SPECIAL ARTICLE

The role of the microbiota-gut-brain axis in neuropsychiatric disorders

Jaqueline S. Generoso, Vijayasree V. Giridharan, Junyoung Lee, Danielle Macedo, Tatiana Barichello

The microbiota-gut-brain axis is a bidirectional signaling mechanism between the gastrointestinal tract and the central nervous system. The complexity of the intestinal ecosystem is extraordinary; it comprises more than 100 trillion microbial cells that inhabit the small and large intestine, and this interaction between microbiota and intestinal epithelium can cause physiological changes in the brain and influence mood and behavior. Currently, there has been an emphasis on how such interactions affect mental health. Evidence indicates that intestinal microbiota are involved in neurological and psychiatric disorders. This review covers evidence for the influence of gut microbiota on the brain and behavior in Alzheimer disease, dementia, anxiety, autism spectrum disorder, bipolar disorder, major depressive disorder, Parkinson’s disease, and schizophrenia. The primary focus is on the pathways involved in intestinal microbiota that can activate the host’s immune system. We also list clinical evidence regarding prebiotics, probiotics, and fecal microbiota transplantation as adjuvant therapies for neuropsychiatric disorders.

Keywords: Prebiotics; probiotics; microbiota-gut-brain axis; neuroinflammation; neuropsychiatric disorders

Introduction

The intestinal microbiota influences the brain and may be involved in neuropsychiatric disorders, partially by modulating the availability of circulating tryptophan, serotonin, kynurenine, and short-chain fatty acids (SCFA), as well as blood-brain barrier (BBB) permeability and activation of peripheral immune cells and brain glial cells. The gut-brain axis involves a biochemical signaling pathway between the gastrointestinal (GI) tract and the central nervous system (CNS). When GI structure is compromised, the functionality of the protective barrier is impaired, leading to increased intestinal permeability and, consequently, penetration by substances that can alter physiological functions. These events lead to activation of the innate immune response, resulting in chronically high levels of inflammation mediators that are known to trigger diseases, including a broad spectrum of psychiatric diseases. It has been suggested that the processes of intestinal dysbiosis and neurological deficits are linked through chronic low inflammation, including direct inflammatory stimulation, the production of pro-inflammatory mediators, and the loss of immune-regulatory function. Neuropsychiatric disorders and inflammation are strictly linked. Bipolar disorder, major depressive disorder (MDD), and schizophrenia patients have high plasma levels of proinflammatory cytokines, inflammation inducers (e.g., damage-associated molecular patterns), activated sensors (e.g., toll-like receptors [TLRs] and inflammasome), increased levels of acute-phase proteins (e.g., C-reactive protein), and adhesion molecules in their blood and cerebrospinal fluid. An association has been demonstrated between inflammation and the clinical progression of neuropsychiatric disorders.

In recent decades, the trillions of microorganisms in the intestines have been shown to regulate the gut-brain axis. Several lines of research have shown that the intestinal microbiota affects the brain. First, studies on germ-free animals have shown that the brain is affected by the absence of microorganisms. Second, behavioral changes occurred in animals treated with specific

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microorganisms (*Lactobacillus*), demonstrating that the intestinal microbiota also affect animal behavior. Third, modulations of the gut-brain axis and behavioral changes were observed in individuals with infectious diseases. Fourth, preclinical and clinical studies have shown that antibiotics affect the brain and the enteric nervous system. Thus, given that they influence the brain and behavior, understanding the complex processes that occur in the gut and microbiota is crucial.

**Gut microbiota: the effects of prebiotics, probiotics, and the synthesis of tryptophan metabolites**

**Gut microbiota**

The gut microbiota encompasses a compact and diverse ecosystem that contains approximately 1,000 to 5,000 different species, of which 99% belong to the phyla *Firmicutes, Bacteroidetes, Proteobacteria*, and *Actinobacteria*. This community comprises more than 100 trillion microbial cells inhabiting the small and large intestine, which is estimated to be 10 times the number of all other cells in the human body. Similarly, there are nearly 3.3 million gut microbial genes, which is 150 times the number of genes in the human genome. SCFAs are the essential gut-microbial derived metabolites formed from dietary and environmental compounds, including acetate, propionate, and butyrate, as well as tryptophan metabolites, which include indole-3-acetic acid, indole 3-proponic acid, indole-3-acetaldehyde, indole acyclic acid, and indole-3-aldehyde (for more details, see Box 1).

**Prebiotics**

According to the International Scientific Association for Probiotics and Prebiotics, prebiotic is defined as “a substrate that is selectively utilized by the host microorganisms, conferring a health benefit.” A typical diet of prebiotics includes inulin (sugar beets, leeks, and asparagus), fructooligosaccharides (bananas, onions, chicory root, garlic, asparagus, and leeks), galactooligosaccharides (lentils, beans, cashews, and pistachios), resistant starch (green banana, beans, peas, and lentils), and soluble fiber (fruits, vegetables, oats, beans, peas, and lentils). The health properties of prebiotics include benefits to the GI tract, such as inhibition of pathogens and immune stimulation; benefits to the cardiac metabolism, such as lower blood lipid levels and insulin resistance effects; and benefits to mental health, such as metabolites that influence brain function, decrease the BBB permeability, decrease neuroinflammation, etc. Studies have shown that prebiotic supplementation reduces stress responsiveness, anxiety, and depressive-like behavior, increases brain-derived neurotrophic factor (BDNF) expression, and improves cognition. In clinical studies, prebiotic supplementation increased SCFA levels, improved social behavior symptoms and sleep patterns in autism spectrum disorder (ASD) patients, and reduced anxiety scores in irritable bowel syndrome patients.

