RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 4, Issue 3, 2026

A COMPREHENSIVE REVIEW OF THE MICROBIOTA-GUT-BRAIN AXIS IN NEUROLOGICAL DISORDERS: MECHANISTIC FOUNDATIONS, CLINICAL PATHOLOGIES, AND THERAPEUTIC FRONTIERS

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DOI: http://doi.org/10.5281/zenodo.19060628

Received	Accepted	Published
17 January 2026	27 March 2026	17 March 2026

ABSTRACT

Background: *The microbiota-gut-brain axis (MGBA) is increasingly recognized as a central regulatory network dictating central nervous system (CNS) homeostasis and neurodevelopment. This review examines the shift from taxonomic associations to causative molecular mechanisms, highlighting the gut's role as a neurobiotic sensor.*

Methods: *The article synthesizes recent studies from utilizing databases like; PubMed and Google Scholar, regarding bidirectional signalling pathways neural, immune, and metabolic that facilitate gut-brain communication. The search span takes around 3 months to study and identify the research gap across the present literature. We then, evaluate clinical correlations and therapeutic efficacy of interventions like probiotics and fecal microbiota transplantation (FMT) in neurodegenerative and psychiatric disorders.*

Results: *Mechanistically, vagal neuropods enable real-time microbial sensing, while dysbiosis compromises the blood-brain barrier (BBB), priming microglia for neuroinflammation. Metabolically, short-chain fatty acids (SCFAs) regulate epigenetic and immune responses. Pathologically, Alzheimer's is linked to lipopolysaccharide-driven amyloid aggregation, and Parkinson's to gut-first alpha-synuclein propagation. Clinically, probiotics significantly reduce depression and anxiety symptoms, while FMT demonstrates potential in improving Parkinson's symptoms and slowing Amyotrophic lateral sclerosis functional decline.*

Conclusion: *The MGBA represents a critical, modifiable target for neurological health, transitioning from theoretical research to clinical application. While artificial intelligence driven diagnostics and precision nutrition offer promise early intervention, large-scale randomized trials are essential to standardize therapeutic protocols.*

Keywords: *Brain-Gut-Axis; Alzheimer disease; Parkinson disease; Depression; Amyotrophic lateral sclerosis; Blood Brain Barrier; Artificial Intelligence.*

INTRODUCTION

The conceptualization of the human body as a supra-organism, harboring a complex symbiotic ecosystem of trillions of microorganisms, has fundamentally disrupted the traditional silos of neurology, immunology, and gastroenterology. The microbiota-gut-brain axis (MGBA) is no longer viewed as a peripheral interest but as a central regulatory network that dictates central nervous system (CNS) homeostasis, neurodevelopment, and the trajectory of neurodegenerative disease [Stanimirov et al., 2025]. This bidirectional communication system operates through an intricate web of neural, endocrine, immune, and metabolic signalling pathways, enabling the gut microbiota to serve as a biological sensor and transducer of environmental and dietary inputs into neurological outputs [Faysal et al., 2025; Ataei et al., 2025]. As research progresses into 2025 and 2026, the focus has shifted from mere taxonomic associations to the elucidation of causative molecular mechanisms, identifying how specific microbial metabolites and neuroactive compounds penetrate the blood-brain barrier (BBB) to modulate microglial phenotypes, synaptic plasticity, and protein aggregation [Yuan et al., 2026; Petrut et al., 2025; Chen et al., 2025]. Refer to **Table 1.**

