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Mechanisms of Gut Microbial Effects on the Human Brain in the Brain-gut Axis and Study of Disease Relevance

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Abstract. The microbiota-gut-brain axis (MGBA) is a pivotal concept for understanding bidirectional gut–brain communication, with mounting evidence that microbial dysbiosis contributes to neurological disorders. The present review explores the underlying mechanisms and assesses potential therapeutic strategies. Mechanistically, the gut microbiota exerts influence on brain function via neural pathways such as vagus nerve signaling, microbial metabolites including short-chain fatty acids and tryptophan derivatives, and immune activity. The study identified a novel sensory mechanism in which TLR5+ neuroglial cells in the colon detect bacterial flagellin within milliseconds, thereby regulating feeding. Furthermore, under dysbiotic conditions, live rumen bacteria have been observed to produce phenylethanolamine (PEA), which can directly trigger neuropathology in cases of hepatic encephalopathy. In a Parkinson's disease model, the therapeutic use of engineered GLP-1-expressing Lactobacillus lactis has been shown to alleviate motor deficits by suppressing neuroinflammation and α-synuclein aggregation. In conclusion, the impact of gut microbiota on brain function is significant, with neural, metabolic, and immune mechanisms being key factors. This positions targeted microbial interventions as a promising avenue for treating neurological disease.

Keywords: Microbiota-Gut-Brain Axis, MGBA, Dysbiosis, Gut Microbiota

1. Introduction

The microbiota-gut-brain axis represents a paradigm shift in neuroscience, depicting a dynamic bidirectional communication network connecting the gut microbiota with central nervous system function through neural, endocrine, immune, and metabolic pathways [1]. Accumulating evidence indicates that the gut microbiota plays an indispensable role in regulating neurodevelopment, cognitive function, and emotional responses, and its dysregulation is increasingly recognized as closely associated with the pathogenesis of various neuropsychiatric disorders, ranging from Alzheimer's disease to autism spectrum disorders.

Despite significant progress, the following core questions remain unresolved: Mechanistic complexity: Specific neural circuits, such as hypothalamic POMC neurons, How can rapid, region-specific regulation of the gut microbiome be achieved within hours [2]? Causal inference: Are microbial metabolites, such as α-synuclein aggregates in Parkinson's disease, direct triggers of neuropathology or secondary phenomena [3]? Clinical translation: How can neuro-microbial

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interactions be harnessed to develop precision intervention strategies, such as engineered probiotics delivering GLP-1 [4]?

This review integrates cutting-edge discoveries from 2023 to 2025 with the aim of: elucidating the multilevel communication mechanisms of MGBA, beginning with an exploration of microbe regulation mediated by neural pathways; assessing the causal contribution of gut microbiota dysbiosis to neurodegenerative diseases and neurodevelopmental disorders; and critically evaluating emerging MGBA-targeted therapies, including fecal microbiota transplantation and genetically engineered probiotics.

Based on this theoretical framework, the following sections will systematically analyze the core communication mechanisms of MGBA, with an initial focus on microbe regulation mediated by neural pathways.

2. Fundamental communication mechanisms of the microbiota-gut-brain axis

2.1. Neurological pathway mechanisms

2.1.1. Neurobiological perception: rapid microbial influence on brain function

The vagus nerve serves as the primary neural pathway connecting the gut to the brain, thus functioning as the central information highway of the MGBA. Recent studies have identified specialized neuroendocrine cells—neuropod cells—in the gut that detect intestinal contents, including microbial signals and nutrients, and transmit these signals to the brain within milliseconds via synaptic connections with vagal nerve terminals. In 2025, Bohórquez et al. demonstrated that Toll-like receptor 5 (TLR5) is expressed on intestinal neurons, where it recognizes bacterial flagellin and activates vagal signaling through release of the neuropeptide PYY. This mechanism, termed "neurobiotic sense," allows the brain to perceive microbial signals in real time [5].

Specifically, microbial flagellin binds to TLR5 on PYY^{+} enteric neurons in the colon, triggering calcium-dependent PYY release. PYY then activates NPY2R receptors on vagal afferents, propagating signals to the brainstem and ultimately suppressing feeding behavior. This process occurs within milliseconds, independent of immune or metabolic mediation, illustrating a direct microbial-neural communication route [5].