**Probiotics**

Probiotics are defined as “live microorganisms that, when dispensed in suitable amounts, provide a health benefit for the host” (p. 2). Although commensal microorganisms in the gut are often the source of probiotic strains, until these strains are isolated, identified, and a credible case presented for their health effects, they cannot be considered probiotics. Preclinical studies have demonstrated that chronic administration of probiotics can reduce anxiety- and depressive-like behavior and can normalize associated physiological outputs, such as corticosterone, noradrenaline, and BDNF levels, as well as immune function. The probiotic *Bifidobacterium infantis* was administered in an animal maternal separation model and, compared to placebo, resulted in normalized immune response, reversed behavioral deficits, and restored basal noradrenaline concentrations in the brain stem. In a mouse model, *Lactobacillus rhamnosus* ingestion was found to regulate emotional behavior and central gamma-aminobutyric acid receptor expression via the vagus nerve. A clinical study demonstrated that ingesting *Bifidobacterium longum* 1714 was associated with reduced stress reduction and memory improvement in healthy volunteers.

In another clinical trial, a double-blind, placebo-controlled, randomized parallel-group study involved daily administration of probiotics for 30 days. Volunteers were evaluated with the Hopkins Symptom Checklist, the Hospital Anxiety and Depression Scale, the Perceived Stress Scale, the Coping Checklist, and with urinary free cortisol levels. Sub-chronic administration of probiotics alleviated psychological distress in terms of global severity index, somalization, depression, anger, hostility, global Hospital Anxiety and Depression Scale and Coping Checklist (problem-solving) scores, as well as urinary free cortisol levels. When taken in combination, *Lactobacillus helveticus* R0052 and *B. longum* R0175 had beneficial psychological effects in healthy volunteers.

**Probiotic metabolites (short-chain fatty acids: acetate, butyrate, and propionate)**

Soluble fiber, protein, and peptides, which are not degraded in the upper gut by digestive enzymes, are metabolized by gut microbiota in the cecum and colon. Their main products are SCFAs, including acetate, propionate, and butyrate. Butyrate is the principal energy source for colonocytes and protects against colorectal cancer and inflammation by inhibiting histone deacetylases (EC 3.5.1.98). Luminal acetate and propionate are endogenous ligands of two G protein-coupled receptors, GPR41 and GPR43, which can modulate inflammation; they also increase the production of glucagon-like peptide-1 and peptide tyrosine-tyrosine, which affect satiety and intestinal
transit. SCFAs also regulate the permeability of the BBB. In a preclinical study, colonization of germ-free mice with *Clostridium tyrobutyricum* (a butyrate producer) or with *Bacteroides thetaiotaomicron* (an acetate and propionate producer) decreased BBB permeability and was associated with increased occludin protein expression in the frontal cortex and hypothalamus. In an animal model, intraperitoneal and intravenous administration of sodium butyrate prevented BBB breakdown and promoted angiogenesis and neurogenesis. Although germ-free mice presented microglia defects with altered cell proportions, leading to impaired innate immune response, microbiota recolonization restored microglia properties, which demonstrates that SCFAs regulate microglia homeostasis.

