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Review

Gut Microbiota and Neuroinflammation: An Interconnected Nexus of Health and Neurodegenerative Disease

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Special Issue: Gut Feelings: The Role of the Human Gut Microbiome in Neurological Health and Ill Health

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Abstract

The gut microbiota, a complex ecosystem of billions of microorganisms in the human digestive tract, plays a crucial role in maintaining health. Recent studies have highlighted a bidirectional communication pathway called the gut-brain axis between the gut and the brain. This communication is significantly influenced by gut microbiota and its interactions with the immune system, which can affect brain function and contribute to inflammation. This study aims to provide a comprehensive overview of the relationship between gut microbiota and neuroinflammation, focusing on the underlying mechanisms and

implications for neurological disorders. A thorough literature review was conducted, examining the impact of gut microbiota on neuroinflammation, the mechanisms of this interaction, and potential therapeutic applications. The gut microbiota modulates neuroinflammation through various pathways, including producing short-chain fatty acids (SCFAs), modulating the immune system, and regulating the nervous system. Dysbiosis, characterized by an imbalance in gut microbiota composition, has been associated with an increased risk of neuroinflammation and various neurological conditions. Interventions such as probiotics, prebiotics, and fecal microbiota transplantation show promise in treating neuroinflammation. Understanding the pivotal role of gut microbiota in neuroinflammation is essential for developing novel strategies to prevent and manage neurological diseases. Further research is needed to elucidate the mechanisms involved, identify specific gut microbiota profiles associated with different neurological disorders, and optimize personalized therapies based on microbiome modulation.

Keywords
Gut microbiota; neuroinflammation; gut-brain axis; dysbiosis; probiotics; prebiotics; fecal microbiota transplantation; neurological disorders

1. Introduction

The complex relationship between brain health and the gut microbiome, especially regarding neuroinflammation [1], is quickly gaining attention in medical studies. Recent data indicates that dysbiosis, or an imbalance in the gut microbiota, is a significant factor in aggravating neuroinflammation and promoting the emergence of several neurological illnesses.

The microbial community known as the gut microbiota, which is present in the gastrointestinal tract, has a broad range of effects on the central nervous system (CNS), one of which is the regulation of neuroinflammation [1, 2]. A vital component of some neurological conditions, including multiple sclerosis, Parkinson's disease, and Alzheimer's disease, is neuroinflammation, which is defined by the activation of glial cells and the production of inflammatory mediators [3]. Growing research indicates that changes in the gut microbiota, or gut dysbiosis, may play a role in the emergence of these illnesses [Figure 1] [4].

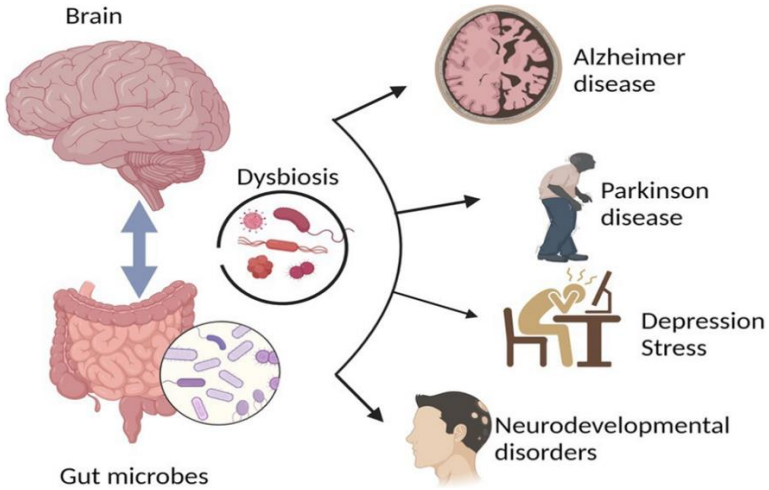

Figure 1 shows how Gut microbiota disruption, or gut dysbiosis, may play a role in the emergence of neurodegenerative diseases [4].

The gut microbiota, a complex ecology of trillions of bacteria, is found in the human gut. The development of the immune system, metabolism, and digestion are all significantly influenced by this microbial community [5]. The gut-brain axis, a previously overlooked connection between the gut microbiota and the central nervous system, has been shown by a recent study [6]. This axis affects different facets of neurophysiology and behavior through intricate interactions involving immunological mediators [7], microbial metabolites, and neuronal pathways. This axis is dependent on intricate networks of communication that include the vagus nerve, immunological signals, and metabolites made by the gut microbiome. Although there is growing evidence that the gut microbiota regulates brain function, the precise mechanisms by which it affects neuroinflammation are still being worked out [8, 9]. Comprehending this complex link is essential to creating new therapeutic approaches for neuroinflammatory disorders. A thorough understanding of the underlying mechanisms of neuroinflammatory illnesses, including multiple sclerosis, Parkinson's disease, and Alzheimer's disease, is crucial due to their increasing incidence [10]. The gut microbiota is a viable target for therapeutic intervention due to its capacity to affect immunological responses and brain function [11]. This review explores the methods via which the gut microbiota can influence neuroinflammation's resolution and its aggravation. Our objective is to provide insight into the possible therapeutic uses of adjusting the gut microbiota composition by investigating the impact of particular microbial species, their metabolites, and their relationship with the immune system.

