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THE GUT–BRAIN AXIS IN MOOD AND ANXIETY DISORDERS: PATHOPHYSIOLOGICAL MECHANISMS, DIAGNOSTIC CHALLENGES, AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Over the past two decades, accumulating evidence has demonstrated bidirectional communication between the gastrointestinal tract and the central nervous system, commonly referred to as the gut–brain axis. This complex network integrates neural, hormonal, immunological, and metabolic pathways and plays a critical role in maintaining both physiological and psychological homeostasis. Increasing attention has been directed toward its involvement in mood and anxiety disorders, which constitute a major global public health challenge.

This narrative review aims to synthesise current human-based research examining gut–brain axis dysfunction in mood and anxiety disorders, with particular emphasis on underlying pathophysiological mechanisms, diagnostic challenges, and emerging therapeutic strategies. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science, focusing on original clinical, neuroimaging, and translational studies published between 2000 and 2025.

The available evidence indicates that alterations in gut microbiota composition, increased intestinal permeability, immune system activation, and changes in microbial metabolite production are consistently associated with depressive and anxiety-related symptoms. Moreover, the high prevalence of psychiatric comorbidity observed in functional and inflammatory gastrointestinal disorders supports the existence of shared biological pathways. Despite significant advances, the clinical translation of gut–brain research remains limited by the lack of standardised diagnostic tools and validated biomarkers.

This review highlights the therapeutic potential of novel interventions, including psychobiotics, dietary modifications, and microbiota-targeted therapies, while emphasising the need for interdisciplinary collaboration and further human studies to support their integration into routine clinical practice.

KEYWORDS

Gut–Brain Axis, Anxiety Disorders, Gut Microbiota, Mood Disorders, Depression, Irritable Bowel Syndrome

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I. Introduction

Mood and anxiety disorders represent a major global health problem and constitute a substantial burden on individuals and healthcare systems worldwide, significantly affecting quality of life, social functioning, and life expectancy. Traditionally, these disorders have been conceptualised primarily as conditions arising from dysfunction within the central nervous system, including alterations in neurotransmitter signalling, neuroendocrine regulation, and neuroplasticity. While this brain-centred framework has contributed to the development of effective pharmacological and psychotherapeutic interventions, it does not fully explain the heterogeneity of clinical presentations or the frequent comorbidity observed in psychiatric practice.

In recent years, growing evidence has challenged this centralised perspective by highlighting the role of peripheral physiological systems in the regulation of emotional and cognitive processes. In particular, the gastrointestinal tract has emerged as a key contributor to mental health through its bidirectional communication with the brain, commonly referred to as the gut–brain axis. This complex network involves interactions between the enteric nervous system, the vagus nerve, immune and inflammatory pathways, microbial metabolites, and neuroendocrine mechanisms, allowing continuous signalling between the gut and the central nervous system.

The human gastrointestinal tract is colonised by trillions of microorganisms collectively known as the gut microbiota. This dynamic ecosystem plays a crucial role in metabolic homeostasis, immune system development, and maintenance of intestinal barrier integrity. Disruptions in microbial composition and function, often described as dysbiosis, have been implicated not only in gastrointestinal diseases but also in a range of neuropsychiatric conditions. Alterations in gut microbiota may influence brain function through

immune activation, changes in intestinal permeability, and modulation of neurotransmitter precursor availability.

Clinical observations provide further support for the relevance of gut–brain interactions in mental health. High rates of depression and anxiety have been consistently reported among individuals with functional gastrointestinal disorders, such as irritable bowel syndrome, as well as inflammatory bowel diseases. Conversely, patients with primary psychiatric disorders frequently report gastrointestinal symptoms in the absence of identifiable structural pathology. These reciprocal associations suggest shared pathophysiological mechanisms rather than coincidental co-occurrence of independent conditions.

Against this background, there is increasing interest in understanding how dysfunction of the gut–brain axis contributes to the development and persistence of mood and anxiety disorders. Improved insight into these mechanisms may help address current diagnostic limitations and inform the development of novel therapeutic strategies that extend beyond traditional brain-focused approaches.

