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Review

The gut microbiota-immune-brain axis: Therapeutic implications

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SUMMARY

The microbiota-gut-brain axis has major implications for human health including gastrointestinal physiology, brain function, and behavior. The immune system represents a key pathway of communication along this axis with the microbiome implicated in neuroinflammation in health and disease. In this review, we discuss the mechanisms as to how the gut microbiota interacts with the brain, focusing on innate and adaptive immunity that are often disrupted in gut-brain axis disorders. We also consider the implications of these observations and how they can be advanced by interdisciplinary research. Leveraging an increased understanding of how these interactions regulate immunity has the potential to usher in a new era of precision neuropsychiatric clinical interventions for psychiatric, neurodevelopmental, and neurological disorders.

INTRODUCTION

The significance of microorganisms in all aspects of human health and disease is increasingly recognized, including brain health. Indeed, the microbiome-gut-brain axis has emerged as a new frontier with implications for our understanding of human physiology.[1] Increasing emphasis is now being placed in disentangling the mechanisms of communication along this axis.

We coexist with trillions of microorganisms including bacteria, viruses, fungi, and other microbes that reside in various body niches and that are recognized as a key determinant of health and disease.[2] The gut microbiome refers specifically to the collective genomes of all the microorganisms that live in the gut.[3] Advances in sequencing technology and bioinformatics have deepened our understanding of microbial communities, highlighting their critical role in programming bodily systems and influencing host health. The gut microbiota, and the bacteriome in particular, has gained attention for its impact on immune maturation, neuroinflammation, and neurobehavioral profiles beyond diversity metrics.[4,5]

Innate immunity acts as the host's first line of defense, integrating signals from the gut microbiota to orchestrate localized and systemic immune responses. Adaptive immunity, with its hallmark specificity and memory, further refines these responses to maintain a delicate balance between tolerance and defense. Together, these two arms of the immune system are important pillars of gut-brain axis communication and mediate many of the effects of the gut microbiota on the central nervous system (CNS), influencing a range of neurological and psychological processes.[6]

This review describes the main pathways through which the microbiota communicates with the brain, emphasizing the roles of innate and adaptive immunity in this complex reciprocal interplay, particularly in the context of relevant immune system disruptions in gut-brain axis disorders. In exploring the immunomodulatory properties of the gut microbiota and its impact on the CNS, we will highlight the therapeutic potential of targeting the microbiome-gut-brain axis, including neurodevelopmental, stress-related neuropsychiatric, and neurological disorders.

INTERACTION OF THE IMMUNE SYSTEM AND THE GUT-BRAIN AXIS

The gut microbiota and the brain communicate through various pathways, encompassing both neuronal connections and chemical messaging, yet the exact details of the mechanisms facilitating these interactions remain to be fully elucidated (see Figure 1). In the following sections, we focus on the main immunomodulatory mechanisms of communication between the gut and the brain, before focusing on specific aspects of the innate and adaptive immune systems that are involved in microbiome-gut-immune-brain axis communication.

THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) is linked to the immune system by the sympathetic and parasympathetic branches, playing a pivotal involuntary role regulating physiological functions and maintaining homeostasis. It facilitates bidirectional communication within the microbiome-gut-brain axis, influencing key gastrointestinal functions and responding to environmental stimuli through feedback loops. The vagus nerve, along with pelvic afferents, is a critical part of this communication network, providing a direct link between the gut and the

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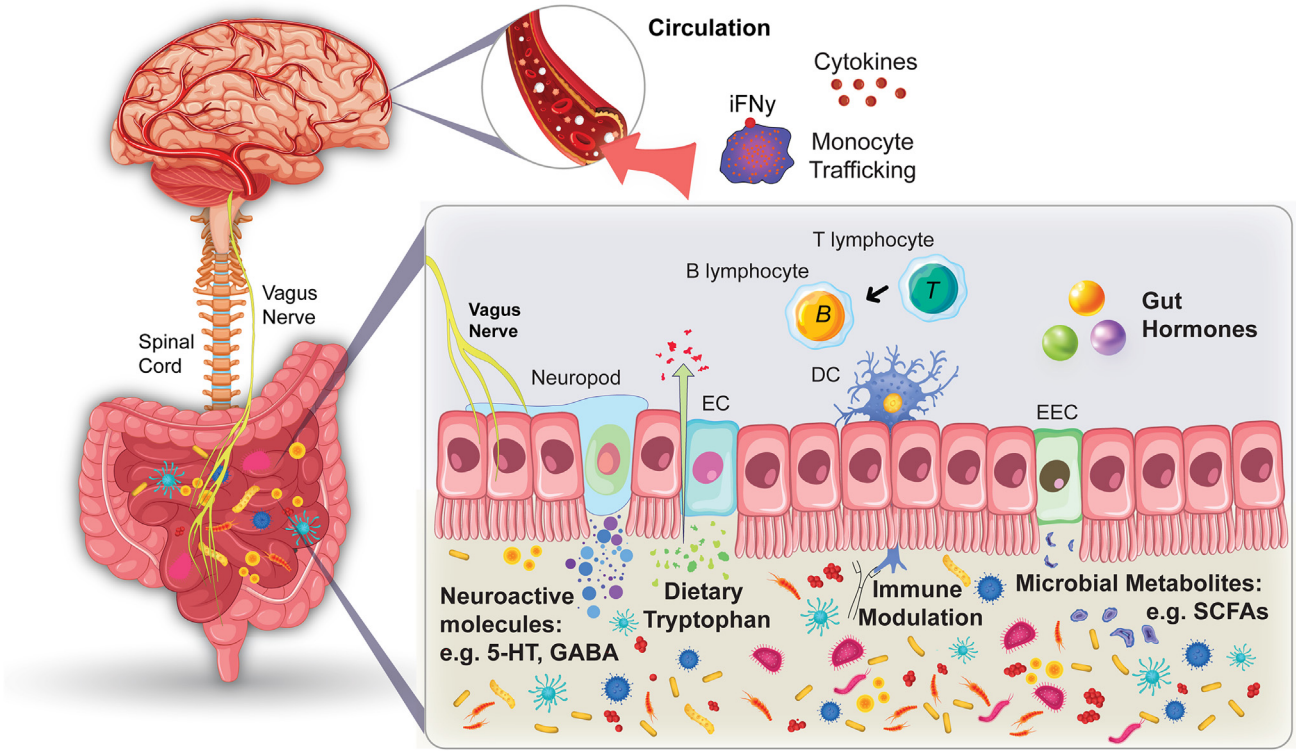


Figure 1. Gut microbiota-immune-brain axis communication mechanisms

Graphical representation of the complex bidirectional communication channels between the gut microbiota and the brain. This includes direct neural connections via the vagus nerve, the enteric nervous system, spinal nerves, neurotransmitters and neuroactive metabolites, as well as mediators such as short-chain fatty acids, cytokines, and essential dietary amino acids; innate and adaptive immune system modulation and enteroendocrine signaling, influencing dendritic cells modulating immune and microglial activities. Additionally, the hypothalamic-pituitary-adrenal axis is involved. Key: short-chain fatty acids (SCFAs), enteroendocrine cell (EEC), enterochromaffin cell (EC), dendritic cell (DC), serotonin/5-hydroxytryptamine (5-HT), γ-aminobutyric acid (GABA), interferon-gamma (IFNγ).

brain.[7] They collect information from the gut through a vast network of afferent fibers and modulate gastrointestinal and immune functions via efferent orthosympathetic/splanchnic nerves and the parasympathetic nervous system, which are relayed to the brain, influencing emotional and behavioral responses.[7] The vagal and pelvic nerves are thought to support homeostasis, while splanchnic innervation primarily transmits nociceptive signals. However, bilateral pelvic nerve sections reduce pain behaviors during noxious colorectal distension in rats, indicating their role in acute pain.[8] Research involving chemical irritants on colonic tissue further suggests pelvic fiber sensitization during inflammation, implicating their involvement in nociception.[9]

The vagus nerve is a key component of the inflammatory reflex: a neural reflex pathway that regulates innate immune responses and inflammation in response to pathogen invasion and tissue damage.[10] Vagal afferents can detect a range of signals from the gut, including stretch, tension, and chemical signals from the microbiota. Research has shown that altering vagal signaling, through methods like vagotomy or vagus nerve stimulation, can impact mood regulation, gut function, and immune response, underscoring the importance of this wandering nerve in gut-brain communication.[11]

While vagal and pelvic pathways primarily convey non-painful stimuli like satiety, distension, and motility to the brain, spinal splanchnic innervation plays a key role in transmitting complex sensory information, including pain, from the gut to the CNS.[12] These signals travel via tracts like the spinoreticular, spinomesencephalic, spinohypothalamic, and spinothalamic pathways, projecting to the brainstem, thalamus, and hypothalamus regions, influencing emotional and autonomic responses to gut-derived stimuli.