1.1 Gut Microbiota Composition and Neuroinflammation

The gastrointestinal tract is home to a diverse colony of billions of microorganisms called the gut microbiota. These microorganisms consist of viruses, fungi, bacteria, and protozoa. The health of humans depends on gut bacteria, as they support healthy nutrient absorption, infection prevention, and food digestion [12]. Furthermore, the gut microbiome is involved in immunological responses, metabolism, and neurodevelopment [Figure 2a]. Microbial metabolites, particularly short-chain fatty acids (SCFAs), are highlighted for their significant role in promoting anti-inflammatory responses and maintaining immune homeostasis. SCFAs are produced through the fermentation of dietary fibers by gut bacteria, and they have been shown to exert direct

effects on the brain by crossing the blood-brain barrier (BBB). This capability underscores the importance of gut microbiota in influencing brain health well beyond the confines of the gastrointestinal tract. Additionally, the involvement of gut microbiota in regulating systemic and brain immunity lays the groundwork for understanding neuroinflammation. By modulating T regulatory cells (Tregs) and T-helper 17 (Th17) cell responses, gut microbiota can sway the balance of pro-inflammatory and anti-inflammatory signals in peripheral and central immune environments. This communication is essential for the maturation and functional regulation of microglia, the resident immune cells in the CNS. An optimal balance of microglial activity is critical for preventing chronic neuroinflammation, which has been implicated in various neurodegenerative diseases. The ability of gut commensals and their metabolites to maintain the integrity of the BBB is another critical dimension highlighted in the figure. A healthy BBB prevents the infiltration of harmful neurotoxic substances and pro-inflammatory cytokines into the brain. Disruption of this barrier, often seen in neurological disorders, can lead to a cascade of neuroinflammatory processes. Thus, the protective role of gut microbiota in bolstering BBB integrity further illustrates its significance in neuroprotection. Interest in the gut microbiota's function in neuroinflammatory disorders [13] has grown recently. Neuroinflammation is one form of persistent inflammation affecting the brain and spinal cord. Many neurodegenerative illnesses, including multiple sclerosis, Parkinson's disease, and Alzheimer's disease, are primarily influenced by neuroinflammation.

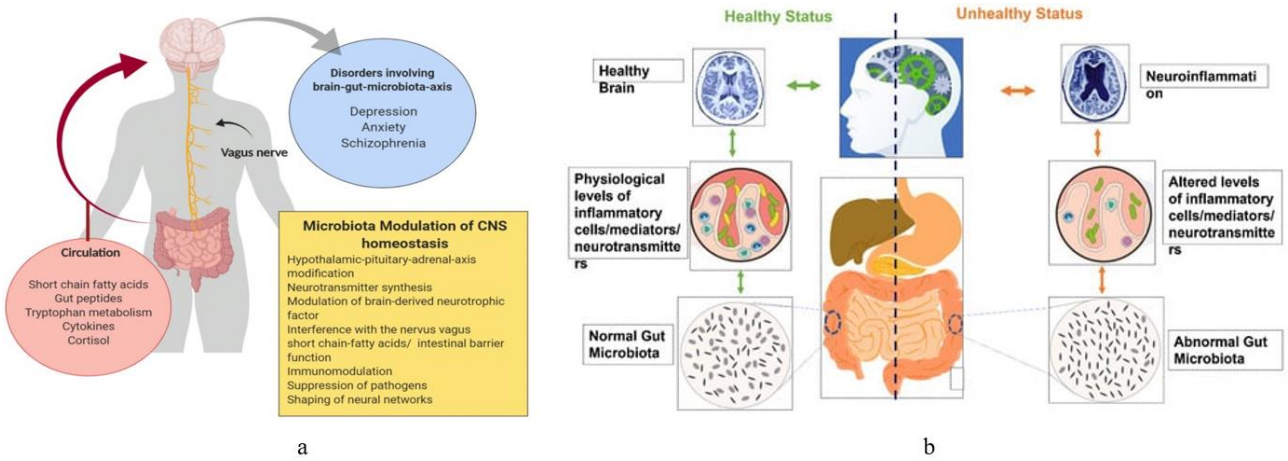

Figure 2 a: succinctly illustrates the multi-faceted role of gut microbiota in modulating gut and brain immunity, emphasizing the importance of microbial products and metabolites in neuroprotection [13]. b: Gut microbiome and neuroinflammation [14].

Numerous chronic disorders, including neuroinflammatory syndromes, are related to dysbiosis, an imbalance in the gut microbiota composition [2]. Lipopolysaccharide (LPS) and other bacterial products may enter the bloodstream due to this imbalance, potentially causing a leaky gut and increased intestinal permeability [15]. LPS initiates an inflammatory cascade that leads to neuroinflammation by stimulating immune cells such as microglia in the brain. This persistent neuroinflammation impairs neuronal function and exacerbates neuronal damage, and it is frequently observed in neurodegenerative diseases [15]. Research has demonstrated that the gut microbiota patterns of individuals with neuroinflammatory diseases differ from those of healthy individuals (Figure 2b) [14, 16]. These variations in the gut microbiota composition may facilitate

the emergence and progression of neuroinflammatory disorders. The immune system is significantly influenced by gut flora, which helps train the immune system to discriminate between beneficial and harmful microorganisms [17]. Additionally, gut flora produces several substances with anti-inflammatory properties. Dysbiosis can disrupt the average balance of the gut microbiota, leading to inflammation. Inflammation occurs as a natural reaction to damage or infection; however, persistent inflammation can harm tissues and cells [2]. One type of persistent inflammation affecting the brain and spinal cord is called neuroinflammation. Neuroinflammation can cause damage to neurons, potentially leading to neurodegenerative diseases [18].

2. Microbial Metabolites and Neuroinflammation

It has been demonstrated that microbial metabolites, in particular short-chain fatty acids (SCFAs) and other microbially produced substances, exhibit immunomodulatory solid and anti-inflammatory properties [19] (Table 1). These metabolites are essential for controlling the immune system, preserving the integrity of the intestinal barrier, and adjusting nervous system function [20].

Table 1 A table that summarizes the gut microbiota and the effects of their metabolites on brain functions [21].

