

Role of the gut-brain axis in neurological diseases: Molecular connections and therapeutic implications (Review)

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Abstract. The gut-brain axis, a bidirectional communication system involving the central nervous system, enteric nervous system and gastrointestinal tract, plays a pivotal role in neurological health and disease. The present review synthesizes current evidence on its anatomical foundations, functional mechanisms and the role of gut microbiota in neurological diseases. It is explored how dysregulation of the gut-brain axis contributes to neurodegenerative, neuroinflammatory, neurodevelopmental, cerebrovascular and epileptic disorders through molecular mechanisms including neuroinflammation, neurotransmitter modulation, oxidative stress, and blood-brain barrier changes. Furthermore, therapeutic strategies targeting this axis, such as dietary interventions, probiotics, pharmacological approaches and emerging therapies were evaluated. The present review highlights the potential for developing biomarkers and personalized medicine approaches based on gut-brain axis components, while acknowledging translational challenges. However, significant heterogeneity in probiotic strains, FMT protocols, and patient microbiota baselines limits immediate translation. Future trials must address these

variables through standardized designs and multi-omics biomarker integration.

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1. Introduction

The gut-brain axis is a bidirectional communication system that connects the gastrointestinal tract with the central nervous system (CNS). This complex network comprises several key components that facilitate constant interactions between the gut and the brain (1). The enteric nervous system, often referred to as the 'second brain' is embedded within the walls of the gastrointestinal tract and contains over 500 million neurons that functioning independently to regulate gastrointestinal motility, secretion and blood flow (2). The vagus nerve, a crucial component of the parasympathetic nervous system, serves as a direct neural pathway between the gut and the brain, transmitting signals bidirectionally (3). Additionally, the gut microbiota, which consists of trillions of microorganisms, plays a vital role in shaping the gut environment and influencing both local and systemic immune responses (4). Immune pathways, including those involving gut-associated lymphoid tissue and circulating immune cells, further contribute to the communication between the gut and the brain, thus enabling the exchange of immune signals and the modulation of inflammatory responses throughout the body (4).

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The gut-brain axis employs multiple bidirectional communication pathways to maintain homeostasis and coordinate responses to internal and external stimuli (5). Neural pathways primarily involve the vagus nerve, which transmits signals from the gut to the brainstem and vice versa, influencing functions such as appetite, digestion and stress responses (6). The endocrine system also plays a significant role, with gut hormones such as ghrelin, leptin and peptides being released in response to nutrient intake and acting on distant targets in the brain to regulate feeding behavior, energy balance and metabolic processes (7). Immune pathways facilitate communication through the production of cytokines, chemokines and other immune mediators by gut-resident immune cells, which can enter the circulation and affect CNS function (8). Conversely, the brain can modulate immune responses in the gut through the release of neuropeptides and hormones, thus creating a dynamic interplay that impacts both gastrointestinal and neurological health (9).

Emerging epidemiological evidence highlights significant associations between gut dysbiosis and various neurological diseases (10). Previous studies have demonstrated alterations in gut microbiota composition in patients with Alzheimer's disease (AD), characterized by decreased diversity and changes in specific bacterial taxa such as *Bifidobacterium* and *Lactobacillus* (11-13). Similarly, in Parkinson's disease (PD), a shift towards pro-inflammatory microbiota profiles has been observed, with correlations between microbial composition and disease severity (14). Epidemiological data also suggest that individuals with inflammatory bowel disease (IBD) have an increased risk of developing neurological conditions such as multiple sclerosis (MS) and depression, indicating a potential shared pathophysiology (15,16). Furthermore, the incidence of autism spectrum disorders (ASD) have been linked to early-life gut microbiota perturbations, with numerous patients with ASD exhibiting gastrointestinal symptoms and altered microbial communities (17,18). These findings underscore the importance of gut microbiota in neurological health and point towards potential therapeutic targets for modulating the gut-brain axis.

The present review aims to comprehensively synthesize current knowledge on the molecular mechanisms underlying the gut-brain axis in neurological diseases and evaluate existing and emerging therapeutic strategies targeting this axis. By integrating findings from recent preclinical and clinical studies, it is aimed to provide a deeper understanding of how perturbations in the gut-brain axis contribute to disease pathogenesis and progression. Furthermore, current therapeutic approaches are critically assessed, including dietary interventions, probiotics, prebiotics and pharmacological agents, highlighting their efficacy, limitations and potential for future development. This synthesis of evidence will not only offer valuable insights for researchers and clinicians but also identify gaps in knowledge and suggest directions for future investigation, ultimately aiming to advance the translation of gut-brain axis research into effective clinical applications for neurological diseases.

2. Methods

A comprehensive, non-systematic narrative review was conducted by querying PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) from inception to 30 June 2025. Search terms combined

MeSH and free-text keywords ('gut-brain axis', 'microbiome-gut-brain axis', 'gut microbiota') with disease-specific terms ['neurodegeneration', 'Parkinson', 'Alzheimer', 'MS', 'epilepsy', 'autism', 'stroke', 'traumatic brain injury' (TBI)] and mechanistic terms ('molecular mechanism', 'therapy', 'probiotic', 'prebiotic', 'fecal microbiota transplantation (FMT)', 'short-chain fatty acid'). English, full-text, peer-reviewed original articles, systematic reviews, meta-analyses and phase I-III clinical trials were retained. Animal or *in vitro* mechanistic studies were included only when corroborated by human data or published within the last twelve years. Reference lists and trial registries (ClinicalTrials.gov, WHO ICTRP) were hand-searched for additional records. Data were narratively synthesized without formal meta-analysis.

3. Gut-brain axis: Anatomical and functional foundations

The bidirectional communication network between gastrointestinal and CNS involves integrated anatomical structures and signaling pathways. Key neural connections include the vagus nerve and spinal cord routes, while endocrine signaling features brain-gut peptides such as ghrelin and leptin. Parallel communication occurs via microbial metabolites, immune mediators and neuroendocrine mechanisms [for example, hypothalamic-pituitary-adrenal (HPA) axis activation], collectively enabling dynamic crosstalk that regulates neurological function (Table I).

Anatomical connections: Vagus nerve, spinal cord and brain-gut peptides. The gut-brain axis relies on anatomical connections that facilitate bidirectional communication between the gastrointestinal tract and the CNS (19). The vagus nerve, a major component of the parasympathetic nervous system, serves as a direct neural pathway between the gut and the brain. It transmits signals from the gut to the brainstem and vice versa, influencing functions such as appetite, digestion and stress responses (3). The spinal cord also plays a role in this communication, processing sensory information from the gut and sending motor commands that regulate gastrointestinal motility and secretion (20). Additionally, brain-gut peptides such as ghrelin, leptin and peptides are released in response to nutrient intake and act on distant targets in the brain to regulate feeding behavior, energy balance and metabolic processes (21). These anatomical connections form the structural basis for the complex interactions that occur within the gut-brain axis.

Microbiota-gut-brain communication pathways: Metabolites, immune system and neural pathways. The gut microbiota, comprising trillions of microorganisms, plays a crucial role in shaping the gut environment and influencing both local and systemic immune responses (22). Microbiota-gut-brain communication occurs through several pathways. Metabolites produced by gut bacteria, such as short-chain fatty acids (SCFAs), secondary bile acids and tryptophan metabolites, can enter the bloodstream and affect brain function (23). These metabolites have been shown to influence neuroinflammation, neurotransmitter synthesis and blood-brain barrier (BBB) integrity (24). The immune system also serves as a

Table I. Studies of gut-brain axis disorders in nervous system diseases.

Authors, year	Related diseases	Object of study	Main findings	(Refs.)
Sampson <i>et al</i> , 2016	PD	PD model	Antibiotic treatment could reduce motor dysfunction and microglial activation, indicating a potential therapeutic avenue for PD by targeting gut microbiota.	(50)
Perez-Pardo <i>et al</i> , 2019	PD	PD model	TLR4 signaling plays a crucial role in the gut-brain axis in PD. The research suggested that TLR4 might be a promising therapeutic target for PD treatment.	(51)
Srivastav <i>et al</i> , 2019	PD	MPTP and rotenone-induced	A probiotics mixture increases butyrate levels, which rescues nigral dopaminergic neurons from neurotoxicity induced by MPTP and rotenone. This finding highlights the potential of probiotics in PD therapy.	(52)
Honarpisheh <i>et al</i> , 2020	AD	Tg2576 mice	Dysregulated gut homeostasis precedes amyloid- β accumulation in the brain. This suggests that gut dysbiosis might be an early indicator or contributor to AD pathology.	(54)
Kim <i>et al</i> , 2021	AD	APP/PS1 mice	Transplantation of gut microbiota from AD mouse models impairs memory function and neurogenesis in recipient mice. This indicates that gut microbiota may influence cognitive decline in AD.	(55)
Shi <i>et al</i> , 2021	AD	APP/PS1 mice	A fiber-deprived diet causes cognitive impairment and hippocampal microglia-mediated synaptic loss through the gut microbiota and metabolites. This study emphasizes the impact of diet on gut microbiota and AD.	(56)
Castelli <i>et al</i> , 2021	AD	Not specified	Probiotics may reduce neuroinflammation, offering a potential therapeutic strategy for AD.	(58)
Yuan <i>et al</i> , 2019	AD	APP/PS1 mice	Sesamol exerts protective effects via the microbiome-gut-brain axis, potentially benefiting AD treatment.	(59)
Shi <i>et al</i> , 2020	AD	Diet-induced obese Mice	Prebiotics prevent neuroinflammation and cognitive decline by improving the gut microbiota-brain axis. This suggests a dietary approach to AD management.	(60)
Bianchimano <i>et al</i> , 2022	Multiple sclerosis	Mice	Specific gut commensals modulate neuroinflammation, highlighting the gut microbiota's role in MS pathogenesis and potential therapeutic targets within the gut microbiota.	(61)

Table I. Continued.

Authors, year	Related diseases	Object of study	Main findings	(Refs.)
Celorrio and Friess, 2022	TBI	Mice	The gut-brain axis impacts neuroinflammation following TBI. This study suggests that targeting the gut microbiota could mitigate post-injury inflammation.	(62)
Lee <i>et al</i> , 2022	Cognitive impairment	Polystyrene microplastics exposure model	Exposure to polystyrene microplastics impairs hippocampus-dependent learning and memory in mice, with gut microbiota alterations preceding neuroinflammatory changes. This indicates environmental factors' impact on cognitive health via the gut-brain axis.	(65)
Yuan <i>et al</i> , 2022	Neuroinflammation	APP/PS1 mice	Treadmill exercise modulates intestinal microbes and suppresses LPS displacement, alleviating neuroinflammation. This demonstrates exercise's beneficial effects on gut-brain axis modulation.	(66)
Hu <i>et al</i> , 2023	Neuroinflammation	TBI model	FMT inhibits neuroinflammation following TBI by regulating the gut-brain axis, indicating its potential as a treatment for neuroinflammatory conditions.	(67)
Li <i>et al</i> , 2023	Cognitive deficits	Rats	<i>Lactobacillus rhamnosus</i> GG ameliorates noise-induced cognitive deficits and systemic inflammation by modulating the gut-brain axis. This suggests probiotics' utility in cognitive deficit management.	(68)
de Theije <i>et al</i> , 2014	ASD	ASD model	Intestinal inflammation is present in a murine model of ASD, suggesting a potential link between gut dysfunction and behavioral abnormalities.	(71)
Slob <i>et al</i> , 2021	ADHD and ASD	Discordant twin study	Early-life antibiotic use is linked to increased risk of ADHD and ASD, indicating that gut microbiota perturbations during critical developmental windows may have long-term neurological consequences.	(81)
Bundgaard-Nielsen <i>et al</i> , 2023	Neurodevelopmental disorders	Children and adolescents with ADHD and ASD	Distinct microbiota compositions are found in children and adolescents with ADHD and ASD, suggesting shared and unique gut microbiota signatures across neurodevelopmental disorders.	(82)
Gonçalves <i>et al</i> , 2020	Behavioral changes	Young zebrafish	Exposure to high doses of amoxicillin causes behavioral changes and oxidative stress in young zebrafish, suggesting potential developmental consequences of antibiotic use.	(84)

Table I. Continued.

Authors, year	Related diseases	Object of study	Main findings	(Refs.)
Volkova <i>et al</i> , 2021	Brain development	Early-life penicillin exposure model	Early-life penicillin exposure alters frontal cortex and amygdala gene expression, highlighting the developing brain's sensitivity to gut microbiota perturbations.	(85)
Benakis <i>et al</i> , 2016	Ischemic stroke	Ischemic stroke model	Commensal microbiota affects stroke outcome via intestinal $\gamma\delta$ T cells, highlighting the role of gut immunity in stroke pathogenesis.	(86)
Dou <i>et al</i> , 2019	Focal cerebral ischemia/ reperfusion injury	Mice	Resveratrol exerts neuroprotection against focal cerebral ischemia/ reperfusion injury in mice through a mechanism targeting the gut-brain axis.	(87)
Park <i>et al</i> , 2020	Reproductive senescence and ischemic stroke	Female rats	Reproductive senescence and ischemic stroke remodel the gut microbiome and modulate the effects of estrogen treatment in female rats.	(90)
Sadler <i>et al</i> , 2020	Stroke	Mice	SCFAs improve poststroke recovery via immunological mechanisms, suggesting a potential therapeutic avenue.	(91)
Aswendt <i>et al</i> , 2021	Acute brain ischemia	Mice	Gut microbiota modulation affects brain network connectivity under physiological conditions and after acute brain ischemia.	(92)
Henry <i>et al</i> , 2021	Acute ischemic stroke patients	SCFAs at thrombectomy	SCFAs taken at the time of thrombectomy in acute ischemic stroke patients are associated with inflammatory markers and worse symptoms at discharge.	(94)
Jiang <i>et al</i> , 2021	Post-stroke depression	Gut microbiome and lipid metabolism	Alterations in the gut microbiome and correlated lipid metabolism are found in post-stroke depression, indicating potential metabolic links between gut dysbiosis and neurological symptoms.	(95)
Huang <i>et al</i> , 2019	Cerebral palsy and epilepsy	Children with cerebral palsy and epilepsy	Distinct gut microbiota composition and functional categories are observed in children with cerebral palsy and epilepsy, suggesting a potential link between gut dysfunction and seizure activity.	(96)
Lindfeldt <i>et al</i> , 2019	Severe epilepsy	Children with severe epilepsy	The ketogenic diet influences the taxonomic and functional composition of the gut microbiota in children with severe epilepsy, indicating that dietary interventions can modulate gut microbiota to reduce seizure frequency.	(97)
He <i>et al</i> , 2017	Epilepsy and Crohn's disease	Epilepsy and Crohn's disease	FMT cured epilepsy in a patient with Crohn's disease, highlighting the potential of microbiota-based therapies.	(98)

Table I. Continued.

Authors, year	Related diseases	Object of study	Main findings	(Refs.)
Avorio <i>et al</i> , 2021	Epilepsy	Epilepsy patients	Functional gastrointestinal disorders are common in patients with epilepsy and may influence seizure occurrence, suggesting that targeting gut dysfunction could improve seizure control.	(99)
Citraro <i>et al</i> , 2021	Absence epilepsy	WAG/Rij rat model of absence epilepsy	Altered microbiota and intestinal damage are present in a genetic animal model of absence epilepsy, indicating a potential pathway linking gut dysfunction to seizure activity.	(100)
Gallucci <i>et al</i> , 2021	Acute seizures	Theiler murine encephalomyelitis virus-induced acute seizures	Gut metabolites may modulate neuronal excitability and contribute to epileptogenesis, suggesting new therapeutic targets.	(101)

PD, Parkinson's disease; AD, Alzheimer's disease; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TLR4, Toll-like receptor 4; TBI, traumatic brain injury; ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder; FMT, fecal microbiota transplantation; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; APP/PS1, amyloid precursor protein/presenilin 1 (transgenic mouse model of AD); CUMS, chronic unpredictable mild stress; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; GABA, gamma-aminobutyric acid; BDNF, brain-derived neurotrophic factor; TNF- α , tumor necrosis factor-alpha; IL-6, interleukin-6.

key communication pathway, with gut-resident immune cells producing cytokines and chemokines that can modulate CNS function (25). Furthermore, neural pathways, including the vagus nerve, transmit signals from the gut to the brain and vice versa, allowing for rapid communication and coordinated responses to internal and external stimuli (3) (Fig. 1). This intricate network of communication pathways enables the gut microbiota to exert profound effects on neurological health.

