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THE GUT–BRAIN AXIS IN NEUROLOGICAL DISORDERS: FROM MICROBIAL DYSBIOSIS TO THERAPEUTIC INTERVENTION

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ABSTRACT

The gastrointestinal tract, gut bacteria, immune system, endocrine pathways, and central nervous system are all connected by the intricate bidirectional communication network known as the gut–brain axis. There is mounting evidence that dysbiosis—a term used to describe changes in gut microbial composition and function—may have an impact on neurological health through alterations in microbial metabolites, intestinal barrier integrity, immune signaling, blood–brain barrier function, and neuroinflammation. The architecture and physiological roles of the gut-brain axis are summarized in this overview, which also looks at the main causes of microbial dysbiosis, such as nutrition, aging, antibiotics, stress, lifestyle, and drug use. With a focus on short-chain fatty acids, tryptophan metabolites, bile acids, immunological mediators, and microbial components like lipopolysaccharide, the molecular pathways connecting gut microbial changes with the brain are examined.

The link between gut dysbiosis and clinically significant neurological disorders including multiple sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy, stroke, and neuropsychiatric disorders is extensively analyzed, taking into account the difference between an association and a causative role. In addition, the research considers novel microbiome-based approaches, probiotics, prebiotics, synbiotics, postbiotics, microbial metabolites, fecal microbiota transplantation, and dietary interventions for targeting the gut-brain axis. Finally, the possibility of using multi-omics and precision microbiome medicine is highlighted, together with current challenges and translational limitations. Individualized treatment strategies for the management and prevention of neurological diseases can benefit from an improved understanding of host-microbe interactions.

KEYWORDS: Gut–brain axis; gut microbiota; microbial dysbiosis; neuroinflammation; neurological disorders; microbial metabolites

INTRODUCTION

Neurological disorders are a major and growing global health issue, covering everything from neurodegenerative and seizure-related conditions to neuroinflammatory, neurodevelopmental, and cerebrovascular diseases. Though the causes differ widely, more evidence points to metabolic, immune, and environmental factors playing a role in triggering or worsening neurological issues. Here, the gut-brain axis serves as a crucial biological bridge between gut function and activity in the central nervous system. The gut-brain axis is a bidirectional communication network that connects your gut, its microbes, the nervous system, immune responses, hormone signals, microbial byproducts, and your brain—all working together in real time. Through these linked pathways, gut microbes can sway brain activity, immune health, hormone signaling, brain growth, thinking abilities, and behavior—while the brain also sends signals back that shape digestion and the gut's microbial makeup. (Morais et al., 2021; Ohara & Hsiao, 2025).

The gut microbiome is a wildly diverse community of microbes, and together they can do way more than any one species could on its own. These tiny microbes help break down nutrients, keep the gut lining strong, support immune system growth, and even make or tweak important biological compounds. Signals zip between the gut and brain through a web of connections—like the vagus nerve, gut-brain axis, HPA system (hypothalamic–pituitary–adrenal), immune messengers in the blood, and compounds made by gut microbes. Short-chain fatty acids (SCFAs), along with tryptophan metabolites, secondary bile acids, and microbial stuff like lipopolysaccharide (LPS), can tweak immune cells, glial cells, nerve signals, and gut barriers—linking gut microbes directly to brain function. (Park & Kim, 2021; Loh et al., 2024).

In a healthy body, the right mix of gut microbes helps keep the immune system balanced, supports steady metabolism, and protects both the gut and blood-brain barrier. However, shifts in microbial makeup and activity—often called microbial dysbiosis—can disrupt these processes. Dysbiosis can involve a drop in microbial variety, loss of helpful or metabolite-producing bacteria, overgrowth of harmful microbes, and shifts in how microbes function metabolically. These

changes can be influenced by what you eat, how old you are, stress, your daily habits, environmental exposure, your genes, and the meds you take. Medications commonly used for neurological and other chronic conditions often change the gut microbiome's makeup and behavior, which complicates figuring out how the microbiome relates to disease. (Nakhal et al., 2024; You et al., 2024).

A substantial number of experimental and clinical data suggest that dysbiosis might be involved in neurodegeneration by a series of overlapping mechanisms: Alteration in microbial composition of the intestine is associated withchanges in the metabolism and production of SCFA, tryptophan metabolites, bile acids, neurotransmitters and others bio-active metabolites, that might affect the peripheral immune system activity inducing local inflammation which can promote secondary immune reactions in the CNS, leading to microglial and astrocyte dysregulation. Furthermore, an increase in gut permeability associated with the dysbiosis might foster the passage of microbe derived molecules, inflammatory mediatiors and toxins into the blood stream. Increased blood brain barrier permeability could facilitate entrance of the neuro-inflammatory signal released by the periphery in the CNS. Consequently sustained input from the gut (metabolic, immune) to the CNS might mediate inflammatory processes, oxidative stress, mitochondrial failure and impairment of synaptic transmission and neuronal loss. (Park & Kim, 2021; Loh et al., 2024).

They have been investigated in relation to their importance for many different neurological disorders. Changes in the gut microbiome were detected in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) and in neuroinflammatory diseases like multiple sclerosis (MS), epilepsy, amyotrophic lateral sclerosis (ALS), stroke, and others. In the case of neurodegenerative diseases, scientists paid attention to the interactions between altered gut microbiota and neuroinflammation, dysfunctions of glial cells, and protein aggregation, particularly the accumulation of amyloid-β tau and α-synuclein. In relation to immune-mediated neurological diseases, microbial products and antigens affect the differentiation of peripheral immune cells and inflammation, thereby affecting the brain homeostasis. (Morais et al., 2021; Loh et al., 2024).

Despite all these advancements, it is important to distinguish between microbial association and biological causation. Much of the human literature consists of observations, and microbiome profiles associated with disease are influenced by factors such as age, dietary habits, geographical location, medication, the extent of disease, among others. Furthermore, the disease state affects the diet, digestive process, physical exercise, and medications, and thereby causes alterations in the microbiome. Hence, the question about whether dysbiosis is the cause, consequence, or modifier of disease still stands. Recent advancements in germ free models, fecal microbiota transplantation, longitudinal studies, metagenomics, metabolomics, and other omics technologies are starting to make up for these shortcomings. (Loh et al., 2024; You et al., 2024).

