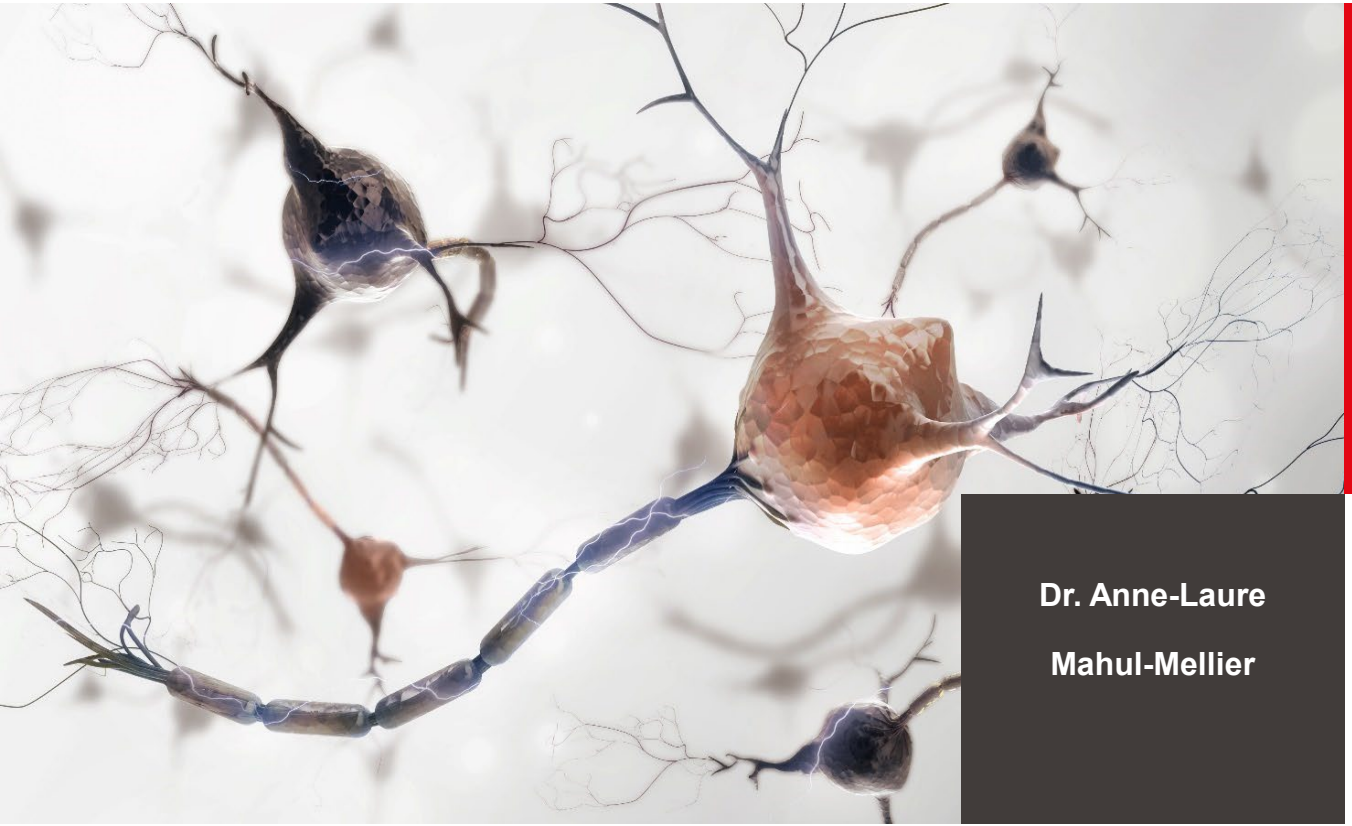
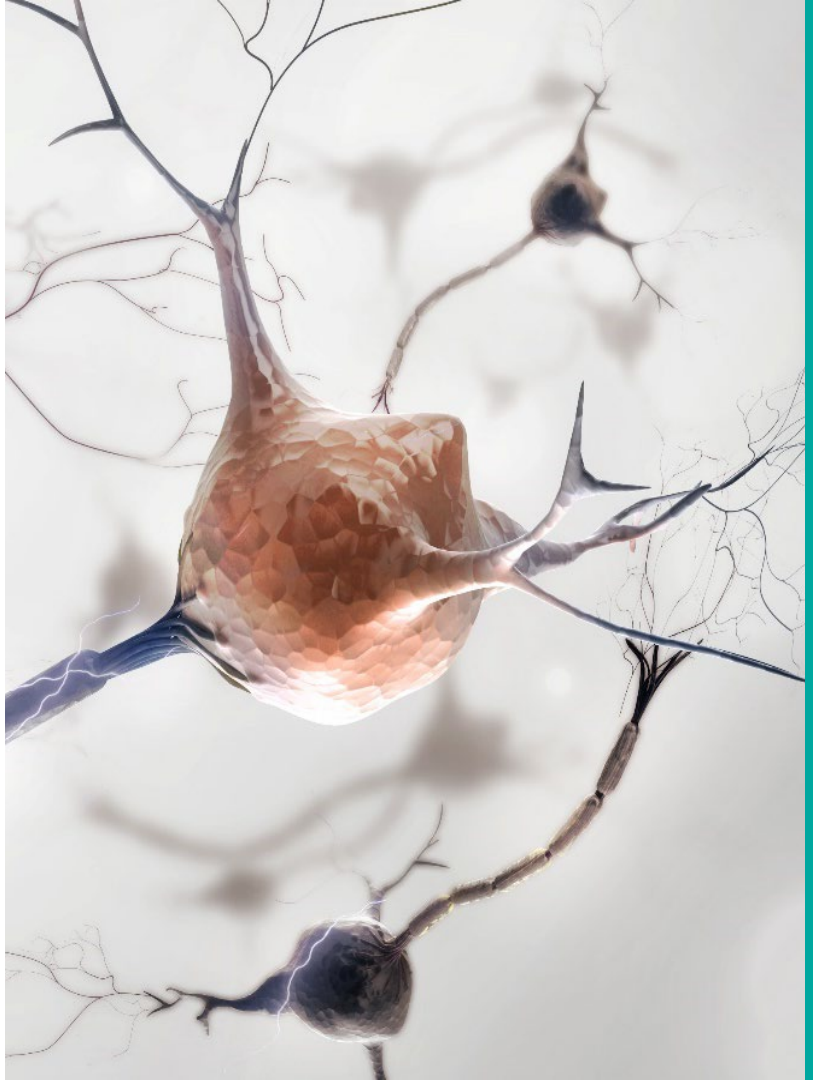


Welcome To BIO480 – NDDs lectures 2024-2025

Dr. Anne-Laure Mahul-Mellier



Instructor:

Dr Anne-Laure Mahul-Mellier
Laboratory of chemical biology of neurodegeneration
IBI Institute, Life sciences Faculty

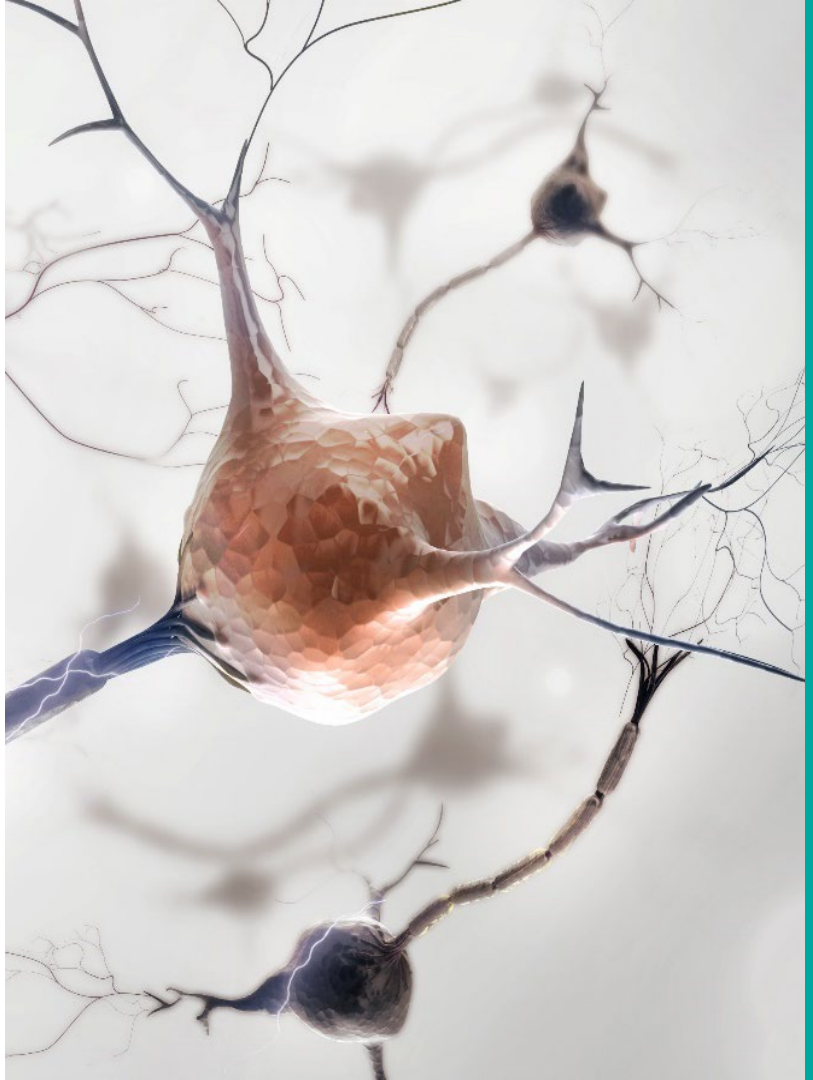
anne-laure.mahul@epfl.ch

Teaching Assistants:

Manel Boussouf, PhD student
manel.boussouf@epfl.ch

Moodle Link:

https://moodle.epfl.ch/course/view.php?id=14320

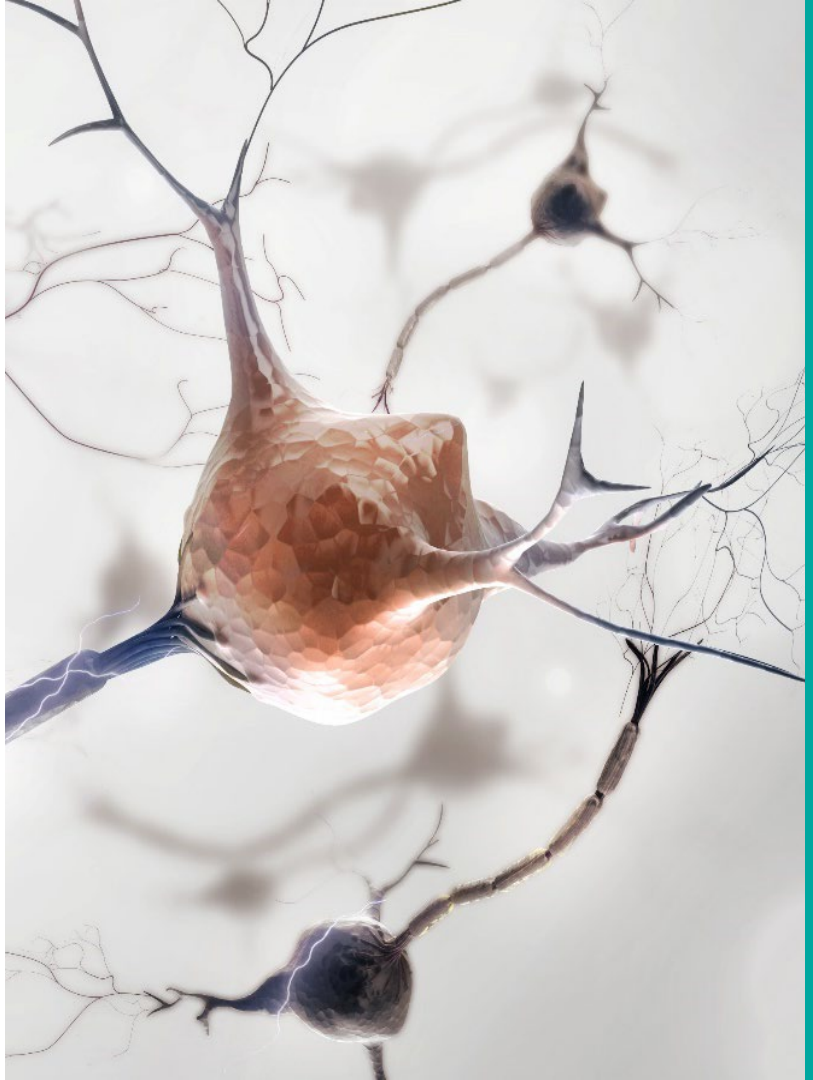


BIO480- Neurodegenerative disease (NDDs) lectures at glance

1. Instructor and TAs

2. Overview of the Bio480 course contents

3. Role of the misfolded proteins in NDD



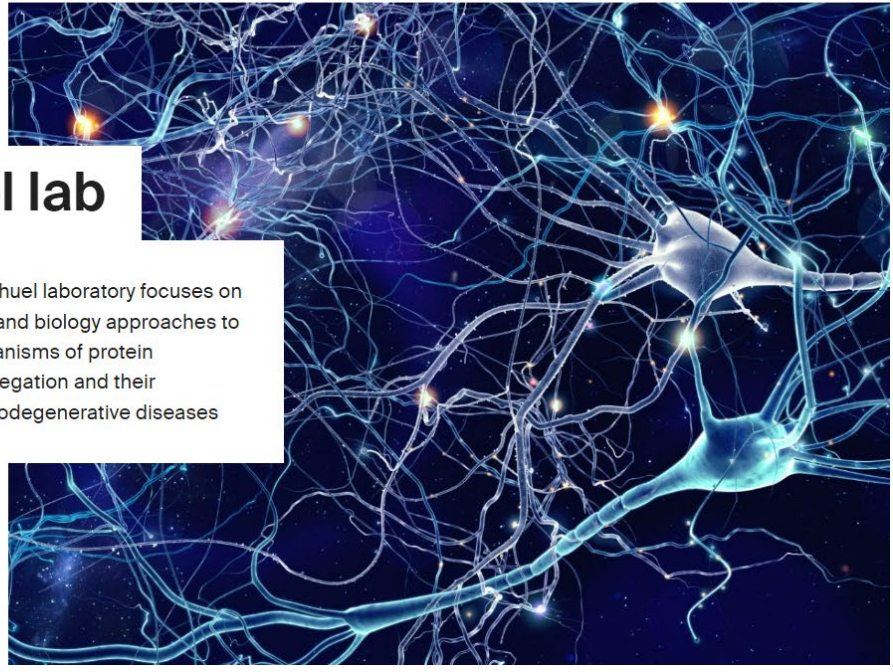
BIO480- Neurodegenerative disease (NDDs) lectures at glance

1. Instructor and TAs

Instructor and TAs

Who are we ?

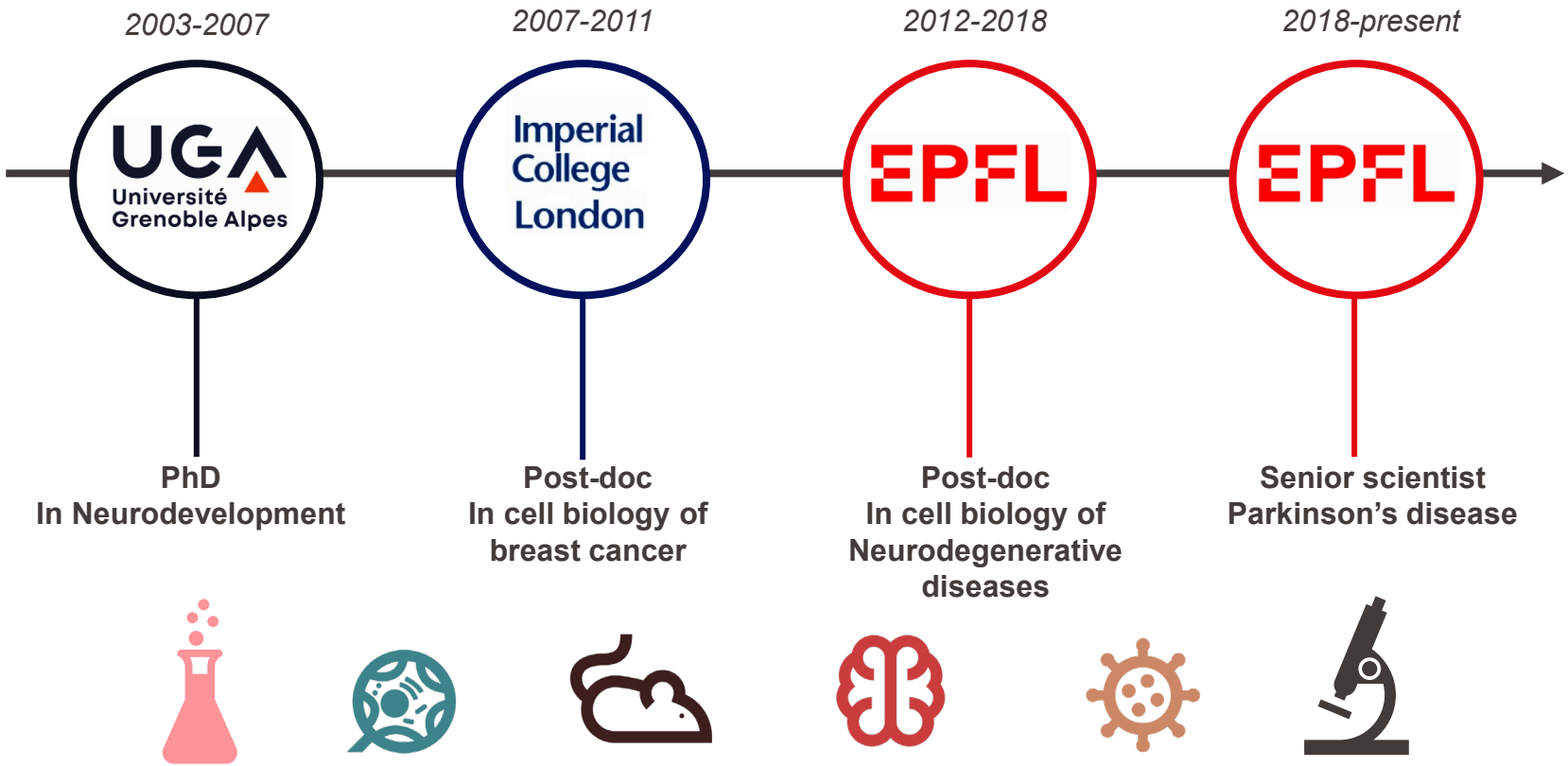
- International Consortia
- Our Open Science Manifesto
- Science and Society
- Upcoming Webinars
- Funding
- Open Positions
- News
- Contact
- Useful Links



Lashuel lab

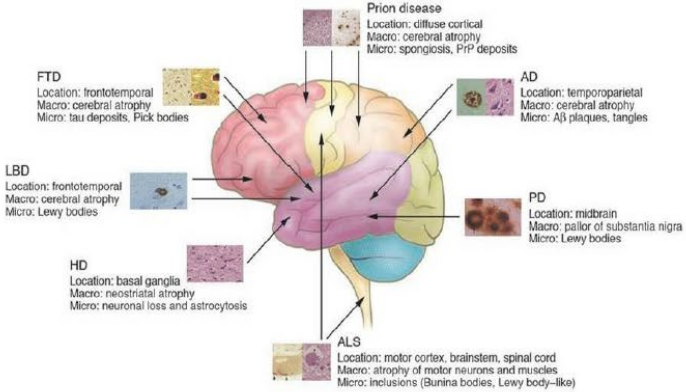
Research in the Lashuel laboratory focuses on applying chemistry and biology approaches to elucidate the mechanisms of protein misfolding and aggregation and their contribution to neurodegenerative diseases