**Box 1 The essential gut-microbial derived metabolites and their effect**

<table>
<thead>
<tr>
<th>Metabolites/producers</th>
<th>Molecular target and/or effect on host</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-chain fatty acids</strong></td>
<td></td>
</tr>
<tr>
<td>Acetate</td>
<td>AhR agonists that block the production of pro-inflammatory cytokines and chemokines. Microglia homeostasis via AhR in experimental study.</td>
</tr>
<tr>
<td><em>Akkermansia muciniphila</em></td>
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<tr>
<td><em>Bacteroides</em> spp.</td>
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<tr>
<td><em>Bifidobacterium</em> spp.</td>
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<tr>
<td><em>Prevotella</em> spp.</td>
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<tr>
<td><em>Ruminococcus</em> spp.</td>
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<tr>
<td>Butyrate</td>
<td>AhR agonists that block the production of pro-inflammatory cytokines and chemokines. Intracellular butyrate inhibits the activity of HDACs. Butyrate-producing gut bacteria decrease gut permeability and inflammation. Microglia homeostasis via AhR in an experimental study. Suppressed lysolecithin-induced demyelination and enhanced remyelination in an <em>in vitro</em> study.</td>
</tr>
<tr>
<td><em>Anaerostipes</em> spp.</td>
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<tr>
<td><em>Coprococcus catus</em></td>
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<tr>
<td><em>C. catus</em></td>
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<tr>
<td><em>C. eutactus</em></td>
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<tr>
<td><em>Eubacterium rectale</em></td>
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<tr>
<td><em>E. hallii</em></td>
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<tr>
<td><em>Faecalibacterium prausnitzii</em></td>
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<tr>
<td><em>Roseburia</em> spp.</td>
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<tr>
<td><strong>Propionate</strong></td>
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<tr>
<td><em>Bacteroides</em> spp.</td>
<td>AhR agonists that block the production of pro-inflammatory cytokines and chemokines. Intracellular propionate inhibits HDAC activity. Propionate regulates microglia homeostasis.</td>
</tr>
<tr>
<td><em>Phascolarctobacterium succinatutens</em></td>
<td></td>
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<tr>
<td><em>Dialister</em> spp.</td>
<td></td>
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<tr>
<td><em>Veillonella</em> spp.</td>
<td></td>
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<tr>
<td><strong>Tryptophan metabolites</strong></td>
<td></td>
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<tr>
<td>Indole-3-acetic acid</td>
<td>AhR ligands decrease the production of pro-inflammatory cytokines. Indole-3-acetic acid affects the severity of intestinal inflammation.</td>
</tr>
<tr>
<td><em>Bacteroides</em> spp.</td>
<td></td>
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<tr>
<td><em>Bifidobacterium adolescentis</em></td>
<td></td>
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<tr>
<td><em>B. longum</em></td>
<td></td>
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<tr>
<td><em>B. pseudologum</em></td>
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<tr>
<td><em>Clostridium</em> spp.</td>
<td></td>
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<tr>
<td><em>Enterobacter cloacae</em></td>
<td></td>
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<tr>
<td>Indole-3-aldehyde</td>
<td>AhR ligands. Indole-3-aldehyde increases AhR-dependent IL-22 transcription, maintaining intestinal homeostasis. Indole-3-aldehyde activates cell lymphoids and confers resistance against pathogens.</td>
</tr>
<tr>
<td><em>Lactobacillus acidophilus</em></td>
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<tr>
<td><em>L. reuteri</em></td>
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<tr>
<td><strong>Indole 3-propionic acid</strong></td>
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<tr>
<td><em>Clostridium</em> spp.</td>
<td>AhR ligands. Indole 3-propionic acid is a free radical scavenger. Indole 3-propionic acid protects against amyloid β in Alzheimer disease. Indole 3-propionic acid causes better insulin secretion and sensitivity and decreased type 2 diabetes.</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> spp.</td>
<td></td>
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<tr>
<td><strong>Indole acrylic acid</strong></td>
<td></td>
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<tr>
<td><em>Clostridium sporogenes</em></td>
<td>AhR ligands. Indole acrylic acid have anti-inflammatory function and increase the intestinal epithelial barrier.</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> spp.</td>
<td></td>
</tr>
</tbody>
</table>

AhR = aryl hydrocarbon receptor; HDAC = histone deacetylase; IL-22 = interleukin-22.

Probiotics in tryptophan metabolite synthesis

The essential amino acid tryptophan is a common constituent of protein-based foods, including eggs, fish, meat, and cheese. Tryptophan metabolism follows three essential pathways in the GI tract: first, gut microbiota can metabolize tryptophan into ligands of aryl hydrocarbon receptor (AhR); second, the kynurenine pathway; and third, the serotonin (5-hydroxytryptamine) pathway in enterochromaffin cells via tryptophan hydroxylase 1. *Lactobacillus reuteri* can use tryptophan as an energy source, producing the AhR agonist indole-3-aldehyde as a metabolic product. Other tryptophan metabolites also are produced by commensal microbiota, and their metabolites are AhR agonists, including indole-3-acetic acid.
acid, indole-3-acetyl aldehyde, indole-3-aldehyde, tryptamine, and 3-methylindol.50,51 These AhR agonist metabolites can cross the BBB and activate AhR in astrocytes and microglial cells (the resident macrophages of the brain and spinal cord, acting as the primary source of immune defense in the CNS).52 Thus, AhR activation suppresses the transcription factor nuclear factor-κB (NF-κB), blocking the production of pro-inflammatory cytokines and chemokines. AhR activation also promotes the expression of microglial transforming growth factor-alpha, which acts on astrocytes to suppress their pro-inflammatory activity.53 The concept of neuroinflammation is characterized by microglial cell activation and the presence of peripheral infiltrating leukocytes in the CNS parenchyma.52 When microglial cells are in homeostasis, they do not produce pro-inflammatory mediators. Consequently, there are no infiltrating peripheral immune cells in the brain and neuroinflammation does not occur.

For more details about probiotics and their metabolites in the CNS, refer to Figure 1.

Potential communication pathways between gut microbiota and the brain

The vagus nerve

The vagus nerve is the principal constituent of the parasympathetic nervous system, and it is the most direct intermediary pathway between the gut and the brain (80% afferent and 20% efferent fibers). Afferent fibers in the vagus nerve do not cross the epithelial layer of the digestive wall and are not in direct communication with the gut luminal microbiota.54 Enteroendocrine cells interact with vagal afferents either directly, through the release of serotonin, which activates 5-hydroxytryptamine-3 receptors in vagal afferent fibers, or through gut hormones.

