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Gut Microbiota and Neurological Disorders: Unraveling the Gut-Brain Axis
The Gut-Brain Axis in Neurological Disorders

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ABSTRACT:
Recent scientific advancements have improved our understanding of health and disease, yet some neurological disorders remain poorly understood. Gut microbiota is a diverse community of bacteria residing in the gut, and they play a role in digestion, metabolism, the immune system, and neuronal functions. There is a bidirectional communication system known as the gut-brain axis (GBA) between the central nervous system and the gut microbiota by neural, endocrine, and immunological mechanisms. Gut microbiota produces metabolites such as short-chain fatty acids (SCFAs), neurotransmitters, and hormones that regulate brain function and behavior. Alteration of gut microbiota or dysbiosis is associated with neurological disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and depression. Changes in microbiota composition can cause systemic inflammation, regulate the concentrations of neurotransmitters, and affect the integrity of the blood-brain barrier, resulting in neurodegeneration. New therapeutic modalities, including probiotics, prebiotics, nutritional intervention, and fecal microbiota transplantation, have been developed to re-establish homeostasis within the gut and halt disease progression. Metagenomics and artificial intelligence are transforming microbiome research, enabling targeted treatment based on the individualized microbiota signature. Information on the gut-brain axis offers promising directions for the development of novel therapies in psychiatric and neurodegenerative disorders.

Keywords: Gut Microbiota, Neurological Disorders, Gut-Brain Axis

I. INTRODUCTION:

The gut microbiome contains trillions of microbes that are vital for human health[1,2]. Emerging evidence suggests the gut microbiome influences brain function and behavior through the gut-brain axis[3,4].The complex, bidirectional communications between the gut and brain are regulated by neural, endocrine, and immune pathways for gut microbes to influence cognition, mood, and behavior[5].

This describes the complexity of two-way communication between the Central Nervous System (CNS) and the gastrointestinal tract via neural, hormonal, and immune pathways. The vagus nerve is a key component of this axis, transmitting microbial signals that affect mood, cognition, and behavior. This emerging evidence shows that gut microbes can produce metabolites like Gamma-Aminobutyric Acid (GABA) and serotonin, which influence neurological functions directly[5].

Composition of gut microbiota:

The most complex and dynamic community of microorganisms in the human intestines is gut microbiota, living among bacteria, fungi, archaea, viruses, and protozoa[6,7]. The gut microbiota consists of six major bacterial phyla, with Firmicutes and Bacteroidetes making up about 90%[8].

Firmicutes: It consists of over 200 genera that include Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminococcus. Indeed, the species of Clostridium make up 95% of this Firmicutes category that highly contribute to the production of Short-Chain Fatty Acids (SCFAs) responsible for maintaining the gut barrier function and energy metabolism[8].

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Bacteroidetes: Genera like Bacteroides and Prevotella dominate in this category but play an important role as degraders of complex carbohydrates as well as acting on immune response regulation[9].

Actinobacteria: Though less abundant, Actinobacteria includes Bifidobacterium, which produces vitamins B12 and K and SCFAs.[10].

Other Compositions: Fusobacteria and Verrucomicrobiaamong others hold the most interest in the preservation of mucosa integrity and metabolic regulation[11].

Table 1 Comprehensive Gut Microbiome Table: Types, Functions, Health Benefits, and Dysfunctions

