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The Microbiota-Gut-Brain Axis in Neurological and Neuropsychiatric Disorders: A Literature Review

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Abstract

The gut-brain axis is a bidirectional communication network linking the GI tract and central nervous system via neural, immune, endocrine, and metabolic pathways. Growing evidence suggests that alterations in the gut microbiota are associated with the pathophysiology and clinical features of several neurological and neuropsychiatric disorders, including schizophrenia, autism spectrum disorder (ASD), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety disorders, and amyotrophic lateral sclerosis (ALS). This narrative review used a structured search of PubMed/MEDLINE, ScienceDirect, SpringerLink, and Wiley Online Library to identify relevant literature published from January 1, 2010, through the final search date of June 25, 2026.

Proposed mechanisms linking gut dysbiosis with neurological dysfunction include alterations in intestinal and blood-brain barrier (BBB) integrity, systemic inflammatory signaling, microglial activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, changes in neurotransmitter pathways, and altered production of microbial metabolites such as short-chain fatty acids (SCFAs). Advanced profiling technologies, including 16S rRNA sequencing, whole-genome metagenomics, and metabolomics, have significantly enhanced the identification of disease-associated microbial signatures. These observations have stimulated interest in microbiome-targeted interventions, including probiotics, prebiotics, psychobiotics, synbiotics, fecal microbiota transplantation (FMT), live biotherapeutic products, and dietary modification; however, evidence supporting their clinical efficacy in neurological disorders remains limited and heterogeneous.

Across the disorders reviewed, recurrent findings include alterations in microbial composition, intestinal barrier function, inflammatory signaling, and microbial metabolites. However, specific taxonomic signatures vary considerably among studies. Human evidence remains predominantly associative, while stronger mechanistic evidence is largely derived from animal and microbiota-transfer studies. Clinical studies of microbiome-targeted interventions remain limited and heterogeneous. Large-scale longitudinal studies and randomized controlled trials are critical to establishing causality, refining microbiome-targeted therapies, and developing personalized diagnostic tools for neurodegenerative and psychiatric diseases.

Categories: Therapeutics, Neurology, Preventive Medicine
Keywords: alzhiemer's disease, amyotrophic lateral sclerosis(als), anxiety, autism spectrum disorder (asd), gut-brain axis, gut dysbiosis, gut microbiome, neuroinflammation and mental health, parkinson`s disease, schizophrenia

Introduction And Background

The gut microbiome is an important component of human physiology, contributing not only to digestion and immune regulation but also to metabolic, neuroendocrine, and neurological processes. Bidirectional communication between the GI tract and the CNS, commonly referred to as the gut-brain axis, contributes to the regulation of neural development, stress responses, mood, cognition, and immune homeostasis, as illustrated in Figure *1* [1].

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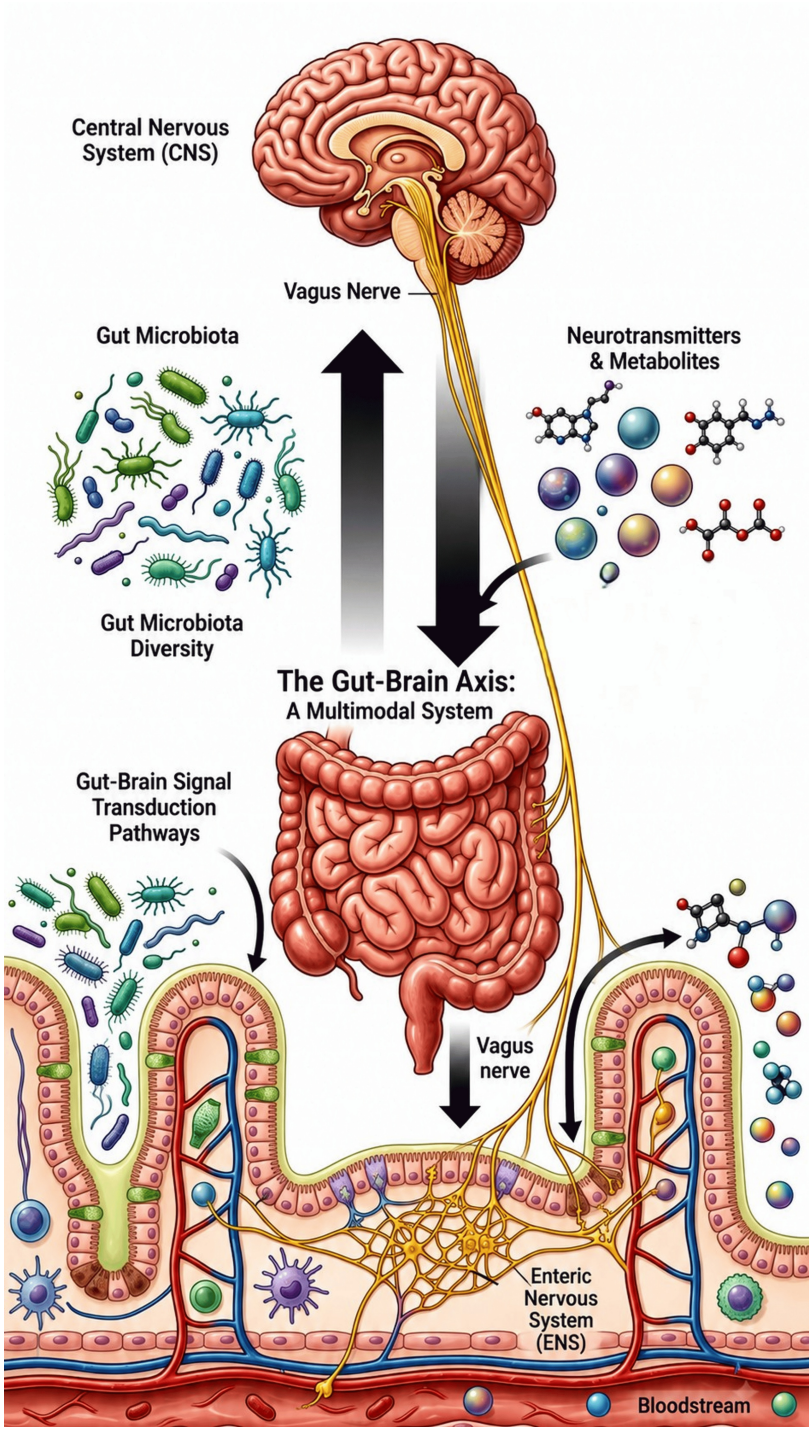


FIGURE 1: Schematic illustration of bidirectional communication between the gut microbiota and the brain via the gut-brain axis.

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The human gut microbiota comprises diverse bacterial taxa, including members of the phyla Firmicutes and Bacteroidetes and numerous genera such as *Lactobacillus* and *Bacteroides*. Dysbiosis refers to alterations in microbial composition, diversity, or function that may disrupt normal host-microbiome interactions [2]. Recent technological advances, including 16S rRNA sequencing, whole-genome metagenomics, metabolomics, fecal microbiota transplantation (FMT) models, and biomarker-based diagnostic tools, have significantly improved our ability to characterize gut microbial communities, identify disease-associated microbial signatures, and investigate potential causal relationships, as shown in Figure *2* [3].

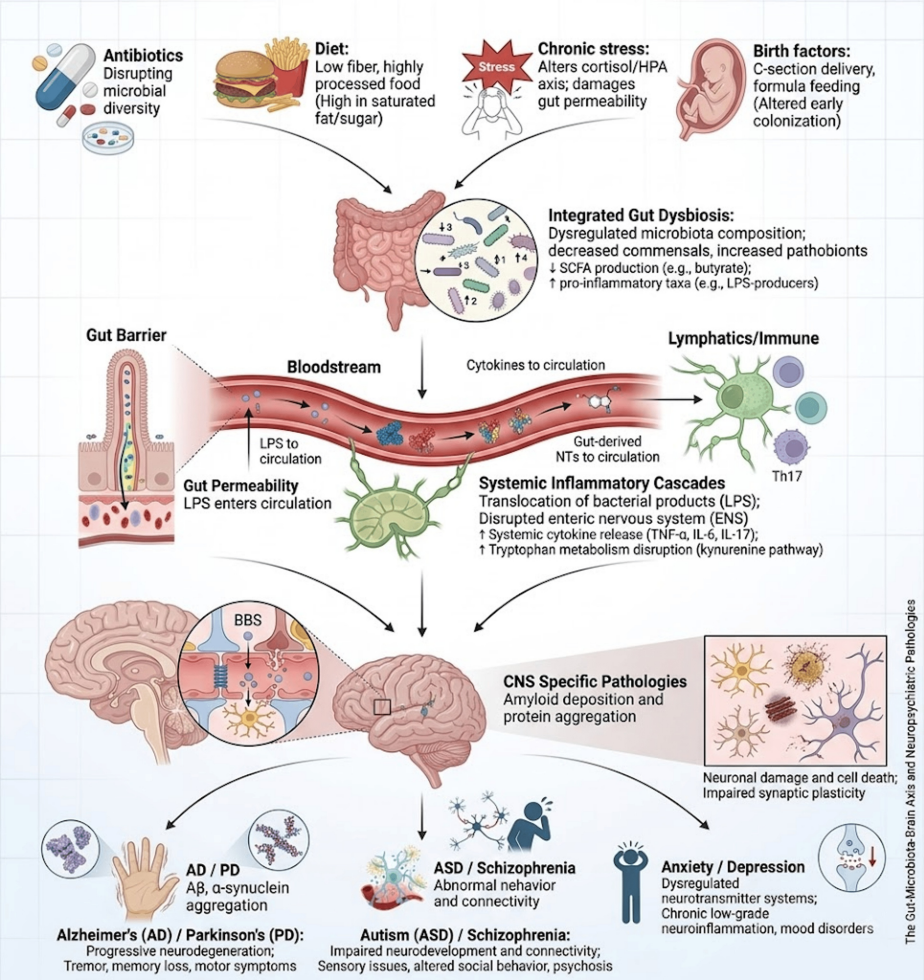


FIGURE 2: Proposed mechanisms linking the microbiota-gut-brain axis with neurological and neuropsychiatric disorders. Environmental and host factors may contribute to gut dysbiosis, altered intestinal permeability, immune activation, changes in microbial metabolites and neurotransmitter signaling, and neuroinflammation. These interconnected processes have been proposed as potential contributors to AD, PD, ASD, schizophrenia, anxiety, and related disorders.

