

Chapter 14: Parkinson's, Alzheimer's, and the Gut

Summary

Parkinson's disease is best known for tremor and slow movement, but many people have gut problems, especially constipation, years before any movement symptoms appear. This chapter explains how Parkinson's damages dopamine neurons, how a misfolded protein called alpha-synuclein may spread from cell to cell, and why some scientists think the disease can sometimes begin in the gut and travel up the vagus nerve. You will weigh the evidence from autopsy studies, mouse experiments, and large health-record studies of people who had their vagus nerve cut or their appendix removed, and you will compare the "gut-first" and "brain-first" ideas side by side. The chapter ends with Alzheimer's disease, where gut microbe research is much younger, and with practical points about how the gut affects Parkinson's medicine.

Concepts Covered

1. Neurodegeneration
2. Parkinson's Disease
3. Dopamine Neuron Loss
4. Alpha-Synuclein
5. Lewy Body
6. Prodromal Symptoms
7. Constipation
8. Braak Hypothesis
9. Prion-Like Spread
10. Gut-First Subtype
11. Brain-First Subtype
12. Truncal Vagotomy Studies
13. Appendix and Parkinson's
14. Levodopa Absorption
15. Alzheimer's Disease
16. Amyloid Beta

Prerequisites

- [Chapter 1: The Brain in Your Belly \(and Why That Phrase Is Misleading\)](#) for the enteric nervous system
- [Chapter 2: The Vagus Highway](#) for the vagus nerve and the brainstem
- [Chapter 3: Meet the Microbiome](#) for gut microbes and correlation versus cause
- [Chapter 13: Autism, ADHD, and the Gut](#) for confounding and small studies

A mystery that starts far from the brain



Parkinson's and Alzheimer's are brain diseases, so why would a gut book spend a whole chapter on them? Because one of the biggest open questions in neurology right now is whether Parkinson's sometimes starts in the gut and climbs up the vagus nerve. (That's me!) Many families, maybe yours, are touched by these diseases, and the online claims about them run far ahead of the evidence. Let's check the evidence together.

14.1 Riya's Grandfather and a Clue From Years Ago

Riya's grandfather, whom she calls Nanaji, is 72. Two years ago his right hand started shaking when it rested in his lap, and his walk turned into small, shuffling steps. His neurologist diagnosed Parkinson's disease. At a family dinner, Riya's grandmother mentioned something odd: "His stomach trouble started long before the shaking. He was constipated for years, and he stopped being able to smell my cooking." Riya, who had just learned in biology club that the gut has its own nervous system, sat up. Could a brain disease have started in the gut? (Riya and her family are fictional and appear throughout this book.)

Riya's question is a real one that scientists are arguing about right now. Her grandmother's observation matches a pattern doctors have noticed in many people with Parkinson's: gut problems, smell loss, and certain sleep problems often show up years before any shaking. This chapter follows that clue. We'll see where the evidence is strong, where it is mixed, and where it turns into hype.

Here's the plan. First, what goes wrong in the brain in Parkinson's. Then the early clues, the idea that the disease can travel from gut to brain, and the experiments that test it in mice and people. Finally, Alzheimer's disease, where the gut story is younger and less certain.

14.2 When Brain Cells Wear Out: Neurodegeneration

Picture a row of old houses on a street. Most stay standing for a century. But in one neighborhood, the houses start to fall apart one after another, and the damage seems to move from one house to its neighbors. That's a rough picture of what happens in some brain diseases.

Neurodegeneration is the slow, progressive loss of the structure and function of neurons, ending in their death, in particular parts of the nervous system. "Progressive" means it gets worse over time. Neurons in the

adult brain are mostly not replaced when they die, so the loss adds up. Parkinson's disease and Alzheimer's disease are the two most common neurodegenerative diseases, and both mostly affect older adults.

You already know the basics of neurons and how they signal to each other. If you'd like a deeper review of how the aging brain changes and how these diseases affect it, see [From Neuron to Bedside, Chapter 13](#). For how the brain controls movement, see [From Neuron to Bedside, Chapter 7](#).

14.3 Parkinson's Disease: Losing the Dopamine Neurons

Parkinson's disease (PD) is a progressive disorder of the nervous system that mainly affects movement, caused by the gradual damage and death of nerve cells in certain parts of the brain. [The National Institute of Neurological Disorders and Stroke \(NINDS\)](#) lists four common movement symptoms:

- **Tremor:** rhythmic shaking, often starting in one hand and most obvious when the hand is at rest. Some people with PD never develop a tremor.
- **Rigidity:** muscles that stay tight and stiff.
- **Bradykinesia:** slowness of movement, so everyday tasks like dressing take longer, and the face may show less expression.
- **Postural instability:** balance problems that raise the risk of falls.

Why these symptoms? Deep in the brain is a small region called the substantia nigra ("black substance," because its cells look dark). Its neurons make dopamine, a chemical messenger that helps the brain produce smooth, purposeful movements. **Dopamine neuron loss** is the death of these dopamine-making neurons in the substantia nigra, the main cause of the movement symptoms of Parkinson's. According to NINDS, by the time movement symptoms appear, most people have already lost 60 to 80% or more of these cells.

Read that number again. The brain has a lot of backup capacity, so it can lose most of these neurons before anything looks wrong from the outside. That means the disease process has been running quietly for a long time before diagnosis. This is the window where the gut clues live.

Parkinson's is not only about dopamine. NINDS notes that people with PD also lose cells that make norepinephrine, a messenger the body uses for automatic jobs like keeping blood pressure steady. That may explain some symptoms that aren't about movement, such as tiredness and blood pressure changes. NINDS also lists other symptoms: depression or anxiety (sometimes even before movement problems), sleep problems, speech changes, bladder problems, and digestive problems like nausea and constipation.

Who gets Parkinson's? NINDS says the average age when symptoms start is the early to mid-60s, and the chance rises with age. A small percentage of people get "early-onset" PD at younger ages. In most people the cause is unknown; researchers think both genes and environmental exposures play a part.

14.4 A Protein That Folds Wrong: Alpha-Synuclein and Lewy Bodies

Proteins are like long strings that must fold into exact shapes to work, the way a paper airplane only flies if it's folded correctly. Crumple it the wrong way, and it's useless. Worse, some wrongly folded proteins stick together into clumps.

Alpha-synuclein is a protein found in neurons, especially at their tips where they send signals, that can misfold and clump together; these clumps are a hallmark of Parkinson's disease. In healthy neurons it is thought to help with releasing chemical messengers, though its normal job is still being studied.

When alpha-synuclein misfolds, it forms clumps inside neurons. A **Lewy body** is an abnormal round clump, made mostly of misfolded alpha-synuclein, found inside nerve cells in Parkinson's disease and some related conditions. NINDS says damaged brain cells in most people with PD have Lewy bodies, though researchers don't yet know exactly why they form or how much harm they do themselves. Pathologists also see thinner threads of the same protein in nerve fibers, called Lewy neurites. Together, these are what scientists mean by "Lewy pathology."

