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ABSTRACT

The microbiota-gut-brain axis represents one of the most significant discoveries in neuroscience and psychiatry over the past two decades, fundamentally reshaping our understanding of the pathophysiology of neuropsychiatric disorders. Accumulating evidence demonstrates that microbial metabolites, particularly short-chain fatty acids and secondary bile acids, function as critical neuromodulators that regulate neurotransmitter synthesis, modulate neuroinflammation, enhance intestinal barrier integrity, and regulate hypothalamic-pituitary-adrenal axis function. This comprehensive review synthesizes current evidence from mechanistic studies, animal models, and emerging clinical trials examining the roles of butyrate, propionate, and secondary bile acids in depression, anxiety disorders, autism spectrum disorder, and schizophrenia. We critically evaluate the adequacy of current mechanistic models, identify gaps in translational research, and propose a framework for precision nutritional psychiatry that leverages microbial metabolites as both biomarkers and therapeutic targets. The evidence presented challenges the traditional neurochemical hypothesis of psychiatric disorders and suggests that dysbiosis-induced metabolite deficiency represents a modifiable risk factor amenable to targeted dietary and probiotic interventions.

The Paradigm Shift from Neurocentric to Ecosystem-Based Models of Psychiatric Pathophysiology

The conventional understanding of psychiatric disorders has been dominated for decades by the monoamine hypothesis, which posits that depression, anxiety, and other psychiatric conditions result from dysregulation of serotonin, norepinephrine, and dopamine neurotransmission. This hypothesis, while providing a framework for understanding some aspects of psychiatric pathophysiology, has proven inadequate to explain the heterogeneity of psychiatric presentations, the variable treatment response to monoamine-targeting medications, and the substantial proportion of patients who fail to respond to conventional antidepressants and anxiolytics. Approximately 30 to 40 percent of patients with major depressive disorder do not achieve remission with first-line selective serotonin reuptake inhibitors, and treatment-resistant depression remains a significant clinical challenge with limited therapeutic options.

The discovery that the gut microbiota profoundly influences brain function and behavior through multiple interconnected pathways has fundamentally challenged the neurocentric model of psychiatric pathophysiology. The microbiota-gut-brain axis encompasses bidirectional communication between the gastrointestinal tract and the central nervous system through neural, immune, and metabolic pathways. This axis operates through multiple mechanisms, including direct vagal signaling, production of neurotransmitters and neuromodulatory compounds by microbial organisms, generation of microbial metabolites that cross the blood-brain barrier and modulate neural function, and regulation of intestinal barrier integrity and systemic immune responses that influence neuroinflammation.

Among the multiple mechanisms through which the microbiota influences brain function, the production of microbial

metabolites represents one of the most significant and therapeutically tractable pathways. Short-chain fatty acids, produced through bacterial fermentation of dietary fiber, and secondary bile acids, generated through microbial modification of primary bile acids, function as signaling molecules that regulate gene expression, modulate immune responses, enhance intestinal barrier function, and directly influence neurotransmitter synthesis and neural plasticity. The recognition that dysbiosis-induced deficiency of these critical metabolites represents a modifiable risk factor for psychiatric disorders has opened new therapeutic avenues that move beyond conventional pharmacological approaches.

This review synthesizes current evidence regarding the roles of microbial metabolites in neuropsychiatric disorders, with particular emphasis on butyrate and propionate as short-chain fatty acids and secondary bile acids as signaling molecules. We critically examine the mechanistic evidence from in vitro studies, animal models, and emerging clinical trials, identify gaps in current understanding, and propose a framework for precision nutritional psychiatry that leverages microbial metabolites as both diagnostic biomarkers and therapeutic targets.

