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The Gut–Brain Axis in Neurodegeneration and Neural Repair: Microbiome-Driven Modulation of CNS Inflammation, Neurogenesis, and Recovery

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ABSTRACT:

Background: *The gut–brain axis represents a dynamic, bidirectional communication network linking the gastrointestinal microbiota with central nervous system (CNS) function. Emerging research implicates gut dysbiosis in the progression of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as in the regulation of neuroinflammatory tone and adult neurogenesis. Understanding the microbial regulation of CNS integrity offers a novel vantage point for both neuropathology and recovery.*

Methodology: *This review synthesizes findings from recent preclinical and clinical studies that explore the mechanistic underpinnings of the gut–brain axis in neurodegeneration and neural repair. Emphasis is placed on germ-free models, microbiome sequencing in human cohorts, and interventional trials involving probiotics, dietary strategies, and fecal microbiota transplantation (FMT).*

Results: *Microbiota-derived metabolites such as short-chain fatty acids (SCFAs) and tryptophan catabolites influence neuroimmune responses, blood–brain barrier (BBB) integrity, and neurogenesis in the hippocampus and subventricular zone. Dysbiosis is associated with heightened microglial activation, impaired Aβ clearance, and α-synuclein aggregation. Conversely, modulation of the microbiota through probiotics or dietary interventions can attenuate neuroinflammation and improve cognitive and motor outcomes in both animal models and early-stage clinical trials.*

Conclusion: *The gut–brain axis is a critical modulator of CNS health, with disruptions contributing to neurodegeneration and offering a therapeutic window for repair. Future work should address causality, interindividual variability, and ethical considerations of microbiome manipulation to enable precision interventions targeting brain resilience and regeneration.*

KEYWORDS:

Gut–brain axis, microbiota, neurogenesis, neurodegeneration, short-chain fatty acids.

1. Background:

The gut–brain axis represents a complex, bidirectional communication network linking the central nervous system (CNS) with the gastrointestinal tract, primarily mediated through neural, endocrine, immune, and microbial pathways. Recent advances in neurogastroenterology have identified the gut microbiota—comprising trillions of microorganisms—as a key modulator of brain development, function, and disease[1]. Microbiota-derived metabolites such as short-chain fatty acids (SCFAs), tryptophan catabolites, and neuroactive peptides influence neuronal excitability, glial function, and synaptic plasticity through blood-brain barrier (BBB) signaling, immune pathways, and vagal modulation[2,3].

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Disruption of the gut microbial ecosystem, or dysbiosis, has emerged as a contributing factor in a range of neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). Mounting clinical and experimental evidence suggests that microbial imbalance not only precedes neurodegeneration but also amplifies neuroinflammation, BBB breakdown, and synaptic dysfunction, thereby exacerbating disease progression[4,5].

The gut microbiome functions as a systemic regulator of immune and neuroendocrine homeostasis, shaping host physiology far beyond the confines of the intestine. Mechanistic insights have shown that microbial signals can influence microglial maturation, astrocyte reactivity, and neurotrophic factor expression—all critical components of CNS health and repair[6,7]. Furthermore, gut microbiota regulates the integrity of the BBB, modulating tight junction expression and endothelial permeability, thus affecting CNS susceptibility to circulating immune signals and toxins[8].

This microbial influence extends into the degeneration-repair continuum of CNS disorders. While dysbiosis exacerbates neurodegeneration through immune priming and metabolic dysregulation, restoration of microbial balance has shown promise in enhancing neurogenesis, resolving inflammation, and facilitating recovery after injury (9, 10).

While previous reviews have broadly described gut–brain interactions, this review's unique contribution is a focused synthesis of how microbiota-derived signals regulate neuroinflammation, neurogenesis, and recovery, bridging mechanistic insights with translational strategies.

