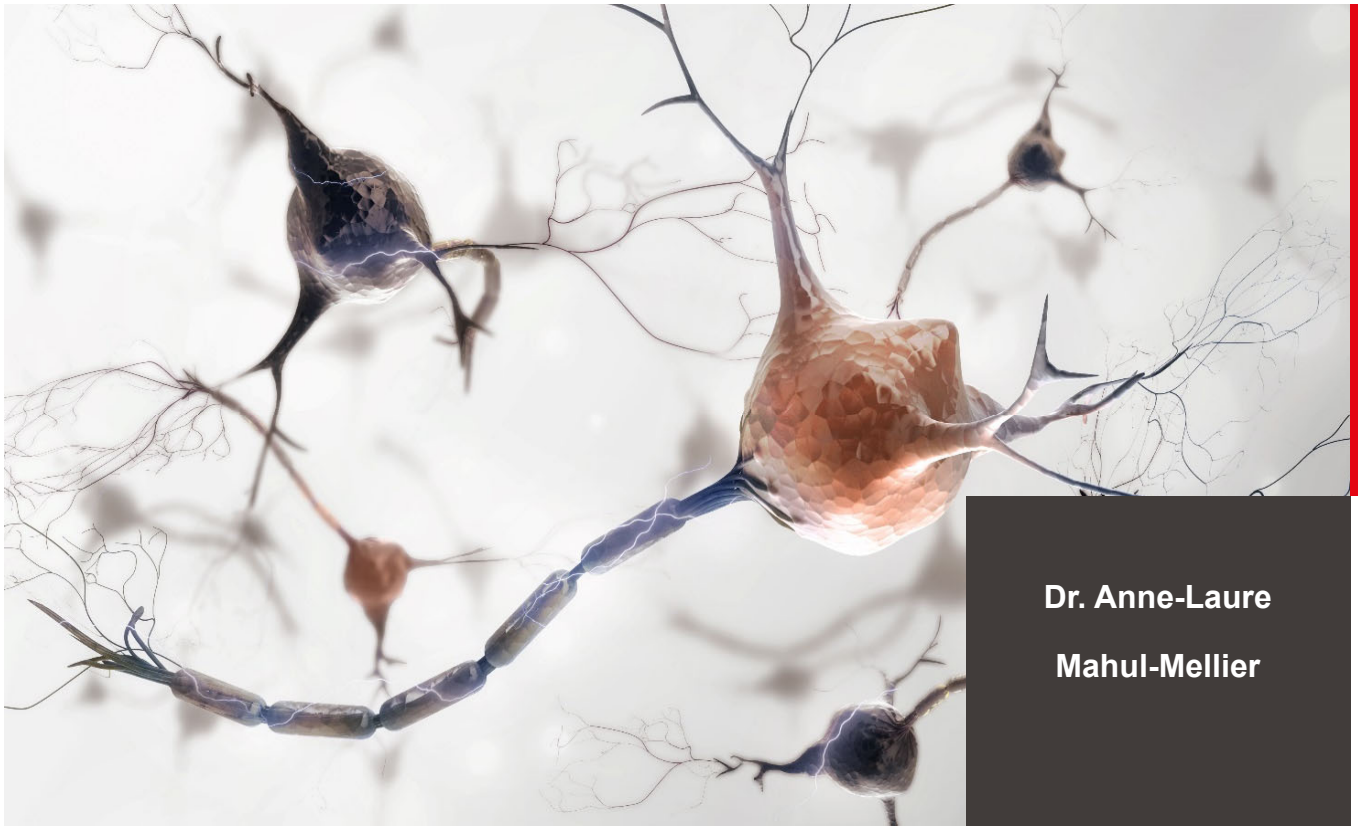
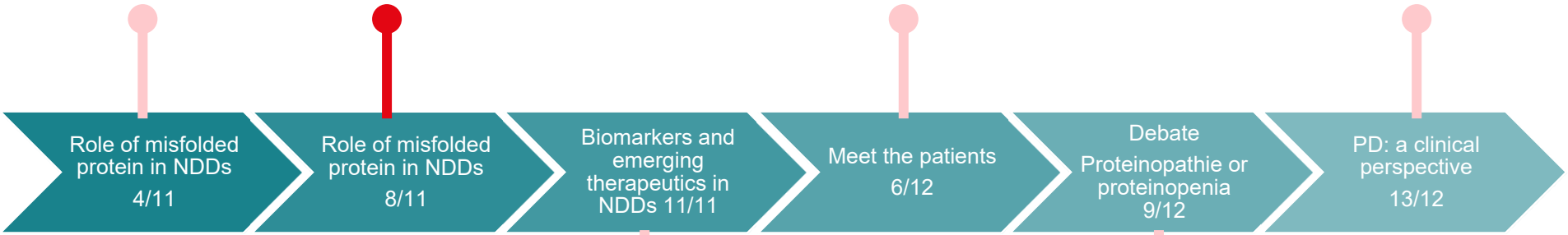


Welcome To BIO480 – NDDs lectures 2024-2025

Dr. Anne-Laure Mahul-Mellier

Course organisation:

From proteins misfolding, to aggregation pathways, through spreading in NDDs



PD and AD patients and family care taker

Dr. Julien Bally, neurologist at the CHUV

Overview of the latest advances in drug design and therapies

Shared session with Bernard Schneider

Introduction to neurodegenerative diseases (NDDs): Comparative pathophysiology of AD, PD, HD, and ALS

I. Global health and economic burden of NDDs (4/11)

II. Main features of the neurodegenerative diseases (NDDs) (4/11)
a. ID card of AD, PD, ALS and HD
b. Origin of the diseases

III. NDDs: the role of misfolded proteins (4/11)

IV. The prion-like hypothesis (4/11)

V. Spreading of pathology in the brain: the gut-brain axis hypothesis (8/11)

VI. Gain-of-Function vs. Loss-of-Function hypotheses (8/11)

★ Key concepts to memorize

Introduction to neurodegenerative diseases (NDDs): Comparative pathophysiology of AD, PD, HD, and ALS

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★ Key concepts to memorize

Origin of the prion-like diseases – case of the PD

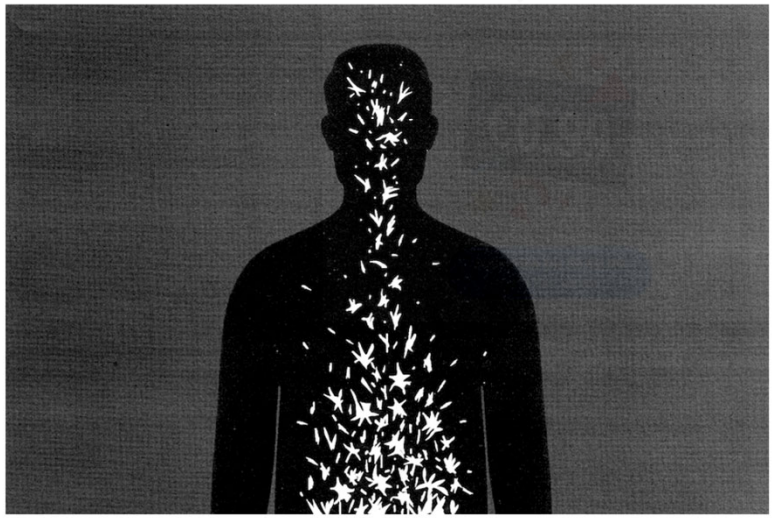
BRAIN MATTERS

Origins of Parkinson's may lie in the gut. Researchers hope to prove it.

If the hypothesis that misfolded proteins start in the gut and travel to the brain is proved, it could lead to early detection and treatment of Parkinson's

By Meeri Kim

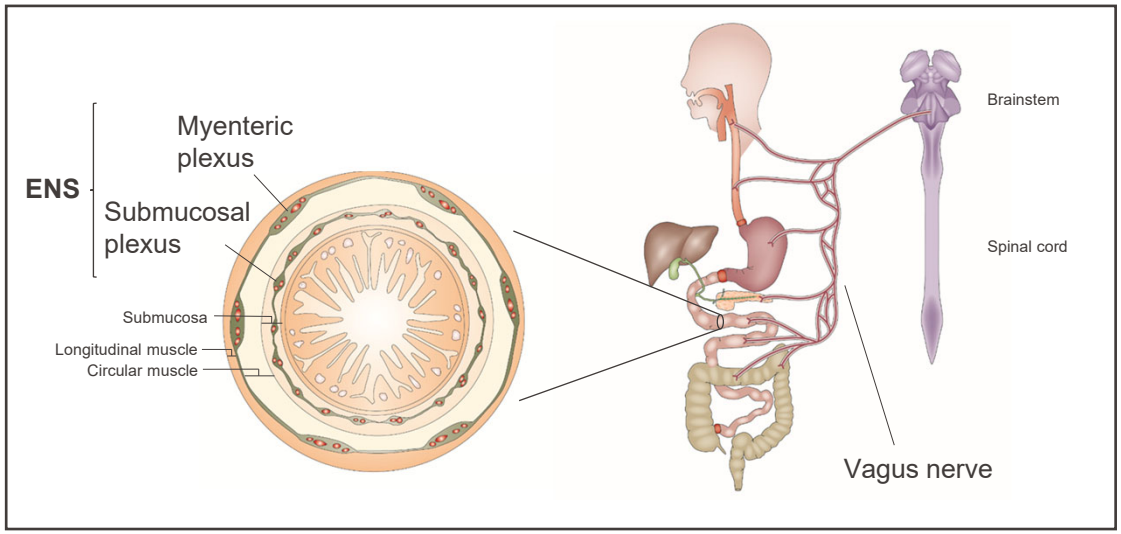
September 28, 2023 at 6:00 a.m. EDT

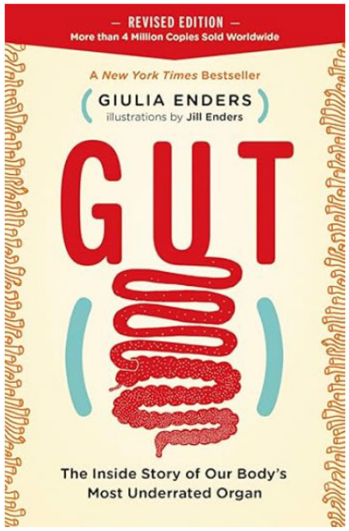


(George Wylesol for The Washington Post)

Origin of the prion-like diseases – case of the PD

The enteric nervous system (second brain)





The **enteric nervous system (ENS)** is the largest component of the autonomic nervous system (≈100 millions of neurons: motor, sensory and interneurons) and is able to **orchestrate gastrointestinal function independently** of CNS input.

The ENS mantains a bidirectional information flow with the CNS via vagus nerve and sympathetic ganglia

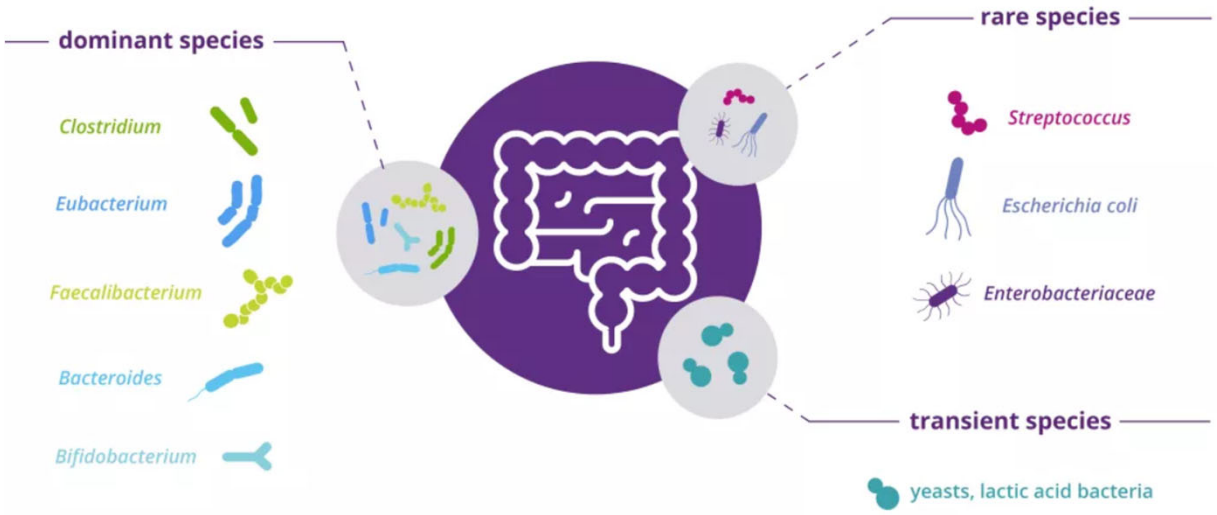
Divided in two types of ganglia:

Myenteric (Auerbach's) plexus: Motor control of gut motility

Submucosal (Meissner's) plexus: Sense luminal conditions, controls gut mucosal secretion and blood flow

Origin of the prion-like diseases – case of the PD ★

Composition of the gut Microbiota



The gut microbiota refers to the community of **trillions** of microorganisms, including bacteria, fungi, and viruses, that live in the human digestive tract.

Dysbiosis is when the balance of good and bad bacteria in the gut is disrupted. This imbalance can affect the brain and may play a role in neurodegenerative diseases like PD and AD.
In these diseases, changes in the gut bacteria might **make symptoms worse** by affecting **inflammation**, brain health, or **how medications like levodopa are processed**.
So, a healthy gut balance is important for better managing these conditions.

Origin of the prion-like diseases – case of the PD

BRAIN MATTERS

Origins of Parkinson's may lie in the gut. Researchers hope to prove it.

