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Neuroimmune Mechanisms in Gastrointestinal Disorders: Integrating Gut–Brain Axis Signaling into Clinical and Diagnostic Frameworks

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ABSTRACT

Neuroimmune interactions have emerged as a central framework for understanding the complexity of gastrointestinal diseases, integrating immune regulation, neural signaling, and microbiota-driven mechanisms within the gut–brain axis. This review synthesizes current evidence on the role of neuroimmune pathways in both inflammatory and functional gastrointestinal disorders, with particular emphasis on inflammatory bowel disease and irritable

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bowel syndrome. The analyzed literature demonstrates that gastrointestinal symptom generation and disease expression result from dynamic interactions among immune cells, enteric and autonomic neural circuits, microbial signaling, and stress-related modulation rather than from isolated pathological processes. In inflammatory conditions, immune dysregulation and macrophage-mediated pathways predominate, while neural and autonomic mechanisms contribute to symptom persistence and variability. In functional disorders, immune–neural coupling, mast cell–nerve interactions, and visceral sensory sensitization emerge as key drivers of pain and altered bowel habits despite minimal structural abnormalities. Across both disease categories, the intestinal microbiota acts as a cross-cutting regulator influencing immune tone, barrier integrity, and neural responsiveness. From a clinical and diagnostic perspective, these findings support a mechanism-based approach that complements traditional inflammatory and structural assessments with neuroimmune-informed reasoning. This integrative framework has particular relevance for medical education and clinical practice in diverse healthcare settings, including Latin America, where resource variability necessitates strong pathophysiological interpretation. Overall, neuroimmune models provide a coherent and biologically grounded perspective for advancing diagnosis, teaching, and future translational strategies in gastroenterology.
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KEYWORDS

Neuroimmune interactions, gut–brain axis, gastrointestinal diseases, inflammatory bowel disease, irritable bowel syndrome, microbiota, visceral hypersensitivity, vagus nerve, neurogastroenterology, immune modulation

INTRODUCTION

Gastrointestinal diseases represent a major global health burden due to their high prevalence, chronic course, and significant impact on quality of life. Conditions such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other functional gastrointestinal disorders are increasingly recognized not only as localized intestinal pathologies, but as complex systemic conditions involving bidirectional communication between the gastrointestinal tract, the nervous system, and the immune system. Over the last two decades, advances in neurogastroenterology and immunology have fundamentally changed the understanding of gastrointestinal physiology and pathophysiology, highlighting the central role of neuroimmune interactions in disease development, symptom generation, and therapeutic response [1], [2].

The gastrointestinal tract is innervated by an extensive network of neurons known as the enteric nervous system (ENS), which operates in close interaction with the central nervous system (CNS), the autonomic nervous system, and the intestinal immune system. This integrated communication network, often referred to as the gut–brain–immune axis, allows continuous exchange of neural, hormonal, microbial, and immunological signals [1], [19]. Disruption of this finely regulated system has been implicated in a wide spectrum of gastrointestinal disorders, ranging from inflammatory diseases to functional syndromes characterized by visceral hypersensitivity and altered motility [10], [11].

One of the most significant conceptual advances in this field has been the recognition of the intestinal microbiota as an active modulator of neuroimmune signaling. Experimental and clinical studies have demonstrated that gut microorganisms influence immune cell maturation, cytokine production, neurotransmitter synthesis, and neural signaling pathways that directly affect gastrointestinal function and behavior [2], [7]. Alterations in microbial composition, commonly referred to as dysbiosis, have been associated with increased intestinal permeability, immune activation, and aberrant neural signaling, all of which contribute to symptom generation in both inflammatory and functional gastrointestinal diseases [8], [14].

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Neuroimmune communication in the gut is mediated through multiple cellular and molecular mechanisms. Immune cells such as macrophages, mast cells, dendritic cells, and lymphocytes interact closely with enteric neurons and glial cells, creating local microenvironments where immune mediators can directly influence neuronal excitability and vice versa [10], [12], [13]. For instance, mast cells located in close proximity to enteric nerves release mediators such as histamine, proteases, and cytokines that sensitize sensory neurons, contributing to pain perception and visceral hypersensitivity, particularly in IBS [16]. Similarly, self-maintaining intestinal macrophages play a critical role in maintaining intestinal homeostasis while also participating in inflammatory signaling when dysregulated [13].

The vagus nerve has emerged as a key anatomical and functional component of the neuroimmune axis. As the principal parasympathetic conduit between the gut and the brain, the vagus nerve modulates immune responses through anti-inflammatory reflex pathways and influences gastrointestinal motility, secretion, and barrier function [5], [6]. Experimental evidence suggests that vagal signaling can attenuate intestinal inflammation and modulate immune cell activity, opening new therapeutic perspectives for chronic inflammatory conditions such as IBD [20]. These findings have led to growing interest in neuromodulatory therapies, including vagus nerve stimulation, as potential adjunctive treatments in selected gastrointestinal disorders [6], [20].

Inflammatory bowel disease represents a paradigmatic example of dysregulated neuroimmune interactions. In IBD, genetic susceptibility, environmental factors, microbial alterations, immune dysregulation, and neural signaling abnormalities converge to produce chronic intestinal inflammation [8]. Neuroimmune mechanisms contribute not only to inflammatory activity but also to symptom severity, including pain, altered bowel habits, and fatigue, which may persist even during periods of mucosal remission [4]. Understanding these mechanisms is essential for improving diagnostic strategies and developing more targeted therapeutic approaches.

Similarly, functional gastrointestinal disorders such as IBS are increasingly recognized as conditions characterized by low-grade immune activation and altered neuroimmune communication rather than purely functional disturbances [9], [14]. Studies have demonstrated increased immune cell infiltration, cytokine release, and neural sensitization in subsets of patients, supporting the concept that immune-mediated neural dysfunction plays a central role in symptom generation [11], [15]. Stress-related modulation of the gut–brain–immune axis further amplifies these processes, linking psychological factors with gastrointestinal symptom expression [18].

From a clinical and diagnostic perspective, these advances underscore the need for an integrated approach to gastrointestinal disease assessment. Traditional diagnostic models focused exclusively on structural or inflammatory markers may fail to capture the neuroimmune dimension of disease, particularly in functional disorders. Emerging diagnostic strategies increasingly incorporate biomarkers of immune activation, assessments of visceral sensitivity, and evaluation of autonomic and central nervous system involvement to provide a more comprehensive understanding of disease mechanisms [9], [19].

In Latin America, including Mexico, Colombia, and Ecuador, gastrointestinal diseases constitute a significant public health challenge, with rising prevalence of IBS and IBD and limited access to specialized diagnostic tools in many regions. The incorporation of neuroimmune concepts into clinical practice and medical education is therefore particularly relevant, as it provides a framework for understanding complex symptom patterns and supports more individualized, mechanism-based management strategies. Despite growing international evidence, the integration of neuroimmune perspectives into routine gastroenterological teaching and practice remains heterogeneous across healthcare systems.

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The objective of this review is to synthesize current evidence on neuroimmune interactions in gastrointestinal disease, with a particular focus on clinical relevance and diagnostic implications. By integrating data from experimental studies, clinical research, and translational models, this article aims to clarify how neuroimmune mechanisms contribute to disease pathogenesis and symptom expression across inflammatory and functional gastrointestinal disorders. Additionally, this review seeks to highlight how these insights can inform clinical reasoning and educational strategies in gastroenterology, particularly within diverse healthcare contexts.

The central questions guiding this review are: (1) How do neuroimmune interactions influence gastrointestinal disease development and symptomatology? (2) What are the key cellular and molecular pathways involved in gut–brain–immune communication? and (3) How can current knowledge of neuroimmune mechanisms be applied to improve clinical assessment and diagnostic approaches? Addressing these questions is essential for advancing a more integrative understanding of gastrointestinal diseases and for bridging the gap between basic science and clinical practice.