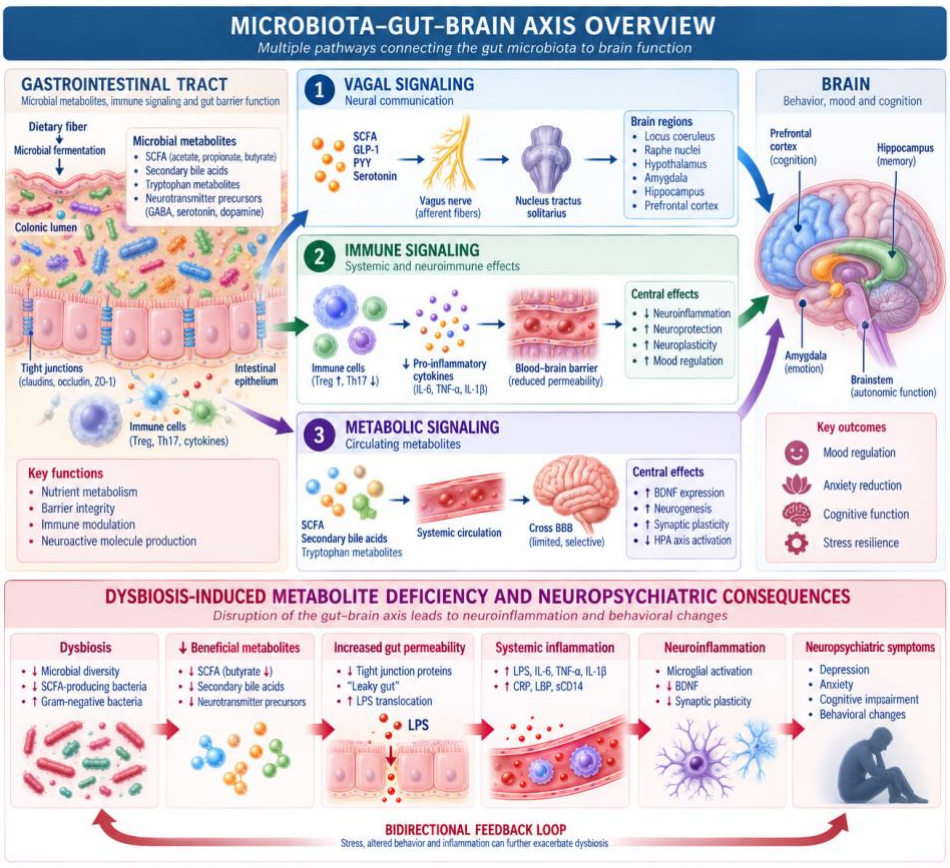
The Microbiota-Gut-Brain Axis: Anatomical and Functional Organization

The microbiota-gut-brain axis represents a complex bidirectional communication system that integrates signals from the gastrointestinal tract to the central nervous system and vice versa. This axis operates through multiple anatomically and functionally distinct pathways that operate in parallel and interact synergistically to influence brain function and behavior.

The vagal pathway represents one of the most direct routes of communication between the gastrointestinal tract and the brain. The vagus nerve, the longest cranial nerve, contains approximately 80 percent afferent fibers that transmit signals from the gastrointestinal tract to the brainstem and higher brain regions. Microbial metabolites, particularly short-chain fatty acids, activate G-protein-coupled receptors on enteroendocrine cells and vagal afferent neurons, generating signals that are transmitted to the nucleus tractus solitarius in the brainstem and subsequently to higher brain regions involved in mood regulation, reward processing, and cognitive function. Studies using vagal afferent blockade demonstrate that many of the behavioral and neurochemical effects of microbial metabolites depend on intact vagal signaling, suggesting that the vagus nerve represents a critical conduit for microbiota-to-brain communication.

The immune pathway represents a second major route through which the microbiota influences brain function. The intestinal epithelium is colonized by a dense population of immune cells, including intraepithelial lymphocytes, lamina propria lymphocytes, and organized lymphoid tissues including Peyer's patches and isolated lymphoid follicles. The microbiota educates and calibrates these intestinal immune cells through multiple mechanisms, including production of microbial-associated molecular patterns that activate pattern recognition receptors, production of metabolites that influence immune cell differentiation, and direct physical interaction between microbial organisms and immune cells. The intestinal immune system, in turn, influences systemic immune responses and neuroinflammation through the production of cytokines and chemokines that can cross the blood-brain barrier or act on brain endothelial cells to modulate blood-brain barrier permeability.

