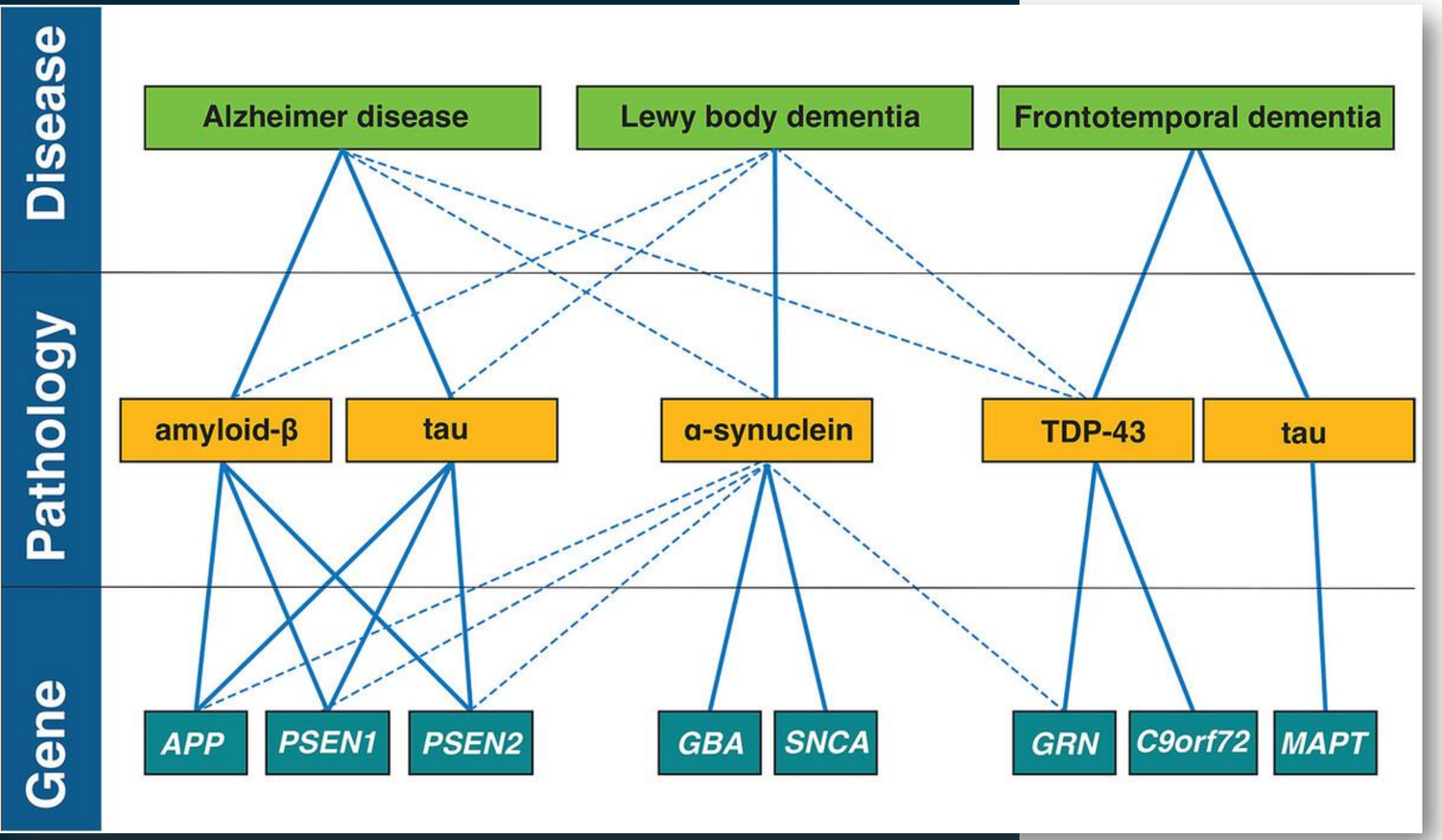
BEACON 2026

Proteinopathies and Neurodegeneration

How misfolded proteins disrupt brain systems over time

A PRESENTATION BY
Evan Nelson, DO

Why Neurodegenerative Diseases Develop



- Many common dementias are linked to proteins that lose their normal shape, accumulate abnormally, and interfere with how the brain functions
- Proteins normally help brain cells build, signal, repair, and adapt.
- Disease begins when certain proteins misfold, accumulate, or are not cleared well.

Neurodegenerative conditions share a common biologic theme**: abnormal proteins accumulating where they should not.**

- Alzheimer's disease (AD)
  - Changes in memory and cognitive impairment.

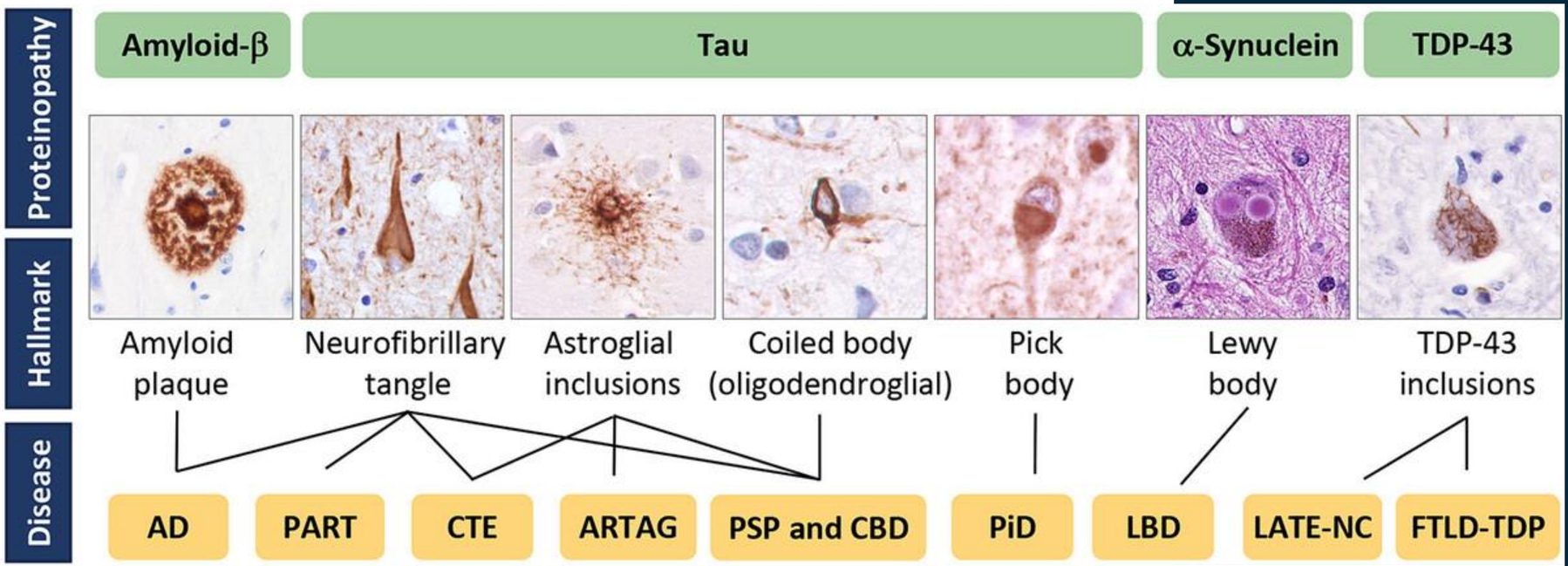
Beta-amyloid and Tau

- Frontotemporal dementia
  - Changes in personality, motor or/and language.

Tau and TDP-43

- Parkinson/Lewy body disease
  - Changes in motor, sleep, and/or hallucinations.

