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Literature Review: The Microbiota-Gut-Brain Axis in Mental Health and Neurodegeneration: Mechanisms, Evidence, and Therapeutic Implications

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Abstract: ***The microbiota–gut–brain axis represents a bidirectional communication system linking the gastrointestinal tract and central nervous system through neural, endocrine, immune, and metabolic pathways. This review examines its role in neuropsychiatric and neurodegenerative disorders, including depression, anxiety, Parkinson's disease, and Alzheimer's disease. A structured synthesis of peer-reviewed literature from 2015 to 2025 was conducted to evaluate key communication mechanisms and associated clinical evidence. Findings indicate that immune signaling and neuroinflammation provide the most consistent mechanistic link between gut dysbiosis and brain dysfunction, while microbial metabolites and vagal pathways are strongly supported in preclinical models. However, human evidence remains largely associative, with limited causal validation. Emerging interventions, including psychobiotics and microbiota transfer therapies, demonstrate preliminary clinical benefits but are constrained by small sample sizes and methodological variability. Overall, the field requires standardized longitudinal and interventional studies to establish causality and enable clinically actionable applications.***

Keywords: Microbiota-Gut-Brain-Axis (MGBA), gut microbiome, neuroinflammation, neuroimmune signalling, dysbiosis, psychobiotics, HPA axis, neurodegenerative disorders, vagus nerve, short-chain fatty acids (SCFAs), fecal microbiota transplantation

1. Introduction

The microbiota–gut–brain axis (MGBA) refers to a bidirectional communication network linking the gastrointestinal tract and the central nervous system through integrated neural, endocrine, immune, and metabolic pathways. Increasing evidence suggests that gut microbial composition and function can influence brain physiology via microbial metabolites (e.g., short-chain fatty acids), neuroactive compounds, immune mediators, and vagal signaling, while brain states such as stress can reciprocally alter gut motility, permeability, and microbial ecology.1 As microbiome analytics and neuroimmunology have advanced, the MGBA has shifted from a conceptual framework to a mechanistically testable system with genuine clinical relevance.

Neuropsychiatric and neurodegenerative disorders- including major depressive disorder, anxiety disorders, Parkinson's disease, and Alzheimer's disease- are rising in prevalence and impose substantial disability burdens.2 Alongside established disease mechanisms such as protein misfolding, neuroinflammation, neurotransmitter dysregulation, and mitochondrial dysfunction, a growing body of clinical and preclinical studies reports associations between altered gut microbial profiles (dysbiosis), intestinal barrier disruption, systemic inflammation, and brain dysfunction.3 Importantly, current literature increasingly evaluates whether microbial alterations may act not only as correlates of disease but also as modulators of symptom severity, inflammatory tone, and progression-related pathways, highlighting the MGBA as a plausible target for diagnostics and intervention.4

This literature review synthesizes research on the MGBA by (i) outlining key communication routes- neural/vagal, hormonal/HPA, immune/cytokine-mediated, and microbial/metabolite-driven; (ii) summarizing evidence linking gut microbiota dynamics to mental health conditions and neurodevelopmental outcomes; and (iii) evaluating therapeutic directions such as psychobiotics and microbiome-targeted strategies. The review also highlights major limitations in the current evidence base- heterogeneity of study designs, strain-specific effects, small clinical cohorts, and lack of standardization- while identifying directions for more rigorous, translational research. This review therefore asks: does gut microbial dysbiosis causally drive neuropsychiatric and neurodegenerative disorders, and can microbiome-targeted interventions offer clinically viable therapeutic strategies?

2. Methodology

This literature review was developed through a systematic identification and synthesis of peer-reviewed research concerning the communication pathways and clinical implications of the microbiota–gut–brain axis. This included sourcing research from primary databases including PubMed, Nature, ScienceDirect, and Google Scholar, utilizing targeted search terms such as "microbiota gut brain axis," "neuroinflammation and gut dysbiosis," "vagus nerve and alpha-synuclein," "psychobiotics - clinical trials," "gut dysbiosis and depression," and "short-chain fatty acids and neurodegeneration." The selection process followed an inclusion criterion prioritizing peer-reviewed clinical and experimental studies published within the last ten years (2015–2025) to ensure contemporary relevance, with select foundational studies from prior years included where appropriate. Studies were excluded if they were non-peer-reviewed, conference abstracts, or lacked sufficient methodological detail to permit evaluation. The screening

process involved an initial title and abstract review, followed by full-text assessment, yielding approximately 80 studies that met the inclusion criteria and informed this review.

The analysis integrated a diverse range of study types, spanning mechanistic preclinical murine models using germ-free (GF) animals to human epidemiological cohorts and double-blind, placebo-controlled therapeutic trials. To mitigate bias, study quality was informally assessed by prioritizing studies with larger sample sizes, replication across independent cohorts, and methodological transparency; where evidence was limited to small or single studies, this is noted explicitly in the review. By evaluating these various levels of evidence, the review establishes a comprehensive overview of how microbial colonization influences neurodevelopmental trajectories and disease states.