THE ENTERIC NERVOUS SYSTEM

The enteric nervous system (ENS), which is often considered a third arm of the ANS,[8] functions as a neural network within the gastrointestinal tract, interfacing with the gut's immune cell population, including macrophages, T cells, and innate lymphoid cells. This interaction enables the ENS to interpret environmental chemical signals into neural responses, pivotal for managing the gut's interaction with its diet, pathogens, and microbiome, influencing overall health. The development and function of the ENS can be affected by the gut microbiota, with studies indicating that microbial components can influence ENS development, activity, and the gut immune response.[8] The absence of the gut

microbiota, in germ-free preclinical models, results in notable ENS immaturity[13] and immune dysregulation, underscoring the important role of the gut microbiota in ENS development and immune function.[14] Antibiotics and diet can alter ENS architecture and immune function, affecting gut motility and intestinal secretion. This interaction suggests the potential for targeting the microbiota or its metabolic products for therapeutic interventions in neuropsychiatric and neurological disorders.

ENS neurons can modulate immune cell activity through neurotransmitter interactions, particularly involving catecholamines, which influence the function of macrophages within the mucosa.[15] Recent studies suggest that ENS activity not only responds to but also actively shapes immune signaling, playing a pivotal role in maintaining gastrointestinal homeostasis and responding to microbial stimuli.[8] This bidirectional communication between the ENS and immune cells underscores the complexity of neuro-immune interactions in the gut, which may have significant implications for broader physiological and pathological processes.

Additionally, emerging evidence highlights the significant impact of microbiota-host interactions at the gut level, which lead to the release of cytokines, chemokines, neurotransmitters, neuropeptides, endocrine messengers, and microbial by-products (Figure 1). These molecules can infiltrate the blood and lymphatic systems or modulate neural messages carried by both vagal and spinal afferent neurons. Through these mechanisms, the gut constantly communicates with the brain, updating it on health status and regulating brain function and behavior. Although a detailed exploration of this pathway is beyond the scope of this review, we refer readers to comprehensive reviews on the subject for further reading.[8,16]

ENDOCRINE PATHWAYS

Microbial endocrinology highlights a shared neurochemical language between host and microbes, with bacteria producing and responding to neurochemicals like serotonin (5-hydroxytryptamine [5-HT]), γ-aminobutyric acid, catecholamines, and indole derivatives, impacting host mood, cognition, and immune responses.[17,18] Tryptophan metabolism, shared by mammals and bacteria, generates 5-HT and kynurenine, influencing gastrointestinal serotonergic systems, immune regulation, and mental health.[19] Bacterial tryptophan-derived metabolites like indoles affect intestinal barrier integrity, inflammation, and metabolic health, while their production is stress-responsive and diurnal.[20] Bacterial-derived histamine induces visceral hyperalgesia, while β-glucuronidases, enzymes produced by host and microbes, affects detoxification, inflammation, and disease.[21,22]

Enteroendocrine cells play a key role in gut-brain communication by sensing microbial metabolites and releasing hormones like glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), influencing satiety, immune responses, and food intake.[8] Notably, L cells form direct synaptic connections with the ENS via neuropods, enabling rapid gut-to-brain signaling.[23] Spore-forming *clostridia* enhance colonic 5-HT biosynthesis, indirectly influencing brain function via vagal activity and immune responses.[24,25] Further, the neonatal gut is rich in 5-HT produced by specific bacteria, which also down-regulate monoamine oxidase A to enhance 5-HT availability. In neonates, gut bacteria-derived 5-HT supports immune tolerance by promoting regulatory T cell differentiation, emphasizing its critical role in early immune development.[26]

MICROBIAL METABOLITE SIGNALING BETWEEN THE GUT AND THE BRAIN

Microbial metabolites such as short-chain fatty acids (SCFAs) and secondary bile acids enhance the secretion of gut peptides, GLP-1 and PYY, particularly in the distal gut.[27] Secondary bile acids like deoxycholic acid and lithocholic acid polyamines can compromise the epithelial barrier, allowing bacterial components like lipopolysaccharide, peptidoglycan, and flagellin to translocate into the bloodstream or other tissues, triggering immune responses and systemic inflammation (see Figure 2[28]). Bacteriocins, small ribosomal synthesized antimicrobial peptides or proteins, are also produced by bacteria that can have a narrow or broad spectrum of activity against other bacteria, often targeting closely related species or specific strains.[29]

The breakdown of the gut barrier also increases intestinal permeability, often termed "leaky gut", and has links to conditions ranging from inflammatory bowel disease to metabolic disorders. However, this term oversimplifies the complex regulation of barrier permeability.[30] SCFAs, produced by the gut microbiota from indigestible fibers, influence immune function, blood pressure, and brain physiology.[27] Acetate, propionate, and butyrate can modulate enteroendocrine signaling, gut-brain pathways, and host immunity.[31] Indeed, SCFAs interact with cell membrane G protein-coupled receptors like free fatty acid receptor 2 (FFAR2, or GPR43), FFAR3 (or GPR41), and hydroxycarboxylic acid receptor 2; FFAR2 is highly expressed on regulatory T cells (Tregs) in the intestinal mucosa, regulating the regulation of intestinal immune balance.[27]

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The hypothalamic-pituitary-adrenal (HPA) axis is central to stress response coordination and a key communication route within the microbiome-gut-brain axis.[32] Immune-HPA interactions, demonstrated through microbial translocation and inflammatory cytokine activation, underscore the gut microbiota's role in HPA signaling. Stress activates the hypothalamus to release corticotrophin-releasing factor, prompting the anterior pituitary to secrete adrenocorticotrophic hormone, stimulating glucocorticoid release from the adrenal cortex. These glucocorticoids prepare the body for "fight or flight" responses, prime the immune system response, and provide negative feedback to the hypothalamus and pituitary. Stress not only impacts the composition[33] and activity[34] of the gut microbiota but also promotes microbial translocation, enhancing inflammatory cytokine activation (e.g., tumor necrosis factor alpha [TNF-α]) and increasing intestinal permeability, exacerbating stress-related symptoms. Cytokine-mediated inflammation allows microbial products to influence systemic and neurological functions, impacting HPA axis activity, as seen in germ-free mice showing heightened stress responses.[17] Interventions like probiotics can modulate cytokine levels, mitigating the adverse effects of stress on the