Image credit: Authors. Created using BioRender.

AD: Alzheimer's disease; PD: Parkinson's disease; ASD: Autism spectrum disorder.

Despite rapidly increasing research on the microbiota-gut-brain axis, findings across neurological, neurodevelopmental, and neuropsychiatric disorders remain heterogeneous, and the clinical significance of many reported microbial changes remains uncertain. This narrative review therefore summarizes and critically compares current evidence across schizophrenia, autism spectrum disorder (ASD), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety disorders, and amyotrophic lateral sclerosis (ALS), with emphasis on disease-associated microbial patterns, proposed biological mechanisms, biomarkers, microbiome-targeted interventions, and the distinction between human clinical and preclinical evidence.

Review

Literature review methods

This narrative review employed a structured literature search of PubMed/MEDLINE, ScienceDirect, SpringerLink, and Wiley Online Library for publications examining the microbiota-gut-brain axis in schizophrenia, ASD, AD, PD, anxiety disorders, and ALS. Literature published between January 1, 2010, and June 25, 2026, was considered, with emphasis on human observational and clinical studies and relevant experimental and preclinical investigations.

Search terms were organized into three major domains and combined using Boolean operators where appropriate. The microbiome-related terms included "gut microbiota", "gut microbiome", "dysbiosis", "intestinal microbiota", "gut-brain axis", "metabolites", "bile acids", and "trimethylamine N-oxide (TMAO)". Terms related to neurological, neurodevelopmental, and neuropsychiatric disorders included "schizophrenia", "Alzheimer's disease", "autism spectrum disorder (ASD)", "Parkinson's disease", "anxiety", and "amyotrophic lateral sclerosis". Therapeutic and diagnostic terms included "probiotics", "prebiotics", "psychobiotics", "antipsychotics", "biomarkers", "fecal microbiota transplantation (FMT)", and "modulators". Formal backward-reference screening and forward-citation tracking were not performed as separate systematic search procedures. The database-specific search strategies, including search fields, Boolean operators, and date limits, are summarized in the Appendices.

Eligible publications included peer-reviewed human studies and relevant preclinical studies examining microbial composition, microbial metabolites, intestinal barrier function, gut-brain signaling pathways, biomarkers, or microbiome-directed interventions in the selected disorders. Eligible study designs included observational studies, clinical trials, experimental studies, systematic reviews, meta-analyses, and relevant narrative reviews. Non-peer-reviewed reports, gray literature, articles without substantive microbiome-related data, and studies focused exclusively on gastrointestinal conditions without relevance to the microbiota-gut-brain axis were excluded. Duplicate publications were considered only once. When reviews substantially overlapped, preference was given to the most recent or comprehensive source, while primary studies were used where appropriate to support specific findings. Publications were limited to English-language articles. Reference lists of relevant reviews and key articles were screened to identify additional publications pertinent to the scope of this narrative review. Formal forward-citation tracking was not performed.

Because this was a narrative review rather than a systematic review, formal study-level risk-of-bias scoring was not performed. Evidence was synthesized qualitatively, with consideration of study design, consistency of findings, sample characteristics, relevance to human disease, and whether evidence was derived from human observational studies, clinical interventions, or preclinical models. Greater interpretive weight was given to replicated human findings and controlled clinical evidence, while mechanistic findings from animal and microbiota-transfer models were identified as preclinical evidence.

Schizophrenia

Schizophrenia is a complex neuropsychiatric disorder characterized by positive symptoms, including delusions and hallucinations; negative symptoms, such as diminished emotional expression and avolition; and varying degrees of cognitive impairment [4,5]. Growing evidence has identified alterations in the gut microbiota of individuals with schizophrenia; however, whether these changes contribute causally to disease pathogenesis or arise secondary to disease-related factors, medications, diet, or lifestyle remains uncertain.

Bacterial Changes in Schizophrenia

Alterations in gut microbial composition have been reported in individuals with schizophrenia, although findings vary considerably across studies. Studies comparing individuals with schizophrenia with unaffected controls have reported differences in microbial diversity and relative abundance across several taxa; however, the direction and magnitude of these differences vary among studies. Reported alterations include differences at the phylum level, including Firmicutes, Proteobacteria, Bacteroidetes, and Actinobacteria, as well as genus-level differences involving *Lactobacillus* and *Clostridium* [6-8]. Collectively, these findings support an association between schizophrenia and altered gut microbial composition, but no reproducible schizophrenia-specific microbial signature has yet been established. Microbial metabolites, including SCFAs, can influence intestinal barrier function and host immune responses, whereas inflammatory cytokines such as IL-6, IL-8, TNF-α, and IL-10 are predominantly produced by host immune and other host cells rather than by gut bacteria. Gut dysbiosis may therefore influence cytokine signaling indirectly by altering microbial metabolites, intestinal permeability, and exposure to microbial products such as lipopolysaccharide (LPS). However, the direction and magnitude of these changes have not been consistent across studies, and no reproducible schizophrenia-specific microbial signature has been established. Differences may also be influenced by antipsychotic medication use, diet, lifestyle, disease duration, and other host factors. Experimental studies in which fecal microbiota from patients with schizophrenia were transferred to microbiota-depleted or germ-free recipient mice have produced behavioral and metabolic alterations, providing preliminary evidence that microbiota-related factors may influence schizophrenia-associated phenotypes [9,10]. Additional well-controlled longitudinal studies are required to identify reproducible microbial signatures and determine whether observed alterations represent causes, consequences, or modifiers of schizophrenia.

Mechanisms Linking Gut Dysbiosis Associated With Schizophrenia

Individuals with schizophrenia have been reported to show alterations in short-chain fatty acid (SCFA)-producing gut bacteria. Such microbial changes may affect intestinal barrier integrity and host immune signaling. Increased exposure to microbial products, including LPS, may promote host-derived inflammatory

responses involving cytokines such as IL-6, IL-8, and TNF-α, whereas SCFAs produced by selected commensal bacteria may exert immunomodulatory effects [4,7]. Gut dysbiosis may contribute to altered immune signaling by affecting intestinal barrier integrity and facilitating exposure to microbial products such as LPS. These changes may promote systemic cytokine production and neuroimmune activation. In parallel, afferent signaling through the vagus nerve represents an important neural route through which intestinal microbial activity may influence CNS function [7]. Another observation made in these studies is that gut dysbiosis influenced tryptophan-kynurenine metabolism, as reflected by decreased tryptophan levels and increased kynurenine and serotonin levels in the blood [10]. Kynurenine can be metabolized to kynurenic acid, which modulates glutamatergic and cholinergic neurotransmission and has been implicated in the neurobiology of schizophrenia [9]. Serotonin is an important neurotransmitter and signaling molecule involved in mood, cognition, and several other central and peripheral physiological processes [9]. Dopaminergic dysregulation remains central to current models of schizophrenia pathophysiology, particularly increased presynaptic dopamine synthesis and signaling within striatal pathways associated with positive symptoms [7]. Proposed interactions among gut dysbiosis, inflammatory signaling, microbial metabolites, and neurotransmitter dysregulation in schizophrenia are summarized in Figure 3.

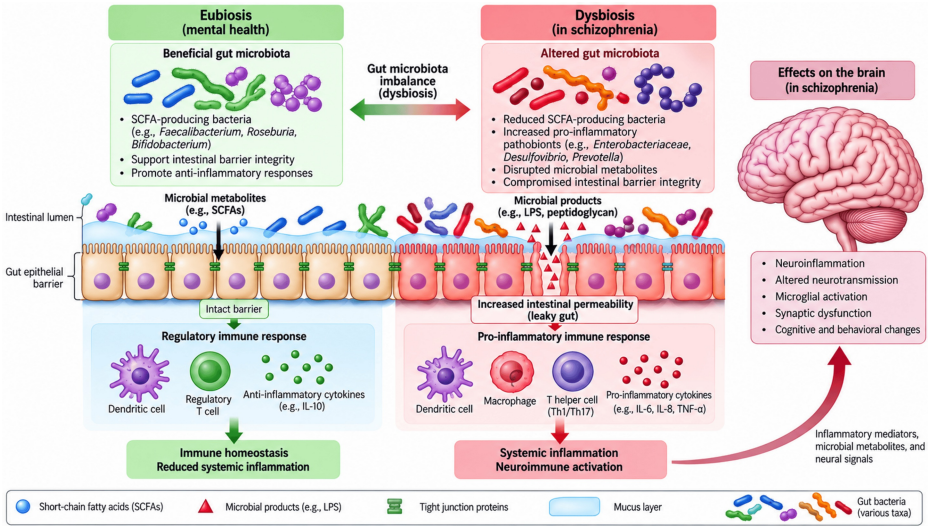


FIGURE 3: Gut dysbiosis-driven inflammation, microbial metabolites, and neurotransmitter dysregulation in the pathophysiology of schizophrenia.

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Microbiome-Targeted Interventions in Schizophrenia

Management of schizophrenia primarily involves antipsychotic pharmacotherapy combined with appropriate psychosocial interventions, including cognitive behavioral and supportive therapies [6]. Antipsychotic medications remain the primary pharmacological treatment for controlling psychotic symptoms and reducing relapse risk. Several studies suggest that antipsychotic medications may alter gut microbial composition and metabolic function, which should be considered as potential confounders when interpreting microbiome differences in schizophrenia [6].

Psychobiotics, including selected probiotics and prebiotics, are being investigated as potential adjunctive interventions; however, current evidence is insufficient to support their use as alternatives to established antipsychotic therapy. Preclinical studies of selected *Lactobacillus* strains have reported alterations in GABA receptor expression, reductions in corticosterone levels, and changes in anxiety- and depression-like behaviors; however, these findings cannot yet be directly extrapolated to the treatment of schizophrenia in humans.