Endocrine and neuroendocrine mechanisms linking the gut and brain. Endocrine and neuroendocrine mechanisms further contribute to the bidirectional communication between the gut and the brain (23). Gut hormones such as ghrelin, leptin and peptides are released into the bloodstream and act on receptors in the brain to regulate appetite, energy expenditure and metabolic processes (26). These hormones can influence neurotransmitter release and affect brain regions involved in reward, motivation and stress responses (27). Additionally, the HPA axis, a key neuroendocrine system, plays a significant role in stress response and regulation of the gut-brain axis. Stress-induced activation of the HPA axis leads to the release of corticotropin-releasing hormone and subsequent increases in cortisol levels, which can modulate gut motility, secretion and barrier function (28) (Fig. 1). Conversely, signals from the gut can feedback to the HPA axis, creating a dynamic interplay that impacts both gastrointestinal and neurological health (29). This complex web of endocrine and neuroendocrine interactions underscores the intimate connection between the gut and the brain in maintaining overall homeostasis and health.

4. Role of gut microbiota in neurological health

Gut microbiota composition-shaped by genetics, diet and environmental exposures-critically influences neurological outcomes through metabolite production. Microbiota-derived SCFAs, secondary bile acids and tryptophan metabolites modulate neurodevelopment, neurotransmitter synthesis [for example, serotonin and γ -aminobutyric acid (GABA)], and neuroinflammatory responses, thereby serving as fundamental regulators of brain homeostasis.

Composition and diversity of gut microbiota. The human gut microbiota comprises a complex community of microorganisms, including bacteria, archaea, viruses and eukaryotic microbes, with bacterial species being the most predominant and diverse (30). The composition of gut microbiota varies significantly among individuals and is influenced by factors such as genetics, diet, age, geographical location and lifestyle (31). The gut microbiota is established at birth, with the initial microbial colonization influenced by the mode of delivery and breastfeeding (32). During infancy and childhood, the microbiota continues to develop and diversify, reaching a relatively stable state in adulthood. However, this stability can be disrupted by various factors, including antibiotics, stress and changes in diet, leading to dysbiosis, which is associated with numerous health issues, including neurological disorders (33).

Microbiota-derived metabolites: SCFAs, secondary bile acids and tryptophan metabolites. Gut microbiota produces a wide

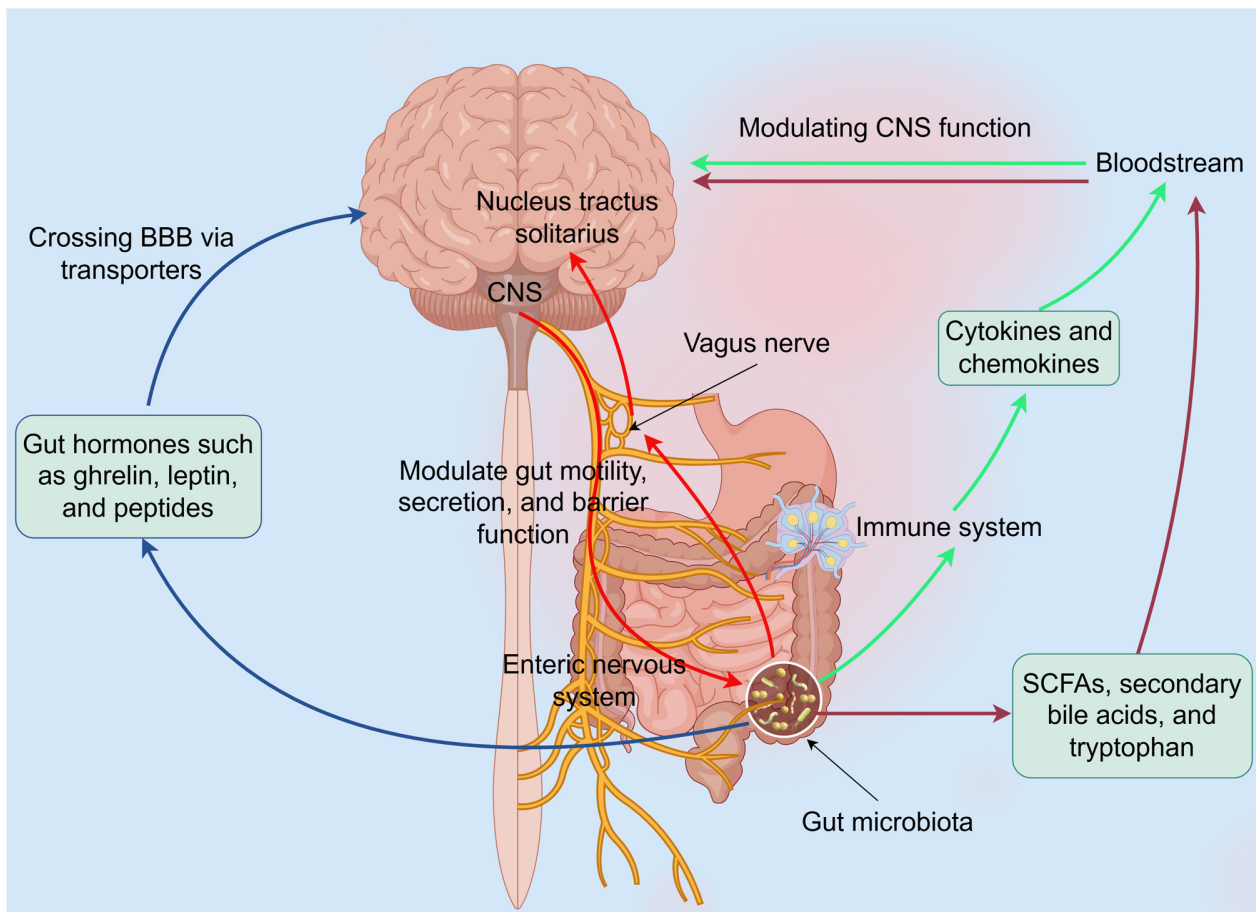


Figure 1. Gut-brain axis: Multidirectional communication network. Schematic summarizing the four principal bidirectional pathways between gut microbiota and brain. Neural route: Vagus nerve afferents carrying microbial signals to nucleus tractus solitarius. Endocrine route: Gut hormones (for example, ghrelin, GLP-1) crossing BBB via transporters. Immune route: Cytokines (IL-6 and TNF- α) released from gut-associated lymphoid tissue entering systemic circulation. Microbial metabolite route: SCFAs (butyrate, propionate), tryptophan catabolites (kynurenine, indole-3-lactic acid) and secondary bile acids (deoxycholic acid) modulating BBB integrity, microglial activation and neurotransmitter synthesis. Schematic illustration created with Figdraw (<https://www.figdraw.com>) under an academic license. BBB, blood-brain barrier; CNS, central nervous system; SCFAs, short-chain fatty acids.

range of metabolites that play crucial roles in host physiology and pathology. Tryptophan metabolites-indole derivatives (for example, indole-3-lactic acid, indole-3-acetic acid) and kynurenine pathway metabolites (kynurenine, kynurenic acid, 3-hydroxykynurenine)-are synthesized by gut bacteria (for example, *Clostridium sporogenes*, *Lactobacillus* spp.) via tryptophanase or indoleamine-2,3-dioxygenase. Dysbiosis-induced accumulation of neurotoxic kynurenine metabolites (3-hydroxykynurenine, quinolinic acid) and reduction of neuroprotective indole-3-lactic acid have been implicated in neurological disorders. In patients with AD, reduced serum indole-3-lactic acid correlates with cognitive decline (34), while elevated 3-hydroxykynurenine levels are associated with neuroinflammation in PD (35). SCFAs, including acetate, propionate and butyrate, are the primary metabolites produced by the fermentation of dietary fiber by gut bacteria (36). SCFAs have been shown to modulate neuroinflammation, reinforce the integrity of the BBB, and regulate neurotransmitter synthesis (37). Secondary bile acids, such as deoxycholic acid and lithocholic acid, are generated by the microbial transformation of primary bile acids and have been implicated in influencing neuroinflammation and cognitive function through interactions with specific receptors (38). Tryptophan

metabolites, including indole derivatives and kynurenine, are another important group of microbiota-derived metabolites that impact serotonin production and immune responses, potentially affecting neuropsychiatric conditions (39).

Microbiota influence on neurodevelopment, neurotransmission and neuroinflammation. The gut microbiota significantly influences neurodevelopment, with animal studies demonstrating that germ-free mice exhibit altered brain development and behavior compared with conventionally raised animals (40). The microbiota also plays a vital role in neurotransmission, as gut bacteria are capable of producing or stimulating the production of neurotransmitters such as serotonin, dopamine and gut luminal GABA (41,42). In total, ~90% of the body's serotonin is synthesized by enterochromaffin cells in the gut, and this peripheral serotonin can influence both gut function and brain activity (43). Furthermore, the gut microbiota is a key regulator of neuroinflammation, modulating the host's immune response and influencing the activation of microglia, the resident immune cells of the CNS (44,45). Dysbiosis has been associated with increased neuroinflammatory responses, which are implicated in the pathogenesis of various neurological disorders, including AD, PD and MS (46-48).

5. Gut-brain axis dysregulation in neurological diseases

Emerging evidence implicates gut-brain axis perturbations across diverse neurological disorders through distinct yet overlapping mechanisms (Table II). Dysbiosis precedes motor symptoms in PD, exacerbates neuroinflammation in MS and stroke, correlates with behavioral deficits in ASD, and influences seizure susceptibility in epilepsy, suggesting pathway-specific pathophysiological contributions.

Neurodegenerative diseases. In PD, research has shown that gut microbiota dysbiosis precedes motor symptoms and may contribute to neuroinflammation and α -synuclein aggregation (49). Sampson *et al* (50) demonstrated that gut microbiota regulates motor deficits and neuroinflammation in a PD model, with antibiotic treatment reducing motor dysfunction and microglial activation. Perez-Pardo *et al* (51) further explored the role of Toll-like receptor 4 (TLR4) in the gut-brain axis in PD, suggesting that TLR4 signaling may be a therapeutic target. Additionally, Srivastav *et al* (52) found that a probiotics mixture increases butyrate, rescuing nigral dopaminergic neurons from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone-induced neurotoxicity.

In PD, α -synuclein pathology is closely linked to gastrointestinal dysbiosis; increased α -synuclein expression correlates with reduced *Lachnospiraceae* and elevated *Enterobacteriaceae*, accelerating neurodegeneration via gut-derived inflammation (53). Homogeneously, emerging evidence suggests that gut microbiota alterations may contribute to amyloid- β plaque formation and neuroinflammation. Honarpisheh *et al* (54) observed dysregulated gut homeostasis prior to brain amyloid- β accumulation in Tg2576 mice. Kim *et al* (55) found that transplantation of gut microbiota from mouse models with AD impairs memory function and neurogenesis in recipient mice. Shi *et al* (56) demonstrated that a fiber-deprived diet causes cognitive impairment and hippocampal microglia-mediated synaptic loss through the gut microbiota and metabolites. Furthermore, chronic PD progression is associated with gut microbiota-driven protection of dopaminergic neurons. *Clostridium butyricum* supplementation increased butyrate-producing taxa, suppressed substantia nigra inflammation, and improved motor deficits in mice with MPTP-induced PD (57).

Recent advances have highlighted the potential therapeutic role of probiotics and prebiotics in neurodegenerative diseases (57). Castelli *et al* (58) discussed the emerging role of probiotics in PD, suggesting new therapeutic possibilities. Yuan *et al* (59) explored the ApoE-dependent protective effects of sesamol on high-fat diet-induced behavioral disorders through regulation of the microbiome-gut-brain axis. Additionally, prebiotics such as microbiota-accessible carbohydrates (a class of prebiotics), have been shown to prevent neuroinflammation and cognitive decline by improving the gut microbiota-brain axis in diet-induced obese mice (60). While these preclinical studies are encouraging, a recent randomized controlled trial (RCT) in early PD reported no motor benefit from multi-strain probiotics after 12 weeks (14), underscoring the need for larger, longer-duration trials that stratify patients by baseline microbiota profiles.

Neuroinflammatory diseases. In MS, research has identified specific gut commensals that modulate neuroinflammation. Bianchimano *et al* (61) utilized microbiota profiling to pinpoint gut bacteria influencing MS-like disease in mice, revealing potential therapeutic targets within the gut microbiota. Similarly, in TBI, the gut-brain axis plays a pivotal role in neuroinflammatory responses. Celorrio and Friess (62) highlighted the impact of gut microbiota dysbiosis on neuroinflammation following TBI, suggesting that targeting the gut microbiota could mitigate post-injury inflammation. Furthermore, first-episode psychosis (FEP) exhibits gut dysbiosis characterized by decreased *Faecalibacterium prausnitzii* and elevated *Enterococcus*, correlating with increased kynurenine/tryptophan ratios and peripheral inflammation (63). These findings implicate microbial tryptophan metabolism in FEP pathophysiology.

Environmental factors also contribute to neuroinflammation through the gut-brain axis (64). Lee *et al* (65) demonstrated that exposure to polystyrene microplastics impairs hippocampus-dependent learning and memory in mice, with gut microbiota alterations preceding neuroinflammatory changes. Exercise has shown promise in modulating the gut microbiota to reduce neuroinflammation. Yuan *et al* (66) found that treadmill exercise modulates intestinal microbes and suppresses lipopolysaccharide (LPS) displacement, alleviating neuroinflammation in APP/PS1 mice.

FMT represents a novel therapeutic approach. Hu *et al* (67) showed that FMT inhibits neuroinflammation following TBI in mice by regulating the gut-brain axis, indicating its potential as a treatment for neuroinflammatory conditions. Additionally, specific probiotics have demonstrated neuroprotective effects. Li *et al* (68) revealed that *Lactobacillus rhamnosus* GG ameliorates noise-induced cognitive deficits and systemic inflammation in rats by modulating the gut-brain axis.

Recent research has also focused on the role of microbial metabolites in neuroinflammation. Wei *et al* (69) showed that butyrate ameliorates chronic alcoholic CNS damage by suppressing microglia-mediated neuroinflammation and modulating the microbiome-gut-brain axis. Similarly, Zhu *et al* (70) demonstrated that *Bifidobacterium breve* HNX26M4 attenuates cognitive deficits and neuroinflammation in APP/PS1 mice through gut-brain axis regulation.

Neurodevelopmental disorders. In ASD, research has identified specific gut microbiota alterations associated with disease severity. De Theije *et al* (71) demonstrated intestinal inflammation in a murine model of ASD, suggesting a potential link between gut dysfunction and behavioral abnormalities. Stilling *et al* (72) found that absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala, highlighting the role of gut microbiota in neurodevelopmental programming. Kantarcioglu *et al* (73) identified specific yeast species in the stool samples of children with ASD, suggesting a potential role of fungal microbiota in disease pathogenesis. Furthermore, recent comparative analyses revealed significant differences in gut microbiota composition between children with ASD and their neurotypical siblings, with reduced *Bifidobacterium* and *Akkermansia* abundance in ASD cohorts (74). These alterations correlated with increased serum zonulin levels,

Table II. Molecular mechanisms that connects the gut and the brain.