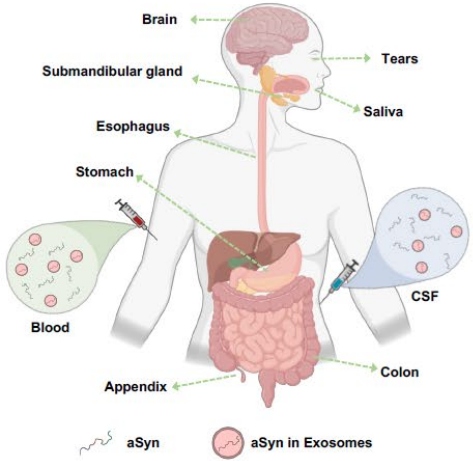
Dr. Anne-Laure Mahul-Mellier

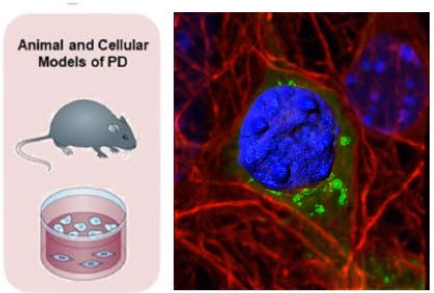


Lashuel Lab: Neurodegenerative diseases

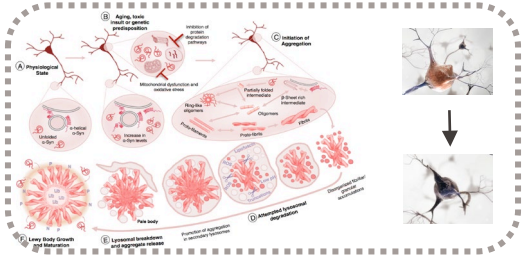
From mechanisms to novel therapies and diagnostics

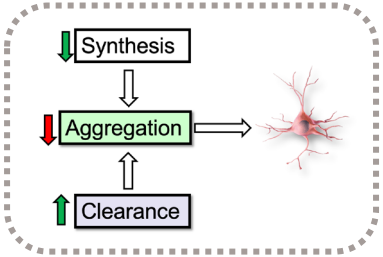


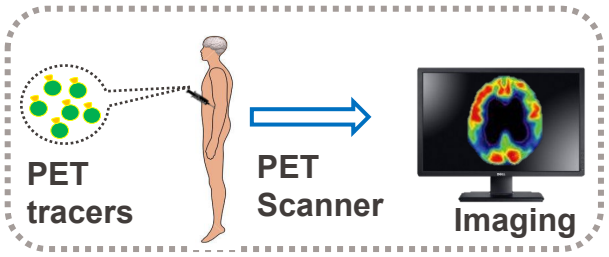


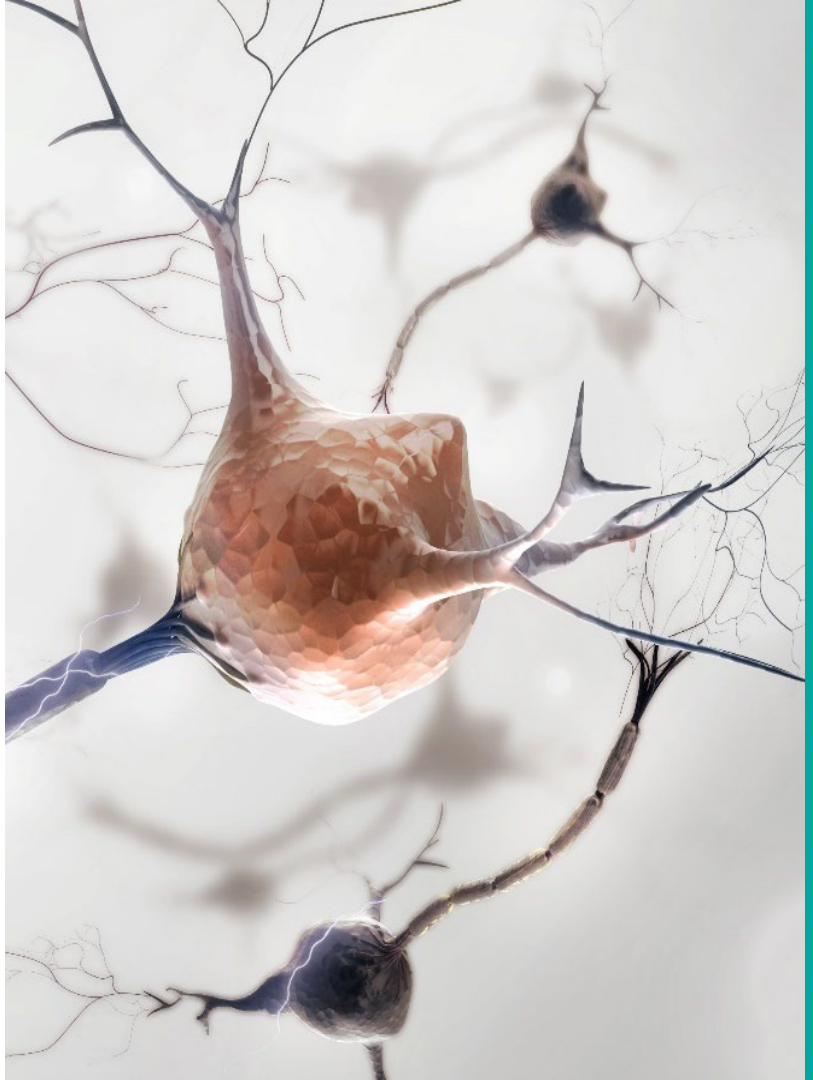


Cellular and molecular mechanisms → **Novel targets and therapies** → **Identify Biomarkers for imaging** → **Biomarkers for diagnosis**





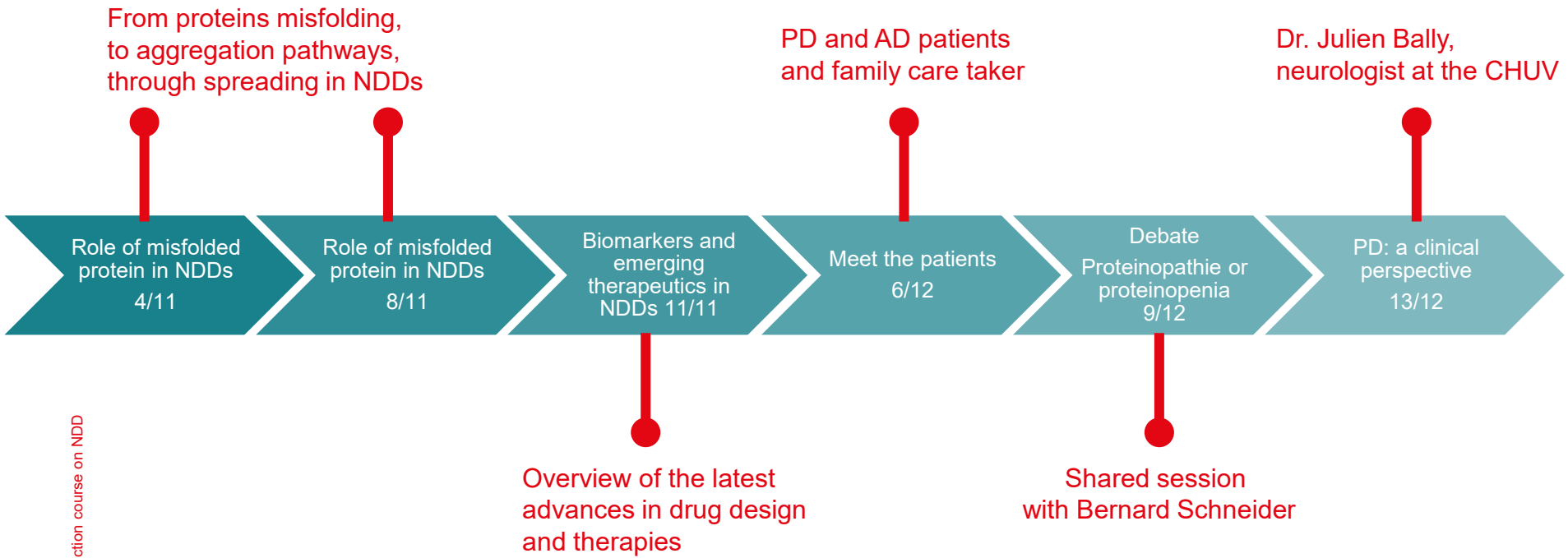


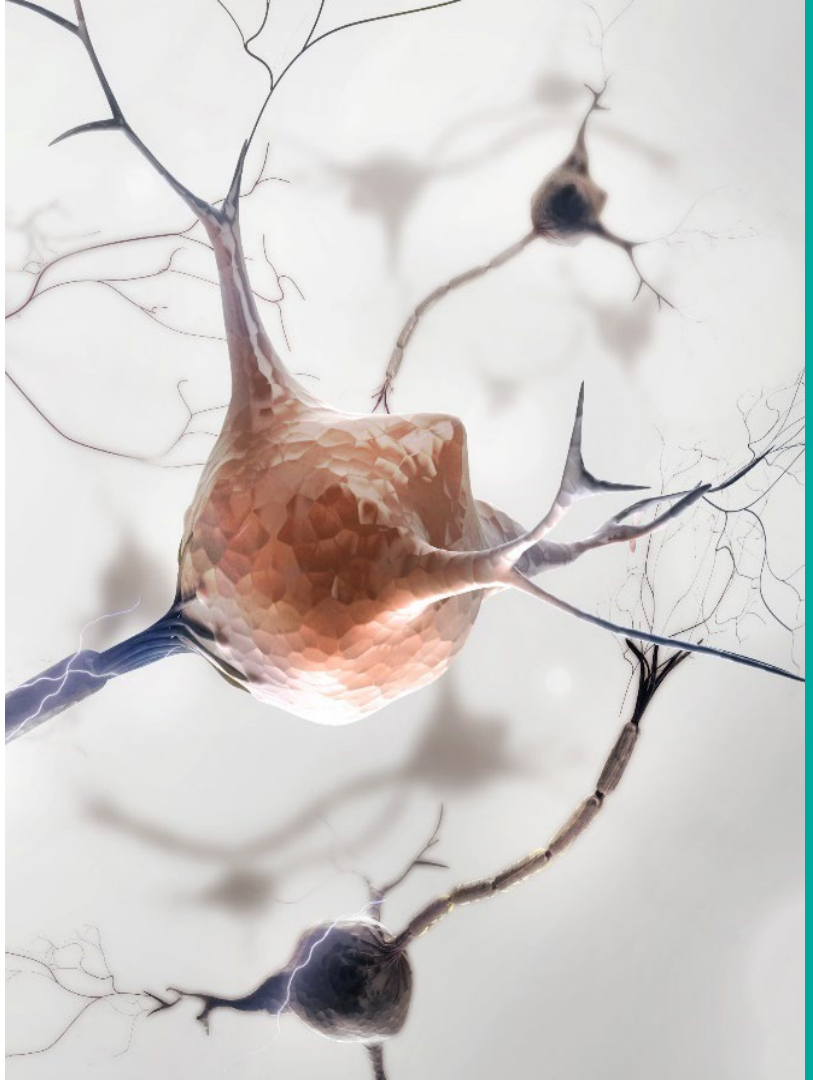


BIO480- Neurodegenerative disease (NDDs) lectures at glance

2. Overview of the Bio480 course contents

Course organisation:





BIO480- NDDs lectures at glance

3. Content of the 4/11 and 8/11 classes:

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)

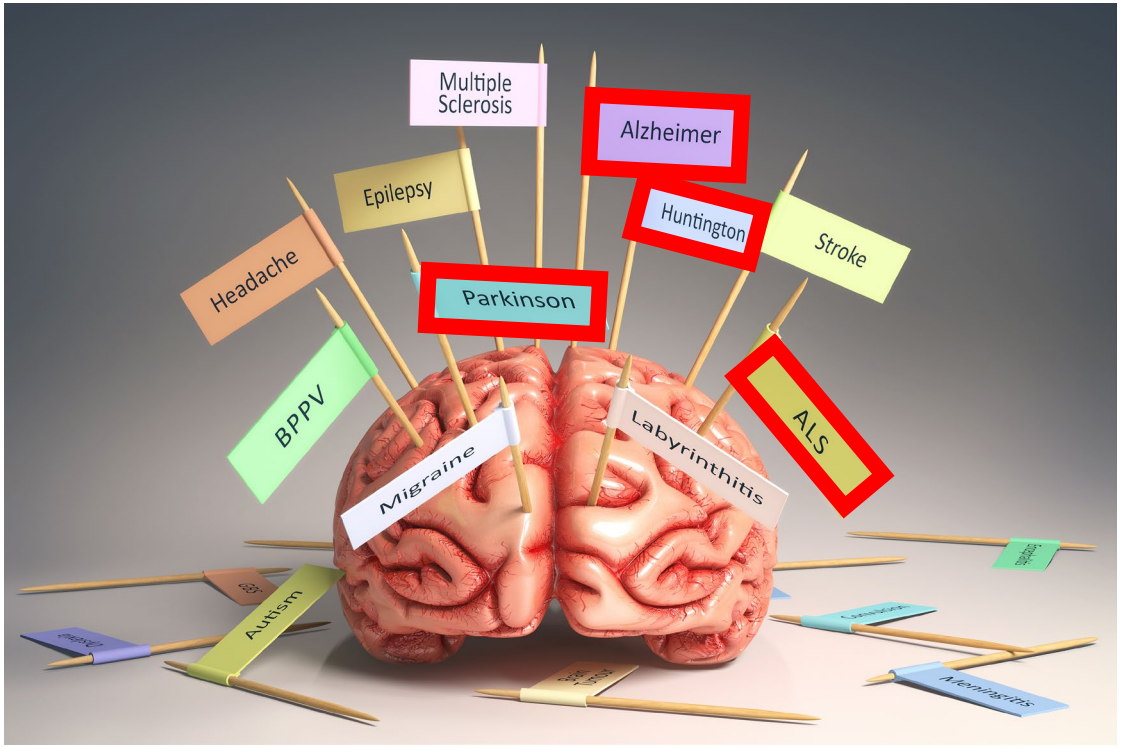
IV. The prion-like hypothesis (4/11)

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

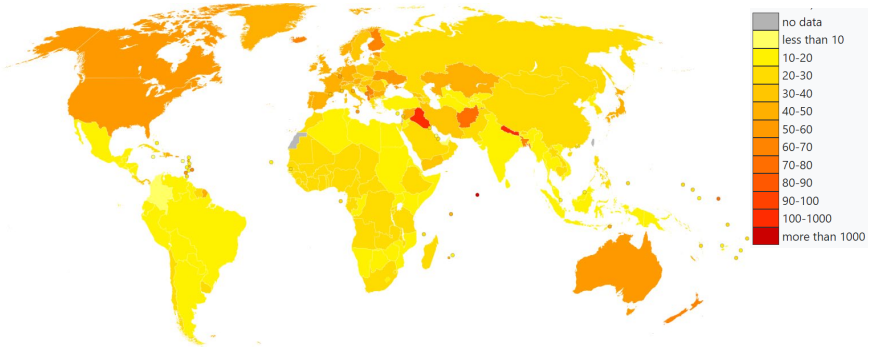
Global health and economic burden of NDDs

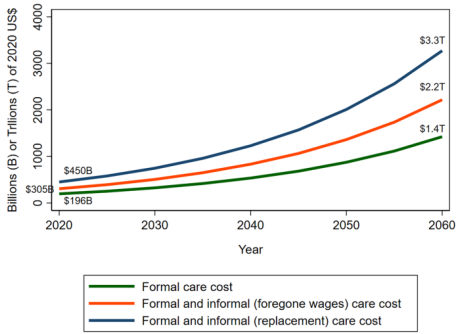
- **Global Prevalence**: Over 60-80 million people globally suffer from neurodegenerative diseases, and this number is expected to more than double by 2050 due to aging populations.

- **Economic Costs**:

The combined annual cost of neurodegenerative diseases globally is projected to surpass **$1 trillion by 2030**.

Alzheimer's disease alone currently costs the US around **$321 billion annually**, a number expected to increase to **$1 trillion by 2050**.





https://ourworldindata.org/grapher/alzheimers-parkinsons-prevalence?tab=table
https://www.nature.com/articles/s41514-024-00136-6

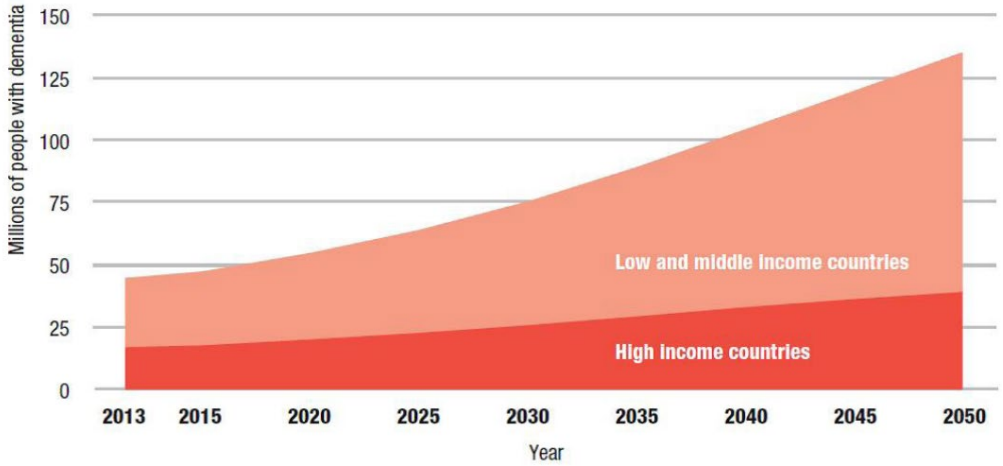
Global health and economic burden of NDDs

- **Healthcare Disparities**:

Higher prevalence and diagnosis rates in high-income countries due to better healthcare infrastructure.

Low- and middle-income countries face rising cases but lack the resources to adequately diagnose, treat, or manage neurodegenerative diseases.

Most cases are currently concentrated in high-income countries like the **US, Western Europe**, and **Japan**, but as the world population ages, developing regions are also seeing a dramatic increase.



https://indjst.org/articles/diagnosis-of-alzheimers-disease-using-rule-based-approach

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★ Key concepts to memorize

Clinical symptoms of the NDDs

Alzheimer's disease (AD)

Memory loss, cognitive decline

Parkinson's disease

Tremor

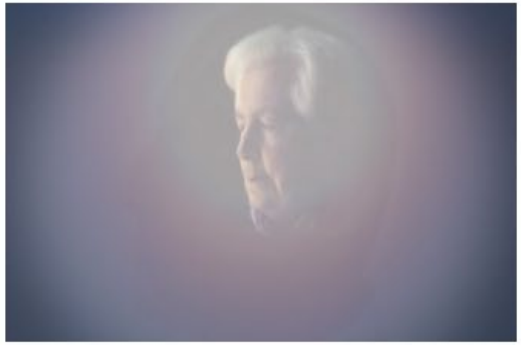
Huntington's disease (HD)

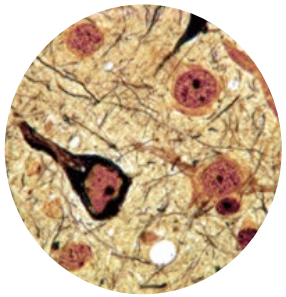
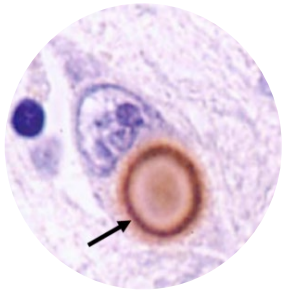
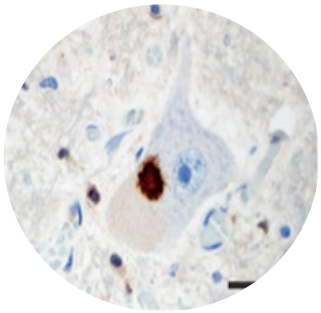
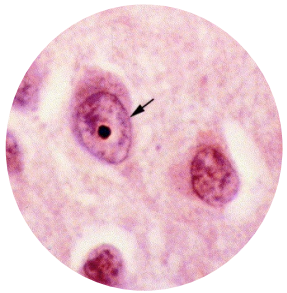
Chorea (involuntary movements)

Amyotrophic lateral sclerosis (ALS)

Progressive muscle weakness

Clinical symptoms of the NDDs

Alzheimer's disease (AD)	Parkinson's disease	Huntington's disease (HD)	Amyotrophic lateral sclerosis (ALS)
			
Memory loss, cognitive decline	Tremor	Chorea (involuntary movements)	Progressive muscle weakness

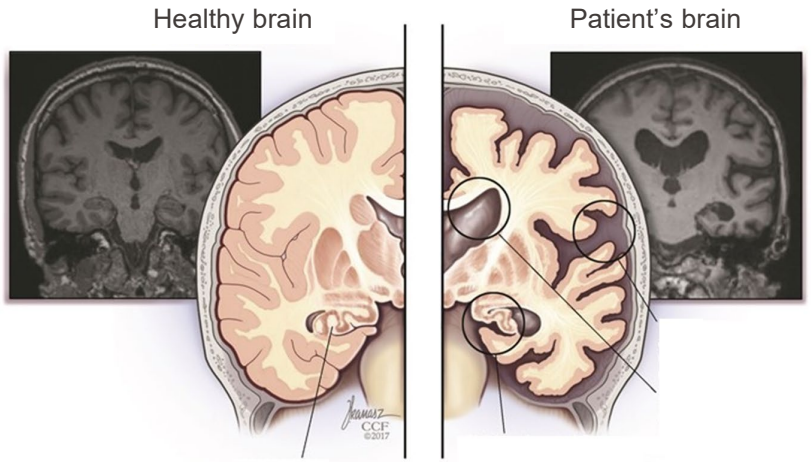
AD, PD, HD, ALS - Different clinical symptoms but a shared mechanism

Protein aggregation is the common thread disrupting brain function and leading to neurodegeneration in all these diseases.

