Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Imbalance of the Brain–Gut–Microbiota Axis in Major Depressive Disorder: From Pathogenesis to Clinical Translation

Tao Wu[1,*], Haoran Xing[2,3,*], Tianzhong Wu[1], Xian Xie[1], Long Ji[1], Wei Wang[1], Xiaolina Zhang[2,4], Yingying Zhang[2], Chengrong Jiang[1], Tianhao Bao[2]

[1]Department of Child and Adolescent Psychiatry, Zhaotong Mental Health Center, Zhaotong, Yunnan, People's Republic of China; [2]Department of Research and Education, The Affiliated Mental Health Center of Kunming Medical University, Kunming, Yunnan, People's Republic of China; [3]Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China; [4]Department of Pain Medicine, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chengrong Jiang, Department of Child and Adolescent Psychiatry, Zhaotong Mental Health Center, Zhaotong, Yunnan, People's Republic of China, Email 824496472@qq.com; Tianhao Bao, Department of Research and Education, The Affiliated Mental Health Center of Kunming Medical University, Kunming, Yunnan, People's Republic of China, Email doctor@kmmu.edu.cn

Abstract: Major depressive disorder (MDD) is one of the most common psychiatric conditions, characterized by complex pathogenesis and marked inter-individual variability in treatment response, leading to persistent impairment of physical and mental health as well as social functioning. In recent years, the brain–gut–microbiota axis (BGMA) has emerged as a key biological pathway linking the gut microbiota with the central nervous system, and its role in MDD has become a major research focus. Although substantial progress has been made in elucidating the association between MDD and the BGMA, the precise mechanisms, critical pathways, and their integrated clinical applications remain to be fully clarified. On the basis of a comprehensive overview of the physiological functions, structural components, and disease associations of the BGMA, this review systematically summarizes the bidirectional interactions between MDD and the BGMA. Integrating the latest findings from preclinical and clinical studies, we further dissect the key regulatory pathways of this axis in MDD and highlight the therapeutic potential of BGMA-based interventions, including pharmacotherapy, fecal microbiota transplantation, dietary modulation, and physical therapies. This work aims to provide a theoretical foundation for developing novel treatment strategies for patients with MDD and for improving their prognosis and quality of life.

Keywords: major depressive disorder, brain–gut–microbiota axis, pathogenesis, treatment

Introduction

The brain–gut–microbiome axis (BGMA) has emerged as a rapidly expanding interdisciplinary research field. It comprises the gut microbiota, the enteric nervous system, the autonomic nervous system, the neuroimmune and neuroendocrine systems, and the central nervous system; these components interact through intricate signaling networks to regulate key physiological processes. At the level of neural pathways, vagal afferent fibers integrate mechanical activity and chemical cues originating from the gut and relay this information to the nucleus tractus solitarius, thereby modulating limbic circuitry. In parallel, the central nervous system regulates intestinal motility, secretion, and local homeostasis via autonomic efferent outputs, establishing a coupled closed-loop system with coordinated top-down and bottom-up control. At the level of endocrine pathways, enteroendocrine cells secrete diverse peptide hormones into the circulation, and some of these signals act on key brain regions such as the hypothalamus to influence energy metabolism and feeding behavior.[1]

https://doi.org/10.2147/NDT.S591429
Received: 24 December 2025
Accepted: 5 March 2026
Published: 30 March 2026

In addition, the canonical hypothalamic–pituitary–adrenal (HPA) axis is initiated by corticotropin-releasing hormone released from the paraventricular nucleus, which activates downstream pituitary and adrenal glucocorticoid production; glucocorticoids then act systemically through the bloodstream. Stress-related signals transmitted via this axis can reach the gut and subsequently alter intestinal barrier permeability, mucosal immune responses, and microbial ecological composition. Conversely, microbiota-derived metabolites can also facilitate HPA-axis activation, forming a bidirectional regulatory circuit.[2]

At the level of immune pathways, cytokines and other mediators produced by intestinal mucosal immune cells can participate in central regulation through vagus nerve–mediated immune reflexes, and can also enter the brain via the systemic circulation to shape neuroinflammatory states.[3,4] Consistently, the activation phenotype and homeostatic maintenance of microglia are modulated by peripheral signals, including microbiota-derived metabolites.[5]

Within this network, the blood–brain barrier (BBB) serves a crucial "filtering–gating" function. Gut-derived molecules such as lipopolysaccharide can increase BBB permeability by disrupting tight junctions, thereby facilitating the entry of inflammation-related peripheral signals into the central nervous system.[6] Conversely, BBB dysfunction may also reshape the gut microenvironment and microbial composition through neuroimmune feedback, further reinforcing the bidirectional nature of this axis.[7] Overall, neural, endocrine, and immune pathways are not independent; rather, they are highly interconnected and synergistic, jointly constituting a multilayered mechanistic framework linking the gut microbiota–host–brain function.

Major depressive disorder (MDD) are heterogeneous psychiatric conditions with complex etiologies and are frequently associated with substantial functional impairment.[8] In recent years, accumulating evidence has linked MDD to dysregulation of the BGMA. Clinical studies indicate that patients with depression often present with gastrointestinal manifestations, including altered gut motility and increased intestinal permeability.[9]

From a microbial ecology perspective, depression has been associated with reduced gut microbiota diversity, decreased abundance of butyrate-producing genera such as Faecalibacterium and Coprococcus, and increased relative abundance of pro-inflammatory taxa including Eggerthella and Escherichia–Shigella.[10] Additional causal clues come from fecal microbiota transplantation(FMT) studies: transplantation of microbiota from patients with depression into germ-free or antibiotic-treated rats can induce depression-like phenotypes such as anhedonia and behavioral despair, whereas transplantation from healthy donors does not produce comparable changes, suggesting that microbial alterations may contribute to pathophysiology rather than merely reflecting comorbidity.[11]

At the level of neural pathways, patients with MDD exhibit reduced vagal tone, which correlates with symptom severity.[12] Microbiota-derived metabolites can activate vagal afferents and signal via the nucleus tractus solitarius and hypothalamic paraventricular nucleus, thereby influencing the HPA axis and the mesolimbic dopaminergic system; through these routes, they may modulate stress responsivity and reward processing and ultimately promote dysregulated emotion control.[13]

At the level of endocrine pathways, microbiota-derived metabolites (eg., butyrate among short-chain fatty acids, SCFAs) have been linked to HPA-axis hyperactivation and are associated with more severe depressive symptoms and a lower likelihood of remission.[14] Along inflammatory–immune pathways, dysbiosis may facilitate the translocation of microbiota-derived lipopolysaccharide into the bloodstream via the portal circulation, activating peripheral immune cells and triggering the release of pro-inflammatory cytokines; in the context of BBB disruption, these inflammatory signals can access the central nervous system, activate microglia, and drive neuroinflammatory processes.[15] In addition, cytokines such as Interleukin-1β and Interleukin-6 secreted by intestinal mucosal immune cells may act on the nucleus tractus solitarius through vagus nerve–mediated immune reflexes, thereby influencing limbic-system function and depressive affect.[16] Beyond these pathways, studies also suggest that microbiota alterations in depression may bias tryptophan metabolism toward the kynurenine pathway, reducing serotonin (5-hydroxytryptamine) synthesis and impairing mood regulation.[17]

Despite multi-level evidence supporting an association between MDD and BGMA dysregulation, key uncertainties remain, including the directionality of causality, the relative contribution of distinct pathways, and the moderating role of inter-individual differences. This review therefore aims to systematically synthesize evidence linking MDD to the BGMA, with emphasis on (i) key nodes within the mechanistic cascade, (ii) translational continuity between preclinical and clinical findings, and (iii) the feasibility and limitations of BGMA-targeted interventions. We will integrate evidence

across vagal signaling, HPA-axis regulation, immune–inflammatory responses, and neurotransmitter-related metabolism; compare animal models with clinical cohort data; and evaluate preliminary efficacy signals and remaining gaps in long-term safety evidence for strategies such as probiotics, FMT, dietary modulation, and physical therapies, with the goal of informing future research and translational application.

Research on the BGMA

Composition of the Gut Microbiota

The gut microbiota is a complex ecosystem comprising trillions of microorganisms that shape host metabolism, immunity, and other physiological processes. Dysbiosis can substantially increase host susceptibility to disease, underscoring the importance of characterizing the composition and structure of the gut microbial community. Current evidence suggests that the gut microbiota is primarily composed of bacteria, fungi, viruses, and other microorganisms; among these, bacteria predominate and can be classified across seven hierarchical taxonomic ranks: domain, phylum, class, order, family, genus, and species.[18,19]

Within this ecosystem, beneficial taxa such as Bifidobacterium, Lactobacillus, and Akkermansia muciniphila contribute to carbohydrate fermentation and immune modulation, support microbial homeostasis, help preserve intestinal barrier integrity, and exert anti-inflammatory effects. By contrast, pathogenic bacteria—including enterotoxigenic Escherichia coli and Clostridioides difficile—can produce toxins that cause intestinal injury and diarrhea, whereas Salmonella, Helicobacter pylori, and Bacteroides fragilis have been implicated in tumorigenesis, inflammation, and other adverse health outcomes.[20] Diet is a major determinant of microbial composition and function; for example, high-fiber diets, following fermentation in the large intestine, can increase the abundance of beneficial bacteria such as Lachnospiraceae and Lactobacillus and enhance the production of SCFAs, key metabolites derived from microbial metabolism.[21]

The dominant bacterial taxa also vary substantially across the life course. During the neonatal period, Bifidobacterium commonly predominates; as individuals transition into adulthood, the microbiota becomes more stable and is largely represented by several major bacterial phyla, including Firmicutes and Bacteroidetes.[22] With advancing age, microbial diversity tends to decline, a pattern that may contribute to increased vulnerability to age-related diseases.[23] In addition to age, sex is another important source of inter-individual variation. Multiple studies have described sex-associated differences in gut microbial composition and functional capacity, potentially reflecting variation in sex hormones, obesity prevalence, insulin resistance, and related host factors.[24]

Association of the BGMA with Multiple Diseases

Gut microbes and their metabolites can influence brain function via multiple routes—most notably HPA-axis activation, vagal signaling, and immune–inflammatory pathways—and have been implicated in susceptibility to several psychiatric conditions, including schizophrenia, bipolar disorder, post-traumatic stress disorder, anxiety disorders, and autism spectrum disorder.[25] In schizophrenia, increased intestinal permeability has been reported. In parallel, overrepresentation of Prevotella has been associated with elevated markers of immune activation, suggesting a potential role in shaping symptom phenotypes by engaging vagus nerve–mediated immune reflexes and thereby influencing central dopaminergic function.[26] For bipolar disorder, available findings suggest that dysbiosis may impair the intestinal barrier and facilitate the translocation of pro-inflammatory mediators into the circulation, which may in turn promote neuroinflammation and microglial activation and disrupt neurotransmitter homeostasis. Meanwhile, abnormalities in vagal tone and HPA-axis function may jointly contribute to mood instability, cycling between manic and depressive states, and cognitive decline.[27] In anxiety disorders, reduced microbial richness often co-occurs with decreased vagal tone. HPA-axis hyperactivation and an increased abundance of pro-inflammatory taxa may form a positive feedback loop that alters the activity and plasticity of anxiety-related neural circuits.[28] In post-traumatic stress disorder, trauma exposure can remodel HPA-axis responsivity and is accompanied by reduced glucocorticoid receptor sensitivity. Dysbiosis may weaken stress-regulatory capacity and, via vagal pathways, enhance amygdala reactivity—mechanisms that may contribute to persistent intrusive trauma memories and recurrent recollection.[29] Moreover, BGMA-related mechanisms in autism spectrum disorder appear to exhibit developmental stage specificity. Maternal dysbiosis during pregnancy and early-life antibiotic exposure may

alter HPA-axis "programming". Overgrowth of Clostridium and its potentially neuroactive/toxic products may signal to the brain through vagal afferents, while increased intestinal permeability can amplify systemic inflammation. Collectively, the gut microbiota may serve as a key mediator between genetic vulnerability and environmental exposures in specific autism spectrum disorder subtypes.[30]

