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Role of Gut Microbiota in Psychiatric Disorders: From Mechanistic Insights to Therapeutic Strategies

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ABSTRACT

Mental health disorders are a global health challenge, and the underlying biological mechanisms remain unclear. Recent evidence has linked gut microbiota to psychiatric symptoms through complex bidirectional interactions along the gut-brain axis, which involve neural, endocrine, and immune pathways. This narrative review aims to synthesize current findings on how gut microbiota contributes to the pathophysiology of major psychiatric disorders, and explore microbiota-based therapeutic interventions, and discusses emerging strategies for personalized treatment. Relevant literature up to July 2025 was reviewed using targeted keywords in major databases, including PubMed and Google Scholar. Rather than applying formal systematic review criteria, we focused on selecting influential and high-impact studies, and the findings were synthesized thematically to provide a comprehensive overview. Consistent findings across psychiatric conditions include a decreased abundance of short-chain fatty acid-producing bacteria and an increased presence of pro-inflammatory taxa. These shifts correlate with heightened systemic inflammation, disrupted neurotransmitter synthesis, and dysregulation of the hypothalamic–pituitary–adrenal axis. Thus, the gut microbiota is increasingly recognized as playing a potential role in the pathophysiology of psychiatric disorders through multifaceted mechanisms involving the gut-brain axis. Probiotics, prebiotics, and dietary modifications show promise in modulating gut microbiota and alleviating psychiatric symptoms, although clinical outcomes remain heterogeneous. Emerging precision medicine strategies indicate promising potential for personalized microbiota-based treatments. Although microbiota-targeted therapies offer promising adjunctive strategies, large-scale, mechanistically informed clinical trials remain warranted. Future research should leverage artificial intelligence and multi-omics tools to develop personalized interventions tailored to individual microbiome profiles.

Keywords: Gut Microbiota; Psychiatric Disorders; Gut-Brain Axis; Neuroinflammation; Psychobiotics; Personalized Medicine

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INTRODUCTION

Mental disorders are a major global health concern, ranking among the leading causes of disability. According to the Global Burden of Disease Study 2019, mental disorders accounted for approximately 125.3 million years lived with disability (14.6% of the global total), with little advancements in this field since 1990.[1,2] The economic burden is substantial; mental disorders contributed to an estimated 418 million disability-adjusted life years in 2019 (approximately 16% of the global total), translating to approximately 5 trillion USD.[3]

Despite significant advancements in neuroscience and psychopharmacology, the biological underpinnings of many psychiatric disorders remain elusive. The conventional wisdom has long suggested that mental illnesses stem from neurochemical imbalances or structural brain abnormalities. However, definitive biomarkers for most psychiatric conditions have yet to be identified.[4] In addition, the efficacy of pharmacological treatments is limited; for instance, a substantial proportion of patients with major depressive disorder (MDD) or schizophrenia exhibit partial or no response to standard pharmacotherapy.[5-7] This reflects the complexity of psychiatric conditions and suggests the involvement of factors beyond the currently identified neurobiological mechanisms in their manifestation and progression. The brain does not function in isolation; instead, it interacts actively with other bodily systems. Scholars are increasingly recognizing the need for more integrative models to explain the pathophysiology underlying mental health disorders. In this context, growing evidence suggests that the gut microbiota plays a role in mental health through neuroimmune and neuroendocrine pathways.[8-12]

This narrative review aims to synthesize current evidence on the relationship between gut microbiota and major psychiatric symptoms. We examine the biological pathways through which the gut microbiota influences mental health, including neuroimmune, neuroendocrine, and microbial metabolite signaling, and explore how these mechanisms contribute to the pathophysiology of disorders such as depression, anxiety, and schizophrenia. Furthermore, in this review, we provide a comprehensive overview of microbiota-targeted therapeutic strategies, including the use of probiotics, prebiotics, and psychobiotics and dietary interventions, for psychiatric disorders. We also examine the application of multi-omics and artificial intelligence (AI) approaches aimed at enabling personalized medicine, highlighting critical experimental and computational challenges such as sample processing variability, data heterogeneity, and model interpretability, which currently limit the scalability and clinical translation of individualized interventions. By addressing both therapeutic applications and methodological limitations, this review offers a balanced perspective on current opportunities and future directions in microbiome-guided personalized psychiatry.

BIOLOGICAL MECHANISMS LINKING THE GUT AND BRAIN: THE GUT-BRAIN AXIS (GBA)

The GBA encompasses multiple interconnected pathways through which the gut microbiota communicates with the central nervous system (CNS), influencing brain function and behavior.

Neural pathways

The vagus nerve enables two-way communication between the gut and brain, playing a central role in the GBA.[13] This mixed cranial nerve contains afferent (sensory) and efferent

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(motor) fibers, enabling it to transmit information from the gut to the brain and vice versa. Approximately 80% of vagal fibers are afferent fibers that relay gut-derived sensory input to the brain, whereas the remaining efferent fibers regulate gastrointestinal motility, secretion, and immune responses.[13]

Key evidence 1: intestinal evidence from germ-free mice

Evidence highlighting the role of the vagus nerve in microbiota–brain communication originated from studies using germ-free (GF) mice. Jameson et al.[14] observed that GF mice exhibited markedly reduced vagus nerve activity compared to conventionally colonized controls.[15] After colonization with microbiota from healthy mice, vagal activity in GF mice normalized, underscoring the importance of microbial presence.[14]

Key evidence 2: role of the vagus nerve in microbial signaling

Vagal afferent fibers can detect gut microbiota and their metabolites and transmit the information to the CNS. This sensory detection is mediated by neuropods, which are specialized epithelial cells in the gut.[16] Neuropods serve as a critical interface, enabling the gut to convert chemical and microbial cues from the intestinal environment to rapid synaptic communication with vagal neurons.[17]

Psychiatric relevance

Vagal nerve activity is positively linked to indicators of physical and psychological well-being, including relaxation and prosocial emotions, such as empathy. In contrast, reduced vagal tone, particularly cardiac vagus activity, is associated with increased vulnerability to stress-related disorders, morbidity, and mortality.[18]

Remaining questions

A key remaining question regarding vagus nerve pathways in the GBA is "Which specific microbial strains, metabolites, or intestinal cells activate particular vagal afferents?" The brain regions that receive and process these vagus nerve-mediated gut-derived signals and how they are integrated into neural circuits that govern behavior, emotion, and cognition also remain unclear. Finally, the mechanisms underlying bidirectional signaling between the brain and gut via the vagus nerve require further elucidation.

