

# The Role of the Gut-Brain Axis in Diseases

Jing Chen,<sup>1</sup> Yijia Xu,<sup>2</sup> and Peng Cao<sup>2,3</sup>

<sup>1</sup>Department of Neurosurgery, Xuanwu Hospital, China International Neuroscience Institute, Capital Medical University, Beijing, China; <sup>2</sup>National Institute of Biological Sciences, Beijing, China; and <sup>3</sup>Tsinghua Institute of Multidisciplinary Biomedical Research, Tsinghua University, Beijing, China  
caopeng@nibs.ac.cn

Accumulating evidence highlights the crucial role of the gut-brain axis in diseases. This bidirectional signaling connects the gastrointestinal tract (GI) and the brain via neural, immune, and endocrine pathways, orchestrating a range of physiological processes. Dysregulation of the gut-brain axis has been related to a variety of neuropsychiatric, neurodegenerative, and neurodevelopmental disorders, as well as to disturbances in emotional regulation, cognition, and feeding-related conditions. The complex molecular interactions underlying this axis are necessary for maintaining homeostasis and overall health. Emerging pharmacological interventions and therapeutic targets have demonstrated potential in modulating gut-brain signaling to influence disease outcomes. This review provides a comprehensive view of the gut-brain axis, detailing its pivotal role in disease pathogenesis and exploring its therapeutic relevance.

*brainstem; gut-brain axis; mental health; neurodegenerative diseases; neurological diseases*

## Introduction

The interactive communication between the gastrointestinal tract (GI) and the central nervous system (CNS), termed the gut-brain axis, is indispensable for regulating physiological functions and disease progression. This complex signaling network operates through neural, immune, and endocrine neuropathways, integrating gut-derived signals with central regulatory mechanisms. Growing evidence has established a compelling relationship between the gut-brain axis and various pathological conditions, including neuropsychiatric disorders, neurodegenerative diseases, and gut-related pathologies. Disruptions within the gut-brain axis trigger maladaptive physiological responses, contributing to disease progression. This review explores recent advances in gut-brain axis research, emphasizing its role in both health and disease. Furthermore, emerging therapeutic strategies targeting gut-brain communication are discussed, highlighting their potential for disease modulation and intervention.

## Multiple Pathways Linking the Gut and Brain

The gut interacts with the brain through neural network, immune system, and endocrine pathway, forming an intricate bidirectional network essential for maintaining homeostasis and influencing disease pathogenesis (FIGURE 1) (1, 2). This cross talk modulates CNS function

and is increasingly recognized as a key determinant of neurological and metabolic health.

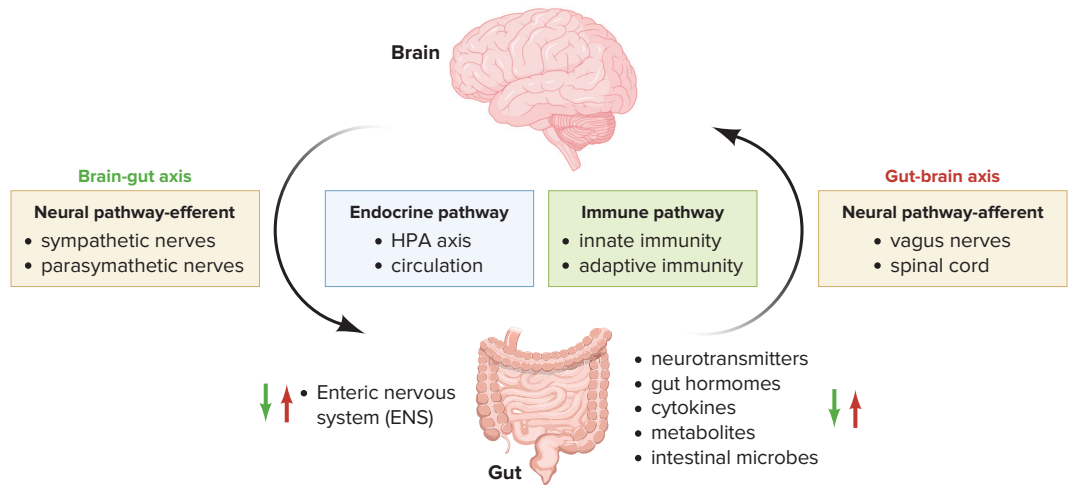
### Neural Pathways

The neural connection between the GI and CNS includes afferent (sensory) signals, efferent (motor) signals, and the enteric nervous system (ENS) (FIGURE 1). Afferent (sensory) pathway transmitted GI signals through vagal (nodose ganglion), spinal (dorsal root ganglion), and enteric pathway to CNS (3). Meanwhile, the efferent (motor) pathway, also called the autonomic nervous system (ANS), regulates GI function from the brain via sympathetic and parasympathetic (vagal) efferent fibers (4). In addition to direct neural transmission, gastrointestinal hormones, short-chain fatty acids (SCFAs), and intestinal microbes modulate CNS activity through these neural pathways.