Here's the part that made scientists think about the gut. In some diseases, a misfolded protein can act like a bad template. When it touches a normal copy of the same protein, it can push that copy to misfold too, and the misfolding spreads.

Prion-like spread is the idea that a misfolded protein, such as alpha-synuclein, can pass from one neuron to a connected neuron and make normal copies of the protein misfold, so the damage moves along nerve pathways over time. The name comes from prions, the misfolded proteins behind mad cow disease. "Prion-like" does **not** mean Parkinson's is contagious between people. It describes how the protein may spread from cell to cell inside one person's nervous system.

Think of falling dominoes. The first domino tips the next, which tips the next, and the wave follows the line of dominoes wherever it goes. In 2003, the German neuroanatomist [Heiko Braak and his colleagues](#) used that very image, a falling row of dominoes, to describe how Lewy pathology seems to march through connected brain regions in a set order. If the dominoes follow nerve connections, then where is the first domino? That question leads straight to the gut.

Lots of new protein words



Alpha-synuclein, Lewy bodies, prion-like spread: that's a lot at once. Here's my shortcut: alpha-synuclein is the protein, a Lewy body is the clump it forms, and prion-like spread is the idea that the clumping moves from neuron to neuron like dominoes.

14.5 Clues Before the Tremor: Prodromal Symptoms

Doctors use the word "prodrome" for early warning signs that come before the main symptoms of a disease.

Prodromal symptoms are early signs that can appear years before the main symptoms of a disease and

before it can be diagnosed; in Parkinson's they include constipation, loss of smell, acting out dreams during sleep, and mood changes.

[The National Institute on Aging \(NIA\)](#) says many people with Parkinson's notice that before their stiffness and tremor began, they had sleep problems, constipation, loss of smell, and restless legs. NINDS adds that depression or anxiety may appear early, even before movement problems. One sleep problem gets special attention: REM sleep behavior disorder (RBD), in which a person physically acts out vivid dreams, kicking, punching, or shouting, because the normal "freeze" of the muscles during dreaming sleep doesn't work.

The table below collects the main prodromal signs you just read about. Notice that none of them is about movement.

Early sign	What the person notices	Part of the nervous system that may be involved
Constipation	Fewer, harder bowel movements	Gut nerves (enteric nervous system) and the vagus nerve
Loss of smell	Food tastes flat; can't smell smoke or flowers	Smell centers in the brain
REM sleep behavior disorder	Acting out dreams, sometimes injuring a bed partner	Brainstem circuits that control sleep
Depression or anxiety	Low mood, worry	Several brain systems, including ones that make serotonin and norepinephrine

Constipation: the most famous gut clue

Constipation means having fewer bowel movements than usual (often fewer than three a week), or stools that are hard, dry, or difficult to pass. It's very common. [The National Institute of Diabetes and Digestive and Kidney Diseases \(NIDDK\)](#) says about 16 out of 100 adults have constipation symptoms, rising to about 33 out of 100 adults aged 60 and older. It usually has ordinary causes, like low fiber, not enough fluid, travel, stress, or certain medicines.

So how strong is the link to Parkinson's? In 2016, [Adams-Carr and colleagues](#) combined 9 observational studies including 741,593 people. People with constipation had about twice the odds of being diagnosed with Parkinson's later (an odds ratio of 2.27). Even when they looked only at constipation that started **more than 10 years** before diagnosis, the link held (an odds ratio of 2.13). Doctors had already recognized constipation as a non-motor feature of Parkinson's; this study showed it can come more than a decade before diagnosis.

Now the most important part, especially if you or someone you love is constipated. An odds ratio of about 2 is a **relative** number. It compares two groups. It does not tell you that constipation is likely to lead to Parkinson's.

Parkinson's is uncommon, so doubling a small chance still gives a small chance. The great majority of constipated people never develop Parkinson's. Constipation is a clue that researchers can study across huge groups of people, not a warning sign for any one person.

Twice as likely, but of what?



Whenever you hear "twice as likely," ask "twice as likely as what?" Doubling a small chance still leaves a small chance, and that's exactly why constipation tells researchers a lot about Parkinson's while telling a single constipated teen almost nothing.

Notice what kind of evidence this is: observational studies of people, showing a correlation over time. Constipation coming first fits the idea that the gut is involved early. But it could also mean that the disease affects many parts of the nervous system at once, and gut nerves simply show it first. Timing alone can't prove where the disease began.

14.6 The Braak Hypothesis: Does the First Domino Fall in the Gut?

In 2003, Braak's team published two influential papers. In the first, they examined the brains of many people who had died with Parkinson's, and of some people who had Lewy pathology but had never shown symptoms. They proposed a staging system. Lewy pathology, they reported, first shows up in two places: a cluster of neurons low in the brainstem that sends fibers down the vagus nerve (the dorsal motor nucleus of the vagus), and a smell-processing area at the front of the brain. From the brainstem, the pathology seems to climb upward through connected regions, reaching the substantia nigra in the middle stages and the outer brain (the cortex) last.

The second paper made a bolder suggestion. Some people who had no symptoms already had Lewy pathology in both the gut's nervous system and the brainstem vagus nucleus. Braak's team asked whether an unknown trigger, perhaps something swallowed, might cross the gut lining, get into enteric neurons, and travel up the vagus nerve into the brain, tipping dominoes all the way.

The **Braak hypothesis** is the proposal, published by Heiko Braak and colleagues in 2003, that Parkinson's pathology spreads through the nervous system in a predictable order, beginning low in the brainstem and in the smell system, and that in some cases it may start in the gut and travel up the vagus nerve to the brain. Notice the two parts: a **staging pattern** in the brain (based on what they saw at autopsy) and a **gut origin idea** (a hypothesis about where it starts).

Why was this exciting? It tied together several puzzles. It explained why constipation and smell loss can come years before movement symptoms, and why the vagus nucleus is hit so early. It also suggested new ways to detect Parkinson's early, perhaps by sampling gut tissue, long before the dopamine neurons are mostly gone.

Why is it still a hypothesis? Autopsy studies show where pathology is at the moment of death, not where it started. It's like finding fallen dominoes after the fact: you can guess where the first one fell, but you didn't see

it fall. And not every brain fits the pattern. In 2019, [Borghammer and Van Den Berge](#) pointed out that a small fraction of people with Parkinson's don't have pathology in the vagus nucleus at all, which is hard to explain if every case climbs up from the gut.

Here's how this book grades the popular version of the idea.

Hype Meter: "Parkinson's can start in the gut"

Strong

Moderate

Preliminary

Hype

Verdict: Moderate (as a hypothesis for some patients). Human autopsy studies show Lewy pathology early in the vagus nucleus and sometimes in gut nerves, large observational studies show constipation can come more than 10 years before diagnosis, and mouse experiments show misfolded alpha-synuclein can travel from gut to brain along the vagus nerve. But human evidence is mostly correlation, studies of vagus surgery and appendix removal in people disagree, and some patients don't fit the pattern at all. Saying "Parkinson's starts in the gut" for everyone is too strong; "Parkinson's may start in the gut in some people" is a fair summary, and that narrower claim is what this grade covers. **What would change the grade:** Long-term human studies that track alpha-synuclein in the gut and brain of the same people over many years, and show the gut changes come first and predict who develops the disease, could move it up. Large studies showing no gut-first group would move it down.