Endocrine signaling

Overall, gut microbes affect neurotransmission through 3 interrelated pathways: the local synthesis of signaling molecules, the bioconversion of nutritional substrates into neuroactive agents, and host receptor system modulation via microbial metabolites.[19,20]

Key evidence 1: microbiota-derived neuromodulators as hormonal messengers

Gut microbes synthesize and secrete various neuroactive compounds, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and glutamate precursors, into the intestinal lumen. These compounds circulate via enteroendocrine and paracellular pathways, where they act either directly or indirectly as hormonal signals, reaching distant targets, including the brain.[21,22]

Key evidence 2: enteroendocrine cell activation

Specialized gut epithelial cells (enterochromaffin cells and L-cells) are stimulated by microbial metabolites and neurotransmitter intermediates to secrete hormones such as serotonin, peptide YY, and glucagon-like peptide-1. These hormones enter the bloodstream to regulate gut motility, appetite, metabolic function, and CNS activity.[11,22-26]

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Psychiatric relevance

Gut microbes affect host neurotransmission by modulating the production and availability of major neuroactive compounds, including serotonin, dopamine, GABA, and glutamate, all of which are closely linked to alterations in mood, cognition, and psychiatric symptomatology.[11,22,27] Microbial metabolites and gut hormones such as glucagon-like peptide-1, peptide YY, and serotonin influence vagal and hypothalamic signaling, thereby modulating stress responsivity and dopaminergic reward pathways.[28] Dysbiosis-induced disruption of this endocrine coupling alters hormonal feedback and excitatory–inhibitory balance within limbic circuits, impairing motivation, cognitive control, and affective regulation.[29]

Remaining questions

How these hormone signals reach the CNS once released into the bloodstream, and the brain regions they functionally influence remain unclear. The effects of contextual factors, such as nutritional status, gut environment, and microbiota composition, on this signaling pathway are not fully understood. Furthermore, the temporal dynamics linking microbial metabolite production, hormone secretion, and CNS responses require further elucidation.

Immune mechanisms

Gut microbiota influence local and systemic immune responses, contributing to neuroinflammation and psychiatric symptomatology.[29-31]

Key evidence 1: commensal-induced immune training

Al Bander[31] highlighted that early colonization by commensal microbes supports immune maturation, including the formation of Peyer's patches, Treg cells, and IgA-secreting plasma cells, which are essential for maintaining homeostasis. Similarly, Mazmanian et al.[32] showed that polysaccharide A from *Bacteroides fragilis* promotes Treg expansion via Toll-like receptor (TLR) 2, thereby protecting against experimental colitis and reinforcing the immune-regulatory role of gut microbes.[30,33-35]

Key evidence 2: cytokine modulation and barrier integrity

Dysbiosis-induced damage to the gut epithelium enables microbial components, such as lipopolysaccharide (LPS) and peptidoglycan, to translocate and trigger innate immune responses through TLR and nucleotide-binding oligomerization domain-like receptor pathways. These events lead to Th17 cell activation and increased levels of cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which are involved in neuroinflammatory processes. At the same time, short-chain fatty acids (SCFAs) strengthen epithelial integrity and modulate immune signaling by inhibiting histone deacetylases and activating GPR109A and FFAR2, promoting Treg cell differentiation and IL-10 production. Therefore, SCFA-producing gut microbes contribute to maintaining immune homeostasis and regulating excessive inflammatory responses.[29-31,34-37]

Psychiatric relevance

Gut microbiota critically shape host immune signaling by regulating intestinal barrier integrity, cytokine balance, and microglial activation. Sustained immune activation impairs synaptic plasticity and monoaminergic transmission, disrupting fronto-limbic circuits that regulate motivation, attention, and emotional control. Consequently, immune-mediated neuroinflammation contributes to symptoms such as fatigue, cognitive slowing, and affective dysregulation.[29]

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Remaining questions

The specific pathways through which gut–brain signals are transmitted via the immune system, including the relative contributions of the bloodstream, lymphatic system, and vagus nerve–immune interactions, remain unclear. In addition, how immune-mediated signals are integrated with neural and hormonal gut–brain signals and how this integration influences behavior, emotion, and cognition are not fully understood. Furthermore, the effects of contextual and individual factors, such as age, sex, genetics, environment, and disease state, on immune–gut–brain signaling require further investigation.

Tryptophan-kynurenine pathway

The gut microbiota modulates the tryptophan-kynurenine pathway by influencing host indoleamine 2,3-dioxygenase (IDO) activity through microbial metabolites and immune signaling. Dysbiosis often enhances kynurenine production at the expense of serotonin synthesis, leading to neuroactive imbalances.[38]

Key evidence 1: activating IDO through microbial metabolites and immune signaling

Microbial components such as LPS and pathogen-associated molecular patterns stimulate pattern recognition receptors, inducing cytokines such as interferon-γ, TNF-α, and IL-6, which in turn upregulate IDO-1. In addition, gut microbiota produce metabolites such as SCFAs (e.g., butyrate) or tryptophan-derived indoles that deactivate IDO-1 via anti-inflammatory signaling and aryl hydrocarbon receptor pathways.[39]

Psychiatric relevance

Gut microbiota can influence the kynurenine pathway by regulating immune system-associated IDO-1 activity or modulating tryptophan availability. Clinical studies have demonstrated that immune activation and microbial dysbiosis jointly promote IDO-1 induction, leading to enhanced tryptophan catabolism and reduced serotonergic tone in circulation and in the brain, which are mechanistically linked to affective and cognitive symptoms.[40] A higher kynurenine/tryptophan ratio and elevated IDO levels have been observed in patients with MDD and in those with comorbid inflammation.[41] These biochemical changes are associated with anhedonia, cognitive fatigue, and blunted emotional reactivity, representing trans-diagnostic features observed across mood and stress-related disorders.[38]

Remaining questions

How tryptophan–kynurenine metabolites produced in the gut differentially affect peripheral immune and metabolic functions versus neural activity in the brain remains unclear. Furthermore, the primary pathways and mechanisms through which these metabolites (e.g., kynurenine, kynurenic acid, and quinolinic acid) influence the CNS—whether via the vagus nerve, immune signaling, or circulation—remain unclear.

The hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is the primary stress response system of the body, and it converts microbial signals into hormonal outputs, such as cortisol, that significantly impact mood, cognition, and overall physiology.[42]

Key evidence 1: causal effects on adrenal function

Liu et al.[43] conducted a two-sample Mendelian randomization analysis and identified 27 potential causal associations between specific microbial genera and adrenal gland regions involved in the regulation of cortisol and aldosterone. *Sellimonas* enhances adrenal

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zona reticularis function, demonstrating the direct influence of gut microbes on adrenal steroidogenesis pathways.[43-45]

Key evidence 2: microbial modulation of HPA reactivity: bidirectional feedback loop

Gut microbiota affect HPA axis function by regulating the hypothalamic release of corticotropin-releasing hormone and pituitary production of adrenocorticotropic hormone via microbial metabolites, such as SCFAs, bile acids (BAs), and microbial-associated molecular patterns, that engage immune and endocrine receptors.[23] These regulate glucocorticoid secretion from the adrenal cortex, thereby influencing systemic cortisol/corticosterone levels, as well as the circadian rhythms of stress hormone release.

Moreover, microbial neurotransmitters (GABA and serotonin precursors) and cytokine signaling can directly influence afferent vagal pathways and central glucocorticoid receptor sensitivity, underscoring the interplay between microbial-derived signaling molecules and host neuroendocrine regulation.[22,23,46,47]

Concurrently, HPA activation by stress-induced cortisol can alter gut permeability and microbial community structure, thereby facilitating a bidirectional feedback loop where dysbiosis exacerbates HPA axis responsiveness through increased intestinal endotoxin translocation.[23,46-49] This integrated mechanistic framework reveals how microbial modulation of HPA activity may contribute to psychiatric phenotype emergence and highlights novel microbiota-targeted strategies for stress-related and mood disorders.[23,46,47,49-52]

Psychiatric relevance

The HPA axis mediates the stress response and is intimately linked to mood and anxiety regulation. HPA dysregulation, often driven by gut microbial perturbations, can impair limbic circuitry and neuroplasticity, linking microbial signals to a broad spectrum of psychiatric symptoms (mood lability, anxiety, and cognitive slowing) across depression, anxiety, schizophrenia, and other disorders.[53] Excess glucocorticoids from HPA overdrive impair hippocampal and prefrontal function, contributing to memory deficits, negative affect, and rumination in these conditions.[51]

Remaining questions

How HPA axis–mediated hormonal signals are integrated with vagus nerve activity, cytokines, and neurotransmitters within the gut–brain signaling network remain unclear. Furthermore, the effects of contextual and individual factors, such as stress, inflammation, nutritional status, age, and sex, on HPA–gut–brain interactions require further investigation.

Bile acid signaling (farnesoid X receptor [FXR]/takeda G protein–coupled receptor 5 [TGR5])

Microbial transformation of primary BAs into secondary BAs generates a pool of metabolites that can activate the nuclear receptor FXR and the TGR5, which regulate metabolic, immune, and endocrine signaling. Activation of these receptors influences gut hormone release, inflammatory tone, and vagal pathways. Through these mechanisms, FXR and TGR5 serve as key mediators linking gut microbiota to brain function.[54]

Key evidence 1: microbial modification of BAs

Gut microbes chemically transform host BAs, reshaping the pool of BA signaling molecules. In the intestine, microbial bile salt hydrolases deconjugate primary BAs (e.g., cholic acid and

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chenodeoxycholic acid) into free BAs, and further enzymes (hydroxylases and dehydrogenases) convert them into secondary BAs (deoxycholic acid, lithocholic acid, etc.).[55] These microbial transformations drastically alter the composition and abundance of circulating BAs that reach host receptors. In effect, gut microbes control the ratio of primary-to-secondary BAs and thus the repertoire of ligands available for nuclear and GPCR receptors (full term) such as FXR and TGR5. Therefore, this microbe-driven modification of the BA pool is a critical first step linking the microbiome to downstream FXR/TGR5 signaling pathways.[54,55]

Key evidence 2: regulation of immune and inflammatory signaling

Microbiota-driven BAs serve as ligands for host receptors that modulate immunity. Activation of the nuclear receptor FXR or the membrane receptor TGR5 by specific BAs suppresses pro-inflammatory pathways: FXR inhibits NF-κB–mediated cytokine production and TGR5 dampens the NLRP3 inflammasome.[56] In effect, a balanced BA pool maintains immune homeostasis, whereas dysbiosis-induced shifts (e.g., excess deoxycholate) can promote inflammatory signaling.

Key evidence 3: direct CNS effects

Certain BAs and their receptors act directly on the brain. BAs can cross the blood–brain barrier or signal via vagal afferents, engaging CNS receptors (FXR and TGR5) to influence neurons and glia. For instance, hippocampal TGR5 regulates synaptic plasticity; activating TGR5 in mice restored hippocampal synapse function and reduced anxiety-/depression-like behaviors.[57]

Psychiatric relevance

BAs link gut microbiota to brain function through FXR/TGR5 signaling. Dysregulated BA profiles can induce neuroinflammation and affect neurotransmitter systems. Clinically, an altered BA metabolism is associated with deficits in cognition and mood. For example, disturbed BA patterns were found in cases of major depression and correlated with cognitive impairment.[58] Notably, certain secondary BAs (e.g., glyco- and tauro-ursodeoxycholic acids) positively correlate with attention and memory performance, while others (e.g., glycolithocholic acid) correlate with poorer cognition.

Remaining questions

How contextual factors, including nutritional status, microbiota composition, inflammation, and disease states, influence BA–gut–brain signaling is not fully understood. Furthermore, the temporal dynamics and dose–response relationships between BA levels and GBA activity require further elucidation.

Glial cell modulation

Gut microbiota influence glial cell function by producing metabolites such as SCFAs, tryptophan derivatives, and secondary BAs. These microbial signals modulate microglia and astrocyte activation, maturation, and inflammatory responses. Through this glial regulation, the GBA affects neuroinflammation, synaptic function, and ultimately behavior and cognition.[59]

Key evidence

Gut microbes produce metabolites that regulate glial development and activation. In particular, bacterial SCFAs shape microglial maturation and phenotype. GF mice have immature, dysfunctional microglia; however, supplying SCFAs (acetate, propionate, and butyrate) restores their normal morphology and function. Moreover, SCFAs such as butyrate

inhibit microglial pro-inflammatory cytokine production and promote a homeostatic, anti-inflammatory microglial profile.[60]

Psychiatric relevance

Glial cells (microglia and astrocytes) modulate synaptic and inflammatory brain states. Gut-driven glial activation alters neuroinflammatory tone and synaptic pruning, which can profoundly affect psychiatric symptoms. Excessive microglial activation (e.g., from dysbiosis) can lead to neuronal damage and excessive synaptic loss, disrupting networks for cognition and emotion. Such glial dysregulation has been linked to symptoms like cognitive fog, anhedonia, and heightened negative affects. In depression models, aberrant microglial activation and cytokine release drive synaptic disruption and behavioral deficits.[61]

Remaining questions

The specific glial cell types, such as microglia, astrocytes, or oligodendrocytes, that are most responsive to gut-derived signals remain unclear. Furthermore, the regional specificity of these effects within the CNS and their functional consequences have not been fully characterized. In addition, the precise molecular signaling pathways through which gut-derived metabolites, neurotransmitters, or cytokines modulate glial cell activity require further elucidation.