2. Gut Microbiota and CNS Homeostasis

Gut-Brain Axis: Microbiome-Derived Pathways Influencing CNS Neuroimmune Crosstalk

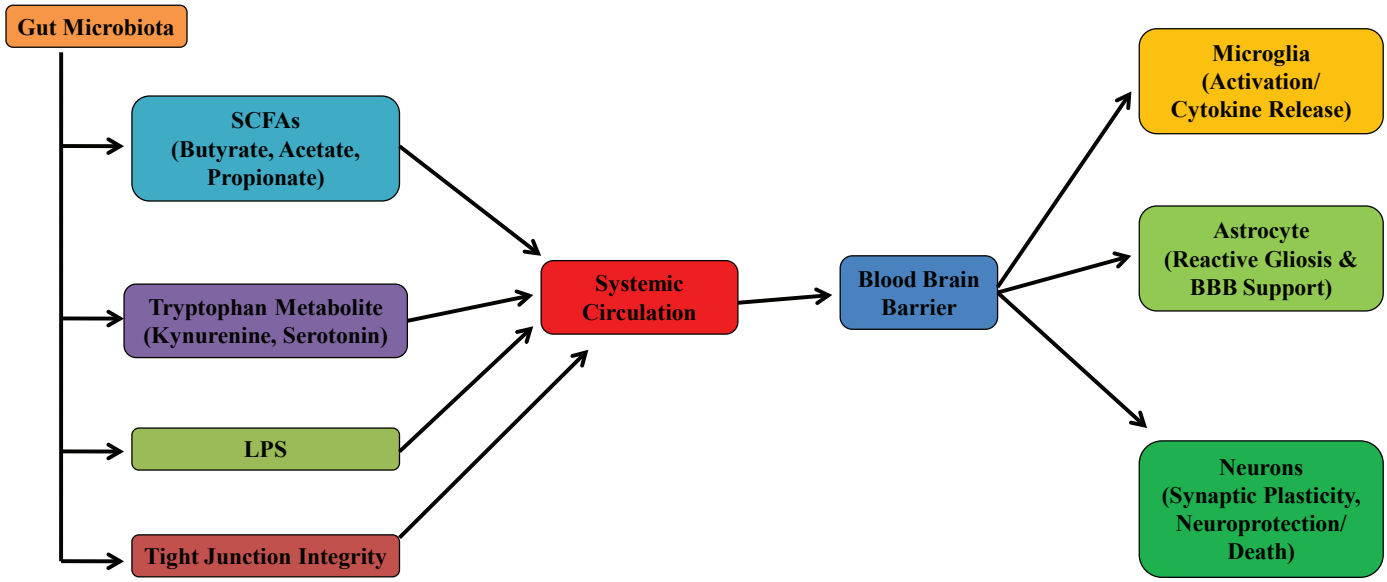

Figure 1: Schematic illustration of microbiome-derived signals influencing CNS function.

Short-chain fatty acids (SCFAs), tryptophan metabolites, and lipopolysaccharide (LPS), along with changes in gut barrier integrity, enter systemic circulation and interact with the blood–brain barrier (BBB). These signals modulate microglial activation, astrocytic reactivity, and neuronal function, leading to outcomes ranging from cytokine release and gliosis to altered synaptic plasticity, neuroprotection, or neurodegeneration.

2.1 Microbial Metabolites and Neuroactive Compounds

The gut microbiota produces a wide range of metabolites and neuroactive compounds that profoundly influence CNS physiology. Short-chain fatty acids (SCFAs)—notably butyrate, acetate, and propionate—are produced by bacterial fermentation of dietary fibers and have been shown to modulate microglial maturation, inflammatory responses, and even blood-brain barrier (BBB) function[11]. Butyrate, in particular, functions as a histone deacetylase (HDAC) inhibitor, enhancing gene expression linked to neuroprotection and synaptic plasticity.

Another essential pathway is the tryptophan–kynurenine axis, which connects gut microbiota activity with serotonergic and glutamatergic signaling in the brain. Commensal bacteria such as Bifidobacterium and Lactobacillus can shift tryptophan metabolism away from kynurenine production—associated with neurotoxicity—and toward serotonin biosynthesis[3]. Dysregulation of this pathway has been implicated in mood disorders, neuroinflammation, and cognitive decline.