You can find how each grade is defined on [the Hype Meter page](#).

14.7 Testing the Idea in Mice

If the dominoes really can fall from the gut to the brain, you should be able to start them in the gut on purpose and watch. You can't do that in people, but you can in mice.

In 2019, [a team at Johns Hopkins](#) led by Sangjune Kim, Ted Dawson, and Han Seok Ko did exactly that. They made small, pre-formed fibers of misfolded mouse alpha-synuclein (called "seeds") and injected them into the muscle wall of the upper gut of mice. Then they looked at the brains at 1, 3, 7, and 10 months.

The misfolded protein showed up first in the vagus nucleus of the brainstem, then in other parts of the lower brainstem, and much later in regions including the amygdala and the substantia nigra. The mice gradually lost dopamine neurons and developed movement problems as well as non-movement problems, such as poorer scores on memory and smell tests. Then came the key test. In mice whose vagus nerve was cut (a truncal vagotomy), and in mice bred without the alpha-synuclein protein, the spread to the brain didn't happen, and neither did the neuron loss.

How to read a gut-brain claim: the 2019 gut-to-brain mouse study

Question	This study
Mouse or human?	Mouse only. No people were studied.
Correlation or cause?	Cause, within the mouse model. Researchers injected seeds on purpose and showed that cutting the vagus nerve, or removing alpha-synuclein, blocked the spread. But the seeds were injected by a needle, which is not how Parkinson's begins in people.
How many?	Small groups: about 7 to 12 mice per group in the behavior tests.
How long?	Up to 10 months after injection, which is a large part of a mouse's life.
Who paid for it?	The JPB Foundation and the US National Institutes of Health (National Institute of Neurological Disorders and Stroke), with support from the Adrienne Helis Malvin Medical Research Foundation. The authors declared no competing interests.
Is something being sold?	No. This was basic research with no product.

The conclusion: this careful experiment shows that the gut-to-brain route is **possible** in mice, and that the vagus nerve can carry misfolded alpha-synuclein. It does not show that this is how Parkinson's starts in people, or how often. The first domino in a human, if it is in the gut, would not be a needle full of lab-made protein.

A second famous mouse study came from Caltech in 2016. [Sampson and colleagues](#) used mice engineered to make too much alpha-synuclein. Mice raised germ-free (with no microbes) or treated with antibiotics had fewer movement problems, while adding gut microbes back made the problems worse. Mice that received gut microbes from people with Parkinson's developed worse movement problems than mice that received microbes from healthy donors. This suggests gut microbes can **influence** how a Parkinson's-like disease plays out in this mouse model. It does not show that microbes cause Parkinson's in people.

A mouse is not a mini-person



When a headline says "Scientists prove Parkinson's starts in the gut," check whether the study used mice. These two studies are strong experiments, but they show what can happen in a mouse model, not what does happen in people.

14.8 Testing the Idea in People: Vagus Surgery and the Appendix

Scientists can't cut people's vagus nerves to test a hypothesis. But for decades, surgeons cut the vagus nerve for another reason: to reduce stomach acid in people with severe ulcers, before modern ulcer medicines made the operation rare. (Chapter 2 tells that story.) That history created a natural experiment.

Truncal vagotomy studies are large health-record studies that compare people who had their main vagus nerve trunks surgically cut (a truncal vagotomy, usually for ulcers) with people who did not, to test whether cutting the gut-to-brain vagus route lowers the later risk of Parkinson's disease. A "selective" or "superselective" vagotomy cuts only some branches, so it acts as a useful comparison: if the vagus route matters, a full cut should protect more than a partial one.

Here's what two big studies found.

- **Denmark, 2015 (Svensson and colleagues).** The team used [national registries](#) of people who had a vagotomy between 1977 and 1995. Overall, truncal vagotomy was not clearly linked to Parkinson's risk (a hazard ratio of 0.85, a result that could easily be chance). But among people followed for more than 20 years, those with a truncal vagotomy had about half the risk of the general population (a hazard ratio of 0.53). The researchers noted that the estimates weren't very precise, and the confidence interval for that result came very close to "no difference." Superselective vagotomy showed no change.
- **Sweden, 2017 (Liu and colleagues).** [This larger study](#) compared 9,430 people who had a vagotomy (3,445 truncal) with 377,200 matched people. Overall, vagotomy was **not** linked to Parkinson's risk (a hazard ratio of 0.96). There was only a suggestion of lower risk after truncal vagotomy (0.78, which could be chance), and a lower risk when the truncal vagotomy happened at least 5 years before diagnosis (0.59).

So: some, but not all, results point the way the gut-first idea predicts, and the clearest signals come from small subgroups. These are also observational studies. People who needed vagus surgery may differ from other people in smoking, diet, other illnesses, or medicines, and those differences could affect Parkinson's risk too. The Danish team did adjust for several of these, but no adjustment is perfect.

Vagus surgery is also not a way to prevent Parkinson's. The operation has real side effects (Chapter 2's bedside case describes some), and the evidence doesn't come close to supporting it as prevention.

The appendix puzzle

The appendix is a small, finger-shaped pouch attached to the large intestine, packed with immune tissue and nerves. **Appendix and Parkinson's** refers to the research question of whether removing the appendix (an appendectomy) changes a person's later risk of Parkinson's disease, based on the idea that the appendix might store misfolded alpha-synuclein that could seed the disease.

The results are a good lesson in why one study is never the final word.

Study	What it found
Killinger et al. 2018 (two data sets, more than 1.6 million people)	Appendix removal decades before diagnosis was linked to lower Parkinson's risk. Healthy human appendixes also contained clumped alpha-synuclein.
Svensson et al. 2016 (Denmark, 265,758 people with appendectomy)	Appendix removal was linked to a slightly higher risk (hazard ratio 1.14).
Lu et al. 2020 meta-analysis (6 studies, about 3.55 million people)	No overall link (relative risk 1.02).
Chin et al. 2025 meta-analysis (9 studies)	No overall link (relative risk 1.01).

The 2018 study made headlines around the world. But when researchers pooled all the available studies, the effect disappeared. The finding that healthy appendixes contain clumped alpha-synuclein is still interesting, because it shows the gut can hold the protein in its problem form. But it doesn't mean the appendix starts the disease, and removing it doesn't seem to change risk overall.

Hype Meter: "Removing your appendix prevents Parkinson's"

Strong

Moderate

Preliminary

Hype

Verdict: Hype. One large 2018 study linked appendix removal to lower Parkinson's risk, but a Danish study of 265,758 people found a slightly higher risk, and two meta-analyses (6 studies with about 3.55 million people, and 9 studies in 2025) found no overall link. No study tested appendix removal as prevention, and surgery has its own risks. **What would change the grade:** New, large studies that consistently find lower risk after appendix removal, with a clear biological explanation, could move the association to Preliminary. Even then, it would not make surgery a prevention strategy.