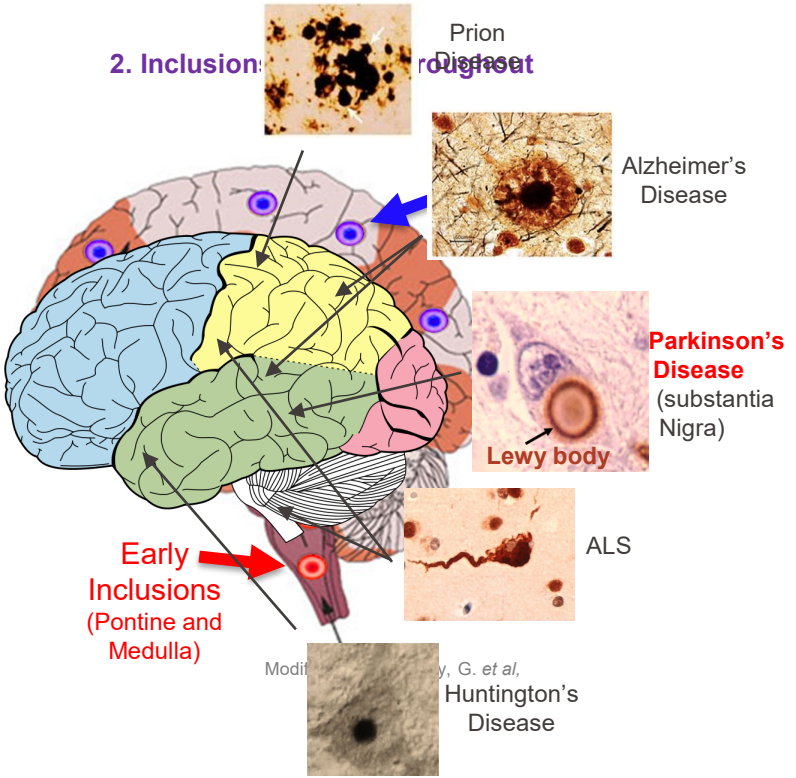
Main features of the neurodegenerative diseases (NDDs)

1. Protein Inclusions in the Brain

3. Neuronal loss in the brain



2. Inclusions throughout



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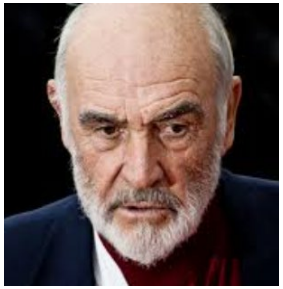
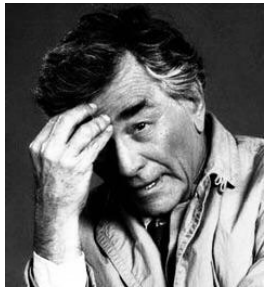
NDDs Overview: Alzheimer's Disease (AD)

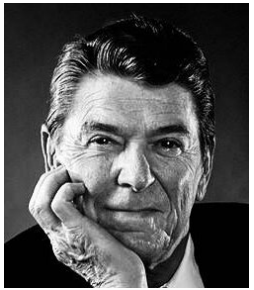


Sean Connery



Peter Falk

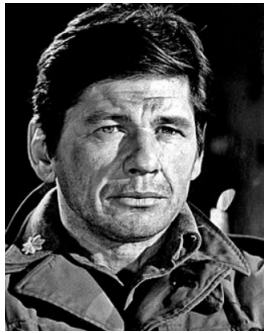
Margaret Thatcher



Ronald Reagan

Rita Hayworth

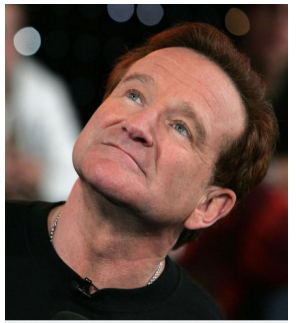
Agatha Christie



Charles Bronson

Rosa Park

Charlton Heston



Robbin Williams

NDDs Overview: Alzheimer's Disease (AD)

•Prevalence:
Affects **50 million people worldwide** today (150'000 in Switzerland).
Projected to rise to **152 million globally by 2050**.

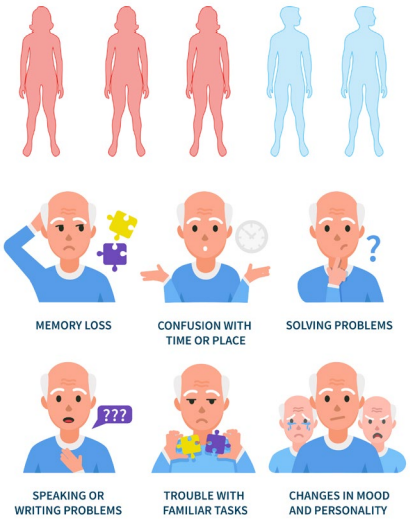
•Male/Female Distribution:
Women: 65% of cases - **Men**: 35% of cases

•Age of Diagnosis:
Typically: After age **65**.
Early-onset AD: ~5% cases occur between ages **30-60**

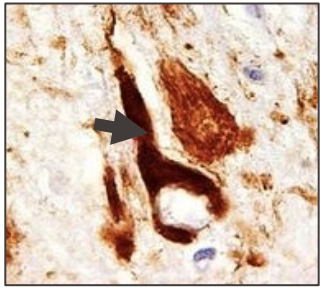
•Key Symptoms: ★
Memory loss, cognitive decline, confusion, language difficulties, personality changes.

•Affected Brain Areas: ★
Initially: **Hippocampus** (responsible for memory).
Later: **Cortex** (cognition, reasoning, language).

•Pathological Features: ★
Amyloid-beta (Aβ) plaques, tau neurofibrillary tangles.



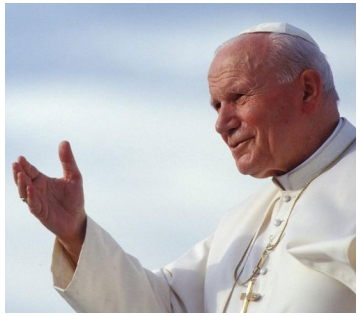
Tau tangles deposition in cortical neurons



NDDs Overview: Parkinson's Disease (PD)


Michael J. Fox

Robbin Williams



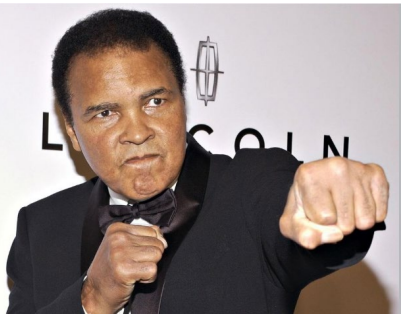
Jean-Paul II

Johnny Cash

Salvadore Dali

Sonia Rykiel

Mao Zedong



Mohamed Ali

Charles Schulz

NDDs Overview: Parkinson's Disease (PD)

Prevalence: 10 millions patients *2024*

worldwide

12-17 millions
2040

60% increase in the number of cases over 20 years

Cost: €250 billions annual

Wijers et al., 2024

Prevalence: 15'000 patients *2007**

In Switzerland

3'000
new cases/year

https://neurochirurgie.insel.ch/fr/maladies-traitees-specialites/neurochirurgie-fonctionnelle-et-douleur/maladie-de-parkinson

CHFs 1-2 billions annual

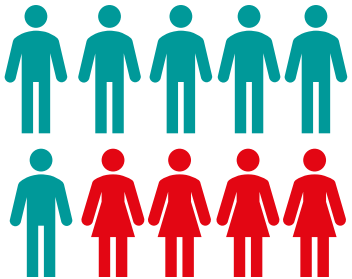
***No recent data for Switzerland**

- Prevalence : 0,2 à 0,3 % of the global population – estimation 15'000 < Swiss patients < *28'000 ?*

NDDs Overview: Parkinson's Disease (PD)

58 years old
Average diagnosis

10%
Of the cases <40 years old



60% men

40% women

NDDs Overview: Parkinson's Disease (PD)

10%

Genetic cases

90%

sporadic cases

NDDs Overview: Parkinson's Disease (PD)

Motor Symptoms

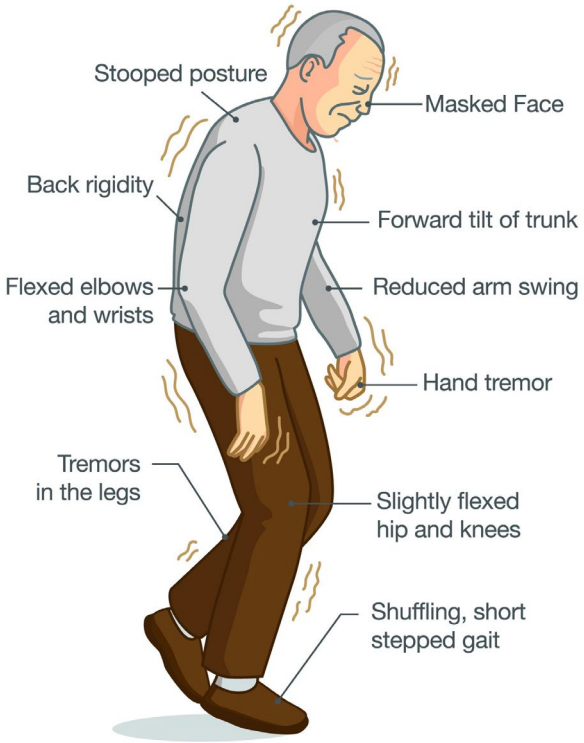
Tremor (involuntary, rhythmic shaking)
Freezing
Bradikinesia (slowness of movement)

Non-motor symptoms !!!

Constipation
Depression
Sleep disorders
Loss of smell

NDDs Overview: Parkinson's Disease (PD)

Definition of the key motor symptoms



1. Bradykinesia:

•**Definition**: **Bradykinesia** refers to the **slowness of movement** and is one of the most disabling motor symptoms in Parkinson's disease. It affects voluntary movements, making everyday tasks such as walking, dressing, and writing difficult. Patients may also experience **reduced facial expression** (hypomimia).

•**Clinical Significance**: Bradykinesia often presents as **hesitation** in initiating movements or slowing down during tasks. It's a hallmark of PD and a required symptom for diagnosis.

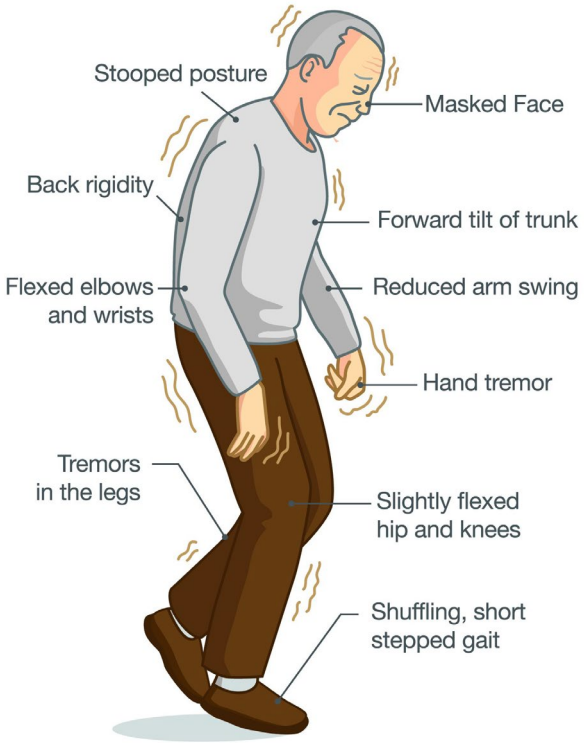
2. Tremor (Resting Tremor):

•**Definition**: **Resting tremor** is an **involuntary, rhythmic shaking** that occurs when muscles are relaxed. It is most often observed in the hands or arms but can also affect the legs, jaw, or chin. The tremor typically diminishes with voluntary movement.

•**Clinical Significance**: Tremors are often one of the first symptoms noticed in Parkinson's disease, though they are not present in all patients. The tremor typically occurs on one side of the body before spreading to the other.

NDDs Overview: Parkinson's Disease (PD)

Definition of the key motor symptoms



3. Rigidity:

•**Definition**: **Rigidity** refers to the **stiffness or inflexibility of the muscles**. In Parkinson's disease, this symptom is characterized by resistance to passive movement through the range of motion. This can affect any part of the body, leading to discomfort and pain.

•**Clinical Significance**: Rigidity can contribute to the **mask-like facial expression** seen in Parkinson's patients, as well as generalized muscle pain and difficulty moving. It often presents in the arms, legs, or neck.

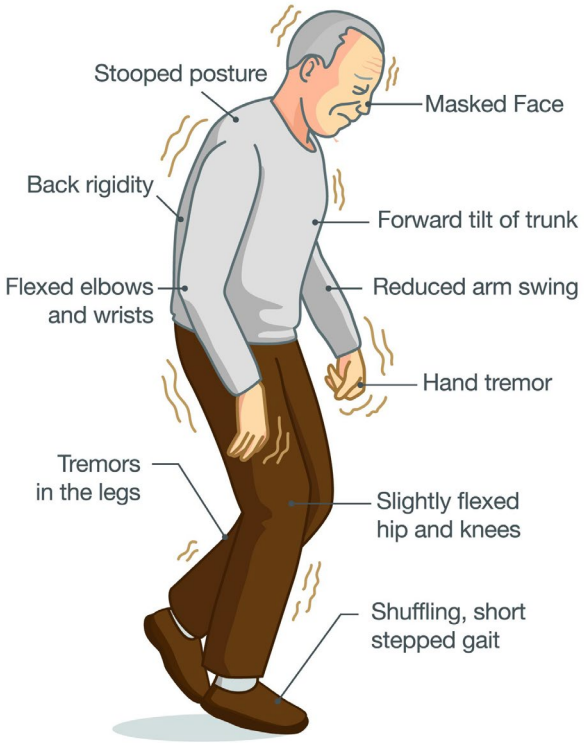
4. Postural Instability:

•**Definition**: **Postural instability** is the **impaired balance and coordination** that leads to difficulty maintaining an upright posture. Patients with postural instability are prone to **falls**, especially when turning or making sudden movements.

•**Clinical Significance**: Postural instability typically emerges in the **later stages** of Parkinson's disease and significantly impacts a patient's mobility and independence. It often results from a combination of bradykinesia, rigidity, and tremor.

NDDs Overview: Parkinson's Disease (PD)

Definition of the key motor symptoms

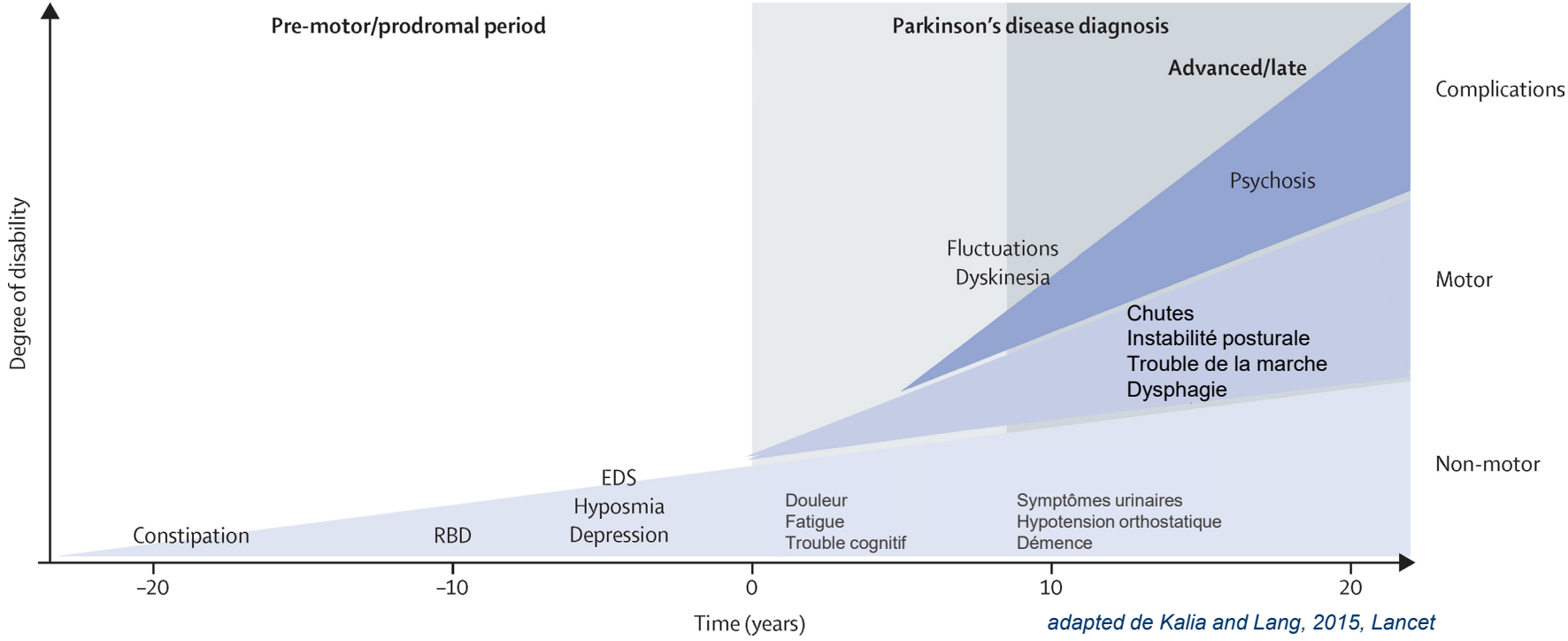


5. Freezing of Gait (FOG):

•**Definition**: **Freezing of gait** refers to a **sudden, temporary inability to move** the feet while walking, even though the person wants to move. It often occurs when a person is trying to initiate walking or when turning.

•**Clinical Significance**: FOG can increase the risk of falls and is often triggered by tight spaces or stressful situations. It can be particularly challenging for patients during transitions like entering a doorway or turning around.

Parkinson's Disease:
begins years before motor symptoms appear



adapted de Kalia and Lang, 2015, Lancet

Non-motor symptoms start 10-20 years before the motor symptoms.

