Measuring Cholinergic Dysfunction in Parkinson's Disease

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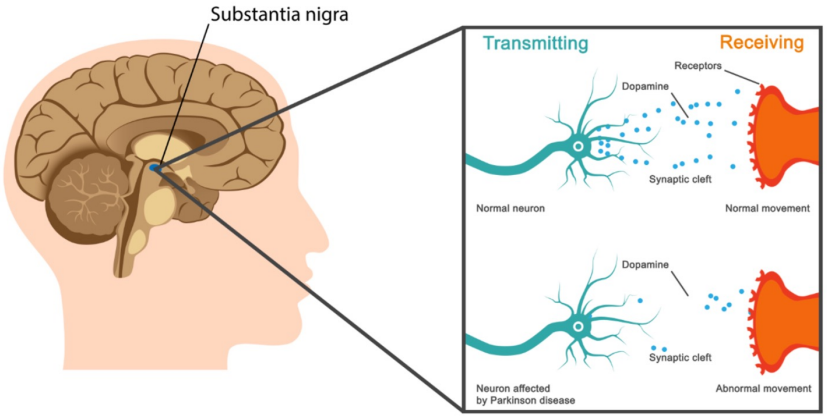
1

What is Parkinson's disease?

Second most common neurodegenerative disorder but most common **movement** disorder



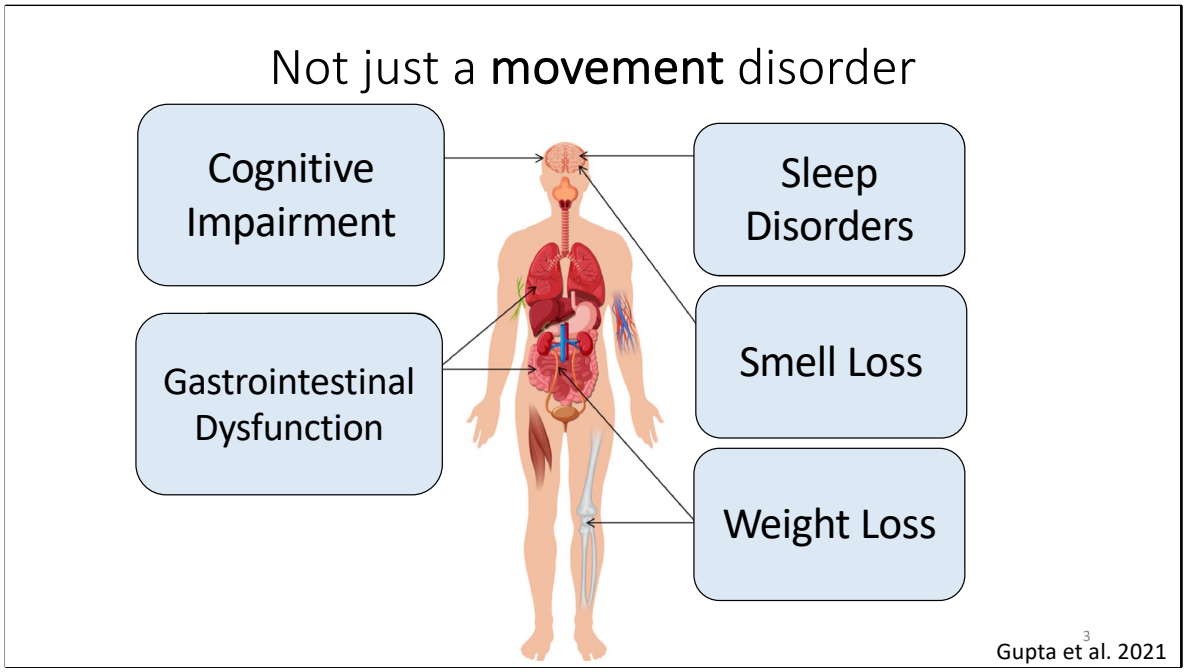
Common motor symptoms:
-Tremor
-Rigidity
-Bradykinesia

2

Parkinson's Disease is the second most common neurodegenerative disorder but most common movement disorder.