The vagus nerve (VN) serves as a vital route for gut-derived signals to the brain. Various gut hormones act through VN-mediated pathways, influencing central processes such as appetite regulation, metabolism, and inflammation.

Gut hormones, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY), modulate brain function through the VN (5). Sensory neurons in the VN express various gut hormone receptors. For instance, CCK produced in the proximal small intestine interacts with CCK1 receptors (CCK1R) on VN afferents, regulating satiety and inflammatory





**FIGURE 1. Multiple pathways linking the gut and brain**

Gut bidirectionally communicates with the brain through 3 pathways, including the neural, immune, and neuroendocrine pathways. HPA, hypothalamus pituitary adrenal. Figure created with a licensed version of BioRender.com.

responses (6). GLP-1, produced by intestinal L cells, modulates food intake via VN GLP-1 receptors (GLP1R) (6). Similarly, PYY, also secreted by L cells, transmits feeding-related information through VN neuropeptide Y receptor Y2 (NPY2R or Y2R) to the nucleus of the solitary tract (NTS) (7).

Beyond VN-mediated communication, the spinal cord can also transfer gut information to the brain (8). Sensory afferents synapse in the spinal cord, projecting gut-derived information to the NTS and hypothalamus (9). The visceral spinal nerves surrounding the portal vein detect glucose signals through specialized receptors, influencing metabolic and autonomic responses (10). Moreover, clinical studies have demonstrated that gut-derived metabolites can also engage spinal cord pathways to modulate CNS activity (11).

The ENS is an independent and complex neural network within the GI (12). The ENS contains the myenteric/Meissner’s plexus and submucosal/Auerbach’s plexus, which control motility, secretion, and sensory processing (13). The ENS functions autonomously (14) and can transfer information from the gut to the brain via spinal afferent and vagal afferent nerves (1). Mechanical, chemical, and microbial stimuli activate ENS neurons, triggering gut-brain signaling through the sympathetic and parasympathetic neurons (13).

**Immune Pathways**

The gut serves as a primary immunological hub, and the gut-associated lymphoid tissue (GALT) houses 70% of the body’s immune cells (15). This complex immune network comprises both innate and adaptive immune components (16–18). Innate immune response involves cells like natural killer (NK) cells, mast (M) cells, dendritic cells, eosinophils, basophils, neutrophils, and monocytes/macrophages, while adaptive immune cells include T lymphocytes, B lymphocytes, and memory cells (19, 20). Notably, both enteric

neurons and glial cells are implicated in the regulation of intestinal immunity. However, immunity interactions with the gut-brain axis are not always beneficial; in some cases, it exacerbates disease processes (21, 22).

A variety of factors, including gut microbiota, dietary components, environmental stimuli, and pathological injury, can influence immune cell activity within the gut. These immune responses can affect the CNS through several mechanisms, including disruption of the blood-brain barrier (BBB) or transmission through neural pathways (23). The immune system is increasingly acknowledged as a gatekeeper and essential regulator of gut-brain communication (20). Inflammatory signaling is initiated bidirectionally between the gut and brain, involving both “gut-to-brain” and “brain-to-gut” pathways (19, 24). Gut-innervating afferent signaling originates from the dorsal root ganglia (DRG) and the vagal nodose ganglion (NG)/jugular ganglion, transmitting immune-derived signals from the GI to CNS (18, 25). Gut-produced proinflammatory cytokines, including NLRP6, interleukin-18 (IL-18), and IL-6, have been implicated in the progression of various diseases (26, 27). Additionally, gut microbiota significantly influences neuroimmune interactions through the production of bioactive compounds, like lipopolysaccharides (LPS) (28). LPS can exacerbate neuroinflammation and promote the progression of neurological disorders (29). Collectively, accumulating evidence emphasizes the indispensable role of immune pathways in the reciprocal communication between the gut and brain, highlighting their significance in both physiological homeostasis and disease progression.

**Endocrine Pathways**

The hypothalamus-pituitary-adrenal (HPA) axis serves as a principal endocrine pathway connecting the CNS and GI, orchestrating physiological responses to peripheral stimuli and stressors (30). This axis modulates gut

motility, intestinal permeability, and inflammatory processes, thereby influencing overall gut function and homeostasis (31). In parallel, endocrine cells within the GI synthesize and release multiple hormones, cytokines, and metabolites that enter the circulation and affect CNS activity (32) (FIGURE 1). Neurotransmitters and bioactive metabolites produced in the gut, such as glutamate, gamma-aminobutyric acid (GABA) (33), catecholamine (34), 5-hydroxytryptamine (5-HT) (35), SCFAs (36), melatonin (37), histamine (38), and acetylcholine (39), also directly modulate brain function via neural or immune pathways. For example, galanin, secreted by the gut, is critical for sleep, blood pressure, and mood regulation (40), while 5-HT, secreted by enterochromaffin cells, regulates emotion, cognition, and sleep (41). Catecholamines produced in the gut have been involved in psychiatric disorders and neurodegenerative diseases (41), while GABA modulates emotional and cognitive functions and is associated with neuropsychiatric conditions (42). SCFAs, key microbial metabolites generated by the intestine, play a vital role in gut-to-brain regulation through the BBB or the ANS (43, 44). In general, these findings illuminate the complex bidirectional cross talk between endocrine signaling and the gut-brain axis, revealing profound perspectives on their contributions to neurological function and disease development.