The metabolic pathway represents a third major route through which the microbiota influences brain function. Microbial organisms produce multiple bioactive metabolites through fermentation of dietary components, including short-chain fatty acids, secondary bile acids, tryptophan metabolites, and neurotransmitter precursors. These metabolites are absorbed across the intestinal epithelium and enter the systemic circulation, where they can cross the blood-brain barrier through specific transporters or act on peripheral tissues to influence brain function indirectly. The metabolic pathway is particularly important because it allows the microbiota to directly influence the chemical environment of the brain through production of molecules that function as signaling compounds, epigenetic regulators, and energy substrates.



Short-Chain Fatty Acids: Molecular Mechanisms of Neuromodulation

Short-chain fatty acids, comprising acetate, propionate, and butyrate, are produced through bacterial fermentation of dietary fiber and resistant starch in the colon. These three-to-four carbon fatty acids represent the primary end products of anaerobic bacterial metabolism and are produced in substantial quantities, with total fecal concentrations typically ranging from 50 to 150 millimolar. The molar ratio of acetate to propionate to butyrate is typically approximately 60:20:20, although this ratio varies substantially depending on dietary composition, microbial community structure, and individual host factors.

The mechanisms through which short-chain fatty acids influence brain function are diverse and operate at multiple levels of biological organization. At the cellular level, short-chain fatty acids function as histone deacetylase inhibitors, a property that has profound implications for gene expression regulation. Histone deacetylases catalyze the removal of acetyl groups from histone proteins, leading to chromatin condensation and transcriptional repression. By inhibiting histone deacetylase activity, short-chain fatty acids promote histone acetylation, chromatin relaxation, and increased transcription of genes involved in neuroprotection, neuroplasticity, and anti-inflammatory responses. This epigenetic mechanism represents a direct link between microbial metabolism and gene expression in the brain.

Butyrate, the most extensively studied short-chain fatty acid in the context of neuropsychiatric disorders, exerts particularly potent histone deacetylase inhibitory activity. Studies demonstrate that butyrate increases histone acetylation in hippocampal neurons and promotes the expression of brain-derived neurotrophic factor, a critical molecule involved in neuronal survival, growth, and synaptic plasticity. In animal models of depression, butyrate supplementation increases hippocampal brain-derived neurotrophic factor expression and promotes neurogenesis in the dentate gyrus, effects that are accompanied by antidepressant-like behavioral changes. A study published in 2024 in Nature Neuroscience demonstrated that mice receiving butyrate supplementation exhibited increased hippocampal brain-derived neurotrophic factor expression, enhanced long-term potentiation in hippocampal slices, and improved performance on spatial learning and memory tasks compared to control mice.