Parkinson's Disease:
begins years before motor symptoms appear

Average age diagnosis: 58 year old
(10% cases < 40 years old)

Non-motor symptoms
Constipation, loss of smell, sleep disorder, cognitive impairment…

Impossibility of early diagnosis

Lack of specific tests available

Inadequate clinical imaging

No dopaminergic neuronal loss

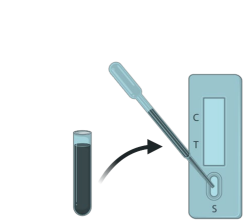
Motor symptoms
Tremor, bradykinesia, muscle rigidity, postural instability

Disease diagnosis overview

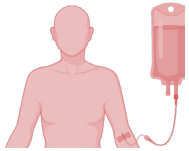
Primary indicators: presence of motor symptoms

Diagnostic confirmation: medical imaging techniques

Critical threshold: > 50% loss of dopaminergic neurons



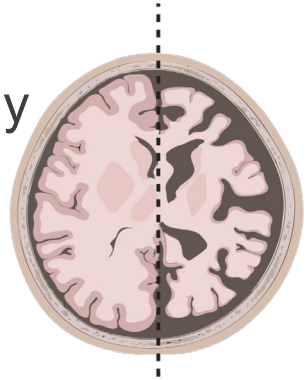
No test available for early diagnosis



No therapies to treat, prevent or slow the progression of Parkinson's disease

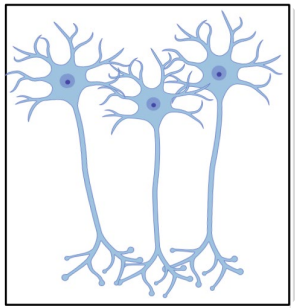
Parkinson's Disease:
Main pathological features

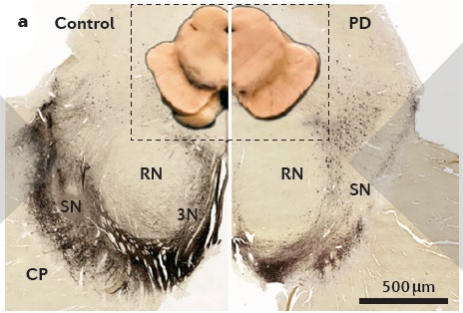
Healthy



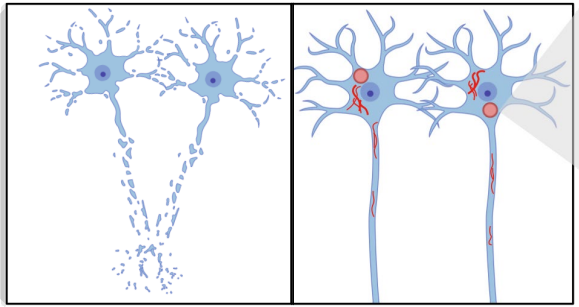
Parkinson's

1. Neuronal loss





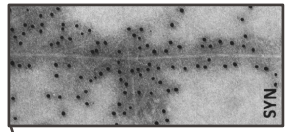
substantia nigra



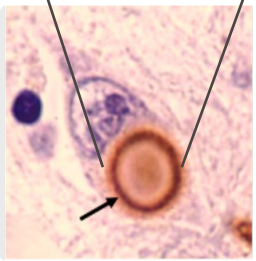
2. Neurodegeneration of dopaminergic neurons

3. Accumulation of inclusions

Alpha-Synuclein fibrils
(pathological form)

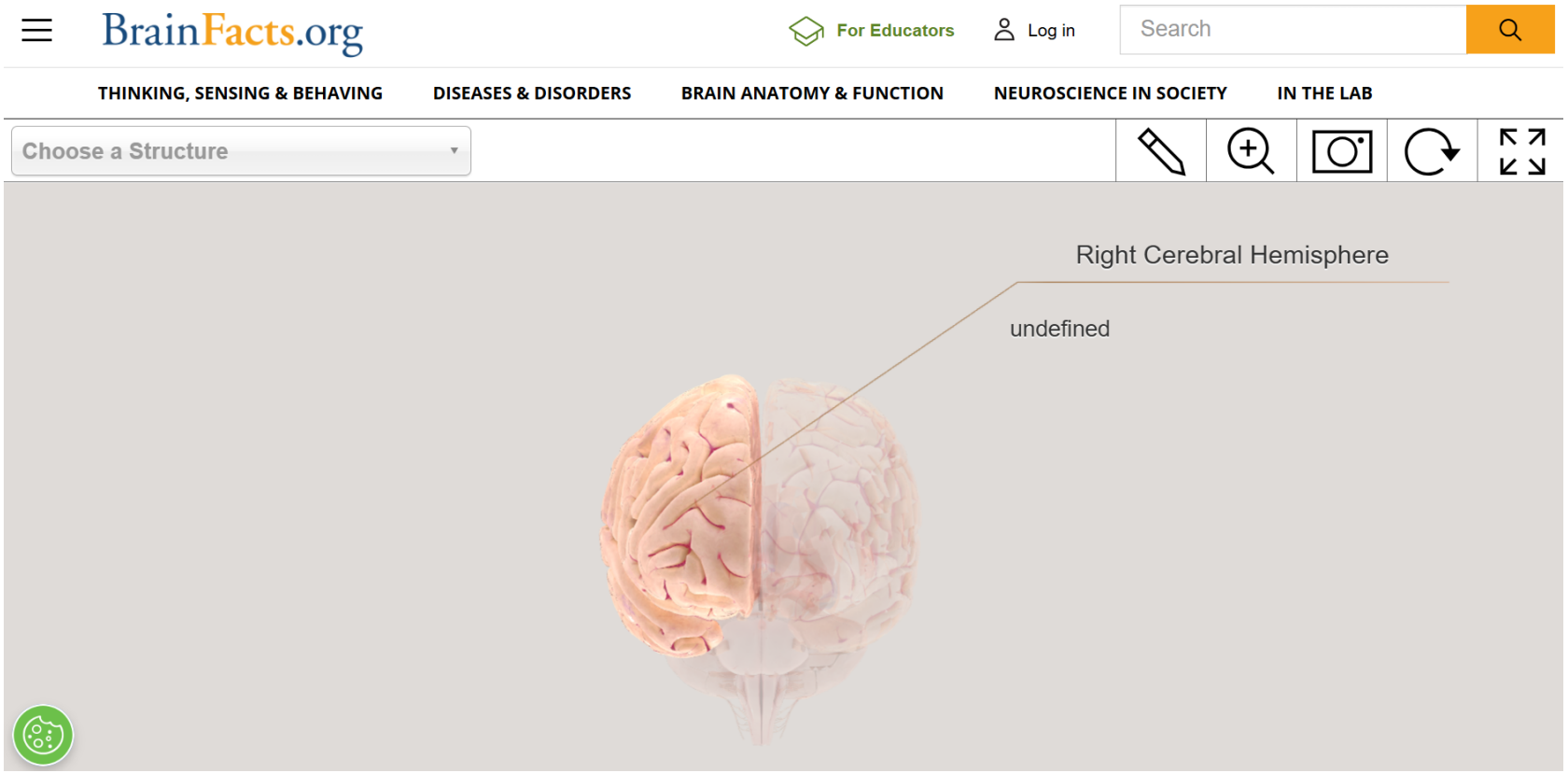


Goedert and Spillantini 1998



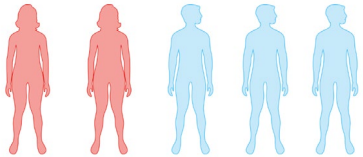
Lewy Body

3D brain interactive map



NDDs Overview: Parkinson's Disease (PD)

•Prevalence:
Affects **10 million people worldwide** today (15'000-30'000 in Switzerland).
Projected to rise to **12-17 million globally by 2040**.



•Male/Female Distribution:
Women: 40% of cases - **Men**: 60% of cases

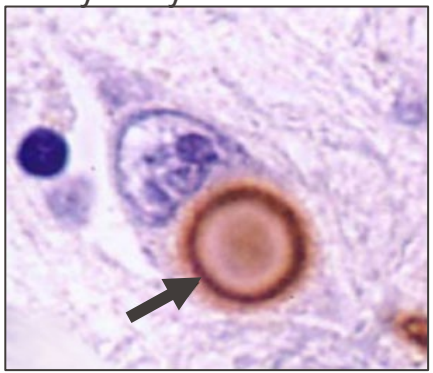
•Age of Diagnosis:
Typically: After age **58**.
Early-onset AD: 10% cases occur before 40 years old

•Key Symptoms:★
Motors: Tremors, bradykinesia (slowed movements), muscle rigidity, postural instability.
Non motors: Constipation, loss of smell, depression, sleep disorders

•Affected Brain Areas:★
Initially: **Substantia nigra** (responsible for motor control).
Later: **Basal Ganglia** (Worsening motor symptoms), **Cortex** (cognition, language)
Brainstem (Gait problems, sleep disorders), **Amygdala** (Depression)

•Pathological Features:★
Misfolded alpha-synuclein accumulates in **Lewy bodies**.
Dopamine deficiency leads to **impaired motor control**.

Lewy body in DA neurons



NDDs Overview: Amyotrophic Lateral Sclerosis (ALS)

Stephen Hawking

NDDs Overview: Amyotrophic Lateral Sclerosis (ALS)

•Prevalence:
Affects **200 000-500 000 people worldwide** today (700 in Switzerland).
Projected to rise due to aging population but not exponential like AD and PD

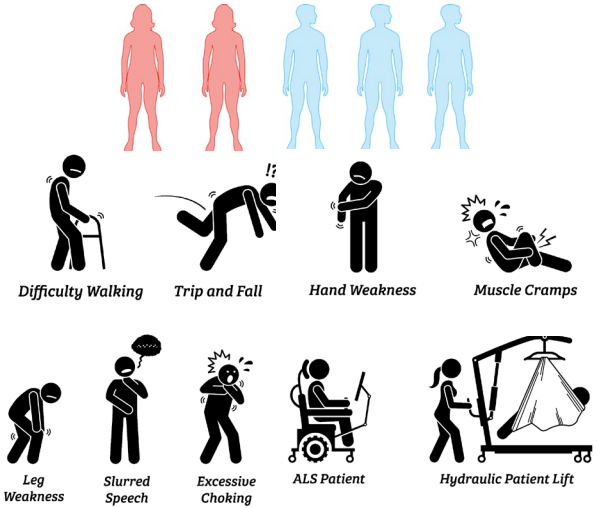
•Male/Female Distribution:
Women: 40% of cases - **Men**: 60% of cases

•Age of Diagnosis:
Typically: 40-70 years - Peak diagnosis: Age **55**.
>80% of ALS patients live between **2 to 5 years** after diagnosis

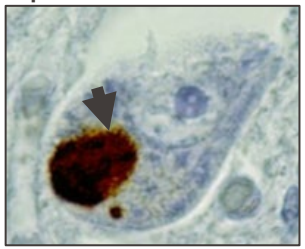
•Key Symptoms: ★
Progressive muscle weakness, difficulty speaking/swallowing, respiratory failure.

•Affected Brain Areas: ★
Motor neurons in the **cortex**, **brainstem**, and **spinal cord**.

•Pathological Features: ★
Intracellular aggregates of **TDP-43**, **SOD1**, and **FUS** proteins.

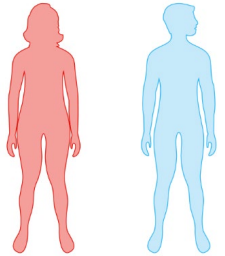


TDP-43 deposition in motor neurons



NDDs Overview: Huntington's disease (HD)

•Prevalence:
Affects **250'000-400'000 people worldwide** today (400 in Switzerland).
The prevalence of HD is expected to increase proportionally with global population growth but not exponential like AD and PD



•Male/Female Distribution:
Women: 50% of cases - **Men**: 50% of cases

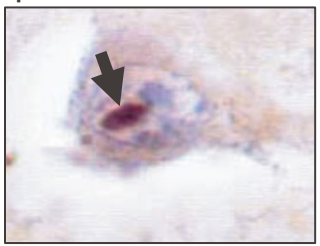
•Age of Diagnosis:
Typically: 30-50 years
Juvenile cases: 5-10 % before 20 years old

•Key Symptoms: ★
Chorea (involuntary movements), cognitive decline, psychiatric disturbances (depression, anxiety, irritability).

Saint Guy Dance

•Affected Brain Areas: ★
Primarily affects the **basal ganglia** and the **striatum** which is involved in motor control.

HTT deposition in striatal neurons



Pathological Features: ★
Intracellular aggregates of mutant **huntingtin protein** with expanded **CAG repeats**.

NDDs Overview: Origin of the diseases - wording ★

Idiopathic:

•**Definition**: A disease is termed **idiopathic** when its cause is **unknown**. The word comes from the Greek "idios," meaning "one's own," and "pathos," meaning "suffering."

•**Context in Diseases**: Many neurodegenerative diseases, like Parkinson's and ALS, have idiopathic forms, where the exact cause of the disease cannot be determined, and there is no clear genetic or environmental trigger.

Sporadic:

•**Definition**: **Sporadic** diseases occur **randomly** or **occasionally**, without a clear genetic link or pattern of inheritance.

•**Context in Diseases**: **Sporadic ALS**, for example, accounts for 90% of ALS cases, where the disease appears randomly and there is no known family history or genetic mutation involved.

Idiopathic and **sporadic** are terms often used interchangeably but have slightly different meanings, particularly in the context of disease classification.

NDDs Overview: Origin of the diseases - wording ★

Genetic:

•**Definition**: A **genetic disease** is caused by a **mutation in genes**, which may be passed down from one or both parents. These mutations can be inherited or occur spontaneously during development.

•**Context in NDDs**: Diseases like **Huntington's disease** are purely genetic, where a mutation in the **HTT gene** leads to the disease, and it is passed down through families in an autosomal dominant pattern.

Familial:

•**Definition**: A **familial disease** is one that **runs in families** and is passed down from one generation to another. Familial diseases are **inherited** and are typically caused by genetic mutations.

•**Context in NDDs**: In **familial PD** or **familial ALS**, there is a clear family history, and specific gene mutations (like **LRRK2** in Parkinson's or **SOD1** in ALS) are often the cause.

! Genetic but not always familial: A person could have a genetic disease caused by a **de novo (new)** mutation that occurred in them for the first time and not inherited from their parents. In this case, the disease is **genetic**, but not **familial**.

! Familial but not always genetic: Some diseases run in families and may be considered **familial** but not necessarily linked to a specific gene mutation.
E.g., diabetes type II, shared lifestyle habits (e.g., diet, exercise patterns) and other risk factors, like obesity, play a significant role. Environmental factors might contribute to the disease in these cases (cancers).

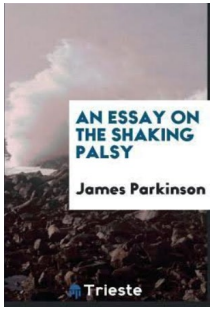
Genetic = Caused by a mutation in the DNA (can be inherited or arise spontaneously).

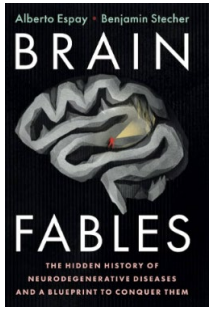
Familial = Runs in families (may be due to genetic or environmental factors, or both).

NDDs Overview: Origin of the diseases ★

NDDs	Origin and risk factor	Genetic Component	% Genetic vs. Sporadic
AD	Risk factors: Age, environmental factors (e.g., pesticides), and family history (genetic).	**Early-onset AD** is caused by mutations in the APP, PSEN1, or PSEN2 genes. Late-onset AD risk is increased by the APOE ε4 allele.	1% to 5% genetic (early-onset AD) 95% to 99% idiopathic (late-onset AD)
PD	Risk factors: Age, environmental factors (e.g., pesticides), and family history (genetic).	**Early-onset PD** is frequently associated with genetic mutations (e.g., LRRK2, PARK7, SNCA, PINK1, DJ-1) **Late-onset PD** is primarly associated with aging and environmental factor	10-15% genetic 85-90% sporadic
ALS	No clear evidence of risk factors although smoking, head trauma, and environmental exposures have been studied	**Familial cases of ALS cases** are frequently associated with the genetic mutations **C9orf72**, **SOD1**, **TARDBP**, and **FUS**.	10% genetic 90% sporadic
HD	Caused by a mutation in the HTT gene (expanded CAG repeat).	Fully genetic. Inherited in an autosomal dominant pattern = One mutated copy of the HTT gene leads to HD.	100% genetic (autosomal dominant inheritance)

Supportive literature, movies and documentaries





PD early onset

Apple TV+ CANAL+

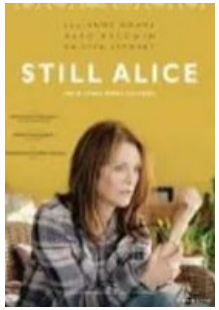
PD early onset

Gina Lupino's journey
https://www.youtube.com/watch?v=-Hmp9l9iJ0o&t=506s

PD early onset

Yves Auberson's journey
https://defi-parkinson.ch/rts-36-9-emission-avec-yves-auberson/

AD early onset



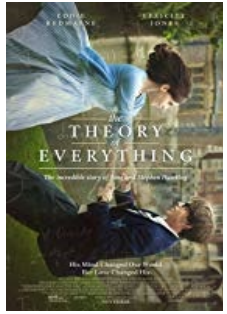
AD early onset

AD Late onset

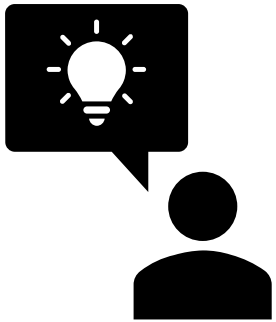
HD

https://www.youtube.com/watch?app=desktop&v=wTTq9Z2QG84

ALS



Any questions ? Or Thoughts ?



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

What did you learn so far in Bio-480?

Quizz

(Answers and questions are in the moodle – "Neurodegenerative Diseases Quiz_Introduction")

NDDs: the role of misfolded proteins – Practical exercices

See Exercices in the Moodle

Part I: “Neurodegenerative diseases quiz”

Part II: **“**Practical exercices – Main features of NDDs**”**

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

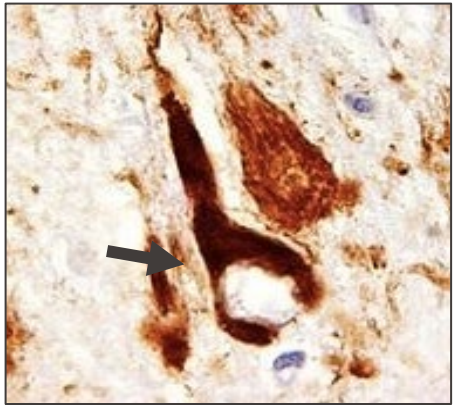
V. Spreading of pathology in the brain: the gut-brain axis hypothesis

VI. Gain-of-Function vs. Loss-of-Function hypotheses

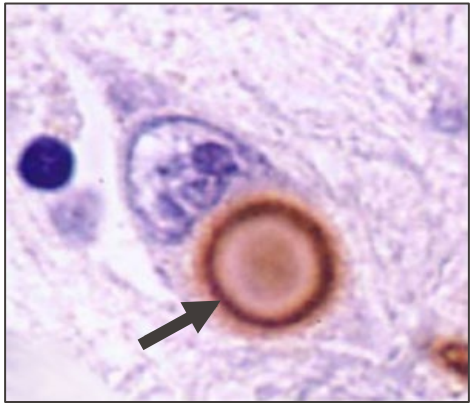
★ Key concepts to memorize

NDDs: the role of misfolded proteins ★

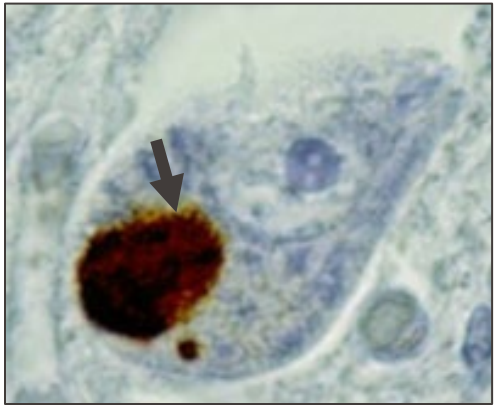
AD



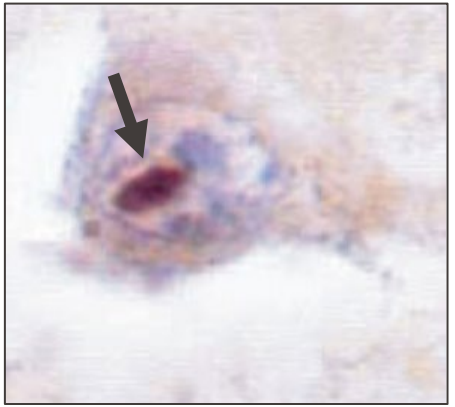
PD



ALS



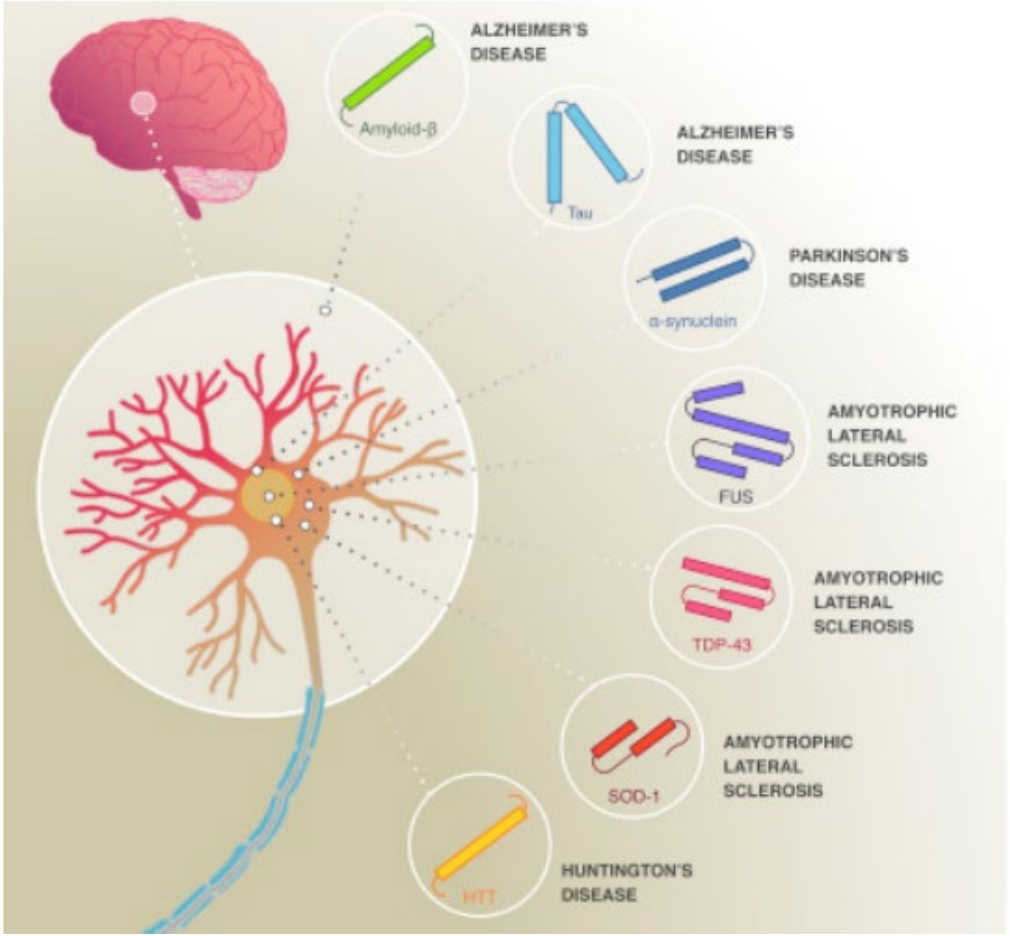
HD



Despite their differing causes, genetic backgrounds, clinical presentations, and progression, **AD**, **PD**, **HD**, and **ALS** share a key pathological feature: the **accumulation of misfolded proteins** in the brain.