If you're going through this

If you have a gut condition like IBS, Crohn's, or ulcerative colitis, reading about constipation and Parkinson's might make you worry. Please hold onto the numbers: Parkinson's mostly begins in older adults, the constipation link comes from comparing huge groups, and most people with gut symptoms never develop it. Your gut condition is its own diagnosis with its own care plan. If you're worried, write the question down and ask your care team; they can explain what your symptoms do and don't mean.

14.9 Two Routes? Gut-First and Brain-First Parkinson's

If some patients fit Braak's climb from the brainstem and others don't, maybe there's more than one kind of Parkinson's. In 2019, the Danish researcher Per Borghammer and his colleague Nathalie Van Den Berge proposed exactly that.

The **gut-first subtype** (also called "body-first") is a proposed form of Parkinson's disease in which alpha-synuclein pathology starts in the gut or other body nerves, reaches the brainstem through the vagus nerve, and climbs up to the dopamine neurons later. Because the body's automatic nerves and the brainstem sleep circuits are damaged early, this subtype is predicted to have constipation, other automatic-nerve problems, and REM sleep behavior disorder years **before** movement symptoms.

The **brain-first subtype** is a proposed form of Parkinson's disease in which alpha-synuclein pathology starts inside the brain, reaches the dopamine system early, and spreads down to the brainstem and the body's nerves later. This subtype is predicted to show movement symptoms earlier, with REM sleep behavior disorder and gut problems usually absent before diagnosis and appearing later, if at all.

Before we compare them, notice that both subtypes share the same machinery from Section 14.4: misfolded alpha-synuclein and prion-like spread along nerve connections. What differs is where the first domino falls. The table below lays out the predictions.

Feature	Gut-first subtype	Brain-first subtype
Proposed starting place	Gut or other body nerves	Inside the brain (the exact site is debated)
Route to the dopamine neurons	Up the vagus nerve, through the brainstem	Directly within the brain
Constipation and other automatic-nerve problems	Early, often years before diagnosis	Later

Feature	Gut-first subtype	Brain-first subtype
REM sleep behavior disorder before diagnosis	Common	Usually absent
Movement symptoms	Come later in the sequence	Come earlier in the sequence

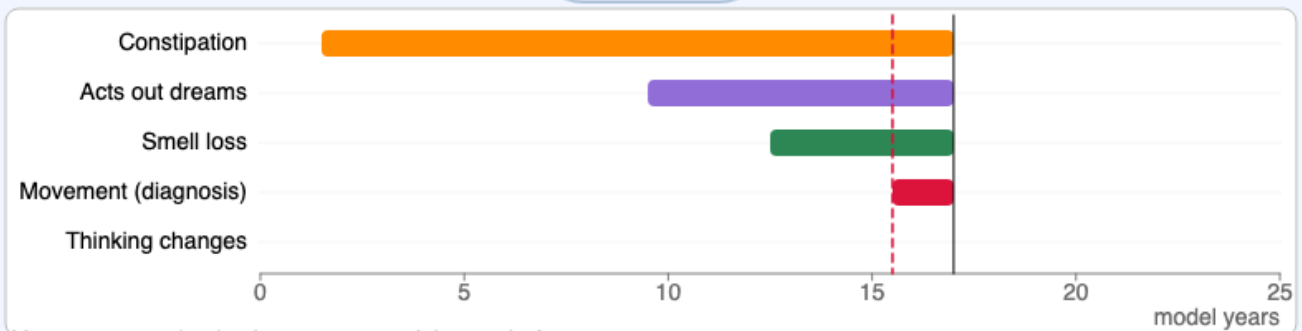
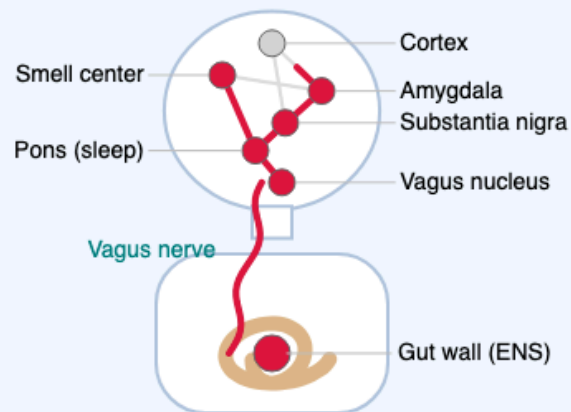
Borghammer and Van Den Berge supported their proposal with brain imaging studies comparing people with and without REM sleep behavior disorder, plus autopsy findings, and noted that it could explain several puzzles in the earlier research. But they called it a hypothesis themselves, a framework for designing new studies. It is one of the most active debates in Parkinson's research.

The MicroSim below lets you compare the two routes. In it, "pathology" means misfolded alpha-synuclein building up in a region, and a symptom appears on the timeline once a region is damaged enough. The years are made-up teaching numbers, chosen only to show the order of events each idea predicts.

Diagram: Gut-First or Brain-First?

Gut-First or Brain-First?

A model of two competing ideas. Pick a start, press Start, and compare the symptom order.



☐ Cut the vagus nerve

Speed: 2.0 yr/s



[Back to Gut-First or Brain-First? Lesson Plan](#)

Interactive simulation: <https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch14-two-routes/main.html>

[Open the Gut-First or Brain-First? MicroSim fullscreen](#)



MicroSim specification: Gut-First or Brain-First?



Type: microsim **sim-id:** ch14-two-routes

Library: p5.js

Status: Implemented

Bloom Level: Analyze, Evaluate

Bloom Verb: compare

Learning Objective: The learner will compare the gut-first and brain-first hypotheses of Parkinson's disease by the order of early symptoms each predicts, and explain why cutting the vagus nerve matters only in the gut-first route.

Canvas: 560 px drawing area plus 110 px controls (iframe 672 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset; Starting point select (Gut-first: starts in the gut wall; Brain-first: starts inside the brain); "Cut the vagus nerve" checkbox; Speed slider (0.5 to 4 model years per second).

Rules: Seven regions (gut wall, vagus nucleus, pons sleep circuits, smell center, amygdala, substantia nigra, cortex) connected by edges with illustrative travel delays. Pathology arrives at each region along the shortest path from the starting point; a symptom bar starts 1.5 model years after arrival (gut wall: constipation; pons: acting out dreams; smell center: smell loss; substantia nigra: movement symptoms, marked as diagnosis; cortex: thinking changes). Cutting the vagus nerve removes the gut to vagus nucleus edge.

Feedback: A body diagram colors regions by pathology level and draws spread along connections; a symptom timeline (0 to 25 model years) shows bars and a dashed diagnosis line; a status line reports how many years before diagnosis constipation appeared.

Provenance: Braak et al. 2003; Borghammer and Van Den Berge 2019; [Kim et al. 2019](#) (vagotomy blocked spread in mice). All timings are illustrative. Labeled on screen as a model of competing ideas.