Autism spectrum disorders

ASD is a complex neurodevelopmental condition characterized by persistent differences in social communication and interaction, along with restricted or repetitive behaviors and interests. Increasing evidence suggests that the gut microbiome may contribute to ASD through the bidirectional gut-brain axis, which involves microbial metabolites, immune signaling, intestinal barrier function, and neural pathways [11].

Bacterial Changes in ASD

Numerous studies have reported differences in gut microbial composition and diversity between individuals with ASD and neurotypical controls; however, the direction and magnitude of these alterations are not consistent across studies. Reduced species richness and a lower Bacteroidetes-to-Firmicutes ratio have frequently been reported, often attributed to a reduction in Bacteroidetes [11,12]. Similarly, an increase in bacteria from the phylum Firmicutes, such as *Clostridium spp*., including *C. bolteae*, *C. perfringens*, and *C. botulinum*, has been reported, which have been strongly associated with ASD symptom severity [11,13,14]. Other taxa reported at higher abundance in some ASD populations include the genera *Lactobacillus*, *Ruminococcus*, *Escherichia*, and *Shigella*, as well as members of the families Enterobacteriaceae and Pasteurellaceae [11,12]. In contrast, decreases in beneficial or fiber-fermenting bacteria, such as *Bifidobacterium*, *Akkermansia*, *Coprococcus*, *Prevotella*, and *Roseburia*, as well as members of the families Coriobacteriaceae and Actinomycetaceae, have often been reported [11,12,15].

Inconsistencies across studies, such as those involving *Prevotella*, *Turicibacter*, and *Oscillospira*, suggest individual variability, potentially due to differences in diet, antibiotic use, genetics, delivery mode, and geographic factors [12,15]. Elevated levels of *Sutterella* and *Desulfovibrio* have been associated with ASD, while reductions in *Sutterella* following specific interventions may correlate with symptom improvement [11,14,15].

Children with ASD have also been found to exhibit fungal dysbiosis, with higher levels of *Saccharomyces cerevisiae* and lower levels of *Aspergillus versicolor* [11]. Butyrate and propionate are examples of SCFAs, which are byproducts of microbial fiber fermentation and may influence behavior and neurodevelopment; higher levels of these SCFAs are seen in children with ASD [14]. Despite these reported differences, no single microbial taxon or community profile has demonstrated sufficient reproducibility to constitute an ASD-specific microbiome signature. Variability among studies may reflect differences in age, diet, gastrointestinal symptoms, antibiotic exposure, geography, sequencing methodology, and ASD phenotypic heterogeneity [12,15].

Several interventions, including microbiota transfer therapy (MTT), probiotics, prebiotics, synbiotics, selected antibiotics, and dietary approaches, have been investigated for their ability to modify the gut microbiota and improve gastrointestinal or behavioral outcomes. Although some studies report favorable findings, results remain heterogeneous, and the overall evidence base is limited [15]. Emerging studies have identified differences in early-life microbial profiles among infants who are subsequently diagnosed with ASD; however, these findings remain exploratory and are not sufficiently validated for clinical prediction or diagnosis [13].

Mechanisms Linking Gut Dysbiosis to ASD

Alterations in the gut microbiome have been proposed to influence several physiological pathways relevant to ASD, including intestinal barrier function, immune signaling, microbial metabolism, neurotransmitter pathways, and neuroendocrine responses. Dysbiosis in ASD is characterized by changes in microbial composition that may influence gut permeability, immune responses, metabolic function, neurotransmitter production, and neuroendocrine signaling. Increased intestinal permeability has been reported in subsets of individuals with ASD and may facilitate systemic exposure to microbial products such as LPS, potentially contributing to immune activation and inflammatory signaling [11,12,15].

Microbial metabolites, particularly SCFAs such as butyrate, propionate, and acetate, are among the candidate mediators proposed to link microbial activity with host immune, metabolic, and neural function. Butyrate generally supports CNS health by promoting blood-brain barrier (BBB) integrity and inhibiting histone deacetylases, thereby enhancing neuroprotection. However, excessive propionate has been linked to autistic-like behaviors, neuroinflammation, and mitochondrial dysfunction [11,12,14]. Reduced SCFA production, especially butyrate, may result from decreased populations of fiber-fermenting bacteria such as *Prevotella* and *Bifidobacterium* [15].

Gut microbes also modulate neurotransmitter systems critical for brain function. Certain gut microorganisms, including *Bifidobacterium* species, may influence tryptophan metabolism and serotonergic signaling, providing a potential mechanism through which the microbiome could affect neurobehavioral processes. Alterations in excitatory/inhibitory neurotransmitter balance, notably involving gamma-aminobutyric acid (GABA), have been implicated in ASD neurophysiology [12,14,15]. The gut microbiota influences the hypothalamic-pituitary-adrenal (HPA) axis, which mediates stress responses via cortisol release. Dysregulation of this pathway has been associated with heightened anxiety and cognitive impairments observed in ASD [11,12]. Proposed interactions among gut dysbiosis, intestinal barrier dysfunction, inflammatory signaling, and neurological pathways in ASD are summarized in Figure *4*.

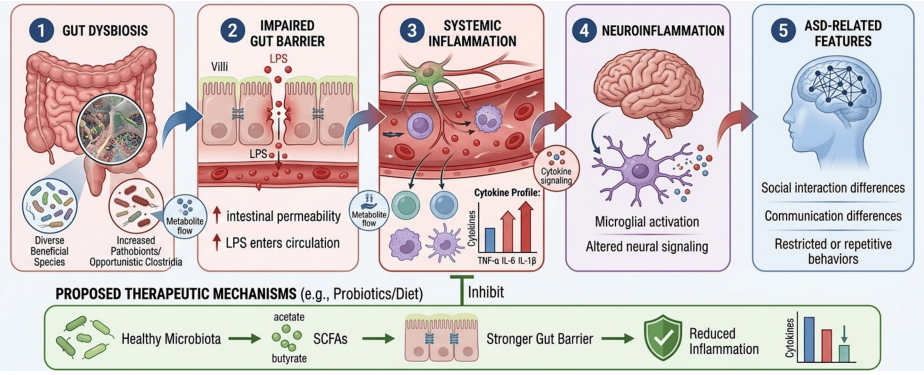


FIGURE 4: Gut dysbiosis-driven inflammation and dysregulation in the pathophysiology of autism spectrum disorder.

Image credit: Authors. Created using BioRender.

At a structural level, microbial disruption can compromise the BBB, permitting peripheral neurotoxic molecules and microbial metabolites to infiltrate the CNS, causing neuronal damage and neuroinflammation [12,13]. Bacterial outer membrane vesicles (OMVs) may also activate glial cells and further impair neuronal function [13]. Finally, metabolic dysfunction in the microbiome's amino acid, carbohydrate, and lipid processing corresponds to alterations in brain metabolism in ASD, highlighting systemic metabolic crosstalk between the gut and brain [12,13].

Microbiome-Targeted Interventions in ASD

Emerging evidence supports modulating the gut microbiome as a promising avenue for managing ASD symptoms, including both gastrointestinal and neurobehavioral manifestations [11,12,15]. Therapeutic strategies broadly fall into additive, subtractive, and modulatory categories.

Additive therapies: These involve introducing beneficial microbes to restore gut microbial balance. Probiotics containing species such as *Lactobacillus* and *Bifidobacterium* have been shown to improve gastrointestinal symptoms, anxiety, sleep, communication, sensory awareness, and specific behavioral outcomes [11,14]. Small, primarily open-label studies of FMT and MTT have reported improvements in gastrointestinal symptoms and selected behavioral measures, with some benefits persisting during follow-up [15]. However, the absence of large, adequately blinded randomized controlled trials limits conclusions regarding efficacy, durability, and effects on core ASD features.

Subtractive therapies: These utilize engineered bacteriocins or bacteriophages to selectively target pathogenic bacteria without disrupting beneficial species, offering a precision approach to microbiome modulation [14].

Modulatory therapies: These focus on lifestyle and dietary changes to promote beneficial microbial colonization. Dietary interventions, including gluten-free/casein-free and ketogenic approaches, have been evaluated in ASD, but reported benefits are inconsistent, and study quality varies considerably. Dietary modification should therefore be considered investigational with respect to core ASD symptoms rather than an established microbiome-directed therapy [11,14]. Some studies have reported improvements in selected behavioral or attentional outcomes following omega-3 supplementation, although findings across clinical studies remain inconsistent [11].

While many interventions show promise, limitations exist. FMT safety concerns necessitate rigorous donor screening [15]. Furthermore, much of the clinical evidence, especially for MTT, is based on open-label or small-scale studies, highlighting the need for larger, double-blind randomized controlled trials [14]. Personalized treatment strategies tailored to individual microbiota profiles, genetics, and health conditions are emerging as critical to optimizing outcomes [12]. Future research should aim to identify the most effective probiotic strains, dosages, and combinations of therapies, alongside standardized assessment protocols to validate long-term safety and efficacy [11,15]. Collectively, these gut microbiome-targeting approaches represent a multifaceted and evolving frontier in ASD therapy [11-15].

The literature collectively explores various factors influencing the gut microbiome and their potential implications for ASD, though direct preventive strategies through microbiome manipulation remain largely unestablished.

Several prenatal, natal, and postnatal risk factors are associated with ASD. Maternal infection, nutritional deficiencies such as folate and iron deficiencies, and gestational drug use are all prenatal influences that can affect fetal brain development and early microbiota colonization [11]. Natal factors such as fetal and umbilical cord complications, hypoxia, cesarean delivery, and abnormal gestational age may also contribute to altered microbiota development [11]. Postnatal factors, including breastfeeding practices, antibiotic exposure, air quality, and nutrition, play a significant role in shaping the infant's gut microbiome, with antibiotic overuse notably linked to decreased microbial diversity and potentially increased ASD risk [11,12].

Microbiota development begins in utero and continues to be shaped by delivery mode and infant feeding methods. Vaginal delivery promotes colonization with a more diverse and beneficial microbial community compared with cesarean delivery [12,14]. Early-life antibiotic exposure can disrupt immune system maturation and microbial balance, possibly leading to long-term consequences for neurodevelopment [12,14]. These observations highlight the importance of understanding how maternal and early-life microbial exposures influence neurodevelopment; however, current evidence does not establish microbiome modification as an effective strategy for preventing ASD.