Moreover, microbial species can synthesize or modulate levels of γ-aminobutyric acid (GABA), serotonin (5-HT), dopamine, and acetylcholine, influencing neural excitability and emotional behavior through vagal pathways or direct circulation of these metabolites[12].

2.2 Microbiota–Immune Interactions

The gut microbiota exerts profound effects on both systemic and CNS-resident immune cells, playing a pivotal role in shaping neuroimmune tone. Microbial-associated molecular patterns (MAMPs), including lipopolysaccharides (LPS) and peptidoglycans, are recognized by Toll-like receptors (TLRs) on immune and glial cells. Activation of TLR2 and TLR4 on microglia, for instance, can shift them toward a proinflammatory phenotype, promoting synaptic loss and neuronal dysfunction [13].

SCFAs also influence immune homeostasis by inducing regulatory T cell (Treg) differentiation, which can modulate neuroinflammation through peripheral cytokine profiles[14]. In addition, microbial signals have been shown to prime astrocytic IL-10 production, creating a neuroprotective milieu under homeostatic conditions.

However, dysbiosis—especially involving overgrowth of pathobionts—can tilt this balance toward a systemic inflammatory state, increasing levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, which can breach the BBB and disrupt neuronal signaling[15].

2.3 Maintenance of BBB Integrity

The integrity of the blood–brain barrier (BBB) is critical for maintaining CNS immune privilege. Gut microbiota modulates BBB function by regulating the expression of tight junction proteins—such as occludin, claudin-5, and ZO-1—via SCFA signaling and anti-inflammatory cytokine induction[16,17]. In germ-free mice, BBB permeability is significantly increased, a phenotype reversible by colonization with SCFA-producing bacteria.

Beyond SCFAs, other microbial signals directly or indirectly regulate BBB integrity. Tryptophan-derived indoles, produced by commensal bacteria such as *Lactobacillus* and *Clostridium* species, activate the aryl hydrocarbon receptor (AhR) on astrocytes and endothelial cells, upregulating tight junction proteins and exerting anti-inflammatory effects[18]. Secondary bile acids, generated by microbial metabolism of primary bile acids, influence endothelial signaling through farnesoid X receptor (FXR) and Takeda G protein receptor 5 (TGR5), modulating barrier permeability and vascular inflammation[19]. Additionally, polyphenol metabolites produced via microbial fermentation (e.g., urolithins, phenolic acids) have been shown to reduce oxidative stress and preserve endothelial tight junction integrity, thereby protecting BBB function[20].

Conversely, gut dysbiosis—through overproduction of endotoxins like LPS—disrupts BBB architecture and enhances

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leukocyte infiltration, thereby exacerbating CNS inflammation[21]. This breach in BBB integrity has been implicated in the pathophysiology of Alzheimer's disease, Parkinson's disease, and multiple sclerosis, providing a mechanistic link between microbial imbalance and neural vulnerability.

2.4 Role of the gut virome and mycobiome in gut-brain axis modulation

While most gut–brain axis studies emphasize bacterial communities, emerging evidence highlights important contributions from the gut virome and mycobiome. The gut virome, dominated by bacteriophages, can indirectly modulate host–microbiota interactions by altering bacterial population dynamics and metabolite production, thereby influencing systemic immunity and CNS function[22]. Similarly, fungal communities, though less abundant, play a role in gut–brain communication. Altered fungal diversity and overgrowth of *Candida* species have been reported in neurodegenerative conditions, where fungal cell wall components such as β-glucans can activate innate immune receptors and exacerbate neuroinflammation[23]. Although still underexplored, integrating bacterial, viral, and fungal interactions will be essential for a more comprehensive understanding of gut-derived signals in CNS homeostasis and neurodegeneration.