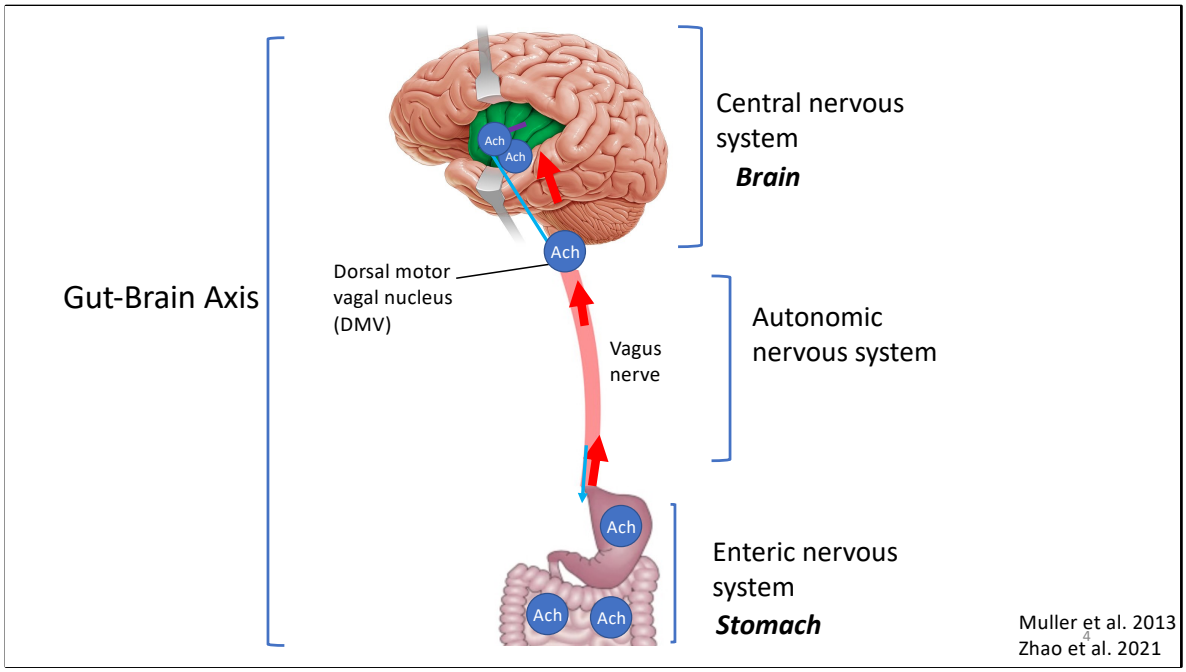
PD is most commonly characterized by the degeneration of dopamine-producing neurons in a deep brain region known as the substantia nigra.

Which causes common motor symptoms such as tremor, rigidity, and/or bradykinesia.



A key issue is that current PD therapies focus on treating this deficit in dopamine when, in fact, the pathology of PD is much more complex Here we can see many other nonmotor systems in the body become affected…so I propose that PD is not just movement disorder…

If this is the case, how can we begin to more accurately characterize the disease?



Taking a look at some of these nonmotor systems in the body….
Neurons in the DMV **produce acetylcholine**

Taking a step back, we know that the stomach, part of the gastrointestinal enteric nervous system, and brain, part of the central nervous system, are electrically connected through the gut-brain axis. They are connected bidirectionally by the vagus nerve. 80% of the fibers in the vagus are afferent (stomach to brain) and 20% are efferent (brain to stomach). A major source of information transmission in the gut-brain axis is via neurotransmitter acetylcholine.

Recent evidence has shown that as early as 10-15 years prior to PD diagnosis, degeneration of cholinergic neurons was found in the ENS. This causes impaired cholinergic synaptic neurotransmission which travels through the gut-brain axis via the cholinergically innervated vagus nerve, the largest nerve in the autonomic nervous system up to brainstem regions and then up to sensory regions in the CNS.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6706297/
EVIDENCE:
αSyn is a natively unfolded protein enriched in presynaptic terminals and plays a role in synaptic vesicle release
αSyn misfolding and abnormal aggregation (misfolded α-synuclein aggregates=Lewy bodies) can cause severe damage to neurons by impairing synaptic neurotransmission
Misfolding of alpha syn=spread of α-synucleinopathy via transneuronal means (thru vagus) between interconnected areas of the peripheral and central nervous system (CNS)
α-synuclein is present in the ENS since the early stages in untreated patients with PD, caudal spread of α-synucleinopathy to the lower brainstem