DETERMINANTS OF GUT MICROBIOTA COMPOSITION AND INTERINDIVIDUAL VARIATION

The human gut microbiota varies significantly among individuals owing to a combination of genetic background, dietary habits, environmental exposure, and lifestyle choices.[62-64]

Geographical location and ethnicity

Geographical location and ethnicity are among the most well-recognized determinants of gut microbiota composition. Environmental factors associated with geographic location, including climate, sanitation, and dietary habits, have a significant influence on microbial communities. Studies across populations have revealed that plant-based, fiber-rich diets enrich *Prevotella*, while Western-style diets favor *Bacteroides*-dominated microbiomes.[65]

In contrast, ethnicity reflects intrinsic genetic differences (as well as socio-cultural factors) and modulates gut microbial composition. Twin studies in European cohorts have identified host genetic determinants influencing the abundance of several taxa, including the heritable Christensenellaceae family.[66,67] Furthermore, genome-wide association studies reveal multiple host loci linked to microbial variation, establishing genotype-microbiome associations across diverse ethnic backgrounds.[67,68] However, environmental influences outweigh host genetic effects, underscoring the dominance of environmental factors in microbiome structuring.[65]

Age

Age affects the diversity and composition of the gut microbiome, with notable shifts during adolescence and aging.[69] With age, the immune system undergoes immunosenescence, marked by reduced adaptive responses, such as naïve T cell production and an increase in low-grade chronic inflammation, or "inflammaging." This persistent, mild inflammation disrupts the gut lining, increasing permeability and allowing harmful bacteria to outcompete

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beneficial microbes.[70,71] Aging also involves hormonal changes, such as reduced anabolic hormones (growth hormone and sex steroids) and increased cortisol, which weaken the gut barrier and alter microbial composition.[70] Together, immune and hormonal changes alter gut conditions, reducing helpful SCFA-producing microbes and encouraging harmful inflammatory bacteria. Studies in older cohorts consistently report reduced microbial diversity and a weakened production of anti-inflammatory metabolites, which are linked to frailty and metabolic decline.[72-76] These age-related changes in the gut microbiota—marked by decreased diversity and reduced anti-inflammatory metabolites—may have broader implications. Altered microbiome-immune interactions in later life have been associated with increased susceptibility to neurodegenerative diseases and may contribute to the rising prevalence of depressive disorders in the elderly population.[77-79]

Sex

Sex is another biological factor that influences the composition of gut microbiota. Research indicates that males and females have distinct gut microbial communities, partly due to hormonal differences (i.e., estrogen and testosterone), which modulate gut physiology and immune responses, and thus affect microbial communities.[80,81] For instance, estrogen is associated with an increased abundance of *Lactobacillus* species, which support gut barrier integrity and immune modulation.[82] Elevated testosterone selectively enriches BA-transforming taxa, most notably *Bacteroides vulgatus* and *Clostridium scindens*, which possess metabolic pathways for steroid and BA turnover.[83] These sex-based differences in microbiota may contribute to variations in disease susceptibility and treatment response, emphasizing the importance of considering sex as a variable in microbiome-related research.[80] Given that the prevalence of psychiatric disorders such as depression and anxiety differs by sex,[84] future studies should examine whether sex-specific gut microbiota profiles contribute to differential vulnerability to these conditions.

Diet

Diet has a long-lasting impact on gut microbiota. In the short term, dramatic shifts, such as switching between plant-based and animal-based diets, can rapidly alter microbial composition, often overpowering baseline individual differences within days.[85] In contrast, long-term dietary habits, particularly fiber, fat, and protein intake, gradually modulate the diversity and metabolic function of gut microbes. Diets high in fiber, including resistant starches and inulin, selectively promote the growth of SCFA-producing bacteria such as *Bifidobacterium* and *Faecalibacterium*, which enhance gut barrier integrity and modulate immune responses.[86,87] In contrast, high saturated fat intake reduces microbial diversity and promotes bile-tolerant, pro-inflammatory taxa (e.g., *Alistipes* and *Bilophila*), whereas polyphenols and omega-3 fatty acids—found in plant-based foods and fish—support beneficial microbes through prebiotic-like effects.[85-87] Because chronic low-grade inflammation plays a central role in the pathophysiology of many psychiatric disorders, dietary patterns that enhance SCFA production and reduce inflammatory metabolites may mitigate psychiatric risk.[88-90] Over time, healthy eating habits promote a stable and balanced microbiome. In contrast, diets consistently low in fiber or high in ultra-processed foods can lead to dysbiosis, characterized by reduced microbial diversity, fewer SCFA-producing bacteria, and a higher presence of opportunistic pathogens.

Pharmaceutical agents

Pharmaceutical agents can disrupt the gut microbial ecosystem, influencing its composition and functional stability.[91] Perturbations such as antibiotic use can disrupt microbial

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equilibrium, leading to decreased diversity and potential dysbiosis.[91] In addition to antibiotics, several non-antibiotic medications, including proton pump inhibitors (PPIs), metformin, and psychotropic drugs, have been shown to affect gut microbial composition.[92] PPIs can reduce microbial diversity by altering gastric pH, whereas metformin has been associated with increased levels of beneficial taxa, such as *Akkermansia muciniphila*, potentially contributing to its metabolic effects.[93,94] Psychotropic medications, including certain antidepressants and antipsychotics, influence microbial communities, which may impact therapeutic efficacy and side effect profiles.[95]

A recent meta-analysis reported that antidepressant use is associated with reduced microbial diversity and taxonomic shifts in humans, likely due to their antimicrobial properties, suggesting effects similar to antibiotics on gut microbiota.[96] Typical and atypical antipsychotics alter the gut microbiota and contribute to metabolic side effects such as weight gain.[97-101] Proposed mechanisms include microbial suppression, increased bile-tolerant species (e.g., elevated Firmicutes/Bacteroidetes ratio), impaired gut barrier, and low-grade inflammation due to a "leaky gut."[97,99-102] Importantly, although psychiatric drugs can directly impact the microbiome, co-administered non-psychiatric medications may indirectly modify the gut environment (e.g., via pH, BAs, or microbial competition), thereby influencing metabolism and the clinical response to psychiatric treatments.[103] This highlights the need for a microbiome-aware, integrated prescribing approach, especially in patients with polypharmacy.