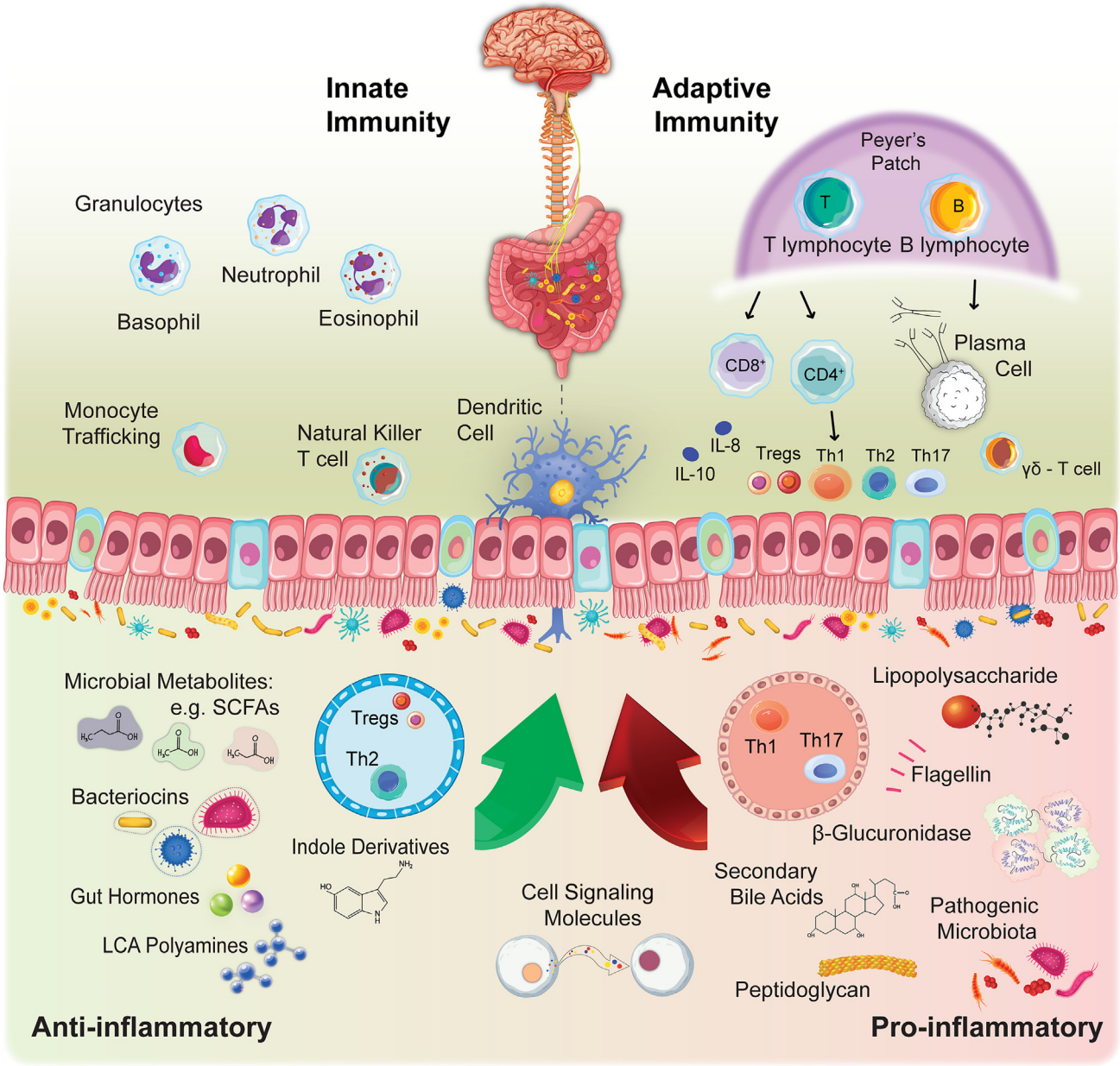


Figure 2. Innate vs. adaptive immunity and the gut microbiome

Microbes throughout the gastrointestinal tract play a key role in the development and maturation of the host's immune system. In addition, innate and adaptive immune cells play a crucial role in regulating the commensal microbiome ecosystem. The broad categories "Anti-inflammatory" and "Pro-inflammatory" refer to the general classification of gut microbiome components based on their predominant effects acknowledging that context-dependent exceptions may exist. Key: regulatory T cell (Treg), T helper cell (Th), interleukin (IL), gamma delta (γδ), cluster of differentiation (CD), short-chain fatty acids (SCFAs).

HPA axis and restoring gut homeostasis.[35] These interactions highlight the significant role of inflammatory cytokines in gut-brain communication, presenting them as potential therapeutic targets for managing stress-related disorders. The dialogue between the HPA axis and other microbiota-brain communication pathways, including vagus nerve stimulation and immune interactions, highlights complex interplays influencing stress and inflammatory responses.[36] More recently, a growing emphasis has been placed on the role of the microbiota in integrating HPA axis responses across the circadian cycle.[37]

GUT MICROBIOTA-IMMUNE-BRAIN AXIS: FOCUS ON THE INNATE AND ADAPTIVE IMMUNE SYSTEM

The immune system was originally perceived as defending against pathogenic microbes; it is now recognized that our

immune system interacts extensively with the gut microbiota, which contribute to host health (Figure 2).[5] Commensals (microorganisms that live in or on the body of a host without causing harm) play essential roles including providing nutrients, metabolizing indigestible compounds, and preventing the colonization of opportunistic pathogens. The interaction between the host immune system and gut microbes involves recognition, interpretation, and response mechanisms. Host recognition occurs through various pathways described previously (i.e., SCFAs, tryptophan metabolites, and bile acids).[27]

There is also growing interest in how cells of the immune system can impact behavior and cognition, while immune function also affects key brain processes like response to infection, injury, or autoimmunity.[5] Immune cells can infiltrate the brain, triggering inflammatory responses. Neuroinflammation can lead to changes in brain function and structure, subsequently influencing cognition, mood, and behavior.[38] Cytokines and chemokines can cross the blood-brain barrier (BBB) where they influence neuronal activity, synaptic transmission, and neurogenesis.[39] Moreover, the skin and mucosal surfaces harbor a multitude of microorganisms. Over time, the immune response to commensal bacteria has shaped innate and adaptive immunity (including B and T lymphocytes within Peyer's patches, plasma cells, and differentiated cytokines), forming intimate links between all three systems (Figure 2). However, the mechanisms underlying these connections are not yet fully understood.

THE GUT MICROBIOME, STRESS, AND IMMUNE SYSTEM: IMPLICATIONS FOR BRAIN DISORDERS

There is increasing focus on the cellular processes facilitating immune cell migration to the brain, particularly the role of the gut microbiota in these dynamics. While the CNS was historically considered isolated from the peripheral immune system, it is now understood that circulating cytokines influence brain function and behavior.[40] Peripheral leukocytes, including monocytes, T and B cells, and natural killer T cells, can access the cerebrospinal fluid, meninges, choroid plexus, and brain. Within the CNS, the choroid plexus, meningeal and perivascular macrophages, mast cells, and microglia (the macrophages of the brain) detect pathogens or tissue damage and initiate immune responses.[30] Chemokine-driven lymphocyte recruitment to perivascular spaces further supports CNS immunity.[41] Imbalances in cytokine levels and increased monocyte migration may contribute to neuroinflammatory conditions, potentially influenced by the gut microbiota.[42] Such changes in immune status, possibly influenced by the gut microbiota, could have profound effects on neuroinflammatory responses, potentially exacerbating neuropsychiatric and neurological conditions.

Microglia exemplify how gut microbiota affect the brain through innate immune mechanisms.[43] Indeed, germ-free mice display microglial defects, including altered numbers, maturation, morphology, and metabolic function, linked to impaired responses to infection.[44] These processes appear to be regulated by microbial-derived SCFAs, specifically acetate. Bacterial-derived acetate modulates key metabolic processes of microglia at steady state and could rescue impaired microglial maturation in germ-free mice.[45] N6-carboxymethyllysine, a microbial metabolite, also induces mitochondrial dysfunction in aging microglia.[46]

Neutrophils influence the gut microbiota and vice versa, with metabolites modulating neutrophil production and function.[47] Also, neutrophil-driven intestinal inflammation has been linked to autism spectrum disorder (ASD),[48] Parkinson's disease (PD),[49] and Alzheimer's disease (AD).[50] In AD, neutrophils accumulate near β-amyloid (Aβ) deposits, and their depletion in early disease stages improves memory in mouse models.[51] A recent study suggested that acute intestinal inflammation accelerates Aβ accumulation via neutrophil extravasation, which can be mitigated by neutrophil depletion.[50] These findings highlight a potential therapeutic role for targeting neutrophils via the gut-brain axis, though further research is required.

STRESS EXPOSURE

The gut microbiome is also impacted by stress.[33] Research has consistently replicated these findings across different bacterial strains, organisms, and stress paradigms. Moreover, stress is known to alter gut microbiome composition and gastrointestinal physiology and function.[52,53] One recent study showed that transplantation of the gut microbiota from a chronic unpredictable mild stress (CUMS)-induced mouse model into specific pathogen-free (SPF) mice could induce depressive-like behavior. The gut microbiome transfer was able to induce complement C3 activation and microglia-mediated synaptic pruning in SPF mice, a manifestation associated with depressive-like behavior in the CUMS mice.[54]

Dendritic cell (DC) activation has also been implicated in preclinical models of stress exposure and ensuant anxiety.[55] Male mice treated with *Lactobacillus rhamnosus* (JB-1) had decreased stress-induced anxiety-like behavior compared to vehicle-treated animals. This JB-1 strain was also shown to attenuate stress-related activation of DCs while increasing interleukin (IL)-10^{+} regulatory T lymphocytes.[55] Such studies suggest that the microbiota may influence certain neurological and behavioral outcomes through communication with DCs.

