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The Role of Gut Microbiome Dysbiosis in the Pathogenesis of Neurodegenerative Diseases (Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis) – A Comprehensive Review

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Abstract

Background: The gut microbiome interacts with the nervous system through the gut–brain axis (GBA), which is essential for understanding mechanisms contributing to neurodegenerative diseases via neuronal, endocrine, and immune pathways. Gut dysbiosis disrupts microbial balance and is associated with Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), contributing to impaired blood–brain barrier integrity and protein aggregation. Effective treatment is crucial to maintain patients' independence, daily function, and quality of life while reducing long-term healthcare costs.

Aim: This study aimed to synthesize and critically evaluate recent evidence on the role of the gut microbiome and its metabolites in AD, PD, and MS, and to discuss potential diagnostic and therapeutic implications within the GBA. It also highlights the relevance of these findings for health education and future interventions.

Materials and methods: Studies on the impact of the gut microbiome on neurodegenerative diseases were analyzed using PubMed, Scopus, and Web of Science. The search included terms such as "gut microbiome," "dysbiosis," "gut–brain axis," "Alzheimer's disease," "Parkinson's disease," and "multiple sclerosis," covering publications from 2018 to 2025.

Results: Altered levels of short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), and biogenic amines influence neuroinflammation, blood–brain barrier function, and protein aggregation. Preliminary data suggest that modulating the microbiome may help regulate inflammatory responses.

Conclusions: Evidence indicates that the gut microbiome plays a significant role in neurodegenerative disease development. Dysbiosis may serve as a biomarker and therapeutic target. Integrating gut health into preventive programs may enhance effectiveness and support early detection and management strategies.

Keywords: Gut microbiome; Neurodegenerative diseases; Gut–brain axis; Dysbiosis; Short-chain fatty acids

Introduction:

Neurodegenerative diseases (NDs), encompassing conditions such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and Multiple Sclerosis (MS), pose one of the most formidable global health challenges of our era. Their escalating incidence, largely attributable to an aging global population (Global Burden of Disease Study 2019), underscores a pressing need for a deeper comprehension of their pathogenic mechanisms and the identification of modifiable risk factors. Such understanding is not only crucial for medical advancement but also forms the bedrock of effective public health strategies and educational programs aimed at prevention and early intervention.

In recent years, we have learned more about brain diseases. New studies show that the nervous, immune, and digestive systems are strongly connected through immune mechanisms. Microbial

metabolites, such as short-chain fatty acids (SCFAs), like propionate and acetate, are important because they support the function of the gut and brain (Kim et al., 2024). SCFAs provide energy to colon cells, strengthen the gut barrier, help combat inflammation, and protect the nervous system. When dysbiosis occurs in the intestines and the number of Gram-negative bacteria begins to dominate, the production of lipopolysaccharides (LPS) increases.

Among the critical mediators of GBA communication are bioactive microbial metabolites, such as Short-Chain Fatty Acids (SCFAs), including butyrate, propionate, and acetate (Kim et al., 2024). These compounds are vital, serving as primary energy sources for colonocytes, bolstering the integrity of the intestinal barrier, and exerting systemic anti-inflammatory and neuroprotective effects. Conversely, an imbalance in the gut microbial community, termed dysbiosis, often involves the overgrowth of Gram-negative bacteria. This leads to an increased production of Lipopolysaccharides (LPS), which, upon compromising the intestinal barrier, can translocate into systemic circulation and induce widespread immune activation and neuroinflammation (Sampson et al., 2021). This review aims to comprehensively examine the intricate link between gut microbiome dysbiosis and the pathogenesis of AD, PD, and MS (Hansson et al., 2023; Mulak & Varghese, 2019), thereby contributing to a better understanding of these conditions within the broader context of health and education.

Methodology: We analyzed available publications using databases such as PubMed, Google Scholar, and Web of Science. We included only those studies that directly addressed the role of the gut microbiome in Alzheimer's disease, Parkinson's disease, or multiple sclerosis at the population, immunological, or molecular level. Search terms included: "gut microbiome", "dysbiosis", "gut-brain axis", "Alzheimer's disease", "Parkinson's disease", "multiple sclerosis", "neuroinflammation", and "SCFAs". Articles published between 2018 and 2025 were considered. Priority was given to peer-reviewed original research articles, systematic reviews, and meta-analyses written in English. Reference lists of selected papers were also screened to identify additional relevant sources. Only studies addressing the role of the gut microbiome and its metabolites in the pathogenesis of Alzheimer's Disease, Parkinson's Disease, or Multiple Sclerosis at the epidemiological, immunological, or molecular level were included in this review.