Microbe	Type	Function	Health Benefits	Dysfunctions	References
Faecalibacteriumprausnitzii	Anaerobic Bacterium	SCFA (butyrate) producer, anti-inflammatory effects	Supports gut lining integrity, reduces systemic inflammation	Depletion is linked to inflammatory bowel disease (IBD) and metabolic syndrome.	[12,13]
Lactobacillus rhamnosus	Probiotic Bacterium	Modulates GABAergic signaling and balances neurotransmitters	Reduces stress, anxiety, and depression; improves mood	Dysbiosis is associated with mood disorders and increased anxiety.	[14,15]
Akkermansiamuciniphila	Mucin-degrading Bacterium	Maintains mucosal integrity, SCFA production	Enhances gut barrier function, improves metabolic health	Depletion was observed in obesity, type 2 diabetes, and cognitive decline.	[16,17]
Bacteroides fragilis	Anaerobic Bacterium	Produces polysaccharide A (PSA) for immune modulation	Mitigates neuroinflammation enhances resilience to stress	Dysbiosis is linked to inflammatory conditions and neurodevelopmental disorders like autism spectrum disorder (ASD).	[18]
Bifidobacterium longum	Probiotic Bacterium	Supports serotonin synthesis, SCFA production	Promotes mental well-being, reduces symptoms of anxiety and depression	Dysbiosis contributes to increased gut permeability ("leaky gut") and inflammation-related mood disorders.	[19]
Clostridium butyricum	SCFA-Producing Bacterium	Butyrate production, immune modulation	Enhances brain plasticity via Brain-Derived Neurotrophic Factor(BDNF), regulates inflammation	Dysbiosis is linked to reduced neuroplasticity and increased systemic inflammation.	[20]
Roseburia intestinalis	Butyrate-Producing Bacterium	Supports gut epithelium	Reduces systemic inflammation, prevents metabolic and	Reduction associated with IBD and heightened risk of	[21]

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			cognitive dysfunction	Alzheimer's disease.	
Ruminococcusbromii	Anaerobic Bacterium	Resistant starch fermentation, SCFAs production	Improves gut microbiota diversity and metabolic health	Dysbiosis is linked to poor digestion and suboptimal microbial diversity.	[22]
Methanobrevibacter smithii	Methanogen (Archaea)	Methane production, energy regulation	Optimizes caloric extraction from food, supports metabolic efficiency	Overgrowth is linked to small intestinal bacterial overgrowth (SIBO) and altered gut motility.	[23]
Candida albicans	Yeast	Balances gut microbial ecosystem in healthy populations	Maintains microbial equilibrium in low quantities	Overgrowth contributes to neuroinflammation and diseases like Alzheimer's and candidiasis.	[24]

Fungal, and Viral Components

Fungi and viruses also comprise the gut microbiota ecosystem:

Fungi: Though less in number, Candida, Saccharomyces, and Malassezia, among others, can profoundly alter gut immune responses and intestinal inflammation[25].

Viruses: Bacteriophages are the most abundant species in the gut virome and have been shown to regulate bacterial populations and, hence, influence microbial diversity[26].

Archea and Protozoa: Methanogens Methanobrevibacter smithii are involved in the fermentative process whereas protozoa such as Blastocystis hominis might play context-dependent roles in digestion or pathology[27].

Intrinsic and Extrinsic Determinants of Microbial Diversity

Gut microbiome diversity is determined by intrinsic and extrinsic determinants, such as diet, genetics, age, and exposures

Diet: High-fiber diets increase Bacteroidetes and decrease Firmicutes, whereas high-fat, high-sugar diets increase Firmicutes and decrease Bacteroidetes, changing the balance and function of the microbiota[28].

Age and Development: The microbiota matures dynamically from birth, stabilizes in adulthood, and changes with aging. Delivery by vagina allows maternal microbes, whereas delivery by cesarean often results in different microbial signatures[29].

Lifestyle and Environment: Location, exercise, stress, and antibiotic use significantly impact the composition and the robustness of microbes[30].

Stability, Variability, and Dynamics

The colon had been linked to the largest population size of anaerobic domination including fermentation of metabolite that might be excreted[31]. It has seasonal variation and variation between regions: It implies that there is variation in the microbiota itself which has physiological implications for hosts.

The number of human cells is significantly lesser compared to the number of gut microbiotas, and its genome size is at least 100 times that of human ones[32].

