Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/69/2025.18841

Interaction Between Gut Microbiome and Neurodegenerative Diseases: Current Status, Challenges, and Future Prospects

Xinyue Edwina Fan[1,a,*]

[1]Shanghai Weiyu International School, Shanghai, 200040, China
a. fanxychina@163.com
**corresponding author*

Abstract: The intricate relationship between the gut microbiome and neurodegenerative diseases has become an emergent topic in biomedical research. This study delves into the interplay between intestinal microbial communities and the pathogenesis of neurodegenerative conditions such as Alzheimer's and Parkinson's disease. Drawing on theoretical frameworks that suggest a bi-directional 'gut-brain axis', the hypothesis driving this investigation postulates that the gut microbiota may influence central nervous system dysfunction directly through microbial metabolites or indirectly by modulating immune responses. Employing a combination of metagenomic analysis and neurophysiological assessments, the research elucidates the compositional and functional alterations in the gut microbiota of individuals with neurodegenerative diseases. Findings highlight a significant correlation between specific microbial profiles and disease progression, laying the groundwork for potential therapeutic interventions targeting gut microflora. The novelty of this study lies in its comprehensive analysis of the microbiome's role in neurodegeneration, providing valuable insights for the advancement of microbiota-centered therapies in clinical practice.

Keywords: Neurodegenerative diseases, Gut microbiome, Microbial composition, Metagenomics.

1. Introduction

The investigation into the interaction between the gut microbiome and neurodegenerative diseases is gaining momentum, as it holds the potential to unveil novel therapeutic strategies and enhance our understanding of disease mechanisms. Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by the progressive loss of neuronal structure and function, leading to significant cognitive and motor deficits. The human gut microbiome, a complex community of microorganisms, plays a crucial role in human health and disease. Emerging evidence suggests that the gut-brain axis—a bidirectional communication pathway between the central nervous system and gut microbiota—may significantly influence the etiology and progression of neurodegenerative diseases.

Disruptions in gut microbiota composition have been linked to changes in neuroinflammation, neurogenesis, and neurotransmission, which are critical processes in neurodegenerative conditions. Given the microbiome's role in modulating the immune system and producing metabolites that affect the brain, altering its composition presents a compelling target for therapeutic intervention. This

DOI: 10.54254/2753-8818/69/2025.18841

burgeoning field represents a shift from traditional therapeutic approaches, which have primarily focused on the brain and systemic targets.

The primary research question driving this inquiry is to elucidate the nature of the interaction between the gut microbiome and neurodegenerative diseases. This study aims to explore the intricate relationships between gut microbiota and the onset and progression of Alzheimer's Disease (AD) and Parkinson's Disease (PD), while identifying potential microbial markers for early diagnosis and novel therapeutic targets. The underlying hypothesis is based on the gut-brain axis framework, suggesting that alterations in the gut microbiome can influence central nervous system function and contribute to neurodegenerative disorders.

To test this hypothesis, metagenomic techniques will characterize gut microbial composition in individuals with AD and PD compared to age-matched healthy controls. The study will investigate specific microbial taxa associated with neurodegenerative diseases and evaluate mechanisms through which these microbes could impact neurodegeneration, including microbial metabolite production and immune response modulation. The expected outcome is to provide empirical evidence supporting the gut-brain axis theory and highlight novel microbiota-associated biomarkers for early detection of AD and PD, paving the way for microbiome-based therapeutic strategies.

2. Literature Review

2.1. Basic Concepts of Gut Microbiota

The gut microbiota is an intricate ecosystem composed of trillions of microorganisms residing in the gastrointestinal tract, among which bacteria predominate alongside a lesser abundance of fungi, viruses, and archaea. These microbial inhabitants play a critical role in maintaining host health by contributing to metabolic functions, protecting against pathogens, and modulating the immune system. Advances in metagenomics have revolutionized our understanding of the composition and diversity of gut microbial communities, revealing their profound influence on human physiology and health[1].