Mechanisms Underlying the Role of the BGMA in Depressive Disorder

Vagus Nerve

The vagus nerve is a core component of the BGMA and may participate in the pathophysiology of MDD by modulating the transmission of inflammatory signals between the periphery and the central nervous system (Figure 1).[16] Animal studies have shown that vagotomy in mice exhibiting depression-like behaviors can significantly ameliorate these

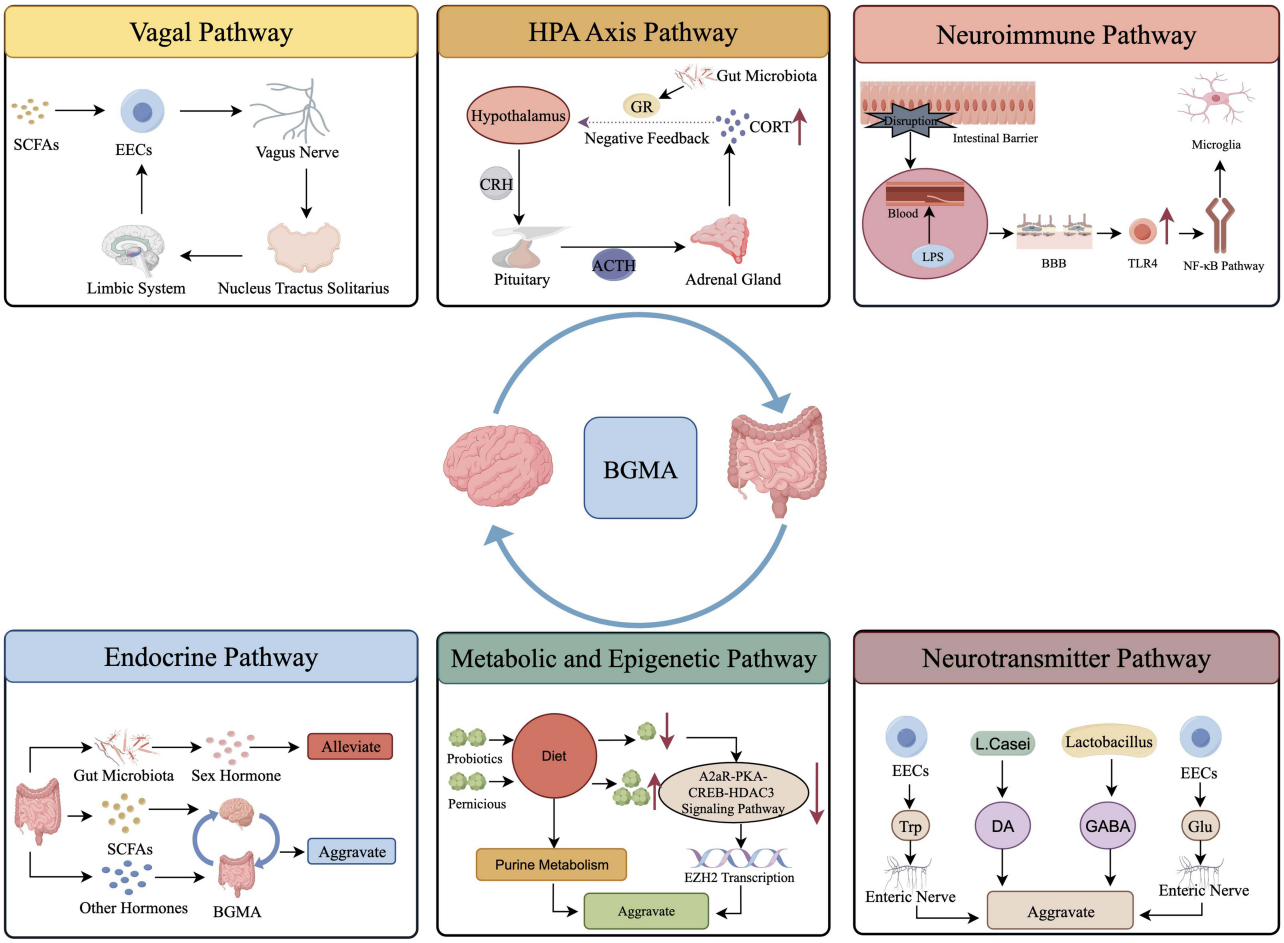

Figure 1 Schematic of an integrated six-pathway model of the brain–gut–microbiota axis implicated in major depressive disorder. The figure highlights that the brain and gut communicate bidirectionally through multiple parallel and interconnected pathways, which together shape depression-related phenotypes. The vagal pathway illustrates how microbiota-derived metabolites activate enteroendocrine signaling and vagal afferents, thereby influencing the nucleus tractus solitarius and limbic circuits. The hypothalamic–pituitary–adrenal axis pathway depicts potential microbial modulation of the CRH–ACTH–cortisol/corticosterone cascade and glucocorticoid receptor–mediated negative feedback. The neuroimmune pathway shows that intestinal barrier disruption permits endotoxin translocation into the circulation and triggers central immune activation via receptor-driven inflammatory signaling. The endocrine pathway summarizes how microbial signals may regulate brain–gut function through sex hormones and other hormonal axes, with the potential to exacerbate or alleviate symptoms. The metabolic and epigenetic pathway integrates diet- and microbiota-related changes that act through purine metabolism and key signaling axes to induce transcriptional and epigenetic regulation, thereby affecting depressive phenotypes. The neurotransmitter pathway summarizes microbial involvement in tryptophan metabolism and the synthesis and transformation of multiple neurotransmitters, with downstream effects on central function via the enteric nervous system.

Abbreviations: ACTH, adrenocorticotropic hormone; A2AR, adenosine A2A receptor; BBB, blood–brain barrier; BGMA, brain–gut–microbiota axis; CORT, cortisol/corticosterone; CREB, cAMP response element-binding protein; CRH, corticotropin-releasing hormone; DA, dopamine; EECs, enteroendocrine cells; EZH2, enhancer of zeste homolog 2; GABA, γ-aminobutyric acid; Glu, glutamate; GR, glucocorticoid receptor; HDAC3, histone deacetylase 3; HPA, hypothalamic–pituitary–adrenal; LPS, lipopolysaccharide; MDD, major depressive disorder; NF-κB, nuclear factor kappa B; NTS, nucleus tractus solitarius; PKA, protein kinase A; SCFAs, short-chain fatty acids; TLR4, Toll-like receptor 4; Trp, tryptophan.

https://doi.org/10.2147/NDT.S591429

behavioral phenotypes.[31] However, this approach is not readily translatable to clinical settings, precluding direct evaluation of its safety and real-world efficacy in humans.

Concurrently, the gut microbiota and its metabolites can stimulate vagal sensory endings and relay signals centrally. Sumel et al reported that SCFAs can activate specific receptors on the vagus nerve and modulate neural activity in the brain.[32] Although this evidence is largely derived from rodent models—and receptor expression profiles and anatomical distribution may differ in humans—it provides an important mechanistic lead for the proposed "metabolite–vagus–brain" signaling cascade. Additional animal experiments further suggest that the microbiota can facilitate vagus nerve–mediated gut–brain communication by shaping the intestinal metabolite landscape.[33]

At the population level, patients with MDD may exhibit remodeling or impairment of vagal function. Available evidence suggests that the sensitivity of vagal afferent neurons to peripheral signals may be reduced.[34] This view aligns with observations by Toya et al in animals: mice that are more prone to developing depression-like phenotypes after stress more frequently show impaired vagal afferent sensitivity than stress-resilient mice.[35] Nevertheless, whether the link between stress susceptibility and vagal afferent hyporesponsiveness is consistent and reproducible in humans requires further verification. Conceptually, reduced vagal afferent encoding efficiency could weaken the effective transmission of microbiota-related signals to the brain, thereby increasing the likelihood that neuroendocrine and neuroimmune regulation deviates from homeostasis and, at least in part, contributing to symptom persistence and exacerbation.

Based on these converging lines of evidence, vagus nerve stimulation has been proposed as a potential intervention target for MDD. Transcutaneous vagus nerve stimulation has been applied in the management of certain conditions and may alleviate depressive symptoms by modulating BGMA-related functions.[36] However, clinical evidence supporting its indication for depression remains at an early stage, and the robustness of efficacy, optimal target populations, and underlying mechanisms still need to be established through higher-quality studies.

HPA Axis

The HPA axis is the central hub of the stress response, and its activity can be modulated by the gut microbiota; however, the key pathways linking the "microbiota–HPA axis" in humans have not yet been clearly delineated. Some studies suggest that specific microorganisms may produce catecholamine-like molecules associated with affective phenotypes and may participate in regulating the initiation phase of HPA-axis activation.[37] Nevertheless, the current evidence is derived predominantly from in vitro systems and rodent models, and its clinical reproducibility and effect size remain to be established. Other work indicates that Lactobacillus and Bifidobacterium can influence HPA-axis reactivity, but the magnitude and direction of effects vary substantially across strains, and generalizable parameters for optimal dose and treatment duration are still lacking.[38] In animal studies, gut dysbiosis is accompanied by altered expression of HPA-axis–related genes and is associated with phenotypes indicative of impaired neuroplasticity and disrupted neurotransmitter homeostasis.[11]

Under stress conditions, elevated circulating cortisol often co-occurs with impaired HPA-axis negative feedback and reduced serotonergic system activity, thereby increasing vulnerability to depression-like phenotypes.[39] Chen et al reported that when stress is intensified, microbiota alterations may promote HPA-axis hyperactivation and increase the secretion of stress hormones such as cortisol, ultimately compromising emotion regulation.[40] Conversely, certain probiotic interventions may attenuate stress-induced HPA-axis activation and lower cortisol levels.[41] However, meaningful cross-study comparisons and evidence synthesis remain constrained by substantial heterogeneity in strains, dosing regimens, treatment duration, and outcome measures. It has been proposed that the microbiota may modulate hypothalamic corticotropin-releasing hormone output by influencing the expression of brain-derived neurotrophic factor (BDNF) and (N)-methyl-(D)-aspartate receptors, thereby inducing HPA-axis dysfunction and shaping affective phenotypes.[42] In addition, stress exposure can impair prefrontal cortical function in rodents and co-occur with depression-like behaviors, HPA-axis hyperactivation, and increased cortisol; these changes may further reshape peripheral immune responses and reduce gut microbial diversity and abundance.[43]

Overall, existing evidence supports the HPA axis as a plausible candidate pathway linking the gut microbiota to depression. Nonetheless, the research emphasis remains weighted toward animal experimentation. In human studies, major challenges include the lack of standardized stress paradigms, the reliance on cortisol as a downstream surrogate that may not capture central dynamics, and inconsistent strain-specific effects. Meanwhile, the relative contributions of—and boundaries of interaction among—the HPA axis, vagal pathways, and immune-inflammatory mechanisms remain

insufficiently resolved. Future work should incorporate longitudinal designs that track multidimensional HPA-axis readouts before and after microbiota-targeted interventions to clarify temporal ordering and strengthen causal inference.