Functions of the Gut Microbiota

Metabolism of Dietary Fibers by Gut Microbiota

Gut microbiota ferments dietary fibers into SCFAs like acetate, propionate, and butyrate. Ruminococcusbromii and Bifidobacterium adolescentis metabolize resistant starches[33,34]. Bacteroides and Bifidobacterium produce acetate for cholesterol synthesis[35]. Prevotella and Veillonella generate propionate for glucose regulation[36,37], while Faecalibacteriumprausnitzii and Roseburia produce butyrate, supporting colonocyte energy and gut barrier integrity[38]. Microbial metabolism of proteins and fats yields beneficial branched-chain fatty acids but also harmful byproducts like ammonia. Bacteroides and Clostridium convert bile acids, influencing lipid absorption[39,40]. There are also complex carbohydrates, cellulose, and hemicelluloses, that the bacterium Bacteroides thetaiotaomicron breaks down into precursors for SCFAs production, with higher microbial diversity[41].

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SCFAs regulate appetite, immunity, and metabolism via GPR41/GPR43[42]. Butyrate prevents colorectal cancer and aids in IBD[43,44], while propionate improves glucose and lipid metabolism, reducing type 2 diabetes risk[45]. Low fiber intake lowers SCFAs, contributing to inflammation, metabolic syndrome, and gut dysfunction[46].

Vitamin Production by Gut Microbiota

Gut microbiota synthesizes essential vitamins for physiological functions. Bacteroides fragilis produces menaquinones (vitamin K2) for blood coagulation and bone formation[47]. Propionibacterium and Lactobacillus reuteri produce vitamin B12, though absorption occurs in the ileum[48].Bifidobacterium and Lactobacillus synthesize folate (B9) for DNA synthesis[49,50]. Bifidobacterium and Escherichia coli generate riboflavin (B2) for energy metabolism[51]. Lactobacillus produces vitamin B6, essential for neurotransmitter synthesis and amino acid metabolism[52]. Vitamin bioavailability depends on diet, gut health, and microbiota composition.

Immune system regulation by gut microbiota

Gut microbiota modulates immune responses by interacting with dendritic cells (DCs) and macrophages, influencing innate and adaptive immunity. Bacteroides fragilis produces PSA, promoting regulatory T-cell differentiation and immune tolerance[53,54].SCFAs like butyrate drive macrophages toward an anti-inflammatory phenotype[55], Microbial components such as lipopolysaccharides and flagellin activate immune pathways via Toll-like receptors, balancing defense without overactivation[56].Faecalibacteriumprausnitzii butyrate inhibits IL-6 and TNF-α while increasing IL-10, modulating inflammation and gene expression via HDAC activity[57]. The gut microbiota also supports Gut-Associated Lymphoid Tissue (GALT) and secretes IgA, reinforcing the intestinal barrier against pathogens[58].
Dysbiosis disrupts immune homeostasis, contributing to inflammatory bowel disease, and rheumatoid arthritis[59,60]. Low microbial diversity is linked with allergies, asthma, and systemic inflammation-allergies, asthma, and systemic inflammation[61], Probiotics, prebiotics, and fecal microbiota transplantation offer promising therapeutic approaches to restoring immune balance.