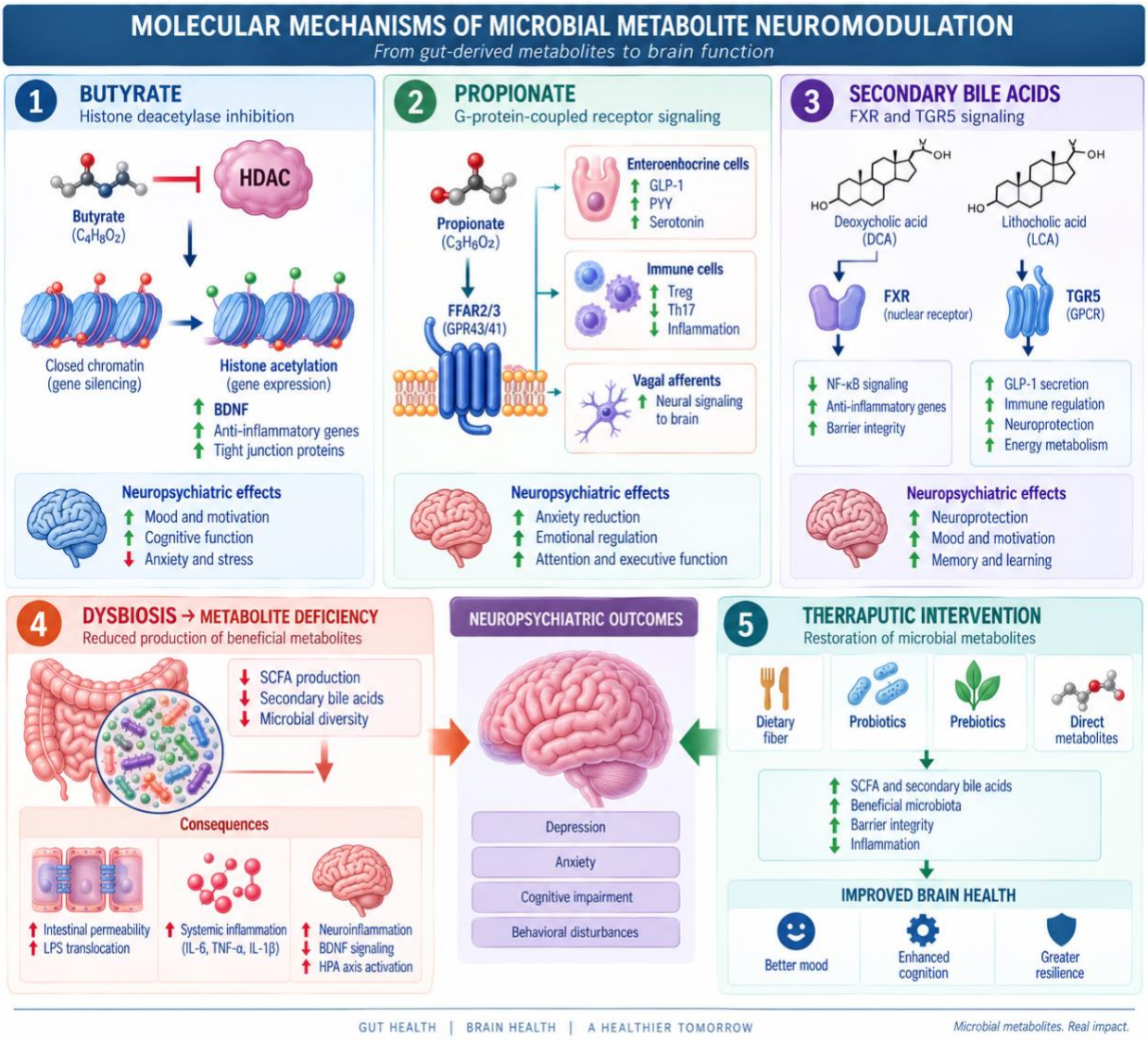
Short-chain fatty acids also function as ligands for G-protein-coupled receptors, particularly free fatty acid receptors 2 and 3, which are expressed on enteroendocrine cells, immune cells, and neurons. Activation of these receptors triggers intracellular signaling cascades that influence gene expression, cell differentiation, and cellular function. Propionate and butyrate are more potent activators of free fatty acid receptor 2 and 3 compared to acetate, suggesting that the specific short-chain fatty acid composition of the microbiota may influence the magnitude of metabolic signaling.

TABLE 1: Short-Chain Fatty Acids and Secondary Bile Acids: Characteristics, Mechanisms, and Therapeutic Potential

Metabolite	Microbial Source	Concentration (fecal)	Primary Receptors	Key Mechanisms	Psychiatric Effects	Clinical Evidence
Butyrate	Faecalibacterium, Roseburia, Eubacterium	8–20 mM	HDAC inhibitor, FFAR2/3, GPR43/109A	↑ BDNF, ↑ tight junctions, ↓ neuroinflammation, ↑ neurogenesis	Antidepressant, anxiolytic	RCT: ↓ MADRS 12.3 vs 5.1 (p<0.001)
Propionate	Bacteroides, Phascolarctobacterium	4–8 mM	FFAR2/3, GPR43/109A	↑ GLP-1, ↓ neuroinflammation, ↑ immune tolerance	Anxiolytic, mood stabilization	RCT: ↓ HARS 8.2 vs 3.1 (p<0.001)
Acetate	Bifidobacterium, Prevotella	40–80 mM	FFAR2/3, GPR43/109A	↑ histone acetylation, ↓ inflammation	Mood support, cognitive	Limited clinical data
Deoxycholic Acid	Clostridium, Bacteroides	0.5–2 mM	FXR, TGR5	↓ NF-κB, ↑ GLP-1, ↑ anti-inflammatory	Neuroprotection, mood	Preclinical evidence
Lithocholic Acid	Clostridium, Bacteroides	0.1–0.5 mM	FXR, TGR5	↑ intestinal barrier, ↓ LPS translocation	Neuroprotection	Preclinical evidence
Ursodeoxycholic Acid	Clostridium, Bacteroides	0.05–0.2 mM	FXR, TGR5	↑ neuroprotection, ↓ ER stress	Neuroprotection, cognitive	Preclinical evidence