Although maintenance of overall maternal and infant health is important for development, there is currently insufficient evidence to conclude that specific microbiome-directed interventions reduce the risk of ASD. The role of the gut microbiome in ASD pathogenesis remains a focal point for research, particularly concerning its diagnostic and therapeutic potential, rather than direct prevention [13].

Alzheimer's disease

AD is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and the accumulation of amyloid-β plaques and hyperphosphorylated tau protein in the brain. Growing evidence suggests that the gut microbiome may influence the development and progression of AD through the bidirectional gut-brain axis, involving microbial metabolites, immune signaling, intestinal permeability, and neural pathways. Alterations in gut microbial composition, commonly referred to as gut dysbiosis, may promote systemic inflammation and neuroinflammation, which can contribute to neuronal dysfunction and cognitive decline [16].

Bacterial Changes Found in the Gut Microbiome of AD Patients

Meta-analyses of 16S rRNA data show an overall decline in species richness (alpha-diversity metrics such as Sobs, ACE, and Chao indices) among individuals with AD [17-19]. Relative abundance shifts include nonsignificant increases in Firmicutes and nonsignificant decreases in Bacteroidetes, while the genus *Bacteroides* shows a significant moderate decrease [17]. Reductions in Bacteroidaceae and Lachnospiraceae and increases in Bifidobacteriaceae have been observed [17]. LEfSe analysis identified elevated levels of Enterobacteriaceae, Lactobacillaceae, *Bifidobacterium*, and *Akkermansia*, along with decreased levels of *Anaerostipes* and *Lachnospira* [17]. Pro-inflammatory *Escherichia* and *Shigella* levels were elevated, while anti-inflammatory species such as *Eubacterium rectale* were reduced [17].

Decreases in beneficial SCFA-producing Firmicutes (Clostridiaceae, Lachnospiraceae, *Ruminococcus*, and Eubacterium) and increases in Proteobacteria (*Escherichia/Shigella*) have been consistently documented [18,19]. Reductions in Rikenellaceae, *Lachnospira*, and *Ruminiclostridium* correlate with lower cognitive performance, and anti-inflammatory *Faecalibacterium* is reduced in subjective cognitive decline and cognitive impairment [19].

Mechanisms Linking Gut Dysbiosis to AD

Gut microbiome alterations have been associated with several immune and metabolic pathways that may contribute to neuroinflammation in AD. One important mechanism involves Th17 cells, which are affected by changes in the gut microbiome and produce IL-17. By stimulating astrocytes and microglia, IL-17 can trigger neuronal death, neuroinflammation, neuronal loss, and cognitive impairment [20]. High-mobility group box 1 (HMGB1), a protein that can trigger immunological pathways and the release of pro-inflammatory mediators such as IL-1, IL-6, and TNF-α, can also increase as a result of gut microbiota alterations [21].

The formation of gut-associated lymphoid tissue contributes to innate immune system priming, and the gut microbiota affects adaptive local and systemic immune responses. In AD mouse models, changes in the gut microbiota are linked to greater peripheral Th1 immune cell penetration across the BBB, enhanced microglial activation, Aβ accumulation, and cognitive loss. In human AD brains, LPS, a bacterial endotoxin produced by Gram-negative bacteria, including Bacteroidetes, is found in perivascular Aβ aggregates and amyloid plaques. LPS can activate Toll-like receptor 4 (TLR4)-dependent inflammatory signaling and stimulate the production of cytokines, including IL-1, IL-6, and TNF-α; these pathways have been proposed as one mechanism linking peripheral inflammation with neuroinflammatory processes in AD [22].

The intestinal barrier and brain endothelium express the efflux transporter P-glycoprotein (P-gp), which aids

in the removal of amyloid across the BBB. Compared with healthy controls and individuals with other dementias, AD is linked to decreased intestinal epithelial P-gp levels, decreased brain endothelial expression, and impaired P-gp activity, promoting amyloid accumulation. P-gp levels are altered by gut microbiome components, primarily Gram-negative *Bacteroides*: higher P-gp levels are linked to a greater abundance of *B. dorei*, whereas lower P-gp levels are linked to higher abundances of *B. fragilis* and *B. vulgatus* [23].

Alterations in bile acid metabolism represent another pathway. High levels of anaerobic gut microbiota are associated with greater serum and stool levels of secondary bile acids created when gut bacteria deconjugate primary bile acids. In a study involving 1,464 individuals with AD-related dementia or MCI and healthy controls, patients with AD had higher levels of deoxycholic acid (DCA) and its 7α-dehydroxylated derivative and lower levels of cholic acid [16].

SCFAs, such as butyrate, acetate, and propionate, preserve gut structural and functional integrity and mediate immunomodulatory processes. Under normal physiological conditions, butyrate primarily exerts anti-inflammatory effects; however, higher doses of butyrate may cause inflammation by inducing T-bet and IFN-γ production [16]. Through epigenetic changes and G-protein-coupled receptor signaling (GPR41/GPR43), SCFAs can affect T-cell fate. Butyrate-producing Ruminococcaceae are far less common in carriers of the APOE4 allele (the primary genetic risk factor for AD) than in APOE2/3 carriers.

BBB disruption, including the loss of pericytes and endothelial tight junctions, is documented even in the early stages of AD, reducing Aβ clearance. Animal research indicates that changes in the BBB may occur before tau and Aβ aggregation or neuronal death, and clinical research indicates that BBB dysfunction in hippocampal and cortical regions is an early event in AD pathogenesis.

Certain gut bacteria, particularly members of the Enterobacteriaceae family, such as *Escherichia coli*, can produce extracellular amyloid proteins such as curli. Experimental evidence suggests that bacterial amyloids may stimulate innate immune signaling and potentially influence protein aggregation pathways relevant to neurodegenerative disease [21]. When these peripheral inflammatory mediators infiltrate the brain, TLR2/1 and NF-κB signaling pathways are activated, increasing IL-1β production. Experimental studies have also raised the possibility that microbial amyloids or amyloid-promoting signals originating in the gastrointestinal tract may influence central protein-aggregation pathways through immune, neural, or molecular mechanisms, although direct transport and clinical relevance in humans remain uncertain [20]. Proposed mechanisms linking gut dysbiosis, inflammatory signaling, and amyloid-related pathways in AD are summarized in Figure *5*.

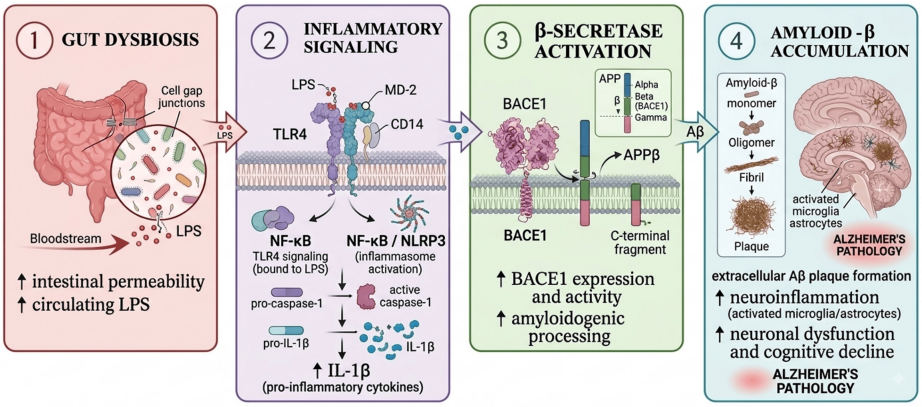


FIGURE 5: Gut dysbiosis-driven inflammation and dysregulation in the pathophysiology of Alzheimer's disease.

Image credit: Authors. Created using BioRender.

Resident gut microorganisms produce physiologically active substances, including toxins, precursors, and signaling molecules (e.g., G-protein-coupled receptor agonists) [24]. Experimental studies suggest that elevated TMAO levels may influence oxidative stress, mitochondrial function, inflammatory signaling, and cellular senescence pathways relevant to neurodegeneration [24]. Higher cerebrospinal fluid TMAO concentrations have been reported in individuals with MCI and AD dementia and have been associated with biomarkers of AD pathology and neuronal injury [24]. Elevated central TMAO levels may also worsen insulin resistance and AD pathogenesis.

Microbiota-derived bile acids (MBAs) influence AD pathology by disrupting BBB integrity, enabling

peripheral metabolites to cross into the CNS, and modulating Aβ accumulation [25]. Specifically, elevated levels of cytotoxic secondary bile acids, such as DCA, are strongly linked to increased amyloid-beta deposition, neurodegeneration, and cognitive decline. This systemic bile acid dysregulation, characterized by elevated DCA levels and altered microbial dehydroxylation ratios (primary-to-secondary bile acid conversion), further directly links gut microbial activity to AD pathogenesis [26].

Microbiome-Targeted Interventions in AD

Experimental microbiome-targeted strategies in AD are being investigated for their potential to improve intestinal barrier integrity, reduce inflammatory signaling, and influence neurodegenerative pathways [26]. A human-origin probiotic formulation containing *Lactobacillus* and *Enterococcus* strains enhanced intestinal tight junction proteins, reduced gut permeability, limited microglial activation, and decreased inflammatory responses across the gut, systemic circulation, and brain in AD models [26].

Specific formulations, such as *Lactobacillus rhamnosus* GG, *Bifidobacterium breve*, VSL#3, and SLAB51, reinforce barrier function and lower systemic inflammation [18]. Supplementation with *Bifidobacterium breve* A1 improved memory performance in older adults with MCI while reducing pro-inflammatory cytokines [27]. Prebiotics (e.g., FOS, GOS, and inulin) promote beneficial microbial growth, while synbiotics enhance Aβ clearance, decrease tau accumulation, and improve cognition in animal models [27].