If the hypothesis that misfolded proteins start in the gut and travel to the brain is proved, it could lead to early detection and treatment of Parkinson's

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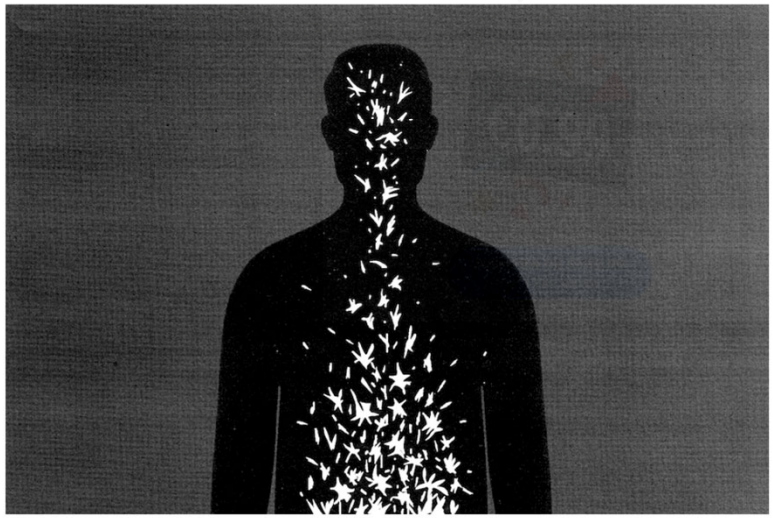
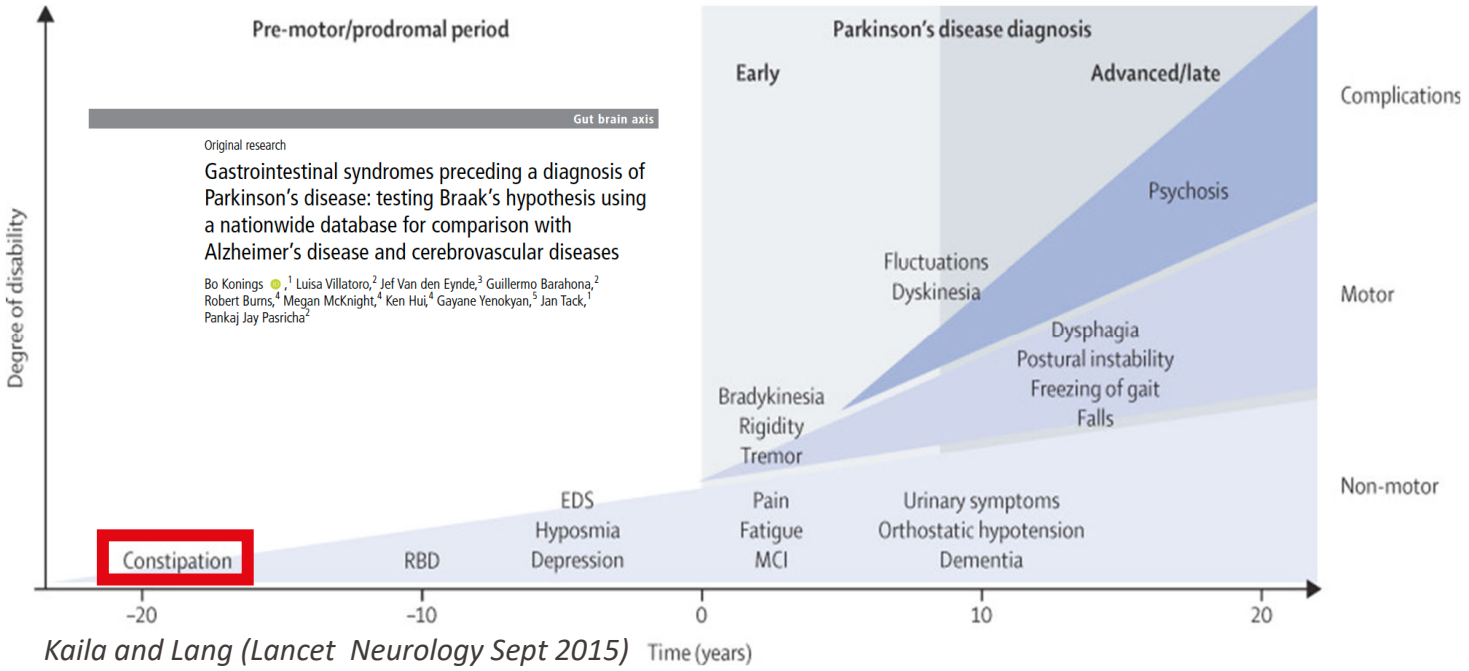


(George Wylesol for The Washington Post)

What are the evidence ?

Origin of the prion-like diseases – case of the PD ★

1. Constipation found in 50-80% of the PD patients 10-20 years before motor symptoms

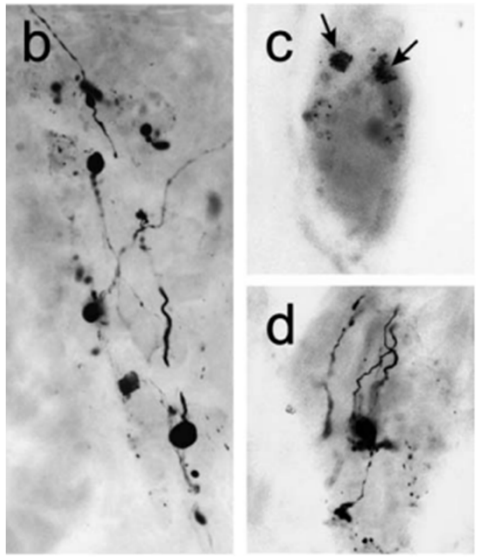


Kaila and Lang (Lancet Neurology Sept 2015)

Constipation is a frequent **early symptom** in PD patients, often occurring years before the onset of motor symptoms. This early involvement of the gastrointestinal system further supports the gut's role in Parkinson's pathogenesis.

Origin of the prion-like diseases – case of the PD ★

2. aSyn aggregates are found in the **Enteric Nervous System in** PD patients

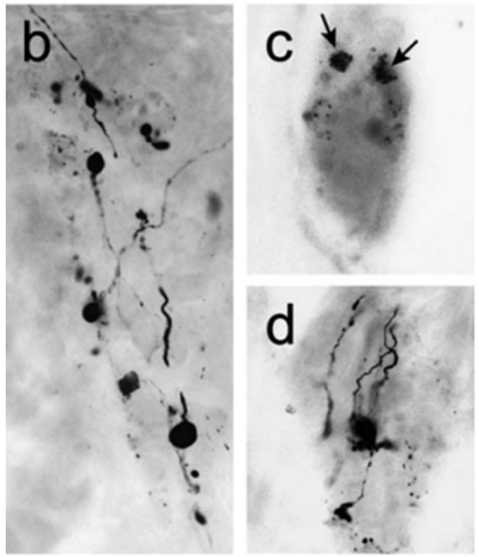


https://pubmed.ncbi.nlm.nih.gov/16330147/

aSyn aggregates are found in the Enteric Nervous System (ENS)
aSyn aggregates, a hallmark of PD, have been found in the **ENS** long before motor symptoms appear. This has led to the hypothesis that PD may begin in the gut

Origin of the prion-like diseases – case of the PD ★

3. aSyn aggregates spread from gut to brain via the vagus nerve



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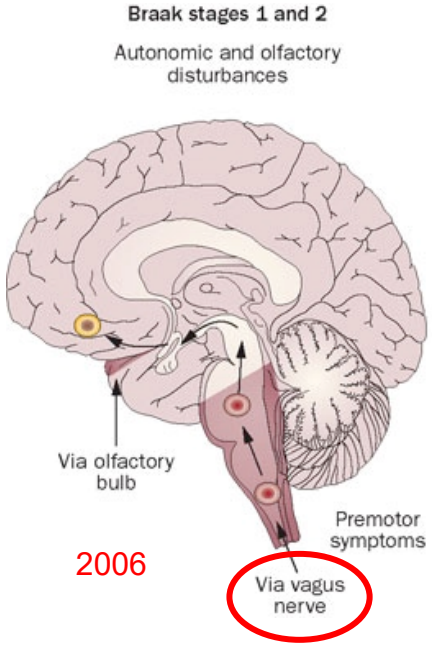
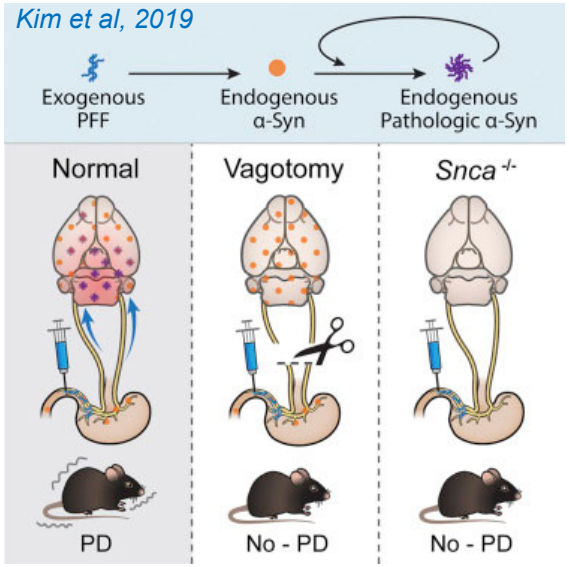


aSyn aggregates are found in the Enteric Nervous System (ENS)

aSyn aggregates, a hallmark of PD, have been found in the **ENS** long before motor symptoms appear. This has led to the hypothesis that PD may begin in the gut and **spread** to the brain via the **vagus nerve**. The **Braak hypothesis** suggests this gut-to-brain transmission is central to PD pathology.

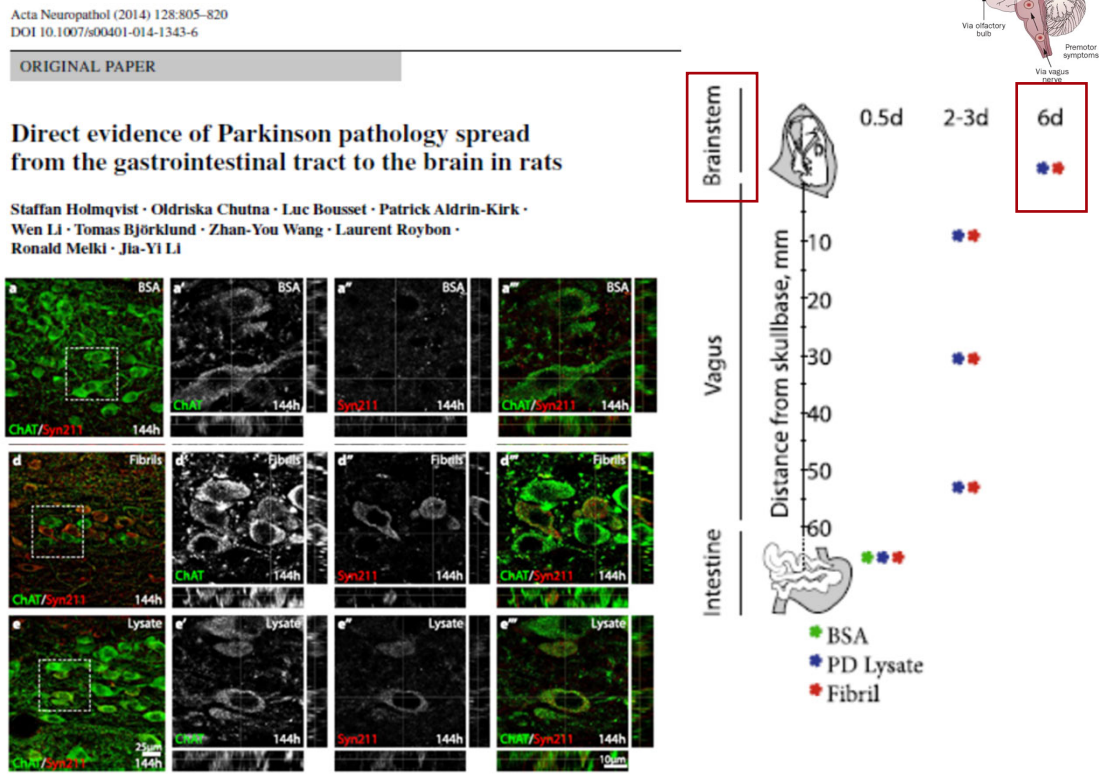
Origin of the prion-like diseases – case of the PD

3. Spreading from gut to brain via the vagus nerve - In vivo models evidence



Highlights

- Gut-to-brain propagation of pathologic α-synuclein via the vagus nerve causes PD
- Dopamine neurons degenerate in the pathologic α-synuclein gut-to-brain model of PD
- Gut injection of pathologic α-synuclein causes PD-like motor and non-motor symptoms
- PD-like pathology and symptoms require endogenous α-synuclein

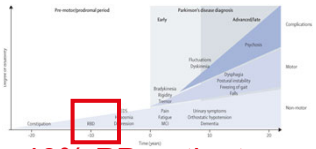


PD brain lysates or aSyn recombinant fibrils injected into the intestinal wall in adult rats. aSyn is transported via vagal projections and present to the brainstem are after 6 days.