Figure 1 The function of SCFAs and TRP metabolites in the gut. Gut microorganisms ferment dietary fibers, producing SCFAs. SCFAs inhibit HDAC. Butyrate presents an effect on G protein-coupled receptor 109A, decreasing inflammation and increasing the synthesis of zonulin, a consequence of preventing gut permeability. Intestinal microbiota can convert TRP from protein-based foods into metabolites with different functions in the host, including decreased gut permeability, AhR activation, increasing serotonin synthesis, and activating the vagus nerve. 5HT = 5-hydroxytryptamine; AhR = aryl hydrocarbon receptor; HDAC = histone deacetylase; IA = indole acrylic acid; IAA = indole-3-acetic acid; IAALD = indole-3-acetaldehyde; IALD = indole-3-aldehyde; IL-22 = interleukin-22; IPA = indole-3-propionic acid; LPS = lipopolysaccharide; NF-κB = transcription factor nuclear factor-κB; PXR = pregnane X receptor; SCFAs = short-chain fatty acids; TRP = tryptophan; TPH-1 = tryptophan hydroxylase 1.
Enteroendocrine cells comprise approximately 1% of the total epithelial cell population. Notably, these cells express TLRs, such as TLR1, TLR2, and TLR4, which mediate the sensing of microorganisms.55

Additionally, enteroendocrine cells identify signals from Gram-negative bacteria by detecting lipopolysaccharide (LPS) through TLR4, by identifying signs from Gram-positive bacteria, and by detecting peptidoglycan through TLR2; these cells also have SCFAs receptors. Consequently, enteroendocrine cells can detect bacterial compounds and have an indirect effect on vagal afferent fibers by regulating G1 motility, secretion, and food intake. For instance, the microbiota can sense the vagus nerve through direct mechanisms, including TLR4, which is activated by LPS. LPS also directly activates vagal afferent fibers at the nodose ganglia level (inferior ganglion of the vagus nerve).54 SCFAs produced by the microbiota activate vagal afferent fibers by different mechanisms, depending on the compound. Interestingly, the results of a Swedish register-based matched cohort study suggested that truncal vagotomies could have a protective effect against Parkinson’s disease.56

**Immune system and bacterial compounds**

There is a high concentration of GI tract cells in the immune system, and these immune cells are in constant communication with the trillions of microbial cells that inhabit the small and large intestine.18 Epithelial goblet cells secrete protective viscous mucus, which form mucus layers, and host-microbiota interaction occurs in this interface. The intestinal immune system maintains tolerance to commensals and immunity to pathogenic bacteria, and the imbalance between the host immune system and microbiota modulates inflammation and can contribute to several diseases. Several bacterial compounds, such as peptidoglycan, lipoteichoic acid (a constituent of the cell wall of Gram-positive bacteria), LPS (a constituent of the cell wall of Gram-negative bacteria), flagellum (motility), pilus (which mediates the attachment of bacteria to cells), DNA, and cell wall fragments57-59 are considered pathogen-associated molecular patterns.60,61 Pathogen-associated molecular patterns are recognized by pattern-recognition receptors and non-pattern-recognition receptors, which are essential constituents of the immune system.62,63 The sensing of pathogen-associated molecular patterns by immune receptors triggers a cascade of signaling pathways that activate several transcription factors and stimulate the production of pro-inflammatory mediators. These mediators include cytokines, chemokines, and antimicrobial peptides, which are required for the elimination of invading pathogens.64 This host-immune response increases intestinal permeability, facilitating the passage of substances into the bloodstream, causing a systemic inflammatory reaction that leads to an increase in BBB permeability, which triggers microglial cell activation.65

Several animal models of neuropsychiatric disorders have administered LPS intraperitoneally or intracerebrally as an inducer of disease. Repeated, intermittent, or single exposure to LPS has been used to model depressive-like behavior in animals.66,67 Maternal immune activation can be produced by LPS, which, in a rat model, has triggered an immune response in pregnant mothers and fetuses and behavioral impairment in surviving adults.68 A clinical study evaluated GI inflammatory markers in the bloodstream of patients with a recent history of suicide attempts (actual, aborted, or interrupted). The study included 90 schizophrenia patients, 72 bipolar disorder patients, 48 MDD patients, and 72 healthy controls and found that recent suicide attempts had higher antibody levels to yeast mannan from *Saccharomyces cerevisiae*, the food antigen gliadin, and bacterial LPS than the healthy group.69 Another study reported finding bacterial LPS in post-mortem brain lysates from the hippocampus and superior temporal lobe neocortex of Alzheimer disease patients.70 A distinctive microbiota composition that favored a pro-inflammatory environment was found in the GI tract of Parkinson’s patients.71

**Tryptophan metabolism**

Tryptophan is an essential aromatic amino acid that can be metabolized by microorganisms in the GI tract into several molecules, including indole-3-aldehyde, indole-3-acetic acid, indole-3-propionic acid, indole-3-acetaldehyde, and indole acrylic acid, which are AhR ligands.26 Gut microbiota affects the brain and may be involved in neuropsychiatric disorders by modulating circulating tryptophan levels. Agonists derived from tryptophan cross the BBB to activate AhR in astrocytes and microglia cells. AhR activation suppresses pro-inflammatory NF-κB signaling, which interferes with transcriptional factors associated with the recruitment of inflammatory monocytes via chemokine production.51

Additionally, AhR activation increases the expression of suppressor of cytokine signaling 2 and indirectly blocks NF-κB signaling. A proteomic study comparing post-mortem hippocampal tissue from schizophrenia patients, bipolar disorder patients, and healthy controls found that the hippocampi of schizophrenia patients had prominent abnormalities in 14-3-3 proteins (proteins that impact neuronal development, and neuroprotection) and in AhR signaling. In contrast, the hippocampi of bipolar disorder patients displayed marked changes in glucose metabolism.72 Another study found an association between AhR-related gene variants and ASD severity73 (for more details, see Figure 2).