## Gut-Brain Axis and Neuropsychiatric Disorders

### *Anxiety and Depression*

Prevalence of anxiety and depression threatens human health, yet the precise pathophysiological mechanisms of these psychiatric illnesses remain incompletely understood (45). Growing evidence suggests the gut-brain axis is involved in the occurrence and development of anxiety-like and depression-related disorders. The gut microbiota, hormones, and metabolites have emerged as key contributors to disease pathology.

The gut microbiota, composed of bacterial and nonbacterial components, as well as their derived metabolites, contributes to the pathogenesis of anxiety and depression (46). Studies proved that gut-derived metabolite 4-ethylphenyl sulfate (4EPS) can modify brain activity and induce anxiety (47). In patients with depression, gut dysfunction disrupts the gut barrier and triggers systemic immune responses (48). Dysfunction of the ENS also aggravates depressive symptoms (49). The VN is significant to the etiology of depression. Notably, the Food and Drug Administration approved the use of stimulation of VN (VNS) to cure refractory depression (50), while subdiaphragmatic vagotomy can also suppress depression (51).

Clinical and preclinical investigations have further emphasized the key role of gut microbiota in modulating depression; meanwhile, the change of the microbial composition contributes to disease onset and severity (52). SCFAs have also emerged as significant mediators of depression development (36). SCFAs exert neuroprotective effects, influencing neuroinflammation, neurotransmitter signaling, and BBB integrity, thereby impacting the incidence and progression of depression (53). Collectively, these studies emphasize the pivotal role of the gut-brain axis in anxiety and depression, offering potential pathways for clinical intervention and treatment.

### *Schizophrenia*

Schizophrenia (SCZ) is a severe mental disorder associated with hallucinations, delusions, and cognitive deficits, significantly impairing daily functioning and social interactions (54). Recent research suggests that gut-brain interactions drive SCZ pathogenesis, with alterations in gut microbiota, microbial metabolites, and neurotransmitter signaling contributing to disease progression. Notably, gut-derived metabolites such as kynurenine-kynurenic acid, SCFAs, and serotonin have been identified as potential contributors to SCZ progression (55, 56). Moreover, recent findings demonstrate that the immune system modulates SCZ through the gut-brain axis (57, 58). Both innate and adaptive immune mechanisms, including humoral and T-lymphocyte-mediated immunity, have been associated with SCZ pathology (59). Increasing studies recognized that the gut-brain axis becomes a potential target for SCZ treatment, including antibiotic diets, probiotics treatment, and fecal microbiota transplantation (FMT) (60). These findings highlight the considerable role of the gut-brain axis in SCZ and indicate novel approaches to managing diseases.

### *Autism Spectrum Disorder*

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that begins in early development and is characterized by impairments in social interactions and communication (61), as well as restricted and repetitive behaviors (62). In addition to core symptoms, ASD is often comorbid with neurological and genetic diseases, such as Down syndrome, epilepsy, and Fragile X syndrome (63). While the precise etiology of ASD remains unclear, emerging evidence suggests that gut microbiota (64) and their metabolites, including SCFAs, LPS, metal ions, cofactors, and vitamins, are essential in both the pathophysiology and potential treatment of ASD (64, 65). Clinical research has identified changes in gut microbiota, disruptions in blood glutathione levels, or abnormalities in phenylalanine metabolism as possible contributors to ASD pathology through gut-brain axis interactions (66). Despite significant advances in both basic and clinical

research, the exact etiopathology of ASD remains incompletely known, requiring further investigation.

### **Bipolar Disorder**

Bipolar disorder (BD) is a complex and severe psychiatric condition, accompanied by alternating episodes of mania (or hypomania) and depression (67), which is different from major depressive disorder (MDD) (68). The World Health Organization (WHO) has indicated that BD impacts ~40 million people globally and is a significant contributor to the worldwide burden of disability. Recent studies suggest that intestinal microbes, metabolites, gut hormones, and neurotransmitters play a fundamental role in BD pathophysiology (38, 69), influencing cognition and mood regulation through endocrine signaling, the VN, and the ENS. Gut hormones, such as GLP-1(70), PYY, GABA (71), adipokines (72), and CCK (73), exhibit dysregulation in BD patients and animal models. Additionally, disturbances in key neurotransmitters, such as brain-derived neurotrophic factor (BDNF), dopamine (74), and serotonin (75), induce the pathogenesis of BD by affecting neuroplasticity, emotional regulation, and cognitive function. Numerous studies have demonstrated that BD is closely linked to immune dysfunction, with immune dysregulation affecting BD progression through the HPA and gut-brain axes (76).

