Neuroscience Research and Clinical Practice

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Review

The Gut-Brain Axis: Emerging Molecular Insights and Therapeutic Opportunities in Neurological Disorders

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Abstract

The microbiota-gut-brain axis (MGBA) represents a pivotal communication network in human health, and its disruption is increasingly implicated in the pathophysiology of neurological disorders. The primary objective of this review is to provide a critical synthesis of the molecular mechanisms governing this connection and its therapeutic implications. We systematically evaluate the neural, immune, endocrine, and metabolic pathways that mediate gut-brain communication. Furthermore, we analyze and synthesize evidence from primary clinical and preclinical studies to assess the role of gut dysbiosis in the pathogenesis of Parkinson's disease, Alzheimer's disease, multiple sclerosis, and autism spectrum disorder. Finally, we critically examine the current landscape of microbiome-targeted therapies, including probiotics, dietary modifications, and fecal microbiota transplantation. By integrating current research, this review identifies key knowledge gaps and highlights the transformative potential of targeting the gut microbiome as a novel therapeutic strategy for neurological disorders.

Keywords

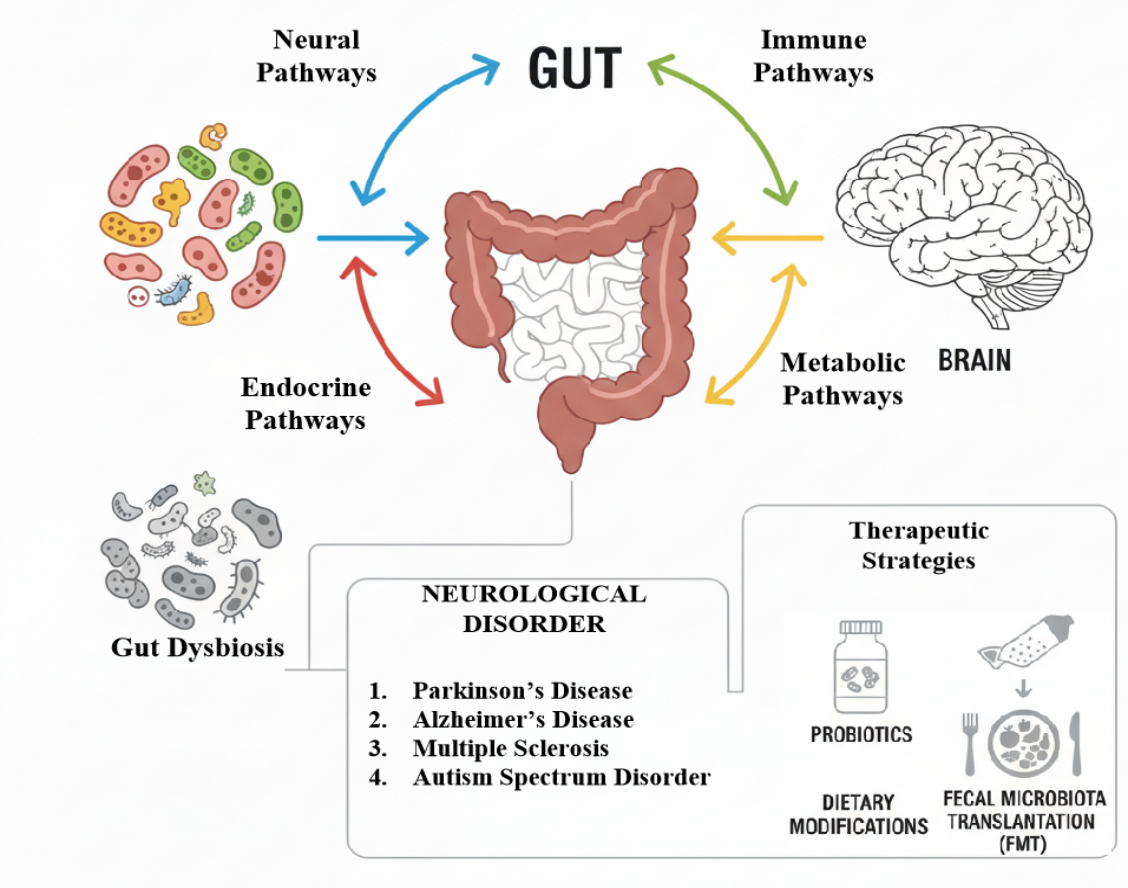
Gut-brain axis, Microbiota, Neuroinflammation, Short-chain fatty acids, Parkinson's disease, Alzheimer's disease, Multiple sclerosis, Autism spectrum disorder

