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MICROBIOME IMMUNE SYSTEM INTERACTIONS IN SELECTED NEUROLOGICAL DISORDER

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Abstract – Neurological disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), autism spectrum disorder (ASD), and multiple sclerosis (MS), have long been thought to affect only the central nervous system. However, recent research sheds light on their complexities, revealing complicated linkages beyond the central nervous system. Gastrointestinal symptoms, gut microbiota dysbiosis, and the gut-brain axis all play critical roles in the development and progression of these illnesses. The interaction between the gut microbiota and neurological function highlights the importance of the gut-brain axis in a variety of illnesses. Furthermore, dysbiosis in the gut microbiome has been linked to the pathophysiology of PD, AD, MS, and ASD. Changes in gut microbiota composition and neuroinflammation mediated by the NLRP3 inflammasome have been observed in AD, suggesting a connection between microbiological variables and the course of the illness. Similarly, studies have found that MS patients have different microbial profiles than healthy people, indicating that the microbiome plays a role in illness development. Anxiety, depression, and stroke have all been linked to changes in the gut microbiota, emphasizing the broader implications of microbiome-immune system interactions in neurological health. Researchers should collaborate, conduct longitudinal studies tracking gut microbiota changes in at-risk populations, use precision medicine approaches tailored to individual microbiota composition, and promote gut health from birth.

Keywords: Neurological disorders, Microbiome, Microbiota, Gut-brain axis, Gastrointestinal tract, Dysbiosis, Immune system.

INTRODUCTION

Neurological disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), autism spectrum disorder (ASD), and multiple sclerosis (MS) have long been thought of as complicated ailments affecting the central nervous system. However, recent research has shed light on the complex nature of many illnesses, demonstrating links beyond the central nervous system[1]. Notably, gastrointestinal symptoms and dysfunctions, as well as gut microbiome dysbiosis, have been linked to the development and progression of a variety of neurological illnesses, including ASD, PD, Alzheimer's disease, and multiple sclerosis. For example, research has highlighted the significance of the gut-brain axis in various disorders, emphasizing the complicated interplay between gut microbiota and neurological function[2]. The human gastrointestinal tract contains a

huge and diverse ecosystem of bacteria known as the gut microbiota, which play critical roles in regulating a variety of physiological processes, including immune system development and function[3]. Furthermore, emerging data emphasizes the gut microbiota's influence on brain function and behavior across the lifespan. While several pathways for gut-brain communication have been hypothesized, new research has underlined the importance of interactions between the microbiota and the immune system in orchestrating this complex bidirectional communication network[4]. With trillions of bacteria in the gastrointestinal tract, the gut microbiota has a significant impact on host health and well-being. Notably, their role goes beyond local gut activities to include systemic processes like immune modulation and neurobehavioral consequences. As our understanding of the microbiota-gut-brain axis grows, unraveling the processes underlying these complex interactions holds promise for developing therapeutic techniques to treat neurological illnesses and improve overall health outcomes[5].

Mammals and commensal microorganisms have evolved in a delicate balance, forming a symbiotic relationship essential for overall health. This balance requires a finely tuned immune system, which protects the host against external threats and internal disruptions. However, environmental factors, like antibiotic usage, dietary changes, and geographical changes, can disrupt this balance, leading to systemic dissemination of microorganisms, increased susceptibility to pathogenic invasion, and abnormal immune responses[6]. Dysregulation of the microbiome-immune axis has been linked to various gastrointestinal disorders, including inflammatory bowel disease (IBD), celiac disease, rheumatic arthritis, metabolic syndrome, neurodegenerative disorders, and malignancy. The relationship between the gut microbiota and host immunity is complex, dynamic, and context-dependent. Understanding these complicated connections is critical for determining the mechanisms that govern immune growth and function[7]. In the face of growing neurological problems caused by modern lifestyles and environmental changes, the involvement of gut microbiota in brain function has emerged as an important topic of research. Recent research has highlighted the active interactions between animals and their microbial populations, exposing their substantial impact on neurological systems via complex immunological, neuronal, and chemical communication pathways[8]. The gut microbiota, which is found in the gastrointestinal system, is recognized as an important factor in controlling cellular processes not just locally but also in distant organs, particularly the brain. Thus, undertaking a thorough assessment of microbiome-immune system interactions in neurological diseases is critical[9]. Therefore, this study aims to thoroughly review the complex relationship between the microbiome, the immune system, and the gut-brain axis and their combined impact on neurological disorders, as well as the potential implications of these interactions in the development, progression, and management of neurological disorders.

METHODOLOGY

We conducted a comprehensive literature search on Scopus, PubMed, and Google Scholar using the boolean operators 'OR' and 'AND' in combination with keywords such as 'Neurological disorders', 'Microbiome', 'Microbiota', 'Gut-brain axis', 'Gastrointestinal tract', 'Dysbiosis', and 'Immune system', to gather pertinent literature published in English with no limit on publication year. We also performed a snowball search of all the included articles to find additional relevant articles for the review. The types of studies included are meta-analysis, systematic literature reviews, original research, commentaries, perspectives, correspondence, and grey literature contributing to the relationship between the microbiome, immune system, and gut brain axis. The articles were included based on their quality and relevance to the study's aim. A comprehensive qualitative summation approach was employed by P.O.O and O.J.O to narratively summarise the data of the articles included under appropriate headings, considering the scope of the review.