Given this expanding understanding, several microbiome-targeted interventions, including diet modifications (77), psychobiotics (78), FMT (38), and vagus nerve stimulation (79), have been investigated as potential strategies to alleviate BD symptoms and enhance quality of life. These findings highlight that the gut-brain axis is merging as a promising strategy for BD treatment.

## **Gut-Brain Axis and Neurodegenerative Diseases**

Neurodegenerative diseases are characterized as persistent neurological disorders that predominantly affect the elderly population (80). There is an increasing awareness that the gut-brain axis is crucial in neurodegenerative disease regulation (FIGURE 2).

### **Parkinson's Disease**

Parkinson's disease (PD) is a neurodegenerative disorder defined by the pathological aggregation of  $\alpha$ -synuclein ( $\alpha$ -Syn) within dopaminergic (DA) neurons of the substantia nigra (SNr) and striatum (81). The disease manifests through motor symptoms, such as resting tremors, muscle rigidity, bradykinesia, and postural instability, alongside nonmotor symptoms including constipation, olfactory dysfunction, sleep disturbances, autonomic dysregulation, and cognitive impairment (82). While PD pathogenesis is complex, involving genetic predisposition, environmental triggers, and

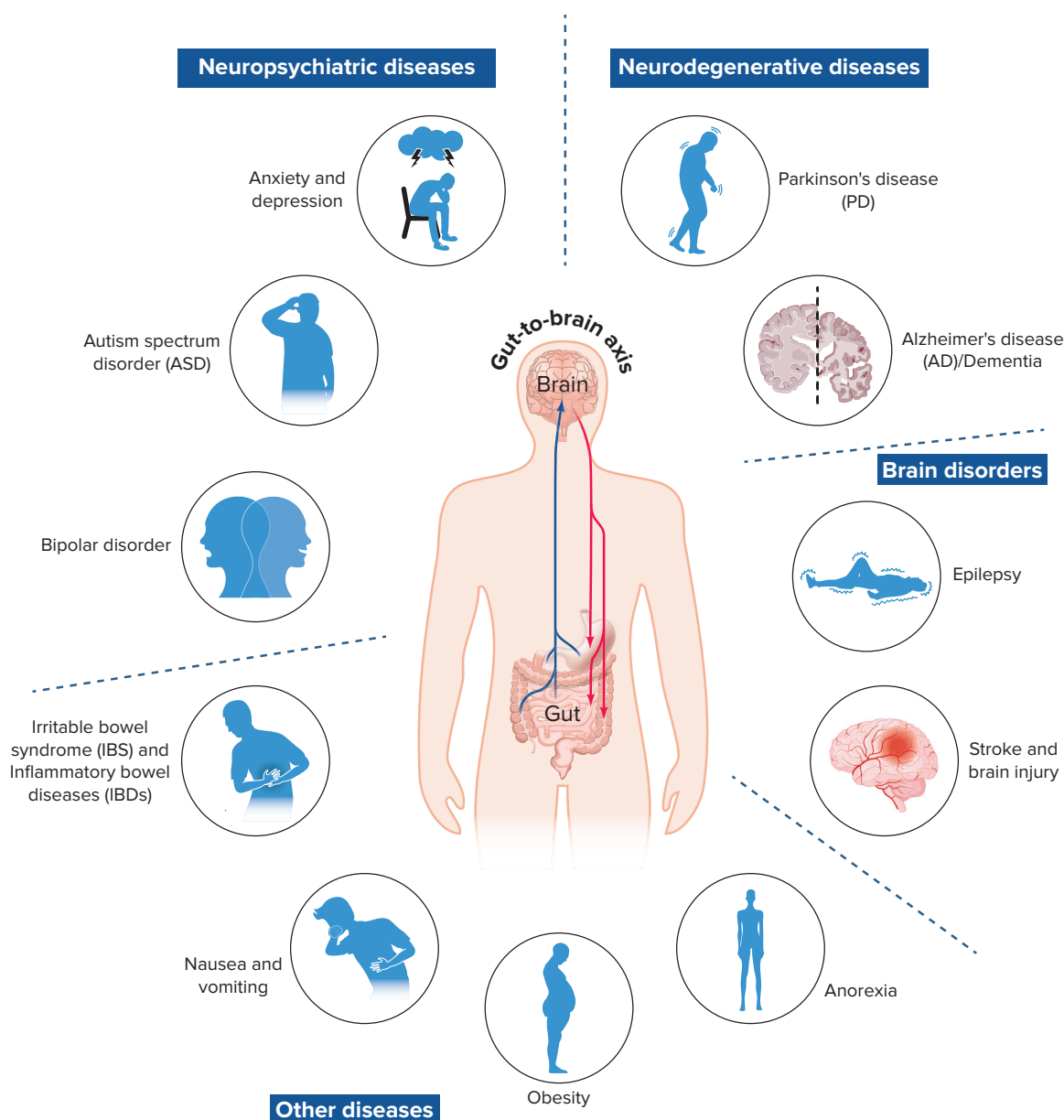
aging, gastrointestinal dysfunction becomes a prominent contributor to disease onset and progression (83). The gut-brain axis is emerging as a vital role in PD pathology, with gut-derived  $\alpha$ -Syn aggregates being transported to the brainstem via the VN, ultimately triggering neurodegeneration (84). Experimental evidence demonstrates that intestinal microbiota derived from PD patients is able to lead to Parkinson-like behaviors in mice when transplanted into wild-type mice, supporting the hypothesis that dysbiosis contributes to disease development (85). Additionally, neuroinflammation, microbial metabolites, and diet-derived compounds influence disease progression by modulating neuroimmune responses and  $\alpha$ -Syn aggregation. Given the influence of the gut on PD pathology, microbiome-targeted interventions have gained attention as potential therapeutic strategies. Approaches such as diet modifications, prebiotics, probiotics, and FMT may benefit patients with PD via gut-brain interactions (86). Furthermore, sodium glycolate (GV-971), a novel gut-brain-targeting compound, can significantly suppress  $\alpha$ -Syn accumulation and aggregation both in vitro and ex vivo models (87). These findings highlight GV-971 as a novel therapeutic candidate for PD.

