Role Of Gut Microbiome In Shaping The Landscape Of Neurological Disorders: A Comprehensive Review

Abdullah Faleh Alharbi[1]*, Aqeel Hamad Albaiji[1], Najah Suliman Albaiji[1], Farhan Hameed Albaiji[1], Ebtesam Hamad Albaiji[1], Salma Matar Alanazi[1], Abdullah Eissa Ali Al-Saheeh[2], Mustafa Ali Alwahamed[2], Dawood Salman AL Uthman[2], Yousef Ali Alsalem[2], Fadel Waheb Al Ali Salem[2], Bader Ahmed Alshagageeg[2], Salah Mahmoud Alabbasi[3], Ibrahim Ahmed Alshehri[3], Mohammed Mahmoud Alabbasi[3]

[1]Directorate of Health Affairs, Hafar Al Batin-39921, Kingdom of Saudi Arabia
[2]Al-Ahsa Health Cluster, Ministry of Health, Rashdiah Street, PO. Box 12944, Al-Ahsa- 31982, Kingdom of Saudi Arabia
[3]Directorate of Health Affairs Jeddah, Al-Rehab, Jeddah-23344, Kingdom of Saudi Arabia
*Corresponding author
E-mail: abdullahfa2@moh.gov.sa (Abdullah Faleh Alharbi)
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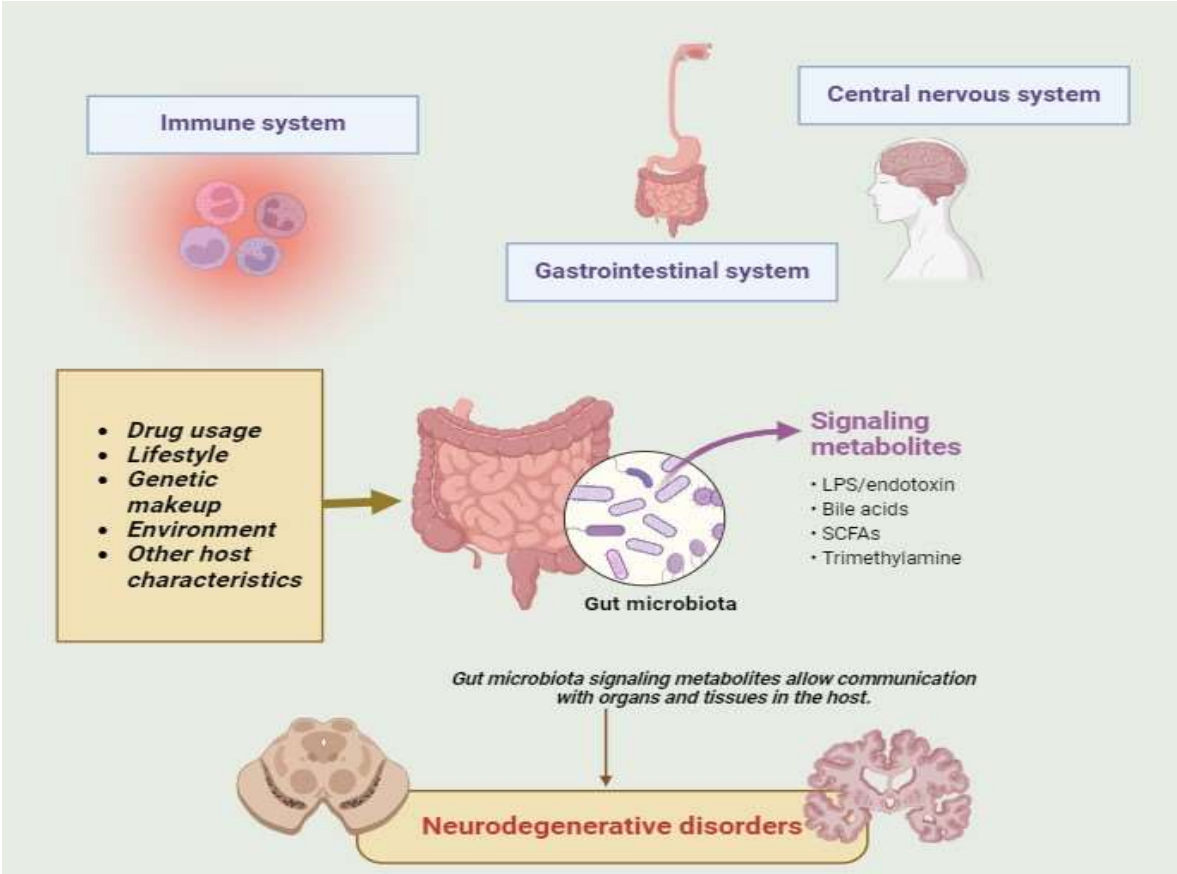
Abstract

The microbial community that makes up the human microbiome has a significant impact on the immune system, central nervous system, and gastrointestinal tract. These microbes, which are derived from both maternal and external sources, are mostly found in the GIT and are important for metabolism and development. Drug usage, lifestyle, environment, and host genetics all affect the makeup of the gut microbiota. An imbalance in gut microorganisms known as dysbiosis is increasingly associated with neurological conditions, highlighting new treatment opportunities. Novel investigations regarding the function of gut microbiome in disorders like epilepsy, Parkinson's, schizophrenia, Alzheimer's, autism, and stroke are promising. Recent research highlights the critical role of gut microbiota in the two-way communication between the gut and the brain, which influences behaviour, neural

development, and the development of neurological disorders. Although research on animals has improved our knowledge, clinical data points to the its possible involvement as a risk factor for neurological conditions. Extensive study investigates the potential impact of gut microbiome beyond gastroenterological diseases, including psychiatric disorders. This review explores the many routes involved in the communication between the nervous system and the gut bacteria, shedding light on the complex relationships between these two systems. It looks at changes in the microbiome and how they relate to neurological diseases and psychiatric illnesses.

Keywords: Gut microbiome; Neurological diseases; Neurodegenerative diseases; Psychiatric diseases, Gut-brain axis; Dysbiosis.