3. The Role of the Gut Microbiome in the Pathogenesis of Neurodegenerative Diseases

3.1. The Role of the Gut Microbiome in Alzheimer's Disease (AD)

Alzheimer's Disease (AD) is intrinsically linked to a profound dysregulation of the gut-brain axis, a connection consistently substantiated by both clinical observations and experimental evidence (Cattaneo et al., 2019; Giavasis et al., 2023). Dysbiosis is a recurring finding in AD patients, typically characterized by a notable decrease in the Firmicutes to Bacteroidetes ratio, primarily due to a reduction in beneficial commensal taxa such as Bifidobacterium and Eubacterium rectale (Cattaneo et al., 2019; Giavasis et al., 2023). Concurrently, there is an observed proliferation of Gram-negative and pro-inflammatory bacteria, including species like Escherichia/Shigella (Cattaneo et al., 2019). This taxonomic imbalance precipitates significant metabolic consequences: a critical deficit of Short-Chain Fatty Acids (SCFAs), arising from the diminished abundance of butyrate-producing bacteria, compromises the integrity of both the intestinal and blood-brain barriers. A pivotal pathogenic mechanism also involves an increase in Lipopolysaccharide (LPS) concentrations. LPS, upon translocation into the systemic circulation, activates Toll-like receptor 4 (TLR4) on microglial cells, initiating intense neuroinflammation and modulating pathways that lead to the accumulation and aggregation of β-amyloid protein (Lei et al., 2023). Encouragingly, interventions targeting the microbiome demonstrate therapeutic potential in AD. Clinical studies have shown that modulating the microbiota with probiotics can lead to improved cognitive function (e.g., in Lee et al., 2023) and a reduction in pro-inflammatory biomarkers (e.g., decreased IL-6 in Cattaneo et al., 2019), thus strongly supporting the premise of the microbiome as a modifiable therapeutic target.

3.2. The Role of the Gut Microbiome in Parkinson's Disease (PD)

In the pathogenesis of Parkinson's disease, the gut microbiome plays a crucial role. This supports the "gut-first" hypothesis, according to which the disease process may begin in the gastrointestinal tract. Numerous studies demonstrate the presence of dysbiosis in PD patients. It is characterized by a reduction in SCFA-producing bacteria such as Prevotella and Roseburia, alongside an increase in Enterobacteriaceae and Proteobacteria (Morais i in., 2023; Sun i in., 2023).

A significant decrease in bacteria from the Lactobacillaceae family is also observed. This change correlates with the severity of motor symptoms and suggests impaired gut barrier

function and increased susceptibility to oxidative stress. Many studies have also noted an increase in Akkermansia muciniphila, whose presence may contribute to the worsening of PD symptoms by degrading mucin and compromising the integrity of the intestinal mucus layer.

According to Braak's hypothesis, the dysbiotic gut environment—including the increased abundance of LPS-producing bacteria—promotes pathological α-synucleinopathy. Aggregates of α-synuclein form within the enteric nervous system and likely travel retrogradely to the central nervous system via the vagus nerve (cranial nerve X) (Sun i in., 2022). Dysbiosis further intensifies this process by promoting systemic inflammation, as evidenced by elevated C-reactive protein (CRP) and TNF-α levels. It also influences neuroactive metabolites such as serotonin and GABA, which modulate both motor and non-motor symptoms (Morais i in., 2023; Sun i in., 2023).

Microbiome-targeted therapies show promising results. Studies, including randomized controlled trials, have demonstrated that interventions such as fecal microbiota transplantation (FMT) can improve motor function and reduce markers of inflammation in the nervous system. At the same time, they help restore the balance of butyrate-producing bacteria (Sun i in., 2022; Barichella i in., 2019).