Article History

Received: 8 September 2025 Revised: 28 September 2025

Accepted: 13 November 2025 Available Online: 25 November 2025

Graphical Abstract



1. Introduction

A paradigm shift is occurring in neuroscience that challenges the traditional, neurocentric view of brain health. This emerging perspective emphasizes an integrated model that recognizes the profound influence of peripheral systems, particularly the gastrointestinal (GI) tract, on brain function and disease [1]. The gut microbiota, consisting of over 100 trillion microorganisms, is now recognized as a critical regulator of host physiology [2,3]. Due to its extensive and complex neural architecture, the enteric nervous system (ENS) is often referred to as a "second brain" and continuously interacts with the central nervous system (CNS) in both directions [4]. This communication network, the microbiota-gut-brain axis (MGBA), has catapulted to the forefront of neuroscience research, revealing that the gut's microbial inhabitants can influence neural development, brain chemistry, and a wide array of behaviors [5,6]. Early clinical evidence for this gut-brain interaction emerged from observations of patients with hepatic encephalopathy, whose neurological symptoms improved significantly following treatment with oral antibiotics. This suggested that gut-derived factors could profoundly impact brain function. [7]. Today, the focus has sharpened on the microbiota itself as a master regulator within this axis, shifting the paradigm toward a holistic view where gut health and brain health are inextricably linked [8]. The MGBA represents a bidirectional signaling network that connects the gut and brain, ensuring the maintenance of homeostasis [9]. This network is not a single pathway but a multifaceted system comprising several core anatomical and physiological components [10].

The CNS and the ENS form the core components of this axis. The ENS, often referred to as the "brain of the gut," contains millions of neurons, enabling it to function both autonomously and in coordination with the CNS [11]. Communication between these neural centers is mediated by the autonomic nervous system (ANS), with its sympathetic and parasympathetic branches, including the vagus nerve, which forms a primary physical conduit [12]. Superimposed on this neural framework is the hypothalamic-pituitary-adrenal (HPA) axis, the primary stress-response system, which both shapes and is shaped by the gut microbiota [13].

This bidirectional network enables the brain's cognitive and emotional centers to regulate gut motility, secretion, and immunity, while microbial signals from the gut influence brain function, mood, and behavior. The rapid expansion of research into the MGBA has unveiled a wealth of molecular details and therapeutic possibilities [14]. This review summarizes current knowledge by outlining the mechanisms underlying gut–brain communication, assessing evidence linking MGBA dysfunction to major neurological disorders, and evaluating therapeutic strategies aimed at modulating the gut microbiota. Schematic representation of the microbiota–gut–brain axis, showing bidirectional communication between the gut and CNS *via* neural, immune, and metabolic routes.