Graphical Abstract:



1. Introduction

The gut microbiome is a complex community of microbes living in the gastrointestinal system which coordinates a symphony

of biochemical reactions vital to human function. This sophisticated ecosystem of fungi, bacteria, and viruses plays a crucial role in maintaining the delicate balance that governs health [1]. The gut microbiota plays a complex role in immunological responses, food absorption, and even brain functioning, in addition to its role in digesting. This microbial environment and the host are intricately linked; they influence each other's metabolic processes, control inflammation, and alter how the body reacts to outside stimuli [2]. The complexity of the gut microbiome, as a field of complex symbiosis, is still being discovered. It presents an intriguing picture of how microbial variety interacts with human health in ways that go beyond current knowledge. The complex ecosystem of the human gut microbiome is essential for promoting communication between the environment and the human host. The relationship between common non-antibiotic drugs and gut microbes is complex and mutualistic: drugs can affect the gut microbiome composition, and the gut microbiome can affect a person's drug response by enzymatically changing the structure of the drug, which can impact the drug bioavailability, bioactivity, or toxicity, popularly known as pharmacomicrobiomics [3].

1.1 Gut microbiome: Historical Significance

Early in the 20th century, Russian scientist Eli Metchnikoff of the Pasteur Institute in Paris carried out groundbreaking studies linking the extraordinary longevity of rural Bulgarians to their regular consumption of fermented milk products. The theory put forth by Metchnikoff was that the lactic acid bacteria, known as "Lactobacillus bulgaricus," found in the fermented milk products these people who endured harsh weather and hard times economically ingested provided an anti-aging benefit that explained why they lived longer than other Europeans [4]. After conducting extensive research, Metchnikoff postulated that consuming fermented milk products could introduce good bacteria into the gastrointestinal tract to counteract harmful bacteria and increase longevity.

Interestingly, he was the first scientist to suggest that good bacteria may be substituted for toxic ones in order to manipulate the gut microbiome. With this groundbreaking breakthrough in immunity, Metchnikoff was awarded the coveted Nobel Prize in 1908 [5]. The subsequent 1928 discovery of penicillin by Scottish biologist Sir Alexander

Fleming signalled a significant change in research focus from using bacteria for therapeutic purposes to investigating derivatives of soil fungi for their antibacterial capabilities. In the golden age of antibiotic discovery, which lasted from 1940 to 1960, most antibiotics were discovered by screening actinomycetes that were obtained from soil. But when the profits on this conventional platform for discovery diminished, the trajectory of new antibiotic discoveries moved in the direction of synthetic molecules [6].

1.2 The composition of gut microbiome

Along the digestive tract, there are variations in the microbial composition of the gut microbiota. A comparatively limited variety of bacterial species are found in the stomach and small intestine [7]. On the other hand, the colon supports a highly populated microbial environment, with roughly 10^12 cells per gramme of intestinal material [8]. There are between 300 to 1000 distinct species in this microbial community, yet only about 30 to 40 species account for 99 percent of the total [9]. It is noteworthy that bacteria make over 60% of the dry bulk of excrement, indicating how common they are in the digestive system. Although they coexist with viruses, protists, fungi, and archaea in the gut flora, little is known about their functions [10]. The gut microbiota is characterised by the high concentration of anaerobic bacteria, which make about 99 percent of the bacterial population [11]. The cecum is notable for having large densities of aerobic microorganisms. Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria are the predominant bacterial phyla found in the human gut. Bacteroides, Clostridium, Peptococcus, Bifidobacterium, Eubacterium, Ruminococcus, Faecalibacterium, and Peptostreptococcus are the most common bacterial genera [12]. Among them, Bacteroides stands out as the most prevalent genus, accounting for about 30% of the total population of gut bacteria. According to Ann and Fergus, this prominence indicates the genus's important involvement in the physiological processes of the host organism [13]. There are several advantageous health effects of the metabolites produced from the gut microbiome, several of which are enlisted under Table 1.

Table 1: A summary of some of the metabolites derived from the gut microbiota and their beneficial health effects.

Metabolic pathway	Metabolite	Microbial agent	Beneficial health effects
Lipid metabolism/ Linoleic acid derivative [14, 15]	10-hydroxy-cis-12-octadecoate	Lactobacillus	Decreased inflammation; maintains the intestinal barrier function; and produces a higher level of intestinal IgA.
Tryptophan metabolism [16-21]	Indole-3-propionate	Clostridium sporogenes	Maintains the intestinal barrier function and mucosal homeostasis; increases the production of antioxidant and neuroprotectants.
	Indole-3-aldehyde	Lactobacillus	Maintains mucosal homeostasis and intestinal barrier function through an increased IL-22 production; protects against intestinal inflammation – reported in colitis mouse models.
	Indole	Lactobacillus	Maintains host-microbe homeostasis at the mucosa, through IL-22 production.
		Bifidobacterium longum	Enhanced barrier function.
		Bacteroides fragilis	Modulates the host metabolism.
Carbohydrate metabolism [22-30]	Propionate	Blautia obeum	Colonic inflammation suppressed.
		Coprococcus catus	Decreases the microbial simulation-associated immune responses.
		Rosebruia inulinivorans	Protects from allergic airway inflammation.
		Prevotella copri	Studies in obese mice have shown improved results in weight control and insulin sensitivity.
	Butyrate	Clostridia	Enhanced intestinal barrier function.
		Faecalibacterium prausnitzii	Modulation of intestinal macrophagic function.
		Coprococcus catus	Colonic inflammation is suppressed.

		Anaerostipes hadrus	Enhanced insulin sensitivity.

1.3 Gut-brain axis

Interactions between the stomach and brain in reciprocity control vital physiological and homeostatic processes, including eating habits, immunological response, and sleep cycles [31]. Over the past ten years, there has been a notable progress in understanding the pathophysiology of gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome (IBS). However, there is still disagreement about the relative contributions of central (spinal cord, brain) and peripheral (intestine) mechanisms to symptom manifestation in these diseases. This lack of clarity also applies to other commonly coexisting disorders such as functional abdominal and functional chest pain. All agreed upon, however, is that the pathophysiology of persistent abdominal pain can be understood as a disturbance in the interaction between gut signalling events, enteric microbiota, enteric nervous system (ENS), and central nervous system (CNS). Changes in immunological response, mood, visceral sensitivity, gut motility, and regional transit are correlated with this dysregulation [32, 33]. Preclinical studies have revealed at least three communication routes and revealed potential signalling molecules by robustly demonstrating reciprocal connections between the gut, brain, and gut microbiota [34]. This complex communication dynamics are nonlinear, bidirectional, and involve several feedback loops. They also probably involve interactions across a variety of channels. Disturbances in the connections between the gut, brain, and microbiota have been observed in rat models that mimic different neurological, psychiatric, and digestive illnesses [35].