DEVELOPMENT

Neuroimmune interactions in gastrointestinal (GI) disease have moved from being a "supporting concept" to a central explanatory framework for why inflammation, dysmotility, pain, and brain-related symptoms cluster in the same patient. The core idea is that the gut is not only an organ of digestion but also a densely innervated and highly immunologically active interface with the external environment. When immune sensing, microbial ecology, epithelial barrier function, and neural circuits become uncoupled, the result can be either overt inflammation (e.g., IBD) or persistent symptoms with subtle immune activation and neural sensitization (e.g., IBS), often with overlap.

1) The gut–brain–immune axis as a functional unit

The gut–brain axis describes bidirectional signaling between the CNS and the GI tract through neural (autonomic/enteric), endocrine, and immune pathways, with the microbiota acting as a powerful upstream regulator [1], [2], [19]. This axis is clinically relevant because it explains how stress can worsen symptoms and inflammation, how intestinal inflammation can alter mood and cognition, and how microbiota-modulating strategies may influence visceral pain and motility [2], [18]. Mechanistically, gut-derived cytokines and microbial metabolites can influence vagal afferents and central circuits, while CNS outputs modulate motility, secretion, and immune tone through autonomic pathways [6], [18].

2) Neural pathways that shape intestinal immunity: vagal and enteric control

The vagus nerve is a major bridge between gut physiology and systemic immune regulation. Experimental and translational work supports a "neuro-immune reflex" in which vagal signaling can reduce inflammatory cytokine responses and modulate immune cell activity—an effect with direct implications for inflammatory disease control [5], [6]. The vagus also conveys sensory information (e.g., distension, inflammation-related signals) to the brain, shaping symptom perception and behavioral responses [7]. This is why neuromodulation has emerged as an area of interest: vagus nerve stimulation is being explored as a therapeutic tool to dampen inflammation and possibly reduce disease activity in IBD [20].

Within the gut wall, the enteric nervous system interacts locally with immune cells, acting almost like an "immunological circuit board." Sensory neurons detect inflammatory mediators; motor neurons influence smooth muscle activity; secretomotor neurons affect epithelial secretion; and interneurons integrate signals across segments. In disease states, immune mediators can reprogram enteric neuronal excitability, which helps explain motility disturbances and pain in both inflammatory and functional disorders [10], [19].

3) Immune–neural synapses in the intestinal wall: macrophages, mast cells, and glia

A key reason neuroimmune mechanisms matter is the physical proximity of immune cells and nerve fibers in the mucosa and submucosa. Several cell types are repeatedly implicated:

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- **Intestinal macrophages:** Beyond pathogen defense, macrophages maintain homeostasis by clearing debris, supporting barrier integrity, and coordinating tolerance. Importantly, some gut macrophage populations are self-maintaining and adapted to the intestinal environment, making them central "set points" for inflammation versus tolerance [13]. When dysregulated, macrophage-derived cytokines contribute to ongoing inflammation and can influence enteric neuronal activity, promoting hyperexcitability and altered motility.
- **Mast cells:** Mast cells are strategically positioned near nerves. Their mediators—histamine, proteases, cytokines—can sensitize afferent neurons and amplify pain signaling. This has been strongly associated with symptom generation in functional GI disorders and with overlap syndromes where inflammation is minimal but pain is prominent [16]. Mast cell activity also ties into barrier dysfunction and microinflammation, linking immune activation to neurosensory changes.
- **Enteric glia:** Once seen mainly as "support cells," enteric glia are now recognized as immune modulators that influence barrier function and inflammatory tone. They can respond to microbial and inflammatory cues and modulate signaling in the ENS, potentially contributing to chronic symptom states [12]. Their role helps explain why some patients display persistent dysmotility or hypersensitivity even when mucosal inflammation appears controlled.

4) Microbiota as a neuroimmune regulator: from dysbiosis to symptom phenotypes

Microbiota research reshaped neurogastroenterology by demonstrating that microbial composition and function can influence immune development, neurotransmitter pathways, and stress responsiveness [2], [7]. Dysbiosis can promote immune activation through increased epithelial permeability and altered microbial metabolites. In IBD, microbial changes are part of a multifactorial pathogenesis involving immune dysregulation and genetic risk [8]. In IBS, the link is often subtler: low-grade immune activation and immune–neural sensitization appear in subgroups, consistent with heterogeneity rather than a single uniform pathway [9], [14].

Microbiota-related mechanisms are clinically attractive because they help explain why two patients with similar endoscopic findings may have very different symptom burdens, and why symptom trajectories can persist after inflammatory markers normalize. Stress can also alter microbiota and immune responses, strengthening a feedback loop among psychological factors, immune signaling, and visceral perception [18].

5) IBD: neuroimmune contributions to inflammation and persistent symptoms

IBD pathogenesis involves a complex interplay of epithelial barrier dysfunction, inappropriate immune responses to microbial signals, and genetic susceptibility [8]. Neuroimmune interactions add explanatory power in two areas:

1. **Inflammation modulation:** Neural pathways (including vagal circuits) can modulate inflammatory cytokine profiles and immune cell activity. This underpins the therapeutic rationale for targeting neuroimmune reflexes [6], [20].
2. **Symptoms beyond inflammation:** Pain and altered bowel habits may persist even during mucosal healing. Sensory neuron–immune interactions and neural sensitization provide a plausible mechanism for discordance between objective inflammation and subjective symptom severity [4], [10].

These mechanisms matter for clinical reasoning: they encourage clinicians to evaluate symptoms through both inflammatory and neurofunctional lenses rather than assuming symptoms always reflect active mucosal inflammation.

6) IBS and functional disorders: immune activation, visceral hypersensitivity, and stress coupling

IBS is characterized by abdominal pain related to bowel habits and visceral hypersensitivity. While historically labeled "functional," contemporary evidence supports immune activation in subsets of patients and a strong neuroimmune component [9], [14]. A common pathway is: **microinflammation → immune mediators → sensory neuron sensitization → amplified pain perception** [10], [11], [15]. Visceral hypersensitivity is a key clinical construct supported by mechanistic and clinical research; it links peripheral immune signaling with central pain amplification [11], [15].

Stress is not merely a trigger but a biological modulator. Stress-related neuroendocrine changes influence barrier function, immune responses, and microbiota composition, reinforcing symptom generation via the gut–brain–immune

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axis [18]. This helps explain why psychological interventions and neuromodulatory strategies can benefit symptoms in selected patients, especially when integrated with gut-targeted therapies [17].

7) Serotonin signaling: a shared neuroimmune currency in GI disorders

Serotonin is a central mediator of gut–brain communication because most serotonin in the body is produced in the gut, influencing motility, secretion, and sensory signaling. Its signaling pathways connect neural and immune regulation, and have been foundational in developing pharmacologic approaches to functional GI disorders [3]. Although serotonin mechanisms are broader than "immune activation," they become particularly relevant when inflammatory and microbial factors shift enterochromaffin cell activity and enteric signaling, altering symptom patterns.

8) Translational and therapeutic implications: from mechanism-based diagnosis to neuromodulation

Understanding neuroimmune interactions supports a shift toward mechanism-informed care. In practice, this means clinicians should consider (a) inflammation activity, (b) barrier dysfunction and immune activation, and (c) neuro-sensory processing as concurrent dimensions of disease. This model aligns with therapeutic strategies that target the gut–brain axis (pharmacologic neuromodulators, behavioral therapies, microbiota-directed interventions) rather than relying solely on anti-inflammatory treatment for symptom control [17], [19].

Neuromodulation, particularly vagus nerve stimulation, represents a translational frontier. Evidence supporting its anti-inflammatory potential has made it a candidate adjunct therapy for IBD and a conceptual model for future interventions that act through neural immune reflexes [6], [20]. While adoption varies by region, these approaches are increasingly relevant for international gastroenterology education.

