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The Role of the Microbiota-Gut-Brain Axis in Psychiatric and Neurological Disorders

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ABSTRACT

The human gut microbiota, comprising trillions of microorganisms, plays a pivotal role not only in digestion and immunity but also in modulating central nervous system (CNS) function through the microbiota–gut–brain (MGB) axis. This bidirectional network integrates neural pathways, endocrine signalling, immune mechanisms, and microbial metabolites, enabling dynamic communication between the gut and brain. Emerging evidence indicates that disruptions in microbial homeostasis, or dysbiosis, contribute to psychiatric and neurological disorders, including depression, anxiety, autism spectrum disorder, schizophrenia, Parkinson's disease, Alzheimer's disease, multiple sclerosis, epilepsy, and stroke. Mechanistically, microbial alterations influence neurodevelopment, neurotransmitter synthesis, tryptophan metabolism, neuroinflammation, and the integrity of the blood–brain and intestinal barriers. Preclinical models using germ-free animals, faecal microbiota transplantation, and probiotic interventions demonstrate causal links between gut microbiota and behavioural or cognitive changes, while clinical studies increasingly highlight the therapeutic potential of psychobiotics, prebiotics, synbiotics, and diet-based strategies. Additionally, short-chain fatty acids, bile acids, and microbial-derived indoles exert neuroactive effects, modulating synaptic plasticity and immune responses. Despite these advances, translation into clinical practice is limited by methodological heterogeneity, interindividual variability, and the challenge of distinguishing causation from correlation.

Keywords: microbiota–gut–brain axis, psychiatric disorders, neurological disorders, psychobiotics, dysbiosis, neuroinflammation

Introduction

The human gastrointestinal tract is colonised by a complex and dynamic population of microorganisms collectively referred to as the gut microbiota. This community, which includes bacteria, archaea, fungi, protozoa, and viruses, is estimated to comprise more than 100 trillion cells, surpassing the total number of human cells in the body [1]. The gut microbiota plays a pivotal role in host metabolism, nutrient absorption, immune modulation, and the maintenance of mucosal integrity.

However, mounting evidence over the past two decades has highlighted an even broader role of these microbial residents: their ability to influence central nervous system (CNS) function, behavior, cognition, and neurodevelopment, via the microbiota–gut–brain (MGB) axis [2,3].

The MGB axis is a complex, bidirectional communication network that connects the gut and the brain through multiple integrated systems.

These include neural pathways such as the vagus nerve and enteric nervous system (ENS), neuroendocrine signaling via the hypothalamic–pituitary–adrenal (HPA) axis, immune mechanisms involving cytokine production and inflammatory responses, and microbial-derived metabolites such as short-chain fatty acids (SCFAs), tryptophan catabolites, and bile acids [4–6]. These channels of communication not only allow the gut to influence brain activity but also enable the brain to affect gut physiology, motility, and microbial composition through top-down modulation [7].

Disruption in the homeostasis of the gut microbiome—termed dysbiosis—has been increasingly implicated in the development and progression of a variety of psychiatric and neurological disorders. For example, alterations in microbial composition and diversity have been reported in individuals with major depressive disorder (MDD), anxiety disorders, autism spectrum disorders (ASD), schizophrenia, Parkinson's disease (PD), and Alzheimer's disease (AD) [8–10]. These microbial shifts are often associated with increased intestinal permeability ("leaky gut"), systemic inflammation, altered neurotransmitter levels, and activation of microglial cells in the CNS, all of which contribute to disease pathophysiology [11–13].

The mechanisms by which the gut microbiota exerts its effects on the brain are diverse and multifaceted. Microbial metabolites such as SCFAs (butyrate, propionate, acetate) are known to influence neurogenesis, neuroinflammation, and synaptic plasticity. Some gut bacteria can synthesise neurotransmitters or modulate their precursors such as gamma-aminobutyric acid (GABA), dopamine, serotonin, and norepinephrinethereby potentially altering mood and behaviour [14,15]. Moreover, gut microbiota can affect the production of kynurenine from tryptophan, linking microbial metabolism with neuroinflammatory pathways commonly observed in depression and schizophrenia [16].

Preclinical studies using germ-free animal models, faecal microbiota transplantation (FMT), and probiotic interventions have provided compelling evidence for the role of microbiomes in brain development and function. Germ-free mice, for instance, show altered anxiety-like behaviour, impaired social interaction, and abnormal stress responses, which can be partially reversed by colonisation with specific microbial strains [17]. Clinical studies, though fewer in number, have started to mirror these findings. Meta-analyses and randomised controlled trials (RCTs) have begun to show that certain probiotic strains collectively termed *psychobiotics*—may reduce symptoms of depression and anxiety, enhance cognitive function, and support emotional regulation [18].

