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Review

The Role of the Gut Microbiota in Neurodegenerative Diseases

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Abstract: The human gut has a rich and dynamic microbial population that plays an important role in many physiological activities. This review explores the complex interaction between the gut microbiota and human health, with an emphasis on its effect on neurodegenerative illnesses. The makeup of the gut microbiome and its impact on brain function through the gut–brain axis is highlighted. Dysbiosis, characterized by changes in the gut microbiota's composition, has been linked to the development of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis. A Bidirectional communication between the stomach and the brain takes place via a variety of channels, including neurotransmitters and metabolites generated by gut bacteria. We investigate the processes through which dysbiosis causes neuroinflammation, oxidative stress, and neuronal damage, which drive disease development. Potential therapeutic approaches that focus on the gut microbiota, such as antibiotics, probiotics, prebiotics, and fecal microbiota transplantation, are reviewed, with promising preclinical and clinical findings. Overall, this study emphasizes the relevance of gut microbiota to neurodegenerative illnesses, as well as the need to understand and target the gut-brain axis for future treatment options.

Keywords: *Firmicutes*; *Bacteroidetes*; gut; neurodegeneration; nerves; disorders; brain; probiotics

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1. Introduction

Different types of microorganisms, including bacteria, viruses, archaea, and unicellular eukaryotes, are present inside the human body. The group of microbes that coexist peacefully living in harmony with their hosts has been called the flora, normal microbiota, or microflora. Nearly every area of the human body that is accessible to the outside world is colonized by microbiota. Microbes proliferate in the gastrointestinal, respiratory, and genitourinary systems, as well as on the skin. The gastrointestinal tract (GIT) is by far the organ that is most densely colonized; it is believed that the colon alone contains more than 70% of all the bacteria in the human body. The predominance of aerobic microorganisms throughout perinatal and postnatal development changes after birth. During the first few weeks of life, the microbiota diversifies to produce a diverse microbial community that is dominated by anaerobes [1]. Strict anaerobes make up the majority of the gut microbiota. Even though more than 50 bacterial species have been identified so far, just two of them *Bacteroidetes* and *Firmicutes*-dominate the human gut microbiota, with smaller numbers of *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria* [2]. The fermentation of indigestible substrates such as food fibers and endogenous intestinal mucus is facilitated by the gut bacteria. The growth of specific microorganisms that generate gases and short-chain fatty acids (SCFAs) is aided by this fermentation. Butyrate, propionate, and acetate are the main SCFAs generated. Higher synthesis of SCFAs has been associated with reduced diet-induced obesity and lower insulin resistance, according to randomized controlled studies [3]. In mice, butyrate and propionate seemed to regulate gut hormones

and lower appetite and the intake of food. A person's physiology is mostly influenced by the microbiota present in their gut. Studies have revealed varied patterns of microbiome composition at various life stages, with major alterations in the dominating phyla and species identified as age progresses. Notably, the quantity of Actinobacteria declines after weaning, whereas *Firmicutes* and *Bacteroidetes* increase in prevalence, particularly in older individuals [4]. When the gut microbiota is compromised, the entire body is impacted. Many different human illnesses are related to the onset and progression of gut microbiota dysbiosis. During the last ten years, research has been aimed at the interactions that occur between the gut microbiota and other body systems, such as the immunological, neurological, and metabolic systems. Neurodegenerative diseases (NDs) are defined as the gradual decline in selectively susceptible neurons. Worldwide, people face significant medical and public health challenges as a result of degenerative illnesses of the neurological system. Among the most common neurological disorders are Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). These illnesses have a sharp increase in incidence and frequency as people age. There has been increasing curiosity regarding the connection between brain development and gut bacteria. Germ-free (GF) mice were shown to exhibit higher levels of motor activity and a decrease in anxiety-like responses in comparison to specific-pathogen-free (SPF) mice. The blood–brain barrier (BBB) is crucial in regulating the flow of nutrients, as well as chemicals, between the blood and the brain. The GF mice exhibited higher blood–brain barrier permeability in comparison to SPF mice [5].

The Pavlov pouch, an externalized section of the dog intestine used to research canine digestive processes, was contributed by Ivan Pavlov [6], who, as well as defining classical conditioning, was also a forerunner in the arena of the gut–brain axis (GBA). He refined the methods by preserving innervation to the intestine section, enabling more precise monitoring of digestive processes in real time over prolonged periods [6]. Our knowledge of the vital role the gut–brain axis plays in homeostatic processes in both illness and health is based on this research, and the bidirectionality of this axis was fully appreciated in the 1980s. The GBA, is a two-way interaction that mediates the significant influence of bacteria on physiological processes in the brain. Neurotransmitters and other metabolites are used by the gut–brain axis to engage in bidirectional communication between the brain and the gut. Many clinical and experimental studies have revealed the significance of the microbiota in NDs via different microbial chemicals that travel through the GBA or neurological system from the gut to the brain [7]. The central, autonomous, and enteric neural systems, together with the immunological, endocrine, and metabolic systems, are all involved in the communication process. However, the precise mechanism regulating the signal propagation and stimulating alterations in host diseases is still unknown [8]. Through these pathways, the metabolites of the gut microbiota, which include SCFAs, histamine, gamma-aminobutyric acid (GABA), norepinephrine, serotonin, etc., affect several cerebral physiological functions. Dysbiosis, or an imbalance in the composition of the gut microbiome, causes the brain to receive signals that lead to low-grade inflammation, increased oxidative stress, disturbed energy metabolism, and increased cellular aging. These pathological processes are involved in a variety of neurological diseases [9]. Gut microbes affect the central nervous system (CNS) through the following three pathways, as shown in Figure 1: first, through enteric nervous system stimulation; second, by inducing the intestinal epithelial secretory cells to produce metabolites or neurotransmitters such as 5-hydroxytryptamine (5-HT), GABA, dopamine, and SCFAs; and third, gut microorganisms influence immune function by generating microbial-associated molecular patterns (MAMPs) that support immune cells or cytokines like IL-6, IL-1a, IL-1b, and TNFa, which then have an impact on the central nervous system [10]. The vagus nerve connects the enteric nervous system (ENS) and the CNS directly. Additionally, bacteria affect the immune system's growth and control, which may change how the immune and CNS systems interact [11].