The aim of this narrative review is to synthesise current human-based research examining gut–brain axis dysfunction in the context of mood and anxiety disorders. The review focuses on key pathophysiological mechanisms, diagnostic challenges, and emerging treatment approaches, with the goal of providing an interdisciplinary perspective relevant to both clinical practice and future research.

II. Methodology

This narrative review was designed to compile original research on the relationship between the gut–brain axis and mood and anxiety disorders. A systematic literature search was conducted across the PubMed, Scopus, and Web of Science databases, covering publications from 2000 to 2025.

A broad set of search terms was used, including gut–brain axis, microbiota, depression, anxiety, irritable bowel syndrome, intestinal permeability, vagus nerve, inflammation, psychobiotics, and faecal microbiota transplantation. Only original medical research studies were considered, including randomised controlled trials, cohort studies, case–control studies, neuroimaging studies, and mechanistic human or translational investigations with clear relevance to human physiology and mental health.

Systematic reviews, meta-analyses, editorials, studies limited solely to animal models without application to human medicine, case reports, and conference abstracts were excluded. Studies were initially screened by reviewing titles and abstracts, followed by a full-text assessment of eligible articles.

Due to the diversity of the included studies and their outcomes, the findings were integrated qualitatively rather than through quantitative synthesis. Ethics committee approval was not required, as this review was based exclusively on previously published data.

III. Results

1. The Gut–Brain Axis: Definition and Clinical Relevance

The gut-brain axis forms a complex, bilateral network of interactions. Key components include the enteric nervous system, the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, immune system signalling pathways, and metabolites produced by microorganisms.

Functional neuroimaging studies have provided initial evidence of disruptions in gut-brain communication in humans, as shown in Tillisch's study.

Tillisch demonstrated that consuming a fermented milk product containing probiotics altered activity in brain regions involved in emotion and sensory processing in healthy female participants. Activated parts include the insula and anterior cingulate cortex. This study provided evidence that modulation of the gut environment can influence central neural processing. In patients with IBS, altered emotional regulation and central pain processing have been consistently observed. Mayer et al. demonstrated that IBS patients exhibit increased activation of limbic areas in response to visceral stimuli, supporting the concept of dysfunctional gut–brain signaling in disorders characterised by both gastrointestinal and psychiatric symptoms.

2. Microbiota Alterations in Mood and Anxiety Disorders

Several original human studies have reported alterations in the gut microbiome of individuals with depression and anxiety. Zheng et al. conducted a significant case–control study that revealed that individuals with major depressive disorder (MDD) had lower microbial diversity and changes in the abundance of specific taxa, including lower Faecalibacterium abundance and higher Enterobacteriaceae abundance. Importantly, microbial composition correlated with the severity of depression.

In a large population-based cohort study, Valles-Colomer et al. reported associations between gut microbial composition and quality-of-life measures, including depression scores. Lower numbers of butyrate-producing bacteria were linked to depressive symptoms, independent of antidepressant use, suggesting a direct microbiota–mental health relationship.

Anxiety disorders have also been associated with microbial changes. In a clinical study of patients with generalised anxiety disorder, lowered microbial diversity and altered short-chain fatty acid profiles were observed, alongside increased markers of systemic inflammation.

3. Gastrointestinal Disorders as Risk Factors for Psychiatric Morbidity

IBS and IBD are strongly associated with mood and anxiety disorders. Long-term cohort studies indicate that psychiatric symptoms often precede gastrointestinal disease onset, which confirms the existence of mutual dependencies.

In a prospective study with patients who were first diagnosed with IBD, Gracie et al. demonstrated that baseline anxiety and depression predicted subsequent disease flares, independent of inflammatory activity. Conversely, persistent intestinal inflammation was associated with worsening psychiatric symptoms over time.

Patients with IBS exhibit particularly high rates of anxiety disorders. A population-based study revealed that up to 60% of IBS patients meet criteria for an anxiety disorder, significantly exceeding rates observed in organic gastrointestinal diseases. These findings suggest that altered gut–brain communication, rather than structural pathology, plays a central role.

4. Pathophysiological Mechanisms Linking the Gut and the Brain

4.1 Intestinal Permeability and Immune Activation

Increased intestinal permeability (“leaky gut”) has been implicated in mood disorders. Maes et al. demonstrated elevated serum antibodies against lipopolysaccharide (LPS) in patients with depression, indicating translocation of bacterial products across the intestinal barrier and subsequent immune activation.

Pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor-α, frequently elevated in depression, can cross the blood–brain barrier or signal via afferent nerves, influencing neurotransmission and neuroplasticity.

4.2 Microbial Metabolites and Neurotransmitter Pathways

The gut microbiota plays an important role in the metabolism of tryptophan, the precursor of serotonin. Altered kynurenine pathway activity has been observed in patients with depression, linking peripheral immune activation to central neurotransmitter imbalance.

Gut bacteria also produce short-chain fatty acids, particularly butyrate, which exert neuroactive properties by modulating blood–brain barrier integrity, microglial activation, and gene expression via histone deacetylase inhibition. These have direct effects on brain function. Notably, lower levels of butyrate-producing bacteria are consistently found in individuals with depressive phenotypes.

4.3 Vagal Signalling

The vagus nerve plays a major role in the communication route between the gut and the brain. In a clinical study, Bravo et al. showed that probiotic mood boosts vanished post-vagotomy, suggesting that vagal pathways are involved.

5. Diagnostic Challenges at the Gut–Brain Interface

Even though research on the gut–brain axis is rapidly expanding, assessing its dysfunction in everyday clinical practice remains difficult. At the moment, there are no validated biomarkers to reliably identify microbiota-driven psychiatric symptoms.

At the same time, research on the microbiome also comes with important limitations. Gut bacterial profiles differ widely due to interindividual variability, dietary influences, medication effects, and the lack of standardised reference ranges. Moreover, causality remains difficult to establish, as psychiatric disorders themselves may alter gut physiology and microbial composition.

Similar challenges arise when assessing intestinal permeability and immune activation. Inflammatory markers lack specificity, as elevated levels are not unique to gut-related inflammation and may instead reflect broader systemic processes.

6. Therapeutic Implications

6.1 Probiotics and Psychobiotics

A number of randomised controlled trials have examined the effects of probiotic supplementation on mood disorders. Akkasheh et al. demonstrated that probiotic supplementation for eight weeks significantly reduced depressive symptoms in patients with major depressive disorder compared with a placebo group. These improvements were paralleled by favourable changes in inflammatory and metabolic markers.

Complementary evidence comes from research in non-clinical populations. Steenbergen et al. showed that probiotic use reduced cognitive reactivity to sad mood in healthy volunteers, suggesting that probiotics may also have preventive or resilience-building effects on emotional health.

6.2 Dietary Interventions

Dietary habits play an important role in shaping the gut microbiota and mental health. In a controlled trial, O'Neil et al. found that people who followed a Mediterranean-style diet experienced significantly greater improvements in depressive symptoms than those who received social support alone.

6.3 Faecal Microbiota Transplantation

Faecal microbiota transplantation (FMT) remains an experimental approach with encouraging potential. An open-label study of patients with IBS and FMT improved gastrointestinal symptoms and also reduced anxiety and depression scores. This outcome supports the idea that changes in the gut microbiota can directly influence psychiatric symptoms.

IV. Discussion

Overall, the available evidence suggests that the gut–brain axis is an important factor in the development of mood and anxiety disorders. Human studies consistently report links between changes in the gut microbiota, immune activation, and psychiatric symptoms. However, variation in study design, analytical methods, and outcome measures makes it difficult to compare results across studies or draw firm conclusions. Disruptions in gut–brain communication seem to affect a range of psychiatric and gastrointestinal conditions. This broader view may help explain why these disorders so often present with overlapping symptoms. Future research would benefit from longitudinal study designs, more standardised methods for assessing the microbiome, and improved patient stratification based on biological characteristics. Closer collaboration between gastroenterology and psychiatry could support the development of more personalised and effective treatment strategies.

V. Conclusions

The gut–brain axis represents an important link between gastrointestinal function and mental health. Disruptions in the gut microbiota, intestinal barrier function, and immune signalling appear to play a role in the onset and persistence of mood and anxiety disorders. Although treatments targeting the gut–brain axis are promising, more evidence is needed before they can be widely applied in clinical practice. Moving forward, closer collaboration between gastroenterology and psychiatry will be essential for improving diagnosis and treatment in this evolving area.

Conflicts of interest: No conflicts of interest to declare.

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