**Short-chain fatty acids**

The primary source of SCFAs is microbial fiber fermentation, while fermented foods can be a secondary source. Endogenous sources of SCFAs include host metabolism of long-chain fatty acids, pyruvate to acetate, and the breakdown of proteins by the microbiota. SCFA levels in human feces generally conform to a 60:20:20 ratio (~ 60 g/kg acetate, ~ 10 to 20 g/kg propionate, and ~ 3 to 30 g/kg butyrate, respectively). SCFAs are metabolized in cells via the citric acid cycle (Krebs cycle) to produce

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energy. All SCFAs present inhibitory effects on histone deacetylase, while butyrate affects specific receptors (GPR43/FFAR2; GPR41/FFAR3; GPR109a/HCAR2), and transporters (MCT1/SLC16A1; SMCT1/SLC5A8), which has led to the use of butyrate as an experimental drug in neuropsychiatric disorders.74

In several neuropsychiatric animal models, the administration of butyrate, 4-phenylbutyrate, or butyrate-producing bacteria has positive effects on brain physiology and function.75 In an Alzheimer model, butyrate treatment increased contextual fear learning, spatial learning, hippocampal synaptophysin, and neural plasticity.75 In animal models of psychosis and drug abuse, animals treated with butyrate decreased cocaine self-administration.76 In mania and bipolar disorder models, animals treated with butyrate presented decreased locomotor activity and increased activity of mitochondrial respiratory chain complexes in the prefrontal cortex, hippocampus, striatum, and amygdala.77 In an animal depressive-like behavior model, decreased depressive-like behavior, increased prefrontal cortical ten-eleven translocation methylcytosine dioxygenase-1, and increased BDNF levels were found in the butyrate treatment group.78 In an ASD model, butyrate treatment increased long-term memory, hippocampal CA1 dendritic spine density, and histone acetylation19 (Figure 2).

The microbiota-gut-brain axis and neuropsychiatric disorders

A large body of accumulated evidence points to the involvement of gut microbiota in several neuropsychiatric disorders. See Tables 1 and 2 for more details.

Alzheimer disease and dementia

Alzheimer disease is an irreversible type of dementia that triggers brain disorders and causes memory and thinking problems, which eventually affect activities of daily living. The characteristic brain pathology includes amyloid plaque deposition and hyperphosphorylation of tau protein in the brain.91 Alzheimer disease can be categorized as familial (5% of all cases) or sporadic (95%).74 Infection plays a role in late-onset disease pathology in sporadic Alzheimer disease. Several studies have suggested that infectious agents, including viruses, parasites, bacteria, and fungi, are trigger factors for the development of Alzheimer disease pathology.18,92,93 The infection hypothesis is not a novel idea; Aloysius Alzheimer (1864-1915) himself proposed that microorganisms could be involved in progression of the disease.94,95

Figure 2 The microbiota-gut-brain axis. SCFAs can increase the expression of claudin and occludin, which decreases BBB permeability. SCFAs and TRP metabolites can prevent astrocyte and microglial cell activation by blocking pro-inflammatory transcript factors, which leads to homeostasis in the brain. AhR = aryl hydrocarbon receptor; BBB = blood-brain barrier; IA = indole acetic acid; IAA = indole-3-acetic acid; IALD = indole-3-acetaldehyde; IALD = indole-3-aldehyde; IPA = indole-3-propionic acid; NF-κB = transcription factor nuclear factor-κB; SCFAs = short-chain fatty acids; SOCS = suppressors of cytokine signaling; TGF-α = transforming growth factor-alpha; TRP = tryptophan; VEGF-β = vascular endothelial growth factor-beta.
### Table 1: Selected studies about prebiotics and probiotics administration in patients diagnosed with neuropsychiatric disorders