Authors, year	Disease model	Study object	Mechanism	Key findings	(Refs.)
Antón <i>et al</i> , 2018	Neuroinflammation	Rat model of alcohol-induced intestinal hyperpermeability	Gut barrier disruption leads to microbial metabolite translocation and systemic inflammation, activating TLR4 signaling in peripheral immune cells and the brain	Alcohol-induced intestinal hyperpermeability promotes systemic endotoxemia, exacerbating neuroinflammatory cascades	(102)
Hoyles <i>et al</i> , 2018	Neuroinflammation and BBB regulation	Mouse model	Propionate protects BBB integrity and suppresses pro-inflammatory cytokines via histone deacetylase inhibition	Propionate reinforces BBB and reduces inflammation	(103)
Ceccarelli <i>et al</i> , 2017	Neuroinflammation in HIV-associated neurocognitive disorders	HIV-1 infected individuals	High-dose multi-strain probiotics modulate CNS immune activation	Probiotics may benefit neurocognitive performance	(104)
Rincel <i>et al</i> , 2019	Sex-specific neuroinflammation	Multi-hit early life adversity in mice	Gut microbiota, brain, and behavior affected differently in males and females	Early life adversity impacts gut-brain axis sex-dependently	(105)
Cuskelly <i>et al</i> , 2022	Neuroinflammation with sexual dimorphism	Neonatal immune challenge in rodents	Microbiota and behavior influenced differently in males and females	Neonatal immune challenge affects microbiota and behavior sexually dimorphically	(106)
Saunders <i>et al</i> , 2020	Neurodevelopmental disorder	Mouse model	Gut microbiota manipulation during prepubertal period shapes behavioral abnormalities	Gut microbiota affects neurodevelopmental behavior	(107)
Duan <i>et al</i> , 2023	Impact of SCFAs on macrophage activities	Disease context	Microbiota-derived SCFAs influence macrophage functions	SCFAs have therapeutic potentials	(108)
Chauhan <i>et al</i> , 2023	Neurodegenerative diseases	Comparative analysis	Microbial dysbiosis may link to neurodegeneration metabolically	Microbial dysbiosis potentially contributes to neurodegeneration	(109)
Zancan <i>et al</i> , 2024	MS	Mendelian randomization analysis	Gut microbiota composition causally linked to MS	Gut microbiota plays role in MS etiology	(110)
Emery <i>et al</i> , 2022	Alzheimer's and PD	High resolution 16S rRNA gene NGS	Brain areas associated with AD and PD have distinct microbiota	Microbiota differs in neurodegenerative diseases	(111)
Boles <i>et al</i> , 2024	Colitis model	Mouse model	Leaky gut dysregulates brain gene networks associated with immune activation, oxidative stress and myelination	Gut permeability affects brain gene regulation	(112)
Luck <i>et al</i> , 2021	Neurotransmitter profiles in gut and brain	Mice mono-associated with <i>Bifidobacterium dentium</i>	Neurotransmitter profiles altered in gut and brain	Gut microbiota influences neurotransmitter profiles	(113)
Pandey <i>et al</i> , 2015	Systemic oxidative stress and neurotransmitters	Probiotic <i>Escherichia coli</i> CFR 16	Protects against 1,2-dimethylhydrazine-induced stress and neurotransmitter alterations	Probiotic modulates systemic stress and neurotransmitters	(114)
Zhu <i>et al</i> , 2020	PD	Mouse model	Potential association between neurotransmitter disturbance and gut microbiota dysbiosis	Gut microbiota may affect neurotransmitters in PD	(115)
Li <i>et al</i> , 2025	Depressive-like behaviors	Mice	<i>Lactiplantibacillus plantarum</i> GOLDGUT-HNU082 modulates gut microbiota and neurotransmitters	Probiotic alleviates depressive behaviors	(116)
Guo <i>et al</i> , 2021	Neurotransmitter metabolism	High sugar and fat diet	Influences neurotransmitter metabolism, affecting brain function via gut microbiota	Diet impacts brain via gut microbiota	(117)
Zhang <i>et al</i> , 2021	Neurotransmitter secretion disorder	Zebrafish exposed to caffeine	Melatonin regulates disorder through microbiota-gut-brain axis	Melatonin modulates neurotransmitter secretion	(118)

Table II. Continued.

Authors, year	Disease model	Study object	Mechanism	Key findings	(Refs.)
Wang <i>et al</i> , 2023	Neurotransmitter disturbances	Methylmercury exposure	Microbiota-gut-brain interaction involved	Methylmercury affects neurotransmitters via microbiota	(119)
Huang <i>et al</i> , 2024	Gut-brain axis in cerebral small vessel disease	Patients	Multi-omics analysis reveals microbial and neurotransmitter signatures	Gut-brain axis altered in cerebrovascular disease	(121)
Margetts <i>et al</i> , 2022	Anti-inflammatory effects	<i>Salvia officinalis</i> L.	Modulates neurotransmitter metabolism	Herbal extract has anti-inflammatory effects	(122)
Kumari <i>et al</i> , 2022	Oxidative stress and brain injury	Mouse model	Lactacaseibacillus rhamnosus-derived exopolysaccharide attenuates oxidative stress and inflammation	Probiotic derivative protects against brain injury	(123)
Cansiz <i>et al</i> , 2021	Gut-brain axis in zebrafish	Rotenone-induced stress	Caprylic acid ameliorates inflammation and oxidative stress	Caprylic acid benefits gut-brain axis	(125)
Pan <i>et al</i> , 2022	MPTP-induced oxidative stress	Probiotic <i>Pediococcus pentosaceus</i>	Alleviates oxidative stress via gut microbiota regulation	Probiotic reduces oxidative stress	(126)
Dong <i>et al</i> , 2023	Cognitive function in mice	Soy protein supplementation	Modifies hippocampal nerve growth, oxidative stress, and intestinal microbiota	Soy protein improves cognitive function	(127)
Nikrad <i>et al</i> , 2023	Gut-brain axis pathway	Obese women with PCOS	Calorie restriction with spinach thylakoids affects gut-brain pathway and oxidative stress	Dietary intervention impacts gut-brain axis	(128)
Rode <i>et al</i> , 2021	Tryptophan transport	Oxidative stress-induced deficits	Butyrate rescues deficits in intestinal epithelial cells	Butyrate may benefit affective disorders	(129)
He <i>et al</i> , 2024	AD model	Hydrogen-rich water	Targets oxidative stress, inflammation, and gut-brain axis	Hydrogen-rich water has therapeutic potential	(130)
Di Chiano <i>et al</i> , 2024	Human microglia	Lactobacilli cell-free supernatants	Modulate inflammation and oxidative stress via NRF2-SOD1 signaling	Probiotic supernatants have neuroprotective effects	(131)
Hsu <i>et al</i> , 2023	Patients with Alzheimer's dementia	Probiotic supplements	Improve BDNF, reduce inflammation and oxidative stress	Probiotics may benefit patients with Alzheimer's disease	(132)
Akhgarjand <i>et al</i> , 2024	Mild to moderate AD	Probiotic supplements	Reduce oxidative stress and inflammation	Probiotics have positive effects	(133)
Chenghan <i>et al</i> , 2025	BBB integrity	SCFAs	Mediate gut microbiota-brain communication, protecting BBB	SCFAs protect BBB integrity	(135)
Stachulski <i>et al</i> , 2023	BBB function	p-cresol glucuronide	Promotes BBB integrity by suppressing pro-inflammatory cytokines	Microbial metabolite benefits BBB	(136)
Connell <i>et al</i> , 2024	LPS-induced BBB disruption	Polyphenol-rich extract	Prevents disruption through modulation of gut microbiota-derived toxins	Dietary polyphenols protect BBB	(137)
Fiorentino <i>et al</i> , 2016	ASD	Patients	Altered gut and brain barriers linked to neuroinflammation	Barrier dysfunction contributes to ASD pathology	(139)
Sun <i>et al</i> , 2021	Post-bone-marrow transplantation	Mice with antibiotic-induced microbiome depletion	Disrupted BBB allows monocyte infiltration	Microbiome depletion affects BBB	(140)
Nelson <i>et al</i> , 2021	Hypertensive stroke-prone rats	Spontaneously hypertensive stroke-prone rats	Gut microbiome contributes to BBB disruption	Gut microbiome affects BBB integrity	(141)
Knox <i>et al</i> , 2022	BBBprotection	Microbial-derived metabolites	Induce actin rearrangement, enhancing barrier resilience	Metabolites protect BBB function	(142)
Wang <i>et al</i> , 2024	Ischemic stroke treatment	Vagus nerve stimulation	Modulates mast cell degranulation via microbiota-gut-brain axis	Vagus nerve stimulation protects BBB	(143)
Marungruang <i>et al</i> , 2018	Postnatal BBB development	Dietary-induced gut maturation	Stabilizes BBB development through metabolic crosstalk	Early dietary intervention benefits BBB	(144)

Table II. Continued.

Authors, year	Disease model	Study object	Mechanism	Key findings	(Refs.)
Schalla <i>et al</i> , 2023	Stem-cell-derived BBB model	Phoenixin-14	Does not cross model, indicating selective transport	Gut-derived molecules have selective BBB permeability	(145)

BBB, blood-brain barrier; SCFAs, short-chain fatty acids; TLR4, Toll-like Receptor 4; HIV, human immunodeficiency virus; CNS, central nervous system; NRF2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; GPx, glutathione peroxidase; LPS, lipopolysaccharide; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine (serotonin); BDNF, brain-derived neurotrophic factor; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NOX2, NADPH oxidase 2; MDA, malondialdehyde; NGF, nerve growth factor; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; Treg, regulatory T cell; IFN- γ , interferon-gamma; IL-17A, interleukin-17A; IL-10, interleukin-10; EVs, extracellular vesicles; PAMPs, pathogen-associated molecular patterns.

suggesting compromised intestinal barrier integrity as a mechanistic link to neuroinflammation.

In addition to ASD, gut microbiota dysbiosis has been implicated in schizophrenia and bipolar disorder. In schizophrenia, patients show reduced microbial diversity and decreased abundance of SCFA-producing taxa such as *Faecalibacterium* and *Roseburia*, which correlates with cognitive deficits and negative symptoms (75). A systematic review by Bioque *et al* (76) further highlighted the role of the microbiome-gut-brain axis in schizophrenia, emphasizing its potential as a therapeutic target (75-77). Similarly, in bipolar disorder, gut dysbiosis is characterized by decreased *Bifidobacterium* and increased pro-inflammatory *Enterobacteriaceae*, which may exacerbate neuroinflammation via kynurenine pathway activation and cognitive dysfunction (63). A pilot study by Reininghaus *et al* (78) demonstrated that probiotic supplementation improved cognitive parameters in patients with euthymic bipolar disorder, suggesting a modulatory role of gut microbiota in psychiatric outcomes.

Recent research has focused on the therapeutic potential of targeting the gut microbiota in ASD. Pulikkan *et al* (79) reported gut microbial dysbiosis in Indian children with ASD, with specific bacterial taxa correlating with disease severity. Bojović *et al* (80) found altered production of SCFAs in children with neurodevelopmental disorders, suggesting a potential metabolic link between gut dysbiosis and neurological symptoms.

In attention-deficit hyperactivity disorder (ADHD), emerging evidence suggests that gut microbiota dysregulation may contribute to disease development. Slob *et al* (81) found an association between early-life antibiotic use and the risk of ADHD and ASD in a discordant twin study, indicating that gut microbiota perturbations during critical developmental windows may have long-term neurological consequences. Bundgaard-Nielsen *et al* (82) reported distinct microbiota compositions in children and adolescents with ADHD and ASD, suggesting shared and unique gut microbiota signatures across neurodevelopmental disorders. Nevertheless, a meta-analysis of 14 pediatric ASD cohorts found no consistent taxonomic signature after adjusting for diet and antibiotic exposure, highlighting the risk of over-interpreting small, uncontrolled studies (83).

Environmental factors and their impact on the gut-brain axis in neurodevelopmental disorders have also been explored. Gonçalves *et al* (84) demonstrated that

exposure to high doses of amoxicillin causes behavioral changes and oxidative stress in young zebrafish, suggesting potential developmental consequences of antibiotic use. Volkova *et al* (85) found that early-life penicillin exposure alters frontal cortex and amygdala gene expression, highlighting the sensitivity of the developing brain to gut microbiota perturbations.

Stroke and cerebrovascular diseases. Research has shown that gut microbiota dysbiosis is associated with increased risk and severity of stroke. Benakis *et al* (86) demonstrated that commensal microbiota affects ischemic stroke outcome by regulating intestinal $\gamma\delta$ T cells, highlighting the role of gut immunity in stroke pathogenesis. Dou *et al* (87) found that resveratrol exerts neuroprotection against focal cerebral ischemia/reperfusion injury in mice through a mechanism targeting the gut-brain axis. Bonsack *et al* (88) discussed the active role of the gut-brain axis in homeostasis and dysbiosis related to stroke. A review highlighted that cerebral ischemia-reperfusion injury triggers gut dysbiosis-mediated neuroinflammation via TLR4/NF- κ B signaling and elevated IL-6/TNF- α levels (89). FMT from healthy donors restored *Lactobacillus* abundance and attenuated microglial activation in rodent stroke models.

Recent studies have focused on the therapeutic potential of targeting the gut microbiota in stroke (89). Park *et al* (90) reported that reproductive senescence and ischemic stroke remodel the gut microbiome and modulate the effects of estrogen treatment in female rats. Sadler *et al* (91) found that SCFAs improve poststroke recovery via immunological mechanisms, suggesting a potential therapeutic avenue. Aswendt *et al* (92) demonstrated that the gut microbiota modulates brain network connectivity under physiological conditions and after acute brain ischemia, indicating its role in both health and disease states.

Environmental factors and their impact on the gut-brain axis in stroke have also been explored (93). Henry *et al* (94) found that SCFAs taken at the time of thrombectomy in patients with acute ischemic stroke are associated with inflammatory markers and worse symptoms at discharge, suggesting complex interactions between gut metabolites and clinical outcomes. Jiang *et al* (95) reported alterations in the gut microbiome and correlated lipid metabolism in post-stroke depression, indicating potential metabolic links between gut dysbiosis and neurological symptoms.

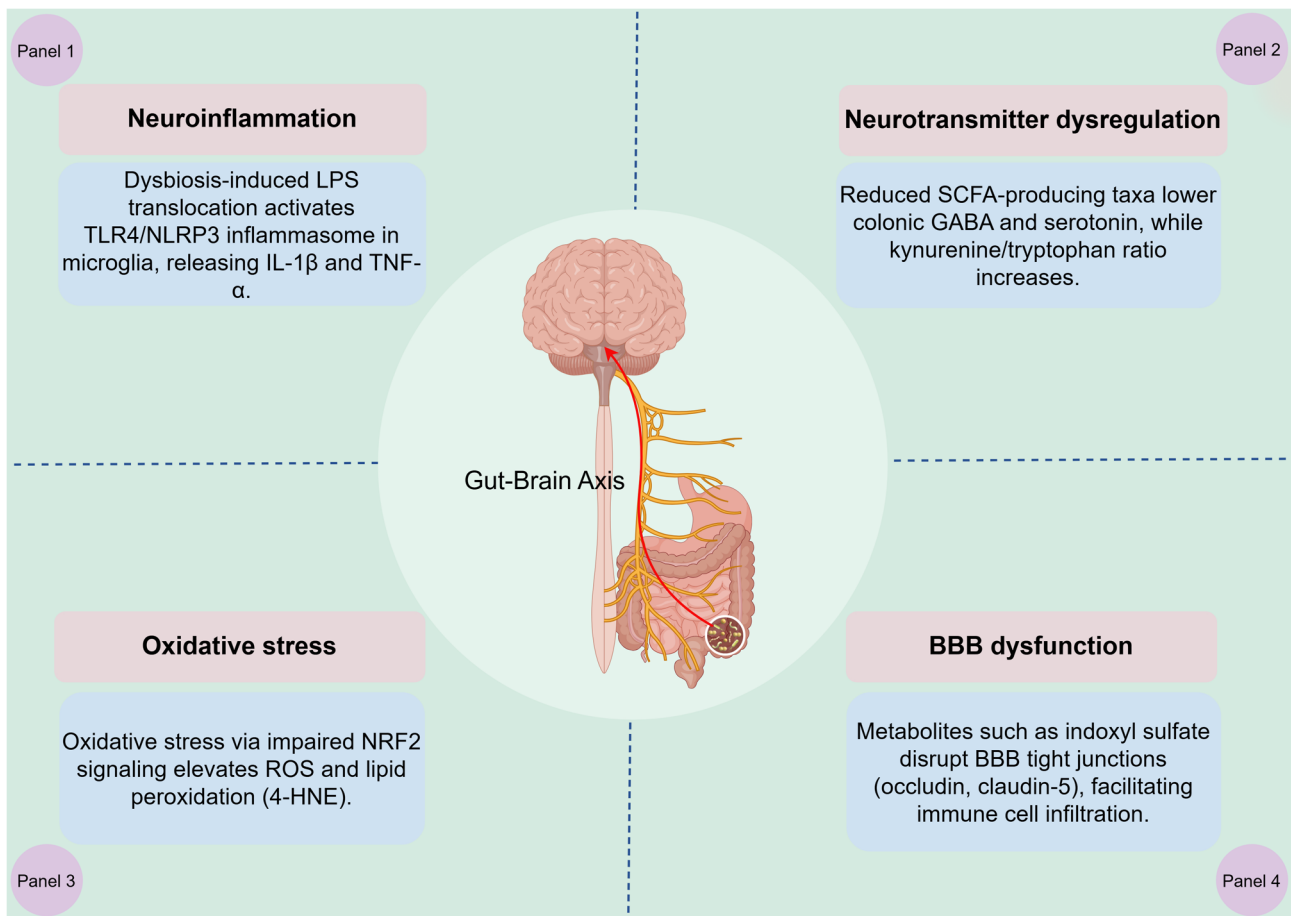


Figure 2. Molecular mechanisms of gut-brain axis dysregulation in neurological diseases. Mechanistic overview of gut-brain axis dysregulation across neurological disorders. Panel 1: Dysbiosis-induced LPS translocation activates TLR4/NLRP3 inflammasome in microglia, releasing IL-1 β and TNF- α . Panel 2: Reduced SCFA-producing taxa lower colonic GABA and serotonin, while kynurenine/tryptophan ratio increases. Panel 3: Oxidative stress via impaired NRF2 signaling elevates ROS and lipid peroxidation (4-HNE). Panel 4: Metabolites such as indoxyl sulfate disrupt BBB tight junctions (occludin, claudin-5), facilitating immune cell infiltration. Mechanistic diagram generated using Figdraw (<https://www.figdraw.com>) under an academic license. LPS, lipopolysaccharide; SCFA, short-chain fatty acid; GABA, gamma-aminobutyric acid; ROS, reactive oxygen species; BBB, blood-brain barrier.