SCFA butyrate-producing bacteria such as *Faecalibacterium prausnitzii* has been shown to exert anti-inflammatory effects in colitis and reduced anxiety- and depression-like behaviors in the open-field test, influencing the Th17/Treg ratio of activated lymphocytes.[56,57] Notably, IL-17A emerged as a key molecule at the interface between the adaptive immune system and the gut microbiome. Further evidence of this relationship was uncovered where a mechanism of neuronal repair coordinated by commensal-specific T cells secreting IL-17A was identified.[58] This cytokine subsequently signals to sensory neurons via the IL-17A receptor A, enhancing neuronal recovery. Thus, at the mucosal surface, cells from the adaptive immune system and the microbiome can coordinate to influence CNS repair.

NEUROPSYCHIATRIC CONDITIONS

Major depressive disorder

Mood disorders like major depressive disorder (MDD) are complex, debilitating conditions influenced by inflammation and the gut microbiome.[59] Disruptions in the HPA axis, altered immune

activation, and gut microbiota disturbances have been shown to contribute to MDD pathology.[38] Chronic low-grade inflammation is recognized as a key element in the development of depression, and elevated levels of circulating immune cells (e.g., monocytes and granulocytes) have been noted in individuals with MDD; suppression of these cytokines reduces depressive-like behavior in animal models.[42,60] Additionally, mast cells, key innate immune regulators, have been implicated in depression through mechanisms linked to tryptophan metabolism and neuroinflammation.[61] Additionally, T cells contribute to MDD pathology, with meta-analyses revealing immune dysfunction, including altered counts of $CD4^+$ helper and activated T cells.[62]

Growing evidence links inflammatory markers such as C-reactive protein (CRP) with depression, anxiety, and cognitive deficits.[63] Mendelian randomization hinted at causal relationships between CRP and anxiety, supporting immune cell profiles as potential MDD biomarkers for patient stratification.[63,64] Collectively, such studies highlight the potential use of immune cell profiles as biomarkers for identifying subtypes of MDD and guiding patient stratification in future trials.

Similarly, such large-scale population studies have also found that bacterial strains of *Coprococcus* and *Dialister* not only indicate better life quality but are also reduced in individuals with untreated depression, while *Butyricicoccus* relates to antidepressant treatment responses.[65] Fecal matter transplants (FMTs) from individuals with MDD induced depressive-like behaviors in recipient animals, implicating the gut microbiome in depression's pathophysiology.[66] Probiotic interventions (e.g., *L. helveticus*, *Bifidobacterium longum* strains, *Clostridium butyricum*, and *L. plantarum*) have demonstrated beneficial effects on depression scores, cognitive function, and treatment responsiveness.[67,68] The gut microbiome's role in adaptive immunity, influencing T and B lymphocyte function, suggests that microbiota-targeted therapies could address MDD. Understanding the interplay between the microbiome, immune system, and depression may inform novel treatments for stress-related disorders.

Social anxiety disorder

Social anxiety disorder (SAD) (a.k.a. social phobia) is a mental health condition marked by a deep and ongoing fear of being scrutinized, judged, or humiliated in social settings. This overwhelming fear leads individuals to avoid social situations or face them with significant distress. Recent studies indicate a significant link between the gut microbiota, immune function, and anxiety in the context of SAD.[69] FMT from individuals with SAD into mice revealed that gut microbiota can induce heightened sensitivity to social fear, mirroring symptoms of SAD.[70] This response was accompanied by notable changes in both central and peripheral immune functions and a reduction in oxytocin expression within the bed nucleus of the stria terminalis. The altered immune responses include diminished IL-17A production and altered T cell profiles in gut-associated lymphoid tissues, indicating disrupted immune signaling that correlates with the behavioral phenotype of increased social fear. The SAD gut microbiome differs in composition and function from that of healthy controls, with elevated levels of *Anaeromassillibacillus* and *Gordonibacter* in patients with SAD and *Parasutterella* in controls.[69] There is a need for larger, longitudinal studies to confirm these findings and explore their clinical relevance.

NEURODEVELOPMENTAL DISORDERS

Schizophrenia

While a neuropsychiatric condition, schizophrenia is also considered a neurodevelopmental disorder resulting from the interaction between genetic susceptibility and prenatal and postnatal environmental stressors.[71] Schizophrenia manifests with positive and negative symptoms, along with cognitive deficits. The interplay between genes and the environment positions the microbiome and the immune system at the forefront of multi-system approaches to treat schizophrenia. Several risk factors for schizophrenia highlight the gastrointestinal tract as a critical area of investigation. These include inflammation,[71] gluten sensitivity, and exposure to *Toxoplasma gondii*.[72]

Strong evidence supports the combined role of the microbiome and the immune system in schizophrenia.[73] Biomarkers of bacterial translocation and intestinal permeability, such as soluble CD14 and lipopolysaccharide binding protein, correlate with CRP levels in individuals with schizophrenia and are influenced by antipsychotic use.[74] Furthermore, individuals with schizophrenia exhibit altered gut microbiome β diversity, with metabolic pathways linked to inflammatory cytokines.[75] Similarly, the oral microbiome showed increased *Streptococcus* and decreased *Prevotella*, with *Streptococcus* associated with elevated TNF-α and IL-9, chronic inflammation, and BBB disruption.[76,77] These pro-inflammatory cytokines were associated with chronic low-grade inflammation and a disrupted BBB. Gut microbiota shifts, such as increased *Eggerthella* and decreased *Bacteroides*, correlate with inflammatory markers like zonulin and CRP.[78] Additionally, enhanced plasma IgM and IgA responses to commensal strains (specifically *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Pseudomonas putida*, and *Klebsiella pneumoniae*) were observed in individuals with neurocognitive impairments, linking the microbiome with innate and adaptive immunity.[79] These findings suggest complex microbiome-immune interactions in schizophrenia, including potential roles in the gene-environment interplay.

ASDs

ASDs are also multifaceted neurodevelopmental disorders characterized by deficits in communication and social skills and repetitive stereotypical behaviors. The high prevalence of gastrointestinal comorbidities in autistic children has spurred interest in the gut microbiome's role in ASD pathogenesis.[80] Fecal samples from ASD showed increased *Bacteroidetes* and alterations in the colonization of *Bifidobacterium*, *Lactobacillus*, *Prevotella*, and *Ruminococcus* genera and were linked to increased inflammation and immune activation. Indeed, *Bifidobacterium* is normally associated with protective anti-inflammatory activity, and therefore its decreased levels in ASD have been suggested to be deleterious rather than protective.[81]

Chronic inflammation in ASD overlaps with inflammatory bowel disease transcriptomes, while peripheral blood mononuclear cells from children with ASD produce elevated mucosa-associated cytokines (IL-5, IL-15, and IL-17) and zonulin, implicating

gut permeability.[82] Maternal immune activation (MIA) due to infections, autoimmune disorders, or inflammation during pregnancy increases the risk of ASD in offspring.[83] Key inflammatory cytokines, including IL-6 and IL-17A, disrupt fetal brain development, leading to neurodevelopmental abnormalities. Mouse models of MIA have demonstrated that maternal inflammation alters offspring brain connectivity, behavior, and immune priming, with IL-17A being a critical mediator. Emerging evidence highlights the role of the maternal gut microbiome in modulating MIA effects, suggesting potential intervention targets.[83]

Further evidence for the gut microbiome-immune system link in ASD comes from studies using probiotics and prebiotics in a valproic acid (VPA) rat model.[84] A multi-strain probiotic (VSL#3) treatment correlated with improved sociability, social interaction, and anxiety-like behaviors, as well as rescue of VPA-induced increases in IL-6 and decreased 5-HT levels in the prefrontal cortex.[84] Moreover, specific prebiotic diets (3% galacto-oligosaccharides [GOS]/fructo-oligosaccharides [FOS]) have been shown to mitigate VPA effects by restoring microbial communities, intestinal permeability, and reducing cerebellum-associated neuroinflammation. It also enhanced Foxp3+ Tregs in VPA-exposed mice, indicating the modulation of immune balance.[85] Taken together, these studies highlight the complex interplay between the gut microbiome and the immune system in ASD and suggest that symptoms could potentially be mitigated through targeting this axis.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by inattention, hyperactivity, and impulsivity, with growing attention on the role of the microbiome in its development.[86] Research indicates that dietary factors, particularly a Western-style diet[87] and elimination diets, may influence ADHD symptoms by affecting the gut microbiota.[86] Increased levels of the genus *Bifidobacterium* in individuals with ADHD could be linked to the regulation of gut-derived dopamine precursors.[88] The effects of a few-foods diet on ADHD symptoms found that 63% of participants showed a significant reduction in symptoms.[89] Although brain activation changes in regions related to inhibitory control did not correlate with symptom improvement, increased activation in the precuneus region was associated with decreased ADHD symptoms, suggesting a neurocognitive mechanism through which the few-foods diet may exert its benefits.