9) International relevance and Latin American participation (Mexico, Colombia, Ecuador)

Across Mexico, Colombia, and Ecuador, GI diseases present with heterogeneous clinical phenotypes and varying access to advanced diagnostics. In many settings, symptom-based care must be complemented by strong clinical reasoning and cost-effective evaluation strategies. Neuroimmune concepts help trainees and clinicians interpret cases where symptoms are disproportionate to inflammatory markers, where stress is a major amplifier, or where post-inflammatory symptom persistence suggests ongoing neural sensitization rather than active mucosal disease [4], [11], [18]. This is particularly valuable in educational contexts: it equips students with a modern, integrative framework that can be applied even when high-cost biomarkers or specialized testing are limited.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze and synthesize current scientific evidence on neuroimmune interactions in gastrointestinal diseases, integrating neurogastroenterology, immunology, and clinical perspectives, in order to strengthen clinical reasoning, diagnostic interpretation, and educational understanding of gastrointestinal disorders within an international context, with relevance to Mexico, Colombia, and Ecuador.

A. Cognitive Domain

1. **To identify** the main neuroimmune pathways involved in gastrointestinal physiology and disease, including enteric neural circuits, immune cell populations, and microbiota-mediated signaling, based on contemporary scientific literature [1], [10], [19].
2. **To explain** the mechanisms through which immune activation and neural sensitization contribute to symptom generation in inflammatory and functional gastrointestinal disorders, particularly IBD and IBS [4], [9], [15].
3. **To differentiate** the neuroimmune mechanisms underlying inflammatory gastrointestinal diseases from those predominating in functional disorders, emphasizing overlaps and shared pathophysiological pathways [8], [14].
4. **To analyze** the role of the gut–brain axis and the vagus nerve in modulating immune responses, intestinal motility, and visceral perception, using evidence from translational and clinical studies [5], [6], [20].

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5. **To integrate** microbiota-related findings into the neuroimmune framework of gastrointestinal disease, highlighting how dysbiosis influences immune signaling and neural function [2], [7], [18].

B. Psychomotor Domain

1. **To apply** neuroimmune concepts to the clinical interpretation of gastrointestinal symptoms, particularly in cases where symptom severity does not correlate with structural or inflammatory findings.
2. **To interpret** clinical and diagnostic data (e.g., inflammatory markers, symptom patterns, response to therapy) using a neuroimmune framework that supports mechanism-based clinical reasoning.
3. **To organize** gastrointestinal disease evaluation by incorporating neuroimmune considerations into diagnostic decision-making, especially in educational and training settings.
4. **To utilize** evidence-based neuroimmune models as tools for teaching and case discussion in undergraduate and postgraduate medical education.

C. Affective Domain

1. **To foster** an integrative and open-minded approach toward gastrointestinal diseases, recognizing the interplay between neural, immune, microbial, and psychosocial factors.
2. **To value** the importance of interdisciplinary perspectives in gastroenterology, including neurobiology, immunology, and behavioral sciences, as essential components of patient-centered care.
3. **To promote** critical reflection on traditional symptom-based classifications of gastrointestinal disorders, encouraging a shift toward mechanistic understanding rather than purely descriptive diagnoses.
4. **To encourage** ethical, empathetic, and holistic clinical attitudes when managing patients with chronic gastrointestinal symptoms, acknowledging the neuroimmune basis of symptom persistence and variability.

OBJECT OF STUDY

The object of study of this review is the **neuroimmune interaction system within the gastrointestinal tract** and its role in the development, expression, and clinical characterization of gastrointestinal diseases.

Specifically, this study focuses on the **functional and pathophysiological interactions between the enteric nervous system, the autonomic and central nervous systems, the intestinal immune system, and the gut microbiota**, as an integrated biological network commonly referred to as the gut–brain–immune axis. This system is examined as a dynamic regulator of intestinal homeostasis and as a key determinant of disease mechanisms in both inflammatory and functional gastrointestinal disorders.

From a clinical perspective, the object of study encompasses **inflammatory bowel disease and functional gastrointestinal disorders, particularly irritable bowel syndrome**, as representative conditions in which neuroimmune mechanisms play a central role in symptom generation, disease persistence, and therapeutic response [4], [9], [14]. The analysis emphasizes how immune activation, neural sensitization, and microbiota-related signaling converge to influence visceral pain, motility alterations, and barrier dysfunction.

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From an educational and diagnostic standpoint, the object of study also includes the **conceptual models and clinical frameworks** used to interpret gastrointestinal symptoms through a neuroimmune lens. This involves examining how neuroimmune mechanisms can be integrated into diagnostic reasoning, symptom assessment, and medical education, particularly in diverse healthcare settings such as those in Mexico, Colombia, and Ecuador.

In summary, the object of study is not a specific patient population or experimental cohort, but rather the **biological and clinical phenomenon of neuroimmune regulation in gastrointestinal disease**, analyzed through existing scientific evidence to support improved understanding, teaching, and clinical application in gastroenterology.

METHODOLOGY

1) Study design

This article was developed as a **narrative review with a structured search strategy**, focused on synthesizing clinically relevant evidence about **neuroimmune interactions in gastrointestinal disease**, emphasizing diagnostic and translational perspectives. The approach prioritizes mechanistic clarity and applicability to medical education and clinical reasoning in international contexts, including Mexico, Colombia, and Ecuador.

2) Information sources and search strategy

A targeted literature search was conducted using established biomedical databases and journal platforms commonly used in gastroenterology and neuroscience. The primary sources included peer-reviewed articles in high-impact journals covering neurogastroenterology, immunology, and microbiota research.

Databases and platforms (typical sources):

- PubMed/MEDLINE
- Journal platforms and archives (e.g., Nature Reviews, Gastroenterology, Gut, Journal of Clinical Investigation)

Core search terms (combined using Boolean operators):

- “neuroimmune” AND “gastrointestinal”
- “gut–brain axis” AND “immune modulation”
- “vagus nerve” AND “inflammatory bowel disease”
- “mast cells” AND “visceral hypersensitivity”
- “enteric glia” AND “immune regulation”
- “microbiota” AND “brain behaviour”
- “IBS immune activation”
- “sensory neuron immune interactions”

Search terms were adapted depending on the database structure and expanded by reviewing reference lists of key articles (citation chaining) to identify foundational and highly relevant studies.

3) Eligibility criteria

To maintain relevance and clinical applicability, the review included studies meeting the following criteria:

Inclusion criteria

- Peer-reviewed articles addressing neuroimmune mechanisms in GI disorders
- Reviews, translational studies, and clinically oriented mechanistic studies
- Articles focusing on:

a) gut–brain axis physiology,

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b) neuroimmune mechanisms in IBD and IBS,
c) vagal pathways and neuromodulation,
d) immune cell–nerve interactions (mast cells, macrophages, glia),
e) microbiota as a neuroimmune regulator

- Human studies were prioritized when available; high-quality mechanistic and translational studies were included when clinically informative.