The bidirectional nature of the MGBA is facilitated by a sophisticated hardware-software architecture that ensures constant feedback between the gastrointestinal (GI) tract and the brain. While the brain regulates GI motility, secretion, and intestinal barrier function via autonomic and neuroendocrine pathways, the gut reciprocates by influencing mood, cognition, and neuroinflammation through "bottom-up" signalling [Yuan et al., 2026; Stanimirov et al., 2025]. The vagus nerve (cranial nerve X) represents the primary physical highway of the MGBA. Historically understood as a slow conduit for satiety signals and autonomic regulation, 2025 research has unveiled its role as a high-speed, real-time sensory system [M. Maya Kaelberer 2026]. Vagal afferent fibers, which constitute approximately 80% of the nerve's composition, do not interact directly with the gut lumen; rather, they synapse with specialized cells known as neuropods. These neuropods act as sensor cells that detect microbial patterns in real-time. For instance, the detection of bacterial flagellin via the Toll-like receptor 5 (TLR5) on these neuropods triggers a neural message that reaches the brain within milliseconds, effectively acting as a neurobiotic sense that informs the CNS of the microbial landscape and influences behaviors such as appetite suppression [Yuchen et al., 2025; M. Maya Kaelberer 2026].

The structural diversity of vagal sensory endings, including intra ganglionic laminar endings in the myenteric plexus, intramuscular arrays serving as stretch receptors, and mucosal endings at the tips of villi, allows the vagus nerve to integrate mechanical, chemical, and microbial signals [Global Rph.com, *accessed on 21st February*]. This neural interface is complemented by the enteric nervous system (ENS), often termed the second brain, which operates semi-independently but remains in continuous dialogue with the CNS to regulate local immune responses and neurotransmitter release [Ataei et al., 2025].

Table 1: Structural and Functional Components of the Neural Gut-Brain Highway

Component	Anatomical Location	Primary Signalling Modality	Neurological/Behavioral Impact
Vagal Afferents (80%)	Intestinal mucosa to Brainstem	Rapid neural firing (60-800ms)	Real-time satiety, mood regulation, and microbial sensing.
Vagal Efferent (20%)	Brainstem to GI tract	Cholinergic signalling	Suppression of pro-inflammatory cytokines; regulation of motility.
Neuropods	Colonic lining	TLR5-mediated flagellin sensing	Neurobiotic sense; millisecond-range appetite regulation.
Enteric Nervous System	Intestinal wall layers	Local neurotransmitter (GABA, 5-HT)	Semi-autonomous control of gut-brain feedback loops.
Enteroendocrine Cells	Gut epithelium	Hormonal (CCK, GLP-1) and synaptic	Integration of metabolic and neural signals to the CNS.

THE IMMUNE-MEDIATED CONDUIT: MICROGLIAL PRIMING AND BARRIER INTEGRITY

The gut is the largest immune organ in the body, and the MGBA serves as a critical regulator of systemic and central immunity. Dysbiosis, or the disruption of microbial eubiosis, triggers the activation of peripheral immune cells, leading to a cascade of pro-inflammatory cytokines such as Interleukin-6 (IL-6), IL-17, and Tumor Necrosis Factor-alpha (TNF- α) [Petrut et al., 2025; Global Rph.com, *accessed on 21st February*]. These cytokines can travel through the bloodstream or signal via the vagus nerve to impact the brain's immune milieu. A hallmark of this interaction is the compromise of the blood-brain barrier (BBB). Elevated systemic lipopolysaccharide (LPS), derived from the outer membrane of Gram-negative bacteria, activates TLR4 receptors on the BBB, increasing its permeability and allowing the infiltration of peripheral immune cells and inflammatory mediators into the CNS [Silva et al., 2020].

Once inside the CNS, these signals drive microglial activation. Microglia, the resident macrophages of the brain, exist in a physiological state (M0) where they maintain immune homeostasis and synaptic plasticity [Ren et al., 2025]. However, chronic systemic inflammation driven by gut dysbiosis "primes" these cells toward an M1 pro-inflammatory phenotype. This shift contributes to a cerebral inflammatory milieu characterized by oxidative stress and neurodegeneration [Petrut et al., 2025; Global Rph.com, *accessed on 21st February*]. Conversely, beneficial microbial metabolites like short-chain fatty acids (SCFAs) are essential for the proper maturation and anti-inflammatory polarization of microglia, highlighting the gut's role in maintaining the brain's innate immune balance [Qian et al., 2022]. The physiological influence of the gut microbiota is largely exerted through their vast metabolic repertoire. These microorganisms produce molecules that serve as ligands for host receptors, epigenetic modulators, and neurotransmitter precursors, effectively bridging

the gap between the gut lumen and the neuronal synapse [Stanimirov et al., 2025].