Barrier Function Maintenance by Gut Microbiota

Gut microbiota helps maintain the intestinal

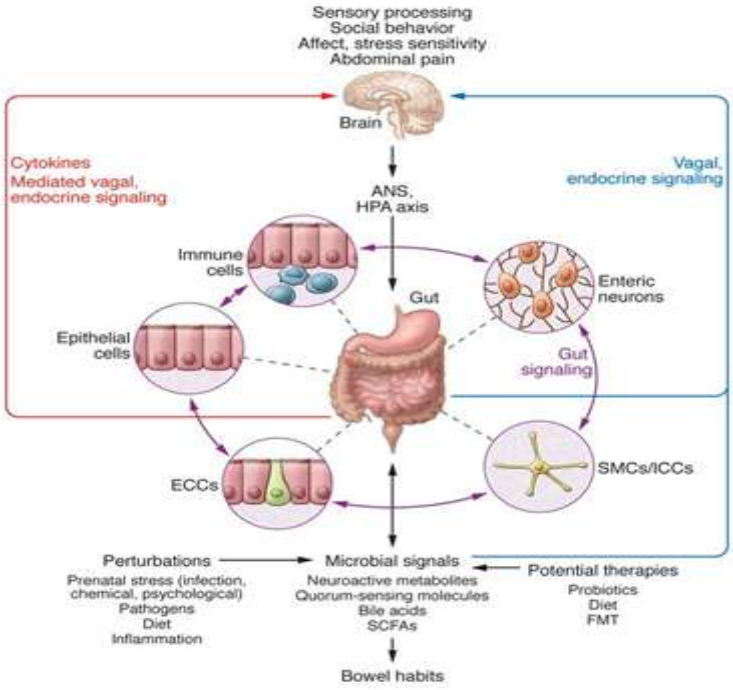

Figure 1: Overview of GBA[69]

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barrier, protecting against pathogens while allowing nutrient absorption. Akkermansiamuciniphila boosts mucin production, forming a protective mucus layer[62]. Lactobacillus rhamnosus strengthens tight junctions, reducing permeability[63]. SCFAs like butyrate, produced by Faecalibacteriumprausnitzii and Roseburia, fuel colonocytes and support epithelial renewal[38,59]. Commensals like Bifidobacterium and Lactobacillus prevent pathogen invasion through competitive exclusion and produce antimicrobial compounds such as lactic acid and reuterin[64]. Microbiota also regulates antimicrobial peptides like RegIIIγ via Toll-like receptors (LPS recognition), enhancing defense mechanisms. SCFA-producing bacteria reduce pro-inflammatory cytokines (IL-6, TNF-α) while increasing IL-10, protecting the epithelial barrier[65,66]. Dysbiosis weakens barrier integrity, increasing intestinal permeability ("leaky gut") and contributing to IBD, type 1 diabetes, rheumatoid arthritis, and metabolic syndrome[19,67].Research into probiotics, prebiotics, and dietary interventions shows promise in restoring barrier function.

Effect on the brain:

Interaction via the Gut-Brain Axis (GBA)

The gut-brain axis works through a two-way signaling mechanism that includes neural, endocrine, immune, and metabolic pathways.The enteric nervous system, known as the 'second brain,' contains about 200 million neurons and constantly interacts with the CNS[68].

Neurotransmitter and Hormonal Activity in the Gut

The sensory nerves of the gut secrete neurotransmitters such as serotonin, histamine, and melatonin that alter the rate of gut motility and secretion[70]. Enterochromaffin cells in the gut produce about 90% of the body's serotonin, influencing mood and stress response.[71]. The other neurotransmitters include acetylcholine, GABA, and catecholamines which further regulate gut and brain functions[72]. For example, GABA is the main inhibitory neurotransmitter that is produced by specific gut microbes and has been associated with anxiety and depressive disorders[73].

The endocrine pathway employs the enteric endocrine cells called EECs, where active peptides are released when microbes signal, dietary components are present, and toxins. It controls nutrient absorption, systemic signaling, and gut immunity[74].Galanin is very significant in influencing mood, sleep-wake cycles, appetite, and stress responses. It stimulates the Hypothalamic-Pituitary-Adrenal (HPA) axis to release hormones of stress, which include glucocorticoids, norepinephrine, and cortisol[70]. The interaction of galanin with the HPA axis demonstrates the role the gut plays in influencing stress-related responses and potentially contributes to neuropsychiatric stress-associated disorders such as anxiety and depression[75].