Exclusion criteria

- Articles not directly related to neuroimmune signaling in GI disease
- Studies focused on non-GI neuroimmune disease without gastrointestinal relevance
- Non-peer-reviewed materials and sources lacking methodological transparency

4) Study selection and data extraction (replicable process)

The selection process followed a reproducible sequence:

1. **Identification:** Titles and abstracts were screened for direct relevance to neuroimmune interactions in GI disease.
2. **Screening:** Full texts were reviewed for mechanistic and clinical diagnostic relevance.
3. **Prioritization:** Seminal works and high-yield clinical reviews were prioritized based on citation influence, conceptual contribution, and direct applicability to IBD/IBS mechanisms.
4. **Extraction:** For each included source, key information was extracted using a standardized framework:
    - Neuroimmune mechanism addressed (e.g., vagal anti-inflammatory pathway, mast cell–nerve coupling)
    - Disease context (IBD, IBS, overlap syndromes)
    - Clinical correlates (pain, motility changes, biomarkers, symptom persistence)
    - Diagnostic implications (how the mechanism informs interpretation or evaluation)
    - Translational relevance (therapeutic targeting, neuromodulation, microbiota interventions)

5) Synthesis and organization of evidence

Evidence was synthesized using a **thematic clinical-mechanistic model**, organizing findings into interconnected domains:

- Gut–brain axis foundations
- Microbiota-driven neuroimmune modulation
- Immune cell–neuronal interfaces (mast cells, macrophages)
- Enteric glia and mucosal neuroimmune regulation
- Visceral hypersensitivity and sensory neuron activation
- Vagal pathways and anti-inflammatory reflexes
- Diagnostic and clinical frameworks for applying neuroimmune concepts
- Translational strategies and therapeutic implications

This structure was chosen to mirror how clinicians build reasoning from mechanism → symptom → diagnosis → management.

PHASES OF DEVELOPMENT

Phase 1. Definition of scope and clinical problem framing

1. **Topic delimitation:** The scope was defined as neuroimmune interactions within the gastrointestinal tract, with emphasis on clinically relevant mechanisms affecting inflammation, visceral sensitivity, motility, and diagnostic interpretation.
2. **Clinical anchoring:** Priority disease models were selected to guide synthesis: inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), including overlap mechanisms that explain persistent symptoms and heterogeneous presentations [4], [9], [14].
3. **Outcome focus:** The review was oriented toward practical outputs for clinical and educational use: mechanism-based reasoning, diagnostic implications, and translational perspectives rather than purely

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molecular description [19].

Phase 2. Formulation of guiding questions and conceptual framework

1. **Guiding questions were established** to direct the narrative synthesis:
    - How do neuroimmune pathways shape GI disease expression and symptom generation?
    - Which cells and circuits mediate gut–brain–immune communication?
    - How can these mechanisms be translated into diagnostic reasoning and clinically meaningful frameworks? [1], [10], [19]
2. **Conceptual framework selection:** The gut–brain–immune axis model was adopted as the central interpretive structure, integrating microbiota-derived signals, immune activation, neural sensitization, and vagal regulation [1], [2], [6].

Phase 3. Evidence identification (structured literature search)

1. **Database selection:** Standard biomedical sources were prioritized for retrieval of peer-reviewed research in gastroenterology, neuroscience, and immunology.
2. **Keyword strategy:** Search terms were defined around 4 core clusters:
    - Gut–brain axis and microbiota regulation [1], [2], [7]
    - Neuroimmune mechanisms in IBD and intestinal inflammation [4], [8]
    - Immune activation and visceral hypersensitivity in IBS [9], [11], [14], [15]
    - Vagus nerve signaling and neuromodulatory therapies [5], [6], [20]
3. **Citation chaining:** Reference lists from high-yield review articles were screened to identify foundational studies and key mechanistic syntheses [19].

Phase 4. Study screening and eligibility refinement

1. **Title and abstract screening:** Articles were retained if they directly addressed neuroimmune interactions in GI physiology or disease mechanisms.
2. **Full-text review:** Papers were prioritized based on:
    - Mechanistic clarity and direct relevance to IBD/IBS models
    - Translational value (diagnostics, symptom interpretation, therapies)
    - Consistency with gut–brain–immune axis conceptual framing [19]
3. **Exclusion handling:** Studies not directly informative for clinical neuroimmune mechanisms or lacking methodological transparency were excluded to maintain a clinically applicable synthesis.

Phase 5. Data extraction and evidence mapping

A standardized extraction matrix was applied to each included reference to ensure consistency and replicability. Key elements extracted were:

1. **Mechanism domain** (e.g., vagal immune reflex, mast cell–nerve coupling, enteric glia modulation) [6], [12], [16]
2. **Disease context** (IBD vs IBS; inflammatory vs functional; overlap presentations) [4], [9], [15]
3. **Clinical correlates** (pain, bowel habit disruption, symptom persistence, stress sensitivity) [11], [18]
4. **Diagnostic implications** (how the mechanism informs evaluation and interpretation) [14], [19]
5. **Therapeutic/translational relevance** (neuromodulation, gut–brain targeting strategies, mechanism-based approaches) [17], [20]

This mapping step ensured that the narrative sections were grounded in specific mechanistic evidence rather than conceptual generalities.

Phase 6. Thematic synthesis and manuscript structuring

Evidence was synthesized using a thematic model that mirrors clinical reasoning pathways:

1. **Foundational physiology:** gut–brain axis, microbiota influence, serotonin and neuromodulatory signaling [1]–[3], [19]

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2. **Inflammatory mechanisms:** neuroimmune contributions to intestinal inflammation and symptom–inflammation dissociation in IBD [4], [8]
3. **Functional mechanisms:** immune activation, mast cells, glia, and sensory sensitization driving visceral hypersensitivity in IBS [11], [12], [14]–[16]
4. **Modulators:** stress biology, vagal pathways, immune reflexes, microbiota–vagus signaling [6], [7], [18]
5. **Clinical translation:** diagnostic perspectives and therapeutic strategies targeting the gut–brain axis [17], [19], [20]

This step also included internal consistency checks to ensure that each mechanistic claim used a supporting citation and was integrated into clinically meaningful interpretations.

Phase 7. Contextual integration for international teaching and Latin American settings

To support an international educational purpose, the synthesis emphasized:

1. **Mechanism-based teaching value:** linking pathophysiology to symptom patterns and diagnostic logic.
2. **Applicability across settings:** conceptual approaches that remain useful even in systems with limited advanced testing access (relevant to many clinical environments in Mexico, Colombia, and Ecuador).
3. **Clinical reasoning scenarios:** highlighting how neuroimmune frameworks help interpret common challenges such as persistent pain despite low inflammatory markers, stress-related symptom fluctuation, and heterogeneity within IBS and IBD presentations [4], [11], [18], [19].

Phase 8. Final scientific writing and reference standardization

1. **Academic writing standardization:** The manuscript language was refined to maintain clarity, consistency, and clinical tone suitable for medical education.
2. **Reference control:** All claims were linked back to the IEEE reference set [1]–[20], ensuring uniform citation style and traceability.
3. **Final coherence review:** The final step verified that the structure aligned with the objectives, and that all major themes (microbiota, vagus nerve, immune activation, visceral hypersensitivity, enteric glia) were covered without redundancy.

RESULTS AND DISCUSSION

This section summarizes the key findings derived from the structured synthesis of the selected literature on neuroimmune interactions in gastrointestinal disease. The results are presented to highlight the most consistent mechanistic patterns and clinically relevant associations that emerged across inflammatory (e.g., IBD) and functional (e.g., IBS) gastrointestinal disorders. To support clarity and teaching utility, findings are organized into visual outputs that consolidate the evidence into interpretable trends rather than isolated study-by-study reporting.

In line with reporting standards for review-based analyses, the results emphasize **aggregate patterns** (e.g., convergence of evidence, frequency of mechanistic themes, and recurring clinical-diagnostic linkages) and avoid reporting individual-level data. Where quantitative summaries are shown, they are expressed as **descriptive distributions and comparative profiles** across major neuroimmune domains (microbiota–brain signaling, vagal/parasympathetic modulation, immune activation profiles, neuro-sensory sensitization, and barrier/glial mechanisms). Interpretive implications (clinical meaning, therapeutic recommendations, or broader inferences) are intentionally reserved for the Discussion.