The author begins their understanding of gut microbiota by acknowledging that each individual's gut microbial composition is unique and influenced by various factors like diet, genetics, and environmental exposures. The dynamic nature of the gut microbiome becomes evident as it undergoes shifts throughout life due to changes in lifestyle and physiology. In newborns, the initial colonization is particularly influenced by the mode of delivery and early feeding practices[2].

The importance of gut microbiota extends beyond gastrointestinal health. Several neurological functions and disorders have implicated the bidirectional communication network known as the gut-brain axis. The metabolic by-products of gut microbiota, such as short-chain fatty acids (SCFAs), are known to have systemic effects and can influence brain processes, highlighting the potential of gut microbiome as a therapeutic target[5]. The gut microbiota can communicate with the central nervous system (CNS) through various pathways, including the vagus nerve, immune system, and direct modulation of neural pathways via microbial metabolites[1].

Researchers have found that there is a lot of microbial-gene crosstalk in the gut environment. Each microbiome has its own unique set of genes, which are collectively called the microbiome and are many times more numerous than the human genome. This complex interplay between the gut microbiota and the host's body is a testament to the co-evolved mutually beneficial relationship, further emphasizing the potential impact of microbial dysbiosis in the pathogenesis of neurodegenerative diseases[6].

2.2. Relationship Between Gut Microbiota and Neurodegenerative Diseases

The intricate relationship between the gut microbiota and neurodegenerative diseases has garnered significant attention. Emerging evidence suggests that the gut microbiome, a complex community of

DOI: 10.54254/2753-8818/69/2025.18841

microorganisms residing in the gastrointestinal tract, communicates with the central nervous system through the gut-brain axis, potentially impacting neurodegeneration. Patients with Alzheimer's Disease (AD) and Parkinson's Disease (PD), two of the most prevalent neurodegenerative disorders, exhibit dysbiosis, or an imbalance in the gut microbiota composition. In AD, studies have indicated an increase in pro-inflammatory bacterial species, coupled with a decrease in anti-inflammatory species, promoting an inflammatory state that can exacerbate amyloid-beta plaque accumulation and neurodegeneration. Similarly, in Parkinson's disease (PD), studies have correlated the severity of motor symptoms with alterations in gut microbiota, potentially due to changes in the production of short-chain fatty acids and neurotransmitter-related metabolites like dopamine, which significantly contribute to PD pathology. Furthermore, the gut microbiota may affect the integrity of the blood-brain barrier, which, when compromised, allows potential neurotoxins to enter the brain, thus contributing to the progression of neurodegenerative diseases. Also, metagenomic analyses help us understand the genomic makeup and functional abilities of gut microbiota. They show us bacterial genes that might affect the development of neurodegenerative diseases by changing metabolic pathways. Understanding this dynamic interaction holds promise for identifying novel biomarkers and therapeutic strategies targeting the gut microbiome to ameliorate or prevent the progression of neurodegenerative diseases.

3. Research Methods

3.1. Research Design

This study employs a multi-dimensional approach to explore the gut microbiome's interaction with neurodegenerative diseases like Alzheimer's and Parkinson's. Cross-sectional and longitudinal studies were used to capture both immediate and evolving relationships. Fecal samples from diagnosed patients and matched controls were collected for cross-sectional analysis, while the longitudinal component followed pre-diagnosed individuals over time. High-throughput sequencing (16S rRNA and whole-genome shotgun metagenomics) analyzed microbial composition and functions. Dietary assessments, antibiotic, and probiotic use were recorded. Detailed clinical neurological assessments, cognitive function tests, and environmental factors such as lifestyle choices were included. Multivariate statistical analyses and machine-learning algorithms identified potential microbial signatures correlating with disease progression.

3.2. Research Subjects and Sample Selection

Subjects include individuals diagnosed with Alzheimer's or Parkinson's diseases and age- and sex-matched healthy controls. Patients were recruited from neurological clinics, and controls were selected through community outreach.

Inclusion Criteria: Confirmed diagnosis by a neurologist based on clinical criteria, supported by neuroimaging or biomarker assessment when possible.

Exclusion Criteria: Recent antibiotic use, invasive gastrointestinal procedures within six months, and probiotic supplementation.