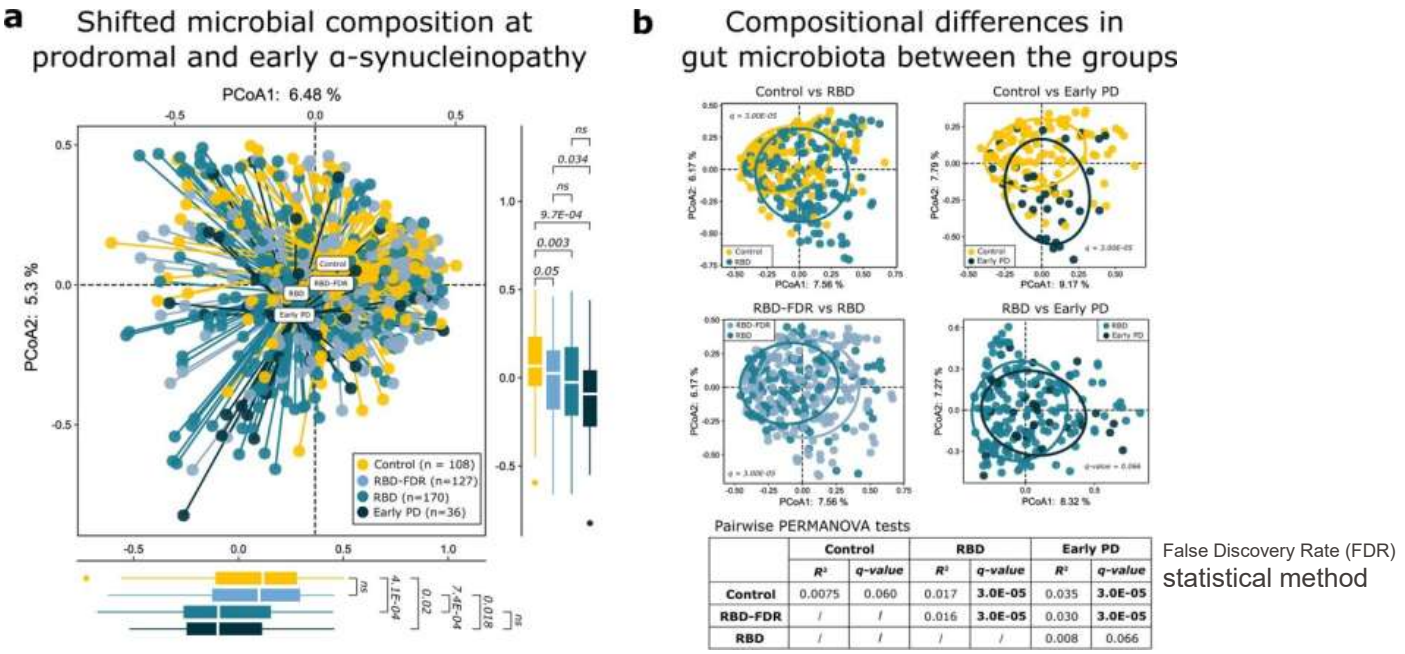
Origin of the prion-like diseases – case of the PD ★

4. Gut microbiota alterations in PD patients

REM (Rapid Eye Movement) Sleep **B**ehavior **D**isorder



40% PD patients



Pairwise PERMANOVA tests

	Control		RBD		Early PD	
	R^2	*q-value*	R^2	*q-value*	R^2	*q-value*
Control	0.0075	0.060	0.017	**3.0E-05**	0.035	**3.0E-05**
RBD-FDR	/	/	0.016	**3.0E-05**	0.030	**3.0E-05**
RBD	/	/	/	/	0.008	0.066

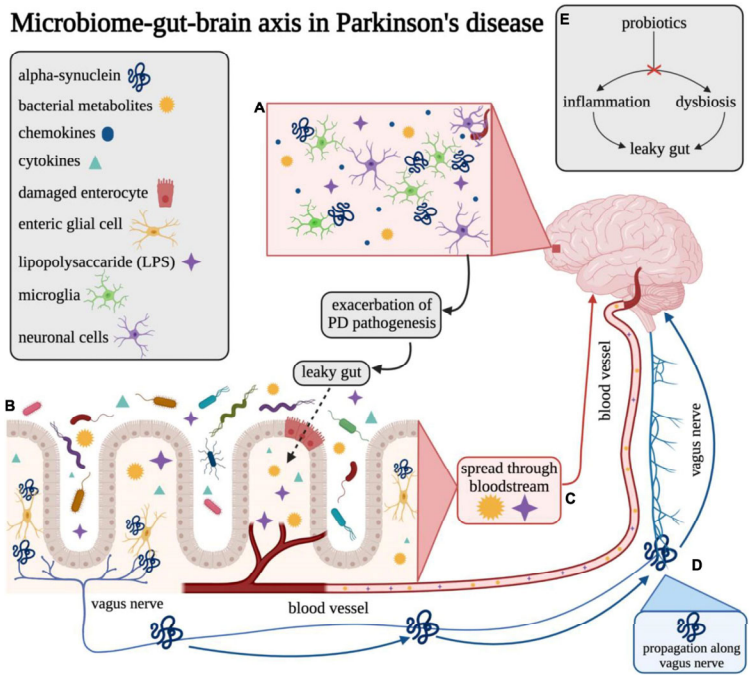
False Discovery Rate (FDR) statistical method

https://medicalxpress.com/news/2023-05-early-parkinson-gut-microbiota-rem.html

- Patients with RBD report having an increased prevalence of constipation and increased phosphorylated α-syn immunostaining in their enteric nervous system.
- The study found gut microbiota compositions significantly altered in early PD and RBD compared with controls and the relative cohort, with an overall microbiota composition shifted closer to those with early Parkinson's.

Origin of the prion-like diseases – case of the PD

4. Gut microbiota alterations in PD patients



https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2021.782082/full

Parkinson's patients exhibit significant changes in gut microbiota (**dysbiosis**), which may contribute to **inflammation** and enhance the aggregation of aSyn in the gut.
These microbiome changes are being explored as a factor in the initiation and progression of PD.

Origin of the prion-like diseases – case of the PD ★

5. Gut bacteria affect the bioavailability of PD medications such as Levodopa

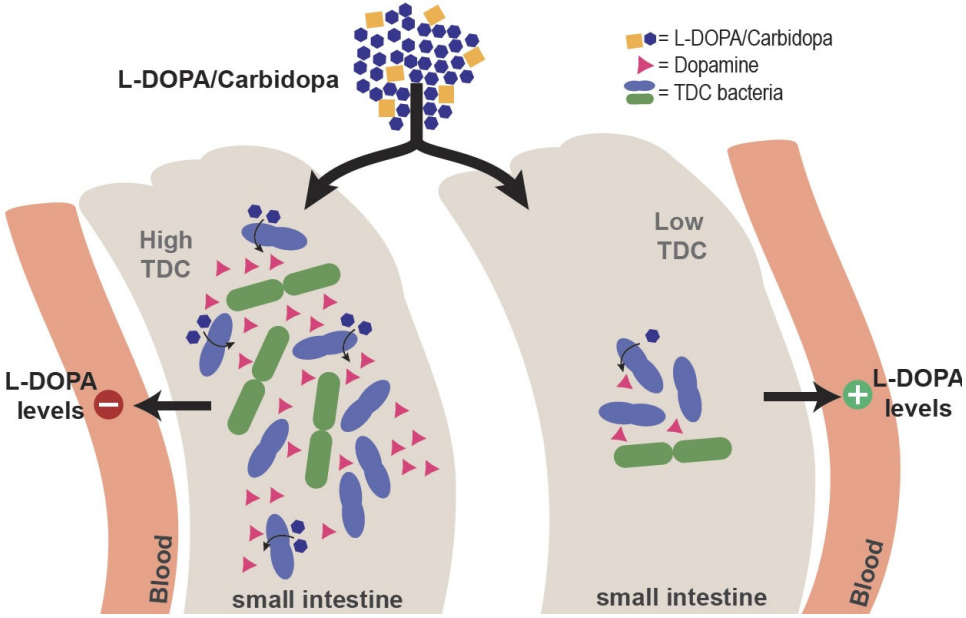
nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-08294-y OPEN

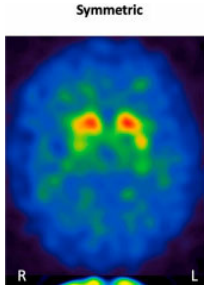
Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease

Sebastiaan P. van Kessel[1], Alexandra K. Frye[1], Ahmed O. El-Gendy[1,4], Maria Castejon[1], Ali Keshavarzian[2], Gertjan van Dijk[3] & Sahar El Aidy[1]



Certain gut bacteria, particularly *Enterococcus faecalis*, produce an enzyme (tyrosine decarboxylase, **TDC**) that converts levodopa into dopamine in the gut, which cannot cross the blood-brain barrier. This premature conversion **reduces the amount of levodopa that reaches the brain**, potentially making the treatment less effective to control de motor symptoms in PD.

Origin of the prion-like diseases – case of the PD

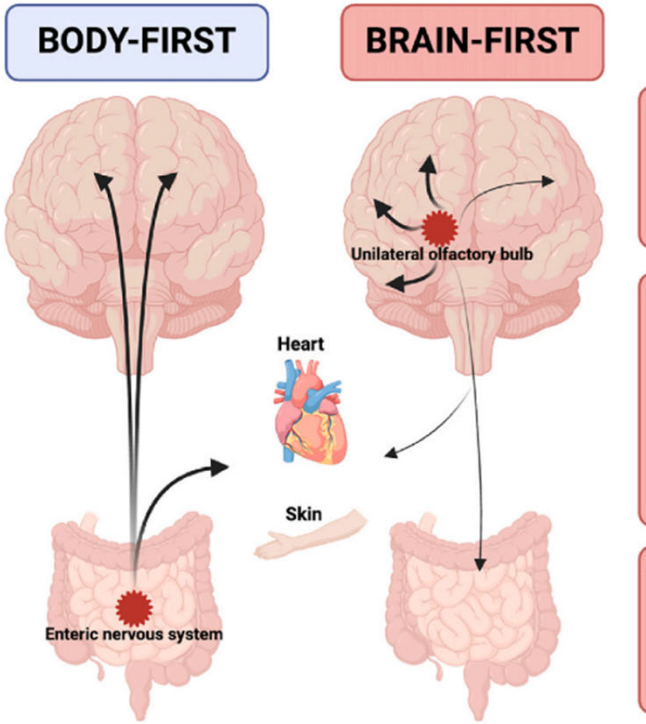


Predicted findings at onset of parkinsonism

Imaging markers
- Dopamine imaging - symmetric loss
- Cardiac sympathetic - pathological
- Structural damage on MRI
  - *potentially symmetric*
  - *potentially greater total grey matter loss*

Clinical markers
- Motor symptoms
  - *less asymmetric*
  - *more often PIGD*
- RBD-positive *
- Often constipation *
- Frequent orthostatic hypotension
- Anosmia *
- Sometimes neuropsychiatric symptoms
- Often mild cognitive impairment

Detection of α-synuclein
- Skin - more often positive *
- Olfactory bulb - often positive
- Postmortem - more pathology in the periphery and brainstem (caudo-rostral pattern) *

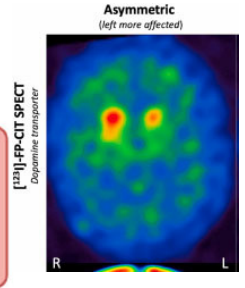


Predicted findings at onset of parkinsonism

Imaging markers
- Dopamine imaging - asymmetric loss
- Cardiac sympathetic - more normal
- Structural damage on MRI
  - *potentially asymmetric*
  - *potentially lower total grey matter loss*

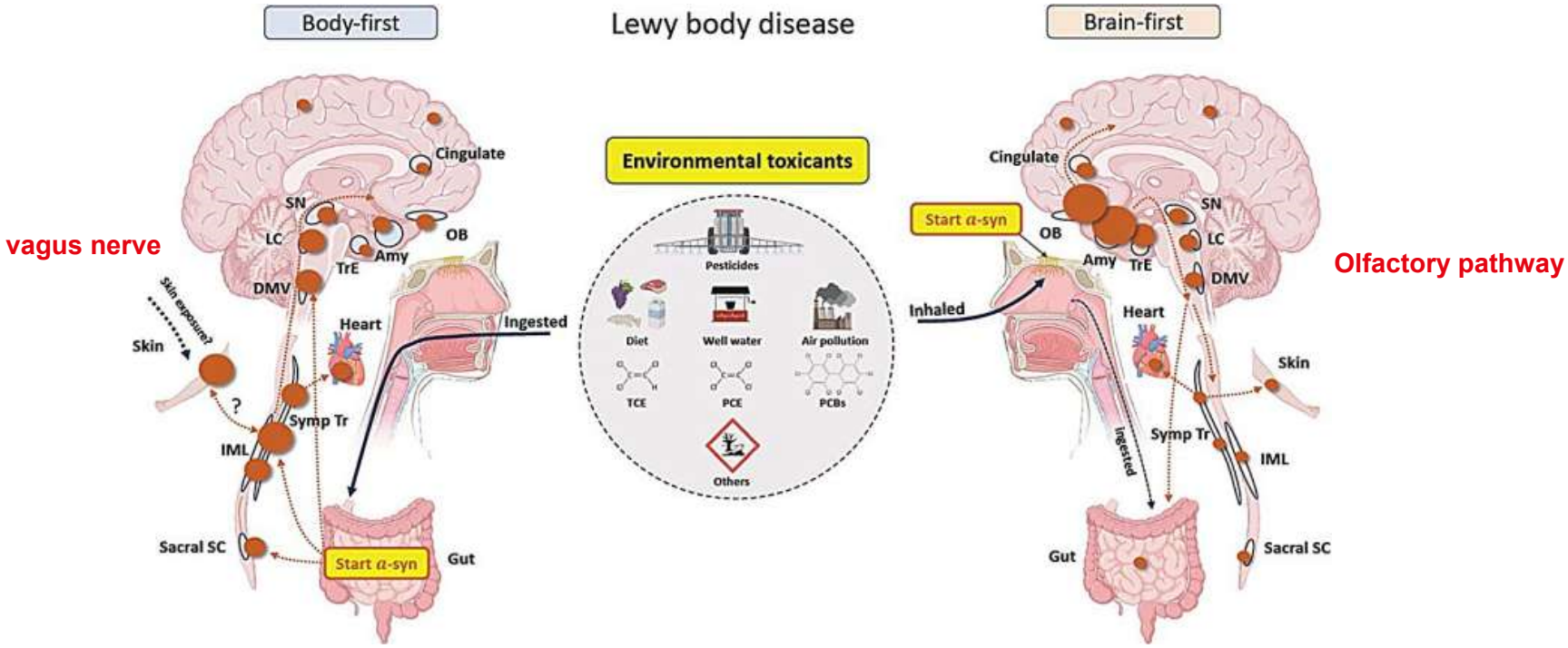
Clinical markers
- Motor symptoms
  - *more asymmetric* *
  - *more often tremor dominant* *
- RBD-negative *
- Sometimes constipation *
- Rare orthostatic hypotension
- Hyposmia or normal olfaction
- Rare neuropsychiatric symptoms
- Normal cognition