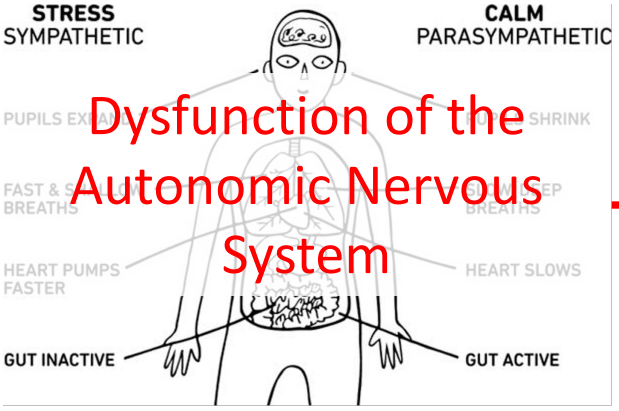
Alpha synuclein is detected in the enteric nervous system prior to clinical diagnosis, suggesting thru the gastrointestinal tract and its neural (vagal) connection.

Many studies recently indicate that αSyn is transported in the long-distance and bi-directional gut-brain axis (Kim et al., 2019). This main transport route is the cholinergic innervated vagus nervous system and central cholinergic neurons (Travagli et al., 2020). In the distal gut, αSyn is selectively expressed in most of the intestinal cholinergic axons. Moreover, in addition to the progressive death of dopaminergic neurons, the degenerative changes and death of cholinergic neurons also run through the pathological process of PD (Perez-Lloret et al., 2016). These findings suggest an involvement of the cholinergic system in αSyn aggregation and transmission.

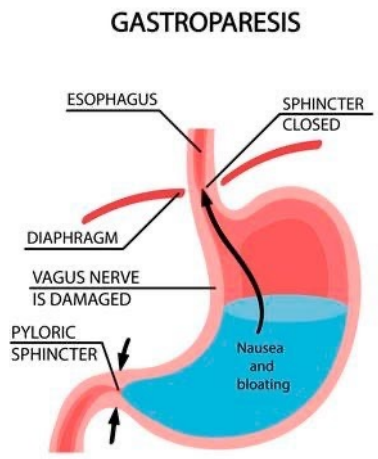
Go through 80:20 afferent to efferent
brain also exerts powerful influences on the gut via multiple descending pathways linking the stomach/brain via vagovagal reflex
mechanical transduction of stomach stretch receptors with afferents to the central nervous system

Parkinson's and Gut Cholinergic (Ach) Pathways

Autonomic Nervous System



Dysfunction of the Autonomic Nervous System



Soliman et al., 2021
Pasricha et al., 2024

5

What does this cholinergic dysfunction look like in terms of PD symptoms?
ANS: involuntary physiological processes
The cholinergic vagus nerve in the ANS plays a central role in controlling gastric motility and emptying.
Its degeneration leads to gastroparesis (delayed gastric emptying).

Supporting Evidence:
Imaging studies (e.g., PET scans with cholinergic tracers) show **reduced cholinergic activity in PD patients with GI dysfunction.**
Postmortem studies reveal **loss of cholinergic neurons in the DMV and ENS in PD patients with severe constipation and gastroparesis**.
Additionally, clinical studies show that **patients with more severe autonomic/cholinergic dysfunction report worse GI symptoms.**

the autonomic nervous system is a component of the peripheral nervous system that regulates involuntary physiologic processes including heart rate, blood pressure, respiration, digestion, and sexual arousal.

Parkinson's and Gut Cholinergic (Ach) Pathways

Enteric Nervous System

Enteric Nervous System Dysfunction

Constipation

Ach = worse GI motility

Yang et al., 2022

6

cholinergic signaling is needed for coordinated bowel movement.
Reduced cholinergic tone = reduced GI motility.