Gut Microorganism	Key Metabolites	Effects on Brain Functions
Lactobacillus	Short Chain Fatty Acids (SCFA), Serotonin, Acetylcholine	- Increases emotional levels - Improves attention, memory, and motivation
Bifidobacterium	Gamma-aminobutyric acid (GABA), Tryptophan	- Reduces anxiety, stress, and fear - Improves symptoms of ADHD - Enhances behavior related to depression
Escherichia	Dopamine, Norepinephrine, Endotoxin, Serotonin	- Improves mood - Enhances blood flow and sleep regulation - Boosts cognition and concentration - Affects hormonal activity
Saccharomyces	Norepinephrine	- Enhances memory retrieval and formation
Enterococcus	Histamine, Serotonin	- Promotes wakefulness - Improves cognition - Orchestrates responses in desperate behavior

Anaerobic bacteria in the gut digest dietary fiber to produce SCFAs, which are organic fatty acids with fewer than six carbon atoms [22]. Acetate, propionate, butyrate are the three primary SCFAs [23]. Numerous immunomodulatory actions of these SCFAs have been demonstrated, including regulating immune cell activity, preserving the integrity of the gut barrier, and

modulation of inflammation [22, 23]. Binding to G protein-coupled receptors (GPCRs) on the surface of immune cells is one of the primary mechanisms by which SCFAs regulate the immune response [24]. When two molecules bind together, signaling pathways are triggered, which reduces the synthesis of pro-inflammatory cytokines and increases the synthesis of anti-inflammatory ones. A study found that butyrate suppresses the activation of nuclear factor kappa B (NF-κB), a critical transcription factor that governs the production of pro-inflammatory genes in immune cells [25]. SCFAs also play a crucial role in preserving the integrity of the gut barrier by regulating the production of tight junction proteins, which help close the spaces between intestinal epithelial cells. By doing this, it is possible to lessen the likelihood that harmful bacteria and the compounds they produce, including lipopolysaccharide (LPS), will enter the bloodstream and cause neuroinflammation and systemic inflammation [21].

SCFAs have been demonstrated to have direct impacts on the immune response, in addition to their ability to alter nervous system function. In a study, acetate has been shown to function as a neuromodulator in the brain, influencing synaptic plasticity and neurotransmitter release [26]. Butyrate has been demonstrated to have neuroprotective properties by reducing the production of inflammatory cytokines and reactive oxygen species (ROS) in the brain [27]. Additionally, it has been demonstrated that microbial metabolites other than SCFAs affect neuroinflammation. Microbial-derived metabolites, including indoles, phenols, and tryptophan derivatives, have been shown to possess anti-inflammatory and immune-modulating properties, according to Gasaly et al. [19]. It has been demonstrated that indoles, which are produced when specific gut bacteria break down tryptophan, have anti-inflammatory properties because they prevent the activation of NF-κB and the generation of pro-inflammatory cytokines [28]. Phenols, which are created when gut bacteria break down aromatic amino acids, have also been shown to have antioxidant properties that lower the production of reactive oxygen species (ROS) and inflammatory cytokines [29].

3. Neuro-inflammation and Tryptophan Derivatives

Neuroinflammation, characterized by the chronic activation of the brain's immune response, has been implicated in a variety of neurodegenerative diseases and psychiatric disorders. An intriguing area of research is the relationship between neuroinflammation and metabolites derived from tryptophan, specifically through the serotonin and melatonin pathways [26]. Tryptophan, an essential amino acid, undergoes various metabolic transformations, including hydroxylation and decarboxylation, producing key neurotransmitters and neurohormones [30]. The critical enzymes involved in these pathways include tryptophan hydroxylase (TPH), which catalyzes the conversion of tryptophan to 5-hydroxytryptophan (5-HTP), and aromatic L-amino acid decarboxylase (ALAAD), converting 5-HTP to Serotonin (5-HT). Additionally, Serotonin can be further processed into melatonin in the pineal gland, primarily through the actions of arylalkylamine N-acetyltransferase (AANAT) and hydroxyindole-O-methyltransferase (HIOMT), with the former catalyzing the N-acetylation of Serotonin to N-acetylserotonin, and the latter facilitating its conversion to melatonin (Figure 3a).