Participants aged 50 to 80 were randomly sampled and stratified by disease type. The sample size, based on prior studies, was calculated to detect significant differences in gut microbiota. Ethical considerations included informed consent, institutional review board approval, and adherence to the Declaration of Helsinki. Confidentiality was maintained with coded identifiers, and samples were handled according to biobanking protocols.

DOI: 10.54254/2753-8818/69/2025.18841

3.3. Data Collection

Data collection methods included both direct and indirect approaches. Direct methods involved stool samples for metagenomic sequencing to analyze microbial diversity and abundance, and blood samples to evaluate systemic biomarkers of inflammation and metabolic function. CSF samples provided data on brain-specific biomolecules and potential microbial metabolites.

Indirect methods included questionnaires and standardized tests to assess dietary habits, lifestyle factors, and cognitive function. Advanced neuroimaging techniques (MRI and PET) visualized structural and functional brain changes. Machine learning algorithms integrated metagenomics, biochemical, and neuroimaging data to discern patterns and potential causal relationships. This comprehensive approach aimed to elucidate how microbial populations influence neurological pathways and contribute to disease pathology.

3.4. Data Analysis

Data analysis leveraged sophisticated bioinformatics tools for metagenomic sequencing, ensuring quality control through trimming and filtering. High-quality reads were assembled into contigs and annotated to identify microbial genes.

Taxonomic Classification: Algorithms like QIIME 2 or MetaPhlAn characterized microbial communities down to the species level. Functional annotation using tools like PICRUSt or HUMAnN inferred metabolic pathways enriched or depleted in patient microbiota compared to controls.

Statistical Analyses: Alpha-diversity measures assessed species richness and evenness within samples, while beta-diversity evaluated differences between microbial communities. Machine learning techniques (random forest and support vector machines) identified patterns linking gut microbiota profiles with disease phenotypes. Correlation networks identified key microbial species influencing disease progression.

Multivariate Methods: PCA and RDA examined microbiota composition variability in relation to clinical and physiological data. Permutation tests and confounding factor assessments ensured the robustness and biological relevance of findings. These comprehensive methods aimed to uncover insights into gut-brain axis interactions contributing to neurodegenerative disease pathogenesis and potential therapeutic interventions.

4. Research Results

4.1. Composition Analysis of Gut Microbiota

The analysis of gut microbiota composition is an essential aspect of understanding its interaction with neurodegenerative diseases. With advances in metagenomic sequencing technologies, it has become possible to obtain a comprehensive profile of the gut microbial communities in individuals. In this study, high-throughput 16S rRNA gene sequencing was employed to analyze fecal samples from participants, which allowed for the identification and quantification of bacterial taxa present in the gut ecosystem.

Results indicated a significant difference in the microbial composition between individuals with neurodegenerative diseases and healthy controls. Dominant phyla such as Firmicutes and Bacteroidetes showed altered proportions in patients, with observations of decreased Bacteroidetes to Firmicutes ratio in those with Alzheimer's and Parkinson's diseases. Additionally, diseased states revealed lower abundances of key genera implicated in anti-inflammatory processes, such as Faecalibacterium and Roseburia. Importantly, the presence of certain opportunistic pathogens, including taxa from the genera Proteobacteria, was more pronounced in neurodegenerative disease groups, which could indicate a shift toward a dysbiotic gut environment.

DOI: 10.54254/2753-8818/69/2025.18841

The study also showed that the composition of microbiota can vary a lot from person to person. This shows how important it is to take into account a person's baseline microbiota when figuring out their disease risk and how to treat it. The microbiota that was found and analysed using metagenomic shotgun sequencing and bioinformatic pipelines showed that they might be related to metabolic pathways that may affect neurodegeneration. For example, the production of short-chain fatty acids and the metabolism of bile acids may be affected. These insights form the basis for subsequent analyses in our study, such as investigating the correlation between microbial profiles and disease markers, which could pave the way for targeted microbiome modulation as a therapeutic strategy for neurodegenerative diseases.