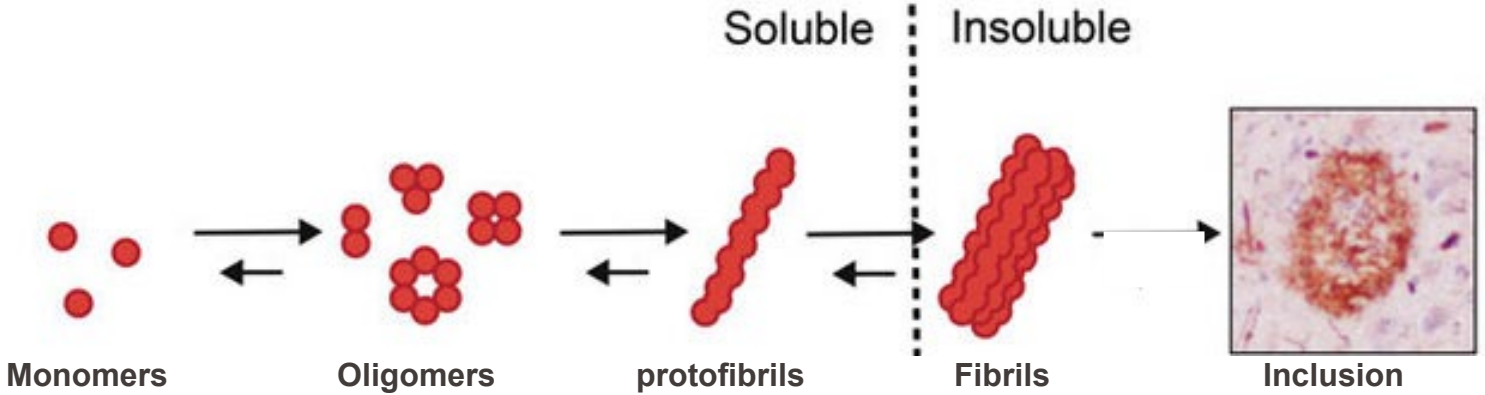
This accumulation is a **hallmark of neurodegeneration** and plays a central role in the damage to neurons in each of these diseases.

NDDs: the role of misfolded proteins ★



https://www.sciencedirect.com/science/article/pii/S0047637416300227

NDDs: the role of misfolded proteins - The aggregation pathway★



Adapted from Elisabeth Nikitidou

A **monomer** is the basic **single unit** of a protein or peptide. In its normal state, a monomer is soluble.

An **oligomer** consists of a few monomer units (usually between 2 and 20 monomers).
Oligomers are intermediate soluble structures in the protein aggregation pathway.

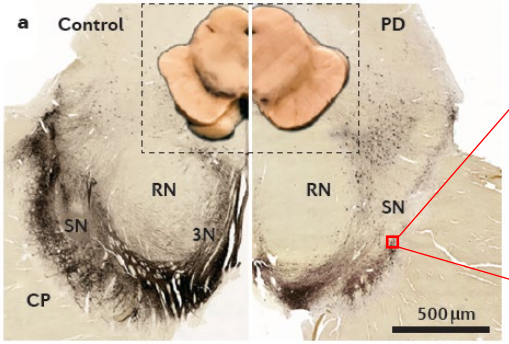
Protofibrils are intermediate structures that form during the transition from oligomers to mature fibrils.
They are **unstable aggregates** of misfolded proteins

Fibrils are **long filaments** made up of misfolded proteins arranged in a stable, **beta-sheet structure**. They are typically **insoluble** and are the hallmark structures of many neurodegenerative disease-related aggregates.

Inclusions are the **final, large aggregates** of misfolded proteins that accumulate inside or outside cells. These inclusions are typically found in the later stages of neurodegenerative diseases and can be seen under a microscope in affected brain tissues.

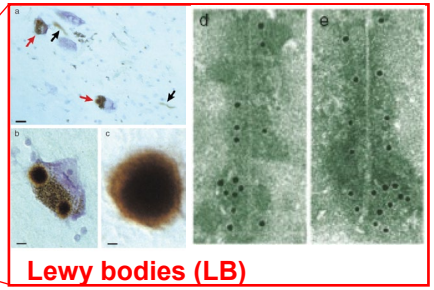
NDDs: the role of misfolded aSyn in PD

Pathological features



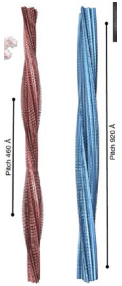
midbrain section Poewe et al., 2017

a-synuclein (aSyn) positive inclusions



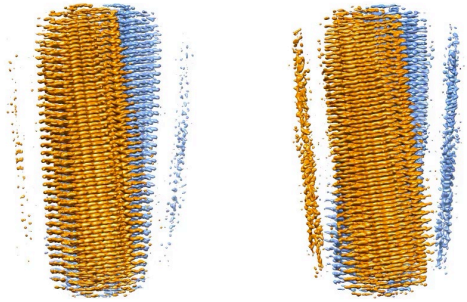
Lewy bodies (LB)

Spillantini et al., 1997



filamentous structures

Alpha-synuclein Polymorphs

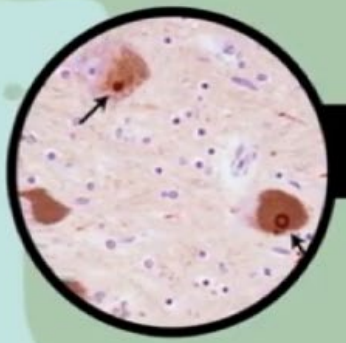


Polymorph 2a Polymorph 2b

Guerrero-Ferreira R et al., 2018, eLife.

Lewy bodies (LB), composed of aggregated alpha-synuclein (aSyn), are observed in affected dopaminergic neurons,

Structural polymorphs of aSyn fibrils (2a and 2b) demonstrate different conformations, highlighting the complexity of alpha-synuclein pathology in PD.

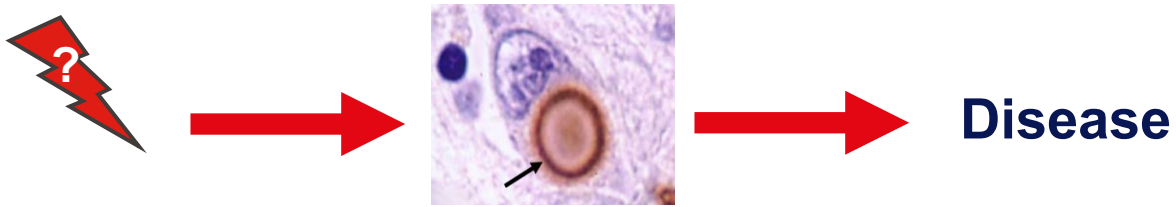


1997 α-synucléine

Présente dans les corps de Lewy

Cambridge

Lewy bodies in PD and Synucleinopathies: Cause or Consequence?



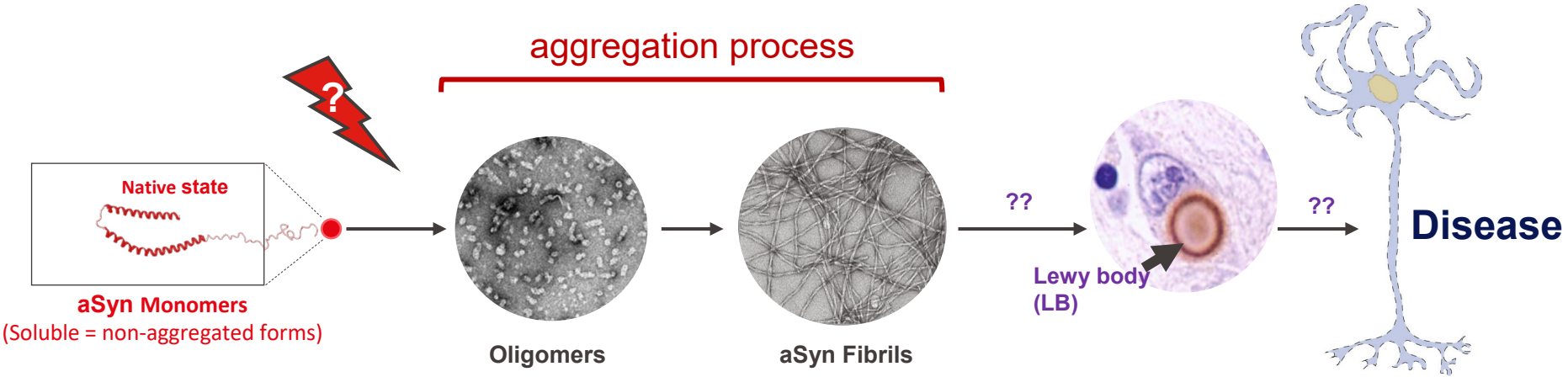
Lewy bodies

The level of LB pathology correlates with disease development, cognitive decline or disease progression and severity

Proteins aggregates are found in the brain of healthy individuals

Protein aggregates are absent in specific genetic forms of PD (LRRK2 cases)

The aggregation pathway of aSyn in PD★



1. What triggers aSyn aggregation?
2. What is the mechanism of LB formation?
3. Are LB toxic or protective or both?

The synucleinopathies: PD and associated disorders★

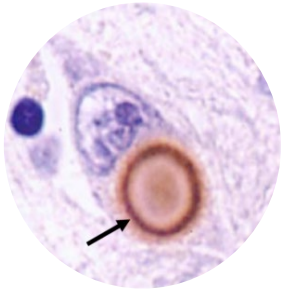
Synucleinopathies are a group of **neurodegenerative disorders** that are all characterized by the **abnormal aggregation and deposition of misfolded aSyn**.

-PD
-PD with Dementia (PDD),
-Dementia with Lewy bodies (DLB)
-Multiple System Atrophy (MSA)

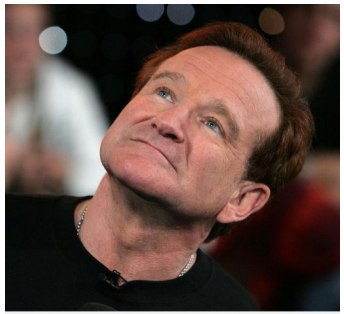
Each of these diseases affects **different brain regions, different types of cells** and involves distinct combinations of symptoms, but the common underlying pathology is the **misfolding and accumulation of aSyn.**

Same protein, different diseases

The synucleinopathies: PD and associated disorders

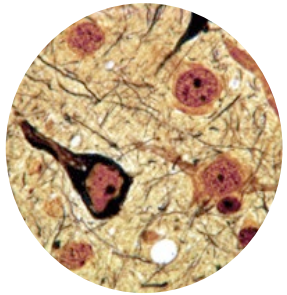


Motor symptoms
LB pathology
(PD-like disease)



Robbin Williams
(DLB)

Dementia with cognitive decline
Amyloid plaques and Tau tangles
(AD-like disease)



Symptoms:
•**Visual and delusional hallucinations**
•**Mood and behavioral Changes**: he suffered from anxiety, depression, and paranoia
•**Movement Issues**: he had symptoms similar to PD, such as tremors and a shuffling gait. This led to an initial misdiagnosis of PD before his death.

Mix of features seen in both **Alzheimer's Disease (AD)** and **Parkinson's Disease (PD)**, which is why it can sometimes be challenging to differentiate from these conditions and make a clear diagnosis. Only an autopsy can confirm which type of synucleinopathies it was.
His experience brought significant public awareness to this complex and challenging disease.

NDDs: the role of misfolded proteins –
Same protein, different diseases

NDDs	Symptoms	Primary affected Brain Areas	Protein Aggregates	Subcellular localization	Type of cells
MSA	**Motor symptoms** (tremors, rigidity, and bradykinesia) **Autonomic dysfunction** (problems with blood pressure regulation, bladder control, and breathing)	Basal ganglia, cerebellum, and brainstem	aSyn Glial like inclusion (GCIs)	Intracellular (soma)	Glial cells (oligodendroytes)
DLB	**Motor symptoms** (stiffness and tremors) **Cognitive symptoms** (memory, problem-solving, and reasoning difficulties) Hallucinations, sleep behavior disorder,	Cerebral cortex SN	aSyn Lewy body	Intracellular (soma)	Neurons
PDD	**Motor symptoms** (tremors, rigidity, and bradykinesia) **Cognitive symptoms** (memory loss, difficulty with executive functions, and visual hallucinations)	SN Cortex	aSyn Lewy body	Intracellular (soma)	Neurons

NDDs: the role of misfolded proteins – Same protein, different diseases

Yes, it is indeed **super complex**!

aSyn is the key player in multiple neurodegenerative diseases, but the clinical outcomes—whether PD, DLB, PDD, or MSA—depend on **which brain regions** and **cell types** are affected by its aggregates. The **same protein** can lead to **different diseases** due to its varying conformations, cellular targets, and the regions of the brain it impacts.

Challenges in diagnosis: The overlap in symptoms makes diagnosis difficult. Understanding the different patterns of aSyn pathology can help in distinguishing these conditions.

Targeted therapies: By understanding how and where aSyn aggregates in different diseases, researchers can work toward developing targeted therapies.
For example, treatments that prevent the spread of alpha-synuclein may slow disease progression.

See chapter IV - Why one protein can cause multiple diseases ?

What regulate protein misfolding and aggregation ? ★

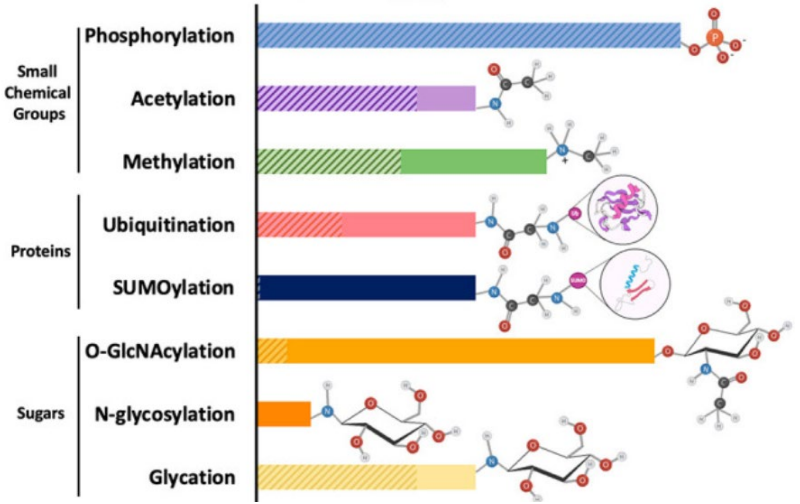
The role of the Post-Translational Modifications (PTMs)

Post-translational modifications (PTMs) play a crucial role in the **aggregation** of misfolded proteins in neurodegenerative diseases such as **AD**, **PD**, **HD**, and **ALS**.

PTMs are chemical changes made to proteins after their synthesis. PTMs can serve as **"tags"** or **signals** that direct proteins toward specific pathways, such as degradation, stabilization, or misfolding and aggregation.

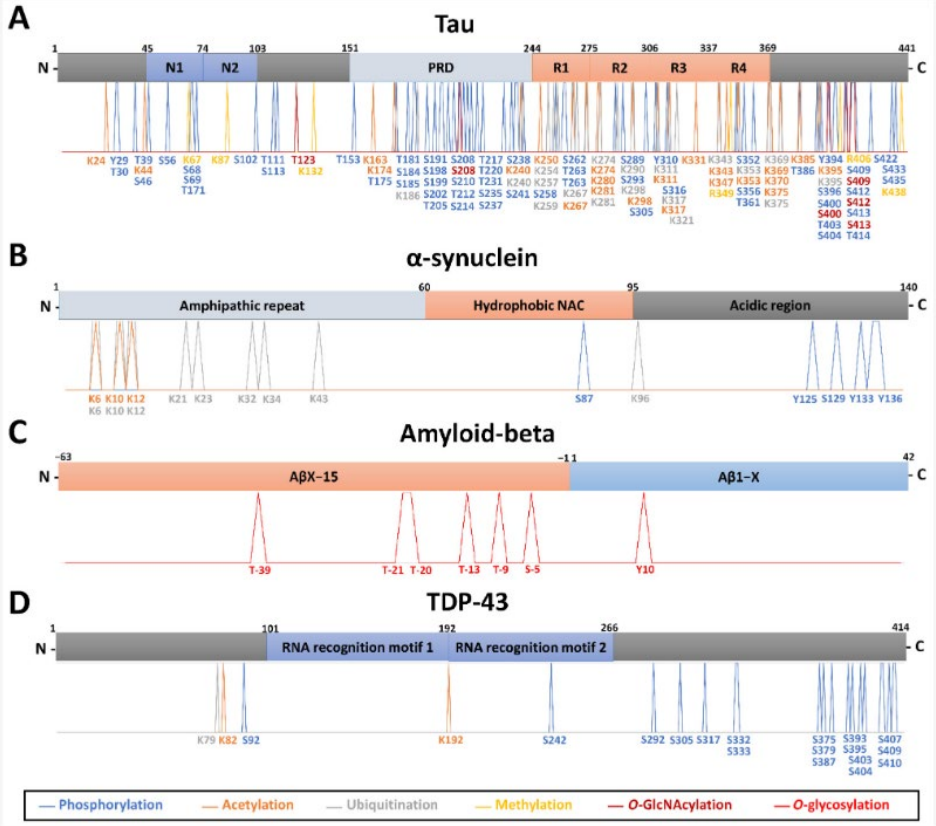
One of the most intriguing aspects of **PTMs** in neurodegenerative diseases is the fact that **multiple** PTMs can occur simultaneously on a single protein.

This introduces **extreme complexity** in how protein aggregation is regulated, as different PTMs can act in concert, antagonistically, or sequentially to modulate a protein's propensity to misfold and aggregate.



What regulate protein misfolding and aggregation ?