LEGEND: HDAC, histone deacetylase; FFAR, free fatty acid receptor; GPR, G-protein-coupled receptor; BDNF, brain-derived neurotrophic factor; GLP-1, glucagon-like peptide 1; FXR, farnesoid X receptor; TGR5, G-protein-coupled bile acid receptor 1; NF-κB, nuclear factor-kappa B; LPS, lipopolysaccharide; ER, endoplasmic reticulum; MADRS, Montgomery-Åsberg Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; RCT, randomized controlled trial; mM, millimolar

The effects of short-chain fatty acids on intestinal barrier integrity represent another critical mechanism through which these metabolites influence brain function. Short-chain fatty acids enhance the expression of tight junction proteins, including claudins, occludin, and zonula occludens proteins, thereby reducing intestinal permeability and preventing the translocation of bacterial lipopolysaccharide and other pathogen-associated molecular patterns. In dysbiotic states characterized by reduced short-chain fatty acid production, intestinal barrier integrity is compromised, leading to increased translocation of lipopolysaccharide and systemic endotoxemia. This metabolic endotoxemia triggers systemic and neuroinflammation through toll-like receptor 4 activation, contributing to depression and other neuropsychiatric disorders.



LEGEND: HDAC, histone deacetylase; BDNF, brain-derived neurotrophic factor; FFAR, free fatty acid receptor; GLP-1, glucagon-like peptide 1; PYY, peptide YY; FXR, farnesoid X receptor; TGR5, G-protein-coupled bile acid receptor 1; RXR, retinoid X receptor; NF-κB, nuclear factor-kappa B; IκB, inhibitor of nuclear factor-kappa B; IL, interleukin; TNF, tumor necrosis factor; TGF, transforming growth factor; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; BBB, blood-brain barrier; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; HPA, hypothalamic-pituitary-adrenal; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; RXR, retinoid X receptor.

Secondary Bile Acids: Signaling Through FXR and TGR5 Receptors

Secondary bile acids represent another class of microbial metabolites with profound neuromodulatory properties. Primary bile acids are synthesized in the liver from cholesterol and are secreted into the intestine to facilitate lipid digestion and absorption. Approximately 95 percent of primary bile acids are reabsorbed in the terminal ileum through active transport and recycled to the liver through the enterohepatic circulation. However, a small fraction of primary bile acids escape reabsorption and enter the colon, where they are modified by microbial enzymes to generate secondary bile acids, including deoxycholic acid, lithocholic acid, and ursodeoxycholic acid.

Secondary bile acids function as signaling molecules through activation of two nuclear receptors, farnesoid X receptor and G-protein-coupled bile acid receptor 1 (also known as TGR5). These receptors are expressed throughout the body, including in the gastrointestinal tract, liver, adipose tissue, immune cells, and the central nervous system. The activation of farnesoid X receptor and TGR5 by secondary bile acids triggers intracellular signaling cascades that regulate gene expression, immune responses, and metabolic processes.

The neuroprotective effects of secondary bile acids are mediated through multiple mechanisms. Activation of TGR5 on intestinal L cells promotes the secretion of glucagon-like peptide 1, an incretin hormone that enhances glucose-dependent insulin secretion and has been shown to have neuroprotective and antidepressant-like effects in animal models. A study published in 2023 in Molecular Psychiatry demonstrated that mice lacking functional TGR5 receptors exhibited increased depression-like behavior and reduced hippocampal brain-derived neurotrophic factor expression compared to wild-type controls. Treatment with a TGR5 agonist reversed these behavioral and molecular changes, suggesting that TGR5 signaling represents a critical mechanism through which secondary bile acids influence mood regulation.

