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**The Gut-Brain Connection in Parkinson's Disease and Its Novel Therapeutic
Possibilities**

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ABSTRACT

Parkinson's disease (PD) has long been characterized by the degeneration of dopaminergic neurons within the central nervous system, manifesting primarily as motor symptoms. However, recent research has ushered in a paradigm shift, highlighting the critical role of the gut-brain axis in the aetiology and progression of PD. This thesis delves into a comprehensive exploration of the intricate relationship between Parkinson's disease and the gut, with a specific emphasis on uncovering therapeutic potentials within this dynamic interplay. The bidirectional communication network of the gut-brain axis has gained prominence, with recent findings indicating the presence of Lewy bodies, a hallmark of PD, not only in the brain but also in the enteric nervous system, underscoring the significance of the gut in the disease process. The focus of this thesis is to unravel the complexities of the gut-brain relationship in PD, elucidating the molecular and cellular mechanisms driving communication between these seemingly disparate systems. Attention is also given to the role of the gut microbiota, a diverse community of microorganisms residing in the gastrointestinal tract, in influencing the progression of PD and its potential as a therapeutic target. The objective extends beyond deepening the understanding of the disease to discerning novel avenues for treatment by examining the intricate connections of the gut-brain axis. This thesis offers insights into the therapeutic potentials residing within these connections in the context of Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD), a progressive neurodegenerative disorder, has been characterized by motor symptoms rooted in the loss of dopaminergic neurons within the central nervous system. However, a paradigm shift in our understanding of Parkinson's disease has recently emerged, emphasizing the integral role of the gut-brain axis in its aetiology and progression. In this thesis I would like to focus on a comprehensive investigation into the relationship between Parkinson's disease and the gut, with a specific focus on uncovering the therapeutic potentials that lie within this dynamic interplay. I would like to devote myself in this paper to the developing new treatments methods based on a gut-brain relationships and on the possibilities of changing the microbiome in the gut.

The gut-brain axis, a bidirectional communication network linking the gastrointestinal tract and the central nervous system, has gained prominence as a potential key player in the pathophysiology of Parkinson's disease. Recent advancements in research have highlighted not only the presence of Lewy bodies, indicative of PD, in the brain but also in the enteric nervous system, underscoring the importance of the gut in the disease process.

This thesis seeks to unravel the complexities of the gut-brain relationship in Parkinson's disease, exploring the molecular and cellular mechanisms that drive communication between these two seemingly disparate systems. I focused on the role of the gut microbiota, a complex community of microorganisms residing in the gastrointestinal tract, in influencing the progression of PD and its potential as a therapeutic target.

My objective is not only to deepen understanding of the disease but also to discern novel avenues for treatment by examining the gut-brain axis. This thesis is offering insights into the novel therapeutic potentials residing within the intricate connections between the gut and the brain in the context of Parkinson's disease.

CHAPTER 1 - PARKINSON'S DISEASE

1.1 Pathophysiology

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons located in the substantia nigra, a region of the brain responsible for motor control. The hallmark pathological feature of PD is the presence of Lewy bodies, abnormal fibrillar aggregates that form within brain cells. These Lewy bodies primarily consist of alpha-synuclein protein, and their accumulation disrupts normal cellular function, playing a pivotal role in the degeneration of dopamine-producing neurons. The impact of misfolded alpha-synuclein protein extends beyond the substantia nigra, affecting not only the central nervous system but also the peripheral and enteric nervous systems. This widespread disruption contributes to the diverse range of symptoms observed in individuals with PD, extending beyond the well-known motor impairments. The misfolding of alpha-synuclein protein influences various neural pathways, leading to disturbances in the intricate balance of neurotransmitters and cellular signalling. One of the key therapeutic strategies in managing PD involves the supplementation or substitution of dopamine, aiming to alleviate the motor symptoms associated with the disease. However, the exact mechanisms that trigger the initiation of PD and the precise pathways through which Lewy bodies exert their detrimental effects remain subjects of active research and exploration (Tan, 2022).

Recent research suggests a potential relationship between the microbiome in a gut and the brain functioning. Alpha synuclein aggregates are mostly located in the brain. However, they also have been found in the enteric nervous system, which is endorsing the idea of brain-gut connection. Based on this research, there is a potential relationship between Parkinson's disease (brain neurodevelopment) and the microbiome in the gut. The nonmotor symptoms such as a gastrointestinal manifestation, support the idea. Involvement of the Enteric Nervous system,

sometimes referred as the 'second brain', which operates independently but is connected to the central nervous system, is a proof of a possible brain-gut connection (Tan, 2022).

Gastrointestinal tract (also referred as gut) is crucial for digestion and for absorption of nutrients which we consume. Microbiome refers to a collection of diverse microorganisms, including viruses, bacteria, fungi, and other microbes. Significant concentration of microbiome is in the digestive system. Human intestine contains approximately quadrillion microbes. The role of bacteria in a gut has been a centre of attention in last years. It is well established that the microbiome is responsible for an overall healthy functioning of an individual. The normal microbiota has several functions to protects an individual and to maintain a structure. The microbiota is influenced by several ways, including lifestyle, diet, and probiotics intake.

1.2 Symptoms

The manifestations of PD encompass a spectrum of both motor and nonmotor symptoms, collectively painting a complex clinical picture. Nonmotor symptoms are adding layers of complexity to its diagnosis and progression. This comprehensive examination sheds light on the various facets of PD symptoms, emphasizing the need for a holistic approach in understanding and managing this debilitating condition (Mulak, 2015).

The motor symptoms are the most recognised and have a great impact on individual's movement abilities. The motor symptoms include the hallmark involuntary shaking known as tremor, which often presents at rest. Additionally, slowness of movement termed bradykinesia, muscle stiffness or rigidity, postural instability, and challenges in maintaining balance. These motor symptoms collectively contribute to the clinical preservation of PD. However, the intricacies of PD extend beyond these motor impairments, as nonmotor symptoms often play a pivotal role. Remarkably, some nonmotor symptoms have been observed to precede the onset of motor symptoms by over a decade, shedding light on the intricate nature of PD's progression

(Shrag, 2015). Among the nonmotor symptoms, olfactory impairment, constipation, sleep disorders, gastrointestinal manifestations, and depression emerge as significant contributors. The intriguing aspect lies in the fact that these nonmotor symptoms, often seemingly unrelated to movement, can act as early indicators of PD, prompting questions about how to effectively assess the risk of developing the disease. Notably, the severity and manifestation of symptoms can widely vary among individuals diagnosed with PD, adding another layer of complexity to its clinical presentation. (Mulak, 2015).

1.3 Risk factors

Despite significant strides in understanding the molecular and cellular underpinnings of Parkinson's disease, there is still much to unravel about the complex interplay of genetic, environmental, and biological factors that contribute to the onset and progression of this debilitating condition. As research continues to advance, unravelling the mysteries surrounding Parkinson's disease holds promise for developing more targeted and effective treatments to improve the lives of those affected by this neurodegenerative disorder (Klann et al., 2022).

Parkinson's disease stands as the second most common neurodegenerative disorder, with an estimated prevalence of approximately 1% among individuals over the age of 65 (Nussbaum, 2003). While the exact cause of developing Parkinson's disease remains unknown, there is a growing understanding that a combination of genetic and environmental factors plays a pivotal role in its manifestation.

Genetic factors contribute significantly to the risk of developing Parkinson's disease. Several genes have been implicated in familial forms of the disease, where a clear hereditary pattern is observed. Individuals with a family history of Parkinson's have an increased risk of inheriting genetic mutations associated with the condition. However, it is important to note that most Parkinson's cases are sporadic, lacking a clear familial link (Nussbaum, 2003).

