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The Gut–Brain Axis in Gastrointestinal Disorders: A Comprehensive Review

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Abstract

The gut–brain axis (GBA) is a bidirectional communication network integrating neural, endocrine, immune and microbial signals between the gastrointestinal (GI) tract and the central nervous system (CNS). Once regarded chiefly as a regulator of motility and secretion, the GBA is now recognised as a central pathophysiological driver across the spectrum of GI disease — from functional conditions such as irritable bowel syndrome (IBS) and functional dyspepsia (FD) to organic disorders including inflammatory bowel disease (IBD), gastro-oesophageal reflux disease (GERD), gastroparesis, chronic constipation, coeliac disease, non-alcoholic fatty liver disease (NAFLD) and GI cancers. The Rome V update (2026) formally consolidates functional GI disorders as *disorders of gut–brain interaction* (DGBI), acknowledging dysregulated gut–brain signalling in their pathogenesis. This review synthesises current evidence on GBA mechanisms across major GI disorders, highlighting shared pathophysiological pathways — dysbiosis, barrier failure, visceral hypersensitivity, neuroimmune activation and altered serotonergic and hypothalamic–pituitary–adrenal (HPA) signalling — together with disease-specific perturbations and evolving axis-directed therapeutics [1].

Keywords: gut–brain axis; microbiota; disorders of gut–brain interaction; irritable bowel syndrome; inflammatory bowel disease; GERD; functional dyspepsia; gastroparesis; constipation; coeliac disease; NAFLD; colorectal cancer; visceral hypersensitivity; vagus nerve; dysbiosis; probiotics; faecal microbiota transplantation

Introduction

The gut–brain relationship has been recognised since William Beaumont documented emotional influences on gastric secretion, but only in the past two decades have microbiome science, neuroimaging and immunology revealed the full complexity of this network. The GBA links the enteric nervous system (ENS), autonomic nervous system, HPA axis, mucosal immune system and gut microbiome into an integrated signalling architecture governing both GI physiology and CNS function [2,3,4].

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GI disorders affect more than one-third of the global population at any time. The traditional binary separating "organic" from "functional" disease has been progressively replaced by the DGBI framework, which recognises that altered gut–brain signalling, visceral hypersensitivity, immune dysregulation and microbiome perturbation are central to virtually all GI conditions [1,5]. This review examines the anatomical and molecular underpinnings of the axis, then addresses its dysregulation across IBS, IBD, FD, GERD, gastroparesis, chronic constipation, coeliac disease, NAFLD and GI cancers.

Anatomy and Physiology of the Gut–Brain Axis

Structural components

Enteric nervous system. The ENS contains over 100 million neurons in submucosal (Meissner) and myenteric (Auerbach) plexuses spanning the GI tract, governing peristalsis, secretion, blood flow and mucosal immunity largely autonomously — hence the "second brain" — and communicating with the CNS through vagal and spinal afferents [6].

Vagus nerve. The principal conduit for bidirectional signalling; 80–90% of fibres are afferent, relaying microbial metabolite, hormonal and mechanical information to the nucleus tractus solitarius and thence to amygdala, hypothalamus and prefrontal cortex. Efferent traffic regulates motility, secretion and mucosal immunity through the cholinergic anti-inflammatory pathway [7,8].

HPA axis. Corticotropin-releasing hormone, ACTH and cortisol translate psychological stress into altered motility, mucosal permeability, secretion and microbial composition [3,9].

Communication pathways

Table 1. Principal channels of gut–brain communication

Pathway	Key mediators	Primary direction	Functional significance
Neural	Vagus nerve, ENS, spinal afferents	Bidirectional	Motility, pain, satiety, mood [10]
Endocrine	Cortisol, GLP-1, ghrelin, PYY, CCK, 5-HT	Gut → brain (systemic)	Appetite, stress response, visceral sensation [11]
Immunological	IL-6, IL-1β, TNF-α, GALT, Treg cells	Bidirectional	Neuroinflammation, barrier integrity, mood [12]