Despite the promising potential of the MGB axis as a therapeutic target, several challenges remain. Human studies are often confounded by inter-individual variability in microbiome composition, dietary influences, medication use (particularly antibiotics and psychotropics), and methodological inconsistencies in microbiota sampling and analysis. Furthermore, distinguishing causality from mere association remains a major hurdle.

As such, future research must employ longitudinal, mechanistic, and multi-omic approaches including metagenomics, metabolomics, proteomics, and neuroimaging to unravel the complexity of gut–brain interactions and validate microbiome-targeted interventions [19].

Aim and Scope:

This narrative review aims to:
(1) provide a comprehensive overview of the biological pathways that constitute the MGB axis,
(2) examine the growing body of evidence linking gut microbiota alterations with psychiatric and neurological conditions, and
(3) Explore the current and emerging therapeutic applications of microbiome-based interventions. By synthesising evidence across disciplines, microbiology, neuroscience, psychiatry, immunology, this review underscores the MGB axis as a promising yet underutilised frontier in the prevention, diagnosis, and treatment of brain-related disorders.

Mechanisms of the Microbiota–Gut–Brain Axis

The microbiota–gut–brain (MGB) axis represents an intricate, multidimensional communication network that integrates signals originating from the gut microbiota with the central nervous system (CNS). This bidirectional system operates through a constellation of interrelated pathways including neural signaling (primarily via the vagus nerve and enteric nervous system), neuroendocrine regulation (notably the hypothalamic–pituitary–adrenal [HPA] axis), immune modulation, microbial metabolite signaling (e.g., short-chain fatty acids [SCFAs], neurotransmitters), and epigenetic mechanisms. These pathways are deeply interconnected and collectively contribute to both the homeostatic regulation and pathophysiological alterations implicated in psychiatric and neurological diseases.

Neural Pathways: Vagus Nerve and Enteric Nervous System

The vagus nerve is the principal afferent conduit transmitting microbial and gut-derived signals to the brain. Comprising approximately 80% afferent fibers, it innervates the gastrointestinal (GI) tract and projects to brainstem regions including the nucleus tractus solitarius and locus coeruleus, modulating autonomic, emotional, and behavioral functions [20]. Stimulation of the vagus nerve by microbial metabolites such as γ-aminobutyric acid (GABA) or short-chain fatty acids can influence mood and cognition. For example, *Lactobacillus rhamnosus* reduced anxiety- and depression-like behavior in mice via vagal activation, an effect abolished by vagotomy [21].

The enteric nervous system (ENS), embedded in the gut wall, functions semi-autonomously but is modulated by the CNS via sympathetic and parasympathetic inputs. Gut microbes modulate the development and excitability of enteric neurons through bioactive molecules such as SCFAs and indoles. Moreover, microbial interactions with enteroendocrine and enterochromaffin cells can modulate 5-hydroxytryptamine (5-HT) release, influencing peristalsis and vagal afferent signaling [22].

Neuroendocrine Pathways: HPA Axis and Stress Reactivity

The hypothalamic–pituitary–adrenal (HPA) axis is the body's central stress response system. Gut microbiota critically regulates HPA axis reactivity, especially during early developmental windows. Germ-free (GF) mice exhibit exaggerated corticosterone responses to stress, which can be attenuated by colonization with specific microbial strains such as *Bifidobacterium infantis* [23]. This suggests a developmental programming role for gut microbes in neuroendocrine maturation.

Microbial regulation of the HPA axis is partly mediated by tryptophan metabolism. Under pro-inflammatory conditions, tryptophan is catabolized via indoleamine 2,3-dioxygenase (IDO) into kynurenine and its downstream metabolites, including quinolinic acid and kynurenic acid. These neuroactive compounds modulate glutamatergic neurotransmission and have been implicated in neuroinflammation and psychiatric disorders such as depression and schizophrenia [24].

Additionally, stress-induced activation of corticotropin-releasing hormone (CRH) receptors in intestinal epithelial cells increases intestinal permeability, facilitating systemic exposure to microbial components such as lipopolysaccharide (LPS), which can further activate the HPA axis and propagate neuroinflammatory responses [25].

Immune System Signalling and Microglial Activation

The gut microbiota plays a fundamental role in shaping both mucosal and systemic immunity. Microbial-associated molecular patterns (MAMPs), including LPS, peptidoglycan, and flagellin, activate host pattern recognition receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), initiating downstream signalling cascades involving NF-κB and MAPK pathways that result in the secretion of pro-inflammatory cytokines [26].

Systemic inflammation and increased gut permeability—hallmarks of dysbiosis—permit the translocation of microbial products into circulation, leading to activation of microglial cells in the CNS. Activated microglia exhibits a pro-inflammatory phenotype (M1), characterised by the release of interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α), and reactive oxygen species (ROS), which contribute to neuronal injury and synaptic loss [27]. Conversely, commensal-derived signals are essential for maintaining microglial homeostasis. GF mice display impaired microglial maturation and dysfunctional responses to immune stimuli, which are normalised following colonisation or SCFA supplementation [28].