Understanding the traditional gut-brain (GB) axis has undergone a paradigm shift in the last 15 years due to the fast growth of microbiome science. This change adopts a systems biology viewpoint and clarifies the complex two-way interactions that occur within the gut–brain–microbiome (GBM) connections [36]. This all-encompassing paradigm goes beyond the brain-gut axis to include dynamic interactions between the gut microbiota, the enteric nerve system (ENS), the enteric neuroendocrine system, and the gut-associated immune system. This revised conceptualization of GB connections has influenced not only how we understand gastrointestinal problems but also how many other brain

disorders that were previously thought to be purely brain-confined processes are pathophysiologically caused [37]. Findings from preclinical and clinical research have opened up the possibility of using the gut microbiota as a therapeutic target for conditions with changed GB interactions, diseases that were previously known as functional GI disorders. Furthermore, the potential encompasses neurological and mental diseases, such as depression, anxiety, Parkinson's disease, Alzheimer's disease, and autism spectrum disorder, among others [38, 39]. **Figure 1** showed a brief representation of the gut-brain-microbiome system.

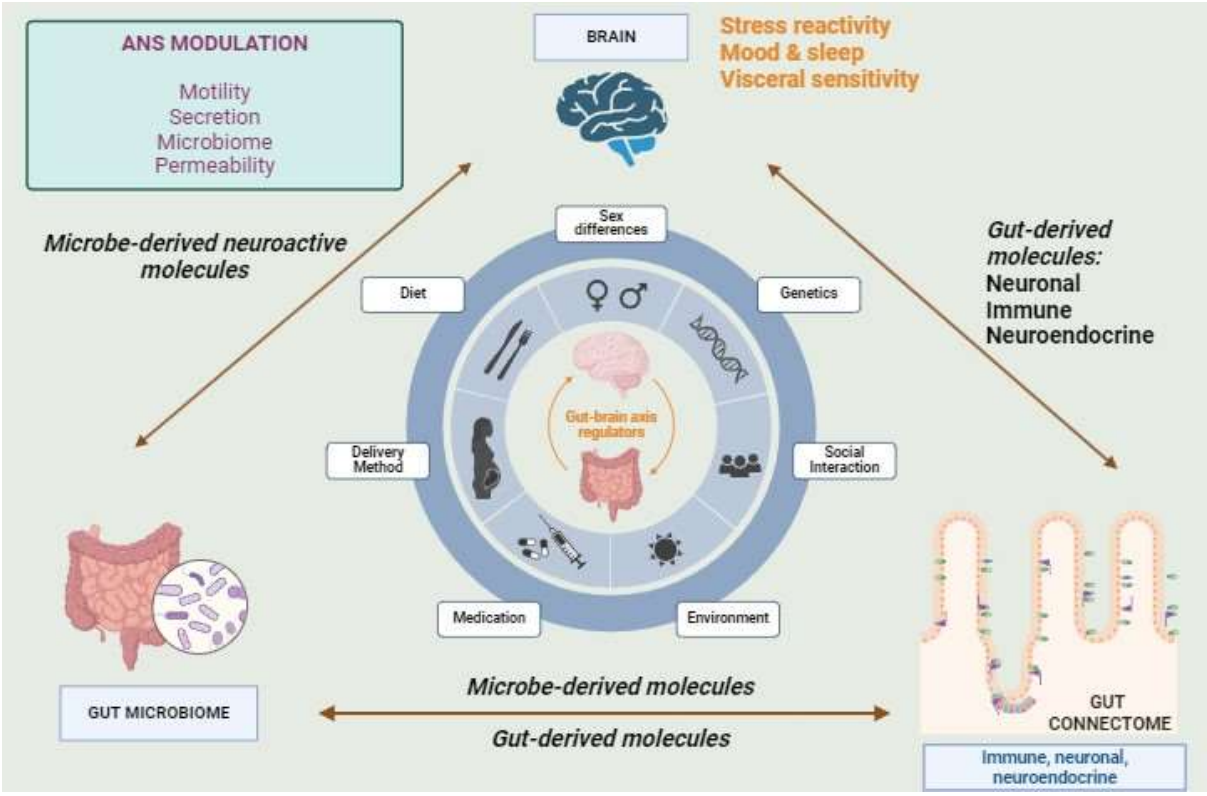


Figure 1: An overview of the gut-brain-microbiome (GBM) systems. The three nodes that comprise the GBM network are the gut microbiota, brain connectome, and gut connectome. A nonlinear system is created when several feedback loops and bidirectional edges link each node. In a similar vein, changes in the gut microbial ecology or direct brain modulation of the microbiome are possible.

2. Neurodegenerative Diseases: An Overview

Neurodegenerative diseases (NDs) are a broad category of complex disorders characterised by progressive degeneration and the slow loss of neurons in different parts of the nervous system [40]. NDs are becoming more common, which presents

a significant worldwide health concern. Although the exact cause of NDs is yet unknown, a complex interaction between genetic, epigenetic, and environmental variables is hypothesised. Effective therapeutic approaches that can impede, stop, or prevent the course of ND remain elusive despite substantial research efforts. Clarifying the molecular subtleties underlying ND development is therefore crucial [41]. Prominent examples in this category include amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD). These disorders are more common and their incidence rises sharply with age, indicating a predicted increase in cases as life expectancies rise in many areas. The exact etiological contributions from genetic and environmental variables are still mostly unknown, with a few significant exceptions. But molecular epidemiology techniques have become indispensable for improving disease diagnosis, defining prognostic markers, identifying susceptibility genes linked to familial neurodegenerative diseases, examining shared genetic variants possibly linked to random variants of these illnesses, and measuring exposure to the environment [42].

Alzheimer’s disease

Alzheimer’s disease is the most common neurodegenerative disease which puts a significant strain on people, families, and society at large. It is characterised by progressive cognitive decline, memory impairment, and disruptions in behaviour and thought processes. The need to relieve pain and provide hope for individuals impacted by this disorder is what motivates us to continue searching for effective interventions even as our understanding of the complex systems behind it changes [43]. Recent studies on the pathogenesis of Alzheimer's disease have highlighted the critical role that tau and amyloid-beta (Aβ) protein aggregation play in the its progression [44]. The accumulation of Aβ-containing plaques in the brain and the development of neurofibrillary tangles (NFTs) made of tau proteins that have been hyperphosphorylated are two of the disease's defining characteristics. These plaques cause disruptions to the hippocampus's circuitry, which hinders the short-term memories' consolidation into long-term traces [45, 46].