Environmental risk factors also play a crucial role in the development of Parkinson's disease. Certain behaviours and exposures are associated with an increased risk of developing the condition. For instance, smoking has been identified as a potential protective factor, reducing the risk of Parkinson's disease. Conversely, high caffeine consumption, exposure to heavy metals, and certain pesticides have been implicated as environmental risk factors (Ascherio, 2016).

Aging is a significant risk factor for Parkinson's disease, with the prevalence of the condition rising sharply in older age groups. The cellular changes and accumulated damage over time may contribute to the increased vulnerability of the aging brain to neurodegenerative processes (Nussbaum, 2003).

PD is a multifactorial disorder with a complex aetiology. The interplay between genetics and the environment, coupled with the influence of aging, creates a landscape of potential risk factors that vary from individual to individual.

Understanding these risk factors is crucial for not only identifying those at higher risk but also for developing preventive strategies and targeted interventions. By unravelling the intricate dance of genetic, environmental, and biological factors contributing to Parkinson's disease, the scientific community is moving closer to a more comprehensive understanding of the condition, offering hope for improved diagnostic accuracy, personalized treatment plans, and ultimately, a future where the impact of Parkinson's disease is significantly mitigated (Klann et al., 2022).

1.4 Diagnosis

PD is the second most common neurodegenerative disorder, accounting for 0.5%–5% of the population older than 65 years (Tanner, 1996). The diagnosis of PD involves a comprehensive evaluation that combines clinical assessments, medical history, and sometimes

additional diagnostic tests. It is crucial to involve a neurologist or movement disorder specialist in the diagnostic process. The diagnosis is primarily clinical, and there is not a definitive test for PD. The key components diagnosing a PD is a review of patient's medical history, physical examination for assessing motor symptoms such as tremor, bradykinesia, and muscle rigidity. Another part of differential diagnosis is the assessment of non-motor symptoms such as constipation, sleep disturbances, and olfactory impairment. Cognitive functions are tested for impairment and for changes. Specialized imaging studies are used to test brain processes and to rule out other conditions (Rao, 2006). Functional imaging is used for diagnosing. It involves dopamine transporter imaging to assess the dopaminergic activity or presence of presynaptic neuronal degeneration (Stoker, 2018). Blood tests and other medical evaluations mainly aim at excluding another disease (Berardelli, 2013). Genetic testing is used when there is a family history of PD.

Diagnosis of Parkinson disease may be very challenging, especially in the early stages when symptoms may be subtle. The involvement of multidisciplinary approach for diagnosing enhances the accuracy and ensures appropriate management and support for PD patients.

Parkinson disease is a progressive disorder, therefore following-up assessments are needed to monitor symptom progression and efficacy of the treatment over time.

1.5 Treatment

Research has started to uncover intriguing connections between gut disorders, dietary factors, and the development as well as the progression of PD (Chao, 2020). This has sparked interest in understanding the potential role of the gut-brain axis in the aetiology of PD. The intricate interplay between the gut and the brain is being explored as researchers delve deeper into the complexities of PD, shedding light on both motor and nonmotor symptoms. This

exploration not only enhances our understanding of PD but also opens new possibilities for potential therapeutic interventions.

The gut-brain axis, a bidirectional communication network between the gastrointestinal system and the central nervous system, has become a focal point in PD research. Recent studies suggest that alterations in gut microbiota may influence the progression of PD, potentially contributing to the neurodegenerative process (Chao, 2020). As scientists uncover these connections, they are paving the way for novel approaches to managing PD, possibly through interventions targeting the gut microbiome.

Despite the significant strides in understanding the intricacies of PD, it remains a disease without a cure. Management of symptoms is primarily achieved through medications such as Levodopa, a dopamine precursor that helps alleviate motor impairments. Other medications, including dopamine agonists and MAO-B inhibitors, are also employed to enhance dopaminergic function and mitigate symptoms. In cases where medication alone is insufficient, Deep Brain Stimulation (DBS) stands as an alternative. This surgical procedure involves the implantation of electrodes into specific brain regions to regulate neuronal impulses and alleviate symptoms (Armstrong, 2020).

The quest for more effective treatments continues, with ongoing research focused on unravelling the root causes of PD. Research is exploring not only the traditional neurological aspects but also venturing into the realms of the gut-brain axis and other potential contributors. Understanding the multifaceted nature of PD is crucial for developing targeted therapies that address both the motor and nonmotor aspects of the disease, ultimately improving the quality of life for individuals affected by PD (Nguyen, 2015).

PD presents a complex tapestry of motor and nonmotor symptoms, intertwined with emerging research on the gut-brain axis. Current therapeutic approaches, while helpful in managing symptoms, fall short of providing a definitive cure. The integration of gut-related

findings into PD research is opening up new avenues for treatment possibilities, underscoring the importance of a comprehensive and multidisciplinary approach in the ongoing battle against this debilitating neurodegenerative disorder. As the scientific community continues to unravel the mysteries of PD, the hope is that this knowledge will lead to breakthroughs in both understanding the disease and developing more effective interventions for those living with Parkinson's (Nguyen, 2015).

1.6 Psychological problems in PD patients

Beyond the well-established motor symptoms, individuals with PD often experience a range of psychological challenges, including depression, anxiety, cognitive impairments, and sleep disturbances. Understanding the underlying mechanisms and reciprocal influences between Parkinson's disease and psychological symptoms is crucial for providing comprehensive care to affected individuals (Won Han, 2018).

Psychiatric symptoms, such as depression, anxiety, hallucinations, delusions, anhedonia, apathy, compulsive behaviours, and cognitive impairments can occur as well as other symptoms. The psychiatric problems affect the quality of life of the patient and of his family. It is important to put the same effort on the non-motor symptoms as well as motor symptoms. The impact of PD extends beyond the realm of motor dysfunction, as patients often grapple with a myriad of psychological challenges that significantly affect their overall well-being. Understanding and addressing these psychological aspects is crucial for comprehensive care and improved quality of life for individuals living with PD.

Depression and anxiety are prevalent psychological issues among PD patients (Aarsland, 2015). The chronic nature of the disease, coupled with the challenges posed by motor symptoms, can lead to feelings of sadness, hopelessness, and frustration. Anxiety may stem from uncertainties about the progression of the disease, fear of falling, or concerns about social

interactions. Both depression and anxiety can exacerbate motor symptoms and diminish the individual's ability to cope with the demands of daily life. The prevalence of suicidal behaviour is 17%-30% higher than general population (Lee T, 2016). Anxiety is often misinterpreted and mistreated for motor symptoms of PD. Anxiety symptoms are often accompanied with social phobia (Won Han, 2018).

Psychosis, including hallucinations and delusions, is a notable concern in advanced stages of Parkinson's Disease. Patients may experience vivid and sometimes distressing hallucinations, affecting their perception of reality. These symptoms can be exacerbated by dopaminergic medications, complicating treatment strategies. Addressing psychosis requires a delicate balance between managing motor symptoms and minimizing adverse psychiatric effects (Won Han, 2018).

Sleep disturbances are common among PD patients. It can cause further psychological disturbances. The visible motor symptoms of Parkinson's Disease can lead to social isolation and stigmatization, contributing to psychological distress. Patients may withdraw from social activities due to embarrassment or fear of judgment, leading to a diminished quality of life. Healthcare providers should emphasize the importance of social support and work towards destigmatizing PD in the broader community (Maffoni. 2017).