Microbial Metabolites and Neurotransmitter Modulation

Short-Chain Fatty Acids (SCFAs)

SCFAs, primarily acetate, propionate, and butyrate, are produced via bacterial fermentation of dietary fibres. These molecules cross the intestinal barrier and can influence CNS activity through multiple mechanisms. Butyrate, a potent histone deacetylase (HDAC) inhibitor, enhances transcription of neuroprotective genes such as BDNF and modulates synaptic plasticity and memory formation [29]. SCFAs also regulate the expression of tight junction proteins, preserving the integrity of both the gut epithelium and the blood–brain barrier (BBB) [30].

Neurotransmitters and Precursors

Several gut bacteria can synthesize or modulate host levels of neurotransmitters:

- Serotonin (5-HT): Although peripheral 5-HT cannot cross the BBB, microbial modulation of serotonin in enterochromaffin cells impacts vagal afferent firing and systemic serotonin signaling [31].
- GABA: Produced by *Lactobacillus* and *Bifidobacterium* species, GABA regulates neuronal excitability and exhibits anxiolytic properties [32].
- Dopamine and Norepinephrine: Certain *Escherichia* and *Bacillus* species can produce these catecholamines, influencing mood and arousal states [33].
- Tryptophan: A key precursor for both serotonin and kynurenine, its availability and metabolic fate are tightly regulated by gut microbiota.

Bile Acids and Secondary Metabolites

Gut bacteria enzymatically convert primary bile acids into secondary bile acids such as deoxycholic acid and

lithocholic acid, which activate receptors including the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). These receptors are expressed not only in the gut and liver but also in the CNS and immune cells, influencing inflammation, energy homeostasis, and potentially cognition [34].
Additionally, microbial-derived indoles from tryptophan metabolism act on the aryl hydrocarbon receptor (AhR), a transcription factor in astrocytes and microglia that modulates neuroinflammatory responses and promotes neuroprotection [35].

Extracellular Vesicles and Microbial RNA

Recent discoveries have highlighted the role of microbiota-derived extracellular vesicles (EVs) as carriers of proteins, lipids, and nucleic acids capable of systemic dissemination. These vesicles can cross biological barriers and deliver cargo such as microRNA-like molecules or small RNAs that modulate host gene expression, immune responses, and neuronal signaling [36].
For instance, *Bacteroides fragilis*-derived EVs have been shown to enhance BBB permeability and induce neuroinflammatory gene expression in mouse models [37]. This adds a new layer of complexity to gut–brain communication, extending beyond traditional metabolites and cytokines.

Epigenetic Regulation

Epigenetic modulation represents a novel and underexplored mechanism of the MGB axis. Butyrate and other SCFAs exert their effects by inhibiting HDACs, thus altering histone acetylation and chromatin accessibility. This facilitates the transcription of genes associated with neuroprotection, neurogenesis, and synaptic remodeling, including BDNF and NTRK2 [38].
Moreover, microbiota can influence the host's epigenome through miRNA modulation. Alterations in the expression of miRNAs implicated in neurodevelopment (e.g., miR-124, miR-132) have been observed in response to microbial dysbiosis, impacting neuronal differentiation, plasticity, and inflammatory signaling [39].

Microbiota Alterations in Psychiatric Disorders

Emerging evidence suggests that psychiatric disorders such as major depressive disorder (MDD), anxiety, bipolar disorder, schizophrenia, and autism spectrum disorder (ASD) are not solely brain-based diseases but are influenced by complex interactions with peripheral systems, including the gut microbiome. Dysbiosis—characterized by reduced microbial diversity, an overgrowth of pathobionts, and depletion of beneficial taxa—has been consistently observed across several psychiatric conditions. These alterations affect host immunity, neuroendocrine responses, neurotransmitter systems, and neuroplasticity, highlighting the microbiota–gut–brain axis as a key modulator in the pathophysiology of mental illness.

Major Depressive Disorder (MDD)

MDD is among the most extensively studied psychiatric conditions in relation to the gut microbiota. Multiple clinical studies have revealed compositional shifts in the gut microbiota of depressed individuals, with consistent findings of decreased levels of Firmicutes (e.g., *Faecalibacterium*, *Coprococcus*) and increased abundance of Bacteroidetes and Proteobacteria, including potentially pro-inflammatory genera such as *Alistipes* and *Oscillibacter* [40].
Functional metagenomic analysis indicates that the microbiota in MDD patients has reduced capacity for SCFA production, impaired GABA and serotonin metabolism, and increased capacity for LPS synthesis, all of which may drive neuroinflammation and HPA axis dysregulation [41]. Transplantation of fecal samples from MDD patients into germ-free rodents induces depressive-like behaviors, confirming causality between microbial dysbiosis and depressive phenotypes [42].