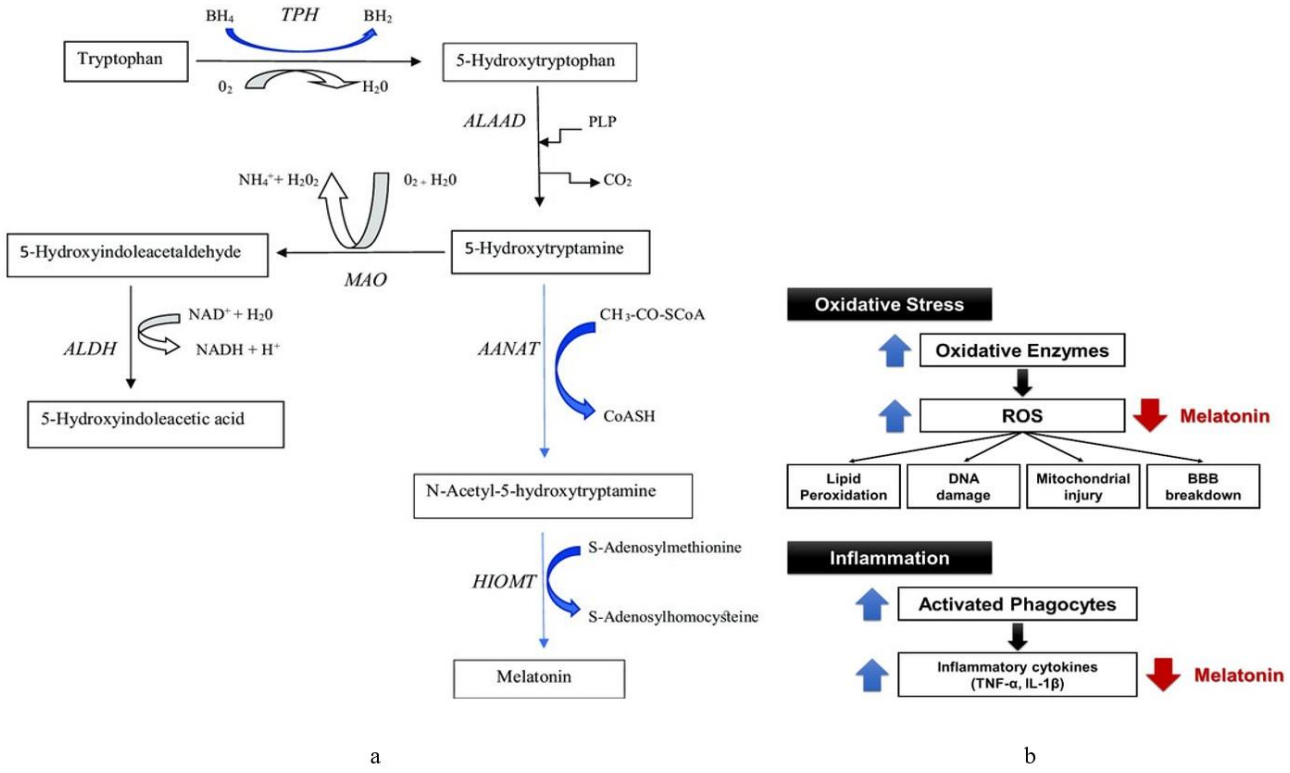

Figure 3 a: shows the brain's hydroxylation or serotonin pathway and the pineal melatonin pathway. Abbreviations include AANAT (arylalkylamine N-acetyltransferase), ALAAD (aromatic L-amino acid decarboxylase), ALDH (aldehyde dehydrogenase), BH2 and BH4 (dihydro- and tetrahydro-biopterin), HIOMT (hydroxy indole-O-methyltransferase), MAO (monoamine oxidase), PLP (pyridoxal 5'-phosphate), 5-hydroxyindoleacetic acid (5-HIAA), aldehyde dehydrogenase (ALDH) and TPH (tryptophan). b: Neuroprotective Effects of Melatonin [31].

Neuroinflammation can alter these metabolic pathways, potentially leading to decreased Serotonin and melatonin levels, both of which have demonstrated neuroprotective properties. It has been demonstrated that tryptophan derivatives, including melatonin and Serotonin, have neuroprotective properties that lessen oxidative stress and inflammation in the brain [30].

Melatonin is a hormone that regulates the circadian rhythm, and it has been the subject of numerous studies [31, 32]. However, new studies have shown that melatonin shields neurons, especially from oxidative stress (Figure 3b). In particular, it is noted for its antioxidant effects and ability to modulate brain inflammatory responses [31]. Due to its hydrophobic nature, melatonin can cross the blood-brain barrier efficiently, making it an attractive candidate for therapeutic intervention in neuroinflammation. Moreover, its synthesis is influenced by dihydrobiopterin (BH2) and tetrahydrobiopterin (BH4), which are essential cofactors for the function of TPH and other enzymes involved in the synthesis of monoamines. Studies have suggested that dietary intake of tryptophan may play a role in preventing or mitigating neuroinflammatory conditions. This import is further supported by the interactions of active metabolites like Serotonin and melatonin with key inflammatory pathways, including the modulation of microglial activation. Melatonin's interaction with signaling pathways such as NF-κB further underscores its potential therapeutic role in managing neuroinflammation [31].

Moreover, Serotonin is a neurotransmitter that moves throughout the brain and is important for many functions, such as sleep and social interaction. Research by Fanibunda et al. [33] claims that the neurotransmitter causes brain cells to have more mitochondria. The mitochondria in brain cells help the cells endure harsh situations by generating energy for biological functions (Figure 4). Serotonin also encourages mitochondria to create more energy.

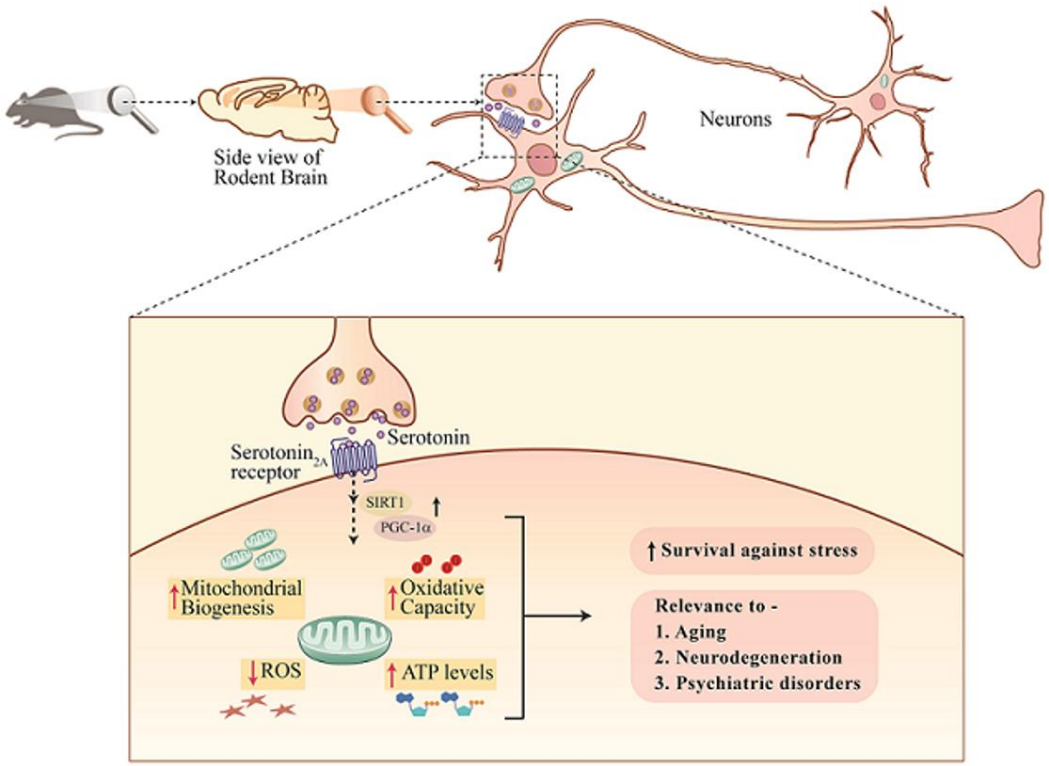

Figure 4 Neuroprotective effect of serotonin-induced increased mitochondria in brain cells under stressful conditions [33].