Detection of α-synuclein
- Skin - more often negative *
- Olfactory bulb - positive (bilateral sampling needed) *
- Postmortem - more pathology in the amygdala and olfactory bulb * (amygdala-based pattern)



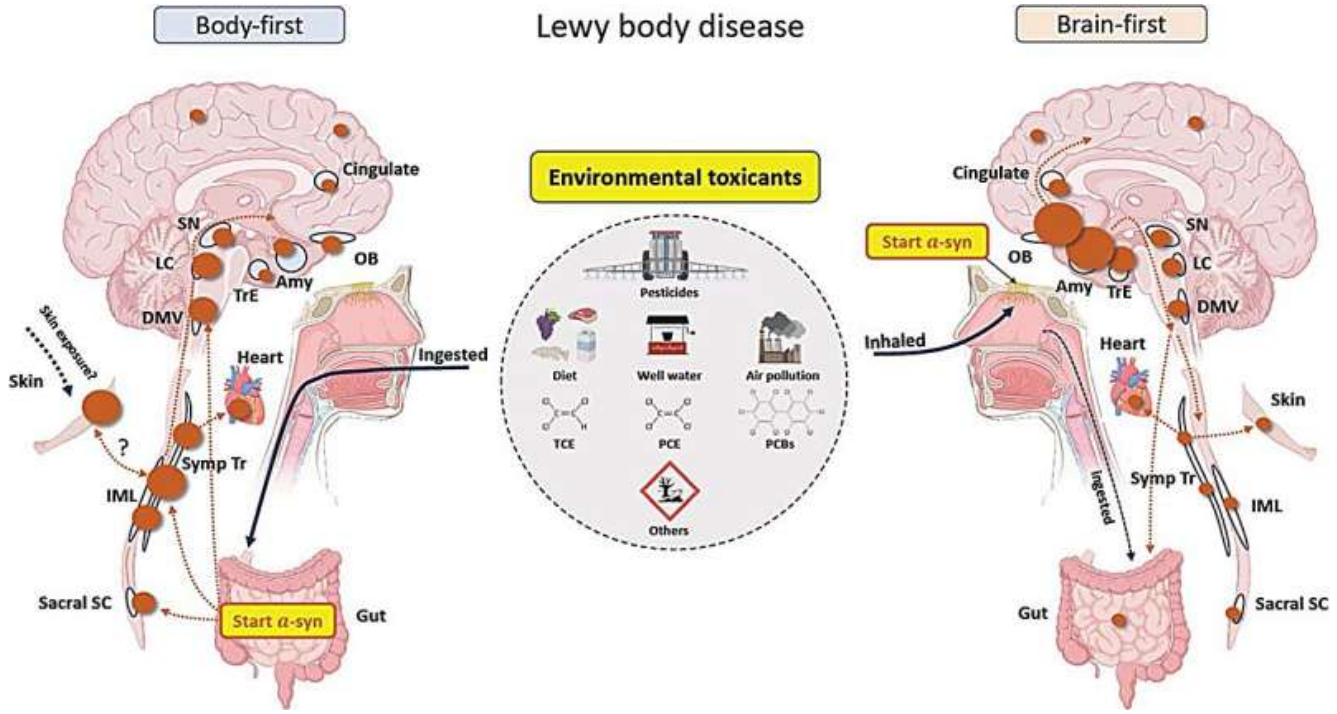
https://www.sciencedirect.com/science/article/pii/S1353802024001135

Origin of the prion-like diseases – case of the PD ★



•It suggests that an environmental trigger, like a **virus, bacteria, or toxin (pesticides, herbicides, metals, industrial chemicals)**, might initiate the misfolding of **aSyn** the gut **(body-first)** or nasal cavity **(brain-first).**
•Misfolded aSyn may then travel along the **vagus nerve** (from the gut to the brain) or the **olfactory pathway** (from the nose to the brain).
•As it spreads, the misfolded aSyn aggregates, potentially "infecting" (prion-like manner) nearby neurons and causing **cell death** in key areas of the brain, such as the substantia nigra, where dopamine-producing cells are located.

Origin of the prion-like diseases – case of the PD ★



Gut-First Hypothesis:

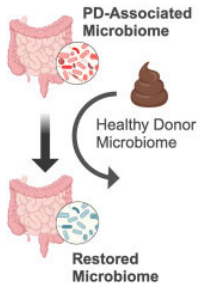
- **Toxicants (e.g., pesticides, dietary toxins)** affect the **gut** first, causing **inflammation** and **dysbiosis**.
- Misfolded **aSyn** spreads from the gut to the brain via the **vagus nerve**.
- **Gastrointestinal issues** often precede motor symptoms.

Brain-First Hypothesis:

- **Toxicants (e.g., MPTP, pesticides)** enter through the respiratory system or bloodstream.
- Directly damage **dopamine neurons** in the brain.
- Leads to **motor symptoms** of PD.

Origin of the prion-like diseases – case of the PD

Microbiome-based therapeutics in recent and ongoing studies

	Fecal Microbiota Transplant (FMT)	Probiotics & Prebiotics	Emerging Alternatives
Approach		**Probiotics:** Lactobacillus Bifidobacterium Bacterial Cocktail **Prebiotics:**  Dietary fiber	**Antibiotics** **Polyphenols?**  **Phage?** **CRISPR?** 
Notable Clinical Trials	1. Bruggeman et al., 2024 2. Scheperjans et al., 2024 3. DuPont et al., 2023 4. Cheng et al., 2023	1. Yang et al., 2023 2. Du et al., 2022 3. Hall et al., 2023 4. Becker et al., 2021	1. Rifaximin (NCT03575195) 2. Ceftriaxone (NCT03413384) 3. Erythromycin (NCT02005029)
Routes & Frequency of Admin	• Oral Delivery[3,4] ◦ 1x wkly, 3 wks[4] ◦ 2x wkly, 12 wks[3] • Nasojejunal, single [2] • Colonic, single [1]	• Oral Delivery[1-4] ◦ Daily[1-4] ◦ 10 days[3] ◦ 8-12 weeks[1,2,4]	• Oral Delivery[1] ◦ 2 wks – Freq NA • Intramuscular[2] ◦ Triweekly – 2 wks • I.V. – single admin[3]
Treatment Properties	• Donor Stool: ◦ Pooled[3] ◦ Single donor[1,2,4]	• Lactobacillus & Bifidobacterium[1,2] • Fiber preparations[3,4]	• Rifaximin[1] • Ceftriaxone[2] • Erythromycin[3]
Major GI Outcomes	• ↓ Constipation[1,3,4] • ↓ Gut transit[1] • No effect[2]	• ↓ Constipation [1,2] • ↓ GI inflammation[3,4]	• In progress: ◦ Not tested[1,2] ◦ Gastric Emptying[3]
Major Motor Outcomes	• ↓ UPDRS scores[1,3,4] • ↓Motor deficits[3] • ↓ Falls[3] • No effect[2]	• No effect[1] • Not tested[2-4]	• In progress: ◦ UPDRS scores[1-3] ◦ DAT SPECT[2] ◦ Motor function[3]

Hamilton et al., 2024

Origin of the prion-like diseases – case of the PD

Fecal microbiota transplantation

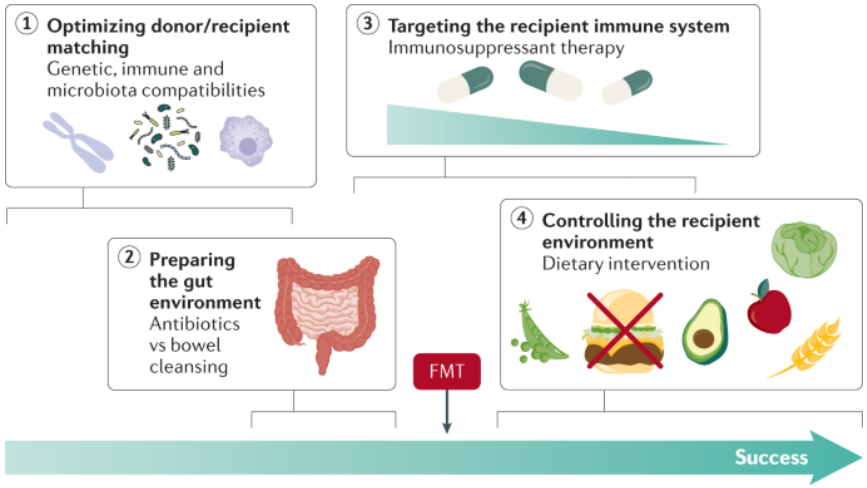
This treatment for an intestinal infection sounds disgusting, but it may be a breakthrough, and it has FDA approval

Vowst is a fecal matter transplant pill that is proving effective at treating C. diff, a potentially deadly illness most widespread among hospital patients

BY **MICHAEL TANENBAUM**
PhillyVoice Staff

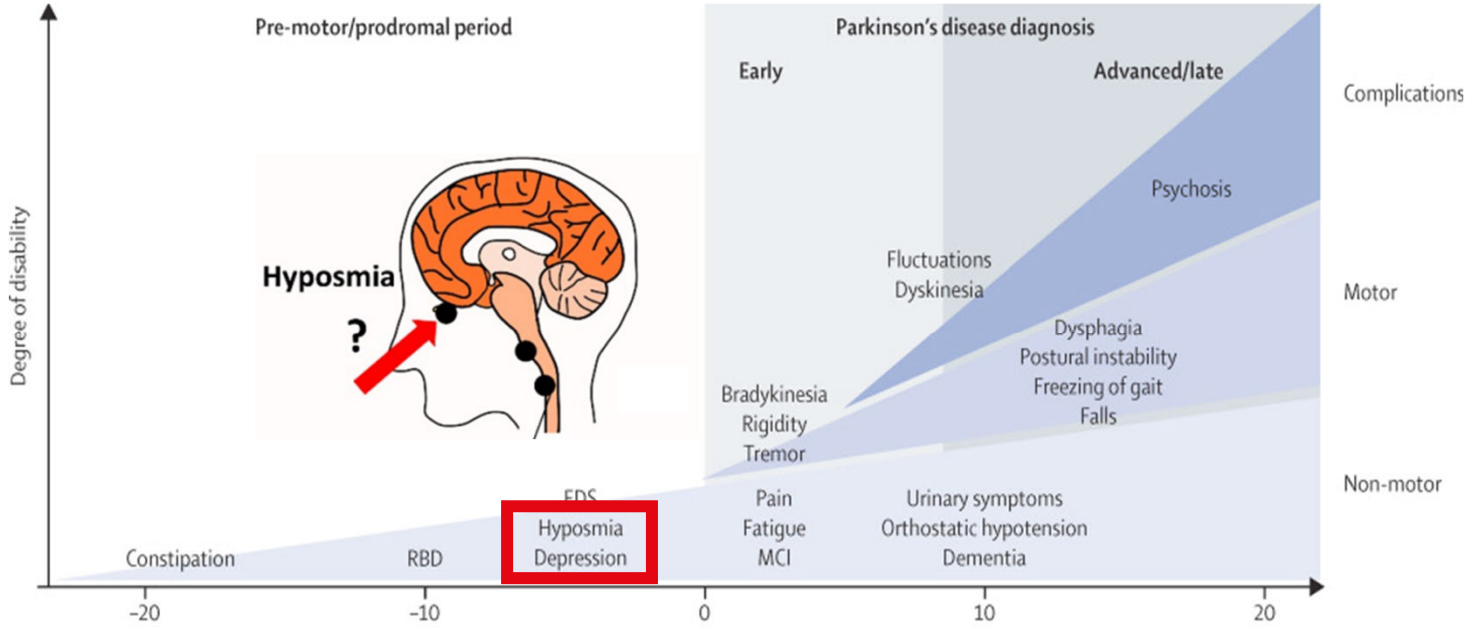
Recipient factors in faecal microbiota transplantation: one stool does not fit all

Camille Danne, Nathalie Rolhion and Harry Sokol



Origin of the prion-like diseases – case of the PD ★

Olfactory bulb as a gateway for PD

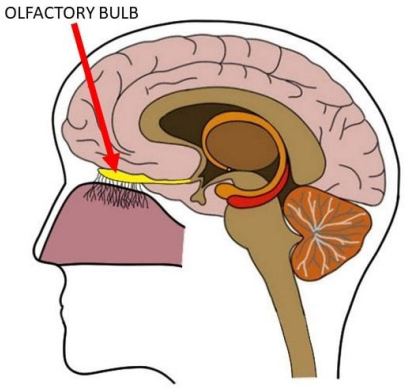


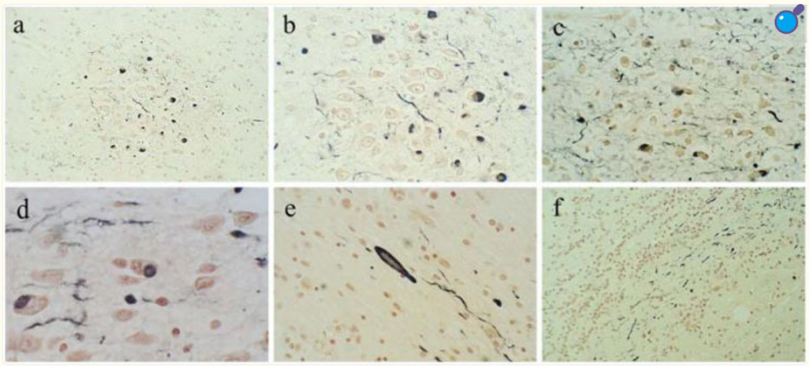
Kaila and Lang (Lancet Neurology Sept 2015)

- The olfactory bulb is a key brain structure involved in **processing smells**. Located at the base of the frontal lobe, it receives sensory input directly from olfactory receptors in the nasal cavity.
- It has connections to brain areas such as the amygdala, hippocampus, and orbitofrontal cortex, regions involved in memory and **emotional processing**, showing its relevance beyond smell alone.