Epilepsy and seizure disorders. Research has shown that gut microbiota dysbiosis is associated with increased risk and severity of epilepsy. Huang *et al* (96) demonstrated distinct gut microbiota composition and functional categories in children with cerebral palsy and epilepsy, suggesting a potential link between gut dysfunction and seizure activity. Lindefeldt *et al* (97) reported that the ketogenic diet influences the taxonomic and functional composition of the gut microbiota in children with severe epilepsy, indicating that dietary interventions can modulate gut microbiota to reduce seizure frequency.

Previous studies have focused on the therapeutic potential of targeting the gut microbiota in epilepsy. He *et al* (98) described a pediatric case where FMT cured epilepsy in a patient with Crohn's disease, highlighting the potential of microbiota-based therapies. Avorio *et al* (99) found that functional gastrointestinal disorders are common in patients with epilepsy and may influence seizure occurrence, suggesting that targeting gut dysfunction could improve seizure control.

The mechanism underlying the gut-brain axis in epilepsy has also been explored. Citraro *et al* (100) provided the first evidence of altered microbiota and intestinal damage in a

genetic animal model of absence epilepsy, the WAG/Rij rat, indicating a potential pathway linking gut dysfunction to seizure activity (100). Gallucci *et al* (101) proposed that gut metabolites may modulate neuronal excitability and contribute to epileptogenesis, suggesting new therapeutic targets.

6. Molecular mechanisms linking the gut and brain in disease

Across neurodegenerative, neuroinflammatory, neurodevelopmental, cerebrovascular and epileptic disorders, convergent evidence implicates four mutually reinforcing gut-brain axis disturbances: i) Gut barrier failure enables microbial translocation, activating TLR4/NLRP3 inflammasomes and microglia; ii) Microbiota dysregulation disrupts neurotransmitter balance (for example, GABA and serotonin); iii) Oxidative stress amplifies neuronal damage via impaired NRF2 signaling; and iv) BBB compromise facilitates neuroimmune crosstalk (Fig. 2). Subsequent disease-specific subsections highlight only the unique nuances of these pathways (for example, α -synuclein aggregation in PD, amyloid- β seeding in AD, Th17 polarization in MS, seizure-associated neuronal hyperexcitability in epilepsy) (Table III).

Table III. Strength of mechanistic evidence linking gut-brain axis pathways to neurological diseases.

Authors, year	Pathway	Disease category	Evidence strength	Key unresolved questions	(Refs.)
Perez-Pardo <i>et al</i> , 2019; Emery <i>et al</i> , 2022; Boles <i>et al</i> , 2024	Neuroinflammation (TLR4/NLRP3)	AD, PD, MS	Moderate-Strong (supported by human tissue and GF-to-conventional transfer studies)	Does dysbiosis precede or follow disease onset?	(51,111,112)
Hoyles <i>et al</i> , 2018; Chenghan <i>et al</i> , 2025; Stachulski <i>et al</i> , 2023; Connell <i>et al</i> , 2024	SCFA-mediated BBB integrity	Stroke, ASD, AD	Moderate (consistent in animal models; limited RCTs)	Inter-individual variability in SCFAs response; dose thresholds unclear	(103,135-137)
Chauhan <i>et al</i> , 2023; Zancan <i>et al</i> , 2024	Microbial amyloid as PD, AD autoantigen		Weak-moderate (correlative human data; GF mice show phenotype reversal)	Lack of longitudinal human cohorts; need for germ-free primate models	(109,110)
Li <i>et al</i> , 2025; Guo <i>et al</i> , 2021; Zhang <i>et al</i> , 2021	Serotonin depletion via gut microbiota	Depression, ASD	Moderate (GF mouse and probiotic RCTs)	Heterogeneity of 5-HT-producing taxa across populations	(116-118)

Evidence strength graded as Strong (meta-analysis or replicated RCT), Moderate (animal-to-human translational data), Weak (single-study or associative only). AD, Alzheimer's disease; ASD, autism spectrum disorder; BBB, blood-brain barrier; GF, germ-free; MS, multiple sclerosis; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; PD, Parkinson's disease; RCTs, randomized controlled trials; SCFAs, short-chain fatty acids; TLR4, Toll-like receptor 4; 5-HT, 5-hydroxytryptamine (serotonin).

Neuroinflammation and immune activation. Emerging evidence highlights that dysregulation of the gut-brain axis contributes to neuroinflammation and systemic immune activation in neurological diseases. For instance, alcohol-induced intestinal hyperpermeability in rats promotes systemic endotoxemia, characterized by elevated LPS levels. This activates TLR4 signaling in peripheral immune cells and the brain, exacerbating neuroinflammatory cascades (102). TLR4 activation has been directly implicated in PD pathogenesis, as demonstrated by elevated TLR4 expression in both human patients and murine models with PD, driving microglial activation and dopaminergic neuron loss (51).

Gut microbiota-derived metabolites play dual roles in modulating neuroimmune responses. SCFAs, such as propionate, exhibit protective effects by reinforcing the BBB and suppressing pro-inflammatory cytokine production (for example, IL-6 and TNF- α) through histone deacetylase inhibition (103). Conversely, dysbiosis-associated reductions in SCFA-producing bacteria (for example, *Faecalibacterium*) correlate with increased CNS immune activation, as observed in HIV-associated neurocognitive disorders (104). Notably, sex-specific differences in gut-immune interactions have been reported; early-life adversity in mice induces persistent gut dysbiosis and neuroinflammation in males but not females, linked to altered IL-10/IL-17A balance and microglial priming (105,106).

The gut microbiome also influences peripheral immune cell trafficking to the brain. In a mouse model of ASD, prepubertal microbiota depletion alters T helper cell polarization, leading to aberrant IFN- γ and IL-17A levels in the prefrontal cortex, which disrupts synaptic plasticity and exacerbates behavioral deficits (107). Similarly, neonatal immune challenges in rodents induce gut-mediated Th1/Th2 imbalances, promoting hippocampal microglial activation and anxiety-like behaviors in adulthood (106). Therapeutic interventions targeting gut-immune crosstalk, such as high-dose probiotics, have shown efficacy in attenuating CNS inflammation by

restoring regulatory T cell (Treg) function and reducing monocyte activation (104,108).

Recent studies further implicate gut-derived extracellular vesicles and bacterial amyloid proteins in priming peripheral immune cells to cross-react with CNS antigens, potentially initiating autoimmune-driven neuroinflammation (109,110). For example, microbiome-induced molecular mimicry between microbial peptides and α -synuclein may contribute to PD pathogenesis by eliciting cross-reactive T cell responses (51,111). Additionally, gut dysbiosis in AD correlates with increased cerebral LPS levels and NLRP3 inflammasome activation, suggesting a feedforward loop between peripheral inflammation and neurodegenerative processes (111,112).

Neurotransmitter regulation. The gut microbiota exerts profound influence over central and peripheral neurotransmitter systems, modulating behaviors and disease progression through bidirectional gut-brain communication. For example, *Bifidobacterium dentium* colonization in mice elevates GABA levels by upregulating glutamate decarboxylase activity, correlating with reduced anxiety-like behaviors and altered hippocampal GABA receptor expression (113). Similarly, gut-resident *Escherichia coli* strains producing pyrroloquinoline quinone mitigate oxidative stress-induced dopamine depletion in rodent models of neurotoxicity, preserving striatal dopaminergic function (114).

Dysbiosis-driven neurotransmitter imbalances are increasingly implicated in neurological disorders. In a MPTP-induced PD mouse model, gut microbiota disruption precedes dopaminergic neuron degeneration, accompanied by diminished colonic serotonin (5-HT) and elevated cerebral norepinephrine, suggesting microbiota-dependent regulation of monoamine metabolism (115). Notably, *Lactiplantibacillus plantarum* supplementation restores CUMS-induced depressive behaviors in mice by normalizing gut microbial diversity and increasing prefrontal cortical 5-HT and brain-derived neurotrophic factor (BDNF) levels, highlighting therapeutic potential (116).

Dietary factors further shape neurotransmitter dynamics via microbiota-mediated pathways. High-sugar/high-fat diets reduce fecal *Lactobacillus* abundance, impairing tryptophan metabolism and lowering hippocampal 5-HT synthesis, which disrupts synaptic plasticity and memory consolidation (117). Conversely, melatonin attenuates caffeine-induced zebrafish hyperactivity by rescuing gut microbial diversity and rebalancing dopamine/GABA ratios in the brain, underscoring diet-microbiota-neurotransmitter interplay (118).

Emerging evidence links environmental toxins to gut-mediated neurotransmitter dysregulation. Methylmercury exposure alters *Bacteroidetes*-to-*Firmicutes* ratios, suppressing colonic dopamine and 5-HT synthesis while elevating glutamate in the hippocampus, a phenotype reversible by *Akkermansia*-enriched probiotics (119). Aluminum oxide nanoparticles, commonly used in food additives, accumulate in juvenile rat brains, reducing striatal dopamine and serotonin while increasing pro-inflammatory cytokines, effects exacerbated by gut barrier leakage (120).

Advanced multi-omics approaches reveal novel microbiota-neurotransmitter networks in disease. In arteriosclerotic cerebral small vessel disease, decreased gut *Roseburia* and *Faecalibacterium* correlate with disrupted tryptophan-kynurenine pathways and reduced cortical GABA, implicating microbial regulation of neurovascular coupling (121). Similarly, *Salvia officinalis* extracts ameliorate neuroinflammation by modulating gut microbial bile acid metabolism, which enhances hypothalamic dopamine signaling and suppresses TNF- α -driven neuronal apoptosis (122).

Indole-3-lactic acid, a tryptophan metabolite produced by *Lactobacillus* spp., protects against neuroinflammation by activating aryl hydrocarbon receptor signaling in microglia (34). Conversely, dysbiotic expansion of *Eggerthella lenta* increases kynurenine/tryptophan ratios, exacerbating neurotoxicity via quinolinic acid production in MS models (35). These findings underscore microbial tryptophan catabolism as a key regulator of neurotransmitter balance (serotonin depletion) and neurodegeneration in neurological disorders (34).

Oxidative stress and antioxidant mechanisms. The gut microbiota plays a critical role in modulating oxidative stress within the gut-brain axis, with dysbiosis exacerbating reactive oxygen species (ROS) accumulation and impairing antioxidant defenses in neurological diseases. For instance, *Lactobacillus rhamnosus*-derived exopolysaccharides mitigate D-galactose-induced brain aging in mice by activating nuclear factor erythroid 2-related factor 2 (NRF2), thereby upregulating superoxide dismutase (SOD) and glutathione peroxidase activity while reducing hippocampal lipid peroxidation (123). Similarly, heat-eliminated *Levilactobacillus brevis* KU15152 attenuates H₂O₂-induced oxidative damage in neuronal cells by enhancing SOD1 expression, highlighting strain-specific antioxidant properties (124).

Gut barrier dysfunction amplifies systemic oxidative stress via microbial translocation. In a rotenone-induced zebrafish model of PD, intestinal hyperpermeability promotes ROS overproduction in the brain, which is reversed by caprylic acid through restoration of tight junction proteins and suppression of NADPH oxidase 2 activity (125). Notably, *Lactiplantibacillus plantarum* GOLDGUT-HNU082 alleviates

MPTP-induced dopaminergic neuron loss by reducing colonic LPS leakage and inhibiting NLRP3 inflammasome-driven oxidative stress in the substantia nigra (126).

Dietary interventions targeting the microbiota-gut-brain axis demonstrate therapeutic potential. Soy protein supplementation enhances cognitive function in mice by increasing hippocampal nerve growth factor levels and reducing ROS, effects mediated by *Lactobacillus*-enriched gut microbiota and upregulated fecal butyrate production (127). Conversely, high-dose amoxicillin exposure in zebrafish depletes *Bifidobacterium*, disrupts glutathione metabolism, and induces behavioral deficits linked to cerebral oxidative damage. Intriguingly, calorie restriction combined with spinach thylakoids in obese women with polycystic ovary syndrome lowers serum 8-OHdG (a DNA oxidative marker) and rescues gut *Akkermansia* abundance, suggesting microbiota-dependent redox balance (128). Emerging evidence implicates microbial metabolites in redox signaling. Butyrate rescues oxidative stress-induced tryptophan transport deficits in intestinal epithelial cells, preserving serotonin synthesis and mitigating depressive-like behaviors in mice (129). In AD models, hydrogen-rich water restores gut *Roseburia* levels, which correlates with reduced hippocampal malondialdehyde and enhanced SOD2 activity via the BDNF/TrkB pathway (130). Furthermore, *Lactobacillus* supernatants suppress microglial ROS production by modulating NRF2-SOD1 crosstalk, offering a novel anti-inflammatory strategy for neuroprotection (131).

Clinical studies underscore translational relevance. Probiotic supplementation in patients with AD reduces plasma 8-isoprostane (a lipid peroxidation marker) and elevates BDNF, correlating with improved cognitive scores (132,133). Similarly, *Agaricus* mushroom-enriched diets in mice lower cortical ROS and normalize gut *Bacteroides* populations, highlighting diet-microbiota interactions in antioxidant defense (134).

BBB integrity and permeability. Gut microbiota-derived metabolites regulate BBB permeability through structural and functional adaptations. For instance, microbial SCFAs, such as propionate, enhance BBB integrity by upregulating tight junction proteins (for example, occludin and claudin-5) and reducing systemic inflammation (103,135). Similarly, the microbial co-metabolite p-cresol glucuronide strengthens BBB function *in vivo* by suppressing pro-inflammatory cytokines and preserving endothelial cell junctions (136). Conversely, dysbiosis-induced uremic toxins, such as indoxyl sulfate, compromise BBB tightness by activating oxidative stress pathways, a mechanism attenuated by polyphenol-rich dietary interventions that restore microbial balance (137,138).

BBB disruption is increasingly recognized in neurodevelopmental and neurodegenerative disorders. In ASD, dual impairment of the BBB and intestinal epithelial barrier correlates with elevated circulating neuroinflammatory markers, suggesting a 'leaky gut-leaky brain' axis (139). Furthermore, gut microbiome depletion via antibiotics exacerbates BBB permeability, facilitating monocyte infiltration into the brain—a process linked to post-infection cognitive deficits (140). In hypertension-related stroke models, gut dysbiosis promotes BBB breakdown through systemic endotoxemia

and endothelial activation, underscoring microbiota-driven vascular pathology (141).

Therapeutic modulation of the gut-BBB axis shows promise. Microbial-derived metabolites, such as butyrate, induce actin cytoskeletal rearrangements in brain endothelial cells, enhancing barrier resilience against inflammatory insults (142). Non-invasive vagus nerve stimulation mitigates ischemia-induced BBB damage by regulating mast cell degranulation via the microbiota-gut-brain axis, highlighting neuro-modulatory approaches (143). Additionally, precocious gut maturation through dietary interventions stabilizes BBB development in early life by shaping microbiota-host metabolic crosstalk (144).

However, not all gut signals permeate the BBB. Phoenixin-14, a neuropeptide implicated in stress responses, fails to cross *in vitro* BBB models, emphasizing selective transport mechanisms (145). This selectivity underscores the need for targeted delivery strategies when leveraging gut-derived molecules for neurological therapies. In summary, the BBB serves as both a gatekeeper and a sensor of gut-derived mediators, with its permeability dynamically shaped by microbial metabolites, systemic inflammation and host-microbe interactions. Restoring BBB integrity via microbiota-centric interventions represents a novel avenue for treating neurological diseases characterized by barrier dysfunction.

Despite converging evidence that gut-brain axis disruption participates in neurological disease, several mechanistic questions remain contentious. First, the temporal and causal relationship between dysbiosis and disease phenotype is unresolved: Mendelian randomization studies yield conflicting signals—some supporting a causal role of reduced SCFA-producers in MS, others finding no causal link in AD—highlighting the need for longitudinal, diet-controlled human cohorts and gnotobiotic humanized-mouse validation. Second, the therapeutic window and inter-individual heterogeneity of SCFA supplementation are unclear; butyrate attenuates neuro-inflammation in AD models yet exacerbates inflammatory markers in a subset of post-stroke patients with high baseline LPS, underscoring the necessity for baseline microbiome/metabolome stratification in future RCTs. Third, extrapolation from germ-free rodent data is limited by the absence of human-equivalent mucosal immunity and dietary complexity; therefore, human intestinal organoid-microbiota co-cultures and phase-0 micro-dosing trials are required. Finally, the ‘microbial amyloid’ hypothesis—where bacterial curli fibers seed α -synuclein aggregation—remains correlative; targeted metagenomic surveys and CRISPR knock-out of curli operons in gnotobiotic mice are proposed as definitive tests. These challenges emphasize the need for standardized multi-omics protocols and precision-medicine frameworks to reconcile associative evidence with causality.