The prospect of using the gut microbiome as a therapeutic target has been generating considerable excitement regarding the possibility of targeting the gutbrain axis to treat neurological disorders. Unlike many CNS targets that can be difficult to manipulate, the gut microbiome can be modified through diet, probiotics, prebiotics, synbiotics, postbiotics, Fecal Microbiota Transplantation (FMT), microbial metabolites, bacteriophages, and engineered microbial communities. Pre-clinical studies and some clinical trials have produced encouraging results on several of these interventions; however, disparities in the microbial composition and other factors still prevent their integration into neurological practice. (Loh et al., 2024; Wadan et al., 2025).

In other words, the gutbrain axis should be understood by going beyond the mere description of the alterations of the microbes in the intestines but also from a holistic viewpoint that includes dysbiosis, mechanisms, disease development, and treatments. The purpose of this literature review is to discuss the structure and physiological functions of the gutbrain axis; understand the reasons and consequences of dysbiosis of the gut microbiota; and explore the neuro-immune-endocrine-metabolic-barrier mechanisms by which the alterations in the intestines lead to neurological dysfunction. In addition, an evaluation of the evidence for the role of the gut brain axis in various neurological diseases, with a distinction of correlation and causation, and the treatment options currently available will be discussed.

Architecture And Physiology Of The Gut–Brain Axis

The gut brain axis is comprised of a complex of interrelated neural, endocrine, immune and metabolic signaling mechanisms rather than an anatomic structure. Enteric nervous system (ENS), autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (HPA) axis, immune system and gut microbiota are components of a physiological communication network between the intestine and brain.

Gut Microbiota as a Functional Component of the Gut–Brain Axis

The gastrointestinal tract is home to a complex microbial ecosystem, primarily made up of bacteria, but also containing archaea, fungi, viruses, and other microorganisms. These microorganisms have broad metabolic functions and play roles in digestion, nutrient absorption, vitamin processing, immune system development, upkeep of epithelial tissue, and the generation of bioactive compounds. Thus, the gut microbiota serves as a critical physiological link between the external environment and the host's nervous system. (Cryan et al., 2019; Zhuang et al., 2024).

Intestinal microbes play a key role by breaking down carbs your body can't digest. This process generates short-chain fatty acids—mostly acetate, propionate, and butyrate. SCFAs can interact with host cells through G-protein-coupled receptors and also tweak cellular behavior by affecting epigenetic pathways. Through these pathways, microbial metabolites influence gut lining health, immune responses, metabolism, and maybe even brain function. (Cryan et al., 2019; Zhuang et al., 2024).

The microbiota also plays a role in breaking down tryptophan and bile acids. Microbes turn tryptophan into indole compounds, and they also convert primary bile acids into secondary bile acids. These metabolites interact with the body's receptors and signaling systems, potentially influencing immune, metabolic, endocrine, and nervous system functions. So,

the microbiota's role isn't just limited to the gut—it actually helps bridge molecular communication between the gut and brain. (Morais et al., 2021; Zhuang et al., 2024).

2.2 Intestinal Epithelial Barrier

The intestinal lining is where microbes first meet the body's cells. It's made up of just one layer of specialized cells—like enterocytes, goblet cells, Paneth cells, enteroendocrine cells, and others. These cells are held together by tight and adherens junctions, carefully regulating what moves from the gut into the bloodstream. The intestinal barrier isn't just a physical wall—it's a dynamic gatekeeper.

It acts as a responsive signaling hub, picking up on nutrients, microbial byproducts, and environmental signals. Goblet cells make mucus, Paneth cells release antimicrobial stuff, and enteroendocrine cells detect nutrients and microbial byproducts in the gut lumen. Together, these cell populations enable the host to maintain a regulated interaction with the intestinal microbiota and to avoid excessive exposure to potentially harmful microbial substances. (Aburto & Cryan, 2024).

Microbial metabolites, particularly SCFAs, are involved in the maintenance of intestinal barrier integrity. For example, butyrate can be used as an energy source for colonic epithelial cells, and can also affect gene expression in colonic epithelial cells and immune regulation. In contrast, an alteration of microbial composition or metabolic activity may lead to impairment of barrier function and enhanced intestinal permeability. This provides a critical mechanistic link between microbial alterations and systemic inflammatory signaling." (Cryan et al., 2019; Aburto & Cryan, 2024).

2.3 Enteric Nervous System and Vagal Signaling

The Enteric Nervous System is an extensive neural system situated in the walls of the gastrointestinal tract, regulating different activities in the gut including movements, secretion, blood supply, and local reflexes. Given the complexity of the ENS, this system has sometimes been described as the "second brain."

The point is that the ENS is not completely independent from the central nervous system; it maintains complex interconnections with the brain through the autonomic nervous system particularly the vagus nerve. In fact, the vagus nerve is one of the primary neural pathways connecting the gastrointestinal tract to the brain. The fibers of the vagus nerve can transfer impulses in both directions; however, mostly, they act as afferent pathways providing sensory information about the internal organs to the brain stem. This information includes data about the mechanical, chemical, metabolic, and immunological conditions in the gut. (Cryan et al., 2019).

Gut microorganisms can influence vagal signaling indirectly through their effects on intestinal epithelial cells, enteroendocrine cells, immune cells, and enteric neurons. Thus, microbial metabolites may modify sensory signaling without needing to enter the brain themselves. This offers a fast neural pathway by which alterations in the gut microbiome can affect central nervous system functions. (Cryan et al., 2019).

2.4 Neuroendocrine Regulation and the HPA Axis

The hypothalamic-pituitary-adrenal axis has a key neuroendocrine role in gutbrain communication . Under stress, the hypothalamus produces corticotropin-releasing hormone, which stimulates the pituitary to produce adrenocorticotropic hormone, which in turn stimulates the adrenal cortex to release glucocorticoids. These hormones affect immune function, metabolism, gastrointestinal function, and the body's capacity to cope with stress. (Cryan et al., 2019).