In preclinical AD models, FMT has been associated with changes in microbial composition, reduced inflammatory signaling, improved barrier-related markers, and reductions in selected neuropathological features [27]. Preliminary human reports and small clinical studies have described microbiome changes and possible improvements in inflammatory or cognitive outcomes following FMT; however, evidence remains insufficient to establish its efficacy or safety for AD treatment [27]. Combined prebiotic and probiotic administration in APP/PS1 mice reduced cortical Aβ accumulation, decreased microglial activation, and shifted astrocytes toward a neuroprotective phenotype, including increased GFAP expression [28].

Specific probiotic strains, including *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Lactobacillus fermentum*, and SCFA-producing bacteria such as *Agathobaculum butyriciproducens* SR79 have been reported to exert neuroprotective effects, reduce microglial activation, and limit Aβ plaque accumulation [29]. The prebiotic sodium oligomannate has been reported to cross the BBB, modulate dysbiosis, and interact directly with Aβ to inhibit aggregation [29]. Some clinical studies have reported improvements in selected cognitive outcomes following probiotic supplementation, particularly in individuals with mild cognitive impairment or early disease; however, findings remain inconsistent and require confirmation in larger trials [29].

Postbiotics are being investigated as potential alternatives to live probiotics because they may retain selected immunomodulatory or metabolic effects while reducing risks associated with administering viable microorganisms; however, clinical evidence for neurological applications remains limited [30].

Technological advances, such as implantable wireless sensors placed in the cecum to measure in vivo oxidation-reduction potential (ORP) in real time, provide novel tools to track microbiome redox dynamics and disease-associated oxidative shifts [31].

Parkinson's disease

PD is a progressive neurodegenerative disorder characterized primarily by motor symptoms such as bradykinesia, rigidity, and resting tremor, along with a range of non-motor manifestations. PD affects over 8.5 million individuals globally. Increasing evidence suggests that the gut microbiome plays an important role in PD through the bidirectional gut-brain axis, which connects intestinal microbial activity with immune, metabolic, and neural processes. Gut dysbiosis in individuals with PD may contribute to intestinal barrier dysfunction, systemic inflammation, altered microbial metabolites, and neuroinflammation, potentially influencing disease progression. Microbial products and metabolites, including SCFAs and bacterial components such as LPS, may affect α-synuclein aggregation, microglial activation, and neuronal function [32,33].

Microbiota-Gut-Brain Communication Pathways

Increasing evidence suggests that the microbiota-gut-brain axis may contribute to selected aspects of PD pathophysiology, particularly gastrointestinal dysfunction, inflammation, and α-synuclein-related processes. Experimental and neuropathological findings have led to the hypothesis that pathological α-synuclein may propagate from the enteric nervous system to the brain through vagal pathways in a subset of patients, consistent with the gut-first component of Braak's hypothesis. However, PD is heterogeneous, and evidence also supports brain-first disease trajectories [32].

Stress-induced activation of the HPA axis releases corticotropin-releasing hormone (CRH), increasing intestinal permeability and mucosal inflammation [33]. Immune signaling via TLR2 and TLR4 recognizes microbial LPS, activating NF-κB pathways and elevating pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) in

intestinal tissues [33]. Reduced SCFA levels impair barrier integrity and accelerate α-synuclein aggregation, while microbial tryptophan metabolites (indoles) further modulate immune and neurochemical signaling [34].

Gut Microbiota and PD

Constipation frequently precedes PD motor symptoms by years. Patients with PD exhibit reductions in SCFA-producing bacteria (*Faecalibacterium prausnitzii*, *Roseburia*, and Lachnospiraceae) and increases in pro-inflammatory taxa (Proteobacteria, Desulfovibrionaceae, and *Akkermansia* muciniphila) [32,35]. An increased abundance of *Desulfovibrio* species has been reported in some PD cohorts. These bacteria produce hydrogen sulfide and other metabolites that have been proposed to influence mitochondrial function, oxidative stress, iron metabolism, and α-synuclein aggregation; however, a direct causal role in human PD has not been established [33]. The proposed role of gut dysbiosis in inflammation and α-synuclein pathology in PD is illustrated in Figure 6.

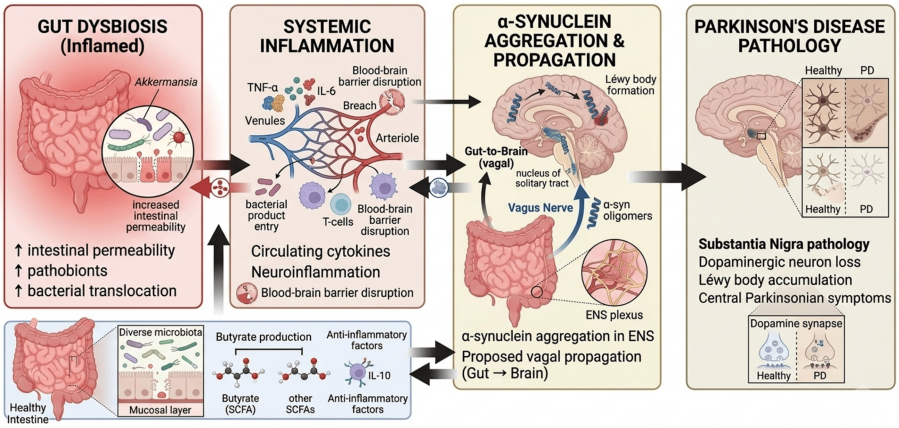


FIGURE 6: Gut dysbiosis-driven inflammation and dysregulation in the pathophysiology of Parkinson's disease.

Image credit: Authors. Created using BioRender.

Increased intestinal permeability may facilitate systemic exposure to LPS and other microbial products, potentially promoting peripheral inflammatory signaling and microglial activation. Whether circulating LPS directly crosses the BBB in clinically meaningful concentrations and contributes to PD progression remains incompletely defined [32].

Microbiome-Targeted Interventions in PD

Growing evidence linking gut dysbiosis to PD has driven interest in microbiome-targeted interventions such as prebiotics, synbiotics, dietary changes, probiotics, and FMT [36,37]. While probiotic trials have demonstrated benefits in alleviating PD-associated constipation and, in some studies, modifying gut microbial composition [37-39], evidence for their impact on motor symptoms or disease progression remains limited [40]. FMT offers a broader microbiome-restoration approach, yet results are mixed: a randomized clinical trial of FMT did not demonstrate clinically meaningful motor improvement and reported a significantly higher frequency of gastrointestinal adverse events [41]. Similarly, a 2026 randomized study found no significant motor benefit following a single FMT, although selected non-motor outcomes improved [42]. In contrast, emerging evidence from a 2026 phase 2 trial suggests that repeated donor FMT in drug-naïve patients may improve both motor and gastrointestinal symptoms, accompanied by favorable changes in gut microbiota and intestinal barrier function [43]. Overall, microbiome-targeted therapies remain promising, particularly for gastrointestinal and other non-motor manifestations of PD; however, substantial heterogeneity in intervention types, probiotic strains, FMT protocols, patient populations, and clinical endpoints necessitates larger, standardized, long-term randomized trials before these approaches can be considered disease-modifying therapies [36,40].

Anxiety

Anxiety disorders are common psychiatric conditions characterized by excessive fear, worry, and behavioral and autonomic symptoms. Emerging evidence suggests that the gut-microbiota-brain axis contributes to anxiety susceptibility and symptom severity through bidirectional interactions involving the vagus nerve, HPA axis, immune signaling, microbial metabolites, and neuroactive compounds. Gut microbiota composition is influenced by diet, genetics, age, medications, geography, and stress, linking environmental

factors with brain function [44-46]. Early work by Foster and Neufeld highlighted neural, endocrine, and immune mechanisms connecting the microbiota with stress-related behavior. Recent human studies demonstrate altered gut microbiota in generalized anxiety disorder (GAD) and social anxiety disorder (SAD), although findings remain heterogeneous and do not establish dysbiosis as a primary cause of anxiety [47].

Bacterial Changes Associated With Anxiety

Human studies indicate that anxiety disorders are associated with alterations in gut microbial composition and function, although findings remain heterogeneous. Ritz NL et al. demonstrated that gut microbiota associated with SAD can influence anxiety-related behavior, as transplantation of SAD-associated microbiota into mice increased social fear, providing experimental evidence for a potential causal role of the gut microbiome in anxiety-related behaviors [47]. Chen YH et al. identified differences in approximately 25 bacterial genera, with *Eubacterium coprostanoligenes*, Ruminococcaceae UCG-014, and Prevotella 9 enriched in controls and negatively associated with anxiety severity, whereas *Bacteroides*, *Escherichia*, and *Shigella* were increased in GAD and positively associated with symptom severity [48]. A 2024 Mendelian randomization study further identified associations between anxiety risk and specific taxa, including inverse associations for *Blautia* and *Butyricicoccus* and positive associations for *Eubacterium* and *Coprococcus* [49]. Collectively, these findings suggest that reduced beneficial/SCFA-producing bacteria and increased potentially pro-inflammatory taxa may contribute to anxiety, although causality remains uncertain.

Similar alterations have been reported in SAD. Functional differences, including enrichment of the aspartate degradation I pathway, were also observed. Across anxiety studies, reductions in potentially beneficial organisms such as *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*, *Blautia*, and *Butyricicoccus*, together with increases in *Escherichia*, *Shigella*, *Fusobacterium*, *Ruminococcus gnavus*, and selected *Bacteroides*, have been reported [48-50]. Butler MI et al. found significant differences in microbial beta-diversity between 31 patients with SAD and 18 controls, with enrichment of *Anaeromassilibacillus* and *Gordonibacter* in SAD and greater abundance of *Parasutterella* in controls; *Anaeromassilibacillus* sp. An250 was particularly prevalent in SAD, while *Parasutterella excrementihominis* was enriched in controls [50]. However, these bacteria should not be universally classified as beneficial or harmful because their effects are species-, strain-, diet-, and host-dependent; therefore, anxiety is more appropriately characterized by functional microbial dysbiosis rather than a single, reproducible bacterial signature.