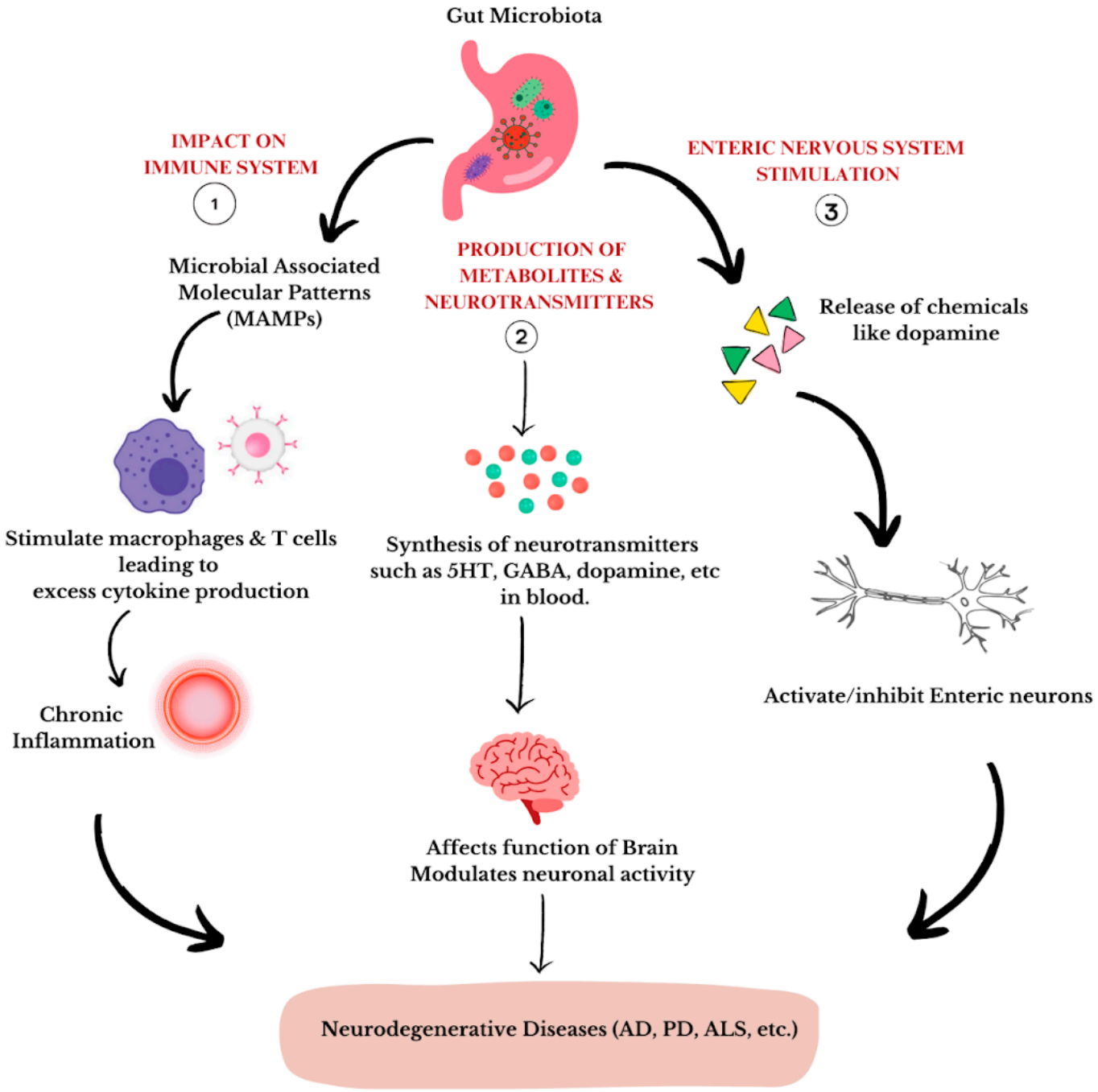

Figure 1. Mechanisms of influence of gut microbiota on the central nervous system.

In the gastrointestinal system, digestion is regulated by the gut bacteria, which also facilitate nutrient and metabolite extraction, synthesis, and absorption. Additionally, commensal bacteria support the first immune response to pathogenic bacteria by competing for resources, generating bacteriocins, and protecting the integrity of the intestinal epithelium [12]. Additionally, short-chain fatty acids are dependent on the variety and composition of the gut bacteria [13]. The function of the nervous system and its growth are both affected by SCFAs. It has been found that the tryptophan–kynurenine (TRP-KYN) pathway and its metabolites are important in the progression of neuroinflammation. Enterochromaffin (EC) cells are principally responsible for producing histamine. It performs as one of the most crucial neurotransmitters in the brain and plays important roles in many

physiological processes, like cell proliferation, wound healing, allergic reactions, immune cell modulation, etc. [9].

2. Gut Microbiota

More than 100 trillion different bacteria are found in the human gastrointestinal tract, or GI tract, which is home to a large and diverse microbial community. According to estimates, there are between 10^{11} and 10^{12} bacteria per milliliter in the colon, making it one of the planet's densest microbial homes. Trillions of microbes occupy our bodies before and after birth. Infants' intestinal tracts are clear of bacteria during pregnancy, but they become contaminated when they are birthed normally and come into contact with maternal vaginal microbes. Cesarean section babies are exposed to maternal skin bacteria, changing the bacterial composition of their guts [14]. Considering the phylum level, the composition of the gut bacteria is similar (mostly *Firmicutes* and *Bacteroidetes*), but the species diversity and richness vary from person to person. The structure of the gut microbiota is determined by the host's genetics, environment, nutrition, illness, stress, and other variables, whereas the microbiota controls the host's health and diseases through genes, proteins, or metabolites [15]. The gut bacteria also differ in different anatomical sections of the intestine, which change with respect to their pH, physiology, O_2 tension, digestion flow speeds, host secretions, and substrate availability. Given its relatively short 3–5 h transit periods and increased bile contents, the small intestine presents a more difficult habitat for microbial colonizers. The greatest microbial community, with mostly obligate anaerobic bacteria, is found in the large intestine, which is distinguished by sluggish flow rates and a pH varying from neutral to mildly acidic. With a steady decline in aerobic bacteria in favor of solely anaerobic bacteria, we can observe an increasing quantitative gradient and a decreasing qualitative gradient for the microbiota [12]. The components of the human microbiome are now well understood due to the use of molecular methods. The mouth cavity and distal GI tract often have the most varied and plentiful microbial populations [16]. Metagenomic analysis of the human microbiome has revealed that there are 3.3 million unique genes in the human gut, 150 times more genes than in our genome [17]. Additionally, an analysis of bacterial diversity revealed that there are about 1000 different bacterial species living in our gut, with the majority of them falling under the *Firmicutes* and *Bacteroidetes* divisions [18]. Human Oral Microbiome Database (HOMD) includes over 800 full-length sequences categorized into 619 taxa. A total of 96% of the species have been classified into six main phyla: *Firmicutes*, *Bacteroidetes*, *Fusobacteria*, *Spirochaetes*, *Actinobacteria,* and *Proteobacteria*. Other phyla, including *Euryarchaeota*, *Chloroflexi*, *Chlamydia*, SR1, *Tenericutes*, *Synergistetes*, and TM7, constitute the remaining 4% of the taxa, as shown in Figure 2. According to a pyrosequencing analysis of distal esophagus samples, *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria*, *Proteobacteria*, and TM7 were found to be present. The most common bacteria were determined to be *Streptococcus*, *Prevotella*, and *Veillonella*, and the distal esophagus' population resembled that of the mouth cavity. The phyla *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Bacteroidetes* are dominant in the complex community of stomach microorganisms. This microbial community differed greatly from the oral and esophageal communities [19].

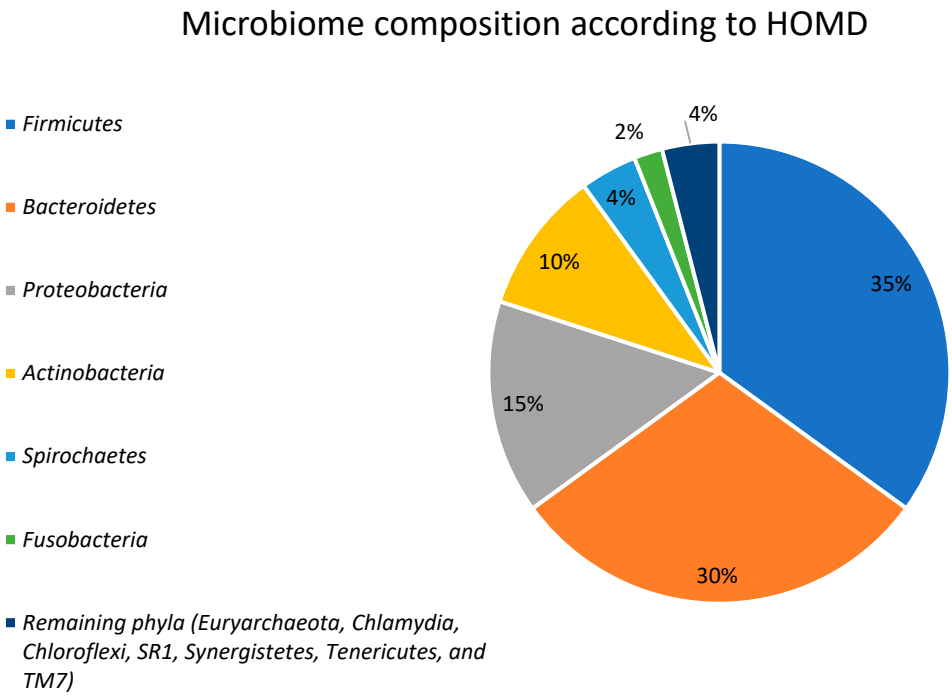

Figure 2. Microbiome distribution based on Human Oral Microbiome Database [19].