THE MICROBIOME AND ITS IMPACT ON THE IMMUNE SYSTEM

The microbiome, which includes bacteria, viruses, and fungi, is an essential component of mammalian beings at a ratio of 1.3 to 1. Research focuses on its interactions with the immune system, with the gastrointestinal tract being the most prevalent. The microbiome provides ben-

efits such as resistance to pathogen colonization, but it can also alter the body's pathogen response and therapeutic efficacy[10]. The development of germ-free (GF) animals has contributed to a better understanding of the microbiome's role in humans. According to research, mice with a healthy microbiota had better macrophage digestion and faster immunological responses. The GI tract microbiome also creates antimicrobial peptides known as bacteriocins, which can kill specific infections without relying on traditional immune responses[11]. Microbiota plays an important role in many aspects of immune function, such as cytokine synthesis, homeostasis maintenance, T cell formation, and immunity modulation. Environmental variables, particularly during birth and infancy, significantly impact the complex interaction between the microbiota and the immune system. Microbiota has been linked to the formation of certain immune system components, such as myeloid cell derivatives, which demonstrate their multifaceted functions in immune response differentiation and efficacy[12]. Notably, the microbiome is extremely vulnerable to changes caused by antibiotics and food. Dietary changes can alter the composition of the microbiota, influencing T-cell responses to microbial stimulation. On the other hand, antibiotic use affects the microbiota's amount and variety, impairing immune response efficacy. As a result, concurrent administration of probiotics with high-dose antibiotics is recommended to reduce the negative effects on the microbiota while maintaining immune function[13]. An unbalanced microbiome causes a variety of diseases and has a wide range of consequences for the immune system. Inflammatory bowel disease (IBD), type 1 diabetes, multiple sclerosis, HIV, and some malignancies have all been linked to changes in the microbiota[14]. The umbrella term for microbiota imbalance is dysbiosis, which is defined by the loss of beneficial microbiota, the expansion of dangerous microbes, and a decrease in microbial diversity, which can be caused by several factors, including excessive antibiotic usage, poor lifestyle choices, recurring illnesses, and environmental impacts[15].

The gut microbiota and gut epithelial barrier both play important roles in protecting the host against pathogen infections. The epithelial barrier, made up of closely packed cells and strengthened with mucus, serves as the initial line of defense against bacterial invasion[16]. Mucus functions as both a physical barrier and a store for antibacterial compounds. The host-microbiota relationship affects mucus formation and breakdown, which influences susceptibility to infection[17]. Constant interaction between the microbiota and the intestinal epithelium results in persistent immunological signaling, which is essential for maintaining intestinal homeostasis. Disruption of this mechanism can lead to inflammation and infection[18]. The immunological response, which includes both the innate and adaptive immune systems, is critical in determining infection susceptibility, persistence, and clearance. The innate immune system provides nonspecific protection *via* physical and chemical barriers such as the skin, mucous membranes, enzymes, and antimicrobial proteins, as well as innate immune cells, such as granulocytes, macrophages, and natural killer cells[19]. The adaptive immune system, which is directed by T and B cells, recognizes and responds to certain foreign antigens. T cells play an important role in cellular immunity, recognizing infectious pathogens within host cells, whereas B cells contribute to humoral immunity by generating antibodies against specific antigens found in body fluids[20]. Notably, research in germ-free and gnotobiotic mice has shown that the development and efficacy of the immune response are inextricably related to the growth and composition of the gut microbiome. These findings highlight the significance of innate immunity in recognizing and responding to microbiota-derived products, which are assisted by pattern-recognition receptors (PRRs) on intestinal epithelial cells. The activation of PRRs generates chemokines and cytokines that are required for a protective immunological response, with MyD88 acting as an important adapter molecule downstream of PRR signalling[21]. However, the deregulation of PRR responses can result in inflammatory disorders and autoimmunity, highlighting the significance of strict regulation. Furthermore, IECs secrete antimicrobial peptides (AMPs), which are essential innate immune effectors that limit pathogen interaction with the epithelium, and their expression is modulated by the microbiota composition, demonstrating the complex interplay between the microbiome and the immune system in shaping innate immune responses[22]. Microbiota significantly impact the immune response by generating metabolites from food substrates, host products, and other microbial byproducts. A wide range of microbial metabolites, including short-chain fatty acids (SCFAs), tryptophan metabolites, and bile acid derivatives, play important roles in immune protection[23]. SCFAs, for example, stimulate the generation of antimicrobial peptides and mucus by intestinal epithelial cells, as well as the maturation and proliferation of colonic regulatory T cells, which help moderate local inflammatory responses to the microbiota. SCFAs also help maintain

TABLE 1. BRIEF OVERVIEW OF MICROBIOME INSIGHTS INTO NEUROLOGICAL DISORDERS.