There is a two-way interaction between the microbiota and HPA axis . Microbial colonization occurs early in life and can affect the development and regulation of neuroendocrine pathways involved in stress, while psychological or physical stress can affect intestinal motility, secretion, permeability, immune function and microbial composition . Thus, the microbiota and HPA axis are involved in a feedback loop that helps to regulate stress physiology and maintain gut homeostasis . (Cryan et al., 2019; Morais et al., 2021).

Another link between intestinal microbial activity and neuroendocrine signaling is provided by enteroendocrine cells. These cells sense nutrients and microbial metabolites and release hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) to regulate appetite, gut motility, glucose processing and signaling to neural pathways. (Morais et al., 2021).

2.5 Immune Communication Between the Gut and Brain

The immune system is another key communication channel in the gutbrain axis. The gastrointestinal tract hosts a large population of immune cells that constantly interact with the resident microbes. Under normal physiological conditions, these interactions support immune tolerance while still ensuring robust defense against pathogens. (Cryan et al., 2019).

Host pattern-recognition receptors may recognize microbial-associated molecular patterns leading to signaling cascades that regulate cytokine production and immune cell function . Microbial metabolites can also affect the differentiation and function of immune cells. For example, SCFAs can promote regulatory immune responses and regulate inflammatory signaling whereas excessive bacterial components such as lipopolysaccharide (LPS) can induce innate immune signaling. (Morais et al., 2021; Zhuang et al., 2024).

Peripheral immune signals can influence the CNS through circulating cytokines and other mediators. The immune cells in the brain are called microglia and they respond to signals from the body and metabolic processes. Experimental evidence suggests that the intestinal microbiota is involved in the microglial maturation and functional regulation, strengthening a major link between microbial balance and immune surveillance in the central nervous system. (Erny et al., 2015).

Dysbiosis: Driven Factors, Characteristics And Effects

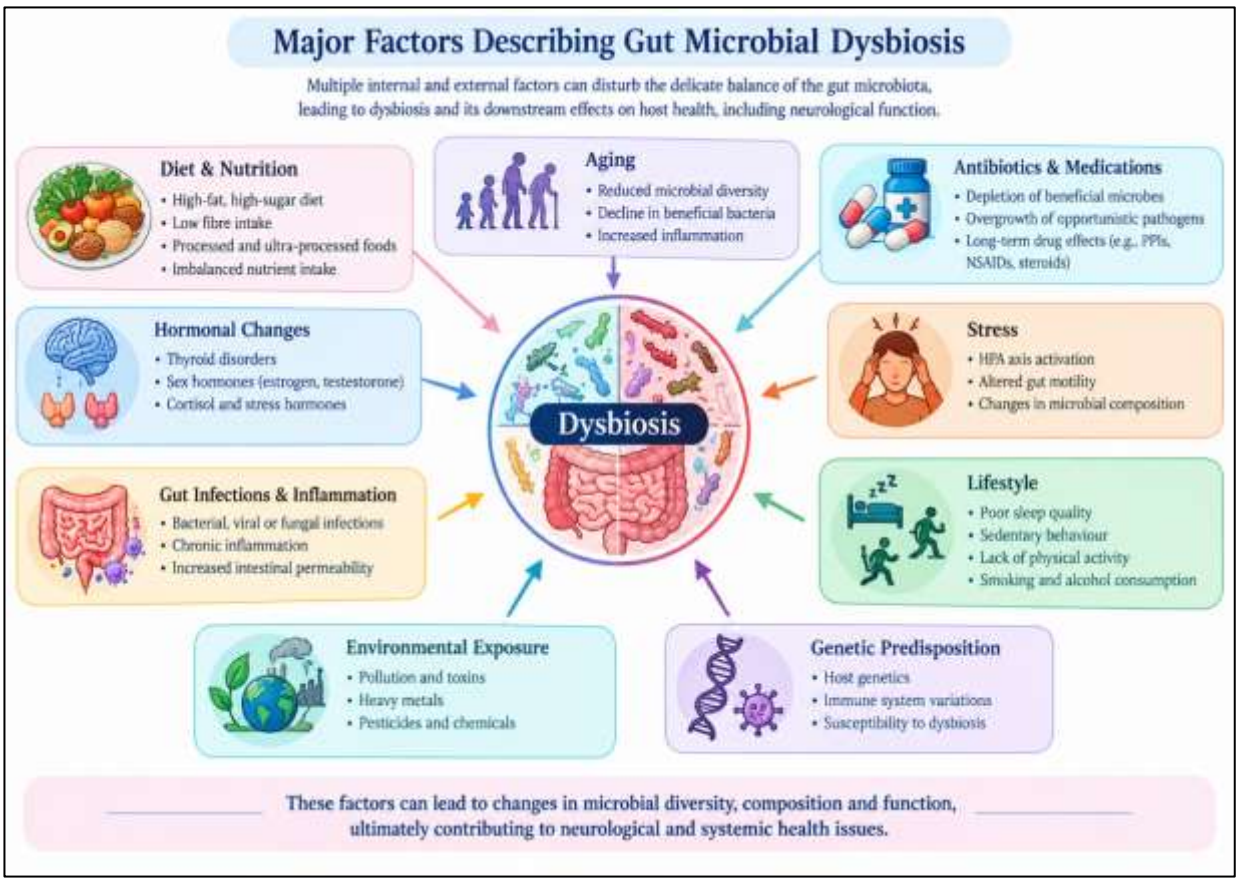
Dysbiosis is defined generally as any change in the composition, diversity and functional activity of the microbial community. Such a definition does not imply necessarily complete loss of beneficial microbes and the presence of "bad" microbial communities. Indeed, microbiome alterations are context dependent and might include changes in microbe population, community structure and metabolism.

Major Factors Driving Dysbiosis

Several factors such as environmental and host-specific characteristics could influence the microbiome in the gastrointestinal tract.

Since diet components supply the substrate for the growth and metabolism of the microbes, nutrition is one of the strongest influences. Although diets rich in processed foods and saturated fat could contribute to an inflammatory microbial environment, diets that contain high amounts of fiber are likely to favor the presence of SCFA-producing microbes (Holmes et al., 2020).