3. Gut Dysbiosis and Neurodegenerative Disorders

3.1 Alzheimer's Disease (AD)

Emerging data demonstrate distinct gut microbiota alterations in Alzheimer's disease (AD). AD patients exhibit reduced levels of beneficial taxa (e.g., Bifidobacterium, Faecalibacterium) and increased abundance of proinflammatory genera (e.g., Escherichia/Shigella, Bacteroides)[24]. This dysbiosis has been implicated in promoting neuroinflammation through increased systemic lipopolysaccharide (LPS) and decreased short-chain fatty acid (SCFA) levels.

Murine studies have provided causal links between gut microbial alterations and AD pathology. For instance, germ-free 5xFAD mice display reduced amyloid-beta (Aβ) plaque load and microglial activation, an effect reversed by recolonization with AD-associated microbiota[25,26]. Similarly, antibiotic-induced depletion of gut microbes leads to reduced Aβ aggregation and alterations in hippocampal microglial morphology, suggesting microbiota-mediated modulation of immune responses involved in Aβ clearance.

Tau pathology is also influenced by microbial metabolites and immune signaling. Tau transgenic mice exhibit increased hyperphosphorylation and neuroinflammation following colonization with dysbiotic microbiota derived from AD donors[7]. Mechanistically, microbial-derived tryptophan catabolites such as kynurenine promote excitotoxicity and oxidative stress, activating kinases including GSK-3β and CDK5, which are key drivers of tau phosphorylation[27]. Similarly, systemic bile acid dysregulation has been linked to abnormal tau aggregation, with certain secondary bile acids (e.g., deoxycholic acid) crossing the BBB and triggering neuronal stress pathways[28]. Inflammatory mediators induced by dysbiosis—particularly IL-6, TNF-α, and IL-1β—further exacerbate tau pathology by enhancing kinase activity and impairing tau clearance[29].

Compared to Aβ mechanisms, which are strongly linked to impaired microglial phagocytosis and altered SCFA signaling, tau pathology appears to be more tightly associated with metabolic and inflammatory pathways involving tryptophan metabolism, bile acid signaling, and proinflammatory cytokine cascades. This highlights how distinct microbial metabolites and immune axes converge on separate yet complementary arms of AD pathology—Aβ aggregation and tau hyperphosphorylation—together driving neurodegeneration.

3.2 Parkinson's Disease (PD)

In Parkinson's disease (PD), gastrointestinal symptoms often precede motor deficits by years, implicating the gut–brain axis in disease initiation. Braak's hypothesis posits that pathological α-synuclein aggregates originate in the enteric nervous system (ENS) and ascend via the vagus nerve to the brainstem. Animal models have recapitulated this pattern, with gut inoculation of α-synuclein fibrils inducing progressive neurodegeneration along the vagal pathway[30].

Clinical studies provide partial support for

this mechanism. A Danish nationwide cohort reported that individuals who underwent truncal vagotomy had a reduced risk of developing PD, suggesting interruption of vagal transmission may be protective[31]. Similarly, a Swedish registry study observed reduced PD incidence following truncal vagotomy, whereas selective vagotomy did not confer protection[32]. However, other population-based studies have failed to confirm this association[33], indicating that vagal involvement may vary by patient subtype, genetic background, or environmental exposures.

Microbial dysbiosis in PD includes increased abundance of proinflammatory *Proteobacteria* and reduced SCFA-producing bacteria. These shifts correlate with intestinal barrier dysfunction, systemic inflammation, and activation of microglia in the substantia nigra[34]. SCFAs, while generally considered neuroprotective, display a dual role in PD. At physiological concentrations, butyrate and propionate enhance gut barrier integrity, promote regulatory T cell differentiation, and support microglial maturation[35]. However, experimental evidence indicates that excessive SCFA exposure, or SCFAs acting in a proinflammatory environment, can exacerbate α-synuclein aggregation and microglial overactivation, thereby worsening motor pathology[35]. This suggests that the effects of SCFAs are highly context-dependent—protective in maintaining homeostasis but potentially harmful once neurodegenerative processes are initiated.