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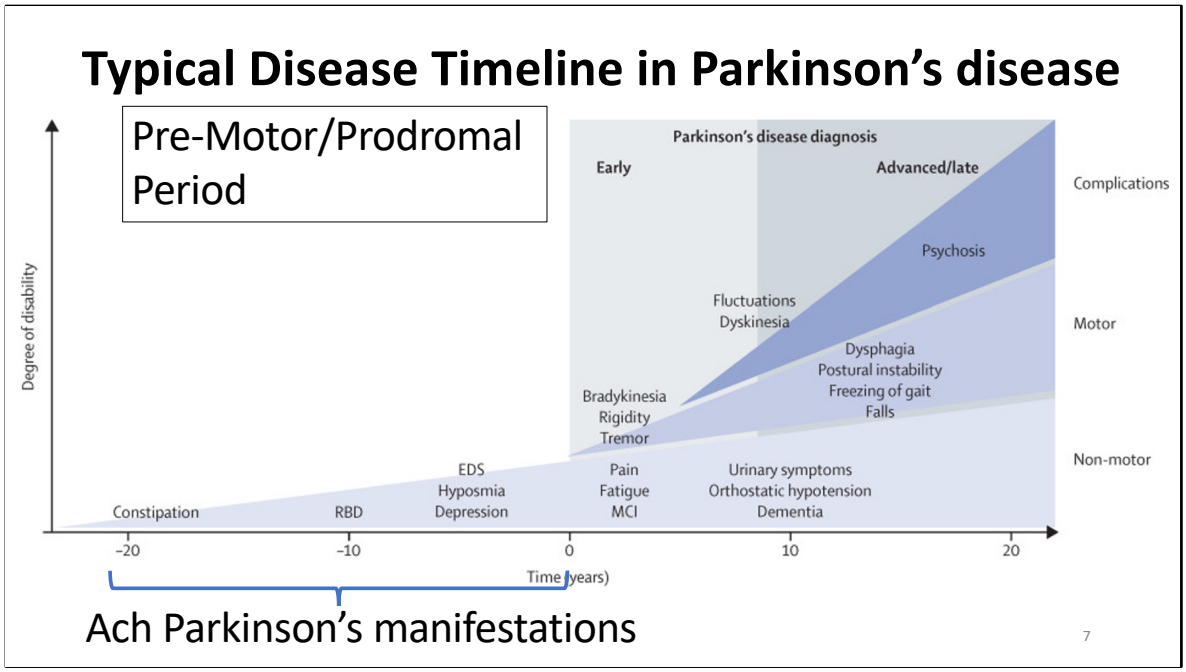

as I mentioned earlier, constipation and other cholinergic nonmotor symptoms such as sleep dysfunction, for example rem sleep behavior disorder known as RBD, and worsened ability to smell, or hyposmia, occur decades prior to PD diagnosis, in the pre-motor/prodromal period

This is a huge issue as the efficacy of disease-modifying therapeutics is dramatically decreased the later one is diagnosed.
To begin to mitigate this issue…….

2 ongoing pharma clinical trials targeted prodromal Parkinson's in 2025

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Prodromal PD

1. REM-sleep behaviour disorder
2. Hyposmia
3. Constipation
4. Autonomic dysfunction
5. Psychiatric symptoms
6. Pathological imaging markers

Benefit: Paradigm shift to focus on the underlying biology rather than symptoms alone

Main limitation: Such *invasive* biomarker screening is infeasible at a population level

8

there were two ongoing pharma clinical trials that targeted prodromal PD in 2025, with an emphasis on individuals with sleep dysfunction and/or smell loss who are biomarker positive (through CSF lumbar puncture).

CLICK *this is a huge development, this signifies the beginning of a paradigm shift in the realm of PD diagnosis to focus on the underlying biology rather than the symptoms alone. This has the potential to aid not only in earlier diagnosis but also to accelerate clinical trials for disease-modifying therapies*

CLICK However, such invasive biomarker screening is infeasible at a population level.

How can we measure the vagal cholinergic pathway **non-invasively** while **leveraging the underlying biology**?