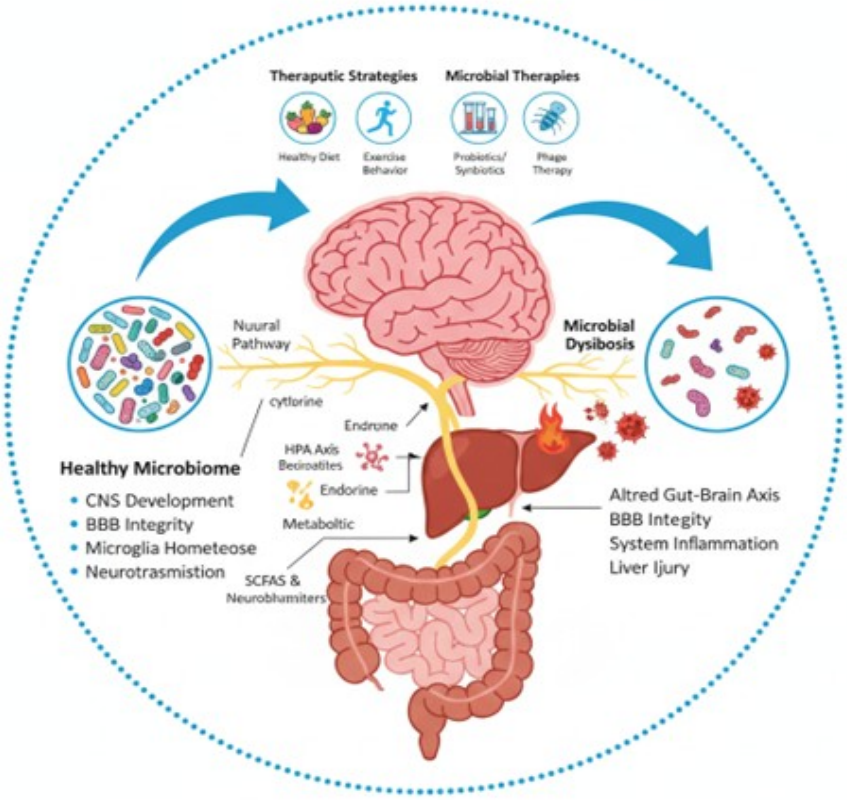


Figure 1. Schematic illustration of the MGBA. A healthy microbiome maintains CNS development, blood-brain barrier integrity (BBB), and overall homeostasis through signaling via neural, immune, and metabolic pathways. Conversely, dysbiosis (microbial imbalance) can drive systemic inflammation and impair neuronal signaling, contributing to neurodegenerative disorders. Interventions such as diet, probiotics, and other therapeutics can restore microbial balance, highlighting the potential of modulating the gut microbiota to prevent and manage neurological diseases [15].

2. Methodology

This review is grounded in an extensive evaluation of the scientific literature, drawing on a systematic search of PubMed, Scopus, and Web of Science to identify original studies, meta-analyses, and reviews published in the past two decades [16-18]. Search terms included "gut-brain axis," "microbiota," "dysbiosis," "neuroinflammation," "neurodegeneration," "short-chain fatty acids," "probiotics," and specific neurological disorders such as "Parkinson's disease," "Alzheimer's disease," "multiple sclerosis," and "autism spectrum disorder [19,20]."

The selected literature, primarily original research, was critically evaluated to synthesize a contemporary understanding of the molecular mechanisms of gut-brain communication, the nuanced role of microbial imbalance in neurological disease pathogenesis, and the efficacy and limitations of emerging microbiome-targeted therapies [21,22]. The information was organized to provide a logical progression from fundamental mechanisms to clinical implications and future therapeutic outlooks [23].

2.1 The Architecture of Gut-Brain Communication: Molecular Pathways and Mediators

Communication between the gut microbiota and the brain occurs via four interconnected molecular pathways that work in concert to translate microbial signals into physiological responses within the CNS [24]. The entire gut-microbiota-ENS complex can be conceptualized as a highly sophisticated chemosensory organ, where the gut lumen represents an internal environment rich with chemical information derived from diet and microbial activity [25, 26]. The microbiota functions as a metabolic bioreactor, converting these inputs into a complex chemical language of SCFAs, neurotransmitters, and other signaling molecules [27]. The ENS and vagus nerve then act as the transduction machinery, converting these chemical signals into neural impulses relayed to the brain [28]. This reframes the MGBA from a simple communication link to a dynamic, integrated sensory system that constantly informs the brain about the host's internal metabolic and inflammatory state [29]. The brain's capacity to rapidly modulate the microbiota represents a feedback loop to fine-tune this sensory input, creating a highly responsive and adaptive system [30].

2.1.1 Neural Pathways

The most direct route of communication is through neural connections, with the cranial nerve X, or vagus nerve, serving as the primary information "superhighway" between the gut and brainstem [31]. The vagus nerve, composed of roughly

80% afferent and 20% efferent fibers, enables the CNS to continuously monitor the gut's luminal environment [32]. The critical role of this nerve is underscored by studies in which the neurochemical and behavioral effects of certain probiotics are nullified in vagotomized mice [33]. Complementing this is the ENS, an intricate network of neurons within the gut wall that serves as a critical relay station, integrating signals from the microbiota and transmitting them to the CNS [34]. This communication is profoundly bidirectional, as demonstrated by recent studies showing that the brain can exert rapid, top-down control over the gut's microbial landscape [35]. Activation of specific neurons in the hypothalamus can reshape the gut microbiota within hours, highlighting a sophisticated feedback loop where the brain not only responds to gut signals but actively prepares the gut environment for anticipated nutritional states [36].