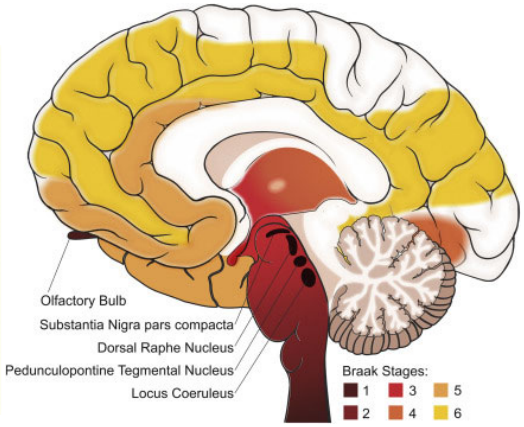
Origin of the prion-like diseases – case of the PD ★

Olfactory bulb as a gateway for PD – Human evidences





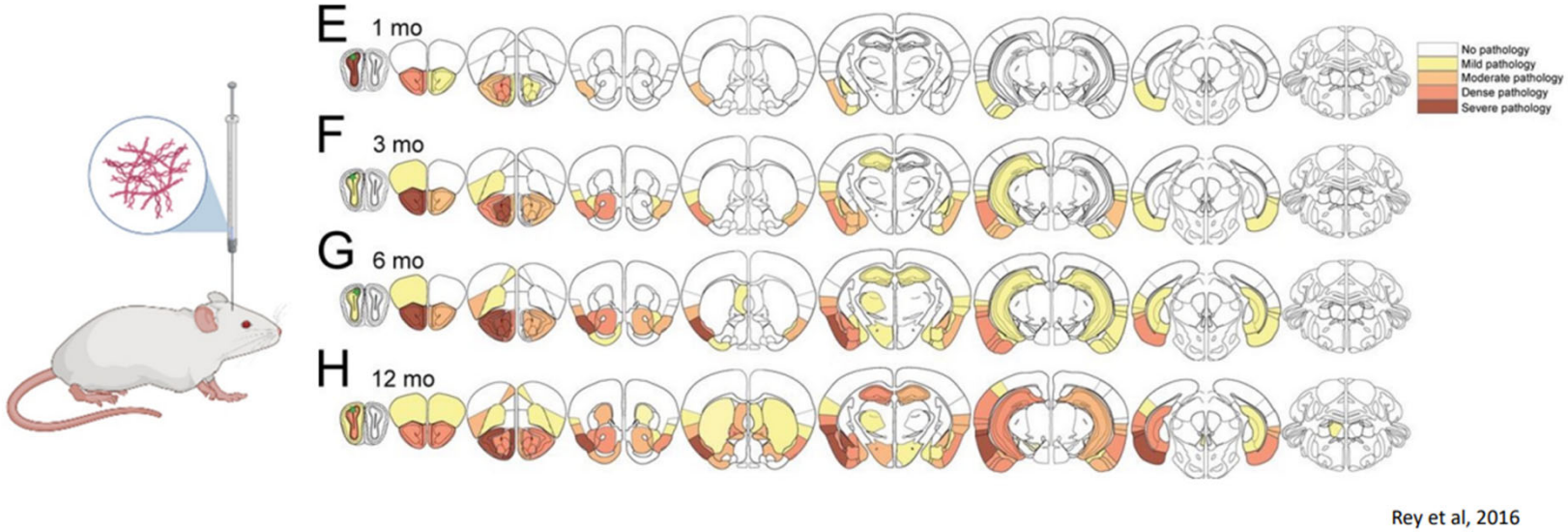
Beach et al, 2010



Pathological studies suggest that Lewy bodies, abnormal aggregates of protein associated with PD, are found in the olfactory bulb in early stages (**Braak stages I and II**), making it a site of early pathological change in PD.

Origin of the prion-like diseases – case of the PD

Olfactory bulb as a gateway for PD – animal models evidences

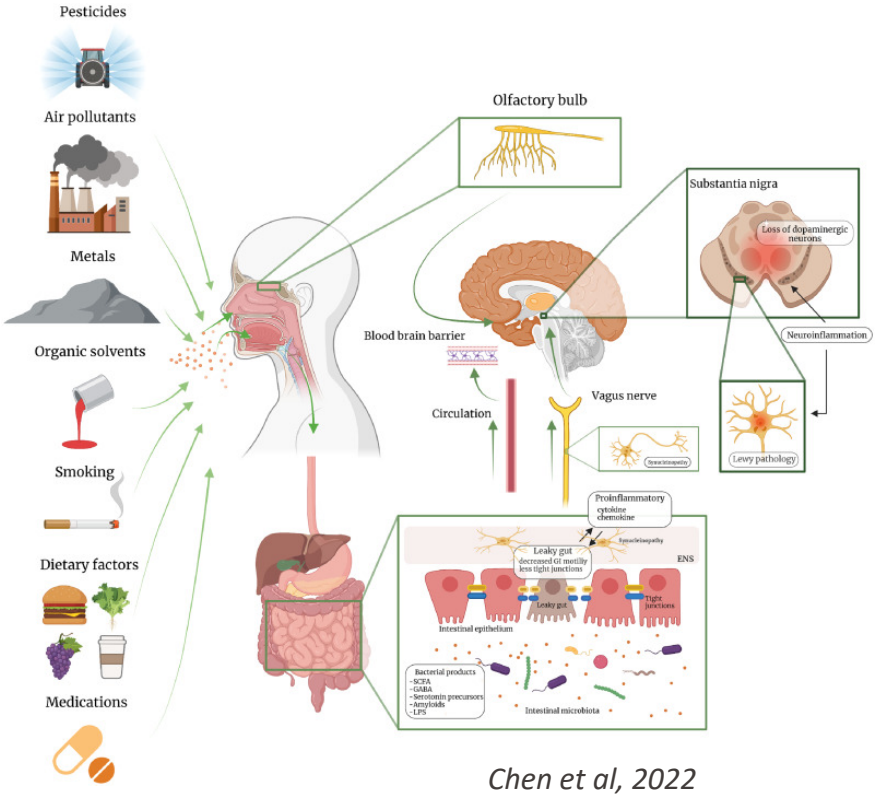


Rey et al, 2016

Olfactory Bulb injection of aSyn pre-formed fibrils is able to recapitulate aSyn pathology and some of the non-motor symptoms

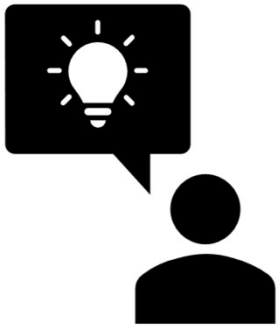
Origin of the prion-like diseases – case of the PD

Body first and environnemental impact



Chen et al, 2022

Any questions ? Or Thoughts ?



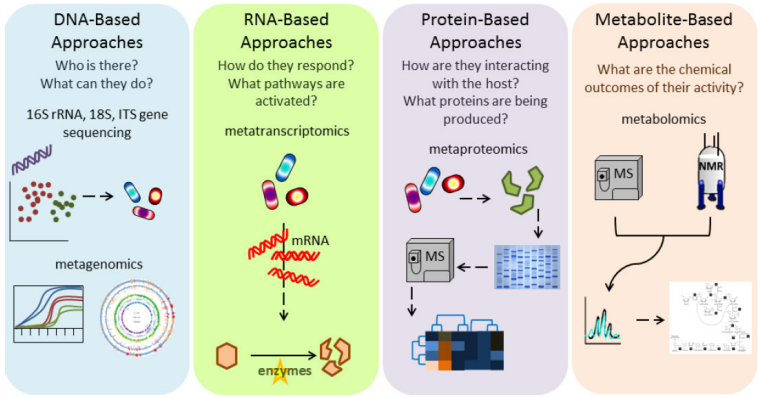
Role of the gut microbiome in PD

See exercices in the Moodle

“Gut-brain-axis”

See assays to do microbiota analysis in the next page

Tools for analyses of the human gut microbiome



See detailed methods in word doc
In the Moodle
"Methods to study the microbiome"

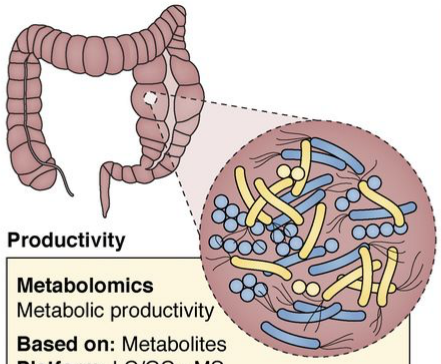
Composition

Biomarker profiling
Microbiota composition

Based on: DNA
Platform: NGS
Pros: Cost-effective; semi-quantitative
Cons: Lacks functional information

Metagenomics
Microbiome functional gene capacity

Based on: DNA
Platform: NGS
Pros: Strain-level resolution
Cons: Expensive; computationally intensive



Productivity

Metabolomics
Metabolic productivity

Based on: Metabolites
Platform: LC/GC - MS
Pros: Semi-quantitative, targeted or untargeted
Cons: Origin of metabolite unclear

Function

Metatranscriptomics
Microbial functional gene expression

Based on: RNA
Platform: NGS
Pros: Host and microbial gene transcripts
Cons: Samples require RNA preservation; host genes may predominate signal

Metaproteomics
Protein expression

Based on: Proteins
Platform: LC/GC-MS
Pros: Semi-quantitative
Cons: Origin of proteins unclear

http://jem.rupress.org/conte

Introduction to neurodegenerative diseases (NDDs): Comparative pathophysiology of AD, PD, HD, and ALS

I. Global health and economic burden of NDDs

II. Main features of the neurodegenerative diseases (NDDs)
a. ID card of AD, PD, ALS and HD
b. Origin of the diseases

III. NDDs: the role of misfolded proteins

IV. The prion-like hypothesis

V. Spreading of pathology in the brain: the gut-brain axis hypothesis

VI. Gain-of-Function vs. Loss-of-Function hypotheses in PD (for class 9/12)

★ Key concepts to memorize

PD: Gain-of-function or Loss-of-function ? ★

What are Gain-of-Function (GoF) mutations in PD?

Definition: Gain-of-function mutations occur when a genetic mutation leads to **increased**, **new**, or **abnormal activity** of a protein, often resulting in toxic effects. These mutations make proteins either more active than normal or cause them to behave abnormally, leading to cellular damage and neurodegeneration in Parkinson's disease.

Mechanisms of Gain-of-Function mutations in PD

1.Increased protein enzymatic activity:
Some GoF mutations make proteins **hyperactive**, leading to abnormal signaling, dysregulation of critical cellular pathways, or cellular stress. E.g. LRRK2 and GBA1

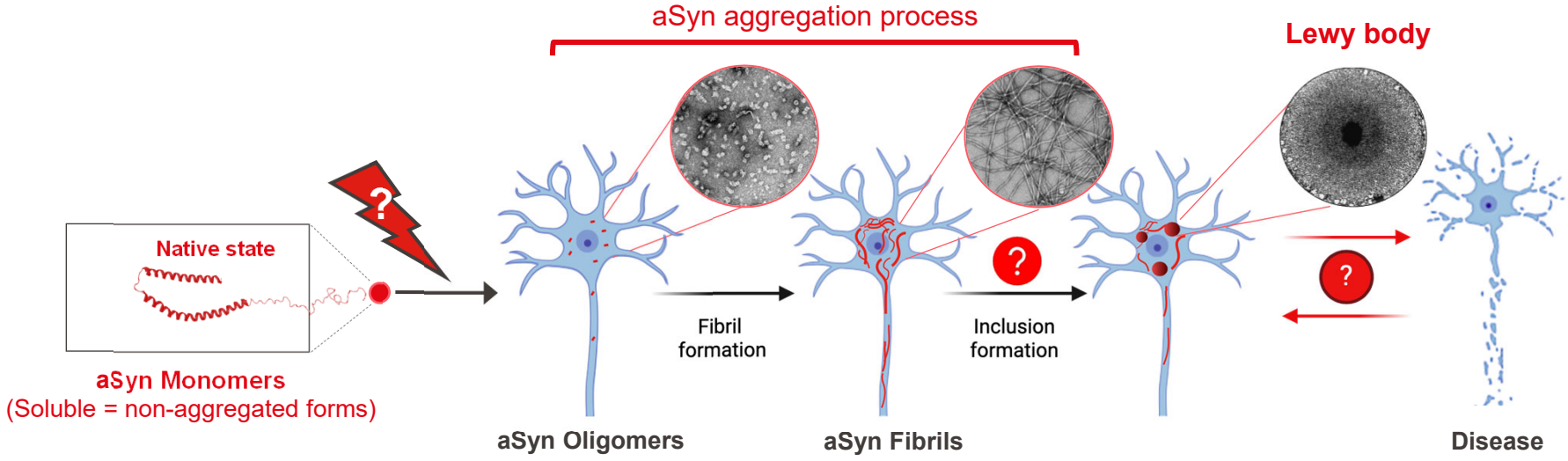
2. Toxic protein aggregation:
GoF mutations can result in the production of **misfolded proteins** that aggregate within cells, causing neuronal dysfunction and cell death. E.g. aSyn

GOF leads to disrupted cellular functions: Overactive or mutated proteins can interfere with key processes such as **mitochondrial function**, **protein clearance**, and **autophagy**, leading to the accumulation of damaged proteins and cellular stress.