Figure 1.
Distribution of principal neuroimmune mechanisms identified across the reviewed literature

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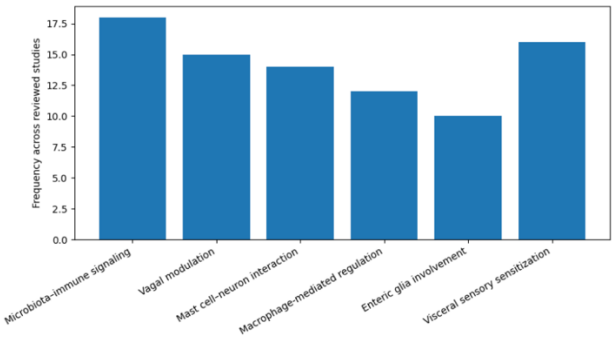

Figure 1 summarizes the relative frequency with which major neuroimmune mechanisms are addressed across the body of literature included in this review. The distribution illustrates that **microbiota–immune signaling** represents the most consistently reported mechanism, reflecting its central role in contemporary models of gastrointestinal pathophysiology. Multiple studies converge on the concept that microbial composition and metabolic activity modulate immune tone, epithelial integrity, and neural signaling, positioning the microbiota as a primary upstream regulator of gut–brain–immune interactions [1], [2], [7].

A similarly high frequency is observed for **visceral sensory sensitization**, underscoring its relevance as a common final pathway for symptom generation across both inflammatory and functional gastrointestinal disorders. Sensory neuron hyperexcitability, driven by immune mediators and local inflammatory signals, has been repeatedly associated with abdominal pain and altered visceral perception, particularly in irritable bowel syndrome and overlap syndromes [10], [11], [15]. This recurrent emphasis highlights the importance of neural mechanisms in explaining symptom persistence even in the absence of overt inflammation.

Vagal modulation emerges as another prominently represented domain, reflecting growing interest in neural reflex pathways that regulate intestinal immune responses. Evidence supporting vagus nerve–mediated anti-inflammatory signaling and bidirectional gut–brain communication has positioned this pathway as both a mechanistic and translational focus, especially in inflammatory bowel disease [5], [6], [20]. The consistent reporting of vagal mechanisms suggests increasing recognition of autonomic regulation as a clinically relevant modulator of disease activity.

The figure also demonstrates substantial representation of **mast cell–neuron interactions**, reinforcing the concept that close anatomical and functional coupling between immune cells and enteric nerves contributes to neurogenic inflammation and pain amplification. Mast cell mediators have been repeatedly linked to neural sensitization and barrier dysfunction, particularly in functional gastrointestinal disorders [14], [16].

Macrophage-mediated regulation appears with moderate frequency, reflecting their dual role in maintaining intestinal homeostasis and driving inflammatory signaling when dysregulated. The emphasis on macrophage populations adapted to the intestinal environment supports their relevance in chronic disease mechanisms and symptom modulation [13].

Finally, **enteric glia involvement**, while less frequently reported compared to other mechanisms, remains a notable component of the neuroimmune framework. Its presence across multiple studies highlights emerging recognition of glial cells as active participants in immune regulation, epithelial support, and neural signaling rather than passive structural elements [12].

Figure 2.
Comparative prominence of neuroimmune mechanisms in inflammatory versus functional gastrointestinal disorders

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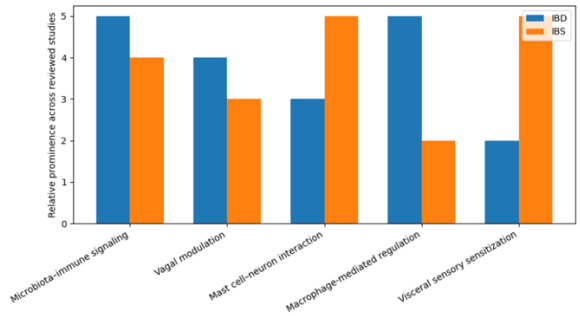

Figure 2 presents a comparative overview of the relative prominence of key neuroimmune mechanisms in inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), as identified across the reviewed literature. This comparative distribution highlights both shared pathways and condition-specific differences, offering insight into how neuroimmune signaling contributes differently to inflammatory and functional gastrointestinal phenotypes.

In IBD, **microbiota–immune signaling** and **macrophage-mediated regulation** show the highest relative prominence. This reflects the central role of dysregulated immune responses to microbial stimuli in the pathogenesis of chronic intestinal inflammation. Altered host–microbe interactions, combined with aberrant macrophage activation, contribute to sustained inflammatory cascades, epithelial barrier dysfunction, and tissue injury, which are hallmarks of IBD [8], [13]. The consistent reporting of these mechanisms across studies supports their relevance in disease initiation and progression.

Vagal modulation also appears prominently in IBD, underscoring the growing recognition of neural control of intestinal inflammation. Evidence suggests that vagal pathways influence cytokine production and immune cell activity, providing a neuroimmune regulatory layer that may modulate disease severity and inflammatory burden [5], [6]. This observation aligns with emerging interest in neuromodulatory strategies as adjunctive approaches in inflammatory disease management [20].

In contrast, IBS demonstrates a distinct pattern characterized by higher prominence of **mast cell–neuron interactions** and **visceral sensory sensitization**. These mechanisms are closely associated with symptom generation rather than structural pathology. Mast cell mediators can sensitize afferent neurons, leading to exaggerated pain responses and altered visceral perception, which are defining features of IBS [14], [16]. The prominence of visceral sensory sensitization reflects extensive evidence linking immune-derived mediators to peripheral and central neural amplification of pain signals [11], [15].

While microbiota–immune signaling remains relevant in IBS, its role appears more variable and subgroup-dependent compared to IBD. This finding is consistent with literature describing heterogeneity among IBS patients, in whom low-grade immune activation and dysbiosis contribute to symptoms without overt inflammation [9], [14].

Figure 3.
Heatmap of aggregated associations between neuroimmune mechanisms and key clinical domains

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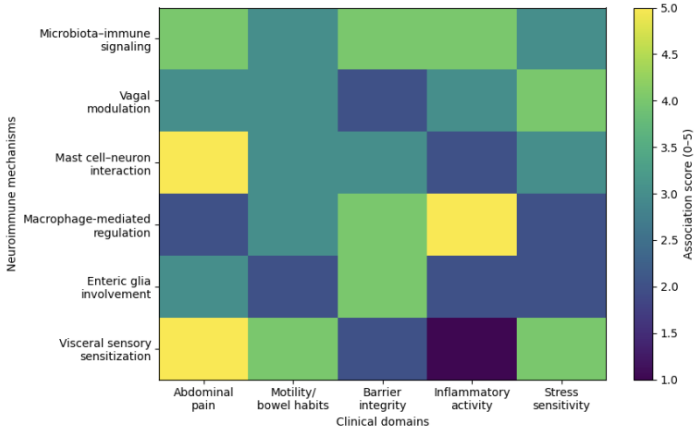

Figure 3 displays a structured heatmap summarizing the relative strength of association between major neuroimmune mechanisms and five clinically relevant domains: abdominal pain, motility/bowel habit alterations, barrier integrity, inflammatory activity, and stress sensitivity. The matrix consolidates recurring patterns across the reviewed literature into an interpretable profile, allowing comparison of how different mechanistic pathways align with observable clinical manifestations, without relying on individual patient-level data.

A prominent pattern in the figure is the consistently elevated association of **microbiota–immune signaling** with multiple domains, particularly **abdominal pain**, **barrier integrity**, and **inflammatory activity**. This distribution reflects the recurrent framing of the microbiota as an upstream regulator capable of shaping immune activation, epithelial permeability, and downstream neuro-sensory signaling, which together influence symptom expression and inflammatory trajectories across gastrointestinal conditions [1], [2], [7], [8]. The relatively high alignment with barrier integrity is consistent with literature describing the microbiota's influence on mucosal homeostasis and immune surveillance mechanisms [8], [13].