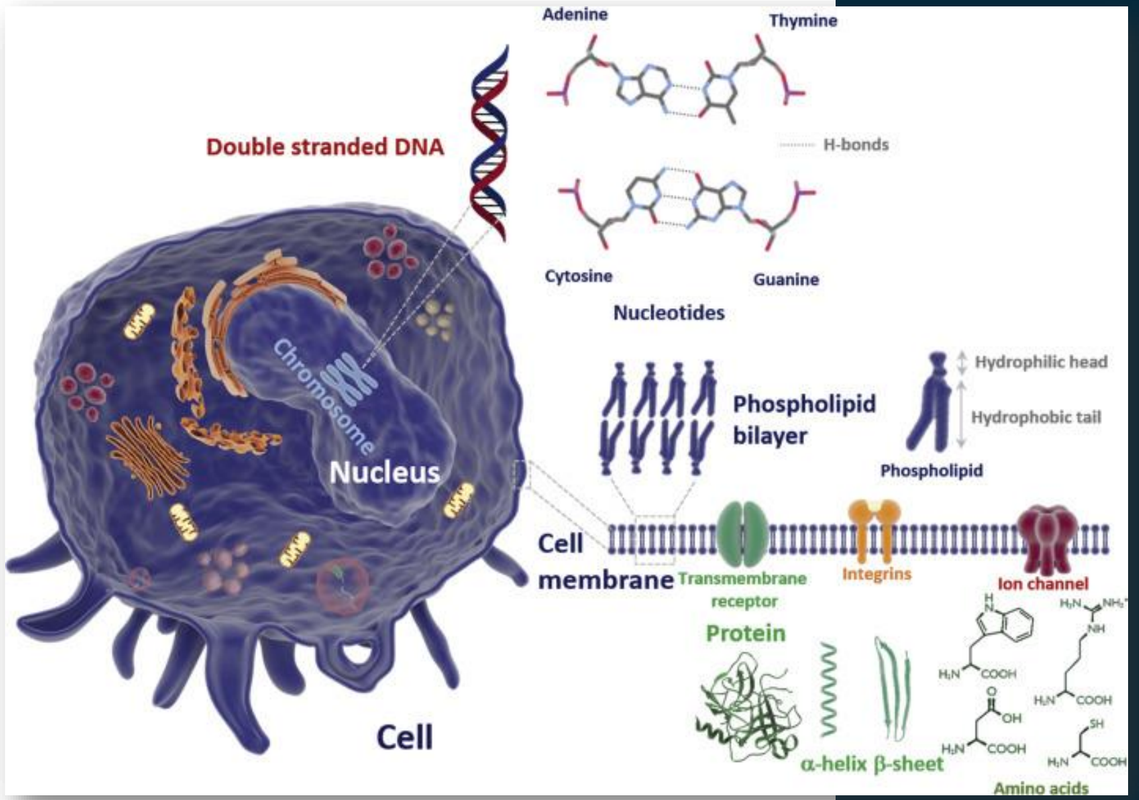
Alpha-synuclein

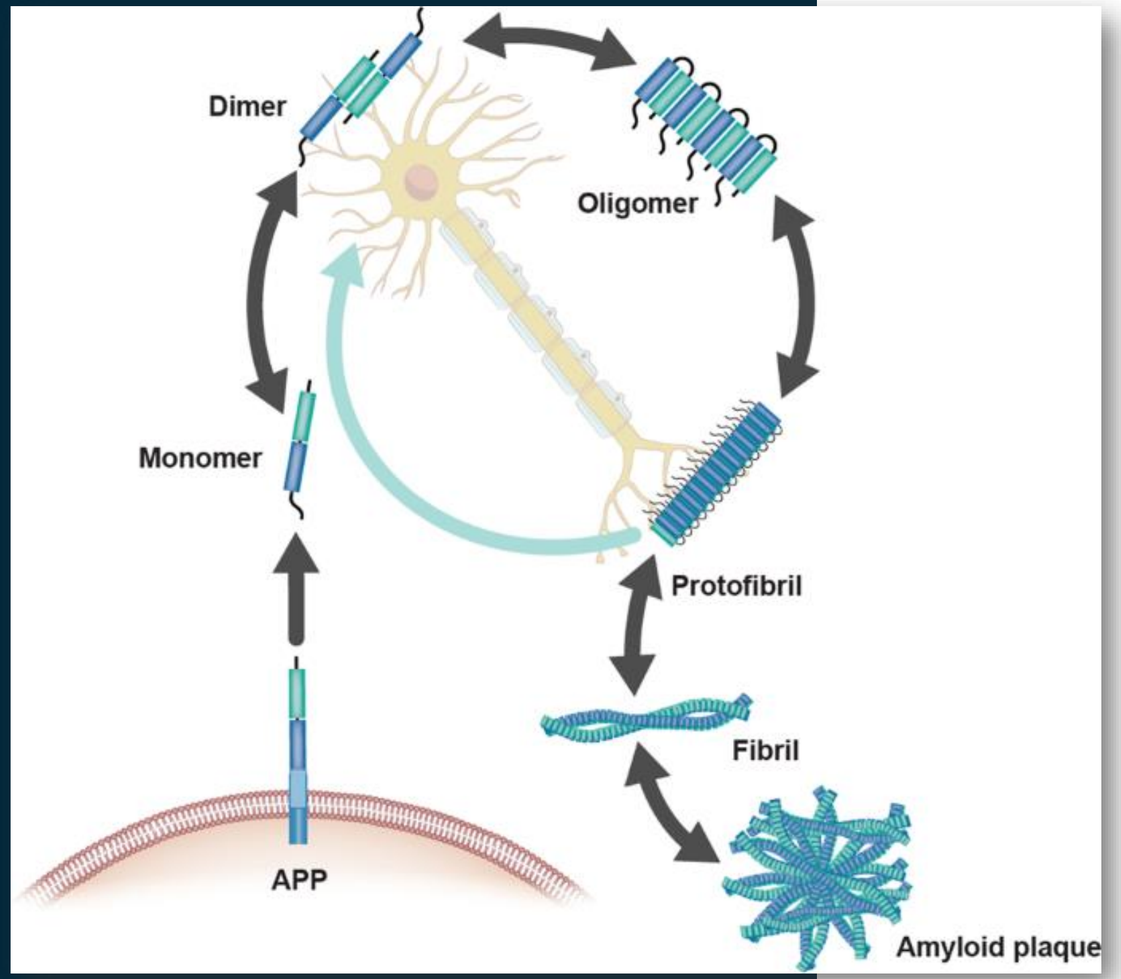


Different proteins → different vulnerable networks → different symptoms

Pievani et al., 2014; Gan et al., 2018

1. The journey starts with DNA
2. DNA is short for “deoxyribonucleic acid”
3. Our DNA is mostly located in the center of the cell—the “nucleus”
4. DNA is “transcribed” into RNA
5. RNA is short for “ribonucleic acid”
6. RNA is then made into protein
7. Protein is further processed, folding for example



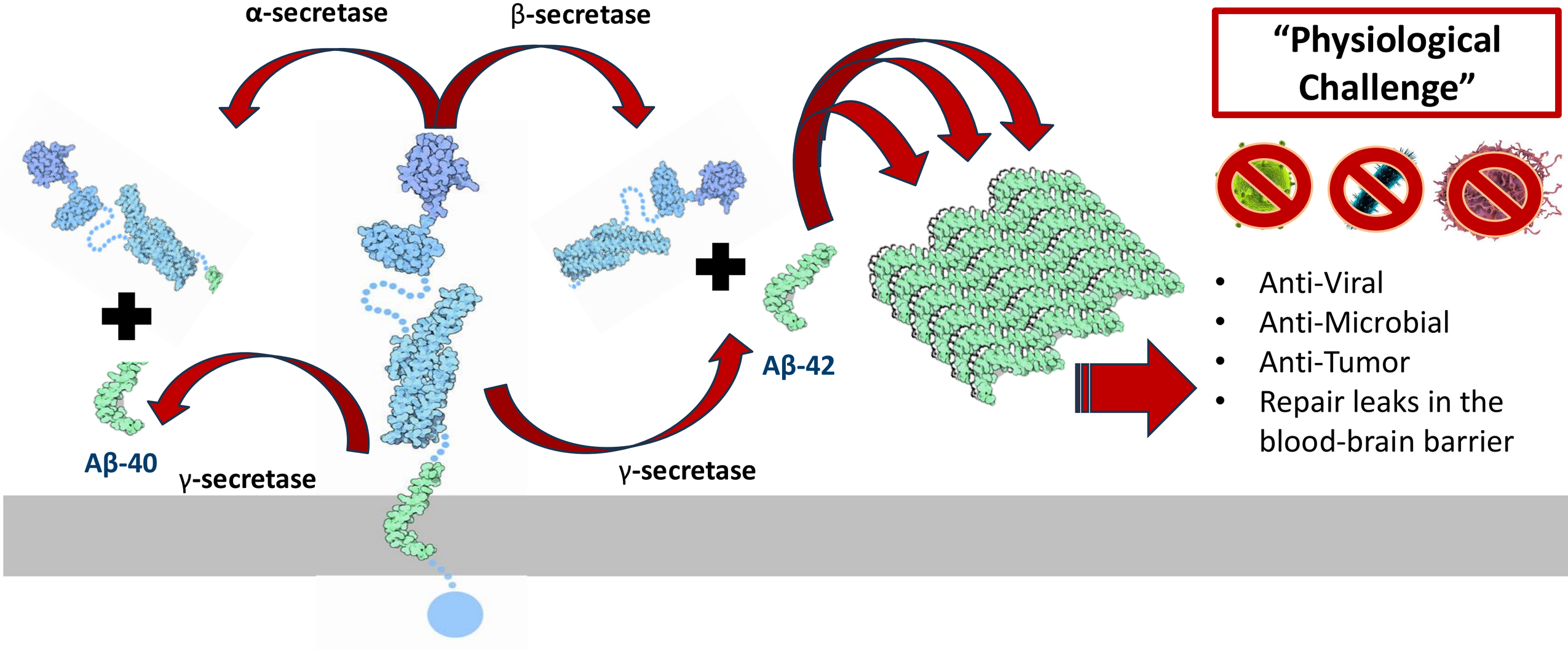


Amyloid

- Amyloid protein serves a multitude of purposes from bacteria to plants to animals
  - anti-microbial/viral
  - anti-tumor effects
  - Repairs defects in the blood-brain barrier