Immune pathway of the GBA

One of the most important ways the composition of gut microbiota engages with brain health is the immune pathway. The gut-associated lymphoid tissue will communicate with microbial-associated molecular patterns identified by Toll-like receptors in the immune cells and cause pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-17, to be secreted across the BBB, hence neuroinflammation[76]. Continuous activation of these pathways has been implicated in the pathogenesis of neurodegenerative disorders such as AD, PD, and MS. For instance, chronic gut inflammation due to microbial dysbiosis may increase the permeability of the gut-the "leaky gut", thereby allowing penetration of microbial toxins and cytokines into the brain, thus increasing neurodegenerative processes[77].

This further affects the immune system's influence on gastrointestinal motility and secretion, thus causing disorders like visceral hypersensitivity, which is a very common finding in irritable bowel syndrome[78]. It also impacts the function of enteroendocrine cells. Such disturbances impact not only gut function but also feedback into the brain and potentially worsen neuropsychiatric symptoms.

Gut Microbiota and Neurological Diseases

Alzheimer Disease

Alzheimer's disease is a progressive neurodegenerative disorder that has continuously been associated with gut microbiota. Dysbiosis disrupts the gut barrier, triggering systemic inflammation and allowing inflammatory signals to reach the brain.[79]. Such pro-inflammatory bacteria include endotoxins containing Escherichia coli, Shigella, and Salmonella, leading to systemic inflammation. The end product of this is the deposition of amyloid-β (Aβ) into the brain, which in turn promotes further deposition and neuroinflammation through the activation of the receptors by microglia, including TLRs, IL-1β, and TNF-α release[80]. Another way by which gut microbiota exerts an effect on oxidative stress in

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the brain is through its role in the Reactive Oxygen Species(ROS) balance that leads to neuron damage in addition to promoting Aβ aggregation[81]. Modulation of gut microbiota by probiotics and their exopolysaccharides may relieve neuroinflammation, and oxidative stress, and slow down the progression of AD by restoring the balance of microbes and improving gut-brain communication[82].

Parkinson's Disease

PD has had a proven profound association with the gut microbiota mainly through the gut-brain axis. The dysbiosis within the gut microbiome is thus likely an important contributing component in the genesis of PD given its impacts on processes of neuroinflammation and aggregations of alpha-synuclein. Aggregations of alpha-synuclein can accumulate within the gut and thereby travel along axons of neurons in the vagus to initiate neurodegenerative events[83,84]. Aggregation may be triggered by a stimulus like microbial metabolites or inflammation associated with the gut.Research studies have shown that, compared to control healthy people, a reduction of Prevotellaceaeis associated with an increase of pro-inflammatory species like Enterobacteriaceae among PD patients[85]. With these changes in microbial ecology, the production of certain short-chain fatty acids-like butyrate, essential for controlling inflammation and maintaining the integrity of the gut as well as the brain, is found to be decreased. This decrease in the quantities of such beneficial SCFAs is associated with neuroinflammation, especially within PD[86]. Besides this, gastrointestinal symptoms in patients with PD occur early[87]. They often occur even years before the onset of motor symptoms such as constipation. The study uses targeted therapy like probiotics, diet intervention, and polyphenols to modulate the gut microbiota and probably reduce the aggregation of alpha-synuclein.

Multiple Sclerosis

This link between the gut microbiota and MS has been found to possess immune-modulating functions. The changed gut microbiota profiles noted in most MS patients are characterized by reduced levels of short-chain fatty acids, such as butyrate and propionate, which are crucial in regulating T-cell responses[88]. Dysbiosis results in increased levels of pro-inflammatory T-helper 1 (Th1) and Th17 cells, causing increased blood-brain barrier permeability and neuroinflammation[89]. SCFAs, in contrast, increase the population of the regulatory T cells, and consequently, inflammation is lessened while maintaining the integrity of BBB[90]. The modulation of gut microbiota by SCFAs supplementation has been very promising in lowering MS relapse rate and stabilizing disease progression.