2.1.2. Brain-mediated rapid regulation of gut microbiota

Contrary to the traditional unidirectional view of gut-brain communication, recent evidence shows that the brain can rapidly modulate gut microbiota via specific neural circuits. The activation of hypothalamic POMC neurons in the arcuate nucleus alters the microbial composition of specific gut regions (e.g., the duodenum) within four hours [6].

Chemogenetic activation of POMC neurons increased abundances of specific bacterial families in the duodenum, while their inhibition shifted composition in the jejunum, ileum, and cecum. AgRP neuron activation had minimal effects, indicating neuron-type and gut-region specificity [6].

Central leptin administration also induced rapid, region-specific microbial shifts: changes occurred in the ileum and cecum after two hours, and shifted to the duodenum by four hours. Certain bacterial families increased twofold in the duodenum but decreased by half in the ileum and cecum. Leptin also elevated duodenal metabolite levels (e.g., pyruvate and nicotinamide increased 1.5- and 2-fold, respectively). These regulatory effects were abolished in diet-induced obese mice, indicating that impaired leptin signaling disrupts microbiota regulation [6].

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Mechanistically, leptin increased gene expression related to neural signaling and synaptic processes in the duodenum (~1.2-fold) and elevated local adrenaline levels, which suggests the involvement of the sympathetic nervous system in gut microbial modulation [6].

2.2. Metabolic pathway mechanisms

The gut microbiota produces key bioactive metabolites that mediate brain-gut communication, primarily through the following categories:

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are generated from bacterial fermentation of dietary fiber. Butyrate, for example, exerts anti-inflammatory effects and maintains blood-brain barrier integrity by inhibiting the NF-κB pathway. It also promotes microglial maturation via epigenetic regulation of HDAC3. SCFAs generally provide neuroprotection by activating GPCRs such as GPR41/GPR43 and inhibiting histone deacetylases [7,8].

Gut microbes play a major role in regulating tryptophan metabolites. One way is that bacteria convert tryptophan into a precursor of serotonin (5-HT). Amazingly, around 95% of the body's 5 - HT is synthesized right in the gut, and this has a notable impact on our mood and cognitive abilities. On the other hand, there's the kynurenine pathway. It gives rise to metabolites such as kynurenic acid. This particular metabolite is neurotoxic, and interestingly, it shows up at abnormal levels in patients with Alzheimer's disease [7,8].

Now, let's talk about bile acid derivatives. Gut bacteria transform primary bile acids into secondary bile acids, and in the process, these derivatives are formed. They function as signaling molecules that can activate certain receptors, like FXR and GPBAR1. By doing so, they have the ability to modulate neuroendocrine functions [7,8].

2.3. Immune-inflammatory axis mechanism

The gut microbiota shapes brain function via immune regulation. When it falls out of balance, “leaky gut” can emerge, weakening the barrier and letting endotoxins like lipopolysaccharide (LPS) into the blood. Once in the blood, LPS triggers systemic inflammation via Toll-like receptor 4 (TLR4) signaling, which disrupts the blood-brain barrier (BBB). As a result, cytokines (TNF-α, IL-1β, IL-6) reach brain tissue, activate microglia, and set off neuroinflammation [7,8].

Enteric glial cells are really important in this immune–inflammatory link. They join local responses by releasing S100β and cytokines like IL-6 and TNF-α. What’s more, they may aid the abnormal spread of α-synuclein from gut to brain—a key factor in Parkinson’s disease [9].Back in 2023, a Nanchang University team dug deeper. They showed that intestinal inflammation activates microglia via TLR4/MyD88/NF-κB, leading to dopaminergic neuron death. Specifically, after TLR4 teams with MD2, a phosphorylation chain involving IRAK1 and TRAF6 activates NF-κB and drives neuroinflammation [4]. Altogether, dysbiosis-driven barrier failure and glial signaling couple peripheral inflammation to central pathology, underscoring the gut–brain immune axis as a therapeutic target. This cascade highlights how gut-derived immune signals can breach neural defenses and shape brain outcomes.

3. The role of the brain-gut axis in neurodevelopment and mental disorders

3.1. Autism Spectrum Disorder (ASD)

Autism spectrum disorder is a neurodevelopmental disorder characterized by social deficits and repetitive behaviors, often accompanied by gastrointestinal symptoms. In February 2025, a research

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team led by Zhao Fangqing from the Institute of Zoology, Chinese Academy of Sciences, published a significant study in Cell Genomics, reporting the first single-cell analysis of gut-brain interaction disorders caused by defects in the ASD high-risk gene Chd8 [9].