PD: Gain-of-function or Loss-of-function ? ★

Examples of Gain-of-Function mutations in PD

1.SNCA (aSyn) mutations:
Alpha-synuclein is a protein involved in synaptic transmission.
GoF mutations in **SNCA gene (point mutations or duplication or triplication)** lead to the **misfolding** and **aggregation** of alpha-synuclein into **Lewy bodies**.
These Lewy bodies accumulate in neurons, causing toxicity and contributing to the death of **dopaminergic neurons** in the substantia nigra.



PD: Gain-of-function or Loss-of-function ?

Examples of Gain-of-Function mutations in PD

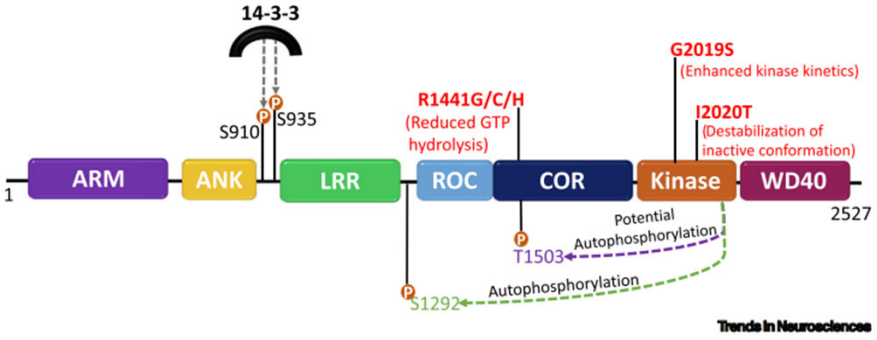
2. LRRK2 (Leucine-Rich Repeat Kinase 2) mutations:

LRRK2 is a kinase that regulates many cellular processes, including vesicle trafficking, autophagy, and mitochondrial function.

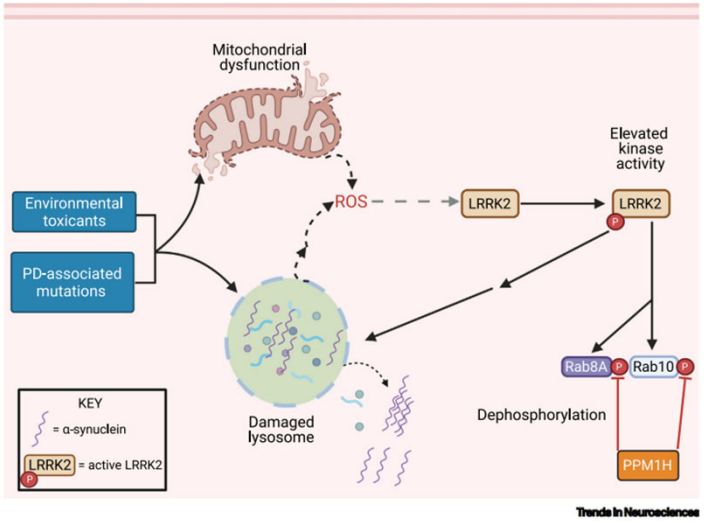
GoF mutations in LRRK2 (e.g., the **G2019S** mutation) result in **hyperactive kinase activity**, leading to:

Mitochondrial dysfunction: Increased oxidative stress and mitochondrial damage.

Autophagy impairment: Disruption of the cell's ability to clear damaged organelles and proteins, leading to their accumulation and neuronal death.



Rocha et al 2022



PD: Gain-of-function or Loss-of-function ? ★

Consequences of Gain-of-Function Mutations in PD

•Lewy Bodies:
Protein aggregates such as **Lewy bodies**, primarily composed of misfolded aSyn, are a hallmark of PD and cause widespread neuronal dysfunction.

•Mitochondrial and autophagy dysfunction:
Overactivity of proteins like LRRK2 leads to mitochondrial damage and impaired autophagy, further contributing to neurodegeneration in PD.

•Neuronal Death:
GoF mutations often result in the **accumulation of toxic proteins** (e.g., aSyn), **overactivity of cellular enzymes** (e.g., LRRK2 kinase), and **defective protein clearance**, all of which contribute to the degeneration of dopaminergic neurons.

PD: Gain-of-function or Loss-of-function ? ★

What are Loss-of-Function (LoF) Mutations?

Definition: Loss-of-function (LoF) mutations occur when a genetic mutation leads to the **reduction** or **elimination** of a protein's normal function. This can impair essential cellular processes, making cells less capable of dealing with stress or damage, ultimately contributing to neurodegeneration in Parkinson's disease.
These mutations usually result in **insufficient protein activity** or the complete **absence of a functional protein**, disrupting the cell's ability to maintain homeostasis.

Mechanisms of Loss-of-Function mutations in PD

1. Depletion of endogenous aSyn during aggregation pathway:
aSyn normally plays a critical role in **synaptic vesicle regulation** and **neurotransmitter release**. As aSyn aggregates form, there is a **depletion of functional, soluble aSyn**, which is essential for normal neuronal function. Thus depleted aSyn might lead to synaptic dysfunctions with impaired synaptic vesicle cycling, which disrupts neurotransmitter release and contributes to neurodegeneration or contribute to the **loss of cellular homeostasis.**

2. Impaired protein degradation:
LoF mutations can disrupt the **ubiquitin-proteasome system (UPS)** or **autophagy**, making it difficult for cells to clear misfolded proteins like alpha-synuclein, which results in the toxic buildup of **aSyn aggregates**.

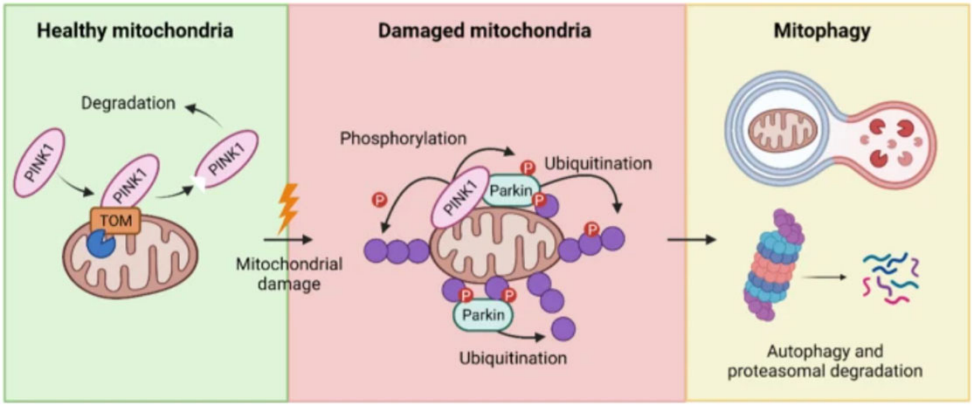
3. Mitochondrial dysfunction:
LoF mutations impair mitochondrial health by disrupting **mitophagy** (the removal of damaged mitochondria), leading to energy failure, oxidative stress, and **dopaminergic neuron loss**.

PD: Gain-of-function or Loss-of-function ?

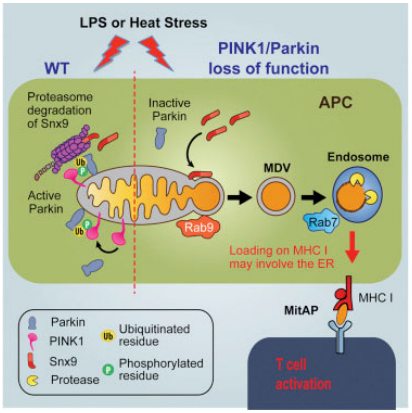
Examples of Loss-of-Function Mutations in PD

PARKIN (PRKN) mutations:

1. **PARKIN** is a key protein involved in tagging damaged proteins and mitochondria for degradation via the **ubiquitin-proteasome system (UPS)**.
2. **LoF mutations in PARKIN** impair the degradation of both **misfolded aSyn** and damaged mitochondria. As alpha-synuclein aggregates form, the loss of PARKIN leads to the **depletion of soluble, functional aSyn**, which disrupts normal neuronal function.
3. PARKIN also plays a major role in **mitophagy**, so its loss of function contributes to mitochondrial dysfunction and cellular energy deficits.



Clausen et al 2024



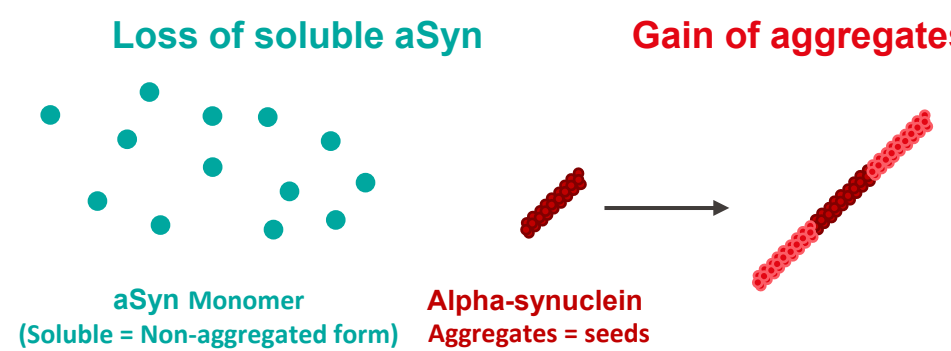
Matheoud et al 2016

PD: Gain-of-function or Loss-of-function ?

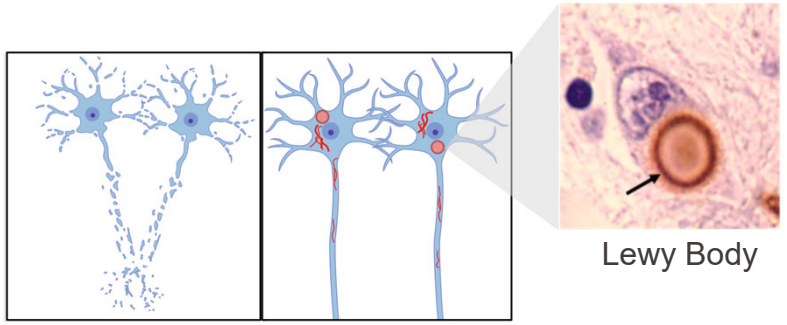
Feature	Gain-of-Function	Loss-of-Function
Mutation Type	Overactivity or toxic function	Reduced/absent function
Protein Impact	Toxic aggregation or activity	Inadequate cellular function
Key Genes	SNCA, LRRK2	SNCA, PARKIN, PINK1
Major Pathways	Aggregation, toxicity	Mitochondrial quality control, protein degradation

aSyn : GOF or LOF ??

aSyn in synucleinopathies: Gain-of-function or Loss-of-function? ★
The Lewy bodies case



Recruitment of endogenous aSyn to the newly formed fibrils



Neurodegeneration of dopaminergic neurons
is concomitant to LB formation and accumulation

1. Pathological aggregation of aSyn leads to **depletion of aSyn endogenous** in neurons
2. The level of LB pathology correlates with disease development, cognitive decline or disease progression and severity