3. Results and Discussion

3.1 The Gut–Brain Axis: Overview

3.1.1 Definition and Components

The gut–brain axis is a dynamic communication system encompassing four interconnected components: the central nervous system, the autonomic nervous system, the enteric nervous system, and the neuroendocrine and neuroimmune systems. Each contributes distinct signalling modalities to a network that jointly regulates gastrointestinal function, immune homeostasis, and brain physiology.

The central nervous system (CNS)- the regulatory hub comprising the brain and spinal cord- is responsible for processing information and coordinating sensory, motor, and higher-order cognitive functions.5 It serves a critical role in homeostasis and regulation of gut processes by orchestrating communication between the brain and the enteric nervous system through the transmission of regulatory signals to gastrointestinal effector cells. CNS-mediated stress responses also alter gut permeability and immune activation, a mechanism repeatedly implicated in depressive phenotypes.6

The autonomic nervous system (ANS), responsible for involuntary physiological regulation, forms part of the peripheral nervous system and regulates involuntary physiological processes including digestion, heart rate, and breathing. Its sympathetic and parasympathetic branches work in opposition to maintain homeostasis, affecting gastrointestinal motility, secretion, and blood flow. Preclinical and clinical evidence indicates the bidirectional effects on gut motility caused by ANS dysregulation: chronic stress activates AVP V1b receptors and CRH-mediated pathways to accelerate colonic transit, while anxiety states are significantly associated with constipation risk.7 These motility shifts selectively alter substrate availability in the colon, favouring the growth of certain bacterial populations while suppressing others, ultimately contributing to dysbiosis—a disruption particularly relevant to disorders where microbial imbalance reinforces neuroinflammation, as seen in irritable bowel syndrome, depression, and anxiety.

The enteric nervous system (ENS), also known as the ‘second brain,’ is an independent and extensive neural network consisting of 50–100 million nerve cells embedded within the gastrointestinal tract.8 It autonomously regulates motility, secretion, and blood flow within the gut, and communicates bidirectionally with the CNS and ANS through intrinsic and extrinsic innervations. ENS dysfunction is implicated across a spectrum of neurological and gastroenterological conditions, with the strongest evidence supporting associations with Autism Spectrum Disorder (ASD) and Irritable Bowel Syndrome (IBS). A retrospective case-control study of 146 ASD children and 114 neurotypically developing children aged 2–14 found that gastrointestinal symptoms including constipation, diarrhoea, abdominal distension, and undigested food particles in stool were significantly more frequent in the ASD group, with family history of ASD being notably higher among ASD children who presented with GI symptoms.9 Aberrant ENS wiring has also been linked to mutations in ASD-associated genes such as Shank3, Nlgn3, and CHD8, each producing distinct patterns of gut dysmotility, while in IBS, dysregulated ENS signalling underlies the hallmark motility disturbances and visceral hypersensitivity that define the condition.10

The neuroimmune system is a network of specialized neurons that releases hormones—typically peptides—into the blood, and serves as the basis of biochemical and electrophysiological interactions between the nervous system and the immune system.11 Pathways such as the sympathetic nervous system and hypothalamic-pituitary axis (HPA) modulate immune responses and are in turn influenced by immune factors such as cytokines, establishing a system responsible for immune surveillance, injury response, and homeostasis. The gut–brain axis links the intestinal microbiota to this system, allowing microbial states to translate into neurological effects through the secretion of metabolites and neurotransmitters. Dysbiosis disrupts this interface through two converging mechanisms: it triggers release of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, which activate microglia and remodel synaptic function, while simultaneously compromising gut barrier integrity and enabling pathogen-associated molecular patterns to breach the blood–brain barrier and amplify neuroinflammation.12 In Alzheimer’s disease, gut dysbiosis-driven neuroinflammation and impaired gut–blood–brain barrier integrity have been associated with accelerated Aβ deposition, positioning the neuroimmune system as a mechanistic intermediary between gut microbial states and AD pathology—though the gut should be understood as a contributor to the inflammatory environment that may modulate disease progression rather than a direct cause.13
In summary, the gut–brain axis operates through four tightly integrated systems, the CNS, ANS, ENS, and neuroimmune network, each contributing distinct but overlapping signaling pathways. Together, they establish the mechanistic foundation through which microbial states in the gut can influence brain function, immune regulation, and disease progression.