CHAPTER 2 – GUT-BRAIN AXIS IN PARKINSON’S DISEASE

2.1 The Enteric Nervous System as the ‘second brain’

The Enteric Nervous System (ENS) serves as a complex and semi-independent neural network often referred to as the 'second brain' due to its extensive capabilities and relative autonomy. While the intricate relationship between specific neurons and complex behaviours like gut motility and secretion remains a challenge, ongoing research is making rapid strides in this domain. The evolving recognition of the ENS as a complex neural network underscores its importance beyond basic gastrointestinal functions, presenting opportunities for novel insights and therapeutic strategies in the realm of neurological and gastrointestinal disorders (Gershon, 1999).

The ENS system is embedded in the lining of the gastrointestinal system, beginning in the esophagus and extending down to the anus (Hall, 2011). ENS is composed of a vast network of neurons, glial cells, and interconnected ganglia. This intricate system is endowed with the capacity for local information processing, enabling it to regulate and modulate gastrointestinal functions independently of the central nervous system. The ENS integrates sensory information from the gut environment, coordinating various processes such as peristalsis, nutrient absorption, and immune responses. Importantly, the ENS communicates bidirectionally with the central nervous system (CNS) through a complex network of pathways, including the vagus nerve, forming the basis for the gut-brain axis (Fung, 2020).

2.2 The gut-brain axis

The gut-brain axis represents a bidirectional communication network between the gastrointestinal tract and the central nervous system. This communication does not follow a singular path. It involves a sophisticated network of neural, hormonal, and immune pathways,

showcasing the complexity of the signals exchanged between these two vital systems. The gut-brain axis is not merely a passive connection but rather a dynamic and intricate system with a pivotal role in shaping distinctive psychological functioning (Mulak, 2015).

The significance of the gut-brain axis transcends its structural complexity, extending into the realm of mental health. Emerging research has underscored its influence on various aspects of psychological well-being. The interdependence between the gut and the brain becomes even more intricate when considering the presence of the microbiota, a complex community of microorganisms residing within the gut. This microbiota, often referred to as the gut microbiome, represents a diverse ecosystem that significantly contributes to overall health, impacting digestion, metabolism, and even cognitive function. The microbiota's role in the communication between the gut and the brain adds an additional layer of complexity to the gut-brain axis. These microorganisms produce bioactive compounds, including neurotransmitters and metabolites, which can influence neural signalling and immune responses. As such, the disturbances in the delicate balance of the gut-brain axis have emerged as crucial factors in the pathophysiology of various neurological disorders, including PD (Liu, 2020). As indicated in figure 1, alpha-synuclein, a neuronal protein highly concentrated at synapses and abundantly present in the brain is linked to neuropathology in Parkinson's disease and related neurodegenerative disorders, such as Lewy Body Disease and Multiple System Atrophy. This association primarily stems from the formation of abnormal aggregates, which have the potential to disrupt cellular homeostasis, synaptic function, and lead to neuronal degeneration (Klann,2022)

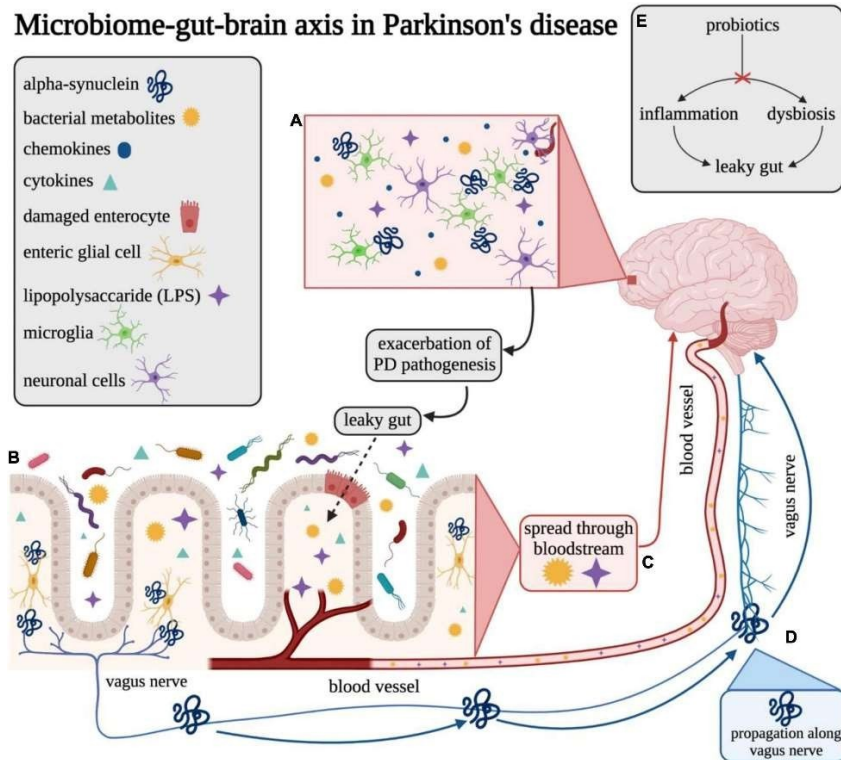


Figure 1. Overview of the gut–brain axis in Parkinson’s disease, presenting a visual summary of the proposed microbiome–gut–brain axis. (A) Bacterial metabolites, like LPS, may breach the blood–brain barrier (BBB), triggering the release of chemokines/cytokines and fostering inflammation in Parkinson’s disease. (B) Microbes in the gut lumen can activate inflammatory pathways, damaging enterocytes and compromising gut epithelial barrier integrity (leaky gut). (C) Bacterial metabolites, including LPS, can move from the gut lumen to the bloodstream through the compromised gut barrier, potentially causing systemic and neuroinflammation. (D) Microbes at the gut–ENS intersection may induce misfolded α -synuclein, which can propagate to brain neurons via the vagus nerve. (E) Probiotic interventions aim to counter dysbiosis, altering microbiome composition, reducing inflammation, and enhancing gut barrier integrity to prevent or decrease microbial translocation. (Source: Klann et al., 2022, p. 3).

Parkinson's disease, a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons, has been linked to disruptions in the gut-brain axis. Studies have

demonstrated alterations in the composition of the gut microbiota in individuals with PD, suggesting a potential role of the microbiome in the development or progression of the disease. Understanding these connections provides valuable insights into the intricate relationship between gut health and neurological disorders, paving the way for innovative therapeutic approaches (Rietdijk, 2017).

Considering these discoveries, the recognition of the gut-brain relationship has opened new options for therapeutic interventions. Targeting the gut microbiota through probiotics, prebiotics, or dietary modifications has emerged as a promising avenue for influencing not only gastrointestinal health but also mental well-being. Influencing the gut-brain axis to enhance overall health and diminish the impact of neurological disorders is an important part in medical research. New discoveries regarding the gut-brain connection could improve treatment strategies in the future and deepen the understanding of the gut and brain connection.

2.3 Aggregation of alpha-synuclein

Alpha-synuclein is a protein at presynaptic terminals abundantly found in the brain. Abnormal accumulation of this protein plays a main role in a neurodegenerative disorder, including PD (Uversky, 2009). Aggregation of alpha-synuclein proteins forms a Lewy bodies, which are the pathological hallmarks of the disease. The accumulation of these proteins disrupts synaptic function and initiates neuronal degeneration, leading to the characteristic motor and cognitive impairments observed in PD. Its abnormal accumulation disrupts the synaptic function and induce neuronal degeneration. While most of the pathology of Parkinson's disease is found in a brain, accumulating evidence suggests that alpha-synuclein pathology may originate in the gut and possibly spread the pathological proteins to the brain (Klann, 2022). This concept challenges the traditional notion that neurodegenerative disorders, particularly

those involving alpha-synuclein, exclusively manifest within the confines of the central nervous system.