3. Impact of the Gut Microbiota on Physiology

The gut microbiota plays a major role in both health and disease. The brain, lungs, liver, cardiovascular system, and other organ systems are linked with the gut bacteria. The SCFA butyrate is one of the major signals that connect the gut microbiota and physiology [15]. Based on a symbiotic connection with the host, the human intestine is the habitat of a wide population of microbiota that supports the digestion and metabolism of food components. Although diet has always been seen as a significant determinant of health and disease, current research on the microbiome has revealed that diet has an impact on the host's metabolic processes and helps shape the gut microbial structure [20]. Cirrhosis, non-alcoholic fatty liver disease (NAFLD), alcohol liver disease (ALD), and even hepatic cancer may be influenced by the gut flora. Probiotics help in preventing the occurrence of NAFLD. Th gut microbiota may regulate hepatic gluconeogenesis. While cecal microbiota from obesity lowered the indicators of hepatic gluconeogenesis, probiotics increased hepatic gluconeogenesis [15]. The gut microbiota offers a variety of advantageous features to the host because of its substantial genetic content and metabolic complement. These microorganisms have some of the most crucial functions in maintaining mucosal barrier integrity, supplying vitamins, and defending against infections. Additionally, a healthy immune system depends on the interaction of the mucosal immune system with commensal bacteria [21]. Human health and illness are greatly influenced by the microbiota; in fact, it is frequently referred to as our "essential organ" [22]. The ability of the microbiota to harvest and store energy, as well as perform a variety of metabolic tasks, including fermenting and absorbing undigested carbohydrates, has likely acted as a powerful evolutionary force in the development of bacteria as symbionts in humans. Perhaps even more crucially, the immune system interacts with the gut microbiota, which sends signals to encourage immune cell maturation and the appropriate development of immunological functions [23].

An essential part of the adaptive immune system is CD4+ T cells. T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), and regulatory T cells are the four main subtypes that naive CD4+ T cells can develop into after activation. Both inside and outside the intestine, the gut microbiota is crucial to the formation of CD4+ T lymphocytes. Recent research even found a link between the development of different T cell subtypes and particular bacterial species. Polysaccharide A (PSA) molecules from *Bacteroides fragilis* have been

found to stimulate the development of a systemic Th1 response [24]. The prevalence of neurodegenerative diseases is currently rising quickly. Though genetic predisposition to neurodegenerative illnesses is a significant risk factor, the environmental circumstances experienced throughout a person's lifetime also have a significant impact on the start, progression, and ultimate severity of such disorders. The current body of clinical and preclinical research indicates that alterations in the gut microbes may, to some extent, increase the risk of neurodegeneration [9]. The idea that gut microorganisms influence neurodegenerative illnesses via the GBA is gaining popularity, even if the underlying processes are still largely unknown.

4. The Microbiota–Gut–Brain Axis

Numerous mechanisms, such as the vagus nerve, the immune system, the ENS, and the metabolic activities of the gut bacteria, can link the gut and the brain. Through the vagus nerve, gut bacteria can impact how the brain functions. The idea of the GBA, a bidirectional communication pathway between the brain in the cranium and the enteric nervous system in the abdomen, connected by the sympathetic and parasympathetic nervous systems and also by circulating hormones and other neuromodulator molecules—has long been envisioned as the mediating factor in the symptoms of stress-related gastrointestinal problems [25]. Bidirectional communication occurs between the microbiota and the brain through several different channels, including the hypothalamic–pituitary–adrenal axis, or HPA axis; the spinal cord; immunological cytokines; and short-chain fatty acids. The neuroactive substances generated by bacteria, such as acetylcholine (ACh), GABA, serotonin, and dopamine, mostly operate locally on the ENS, called "the second brain" or "gut brain". Some of these substances enter the brain through the vagus nerve or through the blood and circumventricular organs [26]. Through the immunological, neuroendocrine, and neurological pathways, the gut microbiota communicates with the host. Preclinical research indicates that these pathways, which are part of the GBA, can be used by the microbiota to affect brain function, development, and even behavior. The GBA functions as an intricate communication network including many signaling channels. The CNS receives visceral stimulation from the intestines, which activates the vagal and spinal sensory nerves to reach higher brain regions. *Bacteroidetes* and *Firmicutes* affect the host through neurological, immunological, and metabolic processes that are part of the microbiota–gut–brain axis [27]. The vagal nerve, metabolites of tryptophan, and bacterial products like SCFAs are involved in this communication. The gut microbiome affects GABA, acetylcholine, dopamine, noradrenaline, serotonin, and other neurotransmission systems. Certain bacteria produce these neurotransmitters and have an impact on brain activity. Although most gut-produced neurotransmitters are unable to cross the blood-brain barrier, there are a few exceptions, such as GABA, and the microbiota affects serotonin levels by metabolizing tryptophan [28].

The neurotransmitters and neuromodulators produced by the gut microbiota may offer the best explanation for how the microbiota interacts with the brain. The precise mechanism regulating the signal transmission and potentiating host pathological disturbances is still unknown. Numerous research studies have looked into how changing the gut flora may affect neurotransmitter release to fill in the gaps caused by pharmaceutical targets that consistently fail. Evidence suggests that many bacterial species, including *E. coli*, *Staphylococcus aureus*, and *Bacillus subtilis*, are capable of synthesizing acetylcholine, one of the main neurotransmitters [8]. The function of the microbiome is demonstrated by the cognitive abnormalities shown in germ-free mice with altered microbiota in animal studies. Certain bacteria can create neurotransmitters that affect brain function, such as serotonin. Through its effects on the GBA, stress, infection, and maternal relationships throughout early life influence cognitive behavior. There are connections between disrupted gut–brain communication, inflammation, and cognitive impairment observed in studies on diseases like irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Also, the microbiota is shaped by dietary practices, which also affect behavior. Giving probiotics

to people or animals has been shown to have positive behavioral effects, which may have implications for mental health [29].