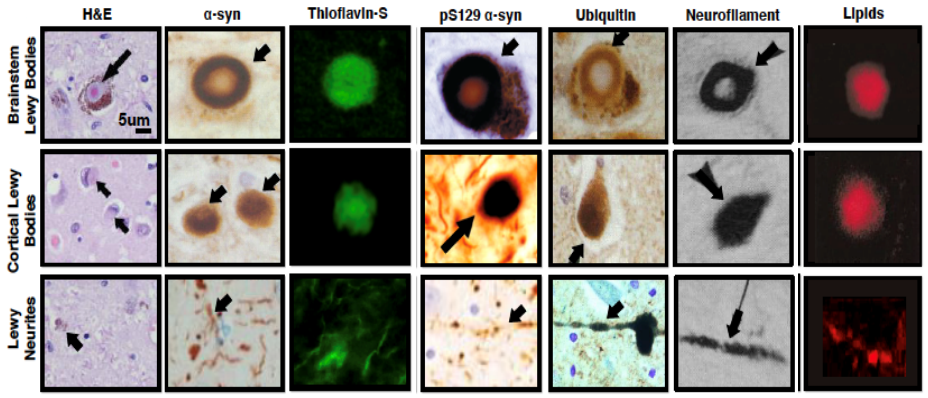
BUT

3. Proteins aggregates are also found in the brain of healthy individuals
4. Protein aggregates are absent in specific genetic forms of PD such as LRRK2 patients

aSyn in synucleinopathies: Gain-of-function

The Lewy bodies case

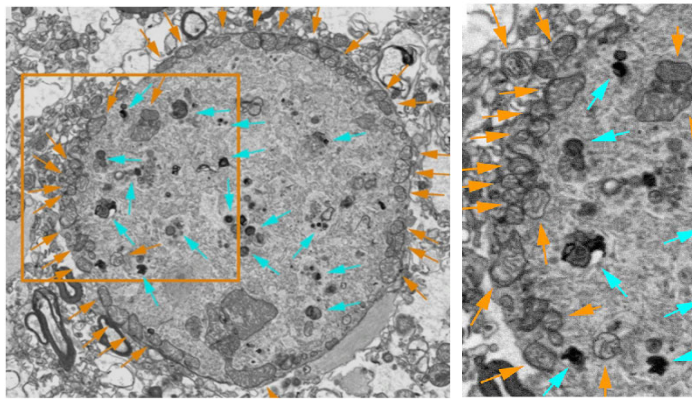
1. Molecular markers

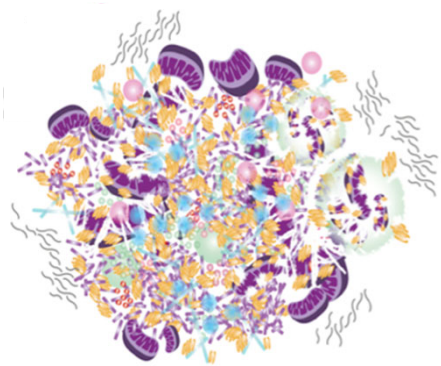


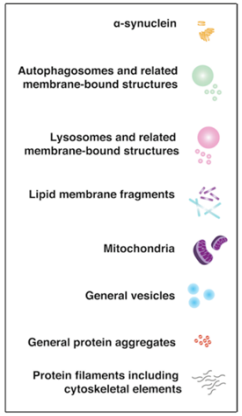
Ibáñez B*, and Lashuel HA*, Nat. Rev. Neuroscience, 2021

β-sheet PTMs > 600 Proteins

2. Membranous structures/abnormal organelles in LBs

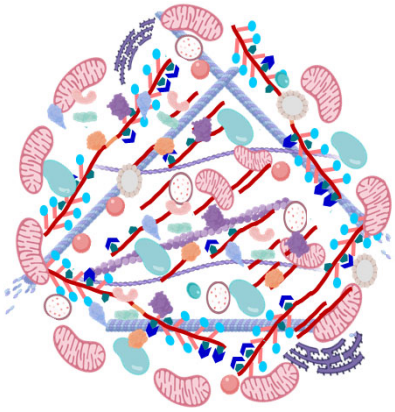




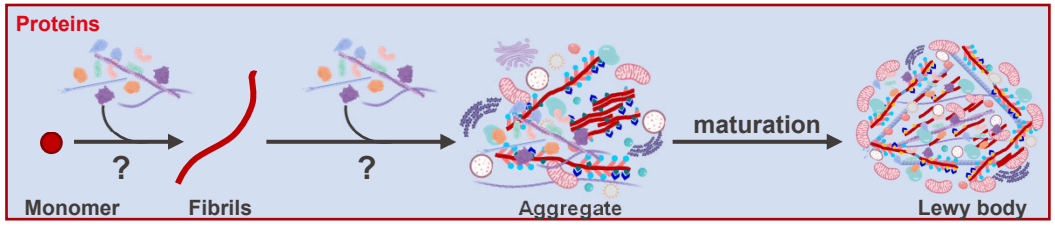


Shahmoradian S et al., Nat. Neuroscience, 2019

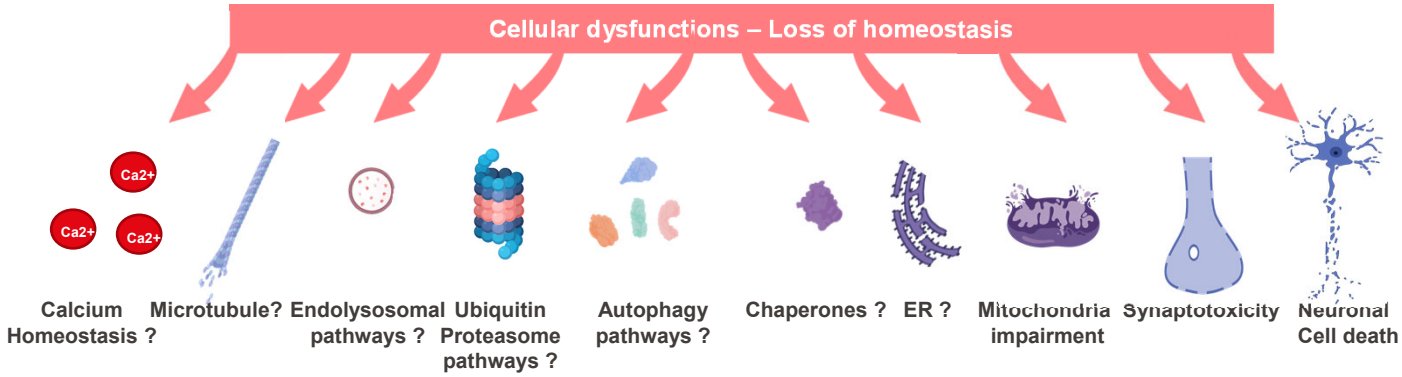
aSyn in synucleinopathies: Gain-of-function
The Lewy bodies case



LB Composition

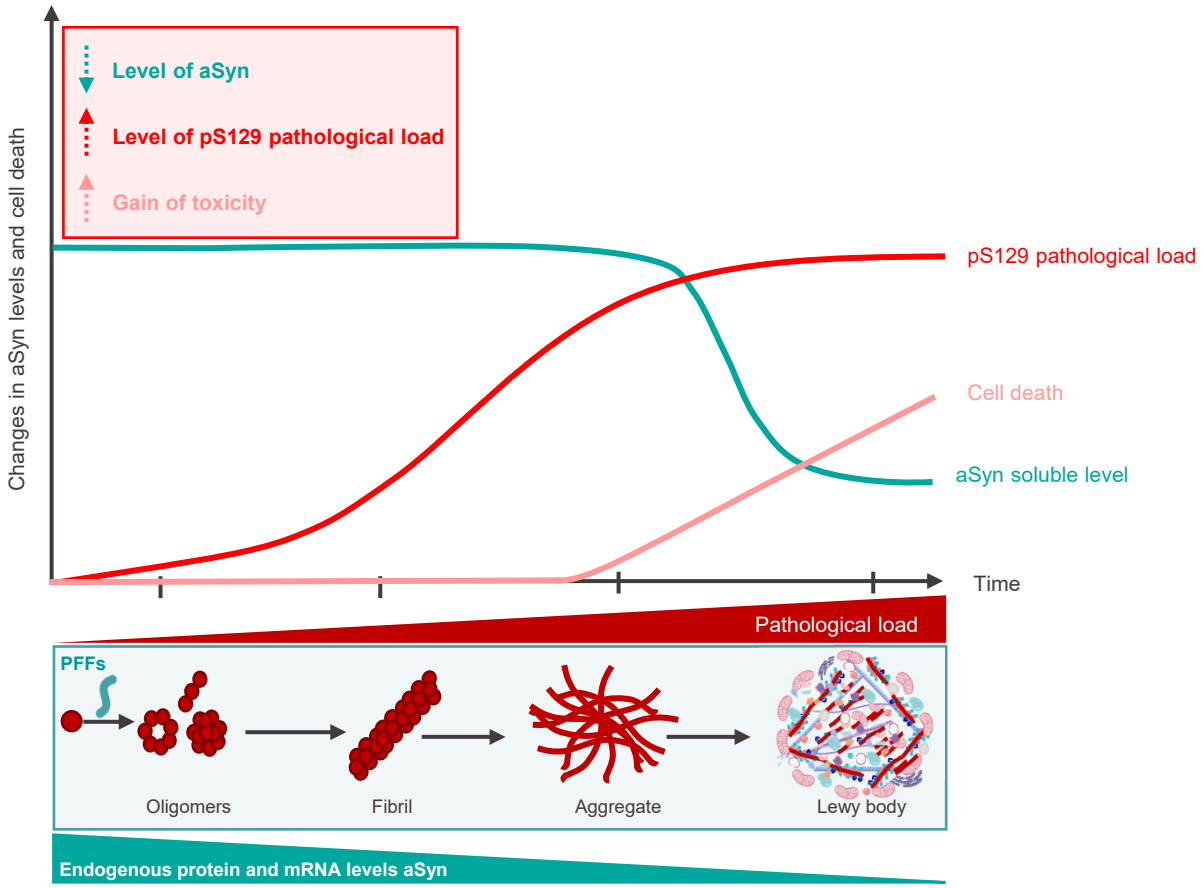


> 600 proteins, lipids, and organelles are sequestered along the LB maturation



aSyn in synucleinopathies: Gain-of-function or Loss-of-function?

The Lewy bodies case



Synucleinopathies: Proteinopathy (GOF) or proteinopenia (LOF)? ★40

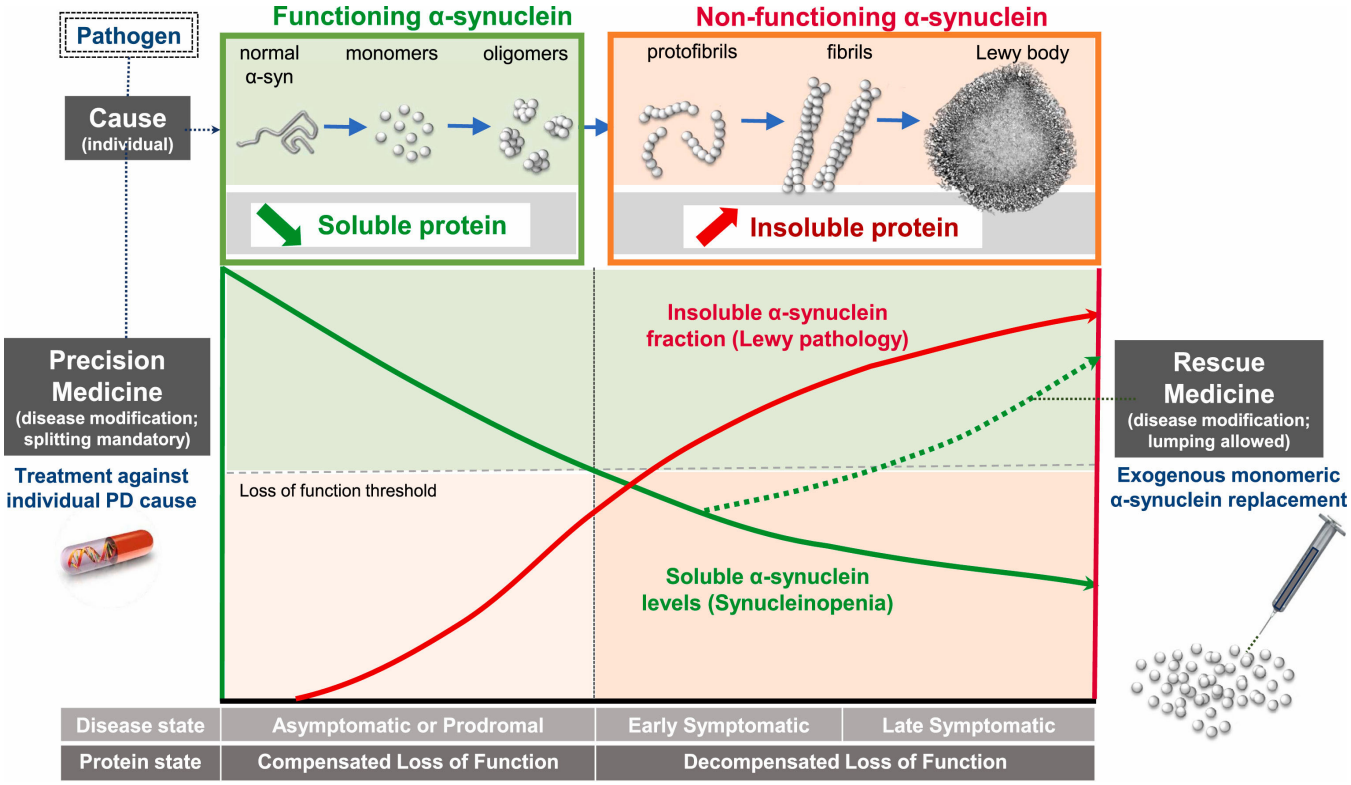
	Synucleinopathy	Synucleinopenia
Alpha-synuclein	Cause of disease	Affected by disease
Pathogenesis	Accumulation of pathology	Depletion of normal synuclein
Lewy pathology	Toxic causal agent	Inert physical consequence
Conformation	Strains (identical copies)	Polymorphs (infinitely diverse)
Pathology spread	Active, Replication	Passive, Nucleation
Treatment approach	Clearance of Lewy pathology	Restoration of normal synuclein

Table 1

Contrasting the 'synucleinopathy' and 'synucleinopenia' hypotheses.