Endocrine System

The endocrine system interacts closely with the BGMA. The gut is increasingly recognized as an important source of endocrine and neuropeptide signals; its secretory products can participate in bidirectional brain–gut communication and influence emotion and cognition.[44] Prior studies suggest that the gut microbiota may be associated with circulating levels of hormones such as testosterone, estradiol, oxytocin, and vasopressin, with potential links to affective phenotypes.[45] However, cross-sectional data cannot readily disentangle whether hormonal alterations are causal drivers of depression, markers of vulnerability, or consequences of disease status and treatment exposure. Gut-derived neuroactive mediators, including cholecystokinin and substance P, have been implicated in brain–gut axis regulation, yet systematic evidence remains limited regarding their peripheral–central concentration gradients, transport across biological barriers, and the effective dose ranges required to elicit behavioral effects.[46] In addition, interactions between gut microbes and hormones such as growth hormone, neurotensin, and melatonin may contribute to BGMA homeostasis.[47] Nonetheless, mechanistic validation of the "microbiota–hormone axis" in human studies remains insufficient, particularly due to a shortage of longitudinal data coupled to well-characterized clinical phenotypes.

Clinically, one study observed increased positive affect in individuals with obesity following insulin treatment, hypothesizing a role for humoral signaling and hypothalamic regulation.[48] However, given the limited sample size and incomplete control of key confounders (eg., diet, sleep, and changes in body weight), stronger designs are needed before these findings can be generalized. Endocrine dysregulation is common in MDD. For example, thyroid hormone levels are associated with depressive phenotypes, and the gut microbiota may contribute to depression by influencing thyroid hormone metabolism or modulating hypothalamic–pituitary–thyroid axis reactivity.[49] With respect to sex hormones, fluctuations in estrogen can affect microbial diversity, while microbial metabolism can in turn modulate estrogen bioactivity. This bidirectional regulation may be relevant to mood variability across the menstrual cycle, pregnancy, and the perimenopausal transition; however, longitudinal studies capable of simultaneously capturing hormonal dynamics, microbiome changes, and symptom trajectories are still lacking.[50]

Overall, endocrine pathways remain a comparatively underdeveloped component of BGMA research. Existing studies often rely on single time-point hormone measurements with low temporal resolution, limiting the ability to characterize circadian rhythmicity and stress reactivity. The causal chain linking "microbiota–hormones–mood" and its key mediating steps has not been established, and the systematic underrepresentation of female physiological stages constrains the delineation of sex-specific mechanisms. Future work should prioritize high-frequency or repeated sampling, integrate controlled interventions with longitudinal follow-up, and concurrently profile hormonal rhythms, the gut microbiome, and symptom fluctuations within the same cohort. Mediation analyses could then be used to quantify the extent to which hormonal dynamics explain associations between microbial features and depressive phenotypes, thereby strengthening mechanistic inference.

Neurotransmitters

Neurotransmitters are widely regarded as a key effector pathway linking the BGMA to MDD. Among them, serotonin (5-hydroxytryptamine, 5-HT) is one of the most central candidate mediators. It is produced predominantly by intestinal enterochromaffin cells from tryptophan and can modulate enteric neural activity and, via brain–gut signaling, influence central function and affective states; dysregulated 5-HT signaling is closely implicated in depression.[51] Beyond 5-HT, evidence also suggests that the gut microbiota may affect systemic dopamine levels by regulating host processes such as the dopamine transporter.[52]

Animal studies provide mechanistic plausibility for microbiota–monoamine links. For example, Lactobacillus casei supplementation has been reported to increase dopamine, 5-HT, and norepinephrine levels in the rat prefrontal cortex, whereas Lactobacillus plantarum PS128 may improve dopamine metabolism and elevate norepinephrine levels.[53] In addition, Lactobacillus spp. and Escherichia coli have been reported to contribute to the production of the inhibitory neurotransmitter (\gamma)-aminobutyric acid (GABA), and alterations in GABA signaling may shape emotional and

behavioral phenotypes.[54] Beyond inhibitory transmission, enteroendocrine cells can synthesize the excitatory transmitter glutamate and relay signals to the brain via vagal afferents; meanwhile, microbial communities may also participate in central glutamate metabolism, thereby modulating circuits involved in emotion regulation.[53]

Importantly, even if the gut microbiota regulates peripheral neurotransmitter synthesis and release, it remains uncertain whether peripherally generated neurotransmitters can cross the blood–brain barrier at sufficient concentrations to exert direct central effects.[55] At present, the relative contributions of different neurotransmitter systems to depressive phenotypes—and their interactions with broader brain–gut pathways—have not been quantified within a unified framework, which constrains the development of precise neurotransmitter-targeted interventions.

Immune and Inflammatory Mechanisms

Immune–inflammatory responses are considered a major biological pathway linking the BGMA to MDD. Studies have reported that patients with depression may exhibit elevated gut-associated inflammatory mediators, including tumor necrosis factor, macrophage colony-stimulating factor, and interleukin-12. These alterations are consistent with bidirectional "gut–immune–brain" communication and often co-occur with impaired intestinal barrier integrity, activation of immune signaling pathways, and blood–brain barrier dysfunction.[56,57] In the context of dysbiosis, microbe-associated molecular patterns can be sensed by host pattern-recognition receptors, triggering innate immune responses and subsequent cytokine release. Such mediators can exacerbate local intestinal inflammation and may also influence the central immune milieu via humoral routes, thereby facilitating depression-like phenotypes.[58]

Beyond these factors, interleukin-6, interleukin-1(\beta), interleukin-10, and C-reactive protein (CRP) have been repeatedly used to characterize depression-related inflammatory states; through cascades and feedback within immune networks, they may couple intestinal immune activation to neuroinflammatory processes.[46] Prior work also suggests that dysbiosis can promote inflammatory mediator release and coincide with HPA-axis hyperactivation, increasing the risk of depression. However, whether inflammatory activation is a precipitating event, a concomitant process, or a downstream consequence remains unclear due to limited longitudinal evidence capable of establishing temporal ordering.[59] As the gut represents a major reservoir of Gram-negative bacteria, outer-membrane lipopolysaccharide can elicit immune activation and, in animal models, more readily induce depression-like behaviors; yet this effect is strongly contingent on mucosal barrier integrity and baseline immune tone, contributing to substantial heterogeneity at the population level.[60,61] In specific contexts, postpartum depression research has implicated hippocampal NOD-like receptor family pyrin domain-containing 3 as a potential mediator of a "microbiota–gut–inflammation–brain" axis and associated depression-like behavior;[62] however, given the constraints of physiological stage and endocrine milieu, extrapolation to broader depressive populations requires cautious validation.

Importantly, inflammation is not a universal feature of MDD: approximately 30–40% of patients show inflammatory markers within the normal range,[63] suggesting that immune mechanisms may characterize a stratifiable "inflammatory subtype" rather than a shared pathway across all patients. Consistently, clinical evidence for anti-inflammatory treatments is mixed. A recent meta-analysis reported that among depressed patients with CRP $\geq$ 2 mg/L, anti-inflammatory therapy reduced symptom severity, but response and remission rates were not significantly superior to placebo.[64] More broadly, the overall effect size of NSAIDs appears close to null with substantial between-study heterogeneity,[65] and tumor necrosis factor-(\alpha)–targeting monoclonal antibodies have also failed to demonstrate clear antidepressant benefit in some trials.[66] These patterns—symptom improvement without robust clinical endpoints—may reflect inadequate biomarker-based stratification at enrollment, discordance between peripheral and central inflammation, and a considerable mechanistic distance between the chosen targets and the outcome measures.

Overall, the immune–inflammatory pathway is among the better-supported domains in BGMA research: associations between inflammatory markers and depression are relatively consistent, but specificity remains limited. In addition, metrics and assay methods for evaluating intestinal and blood–brain barrier function are not yet standardized, constraining cross-study comparability and evidence synthesis. Two priorities appear central for clinical translation: (1) establishing reproducible stratification frameworks (eg., defining inflammatory subtypes using CRP/cytokine signatures/barrier-related indices) to improve signal-to-noise in trials; and (2) within acceptable safety margins, identifying which immune

targets, therapeutic windows, and patient subsets are most likely to benefit, thereby avoiding the risks of non-selective immunosuppression.

Other Factors

Chronic stress exposure can induce structural and barrier-related changes in the gut, thereby increasing susceptibility to intestinal inflammation, weakening BGMA function, and ultimately elevating the risk of depressive- and anxiety-like symptoms.[67] Multiple studies further indicate that depressive phenotypes and microbiota alterations frequently co-occur with perturbations across several metabolic pathways. Taking purine metabolism as an example, under conditions such as a high-fat diet or hypoxia, reductions in beneficial taxa alongside increases in potentially pathogenic bacteria may disrupt purine-metabolic networks relevant to the brain–gut axis. These changes have been linked to decreased levels of metabolites including uric acid, 2-oxohexanedioic acid, acetate, and D-purine, in parallel with depression-like behaviors.[68] However, such studies are often limited by small sample sizes, short intervention periods, and insufficient control for key confounders such as physical activity and energy intake. Beyond purine metabolism, it has been proposed that the microbiota may contribute to depression through effects on central glycerophospholipid and sphingolipid metabolism.[69] Nonetheless, these lipid-related indices generally lack disease specificity and overlap substantially with pathways implicated in metabolic syndrome and cardiovascular disease, which constrains their interpretability as depression-specific biomarkers.

Regarding SCFAs, available evidence suggests that an "excess" state may alter hippocampal BDNF levels and induce depression-like phenotypes, while concomitant disturbances in bile acid metabolism may exacerbate depression-related cognitive impairment.[70,71] Consistent with this, dietary fiber may help preserve intestinal integrity and, via BGMA pathways, influence brain function and mood;[72] yet systematic evaluations of key effector molecules, biological targets, and dose–response relationships remain lacking. Additional work has incorporated D-amino acids into pathophysiological models of depression, suggesting that they may be regulated, at least in part, through BGMA-related mechanisms.[73]

Notably, emerging genetic and epigenetic evidence is moving the "microbiota–metabolite–neural circuit" chain toward more testable mechanistic models. One line of research proposes that depletion of specific genera reduces inosine levels, thereby attenuating A2aR–PKA–CREB–HDAC3 signaling and promoting EZH2 transcription, inducing H3K27me3 reprogramming, suppressing the expression of key genes linked to the serotonergic system, and ultimately resulting in depression-like behaviors.[74] Moreover, dysbiosis may increase BBB permeability and impair brain function, thereby facilitating depressive phenotypes.[75] However, the causal direction between barrier alterations and symptoms, critical thresholds, and reversibility require further validation in longitudinal and interventional studies.

At present, the evidentiary tier for metabolic and genetic mechanisms remains predominantly preclinical. Most metabolomic studies are cross-sectional, limiting causal inference and leaving reverse causation unresolved. Biomarkers such as lipids and amino acids frequently map onto pathways shared across multiple conditions, reducing specificity. Likewise, many genetic and epigenetic observations are derived from animal models or correlational inference, and functional validation remains incomplete. In parallel, chronic stress, dietary patterns, and genetic background are tightly intertwined, increasing the likelihood of residual confounding and attenuation of true effects. Future studies should adopt longitudinal, multi-omics integrative designs with rigorous control of diet and activity exposures, incorporate genetic stratification, and use interventions or mediation analyses to test the causal effects of key metabolites —thereby identifying individualized targets with higher translational potential.

Overall, BGMA-related mechanisms are better conceptualized as a network in which multiple pathways operate in parallel and are reciprocally coupled. The vagus nerve provides a plausible route for rapid gut-to-brain signaling, yet strong causal evidence still largely comes from animal models. The HPA axis and immune–inflammatory pathways can amplify one another under stress, but exhibit marked clinical heterogeneity, contributing to unstable overall intervention effects. Endocrine and neurotransmitter mechanisms are relatively well characterized in basic research; however, translation is constrained by circadian rhythmicity, blood–brain barrier considerations, and measurement limitations. A critical next step is stratified and longitudinal validation: under controlled stress and dietary exposures, multi-omics profiling combined with reproducible mechanistic endpoints should be used to determine which patients are most likely to benefit—and through which pathway—so that "association" can be advanced toward testable causal models and implementable, individualized interventions.