7. Therapeutic strategies targeting the gut-brain axis and related clinical studies

Current therapeutic approaches leverage gut-brain axis modulation through dietary interventions, microbial restoration and pharmacological targeting. Clinical trials demonstrate probiotic efficacy in stress reduction, FMT-mediated motor improvement in PD, and SCFA-mediated neuroprotection,

though challenges persist in strain selection, treatment durability and patient stratification (Table IV).

Dietary interventions. Dietary interventions have emerged as a promising approach to modulate the gut-brain axis and improve neurological health. The Mediterranean diet, rich in vegetables, fruits, whole grains, legumes and olive oil, has been associated with beneficial effects on cognitive function and a reduced risk of neurodegenerative diseases. This diet promotes a healthy gut microbiota composition, increasing the abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, which produce SCFAs that exert anti-inflammatory effects and enhance gut barrier function. For example, Solch *et al* (146) found that adherence to the Mediterranean diet was associated with a lower risk of AD. The mechanisms underlying this effect may involve the production of SCFAs, which can modulate neuroinflammation, reinforce the BBB, and regulate neurotransmitter synthesis.

The ketogenic diet, high in fats and low in carbohydrates, has also gained attention for its neuroprotective effects, particularly in epilepsy and neurodegenerative disorders. By inducing ketosis, this diet alters the metabolic landscape of the brain, providing alternative energy substrates and reducing oxidative stress. Lussier *et al* (147) demonstrated that the ketogenic diet could inhibit tumor growth in a mouse model of glioblastoma multiforme. In addition to its direct metabolic effects, the ketogenic diet can also influence gut microbiota composition, increase the relative abundance of beneficial bacteria and reduce pathogenic species. This modulation of the gut microbiota may contribute to the diet's therapeutic effects on neurological diseases.

Fiber supplementation and prebiotics represent another avenue for targeting the gut-brain axis. Berding *et al* (148) demonstrated that supplementing with microbiota-accessible carbohydrates can prevent neuroinflammation and cognitive decline by improving the gut microbiota-brain axis in diet-induced obese mice. This evidence underscores the potential of fiber supplementation and prebiotics in modulating the gut-brain axis for neurological health. Alcohol addiction exacerbates gut dysbiosis in patients with minimal hepatic encephalopathy, further impairing cognitive function through increased gut-derived ammonia and systemic inflammation (149).

Probiotics and microbial therapies. Specific probiotic strains have been investigated for their effects on neurodegenerative and neuroinflammatory diseases. For instance, *Lactobacillus* and *Bifidobacterium* strains have demonstrated the ability to produce neurotransmitters such as GABA, serotonin and dopamine, which can influence brain function and behavior. Bravo *et al* (150) found that administration of *Lactobacillus rhamnosus* to mice reduced anxiety-like behavior and altered GABA receptor expression in the brain. In animal models of AD, probiotic supplementation with strains such as *Lactobacillus plantarum* and *Bifidobacterium longum* has been shown to reduce amyloid-beta pathology and improve cognitive performance. Srivastav *et al* (52) demonstrated that a probiotics mixture increased butyrate levels, which rescued nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity.

Table IV. Clinical studies on gut-brain axis.

Authors, year	Intervention	Population	Duration	Outcome measures	Results	(Refs.)
Chong <i>et al</i> , 2019	<i>Lactobacillus plantarum</i> DR7	Adults with stress and anxiety	12 weeks	Stress (DASS-21), anxiety (STAI), plasma cortisol, inflammatory cytokines	Reduced stress, anxiety, and cortisol levels; improved gut barrier function	(151)
Lew <i>et al</i> , 2019	<i>Lactobacillus plantarum</i> P8	Stressed adults	12 weeks	Cognitive function (CANTAB), stress (PSS), anxiety (STAI), gut microbiota analysis	Enhanced memory, reduced stress and anxiety; increased <i>Bifidobacterium</i> and <i>Lactobacillus</i> abundance	(152)
Karakula-Juchnowicz <i>et al</i> , 2019	Probiotic supplementation	Patients with MDD (gluten-free/gluten-containing diet)	12 weeks	Mental status (HAMD, MADRS), intestinal permeability (zonulin), inflammatory markers	Improved mental status, reduced inflammation; no significant difference between dietary groups	(153)
Cheng <i>et al</i> , 2023	FMT	PD patients	12 weeks	Motor symptoms (UPDRS), gut microbiota composition, quality of life (PDQ-39)	Improved motor symptoms and quality of life; restored microbial diversity and SCFA production	(154)
Dalile <i>et al</i> , 2020	Colon-delivered SCFAs	Healthy men under psychosocial stress	4 weeks	Cortisol response, psychological stress (VAS), gut microbiota	Attenuated cortisol response to stress; modulated gut microbial composition	(155)
Lei <i>et al</i> , 2022	Disulfiram (bile acid modulation)	Nonalcoholic steatohepatitis patients	24 weeks	Liver function, gut microbiota, bile acid profiles	Improved liver function; restored gut microbiota and bile acid homeostasis	(156)
Fleck <i>et al</i> , 2021	Dietary conjugated linoleic acid	Patients with multiple sclerosis	12 weeks	CNS autoimmunity markers, intestinal inflammation, gut barrier integrity	Reduced CNS inflammation; improved gut barrier function and microbiota diversity	(157)
Martin <i>et al</i> , 2024	Probiotic (<i>Lactobacillus</i> strain)	Irritable bowel syndrome patients	8 weeks	Metabolomic, profiling psychological symptoms (HADS)	Improved psychological comorbidities; altered gut metabolome linked to serotonin pathways	(158)
Mysonhimer <i>et al</i> , 2023	Prebiotic supplementation	Healthy adults	6 weeks	Microbiota biomarkers (cortisol), mental health questionnaires	Modulated microbiota composition; no significant changes in stress/inflammation biomarkers or mental health	(159)
Li <i>et al</i> , 2024	<i>Bifidobacterium breve</i> 207-1	Healthy adults	8 weeks	Lifestyle behaviors, mental wellness (DASS-21), gut microbiota	Improved mental wellness; increased <i>Bifidobacterium</i> abundance and SCFA levels	(160)
Casertano <i>et al</i> 2024	γ -aminobutyric acid-producing <i>Lactobacillus</i>	Healthy adults	4 weeks	Cognitive reactivity (LEIDS-R), mood (POMS), gut-brain metabolites	Reduced cognitive reactivity to negative mood; no improvement in cognitive performance	(161)

DASS-21, depression anxiety stress scales; STAI, state-trait anxiety inventory; CANTAB, Cambridge neuropsychological test automated battery; PSS, perceived stress scale; HAMD, Hamilton depression rating scale; MADRS: Montgomery-Åsberg depression rating scale; UPDRS, unified Parkinson's disease rating scale; PDQ-39, Parkinson's disease questionnaire; VAS, visual analog scale; HADS, hospital anxiety and depression scale; LEIDS-R, Leiden index of depression sensitivity-revised; POMS, profile of mood states.

Clinical trials in humans have also provided encouraging results. An RCT by Chong *et al* (151) found that *Lactobacillus plantarum* DR7 alleviated stress and anxiety in adults. Lew *et al* (152) showed that *Lactobacillus plantarum* P8 alleviated stress and anxiety while enhancing memory and cognition in stressed adults. In patients with major depressive disorder, probiotic supplementation has been associated with improvements in mental status, inflammation and intestinal barrier function. Karakula-Juchnowicz *et al* (153) evaluated the effect of probiotic supplementation on the mental status, inflammation and intestinal barrier in patients with major depressive disorder using a gluten-free or gluten-containing diet. The results showed that probiotic supplementation improved mental status and reduced inflammation in both groups.

FMT, the transfer of microbiota from a healthy donor to a recipient, has gained interest as a therapeutic approach for neurological diseases. FMT aims to restore a healthy gut microbiota composition and function, potentially reversing dysbiosis-associated neurological pathology. Preclinical studies have shown promising results in various neurological disease models. Cheng *et al* (154) investigated the efficacy of FMT in patients with PD. The results showed that FMT improved motor symptoms and quality of life in patients with PD. These preliminary data (n=47) lack blinding and showed transient engraftment (<8 weeks) in 30% of recipients. Adverse events including bloating (23%) and transient delirium (4%) further caution against uncritical adoption outside controlled trials.

However, translating these findings to clinical practice presents several challenges. The mechanisms underlying FMT's therapeutic effects remain incompletely understood, and there is a need for standardized protocols regarding donor selection, preparation of fecal microbiota, and administration routes. Additionally, safety concerns related to the transmission of pathogens or harmful metabolites necessitate rigorous screening of donors and donor materials. Despite these challenges, ongoing clinical trials are exploring the efficacy and safety of FMT in neurological conditions such as MS, AD and PD, which may provide valuable insights into its therapeutic potential in the near future.

Pharmacological approaches. Pharmacological strategies targeting microbiota-derived metabolites offer another avenue for modulating the gut-brain axis. SCFAs analogs and bile acid sequestrants represent two classes of agents with potential therapeutic applications in neurological diseases. Dalile *et al* (155) demonstrated that colon-delivered SCFAs attenuated the cortisol response to psychosocial stress in healthy men.

Bile acid sequestrants, such as cholestyramine, bind to bile acids in the gut, altering their enterohepatic circulation and potentially modulating bile acid signaling pathways. Recent research has shown that bile acids can influence gut microbiota composition and immune responses, suggesting that sequestrants may indirectly affect the gut-brain axis. In animal models of PD, cholestyramine treatment reduced alpha-synuclein pathology and improved motor function, highlighting the potential of this approach in neurodegenerative diseases. Lei *et al* (156) demonstrated that disulfiram ameliorated non-alcoholic steatohepatitis by modulating the gut microbiota and bile acid metabolism.

Immune modulators and anti-inflammatory agents represent a broad category of pharmacological interventions with potential applications in targeting the gut-brain axis. For instance, anti-tumor necrosis factor (TNF) agents, such as infliximab and adalimumab, have been used in the treatment of IBD and have shown promise in ameliorating neurological symptoms in patients with comorbid IBD and neurological disorders. Similarly, interleukin (IL)-17 and IL-23 inhibitors are being investigated for their potential to modulate neuroinflammation in conditions such as MS and PD. Fleck *et al* (157) found that dietary conjugated linoleic acid links reduced intestinal inflammation to amelioration of CNS autoimmunity.

Recent clinical trials have explored the use of these agents in neurological diseases. A phase II trial of the IL-17 inhibitor secukinumab in patients with relapsing-remitting MS demonstrated a reduction in disease activity and MRI lesions, suggesting a potential role for targeting IL-17 signaling in this condition. Additionally, the TNF inhibitor etanercept has shown beneficial effects in patients with PD, with improvements in motor symptoms and quality of life. These findings highlight the potential of immune modulators in targeting gut-brain pathways for neurological health.

Emerging therapies. Advances in synthetic biology and genetic engineering have paved the way for the development of engineered microbiota with tailored functions for therapeutic applications. These engineered bacteria can be designed to produce specific metabolites, enzymes, or anti-inflammatory molecules that target key pathways in neurological diseases. Martin *et al* (158) demonstrated that metabolome-associated psychological comorbidities improved in patients with irritable bowel syndrome receiving a probiotic. Moreover, synthetic biology approaches allow for the creation of bacteria with sensing and responsive capabilities, enabling them to detect specific disease biomarkers and release therapeutic agents in a targeted manner. This precision medicine approach could enhance the efficacy and safety of microbiota-based therapies for neurological disorders. Mysonhimer *et al* (159) found that prebiotic consumption alters microbiota but not biological markers of stress and inflammation or mental health symptoms in healthy adults.

Nanomedicine and advanced drug delivery systems offer innovative strategies to enhance the targeting and efficacy of therapeutics aimed at the gut-brain axis. Nanoparticles can be engineered to encapsulate drugs, probiotics, or bioactive compounds, protecting them from degradation and enabling controlled release at specific sites along the gastrointestinal tract. For instance, chitosan nanoparticles loaded with curcumin, a polyphenol with anti-inflammatory and antioxidant properties, have shown enhanced bioavailability and therapeutic efficacy in animal models of AD and PD. These nanoparticles can traverse the BBB and deliver curcumin to the brain, where it exerts neuroprotective effects. Similarly, lipid-based nanoparticles have been used to deliver probiotics to the gut, improving their survival and colonization efficiency. Li *et al* (160) investigated the effects of *Bifidobacterium breve* 207-1 on regulating lifestyle behaviors and mental wellness in healthy adults based on the microbiome-gut-brain axis. The results showed that *Bifidobacterium breve* 207-1 improved mental wellness and regulated lifestyle behaviors in healthy adults.

Additionally, targeted drug delivery systems can be designed to specifically interact with gut microbiota or immune cells, modulating their function in a precise manner. For example, antibody-conjugated nanoparticles can target specific bacterial strains or immune cells, delivering therapeutic agents directly to the site of action. These approaches hold promise for improving the therapeutic index of existing drugs and developing novel interventions for neurological diseases by leveraging the gut-brain axis. Casertano *et al* (161) demonstrated that GABA-producing lactobacilli boost cognitive reactivity to negative mood without improving cognitive performance.

8. Future directions and challenges

The gut-brain axis serves as a promising source of biomarkers for neurological diseases. Recent studies have identified specific gut microbiota signatures associated with conditions such as AD, PD and MS (162-164). These signatures can potentially be used for early diagnosis, disease progression monitoring and treatment response prediction. For example, certain bacterial taxa such as *Bifidobacterium* and *Lactobacillus* have been found to be decreased in patients with AD, whereas an increase in pathogenic bacteria such as *Escherichia coli* has been observed (165). Similarly, in PD, specific microbial metabolites such as SCFAs and secondary bile acids have shown potential as biomarkers because of their altered levels in patient sera (166). The development of these biomarkers is crucial for improving diagnostic accuracy and personalizing treatment approaches.

Personalized medicine holds considerable promise for treating neurological disorders by tailoring treatments to individual patients on the basis of their unique gut microbiota profiles. This approach involves a comprehensive analysis of a patient's gut microbiota composition, genetic makeup and metabolic status to design targeted therapeutic interventions (14). For example, patients with specific microbial imbalances could be prescribed customized probiotic formulations or dietary plans to restore microbial balance and improve neurological outcomes (45). Additionally, integrating gut microbiota data with other omics data (genomic, proteomic and metabolomic data) can provide a more holistic understanding of disease mechanisms and enable the development of multitargeted therapies (14). Clinical trials are underway to validate the efficacy of such personalized approaches and establish standardized protocols for implementation in clinical practice.

Emerging comparative analyses indicate that precision-medicine paradigms outperform universal interventions across neurological disorders. Multi-strain probiotics co-administered with dietary substrates (prebiotics) currently yield the strongest clinical signal for stress-related disorders and early PD, achieving significant reductions in anxiety and Unified PD Rating Scale motor scores in randomized trials lasting ≥ 12 weeks (167). In AD, SCFA-enriched Mediterranean diets outperform single-probiotic regimens by simultaneously improving gut barrier integrity, systemic inflammation and cognitive composite scores (167,168). FMT retains promise for refractory epilepsy and pediatric ASD, yet pooled data demonstrate 30-40% responder rates only when donor selection is paired with host-microbiome matching algorithms and baseline α -diversity is low (19). In diseases, compared with non-personalized

probiotics, intervention measures integrating multi-omics stratification (baseline microbiota, metabolome, host genetics) have improved effects (167). Consequently, combination strategies that couple dietary modification with targeted microbial restoration appear most effective, whereas single-agent probiotics or unpersonalized FMT offer limited and transient benefits.

Despite promising preclinical evidence, the translation of gut-brain axis research into clinical practice faces several significant challenges (169). One major hurdle is establishing a definitive causal relationship between gut microbiota alterations and neurological diseases. Numerous studies have identified correlations, but determining whether these effects are causative, consequential, or merely bystander responses remains difficult (170). Another challenge is the complexity of the gut-brain axis itself, with its multitude of interacting components and pathways making it challenging to identify specific targets for intervention (171). Furthermore, existing animal models do not fully recapitulate human pathophysiology, thus limiting the translational value of preclinical findings (172). Additionally, there are technical limitations in accurately measuring and manipulating the gut microbiota among humans, as well as regulatory and ethical considerations regarding the use of microbiota-based therapies (173). Addressing these challenges requires multidisciplinary collaboration, rigorous clinical trials and the development of advanced technologies for microbiota analysis and manipulation.