SHORT-CHAIN FATTY ACIDS (SCFAS): THE EPIGENETIC AND METABOLIC MASTER REGULATORS

SCFAs, primarily acetate, propionate, and butyrate, are generated through the anaerobic fermentation of dietary fibers [Silva et al., 2020; Fock and Parnova 2023]. Their role in the MGBA is multifaceted, involving both direct and indirect pathways:

- **Direct Pathway:** SCFAs like acetate can cross the BBB and enter the brain parenchyma, where they are metabolized by microglia into tricarboxylic acid (TCA) cycle intermediates, thereby restoring mitochondrial function and maintaining the "immunological competence" of these cells [Cao et al., 2025].
- **Indirect Pathway:** SCFAs bind to G-protein-coupled receptors (GPCRs) such as GPR41, GPR43, and GPR109A on peripheral immune cells and the intestinal epithelium, triggering signaling cascades that reduce systemic inflammation and strengthen the intestinal barrier [Silva et al., 2020].
- **Epigenetic Modification:** Butyrate, in particular, acts as a potent inhibitor of histone deacetylases (HDACs). By inhibiting the deacetylation of lysine residues such as H3K9 and H3K18, butyrate promotes the expression of neurotrophic factors and anti-inflammatory genes, effectively reprogramming the brain's response to injury or disease [Cao et al., 2025]. Refer to **Table 2** for further details.

Table 2: Functional Comparison of Major Short-Chain Fatty Acids in the MGBA

Metabolite	Primary Mechanism of Action	CNS/Neurological Effect	Key Research Finding
Acetate (C2)	Crosses BBB; enters TCA cycle	Restores mitochondrial function in microglia	Metabolized directly by CNS cells to maintain energy balance.
Propionate (C3)	FFAR2/3 activation; Th17 suppression	Reduces autoimmune neuroinflammation	Decreases infiltration of IL-17-producing cells into the CNS.
Butyrate (C4)	HDAC inhibition; GPR109A binding	Enhances synaptic plasticity; strengthens BBB	Promotes tight junction protein expression (ZO-1, Claudin-1).

BILE ACIDS AND THE NEUROENDOCRINE INTERFACE

Beyond their roles in digestion, bile acids have emerged as potent signalling molecules in the MGBA. Primary bile acids are converted by gut bacteria into secondary bile acids, which act as ligands for the farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor 1 (GPBAR1/TGR5). These receptors are expressed throughout the CNS and participate in the regulation of neuroinflammation, thermogenesis, and energy homeostasis. Recent studies suggest that microbial modulation of the bile acid pool influences hypothalamic regulation of appetite and cognitive processes, linking metabolic health to neurological function [Fock and Parnova 2023; Stanimirov et al., 2025].

TRYPTOPHAN METABOLISM AND THE KYNURENINE TRAP

The gut microbiota significantly influences the bioavailability of tryptophan, an essential precursor for serotonin (5-HT) and melatonin. Under the eubiotic conditions, a balance is

maintained between the serotonin pathway and the kynurenine pathway. However, dysbiosis-driven inflammation induces enzymes like indoleamine 2,3-dioxygenase (IDO), diverting tryptophan away from serotonin synthesis and toward the kynurenine pathway [Ataei et al., 2025]. This diversion leads to two pathological outcomes: a deficit in serotonin, contributing to depression and anxiety, and the accumulation of neurotoxic metabolites such as quinolinic acid, which causes NMDA-mediated excitotoxicity and neuronal death [Luo 2025]. The onset and progression of neurodegenerative diseases are increasingly linked to specific microbial signatures and functional deficits in metabolite production. The multi-hit model suggests that gut dysbiosis acts as a chronic source of pathological signals that exacerbate central neuroinflammation and protein misfolding [Chen et al., 2025; KRUSZEWSKA et al., 2025].