Preclinical Studies on the BGMA and MDD

In recent years, preclinical studies using animal models have highlighted the pivotal role of the BGMA in MDD. Accumulating evidence suggests that the gut microbiota, a key component of the human ecological system, is closely associated with the onset, progression, and maintenance of MDD.[76] Studies using mouse models of depression induced by chronic unpredictable stress have shown that shifts in the relative abundance of gut microbes correlate with depression-like behaviors. Nevertheless, the construct validity of these paradigms and the translational relevance of rodent findings to human clinical phenotypes remain debated.

Feng et al further demonstrated that aberrant stress exposure in female mice alters the gut microbiota and subsequently disrupts hippocampal signaling pathways.[77] In addition, the degree of interaction between depressed dams and their offspring has been associated with microbiota alterations in the offspring, and such dysbiosis may contribute to the intergenerational transmission of depression-like phenotypes,[78] although epigenetic influences and early-life environmental confounding cannot be fully excluded.

Mechanistically, disruption of microbiota homeostasis is often characterized by reduced abundance of putatively beneficial genera such as Bifidobacterium and Lactobacillus and expansion of potentially pathogenic taxa such as Enterobacteriaceae, which may precipitate intestinal injury and compromise epithelial barrier integrity. This, in turn, can facilitate the translocation of bacteria and microbial products into the systemic circulation, provoke systemic inflammation, and ultimately impair neuroplasticity and neurotransmitter metabolism, thereby aggravating depressive symptoms.[79] In a stress-induced mouse model, He et al reported that stress-resilient mice exhibited higher fecal abundance of Lactobacillus, Bifidobacterium, and Romboutsia, alongside lower abundance of Staphylococcus, Psychrobacter, and Corynebacterium.[80]

From a therapeutic perspective, FMT in depressed mice has been shown to increase central levels of 5-hydroxytryptamine, BDNF, and GABA while reducing glutamate levels, collectively alleviating depression-like behaviors.[81] At the genomic level, adenosine has been reported to mitigate depression-like behaviors in mice by modulating the gut microbiota,[82] and its deamination product inosine may also exert antidepressant-like effects via microbiota-related metabolic pathways (Table 1).

Table 1 Preclinical Studies of the BGMA in MDD

Research	Grouping	Duration	Main Findings
[83]	CUMS group: 5 rats Control group: 5 rats	4 weeks	Gut microbiota dysbiosis can lead to the development of depression, and this is related to the ratio between Lactobacillus and Clostridium.
[77]	CUMS group: 8 rats Control group: 8 rats	3 weeks	Prenatal maternal stress in mice leads to emotional abnormalities in the offspring, which are related to hippocampal signaling abnormalities in the offspring induced by gut microbiota dysbiosis.
[80]	CUMS group: 40 mice Control group: 13 mice	4 weeks	After stress, the gut microbiota can be remodeled, reversing stress-induced neural damage and promoting the recovery of depressive symptoms.
[81]	CUMS group: 10 rats CUMS+ FMT group: 10 rats Control group: 10 rats	4 weeks	FMT has an antidepressant effect on depression induced by CUMS.
[84]	CUMS group: 16 mice Bedding-exchange group: 16 mice Control group: 16 mice	4 weeks	Exchanging bedding between control mice and CUMS mice can reverse gut microbial composition and hypothalamic gene expression, thereby improving depressive symptoms.
[85]	CUMS + inosine group: 30 mice CUMS + normal saline group: 30 mice Control + normal saline group: 15 mice	4 weeks	Inosine can improve depressive behaviors in CUMS mice by modulating the gut microbiota and metabolic pathways.
[86]	CRS group: 8 mice Control group: 8 mice	4 weeks	The rhythmicity of the microbiota may influence the host's emotions by regulating different metabolic pathways during the day and at night.

Abbreviations: BGMA, brain–gut–microbiota axis; MDD, Major depressive disorder; CUMS, Chronic Unpredictable Mild Stress; FMT, Fecal Microbiota Transplantation; CSDS, Chronic Social Defeat Stress; CRS, Chronic Restraint Stress; RCT, Randomized Controlled Experiment.

Taken together, a substantial preclinical literature supports the view that the gut microbiota may contribute to the pathogenesis of MDD by modulating neurotransmitter metabolism, neuroplasticity, and genome-related regulatory processes, underscoring the mechanistic relevance of the BGMA in depression. Despite notable limitations—including insufficient consideration of sex-related differences, the lack of standardized microbiome analytic workflows, and short follow-up periods that preclude evaluation of long-term microbiome stability—these findings provide an important foundation for further investigation of BGMA-related mechanisms in MDD.

Clinical Studies on the BGMA in MDD

Clinical evidence further supports an association between the BGMA and MDD. The composition and relative abundance of gut microbial communities appear to be relevant to both depression risk and illness course. In population-based analyses, Escherichia–Shigella and Lachnospiraceae NK4A136 have been reported to be less abundant among individuals at lower risk of depression, with the latter also correlating with depressive severity.[10] By contrast, Bacteroidetes and Prevotellaceae have been observed at higher abundance in groups with increased depression risk.[87] Among patients with depressive disorder, the Gram-negative genus Alistipes—implicated in multiple metabolic pathways and potentially relevant to brain function—has been reported to be enriched in the gut.[88] Adverse childhood experiences may reduce beneficial taxa while increasing pro-inflammatory microbes, thereby heightening vulnerability to MDD in adolescents.[89] In school-aged children with depressive disorder, fecal microbiota profiles show increased abundance of pro-inflammatory bacteria and reduced abundance of anti-inflammatory bacteria, and these alterations have been reported to correlate inversely with the pro-inflammatory cytokine interleukin-17,[90] offering potential mechanistic clues for depression in this population.

Mechanistically, thirteen gut microbial taxa, including Eggerthella, Subdoligranulum, and Coprococcus, have been linked to MDD and may contribute via pathways related to neurotransmitter metabolism (eg., serotonin, glutamate, and GABA).[91] In parallel, obesity and metabolic dysregulation—common comorbidities of MDD—are associated with BGMA dysfunction and involve multiple immunometabolic pathways.[92]

Intervention studies have explored whether probiotics can alleviate depressive symptoms by modulating the gut microbiota. In patients with depression, probiotic supplementation has been associated with reduced depressive symptoms and increased serum BDNF levels.[93] Probiotic administration to students experiencing academic stress has been reported to improve mental health status.[94] In women with postpartum depression, supplementation with a probiotic formulation containing Limosilactobacillus reuteri PBS072 and Bifidobacterium breve BB077 significantly improved maternal mood and breastfeeding quality.[95] In major depressive disorder, Bifidobacterium breve supplementation has been reported to alleviate depressive symptoms, potentially through effects on gut microbial composition and tryptophan metabolism.[96]

From a genomic and metagenomic perspective, Wang et al identified 22 gut fungal biomarkers associated with MDD, six of which showed statistically significant associations,[97] suggesting that gut microorganisms may have value as microbial biomarkers for depression. Moreover, gut microbes can convert dietary phenylalanine into phenylacetic acid, and elevated phenylacetic acid levels may promote the development of MDD (Table 2).[98]

However, not all probiotic studies have reported positive findings. Two recent large randomized controlled trials found no significant difference between specific strain combinations and placebo in reducing depressive symptoms.[99,100] Meta-analytic evidence also highlights this inconsistency: while probiotics showed a significant improvement on the self-rated Beck Depression Inventory (BDI), no significant effects were observed on clinician-rated HAMD or on DASS and MADRS.[101] These discrepancies underscore the importance of strain specificity, the sensitivity and comparability of outcome measures, and baseline microbiome composition in predicting treatment response. They also suggest that current probiotic strategies may be insufficient to address the biological heterogeneity of depression. Future trials may benefit from personalized designs informed by baseline microbiome profiling and inflammatory biomarkers to reduce heterogeneity and improve reproducibility.

Therapeutic Potential of Targeting the BGMA in MDD

Pharmacological Treatment

Pharmacotherapy remains a mainstay for MDD, and drug development targeting the BGMA offers an emerging therapeutic direction. Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors are commonly recommended

Table 2 Clinical Studies of the BGMA in MDD

Research	Grouping	Study Type	Main Findings
[92]	MDD group: 53 participants Control group: 92 participants	Cross-sectional study	MDD exhibit gut microbiota dysbiosis, which is associated with disturbed fatty acid metabolism, obesity, and depressive symptoms.
[94]	Probiotic group:44 participants Placebo group: 46 participants	RCT	Probiotic intake can prevent academic stress–induced gut microbiota dysbiosis, modulate the abundance of specific gut microbial taxa, and is associated with reduced self-reported stress and anxiety.
[97]	Training cohort (Shanxi) MDD group: 20 participants Control group: 16 participants Validation cohort (Wuhan) MDD group: 40 participants Control group: 42 participants Validation cohort (Russia) MDD group: 36 participants Control group: 36 participants	Cross-sectional study	The diversity and composition of the mid-gut fungal community were significantly altered in the MDD group compared with the control group.
[91]	MDD group: 1,054 participants Control group: 1,539 participants	Cross-sectional study	Coprococcus, Eggerthella, and other gut bacterial genera are involved in regulating the synthesis of neurotransmitters associated with MDD, such as glutamate, serotonin, and GABA.
[89]	Depression group: 60 participants Control group: 64 participants	Cross-sectional study	Adolescent MDD are closely associated with adverse childhood experiences and gut microbiota dysbiosis.
[90]	MDD group: 92 participants Control group: 48 participants	Cross-sectional study	The abundance of proinflammatory bacteria such as Prevotella and Bifidobacterium is increased, whereas the abundance of anti-inflammatory bacteria such as Bacteroides and Faecalibacterium is decreased.
[98]	MDD group: 117 participants Control group: 162 participants	Cross-sectional study	Phenaceturic acid and 1-monoheptadecanoyl glyceride were significantly negatively correlated with depressive symptom severity

as first-line agents. Notably, responders and non-responders to these medications show marked differences in gut microbiota composition and functional pathways, providing clues for microbiome-informed treatment stratification and novel intervention development.[102]

Ketamine, a newer antidepressant, also appears to exert antidepressant effects in association with microbiota and metabolite changes, implicating stress-response systems, BDNF expression, inflammatory activity, and neurotransmission.[103] In addition, a recent study in patients with depression reported—reportedly for the first time—that oral butyrate supplementation improved depressive symptoms, supporting the potential of butyrate as a candidate antidepressant agent.[104] Omega-3 polyunsaturated fatty acids have likewise been shown to alleviate depressive symptoms, potentially by improving intestinal barrier integrity, modulating neuroplasticity, and exerting anti-inflammatory and antioxidant effects.[105]

An expanding literature suggests that traditional Chinese medicines may improve depressive phenotypes by modulating the gut microbiota. For example, Xiaoyaosan has been reported to reshape the gut microbiota and inhibit the Toll-like receptor 4/NOD-like receptor family pyrin domain-containing 3 signaling pathway, thereby helping maintain intestinal and blood–brain barrier integrity and reducing depression-like behaviors in rats.[106] Berberine has been shown to increase hippocampal levels of serotonin, norepinephrine, dopamine, and BDNF, improving depression-like behaviors in rats.[107] Magnolia alkaloids have also been reported to regulate BGMA-related pathways and attenuate anxiety- and depression-like behaviors by modulating gut microbiota and specific microbial metabolic pathways.[108]

In parallel, probiotic treatment in stressed rats has been reported to normalize aberrant levels of BDNF, serotonin, inflammatory cytokines, and dopamine in the hippocampus and frontal cortex, restore microbial composition and metabolite profiles, remodel gut–brain signaling, and alleviate depression-like behaviors.[109] Antibiotics have also been proposed to ameliorate depressive symptoms by correcting dysbiosis and reducing intestinal inflammation.[110] However, other evidence indicates that antibiotic use is significantly associated with increased depression risk, suggesting

antibiotics may function as a risk factor for MDD.[111] Thus, the antidepressant impact of antibiotics remains controversial. The seemingly bidirectional effects—beneficial in some contexts yet harmful in others—may reflect class- and spectrum-dependent impacts on microbiome composition; broad-spectrum agents are more likely to induce more severe dysbiosis. Future research should therefore investigate antibiotic effects by specific classes and exposure patterns rather than treating "antibiotics" as a homogeneous intervention.