3.3. Gut Microbiota Changes in Multiple Sclerosis (MS)

Gut microbiome dysbiosis is one of the key factors contributing to autoimmune responses that may lead to demyelination within the central nervous system. In MS, a distinct pattern of disturbances is observed: a decrease in microorganisms supporting immune tolerance, particularly bacteria from the phylum Firmicutes and members of Clostridium cluster XIVa, and an increase in pro-inflammatory microorganisms such as Bacteroidetes and Akkermansia muciniphila (Jangi i in., 2016).

One of the most significant consequences of these changes is the deficiency of short-chain fatty acids (SCFAs), especially butyrate. Studies consistently show a reduction in bacteria capable of producing it (Borbet i in., 2022). Butyrate deficiency impairs the development and proper functioning of regulatory T cells (Tregs), promoting a shift toward pro-inflammatory TH17 cells. TH17 cells play a central role in autoimmune processes and facilitate the penetration of immune cells across the blood–brain barrier, as confirmed by increased IL-17 levels—a cytokine closely associated with disease severity (Cekanaviciute i in., 2017).

The gut microbiota in MS acts as a central immunological regulator. It strongly influences susceptibility to autoimmunity and determines disease progression. These findings underscore the importance of understanding gut microbiome function in autoimmune mechanisms and identifying potential new therapeutic targets.

4. Comparative Analysis and Therapeutic Implications

A comparative analysis of Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis reveals a crucial commonality: a functional deficit of Short-Chain Fatty Acid (SCFA)-producing bacteria is a pervasive feature across all three major neurodegenerative diseases. However, the precise downstream pathological consequences diverge. In AD, the effect is predominantly characterized by LPS-driven microglial activation; in PD, by α-synuclein misfolding and subsequent propagation; and in MS, by a TH17-mediated breakdown of immune tolerance (further summarized in Table 1). This multifaceted role positions the gut microbiome not merely as a potential diagnostic biomarker but also as an exceptionally attractive therapeutic target.

The initial successes observed with microbiome-modulating interventions, which include carefully designed dietary changes (suchally the MIND Diet for AD), targeted probiotic supplementation, and Fecal Microbiota Transplantation (FMT), provide a robust scientific rationale for the development of precision-based microbiome therapies. These advancements hold significant promise for future medical practice and highlight the importance of integrating such knowledge into public health education initiatives.

Table 1. Comparative Analysis and Common Mechanisms.

Feature	Alzheimer's Disease (AD)	Parkinson's Disease (PD)	Multiple Sclerosis (MS)
Key Taxonomic Changes (Dysbiosis)	decrease Firmicutes/Bacteroidetes Ratio, decrease Bifidobacterium, increase Escherichia/Shigella	decrease SCFA-producing bacteria (Prevotella, Roseburia), increase Enterobacteriaceae, increase Akkermansia muciniphila	decrease Tolerogenic bacteria (Clostridium cluster XIVa), decrease Firmicutes, increase Bacteroidetes, increase Akkermansia muciniphila
Main Metabolites / Biomarkers	decrease SCFAs (butyrate), increase LPS, increase IL-6, TNF-α	decrease SCFAs (butyrate), increase LPS, increase Kynurenine (tryptophan metabolite)	decrease SCFAs (butyrate), increase IL-17
Key Pathomechanical Pathway	Neuroinflammation induced by LPS	α-Synuclein migration ("gut-first" hypothesis)	Loss of Immune Tolerance
Mechanism of CNS Damage	LPS causes increase microglial activation; decrease SCFAs weaken BBB; associated with β-amyloid accumulation.	α-Synuclein aggregates migrate from ENS to CNS via the vagus nerve; damage dopaminergic neurons.	SCFA deficiency decrease T_{reg} cells and promotes T_h7 polarization increaseIL-17; T_h17 cells attack myelin.
Therapeutic Potential	MIND Diet, probiotics increase Lactobacillus reduce neuroinflammation and improve cognitive function.	FMT and targeted probiotics/prebiotics improve motor symptoms and inflammation.	Restoration of butyrate-producing bacteria stabilizes the T_{reg}/T_h17 axis.

Abbreviations:

SCFA – Short-Chain Fatty Acid; LPS – Lipopolysaccharide; BBB – Blood-Brain Barrier; ENS – Enteric Nervous System; FMT – Fecal Microbiota Transplantation; T_{reg}– Regulatory T cells; T_h17 – T Helper 17 cells.