The extracellular forms of alpha-synuclein have been found in both, in brain and in the interstitial fluid. These discoveries have added complexity to our understanding of its role in neurodegeneration (Santos, 2019). A study which was using primary neuronal cell cultures found that approximately 70% of extracellular alpha-synuclein originates from neuronal activity dependent pathways (Yamada, 2018). Most of the extra cellular forms originates from neuronal activity-dependent pathways. It brings focus on the relationship between the synaptic function and the presence of alpha-synuclein protein outside of cells. This raises questions about the potential implications of alpha-synuclein in intercellular signalling and communication within the neural network.

Further, it was discovered that there is a connection between neuroinflammation and misfolded alpha-synuclein in PD (Alvarez-Erviti, 2011). However, if neuroinflammation is causing misfolding of the protein or if misfolding of the protein is causing neuroinflammation have not been determined.

2.4 Gut-bran axis and Braak's hypothesis

There are 2 forms of Parkinson's disease: familial and sporadic. Familial disease refers to a genetic cause. It is caused by a mutation of a certain gene. In familial diseases, there is a clear pattern of PD running in families. Most of the cases of PD are sporadic, where causes of the disease are unknow. However, it is believed that a sporadic PD is caused by a combination of genetic and environmental factors. Potential risks include genetics, age (PD is more common among older adults), neurodegenerative processes and environmental factors such as exposure to pesticides and certain toxins. (Rietdijk, 2017). Two twin studies have found that sporadic PD has a significant genetic component (Wirdefeld,2011). It had been found that PD is more

common among Caucasians and Hispanics, than Asians and Afro-Americans, which indicates a potential genetic factor (Wright, 2010). Braak's hypothesis states the sporadic PD.

The research of German neuroanatomist Heiko Braak has significantly contributed to redefining our understanding of PD. Braak and his colleagues have put forth a compelling staging model for PD that challenges the long-standing notion that the disease solely originates within the brain. According to their model, PD may have its roots in the gastrointestinal tract, suggesting a potential prelude to the manifestation of symptoms in the central nervous system. The Braak staging model proposes a sequential progression of PD pathology, starting in the gut before ascending to the brain. This innovative model introduces the possibility that the gastrointestinal tract could serve as a critical focal point for the initiation and early development of PD. The intricate connections between the gut and the brain, often referred to as the gut-brain axis, become a focal point in understanding the complex dynamics involved in the onset and progression of PD. The implications of Braak's model extend beyond challenging established beliefs; they offer a new perspective on potential therapeutic interventions. If the gastrointestinal tract plays a role in the early stages of PD, targeting this aspect of the disease may provide opportunities for intervention and prevention. Investigating the mechanisms by which pathology originates in the gut and understanding how it progresses to the brain could unveil novel targets for therapeutic strategies aimed at halting or slowing the progression of PD. This evolving understanding of PD underscores the importance of interdisciplinary collaboration between neurology, gastroenterology, and related fields. The integration of insights from various disciplines becomes crucial in deciphering the intricate connections between the gut and the central nervous system, shedding light on the multifaceted nature of PD. As research in this area continues to unfold, it holds the potential to revolutionize our approach to both the diagnosis and treatment of PD, offering hope for more effective strategies to manage and mitigate the impact of this complex neurodegenerative disorder.

According to the Braak's hypothesis, a protein alpha-synuclein accumulates in an enteric nervous system (ENS) of the gut. The accumulation starts following events that can lead to motor and non-motor symptoms of PD. The gut triggers misfolding of the protein, which begins in the ENS. Subsequently, it promotes the transfer of the misfolded alpha-synuclein to the brain, where Lewy bodies are formed. Clinical evidence had been stated. PD patients often suffer of altered intestinal permeability, also called 'leaky gut' and inflammation. Intestinal barrier defects occur in some patients early during the onset of the disease. The observations were only true for some patients (Rietdijk, 2017). Therefore, we cannot generalize these findings for all.

As stated by Braak, the sporadic PD starts in two areas. In the neurons of nasal cavity and in the neurons of the gut. It is hypothesized that the pathological neurons spread through specific pathways, through the olfactory tract and through the vagal nerve towards the central nervous system. According to Braak's model, the pathological process commences in the lower brainstem in the dorsal nucleus of the vagus nerve. In the same area the olfactory structures are located. It continues rostrally through other regions of the brain. Eventually it reaches the cerebral cortex.

Another part of Braak's hypothesis is the spread of alpha-synuclein through the enteric route. The enteric route refers to the pathway by which substances are absorbed in the gastrointestinal tract (GI). The GI tract is complex and involves the mouth, esophagus, stomach, small intestine, and large intestine. Braak proposed a potential involvement of the GI in the development and progression of PD. Gut is connected to CNS by vagal and pelvic nerves and through sympathetic pathway. He hypothesized that an unknown pathogen may enter the body through the nasal cavity. The pathogen may induce changes in the normal molecules of alpha-synuclein protein, therefore result in its aggregation. The pathogen could enter the CNS from

ENS through the vagal nerve and the dorsal nucleus of the vagus in the medulla oblongata. It may gain access to the CNS via retrograde transport. The pathogen may spread within the CNS.

Altogether, according to Braak's hypothesis the pathology of Lewy bodies commences in the gut. The supporting factors are high prevalence of gut dysfunction among patients with PD and that the pathology of Lewi bodies is visible in gut tissues prior to the onset of PD disease. Pathological accumulation is spread to the CNS via vagal neve. It is supported by animal studies, where animals received fibril injections in the gut and they developed brain pathology and motor dysfunction only when the vagal nerve was intact (Bindas, 2021). It leads to onset of motor symptoms and to diagnosis of PD. Motor symptoms are getting progressively worse over time and it is correlated with the development of symptoms.

Historically, the hypothesis has been criticized for its lack of applicability. The hypothesis is not universally accepted. Some researches argue that the observed pathology in the ENS is a consequence rather than a cause of PD (Rietdijk,2017). However, Braak provided an insight for understanding the involvement of the ENS and it has significant implications for therapeutic interventions. Several studies provided support for Braak's hypothesis. Researchers discovered a presence of an alpha-synuclein aggregates in the enteric nervous system of individuals with PD, even before the onset of symptoms. Which supports the idea that PD originates in the gut. The potential connection between alpha-synuclein and gastrointestinal symptoms have been discovered. (Rietdijk, 2017). The preceding non motor symptoms, such as problems with olfaction, gastrointestinal problems like nausea, constipation and defecatory difficulty are serving as a support for the Braak's hypothesis. Evidence supports some aspects of this hypothesis such as the presence of alpha-synuclein in the vagus nerve and their ability to spread from the ENS to the CNS (Musgowe, 2019). Additional research is needed to further discover implications of the gut-brain relationship and for further validation. Further findings are necessary to assess whether the pathological alpha-synuclein originates in the gut

independently from the brain. If gut plays a significant role in PD, it opens a new possibility for the treatment and early diagnosis of PD.

2.5 Gut inflammation and neuroinflammation in PD

Individuals diagnosed with PD often exhibit signs of inflammation and disruption in the balance of gut microorganisms, a condition known as intestinal dysbiosis. Furthermore, this dysbiosis might play a role in heightening the permeability of both the intestinal barrier and the blood-brain barrier (BBB) in Parkinson's patients. The compromised integrity of these barriers could potentially facilitate the passage of substances that contribute to inflammation (Baizabal-Carvalho, 2020). Bacterial endotoxins, substances produced by certain bacteria, are believed to amplify inflammation both in the systemic circulation and within the CNS of PD's patients. This systemic and CNS inflammation is considered a significant factor in the progression of PD.