Physical Therapies

Physical therapies show growing promise for the treatment of MDD and may, at least in part, engage the BGMA. In mouse models, transcutaneous auricular vagus nerve stimulation has been reported to alleviate depression-like behaviors by attenuating peripheral inflammation and by partially normalizing bile acid and lipid metabolic disturbances associated with gut microbial dysbiosis.[112] Transcranial magnetic stimulation may likewise improve depressive symptoms through effects on BGMA-related processes; a plausible mechanism is the modulation of central neural activity within circuits that maintain bidirectional communication with the gut, thereby indirectly shaping gut microbial function.[113] However, direct evidence linking post-Transcranial magnetic stimulation clinical improvement to specific, reproducible microbiome changes remains limited, and the observed benefits may be mediated predominantly by primary cortical modulation rather than by downstream gut–brain-axis alterations.

Similarly, transcranial direct current stimulation can modify cortical excitability, enhance vagal tone, suppress cytokine production, and influence intestinal activity, collectively contributing to the alleviation of depressive symptoms.[114] Electroconvulsive therapy, an established and effective intervention for MDD, has also been reported to be associated with shifts in microbial communities.[115] Although the available evidence has focused on the oral microbiota, these findings offer a useful perspective for examining potential links between electroconvulsive therapy and the gut microbiome. In addition, acupuncture has attracted increasing attention as an adjunctive approach for depression and may reduce depressive symptoms by modulating dysbiotic gut microbial profiles and dampening systemic inflammatory responses.[116]

Overall, research connecting physical therapies to the BGMA remains at an early stage, with much of the mechanistic evidence derived from preclinical models. Well-designed clinical studies integrating longitudinal microbiome profiling with standardized psychiatric outcomes and mechanistic endpoints are needed to clarify causal pathways, define therapeutic magnitude, and establish clinical safety.

Fecal Microbiota Transplantation

FMT is a therapeutic strategy in which fecal microbiota from a healthy donor are transferred into a recipient's gastrointestinal tract, with the primary goal of restoring microbial homeostasis. FMT is generally thought to operate through three main mechanisms: engraftment of donor-derived microorganisms, modulation of host immune and metabolic processes, and recovery of microbial diversity.[117] In animal studies, transplantation of fecal microbiota from healthy mice into depression-model mice significantly reduced immobility time in the forced swim test, providing evidence that FMT can attenuate depressive-like behaviors in rodents.[118] Consistent with these findings, Ma et al applied FMT in mice and showed that gut microbiota manipulations can improve depressive-like behaviors, potentially via modulation of BGMA function.[119]

Although clinical evidence remains limited, several exploratory investigations have been conducted. An interventional study using enema-based FMT in patients with major depressive disorder provided preliminary clinical support for the feasibility and practicability of this approach,[120] and another study reported improvements in depressive symptoms that persisted for up to 6 months following FMT.[121] By contrast, other research suggested that a single FMT procedure may exacerbate depressive symptoms,[122] which may reflect heterogeneity in donor screening criteria, donor–recipient matching, and transplantation protocols. In addition, 5-fluorouracil, a fluorinated pyrimidine, has been reported to induce depressive-like behaviors by disrupting the BGMA, whereas FMT can reverse 5-fluorouracil–induced depressive-like phenotypes.[123]

Despite these encouraging findings, the application of FMT in MDD faces substantial challenges. Safety concerns are paramount and extend beyond the risk of infectious transmission and allergic reactions to include potential long-term metabolic consequences observed in FMT recipients treated for other indications, such as weight gain, insulin resistance, and broader metabolic perturbations. Moreover, along with potentially beneficial microbes, FMT may also inadvertently

transfer pro-inflammatory strains or antibiotic-resistance genes. Therefore, rigorous donor screening, standardized preparation and administration procedures, and long-term follow-up are indispensable prerequisites before FMT can be translated into routine clinical practice for MDD.

Dietary Modulation

Diet profoundly shapes the gut microbiota; accordingly, dietary modulation aimed at improving BGMA function may represent a promising strategy for managing MDD. Emerging evidence indicates that optimizing dietary patterns can alleviate depressive symptoms by regulating inflammation, reducing oxidative stress, reshaping gut microbial composition, and enhancing neuroplasticity.[124] For instance, a high-fiber diet has been shown to improve cognitive performance and attenuate depression-like behaviors in mice, accompanied by beneficial microbiota shifts, including enrichment of health-associated taxa and increased production of SCFAs.[21] Beyond serving as key energy substrates for intestinal epithelial cells and supporting mucosal barrier integrity, SCFAs can also influence brain activity via gut–brain signaling pathways.[125]

By contrast, high-sugar diets may promote the expansion of potentially harmful bacteria while suppressing beneficial taxa, thereby contributing to dysbiosis, impairing BGMA function, and adversely affecting brain health, including cognitive decline and mood disturbances.[126] Similarly, diets high in saturated fats can induce microbial imbalance and reduce beneficial bacteria, whereas unsaturated fatty acids tend to exert more favorable effects on the gut microbiome. Notably, omega-3 polyunsaturated fatty acids may act synergistically with probiotics via the gut–brain axis, modulating the hypothalamic–pituitary–adrenal axis and serotonin-related metabolic pathways, and thereby influencing hormonal profiles, neurotrophic factors, and microbial ecology; these effects may reduce depression risk or improve depressive symptoms.[127] Tea consumption may also interact with the microbiota, as intestinal microbes biotransform tea polyphenols into more bioactive metabolites that could, through BGMA-related mechanisms, contribute to symptom relief.[128]

Nevertheless, dietary approaches typically require sustained, long-term adherence, and responses to specific dietary components can vary substantially across individuals. Moreover, dietary interventions are often constrained by poor long-term compliance and difficult-to-control confounding factors, complicating causal attribution of clinical effects specifically to microbiome changes. Digital health tools that enable real-time dietary monitoring and just-in-time adaptive interventions may improve adherence; however, how such tools can be integrated with microbiome-targeted strategies for depression has not yet been systematically explored.

Discussion

The association between the BGMA and depression is unlikely to be explained by a single "pathogenic bacterium" or a single pathway; rather, it reflects a coupled system integrating neural circuits, stress–endocrine regulation, immune–inflammatory networks, neurotransmission, and metabolic–barrier processes. The central challenge in translating preclinical BGMA findings into reproducible clinical benefit is therefore not a lack of mechanistic hypotheses, but fragmentation of the evidentiary chain across levels of analysis: robust behavioral and molecular readouts are often observable in animal models, yet analogous effects are frequently difficult to replicate in human trials. This gap may partly reflect fundamental interspecies differences in microbial ecology and host physiology,[129] and may also be inflated by publication bias toward positive preclinical findings, which can overestimate true effect sizes. At the same time, the heterogeneity of MDD in humans far exceeds standardized animal paradigms: symptom dimensions, comorbidity burden, prior exposures to antidepressants and antibiotics, and differences in diet and sleep–circadian patterns can all reshape microbial composition and alter the "gain" of gut–brain signaling, yielding clinically divergent results.

At present, the frequently noted inconsistency in "depression-associated genera" across studies often appears to arise from the combined effects of methodological and population differences rather than true biological contradiction. Sampling windows, sequencing platforms and bioinformatic pipelines, control of dietary and pharmacological confounding, and reliance on genus/species-level taxonomic signals in place of functional pathway readouts all undermine reproducibility. More importantly, most clinical studies remain cross-sectional, making it difficult to determine whether microbiome alterations represent premorbid vulnerability factors, state-dependent correlates of an episode, or amplifiers that sustain chronicity. Moving from "association" to a testable causal model requires prospective cohorts that begin prior

to illness onset and repeatedly measure, within the same individuals, microbiota profiles alongside metabolites, inflammatory/stress-axis markers, and symptom trajectories to strengthen temporal and causal inference.

Prior reviews have discussed microbiota–neurotransmitter–immune frameworks, while emphasizing that many mechanistic claims still rest largely on preclinical inference;[46] translational gaps and population heterogeneity have likewise been repeatedly highlighted.[130] On the interventional side, meta-analyses of probiotics suggest an overall benefit, but between-study heterogeneity is substantial and mechanistic sources of variability have not been systematically interrogated.[130] The next phase of BGMA research should shift from "identifying single taxa" to "defining stratifiable pathway-based phenotypes," followed by closed-loop mechanistic validation. First, patient-derived intestinal organoids could serve as an intermediate validation platform: they preserve human genetic context while enabling controlled manipulation of candidate microbes or metabolites, allowing direct assessment of barrier integrity, cytokine release, and other key endpoints before advancing the most robust signals into clinical trials.[131] Second, trials should prespecify stratification and matching strategies—for example, defining an inflammation-associated phenotype using inflammatory biomarkers,[132] identifying stress-sensitive subtypes using the cortisol awakening response or histories of childhood adversity,[133] and incorporating vagal metrics, dynamic HPA-axis readouts, and immune/metabolic pathway measures as mechanistic endpoints rather than relying solely on symptom scales.

Finally, methodological standardization and data sharing are practical prerequisites for improving reproducibility. Multi-center consortia focused on psychiatric phenotypes, harmonized metagenomic and metabolomic measurements, and rigorous documentation of diet and medication exposures would substantially reduce the extent to which between-study differences drive inconsistent conclusions. Emerging approaches such as engineered probiotics,[134] together with mechanistic readouts from PET/fMRI, may help shorten the distance from mechanism to clinical translation, but their cost, accessibility, and target populations should be evaluated within real-world implementation frameworks.

Conclusion

This review summarizes evidence for the bidirectional association between MDD and the BGMA. We systematically integrate mechanistic pathways involving the vagus nerve, the HPA axis, immune–inflammatory signaling, neurotransmission, endocrine regulation, and metabolic processes, and we comparatively evaluate the strength and limitations of evidence from preclinical models, clinical observations, and BGMA-targeted interventions. Overall, existing studies support a multi-pathway, coupled role of the BGMA in shaping affective and stress-related phenotypes; however, major bottlenecks remain, including population heterogeneity, methodological variability, and an incompletely established causal chain, which together limit the robustness and reproducibility of some clinical conclusions.

Future work should move beyond describing differences in individual taxa and instead develop pathway-based models that can be directly tested. Longitudinal cohorts and stratified randomized trials should incorporate paired metagenomic and metabolomic profiling, together with dynamic assessments of inflammatory status, HPA-axis reactivity, barrier function, and vagus nerve–related markers. To improve reproducibility, standardized multi-center protocols and data sharing will be essential, providing a more rigorous evidentiary foundation for subsequent personalized BGMA-targeted interventions. In sum, the BGMA offers a biologically interpretable and translationally relevant framework for understanding the onset and maintenance of MDD.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by grants from the following funding programs: National Natural Science Foundation of China (82560282, 82160269, 82360275); the Scientific Research Fund Project of Yunnan Provincial Department of Education (2024Y248); the Program Projects of Yunnan Provincial Science and Technology Department (202301AY070001-020,

202405AC350104, 202203AC100007, 202301AY070001-145); and the Scientific Research Projects of Yunnan Clinical Medical Center for Mental Disorders (2024YNLCYXZX0277, 2024YNLCYXZX0278).