The gut-brain axis exhibits bidirectional cross talk, whereby PD can also impair gut function via descending neural pathways, including sympathetic, parasympathetic, and ENS (88). The damage to the brain in PD patients disrupts the autonomic balance, suppresses intestinal motility, and induces constipation. This persistent colonic dysmotility exacerbates gut dysbiosis and accelerates  $\alpha$ -Syn accumulation, establishing a vicious cycle wherein central pathology amplifies intestinal dysfunction, which in turn drives further neurodegeneration (89).

The interplay between PD and the gut-brain axis forms an intricate network encompassing  $\alpha$ -Syn trafficking, microbial metabolites, immune signals, and endocrine cross talk. Intestinal perturbations (e.g.,  $\alpha$ -Syn aggregation, microbial dysbiosis, barrier damage) may act as either the initiating "spark" or a powerful accelerator of PD, ascending through the gut-brain axis to exacerbate central nervous system pathology. Conversely, the neurodegenerative process within the brain disrupts ANS function and deepens enteric dysfunction. In the future, identifying precise therapeutic targets and developing targeted interventions will be pivotal for advancing PD treatment.

### **Alzheimer's Disease and Dementia**

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, accompanied by a decline in cognitive function and pathological accumulation of  $\beta$ -amyloid plaques (A $\beta$ ) and/or hyperphosphorylated tau proteins (90). Among various forms of dementia, AD is the most prevalent, joined by other subtypes



**FIGURE 2.** The role of the gut-brain axis in the onset and development of various diseases  
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such as frontotemporal dementia, dementia with Lewy bodies, and vascular dementia (91).

With the increasing trend of aging, the population of dementia is expected to reach 150 million by 2050 (92). Emerging evidence implicates the gut-brain axis in AD onset and progression (93), highlighting the function of gut microbiota, microbial metabolites, and neurotransmitters in modulating neuroinflammation and neurodegeneration (94). Gut dysbiosis can alter microbial metabolite production, influencing systemic and central immune responses. These metabolites and immune mediators promote neuroinflammation, disrupt BBB integrity, and accelerate tau aggregation and neuronal loss (95). AD is not driven by a unidirectional gut-to-brain axis alone. The neurodegeneration in the brain also exerts a reciprocal influence on the GI

through autonomic and endocrine pathways. In AD, the disruption between the sympathetic and parasympathetic nervous systems aggravates the microbiota dysbiosis and impairs the intestinal barrier. Furthermore, AD-associated inflammation hyperactivates the HPA axis, amplifying both central and peripheral inflammatory responses. In summary, gut dysbiosis influences AD pathogenesis; meanwhile, the progression of AD reciprocally aggravates intestinal dysfunction. Treatment works on the gut-brain axis, having shown potential in mitigating AD progression. Strategies such as microbiome modulation, FMT, and nutritional interventions can reshape gut microbial composition, reduce systemic inflammation, and influence neurodegenerative pathways, thereby alleviating the onset and progression of AD (96).

## Gut-Brain Axis and Other Brain Disorders

### Epilepsy

Epilepsy is a highly prevalent neurological disorder, affecting over 70 million individuals worldwide (97, 98). Despite advancements in treatment, nearly 30% of epilepsy cases remain drug resistant, necessitating alternative therapeutic strategies. Notably, patients with epilepsy frequently experience gastrointestinal comorbidities, including inflammatory bowel disease (IBD), highlighting a potential gut-brain connection (99). A growing number of studies have revealed that immune dysregulation and neuroinflammation within the gut-brain axis are essential for epilepsy pathogenesis (100). Additionally, the ANS, particularly the vagus nerve, has been reported to modulate epileptic seizures (101). Dysbiosis-induced alterations in gut microbiota composition, endocrine signaling, neurotransmitter balance, and SCFA production may influence seizure susceptibility and disease progression (102). Microbiome-targeted therapies have gained attention as potential adjunctive treatments for epilepsy. Interventions such as probiotic supplementation, FMT, antibiotic therapy, and ketogenic dietary regimes have demonstrated promising benefits through gut-brain axis modulation (103, 104). Further exploration of gut-brain interactions in epilepsy may facilitate the research and development of novel drug targets, enabling more effective and personalized treatment approaches.