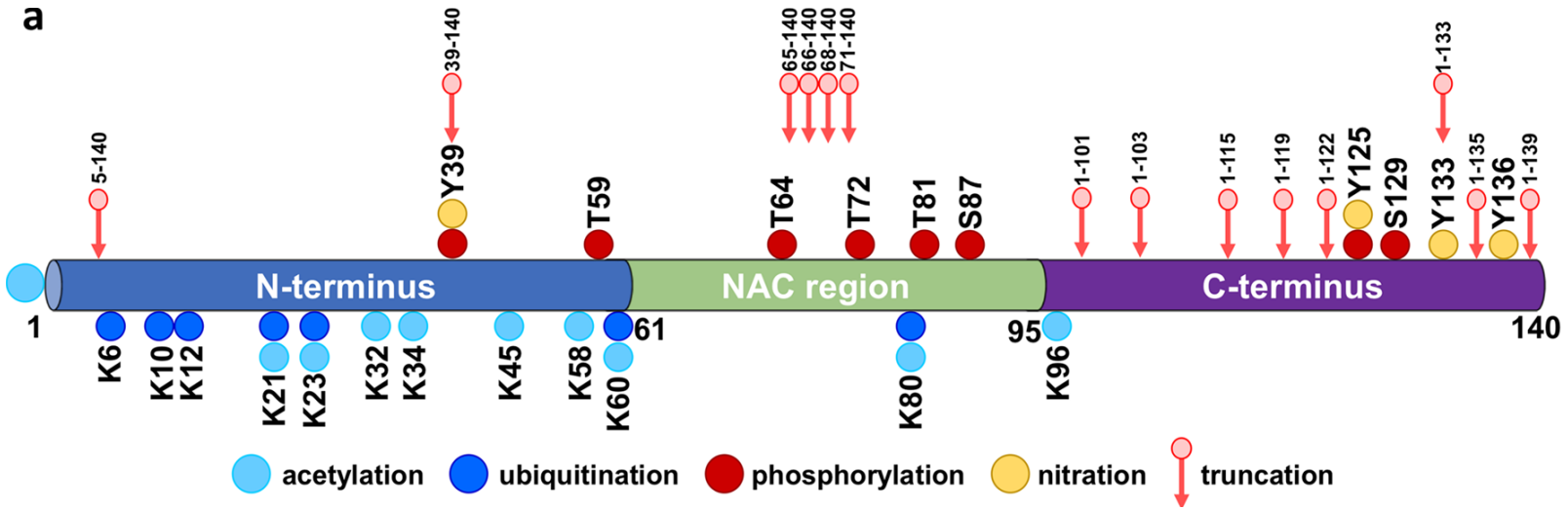
Post-Translational Modifications (PTMs) in NDDs



https://pubmed.ncbi.nlm.nih.gov/35455959/

What regulate protein misfolding and aggregation

aSyn PTMs case in PD

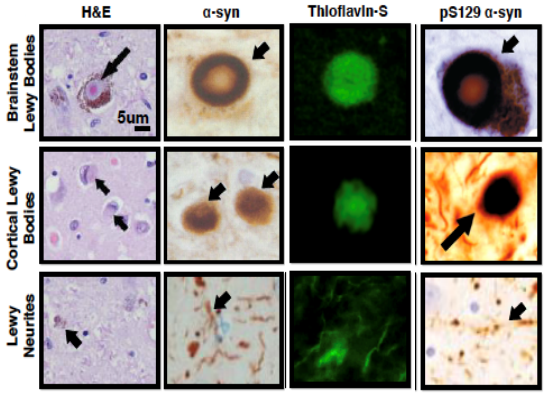


Magalhães et al, NPJ, 2022

The Lewy Bodies are more complex than we initially thought

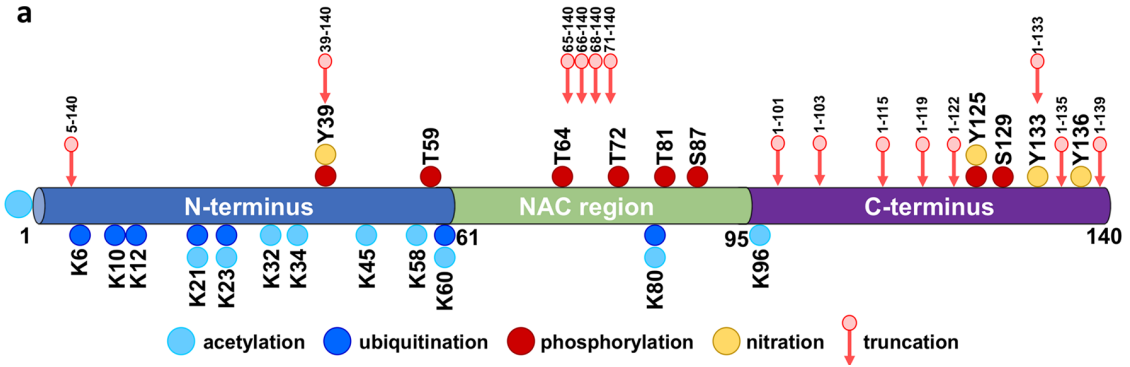
LashuelLab

Molecular markers

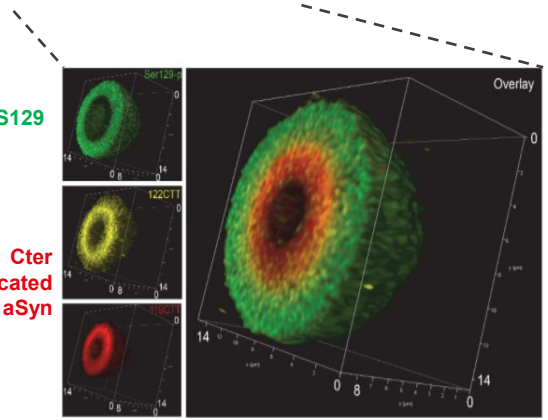


Fares B, and Lashuel HA*, Nat. Rev. Neuroscience, 2021*

β-sheet PTMs



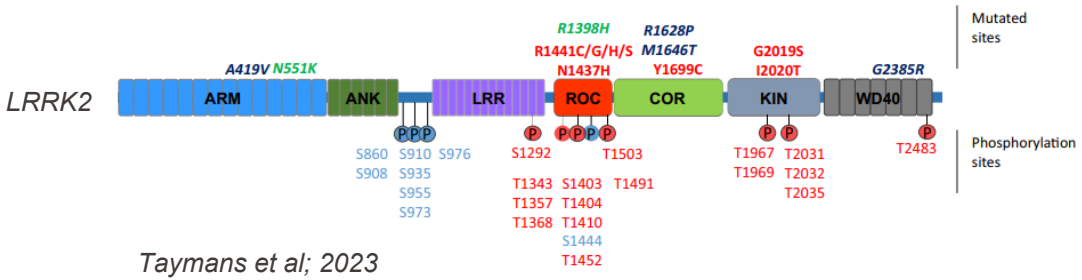
>90% of LBs are pS129+



Moors T et al., 2021

Exception to the rule: PD without LB pathology

The case or LRKK2 patients



Taymans et al; 2023

Aspect	LRRK2-Associated PD	Sporadic PD
Cause	Most common genetic mutation in LRRK2 gene	Multifactorial (environmental)
Clinical Presentation	Similar motor/non-motor symptoms	
LB pathology	Often absent	Typically present
Therapeutic Insight	Target for genetic therapies	Limited genetic targeting

Absence of Lewy Bodies in some cases:
LRRK2-associated PD cases may not show Lewy bodies, challenging the traditional neuropathology of PD.

What regulate protein misfolding and aggregation ?

PTMs in PD

PTM (site/residue)	Enzyme	Experimental model	Aggregation	Cell death	Note	Ref.
Phosphorylation						
Ser87	n.d.	Rat	Reduce	Decrease	Intranigral injection of rAAV2/6-α-syn(WT or S87A) induces α-syn aggregation and loss of DA neurons in rat, but S87E does not.	(76)
Ser87	CK1	Human brain, rat, mouse, *in vitro*	Reduce	n.d.	Phosphorylation at S87 increases conformational flexibility of α-syn.	(64)
Ser87, 129	CK1, CK2	Human brain, mouse, SH-SY5Y, *in vitro*	Reduce	n.d.	Phosphorylation at S87 inhibits α-syn fibril formation *in vitro*, but pS87-α-syn is not abundant in LB; proteasomal dysfunction increases CK2 activity, which results in elevated pS129-α-syn level.	(67)
Tyr125	Shark	Human brain, fly	Reduce	Decrease	Y125-phosphorylation of α-syn is reduced in aged human and fly brains.	(61)
Tyr125, 133, 136	SYK	Mouse, SH-N-BE, CHO	Reduce	n.d.	Syk-mediated phosphorylation prevents α-syn multimerization; Y125-α-syn is the major phosphorylation site by Syk.	(74)
Ser129	n.d.	Mouse, HEK293T	Reduce	Decrease	Prion-like progression and time to disease onset in S129E-α-syn PFFs-injected mouse are elongated.	(75)
Ser129	PLK2	Rat, HEK293T	Reduce	Decrease	S129-phosphorylation of α-syn is mediated by PLK2, and it enhances α-syn autophagic degradation.	(70)
Ser129	GRK2	Fly	Reduce	Increase	S129A-α-syn suppresses DA neuronal cell death induced by α-syn completely and increases inclusion formation; S129D-α-syn or Gprk2-mediated pS129-α-syn enhances α-syn toxicity.	(60)
Ser129	GRK6	Rat	No effect	Increase	Increased levels of pS129-α-syn enhances A53T α-syn toxicity in the rAAV-based rat model.	(62)
Tyr39	c-Abl	Mouse, SH-SY5Y, HEK293T, *in vitro*	Enhance	Increase	Deletion of c-Abl reduces α-syn aggregation and neurodegeneration in the hA53T α-syn mice; overexpression of constitutively active c-Abl accelerates α-syn aggregation and neurodegeneration in the hA53T α-syn mice.	(104)
Ser129	CK2	Human brain, *in vitro*	Enhance	n.d.	Phosphorylation of α-syn at S129 promotes fibril formation *in vitro*.	(57)
Ser129	DAPK1	SH-SY5Y, MEF	Enhance	Increase	DAPK1 plays an important role in stimulating toxic α-syn aggregation and neuronal cell death.	(71)
Ser129	CK2	SH-SY5Y	Enhance	n.d.	H_2O_2 induces S129-phosphorylation of α-syn and the inclusion formation.	(66)
Ser129	GRK2	Fly	Enhance	Increase	Co-expression of Gprk2 with α-syn increases α-syn aggregation; S129A-α-syn reduces α-syn toxicity; S129D-α-syn enhances α-syn toxicity.	(61)
Ser129	CK1	Fly	Enhance	Increase	CK1-mediated S129-phosphorylation of α-syn increases the aggregation.	(65)
Ser129	PLKs	Mouse, SH-SY5Y	Enhance	Increase	METH treatment increases PLK2 and pS129-α-syn levels, the aggregation, and apoptosis; BI2536, pan-PLK inhibitor, treatment reduces S129-phosphorylation of α-syn, the aggregation, and apoptosis, induced by METH.	(69)
Ubiquitination						
N-terminal	UBE2W	*In vitro*	Reduce	n.d.	N-terminal ubiquitination and the proteasome may together disturb α-syn aggregate formation.	(85)
Lys6	n.d.	*In vitro*	Reduce	n.d.	Ubiquitination at K6 results in prominent inhibition of α-syn fibril formation.	(83)
Lys6, 12, 21, 32, 34, 43, 96	n.d.	*In vitro*	Reduce	n.d.	Disulfide-directed ubiquitination at K32C, K34C, K43C or K96C strongly inhibits α-syn aggregation; disulfide-directed ubiquitination at K6C, K12C, or K21C inhibits α-syn aggregation; disulfide-directed ubiquitination at K10C or K23C may not inhibit α-syn aggregation.	(82)

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Yoo et al., 2022

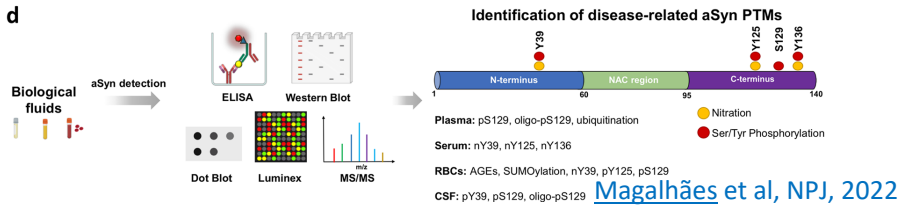
An example of the PTMs complexity….. To be continued for 3 extra pages !

PTMs as biomarkers of NDD - Case of aSyn in PD ★

Biomarkers are measurable indicators of a biological process, condition, or disease.
In NDDs, biomarkers could help with **early diagnosis** before the appearance of clinical symptoms

	Peripheral Tissues						Brain	Bodyfluids		
	Submandibular gland	Esophagus	Stomach	Colon	Skin	Appendix		CSF	Plasma/Serum	RBCs
Acetylation	-	-	-	-	-	-		-	-	
AGEs	-	-	-	-	-	-		-	-	
SUMOylation	-	-	-	-	-	-		-	-	
Ubiquitination	-	-	-	-	-	-		-		X
nY39	-	-	-	-	-	-		X		
pY39	-	-	-	-	-	-			-	-
pS87	-	-	-	-	-	-		-	-	-
nY125	-	-	-	-	-	-		X		-
pY125	-	-	-	-	-	-		-	-	
nY133	-	-	-	-	-	-		-	-	-
nY136	-	-	-	-	-	-		X		-
Truncation	-	-	-	-	-			-	-	
pS129										

- detected by MS approaches; - detected by antibody-based approaches; - detected by both; "-" – not studied; "X" – not detected

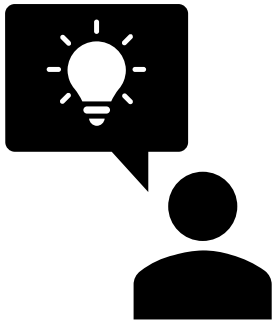


Magalhães et al, NPJ, 2022

Given the strong association between PTMs and protein aggregation, specific PTM patterns could be used to detect abnormal protein states and provide clues about disease stage and severity.

- *More on the biomarkers in the class of the 11/11*

Any questions ? Or Thoughts ?



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

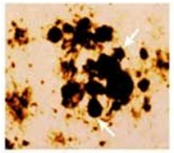
IV. The prion-like hypothesis

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

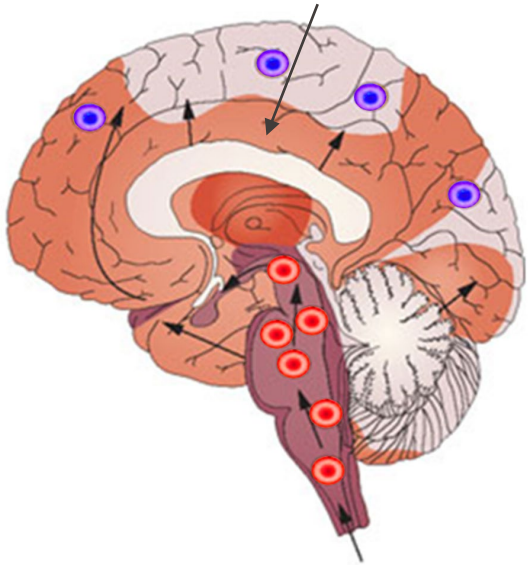
VI. Gain-of-Function vs. Loss-of-Function hypotheses

★ Key concepts to memorize

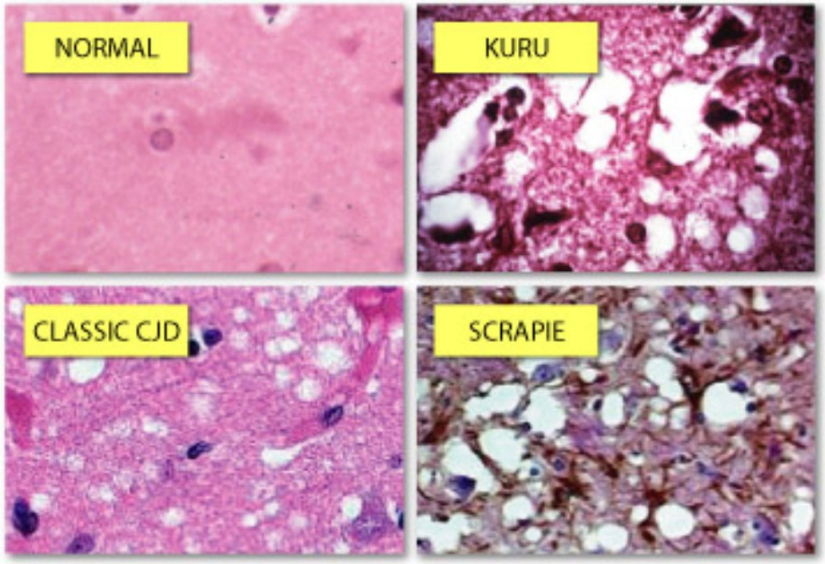
What are the Prion diseases?



Prion Diseases



Creutzfeldt-Jakob disease (vCJD) (human)
Kuru disease (human)
Bovine spongiform encephalopathy (BSE) (Mad cow)
Scrapie (goat, sheep)



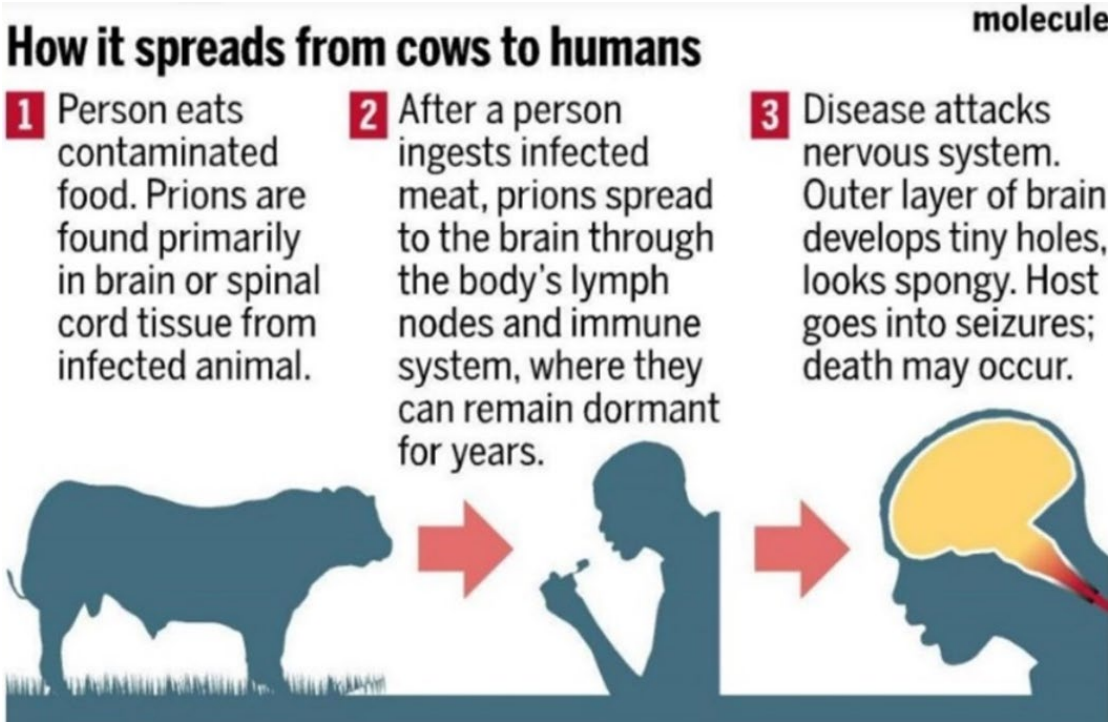
What are the Prion diseases?

What are the Prion diseases?

https://www.bbc.co.uk/programmes/articles/2KbBSZ89QSnkSzK4RFy9PPF/the-cows-are-mad-ten-things-we-learned-about-mad-cow-disease

Between 1997 and 1999, the UK banned the sale of beef on the bone. Following an announcement in 1996, the European Union imposed a global ban on British beef exports. This was in response to a fatal neurological disease in cows that also affected humans. Decades later, scientists and activists still seek answers about the origins of Mad Cow Disease and how it spreads to humans.

What are the Prion diseases?



What are the Prion diseases?