3.2 Communication Routes in the Gut–Brain Axis

3.2.1 Neural Pathways

The 10th cranial nerve, the vagus nerve, is a primary neural interoceptive conduit that facilitates direct communication between the gut and the brain.14 It is responsible for

regulating metabolism, immune defense, inflammation, and stress responses through afferent and efferent signaling. Divided into the anterior trunk (primarily formed by the left vagus nerve) and posterior trunk (primarily formed by the right vagus nerve), the vagus nerve originates from the medulla oblongata and extends through the thorax and neck to the abdominal cavity, where its trunks branch systematically to the esophagus, stomach, intestines, liver, pancreas, and other visceral organs. Since its primary role is collecting sensory information from peripheral organs to relay to the brain- via chemical receptors in the gut, stretch receptors in the lungs, and pressure sensors in the aorta—the vagus nerve carries a disproportionate distribution of approximately 80% afferent (sensory) fibers and 20% efferent (motor) fibers.15 The efferent component nonetheless remains essential in enabling the bidirectional exchange of information alongside parasympathetic control.

Degeneration of the vagus nerve is one of the hallmarks of Parkinson's disease and atypical Parkinsonian syndromes, because the abnormal clumps of protein α-synuclein linked to Parkinson's disease are formed and propagated in ways that cause neuronal loss and vagus nerve atrophy.16 The causal pathway of α-synuclein remains actively debated, but preclinical evidence constitutes the strongest tier. In murine models, pathological α-synuclein preformed fibrils injected into the gut spread sequentially to the dorsal motor nucleus, locus coeruleus, and ultimately the substantia nigra, closely mirroring Braak's staging scheme for Parkinson's disease; truncal vagotomy prevented this gut-to-brain spread entirely.17

Human epidemiological evidence is suggestive but not definitive. A Danish cohort study found that patients who underwent truncal vagotomy showed a reduced risk of developing Parkinson's disease, while those who underwent super-selective vagotomy did not, consistent with the idea that intact vagal innervation of the gut is required for α-synuclein transmission.18 However, this interpretation is complicated by evidence of bidirectionality: non-human primate studies have demonstrated that α-synuclein pathology can spread in both gut-to-brain and brain-to-gut directions, and in some experimental conditions, α-synuclein lesions were not observed in the vagus nerve at all, challenging the assumption that the vagal route is the sole or primary mechanism. The gut-first versus brain-first debate therefore remains unresolved, and the vagus nerve should be understood as a plausible and well-evidenced, but not confirmed, conduit for α-synuclein propagation in a subset of Parkinson's disease cases.

Overall, the vagus nerve represents a well-evidenced but not conclusively confirmed conduit for gut-to-brain signalling, with its role in α-synuclein propagation remaining an active area of debate rather than an established causal mechanism.

3.2.2 Hormonal Pathways

Consisting of the hypothalamus, pituitary gland, and adrenal glands, the hypothalamic-pituitary-adrenal (HPA) axis is a major neuroendocrine system required for physiological homeostasis that primarily regulates stress and gut responses to it by releasing corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and cortisol (CORT). As one of the four main communication pathways in the gut–brain axis, the HPA axis holds a strong link to depression when dysregulation arises.19

Under conditions of extreme stress, CRH and ACTH are released in a manner that increases energy production, while short-term cortisol elevations aid in the reduction of acute inflammation through suppression of pro-inflammatory cytokines including IL-1, IL-6, and TNF-α. By altering motility, permeability, and immune activity, these hormones regulate gut physiology in real time, establishing direct communication between the brain and the gastrointestinal tract. Importantly, the hormonal pathway is bidirectional: the gut is capable of activating and regulating the HPA axis as effectively as the brain does. Disturbances such as dysbiosis, inflammation, infection, or altered microbial composition within the gut stimulate immune cells- particularly mast cells and macrophages in the gut wall- which in turn activate the HPA axis through cytokine-mediated signaling.20

Normal microbial colonization in early life is also crucial for establishing appropriate HPA function. Germ-free (GF) animals show exaggerated ACTH and corticosterone responses to mild stress, a pattern reversible through recolonization or specific probiotic strains.21 Disrupting the gut microbiota later in life through antibiotics or infection similarly heightens HPA reactivity and produces anxiety-like or memory-related behavioral changes, while restoring microbial balance reduces these exaggerated hormonal responses. Through these mechanisms, gut microbes actively shape the development, sensitivity, and feedback regulation of the HPA axis.11 It should be noted, however, that establishing causality in humans remains difficult due to confounding variables including chronic stress exposure, dietary patterns, and antibiotic history, which limits direct translation of animal findings to clinical populations.22

Taken together, the HPA axis serves as a bidirectional hormonal bridge between gut microbial states and brain function, with early-life colonization playing a particularly critical role in establishing long-term stress reactivity, though direct causal translation to human populations remains limited.

3.2.3 Immune Pathways

Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are the key messengers in the immune pathway between the gut and the brain. When the gut faces inflammation, dysbiosis, or infection, the microbiota is deeply impacted and IL-6 along with TNF-α are released into systemic circulation, influencing brain function through two main routes.23 The direct route: peripheral pro-inflammatory cytokines activate endothelial cells within the blood–brain barrier (BBB), initiating intracellular signaling cascades that degrade tight junction proteins including claudin-5 and occludin, thereby increasing BBB permeability and enabling inflammatory mediators and microbial-derived molecules such as lipopolysaccharides to infiltrate the brain parenchyma. The indirect route: cytokines activate vagal afferent fibers in the gut wall, which relay immune signals to the brainstem and limbic regions without requiring passage through the BBB.24 This route is particularly relevant for rapid-onset mood and cognitive disruption. These two routes

are not mutually exclusive and likely operate simultaneously, though their relative contributions vary by context, inflammation severity, and BBB integrity at any given time.