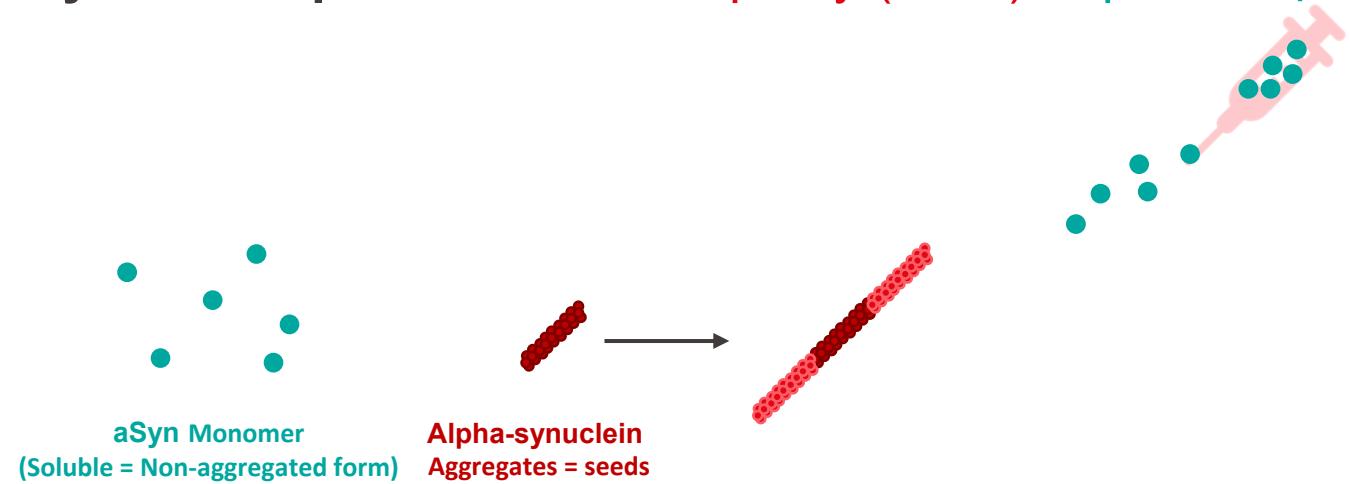
https://www.prd-journal.com/article/S1353-8020(24)00089-0/fulltext?s=09

Synucleinopathies: Proteinopathy (GOF) or proteinopenia (LOF)?



For a pro-proteinopenia rescue medicine is replacement of the endogenous aSyn depleted into the LB

Synucleinopathies: Proteinopathy (GOF) or proteinopenia (LOF)? ★

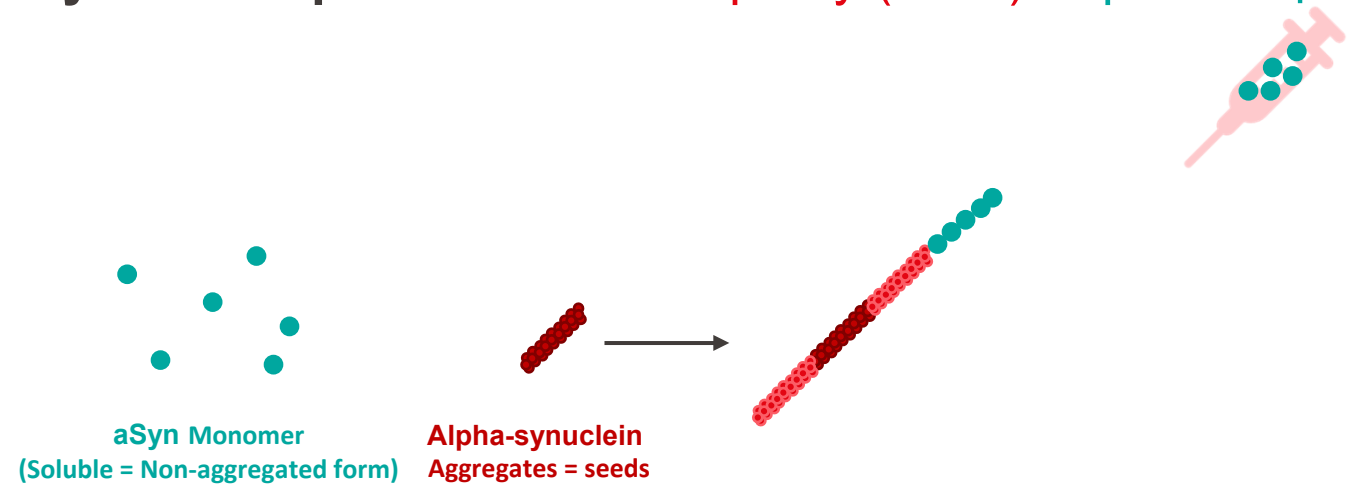


Recruitment of endogenous aSyn to the newly formed fibrils

For a pro-proteinopathy hypothesis, replacement of the endogenous aSyn depleted into the LB will lead to more aggregation and more LB and more neurodegeneration.

Instead Knock-down aSyn endogenous level by siRNA or oligonucleotide antisense to prevent formation or accumulation of LB pathology

Synucleinopathies: Proteinopathy (GOF) or proteinopenia (LOF)? ★



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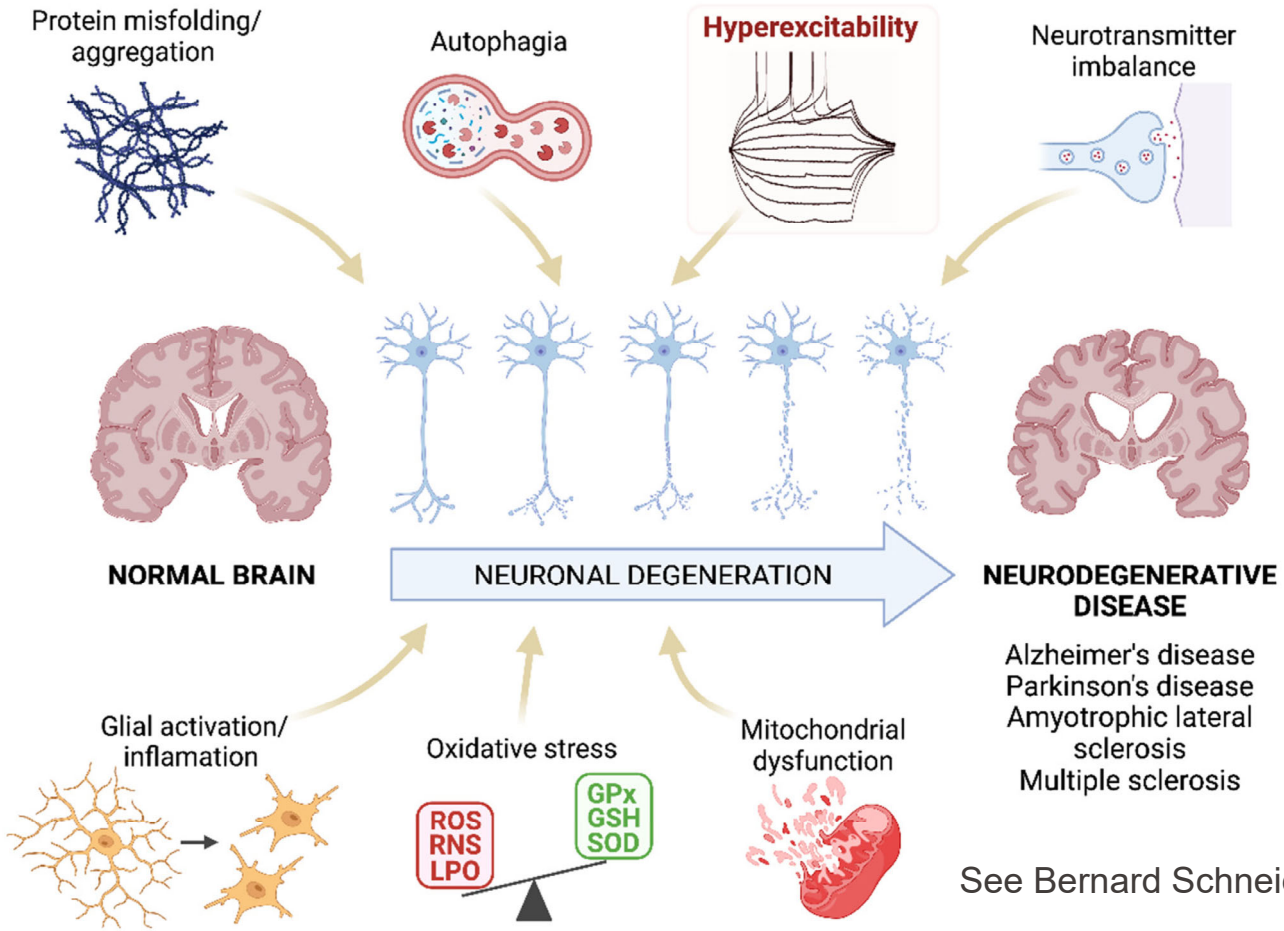
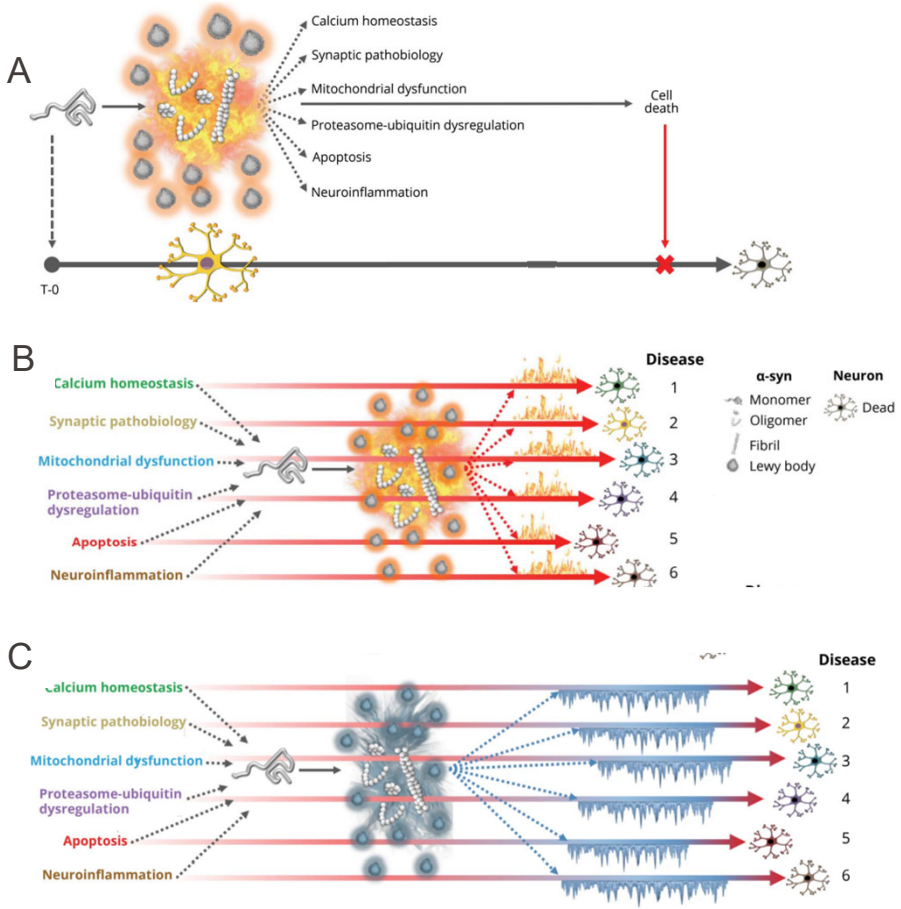
Neuronal cell loss during PD: multifactorial event ★



See Bernard Schneider lecture 15/11

Neuronal cell loss during PD: LB, cause or consequence ? ★

Under investigation and intense debate



Espay et al 2019

Model A LB=toxic (direct):
Abnormal soluble oligomers and fibrils of aSyn that are sequestered into the LBs induce cellular dysregulation leading to cell death.
In this hypothesis, LB pathology and aSyn aggregation are directly pathogenic.

Model B LB=toxic (indirect):
Unknow trigger induce cell dysregulation in neurons, leading to aSyn aggregation and LB formation. While not directly pathogenic, LB act as accelerators of neurodegeneration ("fueling the fire") due to early pathogenic molecular abnormalities

Model C LB = protective:
Unknow trigger induce cell dysregulation in neurons, leading to aSyn aggregation and LB formation. LB are here to sequester the toxic forms of aSyn preventing their toxic effects to the organelles, "cooling" progression of cell degeneration under biological stress

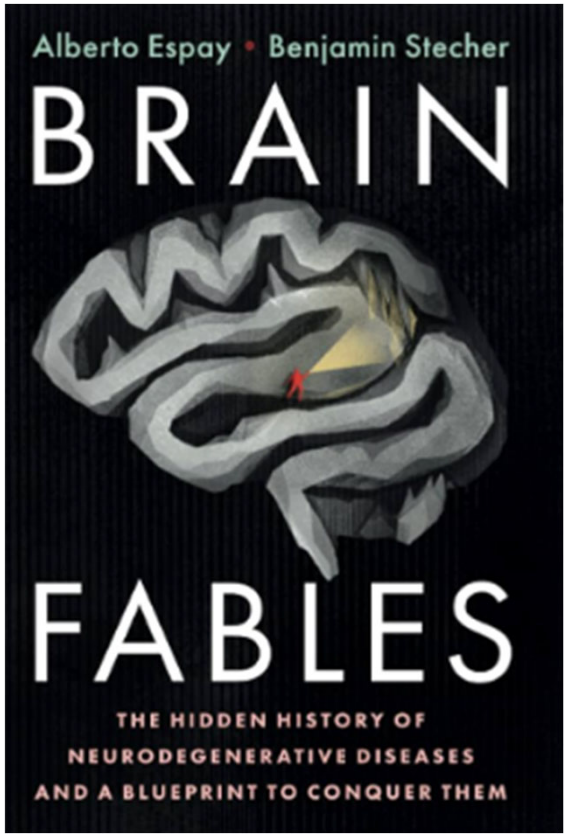
NDDs: GOF or LOF – Practical exercices

Debate "aggregates or non aggregates"

Shared session with Dr. Bernard Schneider

9/12/2024

Supportive litterature



Any questions ? Or Thoughts ?