Imperial Journal of Interdisciplinary Research (IJIR)
Vol-3, Issue-4, 2017
ISSN: 2454-1362, http://www.onlinejournal.in

Bio - Cultural Analysis of Kuru Diseases in Australian Tribe

Delliswararao. Konduru[1] , Chongneikim Hangsang[2] &
Madhu Sudhanarao. T[3]
1M.COM, M.A, (P.HD), PROJECT SCIENTIST "B" (N.M), NIE (I C M R).
2M.A (ANTHROPOLOGY)
3M.Sc. (ANTHROPOLOGY)

Kuru, the First Human Prion Disease †

by Paweł P. Liberski [1,*], Agata Gajos [2], Beata Sikorska [1] and Shirley Lindenbaum [3]

[1] Laboratory of Electron Microscopy and Neuropathology, Department of Molecular Pathology and Neuropathology, Medical University Lodz, 90-419 Lodz, Poland

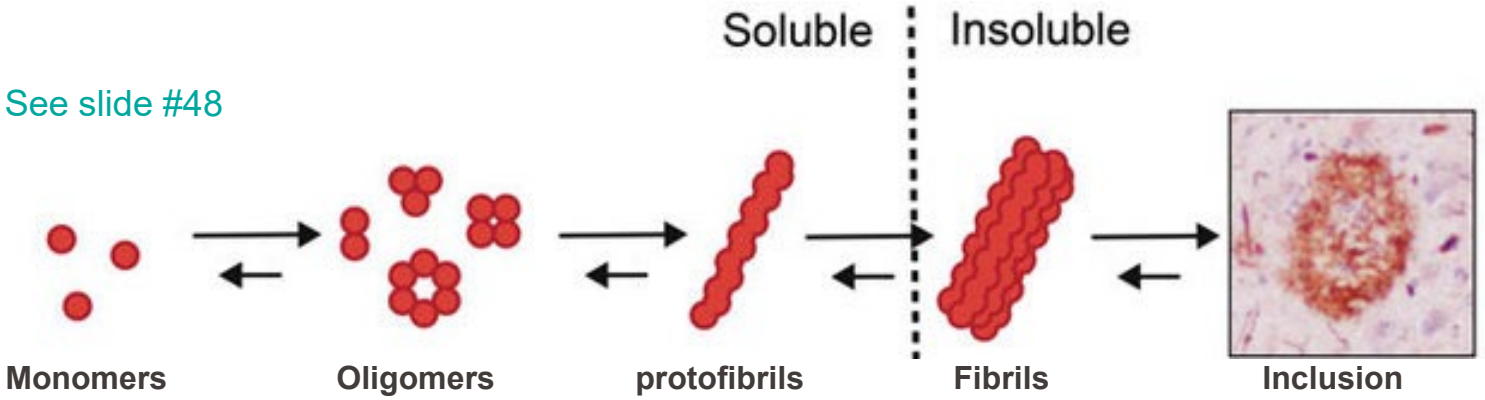
Child with advanced kuru.
He is unable to walk or
sit upright without assistance

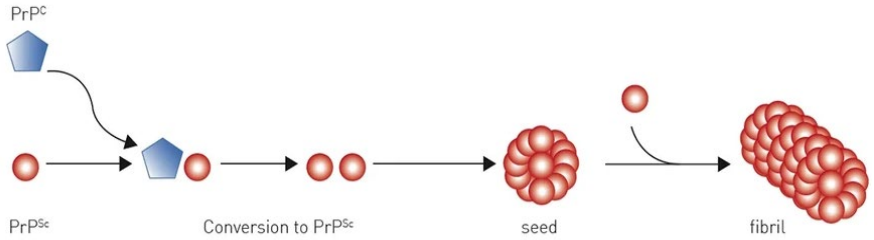
Kuru is a rare and fatal neurodegenerative prion disease that once affected the Fore people of Papua New Guinea. It caused **tremors**, **loss of coordination**, and **severe brain damage**.
Kuru spread through ritualistic **cannibalism**, where people consumed the brains of deceased relatives.
It is incurable and primarily affected women and children.

The Kuru epidemic sharply declined over 50 years, with annual deaths dropping from 200 in 1957 to zero by 2010. This decline followed the end of ritualistic cannibalism among the Fore people, which had been the primary cause of transmission.

What are the Prion diseases?

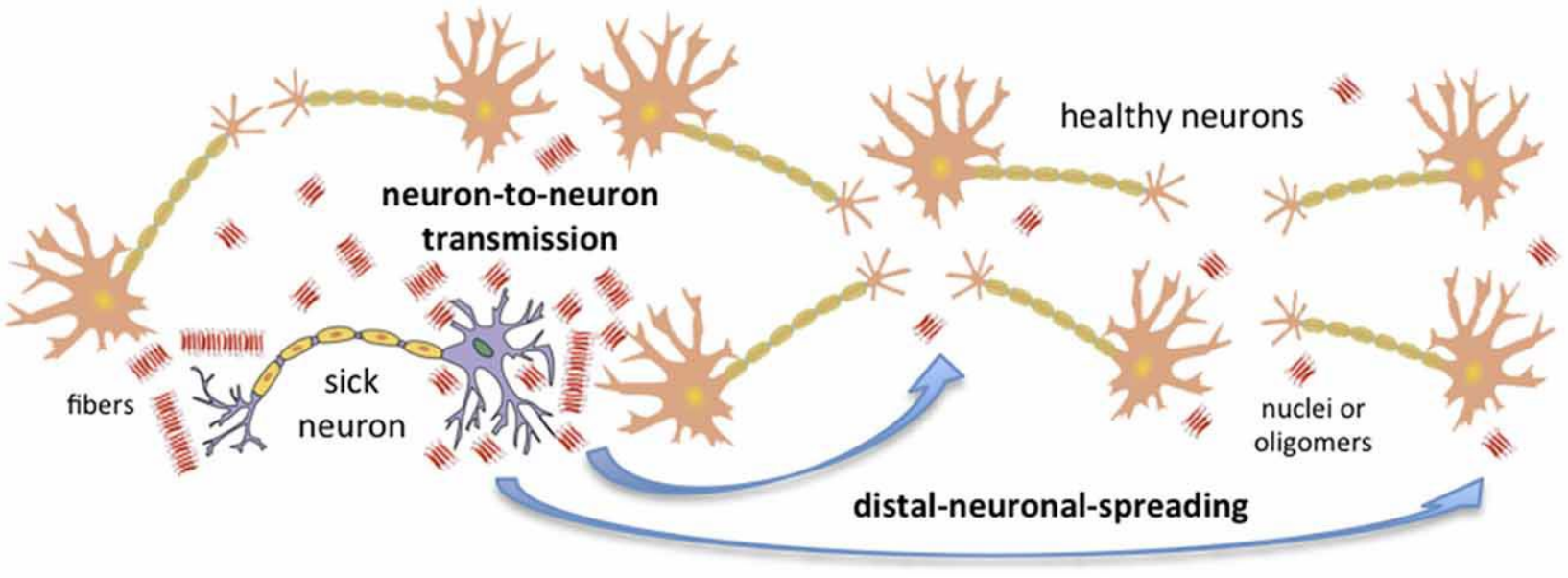
See slide #48





Wild-type PrPC prion protein is converted to the pathological PrPSc prion protein isoform by a PrPSc template. PrPSc prion protein isoforms aggregate to form amyloid fibres.

How do prion diseases spread throughout the brain?



https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2016.00029/full

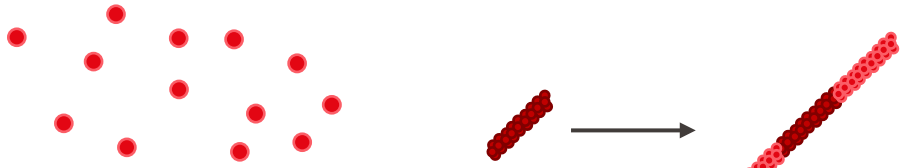
How do prion diseases spread throughout the brain? ★

Criteria	Virus	Prion
Infectivity	High Requires host cells to replicate	Low Requires host cells to replicate by inducing endogenous protein to misfold
Genetic	DNA or RNA	No genetic material, just protein
Transmission	Bodily fluids, air, contact	Contaminated tissue, especially brain
Transmission inter-Species	Common, infects multiple species	Rare, but possible (e.g., Mad Cow Disease, Kuru disease)
Prevalence	Very common e.g., flu, COVID-19	Rare mostly neurodegenerative disorders
Outcome	Varies, some curable, some fatal	Always fatal, no cure

Prion vs Prion-like proteins

Definitions, shared features and differences

	Neurodegenerative Diseases	
Criteria	Prion diseases	Prion-Like diseases
Proteins involved	Scrapie prion protein (PrP^{Sc})	alpha-synuclein, Tau, TDP43, Tau, HTT…..
Associated with a Proteinopathy	Transmissible spongiform encephalopathies (TSEs) Creutzfeldt-Jakob disease (vCJD) Kuru disease Bovine spongiform encephalopathy (BSE)	Parkinson's Disease Alzheimer's Disease Huntington's Disease ALS Disease
Seeding Mechanism	✓	✓



aSyn Monomer
(Soluble = Non-aggregated form)

Alpha-synuclein
Aggregates = seeds

Prion vs Prion-like proteins

Definitions, shared features and differences

	Neurodegenerative Diseases	
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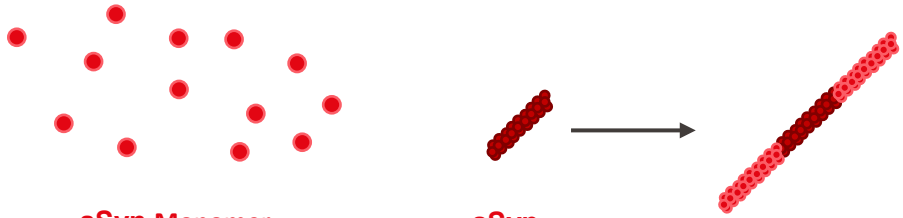
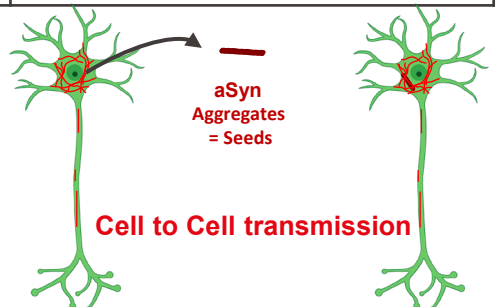
Seeding Mechanism	✓	✓
Cell-to-cell transmission and spreading	✓	✓

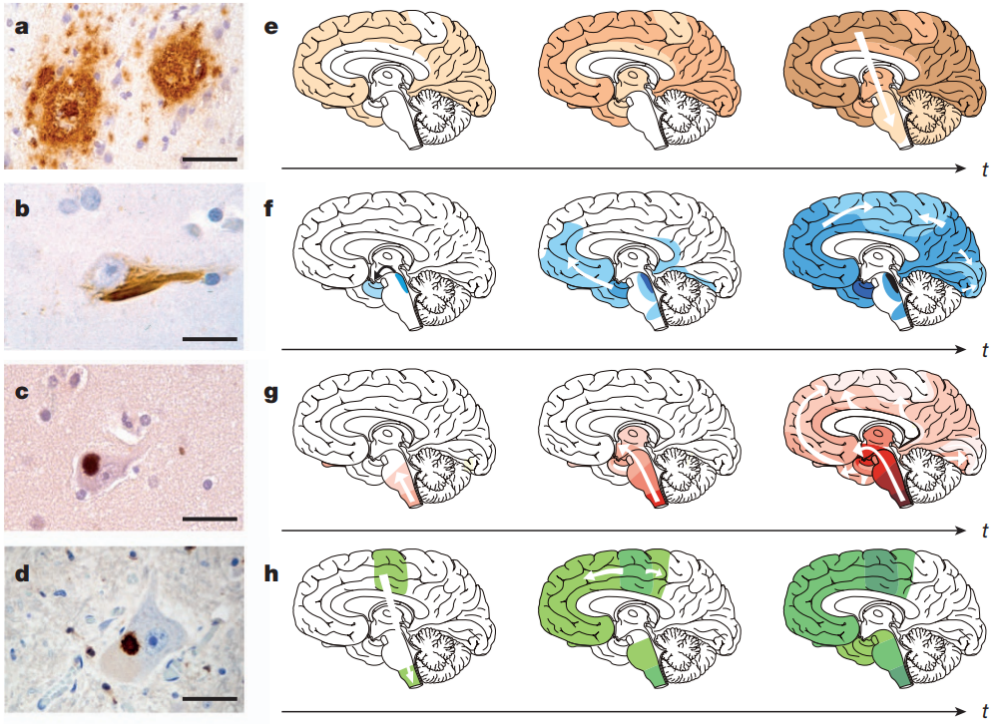




Prion-like diseases: Evidence of Spreading in human brain tissues

Self-propagation of pathogenic protein aggregates in neurodegenerative diseases

Mathias Jucker[1,2] & Lary C. Walker[3,4]



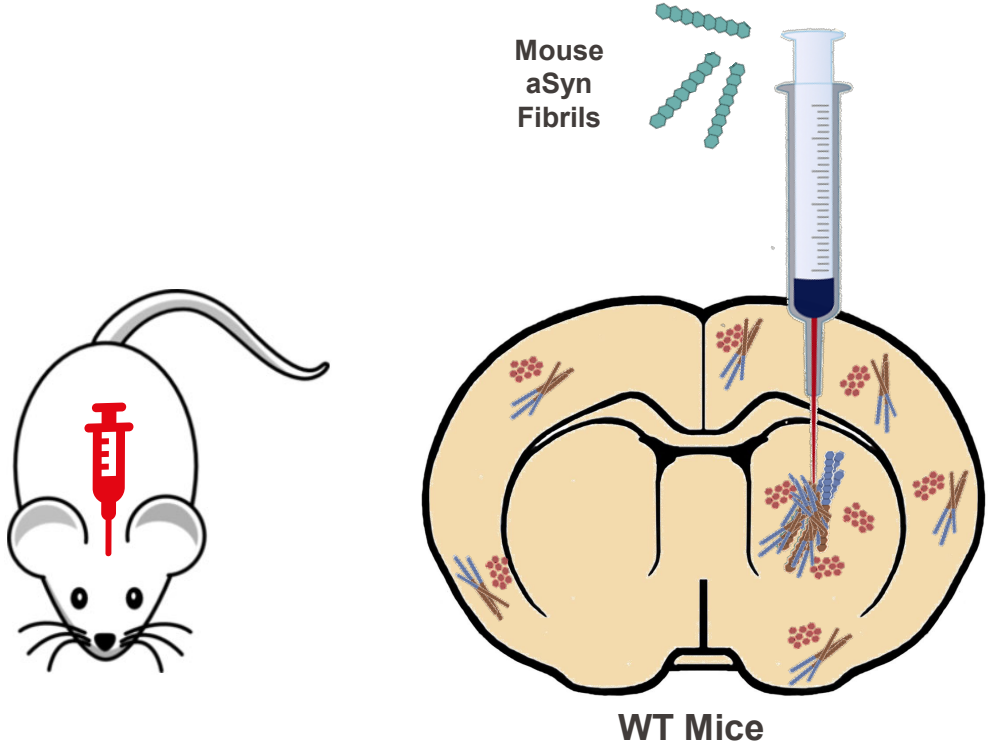
AD
(amyloid β plaques)

AD
(Tau inclusions)

PD
(aSyn)

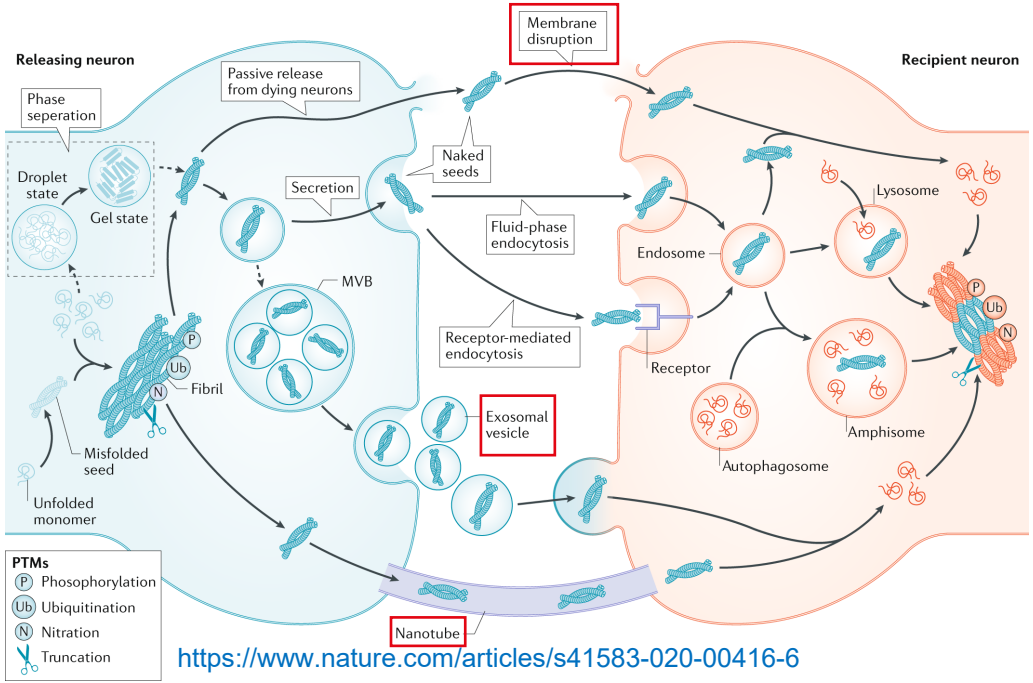
ALS
(TDP-43)

Prion-like diseases: Evidence of Spreading in animal models



Seeding and spreading throughout the brain cause disease **progression**

Prion-like diseases: Routes of Spreading



https://www.nature.com/articles/s41583-020-00416-6

★ **Routes of spreading**: Misfolded proteins, such as prions and prion-like proteins, can spread from one neuron to another through several cellular pathways, contributing to disease progression.

- **Exosomes**: Tiny vesicles released by cells that carry misfolded proteins like Tau or α-Synuclein, allowing these proteins to travel to and infect neighboring cells.
- **Nanotubes**: Direct, tube-like structures connecting two cells, enabling the transfer of misfolded proteins across cells without needing to be released into the surrounding space.
- **Exocytosis species**: Misfolded proteins are packaged inside vesicles and released from one cell via exocytosis. These released proteins can then be taken up by surrounding cells, continuing the spread of pathology.

Prion vs Prion-like proteins

Definitions, shared features and differences

	Neurodegenerative Diseases	
Criteria	Prion diseases	Prion-Like diseases
Proteins involved	Scrapie prion protein (PrP^{Sc})	alpha-synuclein, Tau, TDP43, Tau, HTT…..
Associated with a Proteinopathy	Transmissible spongiform encephalopathies (TSEs) Creutzfeldt-Jakob disease (vCJD) Kuru disease Bovine spongiform encephalopathy (BSE)	Parkinson's Disease Alzheimer's Disease Huntington's Disease ALS Disease
Seeding Mechanism	✓	✓
Cell-to-cell transmission and spreading	✓	✓
Infectivity	✓	?
Transmission between Human-Human or Human/Animals	✓	?

Prion-like diseases:
No evidence of interspecies or Human to Human **transmissions**

Prion diseases

CREUTZFELDT-JAKOB DISEASE AFTER ADMINISTRATION OF HUMAN GROWTH HORMONE

John Powell-Jackson [a], Philip Kennedy [b], E.M. Whitcombe [d], R.O. Weller [b], M.A. Preece [c], John Newsom-Davis [d]

Potential Epidemic of Creutzfeldt–Jakob Disease from Human Growth Hormone Therapy

Paul Brown, M.D., D. Carleton Gajdusek, M.D., C.J. Gibbs, Jr., Ph.D., and David M. Asher, M.D.

1. **CJD can be transmitted between Cow/Human (public health crisis in 80's).**

2. Humans/Humans transmission has been demonstrated based on the data from the use of post-mortem human pituitary extracts to treat thousands of children with growth hormone deficiency from 1958 to 1985

Prion-like diseases

Evaluation of Potential Infectivity of Alzheimer and Parkinson Disease Proteins in Recipients of Cadaver-Derived Human Growth Hormone

David J. Irwin, MD; Joseph Y. Abrams, MPH; Lawrence B. Schonberger, MD, MPH; et al

1. John Trojanowski Group in collaboration with the Centre for Disease Control and Prevention (USA), found **no similar reports** of the transmission of PD, AD, ALS or FTLD to this cohort, a small number of whom developed CJD ~20 years after treatment.