ALZHEIMER'S DISEASE (AD): THE LPS-AMYLOID NEXUS

Alzheimer's disease is characterized by the accumulation of amyloid-beta (*Aβ*) plaques and tau tangles. Current research suggests that gut microbiota alterations promote *Aβ* pathology through several mechanisms. Patients with AD often show a decrease in the Firmicutes/Bacteroidetes ratio and a reduction in beneficial taxa like *Bifidobacterium* and *Akkermansia* [Pfaffinger et al., 2025; KRUSZEWSKA et al., 2025].

The reduction in *Akkermansia* is of particular interest, as its abundance is negatively correlated with brain *Aβ* levels [Ren et al., 2025]. Concurrently, an increase in pro-inflammatory taxa such as *Escherichia/Shigella* leads to higher systemic LPS levels. LPS not only facilitates *Aβ* aggregation but also impairs the BBB, allowing inflammatory cytokines to further activate microglia and inhibit the phagocytic clearance of *Aβ* plaques. Animal models demonstrate that fecal transplantation from AD-model mice into healthy recipients can transmit memory deficits and increase *Aβ* burden, underscoring the potential causal role of the gut microbiota [Chen et al., 2025; Ren et al., 2025].

PARKINSON'S DISEASE (PD): THE GUT-FIRST HYPOTHESIS AND ALPHA SYNUCLEIN PROPAGATION

The gut-first hypothesis of Parkinson's disease posits that α-synuclein misfolding begins in the enteric nervous system (ENS), triggered by gut dysbiosis or toxins, and subsequently spreads to the brain via the vagus nerve [KRUSZEWSKA et al., 2025]. This is supported by the fact that non-motor symptoms, particularly chronic constipation, often precede motor symptoms by up to 20 years [Chen et al., 2025].

The microbial signature of PD includes a significant reduction in SCFA-producing bacteria such as *Prevotella* and *Roseburia*, alongside an increase in *Enterobacteriaceae* and *Akkermansia muciniphila* [KRUSZEWSKA et al., 2025]. While *Akkermansia* is typically beneficial, its overabundance in PD may indicate a compensatory response to mucus layer thinning, which exposes the ENS to pro-inflammatory signals. Furthermore, elevations in kynurenine and reductions in butyrate create a neuroinflammatory environment that promotes the death of dopaminergic neurons in the substantia nigra. The MGBA is essential for the trajectory of brain development, and early-life perturbations in the microbiota can have long-lasting consequences on behavior and mental health [Silva et al., 2020]. Refer to **Table 3** for pathogenesis and comparison between neurological conditions.

Table 3: Comparative Microbial Signatures and Pathological Mechanisms

Disease	Characteristic Microbial Shifts	Metabolic/Immune Impact	Primary Pathological Link
Alzheimer's	↓ *Bifidobacterium*, ↑ *Proteobacteria*	↑ LPS, ↓ Butyrate	Microglial activation; *Aβ* plaque accumulation.
Parkinson's	↓ *Prevotella*, ↑ *Enterobacteriaceae*	↑ Kynurenine, ↓ SCFAs	α-synuclein misfolding in ENS; vagal spread.
Multiple Sclerosis	↓ *Clostridium* cluster XIVa, ↓ Firmicutes	↑ IL-17, ↓ Immune tolerance	TH17-mediated breakdown of immune tolerance.
ALS	Altered SCFA-producing taxa	↓ Regulatory T-cells (Tregs)	Neuroinflammation; rapid functional decline.