5. Microbiota and Mental Health

The gut microbiome affects the brain's emotional and cognitive regions directly as well as indirectly. Studies indicate that modifications to these communication networks are associated with variations in the microbiome. There are now distinct links between functional gastrointestinal disturbances and mood disorders, including anxiety and depression. The brain may affect the functional immune effector cells in the gut, which can affect cognition, mood, and mental health. These connections are made possible via the autonomic nervous system, the HPA axis, and the nerves inside the gastrointestinal tract [30]. A wide range of chronic abnormalities are referred to as functional gastrointestinal disorders (FGIDs), some of which are caused by aberrant brain–gut connections that can result in dysmotility and hypersensitivity. Individuals with FGIDs have episodes of depression and anxiety more frequently than those in good health [31]. The increased co-morbidity of stress-related psychological symptoms, such as anxiety, and gastrointestinal illnesses, such as IBS and inflammatory bowel disorder, demonstrates the relevance of this axis to pathogenesis. There are fewer studies on the gut microbiota in individuals with depression. On the other hand, information from related conditions like IBS, associated with signs of depression, shows that fecal samples from affected individuals showed increased *Firmicutes* and decreased *Bacteroidetes* patterns [32]. These findings reveal the potential of targeting the microbiome in therapeutic methods. Altering the gut microbiota of the host has the potential to improve people's mental health and provide a path for future treatment approaches. Also, some 20 neuropeptides made by the enteroendocrine cells function as secondary messengers in the brain, controlling mood and cognition. Some gut bacteria also create neurotransmitters, including neuropeptide Y (NPY), substance P, calcitonin, corticotropin-releasing factor, vasoactive intestinal polypeptide, glucagon-like peptide-1, and somatostatin. The release of ghrelin and other neurotransmitters generated by the gut bacteria is regulated by the endocrine system. These neurotransmitters affect our mood and emotions by controlling the levels of dopamine and other neurotransmitters [33].

Sudo and colleagues demonstrated the important role the intestinal microbiota plays in the development of the HPA axis. They found that, in comparison to control mice, germ-free animals under mild restraint stress showed an increased release of corticosterone and adrenocorticotropic hormone. By colonizing germ-free mice with feces from control animals, this stress reaction was partially reversed; it was fully reversed through mono-association with *Bifidobacterium infantis.* Another important factor was the time of colonization; the earlier the colonization, the stronger the reversal effects. Additionally, the adult offspring of germ-free mothers who were administered specific bacterial strains before delivery saw a complete reversal [34]. In different research, administering rats an antibiotic cocktail changed the range of brain-derived neurotrophic factors and enhanced visceral pain sensitivity and hyperlocomotion, along with depleting the microbiota of the animals. Interestingly, there was no behavioral effect in germ-free mice given the same antibiotic therapy. However, when the microbiota of BALB/C mice was introduced into these germ-free animals, substantial increases in anxiety-like symptoms were observed [35]. These findings emphasize the key role that the microbiota in the gastrointestinal tract plays in the formation of an appropriate stress response.

6. Neurodegenerative Diseases Associated with the Gut Microbiota

By enhancing lipopolysaccharides, T helper cells, pro-inflammatory cytokines, and monocytes, gut dysbiosis can also lead to high permeability of the intestine and blood–brain barrier through the GBA. As a result, misfolded protein buildup, demyelination of the neurons, and damage to the axons occur, which contributes to the development of neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, etc. The effects of dysbiosis on neurodegenerative diseases are depicted in Figure 3.

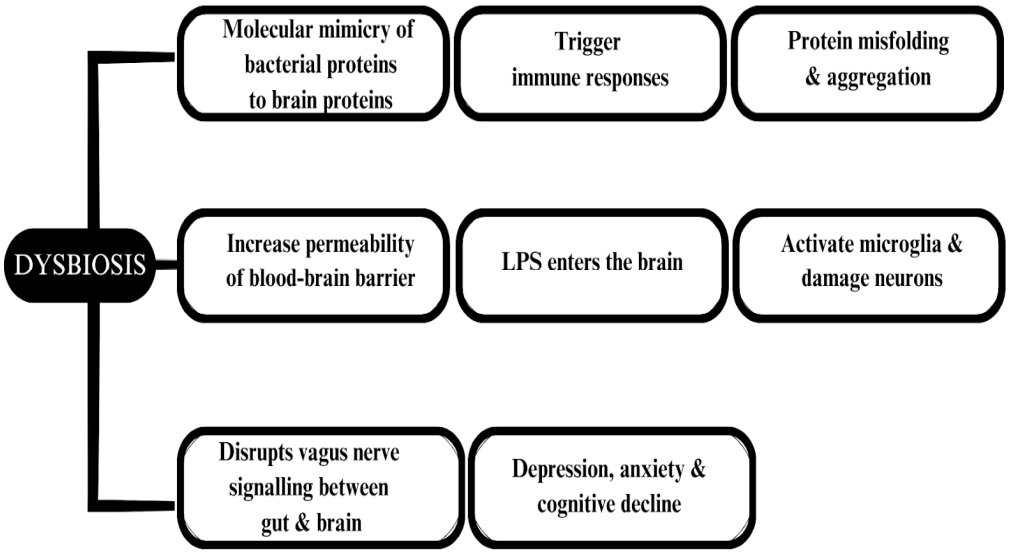

Figure 3. Effects of dysbiosis on neurodegenerative diseases.

6.1. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative illness that causes the decline in the motor neurons in the brain and spinal cord. Microglial activation and persistent neuroinflammation are two of the main characteristics of ALS, which cause symptoms including twitching, spasms, paralysis, and impaired coordination. The most common genetic variation linked with ALS is the C9ORF72 hexanucleotide GGGGCC-repeat expansion. This mutation contributes to ALS pathogenesis through both gain- and loss-of-function mechanisms, including pathways important to neural degeneration [36]. While it is not a complete loss-of-function mutation, ALS patients frequently show lower expression of endogenous C9ORF72. Recent research using C9ORF72-null animals demonstrated a pro-inflammatory phenotype caused by the absence of C9ORF72, which was interestingly mitigated by lowering the microbial load in the gut [37]. This association highlights the complex link between the C9ORF72 mutation, the gut microbiota, and the pro-inflammatory response, offering information on prospective therapeutic interventions in ALS. Research shows that in people with ALS, gastrointestinal problems frequently occur before neurological symptoms. Fecal analysis indicates that individuals with ALS have a microbiota with reduced diversity in the gut than healthy individuals. A pro-inflammatory gut microbiome disease may be indicated by variations in the gut microbiome, such as a decreased *Firmicutes*/*Bacteroidetes* ratio and a reduction in the population of certain bacteria. The intestinal barrier may be damaged by this imbalance, which might lead to immunological reactions and impair bowel movement. According to some studies, toxins can enter the circulation through a malfunctioning intestinal barrier, which may play a role in the etiology of ALS [38].

The gut plays a vital role as a barrier, shielding the body from harmful substances. Gut dysbiosis could be a factor in increased intestinal permeability. This impaired barrier function is concerning since it might make it easier for different dietary toxins to enter. A variety of dietary toxins have been linked to the cause of ALS. The amino acid Beta-methylamino-L-alanine (BMAA), which may be incorporated during brain protein synthesis, is one such toxic substance. In the brains of people suffering from ALS, elevated amounts of BMAA have been found, probably ingested through food [39]. The use of the G93A SOD1 transgenic mice model has been useful in researching the effect of the gut bacteria on the development of ALS. The mice showed reduced levels of transmembrane proteins that help in cell–cell adhesion, such as ZO-1 (Zonula Occludens-1) and E-cadherin (Epithelial cadherins), along with increased gut permeability and an impaired blood–brain barrier during the pre-onset period (60-70 days). Decreased butyrate-producing bacteria were detected

in the feces, which may be linked to higher amounts of IL-17. Butyrate administration slowed the development of ALS, pointing to a potential therapeutic advantage. Patients with ALS had similar changes in butyrate-producing bacteria [40]. Figueroa-Romero et al. studied the temporal evolution of the immune system and gut bacteria in relation to the onset of ALS symptoms using the G93A SOD1 mouse model. The findings offered more proof that changes in the microbiota occur before motor impairment and muscle atrophy in individuals with ALS. Notably, compared to their wild-type littermates, the microbes from G93A SOD1 mice included lower concentrations of *Akkermansia muciniphila* and *Bacteroides caccae*, indicating possible links between certain microbial alterations and the development of ALS [41]. Though still in its early stages, microbiome research in ALS is regarded as one of the most promising areas of study from the past ten years. Although it was once thought that ALS could only occur within the CNS, new information is beginning to cast doubt on this theory. The increasing awareness of the involvement of the gut bacteria in various aspects of human health adds even more fuel to the investigation of its relationship to ALS. The involvement of the gut microbiota in the development of ALS is shown in Figure 4.