Widespread neuronal loss, abnormal synaptic connections, and malfunctioning of key neurotransmitter systems essential

for cognitive functions, most notably memory, are the hallmarks of AD. As a result, in the early stages of AD, selective memory impairment becomes the main clinical sign. Moreover, there is often impairment in functions that rely on the hippocampal and medial temporal lobe, such as declarative episodic memory. Furthermore, difficulties with problem-solving, poor judgement, and deficiencies in executive function frequently appear early in the course of the illness [47, 48].

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease, after AD. The neuronal inclusions known as Lewy bodies and Lewy neurites, along with cell loss in important brain areas like the substantia nigra, are the hallmark pathological feature of Parkinson's disease. Parkinson's disease is classified as a synucleinopathy because Lewy bodies are primarily composed of these aggregated and misfolded forms of α-synuclein proteins [49]. Braak et al. describe a pattern of Lewy pathology propagation that starts in the caudal brainstem and moves cranially through limbic areas, the upper brainstem, and finally ends in the neocortex. It should be emphasised that not all cases may see this kind of dispersion [50]. Recent research has produced strong evidence that the prion-like transfer of synuclein between cells and the promotion of synuclein templating are important processes that propel the development of illness [51]. The main clinical sign of Parkinson's disease is a motor condition characterised by bradykinesia, stiffness, and resting tremor, along with changes in gait and posture. These motor disabilities cause a slow reduction in functioning, which impedes the ability to carry out everyday tasks and lowers quality of life in general. While the traditional motor symptoms appear early and are essential components of current diagnostic standards, postural instability, increasing gait difficulties, and swallowing and speech difficulties hasten the process of motor weakness [52].

Although movement disorders are the main characteristic of Parkinson's disease, the condition also includes a range of non-motor symptoms (NMS) that are present in almost all affected individuals. Olfactory dysfunction, constipation, urinary abnormalities, orthostatic hypotension, discomfort, mental disorders, and sleep disturbances are some of these symptoms [53]. While the degeneration of substantia nigra and dopamine depletion in the striatum are thought to be the causes of the conventional motor manifestations of Parkinson's disease,

NMS are most likely the result of neurodegeneration affecting other anatomical locations, such as the peripheral autonomic nervous system. Although these non-motor symptoms may cause anguish to some patients, observational studies indicate that they are generally modest in most cases, with intensity commonly increasing over time. These symptoms often appear early in the course of the disease. Non-motor symptoms are a major burden that reduces quality of life and raises overall healthcare costs when they persist throughout the course of Parkinson's disease. Remarkably, in people with advanced Parkinson's disease, cognitive deterioration and hallucinations appear to be common triggers for hospitalisation and institutionalisation [54, 55].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting the central nervous system, which has an extremely difficult diagnosis. Due to its rarity, doctors frequently diagnose more prevalent illnesses before ALS, which causes delays in ALS diagnosis. On the other hand, new knowledge about the various clinical signs of ALS, such as behavioural abnormalities, helps with better early identification. Further developments that could speed up diagnostic procedures include the discovery of genetic predispositions and the development of new diagnostic criteria. With regard to prognosis, our growing understanding of ALS as a multisystem illness with behavioural changes and cognitive impairment has significant consequences for providing care and making end-of-life decisions. Moreover, new prognostic models, scales, and scoring systems have emerged, offering ALS patients and their doctors better understanding of how the disease is progressing [56].

A combination of dysfunction affecting both upper motor neurons (UMN) and lower motor neurons (LMN) that affect portions of the bulbar, cervical, thoracic, and/or lumbar regions is the hallmark of ALS [57]. As a result, the voluntary skeletal muscles necessary for breathing, speaking, eating, and limb movement gradually weaken and present a variety of clinical manifestations [58]. The sphincter and extraocular muscles have historically been spared, although autonomic dysfunction in ALS is becoming more widely recognised, as evidenced by symptoms including incontinence and urgency in the urine [59, 60]. Clinically, weakness usually follows an anatomically continuous pattern, spreading contralaterally and

progressively in both rostral and caudal directions. According to a recent assessment of ALS patients, 85 percent of them reported a localised start in one body segment that proceeded contralaterally to adjacent anatomical parts. There was less frequent disease transmission to non-contiguous parts [61].

Huntington's disease

Huntington's disease (HD) is a rare genetic neurodegenerative illness that causes progressive movement deficits, cognitive decline, and mental symptoms. Although a diagnosis can happen at any time in life, it usually shows up in middle adulthood. During its early stages, people often retain some degree of independence while displaying modest executive function difficulties, melancholy, and involuntary movements. Nevertheless, help is required when the illness worsens [62]. Patients may become unable of operating a vehicle or maintaining employment, and their inability to solve problems and coordinate their movements may worsen, increasing their risk of falling. Later stages of HD can cause a person to lose their capacity to communicate due to increased involuntary movements and less voluntary motor control, as well as make them immobile and require feeding tubes [63]. In addition, at this stage of the disease's course, severe dementia frequently affects all cognitive processes. After symptoms appear, the median survival is about 18 years, and infections, most notably aspiration pneumonia are the leading cause of death [64].

HD is caused by the growth of a cytosine-adenine-guanine (CAG) trinucleotide repeat in the coding domain of the HD gene, which is located on chromosome 4p16.3. HD is inherited autosomally dominantly. The huntingtin protein (HTT), which is expressed in many bodily tissues, including the central nervous system (CNS), is encoded by the HD gene. It is involved in important cellular processes as protein trafficking, vesicle transport, and selective autophagy, even if its exact roles are still unclear [65]. The CAG sequence becomes unstable when it exceeds the normal range of 6–26 repeats and may continue to grow in future generations, especially through paternal transmission. There are rarely any clinical symptoms seen in the middle range, which extends from 27 to 35 repetitions. While full penetrance is not apparent until 40 repeats are present, the threshold for HD onset is generally thought to be 36 repeats and above. Furthermore, a higher number of CAG repeats is linked to a faster pace of illness progression, an earlier beginning of the disease, and a more severe form of the

disease. Additionally, the genesis and course of HD may be influenced by additional factors, including as genetic predispositions and environmental factors [66, 67].