Anxiety Disorders

Anxiety and depression frequently co-occur and share overlapping microbial signatures. Preclinical studies have demonstrated that GF mice display exaggerated anxiety-like behaviours, increased plasma corticosterone, and altered expression of BDNF in the hippocampus and amygdala, effects reversible by microbial colonisation [43]. Administration of certain probiotic strains, such as *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175, reduces anxiety scores in both animals and humans, potentially by modulating GABAergic pathways and attenuating systemic inflammation [44].
Microbiome-based studies have also linked chronic anxiety to increased intestinal permeability ("leaky gut") and systemic low-grade inflammation, marked by elevated IL-6, TNF-α, and C-reactive protein (CRP) cytokines known to influence CNS excitability and HPA axis responsiveness [45].

Autism spectrum disorder (ASD)

ASD is a neurodevelopmental disorder characterized by impaired social communication and repetitive behaviors. Children with ASD frequently exhibit gastrointestinal symptoms, and alterations in the gut microbiota are well-documented. Common findings include elevated levels of Clostridium, Desulfovibrio, and Sutterella, and depletion of beneficial bacteria such as *Bifidobacterium* and *Prevotella* [46].
These microbial shifts may contribute to systemic immune activation, mitochondrial dysfunction, and

alterations in neurotransmitter synthesis—particularly GABA and dopamine. Children with ASD show elevated urinary levels of 4-ethylphenyl sulfate (4EPS), a gut-derived neuroactive metabolite linked to behavioral abnormalities in animal models [47]. Fecal microbiota transplantation (FMT) has been associated with improvements in both GI symptoms and core behavioral traits in ASD, further reinforcing the causal role of dysbiosis [48].

Schizophrenia

Schizophrenia has traditionally been viewed through a dopaminergic lens; however, emerging studies suggest a potential microbial component. Patients with schizophrenia often exhibit gut dysbiosis characterized by increased *Lactobacillus* spp., reduced SCFA-producing bacteria, and altered tryptophan metabolism [49].

These microbial imbalances may influence glutamatergic signaling and neuroimmune activation. Notably, increased kynurenine/tryptophan ratios have been reported in schizophrenia, reflecting enhanced IDO1 activity and a neurotoxic metabolic shift [50]. A study by Zheng et al. demonstrated that FMT from schizophrenia patients induced behavioral deficits and neurochemical changes in mice, providing further mechanistic insights [51].

Bipolar Disorder

Though less explored than MDD or schizophrenia, bipolar disorder (BD) is increasingly linked with microbial alterations. A pilot study reported reduced abundance of Faecalibacterium prausnitzii and increased Actinobacteria during manic and depressive episodes [52]. Dysbiosis in BD has been correlated with oxidative stress markers and immune activation, notably higher IL-6 and CRP levels.

Moreover, mood stabilizers such as lithium and valproate can influence microbial composition, suggesting a bidirectional interaction between psychotropic treatment and the microbiome [53]. Studies are underway to determine whether microbial profiles can predict treatment response or risk of relapse in BD patients.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Emerging evidence suggests that gut microbiota may also play a role in the neurodevelopmental underpinnings of ADHD. Children with ADHD show a relative increase in *Bacteroides* and a decrease in *Faecalibacterium* and *Bifidobacterium* [54]. These changes may influence dopaminergic pathways critical for attention and reward processing.

Furthermore, a recent study demonstrated that microbial metabolites affect expression of tyrosine hydroxylase and dopamine transporter genes, suggesting a mechanistic basis for altered dopamine signaling in ADHD [55].

Common Mechanistic Threads Across Disorders

Despite clinical heterogeneity, several recurring features connect psychiatric disorders through the lens of the gut–brain axis:

- Reduced microbial diversity and SCFA-producing taxa
- Upregulated inflammation, both systemic (IL-6, TNF-α) and neuroinflammatory (microglial activation)
- Altered tryptophan metabolism, leading to imbalanced kynurenine pathways
- Disrupted gut barrier and BBB integrity
- Neurotransmitter dysregulation (GABA, serotonin, dopamine)
- Modifiable by probiotics, prebiotics, FMT, and dietary interventions

These findings collectively reinforce the therapeutic potential of microbiome-targeted strategies in psychiatry.

Microbiota and Neurological Disorders

Beyond psychiatric illnesses, compelling evidence now links gut microbial dysregulation to various neurological disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), epilepsy, and stroke. While each of these disorders has unique etiological mechanisms, they all share common pathophysiological threads involving neuroinflammation, oxidative stress, blood–brain barrier (BBB) dysfunction, and abnormal protein aggregation, many of which are modulated by the gut microbiota. This section delineates current insights into how microbial alterations contribute to the onset and progression of these neurological diseases.