The research group carried out cross - developmental stage dynamic analyses on brain and intestinal tissues of Chd8+/0-mice and wild-type mice, spanning from the embryonic stage to adulthood. They then constructed an extensive atlas that included over 460,000 cells.This study found that in the brain, CHD8 deficiencies lead to a delay in the development of crucial precursor cells in the embryonic brain. Later, in adulthood, this sets off a so-called "neuroinflammatory storm." You can recognize this by the abnormal activation of microglia. There's also a 2.3-fold jump in the secretion of pro-inflammatory factors, and an excessive amount of neuronal apoptosis.At a more fundamental level, CHD8 defects bring about a "dual crisis." First, there's a problem with the immune system. T and B lymphocytes don't differentiate in sync, and the level of protective IgA antibodies drops by nearly 40%. Second, gut epithelial cells multiply too much, causing the villi to elongate abnormally by 27%.Here's something interesting. Genes like Klf4 and Ezr, which play roles in both the brain and the gut, show a kind of "see-saw" expression pattern. That is, when their expression goes down in the brain, it goes up abnormally in the gut. This finding uncovers a delicate cross-organ regulatory balance [9].

The research team further generated Chd8 conditional knockout mice, specifically Chd8-AIEC mice with intestinal epithelial cell-specific Chd8 knockout. The results showed that while these mice retained basic social abilities, they lost interest in exploring new social partners, and their cerebral cortex exhibited disrupted glutamate/GABA balance [9]. This suggests that changes in the local intestinal microenvironment can remotely regulate neural function via the gut-brain axis.

In terms of treatment, the research team screened the intestines of Chd8-deficient mice to identify Lactobacillus murinus, a strain with restorative potential. After a one-month probiotic intervention, the social novelty deficits in Chd8-AIEC mice were significantly improved, accompanied by an increased proportion of Drd2-positive neurons and the restoration of synaptic plasticity-related pathways (e.g., those involving Gria2 and Snap25) [9]. This suggests that probiotics may reshape the interaction network between neurons and glial cells in the brain by regulating intestinal inflammation, metabolite secretion, or vagus nerve signaling.

3.2. Hepatic Encephalopathy (HE)

Hepatic encephalopathy is a severe complication of cirrhosis, traditionally based on the “ammonia intoxication theory.” In January 2025, Professor Zhou Hongwei's team from Southern Medical University published a study in Nature Medicine, challenging this long-held view and identifying for the first time the key role of Ruminococcus gnavus and its metabolite phenylacetic acid in hepatic encephalopathy [10]. The study found that Ruminococcus gnavus was significantly enriched in the gut microbiota of patients with hepatic encephalopathy, with the expression of the phenylalanine decarboxylase gene it carries increasing by approximately 10-fold.

This bacterium converts dietary phenylalanine into phenethylamine through decarboxylation. In cirrhotic states, reduced activity of monoamine oxidase B in the liver and serum leads to phenethylamine accumulation and its entry into the brain. Phenethylamine causes specific neuronal loss, memory impairment, and symmetrical tremors in the brain, all of which are the core symptoms of hepatic encephalopathy [10].

In terms of mechanism validation, the research team transplanted fecal microbiota from hepatic encephalopathy patients into germ-free cirrhotic mice, successfully replicating the symptoms of hepatic encephalopathy. Targeting the phenylalanine decarboxylase enzyme using the antibiotic

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rifaximin or targeting phenethylamine using monoamine oxidase B inhibitors reversed these neurological symptoms. Clinical studies further confirmed that cirrhotic patients with high baseline phenethylamine levels had a sevenfold increased risk of hepatic encephalopathy after undergoing transjugular intrahepatic portosystemic shunt [10].

This finding expands our understanding of the gut-liver-brain axis and provides new therapeutic targets for hepatic encephalopathy. The research team is currently developing a phage therapy that specifically targets active rumen bacteria. This approach shows promise for enabling more precise treatment strategies for hepatic encephalopathy [10].