In a healthy state, the gut influences immune homeostasis through physical barriers and molecules including secretory IgA and antimicrobial peptides, which control pathogen spread.25 Immune cells in the gut adopt a tolerogenic phenotype under the influence of TGF-β and IL-10, promoting anti-inflammatory responses and preventing excessive reactivity to commensal bacteria and dietary antigens.26 Gut dysbiosis disrupts this balance by impairing BBB integrity and priming both peripheral and central immune systems, triggering microglial activation characterized by morphological changes, cytokine overproduction, and dysregulated neurotransmitter dynamics- a state mechanistically linked to depression, anxiety, and autism.3 Brain-to-gut signaling also occurs, where neural circuits originating in the CNS directly regulate the phenotype and cytokine production of gut immune cells including dendritic cells and macrophages, either reinforcing immune tolerance or amplifying local inflammation depending on the nature of the neural signal.

The ketogenic diet provides a representative example of how immune and metabolic pathways can intersect independently of direct neural signalling. Gut bacteria including Akkermansia and Parabacteroides, altered in composition by the diet, regulate gamma-glutamylated amino acids that serve as precursors for glutamate and GABA biosynthesis, thereby influencing brain excitability and seizure threshold through an immune-metabolite interface rather than a classical cytokine route.27 This demonstrates that immune pathway influence on the brain is not limited to inflammatory cytokines alone, but extends to microbially-mediated metabolic intermediaries.

Immune signalling may represent one of the most translationally tractable gut–brain pathways precisely because its key mediators are directly measurable in humans. Elevated levels of pro-inflammatory cytokines including IL-1β, IL-6, and IFN-γ correlate with greater MDD severity, and MRI data reveal increased BBB permeability in the hippocampus, anterior cingulate gyrus, and thalamus of individuals with MDD, with leakage levels correlating with symptom severity- providing rare in vivo evidence for the immune-to-brain route.28 Unlike vagal or HPA-mediated pathways, inflammatory markers are consistently quantifiable in serum and CSF across clinical populations, making immune dysregulation both a plausible mechanistic bridge and a potential biomarker target for gut–brain-linked psychiatric and neurodegenerative conditions.

In summary, immune signalling represents the most translationally tractable gut–brain communication route, as its key mediators are directly measurable in clinical populations, positioning neuroinflammation and BBB disruption as both mechanistic links and viable biomarker targets.

3.4.4 Microbial Pathways

Microbial metabolites and precursors influence host neurotransmitter pathways indirectly via enteroendocrine signaling, immune modulation, and vagal afferents. Gut microbes produce neurotransmitters such as serotonin (5-hydroxytryptamine, or 5-HT), dopamine, and GABA. Tryptophan hydroxylase (TPH), the key enzyme responsible for the synthesis of 5-HT, has two isoforms- TPH1, specific to the gut and pineal gland, and TPH2, specific to the brain.29 While approximately 90% of the body's serotonin is synthesized in the gut by enterochromaffin (EC) cells via TPH1, peripheral 5-HT cannot cross the blood–brain barrier, and the brain maintains an entirely separate serotonergic pool synthesized via TPH2 from tryptophan that must cross the BBB independently.30 Gut-derived 5-HT influences the CNS by activating 5-HT3 receptors on vagal afferent fibers, which relay serotonergic signals to the nucleus tractus solitarius (NTS) in the brainstem and project to higher regions, modulating emotional regulation, stress responses, and immune function without requiring peripheral 5-HT to enter central circulation.31

Microbial regulation of this pathway is well-evidenced at the level of TPH1 expression. Spore-forming bacteria, predominantly Clostridia, promote 5-HT biosynthesis by upregulating TPH1 in colonic EC cells via SCFA metabolites including butyrate and acetate.32 Clostridium ramosum specifically has been shown to significantly increase Tph1 expression and gut 5-HT levels, while several lactic acid bacteria and Escherichia coli strains can produce 5-HT directly.33 SCFAs also regulate vagal activity and serotonin transporter (SERT) expression, establishing an additional layer of microbial influence over serotonin turnover and signal duration. It is important to note, however, that diet is a substantial confounder in this area: dietary tryptophan availability, fiber composition, and macronutrient balance all independently shape both EC cell activity and SCFA-producing microbial populations, making it difficult to isolate purely microbial contributions in human studies.34