AUTISM SPECTRUM DISORDER (ASD): MATERNAL INFLUENCE AND METABOLITE TOXICITY

ASD is characterized by social deficits and repetitive behaviors, frequently accompanied by severe GI disturbances [Chen et al., 2025]. Research highlights the role of the maternal microbiome during pregnancy; maternal immune activation (MIA) can disrupt neurogenesis and synaptogenesis in the fetus via cytokine signalling [Silva et al., 2020].

Children with ASD often exhibit dysbiosis characterized by a higher Firmicutes/Bacteroidetes ratio and elevated levels of *Clostridium* species [Valencia-Buitrago et al., 2025]. A specific microbial metabolite, 4-ethylphenylsulfate (4EPS), has been implicated in inducing anxiety-like behaviors in ASD models. Furthermore, disruptions in the production of GABA and serotonin by gut taxa like *Lactobacillus* and *Bifidobacterium* contribute to the excitatory/inhibitory imbalance often seen in ASD [Hughes et al., 2018]. Interestingly, some studies suggest that these microbiota differences may be partially driven by the restrictive dietary preferences of children with ASD, suggesting a complex bidirectional relationship [Valencia-Buitrago et al., 2025; Kadiyska et al., 2025].

DEPRESSION, ANXIETY, AND THE HPA AXIS

The Hypothalamic-Pituitary-Adrenal (HPA) axis is the brain's primary stress response system, and its dysregulation is a hallmark of depression and anxiety. Gut microbes help regulate corticosterone rhythms and influence time-specific stress responsivity [Gut Microbiota for Health.com, *accessed on 21st February*]. Dysbiosis-induced intestinal permeability allows the translocation of bacterial endotoxins, which activate the HPA axis and promote chronic systemic inflammation [Petrut et al., 2025]. Meta-analyses of psychiatric patients reveal significant reductions in the abundance of beneficial taxa like *Faecalibacterium*, which are known for their anti-inflammatory properties and ability to maintain gut barrier integrity [Zhang et al., 2025].

THERAPEUTIC STRATEGIES AND MICROBIOME MODULATION

The therapeutic landscape of neurology is being transformed by interventions that target the MGBA, including probiotics, prebiotics, dietary modification, and fecal microbiota transplantation.

1. PROBIOTICS AND PSYCHOBIOTICS IN CLINICAL PRACTICE

Probiotics are being rigorously tested for their ability to restore microbial balance and alleviate neurological symptoms. Refer to **Table 1**. Strains that confer mental health benefits are categorized as 'psychobiotics' [Jafari et al., 2025; Fekete et al., 2024].

Clinical trials in 2024 and 2025 have yielded promising results across several conditions:

- **Depression and Anxiety:** Systematic reviews involving over 2,800 participants for depression and 2,100 for anxiety demonstrate that probiotic and prebiotic interventions significantly reduce symptom severity compared to placebo [Zhang J et al., 2025].
- **Cognitive Impairment:** In AD and MCI patients, 12 weeks of probiotic supplementation (typically multi-strain formulations including *Lactobacillus* and *Bifidobacterium*) improved MMSE scores, increased BDNF levels, and reduced oxidative stress markers [Yuchen et al., 2025; Ma et al., 2025].
- **Epilepsy:** Probiotic adjunct therapy has been shown to significantly reduce seizure frequency and duration, potentially by increasing the seizure threshold through microglial modulation and normalized neurotransmitter synthesis [Tan et al., 2025].

Table 4: Clinical Efficacy of Probiotic Interventions in Neurological Health

Condition	Intervention Type	Primary Outcome Measure	Statistical Impact (SMD/RR)
Depression	Probiotics/Prebiotics/ Synbiotics	Depressive Symptoms	SMD = -0.53 ($p < 0.001$).
Anxiety	Probiotics/Prebiotics/ Synbiotics	Anxiety Scores	SMD = -0.44 ($p < 0.001$).
AD/MCI	Single/Multi-strain Probiotics	MMSE (Cognitive Function)	SMD = 0.52 to 0.88.
Epilepsy	Probiotic Combination	Clinical Efficacy Rate	RR = 1.16 ($p < 0.00001$).
Sleep Disorders	Probiotics	Sleep Quality Index	SMD = -0.39 ($p < 0.001$).