Start with **Gut-first** and press Start. Watch the red pathology climb from the gut wall up the vagus nerve to the brainstem, then to the sleep circuits and smell center, and only much later to the substantia nigra. On the timeline, constipation and dream-acting appear long before the dashed "diagnosis" line. Then switch to **Brain-first** and run it again. Movement symptoms come early, and constipation shows up last, after the disease has worked its way down to the body.

Now test a prediction. Check **Cut the vagus nerve** and run each route. In the gut-first route, the spread stays in the gut, which mirrors what happened in the 2019 mouse study. In the brain-first route, cutting the vagus changes nothing in the brain, because the disease never needed that road. Ask yourself: if the human vagotomy studies had found a big, clear protective effect, which hypothesis would that support? What does the mixed result you read in Section 14.8 suggest?

What this model leaves out

- It is a model of two competing hypotheses, not a proven map. Many scientists think real Parkinson's is messier, and some think neither route explains every case.
- The years, the regions chosen, and the order of connections are simplified teaching values; real timelines vary widely from person to person, and nobody can watch the spread happen in a living human.
- Real spread involves both sides of the brain, many more regions, and probably genes, aging, inflammation, and the environment, which the model ignores.
- In the model, cutting the vagus fully blocks gut-first spread, as it did in mice; human vagotomy studies give mixed results, and other nerve routes may exist.
- Symptoms appear at a single fixed threshold here. In real life, symptoms like constipation and low mood have many other causes, and many people with them never develop Parkinson's.

14.10 The Gut Matters for Treatment Too: Levodopa Absorption

Even if Parkinson's turns out to start in the brain for most people, the gut still matters every day for people living with it, because of how the main medicine works.

People can't simply take dopamine, because dopamine in the blood doesn't easily cross the blood-brain barrier, the protective layer of cells that controls what gets into the brain. Instead, NINDS explains, the main Parkinson's medicine is levodopa, which the brain converts into dopamine. It's almost always combined with a second medicine, carbidopa, which keeps the body from breaking levodopa down too early, so more of it reaches the brain.

Levodopa is usually swallowed as a pill, so it has a long trip before it can work. It has to leave the stomach, get absorbed into the blood from the upper part of the small intestine, and then cross into the brain. **Levodopa absorption** is the process by which levodopa taken by mouth passes from the gut into the bloodstream; in Parkinson's it can be delayed or uneven because of slow stomach emptying, constipation, and competition from protein in meals.

Each step can go wrong:

- **Slow stomach emptying.** Parkinson's can slow the stomach. A 2020 review by [Pfeiffer and colleagues](#) says delayed stomach emptying has been reported in a substantial fraction of people with Parkinson's and is linked to delayed levodopa levels in the blood and more "off" periods, times when symptoms come back because the medicine isn't working well.
- **Constipation and other gut problems.** A 2023 review by [Leta and colleagues](#) lists swallowing problems, slow stomach emptying, constipation, a stomach infection called *H. pylori*, bacterial overgrowth in the small intestine, and changes in gut microbes as possible barriers to levodopa reaching the blood.

- **Protein in meals.** Levodopa is carried across the gut wall by the same transport system that carries some amino acids (the building blocks of protein). A 2019 review by [van Kessel and El Aidy](#) notes that dietary amino acids can interfere with levodopa absorption, and NINDS notes that too much protein may limit how well people absorb carbidopa-levodopa.

This is why people with Parkinson's sometimes have unpredictable days when the medicine kicks in late or not at all. Their neurology team may adjust timing, treat the gut problems, or use forms of treatment that skip the gut entirely. One example is a levodopa-type medicine pumped slowly and steadily under the skin through a thin tube ([Vyalev](#)), which the FDA approved in October 2024 for motor fluctuations (swings between good and "off" periods) in adults with advanced Parkinson's. Those decisions belong to the care team; NINDS warns that people should never stop carbidopa-levodopa suddenly without talking with a doctor.

14.11 Alzheimer's Disease: Is the Gut Involved?

Now for the other big neurodegenerative disease. If Parkinson's is the disease of movement, Alzheimer's is the disease of memory and thinking.

Alzheimer's disease is a progressive brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out everyday tasks; it is the most common cause of dementia in older adults. The Alzheimer's Association's [2026 Alzheimer's Disease Facts and Figures report](#) estimates that about 7.4 million Americans aged 65 and older are living with Alzheimer's in 2026. Dementia means losing thinking, remembering, and reasoning abilities to the point that it interferes with daily life.

In 1906, Dr. Alois Alzheimer examined the brain of a woman who had died after memory loss, language problems, and unpredictable behavior. He found two kinds of abnormal deposits. Scientists now call them amyloid plaques and tau tangles, and the NIA says they're still considered main features of the disease.

Amyloid beta is a small protein fragment, cut from a larger protein in the brain, that can clump together into sticky plaques between neurons; these plaques are one of the main signs of Alzheimer's disease. Tau is a different protein that normally helps hold up the internal "railway tracks" of neurons; in Alzheimer's, it twists into tangles inside the cells. According to the NIA, these changes can begin a decade or more before symptoms appear, and damage often starts in memory areas such as the hippocampus.

Notice the pattern you saw in Parkinson's: a misfolding protein, a long silent period, and spread through connected regions. That has led researchers to ask whether gut microbes might nudge Alzheimer's too.

The human evidence is very early. In 2017, [Vogt and colleagues](#) compared stool samples from 25 people with Alzheimer's dementia and 25 people without it, matched for age and sex. The Alzheimer's group had less diverse gut bacteria and a different mix of bacterial groups, and some bacterial levels correlated with Alzheimer's markers in spinal fluid. That's interesting, but it's a single snapshot of 50 people.

It can't tell us which came first. People with dementia often eat differently, move less, take different medicines, and live in different settings, and any of those could change their gut microbes. In a 2024 review, [Seo and Holtzman](#) described research on gut microbes and Alzheimer's as "still in their infancy."

That hasn't stopped supplement marketing.

Hype Meter: "Probiotics prevent Alzheimer's"

Strong

Moderate

Preliminary

Hype

Verdict: Hype. People with Alzheimer's have different gut bacteria in small studies, such as one comparing 25 patients with 25 matched controls, and mouse studies (summarized in a 2024 review by Seo and Holtzman) suggest microbes may affect amyloid buildup in mice. But a 2024 review describes the field as being in its infancy, and no large, long human trial has shown that any probiotic prevents Alzheimer's. The difference in microbes could be a result of the disease or of lifestyle, not a cause. **What would change the grade:** Large, long randomized trials in people, following them for years and showing fewer Alzheimer's diagnoses or slower decline with a specific product, could move it to Preliminary or higher. You'll learn how to read probiotic trials in [Chapter 16](#).

For families

If a grandparent or parent has Parkinson's or Alzheimer's, you might be the one who notices changes first, like constipation, smell loss, low mood, or medicine that seems to wear off at certain times. These are worth mentioning to their doctor, because many of them are treatable. Try not to blame them for being slow, forgetful, or withdrawn; these are symptoms of the disease, and depression and anxiety in Parkinson's can be treated. Be cautious with supplements that promise to "protect the brain through the gut," and bring any product to the care team before trying it.