Dr. Kathleen Poston
Chief of Movement Disorders Division at Stanford Neurology

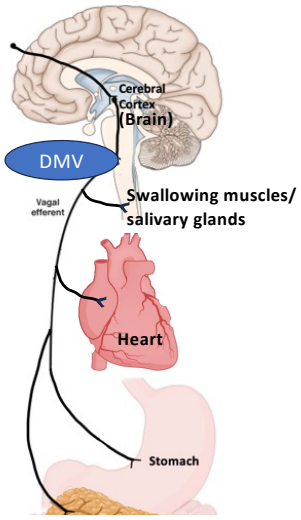
9

As much of the prodromal period is tied to degeneration of the vagal cholinergic pathway, we asked – how can we measure this pathway **non-invasively** and **screen with high specificity** while **still leveraging the underlying biology**?

CLICK We sought to tackle this question with our collaborator Dr. Kathleen Poston, chief of movement disorders at Stanford and an expert in the space of diagnosing and treating nonmotor Parkinson's disease

Goals:
Isolate pathway using physiology (multimodal)
We can screen w high specificity
Physiologic measure that is easy to screen that can tell us about these deficits

Let's focus on the underlying biology…



What organs are involved?

Stomach	Heart	Swallows	Brain

What cholinergic area in gut-brain axis engages all these organs?

Dorsal Motor Nucleus of the Vagus (DMV)

Key Takeaway: DMV Activates the Vagal Cholinergic Pathway

10

CLICK - Taking in the underlying biology, we first asked, what organs are involved in this pathway? **CLICK**

CLICK - Furthermore, what nucleus engages these organs? **CLICK …the DMV is also one of the most cholinergically innervated nuclei in the CNS**

How does the DMV regulate each organ involved? **CLICK**

In the stomach, the DMV regulates gastric motility

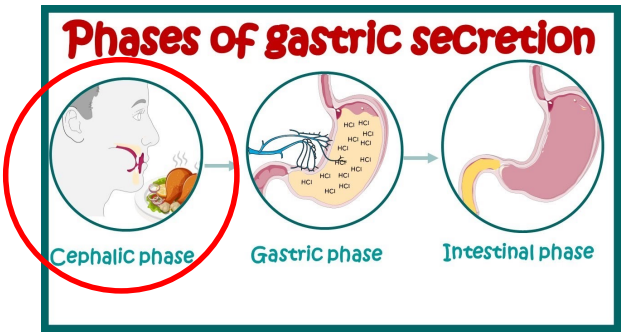
In the heart, the DMV talks to the cardiac ganglia to regulate heart rate

For swallowing, it helps coordinate motor control of swallowing muscles and in the brain, it sends inputs from sensory areas down to the gut

CLICK – to summarize, activation of the cholinergic DMV will thus allow for multimodal, physiological activation of this vagal cholinergic pathway

How do we activate the DMV?