Additionally, toxins originating from the gastrointestinal (GI) tract may expedite the degeneration of neurons and contribute to the development of dyskinesia, the involuntary, erratic movements commonly observed in Parkinson's patients (Baizabal-Carvalho, 2020).

Exploring potential therapeutic avenues, some propose that modifying the dysbiosis in the gut could offer benefits for individuals with Parkinson's disease. However, it is worth noting that comprehensive studies in this area are currently limited, and further research is needed to establish the efficacy of such interventions.

CHAPTER 3 – THE GUT MICROBIOME IN PARKINSON’S DISEASE

3.1 Gut microbiome

In the intricate and symbiotic relationship between humans and their microbiome, a key player resides within the gut – the complex communities of microorganisms collectively known as the gut microbiota. Recent scientific inquiry has unveiled the pivotal role of the microbiome in mediating communication between the ENS and the CNS. This intricate and bidirectional interaction has gained significant attention, particularly in the context of CNS-related co-morbidities, spanning anxiety disorders, mood disorders, autism spectrum disorders, Alzheimer's disease, PD (Santos, 2019).

As the body of evidence linking disruptions in the microbiome to various CNS-related conditions continues to grow, Johnson (2018) highlights that the composition of the microbiome can exert profound effects on behaviour and mood. Notably, specific bacterial strains, such as *Lactobacillus* and *Bifidobacterium* species, have been suggested to have anxiolytic effects in both animal models and human studies, underscoring the potential therapeutic implications of modulating the gut microbiota for mental health.

The link between the gut microbiome and PD has emerged as a particularly intriguing avenue of research. According to Per Saris from the University of Helsinki, the composition of the microbiome in the gut could be a contributory factor in the development of PD. Building on this, the findings of Huynh (2023) suggest that exposure to *Desulfovibrio* bacterial strains may be associated with the development of PD. Statistical analyses revealed significant disparities in nematode (worm) models fed *Desulfovibrio* bacteria obtained from PD patients compared to those fed bacteria from healthy individuals or *E. coli* strains. Worms fed *Desulfovibrio* from PD patients exhibited higher quantities and larger alpha-synuclein

aggregates, a protein hallmark of PD. Additionally, nematodes fed *Desulfovibrio* strains from PD patients experienced elevated mortality rates compared to those fed *E. coli* LSR11 bacteria. These findings strongly suggest that *Desulfovibrio* bacteria may play a significant role in the development of Parkinson's disease by promoting the aggregation of alpha-synuclein. As indicated in the figure 2., the dispersion of alpha-syn aggregate volume is illustrated, with individual worms analyzed in (A) represented by dots, and outliers emphasized in (B). The boxes in the graphs illustrated the first and third quartiles, with the lower and upper edges representing the interquartile range, and the medians were depicted by horizontal lines within the boxes. This comprehensive analysis, as reported by Huynh et al. (2023, p.7), contributes valuable data to our understanding of the impact of bacterial diets on alpha-syn aggregation in *C. elegans*, potentially shedding light on relevant factors in neurodegenerative processes.

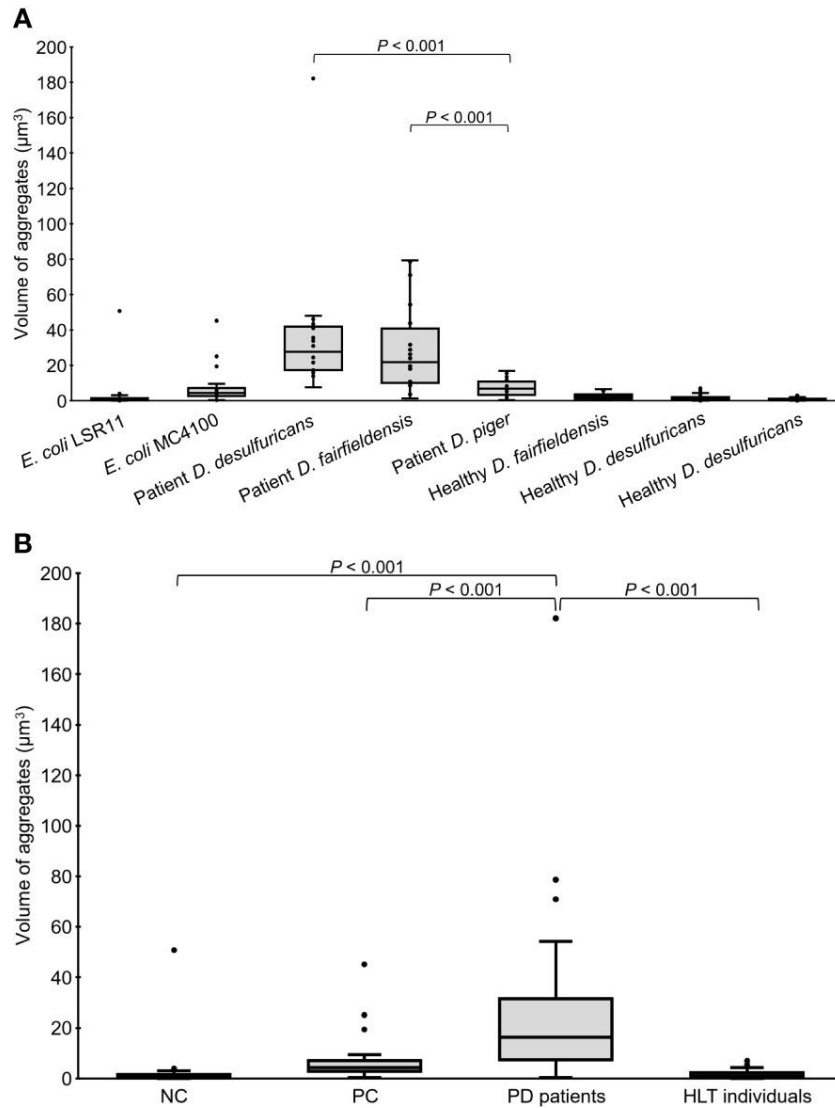


Figure 2. The alpha-syn aggregate volume in the head region of *C. elegans* at the day 4 adult stage, when fed with various bacteria, was assessed both individually (as shown in A) and collectively (as depicted in B). The bacterial diets included NC (negative control: *E. coli* LSR11), PC (positive control: *E. coli* MC4100), PD patients (DSV strains from individuals with PD), and HLT individuals (DSV strains from healthy individuals). Analysis was conducted on twenty worms per bacterial diet. In the graphical representation, dots indicate the worms analyzed in (A) or outliers in (B). The boxes depict the first and third quartiles (lower and upper edges, respectively), and the medians are represented by horizontal lines within the boxes. (Source: Huynh et al., 2023, p.7).

A pivotal study by Li et al. (2015) observed marked differences in the microbiome composition between individuals with PD and those without. PD patients exhibited alterations in various bacterial genera, emphasizing the potential role of the gut microbiome in the complex landscape of neurodegenerative disorders.

Expanding the scope of microbial dysbiosis, researchers are now delving into not only bacteria but also bacteriophages within the microbiome. Bacteriophages, or phage, are viruses that parasitize bacteria, exerting significant influence on the regulation of interactions within the microbiome. These entities participate in processes such as horizontal gene transfer and antagonistic coevolution, thereby impacting the overall balance within the microbial community. Beyond their role in bacterial dynamics, phage can directly influence human health by participating in intestinal inflammatory processes and potentially contributing to the misfolding of α -synuclein, a protein intricately linked to the pathogenesis of PD (Santos, 2019).