At the Bedside: Nanaji's Long Road to a Diagnosis



Meet the patient (fictional)

Nanaji is Riya's 72-year-old grandfather. Over the past two years his right hand has shaken at rest, his handwriting has gotten tiny, and he walks with small steps. Looking back, his family remembers other changes: constipation for many years, losing his sense of smell, and, according to Riya's grandmother, shouting and swinging his arms in his sleep as if fighting someone in a dream. Lately he seems quieter and more worried than he used to be.

What the doctor checks: A neurologist takes a careful history, including the non-movement symptoms that came first, and asks about medicines that can cause Parkinson-like symptoms. The physical exam looks for tremor at rest, rigidity, slowness, and balance problems. There's no single blood test for Parkinson's; the diagnosis is mainly based on the history and exam. In some cases, brain imaging helps rule out other causes. A sleep study can confirm REM sleep behavior disorder.

Connecting the signals: Nanaji has the classic movement symptoms caused by dopamine neuron loss. But his story also includes years of constipation, smell loss, and acting out dreams before the tremor. In the gut-first hypothesis, this order of events is what you'd predict if alpha-synuclein pathology began in body nerves and climbed through the brainstem's sleep circuits before reaching the substantia nigra. His doctor explains that this is an interesting fit, but no test can tell where his disease actually started.

Diagnosis: Parkinson's disease.

Why it happens: Dopamine-making neurons in his substantia nigra have been dying for years, probably along with neurons in his gut, smell system, and brainstem. Lewy bodies made of misfolded alpha-synuclein are found in damaged cells in most people with Parkinson's. Why the process started in him is unknown, as it is for most patients.

The mind-body side: Depression and anxiety are common in Parkinson's and can even appear before movement problems, according to NINDS. They are part of the disease, not a weakness, and they're treatable with therapy, medicine, or both. Nanaji's team screens for low mood, and his family learns that his quietness may be a symptom, not a sign that he's lost interest in them. Staying active and connected helps too; Riya plans a weekly cooking session with him and her grandmother.

Treatment today: The main treatment is carbidopa-levodopa, which usually works well for movement symptoms early in the disease but doesn't stop it from progressing. Because the medicine must be absorbed from the gut, his team also treats his constipation, for example with more fiber and fluids as NINDS suggests, and pays attention to meal timing and protein, which can affect levodopa absorption. Physical, occupational, and speech therapy help with walking, daily tasks, and voice. Exercise is encouraged. All medicine choices and changes are made with his neurologist.

What's new in research: In 2023, the Parkinson's Progression Markers Initiative reported results for a test that detects misfolded alpha-synuclein "seeds" in spinal fluid ([Siderowf and colleagues, *Lancet Neurology*](#)). Among 1,123 participants, the test was positive in 87.7% of people with Parkinson's and negative in 96.3% of healthy controls, and it found the seeds in 44 of 51 people with early warning signs (REM sleep behavior disorder or smell loss) who had not been diagnosed.

The test missed more often in some groups, though: it was positive in only 67.5% of people whose Parkinson's is linked to variants in a gene called *LRRK2*. Several of the study's authors work for Amprion, the company that developed the test.

In 2024, two expert groups used tests like this one to propose new "biological" definitions and stages of Parkinson's that start with finding misfolded alpha-synuclein rather than with symptoms (Simuni and colleagues; Höglinger and colleagues, both in *Lancet Neurology*). Both groups said their systems are for research only, and experts still debate them, partly because the test can be negative in some people with typical Parkinson's. **Evidence grade: Moderate** as a research tool for identifying Parkinson's biology; it is not a routine screening test for the general public, and it can't say where the disease began.

? Your turn: reason through a variation



Nanaji's friend Mr. Okafor, also in his 70s, developed a tremor and slowness, but he never had constipation, smell loss, or dream-acting beforehand. His movement symptoms got worse fairly quickly, and only later did he develop constipation. Which proposed subtype does his story fit better, and what's the limit of that conclusion?

Answer: His story fits the brain-first subtype better: movement symptoms first, without REM sleep behavior disorder or gut problems beforehand, and gut problems later. But the subtypes are a hypothesis, symptoms like constipation have many causes, and memory of past symptoms can be fuzzy. No test available in routine care can show where his pathology started, so this is a teaching exercise, not a diagnosis.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: If you're constipated, you'll probably get Parkinson's.

Reality: People with constipation have about twice the odds of being diagnosed with Parkinson's later, but that's a relative comparison across huge groups. Constipation is very common and has many causes, Parkinson's mostly begins in older adults, and the great majority of constipated people never develop it.

Myth: The Braak hypothesis has been proven.

Reality: Braak's staging pattern is based on autopsies, which show where pathology is at death, not where it started. Mouse studies show gut-to-brain spread is possible, but human studies of vagus surgery are mixed, and a small fraction of patients don't fit the pattern. It's an influential hypothesis, not a settled fact.

Myth: Removing your appendix prevents Parkinson's.

Reality: One 2018 study found a lower risk, but another large study found a slightly higher risk, and two meta-analyses found no overall link. Appendix removal is not a prevention strategy.

Myth: Alzheimer's is caused by gut bacteria.

Reality: Small studies, such as one comparing 25 people with Alzheimer's to 25 without, found differences in gut bacteria. These are correlations, and the disease itself, along with diet, medicines, and activity, could change the microbes. The field is described by experts as still in its infancy.

Myth: "Prion-like" means Parkinson's is contagious.

Reality: "Prion-like spread" describes how misfolded alpha-synuclein may pass from one neuron to a connected neuron inside one person's nervous system. It does not mean you can catch Parkinson's from someone.

Your Gut Check

Test yourself. Try each one before you open the answer.

? 1. Claim Check: "New science proves Parkinson's starts in your gut. Heal your gut with our probiotic and protect your brain for life!" ✓

Grade: Hype. The gut-first idea is a serious hypothesis (Moderate for some patients), supported by autopsy patterns, the constipation link, and mouse experiments. But nothing has "proven" it, human vagotomy and appendix studies are mixed, and no trial has shown that any probiotic prevents Parkinson's. The ad jumps from a contested hypothesis to a product. A careful version: "Some scientists think Parkinson's may begin in the gut in some people; researchers are still testing this idea."

? 2. Predict: Sam reads that Riya's grandfather has Parkinson's and asks whether Riya's Crohn's disease means she'll get it too. Using this chapter, what would you predict, and why? ✓

There's no good reason to predict that Riya will get Parkinson's. Parkinson's mostly starts in people in their 60s or later, and most of the gut evidence in this chapter is about constipation as an early sign in older adults. Sam's question isn't silly, though: large studies of adults have found that people with inflammatory bowel disease, including Crohn's, are diagnosed with Parkinson's somewhat more often later in life (about 1.4 times as often in a [2024 pooled analysis of 7 cohort studies](#)). That is a relative number for an uncommon disease, it comes from observational studies that can't show cause, and most people with Crohn's never develop Parkinson's. Having a grandparent with Parkinson's can matter a little in some families because genes play a part, but in most people the cause is unknown. If Riya is worried, the right step is to ask Dr. Alvarez, not to assume.