Fecal microbiota transplantation (FMT) has been explored as an experimental therapy. Transplanting PD patient microbiota into α-synuclein–overexpressing mice worsens motor symptoms and dopaminergic neurodegeneration, whereas microbiota from healthy controls confer neuroprotection[36]. These findings highlight the causal impact of microbial communities on PD progression and underscore the therapeutic potential of microbiota-targeted interventions.

3.3 Multiple Sclerosis, ALS, and Other Disorders

In multiple sclerosis (MS), gut microbiota influences immune cell polarization, particularly the balance between proinflammatory Th17 cells and anti-inflammatory Tregs. Dysbiosis in MS patients often includes reduced levels of Prevotella and Faecalibacterium, both implicated in SCFA production and Treg induction[37,38]. Colonization of germ-free mice with MS-derived microbiota enhances demyelination and CNS infiltration of Th17 cells, suggesting a microbiota-driven amplification of autoimmune pathology.

Amyotrophic lateral sclerosis (ALS) also shows evidence of gut-brain interactions. In SOD1-G93A mouse models, gut microbial depletion or dysbiosis accelerates disease progression, while specific taxa such as Akkermansia muciniphila are associated with improved motor performance and metabolic profiles[39]. Although human studies are limited, altered microbial compositions have been reported in ALS cohorts, potentially linked to neuroinflammation and intestinal permeability.

Table 1. Disease-specific gut microbial alterations and proposed CNS consequences in neurodegeneration

Disorder	Enriched taxa	Depleted taxa	Key consequences for CNS
Alzheimer's disease (AD)	*Escherichia/Shigella*, *Bacteroides*[24]	*Bifidobacterium*, *Faecalibacterium*[24]	↑ systemic LPS, ↓ SCFAs → microglial priming, impaired Aβ clearance, tau hyperphosphorylation (via kynurenine, bile acids, cytokines)[7,27-29].
Parkinson's disease (PD)	*Proteobacteria*, *Enterobacteriaceae*[34]	SCFA-producers (*Faecalibacterium*, *Roseburia*)[34]	Gut barrier dysfunction, systemic inflammation, dual role of SCFAs (protective vs. pro-aggregatory), α-synuclein aggregation, vagal propagation[30,35].
Multiple sclerosis (MS)	Proinflammatory taxa (*Akkermansia*)[37]	*Prevotella*, *Faecalibacterium*[37,38]	Skewed Th17/Treg balance, ↑ demyelination, ↑ CNS infiltration of autoreactive T cells
Amyotrophic lateral sclerosis (ALS)	Variable, some evidence of *Escherichia* overgrowth	Reduced *Akkermansia muciniphila*[39]	Gut barrier disruption, altered metabolism, accelerated motor neuron loss, systemic inflammation

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4. Gut Microbiota in Neurogenesis and Neural Repair

Short-chain fatty acids (SCFAs), particularly butyrate, cross the blood–brain barrier and modulate histone acetylation in neural stem cells. This epigenetic effect enhances the expression of neurogenic and plasticity-associated genes such as BDNF and Neurog2, thereby supporting basal hippocampal neurogenesis under homeostatic conditions[11]. Germ-free and antibiotic-treated mice exhibit reduced proliferation of neural progenitors in both the dentate gyrus and SVZ, highlighting the necessity of a healthy microbiota for sustaining adult neurogenesis. Restoration of microbial balance via colonization or SCFA supplementation rescues these deficits [9, 40].

In contrast, during injury or disease, microbiota influence neurogenesis through both systemic immune modulation and local CNS cues. After traumatic brain injury (TBI) or stroke, dysbiosis accelerates systemic inflammation and worsens neurological outcomes. Murine stroke models show that oral *Lactobacillus rhamnosus* GG enhances neural progenitor proliferation and increases BDNF, thereby improving recovery[41]. Conversely, antibiotic-induced dysbiosis impairs post-stroke neurogenesis, while fecal microbiota transplantation (FMT) from young or healthy donors restores hippocampal neurogenesis, enhances synaptic density, and improves behavior[42]. Probiotics such as *Bifidobacterium longum* have also been associated with better neurocognitive recovery post-injury[43].