In a Li's (2023) comprehensive analysis distinctions in the microbial composition between individuals with PD and healthy controls were evident. Among the genera consistently elevated in PD, were *Bifidobacterium*, *Alistipes*, *Christensenella*, *Enterococcus*, *Oscillospira*, *Bilophila*, *Desulfovibrio*, *Escherichia/Shigella*, and *Akkermansia*. On the contrary, *Prevotella*, *Blautia*, *Faecalibacterium*, *Fusicatenibacter*, and *Haemophilus* consistently exhibited lower levels in PD patients. Moreover, multiple reports indicated alterations in both directions for *Bacteroides*, *Odoribacter*, *Parabacteroides*, *Butyricicoccus*, *Butyrivibrio*, *Clostridium*, *Coprococcus*, *Lachnospira*, *Lactobacillus*, *Megasphaera*, *Phascolarctobacterium*, *Roseburia*, *Ruminococcus*, *Streptococcus*, and *Klebsiella*. This wealth of evidence underscores the intricate and multifaceted nature of the microbial differences associated with Parkinson's disease (Li, 2023).

As our comprehension of the gut-brain axis continues to unfold, these insights into the complex interplay between the microbiome, CNS, and various health conditions pave the way

for innovative therapeutic strategies. Targeting the microbiome, inclusive of both bacteria and bacteriophages, holds promising potential for therapeutic interventions in PD. This interdisciplinary approach not only broadens our understanding of the intricate relationship between the gut microbiota and neurodegenerative diseases but also opens avenues for exploring novel treatment modalities that address this multifaceted interplay. The evolving field of microbiome research promises to unravel new dimensions in our quest for effective interventions in neurodegenerative disorders, offering hope for improved outcomes and quality of life for individuals affected by these conditions.

3.2 Gut Permeability and PD's

Modifications in the composition of the gut microbiota can exert far-reaching effects on the function of the gut barrier and intestinal permeability. This intricate relationship involves not only GI epithelial cells and the immune system but also extends to the END encompassing both neurons and glial cells (Vizcarra, 2015).

In the context of PD, heightened intestinal permeability, colloquially termed "leaky gut," has been identified as a noteworthy phenomenon. The integrity of the intestinal barrier plays a pivotal role in preventing the translocation of harmful substances from the gut into systemic circulation. Disruptions in gut permeability, as observed in PD patients, may create a gateway for the entry of proinflammatory molecules, contributing to the initiation and progression of neuroinflammation associated with PD (Anderson, 2016).

Several mechanisms have been proposed to elucidate the observed increase in gut permeability in PD. Chronic inflammation, dysregulation of tight junction proteins, and alterations in the gut microbiota are implicated as potential contributors. This multifaceted interplay may collectively compromise the integrity of the intestinal barrier, fostering an

environment conducive to the entry of proinflammatory molecules, thereby influencing systemic inflammation and potentially impacting the central nervous system (Anderson, 2016).

Recent investigations into the gut phage composition (phagobiota) have revealed significant differences between individuals with PD and healthy counterparts. Notably, PD patients exhibited a depletion of *Lactococcus* bacteria, a key player in regulating gut permeability and dopamine production—two factors intricately linked to early signs of PD within the gut (Tetz, 2018).

Probiotic bacteria have emerged as potential allies in alleviating gastrointestinal symptoms in PD. Probiotics exert their influence on the central nervous system by fostering positive interactions with the commensal gut microbiota and modulating inflammation originating from the gut. The gut microbiota in PD patients often displays a pro-inflammatory profile due to increased permeability to endotoxins such as lipopolysaccharide, and bacterial amyloids may contribute to an inflammatory environment in the gut. Probiotic interventions have demonstrated anti-inflammatory responses in patients with conditions like multiple sclerosis, suggesting potential benefits for PD patients, although specific confirmatory reports are still lacking. One promising strategy involves leveraging the ability of *Lactobacilli* to inhibit the formation of biofilms by pathogenic bacteria. However, it is crucial to note that the effects of probiotics can exhibit considerable variability from person to person, as highlighted by recent studies (Santos, 2019). As the intricate connections between the gut microbiota, gut permeability, and PD unfold, ongoing research endeavours are poised to unveil novel therapeutic strategies for managing this complex neurodegenerative disorder.

3.3 Gut dysbiosis

Gut dysbiosis in PD is characterized by an imbalance or disturbance in the composition and functioning of the gut microbiota. This phenomenon is multifaceted, involving several key

aspects that contribute to our understanding of its implications in PD. One significant aspect is the occurrence of small intestinal bacterial overgrowth (SIBO) in PD, a condition marked by the excessive growth of bacteria in the small intestine. SIBO is not uncommon in PD and has been associated with GI motility, a prevalent issue in individuals with PD. Tan (2014) highlighted the link between SIBO and decreased GI motility in PD, offering insights into potential mechanisms contributing to gut dysbiosis.

According to Guo et. al (2022), the connection among gut microbiota dysbiosis, the integrity of the intestinal barrier, and gut inflammation reveals a reciprocal interaction. Changes in gut microbiota can elevate the permeability of the intestinal epithelial barrier, exposing the enteric nervous system and the immune system to bacteria and their byproducts, thereby fostering gut inflammation. In turn, the inflammatory milieu exacerbates both the malfunction of the intestinal barrier and the dysbiosis of gut microbiota. The figure 3. Illustrates the connections between gut microbiota dysbiosis, inflammation, and PD. Dysbiosis disrupts the intestinal barrier, leading to gut inflammation, pro-inflammatory cytokine production, and α -syn misfolding. Misfolded α -syn may reach the brain via the vagus nerve or bloodstream, and pro-inflammatory cytokines can access the CNS through the humoral pathway. Both α -syn and cytokines may compromise the blood–brain barrier, activating microglia and contributing to neuroinflammation and neurodegeneration in PD.