### Stroke and Brain Injury

Stroke, clinically defined as a cerebrovascular accident, is a severe neurological event caused by either an obstruction of cerebral blood flow (ischemic stroke) or intracranial hemorrhage (hemorrhagic stroke). As the second most common cause of death and the third most common cause of disability worldwide, stroke is associated with high incidence, recurrence, and mortality rates (105, 106). Beyond direct brain injury, stroke triggers systemic immune responses, disrupts homeostasis, and alters gut function. Recent studies have demonstrated that the gut microenvironment is vital for the pathophysiology of stroke and that regulation of the gut-brain axis may be an innovative strategy for stroke prevention and treatment (107, 108). The gut-brain axis regulates stroke pathology through four primary mechanisms: intestinal epithelial barrier (IEB), gut microbiome, gut immune system, and ENS.

The IEB serves as both a physical and immunological barrier, composed of epithelial, goblet, Paneth, and enterochromaffin cells, which collectively maintain intestinal integrity (109, 110). These cells secrete mucus, antimicrobial peptides, and immune mediators

to protect against pathogenic invasion and maintain gut homeostasis (111, 112). Structural integrity is dependent on apical junction complexes, which include tight junctions, adherent junctions, and desmosomes (113). Stroke-induced IEB disruption increases intestinal permeability, leading to villus atrophy, mucus depletion, and tight junction dysfunction (114–116). The disruption ultimately leads to microbial translocation, where gut microbiota and microbial components breach the IEB, enter extra-intestinal organs, and exacerbate neuroinflammation (117, 118). Stroke-associated infections further impair neurological recovery, emphasizing the critical function of gut integrity in stroke prognosis (51).

The gut microbiome is a complex ecosystem that regulates digestion, metabolism, immune function, and intestinal homeostasis (119). Beyond gastrointestinal roles, the gut microbiota also contributes to IEB integrity, epithelial cell proliferation, differentiation, and migration, mucus secretion, antimicrobial peptide gene expression, and tight and adherent junction function (116, 120). Stroke can significantly alter gut microbial composition, reducing microbial diversity while shifting the balance of key bacterial populations. Poststroke changes include reduced *Bacteroides* and *Prevotella* abundance, altered SCFA production, and increased inflammatory cytokines, all of which contribute to neuroinflammation (117, 121, 122). Notably, gut dysbiosis exacerbates stroke outcomes by promoting systemic immune activation and BBB permeability (120, 123–125). In conclusion, therapeutic strategies aimed at the gut microbiome, such as FMT, antibiotics, prebiotics, and probiotics therapy, have shown potential in stroke prognosis, neurological recovery, and injury repair.

As the largest immune organ, the gut-associated lymphoid tissue (GALT) is essential for human health and immune function, comprising Peyer's patches, mesenteric lymph nodes (MLN), isolated lymphoid follicles (ILF), and intraepithelial lymphocytes (IEL) (126). Lymphocytes within the gut-associated lymphoid tissue, including T cells, B cells, and macrophages, migrate to the peripheral circulation, triggering immune responses before undergoing lymphatic homing to return to the gut. Dendritic cells within isolated lymphoid follicles process intestinal antigens and provide them to secondary lymphatic tissues, thereby initiating adaptive immune reactions (127). Beyond maintaining intestinal immunity, gut-derived immune cells influence systemic inflammation and neurological outcomes, particularly in stroke. Following a stroke, immune cells from the gut move to the brain, leading to poststroke neuroinflammation and influencing disease progression (128). Additionally, stroke-induced immune dysregulation leads to a reduction of B cells and dendritic cells, weakening systemic immunity and increasing susceptibility to infections (129).

The ENS functions as an autonomous neural network, regulating gastrointestinal motility, digestive

fluids, and mucus secretion, local blood flow, and immune and endocrine signaling (130, 131). The ENS communicates extensively with the gut microbiota, microbial metabolites, nutrients, immune cells, stromal components, and epithelial cells, collectively maintaining intestinal homeostasis (132, 133). Emerging evidence suggests that stroke profoundly influences gut physiology, disrupting gut barrier integrity, microbial composition, and immune responses. Notably, stroke-induced alterations in the ENS may contribute to intestinal dysmotility, impaired nutrient absorption, and gut-driven neuroinflammation, although the precise mechanisms remain incompletely understood, requiring further research.

Brain injury encompasses both acute cerebrovascular events (stroke) and traumatic brain injury, the latter of which results from external mechanical forces and exhibits chronic, progressive pathology. Both types of brain injury are associated with inflammatory changes and gut dysbiosis, reinforcing the gut-brain axis as a key regulator or promising therapeutic intervention for disease prevention, intervention, and recovery.