Parkinson's Disease (PD)

PD is characterised by progressive loss of dopaminergic neurons in the substantia nigra, leading to tremors, bradykinesia, rigidity, and non-motor symptoms such as constipation, anosmia, and mood disturbances—all of which may precede motor signs by years. The early appearance of gastrointestinal symptoms has led to the hypothesis that PD may originate in the gut.

Postmortem analyses have identified aggregated α-synuclein in the enteric nervous system (ENS) and vagus nerve even before reaching the CNS. The Braak hypothesis proposes that misfolded α-synuclein propagates from the gut to the brain via vagal retrograde transport [60]. This idea is supported by evidence that truncal vagotomy reduces PD risk [61].

Several studies have revealed distinct microbial signatures in PD patients: a decrease in SCFA-producing taxa such as *Faecalibacterium* and *Roseburia*, and an increase in pro-inflammatory species like *Akkermansia*, *Proteobacteria*, and *Desulfovibrio* [62]. These changes contribute to a leaky gut barrier, heightened systemic inflammation, and microglial activation—critical events in dopaminergic neurodegeneration [63].

Additionally, SCFAs like butyrate have neuroprotective and anti-inflammatory effects, enhancing regulatory T-cell (Treg) function, promoting anti-inflammatory cytokines (e.g., IL-10), and maintaining blood–brain barrier (BBB) integrity through upregulation of tight junction proteins such as claudin-5 and occludin. However, in the context of Parkinson's disease, emerging data suggest that excessive or dysregulated SCFA production may paradoxically exacerbate neuroinflammation. In mouse models overexpressing human α-synuclein, microbial-derived SCFAs were shown to induce microglial activation, intensify pro-inflammatory responses, and accelerate motor dysfunction and dopaminergic neuron loss [64].

These dual roles of SCFAs highlight the context-dependent nature of microbiota-derived metabolites—offering either neuroprotection or neurotoxicity based on microbial composition, host immune status, and disease stage. Thus, targeted modulation of gut microbiota to restore beneficial SCFA profiles without tipping the balance toward pro-inflammatory signaling represents a promising but challenging therapeutic frontier in PD.

Alzheimer's Disease (AD)

Alzheimer's disease is the most common form of dementia, clinically characterised by progressive cognitive decline and pathologically by extracellular β-amyloid (Aβ) plaques, intracellular tau neurofibrillary tangles, synaptic loss, and neuroinflammation. Though traditionally considered a brain-restricted disorder, recent advances reveal that gut microbiota dysbiosis may significantly contribute to AD pathogenesis via multiple mechanisms: neuroimmune modulation, systemic inflammation, altered amyloid processing, and impaired neurotransmitter balance [65].

Gut Dysbiosis and Amyloidogenesis

Multiple studies have identified altered gut microbial profiles in AD patients, often marked by:

- Depletion of anti-inflammatory genera: *Eubacterium*, *Faecalibacterium*, and *Bifidobacterium*
- Enrichment of pro-inflammatory taxa: *Escherichia/Shigella*, *Proteobacteria*, and *Firmicutes/Bacteroidetes* imbalance [66]

This dysbiosis contributes to increased gut permeability and systemic translocation of lipopolysaccharide (LPS) and bacterial amyloids. These molecules activate Toll-like receptor 4 (TLR4) and NF-κB pathways, upregulating pro-inflammatory cytokines (IL-1β, TNF-α), which can cross the BBB and promote microglial activation, Aβ deposition, and tau hyperphosphorylation [67].

Interestingly, bacterial amyloids (e.g., *Curli* from *E. coli*) share structural homology with human Aβ, potentially acting as cross-seeding agents that accelerate Aβ aggregation in the brain [68]. This hypothesis has been demonstrated in preclinical models where oral administration of curli-expressing bacteria exacerbated Aβ pathology and cognitive deficits [69].

SCFAs, Neuroprotection, and the BBB

SCFAs, particularly butyrate, exert anti-inflammatory and neuroprotective effects via:

- Histone deacetylase (HDAC) inhibition, enhancing memory-related gene transcription
- Maintenance of tight junction proteins, preserving BBB integrity
- Modulation of neurotrophic signaling, including BDNF and IGF-1 pathways [70]

Animal studies show that dietary fiber supplementation or butyrate administration improves cognitive function and reduces Aβ load in AD models [71]. However, these effects are absent in GF or dysbiotic animals, highlighting the microbiome's central role.

Multiple Sclerosis (MS)

MS is an autoimmune demyelinating disease of the CNS, often associated with relapsing-remitting neurological symptoms, chronic neuroinflammation, and axonal degeneration. While the exact trigger is unknown, increasing evidence implicates the gut microbiome as a modulator of immune tolerance, T-cell differentiation, and BBB integrity in MS pathogenesis.