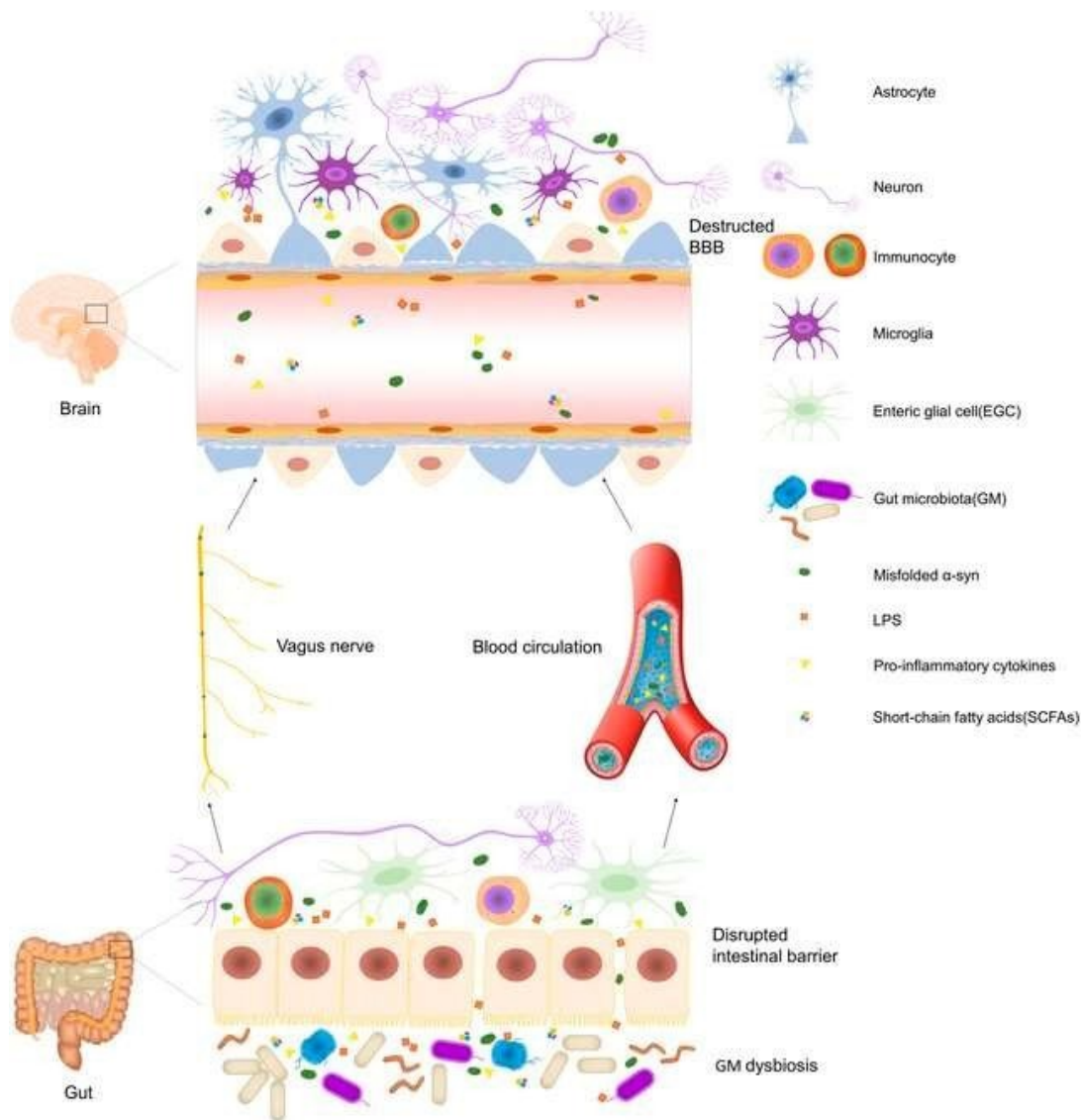


Figure 3. Schematic depiction outlines the mechanisms connecting gut microbiota dysbiosis, inflammation, and PD. GM dysbiosis is implicated in disrupting the intestinal barrier and inducing gut inflammation, fostering the production of pro-inflammatory cytokines, and triggering the accumulation and misfolding of α -syn. The misfolded α -syn may propagate to the brain either through the vagus nerve or the bloodstream, while pro-inflammatory cytokines can reach the CNS through the humoral pathway. Both α -syn and pro-inflammatory cytokines have the potential to compromise the blood–brain barrier and activate microglia within the CNS, leading to neuroinflammation and neurodegeneration in PD. (Source: Guo et al., 2022, p.5)

Constipation is a common symptom in PD, and alterations in the gut microbiota composition have been associated with this gastrointestinal issue. For instance, the increased abundance of the genus *Lactobacillus* in PD patients may be attributed to the higher prevalence of constipation. Conversely, individuals with diarrhoea-type irritable bowel syndrome exhibit an opposite trend (Liu, 2017), emphasizing the complexity of microbial changes in PD.

Bacteriophage viruses, which infect bacteria, have emerged as potential contributors to bacterial imbalance and dysbiosis in PD. Recent research has indicated an overrepresentation of lytic *Lactococcus* phage in PD patients. This overrepresentation may lead to a reduction in the abundance of *Lactococcus* bacteria, a species implicated in the production of intestinal dopamine. The reduction of *Lactococcus* spp. could be linked to early GI dysfunction in PD (Tetz, 2018). However, the origins of this increase in lytic phage remain unclear, raising questions about whether it is a manifestation of dysbiosis or a consequence of external factors, such as the introduction of lytic *Lactococcus* phage commonly found in various dairy products (Tetz, 2018).

The intricate relationship between gut dysbiosis and PD involves various factors, including SIBO, constipation-related microbial changes, and the potential influence of bacteriophage viruses. While these findings shed light on the microbial aspects of PD, the exact causes, and implications of gut dysbiosis in the context of PD still require further exploration and understanding.

CHAPTER 4 – THERAPEUTIC OPTIONS

4.1 Intervention mediated by the microbiota-gut-brain axis

As our understanding of the intricate relationship between the gut microbiome and PD continues to evolve, it opens new possibilities for therapeutic interventions. Modulating the microbiome through dietary interventions, probiotics, prebiotics, and other strategies may hold promise for managing PD symptoms and potentially slowing disease progression. However, it is essential to recognize that the field is still in its early stages, and further research is needed to elucidate the specific mechanisms and establish effective therapeutic strategies. Nonetheless, the growing body of evidence linking the gut microbiome to PD highlights the importance of considering the role of the gut in neurodegenerative diseases and provides a foundation for future investigations and therapeutic developments.

4.2 Diet

Dietary interventions constitute another area of focus in the quest for microbiota-based therapeutic options. Emerging research suggests that specific dietary patterns may impact the gut microbiome and, subsequently, influence PD symptoms. Diets rich in fiber, antioxidants, and polyphenols, commonly found in fruits, vegetables, and whole grains, have been associated with a more diverse and beneficial gut microbiota. Adopting a diet that supports microbial diversity may potentially contribute to better outcomes in individuals with PD. By modifying dietary patterns, notable changes occur in microbial abundance and the production of fermentation products such as SCFAs and phytochemicals. The influence of diet extends to the composition of the gut microbiota and neural activity within the central nervous system through the intricate microbiota-gut-brain axis. One well-recognized exemplar in this context

is the Mediterranean diet, renowned for its health-promoting attributes. This dietary model is characterized by an abundance of plant-based foods, including fruits, vegetables, cereals, legumes, nuts, and bread. It features moderate consumption of dairy products, with olive oil as the primary fat source, and incorporates limited amounts of fish and meat, particularly red meat, favouring the use of spices over salt. Moreover, the Mediterranean diet emphasizes the significance of enjoying meals in a pleasant and familiar setting, resting after eating, and engaging in simultaneous physical and social activities. Numerous studies have linked the Mediterranean diet to favourable health outcomes across various conditions such as cardiovascular disease, obesity, metabolic syndrome, and cancer (Wang, 2021).

The case study of Alcalay (2012), revealed an inverse relationship between adherence to the Mediterranean diet and the risk of Parkinson's disease, suggesting that higher compliance was associated with a reduced risk. Additionally, the study indicated that a lower Mediterranean diet score correlated with earlier onset of Parkinson's disease. However, it did not conclusively establish whether reduced compliance with the Mediterranean diet was a consequence or a contributing factor to the development of Parkinson's disease. Furthermore, an association between strict adherence to the Mediterranean diet and a lower incidence of prodromal Parkinson's disease has been observed, implying the potential beneficial effects of this dietary pattern on disease prevention.

4.3 Probiotics

Probiotics present a potential avenue for reversing alterations in gut microbial composition associated with PD, leading to restored GI function and reduced gut leakiness and ENS inflammation. Strains like Bifidobacteria and Lactobacilli have been found to produce vitamins, antioxidants, and bioactive molecules, mitigating oxidative stress, and preventing further neuroinflammation and α -synuclein aggregation (LeBlanc, 2014).