Antibiotic intake could be another important determinant. As antibiotics are needed in treating bacterial infections, antibiotics could change the balance of both beneficial and potentially pathogenic bacteria in the gastrointestinal tract while lowering microbial diversity. Changes in immune function and microbial metabolites could occur and could persist even after finishing antibiotic treatment (Ramakrishna & Patankar, 2023).



Age is another aspect highly associated with microbiome alterations. This dysbiosis can occur due to alterations in physiological conditions of the intestines, immunological conditions, drug use, nutrition, and microbial communities as one ages. The fact that aging predisposes an individual to neurodegeneration makes this point relevant to the development of neurological disease (Holmes et al., 2020).

Host genes, infections, drug use, lifestyle, geographical location, sleep disorders, and psychological stress can alter the microbiome composition. It is difficult to determine a "healthy" microbiome for every individual considering these factors (Vuotto et al., 2020).

Changes in Microbial Diversity and Composition

Dysbiosis includes changes in microbial diversity, which is studied quite often. Although some neurological diseases include changes in community structure without having diversity reduction, some others have been associated with reduced microbial diversity. It suggests that the functional capacity of the microbiome can play a more important role than diversity alone (Cryan et al., 2020).

Thus, for example, the first studies of Alzheimer's disease showed lower microbial diversity and differences in various bacteria when compared to age-matched individuals (Vogt et al., 2017). Changes in specific microbial community were also associated with the clinical symptoms of Parkinson's disease, such as gastrointestinal problems (Scheperjans et al., 2015).

Dysbiosis and Microbial Metabolites

Changes in bacterial abundance are not the only effects of dysbiosis. The synthesis of physiologically active metabolites, which serve as crucial messengers between the gut and the brain, can be altered by altered microbial populations. Microbial fermentation of dietary fiber is the primary source of short-chain fatty acids (SCFAs), specifically acetate, propionate, and butyrate. They can affect immunological responses, neuronal signaling, and gut epithelial health. Therefore, some of the gut microbiota's beneficial roles may be weakened by a decrease in SCFA-producing bacteria (Cryan et al., 2020).

Moreover, microorganisms participate in tryptophan metabolism through the production of indoles and influence the pathways associated with kynurenine and serotonin metabolism. The neuronal communication, emotions control, and the immune system of the gut can be affected by these metabolic pathways. Metabolite profiles that are neuroactive in nature may differ between individuals with or without depressive symptoms based on metagenomic studies in humans (Valles-Colomer et al., 2019).
Other microbial metabolites that might influence brain activity and systemic inflammation include bile acid derivatives, lipopolysaccharide (LPS), and trimethylamine metabolism-related products. Therefore, dysbiosis can alter the chemistry used by the stomach to communicate with the brain (Pusceddu & Del Bas, 2020).

Dysbiosis as a Potential Contributor to Neurological Disorders
The current evidence suggests that microbial dysbiosis may influence neurological health through several interconnected pathways:
Diet/environment → microbial alteration → changed microbial metabolites → intestinal barrier disruption → systemic immune activation → altered BBB signaling → neuroinflammation → neuronal dysfunction.
Biologically, the links between the gut bacteria and diseases such as depression, multiple sclerosis, Parkinson's disease, Alzheimer's disease, and others are understood through this model (Cryan et al., 2020; Holmes et al., 2020).
However, patient-to-patient variation is extensive. The constitution of the microbiome can vary due to age, diet, location, medication, disease progression, and genetics. Thus, modern studies pay more attention to the functions, metabolisms, and interaction between hosts and microbes rather than trying to find a particular "bad" or "good" microbe.

The Molecular Connections Between The Gut And Brain
The role played by the gut-brain axis in biology becomes evident upon a closer look at the molecular mechanisms underlying it.
4.1 Short-chain fatty acids
The main mechanism for the production of SCFAs such as acetate, propionate and butyrate relies on microbial fermentation of dietary carbohydrates and fibre.
These molecules might modulate the functioning of the intestinal epithelium, immune reactions and metabolic processes. In particular, butyrate has been suggested to play a specific role in these areas. SCFAs can also affect the brain indirectly through immune and hormonal mechanisms and possibly via glial cells.
Thus, the link between the diet, microbiota and neurological functioning has been identified. (Cryan et al., 2019).
4.2 Tryptophan Metabolism
Tryptophan is an essential amino acid which can undergo a number of metabolic transformations. Some of those are conducted by bacteria and other microorganisms living in the intestine and yield metabolites capable of interacting with the host organism.
One example of such interaction is AhR-mediated effects on immune and epithelial cells. (Agus et al., 2018).
4.3 Bile acid signaling
Primary bile acids produced by the host can undergo modification by microbes in the intestine to form secondary bile acids. The metabolites bind host receptors like FXR and TGR5 and impact metabolism and immunity.
Bile acid metabolism abnormalities have, therefore, become a novel research field in neurological conditions, especially neurodegenerative disease. (Appleton, 2018).
4.4 Neurotransmitter-related signaling
Gut microbes may be involved in the regulation or metabolism of neurotransmitter-related molecules like GABA, serotonin, dopamine, and glutamate.
However, it is unscientific to presume that the synthesis of a neurotransmitter by microbes in the gut necessarily means direct transport of the neurotransmitter to the brain. The physiological effects could be via precursor availability, immune signaling, enteroendocrine signaling, or neuronal signaling. Some recent reviews discuss the complex interplay between the metabolism by the microbiota and neurotransmitter regulation. (Cryan et al., 2019).
4.5 Neuroinflammation and microglia
Microglia function as immune surveillance cells in the CNS and are modulated by systemic immune and metabolic cues. Signals from the microbiota may modulate microglia maturation and activation.
This process plays an important role in neurodegenerative diseases in which the chronic presence of inflammation and glia abnormalities results in neuronal damage.
4.6 Oxidative stress and mitochondrial processes
Dysbiosis can result in redox imbalance through microbial products, inflammatory factors and host metabolism. Overproduction of oxidative stress may lead to cellular protein, lipid and nucleic acid damage and may be associated with mitochondrial dysregulation.
This suggests a possible pathogenic link between the impaired activity of intestinal microorganisms and neurological diseases that are associated with progressive neuronal dysfunction.