- However, overproduction and/or underexcretion may eventually lead to disease

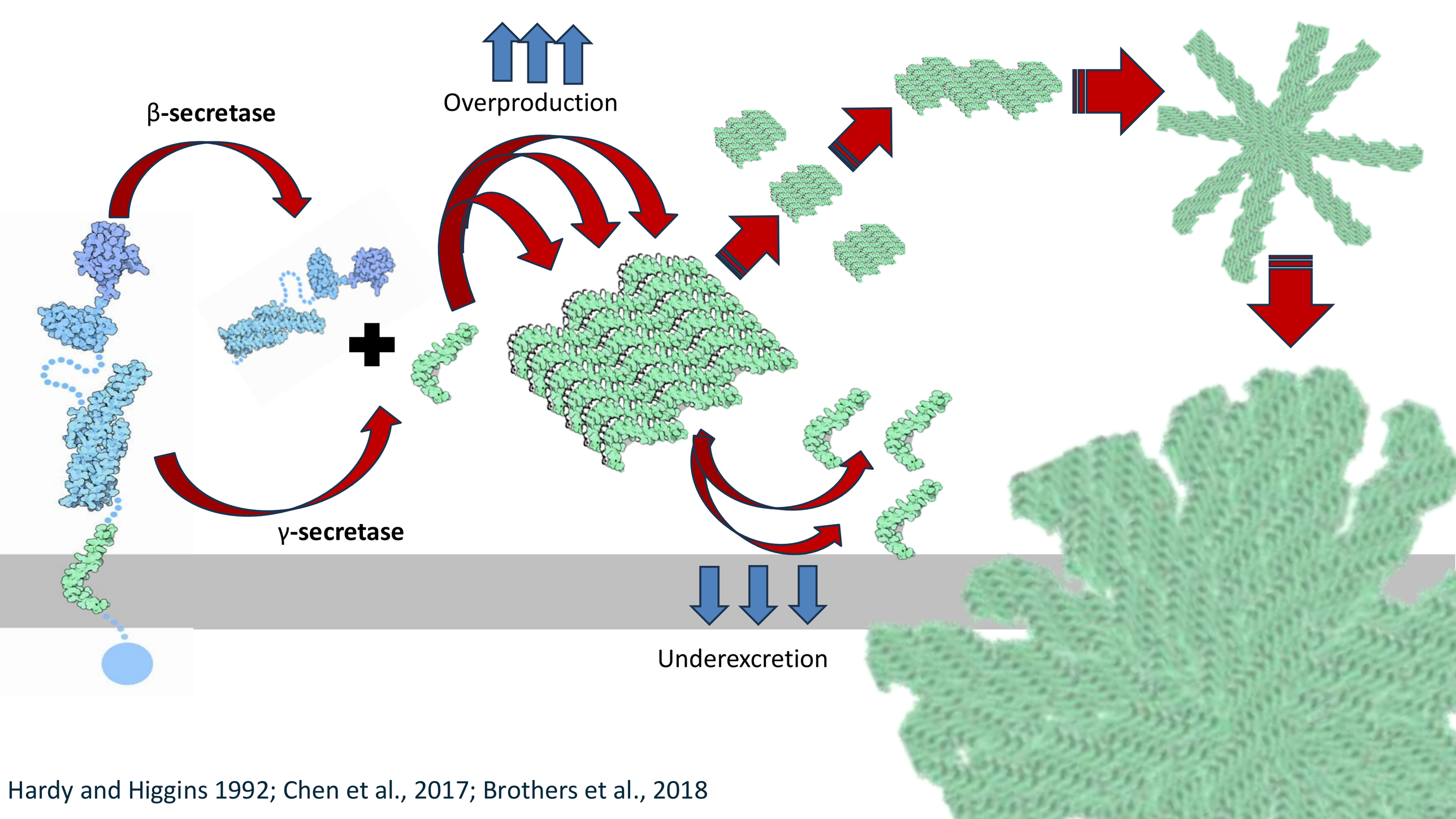
Hardy and Higgins 1992;
Olsson et al., 2016;
Chen et al., 2017;
Brothers et al., 2018
Hansson., 2021;



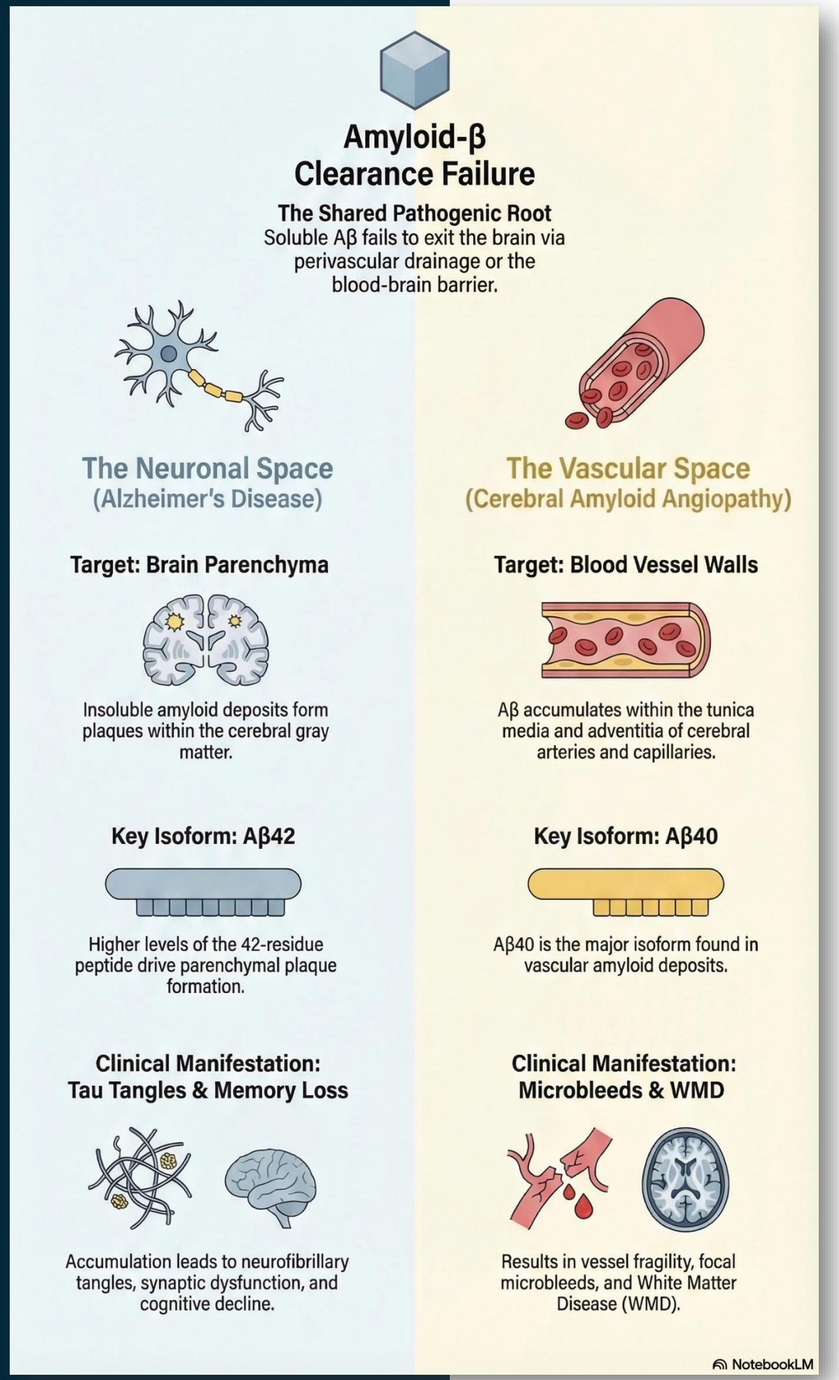
“Physiological Challenge”

- Anti-Viral
- Anti-Microbial
- Anti-Tumor
- Repair leaks in the blood-brain barrier