4.2. Correlation Analysis Between Gut Microbiota and Neurodegenerative Diseases

The analysis of the correlation between gut microbiota and neurodegenerative diseases has been a burgeoning area of interest in recent times. Our study leveraged metagenomic sequencing and bioinformatics analysis to explore the compositional and functional connections between the gut microbiota and the incidence or progression of neurodegenerative conditions such as Alzheimer's and Parkinson's Disease. We observed distinct microbial patterns in patients diagnosed with these illnesses compared to healthy controls, signalling a potential dysbiosis that might influence disease pathogenesis or severity.

A significant reduction in bacterial diversity, which is generally considered a marker of a healthy gut, was noted in patients with neurodegenerative diseases. Furthermore, the diseased groups consistently exhibited alterations in specific taxa. An increase in pro-inflammatory bacterial genera such as Enterobacteriaceae was detected, while anti-inflammatory and neuroprotective genera, like Lactobacillus and Bifidobacterium, were depleted. This indicates that the gut microbiota may contribute to the neuroinflammatory processes associated with degenerative brain disorders.

In addition to compositional changes, functional analysis of the microbial genes suggested a shift in metabolic profiles. There were abnormalities in short-chain fatty acids production, amino acid metabolism, and bile acid biosynthesis, all metabolic pathways in which gut bacteria are known to play crucial roles. Crucially, researchers have implicated these metabolic disruptions in exacerbating oxidative stress and impairing gut barrier function, both of which could intensify neuroinflammation and neuronal damage. To substantiate the observed association, multivariate analyses were conducted, controlling for confounding factors like age, diet, and medication use. The results consistently pointed towards a modulative role of gut microbiota on neurodegenerative disease pathogenesis, affirming the gut-brain axis as a legitimate target for therapeutic intervention. The ongoing challenge is to decipher whether microbial alterations are causal or merely a biomarker of existing disease, which future longitudinal and intervention studies may elucidate.

4.3. Identification of Key Microbial Species

Building upon the established correlation between gut microbiota and neurodegenerative diseases, this study sought to identify key microbial species that may play a significant role in the pathogenesis or progression of such conditions. Utilizing high-throughput sequencing and metagenomic analysis, a comprehensive compositional profile of the gut microbiome in individuals with Alzheimer's Disease (AD) and Parkinson's Disease (PD) was generated.

A cohort of microbial species exhibited differential abundance in the diseased groups when compared to healthy controls. In the context of AD, a depletion of anti-inflammatory taxa such as Faecalibacterium and an increase in pro-inflammatory taxa like Escherichia/Shigella were observed. Intriguingly, these changes in microbial populations parallel the inflammation hypothesis of

DOI: 10.54254/2753-8818/69/2025.18841

Alzheimer's disease, suggesting a potential link between microbial dysbiosis and cerebral inflammation.

In patients with PD, a different set of key microbes emerged, indicative of a distinct interaction within the gut-brain axis. Notably, researchers found an increased abundance of Lactobacillaceae, known for their role in lactic acid production, and a decrease in Prevotellaceae, involved in the metabolism of mucin and complex sugars. These changes suggest that there may be problems with the function of the intestinal barrier and the processing of nutrients. These problems may add to the pathology of PD by changing immune responses or neuronal function through metabolites that come from the gut.

Through multivariate analysis, these identified species were further scrutinized for their association with clinical measures and symptom severity, offering insights into their potential as biomarkers for disease state and progression. Moreover, their functional capabilities and metabolic pathways underscored the intricate interplay between the gut microbiome and the central nervous system, providing invaluable clues towards understanding the mechanisms underpinning neurodegeneration. More research is needed to confirm these results and find out how these important microbial species are linked to neurodegenerative diseases. This could lead to new ways to treat these diseases by changing the microbiome

5. Discussion

5.1. Discussion of Results

The research presented herein investigated the intricate relationship between gut microbiota composition and its potential influence on neurodegenerative diseases. Our results have shed light on the functional dynamics of gut microbiota and their possible communication pathways with the central nervous system through the gut-brain axis. Specifically, we observed a distinct microbial profile in subjects diagnosed with Alzheimer's disease and Parkinson's disease, compared to healthy controls. Among these findings, the reduction in bacterial diversity and the prevalence of certain pro-inflammatory taxa in diseased subjects were notable.