S/N	Microbiome and Neurological Health	Overview
1.	Neurological Disorders	Neurological disorders like Parkinson's disease (PD), Alzheimer's disease (AD), autism spectrum disorder (ASD), and multiple sclerosis (MS) are complex conditions involving the central nervous system. Recent research highlights links between gastrointestinal symptoms, dysfunctions, gut microbiome dysbiosis, and the progression of these disorders through the gut-brain axis.
2.	Gut Microbiota	The gut microbiota, comprising diverse bacteria in the gastrointestinal tract, influences physiological processes such as immune system modulation and neurobehavioral function. It interacts with the gut-brain axis, affecting systemic health beyond local gut activities. Understanding these interactions is crucial for developing therapies for neurological disorders.
3.	Microbiome-Immune System Axis	The microbiome's delicate balance is essential for overall health, influencing immune responses and susceptibility to diseases. Dysregulation, caused by factors like antibiotics and diet, can lead to dysbiosis and increased vulnerability to infections and inflammatory conditions across various body systems.
4.	Gut Epithelial Barrier	The gut epithelial barrier, reinforced by mucus and antimicrobial peptides, defends against pathogen invasion. Disruption of the microbiota-host relationship can compromise this barrier, leading to inflammation and infections.
5.	Immune System	The immune system's innate and adaptive components are influenced by the gut microbiota through mechanisms like cytokine synthesis, T cell regulation, and antimicrobial peptide production. These interactions are crucial for maintaining intestinal homeostasis and systemic immunity. Dysbiosis can lead to inflammatory diseases and affect immune cell function throughout the body.
6.	Microbial Metabolites	Metabolites produced by gut microbiota, such as short-chain fatty acids (SCFAs), tryptophan metabolites, and bile acid derivatives, play vital roles in immune protection and maintaining intestinal health. These compounds modulate inflammatory responses and aid in epithelial barrier function, influencing overall immune function and susceptibility to infections.
7.	Impact on Systemic Immunity	The gut microbiome influences systemic immune responses via metabolite circulation and modulation of T cell populations (e.g., Th1, Th2, Th17, Treg). This systemic influence affects immune cell formation, responses to infections, and overall immunological balance throughout the body.
8.	Clinical Implications	Understanding the microbiome's influence on the immune system has implications for treating inflammatory disorders, enhancing vaccine responses, and improving overall health outcomes. Targeted modulation of the microbiome may offer therapeutic avenues for managing immune-related illnesses and optimizing vaccine efficacy.
9.	Gut-Brain Axis Overview	The Gut-Brain Axis (GBA) is a complex bidirectional communication network linking the intestine to the central nervous system (CNS) via pathways like the autonomic nervous system, enteric nervous system (ENS), vagus nerve, neuroendocrine system, and metabolic pathways. It influences physiological processes and neurological conditions through neurotransmitters, metabolites (e.g., SCFAs, bile acids), and immune system modulation.
10.	Microbiota and CNS Regulation	The gut microbiota plays a crucial role in CNS function, influencing neurodevelopment, ageing, and homeostasis via processes like neurotrophic factor modulation and NMDA receptor regulation. Microbes affect the CNS through chemical transmitters, immune responses, neuronal path ways, and endocrine signalling, highlighting their role in neurological disorders.
11.	Neuroactive Compounds and Pathways	Neuroactive compounds produced or influenced by gut bacteria (e.g., neurotransmitters like dopamine, serotonin; SCFAs) impact brain function and neuroinflammation. SCFAs, in particular, influence gut hormones (PYY, GLP1) that affect mood, memory, and metabolic regulation, potentially impacting diseases like Alzheimer's and other neurodegenerative disorders.
12.	Immune System Interactions	The gut microbiota modulates peripheral immune system formation and function, affecting psychiatric diseases via immune responses and inflammation. Immune cells interact with the CNS through cytokine release, impacting brain health and neurological conditions.
13.	Blood-Brain Barrier (BBB) Regulation	Gut microbiota influence the BBB, altering its permeability and controlling chemical passage to the CNS. Dysregulation of microglia, the brain's immune cells, is linked to psychiatric diseases, highlighting the microbiota's role in neurological health.
14.	Vagus Nerve and Neural Communication	The vagus nerve mediates bidirectional gut-brain communication by transmitting signals such as inflammatory chemicals, metabolites, and gut peptides to the CNS. Probiotic treatments impacting anxiety symptoms via vagus nerve activity underscore its role in neurological disorders.
15.	Microbial Dysbiosis in Neurological Disorders	Alterations in gut microbiota composition are associated with neurological disorders like ASD, PD, AD, depression, and anxiety. Changes in microbiota diversity correlate with these conditions, indicating the microbiota's emerging significance in brain function and disease pathogenesis

intestinal homeostasis by altering epithelial barrier function and promoting intestinal cell repair[24]. Tryptophan metabolites, notably indoles, act as ligands for the aryl hydrocarbon receptor (AhR), which is essential for intestinal homeostasis, and their loss has been linked to the development of inflammatory bowel disease[25]. Furthermore, bile acid derivatives, which are activated by receptors, such as the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor (TGR5), help to maintain intestinal homeostasis and regulate a variety of host activities[26]. These compounds are generated by bacterial bile salt hydrolases (BSHs), and their low abundance is linked to inflammatory bowel illness. The complex interaction of gut microbiota, microbial metabolites, and host factors maintains mucosal homeostasis by controlling a physiological low-grade inflammatory state that is essential for optimal host defense and influences susceptibility to infections[27] (Table 1).

The gut microbiome influences systemic innate and adaptive cell-mediated immune responses *via* a variety of mechanisms in addition to local mucosal immunity. Microbially soluble products generated by the gut microbiota can enter the bloodstream and stimulate immune cells in distant organs, influencing overall immune function and susceptibility to infection[28]. Notably, the gut microbiome has a major impact on the development of T cell populations in the adaptive immune system, specifically T-helper cells (Th1, Th2, and Th17) and regulatory T cells (Treg). Short-chain fatty acids (SCFAs), such as butyrate, enhance the development of regulatory T cells, reducing systemic inflammation and reprogramming metabolic activity to induce regulatory B cells and decrease Th17 cell production[29]. Furthermore, microbiota-produced chemicals like ATP, tryptophan breakdown products, and bacterially derived polysaccharides influence T-cell responses and aid in the regulation of inflammatory reactions. Commensal memory T cell activation and anti-inflammatory response modulation are critical for bacterial infection resistance[30]. Furthermore, the gut microbiota's signaling molecules can affect immune cell formation during hematopoiesis, altering infection response. For example, SCFA butyrate promotes the differentiation of bone marrow monocytes into a tolerogenic phenotype, whereas activation of pattern recognition receptors (PRRs) on hematopoietic stem and progenitor cells (HSPCs) induces trained immunity or tolerized macrophages, depending on the PRR activated[31]. Activation of HSPCs with aryl hydrocarbon receptor (AhR) ligands produces myeloid-derived suppressor cells capable of immunosuppression. These findings emphasize the gut microbiome's diverse function in influencing systemic immune responses as well as its potential as a therapeutic target for immunological-related illnesses[32]. The gut microbiota influences innate immune defenses through a variety of mechanisms, including lymphoid stimulation in the spleen, modulation of neutrophil migration and function, macrophage induction and activation, and stimulation of natural killer (NK) cell maturation and function. Specific bacterial species have also been demonstrated to modulate inflammatory responses by lowering plasma corticosterone levels, which are critical in modulating the inflammatory response to mucosal injury[33]. Dysbiosis in the gut microbiota can affect local and systemic immune responses, resulting in inflammatory disorders in the gut and other locations. The gut-lung axis is particularly interesting, as antibiotic-induced changes in the gut microbiota have been related to the development and increase of allergic airway disorders[34]. In contrast, the gut microbiome directly influences innate and adaptive immune responses, hence guarding against bacterial and viral respiratory infections. Clinical research has demonstrated that using probiotics reduces the frequency of respiratory infections and improves their outcomes[35]. Furthermore, the gut-lung axis is mediated by the shared mucosal immune system, in which antigen-specific B lymphocytes primed in the gut travel to distal regions *via* the thoracic duct. However, identifying whether changes in the gut microbiota are causative or consequential in illness development remains difficult, emphasizing the importance of longitudinal research to better understand the impact of the gut microbiota on the severity and progression of lung disorders[36]. The effect of the microbiome on the immune system, particularly in the gut, has important implications for vaccine reactions. Emerging research suggests that the composition of the microbiota may influence the systemic response to vaccines, with some microbial species potentially improving vaccine efficacy while others reducing it[37]. For example, Bifidobacteria have been connected to increased CD4+ T cell responses to several vaccines, but other taxa, such as Pseudomonadales, Enterobacteriales, and Clostridiales, have been linked to lower vaccine responses. Understanding these connections could lead to therapies that optimize immune memory and improve protection against viral infections through targeted modification of the microbiome[38]. However, despite improvements, there is still a gap in converting preclin-