2. Human growth hormone (c-hGH) recipients had **no transmitted Prion-like pathology (AD or PD)**

Prion-like diseases:
No evidence of interspecies or Human to Human **transmissions**

Pathological alpha-synuclein propagates through neural networks

Masami Masuda-Suzukake[1], Takashi Nonaka[1], Masato Hosokawa[2], Maki Kubo[1], Aki Shimozawa[1], Haruhiko Akiyama[2] and Masato Hasegawa[1*]

aSyn pathology was **not induced** in WT mice **by oral inoculation** of even large amounts of synthetic aSyn fibrils **(400 µg)** at 6 or 14 months

Prion vs Prion-like proteins

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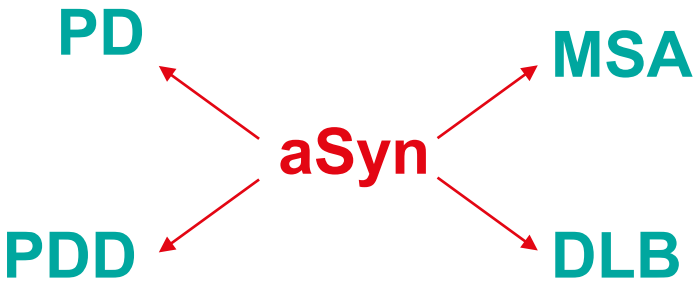
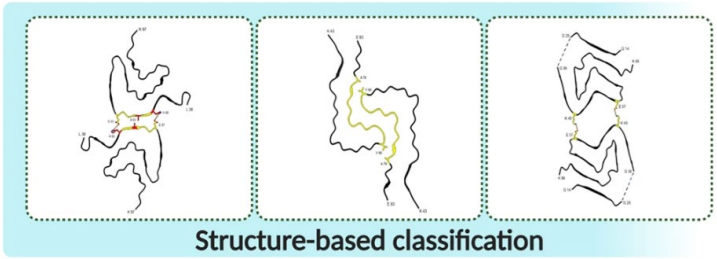
Seeding Mechanism	✓	✓
Cell-to-cell transmission and spreading	✓	✓
Infectivity	✓	X
Transmission between Human-Human or Human/Animals	✓	X

Prion-like diseases - How a same prion-like proteins can give different diseases?

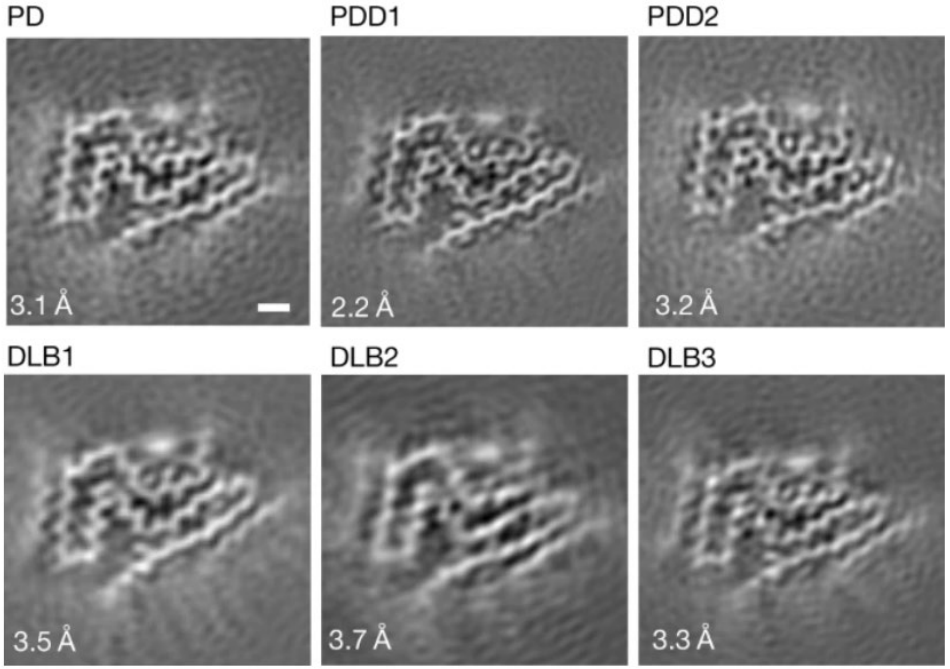
The case of aSyn





Magalhães et al, NPJ, 2022

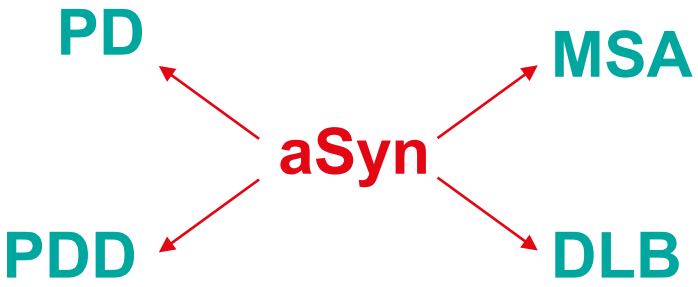
Fig. 1: Cryo-EM cross-sections of α-synuclein filaments (Lewy fold).

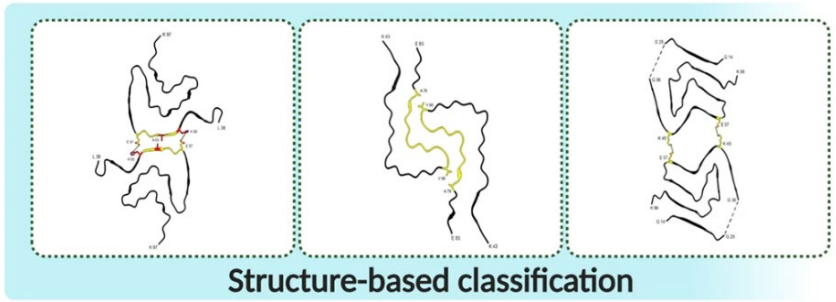


Yang et al, Nature, 2022

Prion-like diseases - How a same prion-like proteins can give different diseases?

The case of aSyn





Magalhães et al, NPJ, 2022

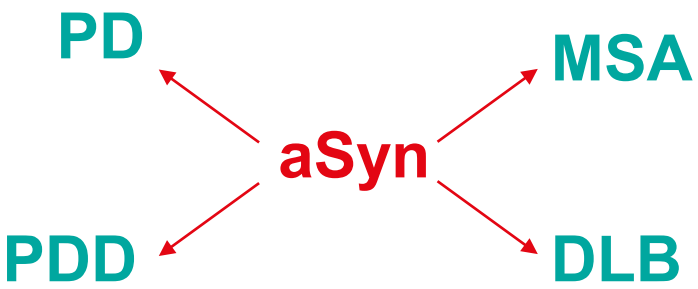
• **aSyn strains**: aSyn can misfold into different **structural strains** (recently identified by Cryo-EM).

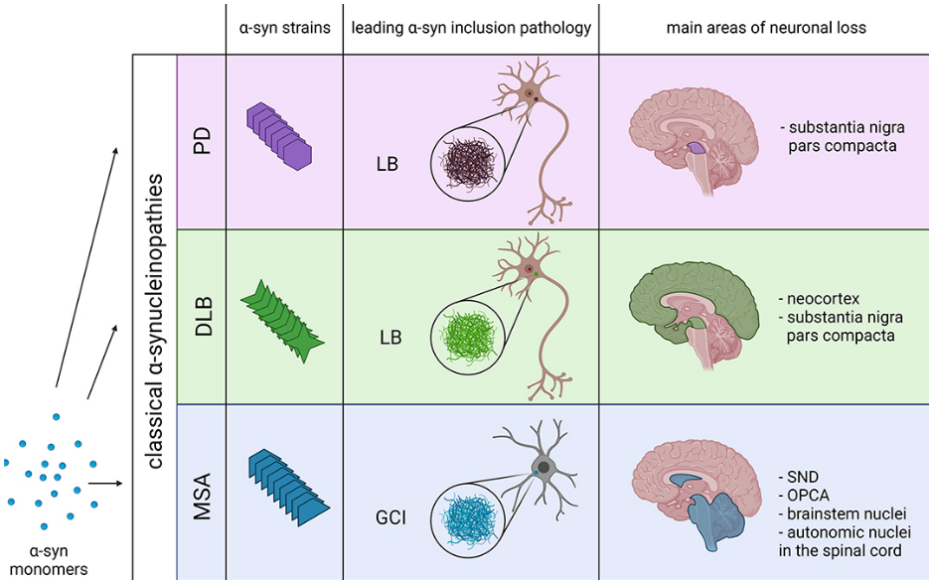
• **Cellular environment**: The biochemical environment influences which **aSyn strain** forms, contributing to **disease heterogeneity**.

• Each strain has **unique properties** of :
Aggregation kinetics (how quickly the misfolded proteins form clumps)
Cellular vulnerability (how they affect specific brain regions or specific cell types)
Toxicity (how damaging the strain is to neurons)

Prion-like diseases - How a same prion-like proteins can give different diseases?

The case of aSyn





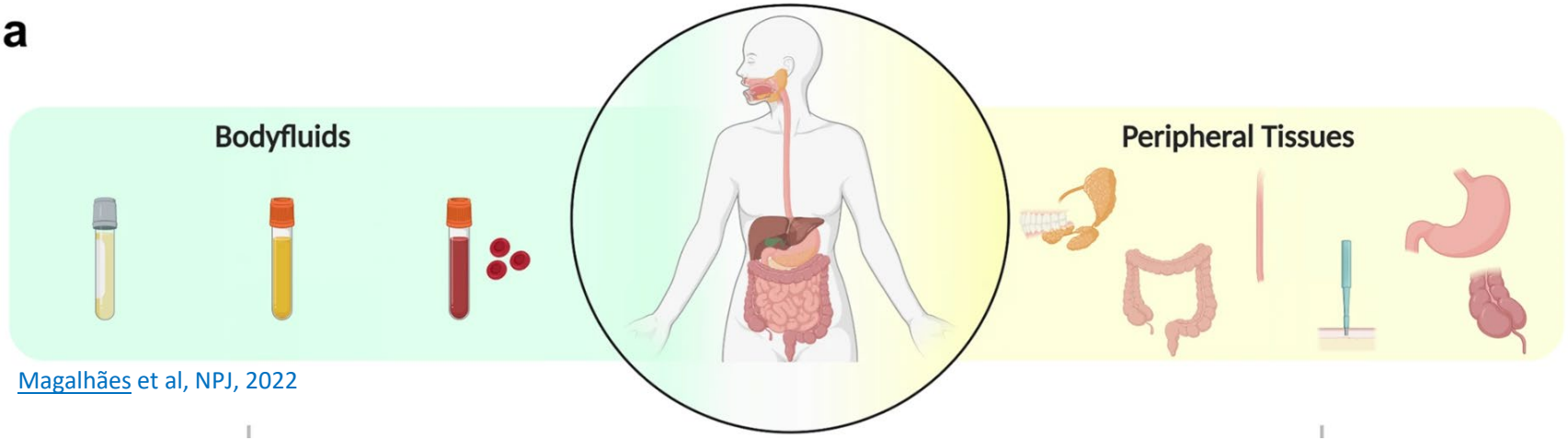
https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.737195/full

- In **PD**, aSyn aggregates primarily in the **substantia nigra**, leading to motor symptoms.
- In **DLB**, aggregates are widespread in both the **cortex** and **limbic areas**, affecting cognition and causing hallucinations.
- In **MSA**, the protein accumulates in **oligodendrocytes** (glial cells), affecting the autonomic nervous system and motor control.

These distinct strains may explain why aSyn-related disorders (like PD, DLB, and MSA) exhibit **different clinical symptoms**, **pathological patterns, and rates of progression, despite being driven by the same protein.**

Prion-like diseases - How a same prion-like proteins can give different diseases?

Therapeutical implications



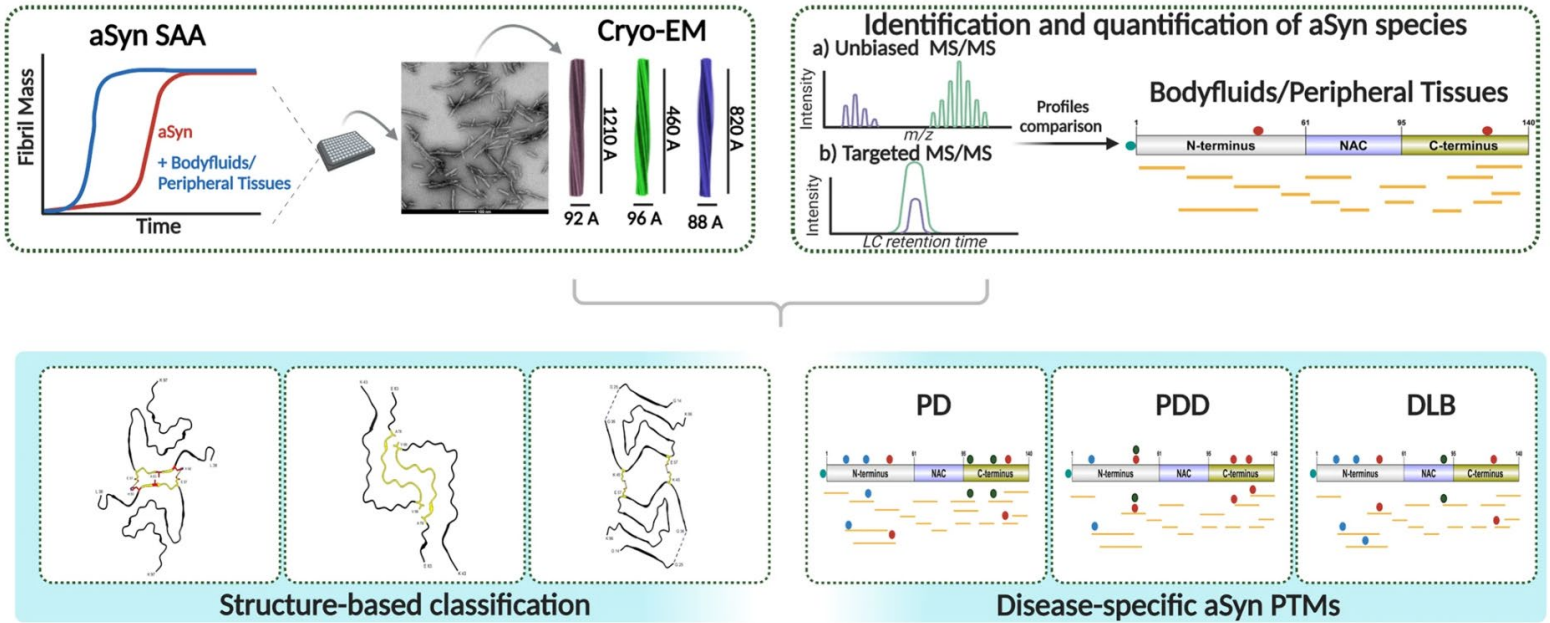
Magalhães et al, NPJ, 2022

aSyn **strains** spread in the body, providing important insight into **early diagnosis** of PD and other **synucleinopathies**. Misfolded aSyn strains can be detected in **body fluids** (e.g., cerebrospinal fluid, blood, saliva, urine) and **peripheral tissues** (e.g., gastrointestinal tract, skin, appendix), which are accessible for diagnostic testing.

Early diagnosis: Detecting specific aSyn strains in body fluids or peripheral tissues could serve as a **biomarker** for early detection of synucleinopathies before severe neurological damage occurs.

Prion-like diseases - How a same prion-like proteins can give different diseases?

Therapeutical implications



Magalhães et al, NPJ, 2022

Strain-specific detection: Different **aSyn strains** exhibit distinct properties in terms of aggregation kinetics, PTMs signature, toxicity, and affected brain regions. By distinguishing between these strains in peripheral tissues or fluids, clinicians could potentially **differentiate between synucleinopathies**, such as PD, MSA, and DLB. This could lead to more **accurate and personalized diagnosis**.

Prion vs Prion-like proteins

Definitions, shared features and differences★

1. Misfolding:
Definition: The abnormal structural change in a protein from its normal conformation to a pathological, disease-causing form. Misfolding is a hallmark of prion diseases and prion-like proteinopathies.
Applies to: **Both prions and prion-like proteins**. For example, in prion diseases, PrP misfolds into a prion form, while in AD, Tau misfolds into tangles, and in PD, aSyn misfolds into Lewy bodies.

2. Templating:
Definition: A mechanism where misfolded proteins act as a template to induce normal proteins to adopt the same abnormal structure. This is a central process in how prions replicate.
Applies to: **Both prions and prion-like proteins**. Misfolded aSyn, Tau, and TDP-43 can also template normal proteins into the same misfolded state, as seen in neurodegenerative diseases like AD, ALS, and PD.

3. Seeding:
Definition: The process where small aggregates of misfolded proteins (seeds) initiate the misfolding of normal proteins. These seeds act as a catalyst for the rapid aggregation and spread of misfolded proteins.
Applies to: **Both prions and prion-like proteins**. In prions, small prion aggregates serve as seeds that accelerate the misfolding of normal prion proteins (PrPC). Similarly, prion-like proteins such as Tau, aSyn, and TDP-43 can form seeds that promote the misfolding and aggregation of these proteins, contributing to neurodegenerative diseases like AD or PD.

Prion vs Prion-like proteins

Definitions, shared features and differences★

4. Spreading:
Definition: Refers to the movement of misfolded proteins within an organism, often starting from one site (such as the digestive system or nervous tissue) and spreading to other parts, particularly the brain.
Applies to: **Both prions and prion-like proteins**. For example, in PD, misfolded aSyn is known to spread between neurons, similar to how prions spread in prion diseases.

5. Propagation:
Definition: The process by which misfolded proteins multiply within the body. In prions, this involves converting normal proteins into the misfolded, infectious form.
Applies to: **Both prions and prion-like proteins**. For instance, in AD, misfolded Tau can propagate and spread misfolding to healthy Tau proteins, just as prions propagate by recruiting normal proteins.

Prion vs Prion-like proteins

Definitions, shared features and differences★

6. Transmission (inter-species):

Definition: The process of passing misfolded proteins between organisms, often through exposure to contaminated tissues (e.g., brain tissue) or bodily fluids. In prion diseases, this can occur through food, medical instruments, or inherited mutations.

Applies to: **Primarily prions**. While transmission is well-documented in prions (e.g., Mad Cow Disease to humans), there is limited or no evidence that prion-like proteins like Tau or α-Synuclein can transmit between organisms in natural conditions, although some experimental settings suggest this may be possible.

7. Infectivity:

Definition: Refers to the ability of a disease-causing agent to invade, replicate, and spread within a host. In prions, infectivity refers to the ability of misfolded prions to spread between cells and even between organisms.

Applies to: **Primarily prions**. Prions are highly infectious and can spread through direct contact with infected tissues or fluids (e.g., through contaminated food or surgical instruments). Prion-like proteins, on the other hand, generally do not spread between organisms, although they can spread within an organism from one brain region to another (e.g., aSyn in PD). However, prion-like proteins do not exhibit the same infectious potential across species as prions do.

In summary, **infectivity** is a major difference, as prions are capable of transmitting and causing disease between organisms, while prion-like proteins mainly spread within the brain and nervous system but are not naturally infectious between individuals.

Prion vs Prion-like proteins

Definitions, shared features and differences★

8. Strains:

Definition: Variants of misfolded proteins that differ in their biochemical properties, such as structure, infectivity, and disease progression, despite being composed of the same protein. Strains can cause different patterns of disease.

Applies to: **Both prions and prion-like proteins**. Prions exhibit well-characterized strains that lead to different forms of disease with varying severity (e.g., different strains of CJD). Emerging evidence suggests that prion-like proteins, such as Tau and aSyn, may also form distinct strains, which could explain variations in clinical presentations of diseases like AD, PD and ALS.

Prion vs Prion-like proteins ★
Conclusions

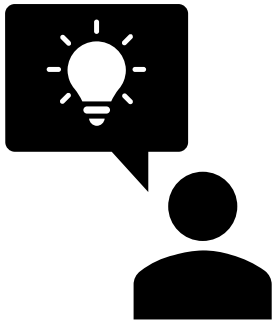
While **infectivity and interspecies transmission** is primarily a feature of prions, the other processes—**spreading**, **propagation**, **templating**, **misfolding**, **nucleation**, and **seeding**—are common to both prions and prion-like proteins involved in neurodegenerative disorders.

Prion vs Prion-like proteins
Practical exercices

See word documents in the Moodle

«Practical exercices – Prion vs. Prion-like proteins»

Any questions ? Or Thoughts ?



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 (8/11)

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

★ Key concepts to memorize