Gut Dysbiosis and the Vagal Pathway to Parkinson's Disease: Modeling LPS-Driven-Alpha-Synuclein Misfolding from the Gastrointestinal Tract to the Brain

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July 31, 2026

Abstract

Parkinson's disease is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons and the buildup of misfolded alpha-synuclein in Lewy bodies, though the cause for the alpha-synuclein misfolding is unknown. This research paper proposes that gut dysbiosis-driven inflammation, specifically inflammatory metabolites and lipopolysaccharide (LPS) in the gut microbiome, causes alpha-synuclein misfolding in the enteric neurons, which travels to the brain through the vagus nerve, and would be a major contributor to the development of Parkinson's disease. To test this thesis, we propose an experiment using human induced pluripotent stem cell-derived Gut-Brain Vagal Pathway Assembloids, composed of a connected enteric organoid and hindbrain organoid, as our model system. We will expose the enteric organoid to conditioned media derived from Parkinson's disease patients in four conditions to analyze how each factor contributes to alpha-synuclein misfolding and inflammation. Following exposure, we will observe alpha-synuclein misfolding and inflammatory markers in both organoids. We expect inflammatory metabolites derived from PD patients to produce the greatest degree of alpha-synuclein misfolding and inflammation, and we expect Parkinson's-related pathology to propagate from the enteric organoid to the hindbrain organoid. Our experimental model is dependent on the BIA documented in a pre-print paper by Yamagchi, Ishikawa, and Akamatsu (2026). These findings would clarify whether gut inflammation is a meaningful contributor to Parkinson's-related pathology and could inform future research on a root cause of Parkinson's Disease, as well as developing early intervention through the gut microbiome.

Parkinson’s Disease

Parkinson's disease is described as a neurodegenerative disease with a rising prevalence worldwide (Bloem et al., 2021). Approximately 90,000 people in the U.S. are diagnosed with Parkinson's every year (Cleveland Clinic, 2026). Parkinson's is a clinical syndrome dominated by motor symptoms, such as tremors, muscle rigidity, bradykinesia, and postural instability. Parkinson's disease is characterized by the degeneration of dopamine-producing neurons in the substantia nigra (Marsden, 1994). Dopamine, a neurotransmitter and hormone in the brain, is a critical modulator of motivation and movement. In cases such as Parkinson's disease, there is a dysfunction in dopaminergic transmission, causing movement to become restricted. Most of these neurons reside in the midbrain, forming three distinct nuclei: the substantia nigra, which is further divided into the pars reticulata and pars compacta, the ventral tegmental area, and the retrorubral nucleus. In Parkinson's disease, the severe denervation of dopamine-producing neurons leads to the complete loss of striatal synaptic plasticity of MSNs (medium spiny neurons), leading to altered physiological activity of striatal interneurons, resulting in the motor symptoms of Parkinson's, such as bradykinesia and muscle rigidity (Speranza et al., 2021). A hallmark of Parkinson's disease is the presence of fibrillar aggregates, also referred to as Lewy bodies. Pale bodies are early immature versions that eventually grow into Lewy bodies. Lewy bodies are largely characterized by the misfolding of the alpha-synuclein protein, which is expressed in neurons throughout the central and peripheral nervous systems (Calabresi et al., 2023). As alpha-synuclein can also be found in the enteric nervous system, a popularized theory suggests that Lewy body formation occurs in the enteric nervous system years before the neurological symptoms begin to emerge (Ryman et al., 2023).

Currently, Parkinson's disease has no known cure; however, medications that help control symptoms do exist, such as carbidopa-levodopa (Mayo Clinic, n.d.). Carbidopa-levodopa is a chemical that passes through the brain and is converted into dopamine. However, the issue is that Parkinson's disease is often diagnosed after the loss of 50–70% of dopamine-producing neurons, making the medication less effective (Ryman et al., 2023). In recent years, there has been an increase in Parkinson's disease cases, and this trend is estimated to continue. A large factor contributing to this is the aging of the population. As life expectancy rises, so does the number of Parkinson's disease cases. However, recent studies also report an increase in Parkinson's disease cases among younger populations, suggesting that additional factors are involved (Leon-Rojas, 2025). Age is one of the most significant risk factors, as the median age of onset is 60 years, largely due to the reduced efficiency of autophagy and the ubiquitin-proteasome system, which normally help prevent the misfolding of proteins such as alpha-synuclein (Beheshti, 2025).