Dysbiosis and Immune Dysregulation

Patients with MS display a decrease in butyrate-producing taxa such as *Clostridia XIVa* and *Faecalibacterium prausnitzii*, and an increase in pro-inflammatory bacteria like *Akkermansia muciniphila*, *Methanobrevibacter*, and *Desulfovibrio* [72]. These changes skew immune responses toward a pro-inflammatory Th1/Th17 phenotype, reduce Treg populations, and increase CNS infiltration by autoreactive lymphocytes.

In experimental autoimmune encephalomyelitis (EAE) models, colonisation with Clostridium clusters IV and XIVa has been shown to induce colonic Tregs and suppress CNS autoimmunity [73]. Moreover, SCFAs like butyrate and propionate suppress microglial activation and modulate epigenetic programs in astrocytes, offering neuroprotective benefits [74].

Gut–Brain Barrier Crosstalk

Increased intestinal permeability commonly observed in MS is associated with elevated systemic levels of zonulin, microbial antigens, and cytokines, which can compromise the BBB and promote CNS infiltration of immune cells [75]. These findings underscore the gut as a potential site of initial immune dysregulation in MS.

Epilepsy

Epilepsy is characterized by recurrent unprovoked seizures due to abnormal neuronal hyperexcitability. While traditionally managed with anticonvulsants, increasing attention has been given to gut microbiota modulation as both a contributor and therapeutic target in drug-resistant epilepsy.

Microbiota–Seizure Link

Several studies indicate that children with refractory epilepsy have distinct microbial compositions compared to controls, often with lower microbial richness and reduced SCFA-producing bacteria [76]. Dysbiosis may influence seizure susceptibility by:

- Altering GABA/glutamate balance
- Promoting systemic inflammation
- Modulating neurotransmitter precursors and transporters

Ketogenic Diet and Microbial Modulation

The ketogenic diet (KD), high in fat and low in carbohydrates, is effective in reducing seizure frequency—especially in drug-resistant cases. Interestingly, its antiepileptic effects may be partly microbiota-mediated. Olson et al. (2018) demonstrated that the KD alters gut flora composition (e.g., increased *Akkermansia* and *Parabacteroides*), which in turn modulates γ-glutamylation pathways and elevates GABAergic tone, reducing excitability and seizure activity [77].

Moreover, antibiotic-induced microbiota depletion abolishes the seizure-protective effects of KD, highlighting the microbiota's necessity for full therapeutic response [78].

Stroke and Post-Stroke Cognitive Impairment

Stroke is a leading cause of mortality and long-term disability, with post-stroke cognitive decline often being a major consequence. Recent studies reveal that gut microbiota dysbiosis occurs immediately after ischemic stroke, influencing infarct volume, neuroinflammation, and neurological recovery.

Post-Stroke Dysbiosis

Stroke induces bidirectional gut–brain changes:

- Reduced gut motility and blood flow impair microbial diversity
- Systemic inflammation and CNS injury increase gut permeability
- Microbial translocation contributes to systemic infection and poor outcome [79]

These changes promote a shift toward pro-inflammatory microbiota (e.g., *Enterobacteriaceae*, *Clostridium difficile*), exacerbating brain injury via peripheral immune activation and microglial overreaction. Restoration of microbial balance via prebiotics, probiotics, or FMT in animal models reduces infarct size and improves neurobehavioral outcomes.

Therapeutic Implications and Future Directions

The expanding recognition of the microbiota–gut–brain axis in psychiatric and neurological disorders offers a paradigm shift in how we conceptualise, diagnose, and manage these complex diseases. With mounting evidence linking microbial dysbiosis to mental and cognitive health, attention has increasingly turned to modulating the gut microbiota as a therapeutic strategy. These approaches include probiotics, prebiotics, synbiotics, faecal microbiota transplantation (FMT), dietary interventions, psychobiotics, and even targeted microbial metabolite therapies.

However, translating preclinical and early-phase clinical insights into standardised, evidence-based interventions remains a substantial challenge. This section explores the therapeutic landscape, the current clinical evidence, and the key future directions for harnessing the microbiome in neuropsychiatric care.

Probiotics and Psychobiotics

Probiotics, defined as live microorganisms that confer health benefits to the host when administered in adequate amounts, have garnered significant interest in mental health. When these strains show efficacy in modulating mood, cognition, or behavior, they are often referred to as psychobiotics [80].