2. DIETARY MODULATION AND PRECISION NUTRITION

Dietary interventions represent a scalable and low-risk approach to modulating the MGBA. The Mediterranean and DASH diets, which prioritize high fiber and phytochemical intake, are robustly associated with reduced neuroinflammation and improved cognitive aging [Luo 2025].

Recent breakthroughs in precision nutrition focus on individualized responses to diet. For instance, the *A. muciniphila/R. ilealis* ratio has been identified as a sex-specific biomarker for cognitive response to metformin and dietary change in males [Bagheri et al., 2026]. Furthermore, the Dietary Index for Gut Microbiota (DI-GM) has demonstrated a linear correlation between gut-healthy dietary scores and cognitive performance in elderly populations, suggesting that dietary modifications can directly counteract age-related cognitive decline [Sun et al., 2025; Alaeddin et al., 2025].

3. FECAL MICROBIOTA TRANSPLANTATION (FMT): RECONSTITUTING THE NEURAL ECOSYSTEM

FMT is emerging as a potent tool for 'resetting' the gut microbiome in severe neurodegenerative conditions. By transferring the diverse microbial community of a healthy donor to a patient, FMT aims to restore eubiosis and reduce the source of pathological neuroinflammatory signals. Evidence regarding neurological diseases showed:

- **Parkinson's Disease:** Systematic reviews of trials involving 104 patients show improvements in UPDRS and Non-Motor Symptom Scale (NMSS) scores. Responders typically showed an increase in alpha diversity and a rise in beneficial genera like *Blautia* and *Roseburia* [Chen et al., 2025; ClinicalTrials.gov. NCT03808389, *accessed on February 21, 2026*].
- **Amyotrophic Lateral Sclerosis (ALS):** Trials have demonstrated that FMT is safe and may slow functional decline, particularly in bulbar and respiratory symptoms, by increasing the number of neuroprotective regulatory T-cells [ClinicalTrials.gov. NCT03766321. *Accessed on February 21, 2026*].
- **Multiple Sclerosis:** A landmark case study of combined FMT (colonoscopy followed by 3 months of daily oral capsules) reported significant neurological improvements, including reduced spasticity and better fine motor skills, coinciding with a peak in microbiota eubiosis at 90 days [Bibbò et al., 2025].

FUTURE DIRECTIONS: AI-DRIVEN DIAGNOSTICS AND PERSONALIZED MEDICINE

The trajectory of MGBA research is moving toward a highly mechanistic, biomarker-driven future. The traditional "bacterial count" approach is being replaced by an understanding of complex metabolic networks and nutrient exchanges that support whole-body wellness [DSM-Firmenich.com, *accessed on February 21, 2026*]. The integration of artificial intelligence is revolutionizing the early detection of neurological diseases. AI models trained on millions of medical images and longitudinal microbiome data can now predict the onset of AD and PD with over 95% precision, years before the first clinical signs appear [DSM-Firmenich, *accessed on February 21, 2026*]. These tools enable a shift from reactive to proactive care, where 'personalized probiotic therapies' are tailored to a patient's unique microbial composition to prevent disease progression [Gut Microbiota for Health.com, *accessed on February 21, 2026*].

NANOTECHNOLOGY AND TARGETED DELIVERY

Innovation in drug delivery is utilizing the gut as a gateway to the brain. Researchers are developing microbially derived nanoparticles, microbiota-modulating hydrogels, and engineered 'living therapeutics', probiotics that have been genetically modified to produce specific neuroactive compounds at precise locations in the GI tract [GlobalRph.com, *accessed on February 21, 2026*]. These technologies offer a way to bypass the BBB and deliver therapeutic agents with high specificity and minimal systemic toxicity [Ugwu et al., 2025].