Microbiota-derived signals further shape microglial polarization, which critically determines neurodegeneration versus repair. Germ-free mice exhibit immature or hyperactivated microglia, a phenotype normalized by SCFA administration[6,44]. Butyrate and propionate promote anti-inflammatory M2 polarization, characterized by enhanced phagocytosis, trophic factor release, and remyelination in models of spinal cord injury. By contrast, LPS and other microbial-associated molecular patterns drive proinflammatory M1 polarization, marked by TNF-α, IL-1β, and ROS production, thereby amplifying neuronal injury. Tryptophan metabolites also modulate polarization: kynurenine pathway activation favors M1-like states, while indole derivatives engage aryl hydrocarbon receptor (AhR) signaling to promote M2 phenotypes and neuroprotection[3,18]. Astrocytes, likewise, integrate microbial cues. Probiotics enhance astrocytic production of neurotrophic factors such as GDNF and BDNF, facilitating synaptic recovery after TBI[43]. Moreover, astrocytic modulation of glutamate uptake and BBB integrity in response to microbial metabolites underscores the broad role of gut-derived signals in orchestrating CNS homeostasis and repair.

5. Experimental and Clinical Insights

Germ-free (GF) and antibiotic-treated rodents exhibit significant alterations in CNS development, including reduced hippocampal neurogenesis, altered microglial morphology, and impaired stress reactivity[9,11]. These models demonstrate that the absence or depletion of microbiota impacts synaptic plasticity and gene expression related to neurodevelopment and plasticity. More recently, GF mice showed blunted BDNF expression in the prefrontal cortex and hippocampus, affecting emotional resilience[40].

Large-scale microbiome analyses in Alzheimer's and Parkinson's cohorts have identified disease-specific microbial signatures. For instance, *Prevotella* and *Faecalibacterium* were consistently depleted in PD patients, correlating with motor severity and inflammatory cytokine profiles[45]. Similar microbial alterations in AD patients have been linked to increased serum LPS and impaired Aβ clearance[46]. Integration with neuroimaging data suggests that dysbiosis correlates with hippocampal atrophy and cortical thinning[23].

Fecal microbiota transplantation (FMT) from healthy or young donors has improved cognitive performance and synaptic integrity in aged or AD-model mice[42]. Small clinical trials have also reported mild cognitive or motor improvements in PD patients receiving FMT or targeted probiotics, although findings are preliminary and require validation in larger cohorts [47, 48]. Limitations include interindividual microbiota variability, absence of standardized protocols, and inconsistent clinical endpoints.

6. Therapeutic Potential and Translational Strategies

Targeted microbial supplementation has shown promise in modulating neuroinflammatory markers and cognitive function. Specific

strains such as *Lactobacillus plantarum* PS128 improved motor symptoms and reduced anxiety in Parkinson's patients in a double-blind randomized trial[49]. Similarly, synbiotic supplementation attenuated cognitive impairment and oxidative stress in murine Alzheimer's models[50]. Prebiotics—non-digestible dietary fibers that selectively stimulate beneficial bacteria—are emerging as complementary tools. For instance, inulin and fructo-oligosaccharides (FOS) increase SCFA production, modulate immune tone, and improve cognitive outcomes in preclinical AD models[51]. Synbiotics, combining probiotics with prebiotics, provide synergistic effects by improving microbial survival and enhancing metabolite production, representing a distinct therapeutic avenue beyond general dietary modulation.

Dietary patterns such as the Mediterranean and ketogenic diets have been associated with neuroprotective microbiota shifts and reduced systemic inflammation[52,53]. In murine models, supplementation with sodium butyrate or polyphenol-rich extracts (e.g., resveratrol) restored synaptic plasticity and enhanced hippocampal BDNF levels[54]. Tryptophan supplementation also modulated serotonergic signaling and gut–brain axis responses post-stroke[55]. Importantly, environmental factors—including early life exposures, stress, sleep, and exercise—also shape microbiome composition and function, intersecting with neurodegeneration risk and resilience[1]. Chronic stress alters microbial diversity and increases gut permeability, while aerobic exercise enhances SCFA production and hippocampal neurogenesis, highlighting the need to view microbiome interventions within broader lifestyle contexts.