Spinal muscular atrophy

A collection of hereditary diseases known as spinal muscular atrophy (SMA) are distinguished by the degeneration of anterior horn cells, which causes atrophy and weakening in the muscles. Approximately 95% of cases with SMA are of the most common variety, which is caused by an autosomal recessive disorder resulting from a homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. In an extensive multi-ethnic investigation, the total carrier frequency was determined to be one in 54, with an incidence rate of one in 11,000, to evaluate the viability of high-throughput genetic testing for SMA carriers [68]. Based on the age at which symptoms first appear and the maximum motor function attained, clinical characteristics of SMA are divided into four main phenotypes, each of which has a wide range of severity [69]. Although there is still no treatment for SMA, pre-clinical models and a wide range of possible therapeutic approaches have been made possible by developments in our understanding of the disease's molecular genetics [70, 71].

Muscle weakness and atrophy are the main clinical characteristics of SMA; these usually manifest as symmetric weakness that affects proximal muscles more than distal groups, similar to NP7 (Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS). Reports published over the previous 125 years have continuously highlighted anterior horn cell degeneration as the primary pathology along with prominent clinical symptoms such proximally predominant, symmetrical weakening of the limbs affecting the axial, intercostal, and bulbar muscles [72]. During an International Consortium on Spinal Muscular Atrophy, which was supported by the Muscular Dystrophy Association (MDA), these diverse phenotypes were formally arranged into a classification system in 1991 [73]. Based on the age of onset and the greatest level of motor function attained (such as sitting or standing), this classification distinguished three SMA kinds. Subsequent improvements included type 0 for patients with prenatal onset and death within weeks, type 4 for cases with adult onset, and subdivisions within type 3 based on age of onset [74, 75]. Even with the intrinsic heterogeneity in severity within a single type and the difficulty

of accurately classifying up to 25% of patients, this classification scheme is still relevant in the genetic era and provides useful information for prognosis and clinical management [76].

3. Chemical Signaling between the Gut and the Brain

The network of communication that runs both ways between the brain and the gastrointestinal system is known as the gut-brain axis (GBA). Neural, hormonal, and immunological signaling are just a few of the complex pathways involved in this system that are essential for preserving homeostasis and affecting behavior and thought processes. One significant component of the GBA is the vagus nerve, a long cranial nerve that connects the brainstem to the gut [77]. Through this pathway, signals originating in the gut can travel to the brainstem and then to higher brain regions, influencing processes such as appetite regulation, mood, and stress response. Furthermore, millions of bacteria living in the gastrointestinal tract, known as the gut microbiota, also play a role in gut-brain communication. These microorganisms create short-chain fatty acids (SCFAs), which can influence mood and behavior, as well as neurotransmitters including serotonin and gamma-aminobutyric acid (GABA) [78].

There is growing recognition of the role of the GBA in neurodegenerative illnesses like PD and AD. Research has indicated that these disorders are associated with modifications in the makeup and function of the gut microbiota. The pathophysiology of neurodegenerative illnesses is linked to neuroinflammation, oxidative stress, and neuronal damage, all of which may be facilitated by dysregulation of the GBA. Furthermore, new research indicates that therapies including probiotics, prebiotics, and dietary changes that target the gut microbiota may be therapeutically useful in the treatment of neurodegenerative illnesses. These therapies have the potential to improve cognitive function and mitigate the course of disease by restoring microbial balance and altering gut-brain connection [79]. **Figure 2** represents a brief functioning and interaction of the gut-brain-axis and shows the gut-neurotransmitter signaling. **Table 2** showed some examples of the involved gut microbiota in neurodegenerative diseases.

Table 2. Representation of the gut microbiome involvement in neurogenerative disease.

Genus of Bacteria	**Mechanism/Pathway involved**	**Manifested Neurogenerative disease**
Hydrogen-producing bacteria	Reduced dopaminergic loss	Parkinson's disease
Clostridium, Bacteroides, Prevotellaceae	NA	
Enterobacteriaceae	Curli, α-synuclein aggregation	
Pseudomonas	Fap, α-synuclein change	
Roseburia, Faecalibacterium	SCFA production	
Coriobacteriales, Erysipelotrichales, Bacteroidales, Burkholderiale	NA	Huntington disease
Bifidobacterium	Regulates cortical excitability and neural excitation-inhibition	Alzheimer's disease
Proteobacteria, Bacteroidetes, Firmicutes, Actinobacteria, Lachnospiracea	NA	