A recent systematic review of the beneficial effects of prebiotics, probiotics, and synbiotics on ADHD[90] found that specific strains of bacteria, such as *L. rhamnosus* and *Bifidobacterium bifidum*, may positively influence neurocognitive and behavioral outcomes. Another systematic review identified differences in gut microbiome characteristics associated with ADHD, highlighting an increased abundance of genera like *Odoribacter* and *Eggerthella*, linked to dopamine metabolism, and a decreased abundance of *Faecalibacterium*, associated with inflammation.[86] While some correlations between gut microbiota features and ADHD symptomatology emerged, the review underscores the need for further studies to explore these relationships, considering factors like geographic variations, age, and dietary habits, which may influence the gut-brain connection in ADHD.

AUTOIMMUNE DISORDERS

Multiple sclerosis

The links between microbiota-immune communication and autoimmune disorders, such as multiple sclerosis (MS), are well established. MS, a chronic autoimmune disease characterized by CNS myelin destruction, is associated with microbiome alterations correlating with increased expression of inflammatory pathways in monocytes.[91] Probiotics containing taxa depleted in patients with MS (*Lactobacillus*, *Bifidobacterium*, and *Streptococcus*) induced anti-inflammatory responses and reduced monocyte activation, highlighting gut-immune communication in MS pathology.[92]

At the interface between innate and adaptive immunity are DCs, professional antigen-presenting cells that play an important role in activating T lymphocytes. DCs are regulated by the gut microbiome, with SCFAs promoting DC hematopoiesis via Fms-related tyrosine kinase 3 ligand expression.[93,94] Performed in preclinical MS models (experimental autoimmune encephalomyelitis [EAE]), probiotics like Lactibiane Iki improved clinical outcomes by reducing demyelination and inducing a tolerogenic DC phenotype.[95] Similarly, *Saccharomyces cerevisiae* and its derivative Selemax increased $CD103^+$ DCs and reduced intestinal inflammation.[96]

Recent research has highlighted the role of the meninges in immune surveillance.[97] Meningeal IgA+ cells, which depend on the gut microbiome, increase in response to gut inflammation and dampen EAE-associated inflammation.[98,99] Molecular mimicry also contributes to EAE, with *L. reuteri* producing peptides mimicking myelin oligodendrocyte glycoprotein (MOG), exacerbating autoimmunity.[100] Overall, given that the complexity of the microbiome leads to an increase in the diversity of IgA, it is tempting to speculate that targeting or modifying IgA in the gut may pose a therapeutic pathway for treating brain disorders.

Diet influences B cell function, with implications for neuronal development, particularly the B1a subtype involved in myelination. As mentioned earlier, there is increasing evidence implicating the gut microbiome in the onset and progression of MS with researchers observing changes in the composition of certain commensals in patients with MS. These include low-level translocation of bacterial cell wall components, disruption of the BBB, or alterations in the expression of genes involved in myelination. FMT from individuals with MS into germ-free mice worsened EAE symptoms, reducing IL-10+ Tregs and enhancing anti-MOG antibody production, underscoring the microbiome's role in MS pathology.[101,102] Antibiotics pre-treatment enhanced the population of regulatory T and B cells, leading to a reduction in EAE severity by altering cytokine profiles, suggesting that modulation of the microbiota may impact MS autoimmunity.[103] Overall, these studies suggest the potential to utilize the gut microbiome to reduce autoimmune responses in disorders like MS.

NEURODEGENERATIVE DISEASES

PD

It is now over two decades since seminal research postulated that the cause of PD might begin in the gut.[104] This age-related neurodegenerative disorder, marked by dopaminergic neuron

loss, α-synuclein accumulation, and neuroinflammation, often presents with constipation years before diagnosis.[105] α-synuclein has been identified in gut nerve fibers and ganglia, and mouse models show that the gut microbiota influence α-synuclein aggregation and protein clearance.[106,107] Moreover, the vagus nerve may mediate gut-to-brain α-synuclein transport, supported by findings that truncal vagotomy decreases PD risk and halts α-synucleinopathy progression in mice.[108] Yet, there is no consensus on whether there is a distinct microbial pattern specific to PD partly due to limited longitudinal studies and small sample sizes.

Immunological links to PD are well documented, with genes regulating immune activity and cytokine signaling associated with PD risk.[109] Emerging research suggests that inflammation originating from the gut plays a pathological role in PD, driving the development of immune-based therapies targeting α-synuclein and immune mediators. Postmortem analysis of PD brain tissue shows an increase in the activation of complement, cytokine and chemokine production, and inflammasome activation, all coupled with microglial activation, indicating immune system involvement throughout disease progression.[109]

Microbiome studies have revealed consistent findings across populations. Reduced *Prevotella* abundance has been reported in cohorts from Germany, Finland, Russia, and Japan, suggesting a global pattern independent of ethnicity or diet.[110,111] Increased *Akkermansia muciniphila* correlated with constipation in patients with PD, while altered SCFA-producing bacteria are hallmarks of PD, potentially linking SCFA dysregulation to neuroinflammation.[112] Associations between *Bacteroides* and TNF-α, as well as *Verrucomicrobia* and interferon-gamma (IFNγ), further highlight microbiota-immune interactions in PD.[113] It is becoming clear that the microbiome is required for PD progression, and future work should identify the microbiome composition at distinct time points during the development of the disease, including the prodromal phase.

AD

AD is the most prevalent neurodegenerative disorder, leading to dementia, and is characterized by the formation of Aβ plaques,[114] hyperphosphorylated tau protein and neurofibrillary tangles, neuronal loss, and neuroinflammation.[115] The disease progresses from the transentorhinal cortex to the hippocampus and cortical areas. Although Aβ accumulation is central to AD, neuroinflammation accelerates cognitive decline, with Toll-like receptor activation by Aβ triggering inflammasome complexes and microglial-driven inflammation.[114] Misfolded tau disrupts protein turnover at synapses, further contributing to neuronal dysfunction. However, whether Aβ accumulation is a dysregulated immune response or a direct driver of AD remains an open question, necessitating further research.