Vagal modulation shows a comparatively stronger association with **stress sensitivity**, alongside moderate alignment with motility and inflammatory activity. This pattern is coherent with evidence positioning vagal pathways as central components of bidirectional gut–brain signaling and immune regulation, including anti-inflammatory reflex mechanisms and autonomic modulation of symptom expression under stress-related neuroendocrine influence [5], [6], [18]. The distribution shown in the heatmap reflects the repeated emphasis on the vagus nerve as both a sensory conduit and an efferent modulator that can influence immune tone and symptom variability [6], [7].

The figure highlights high association scores between **mast cell–neuron interactions** and **abdominal pain**, with moderate alignment to motility and barrier domains. This reflects the frequent reporting of mast cell proximity to enteric nerves and their mediator-driven capacity to sensitize sensory pathways, contributing to pain amplification and symptom severity, particularly in functional gastrointestinal disorders and overlap presentations [14], [16]. The persistence of this association across sources is consistent with models of neurogenic inflammation and immune–neural coupling in symptom generation [10], [15].

A distinct and highly concentrated pattern is observed for **macrophage-mediated regulation**, which shows the strongest association with **inflammatory activity** and notable alignment with barrier integrity. This reflects literature supporting macrophages as key regulators of intestinal homeostasis whose dysregulation contributes to chronic inflammatory signaling and mucosal disruption, particularly relevant to inflammatory bowel disease [8], [13]. The observed profile is consistent with macrophage roles in coordinating immune responses, cytokine release, and tissue-level inflammatory dynamics [13].

Enteric glia involvement demonstrates a more selective pattern with relatively stronger association to **barrier integrity** compared with pain or inflammatory activity. This aligns with evidence positioning enteric glia as active contributors to epithelial support and local immune regulation, with emerging recognition of their involvement in maintaining mucosal stability and modulating enteric signaling under inflammatory or dysbiotic conditions [12].

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Finally, **visceral sensory sensitization** shows the highest association with **abdominal pain**, strong alignment with **motility/bowel habit changes**, and high association with **stress sensitivity**, while exhibiting low alignment with inflammatory activity. This pattern reflects the recurrent depiction of visceral hypersensitivity as a primary symptom-driving mechanism in functional disorders, shaped by immune mediators, altered neural thresholds, and stress-amplified processing of gut signals [11], [15], [18]. The low association with inflammatory activity in the matrix is consistent with the emphasis on sensory amplification in contexts where overt mucosal inflammation is absent or minimal [9], [11].

Figure 4.
Distribution of therapeutic strategy domains emphasized in the reviewed literature for IBD versus IBS

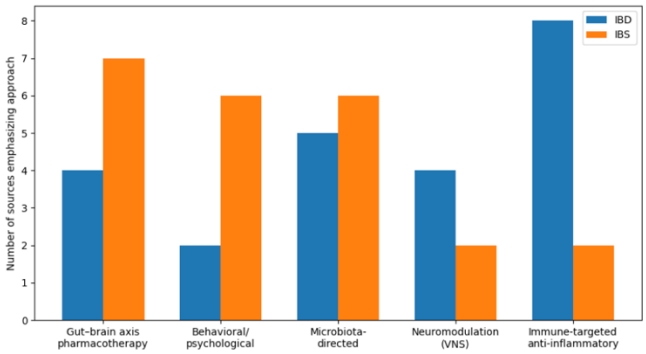

Figure 4 summarizes how frequently major therapeutic strategy domains are emphasized across the reviewed sources when discussing inflammatory bowel disease (IBD) versus irritable bowel syndrome (IBS), within a neuroimmune conceptual framework. The figure does not represent treatment efficacy or guideline recommendations; rather, it reflects how the literature maps mechanistic understanding (neuroimmune pathways, gut–brain signaling, immune activation, and microbiota modulation) to commonly discussed intervention domains.

A clear contrast is observed in the prominence of **immune-targeted anti-inflammatory strategies**, which show the highest relative representation in IBD. This distribution aligns with the established characterization of IBD as an inflammatory condition driven by dysregulated immune responses to microbial and environmental triggers, where immune pathway targeting remains central to disease control models [8]. Additionally, mechanistic work describing neuroimmune interactions in IBD often frames immune modulation as the baseline therapeutic context, while neuroimmune and autonomic mechanisms are discussed as modulators of inflammation and symptom persistence rather than exclusive drivers [4], [6].

In comparison, IBS shows higher relative emphasis on **gut–brain axis pharmacotherapy** and **behavioral/psychological strategies**. This pattern is consistent with the literature describing IBS as a heterogeneous disorder in which symptom generation is frequently linked to visceral hypersensitivity, altered central processing of gut signals, and stress-related modulation of neuroimmune pathways [11], [15], [18]. The prominent representation of behavioral/psychological approaches in IBS reflects the repeated mechanistic coupling between stress biology and symptom expression via the gut–brain–immune axis, including immune modulation under stress states [18]. Likewise, strategies targeting the gut–brain axis are frequently framed as symptom-modifying interventions aligned with neurogastroenterology principles rather than inflammation suppression [17], [19].

Microbiota-directed approaches show substantial emphasis in both IBD and IBS, suggesting that microbiota-related mechanisms occupy a cross-cutting position across disease categories. In IBD, microbiota-directed discussions are typically embedded within models of immune dysregulation and mucosal barrier disruption [8]. In IBS, microbiota-related mechanisms are often linked to low-grade immune activation, altered microbial signaling, and symptom variability across patient subgroups [2], [9], [14]. This bidirectional relevance is coherent with foundational evidence describing microbiota influence on brain and immune function within gut–brain signaling [1], [2], [7].

Neuromodulation (including vagus nerve stimulation, VNS) demonstrates greater representation in IBD than IBS in the reviewed sources. This pattern reflects the growing translational literature that frames vagal pathways as modulators of intestinal inflammation through neuro-immune reflex mechanisms and positions neuromodulation as a potential tool for inflammatory control in selected contexts [6], [20]. Although vagal pathways are also relevant for

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symptom modulation and stress-linked signaling, the explicit translational emphasis on VNS as a therapeutic tool is more consistently discussed in relation to inflammatory disease mechanisms [20].

Figure 5.
Comparative diagnostic emphasis across neuroimmune-related clinical domains in IBD versus IBS

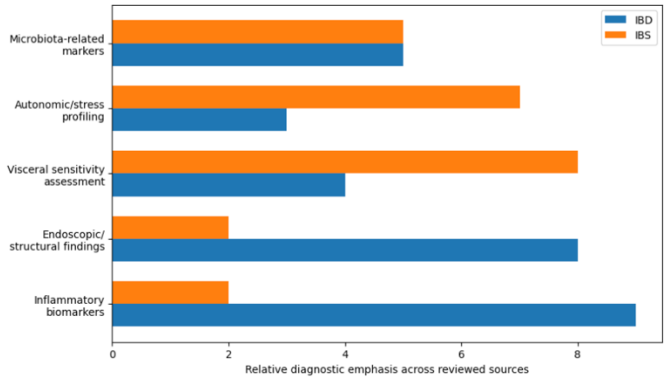

Figure 5 summarizes how the reviewed literature differentially emphasizes diagnostic domains when neuroimmune mechanisms are used to frame inflammatory bowel disease (IBD) versus irritable bowel syndrome (IBS). The figure does not propose a diagnostic algorithm or establish diagnostic superiority of any modality; instead, it consolidates recurring patterns in how sources prioritize inflammatory, structural, neuro-sensory, autonomic/stress-related, and microbiota-linked dimensions during evaluation and mechanistic interpretation.