Dysbiosis In Neurological Disorders
There is now growing evidence to indicate that the alterations in the gut microbiome play an important role in a number of neurological disorders including but not limited to neurodegenerative, neuroinflammatory, cerebrovascular, seizure, neurodevelopmental, and neuropsychiatric disorders. Even though different diseases have their own unique microbial profile, some common features include decreased microbial diversity, reduction in short-chain fatty acid-producing

microorganisms, growth of pro-inflammatory bacteria, metabolic alterations, and compromise in the integrity of gut and blood brain barriers. (Nakhal et al., 2024; You et al., 2024).

5.1 Parkinson's disease

Parkinson's disease (PD) is primarily characterized by motor dysfunction resulting from the degeneration of dopaminergic neurons in the substantia nigra, although other symptoms such as gastrointestinal disorders and autonomic disorders may precede or occur simultaneously with motor symptoms.

Gastrointestinal tract has been given particular importance in the case of Parkinson's disease due to the occurrence of constipation and other gastrointestinal disorders years before the appearance of any motor dysfunction. Human gut microbiome studies have shown differences in fecal and mucosal microflora in patients with Parkinson's disease. Keshavarzian et al., (2015), for instance, have reported differences in the lower abundance of proposed butyrate producers such as Blautia, Coprococcus, and Roseburia as well as an increased abundance of pro-inflammatory bacteria in the case of Parkinson's disease patients.

However, whether the change in the microbiome starts Parkinson's disease or appears as a consequence of the disease development is still unknown.

5.2 Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative dementia and is characterized by progressive cognitive decline, amyloid-β accumulation, tau pathology, synaptic dysfunction, neuroinflammation, and neuronal loss. Increasing evidence suggests that the gut microbiota may influence several of these pathological processes through immune, metabolic, and barrier-related mechanisms.

Amongst the earliest studies conducted by humans, which established a connection between Alzheimer's disease and gut microbe alteration was one that found the presence of differential gut microflora in individuals with cognitive decline relative to those without. Changes in the gut bacteria community were associated with markers for amyloid pathology and systemic inflammation, pointing towards a possible correlation between changes in gut microorganisms and biological features of AD, and not just cognitive impairment (Vogt et al al., 2017).

Potential mechanisms might include increased intestinal permeability, inflammatory signaling in the body, alterations in the microbiota's metabolites, and effects on microglia and neurons. Metabolites from the bacteria such as LPS might stimulate inflammation, while alterations in the SCFAs and other metabolites might influence the microglia function and neuronal balance. Hence, gut dysbiosis might create an inflammatory environment that contributes to AD progression (Morais et al., 2021; Loh et al., 2024).

5.3 Multiple Sclerosis

Multiple sclerosis is characterized by immune-mediated destruction in the central nervous system. As microorganisms in the intestine have such a strong interaction with immune system development and regulation, dysbiosis has become an important research area.

A systematic review of the literature on the MS microbiome revealed consistent taxonomic patterns, such as reduced levels of Prevotella, Faecalibacterium prausnitzii, and certain Bacteroides species, alongside elevated levels of Akkermansia muciniphila and Methanobrevibacter in multiple studies. However, most studies failed to show consistent differences in overall alpha diversity, suggesting that MS-related dysbiosis may stem from alterations in particular taxa or microbial functions rather than a broad reduction in diversity (Tremlett et al., 2017).

Even more importantly, there are experiments that provided some clues on possible functionality of the role of the gut flora. As reported by Berer et al., in 2017, it has been found that the microbiota from multiple sclerosis patients can trigger the development of autoimmune encephalomyelitis in mice that have genetic susceptibility to this condition. Also, as reported by Cekanaviciute et al., in 2017, it was found that the gut bacteria of multiple sclerosis patients could influence human T-cells and contribute to exacerbation of the disease.

5.4 Autism Spectrum Disorder

The research on ASD has found the altered composition of the microbiota in the intestine and various gastrointestinal disorders in some patients. Proposed mechanisms include microbial metabolites, immune signaling, gut permeability, and neurodevelopmental pathways.

However, the results are complicated due to the dietary restrictions, medication, and gastrointestinal symptoms that could also have an effect on the microbial composition. Therefore, microbiome alteration cannot be used as a biomarker of ASD.

5.5 Depression and Anxiety

Research has also been conducted regarding psychiatric conditions using the Microbiota–Gut–Brain Axis concept. Stress can affect the physiological functioning of the gut and the composition of the microorganisms, whereas products produced by the microorganisms can affect the immune response, the hormonal response and the neural signals.

This interaction could be bi-directional:

Stress → change in physiological functioning of the gut → change in microorganisms → change in signaling mechanisms → effect on stress responses

5.6 Epilepsy

Epilepsy entails recurrent seizures that are not caused by external stimuli and arise from aberrant neuronal network activities. Research increasingly shows that the nature of the gut microbiome and its metabolism may impact neuronal excitability and seizure susceptibility.

In a systematic review and meta-analysis done in 2025 comprising 16 case-control studies, significant disparities were observed in the microbiome of people suffering from epilepsy and healthy subjects. While there was no difference in the alpha diversity across studies, beta diversity was different in most of the studies that had measured it. In the meta-analysis results, levels of Verrucomicrobia increased, while Roseburia, Blautia, and Dialister were significantly lower (Mousavi et al., 2025).

The gut microbiota could affect susceptibility to seizures by influencing microbial metabolites, neurotransmitter pathways, immune signaling, and the integrity of the intestinal barrier. The ketogenic diet serves as a particularly significant example of how the microbiome interacts with the brain, as its antiseizure effects may stem not only from direct metabolic impacts on neuronal energy use but also from changes in gut microbial makeup and function.

From Correlation To Causation: How Reliable Is The Evidence?

Despite the fact that many studies have shown that patients with neurological illnesses and healthy people have different gut microbiota, a crucial question still has to be answered: are these microbial alterations a cause of disease, a result of disease, or both? It is challenging to distinguish actual biological effects from variables like nutrition, medicine, age, lifestyle, and illness severity because the majority of human research are observational. As a result, dysbiosis by itself cannot prove a causative connection (Lubomski et al., 2022; Zancan et al., 2024).