Pathway	Key mediators	Primary direction	Functional significance
Microbial metabolites	SCFAs, tryptophan metabolites, bile acids, LPS	Lumen → ENS/BBB	Neuroprotection, neurotransmitter synthesis, BBB integrity [13]

The microbiome as a GBA regulator

The gut harbours some 100 trillion microorganisms of roughly 1,000 species, dominated by Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria [14]. Microbial influence operates through four routes. *Short-chain fatty acids* (butyrate, propionate, acetate) from fibre fermentation modulate barrier integrity, microglial activation and blood–brain barrier (BBB) function [15]. *Serotonin biosynthesis*: 90–95% of body serotonin is produced by enterochromaffin cells, and the microbiota regulate tryptophan availability and its partitioning between serotonin, kynurenine and indole pathways [16,17]. *Neurotransmitter modulation*: gut bacteria produce or regulate GABA, dopamine precursors and acetylcholine [18]. *Immune programming*: gut-associated lymphoid tissue is continuously trained by microbial antigens [19]. Dysbiosis disrupts all four, increasing permeability, promoting systemic inflammation and impinging on CNS function [20].

Barrier integrity

The intestinal epithelium and the BBB operate in parallel as gatekeepers. Dysbiosis degrades tight-junction proteins (claudin, occludin, ZO-1), producing a “leaky gut” that permits lipopolysaccharide (LPS) entry into the circulation; elevated peripheral LPS then increases BBB permeability via TLR4 activation, enabling proinflammatory cytokines to access mood-regulating circuits. The interconnected fragility of both barriers is a unifying theme across GI and neuropsychiatric disease [15].

Disorders of Gut–Brain Interaction: The Evolving Framework

Rome IV (2016) renamed functional GI disorders *disorders of gut–brain interaction*, recognising that altered gut–brain signalling — not merely symptom clusters — defines their pathophysiology. Rome V (2026) extends this with definitions incorporating the gut microenvironment, pharmacogenomics and biopsychosocial factors, generating new diagnostic algorithms and therapeutic approaches [1,5,21]. Shared mechanisms include motility disturbance, visceral hypersensitivity, altered mucosal and immune function, dysbiosis, and altered central processing of gut signals (central sensitisation) [1,5].

Irritable Bowel Syndrome

Epidemiology and clinical features

IBS is the most prevalent DGBI, affecting approximately 11% of the global population. Rome IV defines it as recurrent abdominal pain (≥1 day/week over 3 months) related to defecation and/or change in stool form or frequency, without structural pathology, subtyped as IBS-C, IBS-D, IBS-M and IBS-U. It disproportionately affects women and younger adults [22,23,24].

Pathophysiology

IBS is now understood as a disorder of microbiota–neuroimmune interaction producing GBA dysregulation, through several overlapping mechanisms [25].

Visceral hypersensitivity. Peripheral sensitisation involves mucosal mast cells releasing histamine and tryptase onto nociceptors; central sensitisation involves altered spinal and supraspinal processing with amplified signalling to cortical pain matrices [10,26,27].

Serotonin dysregulation. Enterochromaffin cells release 5-HT, activating intrinsic peristaltic and secretory reflexes and vagal afferents. In IBS-D postprandial plasma 5-HT is elevated, accelerating transit; in IBS-C signalling is blunted. Meta-analysis confirms altered SCFA and 5-HT levels [6,28,29].

Dysbiosis. IBS shows reduced diversity, decreased *Lactobacillus* and *Bifidobacterium*, and increased Proteobacteria. Post-infectious IBS is a compelling model in which documented microbial disruption initiates persistent axis dysregulation, promoting mast cell activation, increased permeability and immune activation [30].

Mucosal immune activation. Increased mast cells, lymphocytes and cytokine expression are consistent biopsy findings; mast cell proximity to enteric nerves is particularly significant [10,24].

Central alterations. Neuroimaging demonstrates altered salience-network connectivity (insula, anterior cingulate), impaired descending pain inhibition and grey-matter changes in emotion-regulating regions [23,31].

Psychosocial factors. Anxiety, depression, early-life adversity and stress worsen symptoms; stress activates the HPA axis, increases permeability and alters microbial composition, creating a self-reinforcing cycle [9,32].