Strains such as *Lactobacillus rhamnosus*, *Bifidobacterium longum*, *L. helveticus*, and *L. plantarum* have been shown to reduce anxiety and depressive symptoms in both preclinical models and small-scale human studies [81,82]. The mechanisms include:

- Increased production of GABA and serotonin
- Modulation of vagal afferent signaling
- Suppression of pro-inflammatory cytokines
- Enhancement of HPA axis resilience

In a double-blind, placebo-controlled trial, Messaoudi et al. demonstrated that a probiotic combination of *L. helveticus* R0052 and *B. longum* R0175 significantly reduced psychological distress and cortisol levels in healthy volunteers [83]. Despite promising findings, replication in larger, heterogeneous psychiatric populations is still limited.

Prebiotics and Synbiotics

Prebiotics are non-digestible food components (e.g., inulin, fructooligosaccharides) that selectively stimulate the growth of beneficial gut microbes. They can enhance the production of short-chain fatty acids (SCFAs) and promote the growth of anti-inflammatory genera like *Bifidobacterium* and *Faecalibacterium* [84].
Preclinical studies show that prebiotics can:

- Normalise microglial morphology
- Improve synaptic plasticity
- Reduce anhedonic behavior in chronic stress models [85]

Synbiotics, the combination of probiotics and prebiotics, may offer synergistic benefits. In schizophrenia, a pilot RCT found that synbiotic supplementation improved cognitive performance and working memory, though larger trials are needed [86].

Fecal Microbiota Transplantation (FMT)

FMT involves transferring stool from a healthy donor to a recipient's GI tract, aiming to reset microbial composition. While established in treating recurrent *Clostridioides difficile* infection, its neuropsychiatric application is emerging.
Notably:

- In ASD, FMT improved both GI and behavioral symptoms, with benefits persisting for two years post-treatment [87].
- In major depression, animal studies show that FMT from healthy donors ameliorates depressive-like behaviors, while FMT from depressed patients induces them [88].
- In PD, a 2021 clinical case series found improved motor symptoms and stool consistency post-FMT [89].

However, standardized protocols, donor screening criteria, long-term safety data, and regulatory oversight are lacking. Moreover, the interindividual variability in microbiota response complicates the predictability of FMT outcomes [90].

Diet-Based Interventions

Diet is a primary modulator of gut microbiota composition. Mediterranean diets, high in fiber, polyphenols, and omega-3 fatty acids, are associated with increased microbial diversity, anti-inflammatory SCFAs, and reduced risk of depression and cognitive decline [91].
Interventional studies have shown that:

- High-fiber diets reduce neuroinflammation and improve cognition in animal models [92]
- Omega-3 supplementation modulates gut flora and enhances BDNF expression in the hippocampus [93]
- Polyphenols (e.g., flavonoids, resveratrol) enhance the growth of Lactobacillus, Akkermansia, and Bifidobacterium, which are linked to improved neurocognitive outcomes [94]

Thus, nutritional psychiatry represents a sustainable, non-invasive strategy for long-term microbiome modulation.

Microbial Metabolite-Based Therapies

An emerging frontier is the direct therapeutic use of microbial metabolites, such as SCFAs, tryptophan derivatives, and bile acid modulators. For instance:

- Butyrate, as a histone deacetylase (HDAC) inhibitor, improves memory consolidation in Alzheimer's models [95].
- Indole-3-propionic acid (IPA), a microbial tryptophan metabolite, has neuroprotective properties through antioxidant and anti-inflammatory effects [96].
- Modulating the kynurenine pathway via dietary or microbial approaches may help re-balance the neurotoxic/neuroprotective metabolite ratio in depression and schizophrenia [97].

These precision therapies aim to bypass variability in

microbial colonization and deliver targeted neuroactive effects.

Challenges and Future Directions

Despite substantial preclinical evidence and early-phase clinical signals, microbiome-based neurotherapeutics face several challenges:

- Interindividual Microbial Variability
  Factors such as age, genetics, medications, and environment affect baseline microbiota composition, complicating standardization of interventions.
- Lack of Large-Scale Randomized Trials
  Most clinical evidence comes from small, underpowered trials with inconsistent strain selection, dosing, and outcome measures.
- Regulatory and Ethical Considerations
  FMT and live biotherapeutics require clear safety regulations, especially in vulnerable populations (e.g., elderly, immunocompromised).
- Causality vs Correlation
  Disentangling whether dysbiosis is a cause or consequence of neuropsychiatric disease remains challenging. Multi-omics approaches, including metabolomics, metagenomics, and neuroimaging, are required to strengthen causal inference.
- Personalized Microbiome Medicine
  Future therapeutics may involve host–microbe matching, real-time microbiome monitoring, and AI-assisted dietary/microbial recommendations tailored to individual profiles.

The next decade promises exciting developments in precision psychobiotics, synthetic microbial consortia, engineered probiotics, and microbiome biomarkers for diagnosis and prediction of treatment response. Tools like CRISPR/Cas9 for microbiota editing, next-generation sequencing, and machine learning-based gut-brain modeling will further refine our understanding of host–microbiota–neurocircuit interactions.