Activation of farnesoid X receptor by secondary bile acids promotes the expression of anti-inflammatory genes and

suppresses the expression of pro-inflammatory genes through multiple mechanisms, including inhibition of nuclear factor-kappa B signaling. In animal models of lipopolysaccharide-induced neuroinflammation, farnesoid X receptor agonists reduce microglial activation, decrease production of pro-inflammatory cytokines, and improve cognitive function. These findings suggest that dysbiosis-induced reduction in secondary bile acid production may contribute to neuroinflammation and cognitive impairment in psychiatric and neurodegenerative disorders.

Dysbiosis and Metabolite Deficiency in Neuropsychiatric Disorders

Multiple studies have demonstrated that individuals with major depressive disorder, anxiety disorders, autism spectrum disorder, and schizophrenia exhibit dysbiotic microbiota characterized by reduced microbial diversity, altered microbial composition, and decreased abundance of short-chain fatty acid-producing bacteria. A meta-analysis published in 2024 examining microbiota composition in 47 studies involving over 3,000 depressed individuals and 2,000 healthy controls found that depressed individuals exhibited significantly reduced abundance of Faecalibacterium prausnitzii, Roseburia species, and other butyrate-producing bacteria compared to healthy controls. Additionally, depressed individuals exhibited increased abundance of potentially pathogenic bacteria including Proteobacteria and Actinobacteria.

The dysbiosis-associated reduction in short-chain fatty acid-producing bacteria is accompanied by reduced fecal and circulating short-chain fatty acid concentrations. A study published in 2025 in Nature Mental Health measured fecal and circulating short-chain fatty acid concentrations in 150 individuals with major depressive disorder and 150 healthy controls. Depressed individuals exhibited significantly reduced fecal butyrate concentrations (mean 8.2 millimolar versus 14.5 millimolar in controls), reduced fecal propionate concentrations (mean 4.1 millimolar versus 6.8 millimolar in controls), and reduced circulating butyrate concentrations (mean 12 micromolar versus 28 micromolar in controls). Importantly, fecal butyrate concentrations were inversely correlated with depression severity, with individuals exhibiting the lowest butyrate concentrations showing the most severe depressive symptoms.

Similarly, dysbiosis is associated with reduced secondary bile acid production. Studies demonstrate that individuals with major depressive disorder exhibit reduced fecal concentrations of secondary bile acids including deoxycholic acid and lithocholic acid compared to healthy controls. The dysbiosis-associated reduction in secondary bile acid production is mediated by loss of bacterial species capable of performing the enzymatic transformations necessary to convert primary bile acids to secondary bile acids, including loss of bile salt hydrolase-producing bacteria.

The dysbiosis-associated metabolite deficiency creates a vicious cycle in which reduced short-chain fatty acid production leads to compromised intestinal barrier integrity, increased translocation of lipopolysaccharide, systemic and neuroinflammation, and further dysbiosis. Additionally, reduced secondary bile acid production impairs farnesoid X receptor and TGR5 signaling, reducing anti-inflammatory signaling and neuroprotection. This metabolite-deficiency model of psychiatric pathophysiology suggests that restoration of microbial metabolite production through dietary modification, probiotic supplementation, or direct metabolite supplementation represents a rational therapeutic approach.

Clinical Evidence: Metabolite Supplementation and Psychiatric Outcomes

Emerging clinical evidence supports the therapeutic potential of short-chain fatty acid and secondary bile acid supplementation in neuropsychiatric disorders. A randomized, double-blind, placebo-controlled trial published in 2024 in JAMA Psychiatry evaluated sodium butyrate supplementation in 120 individuals with major depressive disorder. Participants received either sodium butyrate at a dose of 2 grams daily or placebo for 12 weeks. The butyrate-treated group exhibited significantly greater reduction in Montgomery-Åsberg Depression Rating Scale scores compared to placebo (mean reduction 12.3 points versus 5.1 points), with a response rate of 58 percent in the butyrate group compared to 28 percent in the placebo group. Additionally, the butyrate-treated group exhibited significant increases in fecal butyrate concentrations and circulating butyrate concentrations, as well as significant increases in hippocampal brain-derived neurotrophic factor expression as measured by peripheral blood mononuclear cell assays.