ical discoveries into human vaccination techniques. While studies in axenic or microbiota-depleted animal models have shed light on the role of antibiotics and microbial composition in vaccine responses, more research is required to understand the mechanisms underlying microbiome-mediated immune modulation and its implications for human health. Notably, dietary parameters, such as fiber consumption, influence immunological responses, demonstrating the complex nature of the microbiome-immune system axis. Gaining a better knowledge of these complex relationships may pave the way for novel approaches to improving vaccination efficacy and combating infectious illnesses, particularly in vulnerable populations[39].

THE GUT-BRAIN AXIS AND ITS ROLE IN NEUROLOGICAL DISORDERS

The gut-brain axis (GBA) is a sophisticated bidirectional communication network that connects the intestine to the central nervous system (CNS), affecting a variety of physiological processes and potentially influencing neurological illnesses. This complex relationship involves several pathways, including the autonomic nervous system, enteric nervous system (ENS), vagus nerve, neuroendocrine system, hypothalamic-pituitary-adrenal (HPA) axis, immunological system, and metabolic pathways[40]. Neurotransmitters and metabolites, such as SCFAs, secondary bile acids, vitamins, and amino acids, enable communication along the GBA by modulating immune system pathways and thereby influencing cognition, behavior, learning, mobility, and neurodegenerative disorders[41]. The GBA's impact extends beyond gastrointestinal regulation to include behavior, stress response, and CNS functions, which influence the immune system and digestive tract function[42]. Recent advances in gut microbiota sequencing have highlighted the delicate link between this complex ecosystem and CNS function, sparking renewed interest in researching their interactions and reciprocal influence. The gut-brain axis is thus an important avenue for studying the etiology of neurological illnesses and investigating new treatment strategies that target the gut microbiota[43]. The gut-brain axis allows bidirectional communication between gut bacteria and the brain *via* various chemical signaling systems that include neuronal, immunological, and endocrine pathways. This network of linkages connects several biological systems, including the neurological, endocrine, immunological, and metabolic systems, which are essential for maintaining gastrointestinal, neurological, and microbial homeostasis[1]. The gut microbiota is crucial to this axis, regulating nervous system development, maturation, aging, and homeostasis *via* a variety of processes, including modulation of neurotrophic factors and N-methyl D-aspartate (NMDA) receptor subunits in the hippocampus. Microbes affect the neurological system by direct and indirect transmission via chemical transmitters, immunological responses, neuronal pathways, and endocrine signaling[9]. The gut-brain axis involves direct and indirect communication through various chemical signaling systems[44]. Gut bacteria can produce neuroactive chemicals themselves or boost host synthesis, impacting gut-brain signaling. For example, the intestinal microbiota produces neurotransmitters, such as dopamine, serotonin, and noradrenaline, which can alter brain function[45]. SCFAs, which are metabolic byproducts of gut microbial activity, play an important role in gut-brain communication by affecting immune responses, neuroplasticity, and hormone control. Microbial metabolites, such as indole and SCFAs, influence the production and secretion of neurotransmitters such as serotonin by enteroendocrine cells[46]. Furthermore, neuroactive metabolites, such as lipopolysaccharides and SCFAs can cause neuroinflammation and impair CNS processes. Microbial-associated molecular patterns (MAMPs) link the CNS and the microbiota, regulating CNS function. While the precise mechanisms are still being investigated, the gut microbiota's function in modulating CNS activity, particularly neurotransmitter signaling pathways, is becoming more widely recognized, emphasizing its importance in neurological illnesses[47]. Short-chain fatty acids (SCFAs) influence the production of gut hormones from enteroendocrine cells, including peptide YY (PYY) and glucagon-like peptide 1 (GLP1). These hormones significantly influence mood, memory, learning, and hunger management. SCFAs activate G protein-coupled receptors (GPCRs) in the colon, causing the production of PYY and GLP1, which can directly alter brain function via both humoral and neuronal pathways[48]. GLP1 improves memory, neuroplasticity, and neuroprotection in animal models of Alzheimer's disease (AD) by affecting hippocampus function and lowering β-amyloid plaques and microglia activity. PYY, on the other hand, suppresses hunger and stomach motility while also influencing brain activity via processes that include both blood-brain barrier crossing and vagal afferent pathway activation[49]. Other metabolic hormones regulated by SCFAs, such as ghrelin, leptin, and insulin, also have an impact on brain function, though research on these hormones in the gut-brain axis is limited in comparison to PYY and GLP1. Leptin, for example, controls energy