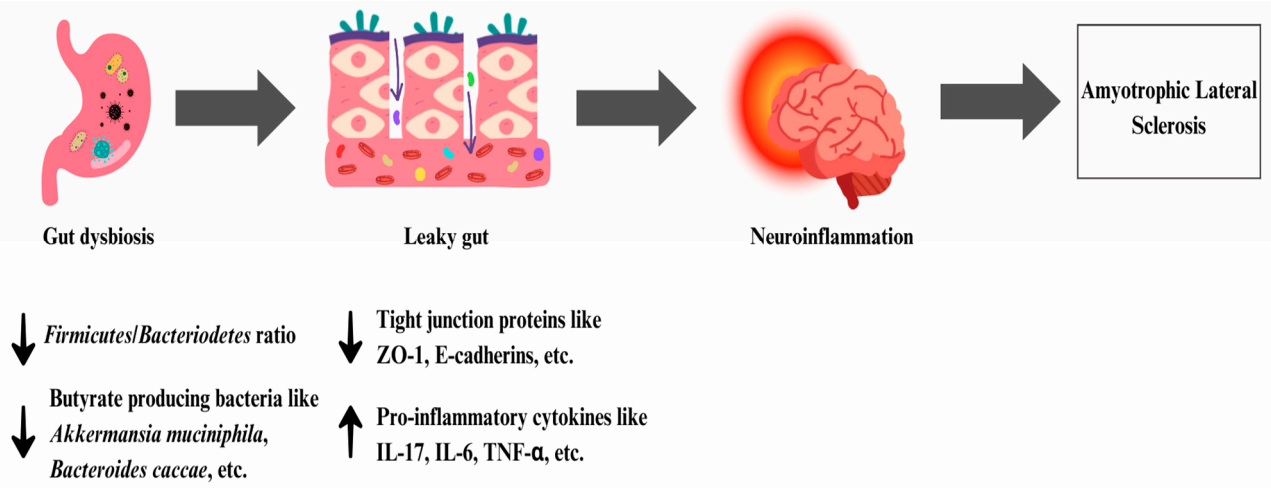

Figure 4. Development of amyotrophic lateral sclerosis.

6.2. Huntington's Disease

A hereditary illness known as Huntington's disease (HD) is marked by a gradual degradation of the brain's nerve cells. A mutation in the huntingtin (HTT) gene on chromosome 4 is the main cause of HD. The GIT and the skeletal muscles are some of the peripheral organs where the HTT gene is extensively expressed besides the brain.

Recent research has revealed a relationship between gut dysbiosis and the development and progression of HD symptoms. GI dysfunction in HD patients has been linked to the existence of mutant HTT (mHTT) in the GI tract. The symptoms include diarrhea, poor gastrointestinal motility, and poor food absorption. Malabsorption is significant since it is associated with weight loss, which is a characteristic of HD shown in both human and transgenic mice models of the illness [42]. Microsatellite repeats are the root cause of many neurological disorders. Trinucleotide repeat expansion disorders, or TREDs, are characterized by these expansions, which are formed by replication mistakes like polymerase disassembly or the formation of a hairpin shape through the sliding of the 5′ and/or 3′ ends of the Okazaki fragment. The TREDs specifically refer to the repeating of the CNG sequence in certain genes, where N is one of the four nucleotides [43]. The genetic mutation causing HD is present in the first exon of the HTT gene, and it is inherited dominantly. This mutation is associated with CAG repeats, where 27–35 repeats raise its risk in progeny but do not cause the illness, and 39 repeats or more show signs of complete penetrance. As a result, the mHTT protein is expressed, leading to the formation of HD-specific intracellular insoluble aggregates. In addition to anatomical changes in the gut, HD is linked to GI dysfunction, which includes diarrhea, malabsorption, and reduced gut motility. According

to mouse model studies, mHTT accumulates in the enteric nervous system before motor symptoms develop [44].

Investigation of the gut microbiota in HD mice has gained more focus. A study found that transplanting the microbiota from wild-type mice into HD mice improved the mice's cognitive abilities, especially in females. However, in males, the effect was not successful, maybe because of instability in the gut flora [45]. Significant compositional alterations, such as increased *Bacteroidetes* and decreased *Firmicutes*, were detected in a thorough investigation using 16S rRNA sequencing in R6/1 mice. In HD males, these alterations were accompanied by a lower body weight, increased food consumption, and a changed water content in the feces [46]. Another detailed study on the impact of the environmental conditions on gut microbiota modulation was conducted on R6/1 mice. In comparison to the controls, the HD mice had more alpha diversity and alterations in the overall composition of their microbiomes as a result of increased physical activity and environmental enrichment [43]. The involvement of the gut microbiota in the development of HD is shown in Figure 5.

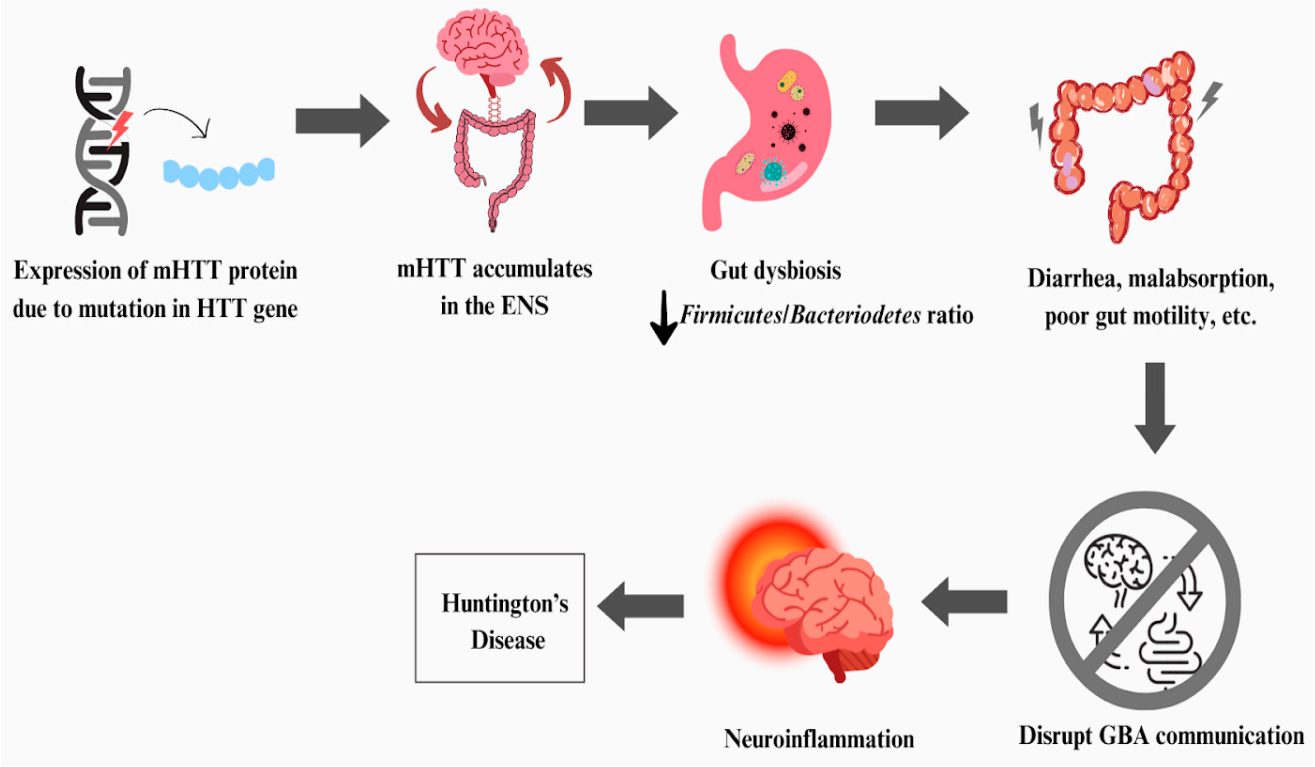

Figure 5. Development of Huntington's disease.