Hardy and Higgins 1992; Chen et al., 2017; Brothers et al., 2018



Hardy and Higgins 1992; Chen et al., 2017; Brothers et al., 2018

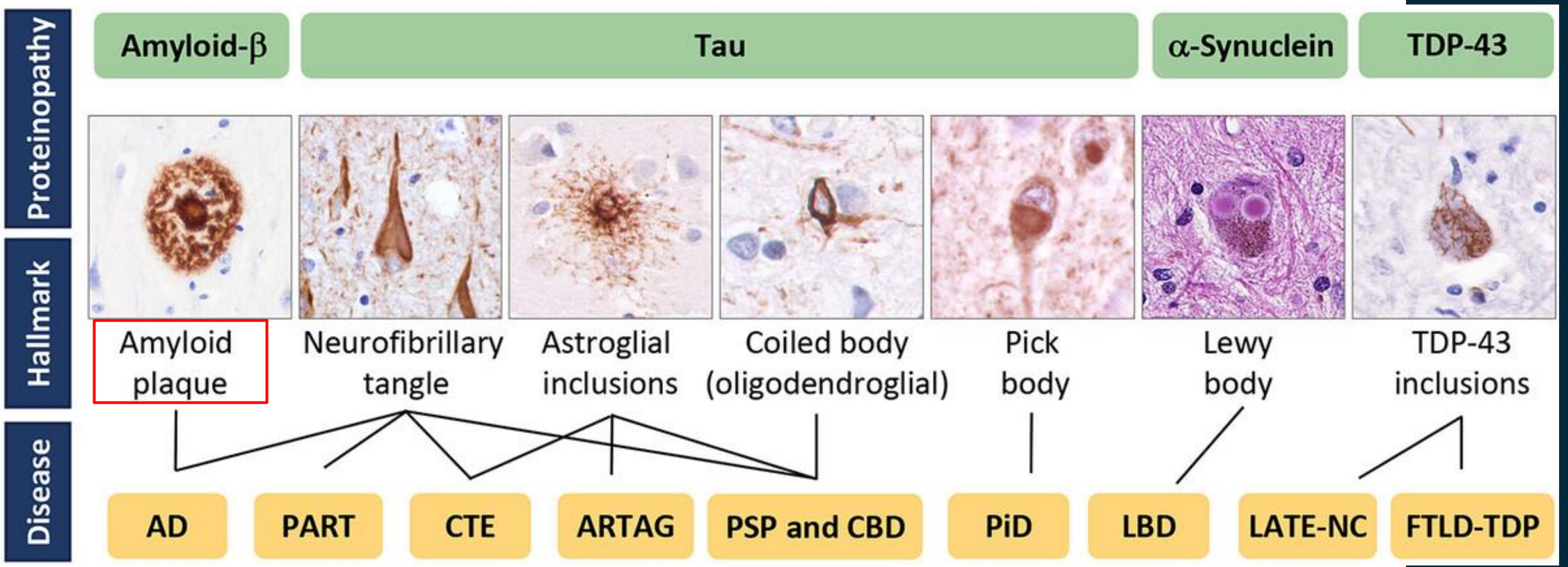


- Excess Amyloid beta deposits **drive disease**

- **Cerebral Amyloid Angiopathy (CAA)**
  - Amyloid deposits occur in the walls of small blood vessels over the surface of the brain

- **Alzheimer’s Disease**
  - Amyloid beta 42 may form extracellular aggregates known as plaques

Plaque formation is only the first step of Alzheimer cognitive impairment, preceding tau pathology, which we will discuss next



Different proteins → different vulnerable networks → different symptoms

- Amyloid builds up in tissue→ AD
- Amyloid build up in the blood vessels→ CAA

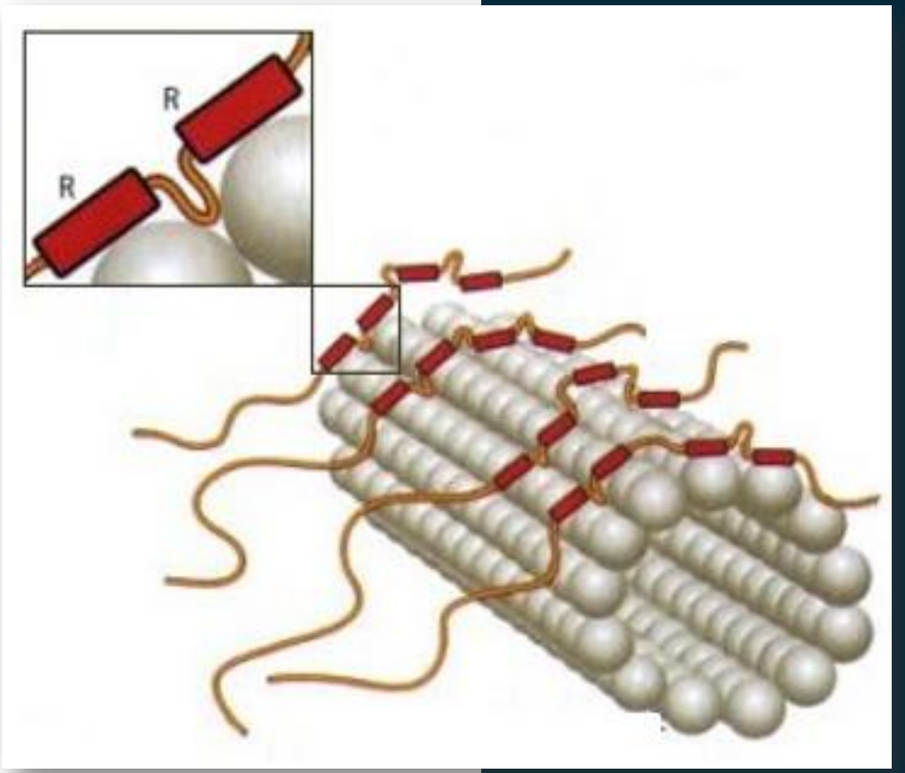
Pievani et al., 2014;
Gan et al., 2018

Tau

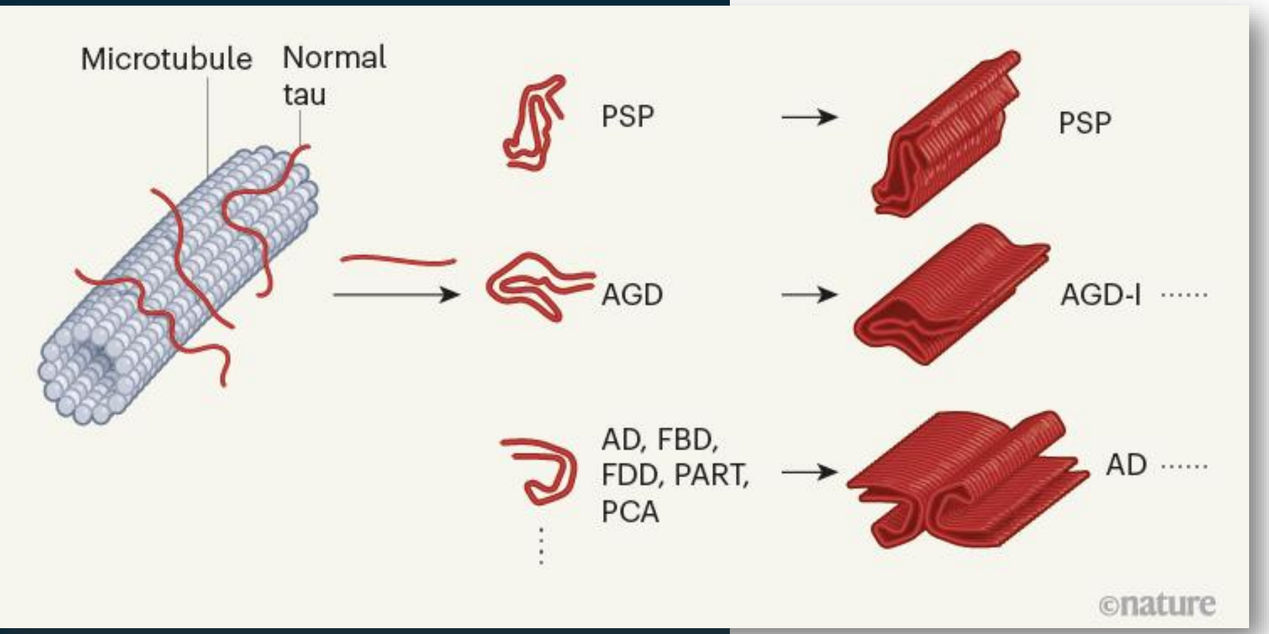
- Tau stabilizes the neuronal backbone (**microtubules**),

- Tau proteins may be phosphorylated at several different locations leading to
  - Adjust microtubule **binding**
  - Allow intracellular **transport**
  - Enable structural **flexibility**

- When tau phosphorylation regulation is lost:
  - Tau detaches from microtubules
  - Microtubules destabilize
  - Tau aggregates into intracellular tangles



Weingarten et al., 1975;
Brion et al., 1985;
Lovestone et al., 1997;
Ballatore et al., 2007;
Luna-Muñoz et al., 2013;
Olsson et al., 2016;
Hansson., 2021;



- Intracellular aggregates of hyperphosphorylated tau are called **“neurofibrillary tangles”**

- Tau aggregation tracks with:
  - Network failure
  - Cognitive decline
  - Disease phenotype (e.g., Alzheimer’s)