2.1.2 Immune Pathways

Gut microorganisms play a central role in shaping the host's immune defenses, making immune modulation an essential mechanism of gut-brain interactions, especially regarding neuroinflammatory processes [37]. Disruption of gut microbial balance, known as dysbiosis, can weaken the intestinal barrier and lead to increased permeability commonly referred to as "leaky gut." This enables microbial molecules such as lipopolysaccharide (LPS) to cross into the bloodstream, promoting systemic inflammation [38]. Systemic inflammation can impair the BBB, permitting the infiltration of inflammatory molecules and immune cells into the brain tissue, which may contribute to neurological dysfunction [39]. This process is mediated by microglia, whose maturation and function are dependent on the gut microbiota [40]. Inflammatory signals originating from a dysbiotic gut can lead to prolonged activation of microglia, which fosters a neurotoxic environment contributing to neuronal injury in neurodegenerative diseases such as Alzheimer's and Parkinson's [41].

2.1.3 Endocrine Pathways

The endocrine system provides another vital communication channel, with the HPA axis at its core. This system, which orchestrates the body's response to stress, is in constant bidirectional communication with the gut microbiota [13]. Chronic stress is known to alter microbial composition, while the microbiota itself plays a fundamental role in calibrating the HPA axis, as demonstrated by studies in germ-free mice which exhibit an exaggerated stress response [42]. Beyond the HPA axis, the emerging field of "microbial endocrinology" recognizes that bacteria can both produce and respond to host neurochemicals, allowing for a direct and intimate level of crosstalk [43]. Certain gut bacteria synthesize neuroactive compounds that stimulate enteroendocrine cells to release hormones such as peptide YY and glucagon-like peptide-1. These hormones regulate appetite and communicate signals to the brain, influencing the host's endocrine functions, including stress response and mood regulation [44].

2.1.4 Metabolic Pathways

One of the most direct ways the microbiota influences the brain is through producing neuroactive molecules that can act locally, circulate systemically, and even cross the BBB to affect brain function [45]. Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are key metabolites produced by bacterial fermentation of dietary fibers. These SCFAs have significant physiological effects and play an important role in gut-brain communication [46]. These potent signaling molecules act as master regulators of the MGBA, strengthening the intestinal barrier, exerting profound anti-inflammatory effects, and directly reinforcing the BBB by increasing the expression of tight junction proteins [9]. However, their effects can be context-dependent, as some evidence suggests they might promote neuroinflammation in specific pathological contexts [47]. The gut microbiota also possesses the remarkable ability to synthesize major neurotransmitters [43]. An estimated 90–95% of the body's serotonin, a key regulator of mood, is produced in the GI tract in a process critically dependent on the microbiota [48]. Similarly, bacterial species like *Lactobacillus* and *Bifidobacterium* can produce In animal models, GABA, the CNS's main inhibitory neurotransmitter, can lessen anxiety-like behaviours [49]. Dopamine, norepinephrine, and acetylcholine are produced by other bacteria and have potent local effects on the ENS. They also activate the vagus nerve, which further affects host neurophysiology [50].

3. Gut Dysbiosis in the Pathogenesis of Neurological Disorders

Disruptions to the homeostatic balance of the MGBA are increasingly implicated in the development and progression of various neurological disorders [51]. A common theme emerges across these diseases: a shift away from a diverse, anti-inflammatory microbial community toward a pro-inflammatory state that compromises barrier functions and promotes neuroinflammation [52].

3.1 Parkinson's Disease

A particularly strong link exists between the gut and Parkinson's disease (PD), as GI symptoms like constipation often precede motor symptoms by decades [53-55]. This observation supports the "gut-first" theory, which posits that the pathological buildup of misfolded α-synuclein protein may begin in the ENS and spread to the brain via the vagus nerve [56]. Consistent evidence from patient studies reveals gut dysbiosis in PD, often characterized by a decrease in beneficial, short-chain fatty acid (SCFA)-producing bacteria like *Faecalibacterium* and *Roseburia* [57]. However, it's important to note that the specific microbial signatures reported often vary between studies, which may be attributable

to differences in methodology, patient genetics, or dietary confounders. This microbial imbalance is thought to promote chronic inflammation via bacterial components like LPS and increase intestinal permeability, creating an environment that facilitates the initial misfolding and aggregation of α-synuclein [58,59]. A key limitation of the current human research is its correlational nature, making it difficult to determine if dysbiosis is a cause or a consequence of PD pathology.