Overlap syndromes

IBS overlaps substantially with other DGBI (FD, GERD, chronic constipation) and with fibromyalgia, chronic pelvic pain, temporomandibular disorder and fatigue syndromes — formalised in the Rome Overlap Working Team Report and reinforcing shared axis pathophysiology [33].

Management

Table 2. Symptom- and mechanism-directed therapy in IBS [23]

Category	Examples	Target mechanism
Dietary	Low-FODMAP diet, soluble fibre	Reduce fermentation, normalise transit
Probiotics	*Bifidobacterium infantis*, *Lactobacillus* spp.	Restore dysbiosis, modulate 5-HT
Antispasmodics	Mebeverine, hyoscine	Visceral smooth muscle relaxation
Secretagogues	Linaclotide, lubiprostone	Increase intestinal fluid (IBS-C)
5-HT modulators	Alosetron (IBS-D), prucalopride	Normalise serotonin-mediated transit
Neuromodulators	Low-dose tricyclics, SSRIs	Central pain modulation, mood
Psychological	CBT, gut-directed hypnotherapy	Central sensitisation, stress reactivity

Inflammatory Bowel Disease

Crohn’s disease (CD) and ulcerative colitis (UC) are chronic relapsing disorders driven by dysregulated mucosal immunity in genetically predisposed individuals. Although structural pathology is present, axis dysfunction is a key determinant of both GI and neuropsychiatric burden [34].

Neuroimmune interface. Chronic inflammation upregulates neurogenic mediators (substance P, VIP, CGRP) and remodels ENS architecture, contributing to altered motility, visceral pain and IBS-type symptoms persisting into remission [35,36].

Gut–immune–brain axis. Proinflammatory cytokines (TNF-α, IL-1β, IL-6) generated in the inflamed gut cross a compromised BBB to activate microglia and astrocytes, producing neuroinflammation that affects mood circuits [7,35].

Dysbiosis. IBD shows depletion of *Faecalibacterium prausnitzii*, *Bacteroides* and *Prevotella* with expansion of Proteobacteria and *Campylobacter concisus*. Loss of *F. prausnitzii* reduces butyrate production, impairing epithelial integrity and anti-inflammatory signalling [7,37].

HPA axis and stress. Stress-induced cortisol elevation impairs barrier function and modulates innate immunity; in experimental colitis, HPA hyperactivation sustains inflammation during remission, while glucocorticoid dysregulation drives synaptic remodelling implicated in depression [12].

Neuropsychiatric comorbidity. IBD carries the highest psychiatric comorbidity of any GI disorder. A 2025 global meta-analysis of more than 150,000 person-years reported 35.7% anxiety and 15.7% depression prevalence [38]; risk is elevated approximately 1.4-fold versus controls and peaks in the first post-diagnosis year, with CD particularly affected (anxiety HR 1.38; depression HR 1.36). Neuroimaging shows reduced grey matter in insula, thalamus, hippocampus, amygdala and prefrontal cortex, correlating with disease duration and activity. The relationship is bidirectional: psychiatric symptoms independently predict flares, greater glucocorticoid requirement, treatment escalation and hospitalisation [7]. Under chronic inflammation, cytokine-induced indoleamine 2,3-dioxygenase redirects tryptophan toward kynurenine, depleting serotonin while generating neurotoxic metabolites capable of crossing the BBB [7].

Therapeutics. Biologics targeting TNF-α (infliximab, adalimumab) and interleukins (ustekinumab, vedolizumab) reduce both inflammation and neuropsychiatric symptoms by interrupting cytokine-driven axis disruption. Neuromodulators address central sensitisation and mood simultaneously; duloxetine with anti-TNF-α therapy targets peripheral inflammation and central monoamine reuptake together. A 2023 multicentre trial of non-invasive vagus nerve stimulation reported significant anxiety improvement in 58% of recipients [7]. Faecal microbiota transplantation (FMT) shows promising Phase II data [39], and adjunctive brain–gut behavioural therapy improves both disease activity indices and psychological burden [12,37].