Tau is not the problem—loss of its regulation is

Weingarten et al., 1975;
Brion et al., 1985;
Lovestone et al., 1997;
Ballatore et al., 2007;
Luna-Muñoz et al., 2013;
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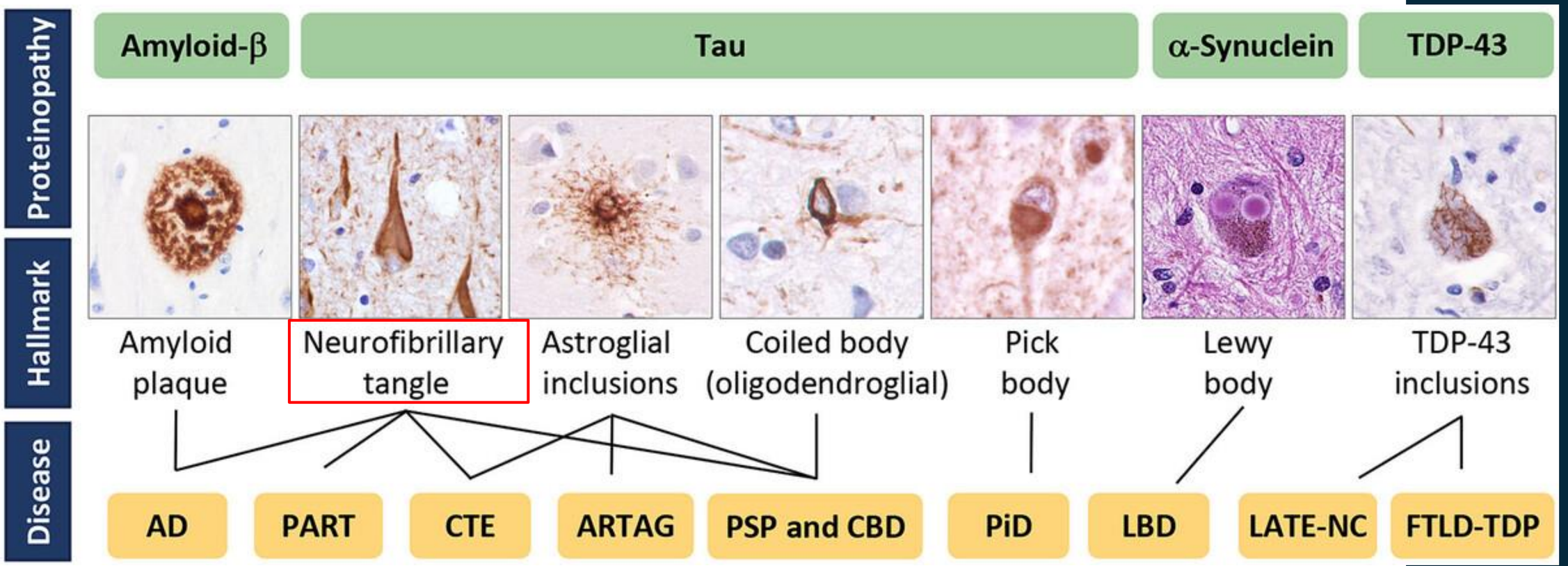


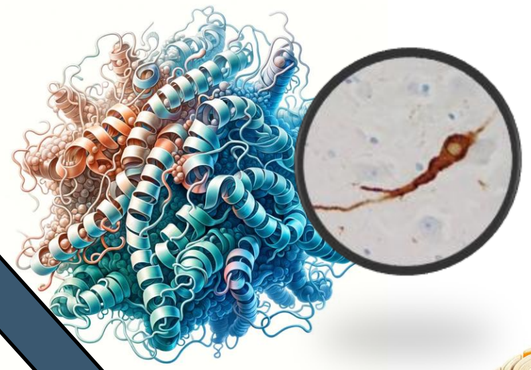
Different proteins → different vulnerable networks → different symptoms

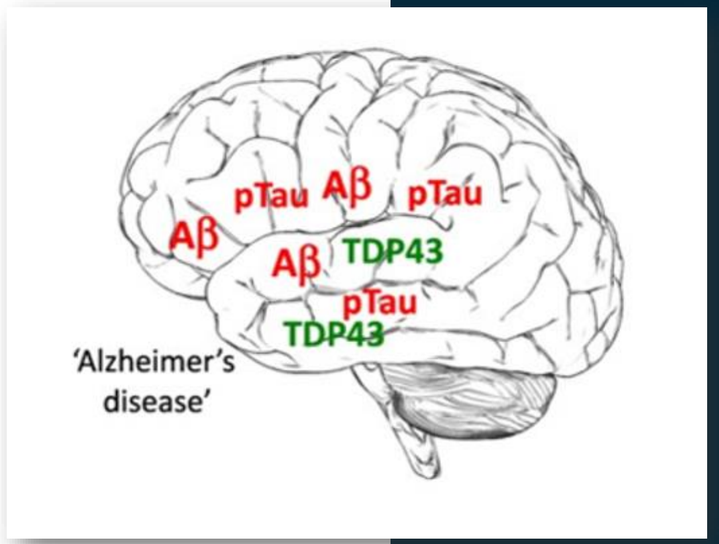
- Tau builds up in memory/attention networks→ AD/LANS
- Tau builds up in motor networks→ PSP, CBD

Pievani et al., 2014;
Gan et al., 2018

A (β-amyloid)

T (Tau)





N (Neurodegeneration)

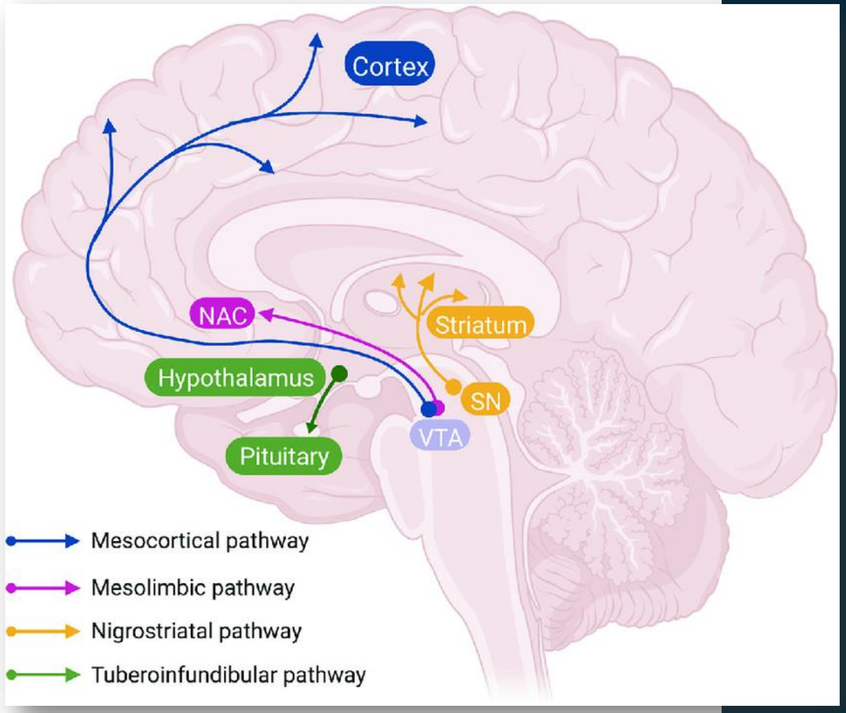
Hardy and Higgins 1992;
Chen et al., 2017;
Brothers et al., 2018

α-Synuclein

- **What α-synuclein does (normal brain):**
  - Organizes synaptic vesicles
  - Regulates neurotransmitter release timing
  - Maintains precision in high-demand circuits

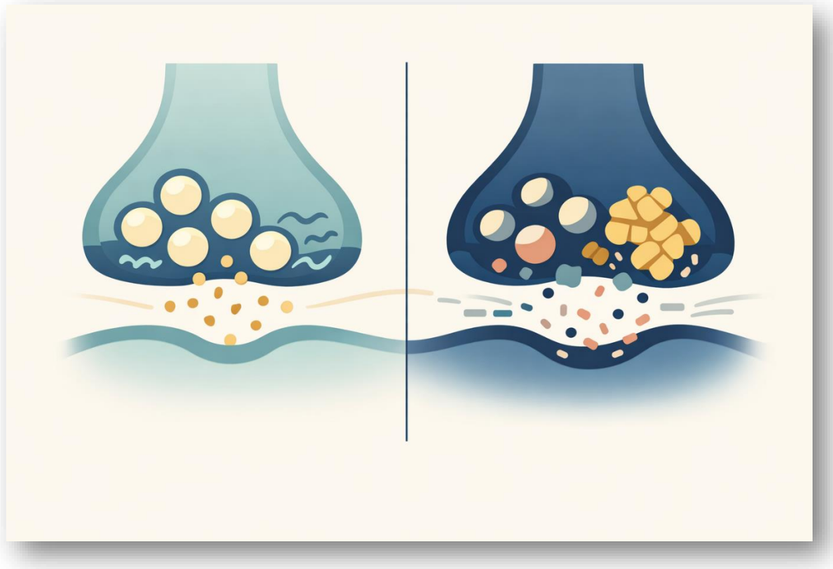
- **Where it matters most:**
  - Nigrostriatal pathway → movement control
  - Mesolimbic pathway → motivation, reward
  - Mesocortical pathway → attention, cognition