Disclosure

The authors declare that they have no competing interests.

References

1. Sun LJ, Li JN, Nie YZ. Gut hormones in microbiota-gut-brain cross-talk. *Chin Med J*. 2020;133(7):826–833. doi:10.1097/CM9.0000000000000706
2. Rusch JA, Layden BT, Dugas LR. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. *Front Endocrinol*. 2023;14:1130689.
3. Müller L, Di Benedetto S. Bridging the brain and gut: neuroimmune mechanisms of neuroinflammation and therapeutic insights. *Front Cell Neurosci*. 2025;19:1590002. doi:10.3389/fncel.2025.1590002
4. Binder LB, Menegatti Bevilacqua L, Gro Lorentzen Thomassen F, Lebel M, Jensen B, Menard C. Across barriers: blood-brain and gut barrier signaling in psychiatric disorders. *J Neurochem*. 2025;169(11):e70282. doi:10.1111/jnc.70282
5. Cao Q, Shen M, Li R, et al. Elucidating the specific mechanisms of the gut-brain axis: the short-chain fatty acids-microglia pathway. *J Neuroinflammation*. 2025;22(1):133. doi:10.1186/s12974-025-03454-y
6. Logsdon AF, Erickson MA, Rhea EM, Salameh TS, Banks WA. Gut reactions: how the blood-brain barrier connects the microbiome and the brain. *Exp Biol Med*. 2018;243(2):159–165. doi:10.1177/1535370217743766
7. Zhuang M, Zhang X, Cai J. Microbiota-gut-brain axis: interplay between microbiota, barrier function and lymphatic system. *Gut Microbes*. 2024;16(1):2387800. doi:10.1080/19490976.2024.2387800
8. Jing Y, Zhang M, Liu Y, et al. Neural mechanisms of suicide thoughts and behaviors in major depressive disorder: abnormal regional brain activity and its functional connectivity. *BMC Psychiatry*. 2025;25(1):1040. doi:10.1186/s12888-025-07483-y
9. Morena D, Lippi M, Scopetti M, Turillazzi E, Fineschi V. Leaky gut biomarkers as predictors of depression and suicidal risk: a systematic review and meta-analysis. *Diagnostics*. 2025;15(13):1683. doi:10.3390/diagnostics15131683
10. Cussotto S, Colle R, Voican CS, et al. The gut microbiota is altered in antidepressant-free depressed patients and is associated with depression severity. *J Neurochem*. 2025;169(7):e70173. doi:10.1111/jnc.70173
11. Kelly JR, Borre Y, O' Brien C, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. *J Psychiatr Res*. 2016;82:109–118. doi:10.1016/j.jpsychires.2016.07.019
12. Böttcher E, Schreiber LS, Wozniak D, Scheller E, Schmidt FM, Pelz JO. Impaired modulation of the autonomic nervous system in adult patients with major depressive disorder. *Biomedicines*. 2024;12(6):1268. doi:10.3390/biomedicines12061268
13. Han Y, Wang B, Gao H, et al. Vagus nerve and underlying impact on the gut microbiota-brain axis in behavior and neurodegenerative diseases. *J Inflamm Res*. 2022;15:6213–6230. doi:10.2147/JIR.S384949
14. Cheng J, Hu H, Ju Y, et al. Gut microbiota-derived short-chain fatty acids and depression: deep insight into biological mechanisms and potential applications. *Gen Psychiatr*. 2024;37(1):e101374. doi:10.1136/gpsych-2023-101374
15. Li J, Wan B, Zhou L, et al. Gut microbiota dysbiosis induces neuroinflammation in major depressive disorders: mechanisms targeting the gut-brain axis. *Front Psychiatry*. 2025;16:1629182. doi:10.3389/fpsyt.2025.1629182
16. Hashimoto K. Neuroinflammation through the vagus nerve-dependent gut-microbiota-brain axis in treatment-resistant depression. *Prog Brain Res*. 2023;278:61–77.
17. Lukić I, Ivković S, Mitić M, Adžić M. Tryptophan metabolites in depression: modulation by gut microbiota. *Front Behav Neurosci*. 2022;16:987697. doi:10.3389/fnbeh.2022.987697
18. Huertas-Díaz L, Vestergaard LG, Marietou A, et al. Insights into the utilisation of 1,2-propanediol and interactions with the cell envelope of Clostridium perfringens. *Gut Pathog*. 2025;17(1):23. doi:10.1186/s13099-025-00689-1
19. Shabani M, Ghoshehy A, Mottaghi AM, et al. The relationship between gut microbiome and human diseases: mechanisms, predisposing factors and potential intervention. *Front Cell Infect Microbiol*. 2025;15:1516010. doi:10.3389/fcimb.2025.1516010
20. Paul JK, Azmal M, Haque A, Meem M, Talukder OF, Ghosh A. Unlocking the secrets of the human gut microbiota: comprehensive review on its role in different diseases. *World J Gastroenterol*. 2025;31(5):99913. doi:10.3748/wjg.v31.i5.99913
21. Tanabe M, Kunisawa K, Saito I, et al. High-Cellulose diet ameliorates cognitive impairment by modulating gut microbiota and metabolic pathways in mice. *J Nutr*. 2025;155(6):1689–1699. doi:10.1016/j.tjnut.2025.04.004
22. Schoultz I, Claesson MJ, Dominguez-Bello MG, et al. Gut microbiota development across the lifespan: disease links and health-promoting interventions. *J Intern Med*. 2025;297(6):560–583. doi:10.1111/joim.20089
23. Bekbossynova M, Saliev T, Ivanova-Razumova T, Andossova S, Kali A, Myrzakhmetova G. Beyond cholesterol: emerging risk factors in atherosclerosis. *J Clin Med*. 2025;14(7):2352. doi:10.3390/jcm14072352
24. Minaya DM, Hoss A, Bhagat A, Guo TL, Czaja K. Sex-Specific effect of a high-energy diet on body composition, gut microbiota, and inflammatory markers in rats. *Nutrients*. 2025;17(7):1147. doi:10.3390/nu17071147
25. Dziedziak M, Mytych A, Szyller HP, et al. Gut microbiota in psychiatric and neurological disorders: current insights and therapeutic implications. *Biomedicines*. 2025;13(9):2104. doi:10.3390/biomedicines13092104
26. Lee JY, Liu YH, Hsieh CL, Lung FW. The clinical utility of the immune status questionnaire as a marker of immune function among persons with schizophrenia. *Sci Prog*. 2025;108(4):368504251405328. doi:10.1177/00368504251405328
27. Lin X, Huang J, Wang S, Zhang K. Bipolar disorder and the gut microbiota: a bibliometric analysis. *Front Neurosci*. 2024;18:1290826. doi:10.3389/fnins.2024.1290826
28. Pasqualette L, Fidalgo T, Freitas-Fernandes LB, et al. Alterations in vagal tone are associated with changes in the gut microbiota of adults with anxiety and depression symptoms: analysis of fecal metabolite profiles. *Metabolites*. 2024;14(8):450. doi:10.3390/metabo14080450

29. Ke S, Hartmann J, Ressler KJ, Liu YY, Koenen KC. The emerging role of the gut microbiome in posttraumatic stress disorder. *Brain Behav Immun*. 2023;114:360–370. doi:10.1016/j.bbi.2023.09.005
30. Mavel S, Pellé L, Andres CR. Impact of maternal microbiota imbalance during pregnancy on fetal cerebral neurodevelopment: is there a link to certain autistic disorders. *Brain Behav Immun Health*. 2025;48:101074. doi:10.1016/j.bbih.2025.101074
31. Yang Y, Eguchi A, Wan X, Mori C, Hashimoto K. Depression-like phenotypes in mice with hepatic ischemia/reperfusion injury: a role of gut-microbiota-liver-brain axis via vagus nerve. *J Affect Disord*. 2024;345:157–167. doi:10.1016/j.jad.2023.10.142
32. Ashique S, Mohanto S, Ahmed MG, et al. Gut-brain axis: a cutting-edge approach to target neurological disorders and potential synbiotic application. *Heliyon*. 2024;10(13):e34092. doi:10.1016/j.heliyon.2024.e34092
33. Jameson KG, Kazmi SA, Ohara TE, et al. Select microbial metabolites in the small intestinal lumen regulate vagal activity via receptor-mediated signaling. *iScience*. 2025;28(2):111699. doi:10.1016/j.isci.2024.111699
34. Krieger JP, Skibicka KP. From physiology to psychiatry: key role of vagal interoceptive pathways in emotional control. *Biol Psychiatry*. 2025;98(6):466–475. doi:10.1016/j.biopsych.2025.04.012
35. Okonogi T, Kuga N, Yamakawa M, Kayama T, Ikegaya Y, Sasaki T. Stress-induced vagal activity influences anxiety-relevant prefrontal and amygdala neuronal oscillations in male mice. *Nat Commun*. 2024;15(1):183. doi:10.1038/s41467-023-44205-y
36. Suica Z, Behrendt F, Ziller C, et al. Comparative effectiveness of non- pharmacological treatments in patients with persistent postural-perceptual dizziness: a systematic review and effect sizes analyses. *Front Neurol*. 2024;15:1426566. doi:10.3389/fneur.2024.1426566
37. Bear T, Dalziel J, Coad J, Roy N, Butts C, Gopal P. The microbiome-gut-brain axis and resilience to developing anxiety or depression under stress. *Microorganisms*. 2021;9(4):723. doi:10.3390/microorganisms9040723
38. Rosas-Sánchez GU, Germán-Ponciano LJ, Puga-Olguín A, et al. Gut-Brain axis in mood disorders: a narrative review of neurobiological insights and probiotic interventions. *Biomedicines*. 2025;13(8):1831. doi:10.3390/biomedicines13081831
39. Alcántara-Alonso V, García-Luna C, Soberanes-Chávez P, Estrada-Camarena E, de Gortari P. Two adverse early life events induce differential changes in brain CRH and serotonin systems in rats along with hyperphagia and depression. *J Integr Neurosci*. 2024;23(2):41. doi:10.31083/j.jin2302041
40. Chen Y, Chen X, Lin S, et al. Effects of psychological stress on inflammatory bowel disease via affecting the microbiota-gut-brain axis. *Chin Med J*. 2025;138(6):664–677. doi:10.1097/CM9.0000000000003389
41. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: regulation by the microbiome. *Neurobiol Stress*. 2017;7:124–136. doi:10.1016/j.ynstr.2017.03.001
42. Gwak MG, Chang SY. Gut-Brain connection: microbiome, gut barrier, and environmental sensors. *Immune Netw*. 2021;21(3):e20. doi:10.4110/in.2021.21.e20
43. Młynarska E, Gadzinowska J, Tokarek J, et al. The role of the microbiome-brain-gut axis in the pathogenesis of depressive disorder. *Nutrients*. 2022;14(9):1921. doi:10.3390/nu14091921
44. Herberger L, Gilliam S, Hosseini M, et al. Assessing the effectiveness of propranolol in treating pediatric airway hemangiomas: a systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol*. 2025;198:112576. doi:10.1016/j.ijporl.2025.112576
45. Robinson JM, Crino OL, Camargo A, Breed MF. Does a microbial-endocrine interplay shape love-associated emotions in humans? A hypothesis. *mSystems*. 2025;10(8):e0041525. doi:10.1128/msystems.00415-25
46. Zhu Z, Cheng Y, Liu X, et al. The microbiota-gut-brain axis in depression: unraveling the relationships and therapeutic opportunities. *Front Immunol*. 2025;16:1644160. doi:10.3389/fimmu.2025.1644160
47. Khan MT, Zohair M, Khan A, Kashif A, Mumtaz S, Muskan F. From gut to brain: the roles of intestinal microbiota, immune system, and hormones in intestinal physiology and gut-brain-axis. *Mol Cell Endocrinol*. 2025;607:112599. doi:10.1016/j.mce.2025.112599
48. Schneider E, Spetter MS, Martin E, et al. The effect of intranasal insulin on appetite and mood in women with and without obesity: an experimental medicine study. *Int J Obes*. 2022;46(7):1319–1327. doi:10.1038/s41366-022-01115-1
49. Mattar L, Delaunay AL, Berthoz S, et al. Exploring the interplay between thyroid hormone levels and symptoms of anxiety and depression in anorexia nervosa. *Brain Behav*. 2025;15(7):e70685. doi:10.1002/brb3.70685
50. Petrine J, Jacques LS, Da Cruz Santos TM, Pereira F, Castelo PM, Borges B. The impact of mental health and psychological stressors on menstrual cycle modulation: exploring the influence of age and hormonal contraceptives. *Arch Womens Ment Health*. 2025;28(2):321–327. doi:10.1007/s00737-024-01499-1
51. Xu M, Zhou EY, Shi H. Tryptophan and its metabolite serotonin impact metabolic and mental disorders via the brain-gut-microbiome axis: a focus on sex differences. *Cells*. 2025;14(5):384. doi:10.3390/cells14050384
52. Qu S, Yu Z, Zhou Y, et al. Gut microbiota modulates neurotransmitter and gut-brain signaling. *Microbiol Res*. 2024;287:127858. doi:10.1016/j.micres.2024.127858
53. Hamamah S, Aghazarian A, Nazaryan A, Hajnal A, Covasa M. Role of microbiota-gut-brain axis in regulating dopaminergic signaling. *Biomedicines*. 2022;10(2):436. doi:10.3390/biomedicines10020436
54. Sendi M, Halko M, Traynor J, et al. Comprehensive mapping of cognitive and emotion networks in stress, anxiety, and depression implicates the precuneus as a critical hub. *Res Sq*. 2025:rs–3.
55. Zhou L, Wu Q, Jiang L, et al. Role of the microbiota in inflammation-related related psychiatric disorders. *Front Immunol*. 2025;16:1613027. doi:10.3389/fimmu.2025.1613027
56. Park JC, Chang L, Kwon HK, Im SH. Beyond the gut: decoding the gut-immune-brain axis in health and disease. *Cell Mol Immunol*. 2025;22(11):1287–1312. doi:10.1038/s41423-025-01333-3
57. Zhao H, Tao L, Tang C, Cai W, Shen W. Do immune system and microbiome-gut-brain axis interactions associate with major depressive disorder. *J Transl Med*. 2025;23(1):1279. doi:10.1186/s12967-025-07176-w
58. Liu P, Liu Z, Wang J, et al. Immunoregulatory role of the gut microbiota in inflammatory depression. *Nat Commun*. 2024;15(1):3003. doi:10.1038/s41467-024-47273-w
59. Atanasova K, Knödler LL, Reindl W, Ebert MP, Thomann AK. Role of the gut microbiome in psychological symptoms associated with inflammatory bowel diseases. *Semin Immunopathol*. 2025;47(1):12. doi:10.1007/s00281-025-01036-x
60. Yu X, Yao H, Zhang X, Liu L, Liu S, Dong Y. Comparison of LPS and MS-induced depressive mouse model: behavior, inflammation and biochemical changes. *BMC Psychiatry*. 2022;22(1):590. doi:10.1186/s12888-022-04233-2