GUT MICROBIOTA AND MAJOR PSYCHIATRIC DISORDERS

Depression

Reduced microbial diversity and increased pro-inflammatory taxa are common in patients with MDD, suggesting a possible microbial contribution to the pathophysiology of the disorder.[104] *Faecalibacterium prausnitzii*, a key bacterium that produces butyrate and exhibits anti-inflammatory properties, tends to be consistently reduced in patients with depression, a pattern observed across nearly all studies investigating the link between gut microbiota and depression.[105-107] Additionally, at the species level, *Eubacterium rectale* is consistently reduced in patients with depression, reinforcing the loss of key butyrate producers observed across cohorts.[108] In contrast, *B. fragilis* and *Bacteroides caccae* are repeatedly found to be enriched in depressive cohorts, with their high abundance linked to an increased inflammatory potential and a compromised gut barrier integrity, supporting a microbial shift toward a pro-inflammatory state in MDD.[109]

Recent meta-analyses have reported trends in microbial alterations in MDD, such as a tendency toward a lower abundance of butyrate-producing genera, such as *Coprococcus*, *Butyricicoccus*, *Fusicatenibacter*, and *Romboutsia*, and a higher abundance of pro-inflammatory taxa, such as *Eggerthella*, *Flavonifractor*, and *Streptococcus*.[109] Similarly, Liu et al.[108] reported an increased abundance of *Desulfovibrio* and *Escherichia/Shigella* and reduced levels of *Bifidobacterium*, suggesting a dysbiotic microbial profile potentially associated with inflammation and neurotransmitter dysregulation. Inflammation derived from dysbiosis can shift host tryptophan metabolism from serotonin synthesis toward the kynurenine pathway, increasing neuroactive and potentially neurotoxic metabolites (e.g., quinolinic acid) that promote excitotoxicity, oxidative stress, and impairment of synaptic plasticity. This biochemical shift reduces central serotonin availability and disrupts synaptic plasticity, contributing to

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depressive phenotypes.[110] *Lactobacillus* and *Bifidobacterium* produce GABA and regulate stress responses via the HPA axis, whereas *Escherichia* and *Streptococcus* influence serotonin levels.

Anxiety

Individuals with anxiety disorders often exhibit reduced levels of SCFA-producing bacteria, such as *Faecalibacterium*, *Coprococcus*, and *Butyricicoccus*, and elevated levels of pro-inflammatory taxa, including *Escherichia-Shigella*, *Fusobacterium*, and *Ruminococcus gnavus* in their gut microbiota.[111-113] This pattern of reduced SCFA production, consistent with findings in other psychiatric disorders, may underlie anxiety-related symptoms.[114,115] Among these, LPS-producing bacteria, such as *Escherichia–Shigella,* may trigger chronic peripheral inflammation and promote dysregulation of the HPA axis, contributing to sustained stress responses and anxiety symptomatology.[116] *E. rectale*, a butyrate-producing Firmicutes species, has been consistently reported to be reduced in patients with generalized anxiety disorder and elevated trait anxiety.[116] In contrast, *Eggerthella lenta* has frequently been found to be enriched in anxiety cohorts, with its abundance positively correlated with anxiety severity in several independent analyses. This species has been associated with anxiety and stress-related phenotypes, possibly through its capacity to dehydroxylate host catecholamines such as dopamine, thereby modulating neurotransmitter availability and gut–brain signaling.[117,118] Similarly, *Bacteroides uniformis* has been reported to increase in individuals with heightened stress or anxiety, although the magnitude of change varies across populations. Its altered abundance has been linked to modulation of intestinal tight junction integrity and tryptophan–serotonin metabolism, which may affect gut–brain signaling and stress responsiveness.[119,120]

Schizophrenia

Altered gut microbial patterns contribute to the schizophrenia pathogenesis.[121] Patients with schizophrenia exhibit reduced microbial diversity and significant shifts in bacterial composition, including decreased levels of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and an increased abundance of pro-inflammatory taxa.[122,123]

Recent studies have identified specific microbial taxa associated with schizophrenia. For instance, the abundance of *A. muciniphila*, a mucin-degrading bacterium, increases in patients with schizophrenia, potentially contributing to gut barrier dysfunction and systemic inflammation. Such mucosal barrier disruption allows microbial components, such as LPS, to enter systemic circulation, activating microglia and promoting neuroinflammation, processes closely tied to the exacerbation of schizophrenia symptoms.[123] Similar to MDD and anxiety, a decrease in SCFA-producing bacteria may contribute to gut–brain dysfunction in schizophrenia.[124]

Streptococcus vestibularis has been repeatedly identified as enriched in patients with schizophrenia, and its overrepresentation has been linked to behavioral alterations and disrupted neurotransmitter metabolism in human-derived microbiota transfer experiments.[125] *Flavonifractor plautii* and *Collinsella aerofaciens* are enriched in patients with schizophrenia, and their relative abundances were positively correlated with cognitive impairment and systemic inflammation in a large metagenomic cohort.[126]

Autism spectrum disorder (ASD)

Distinct shifts in gut microbiota have been observed in individuals with aASD, suggesting a possible microbiota-brain interaction in its pathophysiology. Individuals with ASD often

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exhibit gastrointestinal symptoms and reduced microbial diversity, characterized by imbalance in specific bacterial taxa.[104,127]

Recent studies and meta-analyses have consistently demonstrated that individuals with ASD exhibit distinct patterns of gut microbial dysbiosis. Beneficial bacteria, such as *Bifidobacterium longum* and *Bifidobacterium adolescentis*, which play key roles in maintaining gut health and producing GABA, tend to be low in patients with ASD.[128,129] Similarly, major SCFA-producing bacteria, including *F. prausnitzii*, *B. pullicaecorum*, and *E. rectale*, are frequently depleted, which may be associated with gut barrier function, thus reducing the availability of anti-inflammatory metabolites.[130-133] In contrast, elevated levels of potentially harmful and pro-inflammatory taxa, such as *Clostridium* species, have been frequently observed in ASD populations. These shifts have been linked to gastrointestinal disturbances and systemic immune activation.[130] Together, these findings suggest that altered gut microbiota in ASD may be associated with neurodevelopmental features through immune modulation, disrupted metabolite signaling, and impaired GBA.