Emerging evidence links pathogenic microbes to AD pathogenesis. Elevated *Bacteroides* levels in AD mice correlate with reduced microglial phagocytic activity, promoting Aβ accumulation.[116] Individuals with AD often exhibit gut microbiota imbalances with reduced microbial diversity, a decrease in beneficial bacteria like *Eubacterium rectale*, *Bifidobacterium*, and *Dialister*, and an increase in pathogenic bacteria including *Escherichia/Shigella*, *Bacteroides*, and *Ruminococcus*.[117,118] A noted correlation between elevated levels of *Escherichia/Shigella* and increased pro-inflammatory cytokines (IL-1β and the chemokine CXCL2) in the serum of individuals with AD was reported, suggesting a link between gut microbiota alterations and peripheral inflammation in AD.[117]

Hypotheses propose that Aβ functions as an antimicrobial peptide, trapping pathogens in fibrillar aggregates.[119] Viral involvement, particularly herpes simplex virus 1 (HSV-1), is implicated in AD, as HSV-1 colocalized with Aβ plaques and tau tangles in the brain.[120] Anti-HSV-1 IgM antibodies increased AD risk, suggesting that reactivation, rather than persistence, may drive pathology.[121] Additionally, inoculation of AD homogenates from humans into primates and mice induced the transmissibility of AD-like pathology.[120]

Gut microbiota alterations are increasingly linked to AD. Antibiotic-induced microbiome changes modulate neuroinflammation and Aβ deposition.[122] Germ-free amyloid precursor protein/presenilin 1 mice showed reduced Aβ pathology, while FMT from healthy donors reduced Aβ and tau abnormalities in AD mouse models.[123] From a therapeutic perspective, administration of *L. plantarum* prevented cognitive decline by reducing Aβ plaque formation and tau hyperphosphorylation in an AD mouse model.[124] On the other side, causal evidence is emerging from animal studies showing that microbiota from patients with AD can induce cognitive deficits.[125] Clinical trials have shown mixed results, with some probiotics improving cognition in mild AD but limited effects in advanced cases.[126]

While microbiome-targeted therapies for AD are promising, further research is needed to elucidate mechanisms, develop biomarkers for early detection, and refine interventions. Microbiota-based treatments hold potential as adjunct therapies to slow or halt AD progression, offering a transformative approach to managing this complex disease.

PROPOSED GUT-MICROBIOTA-TARGETED THERAPIES

Emerging evidence linking the gut microbiota to psychiatric and neurological disorders via the microbiome-gut-immune brain axis has led to the development of therapies targeting this axis.[127] These therapies focus on modulating the gut microbiota to influence immune responses and brain function, with probiotics, prebiotics, synbiotics, postbiotics, and FMT, combined with coaching on lifestyle choices and dietary advice, being the main strategies currently under investigation (see Figure 3 and Box 1).

PROBIOTICS

Probiotics, live microorganisms that confer health benefits to the host, have been extensively studied in the context of the microbiome-gut-brain axis.[128] Psychobiotics, initially defined as probiotics that specifically target mental health via gut-brain interactions, improve mood, cognition, and stress responses.[1] This definition has been expanded to include other methods for targeting the microbiome that may enhance brain process.[129,130] Benefits of putative probiotics appear to be strain dependent; in particular, *Lactobacillus* and *Bifidobacterium* have shown promise in improving mood, anxiety, and depression scores in both preclinical models and human studies.[131] For instance,

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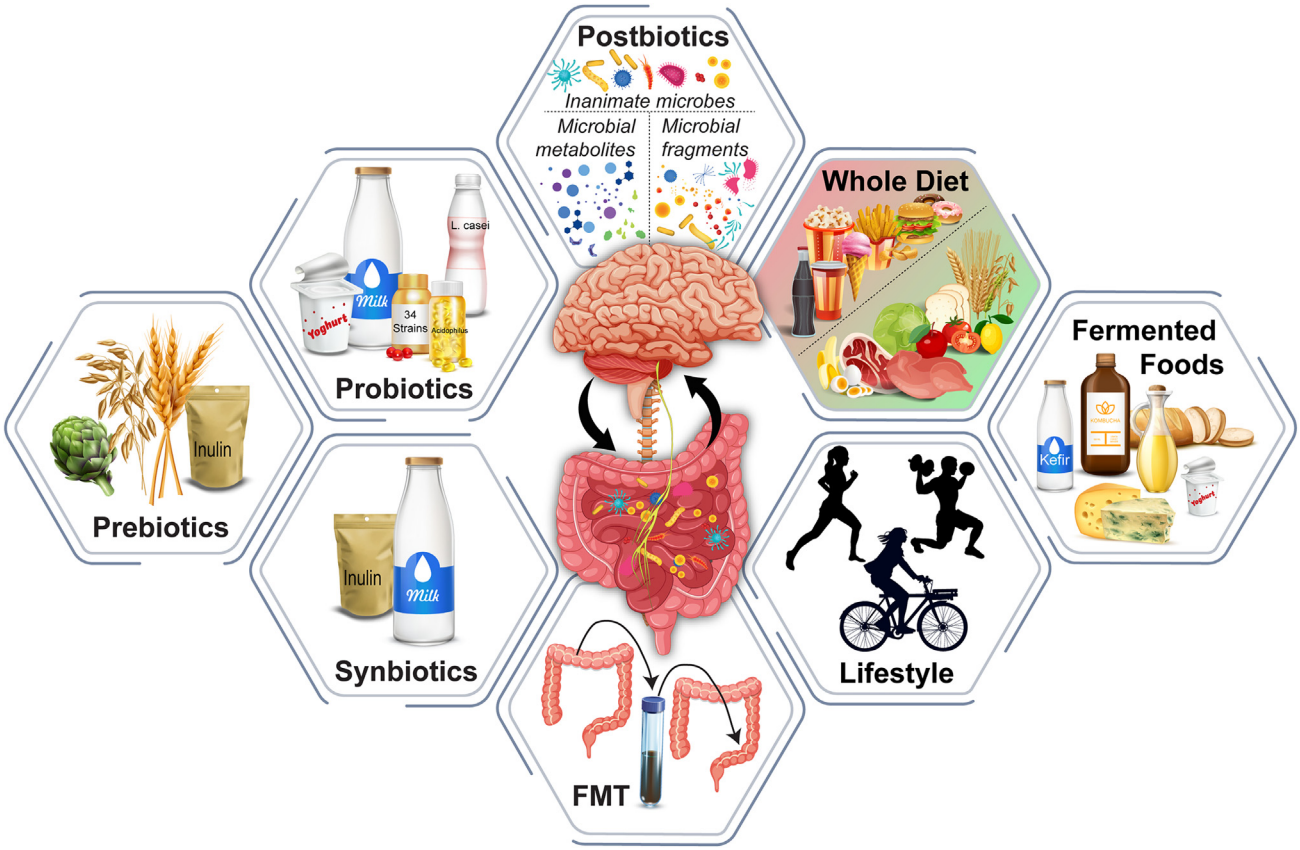


Figure 3. Potential therapeutic interventions that can inform future perspectives

Here, we illustrate various potential therapeutic interventions that could inform future perspectives on gut-brain health. The interventions are categorized into seven main areas: (1) prebiotics: dietary fibers like inulin that promote the growth of beneficial gut bacteria. (2) Probiotics: live beneficial bacteria, commonly found in fermented dairy products and supplements, that support gut microbiota balance. (3) Synbiotics: a combination of prebiotics and probiotics that work synergistically to enhance gut health. (4) Postbiotics: inanimate microbial products, including microbial metabolites and fragments that can have health benefits even in the absence of live bacteria. (5) Whole diet: the overall diet, including the balance between processed foods and whole foods, that influences gut microbiota composition. (6) Fermented foods: yogurt, kefir, and cheese, rich in live cultures, which contribute to a healthy gut microbiome. (7) Lifestyle: physical activities such as running, cycling, and strength training that promote a healthy gut-brain axis. (8) FMT (fecal microbiota transplantation): a method to potentially restore healthy gut microbiota.

L. casei improved mood scores in elderly participants, particularly those with low baseline mood.[132] A combination of *L. acidophilus*, *L. casei*, and *B. bifidum* showed a significant reduction in serum high-sensitivity CRP and depression symptoms in patients with MDD,[133] while *Lactobacillus* and *Bifidobacterium* supplementation lowered CRP and TNF-α levels in patients with gestational diabetes.[134]

Specific strains of bacteria have also reduced inflammation in preclinical models, such as a high-fat diet-induced inflammation model where *Lactobacillus* and *Enterococcus* strains decreased IL-6, TNF-α, and IL-1β.[135] Strain specificity is crucial; for example, *B. longum* alleviated depression in individuals with irritable bowel syndrome (IBS), but not anxiety.[136] Similarly, *L. plantarum* reduced stress and kynurenine in stressed adults but had no effect on TNF-α, IL-6, or IL-1β levels.[68] Such work demonstrates the need for careful selection of probiotic strains in clinical applications, as not all strains have the same therapeutic potential.