6.3. Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of dementia, which is indicated by a gradual decline in cognitive ability. The condition is marked by amyloid beta (Aβ) accumulation, which results in the development of plaques and hyperphosphorylated tau-protein-based neurofibrillary tangles. The neuroinflammation caused by these deposits results in the loss of synapses and neuronal death. Although the precise causes of amyloid plaque development are unknown, it is believed that the gut bacteria have a major involvement in this process. APOε4 is the most prevalent genetic risk factor for sporadic AD. The link between APOε4 and the gut microbiota in AD is not completely known [47]. Research has indicated that the pro-inflammatory gut microbiota contributes to Alzheimer's disease progression. *Collinsella* has been found to be a risk factor for AD diagnosis, showing a positive correlation with the APOε4 risk allele C. In contrast, the *Eubacterium nodatum* group, *Adlercreutzia*, and *Prevotella* act as preventive factors against AD, having a negative

correlation with the APOε4 risk allele C. These findings indicate a complicated interaction in which particular microbial genera and APOε4 may contribute to disease regulation, possibly via shared biological pathways that combine to alter disease risk or protective effects [48]. Bacterial cell attachment and biofilm development are facilitated by the gut bacteria, which are producers of amyloids such as the amyloid curli produced by *E. coli*. Although bacterial and CNS amyloids have different fundamental structures, their tertiary structures are similar. The immune system may be primed by bacterial amyloids in the gut, causing the formation of endogenous neuronal amyloid in the brain. Research indicates that animals subjected to *E. coli* that produce curli showed elevated levels of neuronal alpha-synuclein (α-syn) in both the gut and the brain [49]. This exposure also increased the expression of TNF, TLR2 and IL-6. Using molecular mimicry, the amyloids produced by bacteria can function as prion proteins, resulting in cross-seeding and the adoption of a pathogenic β-sheet structure by other amyloidogenic proteins.

The role of the gut bacteria in the pathogenesis of AD has been demonstrated through investigations conducted on laboratory animals, especially germ-free rodents. The mice exhibit a significant decrease in Aβ pathology, which is subsequently restored upon the reintroduction of the gut bacteria [50]. Infections caused by bacteria or viruses have been linked to AD in humans. Reduced cognitive scores and the production of inflammatory mediators are linked to chronic infection by *Helicobacter pylori* in AD patients. The AD patients with infections such as *H. pylori*, *Chlamydia pneumoniae*, and *Borrelia burgdorferi* had higher amounts of Aβ in their blood. *H. pylori* filtrate leads to the hyperphosphorylation of tau in neuroblastoma cells. Significant amounts of bacterial lipopolysaccharide have also been found in the brains of AD patients [51]. AD is also influenced by metabolites that are released by the gut bacteria like SCFAs, which interfere with protein–protein interactions that are essential to the development of amyloid beta (Aβ) assemblies, linked to AD. Furthermore, β-secretase activity is elevated by trimethylamine N-oxide (TMAO), a metabolite produced by bacteria, which amplifies Aβ buildup and worsens AD pathogenesis. Moreover, TMAO promotes the movement of Aβ from platelets to the brain and releases calcium ions, which, in turn, leads to platelet hyperreactivity [52]. This process suggests the possibility of developing personalized dietary therapies to control the development and aggregation of Aβ in AD. The involvement of the gut microbiota in the development of AD is shown in Figure 6. A study involving the introduction of the fecal microbiota of healthy mice into AD mice showed reductions in glial responses, amyloid plaques, neurofibrillary tangles, and cognitive impairment. Fecal microbiota transplantation (FMT), which is the transfer of healthy gut bacteria from a healthy donor to an affected recipient, significantly reduces circulating inflammatory monocytes in AD animals and restores the abnormal expression of genes linked to intestinal macrophage activity [53]. There are growing opportunities for FMT in the treatment of AD, with various administration routes like colonoscopies, enemas, and capsules providing more flexibility. However, there are limitations in the rodent models and obstacles with FMT, including unclear processes, donor selection, and potential side effects.

6.4. Parkinson's Disease

Parkinson's disease (PD) is a multifocal neurodegenerative condition marked by akinesia, rigidity of the muscles, tremors, slow movement, and issues with gait and walking. Memory loss, depression, and sensory issues are other symptoms in addition to these motor traits. It occurs due to an abnormal Lewy body aggregation of α-synuclein fibrils in the CNS. Surprisingly, the brain is not the only organ affected by PD pathology; there is an additional neurological aspect as well. Around 80% of PD patients experience constipation, which is a common comorbidity of gastrointestinal dysfunction. Constipation is linked to α-synuclein buildup, neurodegeneration, increased local inflammation, oxidative stress, and intestinal permeability in Parkinson's disease [54]. Leucine-rich repeat kinase 2 (LRRK2) is a large, widely expressed, multi-domain, and multifunctional protein. The LRRK2 mutations contribute to both inherited and sporadic PD [55]. Research has found that the

LRRK2 expression levels were greater in microbe-exposed mice as compared to germ-free mice. This finding suggests a strong link between the gut microbiota and LRRK2 expression, emphasizing the importance of additional study to better understand the complex role the indigenous microbiome may play in determining the onset and course of PD [56]. The PD incidence is increased by 22–35% by inflammatory bowel conditions and is reduced by 19% in cases of appendectomy performed more than 30 years ago. These results support the hypothesis that PD is primarily related to increased intestinal permeability. Truncal vagotomy, according to epidemiological research, lowers the risk of PD by about 50% [57].