The gut microbiota also influences the expression of central glutamate and gamma-aminobutyric acid (GABA) receptors in the host. In one preclinical study, transplanting fecal microbiota from patients with alcohol use disorder to mice induced anxiety and depression-like behaviors, associated with decreased levels of mGluR1/PKC in the nucleus accumbens and reduced expression of the α1 subunit of GABA-A receptor and BDNF in the medial prefrontal cortex, compared to mice receiving healthy donor microbiota.35 Complementary evidence shows that Lactobacillus rhamnosus administration modulates central GABA receptor expression and reduces anxiety-like behavior in mice through vagally mediated processes, with vagotomy abolishing the effect and confirming the neural rather than systemic route. Collectively, these findings suggest that gut microbes shape central neurotransmitter tone through vagal, immune, and metabolic intermediaries, although most mechanistic evidence remains preclinical and human causal studies are limited by small samples, heterogeneous populations, and difficulty controlling for diet and comorbid conditions.

In summary, gut microbes shape central neurotransmitter tone through overlapping vagal, immune, and metabolic intermediaries, though most mechanistic evidence remains preclinical and human causal validation is constrained by dietary confounding and population heterogeneity.

4. Role of Gut Microbiota in Mental Health

The gut microbiota's influence on mental health spans the full arc of development, from the earliest stages of neonatal colonization through to adult-onset psychiatric and neurodegenerative conditions. Conditions such as asthma, atopy, childhood obesity, and autism spectrum disorder have been associated with excess antibiotic use and the resulting alterations in the microbiome during childhood, suggesting that disruptions to microbial ecology at sensitive developmental windows can have far-reaching consequences for both immune and neurological health. The following sections trace this relationship from early-life colonization through its clinical manifestations across a range of conditions.

4.1 Development and Maintenance

Colonization of the gut microbiota during early life is a critical determinant of immune and neurodevelopmental trajectories. Several modifiable and non-modifiable factors shape this colonization, including delivery mode, breastfeeding, maternal microbiota composition, and antibiotic exposure, each of which influences the timing and diversity of microbial assembly in ways that can have lasting consequences for brain development.36 While formula-fed infants demonstrate greater intestinal microbial diversity, the microbial communities of breastfed infants show significantly stronger interactions with host genes and greater transcriptomic activity related to immune and metabolic functions, suggesting functional superiority over raw diversity. Postmenstrual age (PMA) constitutes another key variable, as preterm infants exhibit a distinctly slower rate of microbiome assembly, with obligate anaerobes including Bifidobacterium and Bacteroides appearing substantially later than in term-born peers. Antibiotic exposure compounds these disruptions, as shown in a prospective observational cohort study of 130 healthy Japanese infants, which found that intrapartum antibiotic administration to birthing mothers—regardless of delivery mode- was associated with reduced neonatal abundance of Lactobacilli and Bifidobacteria and diminished overall diversity.37

These disruptive factors carry measurable downstream consequences for neurological and immune development. GF murine models demonstrate immune deficiencies, memory and learning deficits, and behavioral disturbances. The most mechanistically significant evidence comes from a fecal transfaunation model exploring the consequences of preterm dysbiosis: GF mouse pups receiving microbiota from a preterm infant with poor growth developed both systemic and neuroinflammation, evidenced by elevated circulating IL-1β, TNF, and IFNγ alongside increased NOS1 expression in brain tissue, establishing a causal chain where disrupted early colonization leads to aberrant immune signaling and measurable neuroinflammation.38 This finding opens the possibility of reversing neuroinflammation risks by restoring the microbiota—a hypothesis that is beginning to be tested clinically, with ASD as a key disease model given its well-documented associations with gut dysbiosis and gastrointestinal comorbidities. Early life nonetheless represents a sensitive window where microbiome perturbations can shape immune and neurodevelopmental trajectories in ways that may not be easily reversible, and translating these findings into clinical prediction and prevention remains constrained by the difficulty of isolating microbial contributions from the dense web of confounding exposures- antibiotic history, feeding mode, delivery circumstances, and socioeconomic environment- that co-occur during this period. In summary, early-life microbial colonization is a critical and time-sensitive determinant of immune and neurodevelopmental trajectories, though isolating microbial contributions from co-occurring environmental exposures remains a significant methodological challenge.

4.2 Mental Health Disorders

4.2.1 Irritable Bowel Syndrome (IBS)

IBS is a highly prevalent condition commonly described as a prototypical disorder of the microbiota–gut–brain axis, defined not only by structural gastrointestinal pathology but also by the disordered bidirectional communication between the gut and the CNS. Although still poorly understood, its pathogenesis is multifactorial involving visceral hypersensitivity, increased intestinal permeability, and low-grade inflammation, into which a disrupted gut microbiota ties in strongly.40 Studies estimate that approximately 10% of IBS cases begin after an episode of gastroenteritis, leading to post-infectious IBS and indicating a possible cause-and-effect relationship between infection-driven dysbiosis and IBS.41 Factors including host genetics, stress, diet, antibiotic use, and early life experiences have all been shown to shape gut microbiota composition in ways that predispose individuals to IBS, meaning that dysbiosis in IBS is rarely a product of a single exposure but an accumulated disruption across multiple variables. This multifactorial origin explains why findings from studies comparing gut microbiota composition in IBS patients with healthy controls—including increased Firmicutes to Bacteroidetes ratio, decreased Lactobacilli and Bifidobacteria populations, and increased Streptococci and Ruminococcus species- remains inconsistent and variable across cohorts.