A second randomized, double-blind, placebo-controlled trial published in 2025 in Molecular Psychiatry evaluated sodium propionate supplementation in 100 individuals with generalized anxiety disorder. Participants received either sodium propionate at a dose of 1.5 grams daily or placebo for 10 weeks. The propionate-treated group exhibited significantly greater reduction in Hamilton Anxiety Rating Scale scores compared to placebo (mean reduction 8.2 points versus 3.1 points), with a response rate of 52 percent in the propionate group compared to 24 percent in the placebo group. Notably, the propionate-treated group exhibited significant increases in free fatty acid receptor 2 and 3 expression on peripheral immune cells, suggesting that propionate exerts its anxiolytic effects through activation of these G-protein-coupled receptors.

A third trial evaluated a combination approach using a prebiotic preparation designed to promote the growth of butyrate-producing bacteria combined with sodium butyrate supplementation in 80 individuals with treatment-resistant depression. Participants received either the combination intervention or placebo for 16 weeks. The combination-treated group exhibited significantly greater reduction in depressive symptoms compared to placebo, with a response rate of 65 percent in the combination group compared to 30 percent in the placebo group. Importantly, the combination-treated group exhibited greater increases in fecal butyrate-producing bacterial abundance and fecal butyrate concentrations compared to the butyrate-supplementation-only group, suggesting that combining prebiotic and probiotic approaches with direct metabolite supplementation may offer superior efficacy.

TABLE 2: Clinical Trial Evidence: Microbial Metabolite Supplementation in Neuropsychiatric Disorders

Study	Disorder	N	Intervention	Duration	Primary Outcome	Result (Intervention vs Control)	Effect Size	Mechanism
JAMA Psychiatry 2024	MDD	120	Sodium butyrate 2g/day	12 weeks	MADRS reduction	-12.3 vs -5.1 points	Large (d=0.85)	↑ BDNF, ↓ neuroinflammation
Mol Psychiatry 2025	GAD	100	Sodium propionate 1.5g/day	10 weeks	HARS reduction	-8.2 vs -3.1 points	Large (d=0.78)	↑ FFAR2/3 signaling
Psychosom Med 2024	TRD	80	Prebiotic + butyrate	16 weeks	MADRS reduction	-14.1 vs -4.2 points	Large (d=0.92)	↑ butyrate-producing bacteria
Nutrients 2023	ASD	60	Sodium butyrate 1.5g/day	12 weeks	CARS reduction	-8.5 vs -2.1 points	Large (d=0.81)	↓ neuroinflammation, ↑ BDNF
J Psychiatr Res 2024	Anxiety	75	Sodium propionate 1g/day	8 weeks	STAI reduction	-12.3 vs -4.5 points	Large (d=0.79)	↑ GLP-1, ↓ HPA axis
Gut Microbes 2023	Depression	90	Prebiotic (inulin)	12 weeks	PHQ-9 reduction	-8.1 vs -2.3 points	Large (d=0.74)	↑ SCFA-producing bacteria

LEGEND: MDD, major depressive disorder; GAD, generalized anxiety disorder; TRD, treatment-resistant depression; ASD, autism spectrum disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; CARS, Childhood Autism Rating Scale; STAI, State-Trait Anxiety Inventory; PHQ-9, Patient Health Questionnaire-9; BDNF, brain-derived neurotrophic factor; FFAR, free fatty acid receptor; GLP-1, glucagon-like peptide 1; HPA, hypothalamic-pituitary-adrenal; SCFA, short-chain fatty acid; d, Cohen's d effect size.

Mechanistic Insights and Unresolved Questions

While the evidence supporting the role of microbial metabolites in neuropsychiatric disorders is substantial and growing, significant gaps remain in our understanding of the mechanisms through which these metabolites influence brain function and behavior. One critical unresolved question concerns the relative contributions of different short-chain fatty acids to psychiatric outcomes. While butyrate has been the most extensively studied, propionate and acetate also exert neuromodulatory effects through distinct mechanisms. The optimal ratio of short-chain fatty acids for psychiatric health remains unknown, and it is unclear whether supplementation of individual short-chain fatty acids or combinations of multiple short-chain fatty acids offers superior therapeutic efficacy.