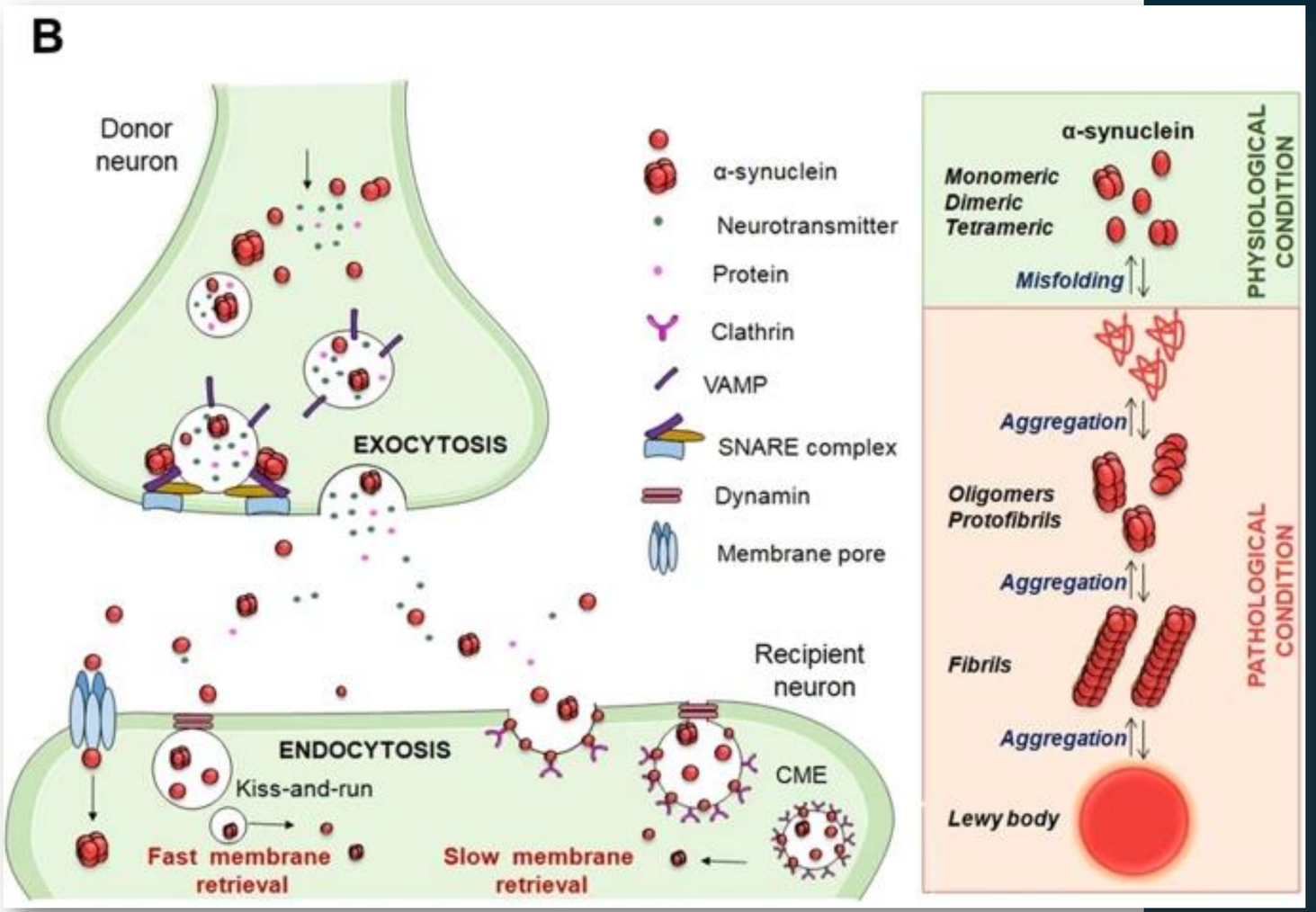
Think of it as a “traffic coordinator” at the synapse—keeping dopamine/norepinephrine release smooth and well-timed.



α-Synuclein

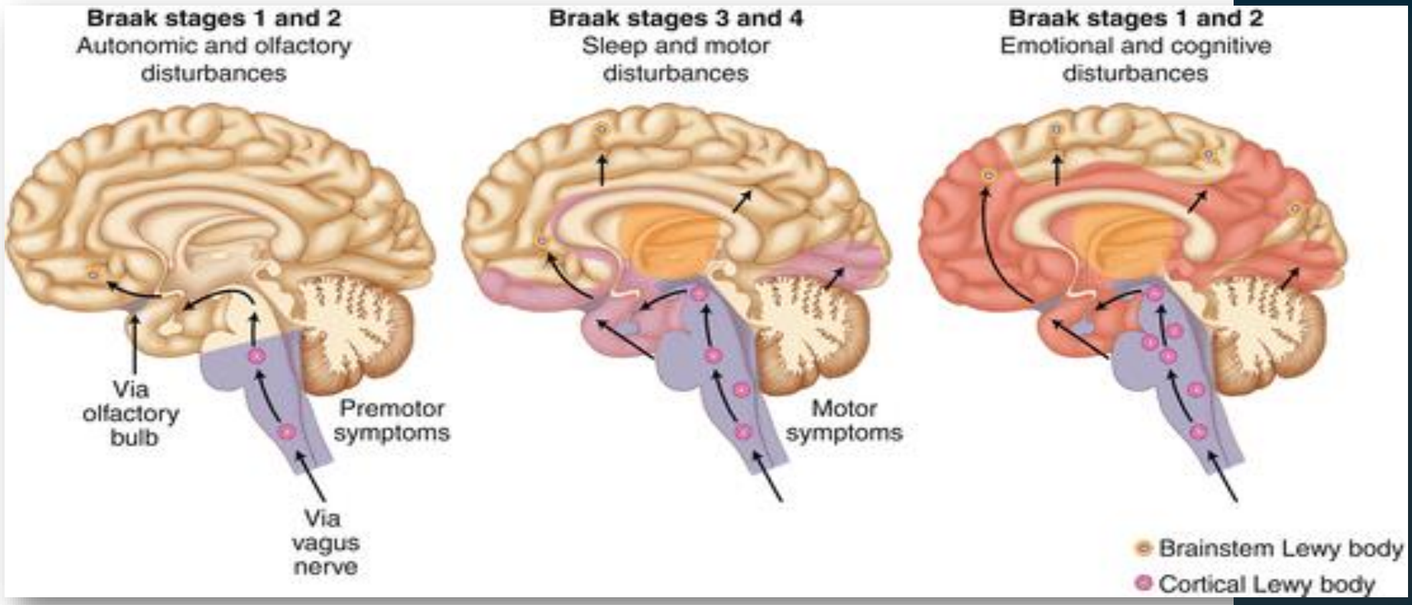
- **What goes wrong**
  - Misfolding → sticky protein
  - Aggregation → Lewy bodies
  - Spread → Disrupts dopamine and norepinephrine signaling





This is not a single-region disease - it is failure across brain signaling networks.

Proteinopathies and Neurodegeneration



- Nigrostriatal
  - Motor slowing, rigidity, tremor

  = Parkinson disease

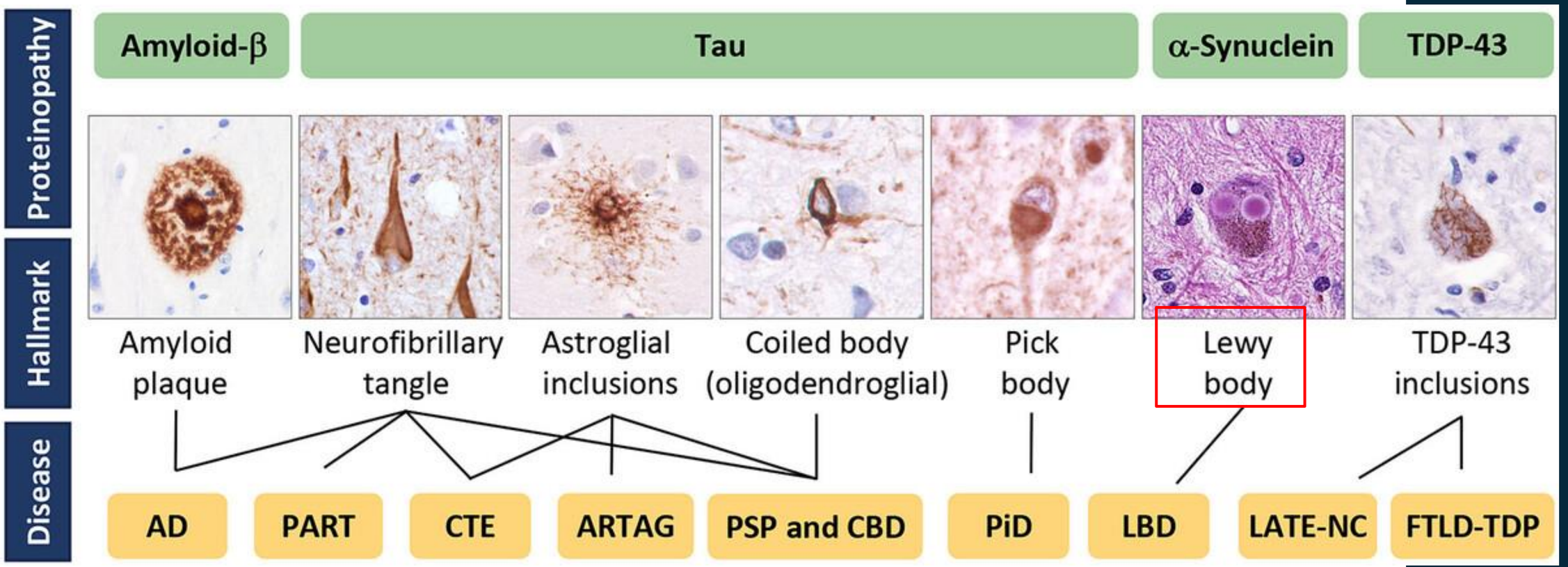
- Mesolimbic / Cortical
  - Hallucinations, fluctuations, cognitive change