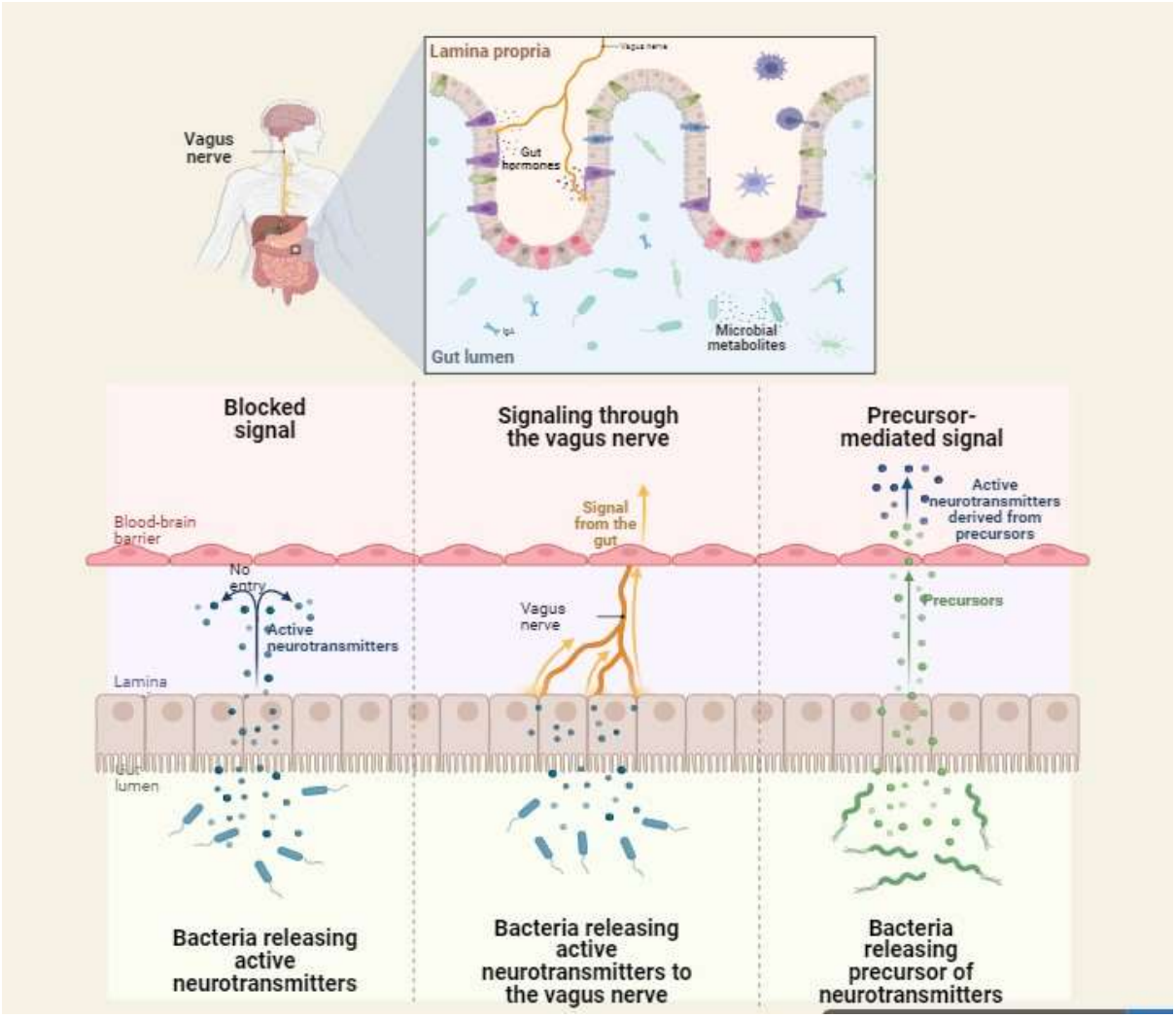


Figure 2. A diagrammatic representation of the gut-brain-axis in a simplified version along with a descriptive pictorial depiction of gut-neurotransmitter signaling. The gastrointestinal tract (the gut) and the central nervous system (the brain) communicate with each other in both directions through a network known as the gut-brain axis. It involves intricate relationships between the immune system, neural system, and gut bacteria, all of which have an impact on mood, cognition, and digestion, among other aspects of health. This axis, which is influenced by a number of variables including nutrition, stress, and drugs, is essential for preserving homeostasis.

4. Role of Microbiome in Neurodegeneration: A Gut Feeling

4.1 Alzheimer's disease

Changes in the diversity of important microbiota groups, including Lactobacilli, Bacteroides, and Prevotella, as well as an increase in the quantity of Ruminococcus, Atopobium, and

Enterobacteriaceae, are associated with host vulnerability. Fascinatingly, these microbial communities have been linked to the host's behaviour and mood, which are known to affect cognitive performance [80]. Research has shown that the gut microbiota makeup of persons with Alzheimer's disease differs from that of healthy people, with Bacteroidetes being more prevalent and Firmicutes, Proteobacteria, and Actinobacteria being less prevalent. Likewise, compared to healthy controls, mice with cognitive impairment similar to AD patients showed clear alterations in the makeup of their gut microbiota, including a reduction in the correlation density and clustering of operational taxonomic units. Furthermore, compared to wild-type mouse models, mice that replicated AD pathology showed comparable changes in the microbiota composition, with higher abundances of Proteobacteria and Erisilopelotrichaeae [81].

Moreover, it has been demonstrated that changes in the variety of the gut microbiota brought on by antibiotic therapy in AD mice models have an impact on amyloidosis and neuroinflammation. Transplanting fecal microbiota (FMT) has become a promising treatment and research avenue for neurodegenerative diseases. Research has indicated that the introduction of FMT from healthy donors into transgenic mice with AD pathology-like traits can successfully mitigate Aβ pathology, neurofibrillary tangles, and cognitive deficit [82]. On the other hand, compared to FMT from healthy donors, FMT from Alzheimer's disease patients or mice models with cognitive impairment to germ-free mice aggravated cerebral Aβ pathology and cognitive impairment. Similarly, glial cell reactivation and amelioration of cognitive impairments were observed upon repeated FMT from healthy wild-type mice to transgenic animals with AD pathology-like characteristics. Changes in microbiological molecules are important in the development of AD, especially when it comes to disturbances in the GBA. Among the major microorganism-associated molecular patterns (MAMPs) linked to AD pathogenesis are lipopolysaccharide (LPS), peptidoglycan (PGN), bacterial DNA, bacterial epigenetics, and bacterial amyloids. Amyloid-beta (Aβ) deposition and neuronal death are caused by microglial activation mediated by the CD14 receptor, which is sometimes referred to as the LPS receptor. Cognitive impairment is correlated with higher levels of LPS in brain areas such as the neocortex and hippocampus in people with AD. Research on

animals has shown that LPS exacerbates AD symptoms by causing neuroinflammation and cognitive decline [83].

Gram-negative bacterial cell walls contain peptidoglycan, which can cross the blood-brain barrier (BBB) and interact with innate immune receptors to affect social behaviours and gene expression. Additionally linked to the pathophysiology of AD, bacterial DNA has been demonstrated in vitro to be able to cause Aβ misfolding and Tau aggregation. Different bacteria species secrete bacterial amyloids, which can pass through the BBB via GBA routes connected to NDs. In animal models, these amyloids exacerbate Aβ pathogenesis and cognitive impairment through their interaction with Aβ nanofibrils. Another class of microbial metabolites that has gained attention as possible therapeutic targets in AD is short-chain fatty acids (SCFAs). In vitro, it has been demonstrated that SCFAs prevent Aβ aggregation and shield neuron cells from Aβ-induced neurotoxicity. When comparing AD animal models to wild-type mice, altered SCFA levels point to a dysregulated gut microbiota and SCFA metabolism linked to AD pathogenesis. To clarify the particular methods by which microbial molecules work, more investigation is required [84, 85].