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Sample</th>
<th>Bacterial species intervention</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazemi et al.(^{80})</td>
<td>Double-blind controlled clinical trial</td>
<td>MDD probiotic group (n=38); 27 F/11 M; age 36.15±7.85 MDD probiotic group (n=38); 27 F/9 M; age 37.35±7.97 MDD placebo group (n=36); 24 F/12 M; age 36±8.47</td>
<td>Probiotic: <em>L. helveticus</em> and <em>B. longum</em> (≥10 x 10^5 CFU)</td>
<td>Probiotic supplementation resulted in lower BDI scores (17.39-9.1) than the probiotic group (19.72-14.14) and the placebo group (18.18-15.55).</td>
</tr>
<tr>
<td>Liu et al.(^{81})</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>ASD probiotic group (n=36); 36 M; age 10.11±2.34 ASD placebo group (n=35); 35 M; age 9.91±2.33</td>
<td><em>L. plantarum</em> PS128 (3 x 10^9 CFU)</td>
<td>Probiotic treatment ameliorated opposition/defiance behaviors, and total SNAP-IV scores for younger children (aged 7 to 12) improved significantly compared with the placebo group. Several others elements were also improved in the probiotic group after 28 days of treatment.</td>
</tr>
<tr>
<td>Reininghaus et al.(^{82})</td>
<td>Cohort study</td>
<td>Euthymic BD probiotic group (n=27); 11 F/16 M; age 50.7±12.2</td>
<td><em>B. bifidum</em> W23, <em>B. lactis</em> W51, <em>B. lactis</em> W52, <em>L. acidophilus</em> W22, <em>L. casei</em> W56, <em>L. paracasei</em> W20, <em>L. plantarum</em> W62, <em>L. salivarius</em> W24, and <em>L. casei</em> W19 (7.5 billion organisms per 1 portion, 3 g)</td>
<td>GI problems were prevalent in more than half of the patients upon inclusion. One-third of the patients reported positive changes (reduced flatulence and more comfortable and frequent bowel movements). Although the patients presented reduced cognitive reactivity to sad mood, significant symptom reduction was found in manic symptom scales.</td>
</tr>
<tr>
<td>Severance et al.(^{83})</td>
<td>Longitudinal, double-blinded, and placebo-controlled</td>
<td>SCZ probiotic group (n=30); 8 F/22 M; age 44.66±11.4 SCZ placebo group (n=26); 11 F/15 M; age 48.11±9.6</td>
<td>Bifiform balance: <em>L. rhamnosus</em> strain GG (10^9 CFUs), <em>B. animalis</em> subspecies</td>
<td>An association was found between <em>C. albicans</em> seropositivity and worse positive psychiatric symptoms. However, probiotics administration normalized <em>C. albicans</em> antibody levels.</td>
</tr>
<tr>
<td>Tamtaji et al.(^{84})</td>
<td>Randomized, double-blind, and controlled clinical trial</td>
<td>AD selenium probiotic group (n=27); 18 F/10 M; age 78.5±8.0 AD selenium group (n=26); 11 F/15 M; age 78.8±10.2 AD placebo group (n=26); age 76.2±8.1</td>
<td><em>L. acidophilus</em>, <em>B. bifidum</em>, and <em>B. longum</em> (2 x 10^9 CFU/g)</td>
<td>Twelve weeks of probiotic and selenium co-supplementation in AD patients improved cognitive function (reflected in increased MMSE scores) and had favorable results for specific inflammation and oxidative stress markers, such as high-sensitivity-CRP, TAC, and GSH, compared to selenium-only and placebo AD groups.</td>
</tr>
<tr>
<td>Tamtaji et al.(^{85})</td>
<td>Randomized, double-blind, placebo-controlled clinical trial</td>
<td>PD probiotic group (n=30); 18 F/12 M; age 68.2±7.8 PD placebo group (n=30); age 67.7±10.2</td>
<td><em>L. acidophilus</em>, <em>B. bifidum</em>, <em>L. reuteri</em>, and <em>L. fermentum</em> (each 2 x 10^5 CFU/g)</td>
<td>Twelve weeks of probiotic treatment by PD patients had a beneficial impact on MDS-UPDRS scores.</td>
</tr>
<tr>
<td>Tankou et al.(^{86})</td>
<td>Cohort study</td>
<td>MS probiotic group (n=9); age 50±10 Healthy control group (n=13); age 35±14</td>
<td><em>L. paracasei</em>, <em>L. plantarum</em>, <em>L. acidophilus</em>, and <em>L. delbrueckii</em> subspecies bulgaricus, <em>B. longum</em>, <em>B. infantis</em>, and <em>B. breve</em>, <em>Streptococcus thermophilus</em> (3,600 billion CFU/g for each strain)</td>
<td>Probiotic treatment was associated with an increased abundance of many taxa, especially <em>Lactobacillus</em>, <em>Streptococcus</em>, and <em>Bifidobacterium</em> species. Probiotics also induced an anti-inflammatory peripheral immune response characterized by a decreased frequency of intermediate monocytes and decreased mean fluorescence intensity of CD80 in classical monocytes, as well as decreased human leukocyte HLA-DR MFI in dendritic cells.</td>
</tr>
</tbody>
</table>

AD = Alzheimer disease; ASD = autism spectrum disorder; BD = bipolar disorder; BDI = Beck Depression Inventory; CFU = colony-forming unit; CRP = C-reactive protein; F = female; FMT = fecal microbiota transplant; GI = gastrointestinal; GSH = glutathione; HLA-DR = human leukocyte antigen-antigen D related; HLA-DR = human leukocyte antigen-antigen D related; M = male; MDD = major depression disorder; MDS-UPDRS = Movement Disorders Society-Unified Parkinson’s Disease Rating Scale; MDS-UPDRS; Movement Disorders Society-Unified Parkinson’s Disease Rating Scale; MFI = mean fluorescence intensity; MMSE = mini-mental state examination; MS = multiple sclerosis; PD = Parkinson’s disease; SCZ = schizophrenia; SNAP-IV = Swanson, Nolan, and Pelham-IV-Taiwan version; TAC = total antioxidant capacity.
Recently, a probiotic combination containing *B. longum* and *Lactobacillus* spp. improved cognitive function and metabolic status in Alzheimer disease patients.96 Probiotic and selenium co-supplementation for 12 weeks in Alzheimer patients led to improved cognitive function (i.e., higher Mini-Mental State Exam scores) and favorable results for specific markers of inflammation and oxidative stress in comparison with selenium-only or placebo groups of Alzheimer patients.84 In an explorative intervention study using probiotic supplementation in individuals with Alzheimer dementia patients, multispecies probiotic treatment influenced gut bacteria composition and tryptophan metabolism in serum. After treatment, these patients showed lower intestinal permeability (reflected in lower fecal zonulin concentrations) and more abundant *Faecalibacterium prausnitzii* (a microorganism that produces SCFAs) than controls.97 Taken together, these results indicate the potential efficacy of probiotics in improving cognitive function in Alzheimer patients and healthy populations.