3.2 Alzheimer's Disease

The MGBA also plays a significant role in the pathophysiology of Alzheimer's disease (AD), the most prevalent form of dementia, which is characterized by amyloid-beta (Aβ) plaques and tau tangles [60,61]. Clinical studies consistently report that AD patients have lower microbial diversity and a higher prevalence of pro-inflammatory bacteria, alongside a reduction in beneficial, butyrate-producing taxa [62]. A primary proposed mechanism is the increase in intestinal and BBB permeability caused by dysbiosis, which allows pro-inflammatory bacterial molecules like LPS to enter the bloodstream and co-localize with Aβ plaques in the brain. This triggers chronic neuroinflammation, a major factor in AD progression, by promoting the activation of microglia. Additionally, some gut bacteria generate amyloid proteins that could potentially cross-seed Aβ aggregation through molecular mimicry, thereby accelerating the pathological cascade [63]. This hypothesis, while intriguing, is primarily supported by preclinical data and requires further validation in clinical settings.

3.3 Multiple Sclerosis

The role of the gut microbiota in multiple sclerosis (MS), a chronic inflammatory and demyelinating disease of the CNS, is increasingly acknowledged for its ability to disrupt immune balance in favor of autoimmunity [64]. Studies have identified distinct microbial alterations in MS patients, frequently involving an imbalance in bacterial populations that regulate T-cell differentiation [65]. The microbiota of MS patients may favor the growth of pro-inflammatory Th1 and Th17 cells—key initiators of the autoimmune attack on myelin—over anti-inflammatory regulatory T-cells (Tregs) [64]. However, the specific microbial taxa responsible for this immune shift are not yet fully consistent across studies, suggesting that the functional output of the microbiome may be more important than the presence of specific species. This immune imbalance, combined with increased intestinal permeability, may enable microbial antigens to enter the bloodstream and trigger or worsen the autoimmune response against CNS components, possibly through molecular mimicry [66].

3.4 Autism Spectrum Disorder

The connection between the MGBA and autism spectrum disorder (ASD) highlights the importance of the gut microbiota during critical early-life neurodevelopmental windows [67]. Individuals with ASD have a high frequency of GI issues and exhibit a unique gut microbial composition marked by decreased diversity and changes in specific genera, such as an increase in some species of *Clostridium* and a decrease in *Bifidobacterium* [68-70]. This early-life dysbiosis is significant because microbial signals are essential for neurodevelopmental processes like synaptic pruning and microglial maturation [71,72]. A key proposed mechanism involves the metabolic consequences of dysbiosis, such as the overproduction of microbial metabolites like propionate [73]. High levels of propionate have been shown to induce ASD-like behaviors in rodent models, indicating direct neurotoxic effects that may alter brain connectivity and function during crucial developmental stages. While these preclinical findings are significant, the translational relevance of rodent models to the complex human etiology of ASD remains a subject of ongoing investigation and a key limitation in the field [74].