Importantly, the future of gut–brain axis therapeutics lies not in single-microbe solutions, but in ecosystem-based approaches that restore resilience, diversity, and metabolic balance to the host microbial community.

Conclusion and Research Gaps

Conclusion

The last decade has witnessed an extraordinary transformation in our understanding of brain health one that acknowledges the microbiota–gut–brain axis (MGBA) as a central player in neuropsychiatric and neurodegenerative disorders. No longer can the brain be viewed as an isolated organ. Instead, it is deeply intertwined with peripheral systems, particularly the intestinal ecosystem, which houses trillions of microorganisms that communicate with the central nervous system via neural, immune, endocrine, and metabolic pathways.

Evidence across disciplines ranging from clinical case-control studies to germ-free animal models and interventional trials has demonstrated that gut microbial dysbiosis plays a causative and modulatory role in conditions such as major depressive disorder, anxiety, autism spectrum disorder, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and epilepsy. Mechanistically, these effects are mediated by:

- Microbial metabolites like short-chain fatty acids (SCFAs), tryptophan catabolites, and bile acids
- Modulation of systemic and neuroinflammatory pathways
- Impact on neurotransmitter synthesis and receptor signalling
- Influence on the integrity of the intestinal and blood–brain barriers
- Regulation of the hypothalamic–pituitary–adrenal (HPA) axis and vagal tone

At the therapeutic level, interventions such as probiotics, prebiotics, synbiotics, fecal microbiota transplantation, dietary strategies, and microbial metabolite-based therapies have shown promising results in both preclinical and early-phase clinical settings. Importantly, these approaches not only offer symptom relief but may also modify disease progression by restoring microbial balance and immune homeostasis.

Yet, despite encouraging insights, microbiome-targeted therapies are not yet ready for routine clinical use in psychiatry or neurology. Their future application demands rigorous evidence, precision delivery systems, and a deeper understanding of host–microbe interactions.

Research Gaps and Future Directions

- Standardization and Reproducibility
  The majority of current microbiota studies suffer from lack of standardization in methodology—including differences in sample collection, sequencing platforms, bioinformatics pipelines, and statistical models. This heterogeneity limits reproducibility across studies and makes cross-trial comparisons difficult. Establishing unified protocols and data-sharing consortia is essential to consolidate findings and move toward clinical applications [100].

- Causality versus Correlation
  While compelling correlations between gut microbial patterns and neurological symptoms exist, causality remains insufficiently established in humans. More robust designs, including longitudinal cohort studies, microbiota depletion or engraftment models, and gnotobiotic humanized mouse experiments, are necessary to delineate causal pathways [101].
- Interindividual Variability
  Host-specific factors such as genetics, age, diet, geography, early-life exposures, comorbidities, and medications influence the baseline microbiome. Consequently, microbial interventions may have differential efficacy between individuals. The future of gut–brain therapeutics lies in personalized medicine, which will integrate microbiome profiling with host transcriptomics, epigenomics, and metabolomics to tailor interventions [102].

- Long-term Safety and Efficacy
  Most human studies on probiotics, FMT, and dietary modulation have been short-term and conducted in relatively healthy cohorts. The long-term safety, efficacy, and durability of microbiome-based treatments in vulnerable populations—especially elderly individuals, immunocompromised patients, and those with progressive neurological diseases—remain poorly characterized [103].

- Microbiome as a Biomarker
  The gut microbiome holds promise not only as a therapeutic target but also as a diagnostic and prognostic biomarker. Studies have shown that microbial signatures may predict disease onset, cognitive decline, treatment response, and relapse risk in depression, schizophrenia, and Parkinson's disease. However, robust biomarker validation across diverse populations is still lacking [104].

- Regulatory and Ethical Considerations
  Regulatory frameworks for microbiome-based interventions, particularly live biotherapeutic products and FMT, remain underdeveloped. There is a pressing need for clear safety guidelines, donor screening protocols, ethical use standards, and pathways for regulatory approval—especially for interventions in psychiatric and pediatric populations [105].

Final Remarks

The gut microbiota has emerged as a missing link between environment, behavior, immunity, and brain function. Its profound influence on mental and neurological health offers a tantalizing prospect: that we may one day prevent, diagnose, and treat brain disorders not only through neuropharmacology or psychotherapy, but also by cultivating a healthy microbial ecosystem.

Realizing this vision, however, will require cross-disciplinary collaboration among microbiologists, neuroscientists, psychiatrists, dietitians, immunologists, and data scientists. It will demand technological innovation, ethical oversight, and a commitment to translational research that bridges basic science and bedside care.

As we enter the era of "psychobiotics and neurobiome medicine," we must ensure that science leads the way—guided by evidence, powered by technology, and grounded in patient-centred care.

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