Evidence Supporting a Causal Role

Experimental research serves as the strongest evidence that gut microbiota influences the function of brain. Indeed, there is evidence from research involving microbiota transplantation that the microbial composition of MS patients could influence the immune system responses of animals (Berer et al., 2017; Cekanaviciute et al., 2017). This proves that changes in the gut microbiota may be both indicative and functional.

Mendelian randomization (MR) studies have provided additional evidence for possible causal relationships lately. By applying genetic markers which have a relationship with microbial traits as instrumental variables, Mendelian randomization reduces certain problems of conventional observational studies. Some clusters of gut microbes have been connected to multiple sclerosis, as reported by Zancan et al. (2024). Nevertheless, it is necessary to say that further investigation should confirm these results on other and more independent samples. According to MR studies, some gut microbes might be causally connected with Alzheimer's disease (Chen et al., 2024; Ning et al., 2024). These results prove the idea that some microbial traits might influence the probability of neurological disorders rather than accompany them.

Evidence from Longitudinal Studies

Because longitudinal studies enable the tracking of microbial changes over time, they are very useful. Lubomski et al. (2022) found permanent changes in a number of microbial groups in Parkinson's disease, including decreased representation of certain bacteria that produce SCFA. Nevertheless, there was insufficient evidence linking these microbial alterations to the advancement of the illness to prove that dysbiosis is the primary cause of neurological decline. This draws attention to a significant limitation: changes in food, medicine, gastrointestinal function, or other disease-related factors may still have an impact on microbial alterations that occur before or throughout the course of the disease.

6.3 Intervention Studies: The Critical Test

The evidence from intervention studies could be considered the most convincing evidence for causality. The biological significance of the involvement of dysbiosis can be proven by showing that changes in the microbiome result in improvements in the neurological outcomes.

In one of the recent randomized clinical trials of FMT in patients with Parkinson's disease, despite the clear effects of FMT on the microbiota, the treatment did not lead to clinically significant improvement in the neurological symptoms in comparison with a placebo group (Scheperjans et al., 2024). Also, after the intervention of FMT, some improvements in non-motor symptoms were observed in another randomized study, but there was no effect on the motor symptom of Parkinson's disease (Figura et al., 2026).

Why Causality Remains Difficult to Establish

Analysis of the existing literature becomes challenging for several reasons. The geographical region, nutrition, age, medications, genetics, and lifestyle will all influence the gut microbiota, and the differences from one person to another can be huge. Some other factors that may affect the microbial community in neurological disorders include the impaired intestinal motility, lack of physical activity, difficulties with swallowing, and the prolonged administration of medications. The focus of the microbiome analysis on the abundance of bacteria rather than their role in the body becomes another issue. The metabolic activity of the bacterial genera may not necessarily change together with the change in the number of bacteria. Hence, using metagenomics, metabolomics, immune profiling, and clinical data together may lead to more insightful analysis.

Therapeutic Manipulation Of Gut-Brain Axis

The growing body of evidence connecting gut dysbiosis to neurological disorders has spurred the creation of therapies aimed at the microbiome. These approaches seek to restore microbial balance, alter microbial metabolites, enhance intestinal barrier function, and modulate neuroimmune signaling (Loh et al., 2024; Wadan et al., 2025).

7.1 Dietary intervention

One of the most potent environmental factors affecting microbial communities and their functioning is diet. Dietary patterns including various plant fibers, fruits, vegetables, whole grains, and plant-derived foods can serve as substrates for fermentation and production of SCFAs.

Therefore, instead of elimination of particular organisms, it would be possible to stimulate proper functioning of microbes in the ecosystem. (Mann et al., 2024).

7.2 Probiotics, Prebiotics, and Synbiotics

Probiotics are live microorganisms intended to provide a health benefit when consumed in adequate amounts. They demonstrate strain specificity which means that the effect demonstrated by some probiotic strains does not necessarily apply to all other strains. Common probiotic genera include Lactobacillus, Bifidobacterium, and Saccharomyces. Their proposed mechanisms encompass altering microbial composition, generating bioactive metabolites, strengthening intestinal barrier function, modulating immune responses, and influencing gutbrain communication.

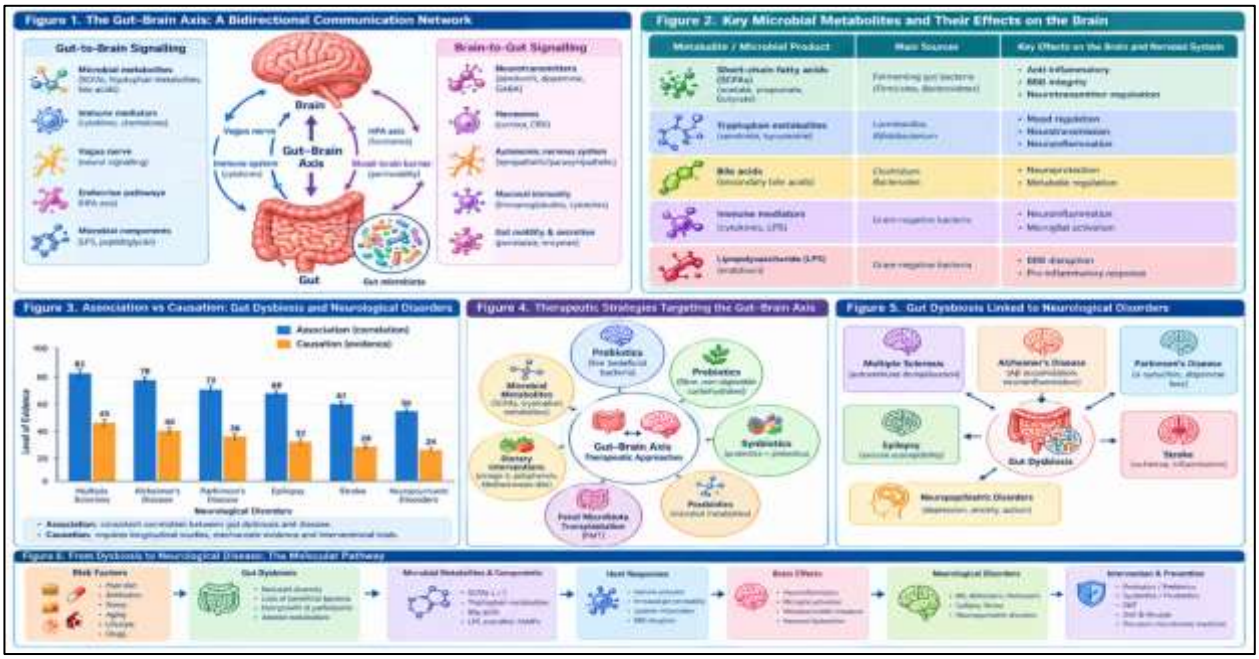
whereas prebiotics are substrates selectively utilized by beneficial microorganisms. A combination of the two is commonly referred to as a synbiotic.