4. Intervention strategies targeting the brain-gut axis

When it comes to disease intervention strategies based on the brain-gut axis, the main thing is to manipulate the gut microbiome in order to affect neurological conditions. Probiotics and prebiotics are used to address this. They work by introducing certain beneficial bacteria to fix gut microbiota imbalances and ease neuroinflammation.Take Lactobacillus plantarum and Bifidobacterium longum for example. These strains have shown to bring about various positive effects. Then there are more targeted methods. In Parkinson's disease, the engineered strain L. lactis-GLP-1 secretes GLP-1, which activates neuroprotective pathways [4]. And in autism spectrum disorder, Lactobacillus rhamnosus has been found to help with social problems [9].Fecal microbiota transplantation (FMT) is another approach. It's all about transferring microbiota from healthy donors to patients to get the gut microbiome back in balance [7]. This method has actually shown some therapeutic results. In models of autism spectrum disorder and Huntington's disease, it has been seen to enhance cognitive and motor functions.Dietary changes can also have a big influence on the microbiome. For example, the Mediterranean diet is known for its high intake of dietary fiber and polyunsaturated fatty acids. Studies have shown that this diet encourages the growth of beneficial bacteria and boosts the production of short - chain fatty acids. Interestingly, a high-fiber diet has shown promise in treating Huntington's disease models [6,7].

Lastly, there's neuroactive substance - targeted therapy. This focuses on blocking harmful microbial metabolites or their pathways. For instance, in hepatic encephalopathy, targeting the phenylalanine decarboxylase enzyme or its product, phenethylamine, can turn around neurological symptoms [10]. And the development of phage therapy, especially when it targets bacteria like Ruminococcus gnavus, shows the potential for precise interventions in this area.

5. Research limitations and future directions

5.1. Limitations of current studies

Despite progress in microbiota–gut–brain research, several issues continue to limit interpretation and hinder clinical application. Causality remains difficult to determine. Most studies cannot confirm whether gut dysbiosis initiates disease or results from it, as microbial shifts may reflect the underlying disorder or medication use. When neurological symptoms and microbial changes co-occur, it remains unclear whether gut alteration precedes brain pathology.

Sample heterogeneity introduces significant confounding. Variation in age, sex, diet, comorbidities, and antibiotic exposure complicates comparison across studies and obscures microbiota–brain associations. A cohort composed of young adults with uniform diets differs substantially from one including older individuals with multiple health conditions, making direct conclusions unreliable.

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Technical limitations constrain taxonomic and functional resolution. Common 16S rRNA (V4) sequencing generally identifies microbes at the genus level, missing species or strains with distinct functional roles. Higher resolution methods like full-length 16S or metagenomics are required to detect meaningful differences. Current tools resemble low-resolution imaging, outlining structures without revealing critical details.

Model systems further restrict translatability. Mouse models only approximate human neuropsychiatric conditions, and germ-free animals lack co-development between the microbiota and immune system, limiting biological relevance to humans.These constraints complicate causal inference, mechanistic understanding, and therapeutic discovery within the gut–brain axis and highlight the need for improved study design, finer analytical resolution, and tighter control of confounders.

5.2. Future research directions

In order to make revolutionary progress, future research ought to focus on the following aspects:

When these efforts work in harmony, they will help brain-gut axis research take a significant step forward, evolving from merely understanding the mechanisms to implementing precision interventions.Integrated multi-omics analyses hold immense significance. When we combine metagenomics, metabolomics, epigenomics, and proteomics, it becomes possible to comprehensively grasp the interactions between hosts and microbes. For instance, consider the single - cell atlas created by Zhao Fangqing's team. It offers a completely new model for revealing the bidirectional regulation between the gut and the brain at various developmental stages [9].

The development of precision microbial interventions is equally vital. These interventions need to be customized based on individual host features. This includes factors like the APOE genotype, epigenetic age, and disease subtype, all with the aim of achieving personalized treatment. Additionally, cutting-edge technologies such as chemogenetics and optogenetics can play a crucial role. They can help us figure out the functions of specific gut - brain neural pathways (for example, different subsets of the vagus nerve) in diseases. By doing so, we can identify new targets for neural modulation therapies [5,6].

Another important aspect is the optimization of engineered microbial therapeutics to boost their efficacy and safety. "Smart probiotics" that are capable of detecting host signals (such as inflammatory markers or metabolites) could potentially deliver neuroactive compounds (like neurotrophic factors or neurotransmitter precursors) precisely in a spatiotemporal manner. This would address the limitations of traditional therapies [4].

When all these endeavors work in tandem, they will propel brain - gut axis research to a new level. It will progress from simply understanding the underlying mechanisms to actually implementing precision interventions.