? 3. Explain: Why did cutting the vagus nerve block the spread of misfolded alpha-synuclein to the brain in the 2019 mouse study? ✓

The misfolded protein was injected into the gut wall, and the vagus nerve is the main nerve line linking the gut to the brainstem's vagus nucleus. Prion-like spread passes from neuron to connected neuron, so the protein needs an unbroken chain of nerve cells to travel. Cutting the vagus removed that chain, so the protein couldn't reach the brainstem, and the dopamine neuron loss and behavior problems didn't happen.

? 4. Apply: Nanaji's levodopa seems to kick in late on days when he's very constipated and after big protein-heavy lunches. Use Section 14.10 to explain why. ✓

Levodopa has to leave the stomach and be absorbed from the upper small intestine before it can reach the brain. Slow gut movement, which often goes along with constipation in Parkinson's, can delay that trip. Protein in meals breaks down into amino acids that compete with levodopa for the same transport system in the gut wall, so less levodopa gets absorbed, or it gets absorbed later. His care team, not his family, should decide on any changes to timing or diet.

5. Read the data. In 2017, Liu and colleagues used Swedish health registers to compare people who had a vagotomy with matched people who didn't. Here are their hazard ratios for later Parkinson's disease (1.0

means no difference; below 1.0 means lower risk). The numbers in parentheses are 95% confidence intervals: the range of values the data are compatible with.

Group compared with matched reference people	Hazard ratio (95% CI)
Any vagotomy (9,430 people)	0.96 (0.78 to 1.17)
Truncal vagotomy (3,445 people)	0.78 (0.55 to 1.09)
Truncal vagotomy at least 5 years before diagnosis	0.59 (0.37 to 0.93)

? 5. What does this data show, and what can't it show? ✓

Overall, vagotomy wasn't linked to Parkinson's risk: 0.96 is close to 1.0, and the interval includes 1.0. For truncal vagotomy, the estimate is lower (0.78), but the interval still includes 1.0, so it could be chance. Only the subgroup with truncal vagotomy at least 5 years before diagnosis has an interval entirely below 1.0, which is consistent with the gut-first idea. But this is an observational study, so it can't prove that cutting the vagus caused the lower risk; people who had surgery may differ in other ways, and testing many subgroups raises the chance of a lucky result. A helpful follow-up would be a pooled analysis of all vagotomy studies, using the same definitions and long follow-up.

Exercises

Remember

1. What protein makes up most of a Lewy body?

Answer ✓

Misfolded alpha-synuclein.

1. Name three prodromal symptoms that can come years before the movement symptoms of Parkinson's disease.

Answer ✓

Any three of: constipation, loss of smell, REM sleep behavior disorder (acting out dreams), and depression or anxiety.

Understand

1. Explain why Parkinson's movement symptoms don't appear until the disease has been present for a long time.



Answer



The brain has a lot of reserve. According to NINDS, most people have already lost 60 to 80% or more of their dopamine neurons in the substantia nigra by the time movement symptoms appear, so the disease process runs quietly for years before it's visible.

1. In your own words, explain the difference between the two parts of the Braak hypothesis.



Answer



The first part is a staging pattern based on autopsies: Lewy pathology appears first in the brainstem vagus nucleus and a smell area, then climbs to higher brain regions. The second part is a guess about the origin: that in some people a trigger may enter through the gut and travel up the vagus nerve. The staging is a description; the gut origin is a hypothesis.

Apply

1. Using the MicroSim, run the gut-first and brain-first routes without cutting the vagus nerve. For each, record the model year when constipation, dream-acting, and movement symptoms begin. Then explain which symptom order each hypothesis predicts and why.
2. A news story says, "Study of 3,445 people shows cutting the vagus nerve protects against Parkinson's." Use the Swedish results in Your Gut Check question 5 to write a two-sentence correction.

Analyze

1. Compare the evidence from the 2019 mouse study (Kim and colleagues) and the 2017 Swedish vagotomy study (Liu and colleagues) using four of the six claim questions. Which one is better at showing cause, and which one tells you more about people?
2. The appendix studies disagree: one found lower risk, one found slightly higher risk, and two meta-analyses found no link. Analyze at least three reasons why large observational studies of the same question might reach different answers.

Evaluate

1. A classmate argues: "Since constipation comes 10 years before Parkinson's, the disease must start in the gut." Evaluate this argument. What does the timing support, and what other explanation fits the same data?
2. Judge which grade you would give the claim "Gut microbes cause Alzheimer's disease." Defend your grade using the Vogt 2017 study, the Seo and Holtzman 2024 review, and at least two of the six claim questions.

Create

1. Design a long-term study in people that could help decide between the gut-first and brain-first hypotheses. Describe who you would enroll, what you would measure (and when), and what result would support each hypothesis. Explain one ethical limit on what you could do.
2. Write a short, kind explanation (under 150 words) that Riya could give her younger cousin about why Nanaji had stomach problems before his shaking started, without scaring the cousin or overstating the science.

Key Takeaways

- Parkinson's disease is a neurodegenerative disease in which dopamine neurons in the substantia nigra die; most are gone before movement symptoms like tremor, rigidity, and slowness appear.
- Misfolded alpha-synuclein forms Lewy bodies, and it may spread from neuron to connected neuron (prion-like spread), which does not mean Parkinson's is contagious.
- Prodromal symptoms, including constipation, smell loss, REM sleep behavior disorder, and mood changes, can come years earlier. Constipation roughly doubles the odds of a later diagnosis, but most constipated people never develop Parkinson's.
- The Braak hypothesis proposes that pathology climbs from the brainstem and may begin in the gut; mouse studies show gut-to-brain spread is possible, but human vagotomy studies are mixed and appendix removal shows no overall link.
- Parkinson's may come in gut-first and brain-first subtypes that predict different symptom orders. This is an active, unresolved hypothesis.
- The gut also matters for treatment: slow stomach emptying, constipation, and protein can affect levodopa absorption.
- Alzheimer's disease involves amyloid beta plaques and tau tangles. Gut microbe differences have been found in small studies, but the research is very early, and claims that probiotics prevent Alzheimer's are hype.

You weighed a real scientific debate!



You just did what neurologists do: compared two competing ideas by the predictions they make and the evidence for each. Next, in Chapter 15, we'll turn from disease to everyday life and ask a question you face at every meal: can food change your mood?

Quiz: Parkinson's, Alzheimer's, and the Gut

Test your understanding of Chapter 14. Choose the best answer, then click **Show Answer** to check.

Question 1

What is the main cause of the movement symptoms of Parkinson's disease?

- A. Loss of dopamine-making neurons in the substantia nigra
- B. Amyloid beta plaques building up in the hippocampus
- C. Damage to the muscles of the arms and legs
- D. Too much serotonin made in the gut

 **Show Answer**



The correct answer is **A**. Movement symptoms come mainly from the death of dopamine-making neurons in the substantia nigra; NINDS says most people have lost 60 to 80% or more of them by the time symptoms appear. Option B describes a hallmark of Alzheimer's disease, not Parkinson's.