These approaches may influence the gut–brain axis by modifying microbial composition, increasing beneficial metabolites, strengthening the intestinal barrier, and regulating immune responses. Some studies have reported improvements in selected neurological or psychological outcomes, although the results are not yet consistent enough to consider these approaches as universal treatments (Wadan et al., 2025).

7.3 Postbiotics and Microbial Metabolites

Interest is increasingly shifting from live bacteria toward their beneficial products, often referred to as postbiotics. These include microbial metabolites and other non-living microbial components that can affect host physiology.

SCFAs, tryptophan-derived compounds, and bile acid derivatives are particularly important because they can influence immune cells, epithelial barriers, microglia, and neuronal signaling. Targeting specific microbial metabolites may eventually provide a more controlled therapeutic strategy than changing the entire microbial community (Park & Kim, 2021; Zhuang et al., 2024)



7.4 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) involves transferring microorganisms from a screened donor to the gastrointestinal tract of a recipient. The approach has demonstrated strong clinical value for recurrent Clostridioides difficile infection and is now being investigated for other conditions, including neurological disorders.

In neurological research, FMT is being explored as a method of restoring microbial communities and altering microbial metabolites. However, evidence for neurological indications remains preliminary, and issues related to donor selection, long-term safety, standardisation, and patient response must be addressed before routine clinical use (Loh et al., 2024).

7.5 Emerging Microbiome-Based Approaches

Newer strategies are moving toward precision microbiome therapy. These include targeted bacterial supplementation, bacteriophages, engineered microorganisms, and interventions designed to increase or suppress specific microbial metabolic pathways.

The future of microbiome therapy may therefore not involve simply "adding good bacteria." Instead, treatment could be personalised according to an individual's microbial composition, metabolic profile, disease stage, diet, and immune status. Multi-omics technologies may help identify the patients most likely to benefit from a particular intervention (You et al., 2024; Wadan et al., 2025).

Precision Microbiome Medicine And Omics

A single treatment using microbiome may not work effectively on all patients because of individual variation in gut bacteria composition. The emergence of precision microbiome medicine that considers microbial composition, microbial function, host characteristics, lifestyle, and clinical factors to aid in diagnosis and treatment has been on the rise for this reason (Ratiner et al., 2024).

8.1 From Microbial Composition to Microbial Function

The main purpose of initial microbiome studies was to assess whether certain bacteria were abundant or rare during disease states. Nevertheless, the biological processes are not defined only by the prevalence of certain bacteria. Given that various microorganisms can perform similar metabolic functions, the shift in the bacterial composition does not necessarily affect the level of microbial activity (Ou et al., 2023).

In this context, instead of focusing on the specific bacterial strain, it might be more useful to look for markers of biological processes that occur during the development of neurological diseases.

8.2 Role of Multi-Omics Approaches

Combining several levels of biological data through multi-omics allows obtaining a more complete view of the gut-brain axis. Where metatranscriptomics describes gene expression in microbes, metagenomics identifies microbes and their gene capacity. In contrast to metabolomics, which examines the metabolites available in the biological samples, proteomics provides data on proteins and biological pathways (Moraes et al., 2022).

It is possible to connect microbial change with its effect on functions through the integration of the datasets. For example, reduction of some bacteria may be connected with changes in genes responsible for SCFA synthesis, resulting in changes in metabolites or inflammatory molecules in circulation. The systems approach may provide a more compelling explanation of the biological process compared to the approach based only on the taxonomic profile (Moraes et al., 2022; Ma et al., 2024).

8.3 Artificial Intelligence and Microbiome-Based Biomarkers

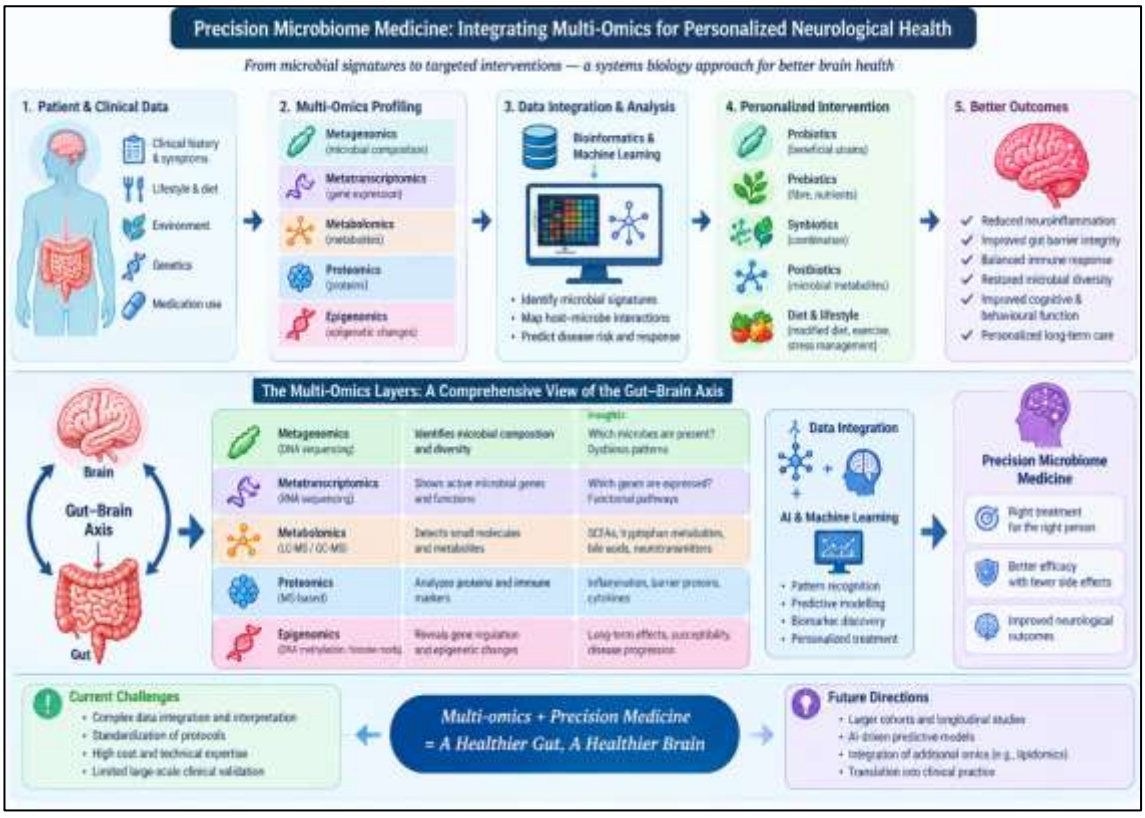
Machine learning techniques have been made possible by virtue of the huge and complicated datasets generated by multi-omics studies. The algorithms can predict the response of patients, uncover microbial signatures associated with diseases, and perhaps also classify individuals based on their physiological characteristics.