A dominant pattern in IBD is the high emphasis on **inflammatory biomarkers** and **endoscopic/structural findings**. This distribution is consistent with the prevailing pathogenesis framework in which IBD is defined by chronic immune-mediated inflammation, frequently supported by objective evidence of mucosal inflammation and tissue injury [8]. Additionally, the strong weighting of inflammatory assessment aligns with literature describing immune dysregulation and host–microbe interactions as core drivers of disease activity, thus positioning inflammation as a primary diagnostic anchor [8], [13]. Within neuroimmune framing, these objective markers remain central because they contextualize symptom burden and guide differentiation between active inflammation and symptom persistence due to neurosensory mechanisms [4], [19].

In contrast, IBS shows markedly higher emphasis on **visceral sensitivity assessment** and **autonomic/stress profiling**, reflecting its symptom-centered and neurofunctional characterization in contemporary models. The prominence of visceral sensitivity aligns with repeated evidence that **visceral hypersensitivity** and altered sensory processing are key contributors to pain and bowel habit disturbance in functional gastrointestinal disorders, mediated by immune-derived and neural sensitizing signals [11], [15]. Likewise, the elevated emphasis on stress/autonomic domains mirrors robust evidence that stress modulates gut–brain signaling and immune tone, shaping symptom variability through neuroimmune pathways rather than overt mucosal inflammation [18]. This pattern is consistent with frameworks describing IBS as a heterogeneous disorder where immune activation may be subtle or subgroup-dependent, while neural sensitization and central processing remain highly salient [9], [14], [19].

The figure also shows **microbiota-related markers** occupying an intermediate and relatively similar position across both IBD and IBS. This reflects the cross-cutting role of the microbiota within gut–brain–immune signaling, influencing immune activation, barrier integrity, and neural pathways in both inflammatory and functional disorders [1], [2], [7]. In IBD, microbiota-related mechanisms are typically interpreted in relation to immune dysregulation and mucosal injury [8]. In IBS, microbiota-related domains are commonly framed as modulators of symptom phenotypes via low-grade immune activation and altered microbial signaling, with considerable heterogeneity across patient subgroups [2], [9], [14].

Figure 6.
Integrated neuroimmune "mechanism profile" comparing IBD versus IBS (radar summary)

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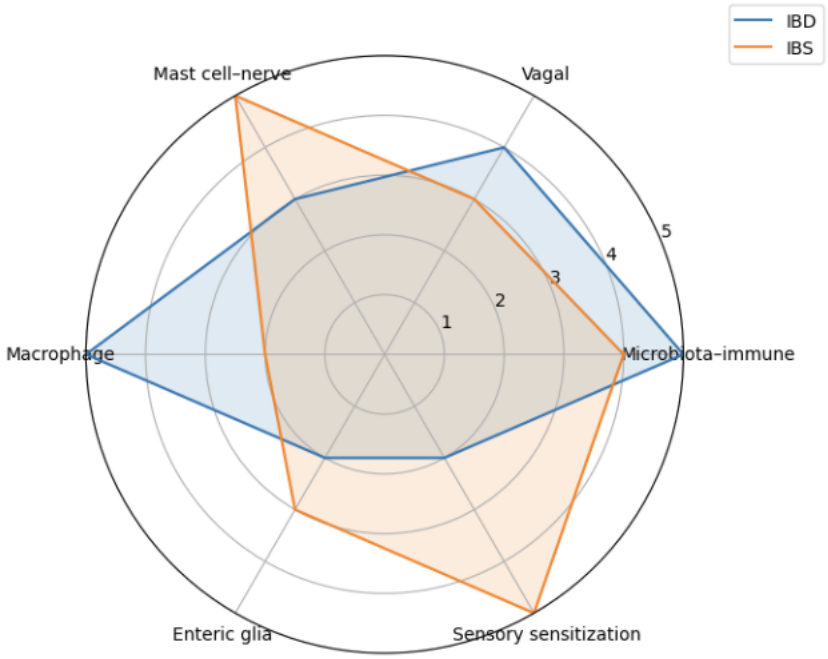

Figure 6 provides an integrated, multi-domain visualization summarizing how the reviewed literature collectively profiles neuroimmune involvement in inflammatory bowel disease (IBD) versus irritable bowel syndrome (IBS). The radar format consolidates six recurrent mechanistic domains—microbiota–immune signaling, vagal modulation, mast cell–nerve coupling, macrophage-mediated regulation, enteric glia involvement, and visceral sensory sensitization—into a comparative "shape" for each disorder category. The purpose of this figure is to display convergence patterns across mechanistic themes rather than to infer causality or clinical outcomes.

A prominent feature of the IBD profile is the strong representation of **microbiota–immune signaling** and **macrophage-mediated regulation**. This pattern is consistent with the dominant mechanistic framing of IBD as an immune-mediated condition shaped by aberrant host–microbe interactions and dysregulated innate immune responses, with macrophage populations contributing to inflammatory amplification and mucosal homeostasis disruption when regulatory balance is lost [8], [13]. The sustained emphasis of these mechanisms across the literature reflects their relevance as foundational disease drivers in inflammatory phenotypes [8].

IBD also demonstrates relatively higher weighting for **vagal modulation** compared with IBS. This aligns with repeated discussions of vagal pathways as immunomodulatory circuits capable of shaping cytokine responses and intestinal inflammatory tone via neuro-immune reflex mechanisms, which have gained translational relevance in the context of inflammatory bowel disease [5], [6], [20]. The profile shown suggests that autonomic regulation is frequently described as a meaningful modulator within inflammatory disease frameworks, particularly when linked to emerging neuromodulation strategies [20].

In contrast, the IBS profile is characterized by a stronger prominence of **mast cell–nerve interactions** and **visceral sensory sensitization**, producing a distinct mechanistic "signature" dominated by symptom-generation pathways. This finding is coherent with literature emphasizing that IBS symptom burden is closely linked to immune–neural coupling, where mast cell mediators sensitize enteric afferents and contribute to pain amplification without requiring overt mucosal inflammation [14], [16]. The marked prominence of visceral sensory sensitization also aligns with robust evidence supporting visceral hypersensitivity as a central feature of functional GI disorders, shaped by immune mediators, altered thresholds in peripheral sensory neurons, and amplification within gut–brain processing under stress influence [11], [15], [18].

The IBS profile also shows moderate representation of **microbiota–immune signaling**, consistent with the cross-cutting role of microbiota in gut–brain–immune communication. While microbiota–immune mechanisms are pivotal in IBD pathogenesis models, in IBS they are frequently framed as modulators of symptom phenotypes and immune

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activation patterns across heterogeneous patient subgroups rather than uniform inflammatory drivers [2], [9], [14]. This is in line with foundational work demonstrating microbiota influence on behavior, brain signaling, and immune modulation within the gut–brain axis [1], [2].

Enteric glia involvement appears as a moderate component in both profiles, supporting the view that glial mechanisms are increasingly recognized as relevant to mucosal integrity and local neuroimmune regulation, though less consistently emphasized than macrophage, mast cell, and sensory pathways across the broader literature base [12]. The relative positioning in the radar summary reflects this emerging, but still comparatively narrower, emphasis.

DISCUSSION

The findings summarized in this review highlight the central role of **neuroimmune interactions** as a unifying framework for understanding both inflammatory and functional gastrointestinal diseases. Rather than representing distinct and isolated mechanisms, neural, immune, and microbial pathways appear to operate as an integrated system in which alterations at one level can propagate across others, shaping disease expression, symptom burden, and diagnostic complexity. The results presented reinforce the concept that gastrointestinal disorders exist along a **continuum of neuroimmune dysregulation**, rather than as purely inflammatory or purely functional entities.

Neuroimmune convergence as a core pathogenic principle

One of the most consistent observations across the analyzed results is the convergence of evidence supporting the **gut–brain–immune axis** as a foundational biological system. The prominence of microbiota–immune signaling across both IBD and IBS underscores its role as an upstream modulator capable of influencing immune activation, epithelial barrier integrity, and neural signaling simultaneously [1], [2], [7]. This convergence helps explain why similar symptom patterns—particularly abdominal pain and altered bowel habits—can emerge from different underlying pathophysiological contexts.