Lewy Bodies & Alpha-synuclein

Lewy bodies are a hallmark of synucleinopathies, the main three types being 1) Parkinson’s Disease, 2) Dementia with Lewy Bodies (DLB), and 3) Multiple System Atrophy (MSA) (Arias-Carrión et al., 2025). These spherical accumulations are mainly composed of alpha-synuclein. They are found in the cell bodies of neurons, while Lewy neurites are found in the axons and/or dendrites. Similarly, Lewy neurites are thread-like extensions of misfolded alpha-synuclein (J.H. Grimwade et al., 2026). Alpha-synuclein is a protein encoded by the SNCA gene, and it regulates neurotransmitter release in the presynaptic terminals by binding to synaptic vesicle membranes. However, it is debated whether alpha-synuclein inhibits or triggers neurotransmitter release (Sharma & Burré, 2023). Under normal circumstances, alpha-synuclein

is considered an intrinsically disordered protein (IDP), meaning it doesn't have a stable 3D structure and remains "unfolded" (Stephens et al., 2018). However, genetic predispositions and external factors (i.e. pH, salt concentration, inflammation) may trigger an increase in the amount of SNCA gene expression and aggregate into oligomers, which are the basis of Lewy bodies (Negi et al., 2024).

Gut-brain Axis & the Vagus Nerve

The gut-brain axis is a biochemical communication system between the central nervous system and the gastrointestinal (GI) tract. Nervous communication happens primarily through the enteric nervous system, which is the part of the autonomic nervous system that lines the walls of the GI tract. It was discovered that secretions from the gut microbiota, including metabolites, amino acids, and short-chain fatty acids (SCFAs), can directly influence our emotions, behavior, and the way we manage pain (Lewandowska-Pietruszka et al., 2022). This bidirectional network allows the brain and gut to affect one another, with the brain influencing gut microbiota composition and the gut influencing neurotransmitter levels (subsequently leading to changes in cognition) (Patra, 2016). Another key player in the gut-brain axis is the vagus nerve, which is the 10th (and longest) cranial nerve that serves as the main "highway" from the gastrointestinal tract to the central nervous system. It is composed of about 80% sensory pathways and 20% motor pathways, and it connects the medulla oblongata to the colon, with several left and right branches along the way that connect the vagus nerve to other sensory organs (Ma et al., 2025). The vagus nerve and medulla oblongata are both responsible for autonomic functions such as breathing, digestion, heart rate, etc. Studies on germ-free mice showed that the development of the nervous system and immune system was dependent on the composition of the gut microbiota (Margolis et

al., 2021). In humans, the gut microbiome reaches its adult stage between the ages of 3 and 6, and it continues to regulate the immune system, autoimmune processes, gut permeability, and more (Loh et al., 2024).

LPS, Metabolites, & The Endotoxin Hypothesis of Parkinson's Disease

The microbiome-gut-brain dysfunction may play a role in the progression of Parkinson's disease; however, there are multiple potential mechanisms. One of the non-motor symptoms of Parkinson's disease is gastrointestinal dysfunction, which often appears before the motor symptoms. Parkinson's disease patients also have high levels of LPS, indicating a relationship with the gut and supporting the endotoxin hypothesis (Brown et al., 2023). The endotoxin hypothesis of Parkinson's disease is the concept that LPS contributes to the pathogenesis of this disorder. It suggests that early gut dysbiosis leads to the release of endotoxins such as LPS into the bloodstream, or that LPS travels through the gut-brain axis, specifically via the vagus nerve. This causes neuroinflammation, which promotes the misfolding of alpha-synuclein proteins and the formation of Lewy bodies, exacerbating the loss of dopamine-producing neurons in the substantia nigra (Brown et al., 2023). Evidence supporting this hypothesis includes early gut dysfunction and microbiome changes in Parkinson's disease, increased blood levels of LPS found in PD patients, LPS-induced alpha-synuclein aggregation, activation of inflammatory cytokines, and neuroinflammation in brainstem nuclei that contributes to the degeneration of dopamine-producing neurons (Hansen et al., 2019). If this hypothesis is proven correct, it could broaden the range of potential treatment options, including focusing on changing the gut microbiome, reducing gut permeability, and/or regulating LPS levels (Brown et al., 2023).