Idea: Probe Cephalic Phase Response

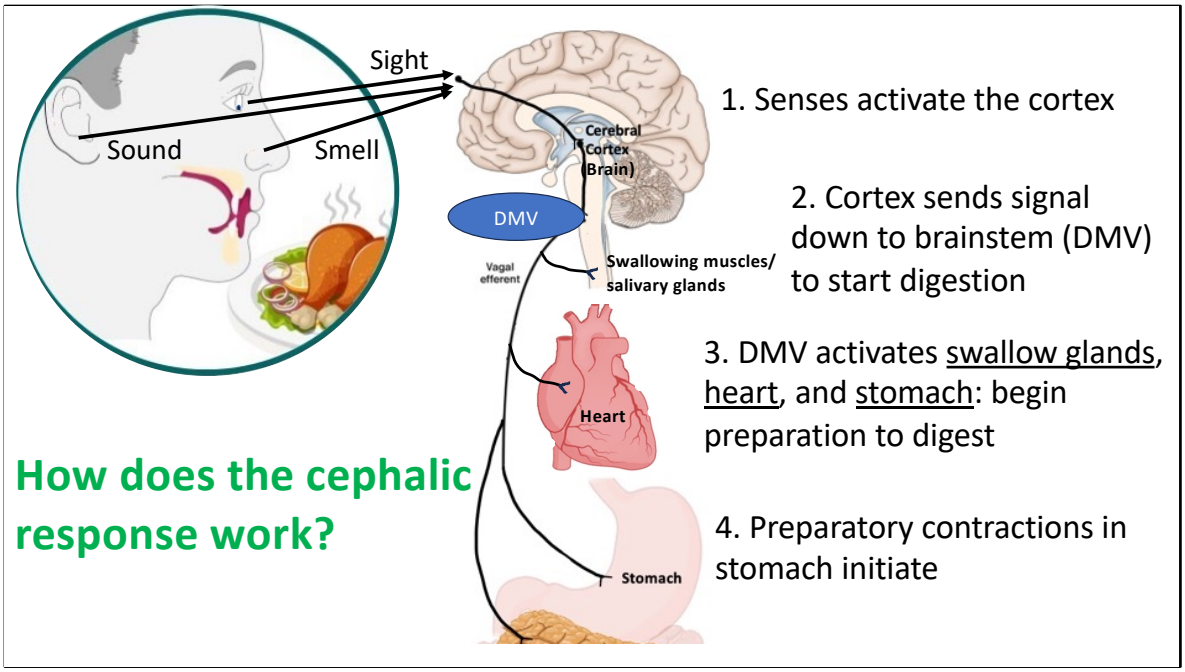


Thought, anticipation, sight, smell, mouth sensations

Nutrient sensing, stomach distension

11

So how do we activate the DMV?
Through the cephalic phase of digestion



How do we plan to interrogate and measure a CPR?

I propose to interrogate downstream efferent vagal activity by triggering a cephalic phase response.
EXPLAIN CEPHALIC PHASE
-initial visual food exposure (brain), the period prior to digestion, **triggers gastric acid secretion and salivation in the stomach and pancreas**, entirely mediated by the efferent vagus nerve and efferent vagal neurons of the DMV

Recent evidence has shown that early to moderate stage

PD patients showed a **decreased pancreatic polypeptide response after triggering** of the cephalic phase, thus suggestive of efferent vagal denervation.

Abnormal cephalic phase response may suggest delayed gastric emptying of the stomach.

-Previous evidence has shown that there are **descending parasympathetic efferents sent downwards from the brain to the gut**.
These motor efferents travel through the cholinergic vagus nerve and thus reach neurons in the cholinergic dorsal motor nucleus of the vagus (DMV).
These descending vagal pathways are **responsible for gastric contractions during digestion**.
-The main neurotransmitter in the parasympathetic nervous system, **acetylcholine**, plays a major role in control of the DMV, so cholinergic degeneration in **PD may alter descending vagal signaling from the brain and negatively impact gut motility and gastric secretion.**

Previous Work Measuring The Cephalic Response

Sham Feeding: activates taste

→ **Take blood sample (Pancreatic Polypeptide)**

Limitations:

- Only using one sense
- Blood sample is invasive
- Measures are only GI readouts

How can we improve this?

Balaji et al. 2002

13

- Gold standard method to quantify vagal integrity currently is **sham feeding and subsequent measurements of pancreatic polypeptide (PP) in blood**

It's a **marker of vagal (parasympathetic) tone**, especially during the **cephalic phase of digestion**.

Its levels rise in response to **sham feeding** (smelling/chewing food without swallowing), showing **neural stimulation of digestion** without actual nutrient contact in the gut.

It's used in research to assess **autonomic nervous system function**, particularly in conditions like **Parkinson's disease**, where PP response is often blunted due to vagal dysfunction.

Pancreatic polypeptide (PP) is a hormone secreted by specialized cells in the pancreas—specifically the **F cells (or PP cells)** located mostly in the **head of the pancreas**, within the **islets of Langerhans**.

🔬 **What does pancreatic polypeptide do?**

PP plays a regulatory role in **digestive physiology**, especially during and after meals.

Its key functions include:

Inhibits pancreatic exocrine secretion

– Reduces the secretion of digestive enzymes and bicarbonate from the pancreas.