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Functional Dyspepsia and Gastroparesis

Functional dyspepsia

FD comprises persistent or recurrent epigastric symptoms — postprandial fullness, early satiation, epigastric pain or burning — without structural explanation, subdivided into postprandial distress syndrome and epigastric pain syndrome [40,41]. Contributing perturbations include delayed gastric emptying in 25–35% of patients, reflecting ENS and vagal dysfunction; impaired gastric accommodation driven by dysregulated serotonergic and nitrergic signalling, causing excessive antral distension; duodenal low-grade eosinophilia and mast cell infiltration sensitising afferent nerves; microbiome alteration, with *Helicobacter pylori* documented in 30–40% of cases and eradication relieving symptoms in a subset; and central sensitisation, with activation of emotion-regulating regions on duodenal distension [40]. FD overlaps with IBS in 25–40% of patients and with GERD; a 2025 study found the brain-to-gut pathway predominates in isolated IBS and FD whereas gut-to-brain disturbance dominates in FD/IBS overlap [42,43].

Gastroparesis

Gastroparesis is delayed gastric emptying without mechanical obstruction, most commonly diabetic, idiopathic or post-surgical [44]. Vagal efferent dysfunction impairs accommodation and antral motility; in diabetes, chronic hyperglycaemia damages both the vagus and the interstitial cells of Cajal (ICC), whose loss disrupts the gastric slow wave and produces disorganised peristalsis. Macrophage infiltration and oxidative stress in the myenteric plexus damage inhibitory nitrergic neurons, impairing pyloric relaxation, while gastric dysbiosis promotes stasis and immune activation [44]. Management combines small low-fat meals, prokinetics (metoclopramide, domperidone, erythromycin), gastric electrical stimulation in refractory disease, and emerging neuromodulation approaches [40].

Gastro-oesophageal Reflux Disease

GERD is defined by troublesome symptoms or mucosal injury from gastric reflux. Although traditionally attributed to lower oesophageal sphincter dysfunction, contemporary evidence assigns a critical role to axis dysregulation: a large proportion of symptoms — particularly those persisting despite acid suppression — reflect peripheral and central sensitisation of oesophageal afferents, so that in hypersensitive oesophagus physiological reflux events generate disproportionate pain, analogous to IBS visceral hypersensitivity [45]. Oesophageal dysbiosis, with Gram-negative anaerobes displacing Gram-positive aerobes, correlates with

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mucosal inflammation and altered ENS signalling [46]. Neuroendocrine profiling indicates brain-to-gut predominance in GERD, IBS and FD, and anxiety, depression and somatisation strongly predict symptom severity and treatment non-response [43]; GERD and FD co-occur frequently, sharing oesophagogastric junction dysfunction, impaired accommodation and central sensitisation [42]. Proton pump inhibitors remain first-line but are limited in hypersensitive oesophagus; neuromodulators, CBT and gut-directed hypnotherapy are effective in refractory cases, with microbiota modulation an emerging adjunct [45].

Chronic Constipation

Chronic constipation (CC) is increasingly understood as a manifestation of brain–gut–microbiome axis dysregulation rather than a simple motility problem [47,48]. Reduced propulsive colonic contractions arise from deficient 5-HT signalling and impaired enteric reflexes [48]. Patients show reduced microbial diversity, decreased *Bifidobacterium*, *Faecalibacterium* and butyrate producers, and increased methanogenic archaea (*Methanobrevibacter smithii*), with excess methane directly slowing transit [47]. Reduced colonic 5-HT release impairs peristaltic reflex initiation; conversely the selective 5-HT4 agonist prucalopride restores propulsive contractions [47]. CC and mood disorders frequently co-occur bidirectionally: depression alters motility via HPA activation and reduced serotonergic tone, while constipation-related discomfort worsens psychological wellbeing [49]. Treatment includes osmotic laxatives, secretagogues (linaclotide, prucalopride), fibre, microbiome-targeted intervention and CBT [47,48].