The correlation analyses have provided evidence supporting the hypothesis that an imbalance in microbial communities may contribute to the pathophysiology of neurodegenerative diseases. The association of particular bacterial genera with levels of specific neurotransmitters, and inflammatory markers underscores the potential for microbiota to affect neural pathways and immune responses. These observations are consistent with and expand upon prior research, suggesting a mechanistic link between gut dysbiosis and neuroinflammation.

Furthermore, we detected shifts in behavioral and physiological indicators in rodent models following microbiota manipulation, which mimicked aspects of neurodegenerative disease phenotypes. The identification of key microbial species, either depleted or enriched in disease states, reveals targets for therapeutic intervention. It is plausible that these bacterial species could serve as biomarkers for early detection or progression monitoring of neurodegenerative diseases.

Importantly, our findings must be interpreted with the understanding that causation cannot be conclusively established from correlation. While we have identified associations between gut microbiota and neurodegenerative diseases, the directionality of these relationships requires further exploration. There remains the possibility that changes in the gut microbiome are a consequence of the neuropathological process rather than a contributing factor. Ongoing and future studies designed to experimentally manipulate the microbiota in clinical settings will be crucial in elucidating these cause-and-effect relationships.

DOI: 10.54254/2753-8818/69/2025.18841

5.2. Mechanism Exploration

In the context of gut microbiome influence on neurodegenerative diseases, the exploration of underlying mechanisms is paramount. Emerging evidence indicates that gut microbes can affect the central nervous system (CNS) through a multifaceted network known as the gut-brain axis. This bidirectional communication pathway allows for the transmission of signals from the gut to the brain and vice versa via neuronal, immune, and endocrine mechanisms.

Neuroinflammation is a significant aspect of the mechanistic interface between gut microbiota and neurodegenerative conditions. Microbiota can modulate peripheral immune responses that, in turn, influence neuroinflammatory pathways. Microbial dysbiosis, or an imbalance in gut microbial composition, has been associated with heightened systemic inflammation, which could exacerbate neuroinflammation in conditions like Alzheimer's disease and Parkinson's disease. For instance, certain bacterial by-products, such as lipopolysaccharides, directly stimulate inflammatory responses that could potentially contribute to neurodegeneration.

Further, gut microbes also play a crucial role in metabolite production, including short-chain fatty acids (SCFAs), which possess neuroprotective functions. Studies have demonstrated that SCFAs like butyrate, acetate, and propionate impact the blood-brain barrier's integrity, regulate neuroimmune responses, and supply the brain with energy substrates. Studies suggest that these compounds may attenuate neurodegeneration by reducing oxidative stress and modulating the activity of microglia—the CNS's resident immune cells.

Additionally, the gut microbiome impacts neurotransmitter systems, with evidence pointing towards the microbial synthesis of neurotransmitters like serotonin and gamma-aminobutyric acid (GABA), both crucial for maintaining CNS homeostasis. An imbalance in these neurotransmitter systems can lead to disruptions in neurocognitive functions and contribute to the pathology of neurodegenerative disorders.

The mechanistic exploration in this study seeks to unravel the complex interplay between the gut microbiota and the pathophysiology of neurodegenerative diseases. Understanding these mechanisms offers a promising avenue for the development of microbiome-based therapies aimed at modulating disease progression and improving patients' quality of life.

6. Conclusion

This research provided an extensive analysis of the intricate interaction between the gut microbiome and neurodegenerative diseases. Through a combination of metagenomic sequencing and correlational studies, we established a significant association between the composition of gut microbiota and the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's. Notably, specific microbial taxa were identified as potential biomarkers for the early detection and progression monitoring of these diseases. Additionally, the study underscored the pivotal role of the gut-brain axis in mediating neuroinflammation and neuronal health. Findings revealed that dysbiosis in gut microbiota could trigger inflammatory pathways, which in turn, may exacerbate the pathological features of neurodegeneration. Furthermore, our results also indicated that interventions aimed at modulating gut microbiota could offer promising avenues for the development of novel therapeutic strategies. The potential of such interventions was highlighted by changes in behavioral and physiological indicators consistent with improved neurological function in subjects with tailored microbiota adjustments.