Numerous clinical trials are currently ongoing or planned to investigate therapies targeting the gut-brain axis in neurological disorders. These trials encompass a range of approaches, including probiotics, prebiotics, FMT, dietary interventions and pharmacological agents. For example, several trials are evaluating the efficacy of specific probiotic strains in improving cognitive function in patients with AD and motor symptoms in patients with PD (174-176). Other trials are exploring the potential of FMT to modulate the gut microbiota and reduce disease activity in patients with MS and IBD with neurological complications (177,178). Additionally, research is ongoing to develop novel drugs that can specifically target gut-brain communication pathways, such as inhibitors of microbial metabolite production or modulators of immune signaling (179). These clinical trials are essential for validating the therapeutic potential of gut-brain axis-targeted strategies and establishing evidence-based treatment guidelines.

Despite emerging evidence, the gut-brain axis field faces three critical gaps: Causality vs. correlation, as most human studies remain associative, and Mendelian randomization and long-term gnotobiotic models are needed to clarify whether dysbiosis initiates or merely mirrors neurological disease; microbiome stability, as the rate of probiotic engraftment falls $<30\%$ after 4 weeks and high interindividual variability undermining reproducibility (180); and clinical heterogeneity, exemplified by recent negative RCTs in AD (NCT04168974) and early PD that reveal 'one-size-fits-all' interventions to be ineffective, thereby requiring precision-medicine frameworks integrating host genetics, metabolomics and real-time dietary data. Furthermore, there is the lack of standardized protocols for FMT-donor selection, dosing and delivery routes vary widely, leading to inconsistent engraftment and safety signals. Adopting consensus guidelines such as those proposed by the International Scientific Association for Probiotics and Prebiotics will be essential to

harmonize endpoints, biomarker panels and adverse-event reporting, ultimately determining whether microbiota-directed therapeutics can deliver reproducible neurological benefits.

9. Conclusion

In conclusion, the gut-brain axis represents a fascinating and promising frontier in neurological research with significant clinical implications. By developing biomarkers based on gut-brain axis components, adopting personalized medicine approaches, overcoming translational challenges and conducting rigorous clinical trials, the therapeutic potential of the gut-brain axis can be harnessed to improve outcomes for patients with neurological diseases. Future research should continue to explore the intricate mechanisms underlying gut-brain communication and expand our understanding of how to effectively modulate this axis for therapeutic benefit.

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Competing interests

The authors declare that they have no competing interests.

References

- Morais LH, Schreiber HL 4th and Mazmanian SK: The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol* 19: 241-255, 2021.
- Chanpong A, Borrelli O and Thapar N: Recent advances in understanding the roles of the enteric nervous system. *Fac Rev* 11: 7, 2022.
- Carabotti M, Scirocco A, Maselli MA and Severi C: The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol* 28: 203-209, 2015.
- Schluter J, Peled JU, Taylor BP, Markey KA, Smith M, Taur Y, Niehus R, Staffas A, Dai A, Fontana E, *et al*: The gut microbiota is associated with immune cell dynamics in humans. *Nature* 588: 303-307, 2020.
- Gwak MG and Chang SY: Gut-brain connection: Microbiome, gut barrier, and environmental sensors. *Immune Netw* 21: e20, 2021.
- Appleton J: The Gut-brain axis: Influence of microbiota on mood and mental health. *Integr Med (Encinitas)* 17: 28-32, 2018.
- Pucci A and Batterham RL: Endocrinology of the gut and the regulation of body weight and metabolism. In: *Endotext*. Feingold KR, Anawalt B, Blackman MR, *et al*. (eds.) MDText.com, Inc. Copyright © 2000-2025, MDText.com, Inc., South Dartmouth (MA), 2000.
- Konsman JP: Cytokines in the Brain and Neuroinflammation: We Didn't Starve the Fire! *Pharmaceuticals (Basel)* 15: 140, 2022.
- Köhler A, Delbauve S, Smout J, Torres D and Flamand V: Very early-life exposure to microbiota-induced TNF drives the maturation of neonatal pre-cDC1. *Gut* 70: 511-521, 2021.
- Hrncir T: Gut microbiota dysbiosis: Triggers, consequences, diagnostic and therapeutic options. *Microorganisms* 10: 578, 2022.
- Quansah M, David MA, Martins R, El-Omar E, Aliberti SM, Capunzo M, Jensen SO and Tayebi M: The beneficial effects of lactobacillus strains on gut microbiome in Alzheimer's disease: A systematic review. *Healthcare* 13: 74, 2025.
- Zhang X, Wang Y, Liu W, Wang T, Wang L, Hao L, Ju M and Xiao R: Diet quality, gut microbiota, and microRNAs associated with mild cognitive impairment in middle-aged and elderly Chinese population. *Am J Clin Nutr* 114: 429-440, 2021.
- Li B, He Y, Ma J, Huang P, Du J, Cao L, Wang Y, Xiao Q, Tang H and Chen S: Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimers Dement* 15: 1357-1366, 2019.
- Tan AH, Lim SY and Lang AE: The microbiome-gut-brain axis in Parkinson disease-from basic research to the clinic. *Nat Rev Neurol* 18: 476-495, 2022.
- Casella G, Tontini GE, Bassotti G, Pastorelli L, Villanacci V, Spina L, Baldini V and Vecchi M: Neurological disorders and inflammatory bowel diseases. *World J Gastroenterol* 20: 8764-8782, 2014.
- Yaqubi K, Kostev K, Klein I, Schüssler S, May P, Luedde T, Roderburg C and Loosen SH: Inflammatory bowel disease is associated with an increase in the incidence of multiple sclerosis: A retrospective cohort study of 24,934 patients. *Eur J Med Res* 29: 186, 2024.
- Hughes HK, Rose D and Ashwood P: The gut microbiota and dysbiosis in autism spectrum disorders. *Curr Neurol Neurosci Rep* 18: 81, 2018.
- Naspolini NF, Natividade AP, Asmus CIF, Moreira JC, Dominguez-Bello MG and Meyer A: Early-life gut microbiome is associated with behavioral disorders in the Rio birth cohort. *Sci Rep* 15: 8674, 2025.
- Doenya C, Clarke G and Cserjési R: Gut-brain axis and neuropsychiatric health: Recent advances. *Sci Rep* 15: 3415, 2025.
- Holmes GM and Blanke EN: Gastrointestinal dysfunction after spinal cord injury. *Exp Neurol* 320: 113009, 2019.
- Su Y, Wang D, Liu N, Yang J, Sun R and Zhang Z: *Clostridium butyricum* improves cognitive dysfunction in ICV-STZ-induced Alzheimer's disease mice via suppressing TLR4 signaling pathway through the gut-brain axis. *PLoS One* 18: e0286086, 2023.
- Fan Y and Pedersen O: Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 19: 55-71, 2021.
- Ahmed H, Leyrolle Q, Koistinen V, Kärkkäinen O, Layé S, Delzenne N and Hanhineva K: Microbiota-derived metabolites as drivers of gut-brain communication. *Gut Microbes* 14: 2102878, 2022.
- Oleskin AV and Shenderov BA: Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. *Microb Ecol Health Dis* 27: 30971, 2016.
- Ramesh G, MacLean AG and Philipp MT: Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. *Mediators Inflamm* 2013: 480739, 2013.
- Person H and Keefer L: Psychological comorbidity in gastrointestinal diseases: Update on the brain-gut-microbiome axis. *Prog Neuropsychopharmacol Biol Psychiatry* 107: 110209, 2021.

27. Mayer EA, Nance K and Chen S: The gut-brain axis. *Annu Rev Med* 73: 439-453, 2022.
28. Makris AP, Karianaki M, Tsamis KI and Paschou SA: The role of the gut-brain axis in depression: Endocrine, neural, and immune pathways. *Hormones (Athens)* 20: 1-12, 2021.
29. Ohara TE and Hsiao EY: Microbiota-neuroepithelial signalling across the gut-brain axis. *Nat Rev Microbiol* 23: 371-384, 2025.
30. Rastogi S and Singh A: Gut microbiome and human health: Exploring how the probiotic genus *Lactobacillus* modulate immune responses. *Front Pharmacol* 13: 1042189, 2022.
31. Parizadeh M and Arrieta MC: The global human gut microbiome: Genes, lifestyles, and diet. *Trends Mol Med* 29: 789-801, 2023.
32. Procházková N, Laursen MF, La Barbera G, Tsekitsidi E, Jørgensen MS, Rasmussen MA, Raes J, Licht TR, Dragsted LO and Roager HM: Gut physiology and environment explain variations in human gut microbiome composition and metabolism. *Nat Microbiol* 9: 3210-3225, 2024.
33. Gomaa EZ: Human gut microbiota/microbiome in health and diseases: A review. *Antonie Van Leeuwenhoek* 113: 2019-2040, 2020.
34. Kearns R: Gut-brain axis and neuroinflammation: The role of gut permeability and the kynurenine pathway in neurological disorders. *Cell Mol Neurobiol* 44: 64, 2024.
35. Kearns R: The kynurenine pathway in gut permeability and inflammation. *Inflammation* 48: 1063-1077, 2025.
36. Koh A, De Vadder F, Kovatcheva-Datchary P and Bäckhed F: From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell* 165: 1332-1345, 2016.
37. Fock E and Parnova R: Mechanisms of Blood-brain barrier protection by Microbiota-derived short-chain fatty acids. *Cells* 12: 657, 2023.
38. Jia M, Fan Y, Ma Q, Yang D, Wang Y, He X, Zhao B, Zhan X, Qi Z, Ren Y, *et al*: Gut microbiota dysbiosis promotes cognitive impairment via bile acid metabolism in major depressive disorder. *Transl Psychiatry* 14: 503, 2024.
39. Hou Y, Li J and Ying S: Tryptophan metabolism and gut microbiota: A novel regulatory axis integrating the microbiome, immunity, and cancer. *Metabolites* 13: 1166, 2023.
40. Luczynski P, McVey Neufeld KA, Oriach CS, Clarke G, Dinan TG and Cryan JF: Growing up in a Bubble: Using Germ-free animals to assess the influence of the gut microbiota on brain and behavior. *Int J Neuropsychopharmacol* 19: pyw020, 2016.
41. Mhanna A, Martini N, Hmaydoosh G, Hamwi G, Jarjanazi M, Zaifha G, Kazzazo R, Haji Mohamad A and Alshehbi Z: The correlation between gut microbiota and both neurotransmitters and mental disorders: A narrative review. *Medicine* 103: e37114, 2024.
42. Gu F, Wu Y, Liu Y, Dou M, Jiang Y and Liang H: *Lactobacillus casei* improves depression-like behavior in chronic unpredictable mild stress-induced rats by the BDNF-TrkB signal pathway and the intestinal microbiota. *Food Funct* 11: 6148-6157, 2020.
43. Hwang YK and Oh JS: Interaction of the vagus nerve and serotonin in the Gut-brain axis. *Int J Mol Sci* 26: 1160, 2025.
44. Sorboni SG, Moghaddam HS, Jafarzadeh-Esfehani R and Soleimanpour S: A comprehensive review on the role of the gut microbiome in human neurological disorders. *Clin Microbiol Rev* 35: e0033820, 2022.
45. Cryan JF, O'Riordan KJ, Sandhu K, Peterson V and Dinan TG: The gut microbiome in neurological disorders. *Lancet Neurol* 19: 179-194, 2020.
46. Liu C, Yang SY, Wang L and Zhou F: The gut microbiome: Implications for neurogenesis and neurological diseases. *Neural Regen Res* 17: 53-58, 2022.
47. Socała K, Doboszewska U, Szopa A, Serefko A, Włodarczyk M, Zielińska A, Poleszak E, Fichna J and Wlaziński P: The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. *Pharmacol Res* 172: 105840, 2021.
48. Hirschberg S, Gisevius B, Duscha A and Haghighi A: Implications of diet and the gut microbiome in neuroinflammatory and neurodegenerative diseases. *Int J Mol Sci* 20: 3109, 2019.
49. Ivan IF, Irincu VL, Diaconu Ș, Falup-Pecurariu O, Ciopleiaș B and Falup-Pecurariu C: Gastro-intestinal dysfunctions in Parkinson's disease (review). *Exp Ther Med* 22: 1083, 2021.
50. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, *et al*: Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167: 1469-1480.e12, 2016.
51. Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Hushens AM, Shaikh M, Voigt RM, Naqib A, Green SJ, Kordower JH, *et al*: Role of TLR4 in the gut-brain axis in Parkinson's disease: A translational study from men to mice. *Gut* 68: 829-843, 2019.
52. Srivastav S, Neupane S, Bhurtel S, Katila N, Maharjan S, Choi H, Hong JT and Choi DY: Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity. *J Nutr Biochem* 69: 73-86, 2019.
53. Lei Q, Wu T, Wu J, Hu X, Guan Y, Wang Y, Yan J and Shi G: Roles of α -synuclein in gastrointestinal microbiome dysbiosis-related Parkinson's disease progression (review). *Mol Med Rep* 24: 734, 2021.
54. Honarpisheh P, Reynolds CR, Blasco Conesa MP, Moruno Manchon JF, Putluri N, Bhattacharjee MB, Urayama A, McCullough LD and Ganesh BP: Dysregulated gut homeostasis observed prior to the accumulation of the brain amyloid- β in Tg2576 mice. *Int J Mol Sci* 21: 1711, 2020.
55. Kim N, Jeon SH, Ju IG, Gee MS, Do J, Oh MS and Lee JK: Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice. *Brain Behav Immun* 98: 357-365, 2021.
56. Shi H, Ge X, Ma X, Zheng M, Cui X, Pan W, Zheng P, Yang X, Zhang P, Hu M, *et al*: A fiber-deprived diet causes cognitive impairment and hippocampal microglia-mediated synaptic loss through the gut microbiota and metabolites. *Microbiome* 9: 223, 2021.
57. Zhang T, Wang T, Chen X, Zhao Z and Chen Z: Gut microbiota relieves inflammation in the substantia nigra of chronic Parkinson's disease by protecting the function of dopamine neurons. *Exp Ther Med* 23: 52, 2022.
58. Castelli V, d'Angelo M, Quintiliani M, Benedetti E, Cifone MG and Cimini A: The emerging role of probiotics in neurodegenerative diseases: New hope for Parkinson's disease? *Neural Regen Res* 16: 628-634, 2021.
59. Yuan T, Chu C, Shi R, Cui T, Zhang X, Zhao Y, Shi X, Hui Y, Pan J, Qian R, *et al*: ApoE-dependent protective effects of sesamol on High-Fat Diet-induced behavioral disorders: Regulation of the microbiome-Gut-brain axis. *J Agric Food Chem* 67: 6190-6201, 2019.
60. Shi H, Wang Q, Zheng M, Hao S, Lum JS, Chen X, Huang XF, Yu Y and Zheng K: Supplement of microbiota-accessible carbohydrates prevents neuroinflammation and cognitive decline by improving the gut microbiota-brain axis in diet-induced obese mice. *J Neuroinflammation* 17: 77, 2020.
61. Bianchimano P, Britton GJ, Wallach DS, Smith EM, Cox LM, Liu S, Iwanowski K, Weiner HL, Faith JJ, Clemente JC and Tankou SK: Mining the microbiota to identify gut commensals modulating neuroinflammation in a mouse model of multiple sclerosis. *Microbiome* 10: 174, 2022.
62. Celorrio M and Friess SH: Gut-brain axis in traumatic brain injury: Impact on neuroinflammation. *Neural Regen Res* 17: 1007-1008, 2022.
63. Theleritis C, Stefanou MI, Demetriou M, Alevyzakis E, Triantafyllou K, Smyrnis N, Spandidos DA and Rizos E: Association of gut dysbiosis with first-episode psychosis (review). *Mol Med Rep* 30: 130, 2024.
64. Torres-Chávez ME, Torres-Carrillo NM, Monreal-Lugo AV, Garnés-Rancurello S, Murugesan S, Gutiérrez-Hurtado IA, Beltrán-Ramírez JR, Sandoval-Pinto E and Torres-Carrillo N: Association of intestinal dysbiosis with susceptibility to multiple sclerosis: Evidence from different population studies (review). *Biomed Rep* 19: 93, 2023.
65. Lee CW, Hsu LF, Wu IL, Wang YL, Chen WC, Liu YJ, Yang LT, Tan CL, Luo YH, Wang CC, *et al*: Exposure to polystyrene microplastics impairs hippocampus-dependent learning and memory in mice. *J Hazard Mater* 430: 128431, 2022.
66. Yuan S, Yang J, Jian Y, Lei Y, Yao S, Hu Z, Liu X, Tang C and Liu W: Treadmill exercise modulates intestinal microbes and suppresses LPS displacement to alleviate neuroinflammation in the brains of APP/PS1 Mice. *Nutrients* 14: 4134, 2022.
67. Hu X, Jin H, Yuan S, Ye T, Chen Z, Kong Y, Liu J, Xu K and Sun J: Fecal microbiota transplantation inhibited neuroinflammation of traumatic brain injury in mice via regulating the gut-brain axis. *Front Cell Infect Microbiol* 13: 1254610, 2023.
68. Li X, Zheng P, Cao W, Cao Y, She X, Yang H, Ma K, Wu F, Gao X, Fu Y, *et al*: *Lactobacillus rhamnosus* GG ameliorates noise-induced cognitive deficits and systemic inflammation in rats by modulating the gut-brain axis. *Front Cell Infect Microbiol* 13: 1067367, 2023.
69. Wei H, Yu C, Zhang C, Ren Y, Guo L, Wang T, Chen F, Li Y, Zhang X, Wang H and Liu J: Butyrate ameliorates chronic alcoholic central nervous damage by suppressing microglia-mediated neuroinflammation and modulating the microbiome-gut-brain axis. *Biomed Pharmacother* 160: 114308, 2023.

