Chapter 6

Gut Microbiota in Neurological Disorders – Parkinson's and Alzheimer's Disease

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Recent scientific investigations increasingly highlight the gut microbiome as a significant contributor to the development of neurodegenerative diseases. Among the most extensively researched conditions in this context are **Parkinson's disease (PD)** and **Alzheimer's disease (AD)**. These disorders are not solely confined to the brain; instead, they are marked by broader physiological disturbances that begin or are influenced by the gut.

A consistent finding in both PD and AD is the presence of **chronic systemic inflammation**, which is thought to be partially driven by microbial imbalances in the gut. Alongside this, individuals with these diseases often exhibit **gut barrier dysfunction**, commonly referred to as "leaky gut." This compromised barrier allows harmful bacterial products—such as lipopolysaccharides (LPS)—to enter the bloodstream, promoting inflammatory responses that may affect the brain over time.

Furthermore, **gut microbiota dysbiosis**—an imbalance in the composition and function of the gut microbial community—has been observed in patients with PD and AD. This dysbiosis can alter immune responses, impact neurotransmitter levels, and influence metabolic pathways, all of which are relevant to the progression of neurodegeneration.

6.1 Parkinson's Disease and the Gut

Parkinson's disease is a progressive neurodegenerative disorder primarily characterized by motor symptoms such as

bradykinesia, rigidity, and tremors. However, gastrointestinal (GI) symptoms like constipation often precede motor features by years, suggesting an early gut involvement[1].

6.1.1 Alpha-Synuclein and Gut Origin Theory

- **Alpha-synuclein (α-syn)** aggregates, the pathological hallmark of PD, have been found in the enteric nervous system (ENS) and vagus nerve in early disease stages[2].
- Braak's hypothesis proposes that PD may originate in the gut, with α-syn pathology spreading to the brain via the **vagus nerve**[3].

6.1.2 Microbiota Composition in PD

PD patients typically show:

- Decreased *Prevotella*, A **decrease in Prevotella**, a genus of beneficial gut bacteria, has been observed in individuals with certain neurological and gastrointestinal disorders, including **Parkinson's disease**. Prevotella plays a key role in the production of **mucin**, a glycoprotein essential for maintaining the protective mucus layer that lines the intestinal wall. Lower levels of Prevotella are associated with **reduced mucin production**, which can compromise **gut barrier integrity**. This weakened barrier—often referred to as a "leaky gut"—allows harmful substances like bacterial toxins and inflammatory molecules to enter the bloodstream, potentially triggering **systemic inflammation** and contributing to **neuroinflammatory processes**. The reduction in Prevotella may therefore play a critical role in gut–brain axis dysfunction and the progression of inflammatory and neurodegenerative conditions.which correlates with lower mucin production and gut barrier integrity.

- Research has shown that individuals with **Parkinson's disease (PD)** often exhibit an increased abundance of **Enterobacteriaceae**, a family of bacteria commonly linked to **pro-inflammatory responses**. Elevated levels of these bacteria in the gut are thought to contribute to **intestinal and systemic inflammation**, which may exacerbate neuroinflammation and the progression of PD. Notably, higher concentrations of Enterobacteriaceae have been correlated with **greater motor symptom severity**, including

tremors, rigidity, and bradykinesia. This suggests that the gut microbiota may influence not only brain function but also the **clinical expression of motor symptoms** in PD. These findings support the theory that **gut dysbiosis** plays a key role in the disease's pathophysiology, possibly by triggering or amplifying immune responses that affect the central nervous system. As a result, modulating the gut microbiome may offer a potential therapeutic avenue for managing motor symptoms in Parkinson's disease.[4]

6.1.3 Fecal Transplantation and Animal Studies

When mice are transplanted with gut microbiota taken from patients with Parkinson's disease (PD), they tend to develop more severe motor impairments—such as difficulty with movement and coordination—compared to mice receiving microbiota from healthy individuals. This experimental finding suggests that the altered microbial communities present in PD patients can actively contribute to worsening neurological symptoms. Additionally, these mice show higher levels of neuroinflammation, meaning their brains have increased immune activity and inflammation, which is a hallmark of Parkinson's disease pathology. This evidence supports the idea that changes in gut microbiota may play a causal role in driving or exacerbating the motor and inflammatory features of PD, highlighting the importance of the microbiota–gut–brain axis in neurodegenerative diseases.[5].