## Gut-Brain Axis and Metabolic Disorders

### *Irritable Bowel Syndrome and Inflammatory Bowel Disease*

Gastrointestinal diseases remain a significant source of mortality and morbidity (134), with chronic intestinal disorders contributing substantially to global health burdens (135). Among these, IBD and irritable bowel syndrome (IBS) represent two distinct yet interconnected conditions, both of which involve gut-brain axis dysregulation and are often accompanied by psychological comorbidities and impaired quality of life (136). IBS is a functional gastrointestinal disorder characterized by abdominal pain, diarrhea, and discomfort are key components (137). In contrast, IBD includes a range of chronic inflammatory disorders, which lead to structural damage in the gastrointestinal tract. Notably, many IBS and IBD patients present with inflammation as well as anxiety- and depression-related disorders (138). Growing studies demonstrate that gut-brain axis dysfunction is a core driver in the pathogenesis of IBS and IBD (139–141), with several factors exacerbating disease severity. CNS hypervigilance, sleep disturbances, and visceral hypersensitivity have been implicated in IBS progression (142). Additionally, the VN has been identified as a key regulator of IBD, exerting anti-inflammatory effects via the cholinergic pathway and improving mood disorders (138), highlighting its potential as a promising approach for IBD treatment. Beyond vagal signaling, the gut microbiota, neurotransmitters, and immune cytokines facilitate reciprocal communication between the gut and brain, influencing IBS/IBD onset and progression (143, 144). Psychological

interventions and antidepressant therapies have demonstrated efficacy in both IBS and IBD, offering a chance to diminish healthcare burdens and enhance living quality.

### *Nausea and Vomiting*

Nausea and vomiting are widespread gastrointestinal disorders mediated by both the gut and brain (145). These responses can be triggered by various factors, including toxins, bacterial and viral infections, fungal pathogens, medications, chemotherapy, pregnancy, and motion sickness (146). Clinical and experimental investigations showed that autonomic pathways, especially the VN, are vital for the regulation of nausea and vomiting (147, 148), with neurotransmitters, 5-HT<sub>3</sub>, dopamine (D2), and histamine (H1) identified as primary mediators of emetic responses (149). More recent findings indicate that the direct involvement of the gut-brain axis in toxin-induced nausea (150), with intestinal toxin signals transmitted to the dorsal vagal complex (DVC) Tac1 neurons via vagal Htr3a neurons (150). In the future, research into the gut-to-brain axis is anticipated to develop new antiemetic drugs or personalized antiemetic treatments.

### *Obesity*

Obesity is a global epidemic driven by complex metabolic, neurological, environmental, and lifestyle factors. Emerging findings support that the gut-brain axis and obesity exhibit bidirectional interactions, which act as essential mediators in energy regulation and metabolic homeostasis. The interactions between obesity and the gut-brain axis occur through multiple pathways, including the vagal afferent system, spinal afferent pathways, and systemic circulation (151, 152). Clinical studies have already leveraged gut-brain communication for obesity treatment through interventions such as gut hormone-based therapies and neuromodulation approaches (153). Furthermore, gut microbes and their metabolites have been shown to contribute to obesity pathophysiology by modulating host metabolism, inflammation, and nutrient absorption through the gut-brain axis (154). Thus, the microbiota-gut-brain axis is a promising target for obesity treatment (155). Notably, intestinal fat absorption is directly regulated by the brain. Recent research has identified that the DMV-vagus-jejunum axis plays a primary role in fat absorption and weight maintenance (156). Enhanced insights into the gut-brain axis in obesity could accelerate the development of more powerful approaches for treating obesity and metabolic disorders.

### *Overeating Disorders and Anorexia Nervosa*

Overeating disorders (ODs) are a class of neuropsychiatric conditions characterized by compulsive