Increased LPS-producing bacteria trigger peripheral inflammation that crosses the blood–brain barrier, driving ASD-associated neuroinflammation.[104,134]

Bipolar disorder (BD)

Patients with BD exhibit distinct alterations in gut microbiota composition compared with healthy individuals. A consistent finding is the reduced abundance of SCFA-producing bacteria, such as *F. prausnitzii*, which may contribute to systemic inflammation, oxidative stress, and impaired regulation of circadian and mitochondrial function—factors implicated in mood stability.[135,136] In addition, increased *Eggerthella lenta* and decreased *Coprococcus* abundance have been repeatedly observed across bipolar cohorts, suggesting a shift toward a pro-inflammatory and metabolically imbalanced gut ecosystem that may further disrupt neurotransmitter homeostasis and emotional regulation.[137]

However, conflicting results have been reported in the literature for *Lactobacillus* in BD. Getachew et al.[138] reported that probiotics such as *Lactobacillus* may alleviate depressive-like behavior by reducing gut IL-6, reflecting their anti-inflammatory effects. In contrast, Painold et al.[139] found that higher IL-6 levels correlated with increased *Lactobacillus*, *Bacilli*, and *Streptococcaceae*. Notably, *Lactobacillus* was associated with reduced depressive symptoms, suggesting that elevated IL-6 in patients with BD may be associated with symptom improvement. A possible explanation for the conflicting results is confounding. Painold et al.[139] reported that BD patients with higher BMI had greater *Lactobacillus* abundance than those with lower BMI, consistent with studies linking elevated *Lactobacillus* levels to obesity. Additionally, although manic and depressive episodes have contrasting phenomenon, some taxa showed changes in relative abundance in the same direction. Reininghaus et al.[140] reported that probiotics containing *Lactobacillus* and *Bifidobacterium* reduced depressive symptoms and rumination in patients with BD, consistent with links to increased serotonin. In contrast, Dickerson et al.[141] found that these probiotics lowered rehospitalization rates and improved manic symptoms, particularly in patients with high baseline inflammation. These discrepancies suggest that inflammation may be a key mediator, and overall the findings support connections between gut microbiota, inflammation, and tryptophan.[22,135] These findings underscore that, in BD, interpreting gut microbiota changes requires consideration of microbial functional capacity and ecological context, not just taxonomic shifts.[136]

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Attention-deficit/hyperactivity disorder (ADHD)

Recent research has identified characteristic shifts in gut microbiota composition among individuals with ADHD, which may be associated with aspects of ADHD pathophysiology. Increased levels of *Enterococcus* and *Bifidobacterium*, both implicated in neurotransmitter metabolism, have been reported in individuals with ADHD. *Enterococcus* species influence dopamine metabolism via decarboxylase activity, which might be linked to attention and executive function.[142,143]

Conversely, a reduction in *F. prausnitzii*, a key butyrate-producing bacterium with anti-inflammatory properties, is associated with increased intestinal permeability.[142,143] Such increased permeability promotes the translocation of microbial components, such as LPS, into the systemic circulation, thereby triggering immune responses and potentially exacerbating symptoms of ADHD.[142] In addition, a decreased abundance of other SCFA-producing bacteria, such as members of the Ruminococcaceae family, has been reported in patients with ADHD. A reduced SCFA-producing taxa may affect the GBA, which is relevant in ADHD.[136,142,144]

Alzheimer's disease (AD)

Recent meta-analyses have synthesized gut microbial alterations in AD and mild cognitive impairment, consistently reporting reduced microbial diversity and specific taxonomic shifts. Notably, a decrease in beneficial taxa such as *F. prausnitzii* and *Bifidobacterium* species—both of which produce SCFAs and exhibit anti-inflammatory properties—has been repeatedly observed.[145-150] These findings are further supported by individual studies reporting that potentially harmful taxa, including members of the Bacteroidetes phylum and *Escherichia-Shigella*, are frequently enriched in individuals with AD. These reductions weaken gut barrier integrity and diminish anti-inflammatory signaling, promoting systemic inflammation. These bacteria produce pro-inflammatory compounds such as LPS, which can cross a compromised gut barrier, elevate systemic cytokine levels, and contribute to blood–brain barrier disruption and amyloid-β accumulation.[150-153] Additionally, microbial alterations can impact BA metabolism, influencing amyloid precursor protein processing and potentially accelerating amyloid-β deposition.[149,154] These factors converge to activate microglia, the brain's resident immune cells, which further sustain neuroinflammatory cascades and contribute to cognitive decline.[155,156] Taken together, gut dysbiosis in AD may promote neuroinflammation and neurodegeneration through multiple interrelated immune and metabolic pathways, emphasizing the central role of the microbiota-GBA in AD pathophysiology.

Research directions for using the microbiome as a psychiatric biomarker

Although numerous studies have reported associations between gut microbiota alterations and psychiatric disorders, the majority of evidence remains correlational, limiting conclusions about causality. Existing studies are often constrained by small sample sizes, cross-sectional designs, and variability in sample collection, processing, and sequencing methods, which may confound observed relationships. To address these limitations, future research should utilize longitudinal designs, fecal microbiota transplantation studies, and causal inference models to better establish mechanistic links between specific microbial taxa and psychiatric phenotypes. Additionally, standardized protocols for sample handling and multi-omics analyses, combined with rigorous control of potential confounders such as diet, medication, and lifestyle factors, are essential to improve reproducibility and support the development of microbiota-targeted interventions (**Table 1**).

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Table 1. Comparative summary of gut microbiota changes and gut-brain axis mechanisms across psychiatric disorders