70. Zhu G, Zhao J, Wang G and Chen W: *Bifidobacterium breve* HNX26M4 attenuates cognitive deficits and neuroinflammation by regulating the Gut-brain axis in APP/PS1 mice. *J Agric Food Chem* 71: 4646-4655, 2023.
71. de Theije CG, Koelink PJ, Korte-Bouws GA, Lopes da Silva S, Korte SM, Olivier B, Garssen J and Kraneveld AD: Intestinal inflammation in a murine model of autism spectrum disorders. *Brain Behav Immun* 37: 240-247, 2014.
72. Stilling RM, Ryan FJ, Hoban AE, Shanahan F, Clarke G, Claesson MJ, Dinan TG and Cryan JF: Microbes & neurodevelopment-Absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala. *Brain Behav Immun* 50: 209-220, 2015.
73. Kantarcioglu AS, Kiraz N and Aydin A: Microbiota-gut-brain axis: Yeast species isolated from stool samples of children with suspected or diagnosed autism spectrum disorders and in vitro susceptibility against nystatin and fluconazole. *Mycopathologia* 181: 1-7, 2016.
74. Abuljadayel D, Alotibi A, Algothmi K, Basingab F, Alhazmi S, Almuhammadi A, Alharthi A, Alyoubi R and Bahieldin A: Gut microbiota of children with autism spectrum disorder and healthy siblings: A comparative study. *Exp Ther Med* 28: 430, 2024.
75. Dai W, Liu J, Qiu Y, Teng Z, Li S, Yuan H, Huang J, Xiang H, Tang H, Wang B, *et al*: Gut microbial dysbiosis and cognitive impairment in bipolar disorder: Current evidence. *Front Pharmacol* 13: 893567, 2022.
76. Bioque M, González-Rodríguez A, Garcia-Rizo C, Cobo J, Monreal JA, Usall J, Soria V, PNECAT Group and Labad J: Targeting the microbiome-gut-brain axis for improving cognition in schizophrenia and major mood disorders: A narrative review. *Prog Neuropsychopharmacol Biol Psychiatry* 105: 110130, 2021.
77. Reddy-Thootkur M, Kraguljac NV and Lahti AC: The role of glutamate and GABA in cognitive dysfunction in schizophrenia and mood disorders-A systematic review of magnetic resonance spectroscopy studies. *Schizophr Res* 249: 74-84, 2022.
78. Reininghaus EZ, Wetzlmair LC, Fellendorf FT, Platzer M, Queissner R, Birner A, Pilz R, Hamm C, Maget A, Koidl C, *et al*: The impact of probiotic supplements on cognitive parameters in euthymic individuals with bipolar disorder: A pilot study. *Neuropsychobiology*: 1-8, 2018 doi: 10.1159/000492537 (Epub ahead of print).
79. Pulikkan J, Maji A, Dhakan DB, Saxena R, Mohan B, Anto MM, Agarwal N, Grace T and Sharma VK: Gut microbial dysbiosis in indian children with autism spectrum disorders. *Microb Ecol* 76: 1102-1114, 2018.
80. Bojović K, Ignjatović ĐI, Soković Bajić S, Vojnović Milutinović D, Tomić M, Golić N and Tolinački M: Gut microbiota dysbiosis associated with altered production of short chain fatty acids in children with neurodevelopmental disorders. *Front Cell Infect Microbiol* 10: 223, 2020.
81. Slob EMA, Brew BK, Vijverberg SJH, Dijs T, van Beijsterveldt CEM, Koppelman GH, Bartels M, Dolan CV, Larsson H, Lundström S, *et al*: Early-life antibiotic use and risk of attention-deficit hyperactivity disorder and autism spectrum disorder: Results of a discordant twin study. *Int J Epidemiol* 50: 475-484, 2021.
82. Bundgaard-Nielsen C, Lauritsen MB, Knudsen JK, Rold LS, Larsen MH, Hindersson P, Villadsen AB, Leutscher PDC, Hagstrøm S, Nyegaard M and Sørensen S: Children and adolescents with attention deficit hyperactivity disorder and autism spectrum disorder share distinct microbiota compositions. *Gut Microbes* 15: 2211923, 2023.
83. Liu S, Gao J, Zhu M, Liu K and Zhang HL: Gut microbiota and dysbiosis in Alzheimer's disease: Implications for pathogenesis and treatment. *Mol Neurobiol* 57: 5026-5043, 2020.
84. Gonçalves CL, Vasconcelos FFP, Wessler LB, Lemos IS, Candiotto G, Lin J, Matias MBD, Rico EP and Streck EL: Exposure to a high dose of amoxicillin causes behavioral changes and oxidative stress in young zebrafish. *Metab Brain Dis* 35: 1407-1416, 2020.
85. Volkova A, Ruggles K, Schuler A, Gao Z, Ginsberg SD and Blaser MJ: Effects of early-life penicillin exposure on the gut microbiome and frontal cortex and amygdala gene expression. *iScience* 24: 102797, 2021.
86. Benakis C, Brea D, Caballero S, Faraco G, Moore J, Murphy M, Sita G, Racchumi G, Ling L, Pamer EG, *et al*: Commensal microbiota affects ischemic stroke outcome by regulating intestinal $\gamma\delta$ T cells. *Nat Med* 22: 516-523, 2016.
87. Dou Z, Rong X, Zhao E, Zhang L and Lv Y: Neuroprotection of resveratrol against focal cerebral ischemia/reperfusion injury in mice through a mechanism targeting Gut-brain axis. *Cell Mol Neurobiol* 39: 883-898, 2019.
88. Bonsack B, Jiang RH and Borlongan CV: A gut feeling about stroke reveals gut-brain axis' active role in homeostasis and dysbiosis. *J Cereb Blood Flow Metab* 40: 1132-1134, 2020.
89. Zhang Y, Yang H, Hou S, Xia Y and Wang YQ: Influence of the brain-gut axis on neuroinflammation in cerebral ischemia-reperfusion injury (Review). *Int J Mol Med* 53: 30, 2024.
90. Park MJ, Pilla R, Panta A, Pandey S, Sarawichitr B, Suchodolski J and Sohrabji F: Reproductive senescence and ischemic stroke remodel the gut microbiome and modulate the effects of estrogen treatment in female rats. *Transl Stroke Res* 11: 812-830, 2020.
91. Sadler R, Cramer JV, Heindl S, Kostidis S, Betz D, Zuurbier KR, Northoff BH, Heijink M, Goldberg MP, Plautz EJ, *et al*: Short-chain fatty acids improve poststroke recovery via immunological mechanisms. *J Neurosci* 40: 1162-1173, 2020.
92. Aswendt M, Green C, Sadler R, Llovera G, Dzikowski L, Heindl S, Gomez de Agüero M, Diedenhofen M, Vogel S, Wieters F, *et al*: The gut microbiota modulates brain network connectivity under physiological conditions and after acute brain ischemia. *iScience* 24: 103095, 2021.
93. Ji W, Zhu Y, Kan P, Cai Y, Wang Z, Wu Z and Yang P: Analysis of intestinal microbial communities of cerebral infarction and ischemia patients based on high throughput sequencing technology and glucose and lipid metabolism. *Mol Med Rep* 16: 5413-5417, 2017.
94. Henry N, Frank J, McLouth C, Trout AL, Morris A, Chen J, Stowe AM, Fraser JF and Pennypacker K: Short chain fatty acids taken at time of thrombectomy in acute ischemic stroke patients are independent of stroke severity but associated with inflammatory markers and worse symptoms at discharge. *Front Immunol* 12: 797302, 2021.
95. Jiang W, Gong L, Liu F, Ren Y and Mu J: Alteration of gut microbiome and correlated lipid metabolism in Post-stroke depression. *Front Cell Infect Microbiol* 11: 663967, 2021.
96. Huang C, Li Y, Feng X, Li D, Li X, Ouyang Q, Dai W, Wu G, Zhou Q, Wang P, *et al*: Distinct gut microbiota composition and functional category in children with cerebral palsy and epilepsy. *Front Pediatr* 7: 394, 2019.
97. Lindefeldt M, Eng A, Darban H, Bjerkner A, Zetterström CK, Allander T, Andersson B, Borenstein E, Dahlin M and Prast-Nielsen S: The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy. *NPJ Biofilms Microbiomes* 5: 5, 2019.
98. He Z, Cui BT, Zhang T, Li P, Long CY, Ji GZ and Zhang FM: Fecal microbiota transplantation cured epilepsy in a case with Crohn's disease: The first report. *World J Gastroenterol* 23: 3565-3568, 2017.
99. Avorio F, Cerulli Irelli E, Morano A, Fanella M, Orlando B, Albini M, Basili LM, Ruffolo G, Fattouch J, Manfredi M, *et al*: Functional gastrointestinal disorders in patients with epilepsy: Reciprocal influence and impact on seizure occurrence. *Front Neurol* 12: 705126, 2021.
100. Citraro R, Lembo F, De Caro C, Tallarico M, Coretti L, Iannone LF, Leo A, Palumbo D, Cuomo M, Buommino E, *et al*: First evidence of altered microbiota and intestinal damage and their link to absence epilepsy in a genetic animal model, the WAG/Rij rat. *Epilepsia* 62: 529-541, 2021.
101. Gallucci A, Patel DC, Thai K, Trinh J, Gude R, Shukla D and Campbell SL: Gut metabolite S-equol ameliorates hyperexcitability in entorhinal cortex neurons following Theiler murine encephalomyelitis virus-induced acute seizures. *Epilepsia* 62: 1829-1841, 2021.
102. Antón M, Rodríguez-González A, Ballesta A, González N, Del Pozo A, de Fonseca FR, Gómez-Lus ML, Leza JC, García-Bueno B, Caso JR and Orio L: Alcohol binge disrupts the rat intestinal barrier: The partial protective role of oleoylethanolamide. *Br J Pharmacol* 175: 4464-4479, 2018.
103. Hoyle L, Snelling T, Umlai UK, Nicholson JK, Carding SR, Glen RC and McArthur S: Microbiome-host systems interactions: Protective effects of propionate upon the blood-brain barrier. *Microbiome* 6: 55, 2018.
104. Ceccarelli G, Brenchley JM, Cavallari EN, Scheri GC, Frattino M, Pinacchio C, Schietroma I, Fard SN, Scagnolari C, Mezzaroma I, *et al*: Impact of High-dose multi-strain probiotic supplementation on neurocognitive performance and central nervous system immune activation of HIV-1 infected individuals. *Nutrients* 9: 1269, 2017.

105. Rincel M, Aubert P, Chevalier J, Grohard PA, Basso L, Monchaux de Oliveira C, Helbling JC, Lévy É, Chevalier G, Leboyer M, *et al*: Multi-hit early life adversity affects gut microbiota, brain and behavior in a sex-dependent manner. *Brain Behav Immun* 80: 179-192, 2019.
106. Cuskelly A, Hoedt EC, Harms L, Talley NJ, Tadros MA, Keely S and Hodgson DM: Neonatal immune challenge influences the microbiota and behaviour in a sexually dimorphic manner. *Brain Behav Immun* 103: 232-242, 2022.
107. Saunders JM, Moreno JL, Ibi D, Sikaroodi M, Kang DJ, Muñoz-Moreno R, Dalmat SS, García-Sastre A, Gillevet PM, Dozmorov MG, *et al*: Gut microbiota manipulation during the prepubertal period shapes behavioral abnormalities in a mouse neurodevelopmental disorder model. *Sci Rep* 10: 4697, 2020.
108. Duan H, Wang L, Huangfu M and Li H: The impact of microbiota-derived short-chain fatty acids on macrophage activities in disease: Mechanisms and therapeutic potentials. *Biomed Pharmacother* 165: 115276, 2023.
109. Chauhan V, Chauhan NK, Dutta S, Pathak D and Nongthomba U: Comparative In-silico analysis of microbial dysbiosis discern potential metabolic link in neurodegenerative diseases. *Front Neurosci* 17: 1153422, 2023.
110. Zancan V, Nasello M, Bigi R, Reniè R, Buscarinu MC, Mechelli R, Ristori G, Salvetti M and Bellucci G: Gut microbiota composition is causally linked to multiple sclerosis: A mendelian randomization analysis. *Microorganisms* 12: 1476, 2024.
111. Emery DC, Davies M, Cerajewska TL, Taylor J, Hazell M, Paterson A, Allen-Birt SJ and West NX: High resolution 16S rRNA gene next generation sequencing study of brain areas associated with Alzheimer's and Parkinson's disease. *Front Aging Neurosci* 14: 1026260, 2022.
112. Boles JS, Krueger ME, Jernigan JE, Cole CL, Neighbarger NK, Uriarte Huarte O and Tansey MG: A leaky gut dysregulates gene networks in the brain associated with immune activation, oxidative stress, and myelination in a mouse model of colitis. *Brain Behav Immun* 117: 473-492, 2024.
113. Luck B, Horvath TD, Engevik KA, Ruan W, Haidacher SJ, Hoch KM, Oezguen N, Spinler JK, Haag AM, Versalovic J and Engevik MA: Neurotransmitter profiles are altered in the gut and brain of mice Mono-associated with *Bifidobacterium dentium*. *Biomolecules* 11: 1091, 2021.
114. Pandey S, Singh A, Chaudhari N, Nampoothiri LP and Kumar GN: Protection against 1,2-di-methylhydrazine-induced systemic oxidative stress and altered brain neurotransmitter status by probiotic *Escherichia coli* CFR 16 secreting pyrrolo-quinoline quinone. *Curr Microbiol* 70: 690-697, 2015.
115. Zhu Y, Huan F, Wang J, Xie X, Yu G, Wang X, Jiang L, Gao R, Xiao H, Ding H and Wang J: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Induced Parkinson's disease in mouse: Potential association between neurotransmitter disturbance and gut microbiota dysbiosis. *ACS Chem Neurosci* 11: 3366-3376, 2020.
116. Li W, Xu M, Liu Y, Zhang S, Wang J, Zhang Z, Xiao G, Wang R, Zhang J and Xue H: *Lactiplantibacillus plantarum* GOLDGUT-HNU082 alleviates CUMS-Induced Depressive-like behaviors in mice by modulating the gut microbiota and neurotransmitter levels. *Foods* 14: 813, 2025.
117. Guo Y, Zhu X, Zeng M, Qi L, Tang X, Wang D, Zhang M, Xie Y, Li H, Yang X and Chen D: A diet high in sugar and fat influences neurotransmitter metabolism and then affects brain function by altering the gut microbiota. *Transl Psychiatry* 11: 328, 2021.
118. Zhang Z, Peng Q, Huo D, Jiang S, Ma C, Chang H, Chen K, Li C, Pan Y and Zhang J: Melatonin regulates the neurotransmitter secretion disorder induced by caffeine through the Microbiota-Gut-brain axis in zebrafish (*Danio rerio*). *Front Cell Dev Biol* 9: 678190, 2021.
119. Wang W, Chen F, Zhang L, Wen F, Yu Q, Li P and Zhang A: Neurotransmitter disturbances caused by methylmercury exposure: Microbiota-gut-brain interaction. *Sci Total Environ* 873: 162358, 2023.
120. Mortensen NP, Moreno Caffaro M, Patel PR, Snyder RW, Watson SL, Aravamudan S, Montgomery SA, Lefever T, Sumner SJ and Fennell TR: Biodistribution, cardiac and neurobehavioral assessments, and neurotransmitter quantification in juvenile rats following oral administration of aluminum oxide nanoparticles. *J Appl Toxicol* 41: 1316-1329, 2021.
121. Huang J, Liu S, Li P, Wei L, Lin G, Lin J, Luo Y, Liu Y, Mao Y, Ruan H, *et al*: Multi-omics analysis of gut-brain axis reveals novel microbial and neurotransmitter signatures in patients with arteriosclerotic cerebral small vessel disease. *Pharmacol Res* 208: 107385, 2024.
122. Margetts G, Kleidonas S, Zaibi NS, Zaibi MS and Edwards KD: Evidence for anti-inflammatory effects and modulation of neurotransmitter metabolism by *Salvia officinalis* L. *BMC Complement Med Ther* 22: 131, 2022.
123. Kumari M, Dasriya VL, Nataraj BH, Nagpal R and Behare PV: *Lactocaseibacillus rhamnosus*-derived exopolysaccharide Attenuates D-Galactose-Induced oxidative stress and inflammatory brain injury and modulates gut microbiota in a mouse model. *Microorganisms* 10: 2046, 2022.
124. Bock HJ, Lee NK and Paik HD: Neuroprotective effects of Heat-killed *Levilactobacillus brevis* KU15152 on H2O2-induced oxidative stress. *J Microbiol Biotechnol* 33: 1189-1196, 2023.
125. Cansız D, Ünal İ, Üstündağ ÜV, Alturfan AA, Altinoz MA, Elmacı İ and Emekli-Alturfan E: Caprylic acid ameliorates rotenone induced inflammation and oxidative stress in the gut-brain axis in Zebrafish. *Mol Biol Rep* 48: 5259-5273, 2021.
126. Pan S, Wei H, Yuan S, Kong Y, Yang H, Zhang Y, Cui X, Chen W, Liu J and Zhang Y: Probiotic *Pediococcus pentosaceus* ameliorates MPTP-induced oxidative stress via regulating the gut microbiota-gut-brain axis. *Front Cell Infect Microbiol* 12: 1022879, 2022.
127. Dong B, Qi Y, Sundas H, Yang R, Zhou J and Li Z: Soy protein increases cognitive level in mice by modifying hippocampal nerve growth, oxidative stress, and intestinal microbiota. *J Sci Food Agric* 103: 4085-4094, 2023.
128. Nikrad N, Farhangi MA, Fard Tabrizi FP, Vaezi M, Mahmoudpour A and Mesgari-Abbasi M: The effect of calorie-restriction along with thylakoid membranes of spinach on the gut-brain Axis Pathway and oxidative stress biomarkers in obese women with polycystic ovary syndrome: A randomized, Double-blind, placebo-controlled clinical trial. *J Ovarian Res* 16: 216, 2023.
129. Rode J, Yang L, König J, Hutchinson AN, Wall R, Venizelos N, Brummer RJ, Rangel I and Vumma R: Butyrate rescues oxidative Stress-induced transport deficits of tryptophan: Potential implication in affective or Gut-Brain axis disorders. *Neuropsychobiology* 80: 253-263, 2021.
130. He J, Xu P, Xu T, Yu H, Wang L, Chen R, Zhang K, Yao Y, Xie Y, Yang Q, *et al*: Therapeutic potential of hydrogen-rich water in zebrafish model of Alzheimer's disease: Targeting oxidative stress, inflammation, and the gut-brain axis. *Front Aging Neurosci* 16: 1515092, 2024.
131. Di Chiano M, Rocchetti MT, Spano G, Russo P, Allegretta C, Milior G, Gadaleta RM, Sallustio F, Pontrelli P, Gesualdo L, *et al*: Lactobacilli Cell-free supernatants modulate inflammation and oxidative stress in human microglia via NRF2-SOD1 signaling. *Cell Mol Neurobiol* 44: 60, 2024.
132. Hsu YC, Huang YY, Tsai SY, Kuo YW, Lin JH, Ho HH, Chen JF, Hsia KC and Sun Y: Efficacy of probiotic supplements on Brain-derived neurotrophic factor, inflammatory biomarkers, oxidative stress and cognitive function in patients with Alzheimer's dementia: A 12-week randomized, double-blind active-controlled study. *Nutrients* 16: 16, 2023.
133. Akhgargand C, Vahabi Z, Shab-Bidar S, Anoushirvani A and Djafarian K: The effects of probiotic supplements on oxidative stress and inflammation in subjects with mild and moderate Alzheimer's disease: A randomized, double-blind, placebo-controlled study. *Inflammopharmacology* 32: 1413-1420, 2024.
134. García-Sanmartín J, Bobadilla M, Mirpuri E, Grifoll V, Pérez-Clavijo M and Martínez A: *Agaricus Mushroom*-enriched diets modulate the Microbiota-Gut-brain axis and reduce brain oxidative stress in mice. *Antioxidants (Basel)* 11: 695, 2022.
135. Chenghan M, Wanxin L, Bangcheng Z, Yao H, Qinxi L, Ting Z, Xiaojie L, Kun Z, Yingqian Z and Zhihui Z: Short-chain fatty acids mediate gut microbiota-brain communication and protect the blood-brain barrier integrity. *Ann N Y Acad Sci* 1545: 116-131, 2025.
136. Stachulski AV, Knausenberger TB, Shah SN, Hoyle L and McArthur S: A host-gut microbial amino acid co-metabolite, p-cresol glucuronide, promotes blood-brain barrier integrity in vivo. *Tissue Barriers* 11: 2073175, 2023.
137. Connell E, Le Gall G, McArthur S, Lang L, Breeze B, Pontifex MG, Sami S, Pourtau L, Gaudout D, Müller M and Vauzour D: (Poly)phenol-rich grape and blueberry extract prevents LPS-induced disruption of the blood-brain barrier through the modulation of the gut microbiota-derived uremic toxins. *Neurochem Int* 180: 105878, 2024.
138. He J, Liu Y, Li J, Zhao Y, Jiang H, Luo S and He G: Intestinal changes in permeability, tight junction and mucin synthesis in a mouse model of Alzheimer's disease. *Int J Mol Med* 52: 113, 2023.