**Table 1. Gut-brain axis mechanisms in diseases**

Diseases	Key Gut-Brain Mechanisms
<b>Neuropsychiatric diseases</b>	
Anxiety and depression	<ul style="list-style-type: none"> <li>• VN</li> <li>• Immune system</li> <li>• BBB integrity</li> <li>• Gut microbiota</li> <li>• Metabolites, e.g., 4EPS</li> </ul>
Schizophrenia	<ul style="list-style-type: none"> <li>• Immune system</li> <li>• Gut microbiota</li> <li>• Metabolites, e.g., kynurenine-kynurenic acid, SCFAs, and serotonin</li> </ul>
Autism spectrum disorder	<ul style="list-style-type: none"> <li>• Gut Microbiota</li> <li>• Metabolites, e.g., SCFAs, LPS, metal ions, cofactors, and vitamins</li> </ul>
Bipolar disorder	<ul style="list-style-type: none"> <li>• VN</li> <li>• ENS</li> <li>• Gut hormones, such as GLP-1, PYY, GABA, adipokines, and CCK</li> </ul>
<b>Neurodegenerative diseases</b>	
PD	<ul style="list-style-type: none"> <li>• VN</li> <li>• Immune system</li> <li>• Gut microbiota</li> <li>• Metabolites</li> </ul>
AD and dementia	<ul style="list-style-type: none"> <li>• Gut microbiota</li> <li>• Metabolites</li> <li>• Neurotransmitter</li> </ul>
<b>Brain disorders</b>	
Epilepsy	<ul style="list-style-type: none"> <li>• ANS</li> <li>• Gut microbiota</li> <li>• Metabolites</li> <li>• Neurotransmitter</li> </ul>
Stroke and brain injury	<ul style="list-style-type: none"> <li>• Gut microbiota</li> <li>• Metabolites</li> <li>• Neurotransmitter</li> </ul>
<b>Metabolic diseases</b>	
IBS and IBD	<ul style="list-style-type: none"> <li>• VN</li> <li>• Immune system</li> <li>• Gut microbiota</li> <li>• Metabolites</li> <li>• Neurotransmitter</li> </ul>
Nausea and vomiting	<ul style="list-style-type: none"> <li>• VN</li> <li>• Neurotransmitter, e.g., 5-HT<sub>3</sub>, D2, and H1</li> </ul>
Obesity	<ul style="list-style-type: none"> <li>• VN</li> <li>• Gut microbiota</li> <li>• Metabolites</li> </ul>
ODs and AN	<ul style="list-style-type: none"> <li>• VN</li> <li>• Gut microbiota</li> <li>• Metabolites</li> </ul>

AD, Alzheimer’s disease; AN, anorexia nervosa; ANS, autonomic nervous system; BBB, blood-brain barrier; CCK, cholecystokinin; D2, dopamine; ENS, enteric nervous system; GLP-1, glucagon-like peptide-1; H1, histamine; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; ODs, overeating disorders; PD, Parkinson’s disease; PYY, peptide YY; SCFAs, short-chain fatty acids; VN, vagus nerve; 4EPS, 4-ethylphenyl sulfate.

consumption of high-calorie foods, primarily triggered by dieting and psychological stress (157). Increasing findings demonstrate that gut-brain axis dysfunction acts as a core regulator in driving binge-eating behaviors. Dieting combined with stress alters gut microbiota composition, leading to reduced probiotics and kynurenic acid levels. These changes excite the gut-vagal-NTS-paraventricular thalamus neural circuit, reinforcing cravings for highly palatable foods and promoting binge-eating behavior (158).

Anorexia nervosa (AN) is now recognized as a serious and complex mental disease characterized by self-imposed starvation, extreme weight loss, and dysregulated appetite perception. Its pathogenesis is mediated by complex interactions among environmental, genetic, and biochemical factors, with growing evidence implicating gut-brain signaling in appetite dysregulation. The gut can transmit hunger and satiety signals to the brain via neural and hormonal pathways (159). Investigations have indicated that the changes

in gut microbiota and microbial metabolites can initiate the pathogenesis of AN (160), highlighting the critical role of the gut-brain axis in treating AN (161). Considering the pivotal role of microbiota in neurotransmitter production and appetite control, probiotics and microbiome-targeted therapies may offer novel strategies for managing and treating eating disorders (162).

GLP-1 is widely recognized for its role in appetite suppression, weight loss, and glucose regulation. The connection of endogenous GLP-1 and the gut-brain axis in appetite regulation and metabolism regulation has been extensively characterized. GLP-1, secreted by ileal L cells, transmits metabolic information through circulation and vagal afferent pathway to the CNS. At the same time, central GLP-1 signaling can modulate peripheral physiological functions via ANS (163). Additionally, intestinal GLP-1-induced gastric distension activates the brain through the spinal afferent pathway (164). Collectively, central and peripheral GLP-1 signaling regulates homeostasis through independent gut-brain circuits.

## Conclusions and Future Perspectives

Accumulating evidence has demonstrated that gut-brain interactions are essential for maintaining homeostasis and overall health, while their disruption is linked to various disease processes (FIGURE 2). Impairments in this regulatory network have been linked to neuropsychiatric, neurodegenerative, and metabolic disorders, yet many underlying biological mechanisms are still incompletely understood. This comprehensive review highlights the role of gut-brain interactions in disease pathophysiology and explores the potential therapy for disease treatment (Table 1). Although gut-brain communication is inherently bidirectional, this review mainly discussed the impact of the gut-brain axis on diseases. Comprehensive studies are warranted to delineate disease-specific mechanisms and to create microbiome-based, neuroimmune, and gut-targeted interventions. Future work is required to decode how gut signals influence neuroinflammation and protein aggregation in neurodegenerative diseases, develop targeted treatment for gut-brain related diseases and translate them to clinical applications, and elucidate the sex-specific differences in gut-brain signaling, particularly sex hormone-related gut-brain communication. ■

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J.C. and Y.X. prepared figures; J.C. drafted manuscript; J.C., Y.X., and P.C. edited and revised manuscript; J.C., Y.X., and P.C. approved the final version of manuscript.

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