Mechanisms Linking Gut Dysbiosis to Anxiety

Gut microbiota communicate bidirectionally with the brain through the enteric and autonomic nervous systems, particularly the vagus nerve, as well as the HPA axis and immune pathways. Experimental studies show that bacterial exposure can activate vagal and central stress-related circuits, while organisms such as *Lactobacillus rhamnosus* can alter enteric neuronal excitability [44]. The microbiota also influence HPA-axis development and stress responsiveness; germ-free animals exhibit exaggerated stress-related corticosterone and ACTH responses, whereas early-life microbial colonization can normalize aspects of stress behavior [44]. Dysbiosis may therefore contribute to a bidirectional stress-microbiota cycle, in which psychological stress alters gut function and microbial composition, while microbial disturbances further enhance HPA-axis activity and anxiety. In addition, impaired intestinal barrier function may increase the translocation of microbial products such as LPS, activating Toll-like receptor signaling and inflammatory cytokine production. Systemic inflammation may subsequently affect the BBB, microglial activity, neurotransmitter metabolism, and neural plasticity. Clinical findings of altered inflammatory markers and gut microbiota in GAD further support interactions among microbial, immune, and host factors [51].

Microbial metabolites provide another important mechanism linking dysbiosis with anxiety. SCFAs, including acetate, propionate, and butyrate, produced through microbial fermentation of dietary carbohydrates and fiber, contribute to intestinal barrier integrity, immune regulation, metabolic homeostasis, and gut-brain communication [52,53]. Reductions in SCFA-producing bacteria such as *Faecalibacterium*, *Blautia*, and *Butyricicoccus* reported in anxiety may therefore reflect impaired microbial metabolic capacity rather than changes in bacterial abundance alone. Gut bacteria can also influence the synthesis and metabolism of GABA, serotonin, dopamine-related compounds, glutamate, acetylcholine, and tryptophan-derived metabolites, which may alter enteroendocrine and neural signaling. Thus, a potential pathway is gut dysbiosis → altered microbial metabolites → immune, endocrine, and neural signaling → altered neurotransmission and stress responsiveness → anxiety symptoms. These interconnected mechanisms may also explain why individuals with similar microbial compositions can exhibit different anxiety phenotypes depending on microbial function and host factors [54,55].

The MGBA links the GI tract and CNS through neural, endocrine, immune, and metabolic pathways. Gut dysbiosis has been associated with alterations in intestinal barrier function and immune signaling that may increase systemic exposure to microbial products and pro-inflammatory mediators. These processes have been proposed to influence neuroinflammatory and stress-related pathways relevant to anxiety disorders [56,57]. Microbial activity may influence brain function through vagal signaling, microbial metabolites, immune mediators, SCFAs, and modulation of neurotransmitter-related pathways, including serotonin, GABA, dopamine, and tryptophan-kynurenine metabolism [55]. Alterations in gut microbial composition

have also been associated with HPA-axis dysregulation and altered stress responses, although the direction and clinical significance of these relationships remain under investigation [58,59]. The role of gut dysbiosis in inflammation, cortisol responses, and neurotransmitter dysregulation in anxiety is shown in Figure 7. In Figure 7, A represents gut microbiota dysbiosis and intestinal barrier disruption; B represents increased intestinal permeability; C represents systemic inflammation and microglial activation; D represents BBB disruption; E represents HPA-axis dysregulation; F represents altered neural signaling and plasticity; and G represents anxiety-related behavioral and cognitive changes.

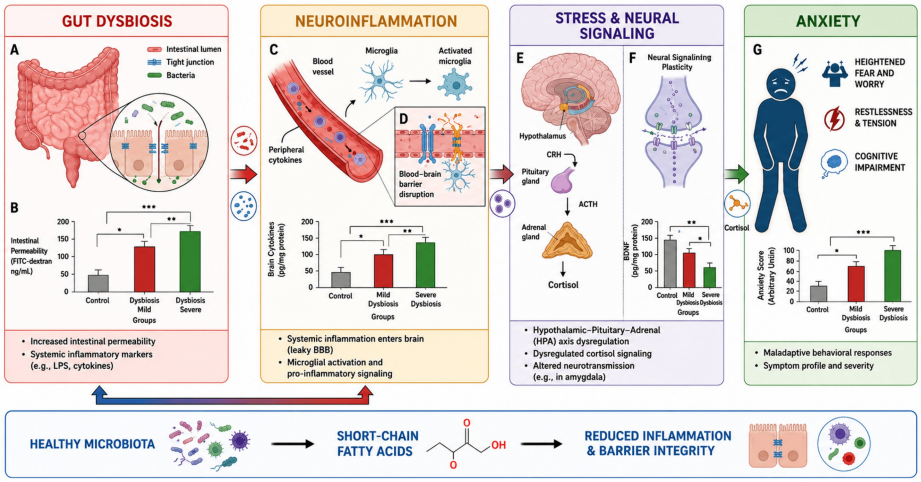


FIGURE 7: Gut dysbiosis-driven inflammation and dysregulation in the pathophysiology of anxiety.

Image credit: Authors. Created using BioRender.

Microbiome-Targeted Interventions in Anxiety

Probiotics are among the most investigated microbiota-directed interventions for anxiety, with proposed benefits including restoration of beneficial bacteria, improvement of intestinal barrier function, enhancement of SCFA production, immune modulation, and regulation of neuroactive metabolites [60-62]. Specific strains such as *Lactobacillus plantarum* and *L. plantarum* P8 have demonstrated reductions in anxiety and stress-related symptoms in randomized controlled studies [60,61]. Potential benefits have also been reported with *L. gasseri* CP2305, which reduced anxiety and sleep disturbances in chronically stressed young adults [62]. In contrast, an 8-week randomized trial of *L. helveticus* R0052 and *Bifidobacterium longum* R075 found no significant differences from placebo in psychological outcomes, illustrating the strain- and population-specific nature of probiotic effects [63]. Another study reported modest improvements in anxiety with probiotic, prebiotic, and synbiotic interventions, but substantial heterogeneity in strains, populations, intervention duration, and outcome measures limits definitive conclusions [64,65]. In a randomized, double-blind, placebo-controlled trial involving 103 stressed adults, *Lactobacillus plantarum* P8 supplementation significantly reduced stress and anxiety symptoms and was associated with reductions in pro-inflammatory cytokines, including IFN-γ and TNF-α, while also improving selected cognitive outcomes [66]. Prebiotics and dietary fibers, including inulin, fructooligosaccharides, galactooligosaccharides, resistant starch, and soluble fiber, may promote beneficial bacteria and SCFA production, while fermented foods and fiber-rich, minimally processed diets may support microbial diversity and metabolic function [67,68]. Overall, these approaches may be considered potential adjunctive strategies rather than replacements for established anxiety treatments.

FMT is another potential strategy for targeting the gut microbiome in anxiety disorders. An increased abundance of *Escherichia-Shigella* has been reported in individuals with GAD, suggesting a potential microbiota-associated target; however, evidence linking FMT-induced changes in this taxon directly to improvement in GAD remains limited. A 2024 systematic review of gastrointestinal studies reported reductions in *Escherichia-Shigella* following FMT in 10 of 14 cases (71.4%), although only four demonstrated statistically significant reductions, providing only indirect evidence relevant to GAD [67]. Conversely, preclinical evidence reported in 2026 showed that FMT from individuals with SAD into antibiotic-treated mice induced anxiety-like behaviors and altered microbial composition, including increases in Bacteroidota and Bacteroidales and decreases in butyrate-producing taxa, and was associated with changes in metabolic pathways and plasma tryptophan levels [68]. These findings provide experimental evidence that anxiety-associated microbiota may influence behavioral and metabolic phenotypes, but they do not establish the therapeutic efficacy of FMT in humans. Recent systematic reviews and meta-analyses suggest that probiotic interventions may improve selected psychiatric and anxiety-related outcomes; however, substantial

heterogeneity in probiotic formulations, study populations, treatment duration, and outcome measures limits the strength of these conclusions [64,65,69]. Although these findings support further investigation of microbiota-targeted interventions, the clinical efficacy and safety of FMT for anxiety disorders remain uncertain. Overall, probiotics, prebiotics, synbiotics, dietary fiber, and fermented foods represent promising microbiota-modulating strategies, whereas FMT remains an experimental approach that should be evaluated in well-designed, adequately controlled clinical trials [64,65,69].

Amyotrophic lateral sclerosis

ALS is a fatal neurodegenerative disorder characterized by progressive motor neuron loss, leading to muscle weakness, atrophy, dysphagia, respiratory dysfunction, and paralysis. Approximately 90% of ALS cases are sporadic and 10% are familial, reflecting complex interactions among genetic, metabolic, immune, environmental, and systemic factors [70,71]. Increasing evidence suggests that ALS may involve gastrointestinal and gut-brain axis abnormalities, as the gut microbiota contributes to nutrient metabolism, intestinal barrier integrity, immune regulation, bile acid metabolism, and the production or modulation of neuroactive metabolites [70-72]. Gastrointestinal dysfunction, including delayed gastric and colonic transit, constipation, and pancreatic abnormalities, has been reported in individuals with ALS and may occur early in the disease course [73]. Experimental studies in SOD1^G93A^ mice have further demonstrated intestinal barrier disruption, increased intestinal permeability, Paneth cell abnormalities, and alterations in gut microbial composition before the onset of overt motor symptoms [74]. Collectively, these findings suggest that gastrointestinal dysfunction and gut microbiota alterations may be associated with ALS pathophysiology; however, current evidence does not establish a causal relationship. Moreover, substantial variability related to disease phenotype, disease stage, diet, medication use, geographic location, sequencing methodologies, and control populations remains an important limitation when interpreting the available evidence [75].

Bacterial Changes Associated With ALS

Human studies have demonstrated substantial but inconsistent alterations in the gut microbiota of individuals with ALS. The 2022 review by Martin S et al. reported alterations involving Bacteroidetes, *Bacteroides*, *Dorea*, *Oscillibacter*, *Anaerostipes*, Lachnospiraceae, Ruminococcaceae, *Clostridium*, *Roseburia*, *E. coli*, and Enterobacteriaceae, with some studies reporting increased Bacteroidetes/*Bacteroides* and others describing reductions in specific Firmicutes and butyrate-producing bacteria [69-70]. This heterogeneity is illustrated by Brenner D et al., who found relatively similar overall fecal microbiome profiles between 25 individuals with ALS and 32 controls, with differences primarily involving operational taxonomic units and uncultured members of the Ruminococcaceae family [76]. In contrast, Zeng Q et al. reported increased Bacteroidetes and reduced Firmicutes and *Megamonas* in individuals with ALS [77]. A recent systematic review similarly concluded that reductions in butyrate-producing bacteria and increases in potentially pro-inflammatory taxa are frequently reported, although findings remain inconsistent [77].