Some probiotics (e.g., *Bifidobacteria* and *Lactobacilli*) have shown potential in improving behavioral and neurochemical disturbances in preclinical models of ASD, where *Bifidobacteria* and *Lactobacilli* improve behavioral and neurochemical disturbances.[137] Human studies are preliminary but indicate potential behavioral improvements with *L. acidophilus*, *L. rhamnosus*, and *B. longum*[138,139]; but again, no significant changes in TNF-α, IL-6, and IL-1b, or cortisol were noted in any group tested in one study.[139]

Peripheral immune abnormalities have been associated with schizophrenia, but probiotics have shown limited psychiatric benefits. Supplementation with *L. rhamnosus* and *Bifidobacterium animalis* reduced von Willebrand factor levels and modulated monocyte chemoattractant protein-1, brain-derived neurotrophic (BDNF), chemokine ligand 5, and macrophage inflammatory protein-1 β.[140] Pathway analysis suggested that these changes relate to the regulation of immune and intestinal epithelial cells via IL-17 cytokines, indicating that probiotics may help manage

Box 1. Definitions of key compounds impacting the gut microbiota

Term	Definition
Fermented food	"foods made through desired microbial growth and enzymatic conversions of food components"[180]
Prebiotic	"a substrate that is selectively utilized by host microorganisms conferring a health benefit"[142]
Probiotic	"live microorganisms, which when administered in adequate amounts, confer a health benefit on the host"[181]
Postbiotic	"preparation of inanimate microorganisms and/or their components that confer a health benefit on the host"[182]
Synbiotic	"a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confer a health benefit on the host"[148]
Psychobiotic	"beneficial bacteria (probiotics) or support for such bacteria (prebiotics) that influence bacteria-brain relationships"[130]

gastrointestinal permeability in schizophrenia. Open-label studies using *Bifidobacterium breve* also reported positive effects on anxiety and depression in schizophrenia and increased levels of TNF-related activation-induced cytokine and IL-22 in responders, though the absence of a placebo arm limits these findings.[141]

Prebiotics: Feeding beneficial gut microbes

Prebiotics, which are non-digestible substrates selectively chosen to target host microorganisms enabling beneficial microbes to thrive, represent another approach to modulating the microbiome-gut-brain axis. Prebiotics can be found in a wide variety of foods including fruit, vegetables, whole grains, and human milk. By promoting the growth of beneficial bacteria like *Bifidobacterium*, prebiotics can enhance gut health and potentially improve mental health.[142] FOS and GOS are among the most studied prebiotics, with research indicating their ability to modulate gut microbial composition and reduce stress responses.[143] Three weeks of GOS supplementation lowered the cortisol awakening response in healthy volunteers, indicating a reduction in stress, albeit without changing biological markers of stress and inflammation or mental health.[144] Another study found that GOS reduced anxiety scores in patients with IBS, highlighting the potential for prebiotics to alleviate both gut and mood-related symptoms.[145] A more recent randomized controlled study demonstrated that a 14-day high-dose prebiotic intervention reduced reward-related brain activation during food decision-making in overweight adults, with concurrent shifts in the gut microbiota, including an increase in SCFA-producing *Bifidobacteriaceae* suggesting a potential link between prebiotics and the modulation of brain functions related to food choices.[146]

Preclinical studies have also demonstrated the antidepressant-like effects of prebiotics. A FOS/GOS mixture was used to mitigate *in utero* VPA-induced alterations in a mouse model of ASD.[85] The prebiotic diet normalized key microbial taxa, improved intestinal permeability, restored immune balance, reduced neuroinflammation (specifically decreasing CD68 expression), and enhanced social behavior and cognition in VPA-exposed offspring.[85] A FOS/GOS mixture administered to mice was also able to reduce corticosterone levels and increase BDNF expression in the hippocampus, which is critical for mood regulation.[147] These findings suggest that prebiotics can influence not only the gut microbiota but also key neurobiological pathways involved in neuropsychiatric conditions. However, human studies on prebiotics and mental health remain limited, and further research is needed to fully understand their therapeutic potential.

SYNBIOTICS: COMBINING PROBIOTICS AND PREBIOTICS FOR ENHANCED EFFECTS

Synbiotics, which combine probiotics and prebiotics,[148] aim to enhance the survival and efficacy of probiotics by providing a fermentable substrate for them to thrive. This approach has shown promise in improving both gut health and psychological well-being. For example, a study in individuals with mild to moderate depression demonstrated that a synbiotic containing *L. helveticus* and *B. longum*, combined with GOS, led to reductions in depression scores and improvements in tryptophan metabolism, a key pathway involved in serotonin production.[67]

In another study, a synbiotic composed of a multi-strain probiotic combined with a prebiotic improved functional gastrointestinal symptoms in patients with PD, suggesting a link between gut health and brain-related outcomes in neurodegenerative disease.[149] A more recent synbiotic approach using *B. longum* (*infantis*) combined with human milk oligosaccharides (HMO) as a prebiotic achieved predictable engraftment in the adult human gut microbiome.[150] *B. infantis*, typically absent in adults, successfully engrafted in an HMO-dependent manner without any pretreatment with antibiotics, reaching up to 25% of the bacterial population and promoting beneficial metabolite changes. The synbiotic also enhanced butyrate levels and inhibited enteropathogen growth, offering a potential novel therapeutic strategy. While synbiotics have shown potential in modulating the microbiome-gut-brain axis, few studies have employed the strategy, and more large-scale clinical trials are needed to establish their efficacy in various psychiatric and neurological conditions.

POSTBIOTICS: NON-VIABLE PREPARATIONS OF MICROORGANISMS WITH POTENTIAL BENEFITS

Postbiotics, which are a non-viable preparation (e.g., heat-inactivated) of inanimate microorganisms and/or their components conferring a health benefit to the host, are gaining attention as a novel approach to modulating the gut-brain axis.[151] A 12-week intervention with heat-killed *L. gasseri* alleviated students' exam-related stress, improving anxiety scores, cortisol levels, and sleep quality.[152] Preclinical studies have also shown that heat-killed *L. paracasei* can exert antidepressant and anxiolytic effects by reversing reduced levels of dopamine in brain regions linked to depression.[153] *Lactobacillus* LB, a postbiotic derived from the fermentation of *Limosilactobacillus fermentum* and *L. delbrueckii*, has been shown to influence ileal ion transport and motility, potentially contributing to its therapeutic effects in acute diarrhea and IBS.[154] Postbiotics offer many advantages over live probiotics, including longer shelf life and potentially enhanced safety.

MICROBIAL METABOLITES

Microbial metabolites, organic compounds produced by gut microbes during their metabolism, influence host physiology and health through immune regulation, inflammation modulation, and gut barrier maintenance.[155] These include a wide range of biochemical products, like SCFAs, amino acids, and vitamins. Microbial metabolites play crucial roles in various biological functions, including regulating immune responses, modulating inflammation, and maintaining gut barrier integrity.[156] Microbial-derived SCFA modulation of microglial activation has been shown to enhance the pathophysiology of PD.[107] However, another study in the context of PD showed that a high-fiber diet that increased SCFA production improved motor deficits, reduced α-synuclein aggregation, and promoted protective macrophage subsets in PD models, effects eliminated by microglia depletion, highlighting a microglia-dependent gut-brain interaction.[157] Similarly, in AD models, SCFA treatment reduced microglia activation, ameliorated plaque burden, and rescued memory impairments in several different studies.[45,158] Taken together, it would suggest that SCFA treatment could be beneficial in treating neurodegenerative disease; however, it could also be dependent on what stage in disease this occurs. Further research in patients with PD identified deficiencies in *Blautia* and butyrate; supplementation with the butyrate-producing bacterium *B. producta* in PD models attenuated microglia-mediated neuroinflammation, improved motor dysfunction, and inhibited microglia activation.[159]

A fiber-deprived diet was also shown to link microglia, the gut-brain axis, and cognitive impairment. Here, mice subjected to long-term fiber deficiency exhibited deficits in object location memory, temporal order memory, and a reduced ability to perform daily activities. These deficits were associated with increased hippocampal inflammation and increased engulfment of synapses by microglia.[160] Further preclinical studies have demonstrated that SCFA supplementation can reduce anxiety and stress-related behaviors in animal models, likely by modulating immune and inflammatory pathways.[161,162]