  = Lewy Body Dementia

- Brainstem / Locus Coeruleus (Norepinephrine)
  - Attention/Arousal dysfunction, REM disorder

  = Contributes across synucleinopathies

Different systems fail at different times → symptoms evolve over years

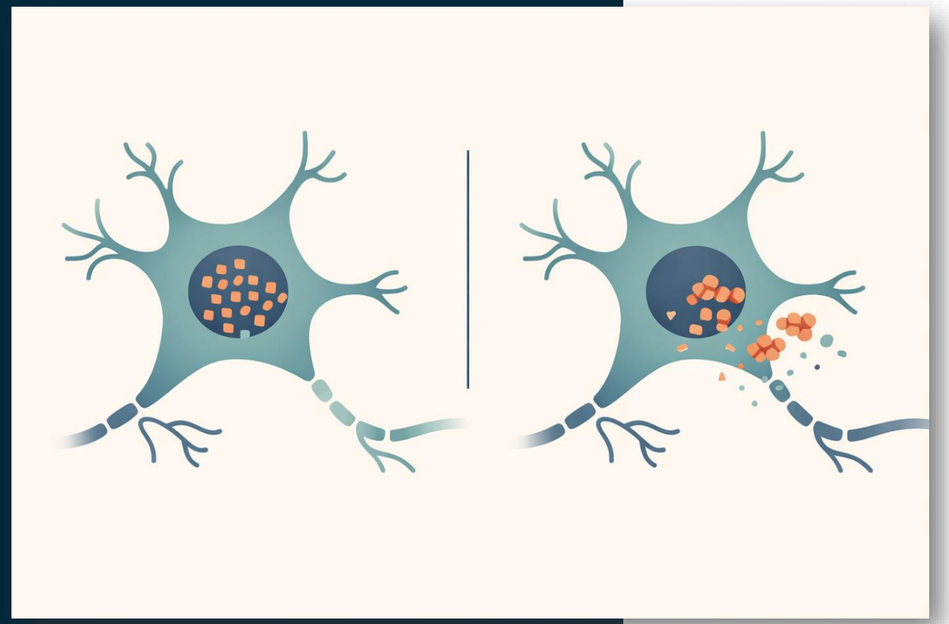


Different proteins → different vulnerable networks → different symptoms

- α-Synuclein builds up in motor networks→ PD
- α-Synuclein builds up in memory/attention networks→ DLB

Pievani et al., 2014;
Gan et al., 2018

TAR DNA-binding Protein 43 (TDP43)

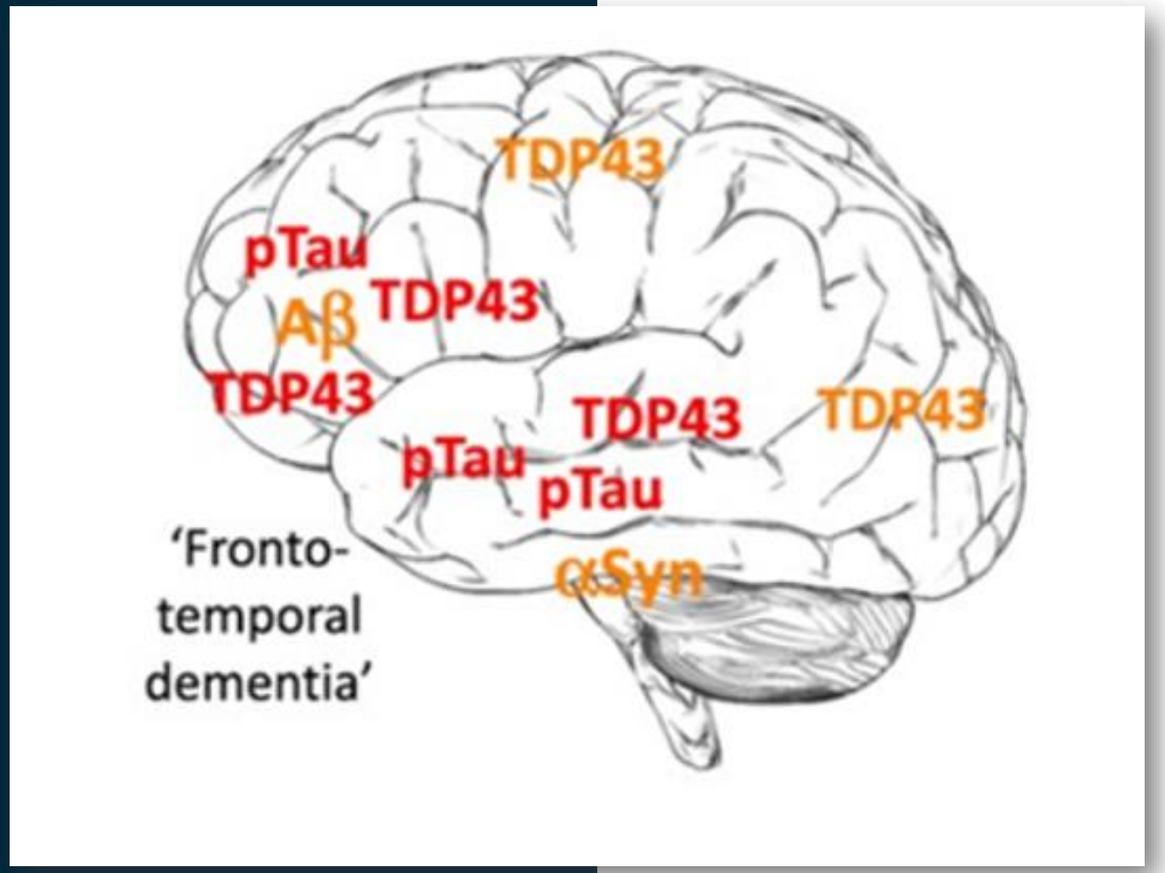


- TDP-43 normally helps
  - Regulates RNA processing
  - Remains predominantly in the nucleus

- In pathological conditions, it shifts to the wrong place
  - Leaves the nucleus
  - Accumulates in the cytoplasm
  - Forms abnormal inclusions

TDP-43 pathology may be associated with various syndromes

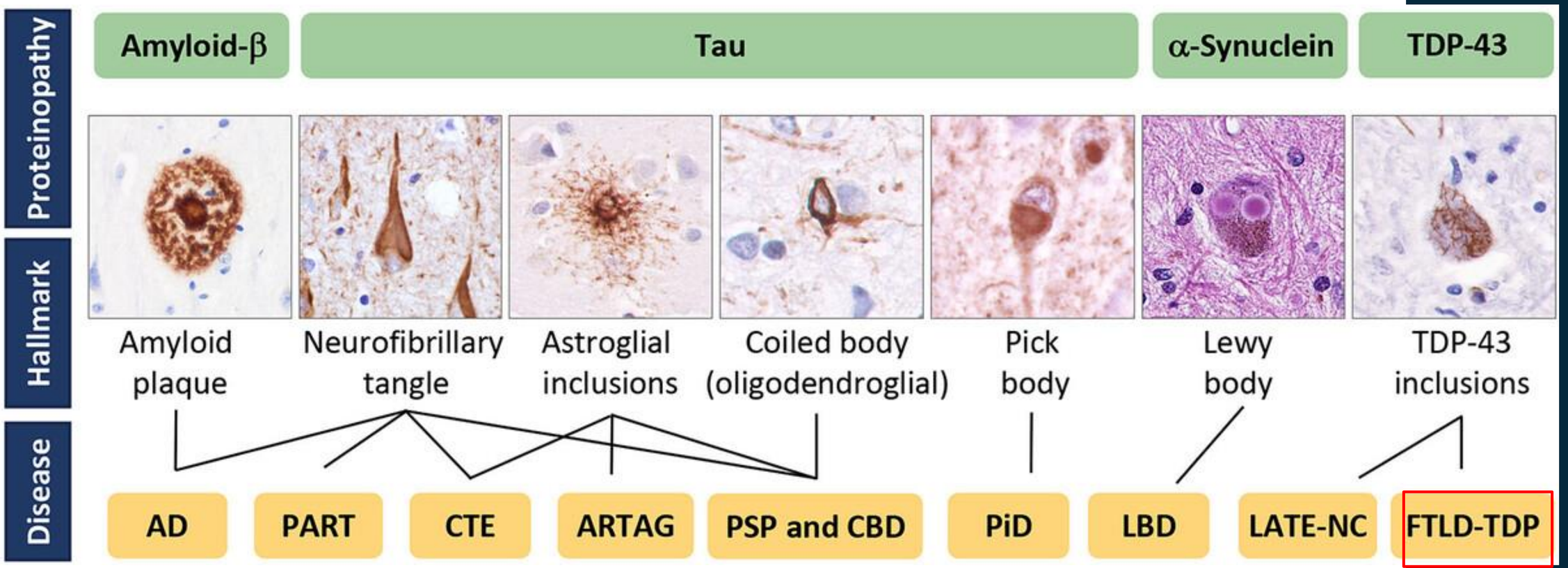
TAR DNA-binding Protein 43 (TDP43)