Given that monoamine oxidase (MAO) is responsible for the degradation of Serotonin, targeting this enzyme or enhancing the availability of its upstream precursors could represent a viable strategy to maintain adequate levels of Serotonin, which in turn may help mitigate neuroinflammatory processes. Moreover, vitamin B6 (pyridoxal 5'-phosphate or PLP) is a crucial cofactor for ALAAD and TPH, suggesting that adequate levels of this vitamin could enhance the synthesis of Serotonin and potentially melatonin [34]. This highlights the importance of nutritional interventions in maintaining neurochemical balance and supporting neuronal health.

4. Gut-Brain Axis and Neuroinflammation

The gut-brain axis is a dynamic network connecting the central nervous system and the gastrointestinal tract. The vagus nerve functions as the main information-transmission pathway, enabling a constant flow of data.

4.1 Vagus Nerve and Other Pathways Mediating Gut-Brain Communication

The longest cranial nerve, the vagus nerve, is the main route via which information travels from the gut to the brain. This complex network, which carries motor and sensory fibers, always makes

information interchange possible. To reach the brainstem and eventually the higher brain centers, sensory fibers carry signals from the stomach that provide information about nutritional content, microbiota composition, and inflammatory conditions [35]. Conversely, motor fibers carry signals from the brain to the stomach, affecting the immune system, gastric motility, and digestion processes [36]. Nonetheless, the vagus nerve is not the only pathway via which information travels from the gut to the brain. This complex dance involves additional channels, such as the sympathetic and parasympathetic neural systems [37]. Brain activity is directly influenced by neurotransmitters generated by enteric neurons in the gut, such as gamma-amobutyric acid (GABA), dopamine, and Serotonin [38]. Furthermore, circulating hormones such as cortisol, ghrelin, and leptin serve as messengers, carrying information from the gut to the brain regarding metabolic conditions and stress levels [39]. The immune system is also critical for gut-brain communication because immune cells in the stomach generate cytokines that affect brain activity and neuronal function [40].

4.2 Role of Gut Microbiota in Activating the Gut-Brain Axis and Promoting Neuroinflammation

The gut microbiota is a critical component of the gut-brain axis, which comprises billions of bacteria, fungi, and viruses. The gastrointestinal tract is home to this complex community essential to immunological development, nutrition absorption, and digestion [41]. There is growing evidence that the gut microbiota significantly influences neuroinflammation and brain function [42]. Brain activity is directly influenced by metabolites from the microbiota, such as SCFAs, which are generated by the fermentation of dietary fiber [43]. Butyrate, propionate, and acetate are examples of SCFAs that function as signaling molecules that affect the synthesis of neurotransmitters, control inflammatory reactions, and even aid in developing the blood-brain barrier [44]. An imbalance in the composition of the gut microbiota known as dysbiosis has been associated with a higher risk of neuroinflammatory diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease [45]. The stomach's Immune cells may excessively generate pro-inflammatory cytokines in response to dysbiosis. These cytokines can then go to the brain via the vagus nerve and other pathways, exacerbating neurological diseases and contributing to neuroinflammation [46, 47].

5. Preclinical and Clinical Evidence

5.1 Preclinical Studies

Various animal studies have revealed critical insights into how gut microbiota influences neuroinflammation. Short-chain fatty acids (SCFAs) are known to exhibit anti-inflammatory effects within the central nervous system (CNS) [48, 49]. By inhibiting the activation of microglia and astrocytes, SCFAs can reduce the release of pro-inflammatory cytokines and enhance neuroprotection [50-52]. For example, specific gut bacteria such as *Bacteroides fragilis*, *Clostridium difficile*, and *Escherichia coli* have demonstrated an ability to provoke neuroinflammation and exacerbate neurological symptoms in models of neurodegenerative diseases, including Alzheimer's and Parkinson's [53, 54].

Evidence also suggests that the gut microbiota can modulate immune responses within the CNS and interact with the immune system in the gut. Certain microbial species promote the

development of anti-inflammatory immune cells, such as regulatory T cells (Tregs), while inhibiting pro-inflammatory cell growth [55]. Alterations in gut microbiota composition can lead to neuroinflammation, as shown in various animal studies [56, 57]. For instance, germ-free mice, which lack gut microbes, exhibit reduced brain inflammation and microglial activation compared to conventionally colonized mice [58]. Overall, research indicates that the gut microbiota significantly influences immune cell activity, particularly in gut-associated lymphoid tissue (GALT), which is crucial for immune regulation and maintaining the gut barrier's integrity [59].

5.2 Clinical Studies

Clinical investigations have linked neuroinflammatory diseases to intestinal dysbiosis. Patients suffering from conditions such as multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), and inflammatory bowel disease (IBD) often present altered gut microbiome compositions. These alterations are characterized by reduced diversity, changes in bacterial abundance, and increased pro-inflammatory bacteria [60, 61]. Notably, comparisons have shown differences in gut microbiota composition between AD patients and healthy controls, with specific microbial species, such as *Akkermansia muciniphila*, associated with decreased cognitive decline and improved brain function [62]. Similarly, alterations in the gut microbiota have been observed in PD, marked by an increase in pro-inflammatory bacteria coupled with a decrease in beneficial bacteria, contributing to increased intestinal permeability, or "leaky gut" [63]. This phenomenon allows for bacterial metabolites and toxins to enter the bloodstream, potentially exacerbating neuroinflammation [64]. Furthermore, in MS, patients exhibit a gut microbiota profile with a higher abundance of pro-inflammatory taxa than healthy individuals [65]. Research has begun to demonstrate the potential of probiotics and fecal microbiota transplantation (FMT) in mitigating neuroinflammation and improving clinical symptoms in MS patients [66].