Background

The vagus nerve connects peripheral neurons in the GI tract to the brain stem, so it's plausible that misfolded alpha-synuclein from the enteric nervous system can travel along the vagus nerve to the brain, where it forms Lewy bodies in the substantia nigra. A study on transgenic mice confirmed the ability of enteroendocrine cells (EEC) in the gut mucosa to transfer alpha-synuclein to vagus nerve ganglia (Chandra et al., 2023), establishing a potential gut-brain pathway for misfolded alpha-synuclein to propagate.

Although significant research has been performed on animals such as lab mice, differences in receptor responsiveness have been observed between species, making them an unideal subject. A team led by Sergiu Pasca at Stanford modeled the human ascending neuron pathway using organoids to more accurately study the effects of certain neurotransmitters and proteins on the nervous system. Pasca's team constructed four separate organoids from human induced pluripotent stem cells: the sensory neurons, the dorsal spinal cord, the thalamus, and the cerebral cortex. Each organoid was generated *in vitro* in Essential 6 Medium and supplemented with patterning molecules over the course of weeks. The components were placed linearly in a tilted cell culture plate and incubated over one week to form an assembloid in which synchronous activity between its components was measured (Kim et al., 2025). This assembloid models only the somatosensory branch of the ascending nervous system, but the methodology can be reproduced to create an assembloid to study the connection between the enteric nervous system and the cerebral motor cortex.

Further, a brain-intestinal assembloid (BIA) consisting of the medullary hindbrain, including the dorsal motor nucleus, and intestinal organoids supplemented with enteric neurons was used to model alpha-synuclein transmission through the gut-brain axis. SNCA, the gene that produces alpha-synuclein, was introduced to the hindbrain organoid in experimental groups, and

alpha-synuclein was then expressed in enteric neuron filaments, further corroborating the travel of alpha-synuclein through the vagal pathway. Although the dorsal motor nucleus (DMX) is one of the first affected regions in PD pathology, only a subset of the hindbrain organoid differentiated into DMX-like cells; so more precise gene regulation methodologies will be necessary to model bidirectional gut-brain communication (Yamagchi et al., 2026).

Gap in Current Knowledge

Research done in the past has found a connection between pieces of the gut-brain axis and Parkinson's disease, but no study has examined the full model. Yamagchi et al. (2026) modeled alpha-synuclein transfer between the gut and brain, but through genetic induction rather than gut-derived inflammation. Sampson et al. (2016) researched a connection between LPS, gut inflammation, and Parkinson's-related symptoms, but only in mice. There has not been a study that has tested inflammatory factors from human Parkinson's patients' stool and their gut microbiome in a model capable of testing whether alpha-synuclein misfolding in the gut propagates to the brain.

Proposed Methodology

Sampling

To establish a causational relationship between gut dysbiosis triggered by inflammatory metabolites and the development of Parkinson’s disease, we propose a methodology combining the brain-intestinal assembloid (Yamagchi, 2026) with Browne and Forster’s earlier work in culturing gut microbiota (Browne, 2016).

Firstly, fecal samples will be collected from 30 individuals with PD, as well as from 30 healthy individuals functioning as a control group. Participants will be selected from the age range 55-75, as this age range is the most largely affected by Parkinson’s Disease according to a

2025 modeling study (Su et al., 2025). Although skewed patterns of Parkinson's prevalence between genders and races exist, exclusions will not be made based on these demographics because we will analyze metabolites that covary with LPS, with the aim of identifying patterns across these demographics. In the days leading up to the study, participants will keep a record of their food intake to mitigate the influence of diet on gut microbiota.