Among potentially beneficial taxa, reductions in SCFA-producing organisms, including *Lactobacillus*, *Prevotella*, *Butyricimonas*, *Roseburia*, *Eubacterium rectale*, and selected members of the Ruminococcaceae and Lachnospiraceae families, have been reported. In particular, Fontdevila L et al. observed reduced *Prevotella*, *Lactobacillus*, and *Butyricimonas*, together with increased *Enterobacter*, *Clostridium*, *Veillonella*, *Dialister*, *Turicibacter*, and *Acidaminococcus* in individuals with ALS [78]. However, total fecal SCFA concentrations were not significantly different, indicating that changes in bacterial abundance do not necessarily correspond directly to fecal metabolite concentrations. Nevertheless, alterations in SCFA-producing taxa may remain biologically relevant because butyrate contributes to intestinal epithelial integrity and may influence immune and anti-inflammatory processes [71,76,79].

Potentially pro-inflammatory or disease-associated changes have also included increases in *E. coli*, Enterobacteriaceae, *Bacteroides*, *Fusobacteria*, *Acidobacteria*, *Veillonella*, *Dialister*, *Acidaminococcus*, and selected *Clostridium* species [78]. Importantly, Kim HS et al. demonstrated that microbiome alterations may differ according to ALS phenotype: spinal-onset ALS was associated predominantly with gut dysbiosis, whereas bulbar-onset ALS showed more prominent oral dysbiosis, with microbial translocation into the bloodstream associated with disease severity [80]. Collectively, these findings suggest that alterations in the gut and oral microbiota may be associated with ALS pathophysiology; however, current evidence does not support the existence of a single, universal ALS-associated microbial signature.

Mechanisms Linking Gut Dysbiosis to ALS

The intestinal epithelial barrier, maintained in part by tight-junction and adherens-junction proteins such as zonula occludens-1 (ZO-1) and E-cadherin, appears to be compromised in experimental models of ALS. Wu S et al. demonstrated reduced ZO-1 and E-cadherin expression, disrupted tight-junction organization, increased intestinal permeability, abnormal Paneth cell morphology, and reduced defensin-5α levels in SOD1^G93A^ mice, with these abnormalities occurring before the onset of overt motor symptoms [73-79]. Increased intestinal permeability may facilitate the translocation of microbial products, such as LPS, into the circulation. Circulating LPS can activate Toll-like receptor 4 (TLR4) signaling and promote host inflammatory responses involving cytokines such as TNF-α, IL-1β, and IL-6. Evidence summarized by

Martin S et al. indicates increased circulating LPS in sporadic ALS, while recent work has proposed a gut-liver-brain pathway in which dysbiosis, impaired intestinal permeability, and altered hepatic clearance may amplify systemic and neuroinflammatory signaling. Thus, a potential sequence is gut dysbiosis → epithelial barrier disruption → microbial product translocation → systemic and hepatic inflammatory signaling → neuroinflammation → motor neuron injury. However, the causal relevance of this pathway to human ALS remains unresolved [69-73].

Microbial metabolites may provide an additional link between dysbiosis and ALS. SCFAs, particularly butyrate, contribute to intestinal barrier integrity and can modulate immune and inflammatory pathways. Although the 2024 study by Fontdevila L et al. did not identify a significant difference in total fecal SCFA concentrations, animal studies have reported that butyrate supplementation can improve microbial homeostasis and intestinal integrity, reduce microglial activation and levels of IL-17 and LPS, and prolong survival in SOD1^G93A^ mice [78]. Alterations in microbial tryptophan-nicotinamide metabolism, including changes in indoleacetate, kynurenine, serotonin, and nicotinamide, may also influence neuronal function and survival [78]. Other proposed mechanisms include microbial modulation of glutamate and other neuroactive metabolites, oxidative stress, mitochondrial dysfunction, and potentially bacterial amyloid-associated effects on protein misfolding involving TDP-43 and SOD1; however, these mechanisms remain incompletely established. Collectively, these findings support a multifactorial gut microbiota-metabolite-immune-brain axis in ALS, although most mechanistic evidence remains preclinical and requires validation in longitudinal human studies [70-77].

The proposed role of gut dysbiosis in inflammatory signaling and HPA-axis alterations associated with ALS is illustrated in Figure *8*. In Figure *8*, Panel A represents immune activation associated with intestinal dysbiosis and epithelial barrier disruption, whereas Panel B illustrates the proposed effects of IL-6- and TNF-α-mediated inflammatory signaling on the BBB.

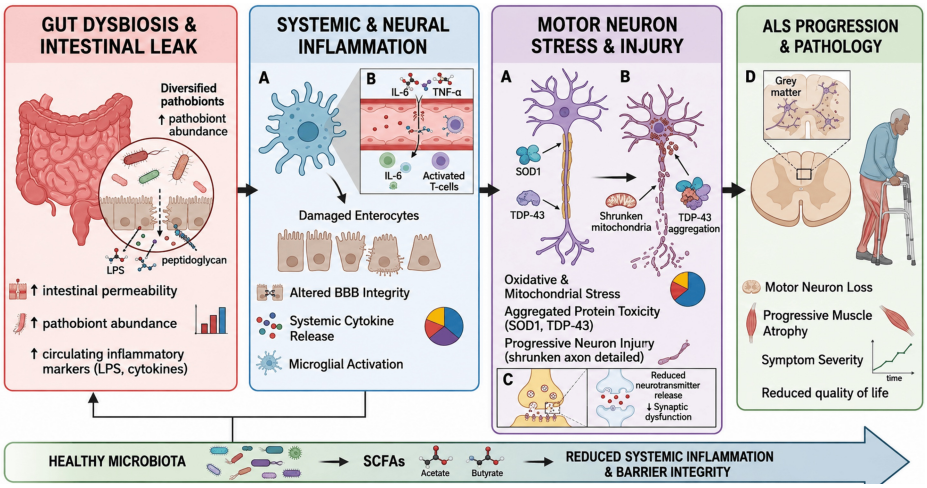


FIGURE 8: Gut dysbiosis-driven inflammation and dysregulation in the pathophysiology of amyotrophic lateral sclerosis.

Image credit: Authors. Created using BioRender.

Treatment for Gut Dysbiosis in ALS

Microbiota-targeted therapies for ALS include probiotics, prebiotics, dietary fiber, butyrate and other postbiotic approaches, and FMT. Probiotics may influence microbial composition, intestinal barrier function, SCFA production, and inflammatory signaling; however, a six-month study using *Lactobacillus fermentum*, *L. delbrueckii*, *L. plantarum*, *L. salivarius*, and *Streptococcus thermophilus* altered gut microbial composition without significantly improving disease progression, indicating that probiotics remain biologically plausible but are not established disease-modifying treatments for ALS [81]. Prebiotics and dietary fibers, including inulin, fructooligosaccharides, resistant starch, and vegetable fiber, may promote SCFA-producing bacteria and support intestinal integrity. Notably, higher vegetable fiber intake was associated with slower disease progression and longer survival in a cohort of 272 individuals with sporadic ALS; however, the observational study design precludes conclusions regarding causality [82,83]. Butyrate and other postbiotic approaches are also promising because butyrate supplementation restored microbial homeostasis, improved intestinal integrity, and prolonged survival in SOD1^G93A^ mice [79]. However, these findings remain preclinical and cannot yet be extrapolated directly to human ALS.

FMT may modify gut microbial diversity and composition and potentially influence inflammatory microbial

communities; however, evidence in ALS remains limited. In a randomized, double-blind, placebo-controlled trial involving 27 individuals with sporadic ALS, FMT resulted in microbiome modification and improvements in some gastrointestinal and behavioral outcomes but did not significantly reduce the rate of decline in the ALS Functional Rating Scale-Revised (ALSFRS-R); gastrointestinal adverse events were also reported [84]. Overall, probiotics, prebiotics, dietary fiber, butyrate, and FMT represent promising microbiome-directed strategies, but current evidence is insufficient to establish any of these approaches as disease-modifying treatments for ALS. FMT, in particular, should remain an investigational intervention evaluated within appropriately designed and adequately controlled clinical trials [80].

Diagnostic, biomarker, and therapeutic potential

The microbiota-gut-brain axis offers potential diagnostic biomarkers, prognostic indicators, and therapeutic targets across neurological, neurodevelopmental, and neuropsychiatric disorders, including AD, PD, schizophrenia, ASD, anxiety, and ALS [84-87]. Alterations span microbial diversity, taxa, and functional metabolites, such as SCFAs, tryptophan metabolites, bile acids, TMAO, and inflammatory markers [85,87]. In PD, bacterial tyrosine decarboxylase has gained attention for its capacity to metabolize levodopa and alter therapeutic bioavailability [88,89]. Therapeutic strategies such as prebiotics, probiotics ("psychobiotics"), synbiotics, postbiotics, dietary modifications, and FMT show preclinical and early clinical promise in reducing neuroinflammation, restoring barrier integrity, regulating neurotransmitter dynamics, and impeding protein aggregation [86,87].

Translating these associations into standardized clinical practice faces challenges due to high interindividual variability and low signature reproducibility across diverse populations [85,86]. Microbiome profiles are heavily confounded by host age, diet, concurrent medications, genetics, lifestyle, and bioinformatic pipelines [85,87]. Advancing beyond basic taxonomic associations requires integrating strain-resolved metagenomics, functional metabolomics, and longitudinal multi-omic datasets paired with machine-learning analytical frameworks [84]. Prospective, multicenter clinical trials with standardized methodologies and appropriate control groups will be essential to validate these biomarkers and establish targeted, individualized microbiome therapies (Table *1*) [85-87].