61. Yu X, Zuo Y, Yang Y, et al. Mechanism of microbiota-gut-brain in perimenopausal depression: an inflammatory perspective. *Expert Rev Mol Med*. 2025;27:e28. doi:10.1017/erm.2025.10011
62. Xu Q, Sun L, Chen Q, et al. Gut microbiota dysbiosis contributes to depression-like behaviors via hippocampal NLRP3-mediated neuroinflammation in a postpartum depression mouse model. *Brain Behav Immun*. 2024;119:220–235. doi:10.1016/j.bbi.2024.04.002
63. Felger JC, Capuron L. Special issue: the intersection of inflammation and metabolism in neuropsychiatric disorders. *Brain Behav Immun*. 2021;93:331–334. doi:10.1016/j.bbi.2020.12.025
64. Mac Giollabhui N, Madison AA, Lydston M, Lenoel Quang E, Miller AH, Liu RT. Effect of anti-inflammatory treatment on depressive symptom severity and anhedonia in depressed individuals with elevated inflammation: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry*. 2026;183(1):70–79. doi:10.1176/appi.ajp.20241115
65. Du Y, Dou Y, Wang M, et al. Efficacy and acceptability of anti-inflammatory agents in major depressive disorder: a systematic review and meta-analysis. *Front Psychiatry*. 2024;15:1407529. doi:10.3389/fpsyt.2024.1407529
66. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 2013;70(1):31–41. doi:10.1001/2013.jamapsychiatry.4
67. De Cillis F, Petrillo G, I D, et al. Prenatal stress rewires the gut-brain axis: long-term, sex-specific effects on microbiota, intestinal barrier, and hippocampal inflammation. *Nutrients*. 2025;17(17):2812. doi:10.3390/nu17172812
68. Qiao Y, Cheng R, Zheng H, et al. The impact of a high-fat diet (HFD) on mouse behavior, neurotransmitters, inflammation, and gut-brain axis metabolism under hypoxic conditions. *Behav Brain Res*. 2025;495:115782. doi:10.1016/j.bbr.2025.115782
69. Cao Y, Fan X, Zang T, et al. Gut microbiota causes depressive phenotype by modulating glycerophospholipid and sphingolipid metabolism via the gut-brain axis. *Psychiatry Res*. 2025;346:116392. doi:10.1016/j.psychres.2025.116392
70. Shen H, Zhang C, Zhang Q, et al. Gut microbiota modulates depressive-like behaviors induced by chronic ethanol exposure through short-chain fatty acids. *J Neuroinflammation*. 2024;21(1):290. doi:10.1186/s12974-024-03282-6
71. Jia M, Fan Y, Ma Q, et al. Gut microbiota dysbiosis promotes cognitive impairment via bile acid metabolism in major depressive disorder. *Transl Psychiatry*. 2024;14(1):503. doi:10.1038/s41398-024-03211-4
72. Yassin LK, Skrabulyte-Barbulescu J, Alshamsi SH, et al. The microbiota-gut-brain axis in mental and neurodegenerative disorders: opportunities for prevention and intervention. *Front Aging Neurosci*. 2025;17:1667448. doi:10.3389/fnagi.2025.1667448
73. Chang L, Wei Y, Hashimoto K. Brain-gut-microbiota axis in depression: a historical overview and future directions. *Brain Res Bull*. 2022;182:44–56. doi:10.1016/j.brainresbull.2022.02.004
74. Zhu S, Li X, Yu Y, et al. EZH2-mediated H3K27me3 links microbial inosine loss to depression: a gut-brain epigenetic switch. *Theranostics*. 2025;15(18):9969–9986. doi:10.7150/thno.120824
75. Liu L, Wang H, Zhang H, et al. Toward a deeper understanding of gut microbiome in depression: the promise of clinical applicability. *Adv Sci*. 2022;9(35):e2203707. doi:10.1002/advs.202203707
76. Ugwu OP, Okon MB, Alum EU, et al. Unveiling the therapeutic potential of the gut microbiota-brain axis: novel insights and clinical applications in neurological disorders. *Medicine*. 2025;104(30):e43542. doi:10.1097/MD.0000000000043542
77. Zhao F, Wang K, Wen Y, et al. Contribution of hippocampal BDNF/CREB signaling pathway and gut microbiota to emotional behavior impairment induced by chronic unpredictable mild stress during pregnancy in rats offspring. *PeerJ*. 2022;10:e13605. doi:10.7717/peerj.13605
78. Zhang H, Wei H, Qin X, et al. Is anxiety and depression transmissible? Depressed mother rats transmit anxiety- and depression-like phenotypes to cohabited rat pups through gut microbiota assimilation. *J Affect Disord*. 2024;366:124–135. doi:10.1016/j.jad.2024.08.164
79. Mao Q, Zhang H, Zhang Z, et al. Co-decoction of lilii bulbus and radix rehmannia recens and its key bioactive ingredient verbascoside inhibit neuroinflammation and intestinal permeability associated with chronic stress-induced depression via the gut microbiota-brain axis. *Phytomedicine*. 2024;129:155510. doi:10.1016/j.phymed.2024.155510
80. He H, Zhao Z, Xiao C, et al. Gut microbiome promotes mice recovery from stress-induced depression by rescuing hippocampal neurogenesis. *Neurobiol Dis*. 2024;191:106396. doi:10.1016/j.nbd.2023.106396
81. Cai T, Zheng SP, Shi X, et al. Therapeutic effect of fecal microbiota transplantation on chronic unpredictable mild stress-induced depression. *Front Cell Infect Microbiol*. 2022;12:900652. doi:10.3389/fcimb.2022.900652
82. Huang Y, You Y, Wang W, et al. Adenosine regulates depressive behavior in mice with chronic social defeat stress through gut microbiota. *Neuropharmacology*. 2025;262:110209. doi:10.1016/j.neuropharm.2024.110209
83. Lv WJ, Wu XL, Chen WQ, et al. The gut microbiome modulates the changes in liver metabolism and in inflammatory processes in the brain of chronic unpredictable mild stress rats. *Oxid Med Cell Longev*. 2019;2019:7902874. doi:10.1155/2019/7902874
84. Jiang W, Li Y, Yang J, et al. Chronic stress in mice: how gut bacteria influence gene activity in key brain neurons. *Transl Psychiatry*. 2025;15(1):262. doi:10.1038/s41398-025-03479-0
85. Liu X, Teng T, Li X, et al. Impact of inosine on chronic unpredictable mild stress-induced depressive and anxiety-like behaviors with the alteration of gut microbiota. *Front Cell Infect Microbiol*. 2021;11:697640. doi:10.3389/fcimb.2021.697640
86. Wang Y, Cui P, Cao M, et al. Chronic restraint stress affects the diurnal rhythms of gut microbial composition and metabolism in a mouse model of depression. *BMC Microbiol*. 2025;25(1):38. doi:10.1186/s12866-025-03764-4
87. Liang S, Sin ZY, Yu J, et al. Multi-cohort analysis of depression-associated gut bacteria sheds insight on bacterial biomarkers across populations. *Cell Mol Life Sci*. 2022;80(1):9. doi:10.1007/s00018-022-04650-2
88. Liu S, Li Y, Shi Y, et al. Multi-omics analyses of the gut microbiome, fecal metabolome, and multimodal brain MRI reveal the role of Alistipes and its related metabolites in major depressive disorder. *Psychol Med*. 2025;55:e190. doi:10.1017/S003329172510072X
89. Bai Y, Shu C, Zhang S, et al. The role of gut microbiota in adolescent depression: insights from adverse childhood experiences. *J Affect Disord*. 2026;392:120141. doi:10.1016/j.jad.2025.120141
90. Ling Z, Cheng Y, Chen F, et al. Changes in fecal microbiota composition and the cytokine expression profile in school-aged children with depression: a case-control study. *Front Immunol*. 2022;13:964910. doi:10.3389/fimmu.2022.964910
91. Radjabzadeh D, Bosch JA, Uitterlinden AG, et al. Gut microbiome-wide association study of depressive symptoms. *Nat Commun*. 2022;13(1):7128. doi:10.1038/s41467-022-34502-3