Coeliac Disease and Non-Coeliac Gluten Sensitivity

Coeliac disease

Coeliac disease (CeD) is a systemic immune-mediated disorder triggered by gluten in HLA-DQ2/DQ8-predisposed individuals, characterised by small-intestinal enteropathy, systemic inflammation and extra-intestinal manifestations [50,51]. Neurological and psychiatric complications are common — gluten ataxia, peripheral neuropathy, epilepsy, headache, cognitive impairment and depression — mediated by antibody cross-reactivity (anti-tissue transglutaminase and anti-gliadin antibodies cross-reacting with neural antigens), dysbiosis that disrupts GBA signalling even before mucosal healing [50], malabsorption of B12, folate, zinc and magnesium impairing neurotransmitter synthesis and myelination, and a proposed gut–liver–brain axis operating through altered bile acid metabolism and hepatic neuroactive metabolites [50]. A 2025 Mendelian randomisation study found a causal association between

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CeD and multiple sclerosis risk (OR 1.19, 95% CI 1.09–1.31) with CCL19 as a key mediator, and a 2026 paediatric review positions CeD as a model of gut–brain autoimmunity [51,52]. Strict gluten-free diet reverses most GBA-mediated neurological complications, with normalisation of serological, neurophysiological and structural findings over time [50].

Non-coeliac gluten sensitivity

Non-coeliac gluten sensitivity — GI and extra-intestinal symptoms (brain fog, fatigue, headache, anxiety) triggered by gluten without CeD serology or enteropathy — is emerging as a distinct GBA-mediated entity. A 2026 study proposed that the microbiome governs immune responses to gluten even in the absence of CeD, with gluten-triggered dysbiosis, neuroinflammation and GBA dysfunction increasing vulnerability to cognitive symptoms [53,54].

Non-Alcoholic Fatty Liver Disease

NAFLD spans simple steatosis, steatohepatitis, cirrhosis and hepatocellular carcinoma, and is now understood through the gut–liver–brain axis [13,55]. Patients show depletion of *F. prausnitzii* and *Akkermansia muciniphila* with enrichment of LPS-producing Gram-negatives; elevated LPS translocating through a disrupted barrier into portal circulation activates hepatic Kupffer cell TLR4 signalling, driving inflammation and steatosis [55,56]. Disrupted GLP-1, FGF19 and bile acid signalling impairs hepatic lipid metabolism and hypothalamic energy sensing, promoting obesity and insulin resistance [13]. Depression and anxiety are elevated, mediated by altered tryptophan metabolism, peripheral cytokines and cortisol dysregulation [55]. Review of the tripartite gut–liver–brain axis identifies FXR and TGR5 agonists, GLP-1 receptor modulators and FGF19 analogues as promising targets [13]. Prebiotics, probiotics, synbiotics, polyphenols and FMT show promise in reducing steatosis [13,57].

Gastrointestinal Cancers

Colorectal cancer

The microbiome is now recognised as a causal contributor to colorectal cancer (CRC) initiation, progression and treatment response, acting through immune, metabolic, neural and endocrine pathways [58]. CRC is characterised by enrichment of *Fusobacterium nucleatum*, pks^{+} *Escherichia coli* and enterotoxigenic *Bacteroides fragilis* with loss of SCFA producers. Colibactin and cytolethal distending toxin directly damage colonocyte DNA, generating mutational signatures identifiable in human CRC genomes [58]; microbial metabolites rewire tumour-infiltrating immune cells toward regulatory T cells and myeloid-derived suppressor

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cells [59]; and tumour cells co-opt enteric and autonomic networks using neurotrophin signals (NGF, BDNF) for perineural invasion, a prognostically adverse feature [19]. A 2025 review mapped the neuroimmune axis in GI cancers, documenting regulation of tumour immunity by serotonin, dopamine, acetylcholine, substance P and VIP, with sympathetic innervation promoting and vagal innervation suppressing tumour growth [60]. Dietary modulation, probiotics, FMT, bacteriophage therapy and engineered live biotherapeutics are under investigation, alongside repurposing of beta-blockers and anticholinergics against neuroimmune pathways [58,60].