6. Gut Microbiota, Oxidative Stress, Neuroinflammation and Ageing

Numerous neurodegenerative and psychiatric diseases have been linked to oxidative stress, which is defined as an imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense systems [67]. It has been discovered that changes in the variety and composition of the microbiota, known as gut microbiota dysbiosis, influence the brain's levels of oxidative stress [68]. While some microbial species, like Escherichia coli, produce toxins and pro-inflammatory chemicals that exacerbate oxidative stress, other species, like Akkermansia muciniphila, have antioxidant capabilities and can lower the generation of ROS [69]. The brain's NF-κB can become chronically activated due to dysregulated gut microbiota composition, which can cause increased generation of ROS and damage to neurons [2]. Numerous neurological conditions have been related to oxidative stress brought on by dysbiosis in the gut microbiota [68]. Increased oxidative damage to neuronal cells is a hallmark of multiple sclerosis, Parkinson's disease, and Alzheimer's disease. An imbalance between the Firmicutes and Bacteroidetes species has been linked to dysbiosis; this imbalance impairs the generation of antioxidant metabolites and increases oxidative stress and inflammation in the brain [68, 70].

Deterioration in physiological performance and an elevated risk of illness are hallmarks of aging, a complex biological process. The intricate link between aging, the brain-gut microbiota, and neuroinflammation has been clarified by recent research, emphasizing how these factors influence

cognitive health and wellbeing [71]. It is well recognized that aging affects the makeup of the gut microbiota, which may cause an imbalance in the gut's homeostasis. In animal studies, Age-associated neuroinflammation and gut microbiota changes have been causally connected [72, 73]. It has been demonstrated that fecal microbiota transplantation from old germ-free mice to young mice induces neuroinflammation and cognitive impairments, indicating a potential role of the gut microbiota in aging [74].

7. Epigenetic Interplay of Gut Microbiota and Neuroinflammation

Epigenetic mechanisms provide a link between gut microbiota and neuroinflammation [75]. Metabolites originating from microbiota can alter epigenetic markers in brain neurons, microglia, and immune cells. For instance, short-chain fatty acids (SCFAs) block histone deacetylases (HDACs), which causes microglia to have more acetylated histones and reduces their pro-inflammatory activation [76]. On the other hand, some microbial metabolites, such as deoxycholic acid, can activate DNA methyltransferases (DNMTs) and hence increase DNA methylation [77]. These epigenetic changes can affect gene expression in immunological responses, metabolic processes, and host-microbe interactions. Furthermore, these changes in the genome can maintain long-term neuroinflammation and contribute to the emergence of neurological disorders [78].

8. Gut Microbiota and Brain-Derived Neurotrophic Factor (BDNF)

Dysregulation of brain-derived neurotrophic factor (BDNF), a protein necessary for synaptic plasticity, neuronal growth, and survival, has been linked to neuropsychiatric diseases. The hippocampus is a portion of the brain associated with memory and cognition. Short-chain fatty acids (SCFAs), especially butyrate, increase the expression of BDNF in this region [79]. It is well established that BDNF affects the composition and function of gut microbiota. Studies have demonstrated that BDNF promotes the growth of beneficial bacteria, including Lactobacillus and Bifidobacterium [80, 81]. Gamma-aminobutyric acid, one of the neuroactive metabolites produced by these bacteria, can alter brain activity. Furthermore, research has demonstrated that while an altered microbiota can decrease BDNF levels, a healthy gut microbiota can encourage the production of BDNF [82]. In animal models, brain BDNF expression is lower in germ-free mice (i.e., lacking a gut microbiome) than in animals with normal microbiota [83]. Studies on humans and animals have shown that administering probiotics-beneficial bacteria that colonize the gut increases BDNF levels [84]. Since electrical stimulation of the vagus nerve has been shown to boost BDNF production, it is thought that the vagus nerve, which connects the gut to the brain, plays a role in this communication [85].

Neuropsychiatric disorders and changes in BDNF levels have been linked to dysbiosis [86]. Dysbiosis and decreased BDNF production, for instance, are features of inflammatory bowel disease that may be responsible for the cognitive and mood abnormalities frequently seen in this condition [87]. In a similar vein, it has been discovered that people with anxiety and depression have lower levels of BDNF and different compositions of their gut flora [88]. It has been demonstrated that fecal microbiota transplantation (FMT), a technique in which a recipient's gut receives fecal material from a healthy donor, enhances BDNF production and alleviates depressive symptoms in individuals with treatment-resistant depression [89]. Furthermore, it has been shown

that dietary interventions, such as taking probiotics and prebiotics that support a healthy gut microbiota, raise BDNF levels and improve mood [90].

9. Gut Microbiota and Toll-like Receptors (TLRs)

A class of pattern recognition receptors (PRRs) known as toll-like receptors (TLRs) is involved in the innate immune response to microbial components [91]. All immune cells in the body, including those lining the GI tract, have TLRs. They identify pathogen-associated molecular patterns (PAMPs), which are particular molecular patterns linked to infections [92]. TLRs attach to PAMPs and initiate intracellular signaling pathways that produce inflammatory cytokines, activate immune cells, and draw additional immune cells to the infection site [92]. TLR ligands, such as peptidoglycan from Gram-positive bacteria and lipopolysaccharide (LPS) from Gram-negative bacteria, are primarily derived from the gut microbiota [93]. These ligands bind to TLRs and are expressed in immune cells, sensory neurons, and intestinal epithelial cells. TLRs' identification of microbial ligands triggers immunological reactions that influence the gut microbiota's function and composition while promoting immune homeostasis [94].

Through the induction of TLR-mediated tolerance, the gut microbiota in healthy individuals maintains a balanced immune response [95]. The generation of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which inhibit excessive immune activation and avert tissue damage, indicates this tolerance [96]. TLR signaling changes brought on by dysbiosis can impair immunological tolerance and encourage chronic inflammation. TLR signaling in the gut also controls metabolic activities [97, 98]. In animal models, TLR deficiency has been linked to metabolic problems and obesity [99]. It has been demonstrated that TLRs control the expression of genes related to insulin sensitivity, glucose homeostasis, and lipid metabolism [100]. Thus, the relationship between TLRs and the gut microbiota impacts metabolic health. Moreover, the formation and operation of the enteric nervous system are influenced by TLR signaling in the gut [101]. In addition to affecting neuronal signaling and modifying intestinal motility, sensation, and immunological responses, microbial ligands have the ability to activate TLRs on sensory neurons [102].