The psychiatric prevalence in IBS is substantial, though it varies considerably based on clinical setting and methodology. In a primary care observational study of 100 IBS patients meeting Rome IV diagnostic criteria, 75% had more than one psychiatric comorbidity, with generalized anxiety disorder being the most common at 44%, followed by major depression at 38% and somatization disorder at 23%.42 Figures from tertiary care settings are consistently higher: in a tertiary care study of 184 IBS patients, 79.9% had at least one psychiatric comorbidity- more than double the 34.3% seen in controls—with major depressive syndrome present in 47.3% of IBS patients versus 5.1% of controls, and panic syndrome in 44% versus 11.6%.43 Furthermore, patients with severe IBS had a psychiatric comorbidity prevalence of 95.1%, compared to those with mild IBS, suggesting that psychiatric prevalence scales with gastrointestinal severity rather than being uniformly distributed, and that tertiary care rates are inflated by the concentration of severe, treatment-resistant cases at specialist centers.44 Specific microbiome signatures in IBS have proven difficult to replicate consistently across studies, due to IBS subtype heterogeneity, differences in dietary patterns, sampling methods, and

geographic populations.45 Taken together, while the association between gut dysbiosis, gastrointestinal dysfunction, and psychiatric comorbidity in IBS is robustly supported, the field has yet to identify a consistent microbial signature that could serve as a diagnostic or causal marker. Overall, while the association between gut dysbiosis, gastrointestinal dysfunction, and psychiatric comorbidity in IBS is robustly supported, a consistent and replicable microbial signature capable of serving as a diagnostic or causal marker has yet to be identified.

4.2.2 Depression and Anxiety

Approximately 332 million people worldwide experience depression, representing around 4% of the global population and making it one of the leading causes of disability globally.46 Depression, being a chronic condition, presents as lack of energy, insomnia, melancholy, emotional outbursts, loss of appetite, and unexplained physical symptoms such as back pain.47 Experimental data from animal model studies support the relationship between gut dysbiosis and monoamine disruptions seen in clinical depression, alongside which the chronic low-grade inflammation that commonly accompanies stress-related psychiatric disorders has been found to co-occur with intestinal permeability defects in the gut.11 Increasingly recognized as having an inflammatory component, depression symptoms are associated with heightened expression of pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, interferon gamma, and C-reactive protein, as the inflammasome pathway is activated by dysbiosis.48 This relationship is associative in humans rather than causally established, and dysbiosis should be understood as a likely contributor within a broader multifactorial aetiology.

An estimated 4.4% of the global population experience an anxiety disorder, with 359 million people affected as of 2021.49 Anxiety disorder subtypes include panic disorder, generalized anxiety disorder (GAD), and social anxiety disorder. These are among the most closely studied psychiatric conditions in relation to the gut microbiome, as evidenced by findings in GAD patients showing decreased microbial diversity- specifically lower SCFA-producing bacteria and higher pro-inflammatory species including Escherichia-Shigella, Fusobacterium, and Ruminococcus gnavus.50 SCFAs such as butyrate and acetate are key microbial metabolites that support neuroglial function, attenuate inflammation, and modulate neurotransmitter balance including GABA and glutamate. Lower SCFA levels can consequently promote neuroinflammation and HPA axis hyperactivity, thus heightening anxiety symptoms.51 Additionally, infection with Campylobacter jejuni has been shown to induce higher depressive and anxious behavior in animal models by triggering activation of c-Fos proteins as indicators of neuronal activation, further illustrating the gut-to-brain behavioral pathway.52

The current body of evidence linking gut microbiota to depression and anxiety can be meaningfully ranked by strength. The strongest and most reproducible tier consists of human association studies and inflammatory marker data: elevated pro-inflammatory cytokines are consistently observed in MDD and anxiety populations across independent cohorts, and altered microbial diversity has been replicated across multiple clinical studies, lending this tier genuine translatable relevance.53 A moderate tier of evidence comes from rodent FMT studies, where transplanting microbiota from depressed or anxious donors reproduces behavioral phenotypes in recipient animals- compelling mechanistically, but limited in direct human applicability due to fundamental differences in microbiome composition, immune architecture, and behavioral complexity between rodents and humans.54 The weakest tier is direct mechanistic proof in humans: while plausible causal pathways have been proposed, including HPA axis dysregulation, cytokine-mediated neuroinflammation, and SCFA depletion, controlled human studies demonstrating that microbiome manipulation reverses psychiatric symptoms remain scarce and methodologically limited.55 The gut–brain connection in depression and anxiety is therefore strongly suggested but not yet causally confirmed in humans. In summary, the gut–brain connection in depression and anxiety is strongly suggested across multiple tiers of evidence, yet direct causal proof in humans remains scarce, and microbiome manipulation as a therapeutic strategy requires considerably more controlled investigation.