Concept Tested: Dopamine Neuron Loss **Bloom's Level:** Remember

Question 2

What is a Lewy body?

- A. A bundle of vagus nerve fibers in the gut wall
- B. A plaque of amyloid beta between neurons
- C. An abnormal clump, made mostly of misfolded alpha-synuclein, inside a nerve cell
- D. A group of gut bacteria found in people with Parkinson's

? Show Answer



The correct answer is **C**. Lewy bodies are clumps of misfolded alpha-synuclein found inside damaged nerve cells in most people with Parkinson's. Option B mixes up Lewy bodies with the amyloid plaques of Alzheimer's disease, which form between neurons rather than inside them.

Concept Tested: Lewy Body **Bloom's Level:** Remember

Question 3

In Braak's 2003 staging system, where does Lewy pathology first appear in the brain?

- A. In the outer cortex, then it moves down to the brainstem
- B. In the substantia nigra only
- C. In the hippocampus and memory areas
- D. In the brainstem vagus nucleus and a smell-processing area

? Show Answer



The correct answer is **D**. Braak's team reported that pathology first shows up in the dorsal motor nucleus of the vagus and an olfactory (smell) area, then climbs upward, reaching the substantia nigra in middle stages and the cortex last. Option A reverses the direction of the proposed spread.

Concept Tested: Braak Hypothesis **Bloom's Level:** Remember

Question 4

A 2016 meta-analysis found that people with constipation had an odds ratio of about 2.27 for a later Parkinson's diagnosis. What is the best interpretation?

- A. Most people with constipation will develop Parkinson's disease.
- B. Constipation is linked to about double the odds of a later diagnosis, but because Parkinson's is uncommon, most constipated people never develop it.
- C. Constipation causes Parkinson's disease by damaging the substantia nigra.
- D. Treating constipation prevents Parkinson's disease.

 Show Answer



The correct answer is **B**. An odds ratio near 2 is a relative comparison between large groups; doubling a small chance still leaves a small chance. Option A is the most common misreading, and options C and D claim cause, which observational studies can't show.

Concept Tested: Constipation **Bloom's Level:** Understand

Question 5

What does "prion-like spread" mean in Parkinson's research?

- A. Parkinson's can be caught from another person, like an infection.
- B. Gut bacteria travel through the blood to the brain.
- C. Misfolded alpha-synuclein may pass to connected neurons and make normal copies misfold, so damage moves along nerve pathways.
- D. Dopamine leaks out of the brain into the gut.

 Show Answer



The correct answer is **C**. Prion-like spread describes misfolding moving from neuron to connected neuron inside one person's nervous system, like falling dominoes. Option A is a common misunderstanding of the word "prion"; Parkinson's is not contagious between people.

Concept Tested: Prion-Like Spread **Bloom's Level:** Understand

Question 6

How do the gut-first and brain-first subtypes differ in what they predict before diagnosis?

- A. Gut-first predicts constipation and REM sleep behavior disorder years before movement symptoms; brain-first predicts movement symptoms earlier, with those problems usually absent before diagnosis.
- B. Gut-first predicts memory loss first; brain-first predicts constipation first.
- C. Both predict exactly the same order of symptoms.
- D. Brain-first predicts that cutting the vagus nerve will prevent the disease.

? Show Answer



The correct answer is **A**. In the gut-first idea, body nerves and brainstem sleep circuits are damaged before the dopamine system, so constipation and dream-acting come first. In the brain-first idea, the dopamine system is hit early. Option D gets it backward: the vagus route matters only in the gut-first idea.

Concept Tested: Gut-First Subtype **Bloom's Level:** Understand

Question 7

A man has had trouble with his Parkinson's medicine kicking in late, especially after large, protein-heavy meals and on days when he is constipated. Which explanation fits the chapter best?

- A. Protein and constipation destroy levodopa in the brain.
- B. Levodopa can't cross the blood-brain barrier at all, so it never works.
- C. His dopamine neurons grow back after meals.
- D. Slow gut movement delays levodopa's trip to the small intestine, and amino acids from protein compete with it for absorption.

? Show Answer



The correct answer is **D**. Levodopa is absorbed from the upper small intestine, so slow stomach emptying and constipation can delay it, and dietary amino acids share its transport system. Option B is wrong because levodopa does reach the brain, where it is converted into dopamine; it's dopamine itself that doesn't cross easily. Any changes should be made by his care team.

Concept Tested: Levodopa Absorption **Bloom's Level:** Apply

Question 8

A headline says: "Cutting the appendix slashes Parkinson's risk!" Based on the evidence in this chapter, what is the best response?

- A. It's true, so people should consider having their appendix removed.
- B. One 2018 study found lower risk, but a Danish study found slightly higher risk and two meta-analyses found no overall link, so the claim is not supported.
- C. It's true only for people with constipation.
- D. It's proven in mice, so it must be true in people.

 Show Answer



The correct answer is **B**. The Killinger 2018 finding was not confirmed when studies were pooled: Lu 2020 found a relative risk of 1.02 and Chin 2025 found 1.01, both meaning no overall link. Option A turns a disputed association into a medical recommendation, which no evidence supports.

Concept Tested: Appendix and Parkinson's **Bloom's Level:** Apply

Question 9

The Danish truncal vagotomy study found a hazard ratio of 0.53 (95% CI 0.28 to 0.99) for people followed more than 20 years, while the larger Swedish study found no overall link (hazard ratio 0.96). What is the most reasonable conclusion?

- A. Cutting the vagus nerve is proven to prevent Parkinson's.
- B. The vagus nerve has nothing to do with Parkinson's.
- C. The human evidence is mixed: some subgroup results fit the gut-first idea, but they are imprecise and observational, so they can't prove cause.
- D. The Swedish study must be wrong because it was larger.

 Show Answer



The correct answer is **C**. The Danish result came from a subgroup, with a confidence interval that nearly reached 1.0, and the Swedish study found no overall effect. Both are observational, so differences between people who had surgery and those who didn't could explain the results. Option A overstates a weak, mixed signal.

Concept Tested: Truncal Vagotomy Studies **Bloom's Level:** Analyze

Question 10

A 2017 study compared stool samples from 25 people with Alzheimer's and 25 matched people without it and found differences in gut bacteria. Which statement best analyzes what this study can show?

- A. It shows a correlation in a small snapshot; the disease, diet, medicines, or activity could explain the bacterial differences.
- B. It proves gut bacteria cause amyloid beta plaques in people.
- C. It shows that probiotics prevent Alzheimer's.
- D. It shows nothing at all because it studied people instead of mice.



Show Answer



The correct answer is **A**. This cross-sectional study of 50 people found an association, but it can't tell which came first, and people with dementia often differ in diet, activity, and medicines. Option B confuses correlation with cause; experts describe this research area as still in its infancy.

Concept Tested: Alzheimer's Disease **Bloom's Level:** Analyze