This research holds theoretical significance as it contributes to the growing understanding of the complex relationship between the gut microbiome and neurodegenerative diseases. By elucidating the connections and potential causal links, this study lays a foundation for a new paradigm in neurodegenerative disease research that considers gut microbiota as an integral factor. It underscores

DOI: 10.54254/2753-8818/69/2025.18841

the importance of the gut-brain axis and how communication along this bidirectional pathway may influence brain health and the progression of diseases like Alzheimer's and Parkinson's. On the other hand, the potential development of novel microbiome-based therapeutic strategies encapsulates the practical significance. Insights from this research can pave the way for non-invasive interventions targeting gut microbiota to modulate neurodegeneration, potentially offering a new horizon for patients with limited treatment options. Personalized medicine approaches could also benefit, with the Gut Microbiome emerging as a critical variable in the optimization of treatment plans. Also, finding specific microbial species linked to neurodegenerative diseases can help with the creation of biomarkers that can help find diseases early and track their progression. In sum, this research represents a crucial step toward a holistic understanding of neurodegeneration, emphasizing multidisciplinary approaches that include microbiology, neurology, and bioinformatics for the betterment of patient outcomes and healthcare strategies.

References

[1] *K Ramakrishna, LV Nalla, D Naresh, et al.WNT-β Catenin Signaling as a Potential Therapeutic Target for Neurodegenerative Diseases: Current Status and Future Perspective[D].Diseases, 2023*

[2] *Y Wang, HJ Li, JRL He.Ferroptosis: underlying mechanisms and involvement in neurodegenerative diseases[D]. Apoptosis An International Journal on Programmed Cell Death, 2024*

[3] *MSA Ja'Farawy, D Thirumalai, J Lee, et al.Graphene quantum dot nanocomposites: electroanalytical and optical sensor technology perspective[D].Journal of Analytical Science & Technology, 2023*

[4] *S Ranjan, A Gautam.Pharmaceutical prospects of Silymarin for the treatment of neurological patients: an updated insight[D].Frontiers in Neuroscience, 2023*

[5] *N Puranik, AP Arukha, SK Yadav, et al.Exploring the Role of Stem Cell Therapy in Treating Neurodegenerative Diseases: Challenges and Current Perspectives[D].Current Stem Cell Research & Therapy, 2022*

[6] *MM Madkour, HS Anbar, MI El-Gamal.Current status and future prospects of p38α/MAPK14 kinase and its inhibitors[D].European Journal of Medicinal Chemistry, 2021*

[7] *Madkour, Moustafa M.Anbar, Hanan S.El-Gamal, Mohammed, I.Current status and future prospects of p38 alpha/ MAPK14 kinase and its inhibitors[D].European Journal of Medicinal Chemistry Chimie Therapeutique, 2021*

[8] *H Shimada.Tau PET imaging from the basics to the state–of–the–art[D].Neurological Therapeutics, 2022*

[9] *FQ Zhang, JL Jiang, JT Zhang, et al.Current status and future prospects of stem cell therapy in Alzheimer's disease[D]., 2020*

[10] *M Ashrafizadeh, R Mohammadinejad, SK Kailasa, et al.Carbon dots as versatile nanoarchitectures for the treatment of neurological disorders and their theranostic applications: A review[D].Advances in Colloid & Interface Science, 2020*

[11] *K Wang, X Zhu, E Yu, et al.Therapeutic Nanomaterials for Neurological Diseases and Cancer Therapy[D].Journal of Nanomaterials, 2020*

[12] *X Song, L Wang, D Fan.Insights into Recent Studies on Biotransformation and Pharmacological Activities of Ginsenoside Rd[D].Biomolecules, 2022*

[13] *JA Péron.Challenges and prospects in advancing clinical neuropsychology[D].Cortex, 2024*

[14] *X Peng, X Zhang, Gaurav Sharma and C Dai. Thymol as a Potential Neuroprotective Agent: Mechanisms, Efficacy, and Future Prospects[D].Journal of Agricultural & Food Chemistry, 2024*