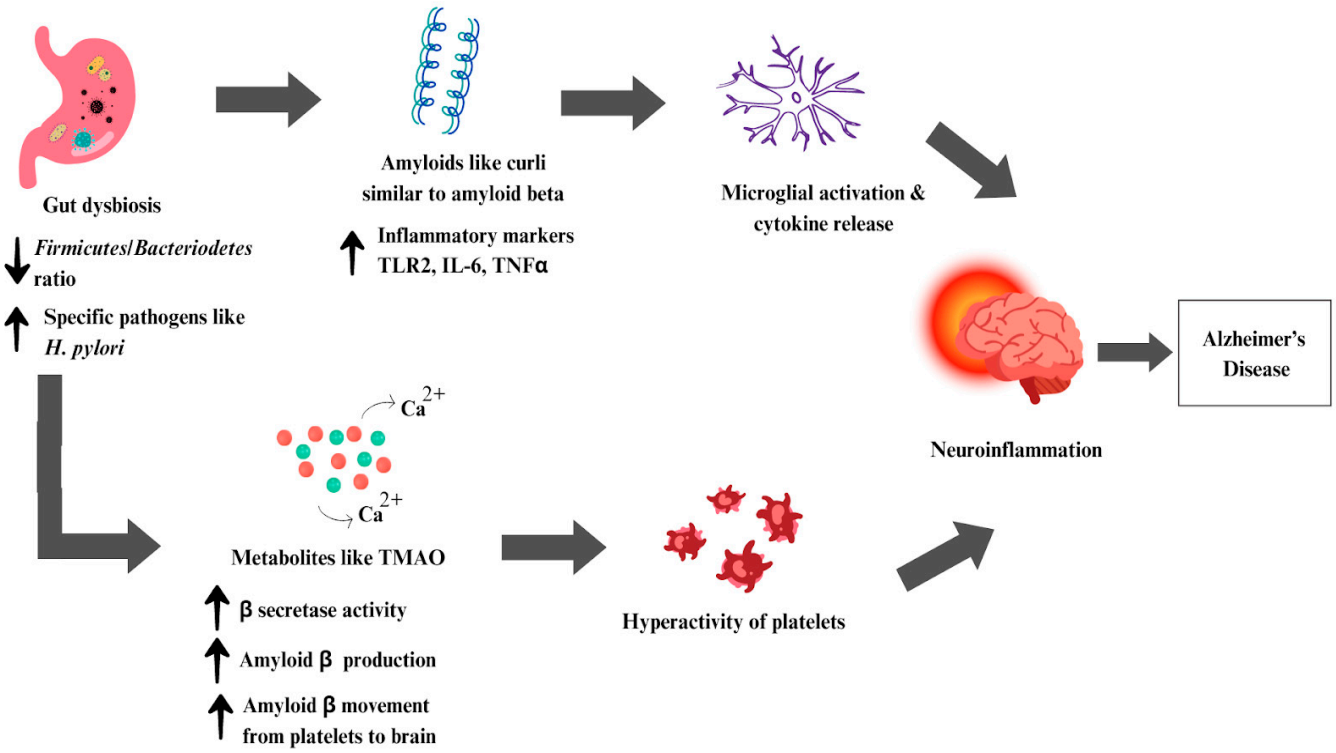

Figure 6. Development of Alzheimer's disease.

Infections, toxin exposure, and brain injury may trigger a PD "clock", causing a cyclic inflammatory process that ultimately leads to neuron death. *H. pylori* is an example of a chronic infection in PD. *H. pylori* can reduce the absorption of L-dopa, a medication used to treat PD, and worsen the disease's symptoms. Antibiotic treatment of *H. pylori* infection has been shown to improve PD symptoms in some patients. However, it is not clear whether *H. pylori* is directly involved in PD pathogenesis or whether its effects are due to other mechanisms, such as inflammation or autoimmunity [58]. Other infectious agents that have been linked to PD include viruses (such as those that cause encephalitis, AIDS, and coronaviruses) and bacteria (such as those that cause Lyme disease and Legionnaires' disease). The pathogenic process in the brain in response to infections has been mimicked in vivo models of PD. A study has revealed higher levels of antibodies against cytomegalovirus, herpes simplex virus type-1, *Borrelia burgdorferi*, Epstein–Barr virus, *H. pylori*, and *Chlamydophila pneumoniae* were associated with PD. This suggests that these infections may play a role in the development of PD [59]. Bacterial proteins can induce the cross-seeded misfolding of proteins in the brain. This misfolding can be mediated by molecular mimicry, which occurs when bacterial proteins have a similar structure to human proteins. The immune system can mistake bacterial proteins for human proteins, and this can trigger an inflammatory response. The inflammatory response can be amplified by CD14 and Toll-like receptors, TLR2/1, which are proteins that are involved in the detection of foreign molecules by the immune system. TLR2/1 and CD14 are activated by bacte-

rial proteins, which can promote the synthesis of inflammatory molecules like cytokines and chemokines. This can also activate nuclear factor kappa B (NFκB), a transcription factor regulating gene expression. NFκB can promote the expression of genes responsible for inflammation and cell death [60]. The combined effects of cross-seeded misfolding, inflammation, and oxidative stress can lead to neurodegeneration and the symptoms of neurodegenerative diseases.

The relationship between PD and the gut microbiome is not fully understood. However, the current evidence suggests that an unknown pathogen may enter the GIT and cause GM imbalance. This imbalance can break the intestinal epithelial barrier, allowing the pathogen to reach the ENS. α-synuclein, a protein associated with PD, may then start to accumulate in the ENS. If it accumulates to a certain level, it can spread to the CNS via a process called trans-synaptic cell-to-cell transmission [61]. The pathogen may also cause GM translocation, which is the movement of bacteria from the gut to other body parts. This can lead to inflammation in the GIT, and these inflammatory signals may be sent to the brain through the blood–brain barrier. Studies have shown that α-synuclein is present in both the gut and brain, suggesting that the gut may not be the only place where α-synuclein pathology starts in PD. The involvement of the gut microbiota in the development of PD is shown in Figure 7. One potential treatment for PD is fecal microbiota transplantation. The FMT is effective in treating other gut-related diseases, and it may also be effective in treating PD. Other potential treatments are new gastrointestinal (GI) biomarkers for the clinical diagnosis of PD. Biomarkers are substances that can be measured in the body to indicate the presence of a disease. The development of new GI biomarkers could help doctors diagnose PD earlier and develop more targeted treatments [62]. Now that the gut–microbiota–brain axis (GMBA) has gained widespread awareness and its dysregulation has been connected to several disorders, there is an urgent need for a proper understanding and new therapeutic approaches. The neurochemistry of the brain, including changes in the neurotransmitter levels, receptor activity, and various neurotrophic factors, is influenced by GMBA. Research on the relationship between GM disorder and PD is still in its early stages. However, the evidence suggests that GM disorder has a role in the progression of PD. Further investigation is needed to confirm this role and to develop effective treatments.

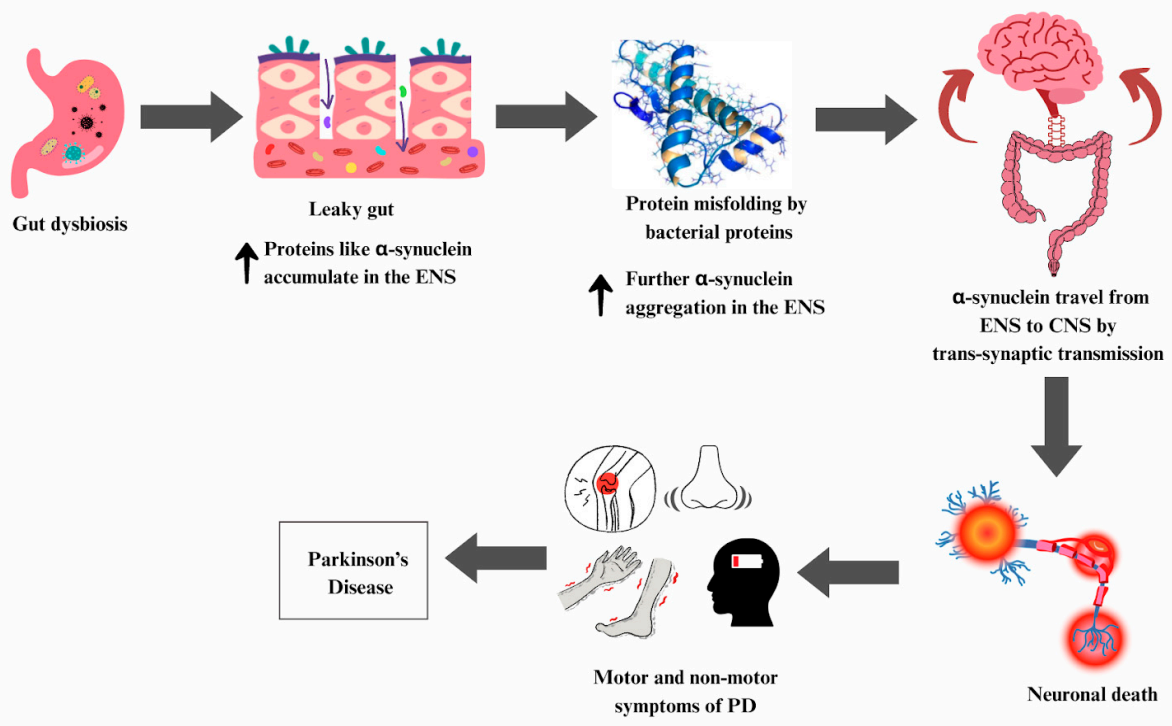

Figure 7. Development of Parkinson's disease.