Slows gastric emptying

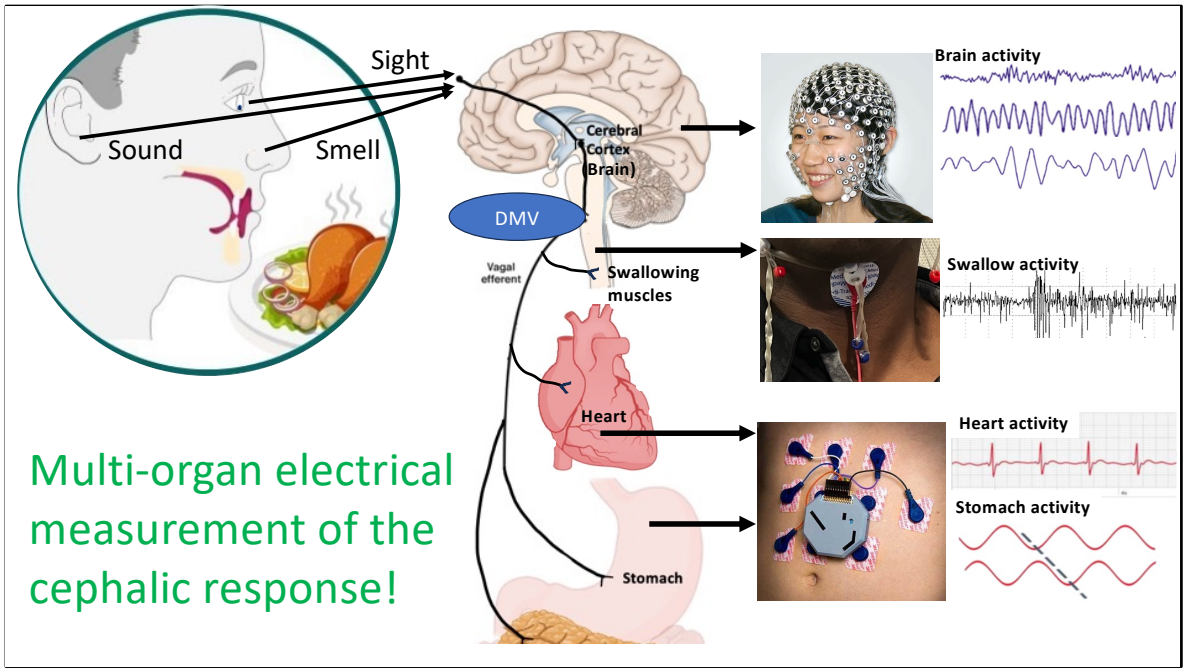
– Delays movement of food from the stomach to the intestine.

Modulates hepatic glycogen stores and gut motility

– Helps regulate energy balance and digestion.

Acts as a signal of satiety

– May reduce appetite, acting through the brainstem and hypothalamus.

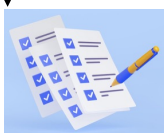


Testing fig 1

Study Design

Experimental Timeline

15 min baseline	Short break	15 min cephalic: Personalized food presented	Short break	15 min ingestion: Eating personalized food



Hunger and Satiety Questionnaires

Personalized food presented (sight, smell, video)

Hunger and Satiety Questionnaires

Hunger and Satiety Questionnaires

15

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Are you interested in advancing research to understand nonmotor symptoms of Parkinson's disease?

Researchers at Stanford University are looking for people with Parkinson's disease to help us ***develop non-invasive measures of non-motor symptoms***.

Are you eligible?
- Diagnosis of idiopathic Parkinson's disease
- No dementia or other neurological disorders
- No allergies to skin adhesives
- Able to sit in chair for 45 minutes

Locations:
- Stanford Neuroscience Health Center (213 Quarry Road)
- Koret Human Neurosciences Lab (Wu Tsai Neuroscience Building, 290 Jane Stanford Way)
- Lucas Center for Imaging (1201 Welch Road)

Study Involvement:
- Data collection including cutaneous electrodes on the abdomen (electrogastrography, EGG), throat (electromyography, EMG), scalp (electroencephalography, EEG), continuous glucose monitor (CGM)
- Two visits: data collected at home and in clinic
- Participants will receive up to two $25 Amazon gift cards as compensation

EGG

EEG

If you're interested or unsure if you meet the requirements, please email or call a member of the research study team:

Yasmine Kehnemouyi, *Study Coordinator*
ykehn97@stanford.edu
650-220-5321

For complaints, concerns, or participant's rights, contact 1-866-680-2906.

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