IMPLICATIONS FOR MENTAL HEALTH AND SOCIETY

The recognition of the 'neurobiotic sense' and the role of the gut in real-time mood and appetite regulation suggests that societal mental health may be intrinsically linked to dietary quality and microbial diversity [GlobalRph.com, *accessed on February 21, 2026*]. As the Western diet and urban lifestyle continue to deplete microbial richness, targeted interventions that restore the MGBA may become essential public health strategies for combating the global rise in neurodevelopmental and neurodegenerative disorders [Fekete et al., 2024].

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The expanding understanding of the microbiota–gut–brain axis (MGBA) has substantial implications for clinical neurology and psychiatry. Accumulating evidence indicates that gut microbial communities function as active regulators of neuroimmune signaling, metabolic homeostasis, and neurotransmitter synthesis.

Through the production of bioactive metabolites including short-chain fatty acids (SCFAs), bile acid derivatives, and tryptophan metabolites intestinal microbiota influence blood–brain barrier integrity, microglial activation, and synaptic plasticity, thereby shaping neurological health and disease susceptibility [Silva et al., 2020; Cao et al., 2025; Stanimirov et al., 2025]. These findings position the gut microbiome as a dynamic and modifiable therapeutic target for a wide spectrum of neurological and neuropsychiatric conditions. In clinical practice, microbiome-modulating strategies are increasingly being investigated as adjunctive or disease-modifying interventions [Li et al., 2025]. Probiotic and psychobiotic formulations have demonstrated beneficial effects in several disorders, including depression, anxiety, cognitive impairment, and epilepsy, where restoration of microbial balance appears to reduce systemic inflammation and normalize neuroactive metabolite production [Zhang et al., 2025; Tan et al., 2025; Jafari et al., 2025]. Similarly, dietary interventions that promote microbial diversity particularly fiber-rich dietary patterns such as the Mediterranean and DASH diets have been associated with improved cognitive resilience and reduced neuroinflammatory burden [Zhang R et al., 2025; Luo, 2025; Sun et al., 2025]. These strategies highlight the potential for scalable, lifestyle-based approaches to complement pharmacological treatment in neurological disease management. More intensive microbiome-directed interventions are also emerging. Fecal microbiota transplantation (FMT) has shown promising early results in neurodegenerative disorders, including Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis, where restoration of microbial diversity has been associated with improvements in clinical symptoms and inflammatory profiles [Chen et al., 2025; Bibbò et al., 2025]. Although these findings remain preliminary, they suggest that large-scale microbial ecosystem restoration may influence disease trajectories in conditions traditionally viewed as irreversible neurodegenerative processes. However, clinical translation requires standardized donor screening, optimized delivery protocols, and rigorous long-term safety monitoring before FMT can be broadly implemented in neurological practice.

Future advances in MGBA research will likely be driven by integrative technologies that combine microbiome science with precision medicine. Multi-omics platforms including metagenomics, metabolomics, and transcriptomics are enabling increasingly detailed characterization of microbial–host interactions and disease-specific microbial signatures [Ataei et al., 2025; Petrut et al., 2025]. These datasets, when integrated with clinical imaging and genetic information, may facilitate the development of predictive biomarkers capable of identifying individuals at risk for neurodegenerative diseases long before clinical onset. Artificial intelligence and machine-learning approaches are further accelerating this transition toward predictive neurology. Emerging computational models trained on large microbiome datasets have demonstrated the capacity to predict neurodegenerative disease risk and progression with high accuracy, suggesting that microbiome-based diagnostics may soon complement traditional neurological assessments [DSM-Firmenich.com, *accessed on February 21, 2026*]. Such predictive frameworks could enable early preventive interventions, including targeted microbiome modulation, dietary strategies, or personalized probiotic therapies tailored to an individual's microbial profile.