**Anxiety**

Most of the evidence demonstrating an association between anxiety and the microbiota-gut-brain axis comes from preclinical studies. Some probiotic administration studies have found improvements in specific anxiety measures. A meta-analysis of randomized controlled trials evaluated the efficacy of probiotics for anxiety behavior and found no significant difference between probiotics and placebo in alleviating anxiety symptoms.98 In a placebo-controlled study in stressed adults, 12 weeks of treatment with *Lactobacillus plantarum* reduced stress and anxiety symptoms, as well as total Depression Anxiety Stress Scales-42 scores. Plasma cortisol levels, as well as plasma pro-inflammatory cytokines, were lower in individuals who received probiotics than placebo. Compared to the placebo and young adult (< 30 years old) groups, *L. plantarum* treatment improved cognitive and memory function in healthy adults > 30 years old, including primary attention, emotional cognition, and associated learning. The administration of probiotics may modulate the serotonin pathway by decreasing the plasma levels of dopamine, 

### Autism spectrum disorder

Several studies have demonstrated the role of GI microbiota in ASD symptomatology. Approximately 70 to 80% of children with ASD also have GI disorders, such as bloating, constipation, and diarrhea, which indicates that there is a relationship between ASD, gut physiology, and altered microbiota.100,101 Children with ASD tend to eat fewer vegetables than other children of the same age. Their fiber intake is also inadequate since they tend to eat more energy-dense foods.102 The microbiota of children with ASD differs from that of other children regarding species and bacterial metabolites, such as SCFAs, etc. These children have fewer genera of beneficial bacteria, such as *Bifidobacterium* spp., along with a greater abundance of potentially pathogenic genera, such as *Desulfovibrio* and *Clostridium*.18 A recent study identified *Clostridium perfringens* and its toxin genes in the gut of children with ASD, associating this toxin with GI-related illnesses.103 In a placebo-controlled trial, probiotic treatment had a positive effect on oppositional-defiant behavior, as well as on total Swanson, Nolan, and Pelham, version IV scale scores for younger children with ASD.

### Table 2 Selected studies about fecal microbiota transplantation and neuropsychiatric disorders

<table>
<thead>
<tr>
<th>Title</th>
<th>Study designer</th>
<th>Sample</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao et al.87</td>
<td>Case report</td>
<td>Patient (n=1); M; age 9-year-old Healthy donor (n=1); F; age 79-year-old</td>
<td>Eight weeks after treatment, the patient's YGTSS score reduced from 31 to 5, his motor severity score reduced from 16 to 5, and his vocal severity score reduced from 15 to 0 (i.e., from severe to mild).</td>
</tr>
<tr>
<td>Cai et al.88</td>
<td>Case report</td>
<td>MDD patient (n=1); M; age 6-year-old Healthy donor (n=1); F; age 79-year-old</td>
<td>Four days after the FMT, the patient felt less sleepy, her appetite improved, and she was more talkative. Two weeks after FMT, the patient was able to live independently and her weight increased. Six months after FMT, the patient's weight had returned to normal, her constipation symptoms improved, and her PHQ-9 score decreased from 21 to 4 (normal).</td>
</tr>
<tr>
<td>Kang et al.89</td>
<td>Open-label clinical trial</td>
<td>ASD patients (n=18); age 7 to 16-years-old</td>
<td>The patients presented an 80% reduction of GI symptoms after treatment, including improvements constipation, diarrhea, indigestion, and abdominal pain symptoms. Clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended.</td>
</tr>
<tr>
<td>Kang et al.90</td>
<td>Follow-up study of a clinical trial</td>
<td>ASD patients (n=18); age 7 to 16-year-old</td>
<td>Two years after the FMT, most GI symptoms improved continued, and autism-related symptoms improved even more. The changes in gut microbiota found at the end of treatment continued in follow-up, demonstrating the long-term safety and efficacy of FMT as a potential therapy for children with ASD who have GI problems.</td>
</tr>
</tbody>
</table>

**ASD** = autism spectrum disorder; **F** = female; **FMT** = fecal microbiota transplantation; **GI** = gastrointestinal; **M** = male; **MDD** = major depression disorder; **PHQ** = Patient Health Questionnaire; **YGTSS** = Yale Global Tic Severity Scale.
Inflammation at baseline.106 Recently discharged after a manic episode. This effect slightly reduced psychiatric rehospitalizations in individuals who had a decreased abundance of sp. compared to healthy controls, which was 77.6% lower in Parkinson’s disease patients than in healthy controls, as well as that the relative abundance of Enterobacteriaceae was positively associated with postural instability and gait difficulty.110 Another study found that Parkinson’s patients have intestinal dysbiosis and reduced serum LPS-binding protein levels. LPS-binding protein opsonizes LPS, and acute LPS concentrations in the bloodstream increase serum levels of LPS-binding protein, whereas chronic LPS invasion somewhat decreases serum levels of LPS-binding protein.111 In a placebo-controlled clinical trial, Parkinson’s patients were treated with probiotics (Lactobacillus acidophilus, B. bifidum, L. reuteri, and Lactobacillus fermentum), and the Movement Disorders Society-Unified Parkinson’s Disease Rating Scale was administered pre- and post-intervention. Compared with placebo, probiotic treatment decreased Movement Disorders Society-Unified Parkinson’s Disease Rating Scale scores, reduced high-sensitivity C-reactive protein, decreased oxidative damage, and increased enzymatic defense.85 Moreover, in a Swedish register-based matched cohort study, Liu et al. suggested that truncal vagotomy had potential protective effect against the development of Parkinson’s disease.86