Gastric and other GI malignancies

H. pylori remains the dominant risk factor for gastric cancer, driving chronic mucosal inflammation through persistent immune activation, and $CGRP^{+}$ nociceptors regulate tumour immunity in preclinical models [60,61]. Across GI cancers the brain–gut–cancer interface involves autonomic regulation of tumour vascularity and immune infiltration, stress-induced catecholamine release with β2-adrenergic activation of pro-tumorigenic gene expression, and microbiota composition predicting response to PD-1/PD-L1 blockade [62,63].

Therapeutic Strategies Across GI Disorders

Table 3. Gut–brain axis-directed therapeutic strategies

Strategy	Mechanism	Disorders	Evidence
Probiotics/psychobiotics	Restore dysbiosis; modulate 5-HT, GABA, SCFAs	IBS, IBD, FD, CC, NAFLD	Moderate–high (IBS, IBD)
Prebiotics/synbiotics	Increase SCFA producers; enhance barrier	IBS, IBD, NAFLD, CC	Moderate
Faecal microbiota transplantation	Recolonise with donor microbiome	IBD (UC), IBS, NAFLD, CRC	High (UC), moderate (IBS)
Low-FODMAP diet	Reduce fermentable substrate	IBS, FD	High
Gluten-free diet	Reverse gluten-triggered neuroimmune dysregulation	CeD, NCGS	High (CeD)

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Strategy	Mechanism	Disorders	Evidence
5-HT modulators	Normalise motility and visceral sensation	IBS, FD, CC	High
Neuromodulators (TCA, SNRI)	Central pain modulation; anti-inflammatory	IBS, IBD, FD, GERD	Moderate–high
Vagus nerve stimulation	Cholinergic anti-inflammatory pathway	IBD, IBS, gastroparesis	Moderate
CBT / gut-directed hypnotherapy	Central sensitisation; stress–HPA modulation	IBS, FD, GERD, IBD	High
Gastric electrical stimulation	Restore gastric pacemaker function	Gastroparesis	Moderate (refractory)
FXR/TGR5 agonists	Bile acid–gut–liver–brain modulation	NAFLD/NASH	Early clinical
GLP-1 receptor agonists	Neuroendocrine gut–brain signalling	NAFLD, obesity-related GI dysfunction	Moderate–high
Anti-cytokine biologics	Interrupt neuroinflammatory cascade	IBD	High
Nanoparticle delivery	Targeted gut/CNS delivery	IBD, CRC, NAFLD	Preclinical–early phase

Emerging Frontiers

Machine learning applied to gut metagenomics, metabolomics and host genomics is enabling identification of disease-specific microbial signatures and prediction of therapeutic response [64]. The enteric virome and mycobiome remain understudied but are emerging as modulators, with phage therapy against CRC-associated pathobionts under early investigation [58,65]. Rome V introduces pharmacogenomics and biopsychosocial profiling into DGBI management, supporting precision therapy tailored to individual axis dysfunction [1], while the tripartite gut–liver–brain axis is emerging as a framework integrating hepatology, gastroenterology and neuroscience [13]. Engineered psychobiotics are in clinical development for IBS–depression and IBD–anxiety comorbidity [64], while microbially derived outer membrane vesicles and lipid nanoparticles are being developed as precision vehicles capable of crossing both intestinal and blood–brain barriers [13].

Conclusion

The gut–brain axis has moved from physiological concept to foundational framework for understanding gastrointestinal disease. Across functional, inflammatory, metabolic and neoplastic conditions, axis dysregulation manifests through shared mechanisms: dysbiosis, barrier disruption, visceral hypersensitivity, neuroimmune activation and altered serotonergic and HPA signalling. Rome V anchors functional GI disorders formally within this axis, while research increasingly extends axis pathobiology to IBD, NAFLD, coeliac disease and GI cancers. Effective management therefore requires axis-centred, multidisciplinary strategies integrating gastroenterology, psychiatry, nutrition and precision microbiome medicine, with future advances likely to emerge from the convergence of multi-omic profiling, artificial intelligence and nanotechnology.

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