Disorder	Decreased taxa	Increased taxa	Potential mechanisms
Depression	*Faecalibacterium*,[105-107] *Coprococcus*, *Butyricicoccus*, *Fusicatenibacter*, *Romboutsia*,[109] *Bifidobacterium*[108]	*Eggerthella*, *Flavonifractor*, *Streptococcus*,[109] *Desulfovibrio*, *Escherichia/Shigella*[108]	↓ SCFA-producing bacteria[9,108,109,182] → impaired gut barrier integrity[10,109,153] → LPS translocation & systemic inflammation[10,109,153] → HPA axis activation[22,23,45-47] → increased stress sensitivity[23,46]; ↓ *Bifidobacterium* & *Lactobacillus*[9,10,22,108] → reduced GABA/serotonin synthesis[21,22,109,182] → mood dysregulation[9,109]
Anxiety	*Faecalibacterium*, *Coprococcus*, *Butyricicoccus*[111-113]	*Escherichia-Shigella*, *Fusobacterium*, *R. gnavus*[111-113]	↓ SCFAs[23,49,111-113] → weakened epithelial junctions[116] → increased permeability[116]; ↑ LPS-producing taxa[111,116] → peripheral inflammation & IL6/TNF-α release[45,116] → HPA axis hyperactivation[23,46,49] → sustained anxiety symptoms[111,113]; Microbial influence on tryptophan metabolism[22,109] → impaired serotonin signaling[22,183]
Schizophrenia	*Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*[122,123]	*A. muciniphila*,[123] *Eggerthella*, *Streptococcus*[124]	Dysbiosis[122-124] → peripheral immune activation[123,124] → ↑ pro-inflammatory cytokines[124,184] → blood–brain barrier penetration[124] → neuroinflammation[123,184]; ↓ SCFAs & neuromodulators[9,22,123] → dopamine/glutamate dysregulation[123,185]; ↑ *A. muciniphila*[123] → mucosal erosion[123] → LPS leakage[123] → microglial activation[123,184]
ASD	*B. longum*, *B. adolescentis*,[128,129] *F. prausnitzii*, *B. pullicaecorum*, *E. rectale*[130-133]	*Clostridium*, *Collinsella*, *Escherichia/Shigella*[130]	↓ SCFA, GABA, serotonin precursors[130-133,186]→ disrupted neuronal maturation & signaling[130,133,186]; ↑ LPS-producing & inflammatory taxa[130,134] → immune activation[130,134] → neuroinflammation[130,134]; Compromised gut barrier[130,133] → systemic antigen exposure[130] → impaired gut–brain communication[130]
Bipolar disorder	*Faecalibacterium*, *Coprococcus*, *Roseburia*[135,136]	*Lactobacillus*, *Eggerthella*, *Ruminococcus*[22,135]	↓ SCFAs[135,136,187] → gut barrier disruption[187,188] → "leaky gut"[187,189] → endotoxemia[187,188] → systemic & neuroinflammation[187,189]; LPS[189] → TLR4 activation[189] → ↑ pro-inflammatory cytokines[187,189] → HPA overactivation[22,23,45-47] → mood instability[135,136]; Mitochondrial & circadian dysregulation[136] → oxidative stress[136]
ADHD	*Faecalibacterium*,[143] *Ruminococcaceae*[144]	*Enterococcus*, *Bifidobacterium*[142,143]	↓ SCFA-producing bacteria[136,142-144] → elevated zonulin/occludin[190] → tight junction disruption[190] → ↑ gut permeability[190]; LPS translocation[191] → immune activation (↑ IL-6 and TNF-α)[191]; ↑ Enterococcus[142,143] → dopamine modulation via decarboxylase activity[142,143] → altered attention & impulse control[142]
Alzheimer's disease	*F. prausnitzii*, *Bifidobacterium*[145-147]	*Escherichia/Shigella*, Bacteroidetes[151-153]	↓ SCFAs & anti-inflammatory microbes[145-147,192] → impaired barrier integrity & immune regulation[147,192]; ↑ LPS-producing taxa[151-153] → systemic inflammation[151-153] → blood–brain barrier disruption[152,153] → microglial activation & neurodegeneration[155,156,193]; Altered bile acid metabolism[154] → amyloidogenic APP processing[154] → Aβ aggregation[154]

SCFA = short-chain fatty acid, LPS = lipopolysaccharide, HPA axis = hypothalamic–pituitary–adrenal axis, GABA = gamma-aminobutyric acid, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-alpha, ASD = autism spectrum disorder, TLR4 = Toll-like receptor 4, ADHD = attention-deficit/hyperactivity disorder, Aβ = amyloid-beta, APP = amyloid precursor protein.

THERAPEUTIC APPROACHES AND CLINICAL IMPLICATIONS

Probiotics, prebiotics, and psychobiotics

Probiotics are live microorganisms that, when administered in sufficient amounts, confer health benefits to the host by modulating the gut microbiota and supporting intestinal and immune functions.[157] Prebiotics are non-digestible food components—typically fermentable fibers, such as inulin or fructooligosaccharides—that selectively stimulate the growth and activity of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, leading to increased production of SCFAs.[158] Psychobiotics, a term first introduced by Dinan and Cryan, are beneficial bacteria (probiotics) or a support for such bacteria (prebiotics) that exert mental health benefits by modulating the GBA through immune regulation, HPA axis modulation, and the production of neuroactive compounds.[159,160]

Based on these definitions, a growing body of research is examining how probiotics and prebiotics can affect mood, cognition, and stress-related behavioral factors. Mechanistically, their effects involve enhancement of gut barrier integrity, suppression of systemic inflammation via cytokine modulation, and alteration of central neurotransmitter levels.[9] For instance, administering *Lactobacillus rhamnosus* to mice has been shown to reduce anxiety-like behavior and altered GABA receptor expression in a vagus nerve-dependent manner.[15] Several clinical studies support the psychotropic potential of specific strains. A 30-day administration of *Lactobacillus helveticus* R0052 and *B. longum* R0175 in

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healthy adults has been shown to reduce HADS-anxiety and HSCL-90 scores and lower salivary cortisol levels.[161] Similarly, *B. longum* NCC3001 significantly improved depression scores in patients with irritable bowel syndrome, although its anxiolytic effects were not significant.[162] In patients with MDD, adjunctive treatment with high-dose multistrain probiotics for 31 days resulted in a greater reduction in Hamilton Depression Rating Scale scores than placebo, with increases in *Lactobacillus* abundance correlating with symptom improvement.[163] However, not all findings have been consistently positive. An 8-week randomized trial of *L. helveticus* and *B. longum* in patients with mild to moderate depression showed only modest improvements, with no significant differences in depressive symptoms or biological markers compared to placebo.[164] Similarly, several studies in healthy populations have failed to identify significant changes in global mood or anxiety scores, possibly due to short trial durations, mild baseline symptomatology, or insufficient control for confounders such as diet, sleep, and physical activity.[165] In addition, existing trials have shown considerable diversity in terms of specific probiotic strains, dosage and duration of intervention, and study populations, resulting in substantial heterogeneity across outcomes. Baseline microbiome composition, psychiatric disease severity, and even placebo effects further contribute to the inconsistent findings.[112] Moreover, most studies have been conducted with relatively small sample sizes, often fewer than 100 participants, which limit statistical power and genralizabilty.[96] These inconsistencies necessitate further well-designed, large-scale randomized controlled trials. Future studies should incorporate stratified randomization based on psychiatric severity, control lifestyle factors, and utilize multidimensional endpoints including neuroimaging and inflammatory biomarkers.[166] Careful selection of strains and standardized dosing regimens are also important for standardizing interventions. Long-term follow-up is essential to determine the durability and clinical utility of psychobiotic interventions in psychiatric populations.