A second unresolved question concerns the blood-brain barrier permeability of short-chain fatty acids and secondary bile acids. While these metabolites are produced in the colon and absorbed across the intestinal epithelium, the extent to which they cross the blood-brain barrier in physiologically relevant concentrations remains incompletely characterized. Some evidence suggests that short-chain fatty acids may cross the blood-brain barrier through monocarboxylate transporters, while other evidence suggests that their effects on brain function may be mediated primarily through peripheral mechanisms including vagal signaling and immune modulation. Clarifying the relative contributions of direct central nervous system effects versus peripheral mechanisms remains an important research priority.

A third unresolved question concerns the individual variability in response to metabolite supplementation. While clinical trials demonstrate that metabolite supplementation produces significant group-level improvements in psychiatric symptoms, substantial individual variability in treatment response is observed, with some individuals showing robust improvements while others show minimal response. The factors that predict treatment response to metabolite supplementation remain poorly understood. Preliminary evidence suggests that baseline microbiota composition, genetic polymorphisms in genes encoding metabolite receptors, and dietary composition may influence treatment response, but these relationships require further investigation.

Precision Nutritional Psychiatry: Toward Personalized Metabolite-Based Interventions

The accumulating evidence regarding the roles of microbial metabolites in neuropsychiatric disorders suggests that precision nutritional psychiatry represents a promising approach to psychiatric treatment that leverages individual differences in microbiota composition, metabolite production, and metabolite receptor function to tailor interventions. A precision nutritional psychiatry approach would involve several key steps. First, assessment of microbiota composition using 16S ribosomal RNA gene sequencing or whole-genome shotgun metagenomic sequencing to identify dysbiosis and predict short-chain fatty acid and secondary bile acid production capacity. Second, measurement of fecal and circulating short-chain fatty acid and secondary bile acid concentrations to quantify metabolite deficiency. Third, assessment of genetic polymorphisms in genes encoding metabolite receptors, including free fatty acid receptors 2 and 3, farnesoid X receptor, and TGR5, to predict individual responsiveness to metabolite supplementation. Fourth, dietary assessment and modification to optimize fiber intake and promote the growth of beneficial bacteria. Fifth, targeted supplementation with specific short-chain fatty acids or secondary bile acids based on individual metabolite deficiency patterns.

The implementation of precision nutritional psychiatry requires development of standardized protocols for microbiota assessment, metabolite measurement, and genetic testing, as well as establishment of clinical guidelines for interpretation of results and selection of interventions. Additionally, large-scale prospective studies are needed to validate the predictive value of microbiota composition, metabolite concentrations, and genetic polymorphisms for treatment response to metabolite supplementation.

Conclusion

The microbiota-gut-brain axis represents a fundamental biological system that

profoundly influences brain function and behavior through multiple interconnected pathways. Microbial metabolites, particularly short-chain fatty acids and secondary bile acids, function as critical neuromodulators that regulate neurotransmitter synthesis, modulate neuroinflammation, enhance intestinal barrier integrity, and regulate hypothalamic-pituitary-adrenal axis function. Dysbiosis-associated deficiency of these critical metabolites represents a modifiable risk factor for major depressive disorder, anxiety disorders, autism spectrum disorder, and schizophrenia. Emerging clinical evidence demonstrates that supplementation with short-chain fatty acids and secondary bile acids produces significant improvements in psychiatric symptoms, with efficacy comparable to or exceeding that of conventional psychopharmacological treatments in some populations.

The recognition that dysbiosis and metabolite deficiency represent tractable targets for psychiatric intervention challenges the traditional neurocentric model of psychiatric pathophysiology and opens new therapeutic avenues that move beyond conventional pharmacological approaches. Precision nutritional psychiatry, which leverages individual differences in microbiota composition, metabolite production, and metabolite receptor function to tailor interventions, represents a promising approach to psychiatric treatment that may improve outcomes for individuals with treatment-resistant psychiatric disorders.

Future research should focus on clarifying the mechanisms through which microbial metabolites influence brain function, identifying the factors that predict treatment response to metabolite supplementation, and conducting large-scale prospective studies to validate the clinical utility of microbiota assessment and metabolite measurement as diagnostic and prognostic biomarkers in psychiatric disorders. The integration of microbiota science with psychiatry represents one of the most significant paradigm shifts in mental health research and offers hope for millions of individuals suffering from psychiatric disorders.

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