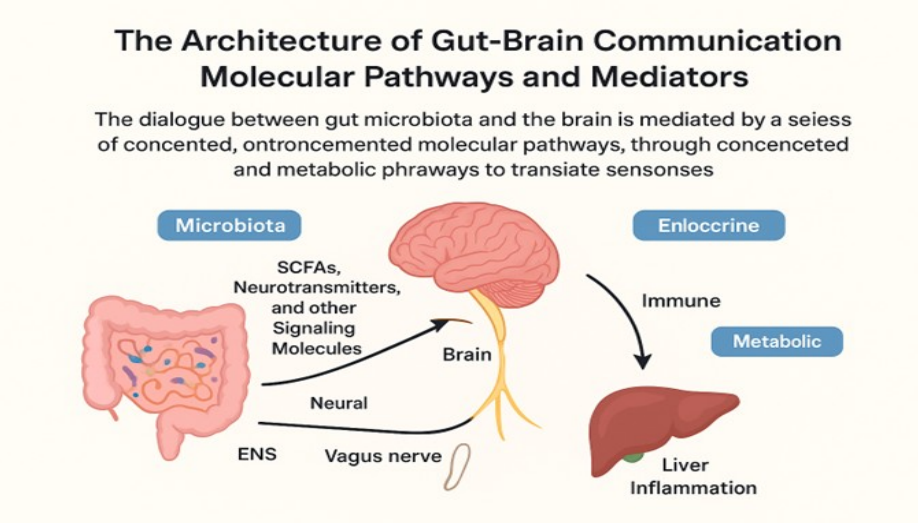


Figure 2. Gut microbiota-mediated communication with the brain and its implications in disease. This diagram illustrates how the gut microbiota produces various metabolites, neurotransmitters, and hormones that communicate signals via the ENS, vagus nerve,

immune system, and HPA to influence brain function. Interruptions in these signaling pathways can lead to inflammation, compromised barrier integrity, and the development of neurological diseases.

Table 1. Comparative Analysis of Gut Microbiota Alterations in Major Neurological Disorders. This table summarizes key microbial changes and the associated pathophysiological mechanisms linked to gut dysbiosis in PD, AD, MS, and ASD.

Table 1. Comparative analysis of gut microbiota alterations in major neurological disorders.

Disorder	Key Microbial Changes	Associated Pathophysiological Mechanisms
PD	Increased: *Akkermansia*, *Lactobacillus*, *Bifidobacterium*. Decreased: SCFA-producing genera, e.g., *Faecalibacterium*, *Roseburia*, *Prevotellaceae*.	Reduced butyrate production leading to increased intestinal permeability ("leaky gut"). Mucin layer degradation. Systemic inflammation (LPS). Promotion of α-synuclein misfolding and aggregation in the ENS and propagation to the CNS *via* the vagus nerve (Braak hypothesis) [75]
AD	Increased: Pro-inflammatory taxa, e.g., *Proteobacteria*, *Bifidobacterium*. Decreased: Overall diversity. Anti-inflammatory/butyrate-prod ucing taxa, e.g., *Firmicutes*, *Clostridiaceae*, *Lachnospiraceae*.	Increased intestinal and BBB permeability. Systemic inflammation driven by bacterial components (LPS, bacterial amyloids). Chronic microglial activation and neuroinflammation. Potential promotion and cross-seeding of Aβ plaque formation [76]
MS	Altered ratios of specific taxa, variable but often involving changes in *Prevotella*, *Bacteroides*, and *Clostridia* clusters.	Immune dysregulation: shift in T-cell balance favouring pro-inflammatory Th1/Th17 cells over anti-inflammatory Tregs. Increased intestinal permeability allowing microbial antigens to trigger or exacerbate autoimmune responses against myelin, possibly *via* molecular mimicry [77]
ASD	Increased: *Clostridium*, Overall diversity. Key beneficial genera, e.g., *Bifidobacterium*, *Prevotella*.	Disruption of critical early-life windows. Altered production of neuroactive microbial metabolites (e.g., excess propionate from *Clostridium* with potential neurotoxic effects). Increased gut permeability and immune dysregulation leading to systemic and neuroinflammation [78]

4. Therapeutic Frontiers: Targeting the Gut Microbiota for Brain Health

An intriguing new therapeutic avenue has been made possible by our increasing understanding of the MGBA's function in neurological disorders [79]. If gut dysbiosis can drive or exacerbate brain pathology, then restoring a healthy microbial ecosystem holds the potential to prevent, slow, or even treat these debilitating conditions [80]. Therapeutic strategies are rapidly evolving, moving from broad-spectrum interventions to more targeted and personalized approaches [81]. Interventions such as probiotics (live beneficial microorganisms), prebiotics (substrates that fuel beneficial microbes), and synbiotics (combinations of both) aim to counteract dysbiosis and modulate the MGBA [82]. Certain probiotic strains, often termed "psychobiotics," can help restore intestinal barrier integrity, compete with pathogens, produce beneficial metabolites, and reduce systemic and neuroinflammation [83]. Probiotic supplementation has been linked to better cognitive function in AD and fewer symptoms in PD, according to preliminary clinical trials [84]. More extensive, carefully monitored clinical trials are required to confirm these findings because the effects are highly strain-specific and the outcomes have been mixed.