Parkinson’s disease
In the course of Parkinson’s disease, the enteric nervous system and parasympathetic nerves are among the first and most frequent structures to be affected by alpha-synuclein pathology. Schepferjans et al. provided the first evidence of an association between the microbiota-gut-brain axis and Parkinson’s disease by comparing the fecal microbiome of Parkinson’s patients with 72 healthy controls. They found that the prevalence of Prevotella ceae was 77.6% lower in Parkinson’s disease patients than in healthy controls, as well as that the relative abundance of Enterobacteriaceae was positively associated with postural instability and gait difficulty.110

Bipolar disorder
In a stool microbiome analysis, bipolar disorder patients had a decreased abundance of Firmicutes and Faecalibacterium spp. compared to and healthy controls, which also correlated with self-reported symptom severity.105 A recent probiotic clinical intervention containing Lactobacillus spp. and Bifidobacterium lactis strains significantly reduced psychiatric rehospitalizations in individuals recently discharged after a manic episode. This effect was increased in individuals who had elevated systemic inflammation at baseline.106

A pilot study evaluated the effects of probiotic treatment on GI symptoms in a cohort of euthymic bipolar disorder patients. GI problems were prevalent in more than half of the patients upon inclusion. Approximately one-third of the patients had positive changes (reduced flatulence and more frequent bowel movements) during treatment. Although the patients presented reduced cognitive reactivity to sad mood, significant symptom reduction was found in the manic symptom scales.82

Major depressive disorder (MDD)
Disturbances in the equilibrium of the gut-microbiota axis have been associated with the pathophysiology of depression. In a recent study, 110 depressed patients were randomized to receive probiotics (B. longum and L. helveticus), prebiotics (galactooligosaccharide), or placebo for 8 weeks. After treatment, Beck Depression Inventory scores were improved in MDD patients, although prebiotic supplementation had no effect.80 In a case report, an older woman diagnosed with depression was treated with FMT. On the fourth day after treatment, she felt less sleepy, had a better appetite, and was more talkative. After 2 weeks, she was able to live independently and her weight increased. Six months later, her weight had returned to normal, constipation symptoms had improved, and her Patient Health Questionnaire-9 score decreased from 21 to 4.88 In a cohort of healthy older adults, treatment with Lactobacillus casei (added to a milk drink) triggered improved mood ratings, and the greatest benefits were observed in those whose mood was initially poor.107 Furthermore, in a placebo-controlled clinical trial that included 40 MDD patients, probiotic treatment including Lactobacillus acidophilus, L. casei, and Bifidobacterium bifidum resulted in improved depression scores.108 A recent open-label study in patients with treatment-resistant depression found that the probiotic Clostridium butyricum, in combination with antidepressants, led to a significant improvement in depression symptoms.109

Schizophrenia
A recent study found differences in gut microbiome composition between chronic schizophrenia patients and healthy controls. Schizophrenia patients had lower levels of the phylum Proteobacteria, higher levels of the genus Anaerococcus, and lower levels of Haemophilus spp., Sutterella spp., and Clostridium spp. than healthy controls. Schizophrenia patients had an abundance of Ruminococcaceae, which is associated with less severe negative symptoms, as well as Bacteroides, which is associated with more severe depressive symptoms, and Coprococcus sp., which is associated with a higher risk of coronary heart disease.112 This trial included 60 patients with chronic schizophrenia and treated them with vitamin D and probiotic co-supplementation. The treatment was associated with a significant improvement in Positive and Negative Syndrome Scale scores, increased total
antioxidant capacity, decreased malondialdehyde, and high sensitivity C-reactive protein levels compared to placebo. In an open-label single-arm study, all participants received *Bifidobacterium breve* for 4 weeks, which improved anxiety and depressive symptoms in schizophrenia patients. A placebo-controlled longitudinal pilot study evaluated the effects of probiotic administration on yeast antibody levels, as well as the association between probiotics, antibody levels, and bowel discomfort in schizophrenia patients. It was found that probiotic treatment significantly reduced *Candida albicans* antibodies in men, but not women. Probiotic treatment has been found to help normalize *C. albicans* antibody levels and *C. albicans*-associated gut discomfort in many men. Additionally, mice that received schizophrenia microbiome fecal transplants had lower glutamate, higher glutamine, and higher gamma-aminobutyric acid in the hippocampus and displayed schizophrenia-relevant behaviors.

### Conclusion

This article has presented a review of current evidence about microbiota-gut-brain axis activity through different pathways, such as the immune system, the vagus nerve, and microbial metabolites, such as SCFAs and tryptophan metabolites. We also showed evidence from preclinical and clinical studies (Tables 1 and 2) that probiotics, prebiotics, and FMT may be involved in several neuropsychiatric disorders, and that the composition of the intestinal microbiota plays an essential role in the physiology and pathophysiology of these disorders.

The complexity of microbiota-host interactions and their relationship with the diseases studied herein requires further investigation of SCFAs and tryptophan metabolites and their functional implications at different stages of life. This will help clarify how the microbiota-gut-brain axis interferes in health and disease, which could refine our goals and lead to therapeutic interventions.

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### Disclosure

The authors report no conflicts of interest.

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