However, accuracy of predictions in one population is no guarantee of similar results in another population. Factors that affect the performance of the model include diet differences, ethnicity, geographical location, drug usage, sequencing methodology, and disease characteristics. Therefore, the validation of microbiome prediction models prior to application as a therapeutic tool is essential (Ratiner et al., 2024; Ou et al., 2023).

8.4 Toward Individualized Therapy

In the future, depending on the microbiological profile and metabolism of the patients, people having the same neurological disorder can be given different types of microbiome-based treatments. This process can be performed through the use of microbiome profiling, metabolomics, immunological profiling, and clinical presentation in order to prescribe an optimal course of treatment for the individual.

This approach represents a new trend towards the transition from a rather general "healthy microbiome" concept to the more realistic goal of restoring the specific functionalities of certain microbes depending on individual needs. Nevertheless, before the usual clinical application, further clinical studies should be conducted because precision microbiome medicine is relatively new (Ratiner et al., 2024; Ma et al., 2024).



Challenges, Controversies, And Translational Issues

The development of research related to the gut-brain axis has progressed at a fast pace. However, there are various challenges that have been encountered when trying to apply findings regarding the microbiome in treatment. The problem lies not in the absence of connections, but in the difficulty in determining if the results are replicable and physiologically important (Ou et al., 2023; Ma et al., 2024).

9.1 High Inter-Individual Variability

The differences between individuals in terms of gut bacteria are very important. The bacterial structure can be affected by many different factors such as age, diet, geographical location, genetics, medication, lifestyle, and the environment. Therefore, microbial markers observed in one population may not be observed in another population (Ratiner et al., 2024).

In terms of neurological diseases, the above statement becomes very important as patients can have different problems related to their gastrointestinal tract.

9.2 Methodological and Technical Differences

Even similar samples could give different microbiomes because of the differences in sample preparation, DNA isolation methods, sequencing technologies, bioinformatics tools, and statistical approaches used. Moreover, shotgun metagenomics could provide more precise data about the gene content of microbial communities, while 16S rRNA sequencing gives mainly taxonomic data (Ou et al., 2023).

Consequently, direct comparison of results between studies could be complicated by the use of different approaches to analyze data. To make research more reproducible, standardization is necessary.

9.3 Correlation, Causation, and Confounding

One of the main barriers is the difficulty of identifying cause-and-effect relations. Microbiome alteration in a patient with epilepsy, Parkinson's disease, or Alzheimer's disease might be associated not only with the disease but also with medication, food intake, reduced mobility, and other aspects.

In this respect, it is important to take into account all the confounding factors like age, gender, body mass index, food, antibiotic treatment, gastrointestinal symptoms, alcohol intake, and medication when conducting microbiome research (Ou et al., 2023). Longitudinal research and experimental confirmation will help determine if the microbial changes occurred before the development of the disease.

9.4 Lack of Universal Microbial Signatures

There is currently no widely recognized microbial profile that can accurately diagnose a severe neurological disease, despite the fact that a number of bacterial taxa have been frequently linked to neurological disorders. Even opposing changes in the same bacterial group may be reported by different investigations.

This implies that the presence or lack of specific bacterial species may not be as closely linked to neurological diseases as changed microbial functions and metabolic networks (Ma et al., 2024).

CONCLUSION

All these biological systems – the gastrointestinal tract, microbiome, immune system, metabolic pathway, and the central nervous system – are interconnected through the gut-brain axis, which has become a highly significant biological network. Recent scientific findings suggest that alterations in the microbial ecology of the gut may influence the immune response signaling, the intestinal barrier function, the blood-brain barrier function, production of microbial metabolites, and neuro-inflammation. This interaction helps explain the role played by gastrointestinal diseases in the development of neurological disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, stroke, and neuropsychiatric diseases.

Nevertheless, there is a complex relationship between gut dysbiosis and brain diseases. Apart from being a potential cause of brain pathology, factors such as changes in diet, drug intake, age, gastrointestinal system function, lifestyle, and physiological changes related to disease may affect disease-linked microbial changes. For this reason, the finding of certain microbial signatures should not necessarily imply causation. The separation between the two concepts needs more attention to the role of microbes, their metabolic pathways, and host-microbe relationships.

The gut–brain axis may be therapeutically adjustable, according to encouraging research on food modification, probiotics, prebiotics, synbiotics, postbiotics, microbial metabolites, and fecal microbiota transplantation. However, the translation of these techniques into standardized neurological therapeutics is still limited by variations in patient characteristics, microbiome makeup, treatment procedures, and clinical outcomes. Thus, multi-omics, mechanistic experiments, well-controlled intervention trials, and longitudinal clinical investigations should all be included in future research.

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