92. Cao B, Lu C, Yan L, McIntyre RS, Teopiz KM, Zhan L. The dysbiosis of gut microbiota in major depressive disorder and comorbidity with overweight/obesity: unraveling biomarkers and metabolic pathways from a microbial perspective. *BMC Psychiatry*. 2025;25(1):1069. doi:10.1186/s12888-025-07388-w
93. Dehghani F, Abdollahi S, Shidfar F, Clark C, Soltani S. Probiotics supplementation and brain-derived neurotrophic factor (BDNF): a systematic review and meta-analysis of randomized controlled trials. *Nutr Neurosci*. 2023;26(10):942–952. doi:10.1080/1028415X.2022.2110664
94. Vázquez-Castellanos JF, Maciel LF, Wauters L, et al. Probiotic-mediated modulation of gut microbiome in students exposed to academic stress: a randomized controlled trial. *NPJ Biofilms Microbiomes*. 2025;11(1):140. doi:10.1038/s41522-025-00776-w
95. Vicariotto F, Malfa P, Torricelli M, Lungaro L, Caio G, De Leo V. Beneficial effects of limosilactobacillus reuteri PBS072 and bifidobacterium breve BB077 on mood imbalance, self-confidence, and breastfeeding in women during the first trimester postpartum. *Nutrients*. 2023;15(16):3513. doi:10.3390/nu15163513
96. Tian P, Chen Y, Zhu H, et al. Bifidobacterium breve CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: a randomized clinical trial. *Brain Behav Immun*. 2022;100:233–241. doi:10.1016/j.bbi.2021.11.023
97. Wang X, Cao D, Chen W, Sun J, Hu H. Metagenomics reveals unique gut mycobiome biomarkers in major depressive disorder - a non-invasive method. *Front Cell Infect Microbiol*. 2025;15:1582522. doi:10.3389/fcimb.2025.1582522
98. Ren S, Qin P, Wang Y, et al. Sex differences in fecal metabolic profiles of major depressive disorder: unveiling sex-specific metabolomic panel. *BMC Psychiatry*. 2025;25(1):720. doi:10.1186/s12888-025-07156-w
99. Ullah H, Di Minno A, Esposito C, et al. Efficacy of a food supplement based on S-adenosyl methionine and probiotic strains in subjects with subthreshold depression and mild-to-moderate depression: a monocentric, randomized, cross-over, double-blind, placebo-controlled clinical trial. *Biomed Pharmacother*. 2022;156:113930. doi:10.1016/j.biopha.2022.113930
100. Sarkawi M, Raja Ali RA, Abdul Wahab N, Abdul Rathi ND, Mokhtar NM. A randomized, double-blinded, placebo-controlled clinical trial on Lactobacillus-containing cultured milk drink as adjuvant therapy for depression in irritable bowel syndrome. *Sci Rep*. 2024;14(1):9478. doi:10.1038/s41598-024-60029-2
101. Nikolova VL, Cleare AJ, Young AH, Stone JM. Updated review and meta-analysis of probiotics for the treatment of clinical depression: adjunctive vs stand-alone treatment. *J Clin Med*. 2021;10(4):647.
102. Du JY, Qin FL, Yang RN, et al. Metagenomic analysis of the gut microbiota in major depressive disorder with different antidepressant efficacy: a prospective cohort study. *J Affect Disord*. 2026;394(Pt B):120709. doi:10.1016/j.jad.2025.120709
103. Hua H, Huang C, Liu H, et al. Depression and antidepressant effects of ketamine and its metabolites: the pivotal role of gut microbiota. *Neuropharmacology*. 2022;220:109272. doi:10.1016/j.neuropharm.2022.109272
104. Korenblik V, Korosi A, Brul S, Bockting C, Nieuwdorp M, Lok A. Feasibility and acceptability of 8-week oral tributyrin supplementation as add on to antidepressant medication in patients with depression: a study protocol paper for a pilot, randomised controlled trial. *BMJ Open*. 2025;15(11):e108423. doi:10.1136/bmjopen-2025-108423
105. De Cillis F, Begni V, Genini P, Leo D, Riva MA, Cattaneo A. Restoring balance: the role of omega-3 polyunsaturated fatty acids on the gut-brain axis and other interconnected biological pathways to improve depression. *Nutrients*. 2025;17(21):3426. doi:10.3390/nu17213426
106. Liu X, Liu H, Wu X, et al. Xiaoyaosan against depression through suppressing LPS mediated TLR4/NLRP3 signaling pathway in "microbiota-gut-brain" axis. *J Ethnopharmacol*. 2024;335:118683. doi:10.1016/j.jep.2024.118683
107. Huang M, He Y, Tian L, et al. Gut microbiota-SCFAs-brain axis associated with the antidepressant activity of berberine in CUMS rats. *J Affect Disord*. 2023;325:141–150. doi:10.1016/j.jad.2022.12.166
108. Wang L, Li M, Dong Y, et al. Magnoflorine alleviates colitis-induced anxiety-like behaviors by regulating gut microbiota and microglia-mediated neuroinflammation. *Microbiome*. 2025;13(1):172. doi:10.1186/s40168-025-02158-y
109. Satti S, Palepu M, Singh AA, et al. Anxiolytic- and antidepressant-like effects of bacillus coagulans unique IS-2 mediate via reshaping of microbiome gut-brain axis in rats. *Neurochem Int*. 2023;163:105483. doi:10.1016/j.neuint.2023.105483
110. Yu DY, Gao JQ, Yang XX, et al. Antibiotic treatment improves gut dysbiosis and depression-like behavior induced by morphine withdrawal. *Neuropharmacology*. 2025;278:110579. doi:10.1016/j.neuropharm.2025.110579
111. Hayer SS, Hwang S, Clayton JB. Antibiotic-induced gut dysbiosis and cognitive, emotional, and behavioral changes in rodents: a systematic review and meta-analysis. *Front Neurosci*. 2023;17:1237177. doi:10.3389/fnins.2023.1237177
112. Zhang X, He X, Zhao Y, et al. Transcutaneous auricular vagus nerve stimulation regulates gut microbiota mediated peripheral inflammation and metabolic disorders to suppress depressive-like behaviors in CUMS rats. *Front Microbiol*. 2025;16:1576686. doi:10.3389/fmicb.2025.1576686
113. Markser A, Vöckel J, Schneider A, Baumeister-Lingens L, Sigrist C, Koenig J. Non-Invasive brain stimulation for Post-COVID-19 conditions: a systematic review. *Am J Med*. 2025;138(4):681–697. doi:10.1016/j.amjmed.2024.07.007
114. Kar SK, Menon V, Agarwal A. Gut-brain interaction: scope of neuromodulation techniques. *CNS Spectr*. 2022;27(5):547. doi:10.1017/S1092852921000651
115. Ammer-Herrmenau C, Hamm J, Neesse A, Günther K, Besse M, Zilles-Wegner D. Response to electroconvulsive therapy is associated with a more diverse oral microbiome- a prospective longitudinal cohort pilot study. *Eur Arch Psychiatry Clin Neurosci*. 2025;275(6):1851–1858. doi:10.1007/s00406-025-01976-3
116. Wei C, Li Y, Tian J, et al. Acupuncture for major depressive disorder: exploring the gut microbiota as a novel therapeutic pathway. *Brain Behav*. 2025;15(11):e71022. doi:10.1002/brb3.71022
117. Wadan AS, El-Aziz M, Ellakwa DE. The microbiota-gut-brain-axis theory: role of gut microbiota modulators (GMMs) in gastrointestinal, neurological, and mental health disorders. *Naunyn Schmiedebergs Arch Pharmacol*. 2025;398(10):13397–13426. doi:10.1007/s00210-025-04155-2
118. Knudsen JK, Michaelsen TY, Bundgaard-Nielsen C, et al. Faecal microbiota transplantation from patients with depression or healthy individuals into rats modulates mood-related behaviour. *Sci Rep*. 2021;11(1):21869. doi:10.1038/s41598-021-01248-9
119. Ma X, Shi W, Wang Z, et al. Butyric acid and valeric acid attenuate stress-induced ferroptosis and depressive-like behaviors by suppressing hippocampal neuroinflammation. *J Transl Med*. 2025;23(1):974. doi:10.1186/s12967-025-06950-0
120. Green JE, Berk M, Mohebbi M, et al. Feasibility, acceptability, and safety of faecal microbiota transplantation in the treatment of major depressive disorder: a pilot randomized controlled trial. *Can J Psychiatry*. 2023;68(5):315–326. doi:10.1177/07067437221150508

121. Cai T, Shi X, Yuan LZ, Tang D, Wang F. Fecal microbiota transplantation in an elderly patient with mental depression. *Int Psychogeriatr*. 2019;31(10):1525–1526. doi:10.1017/S1041610219000115
122. Doll J, Vázquez-Castellanos JF, Schaub AC, et al. Fecal Microbiota Transplantation (FMT) as an adjunctive therapy for depression-case report. *Front Psychiatry*. 2022;13:815422. doi:10.3389/fpsyt.2022.815422
123. Zhang Q, Bi Y, Zhang B, et al. Current landscape of fecal microbiota transplantation in treating depression. *Front Immunol*. 2024;15:1416961. doi:10.3389/fimmu.2024.1416961
124. Lis A, Maj P, Świętek A, Romuk E. The role of various types of diets in the treatments of depressive disorders. *Medicina*. 2025;61(10):1737. doi:10.3390/medicina61101737
125. Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: linking diet, the microbiome and immunity. *Nat Rev Immunol*. 2024;24(8):577–595. doi:10.1038/s41577-024-01014-8
126. Zhang S, Wang X, Liu S, Hu C, Meng Y. Phlorizin ameliorates cognitive and behavioral impairments via the microbiota-gut-brain axis in high-fat and high-fructose diet-induced obese male mice. *Brain Behav Immun*. 2025;123:193–210. doi:10.1016/j.bbi.2024.09.008
127. Cho H, Park Y. Synergistic antidepressant-like effects of biotics and n-3 polyunsaturated fatty acids on dopaminergic pathway through the brain-gut axis in rats exposed to chronic mild stress. *Probiotics Antimicrob Proteins*. 2025;17(4):1769–1781. doi:10.1007/s12602-024-10332-1
128. Zhang Y, Liu C, Zhu Q, Wu H, Liu Z, Zeng L. Relationship between depression and epigallocatechin gallate from the perspective of gut microbiota: a systematic review. *Nutrients*. 2025;17(2):259. doi:10.3390/nu17020259
129. Wos-Oxley M, Bleich A, Oxley AP, et al. Comparative evaluation of establishing a human gut microbial community within rodent models. *Gut Microbes*. 2012;3(3):234–249. doi:10.4161/gmic.19934
130. Zeng L, Zhang S, Liu R, Wang L, Tan Y. The microbiota-gut-brain axis in depression: mechanisms, microbiota-targeted interventions, and translational challenges. *Int J Microbiol*. 2025;2025(1):6750078. doi:10.1155/ijm/6750078
131. Koceva H, Amiratashani M, Akbarimoghaddam P, et al. Deciphering respiratory viral infections by harnessing organ-on-chip technology to explore the gut-lung axis. *Open Biol*. 2025;15(3):240231. doi:10.1098/rsob.240231
132. Paganin W. Stratifying the inflamed endotype in difficult-to-treat depression: a roadmap from biomarkers to precision immunopsychiatry. *Clin Neuropsychiatry*. 2025;22(6):529–539. doi:10.36131/cnfioritieditore20250610
133. Wang HX, Wang YP. Gut microbiota-brain axis. *Chin Med J*. 2016;129(19):2373–2380. doi:10.4103/0366-6999.190667
134. Sadhu S, Paul T, Yadav N. Therapeutic engineering of the gut microbiome using synthetic biology and metabolic tools: a comprehensive review with E. coli Nissle 1917 as a model case study. *Arch Microbiol*. 2025;207(9):213. doi:10.1007/s00203-025-04417-w