Stress:

Multiple direct and indirect pathways are responsible for the gut microbiome that can influence the GBA. These pathways include endocrine (cortisol), immune (cytokines), and neural (vagus and enteric nervous system) routes[91]. The brain also uses these mechanisms to affect the gut microbiome composition, particularly under stress. The hypothalamus-pituitary-adrenal axis regulates cortisol secretion, which can impact immune cells and cytokine secretion both locally in the gut and throughout the body[92]. Additionally, it can also alter gut permeability and barrier function, and change gut microbiota composition. Conversely, the gut microbiome and probiotics can modify circulating cytokine levels, significantly affecting brain function. The vagus nerve and changes in systemic tryptophan levels are key in relaying the influence of the gut microbiome on the brain[93]. Moreover, short-chain fatty acids (SCFAs) which are neuroactive bacterial metabolites of dietary fibers, can also alter brain function and behavior[94].Adrenocorticotropic hormone (ACTH) and Corticotropin-releasing factor (CRF) are also involved in these processes[95].

Depression:

Depression is accompanied by an increase in proinflammatory cytokines and gut microbiota composition alternation in both human subjects and animal depressive patterns[96]. In cases involving depressive patients, the level of Proteobacteria and Bacteroidetes rose, while that of Firmicutes decreased[97].

A recent study has shown that feeding healthy male Balb/C mice the probiotic Lactobacillus rhamnosus (L. rhamnosus) decreased depressive-like behavior. The probiotic-treated mice showed increased entries into the open arms of the Elevated Plus Maze (EPM), spent less time immobile in the Forced Swim Test (FST), and had more entries and spent more time in the center of the Open Field Test (OF)[98]. Another experiment they performed involved using adult rats that had a history of separation from their mothers when they were young. Such rats tend to be depressed. Treatment with probiotics like Bifidobacterium infantis, or B. infantis, reduced depressive-like

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behavior[99]. L. rhamnosus and B. infantis, along with other probiotics, are a likely course of treatment for depression as an alternative or supplement to the prevailing mainstream procedures or treatments.

Conclusion and Future Prospects of Probiotics and Gut Microbiota Research

The area of gut microbiota has witnessed unprecedented growth with the advent of new technologies like multi-omics, i.e., metagenomics, metabolomics, and metatranscriptomics. These have added depth to host-microbiome interaction and correlation with metabolic, autoimmune, and neurological disorders. Such large-scale studies like the Human Microbiome Project, though sample size and cost constrained, attempt to overcome these.

Therapies like microbiota therapies with probiotics have been promising on clinical outcomes but have issues like antibiotic resistance. Some like Lactobacillus rhamnosusare antibiotic-resistant, and gene transfer to pathogen bacteria is feasible. To avoid these, the strain selection has to be made judiciously and genomically screened. Probiotic preparations like Saccharomyces boulardii are also being tested for the prevention of antibiotic-associated diarrhea.

The inclusion of microbiome data in personalized medicine is a reality in the future. This renders personalized therapy based on the microbiota profile of a person based on probiotics, prebiotics, and dietary manipulation a reality. Computational technologies will also aid clinical decision-making; however, cost-effective diagnosis, confidentiality of data, and ethics need to be addressed.

Personalized microbiota-based therapy like fecal microbiota transplantation (FMT) could cure conditions like autoimmune diseases and neurodegenerative diseases. Though promising, such therapy is beset by issues of safety complications, heterogeneity of response, and ethics like consent and security of data. Risk-benefit analysis would have to be done for safe and effective use.

AI and high-throughput sequencing will enhance microbiota research and make microbiome-based therapy scalable. The complex role of gut microbiota and human health, however, remains to be elucidated. Multidisciplinary research will have to be conducted to unlock the full therapeutic potential of microbiota-based therapy.The future will rely on science and technology innovation to bridge microbiome science to the clinic, promoting patient health and well-being.

Conflict of Interest:

The author declares no conflict of interest related to this review.

Author's Contribution:

The author is responsible for the conception, design, literature review, writing, and editing of this manuscript.

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