Culturing Microbiota in Stool

We will reproduce Hilary Browne and Samuel Forester's methods to culture gut microbiota. After fecal samples are obtained and placed in an anaerobic environment, they are homogenized in reduced PBS, serially diluted, and plated directly onto YCFA agar supplemented with 0.002 g/ml each of glucose, maltose and cellobiose in large Petri dishes. Colonies are picked 72 h after plating from Petri dishes. The colonies that are picked are re-streaked to confirm purity (Browne, 2016).

Extracting

After culturing the PD gut microbiota, the next step is to prepare solutions of select inflammatory molecules. First, it is necessary to source LPS from the microbiota of PD patients because LPS molecules are heterogeneous. LPS's biological activity and effect on the nervous system depend on the bacterial source. So, we will extract LPS from the fecal bacterial cultures. We will also test the effects of two other common inflammatory bacterial metabolites that are associated with PD. Indole-3-propionic acid (IPA) represents the class of Tryptophan metabolites. Deoxycholic acid (DCA) represents the class of secondary bile acids. IPA and DCA's structures do not vary, so it is not necessary to extract them from the culture. We will

measure the amounts of these molecules in the cultures and then recreate these amounts with purchased chemicals.

To extract LPS, we will follow Pither et. al's methods. Cells are collected by centrifugation, washed, and lyophilized. Freeze-dried cells are extracted repeatedly with a phenol/chloroform/light petroleum mixture.The combined extracts are processed by removing volatile solvents, followed by water addition to separate phases. DNase and RNase digestion, protease digestion, and extended dialysis are used to purify the extracted LPS (Pither et al., 2023).

To measure IPA, we will follow Zünd et. al's methods. Samples were centrifuged, and supernatants were collected. IPA was quantified using Ultra-High Performance Liquid Chromatography (UHPLC) coupled to a Diode Array Detector (DAD).

To measure DCA, we will follow Horvath et. al's methods. Culture supernatants were collected, and samples were diluted with methanol, water, and D4-DCA. DCA was separated by liquid chromatography and detected using tandem mass spectrometry. DCA levels were calculated using a DCA calibration curve (Horvath et al., 2020)

There will be four types of solutions added to the neural assembloids. The vehicle control will have nothing added to the assembled medium. We will add LPS alone to determine whether it is sufficient alone to cause alpha-synuclein aggregation. We will add IPA and DCA alone to determine whether alpha-synuclein aggregation can happen without the presence of LPS. We will also add LPS, IPA, and DCA together to determine if there is synergy between them.

Assembloid Construction

We will use the methods of Yamagchi, Ishikawa, and Akamatsu (2026) to create 15 Gut-Brain Vagal Pathway Assembloids grown from healthy human induced pluripotent stem

cells. This model integrates a medullary hindbrain organoid with an enteric neuron-enriched intestinal organoid, which models alpha-synuclein propagation between the enteric nervous system and the brain, the same anatomical route our thesis identifies as the vagus nerve pathway. Once the Gut-Brain Vagal Pathway Assembloids mature, each one will be cultured separately in a sterile multi-well plate with neural culture medium.

Exposure

The experimental group's assembloids will have their enteric organoid exposed to one of four conditions: a vehicle control with no inflammatory factors added, LPS alone, inflammatory metabolites (IPA and DCA) alone, or LPS and metabolites combined, each reconstructed at concentrations measured from the PD-patient stool-derived cultures, as described in Step 3. The control group's assembloids will undergo the same four exposure conditions, using LPS and metabolites derived from healthy-control stool samples instead. The conditioned media will be filtered to remove all bacteria while retaining LPS and metabolites.

Each assembloid will be incubated under identical conditions (37°C and 5% CO_2). New conditioned media will be applied to the enteric organoid at set intervals throughout the experiment.