FECAL MICROBIOTA TRANSPLANTATION: RESTORING GUT MICROBIAL BALANCE

FMT involves transferring stool from human or rodent donors to individuals or rodent recipients in order to engraft a gut microbial signature indicative of the donor, transferring a gut microbiome signature and/or a phenotype for treatment or further investigation.[163] While FMT has been successfully used to treat conditions like recurrent *Clostridium difficile* infections and ulcerative colitis, its application in psychiatric disorders is still in its infancy.[164] However, given the strong link between gut disorders, inflammation, and mental health, FMT is being explored as a potential treatment for depression and anxiety.[38,165]

Preclinical studies have shown that transferring the gut microbiota from depressed individuals to healthy animals can induce depressive-like behaviors,[66,166,167] supporting the role of gut microbiota in mood regulation. Indeed, while one study reported no observed differences in either innate or adaptive immune cell populations,[167] another saw a decrease in the production of IL-1β and TNF-α, and a brain region-specific suppression in the activation of Iba1-positive microglia cells and the NLRP3 inflammasome.[166] In humans, small clinical trials have suggested that FMT may alleviate symptoms in patients with IBS, a condition often comorbid with anxiety and depression.[168] Evidence from both clinical and animal studies suggests that FMT may function by reducing systemic inflammation. In mice that have undergone dextran sodium sulfate-induced ulcerative colitis, FMT from healthy donors improved colon inflammation and restored gut microbiota composition, along with reduced mRNA expression of colonic pro-inflammatory markers IL-1 and IFNγ.[169] Clinical studies in patients with ulcerative colitis also demonstrated significant reductions in serum CRP and inflammatory cytokines like IL-6 and IL-1Ra and inflammatory chemokines IP-10 and ENA-78 following FMT, indicating potential immune system modulation.[170,171] Although these findings are promising, larger, controlled trials are needed to fully assess the potential of FMT as a therapeutic option for psychiatric conditions.

FUTURE PERSPECTIVES AND THERAPEUTIC OUTLOOK IN THE MICROBIOME-GUT-IMMUNE-BRAIN AXIS

The utilization of animal models in microbiome research is extensive and has been indispensable for uncovering fundamental biological mechanisms, yet these models often fail to capture the complexities of human condition. Recognizing their limitations encourages a cautious interpretation of these findings, until validated in the context of human health, and prompts a translational focus and shift toward more human-based research. Future investigations should focus on longitudinal and cross-sectional studies that integrate genetic, environmental, social, cognitive, and immune factors to fully understand how these complex interactions influence health and disease. To enhance the scope of translationally relevant animal research, future studies should continue to integrate microbiome analyses with an expanded analysis of immune measures with cognitive and/or behavioral outputs. This approach is particularly relevant in studies using antibiotics and germ-free models, which can

Box 2. Preclinical techniques that provide causality in gut microbiota research

Term	Definition
Germ-free	animals, typically rodents, raised in sterile environments without the opportunity to host microorganisms, are compared to conventionally raised controls that are free from pathogenic microbes (i.e., specific pathogen-free animals)
Fecal microbiota transfer	the process of transferring the entire gut microbiota through fecal transplantation, from a donor (human or animal) exhibiting specific clinical traits of interest, into a human or animal recipient. The assessment of physiological and behavioral modifications in the recipient is conducted to evaluate resemblance to the donor
Antibiotic administration	the use of antibiotics aimed at the gut to modify or reduce the population of gut bacteria

provide important insights into the roles of the gut microbiome under altered conditions (see Box 2). Moreover, expanding research to include cross-species studies, like those involving zebrafish, can offer evolutionary insight into host-microbiome interactions.[172]

The exploration of dietary interventions, including prebiotics and probiotics,[155,173] and evaluating different dietary extremes like vegan versus ketogenic diets,[174] remains critical (see Figure 3). Diet represents a rapid, safe, and significant avenue for modifying the gut microbiome, potentially affecting both the immune system and the brain. Recent studies from our group have demonstrated that increasing dietary fiber intake enhances cognitive performance, while a psychobiotic diet has been shown to stabilize the gut microbiome and improve perceived stress in healthy individuals.[173,175] It is essential to distinguish how these interventions affect the immune system and gut microbiome in both healthy individuals and those in disease states, enabling the development of personalized therapeutic strategies.[38,176] There remain many open questions about FMT regarding its ability to modulate brain and immune system interactions, especially in immune-mediated disorders. Understanding its effects in different health contexts could open new therapeutic avenues. Indeed, new techniques are being developed that use a high-throughput, culture-independent approach that measures systemic IgG against commensal bacteria from the gut in peripheral blood allowing us to highlight interactions between the microbiome and the immune system in inflammatory disease; future work may adapt this technology to neurological conditions.[177]

The integration of CRISPR (clustered regularly interspaced short palindromic repeats) technology for precise microbiome editing may allow us to refine the way we currently target entire microbiomes and reduce the bystander effects of antibiotics. CRISPR in prokaryotic organisms represents the adaptive immune system, and through technical innovation, scientists have harnessed this technology as a powerful tool to treat and target genetic diseases that were once thought to be untreatable. Using CRISPR, we hope to target microbial interactions or remove antibiotic resistance genes among other startling innovations. How CRISPR treatments may modulate the innate and adaptive immune systems in humans remains to be elucidated.

The use of AI in data analysis could revolutionize our understanding of microbiome-gut-immune-brain interactions and enhance disease prediction, treatment strategies, and personalized medicine. Given our ever-expanding capacity to handle vast amounts of biological data, it may allow for a more comprehensive integration of immune-microbe interactions that will surely generate more effective treatments. Machine learning and deep learning can enhance the precision of diagnosis and efficacy of treatment by handling lifestyle factors, immune marker readouts, congenital information, and host data to design tailor-made medical interventions. It also allows for non-invasive diagnostics and disease management, utilizing large dataset microbiome studies and sophisticated genomic techniques to facilitate early identification and improved management of various conditions, like those discussed in this review.

We are also learning a great deal more about the influence of circadian biology on both the immune system and the microbiome.[37,178] We know that host immunity is an energetically demanding process requiring the coordination of a multitude of cell types to perceive and direct responses to microorganisms. Host circadian clock mechanisms entrain immune cell development, function, and trafficking, varying host susceptibility to microbial presence across the cycle.[178] Not only do intestinal microbiota follow diurnal rhythms in the host, but they also generate diurnal rhythms in innate immunity that synchronize to host feeding rhythms to anticipate microbial exposure. Indeed, a detailed understanding of these relationships along the immune-gut-brain axis across the day could improve treatment regimen and timing of interventions for many neurological conditions.

The precise mechanisms of how microbiota influence the gut-brain axis are not yet fully understood, in particular, the role of barriers in the gut-brain axis as critical interfaces between the microbiome and the immune system like the gut epithelial barrier, the BBB, and the blood-cerebrospinal fluid barrier.[30] These barriers serve as vital communication channels, relaying signals from gut microbiota and maintaining compartmental homeostasis. Further detailed mechanistic examination of the potential of targeting these barriers therapeutically to understand and possibly treat the linked pathologies of neurological and gastrointestinal disorders is needed. Finally, further studies of other components of the microbiome on immune-brain interactions will be important. Recent studies have implicated the virome as a therapeutic strategy to modify the effects of chronic stress on immune system and behavior in a mouse model.[179]

Collaborative efforts across disciplines, including immunologists, microbiologists, neuroscientists, and computational biologists among others, are key for navigating the complexity of this

field and developing innovative therapies. Furthermore, prioritizing research into neurological and psychiatric disorders associated with microbiome alterations could lead to significant breakthroughs. Specifically, conditions like ASD, PD, and MDD harbor immune system alterations that may benefit from regulation via microbiome-targeted therapies. Advances in genomic technologies and deeper characterizations of the microbiome will aid in developing precise interventions aimed at modulating the microbiome to improve health outcomes.

In conclusion, the dynamic and rapidly evolving nature of this field continues to yield insights that have the potential to transform the therapeutic landscape for numerous conditions. Embracing a multidimensional approach that incorporates advanced technologies and fosters cross-disciplinary collaboration is vital as we continue to explore the microbiome-gut-immune-brain axis.

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