Dietary interventions and gut health management

Recent clinical trials have demonstrated that specific dietary interventions can positively influence psychiatric symptoms by modulating the gut microbiota. For instance, the SMILES trial showed that adherence to a modified Mediterranean diet combined with dietary support achieved significantly lower depressive symptoms and higher remission rates in patients with MDD than the social support control group.[167] The dietary protocol used in this study is further detailed by Opie et al.[168] Fermented food consumption has been linked to improved mental health. In a recent randomized trial, participants who followed a high-fermented food diet, including yogurt, kefir, kimchi, and kombucha, for 10 weeks exhibited increased gut microbiota diversity and reduced levels of inflammatory markers, such as IL-6, suggesting potential benefits for emotional regulation.[169] Prebiotics, such as galacto-oligosaccharides (GOS), have demonstrated anxiolytic potential. Schmidt et al.[170] conducted a randomized controlled trial showing that GOS supplementation reduced salivary cortisol and attentional vigilance to negative stimuli in healthy adults, indicating reduced stress reactivity. Additionally, polyphenol-rich diets—foods such as berries, cocoa, and green tea—have been associated with improved cognition and mood, likely through anti-inflammatory and neuroprotective mechanisms.[171] These findings suggest that dietary strategies emphasizing fiber, fermented foods, prebiotics, and polyphenols are effective adjunctive tools in managing psychiatric symptoms by restoring gut microbial balance and reducing systemic inflammation. Nevertheless, current dietary intervention studies are relatively few, often limited by small sample sizes and heterogeneity in study design, making it difficult to generalize their efficacy across diverse psychiatric populations. Larger, well-controlled trials are warranted to confirm these preliminary benefits (**Table 2**).

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Table 2. Microbiota-targeted interventions in psychiatric disorders

Intervention type	Intervention	Potential benefits	Study design
Probiotics	*Lactobacillus helveticus* R0052,[161] *Bifidobacterium longum* R0175,[163] multistrain probiotics[164]	Modulate neurotransmitters[161,163] and reduce inflammation[164]	RCT[161,163,164]
Prebiotics	Fructooligosaccharides[165,166]	Enhance gut microbiota activity and SCFA production[165,166]	-
Psychobiotics	*L. rhamnosus*,[15] *B. longum* NCC3001[162]	Reduce anxiety and depression symptoms[15,162]	Preclinical[15]; clinical trial[162]
Dietary interventions	Mediterranean diet,[167] high-fermented foods,[168] polyphenol-rich foods[169]	Improve microbial diversity,[167] SCFA production,[168] and mood regulation[169]	RCT& observational[167-169]

RCT = randomized controlled trial, SCFA = short-chain fatty acid.

PERSONALIZED MICROBIOTA-BASED THERAPIES AND FUTURE DIRECTIONS

Advancements in microbiome research have facilitated personalized interventions targeting the GBA. Variations in gut microbiota composition among individuals highlight the potential benefits of personalized approaches, including tailored medication choices, dose optimization, targeted probiotics, and dietary interventions, for managing psychiatric disorders. The response of the gut microbiota to the antimicrobial effects of escitalopram may be related to its antidepressant efficacy, with individual differences observed. The remitter group showed higher microbial diversity and network robustness, indicating greater resistance to the antidepressant's antimicrobial effects, possibly due to the presence of spore-forming species. Therefore, spore-forming species are potential biomarkers for antidepressant response, enabling the personalization of medication type and dosage.[172] Regarding adjunctive pre- or probiotic therapy, although a recent systematic review suggested that the combination of probiotics with selective serotonin reuptake inhibitors (SSRIs) was more effective in treating MDD and generalized anxiety disorder than SSRI monotherapy, generalization remains limited owing to the heterogeneity of probiotic strains used across studies.[173] Further research is warranted to identify strain-specific probiotic interventions tailored to individual gut microbiome profiles, aiming to improve psychiatric symptoms. Regarding dietary interventions, a paucity of high-quality randomized controlled trials demonstrating that diet-induced normalization of disease-associated dysbiosis is causally linked to clinical improvements exists. Until the objective therapeutic effects of specific dietary interventions are established, clinical applications remain largely limited to recommending a healthy, predominantly plant-based diet that resembles the traditional Mediterranean diet.[174] In this context, emphasizing that microbiota-targeted strategies (including probiotic and prebiotic use and dietary interventions) should be regarded as adjunctive approaches, which complement rather than replace established psychiatric treatments, is important. Positioning these strategies as supportive helps manage expectations and prevents overstatement of their current role in clinical care.[112,175,176] Future studies may benefit from adopting a personalized medicine framework grounded in individual gut microbiota profiling. Metagenomic or metatranscriptomic analyses can characterize patient-specific microbial compositions and functional pathways. Additionally, by leveraging large-scale microbiome datasets, AI can identify latent patterns or subtypes within microbial communities that may not be evident through conventional analyses.[177] These data-driven classifications can stratify individuals into distinct microbiota-based phenotypes, which can inform the selection of specific probiotic strains, prebiotic compounds, or dietary components tailored to the individual's microbial and functional profile. Moreover, integrating microbial, clinical, and behavioral data into an AI-driven framework may enable predictive modeling of treatment response, allowing for more

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dynamic and adaptive therapeutic strategies.[178] Longitudinal studies combining multi-omics data with machine learning-based feedback loops remain warranted to validate the effectiveness and scalability of such personalized interventions. Stool microbiome-guided personalization of medication, supplements, and diet may offer an effective strategy for managing psychiatric symptoms, particularly in treatment-refractory conditions.

Multi-omics analyses face significant challenges at both the experimental and computational levels. Experimentally, each omics layer requires optimized sample processing, as variations in collection, storage, and extraction can substantially influence downstream results. For example, one study evaluating 21 DNA extraction protocols found that the extraction method had the greatest impact on metagenomic results, highlighting the need for a standardized, consensus-based processing pipeline.[179,180] Extending such standardized procedures across multiple institutions and larger datasets is inherently challenging, not only because of resource demands but also because of ethical considerations such as data privacy and informed consent. Computationally, AI-based analyses must contend with heterogeneous datasets, missing or noisy data, high dimensionality relative to sample size, and the need for models that are both robust and interpretable, complicating the extraction of biologically meaningful insights.[181] Addressing both experimental and computational limitations is therefore essential for reliable multi-omics research.

CONCLUSION

Understanding how gut microbial alterations affect brain signaling and mental health remains an active area of research. Although establishing causality remains a challenge owing to the complex and bidirectional nature of gut–brain interactions, evidence has shown that gut dysbiosis is involved in the pathogenesis of psychiatric disorders, such as depression, anxiety, and schizophrenia. Emerging studies have suggested that modulating the gut microbiota through interventions, including probiotic and prebiotic use and dietary changes, offers novel avenues for treatment. To advance personalized medicine, future research should use AI algorithms to distinguish individual gut microbiota patterns and tailor interventions accordingly.

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