Disease	Representative microbial findings	Proposed mechanisms	Human evidence	Therapeutic evidence	Key references
Schizophrenia	Altered Bacteroidetes, Actinobacteria, *Lactobacillus*, and other taxa	Inflammation, LPS, tryptophan-kynurenine pathway, neurotransmitter alterations	Moderate/heterogeneous	Early/preliminary	[4,6,9,10]
ASD	Altered diversity; changes in *Clostridium*, *Bacteroides*, *Bifidobacterium*, *Prevotella*, *Roseburia*, and other taxa	Barrier dysfunction, SCFAs, immune signaling, neurotransmitter alterations	Moderate/heterogeneous	Probiotics/MTT/FMT investigated	[11-15]
AD	Reduced microbial richness; altered *Bacteroides*, Enterobacteriaceae, and SCFA-producing bacteria	LPS/TLR4 signaling, microglial activation, TMAO, bile acids, BBB dysfunction	Increasing	Probiotics/prebiotics/FMT mainly experimental	[16-18,24-28]
PD	Reduced SCFA-producing bacteria; altered Proteobacteria, *Akkermansia*, and *Desulfovibrio*	α-Synuclein aggregation, TLR signaling, SCFAs, LPS, vagal pathways	Moderate	Probiotics benefit constipation; FMT findings are mixed	[32,35,37,41,86,87]
Anxiety	Reduced SCFA-producing bacteria; increased *Escherichia*/*Shigella* and other taxa	HPA axis, vagal signaling, SCFAs, neurotransmitter alterations, inflammation	Moderate but heterogeneous	Selected probiotics show modest effects	[47,48,60,61,66-68]
ALS	Reduced SCFA-producing bacteria; altered Bacteroidetes/Firmicutes and oral microbiota	Barrier dysfunction, LPS, inflammation, SCFAs, microbial metabolites	Limited/heterogeneous	Preclinical and early clinical evidence	[72-75,79-82]

TABLE 1: Summary of studies linking gut microbiome alterations to neurological and neuropsychiatric disorders.

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; ASD: Autism spectrum disorder; BBB: Blood-brain barrier; FMT: Fecal microbiota transplantation; HPA: Hypothalamic-pituitary-adrenal; LPS: Lipopolysaccharide; MTT: Microbiota transfer therapy; PD: Parkinson's disease; SCFAs: Short-chain fatty acids; TLR: Toll-like receptor; TMAO: Trimethylamine N-oxide.

Across the disorders reviewed, the most consistent observations involve altered microbial composition, intestinal barrier dysfunction, inflammatory signaling, and changes in microbial metabolites. However, the specific microbial taxa reported differ substantially across populations and studies, and no reproducible

disease-specific microbial signature has been established. Evidence is also uneven across disorders and study types. Human studies are predominantly observational, while many mechanistic findings derive from animal or microbiota-transfer models. Clinical evidence for microbiome-directed interventions remains limited, with some encouraging findings for gastrointestinal or selected behavioral outcomes but insufficient evidence for consistent disease-modifying effects.

Limitations and knowledge gaps

Interpretation of microbiome research across neurological and neuropsychiatric disorders remains challenging because of substantial heterogeneity among studies. Differences in age, geography, diet, medication exposure, gastrointestinal comorbidities, disease stage, sequencing platforms, sample-processing methods, and bioinformatic pipelines can substantially influence reported microbial profiles. Many studies are cross-sectional and therefore cannot distinguish whether dysbiosis precedes disease, develops as a consequence of disease, or reflects associated lifestyle and treatment factors. In addition, mechanistic findings derived from germ-free animals, microbiota-transfer models, or other preclinical systems may not directly translate to human disease. Although probiotics, prebiotics, dietary interventions, and FMT have produced promising findings in selected studies, clinical trials generally remain small and heterogeneous, and optimal strains, doses, treatment durations, patient selection criteria, and long-term safety have not been established. Standardized longitudinal studies integrating metagenomic, metabolomic, immune, and clinical data will be necessary to identify reproducible microbial signatures and determine whether microbiome-directed interventions can provide clinically meaningful benefits.

This review also has methodological limitations. It was designed as a narrative review with a structured literature search rather than as a systematic review. Formal Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based screening, quantitative meta-analysis, and study-level risk-of-bias assessment were therefore not performed. The inclusion of studies with different populations, methodologies, and levels of evidence also limits direct comparisons across disorders. Accordingly, the findings presented here should be interpreted as a qualitative synthesis of the current literature rather than a quantitative estimate of effect or causality.

Conclusions

The microbiota-gut-brain axis represents a biologically plausible communication network linking intestinal microbial activity with immune, metabolic, neuroendocrine, and neural processes. Across schizophrenia, autism spectrum disorder, Alzheimer's disease, Parkinson's disease, anxiety disorders, and amyotrophic lateral sclerosis, alterations in microbial composition, intestinal barrier function, microbial metabolites, and inflammatory signaling have been repeatedly reported. However, considerable heterogeneity exists among studies, and much of the current human evidence remains associative. Consequently, a universal disease-specific microbial signature or definitive causal relationship between gut dysbiosis and these disorders has not yet been established.

Microbiome-targeted interventions, including probiotics, prebiotics, dietary modifications, psychobiotics, synbiotics, and fecal microbiota transplantation, represent promising areas of investigation but remain largely experimental for neurological and neuropsychiatric indications. Overall, the strongest current evidence supports a biologically plausible association between gut microbial alterations and selected neurological and neuropsychiatric phenotypes, whereas evidence for causality and clinically meaningful disease modification remains insufficient. Future longitudinal studies, standardized microbiome methodologies, multi-omic analyses, and adequately powered randomized controlled trials will be necessary to clarify causality, identify reproducible biomarkers, determine treatment-responsive patient subgroups, and establish the safety and clinical efficacy of personalized microbiome-directed therapies.

Appendices

Database/platform	Search fields	Database-specific search strategy	Date/limits
PubMed/MEDLINE	Title/Abstract; MeSH terms where applicable	("gut microbiota"[Title/Abstract] OR "gut microbiome"[Title/Abstract] OR dysbiosis[Title/Abstract] OR "intestinal microbiota"[Title/Abstract] OR "gut-brain axis"[Title/Abstract] OR metabolites[Title/Abstract] OR "bile acids"[Title/Abstract] OR "trimethylamine N-oxide"[Title/Abstract] OR TMAO[Title/Abstract]) AND (schizophrenia[Title/Abstract] OR "autism spectrum disorder"[Title/Abstract] OR ASD[Title/Abstract] OR "Alzheimer disease"[Title/Abstract] OR "Alzheimer's disease"[Title/Abstract] OR "Parkinson disease"[Title/Abstract] OR "Parkinson's disease"[Title/Abstract] OR anxiety[Title/Abstract] OR "anxiety disorders"[Title/Abstract] OR "amyotrophic lateral sclerosis"[Title/Abstract] OR ALS[Title/Abstract]) AND (probiotic[Title/Abstract] OR prebiotic*[Title/Abstract] OR psychobiotic*[Title/Abstract] OR synbiotic*[Title/Abstract] OR "fecal microbiota transplantation"[Title/Abstract] OR FMT[Title/Abstract] OR biomarker*[Title/Abstract] OR modulators[Title/Abstract] OR therapeutic*[Title/Abstract] OR diagnostic*[Title/Abstract])	2010-2025; peer-reviewed publications; final search date: January 1, 2010 to June 25, 2026
ScienceDirect	Title, abstract, and keywords	("gut microbiota" OR "gut microbiome" OR dysbiosis OR "intestinal microbiota" OR "gut-brain axis" OR metabolites OR "bile acids" OR "trimethylamine N-oxide" OR TMAO) AND (schizophrenia OR "autism spectrum disorder" OR ASD OR "Alzheimer's disease" OR "Alzheimer disease" OR "Parkinson's disease" OR "Parkinson disease" OR anxiety OR "anxiety disorders" OR "amyotrophic lateral sclerosis" OR ALS) AND (probiotic OR prebiotic* OR psychobiotic* OR synbiotic* OR "fecal microbiota transplantation" OR FMT OR biomarker* OR therapeutic* OR diagnostic* OR modulators)	2010-2025; research articles and reviews; final search date: January 1, 2010 to June 25, 2026
SpringerLink	Full text, title, abstract, and keywords, as supported by the platform	("gut microbiota" OR "gut microbiome" OR dysbiosis OR "intestinal microbiota" OR "gut-brain axis" OR metabolites OR "bile acids" OR "trimethylamine N-oxide" OR TMAO) AND (schizophrenia OR "autism spectrum disorder" OR ASD OR "Alzheimer's disease" OR "Alzheimer disease" OR "Parkinson's disease" OR "Parkinson disease" OR anxiety OR "anxiety disorders" OR "amyotrophic lateral sclerosis" OR ALS) AND (probiotic OR prebiotic* OR psychobiotic* OR synbiotic* OR "fecal microbiota transplantation" OR FMT OR biomarker* OR therapeutic* OR diagnostic* OR modulators)	2010-2025; peer-reviewed publications; final search date: January 1, 2010 to June 25, 2026
Wiley Online Library	Title, abstract, and keywords	("gut microbiota" OR "gut microbiome" OR dysbiosis OR "intestinal microbiota" OR "gut-brain axis" OR metabolites OR "bile acids" OR "trimethylamine N-oxide" OR TMAO) AND (schizophrenia OR "autism spectrum disorder" OR ASD OR "Alzheimer's disease" OR "Alzheimer disease" OR "Parkinson's disease" OR "Parkinson disease" OR anxiety OR "anxiety disorders" OR "amyotrophic lateral sclerosis" OR ALS) AND (probiotic OR prebiotic* OR psychobiotic* OR synbiotic* OR "fecal microbiota transplantation" OR FMT OR biomarker* OR therapeutic* OR diagnostic* OR modulators)	2010-2025; peer-reviewed publications; final search date: January 1, 2010 to June 25, 2026

TABLE 2: Database-specific search strategies.

MeSH: Medical Subject Headings; TMAO: Trimethylamine N-oxide; ASD: Autism spectrum disorder; ALS: Amyotrophic lateral sclerosis; FMT: Fecal microbiota transplantation.

Additional Information

Author Contributions

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