7. The Gut Microbiota in Potential Treatment Strategies

Since the gut bacteria have a significant role in both health and illness, modifying the makeup of commensal microorganisms through the use of probiotic, prebiotic, and antibiotic combinations may open up new therapeutic avenues. Adopting a systems approach is essential to comprehending the intricate interactions between the host and bacteria, which allows for the reversal of alterations in the makeup of the gut microbiota associated with disease states. There are two suggested approaches to upcoming treatments that target the intestinal flora. The first is the direct eradication or alteration of certain microbes, similar to antibiotic therapy for peptic ulcers caused by *H. pylori*. The second takes a more comprehensive approach, using profiling techniques such as metabolomics to classify illnesses according to the gut microbiota structures associated with clinical symptoms [63]. To effectively treat the gut microbiota, a combination of antibiotics, probiotics, prebiotics, and maybe laxatives might be utilized. This has the potential to help treat several illnesses, including diabetes. Drug discovery is made possible by culture-independent metagenomic technology, which suggests that the gut microbiome itself may include potential therapeutics. The discovery of genes encoding bioactive chemicals from commensal microbiota is made easier by high-throughput DNA sequencing and bioinformatics techniques, opening up new avenues for medication development [64]. It has been discovered that FMT from normal mice inhibits neuroinflammation and the activation of the glial cells, protecting them against PD caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In contrast, characteristic motor impairments are worsened when the microbiota from PD patients is colonized in mice overexpressing synuclein (Syn) as opposed to when microbiota from healthy human donors is used. In a therapeutic setting, a PD patient's extreme constipation and tremors were successfully reduced using FMT therapy [65].

The gut microbiome may be structurally repaired with the transplantation of microbiota containing *Faecalibacterium prausnitzii*. Interestingly, compared to control individuals, PD patients had a noticeably lower amount of *F. prausnitzii*, suggesting a possible relation. The presence of *F. prausnitzii* might be used as a biomarker for analysis or diagnosis to determine whether FMT is successful [66]. Furthermore, probiotics and/or prebiotics can be used to prevent and treat neurodegenerative illnesses. The use of prebiotics and/or probiotics in the gut microbiota has demonstrated potential in the management of ALS, indicating that adjusting the gut microbiota may be a novel approach to treating ALS [67]. Because of its complexity, the role of the gut microbiota in diseases must be understood in the larger framework of systems biology. Although the microbiome has a role in diseases, it is rarely the sole cause. Comprehending the proportional contribution of the gut microbiota to conditions requires large-scale, well-phenotyped cohort studies employing multi-omics techniques. Drug metabolism, side effects, and the treatment response can all be influenced by several factors. It is simplistic to categorize entire genera as advantageous or detrimental; instead, individual microbiomes should be profiled using higher-resolution approaches. For precision medicine, microbial functions may be more important than taxonomic abundances. Based on improved mechanistic knowledge, therapies should target missing functions and identify various functional challenges among different patients [68].

Table 1 summarizes the impact of different gut microbial species on physiology, emphasizing their involvement in causing or alleviating inflammation and other physiological processes. *Bifidobacterium* and *Lactobacilli* are anti-inflammatory, with the former also showing promise in lowering amyloid formation. Pathogens, such as *Clostridium perfringens type B* and *E. coli*, are known to cause tissue injury, toxin generation, and pro-inflammatory responses through protein misfolding and molecular mimicry. *Proteobacteria*, such as *Acinetobacter calcoaceticus* and *Bacteroides fragilis*, promote inflammation by generating endotoxins, activating cytokines, and interfering with gut–brain communication. *Akkermansia muciniphila* emerges as a beneficial species, strengthening the intestinal barrier and increasing neurotransmitter levels. Furthermore, species such as *Dorea* and *Eubacterium rectale* perform distinct functions, activating immunological responses and generating beneficial

SCFAs, respectively. These findings highlight the complex relationship between the gut microbiota and host physiology, with implications for both health and illness [2–10].

Table 1. Impact of different gut microbial species.

Bacterial Species	Impact on Physiology	References
Bifidobacterium longum	Anti-inflammatory Reduced amyloid aggregation	[69]
Clostridium perfringens type B	Produces toxins Damages tissues and nerves	[40]
Escherichia coli	Protein misfolding through molecular mimicry Pro-inflammatory	[70]
Lactobacilli acidophilus	Anti-inflammatory Strengthen gut barrier Produce beneficial SCFAs	[69,71]
Campylobacter concisus	Pro-inflammatory Produces endotoxins Protein misfolding through molecular mimicry Disrupts GBA communication	[72]
Akkermansia muciniphila	Anti-inflammatory Gut barrier fortification Promotes neurotransmitter levels	[73]
Dorea formicigenerans	Stimulates IFNγ Metabolizes sialic acid Degrades mucin	[70]
Acinetobacter calcoaceticus	Stimulates pro-inflammatory cytokines Depresses regulatory CD4 T cells	[74]
Bacteroides fragilis	Pro-inflammatory Protein misfolding through molecular mimicry Leaky gut	[75]
Eubacterium rectale	Anti-inflammatory Produces beneficial SCFAs	[76]

8. Conclusions

The gut microbiome in humans is a complex environment of bacteria that regulates various physiological systems. The gut bacteria aid in digestion and absorption, the growth of the immune system, and the synthesis of important metabolites like SCFAs. Recent research has revealed the crucial role of the gut bacteria in the progression of neurodegenerative disorders. The bidirectional relationships between the gut bacteria and other physiological systems have been explored. It is important to understand the association between the gut bacteria and brain development in neurodegenerative illnesses. Through neurotransmitters and metabolites, the GBA facilitates gut–brain communication. Dysbiosis, defined as an alteration in the composition of the gut microbiome, is related to low-grade inflammation, high oxidative stress, disturbed energy metabolism, and cellular aging. These pathogenic mechanisms help to develop and advance neurodegenerative diseases. Antibiotics, probiotics, prebiotics, and FMT are some of the potential treatments targeting the gut microbiota. The FMT, in particular, has shown symptom relief in neurodegenerative disorders, with studies showing a good impact on diseases like Parkinson's disease. A systems approach is also required to comprehend the intricate relationships between the human body and the gut bacteria, allowing for the reversal of alterations in the composition of intestinal flora associated with diseases. Understanding the involvement of the gut bacteria in neurodegenerative illnesses gives important insights into how gut microbes impact brain health. It also paves the way for future research into targeted treatment strategies that use the GBA to control and perhaps prevent these chronic illnesses. In short, the gut bacteria have crucial significance in neurodegenerative illnesses, with the involvement of the GBA in maintaining the physiological equilibrium of the body.

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