balance by influencing hypothalamic receptors and the production of neuropeptides involved in hunger regulation. Overall, SCFAs and their related gut hormones play a significant role in communication between the gut and the brain, with consequences for neurological diseases and metabolic regulation[50]. The gut microbiota regulates the formation and function of the peripheral immune system, which has an impact on the pathophysiology of psychiatric diseases that frequently include immunological responses and inflammation. The gut microbiota communicates with the brain *via* immune system interactions and cytokine circulation. Immune cells can breach the blood-brain barrier (BBB) and create cytokines and chemokines in the brain, facilitating this communication[51]. The gut microbiota influences the BBB, a physical barrier that separates the brain microenvironment from the bloodstream, by changing its permeability and controlling the passage of chemicals between the bloodstream and the central nervous system. Dysregulation of microglia, the brain's immune cells, has been related to several psychiatric diseases[44]. Short-chain fatty acids (SCFAs) produced by the gut microbiota directly impact immune cells and immunological modulators, helping maintain homeostasis. SCFAs modulate intestinal mucosal immunity and may lower systemic inflammation by strengthening the intestinal barrier and preventing the transfer of bacteria and their metabolites[49]. SCFAs also regulate the development and activation of many immune cells, including T lymphocytes, macrophages, dendritic cells, and neutrophils, which affects their roles and responses. SCFAs regulate neutrophil activity by influencing cytokine production, chemokine synthesis, and chemotaxis via interactions with particular receptors. Furthermore, SCFAs have the potential to influence T-cell formation and proliferation, either directly or indirectly. As modulated by the gut microbiota and SCFAs, the gut-brain axis plays an important role in the immune-mediated pathogenesis of neurological diseases[52]. The gut-brain axis is crucial in neurological disorders because of the physical connections between the gut and the brain, which are predominantly *via* the vagus nerve. This neural network enables bidirectional communication between the gastrointestinal tract and the central nervous system (CNS)[53]. The vagus nerve, with its afferent and efferent fibers, innervates the digestive system and detects numerous signals, such as inflammatory chemicals, food components, bacterial metabolites, and gut peptides, which it conveys to the CNS. In addition, gut bacteria can directly activate neurons *via* Toll-like receptors and excite intestinal afferent neurons *ex vivo*[54]. Studies have demonstrated that persistent treatment with particular probiotics can decrease anxiety symptoms caused by gut inflammation, and these effects are lost when the vagus nerve is impaired. Microbial metabolites, such as bile acids and short-chain fatty acids (SCFAs), can also directly stimulate neurons in the brain, affecting neuronal activity and gut motility[55]. Furthermore, gut bacteria help to generate enteric glial cells, which are necessary for maintaining neural networks and gut homeostasis. The gut-brain axis, notably through the vagus nerve and chemical communication, plays an important role in neurological disorders by controlling the interaction of gut bacteria with the CNS[56].

Neurological disorders are increasingly being related to alterations in the gut flora. These illnesses affect different sections of the neurological system, such as the brain, spinal cord, and peripheral nerves. Brain hemorrhage, nervous system developmental difficulties, spinal cord injuries, and brain tumors have all been linked to gut microbiota dysbiosis[57]. Studies have found significant changes in gut microbiota makeup between patients with neurological disorders and healthy people. Communication between the

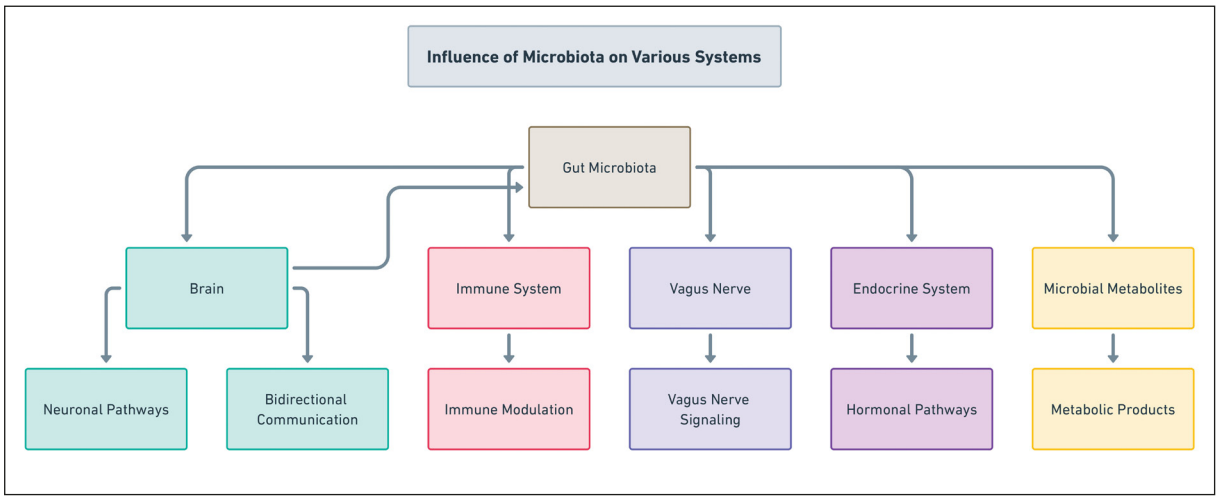

Figure 1. Influence of microbiota on various systems.

gut microbiota and the brain is observed in neurodevelopmental disorders, such as autism spectrum disorder (ASD), neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), and mental health issues, such as depression and anxiety[58]. According to research, changes in microbial variety can harm one's health and the central nervous system. Alterations in microbiota composition have been linked to illnesses such as autism spectrum disorder, depression, and anxiety. Furthermore, research has found correlations between microbiota makeup and various neurological illnesses, emphasizing gut bacteria's evolving significance in brain function[59]. Understanding the relationships between the gut microbiota and neurological illnesses is critical for furthering our understanding of neuromicrobiology. By investigating these connections, researchers hope to offer insight into potential therapy routes for illnesses such as ASD, AD, Parkinson's disease, depression, and anxiety disorders[9] (Figure 1).