5. Discussion

Research on the role of the gut microbiome in nervous system function has progressed rapidly in recent years. Increasing evidence indicates that disturbances in gut microbial balance may play an important role in the development and progression of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Regardless of the underlying cause, dysbiosis promotes inflammatory processes in the brain, weakens the blood–brain barrier, and may lead to the deposition of harmful proteins in neural tissue.

In Alzheimer's disease, reduced levels of beneficial bacteria are frequently observed alongside an increase in microorganisms promoting inflammation, including Bifidobacterium, Eubacterium rectale, and pro-inflammatory taxa such as Escherichia/Shigella. The resulting deficiency of SCFAs disrupts both the intestinal barrier and BBB integrity, allowing increased translocation of bacterial components such as LPS. This systemic and central inflammatory response—mediated by activated microglia—is closely linked to β-amyloid pathology, suggesting that the gut microbiome acts as a major driver of the neuroinflammatory cascade fundamental to AD. As a result, more inflammatory molecules may enter the nervous system, promoting β-amyloid accumulation.

Dietary interventions, such as the MIND diet, and the use of probiotics show promising effects in reducing inflammation and supporting cognitive function. Similarly, emerging findings related to Parkinson's disease are compelling. Increasing evidence suggests that gut disturbances may appear long before the first neurological symptoms. PD patients frequently exhibit reduced levels of Prevotella and Roseburia, which produce SCFAs, as well as increased levels of pro-inflammatory strains. Such changes may facilitate the movement of misfolded α-synuclein from the gut to the brain. Additionally, elevated LPS levels intensify inflammation and may exacerbate the disease.

Research on microbiome modulation—including probiotics and fecal microbiota transplantation (FMT)—is yielding promising results. These therapies may help alleviate PD symptoms and open new therapeutic possibilities.

In multiple sclerosis, strong connections between the gut microbiome and immune function are also observed. Many patients exhibit a deficit of immunomodulatory bacteria and an excess of pro-inflammatory species. Reduced SCFA production, especially butyrate, disrupts immune balance and contributes to nerve damage.

In recent years, increased attention has been directed toward interventions supporting gut health. Such an approach may stabilize immune responses and slow disease progression.

One of the most consistently observed features accompanying these diseases is the reduction of SCFA-producing bacteria. Although the specific consequences of dysbiosis differ across conditions—ranging from intensified inflammation in AD, to pathological protein deposition in PD, to immune dysregulation in MS—the gut microbiome consistently proves to play a key

role. Therefore, it is increasingly viewed as an important reference point in the diagnosis, prevention, and treatment of neurological diseases.

In individuals with Parkinson's disease, the decline in SCFA-producing bacteria is particularly evident, accompanied by an increase in pro-inflammatory species. This shift in the gut environment may promote abnormal α-synuclein folding and its movement from the gut to the brain. Importantly, early studies on microbiome-targeted therapies show highly promising results. Many indications suggest that in the future, treatment may be tailored to an individual's specific microbial profile. This highlights the need for further research and the development of education in this field, which may play a crucial role in shaping new therapeutic strategies.

6. Conclusions

This review demonstrates that changes in the gut microbiome are an important and modifiable factor in the development of neurodegenerative diseases. Research on gut–brain interactions reveals how gut health influences nervous system function.

In Alzheimer's disease, brain inflammation often begins when LPS crosses the weakened blood–brain barrier. In Parkinson's disease, the "gut-first" hypothesis suggests that the disturbed gut environment facilitates the transport of misfolded α-synuclein along the vagus nerve to the brain. In multiple sclerosis, a deficiency of short-chain fatty acids disrupts immune balance, leading to autoimmunity and damage to neural tissue.

All these diseases share one common feature: a reduced number of SCFA-producing bacteria. Therefore, the gut microbiome may serve as an indicator of disease and a foundation for developing new treatment strategies.

Preliminary research on microbiome-modulating therapies is promising. However, further studies are needed to determine which interventions produce the most effective results. These findings also highlight the importance of gut health education. Through such education, patients can make informed decisions that may reduce the risk of neurodegenerative diseases or slow their progression.

Disclosure:

Author Contribution Statement

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