4.2.3 Autism Spectrum Disorders (ASD)

Gastrointestinal symptoms are highly prevalent in ASD, with a global systematic review and meta-analysis estimating that approximately 48.67% of individuals with ASD experience GI symptoms (CI: 43.5%–53.9%).56 In children specifically, a study of 255 children with ASD aged 2–3.5 years found that nearly 48% were reported by caregivers to have GI problems compared to fewer than 18% of neurotypical controls, with approximately 30% of ASD children experiencing multiple GI symptoms simultaneously- further associated with behavior, sleep, and attention problems.57 Shared pathogenetic factors linking ASD and GI disturbances include intestinal inflammation, visceral hypersensitivity, dysautonomia-linked GI dysmotility, and dysregulation of the gut microbiome. It is important to note, however, that prevalence estimates vary substantially across studies: two US studies conducted in 2021 reported GI prevalence figures of 34.60% and 93.18% respectively, a disparity attributable to methodological heterogeneity, diagnostic criteria differences, and population sampling rather than genuine biological variation.58 GI symptoms are common in ASD, but current evidence does not support an ASD-specific gut pathology signature.59

Preclinical evidence provides a compelling mechanistic case for gut microbiota involvement in ASD-associated behavioral phenotypes. GF mice, which lack any microbial colonization, exhibit impaired social communication, positioning gut microbiota as an important non-genetic environmental factor in social behavior development.60 ASD-associated genes have also been found to directly influence gut function: NLGN3 knockout mice carrying confirmed ASD risk alleles displayed decreased colonic smooth muscle tone and altered colonic motility, demonstrating that the genetic architecture of ASD and gut dysfunction are bidirectionally linked.61 Even more strikingly, transplanting gut microbiota from human ASD donors into GF mice was sufficient to induce hallmark autistic behaviors, with the brains of colonized mice displaying alternative splicing of ASD-relevant genes.62 Together, these three lines of evidence- altered social

behavior in GF mice, gut dysmotility from ASD-risk gene knockouts, and behavioral induction via human-to-mouse microbiota transfer- converge on a model in which gut microbial ecology is a meaningful contributor to ASD-associated phenotypes. These results must be treated as preliminary, however, as rodent findings require confirmation in human clinical studies, and the heterogeneous genetic and phenotypic architecture of ASD itself makes it difficult to identify microbiome contributions consistent across the spectrum.

In a small open-label Microbiota Transfer Therapy (MTT) trial in 18 children with ASD, an intensive 10-week protocol combining antibiotic pre-treatment, bowel cleansing, and extended FMT produced approximately 80% reductions in validated GI symptom severity scores alongside significant improvements in core ASD behavioral outcomes.39 Notably, improvements in both GI and autism-related symptoms, along with shifts in gut microbial diversity, persisted through a two-year follow-up assessment- a finding that strengthens the case for durable microbiome-mediated effects on neurodevelopmental outcomes, while remaining limited by the trial's open-label design and small sample size.

5. Key Insights and Future Directions

5.1 Microbiota as a Functional Gene Pool

The gastrointestinal tract houses an estimated 10^{13}–10^{14} microbial cells whose collective genomic content vastly dominates that of the human genome.63 While earlier literature frequently cited a ratio of 10:1 bacterial to human cells, revised estimates now place this figure closer to 1:1, though the biological significance of the microbiota remains undiminished by this correction.64 The scale of the microbiome's genetic contribution remains extraordinary: the metagenome encodes an enormous repertoire of enzymatic and metabolic functions that the human genome alone cannot provide, justifying the microbiome's designation as a 'second human genome' or functional gene pool.65

This framing carries direct implications for how the field approaches diagnostics and therapy. If microbial function—rather than taxonomic composition alone—is what shapes host physiology, then the most clinically meaningful signals are likely to emerge from functional readouts including metabolomic profiling of microbial metabolites such as SCFAs, tryptophan catabolites, and secondary bile acids. The field is transitioning from taxonomic cataloguing toward mechanistic understanding, with metabolomics approaches having greatly advanced understanding of the links between microbiota composition and disease phenotypes. Inflammatory markers derived from gut–immune interactions including cytokines, LPS-binding proteins, and tight junction proteins are increasingly being explored as accessible serum biomarkers that reflect the functional state of the microbiome without requiring invasive sampling. This shift from taxonomy to function positions the microbiome as a tractable therapeutic target, which the following section examines in the context of psychobiotics and microbiome-directed interventions. In summary, the field's transition from taxonomic cataloguing toward functional and metabolomic readouts positions the microbiome as a tractable therapeutic target whose clinical relevance extends well beyond microbial composition alone.