139. Fiorentino M, Sapone A, Senger S, Camhi SS, Kadziński SM, Buie TM, Kelly DL, Cascella N and Fasano A: Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol Autism* 7: 49, 2016.
140. Sun N, Hu H, Wang F, Li L, Zhu W, Shen Y, Xiu J and Xu Q: Antibiotic-induced microbiome depletion in adult mice disrupts blood-brain barrier and facilitates brain infiltration of monocytes after bone-marrow transplantation. *Brain Behav Immun* 92: 102-114, 2021.
141. Nelson JW, Phillips SC, Ganesh BP, Petrosino JF, Durgan DJ and Bryan RM: The gut microbiome contributes to blood-brain barrier disruption in spontaneously hypertensive stroke prone rats. *FASEB J* 35: e21201, 2021.
142. Knox EG, Aburto MR, Tessier C, Nagpal J, Clarke G, O'Driscoll CM and Cryan JF: Microbial-derived metabolites induce actin cytoskeletal rearrangement and protect Blood-brain barrier function. *iScience* 25: 105648, 2022.
143. Wang Y, Tan Q, Pan M, Yu J, Wu S, Tu W, Li M and Jiang S: Minimally invasive vagus nerve stimulation modulates mast cell degranulation via the microbiota-gut-brain axis to ameliorate blood-brain barrier and intestinal barrier damage following ischemic stroke. *Int Immunopharmacol* 132: 112030, 2024.
144. Marungu N, Arévalo Sureda E, Lefrançois A, Weström B, Nyman M, Prykhodko O and Fåk Hållén F: Impact of dietary induced precocious gut maturation on cecal microbiota and its relation to the blood-brain barrier during the postnatal period in rats. *Neurogastroenterol Motil* 30: e13285, 2018.
145. Schalla MA, Oerter S, Cubukova A, Metzger M, Appelt-Menzel A and Stengel A: Locked out: Phoenixin-14 does not cross a Stem-Cell-derived blood-brain barrier model. *Brain Sci* 13: 980, 2023.
146. Solch RJ, Aigbogun JO, Voyiadjis AG, Talkington GM, Darensbourg RM, O'Connell S, Pickett KM, Perez SR and Maraganore DM: Mediterranean diet adherence, gut microbiota, and Alzheimer's or Parkinson's disease risk: A systematic review. *J Neurol Sci* 434: 120166, 2022.
147. Lussier DM, Woolf EC, Johnson JL, Brooks KS, Blattman JN and Scheck AC: Enhanced immunity in a mouse model of malignant glioma is mediated by a therapeutic ketogenic diet. *BMC Cancer* 16: 310, 2016.
148. Berding K, Vlckova K, Marx W, Schellekens H, Stanton C, Clarke G, Jacka F, Dinan TG and Cryan JF: Diet and the Microbiota-Gut-Brain axis: Sowing the seeds of good mental health. *Adv Nutr* 12: 1239-1285, 2021.
149. Zuo Z, Fan H, Tang XD, Chen YM, Xun LT, Li Y, Song ZJ and Zhai HQ: Effect of different treatments and alcohol addiction on gut microbiota in minimal hepatic encephalopathy patients. *Exp Ther Med* 14: 4887-4895, 2017.
150. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J and Cryan JF: Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA* 108: 16050-16055, 2011.
151. Chong HX, Yusoff NAA, Hor YY, Lew LC, Jaafar MH, Choi SB, Yusoff MSB, Wahid N, Abdullah MFIL, Zakaria N, *et al*: *Lactobacillus plantarum* DR7 alleviates stress and anxiety in adults: A randomised, double-blind, placebo-controlled study. *Benef Microbes* 10: 355-373, 2019.
152. Lew LC, Hor YY, Yusoff NAA, Choi SB, Yusoff MSB, Roslan NS, Ahmad A, Mohammad JAM, Abdullah MFIL, Zakaria N, *et al*: Probiotic *Lactobacillus plantarum* P8 alleviated stress and anxiety while enhancing memory and cognition in stressed adults: A randomised, double-blind, placebo-controlled study. *Clin Nutr* 38: 2053-2064, 2019.
153. Karakula-Juchnowicz H, Rog J, Juchnowicz D, Łoniewski I, Skonieczna-Zydecka K, Krukow P, Futyma-Jedrzejska M and Kaczmarczyk M: The study evaluating the effect of probiotic supplementation on the mental status, inflammation, and intestinal barrier in major depressive disorder patients using gluten-free or gluten-containing diet (SANGUT study): A 12-week, randomized, double-blind, and placebo-controlled clinical study protocol. *Nutr J* 18: 50, 2019.
154. Cheng Y, Tan G, Zhu Q, Wang C, Ruan G, Ying S, Qie J, Hu X, Xiao Z, Xu F, *et al*: Efficacy of fecal microbiota transplantation in patients with Parkinson's disease: Clinical trial results from a randomized, placebo-controlled design. *Gut Microbes* 15: 2284247, 2023.
155. Dalile B, Vervliet B, Bergonzelli G, Verbeke K and Van Oudenhove L: Colon-delivered short-chain fatty acids attenuate the cortisol response to psychosocial stress in healthy men: A randomized, placebo-controlled trial. *Neuropsychopharmacology* 45: 2257-2266, 2020.
156. Lei Y, Tang L, Chen Q, Wu L, He W, Tu D, Wang S, Chen Y, Liu S and Xie Z: Disulfiram ameliorates nonalcoholic steatohepatitis by modulating the gut microbiota and bile acid metabolism. *Nat Commun* 13: 6862, 2022.
157. Fleck AK, Hucke S, Teipel F, Eschborn M, Janoschka C, Liebmann M, Wami H, Korn L, Pickert G, Hartwig M, *et al*: Dietary conjugated linoleic acid links reduced intestinal inflammation to amelioration of CNS autoimmunity. *Brain* 144: 1152-1166, 2021.
158. Martin FP, Cominetti O, Berger B, Combremont S, Marquis J, Xie G, Jia W, Pinto-Sanchez MI, Bercik P and Bergonzelli G: Metabolome-associated psychological comorbidities improvement in irritable bowel syndrome patients receiving a probiotic. *Gut Microbes* 16: 2347715, 2024.
159. Mysonhimer AR, Cannavale CN, Bailey MA, Khan NA and Holscher HD: Prebiotic consumption alters microbiota but not biological markers of stress and inflammation or mental health symptoms in healthy adults: A randomized, controlled, cross-over trial. *J Nutr* 153: 1283-1296, 2023.
160. Li J, Li Y, Zhao J, Li L, Wang Y, Chen F, Li Y, Cheng R, He F, Ze X and Shen X: Effects of *Bifidobacterium breve* 207-1 on regulating lifestyle behaviors and mental wellness in healthy adults based on the microbiome-gut-brain axis: A randomized, double-blind, placebo-controlled trial. *Eur J Nutr* 63: 2567-2585, 2024.
161. Casertano M, Dekker M, Valentino V, De Filippis F, Fogliano V and Ercolini D: Gaba-producing lactobacilli boost cognitive reactivity to negative mood without improving cognitive performance: A human Double-Blind Placebo-Controlled Cross-Over study. *Brain Behav Immun* 122: 256-265, 2024.
162. Caradonna E, Nemni R, Bifone A, Gandolfo P, Costantino L, Giordano L, Mormone E, Macula A, Cuomo M, Difruscolo R, *et al*: The Brain-gut axis, an important player in alzheimer and parkinson disease: A narrative review. *J Clin Med* 13: 4130, 2024.
163. Almheiri RT, Hajjar B, Alkhaaldi SMI, Rabeh N, Aljoudi S, Abd-Elrahman KS and Hamdan H: Beyond weight loss: Exploring the neurological ramifications of altered gut microbiota post-bariatric surgery. *J Transl Med* 23: 223, 2025.
164. Park KJ and Gao Y: Gut-brain axis and neurodegeneration: Mechanisms and therapeutic potentials. *Front Neurosci* 18: 1481390, 2024.
165. Manfredi JN, Gupta SK, Vyavahare S, Deak F, Lu X, Buddha L, Wankhade U, Lohakare J, Isaacs C and Fulzele S: Gut microbiota dysbiosis in Alzheimer's disease (AD): Insights from human clinical studies and the mouse AD models. *Physiol Behav* 290: 114778, 2025.
166. Qi A, Liu L, Zhang J, Chen S, Xu S, Chen Y, Zhang L and Cai C: Plasma metabolic analysis reveals the dysregulation of Short-chain fatty acid metabolism in Parkinson's disease. *Mol Neurobiol* 60: 2619-2631, 2023.
167. Nakhal MM, Yassin LK, Alyaqoubi R, Saeed S, Alderei A, Alhammadi A, Alshehhi M, Almehairbi A, Al Houqani S, BaniYas S, *et al*: The Microbiota-Gut-Brain axis and neurological disorders: A comprehensive review. *Life* 14: 1234, 2024.
168. Vaz M and Silvestre S: Alzheimer's disease: Recent treatment strategies. *Eur J Pharmacol* 887: 173554, 2020.
169. Forssten SD, Ouwehand AC, Griffin SM and Patterson E: One giant leap from mouse to man: The Microbiota-Gut-Brain axis in mood disorders and translational challenges moving towards human clinical trials. *Nutrients* 14: 568, 2022.
170. Schächtle MA and Rosshart SP: The Microbiota-Gut-Brain axis in health and disease and its implications for translational research. *Front Cell Neurosci* 15: 698172, 2021.
171. Ericsson AC and Franklin CL: Manipulating the gut microbiota: Methods and challenges. *ILAR J* 56: 205-217, 2015.
172. McGonigle P and Ruggeri B: Animal models of human disease: Challenges in enabling translation. *Biochem Pharmacol* 87: 162-171, 2014.
173. Woodworth MH, Sitchenko KL, Carpentieri C, Friedman-Moraco RJ, Wang T and Kraft CS: Ethical considerations in microbial therapeutic clinical trials. *New Bioeth* 23: 210-218, 2017.
174. Cheng Y, Tan G, Zhu Q, Wang C, Ruan G, Ying S, Qie J, Hu X, Xiao Z, Xu F, *et al*: Efficacy of fecal microbiota transplantation in patients with Parkinson's disease: Clinical trial results from a randomized, placebo-controlled design. *Gut Microbes* 15: 2284247, 2023.
175. Blivet G, Relano-Gines A, Wachtel M and Touchon J: A randomized, double-blind, and sham-controlled trial of an innovative brain-gut photobiomodulation therapy: Safety and patient compliance. *J Alzheimers Dis* 90: 811-822, 2022.

176. Rode J, Edebol Carlman HMT, König J, Hutchinson AN, Thunberg P, Persson J and Brummer RJ: Multi-strain probiotic mixture affects brain morphology and resting state brain function in healthy subjects: An RCT. *Cells* 11: 2922, 2022.
177. Kiliçarslan S and Evrensel A: The effect of fecal microbiota transplantation on psychiatric symptoms among patients with inflammatory bowel disease: An experimental study. *Actas Esp Psiquiatr* 48: 1-7, 2020.
178. Laeeq T, Vongsavath T, Tun KM and Hong AS: The potential role of fecal microbiota transplant in the reversal or stabilization of multiple sclerosis symptoms: A literature review on efficacy and safety. *Microorganisms* 11: 2840, 2023.
179. Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, Foo JB, Ong YS, How CW and Khaw KY: Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct Target Ther* 9: 37, 2024.
180. Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, Kotler E, Zur M, Regev-Lehavi D, Brik RB, *et al*: Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell* 174: 1388-1405.e21, 2018.



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