POTENTIAL IMPLICATIONS IN NEUROLOGICAL DISORDERS

Parkinson's disease (PD)

PD, which affects more than 1% of the elderly and 0.3% of the worldwide population, is the second most common neurodegenerative ailment after Alzheimer's disease. PD is a progressive neurodegenerative condition characterized by a loss of voluntary movement control as a result of severe alterations in the function of the substantia nigra and striatum[60]. These changes include decreased dopaminergic neurons, increased phosphorylated α-synuclein (αSyn), mitochondrial dysfunction, elevated reactive oxygen species, and enhanced microglia activation. α-synucleinopathies, including Parkinson's disease, are mostly caused by inflammation and misfolding of the protein. PD is primarily caused by the accumulation of α-synuclein, a 140-amino-acid protein encoded by a gene on chromosome 4q21.3-q22[61]. Tremors, gait difficulty, slumped posture, and muscle rigidity are common signs of Parkinson's disease. Gastrointestinal problems, notably constipation, can affect up to 80% of Parkinson's patients and may occur several years before the diagnosis[62]. Emerging data suggests that gut dysbiosis contributes to PD onset, progression, and development. Studies comparing individuals with prodromal and/or clinically confirmed PD to controls demonstrated dysbiosis in the gut microbiome of PD patients[63]. Culture-independent high-throughput sequencing techniques were used to analyze the overall structure and composition of the gut microbiota with PD, finding different patterns in the microbiota profiles of patients. Previous research found that PD patients had higher α-diversity but reduced bacterial diversity compared to healthy individuals. There were also differences in β-diversity between PD patients and controls[64].

Alzheimer's disease (AD)

AD is a common neurological ailment that affects around 50 million people worldwide. It is the major cause of progressive, chronic, and irreversible cognitive decline among the elderly, as well as the most common form of dementia in this population. As the disease progresses, symptoms that impair cognition and memory have a significant influence on daily activities[19]. AD is characterized by neuronal loss and synaptic dysfunction caused by the aggregation of β-amyloid precursor protein (Aβ) into soluble or insoluble deposits in the brain. These aggregates set off a chain reaction that results in the creation of neurofibrillary tangles made up of hyperphosphorylated tau proteins, which eventually lead to dementia. Neuroinflammation, particularly as mediated by the NLRP3 inflammasome, has been linked to Alzheimer's disease development and progression[65]. Pro-inflammatory cytokines, including IL-1β and IL-18, have been found in microglia, astrocytes, and neurons around Aβ plaques, indicating that inflammasome activation plays a role in Alzheimer's disease pathology. Patients with tauopathies, characterized by aberrant tau protein buildup, have higher levels of inflammasome components and mature IL-1β in afflicted brain areas, indicating neuroinflammation in AD etiology. Microbiological variables have also been linked to AD, with differences in gut microbiota composition reported in AD patients versus controls[66]. Alzheimer's patients have higher amounts of Bacteroidetes and lower levels of Firmicutes and Actinobacteria in stool samples, with reductions in select Firmicutes families such as Ruminococcaceae, Turicibacteraceae, and Clostridiaceae. Mechanistic linkages have been hypothesized between AD pathogenesis and numerous mi-

croorganisms, including spirochaetes, fungi, and *Chlamydia pneumoniae*. Recent research has highlighted the involvement of the gut microbiota in Alzheimer's disease etiology, with microbiota-derived chemicals detected in AD patients' brain fluid correlating with disease-related indicators. Alterations in fecal microbiomes and short-chain fatty acid (SCFA) levels have been identified in AD animal models, indicating alterations in microbial composition and metabolism[67]. Transgenic AD mouse models have shown alterations in gut microbiota composition, with germ-free mice having lower cerebral β-amyloid pathology compared to conventionally colonized mice. This suggests that the gut microbiota may play a role in modifying AD pathology. These findings highlight the intricate interplay of neuroinflammation, microbiological variables, and gut-brain axis dysfunction in Alzheimer's disease pathogenesis, providing insights into possible treatment targets and diagnostic tools for this severe neurological ailment[68]. *Multiple sclerosis (MS)* MS is a neurological illness characterized by inflammation that affects over 2 million people worldwide. Demyelination, axonal loss, lymphocyte infiltration into the central nervous system (CNS), and neuroinflammation cause a variety of clinical symptoms, including ataxia, poor coordination, hyperreflexia, stiffness, visual and sensory impairment, fatigue, and cognitive deficits[41]. The most prevalent form of MS is relapsing remitting, which is distinguished by progressive neurological function degradation and the recurrence of symptoms over time. In addition to other environmental influences, microbes, and their metabolites play an important role in the pathophysiology of MS. Studies have indicated that MS patients' microbiomes differ from those of healthy people, with unique microbial profiles seen even between MS patients in active disease and those in remission. Pediatric MS patients with high Firmicutes abundance and no Fusobacteria have a shorter time to relapse[69]. Changes in the abundance of particular microbial species, such as Mycoplasma, Dorea, Pseudomonas, Blautia, and Akkermansia, have been found in fecal samples from MS patients *vs.* healthy controls. Preclinical models in germ-free mice showed reduced signs of MS-like illness, indicating a role for gut microbiota in MS development. Furthermore, mice who received the intestinal microbiota of MS patients had more severe experimental autoimmune encephalomyelitis (EAE), a model for MS, and had lower proportions of anti-inflammatory regulatory T cells than mice that received microbiota from healthy individuals. Transplanting MS patients' intestinal microorganisms into genetically predisposed mice dramatically increased the prevalence of EAE compared to transplanting microbes from healthy persons, implying a causal relationship between the microbiome and MS development[70]. Notably, immune cells from mice colonized with MS-derived microbiota produced less of the anti-inflammatory cytokine IL-10, implying that changes in the human microbiome can cause immune system changes that contribute to the onset or progression of MS. However, further study is needed to determine the precise function of the microbiome in MS onset and progression. Nonetheless, the differences in microbiota composition between MS patients and healthy controls emphasize the potential significance of microbial variants in MS pathogenesis, emphasizing the necessity of exploring these differences for therapeutic and diagnostic applications[71].