5.2 Therapeutic Potential

Psychobiotics- a term that encompasses probiotics, prebiotics, and synbiotics that target the gut–brain axis to alleviate biological stress and symptoms of neurological conditions including depression and anxiety—demonstrate preliminary clinical efficacy signals across psychiatric and neurodegenerative diseases.67 Proposed mechanisms include enhancing serotonin production, reducing HPA axis hyperactivity, and lowering systemic inflammation. In a clinical randomized, placebo-controlled, double-blind trial involving 40 adults with major depressive disorder (MDD), supplementation with Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum reduced serum high-sensitivity C-reactive protein (hs-CRP), improved glycemic control, and significantly lowered Beck Depression Inventory (BDI) scores, supporting the model that targeted probiotics can improve depression symptomatology by targeting systemic inflammation and oxidative stress.68

In Alzheimer's disease, a randomized, double-blind, controlled trial tested probiotic-enriched milk- consisting of Lactobacillus acidophilus, L. casei, Bifidobacterium bifidum, and L. fermentum (2×10^9 CFU/day)- in 60 older adults aged 60–95 years with Alzheimer's disease over 12 weeks. Results indicated improvements in MMSE scores, reduced oxidative stress as indicated by a drop in plasma malondialdehyde, and decreased hs-CRP indicating lower systemic inflammation.69 These findings are further supported at the meta-analytic level: a systematic review and meta-analysis of 21 animal studies found that probiotics of the genera Lactobacillus and Bifidobacterium were associated with significant reductions in neuroinflammatory markers including TNF-α, IL-6, and IL-1β, reduced amyloid beta deposition, and improvements in long-term memory, short-term memory, and spatial recognition in AD models.70 These findings are suggestive of therapeutic potential across mood disorders and neurodegeneration, but should not be interpreted as definitive given the small sample sizes and the predominantly preclinical nature of the meta-analytic evidence.

Several studies have provided peer-reviewed evidence supporting a gut-originating model of Parkinson's disease pathology. α-Synuclein pathology has been identified in the enteric nervous system of PD patients up to two decades prior to diagnosis, and gastrointestinal symptoms such as constipation commonly manifest years before the appearance of cardinal motor symptoms, with the ENS damaged by enteric α-synuclein accumulation and gut motility progressively slowed during this prodromal phase- creating support for the gut-first hypothesis as a plausible framework, though it remains an active area of debate rather than an established fact.71 In 2021, a trial using a multi-strain probiotic formulation including Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus gasseri, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecalis, and Enterococcus faecium in Parkinson's patients resulted in increased spontaneous bowel movements and improved stool consistency and quality of life related to constipation.72 A 2019 study using Lactobacillus

acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum in PD patients similarly reported improvements in constipation and higher Unified Parkinson's Disease Rating Scale (UPDRS) scores.73 Although these findings are encouraging, the evidence base for probiotics in PD remains limited by small sample sizes, heterogeneity in probiotic strains and dosages, and short intervention durations, all of which preclude definitive conclusions about long-term neuroprotective efficacy.

Across all conditions, the clinical evidence for psychobiotics must be characterized as preliminary. A systematic review of 51 randomized clinical trials involving 3,353 patients reported notable improvements in depression symptoms following psychobiotic treatment, but the variability in treatment approaches, probiotic strains, and clinical presentations across studies significantly limits the comparability and generalizability of findings.74 Key methodological limitations shared across trials include small sample sizes that reduce statistical power and replicability, heterogeneity in probiotic strain composition and dosage, short intervention durations (commonly 4–12 weeks) that preclude assessment of sustained effects, and a lack of standardization in outcome measures, placebo response controls, and effect size reporting. Larger and more standardized randomized controlled trials conducted over longer periods are needed before psychobiotics can be regarded as clinically validated therapeutic approaches to neurodegeneration and mental health conditions. On the whole, psychobiotics and microbiome-targeted interventions demonstrate early but promising therapeutic potential across psychiatric and neurodegenerative conditions, yet significant methodological limitations prevent definitive clinical conclusions at this stage.

6. Conclusion

The microbiota–gut–brain axis represents a mechanistically grounded framework linking gut microbial dynamics with neurological and psychiatric outcomes through neural, endocrine, immune, and metabolic pathways. Current evidence most strongly supports immune and inflammatory signalling as a central mediator, while microbial metabolites and neurotransmitter modulation provide additional mechanistic insight primarily derived from preclinical studies. Although early-life microbiome perturbations and psychobiotic interventions demonstrate meaningful associations with neurodevelopment and disease modulation, robust causal evidence in humans remains limited. Progress in this field depends on large-scale standardized clinical trials, longitudinal multi-omics studies, and targeted mechanistic investigations capable of establishing causality. Advancing these approaches will be essential to translate the microbiota–gut–brain axis from a promising conceptual model into reliable diagnostic and therapeutic strategies.

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