Neuroinflammation and the emergence of neurological illnesses can be attributed to dysregulation of the gut microbiota and TLR signaling. Changes in the gut microbiome and elevated TLR signaling have been seen in animal models of neurodegenerative illnesses like Alzheimer's and Parkinson's. Research on humans has indicated a connection between the makeup of the gut microbiota and the likelihood of developing depression, autistic spectrum disorder, and multiple sclerosis [103].

10. Mechanisms by Which Gut Microbiota Alter Neuroinflammation

The gut microbiota can modify neuroinflammation through several interconnected mechanisms [104], as illustrated in Figure 5.

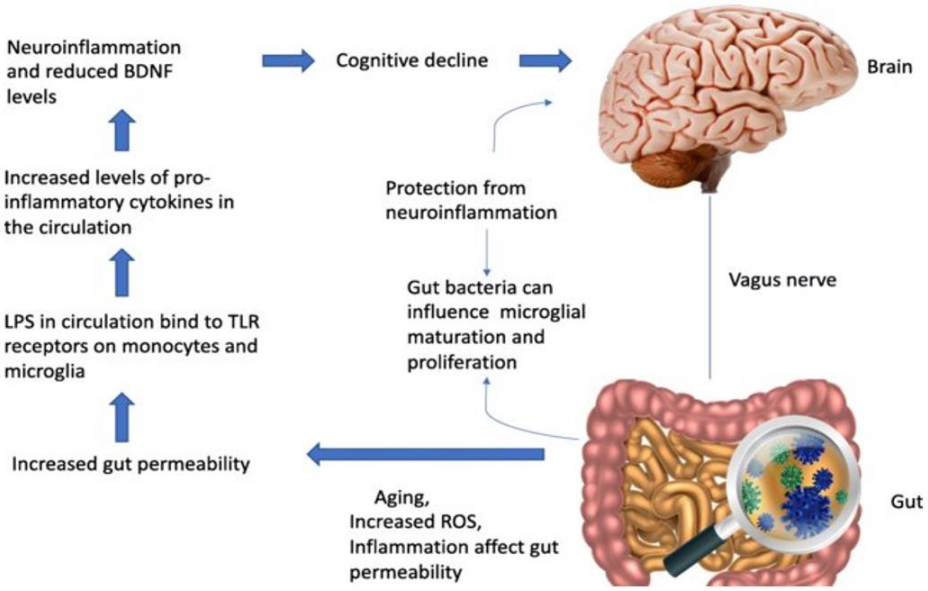

Figure 5 Mechanisms of Gut Microbiota Influence on Neuroinflammation [104].

10.1 Short-Chain Fatty Acids (SCFAs) Production

One of the primary ways in which gut microbiota influence neuroinflammation is through synthesizing short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate. These SCFAs result from the gut microbe's fermentation of dietary fibers [105]. SCFAs have been shown to reduce inflammation in the central nervous system by modulating immune cell activity. For instance, butyrate promotes the differentiation of regulatory T cells and the production of anti-inflammatory cytokines, which help combat neuroinflammation. Additionally, SCFAs can reinforce the integrity of the blood-brain barrier, limiting the entry of neuroinflammatory agents into the brain.

10.2 Activation of the Vagus Nerve

The gut microbiota also modulates neuroinflammatory responses by activating the vagus nerve, a key component in the brain-gut axis [106]. This long nerve transmits signals between the gastrointestinal tract and the brain, influencing peripheral and central immune responses. Vagal activation has been shown to reduce the production of pro-inflammatory cytokines in the brain and spinal cord [107]. Furthermore, the vagus nerve participates in the cholinergic anti-inflammatory pathway, where it directly regulates the activity of splenic macrophages, thereby decreasing systemic inflammation that could contribute to neuroinflammatory processes.

10.3 Immune System Modulation

The composition of gut microbiota plays a crucial role in shaping the immune system, further influencing neuroinflammation [108]. Microbial metabolites, including SCFAs and indole derivatives, can activate immune cells such as macrophages and T lymphocytes, leading to their infiltration into the central nervous system. This infiltration can be beneficial in some contexts, such as in response to injury, but can also exacerbate neuroinflammatory conditions when

dysregulated [109]. Additionally, the gut microbiota can modulate the production of immunoglobulin A (IgA), affecting immune tolerance and the inflammatory state within the brain.

10.4 Microbial Diversity and Its Impact

Recent studies have highlighted the importance of microbial diversity in maintaining a balanced immune response. A diverse microbiota promotes a more resilient immune system, which can better manage inflammation. In contrast, low microbial diversity has been associated with increased neuroinflammatory diseases, suggesting that encouraging microbial diversity through diet and lifestyle might be a potential therapeutic strategy [7].

10.5 Metabolite Signaling and the Microbiota-Gut-Brain Axis

The interaction between microbial metabolites and host receptors (such as G-protein coupled receptors) is another significant mechanism by which gut microbiota can alter neuroinflammation [24]. These metabolites can influence the immune response and neuronal function directly, possibly affecting neurotransmitter release and brain homeostasis. This highlights a direct link between gut health and neural activity that merits further exploration.

11. Potential Therapeutic Implications in Dysbiosis Linked with Neuroinflammation

Targeting the gut microbiota represents a promising avenue for treating and potentially preventing neurological diseases. Modifying the gut microbiota through probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary interventions may reduce neuroinflammation and enhance neurological functioning (Figure 6 & Table 2).