Anxiety and depression

Anxiety and depression, which affect a quarter of the global population, are serious mental and neurological illnesses. Despite being different disorders, they frequently coexist, with a large proportion of people reporting both anxiety and depression symptoms. The clinical presentations of these diseases vary between stages, with an alarming increase in depressive symptoms among teenagers, which has contributed to recent increases in suicide rates[72]. The link between anxiety, depression, and abnormalities in the gut microbiota has received a lot of attention in studies. Numerous studies have been conducted to study the association between intestinal microbiota makeup and patients suffering from anxiety and mood disorders. Human studies have found differences in fecal microbiota diversity and taxonomic makeup between patients and healthy controls. Certain microorganisms have been linked to clinical characteristics and metabolic or inflammatory profiles[73]. While several studies have failed to find a direct link between low microbial diversity and depressive disorders, one study discovered that people with major depressive disorder (MDD) have a higher alpha diversity of gut microbiota than healthy people. This diversity was distinguished by higher levels of Enterobacteriaceae and Alistipes but lower levels of Faecalibacterium, with Faecalibacterium having a negative

TABLE 2. SELECTED NEUROLOGICAL DISORDERS AND GUT MICROBIOTA INTERACTIONS.

S/N	Disease	Burden	Mechanism	Implications
1.	Parkinson's Disease (PD)	Affects >1% of the elderly; second most common neurodegenerative disease after Alzheimer's	Progressive neurodegeneration impacting substantia nigra and striatum; involves α-synuclein accumulation, dopaminergic neuron loss, mitochondrial dysfunction, oxidative stress, and microglia activation.	Gut dysbiosis linked to PD onset and progression; altered microbiota profiles (high α-diversity, reduced bacterial diversity) observed in PD patients; potential for microbiota-based diagnostic and therapeutic strategies.
2.	Alzheimer's Disease (AD)	Affects ~50 million people worldwide; the leading cause of dementia and progressive cognitive decline.	Neuronal loss, synaptic dysfunction due to β-amyloid and tau protein aggregates; neuroinflammation via NLRP3 inflammasome activation; gut microbiota influence through metabolites and microbial composition.	Altered gut microbiota composition (e.g., high Bacteroidetes, low Firmicutes) in AD patients; microbiota-derived chemicals in brain fluid correlate with disease indicators; potential for microbiota-targeted therapies in AD treatment.
3.	Multiple Sclerosis (MS)	Affects >2 million worldwide; autoimmune disease with demyelination, and neuroinflammation.	Microbial dysbiosis linked to MS pathophysiology; unique microbiome profiles in active and remitting MS patients; influence on immune modulation and disease severity (EAE models).	Gut microbiota alterations (e.g., Mycoplasma, Pseudomonas) impact MS progression; potential for microbial therapies to modulate disease outcomes; therapeutic implications in immune regulation and MS management.
4.	Anxiety and Depression	Affects ~25% of the global population; significant mental health disorders with diverse clinical presentations.	Gut microbiota diversity and taxonomic shifts are associated with anxiety and depression; microbial metabolites (e.g., SCFAs, GABA) impact brain function and mood regulation.	Potential for probiotic therapies (e.g., Bifidobacterium, Lactobacillus) to alleviate symptoms; microbial metabolites (e.g., GABA) influence mental health; therapeutic avenues targeting the gut-brain axis for anxiety and depression management.
5.	Autism Spectrum Disorders (ASD)	A complex developmental disorder affecting social interaction and communication.	The gut microbiome regulates neurotransmitter levels (e.g., GABA, serotonin); influences neuroimmune responses; and causes dysbiosis associated with ASD pathogenesis.	Altered gut microbiota composition (e.g., reduced Bacteroides, increased Faecalibacterium) in ASD patients; potential for microbiota-driven therapies in managing ASD symptoms; implications in neurodevelopment and immune modulation in ASD.
6.	Stroke	The second largest cause of death worldwide; significant morbidity and mortality.	Ischemic stroke is linked to changes in gut microbiota composition (e.g., increased opportunistic pathogens, decreased commensals) and their influence on stroke severity and outcomes.	Potential role of gut microbiota in stroke prevention, treatment, and recovery; microbial therapeutic strategies (e.g., targeting microbiota to reduce stroke risk and severity); implications in cerebrovascular health and neurological

connection with depression symptoms[74]. Patients with generalized anxiety disorder (GAD) have lower levels of microbial diversity and richness, which is associated with lower levels of short-chain fatty acid producers like *Eubacterium rectale* and Fecalibacterium and higher levels of Ruminococcus, *Escherichia coli*, Shigella, and Fusobacterium. Probiotic therapies, including *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, and *Lactobacillus casei*, have shown potential for lowering depression symptoms when compared to a placebo[75]. Fecal metagenomic data reveal that bacteria's ability to create 3,4-dihydroxyphenylacetic acid, a dopamine metabolite, may have an impact on mental health. Furthermore, *Lactobacillus rhamnosus* has been shown to release gamma-aminobutyric acid (GABA) and activate GABA receptors in the brain, resulting in the reduction of depression and anxiety-like behaviors in animal models. These data highlight the complex link between gut microbiota and mental health disorders, pointing to possible therapeutic strategies that target the gut-brain axis to reduce anxiety and depression symptoms[76] (Table 2).