Emerging technologies such as CRISPR-based microbiota engineering allow for targeted manipulation of microbial genes affecting metabolite production[56]. Precision medicine approaches are being explored using metagenomic profiling to tailor probiotic or dietary interventions to individual microbiome features, as demonstrated in a pilot personalized nutrition study for Parkinson's patients[57]. However, practical challenges remain: metagenomic sequencing is still costly, time-intensive, and requires advanced bioinformatics pipelines, which limit its feasibility for routine clinical use. Moreover, the interpretation of microbial signatures is confounded by interindividual variability and a lack of standardized reference databases. While these tools hold significant potential, current application is largely confined to research or small pilot studies.

7. Challenges and Future Directions

Despite compelling associations between gut microbiota and brain health, distinguishing causation from correlation remains a central obstacle in translational neuroscience. While rodent models provide mechanistic insights, they often lack clinical fidelity, and human studies remain confounded by diet, genetics, medications, and lifestyle factors. Methodological variability—including inconsistent fecal sampling protocols, differences in sequencing pipelines, heterogeneity in disease staging, and confounds from polypharmacy—further complicates interpretation across cohorts.

A persistent translational challenge lies in defining microbial "dose–response" relationships. Unlike conventional drugs, probiotics or microbial consortia may not follow linear pharmacodynamics; their efficacy depends on concentration, host microbiome context, and competitive niche adaptation. Moreover, the long-term persistence or engraftment of supplemented strains is inconsistent, raising questions about the durability of therapeutic effects and the need for repeated interventions.

Establishing causality requires carefully controlled experimental designs. Germ-free models, targeted gnotobiotic colonization, and humanized microbiome mice have proven invaluable in testing direct microbe–host interactions and their relevance to human disease. Translating these findings to humans will require longitudinal, multi-omics approaches that integrate metagenomics, metabolomics, neuroimaging, and behavioral profiling to identify mechanistic biomarkers of disease progression and therapeutic response.

Ethical concerns also warrant deeper consideration. Fecal microbiota transplantation (FMT) and engineered microbial interventions present particular challenges in obtaining informed consent from cognitively impaired populations, such as patients with advanced Alzheimer's disease or Parkinson's dementia. Safeguards for autonomy and family/guardian involvement must be strengthened to ensure

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ethical trial conduct.

Finally, future research will benefit from leveraging big data analytics and artificial intelligence (AI) to unravel complex microbiome–host interactions. Machine learning models are already being applied to predict disease risk, stratify patient subgroups, and forecast response to microbiome-targeted therapies. Integrating AI with precision microbiome science holds the promise of accelerating biomarker discovery and guiding personalized interventions for neurodegenerative diseases.

Interindividual variability—linked to age, sex, comorbidities, and baseline microbiome composition—remains a fundamental barrier to generalization. The inclusion of diverse populations in research design will be essential for moving toward precision microbiome-based therapies that are capable of enhancing brain resilience and repair.

8. Conclusion

The gut–brain axis represents a fundamental and underappreciated regulator of central nervous system integrity, modulating neuroinflammation, neurogenesis, and circuit repair. Disruptions in microbiota composition and function—collectively termed dysbiosis—have emerged as key contributors to the pathophysiology of Alzheimer's disease, Parkinson's disease, multiple sclerosis, and other neurodegenerative conditions.

Importantly, the gut microbiome is modifiable. This opens therapeutic possibilities through diet, probiotics, targeted metabolite supplementation, or advanced bioengineering approaches. Integrative, cross-disciplinary strategies that combine microbiome science with neuroimmunology, regenerative neuroscience, and systems biology are poised to redefine our understanding of brain resilience and recovery.

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