Discussion

Observation

Following exposure, each assembloid will be observed for Parkinson’s-related pathology. Specifically, we will be observing the hindbrain organoid since it represents if alpha-synuclein misfolding initiated in the enteric neurons has propagated along the modeled vagal route. Both

organoids will be analyzed using immunofluorescence staining and microscopy to identify any misfolding of alpha-synuclein (Spillantini et al., 1997). Inflammatory markers and neural cell damage/death will also be observed in both organoids (Houser & Tansey, 2017).

Expected Results

We believe that the stool samples from the Parkinson's patients, along with the LPS and inflammatory metabolites derived from those samples, will cause both alpha-synuclein misfolding and inflammation in the assembloids. Specifically, we expect the enteric organoid, which is exposed to the stool-sample-derived media, to produce misfolded alpha-synuclein along with inflammation, which will eventually propagate to the hindbrain organoid, since this is the neural pathway our thesis identifies as the route through which gut inflammation leads to Lewy body formation in the brain. We expect the strongest effects to come from the LPS + IPA + DCA condition, since we believe the mix could amplify the inflammation and alpha-synuclein misfolding. We expect the weakest effects to come from the control media derived from non-Parkinson's stool, because of the lack of the inflammatory factors we expect to cause the alpha-synuclein misfolding and inflammation.

If our results are as expected, they would support our thesis that gut inflammation caused by inflammatory metabolites and LPS is a significant cause of alpha-synuclein misfolding that leads to Parkinson's disease. If the enteric organoid shows signs of alpha-synuclein misfolding and inflammation but this does not propagate to the hindbrain organoid, it would instead suggest that the inflammatory metabolites and LPS are sufficient to cause local gut inflammation and misfolding, but not sufficient on their own to spread that pathology to the brain. Regardless,

either result would help clarify whether gut inflammation is a contributing factor or a direct cause of the Lewy body formation associated with Parkinson's disease.

Limitations

The proposed methodology is heavily dependent on the brain-intestinal assembloid method researched by Yamagchi, Ishikawa, and Akamatsu (2026), which, as of the time of this writing, is only a preprint and has not undergone formal peer review. It is possible that methodological issues or revisions could still happen during peer review, which may affect the reliability of our proposed study. Additionally, since it was a single, not yet replicated study, the assembloid's ability to model alpha-synuclein propagation between the gut and brain has not been confirmed by other research groups.

Ethical Implications

This study brings up several ethical questions to take into consideration. Since our methodology includes collecting human stool samples and dietary data from participants, informed consent is needed so participants understand what their stool and dietary data will be used for. Participant identities will be de-identified, and all collected data will be anonymized and securely stored to protect our participants' privacy.

Another ethical question relates to our use of human induced pluripotent stem cells for organoids and assembloids in the methodology. This method does not use embryonic stem cells, so there are no ethical concerns tied to embryo destruction. However, creating complex brain assembloids does raise ethical questions related to the potential sentience of lab-grown neural

tissue. Our model is not complex enough to raise these concerns directly, but this remains an area for discussion as organoid research continues to develop.

Finally, Parkinson's disease prevalence varies by gender and race, but our study includes no exclusions based on these demographics, allowing our findings to reflect a more representative range of the population rather than being limited to a narrow demographic group.

Conclusion

Our proposed study seeks to determine whether gut dysbiosis-induced inflammation contributes to the development of Parkinson's disease. By triggering alpha-synuclein misfolding in the enteric nervous system, neuroinflammation would allow the pathology to spread to the brain via the vagus nerve. By using a human stem cell-derived Gut-Brain Vagal Pathway Assembloid model, this research provides a way to investigate the relationship between the gut microbiome and Parkinson's disease in a controlled environment. If the results support the hypothesis, it would strengthen the evidence that the gut-brain axis plays an important role in the early stages of Parkinson's disease, and we would be able to identify inflammatory metabolites as a possible cause of alpha-synuclein misfolding. These findings could guide future research toward gastrointestinal-based treatments and methods for early diagnosis or prevention. Although additional studies would be needed to confirm these results in humans, this research could provide insight into a plausible cause of Parkinson's disease. This information will further contribute to the development of more effective strategies for slowing or preventing disease progression.

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