Autism spectrum disorder (ASD)

ASD is a complicated mix of neurological developmental alterations characterized by difficulties with social interaction, communication, and repetitive behaviors. Individuals with ASD typically suffer from gastrointestinal symptoms, such as constipation, diarrhea, stomach discomfort, flatulence, and intestinal gas, which are frequently associated with gastrointestinal illnesses[72]. The gut microbiome regulates the levels of chemical transmitters such as GABA, glutamate, oxytocin, and serotonin, all of which are linked to ASD. Microbial impacts on the immune system are also hypothesized to have a role in shaping neuroimmune responses in ASD patients, owing to the low-grade inflammation that is common in these patients. Emerging research using modern technologies emphasizes the role of microbial metabolites such as taurine, bile acid metabolites, SCFAs, and 5-amino valeric acid in regulating ASD symptoms.[44] While research on the role of the microbiome in ASD pathogenesis has been limited and inconsistent, some studies have shown changes in bacterial species between ASD patients and controls. These variations include changes in Clostridiales, Firmicutes, Prevotella, *Clostridium perfringens, and* Bifidobacterium. Such alterations in gut microbiota composition may result in reduced food quality and nutritional insufficiency. According to scientific research, ASD is associated with lower amounts of good bacteria, such as Bacteroides and Bifidobacterium, as well as higher numbers of dangerous bacteria, like Faecalibacterium and *Escherichia coli*[77]. While there is evidence of dysbiosis in people with ASD, it is difficult to establish a causal link between certain bacteria and the start of ASD. Nonetheless, the gut microbiota and its metabolites are rapidly becoming recognized as potentially important components in the etiology of ASD. More studies are needed to understand the complex interplay between gut microbiota composition, immunological function, and neurological development in people with ASD, which could open the way for new treatment strategies targeting the gut-brain axis in ASD management[78].

Stroke

Stroke, the second largest cause of death worldwide, places a significant burden on healthcare systems and individuals, affecting both morbidity and mortality rates. Strokes impact around 15 million individuals each year, posing a significant public health concern. While stroke can be caused by a variety of underlying diseases, including cerebrovascular illness, atherosclerosis, dyslipidemia, diabetes, and arterial hypertension, research into the relationship between hemorrhagic stroke and the gut microbiota has been limited[79]. According to recent research, the gut microbiota (GM) may have an important role in the development and prognosis of stroke. Ischemic stroke, which accounts for the vast majority of stroke cases, has been specifically related to changes in the gut microbiota composition[80]. Patients who have transient ischemic attacks or strokes frequently have changes in their gut microbiota, including an increase in opportunistic pathogens such as Desulfovibrio, Enterobacter, Megasphaera, and Oscillibacter, as well as a decrease in beneficial or commensal bacteria, such as Bacteroides, Faecalibacterium, and Prevotella[81]. Furthermore, some microbial taxa, such as Peptococcaceae and Prevotellaceae, have been linked to stroke severity, implying a possible relationship between gut microbiota composition and illness outcomes. Preclinical research has also revealed a role for the gut bacteria in hemorrhagic transformation (HT), a consequence of ischemic

stroke. In experimental stroke models with hemorrhagic transformation, the gut microbiota changed, with an increase in Proteobacteria and Actinobacteria[82]. However, the precise processes behind the gut microbiota's participation in stroke onset and progression are not well understood. While animal models have provided useful insights, further clinical research is required to fully understand the potential therapeutic implications of addressing the gut microbiota in stroke therapy. Understanding the relationship between gut microbiota makeup, stroke pathogenesis, and illness outcomes could lead to new microbial therapeutic methods for stroke prevention, treatment, and rehabilitation[83].

CONCLUSIONS

The study on microbiome-immune system interactions in neurological disorders has revealed the crucial role these systems play in maintaining brain health and influencing the development and progression of neurological diseases. This understanding offers new insights into the underlying mechanisms of neurological disorders. Research advancements in this field offer promising avenues for enhancing diagnosis, treatment, and potentially preventing neurological disorders. Identifying biomarkers associated with microbiome-immune system imbalances can enable earlier detection and more effective disease management. Tailoring interventions based on individual gut microbiota composition and immune function, such as probiotics, prebiotics, dietary modifications, or targeted therapies, holds considerable potential for personalized treatment approaches. Targeting immune pathways triggered by the gut microbiome presents an opportunity to develop novel therapeutic strategies for neurological disorders. However, further research is needed to fully realize the potential of the microbiome-immune system axis in neurological disorders.

The proposed recommendations aim to transform the field of neurological treatment by leveraging the microbiome-immune system axis. Interdisciplinary collaboration among neuroscientists, immunologists, microbiologists, physicians, and bioinformaticians is required to fully comprehend neurological illnesses' intricacies. Supporting longitudinal research that tracks changes in the gut microbiota and immune profiles over time in at-risk people can provide crucial insights into disease development. Precision medicine approaches based on individual gut microbiota composition, immunological condition, and genetic background improve therapeutic success while minimizing side effects. Facilitating the translation of fundamental research discoveries into clinical practice through well-designed clinical trials is critical, necessitating collaboration across academics, industry, and regulatory bodies. Empowering patients and carers with knowledge about the microbiome-immune system's involvement in neurological health and disease promotes patient participation in research efforts and clinical trials, ensuring that treatment approaches are tailored to patient preferences. Advocating for public health measures that promote gut health and immune resilience from birth to adulthood can help to create a favorable microbiome and immune milieu for brain health. These guidelines jointly increase our understanding and approach to neurological illnesses, resulting in better patient outcomes and public health.

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Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

All datasets generated for this study are available with the corresponding author upon reasonable request.

Authors' Contribution

All authors contributed equally to the writing of this paper and have read and approved the final draft.

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