4.2 Parkinson's disease

The loss of dopaminergic neurons in the midbrain substantia nigra pars compacta (SNpc) area is a common pathology seen in Parkinson's disease (PD), and it largely causes motor impairment. The existence of Lewy bodies, which are intracellular aggregates made of insoluble alpha-synuclein (α-Syn) proteins, is intimately associated with this neuronal degeneration [86]. Six phases have been identified in the development of Lewy pathology in PD, and the data points to a gastrointestinal genesis for the disease before it spreads to the brain. Due to its possible impact on the onset and course of the disease, the gut microbiome's role in PD has drawn interest. Research has demonstrated that PD patients differ from healthy individuals in terms of metabolites and microbial diversity. More specifically, Lactobacillaceae, Barnesiellaceae, and Enterococcacea are more prevalent in PD patients compared to Clostridium coccoides, Bacteroides fragilis, and Prevotellaceae. Furthermore, increased intestinal permeability and bacterial overgrowth in the small intestine are common in PD patients [87]. The important involvement of gut microbiota in Parkinson's disease manifestation is highlighted by experimental findings from α-Syn-overexpressing (ASO) mice

models. When compared to mice receiving fecal transplants from healthy persons, mice receiving fecal transplants from PD patients showed worsened motor symptoms. Furthermore, a case study describing the transplantation of FMT from a healthy donor to a patient with PD shown a transient improvement in leg tremors and other PD symptoms, indicating a promising treatment approach that warrants additional investigation. Changes in gut-derived microbial compounds are becoming more widely acknowledged as important markers of PD, similar to AD. LPS is a key player in the pathophysiology of PD, as exposure to intraneural LPS causes microglial activation and dopaminergic neuron loss. Mice models have provided experimental evidence that the modulation of microglial nicotinamide adenine dinucleotide phosphate oxidase expression by LPS causes mitochondrial malfunction, which intensifies the neurotoxic consequences. Notably, LPS injection is frequently used in animal models to cause PD-like disease in order to conduct research. PRRs bind to PGNs, which are unique bacterial ligands that the host immune system recognizes as foreign substances. PGN recognition protein genes may be involved in the dynamics of the gut microbiota and gut homeostasis, according to recent studies on these genes [88].

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4.3 Amyotrophic lateral sclerosis

Research and interest in the connection between the gut microbiota and Amyotrophic Lateral Sclerosis (ALS) are expanding. Lou Gehrig's disease, also referred to as ALS, is a

progressive neurological illness that affects the brain and spinal cord's motor neurons. Although the precise origin of ALS is still unknown, new research points to the gut microbiota as a potential factor in the onset and progression of the disease [90]. Numerous investigations have documented modifications in the makeup and variety of gut microbiota in individuals with ALS in contrast to those in good health. These alterations include variations in the abundance of particular bacterial species as well as dysbiosis, or imbalance, in the gut microbial population. Furthermore, research using mice models of ALS has demonstrated that modifications to the makeup of the gut microbiota can impact the onset and course of the disease, pointing to a possible link between the pathophysiology of ALS and gut dysbiosis. Although a number of theories have been put up, the processes underlying the connection between the gut microbiota and ALS are still not entirely known [91].

Dysbiosis in the gut microbiota may, for example, result in increased intestinal permeability, which would allow pathogenic bacteria or their metabolites to enter the circulation and set off immunological reactions that would otherwise contribute to neuroinflammation and degeneration of motor neurons. Furthermore, the survival and function of neurons may be influenced, either directly or indirectly, by microbial compounds generated by gut bacteria. Moreover, a key role in the pathogenesis of ALS is believed to be played by the GBA, a bidirectional communication mechanism between the stomach and the central nervous system. This axis is disrupted, and disruptions may be caused by changes in the gut microbiota. These changes may then transmit neuroinflammation and neurodegeneration from the gut to the central nervous system, aggravating symptoms of ALS [92]. Overall, new research indicates that addressing the gut microbiota may offer a unique therapeutic strategy for ALS, even though the precise mechanisms by which the gut microbiome affects the disease are yet unknown. In order to improve patient outcomes and maybe halt the progression of the disease, more research is required to fully understand the role of the gut microbiome in ALS and to develop tailored therapies focused at modifying gut dysbiosis. Table 3 represents some exemplary human studies revealing the role of microbiome in ALS.

Table 3: Various studies on the role of microbiome in ALS.

Study	**Methodology**	**Key Findings**

Evaluation of the Microbial Diversity in Amyotrophic Lateral Sclerosis Using High-Throughput Sequencing [93]	Extracted genomic DNA and high-throughput sequencing	There was a considerable increase in bacteroidetes, bacteroidia, bacteroidales, and dorea in ALS patients. Oscillibacter, Anaerostipes, and Lachnospiraceae were significantly lower in ALS patients than in controls.
The fecal microbiome of ALS patients [94]	Nucleic acid extraction, qRT-PCR, and analysis of 16S rRNA sequencing	Different proportions of Ruminococcaceae
Gut inflammation and dysbiosis in human motor neuron disease [95]	Stool samples collected, bacterial and mycological cultures, mass spectrometry, enzyme immunoassay, commensal bacteria PCR	ALS patients 1, 3, and 5 had low levels of Firmicutes/Bacteroidetes ratio, low levels of Ruminococcus spp., low levels of Clostridium spp. and Roseburia spp., high levels of Bacteroides-Prevotella, Odoribacter spp., Barnesiella spp., and Bacteroides vulgatus, and high levels of Bacteroides vulgatus in patient 3.
The alteration of gut microbiome and metabolism in amyotrophic lateral sclerosis patients [96]	16s rRNA sequencing; Metabolism analysis; Shotgun sequencing (using 10 ALS patients and 10 controls).	Higher concentrations of unclassified Porphyromonadaceae, Mannheimia, Odoribacter, Sporobacter, Parabacteroides, Kineothrix, Eisenbergiella, and Bacteriodetes in ALS patients. ALS patients

		had a much lower number of Firmicutes and Megamonas than control patients.
Progression and survival of patients with motor neuron disease relative to their fecal microbiota [97]	Whole-body composition and resting energy expenditure measurements, DNA extraction, faecal sample collection, and 16s rRNA amplicon sequencing	The distribution of bacteria, protobacteria, and F/B did not significantly change between ALS patients and controls. Patients with ALS who had a faecal microbiome that was more varied and even in terms of richness and evenness fared worse from the start of their symptoms in terms of survival.
Assessment of bidirectional relationships between 98 genera of the human gut microbiota and amyotrophic lateral sclerosis: a 2-sample Mendelian randomizatio n study [98]	Mendelian randomization analysis, genome-wide association research, and discovery of independently significant SNPs	The unclassified Enterobacteriaceae OTU10032 was linked to an increased risk of ALS. Unclassified Acidaminococcaceae was linked to an increased risk of Alzheimer's disease. Gamma-glutamylphenylalanine was associated with a notably higher incidence of ALS. Three-methyl-2-oxobutyrate and 1-arachidonoyl-GPI are two metabolites linked to an increased risk of ALS. The risk of ALS may be reduced by a genetically predicted rise in 4-acetamidobutanoate

		levels. An increase in the relative abundance of OTU4607_Sutterella and Lactobacillales_order was linked to genetically predicted ALS.

