in particular in neurodevelopmental and neurodegenerative disorders, and the interaction between the gut microbiota and the immune system, are promising avenues for future research. In addition, the contribution of the virome, which encompasses the viral entities present in the gut, and its interactions with the gut bacteria, remains an area of active exploration that has not received sufficient

attention. Furthermore, integrating machine learning and artificial intelligence into the analysis of extensive multi-omics imaging and microbiome data sets has the potential to significantly enhance our comprehension of the BGM system at a systems biological level.

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Conflicts of interest
The authors disclose no conflicts.