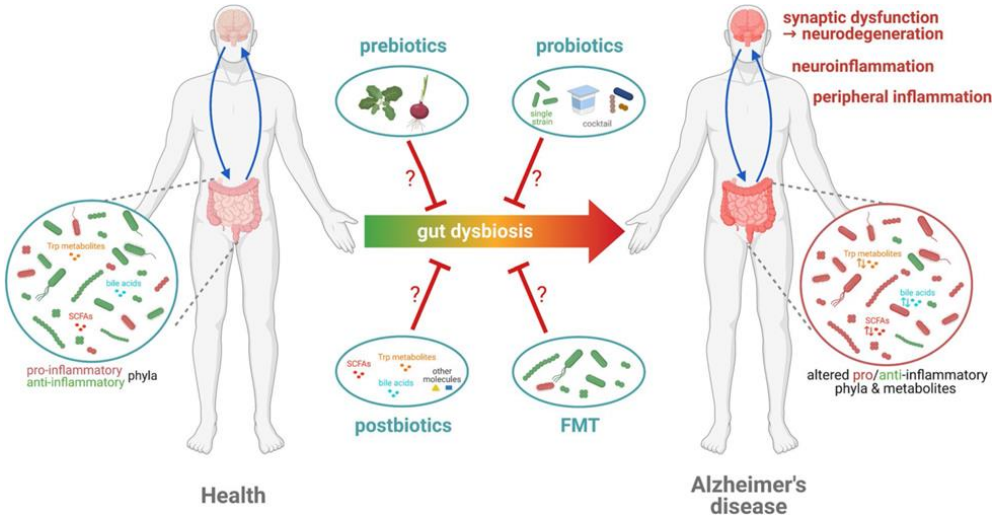

Figure 6 Gut-brain microbiota dysbiosis-based therapeutic interventions.

Table 2 Shows a summary of trials focusing on probiotics, prebiotics, and other related treatments, particularly in the context of dysbiosis and neuroinflammation.

Trial Name	Intervention	Condition	Phase	Status	Details
Probiotic Bifidobacterium longum	Probiotic supplementation	Irritable Bowel Syndrome (IBS)	II	Recruiting	Evaluating effects on depression scores and brain activity in IBS patients [110].
Lactobacillus reuteri for Anxiety	Probiotic treatment	Anxiety Disorders	I	Completed	Investigating the impact of Lactobacillus reuteri on anxiety symptoms [111].
Fecal Microbiota Transplantation (FMT)	FMT from healthy donors	Neurodegenerative Diseases	III	Active, not recruiting/recruiting	Assessing efficacy of FMT in patients with Parkinson’s disease/Alzheimer's disease [112].
Prebiotic Fiber Supplementation	Dietary intervention	Cognitive Decline	II	Recruiting	Studying the effects of prebiotics on cognitive function in older adults [113].
Gut-Brain Axis Modulation Study	Multi-strain probiotic	Major Depressive Disorder	II	Active, not recruiting	Exploring the role of gut microbiota in mood regulation through probiotics [114].

11.1 Probiotics

Probiotics are live microorganisms that confer health benefits when consumed. They can help restore the gut microbiota to a healthier state. Numerous studies have explored the efficacy of specific probiotic strains in alleviating inflammation and improving symptoms in neuroinflammatory disorders [115]. For instance, certain strains of *Lactobacillus* and *Bifidobacterium* have shown promise in reducing neuroinflammation and enhancing cognitive performance in animal models of PD and AD [116].

11.2 Prebiotics

Prebiotics are indigestible components of food that selectively promote the growth and activity of beneficial gut bacteria. Prebiotics can help restore gut homeostasis and mitigate inflammation by fostering the proliferation of these beneficial microbes. In animal models of neuroinflammation, prebiotic fibers such as fructans and inulin have demonstrated the potential to reduce inflammation and enhance cognitive function [117-119].

11.3 Fecal Microbiota Transplantation (FMT)

FMT involves transferring fecal microbiota from a healthy donor to a recipient with intestinal dysbiosis to restore a balanced gut microbial community [120]. Though evidence in the context of neuroinflammatory disorders is still limited, FMT has shown encouraging results in treating inflammatory bowel disease, suggesting potential applications for neuroinflammatory conditions as well [121].

11.4 Dietary Modifications

Dietary changes are essential for lowering neuroinflammation and regulating the gut flora [122]. Antioxidants, fiber, and omega-3 polyunsaturated fatty acids are abundant in the Mediterranean diet, which may offer protection against neurodegeneration. A study found that eating a "Mediterranean diet" high in fruits, vegetables, seafood, and olive oil enhanced gastrointestinal health and decreased the risk of neurodegenerative illnesses [123]. On the other hand, dysbiosis and elevated inflammation are associated with diets heavy on sugar, processed foods, and saturated fat [124].

12. Future Directions and Challenges

Even while the literature shows a strong correlation between gut microbiota and neuroinflammation, more significant and varied clinical trials are needed to make further progress. Small sample sizes and limited diversity in study populations restrict the generalizability of findings. Large-scale, multicenter studies with participants from different geographic areas, ethnicities, and disease backgrounds are essential to establish strong relationships and identify relevant confounders. Identifying the precise bacterial species and metabolites responsible for neuroinflammation should be the primary goal of future studies. The gut microbiota can be thoroughly characterized through metagenomic sequencing techniques, allowing researchers to pinpoint specific bacterial strains linked to illness. Metabolomics research can reveal microbial

metabolites that regulate neuroinflammation and potentially lead to specific therapies. We can create more potent microbiota-based treatments if we understand the precise mechanisms by which bacterial taxa and metabolites interact with the immune system. Neuroinflammatory disorders may benefit from personalized medicine approaches that customize interventions based on individual patient characteristics. Individual differences in gut microbiota composition indicate that customized microbiome-based treatments are necessary. Fecal microbiota transplant (FMT) is a promising treatment for some neurological diseases, involving the transplantation of gut bacteria from a healthy donor to a recipient. More research is necessary to enhance FMT procedures, determine ideal donor selection criteria, and evaluate long-term safety and effectiveness.

13. Conclusion

According to newly available data, the gut microbiota is essential in controlling neuroinflammation. Immune system homeostasis can be upset by dysbiosis, which can also cause CNS inflammation, alter behavior, and impact brain function. To develop novel therapeutic options for neuropsychiatric illnesses, it is imperative to comprehend the mechanisms underlying the interactions between gut microbiota and neuroinflammation. More studies are required to improve current therapies, pinpoint particular microbe targets, and ascertain their long-term impacts on neuroinflammation and general health.

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Data Availability Statement

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