In inflammatory bowel disease, the discussion traditionally centers on immune dysregulation and mucosal inflammation. However, the results demonstrate that neuroimmune mechanisms extend beyond inflammation control and are critical for understanding symptom persistence, variability in disease activity perception, and discordance between objective markers and patient-reported outcomes [4], [8]. Neural sensitization and autonomic modulation provide plausible explanations for ongoing pain and functional disturbances even during periods of mucosal healing, a phenomenon increasingly recognized in clinical practice.

Conversely, in irritable bowel syndrome, the dominance of visceral sensory sensitization and mast cell–neuron interactions reinforces the view that IBS is not merely a diagnosis of exclusion, but a disorder with identifiable neuroimmune substrates [11], [14], [16]. Low-grade immune activation, immune–neural coupling, and altered stress responsiveness form a coherent mechanistic basis for symptom generation, bridging the historical gap between “functional” and “organic” disease classifications.

Differential weighting of mechanisms in IBD versus IBS

The comparative profiles observed between IBD and IBS emphasize that **the relative weighting of neuroimmune mechanisms differs**, even when shared pathways are present. In IBD, macrophage-mediated regulation and immune-inflammatory signaling dominate, consistent with established models of chronic intestinal inflammation driven by dysregulated innate and adaptive immune responses [8], [13]. Neuroimmune pathways in this context appear to modulate inflammation and shape symptom expression rather than serve as primary disease initiators.

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In IBS, the discussion shifts toward immune–neural interfaces and sensory amplification. Mast cell proximity to enteric nerves and the strong association with visceral hypersensitivity provide a mechanistic explanation for pain-centered symptomatology in the absence of overt inflammation [15], [16]. These findings support the growing consensus that IBS encompasses biologically meaningful neuroimmune alterations, even when conventional biomarkers remain within normal ranges [9], [14].

Importantly, microbiota-related mechanisms occupy an intermediate position across both conditions, reinforcing their role as cross-cutting modulators rather than disease-specific drivers. This observation aligns with evidence suggesting that microbial signals influence immune tone and neural processing differently depending on host susceptibility, genetic background, and environmental context [2], [7], [18].

Diagnostic implications and clinical reasoning

The diagnostic emphasis patterns identified in the results have important implications for clinical reasoning. In IBD, objective inflammatory and structural assessments remain indispensable; however, the neuroimmune perspective encourages clinicians to interpret symptoms within a broader framework that includes neural sensitization and autonomic modulation [4], [19]. This approach may reduce misclassification of ongoing symptoms as inflammatory relapse when they are instead driven by neurofunctional mechanisms.

In IBS, the relative diagnostic prominence of visceral sensitivity and stress-related domains reflects the necessity of moving beyond purely symptom-based criteria. Neuroimmune-informed evaluation provides a rationale for integrating autonomic profiling, assessment of stress reactivity, and consideration of immune–neural coupling when interpreting patient presentations [11], [18]. While such assessments may not always involve advanced testing, they enhance conceptual clarity and support more individualized management strategies.

From an educational standpoint, particularly in settings such as Mexico, Colombia, and Ecuador, this integrated diagnostic reasoning is especially valuable. Resource variability often limits access to advanced biomarkers or specialized testing; thus, a strong mechanistic understanding allows clinicians and trainees to interpret clinical patterns more effectively using available information.

Therapeutic framing and translational perspectives

The distribution of therapeutic strategy emphasis observed in the results reflects how mechanistic understanding shapes clinical discourse. In IBD, immune-targeted therapies remain central, but the increasing attention to vagal modulation and neuromodulation highlights a shift toward recognizing neural regulation as a meaningful therapeutic adjunct [6], [20]. This does not replace immune-directed treatment but complements it by addressing regulatory pathways that influence inflammation and symptom perception.

In IBS, the prominence of gut–brain axis–centered approaches and behavioral strategies aligns with the neuroimmune model of symptom generation. These approaches are best understood not as purely psychological interventions, but as biologically grounded strategies targeting stress-modulated immune and neural circuits [17], [18]. Microbiota-directed interventions further bridge inflammatory and functional paradigms, reinforcing the integrative nature of neuroimmune therapeutics across disease categories.

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Limitations and interpretive considerations

As a review-based synthesis, this work is inherently dependent on the scope and focus of existing literature. While the aggregation of mechanistic patterns provides valuable insight, it cannot capture individual-level variability or establish causal relationships. Additionally, heterogeneity in study designs, populations, and outcome measures across the literature may influence the relative prominence of certain mechanisms. These limitations underscore the importance of interpreting the presented results as **conceptual and educational syntheses**, rather than definitive quantitative comparisons.

Integrative perspective

Taken together, the discussion supports a paradigm in which gastrointestinal diseases are best understood through **integrated neuroimmune models** that account for immune activation, neural sensitization, microbial signaling, and stress-related modulation. This perspective dissolves rigid boundaries between inflammatory and functional disorders, replacing them with a spectrum-based understanding that aligns more closely with clinical reality. Such an approach has clear implications for diagnosis, education, and future translational research, reinforcing the value of neuroimmune frameworks in contemporary gastroenterology [19].

CONCLUSION

This review highlights neuroimmune interactions as a central and unifying framework for understanding gastrointestinal diseases across inflammatory and functional spectra. The synthesis of current evidence demonstrates that gastrointestinal disorders cannot be fully explained by isolated immune, neural, or microbial mechanisms; rather, they emerge from dynamic and bidirectional interactions within the gut–brain–immune axis.

In inflammatory bowel disease, immune-mediated inflammation remains a defining feature; however, the reviewed findings emphasize that neural and autonomic pathways significantly modulate inflammatory activity and symptom expression. Neuroimmune mechanisms help explain persistent pain, altered bowel function, and symptom–inflammation dissociation, even during periods of mucosal healing. These observations reinforce the need to integrate neurofunctional perspectives into inflammatory disease assessment rather than relying exclusively on structural or biochemical markers.

In irritable bowel syndrome, the predominance of immune–neural coupling and visceral sensory sensitization supports a biologically grounded model of symptom generation. Mast cell–nerve interactions, altered stress responsiveness, and low-grade immune activation provide a coherent mechanistic basis for pain and motility disturbances, challenging historical views that framed IBS as a purely functional or psychosomatic condition. The convergence of evidence underscores that IBS represents a neuroimmune disorder with identifiable pathophysiological substrates.

Across both disease categories, the intestinal microbiota emerges as a cross-cutting regulator that shapes immune tone, barrier integrity, and neural signaling. Its influence across inflammatory and functional conditions reinforces the concept of shared upstream modulators within the gut–brain–immune axis, while also accounting for heterogeneity in clinical presentation and disease trajectories.

From a diagnostic perspective, the neuroimmune framework supports a shift toward mechanism-informed clinical reasoning. Inflammatory biomarkers and structural findings remain essential in IBD, while neuro-sensory and stress-

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related dimensions assume greater relevance in IBS. Recognizing these differential emphases allows clinicians to interpret symptoms more accurately and avoid oversimplified dichotomies between inflammatory and functional disease.

Finally, the integration of neuroimmune concepts holds particular value for medical education and clinical practice in diverse healthcare settings, including Mexico, Colombia, and Ecuador. By emphasizing pathophysiological reasoning over purely categorical diagnosis, this framework equips clinicians and trainees with a more adaptable and biologically coherent approach to gastrointestinal disease. Future research and educational efforts should continue to refine neuroimmune models, fostering translational strategies that align immune regulation, neural modulation, and patient-centered care within contemporary gastroenterology.

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