A more thorough method is faecal microbiota transplantation (FMT), which involves transferring an entire microbial community from a healthy donor [85]. Its remarkable success in treating recurrent *Clostridioides difficile* infection provides a powerful proof-of-concept [86]. For neurological disorders, FMT is still in early stages, but initial results are intriguing [87]. Open-label trials in ASD have reported significant and long-lasting improvements in both GI and behavioral symptoms, while small studies in PD and MS have suggested potential benefits [88].

FMT has challenges despite this promise, such as the requirement for standardised procedures, guaranteeing long-term safety, and the difficulty of excluding placebo effects in the absence of sizable, double-blind, randomised controlled trials [89]. Diet is one of the most significant and readily modifiable factors that influences the gut microbiome, making it a cornerstone strategy for targeting the MGBA [90]. Beneficial dietary patterns, such as the Mediterranean diet, are rich in plant-based fibers and polyphenols. These compounds function as prebiotics, supporting the growth of beneficial, SCFA-producing bacteria and fostering high microbial diversity [91]. This supports brain function, lowers systemic inflammation, and preserves the integrity of the gut barrier [92].

Conversely, the "Western" dietary pattern, which is low in fiber and high in processed foods, is associated with gut dysbiosis, chronic inflammation, and an increased risk for neurological conditions like AD and PD [93]. Beyond modifying the microbes themselves, a more direct therapeutic strategy involves targeting the essential molecules the microbiota uses to communicate with the host [94]. This approach includes the administration of purified microbial metabolites, often termed "postbiotics." For instance, direct supplementation with butyrate is a promising avenue for

neurological disorders, given its crucial role in strengthening the intestinal and BBB and reducing neuroinflammation [95]. This could offer a more consistent and pharmacologically controllable therapeutic effect, bypassing the complexities of altering the entire microbial ecosystem. While still largely in the preclinical stage for neurological applications, the development of such metabolite-based therapies represents an exciting evolution toward a new generation of targeted, microbiome-inspired pharmaceuticals [96].

5. Conclusion and Future Directions

The MGBA is a complex, two-way communication network that has revolutionized our knowledge of neurological health and illness. It is now well established that the gut microbiota plays a crucial role in maintaining CNS homeostasis through a complex language of immunological, neurological, endocrine, and metabolic signals. A therapeutic landscape where interventions aimed at restoring microbial balance offer novel and promising avenues for treating brain disorders has been revealed by the strong evidence that links gut dysbiosis to the pathophysiology of debilitating neurological disorders. Even though the field is expanding at an exponential rate, there are still many obstacles to overcome before this promise can be realized in clinical settings. A primary challenge in the field is to establish causality beyond mere correlation, as it is often difficult to determine whether dysbiosis is a primary driver of disease pathogenesis or a secondary consequence of the underlying pathology. The translational gap between preclinical animal models and the enormous complexity of the human condition is a second significant obstacle. Lastly, a "one-size-fits-all" strategy for microbiome modification is unlikely to be successful due to the significant inter-individual variability of the human microbiome. The future of MGBA research will be defined by its ability to overcome these challenges through innovation and a commitment to precision. The path forward will likely involve a move toward personalized, microbiome-based medicine, using deep, multi-omics profiling to design tailored interventions. The development of next-generation probiotics, or "live biotherapeutics," and the refinement of postbiotic therapies will offer more controlled and predictable pharmacological effects. Ultimately, successfully leveraging the MGBA will require a more holistic and integrative approach to neurological care, where microbiome diagnostics and targeted therapies are integrated into standard treatment protocols. While the journey from fundamental discovery to widespread clinical application is long, the potential to improve the lives of millions suffering from neurological disorders by targeting the gut is a prospect of profound significance.

Acknowledgements

The authors would like to acknowledge Lovely Professional University, Phagwara for continuous support and encouragement.

Author Contributions

Kamaljeet Singh: Writing, Conceptualization. Suman Samanta: Writing, review & editing. Rakesh Chandra Kalita: Preparation of figures and graphical illustrations. Saminesh Kumar: Methodology, Formal analysis. Shivank Sharma: Visualization, Validation, Supervision.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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