6. Conclusion

The microbiota - gut - brain axis is seen as a complex two-way communication network. It combines neural, endocrine, immune, and metabolic signals between the gut and the central nervous system. Looking closely at the research literature, we can find that microbial metabolites like phenethylamine can directly affect enteric nervous system receptors. Also, certain host genetic factors, especially mutations in the chromatin remodeler gene CHD8, can weaken the intestinal barrier function. This then leads to abnormal signaling through the vagal and spinal afferent pathways.On the other hand, top - down regulatory processes are obvious in some studies. For

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example, in optogenetic experiments, when hypothalamic neurons are activated, it quickly changes the gut's motility and permeability. These changes in the gut then alter the microbial environment through bile acid secretion and changes in the intestinal pH.

There are some promising therapeutic strategies targeting the microbiota-gut-brain axis. These include using engineered probiotics to deliver neuroprotective substances, fecal microbiota transplantation to bring back microbial diversity, and precise dietary changes with prebiotic fibers. In rodent models of diseases like autism spectrum disorder, depression, and Parkinson's disease, these methods have shown good results. For example, fecal microbiota transplantation from healthy donors has been able to reduce repetitive behaviors in autism spectrum disorder models by 40%-60%. This might be because it restores the balance between GABA and glutamate.But, it's not easy to apply these findings in clinical settings. There are still some problems to solve. Figuring out whether microbes are causing the disease or are just a result of it is a big challenge. Also, everyone's microbiome is different, which is affected by things like diet, antibiotic use, and genetic factors.

The future of this area depends on using a variety of strategies. One important thing is to combine long - term metagenomic and metabolomic analysis to keep track of how microbes change as a disease develops. Also, classifying patients according to things like biological age (using things like epigenetic clocks), APOE genotype, and their inflammatory profiles is crucial for coming up with personalized treatments. These could be customized probiotic mixtures or better - designed vagus nerve stimulation methods.

References

[1] Sharon, G.et al.(2019). Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell, 177(6), 1600–1618.e17. https: //doi.org/10.1016/j.cell.2019.05.004

[2] Toledo, M.et al.(2025). Rapid modulation of gut microbiota composition by hypothalamic circuits in mice. Nature metabolism, 7(6), 1123–1135. https: //doi.org/10.1038/s42255-025-01280-3

[3] Kiani L. (2022). Novel plasma markers for Parkinson disease. Nature reviews. Neurology, 18(12), 699. https: //doi.org/10.1038/s41582-022-00746-2

[4] Yue, M., Chen, T., Chen, W., Wei, J., Liao, B., Zhang, J., Li, F., Hong, D., & Fang, X. (2026). The engineered probiotic strain Lactococcus lactis MG1363-pMG36e-GLP-1 regulates microglial polarization and gut dysbiosis in a transgenic mouse model of Parkinson's disease. Neural regeneration research, 21(3), 1211–1221. https: //doi.org/10.4103/NRR.NRR-D-24-00702

[5] Liu, W. W., Reicher, N., Alway, E., Rupprecht, L. E., Weng, P., Schaefgen, C., ... & Bohórquez, D. V. (2025). A gut sense for a microbial pattern regulates feeding. Nature, 1-8.

[6] Toledo, M.et al.(2025). Rapid modulation of gut microbiota composition by hypothalamic circuits in mice. Nature metabolism, 7(6), 1123–1135. https: //doi.org/10.1038/s42255-025-01280-3

[7] Socała, K., Doboszewska, U., Szopa, A., Serefko, A., Włodarczyk, M., Zielińska, A., Poleszak, E., Fichna, J., & Wlaź, P. (2021). The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacological research, 172, 105840. https: //doi.org/10.1016/j.phrs.2021.105840

[8] Wang, M., Ma, Y., Zeng, B., Yang, W., Huang, C., & Tang, B. (2024). Influence of the Gut Microbiota, Metabolism and Environment on Neuropsychiatric Disorders. Current reviews in clinical and experimental pharmacology, 10.2174/0127724328335219241202142003. Advance online publication. https: //doi.org/10.2174/0127724328335219241202142003

[9] Ji, P., Wang, N., Yu, Y., Zhu, J., Zuo, Z., Zhang, B., & Zhao, F. (2025). Single-cell delineation of the microbiota-gut-brain axis: Probiotic intervention in Chd8 haploinsufficient mice. Cell genomics, 5(2), 100768. https: //doi.org/10.1016/j.xgen.2025.100768

[10] He, X.et al.(2025). The gut-brain axis underlying hepatic encephalopathy in liver cirrhosis. Nature medicine, 31(2), 627–638. https: //doi.org/10.1038/s41591-024-03405-9