4.4 Huntington's disease

The classical presentation of Huntington's disease is ultimately brought on by the aberrant growth of HTT, which leads to HTT malfunction in brain development, transcription, histone modification, and mitochondrial function. Even though the pathophysiology and symptoms of HD are clearly understood, there is currently no viable medication for either stopping the disease's progression or curing it [99].

There may be benefits to incorporating gut bacteria into the diagnosis and treatment of Huntington disease (HD) given that recent studies have linked gut microbiota to brain health. HD may be characterized by differences in the diversity or abundance of the gut microbiota, which may be impacted by gender differences. Male HD mice were shown to have lower amounts of Clostridiales and higher levels of Bacteroidales and Lactobacillales in their gut microbiota as compared to wild-type mice in a recent study. On the other hand, female HD mice showed lower levels of Clostridiales and higher levels of Coriobacteriales, Erysipelotrichales, Bacteroidales, and Burkholderiale [100]. In addition, microbial diversity was higher in male HD mice than in female or wild-type mice. In the prefrontal cortex of microbiota-deficient animals, a different study showed reduced amounts of mature oligodendrocytes and myelin-related proteins, which weakened callosal myelination and white matter plasticity. The aggravating role of microbiota deficit on internal HD symptoms was highlighted by this investigation. In addition to the correlation between HD and diversity of the gut microbiota, specific SCFAs and bioactive metabolites derived from the secretion of the gut microbiota have been linked to the start and progression of HD, mainly affecting processes in the GBA. Serotonin, tyrosine, 2-hydroxyphenylacetic acid, 3-hydroxyphenylacetic acid, and 4-hydroxyphenylacetic acid are examples of compounds that can upset the balance of bioactive compounds in the GBA and diet, whereas indole-3-propionic acid can damage intestinal

permeability. It is possible that more research on these metabolites originating from gut microbiota may clarify the complex relationship between gut microbiota and HD and provide guidance for early diagnosis and treatment approaches [101].

4.5 Spinal muscular atrophy

The relationship between the gut microbiota and Spinal Muscular Atrophy (SMA) is one of the newest research topics in the field of neurodegenerative diseases. Although mutations in the Survival Motor Neuron 1 (SMN1) gene are thought to be the primary cause of SMA, recent research has revealed possible connections between the gut microbiota and the development of the illness. Studies have suggested that the gut microbiota of people with SMA may differ from that of healthy people in terms of composition and diversity. These alterations may consist of variations in the abundance of particular bacterial species as well as dysbiosis, or imbalance, in the gut microbial community [102]. Additionally, research using animal models of SMA has demonstrated that alterations to the makeup of the gut microbiota can affect the course and severity of the disease, suggesting a possible involvement for the gut microbiome in the pathophysiology of SMA. Although various theories have been put out, the processes underlying the relationship between the gut microbiota and SMA are still not entirely known. One theory is that oxidative stress and systemic inflammation, which are known to be involved in the pathophysiology of SMA, could be exacerbated by dysbiosis in the gut microbiota. Furthermore, the microbial metabolites generated by gut bacteria have the ability to interact with host cells, impacting neuronal survival and function, and so potentially altering the course of a disease [103]. Furthermore, SMA may be influenced by the GBA, a system of reciprocal communication between the stomach and the central neurological system. Disruptions in this axis may be responsible for the neuroinflammation and motor neuron degeneration seen in SMA, and they may be mediated by changes in the gut microbiota [104].

All things considered, this data indicates that targeting the gut microbiota may offer a unique therapeutic approach for this debilitating condition, even though more investigation is required to clarify the precise processes by which the gut microbiome regulates SMA. For those with SMA, modifying gut dysbiosis and encouraging a balanced composition of the gut

microbiome may slow the course of the disease and enhance quality of life.

5. Conclusion and Way Forward

Neurological disorders (NDs) are systemic illnesses spanning multiple fields, such as microbiology and neurology. The relationship between gut microbiota and brain function, neurological processes, and cognitive behaviors has been highlighted by a wealth of evidence from preclinical, clinical, in vitro, and in vivo studies. Nevertheless, limited sample sizes impair the validity of many investigations. Due to varying microbial profiles and the majority of experiments use animal models, the influence of microbiota on ND pathophysiology in faecal microbiota transplantation (FMT) trials is still unknown. Given the differences in cohorts, lifestyles, ages, and genders across research, comprehensive, standardized, and rigorous analysis and evaluation standards are desperately needed to address these issues. Notably, notable regional differences have been observed; gut Bacteroides abundance, for example, was found to be low in AD patients from China but it was reported to be high in individuals from the USA. Furthermore, research from various Chinese provinces has revealed inverse variations in the quantity of Blautia. Although certain research has examined the impact of particular microbial species on the pathogenesis of ND, the underlying processes are still unclear. While human patients with AD, PD, and MS had higher levels of Akkermansia, intragastric treatment of the bacteria had protective benefits on cognitive deficits in an AD mice model. In mice models of AD and PD, elevated levels of Akkermansia have also been linked to less severe pathology.

These disparities in experimental results could be attributed to the restricted replication of ND pathogenesis in mice models, which mostly depend on gene editing or therapeutic interventions, in contrast to the complex aetiologies found in human NDs. These disparities in experimental results could be attributed to the restricted replication of ND pathogenesis in mice models, which mostly depend on gene editing or therapeutic interventions, in contrast to the complex aetiologies found in human NDs. Furthermore, research has revealed age-related changes in the microbiota's makeup, however it's yet unclear if these changes indicate illness or wellness. Faecal microbiota analysis could be revolutionised by creating a standardised faecal microbiota bank for patients with non-diagnostic ND, providing a noninvasive diagnosis

method. Furthermore, it is critical to create more realistic animal models that replicate the intestinal ecology and pathophysiology of non-diabetic humans. It is imperative to comprehend the ways in which GBA modulation is impacted by BBB permeability and neuronal susceptibility, given the age-related deterioration of the nervous system and BBB integrity.

To evaluate the viability of the gut-brain-axis as a novel "endocrine organ" and its effect on ND pathophysiology, longer-term research is necessary. It is promising to target particular microbial compounds involved in gut-brain signaling chemically and physically as a therapeutic strategy. For example, the use of non-dependent psychotropic drugs targeted to the microbiome may transform treatment for NDs. The gut microbiota affects non-diagnosed neurological diseases by immunological modulation, neuronal signaling, and humoral pathway activation by microbial compounds and additional possibly unknown mechanisms. It will take coordinated efforts from bench to bedside research to unravel these mechanisms and contributing factors in order to improve our understanding of ND pathophysiology and investigate new therapeutic approaches.

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