- Vagotomy, a surgical procedure that involves cutting the vagus nerve, has been linked to a reduced risk of developing Parkinson's disease (PD) in several large population studies. This finding supports the **gut-brain propagation theory**, which suggests that PD may begin in the gastrointestinal tract and spread to the brain via the vagusnerve.By severing this nerve, vagotomy may interrupt the transmission of pathological agents, such as misfolded proteins or inflammatory signals, from the gut to the brain. This epidemiological evidence reinforces the idea that the gut plays a critical role in the early stages of PD and that targeting gut-brain interactions could offer new preventive or therapeutic strategies.[6].

6.2 Alzheimer's Disease and the Microbiota

Alzheimer's disease is the most common form of dementia, marked by progressive memory loss, cognitive decline, and

accumulation of **amyloid-β (Aβ)** plaques and **tau tangles** in the brain.

6.2.1 Gut Dysbiosis and Amyloid Pathology

- Gut microbiota can promote amyloid deposition via systemic inflammation and increased intestinal permeability ("leaky gut")[7].
- Bacterial amyloids (e.g., curli from *E. coli*) may **cross-seed** with human Aβ, accelerating plaque formation[8].

6.2.2 Inflammatory Pathways

- Gut-derived **lipopolysaccharide (LPS)** and **trimethylamine N-oxide (TMAO)** can cross the blood-brain barrier and trigger microglial activation, contributing to neuroinflammation[9].
- Elevated plasma LPS and TMAO levels have been observed in AD patients and correlate with cognitive decline[10].

6.2.3 Microbiota Changes in AD

- AD patients show reduced levels of **anti-inflammatory bacteria** such as *Bifidobacterium* and *Eubacterium*
- Increased abundance of pro-inflammatory species including *Escherichia/Shigella*[11]

6.3 Therapeutic Insights and Interventions

Probiotics and Prebiotics

- *Lactobacillus* and *Bifidobacterium* strains reduce cognitive impairment and amyloid burden in AD mouse models[12].
- Probiotic supplementation has shown to improve Mini-Mental State Examination (MMSE) scores in human AD patients in small trials[13].

Dietary Interventions

- **Mediterranean diet** and **ketogenic diets** have neuroprotective effects mediated partly through microbial modulation. The Mediterranean diet, rich in fiber, polyphenols, and healthy fats, promotes the growth of **anti-inflammatory, SCFA-producing bacteria**, supporting brain health and reducing neuroinflammation. Similarly, the ketogenic diet, high in fats and low in carbohydrates, alters gut microbial composition

in ways that may enhance **mitochondrial function** and reduce **oxidative stress** in the brain. These microbial shifts help regulate the **gut-brain axis**, contributing to improved cognitive function and reduced risk or progression of neurological disorders. [14].

• Still experimental but shows promise in animal models by reducing amyloid pathology and improving cognition. These interventions appear to **modulate neuroinflammation**, improve **gut barrier integrity**, and alter the production of **neuroactive compounds** that can cross the blood–brain barrier or signal through the vagus nerve. As a result, treated animals often demonstrate **enhanced cognitive performance**, such as improved memory and learning in behavioral tests, compared to untreated controls.[15].

6.4 Mechanistic Summary

Mechanism	Effect
α-syn spread via vagus	Parkinson's progression
Gut-derived LPS/TMAO	Microglial activation, inflammation
Bacterial amyloids	Amyloid-β cross-seeding
SCFAs	Anti-inflammatory, neuroprotective

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