Innovative therapeutic technologies are also being explored to refine microbiome-based treatment strategies. Engineered probiotics capable of producing specific neuroactive compounds, microbiota-derived nanotherapeutics designed to bypass the blood–brain barrier, and microbiome-responsive drug delivery systems represent emerging approaches that may enhance treatment precision and therapeutic efficacy [Ugwu et al., 2025]. These next-generation interventions aim to directly manipulate gut-derived signalling pathways that influence neuronal survival, inflammation, and synaptic function. Despite these promising developments, significant challenges remain. The human microbiome exhibits profound interindividual variability influenced by genetics, diet, geography, and environmental exposures, complicating the identification of universal therapeutic targets.

Furthermore, many current studies remain associative rather than mechanistically causal. Future research should therefore prioritize longitudinal cohort studies, mechanistic experimental models, and large randomized clinical trials that directly evaluate microbiome-targeted therapies in neurological disease populations.

CONCLUSION

The microbiota–gut–brain axis has emerged as a central biological network linking the gastrointestinal microbiome with neural, immune, and metabolic regulation of the central nervous system. Increasing evidence indicates that disturbances in microbial composition can influence neuroinflammation, neurotransmitter production, blood–brain barrier integrity, and neuronal signalling, thereby contributing to the pathogenesis and progression of multiple neurological and neuropsychiatric disorders. The mechanistic pathways underlying gut–brain communication including microbial metabolite signalling, immune modulation, and neural transmission via the vagus nerve highlight the profound influence of intestinal microbial ecosystems on brain function. These interactions underscore the concept that neurological disorders may arise not only from intrinsic neural pathology but also from systemic disturbances originating within the gut microbial environment. Therapeutic strategies targeting the gut microbiome are therefore gaining increasing attention as potential disease-modifying approaches. Interventions such as microbiome-supportive dietary patterns, probiotic and psychobiotic supplementation, and microbiota transplantation offer promising avenues for modulating neuroinflammatory pathways and restoring microbial homeostasis. As these approaches continue to be investigated, they may complement existing pharmacological treatments and contribute to more holistic management of neurological diseases.

Ultimately, the recognition of the microbiota–gut–brain axis as a key regulator of neurological health represents a paradigm shift in biomedical research. Continued interdisciplinary investigation integrating microbiology, neuroscience, immunology, and computational biology will be essential to fully elucidate the complexity of gut–brain communication. Advancing this field may enable the development of innovative diagnostic tools and targeted therapeutic strategies that reshape the future of neurological medicine and improve long-term brain health.

Abbreviations

MGBA: microbiota-gut-brain axis. CNS: central nervous system. FMT: Fecal microbiota transplantation. BBB: blood brain barrier. SCFAs: short chain fatty acids. TLR5: toll like receptor 5. ENS: enteric nervous system. GABA: gamma aminobutyric acid. 5-HT: 5-hydroxytryptamine. CCK: cholecystokinin. GLP-1: glucagon like peptide-1. IL-6: interleukin-6. IL-7: interleukin-7. LPS: lipopolysaccharide. GPCRs: G-protein coupled receptor. HDACs: histone deacetylases. FXR: Farsenoid X receptor. GPBAR-1: G-protein coupled bile receptor. IDO: indoleamine 2,3-dioxygenase. NMDA: N-methly-D-aspartate. AD: Alzheimer's disease. PD: Parkinson's disease. MIA: maternal immune activation. EPS: ethyl phenyl sulfate. ASD: autism spectrum disorder. HPA: hypothalamic-pituitary-adrenal. MCI: mild cognitive impairment. MMSE: mini mental state examination. DI-GM: dietary index for gut microbiota. NMSS: non-motor symptom scale. UPDRS: Unified Parkinson's disease rating scale. ALS: amyotrophic lateral sclerosis.

Availability of data and materials

No datasets were generated or analysed during the current study.

Funding

The authors received no extramural funding for the study.

Conflict of Interest

The authors report there are no competing interests to declare.

Author Contributions

All authors equally contributed to the study and approved the final manuscript.

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