The composition of the intestinal microbiota has the potential to influence various organ systems, including the cardiovascular, nervous, immune, and metabolic systems. This has sparked interest in microbial therapy, particularly using probiotics, as a novel strategy for treating Parkinson's disease. Probiotics, characterized as non-viable food components conferring health benefits by modulating the microbiota, have shown promise in recent studies for alleviating gastrointestinal symptoms associated with Parkinson's disease. These symptoms, notably constipation, abdominal pain, and abdominal distension, have demonstrated improvement with probiotic interventions. Probiotics, such as specific strains of *Lactobacillus* and *Bifidobacterium*, have shown promise in preclinical and clinical studies for their potential to alleviate gastrointestinal symptoms in PD and positively impact the gut-brain axis. By fostering a healthier microbial environment in the gut, probiotics may contribute to improved overall well-being in individuals with PD. Despite these positive findings, the precise mechanisms and safety considerations of employing probiotics in Parkinson's disease remain to be fully elucidated. Potential mechanisms may include symptom relief, anti-inflammatory effects, mitigation of antioxidant stress, and micronutrition support (Wang, 2021).

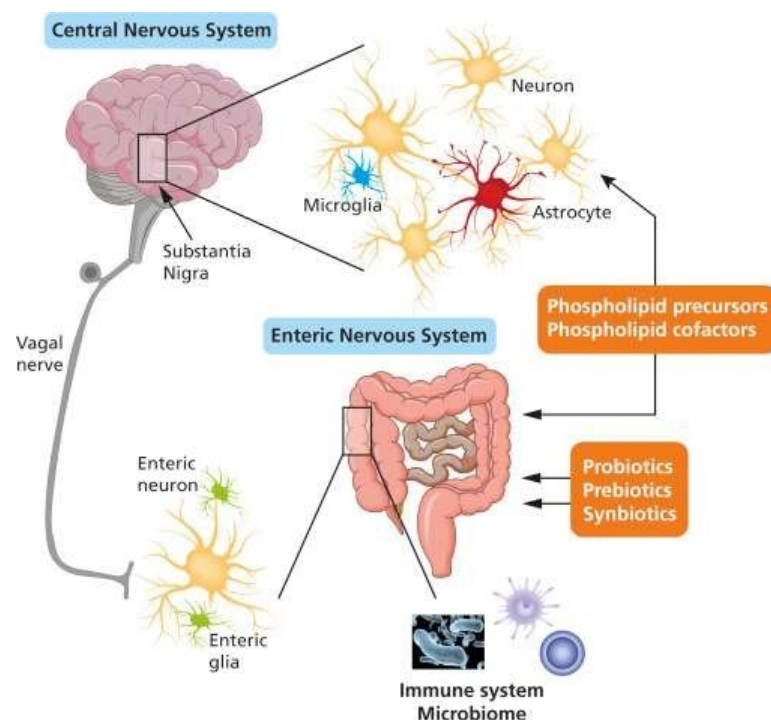


Figure 4. Dietary phospholipid precursors and cofactors improve neuronal function, reduce inflammation in the ENS and CNS, lessening motor and non-motor issues in PD. Probiotics, prebiotics, or synbiotics may alter gut microbiota, enhance intestinal integrity, and reduce inflammation, potentially impacting neurodegenerative processes (Source: Perez-Pardo et al., 2017, p. 89).

4.4 Faecal microbiota transplantation

The use of faecal microbiota transplantation (FMT) is an experimental but intriguing avenue. FMT involves transferring faecal material from a healthy donor into the gastrointestinal tract of the recipient, aiming to restore a healthy microbial balance. While FMT is still in the early stages of investigation for PD, it represents an innovative strategy to address the gut dysbiosis associated with the disease (Tan,2022).

FMT is a procedure in which faecal material from a healthy donor is introduced into GI tract of a patient. The goal of FMT is to reinstate a healthy balance of gut flora. The procedure includes screening the faecal material for pathogens, followed by homogenization,

filtration, and resuspension of the stool sample. The prepared material is then administered to the recipient through various methods such as a nasogastric tube, enema, or colonoscopy (Aas, 2003). FMT appears to play a pivotal role in the interventional treatment of neurological disorders (Fann, 2022).

FMT has the capacity to reconstruct the gut microbiota, modify the diversity of intestinal microbes, and comprehensively restore abnormal intestinal microbiota. Additionally, FMT has been suggested as a therapeutic intervention for neurological conditions such as multiple sclerosis, Parkinson's disease, autism spectrum disorder, Alzheimer's disease, and epilepsy. The regulatory effects of FMT on the intestinal microbiota may influence the symptoms or progression of nervous system diseases through immune, endocrine, metabolic, and neural pathways. In various animal experiments, these effects have been explored (Wang, 2021).

Kuai et al. (2021) found that following FMT treatment, 11 individuals with Parkinson's disease exhibited an augmentation in *Blautia* and *Prevotella*, along with a significant reduction in the abundance of *Bacteroidetes*. This coincided with improvements in non-motor symptom questionnaire scores and alleviation of constipation symptoms.

Several case studies showed that the utilization of FMT proved beneficial in addressing GIT symptoms such as constipation, ulcerative colitis, and bowel disorders. Additionally, this therapeutic approach demonstrated efficacy in alleviating several non-GIT symptoms as well (Parashar, 2017).

4.5 Lifestyle influences

The composition and dynamics of the gastrointestinal microbiota in Parkinson's disease are influenced by various lifestyle factors and potential confounding variables. Lifestyle choices, including diet, physical activity, and stress levels, play a crucial role in

shaping the gut microbial community. Dietary habits, such as the consumption of fiber-rich foods and fermented products, can impact microbial diversity and function. Regular physical activity has been associated with a more diverse and balanced gut microbiota, while chronic stress may contribute to dysbiosis. Other potential confounders encompass medication usage, as certain drugs used in Parkinson's disease management may influence the gut microbiota. Additionally, age, genetics, and environmental exposures contribute to the complexity of the gut microbiome in individuals with Parkinson's disease. Understanding the interplay between lifestyle factors, potential confounders, and the gastrointestinal microbiota is essential for unraveling the intricate relationship between gut health and Parkinson's disease. Further research and exploration of these influences are crucial for developing targeted interventions that address the multifaceted nature of the gut-brain axis in Parkinson's disease (Lubomski, 2020).

While the field of microbiota-based therapeutic options for PD is evolving, it is crucial to approach these strategies with caution. Rigorous scientific investigations, including well-designed clinical trials, are essential to validate the safety and efficacy of these interventions. The potential impact of microbiota-based therapies on not only gastrointestinal symptoms but also the broader spectrum of PD manifestations underscores the exciting prospects for more holistic and personalized approaches in managing this challenging neurodegenerative condition. As our understanding of the intricate relationship between the gut microbiota and PD deepens, the development of targeted and effective therapeutic interventions represents a promising frontier in the pursuit of improved outcomes for individuals living with Parkinson's disease.

CONCLUSION

In conclusion, the thesis has delved into the evolving understanding of Parkinson's disease, moving beyond the traditional focus on dopaminergic neuron degeneration in the central nervous system to explore the crucial involvement of the gut-brain axis. Recent research has revealed Lewy bodies, a characteristic feature of PD, not only in the brain but also in the enteric nervous system, emphasizing the intricate connection between the gut and PD. The bidirectional communication network of the gut-brain axis has emerged as a significant player in the aetiology and progression of PD. The molecular and cellular mechanisms facilitating communication between these two systems have been examined, and they showed the complexity of their relationship.

I particularly focused on the role of the gut microbiota in influencing the course of PD, presenting a potential therapeutic target. By unravelling these complexities, this thesis has contributed to a deeper understanding of the disease and identified novel avenues for treatment. The insights offered into the therapeutic potentials within the gut-brain axis connections provide a foundation for future research and the development of innovative approaches to address Parkinson's disease. Overall, this exploration of the intricate relationship between the gut and PD opens doors to new possibilities in the quest for effective treatments and interventions.

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