- Linked to several major clinical syndromes
  - Frontotemporal degeneration
  - ALS
  - Amnesia in older adults

- Why it matters clinically
  - Underrecognized outside specialty settings
  - Worsens cognitive decline when a co-morbidity

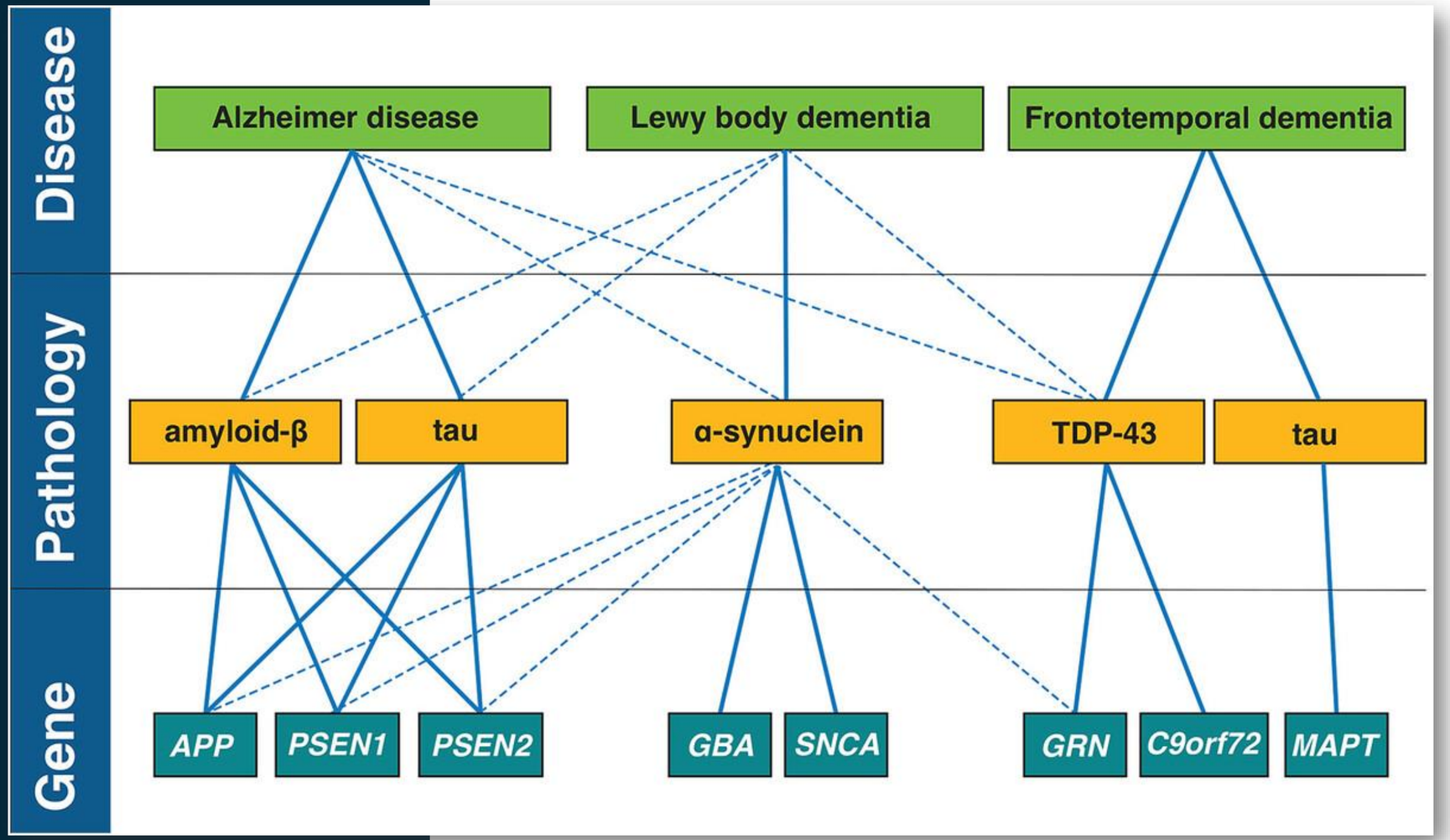
TDP-43 is one of the most important but least publicly recognized proteinopathies in neurology.

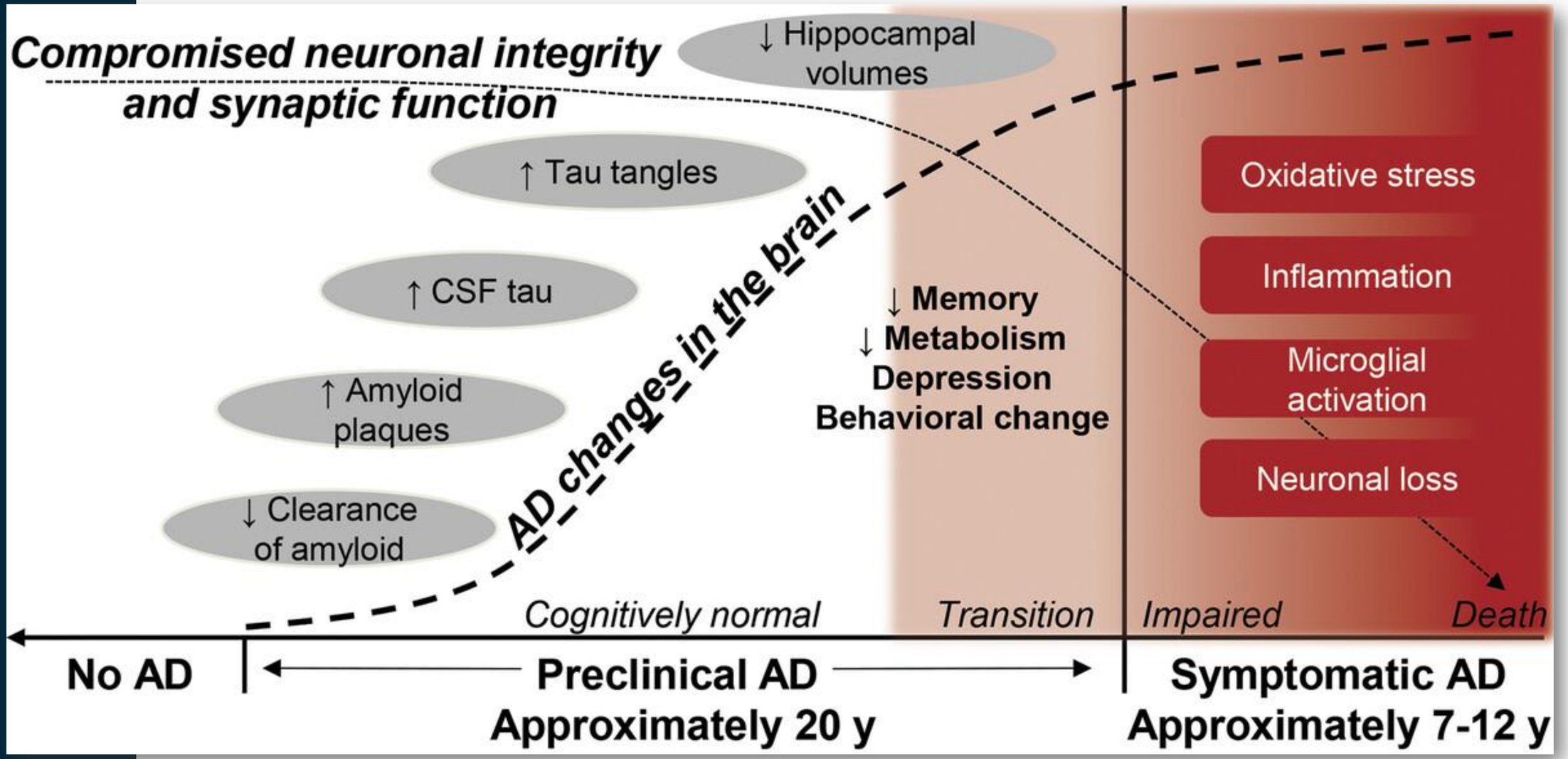


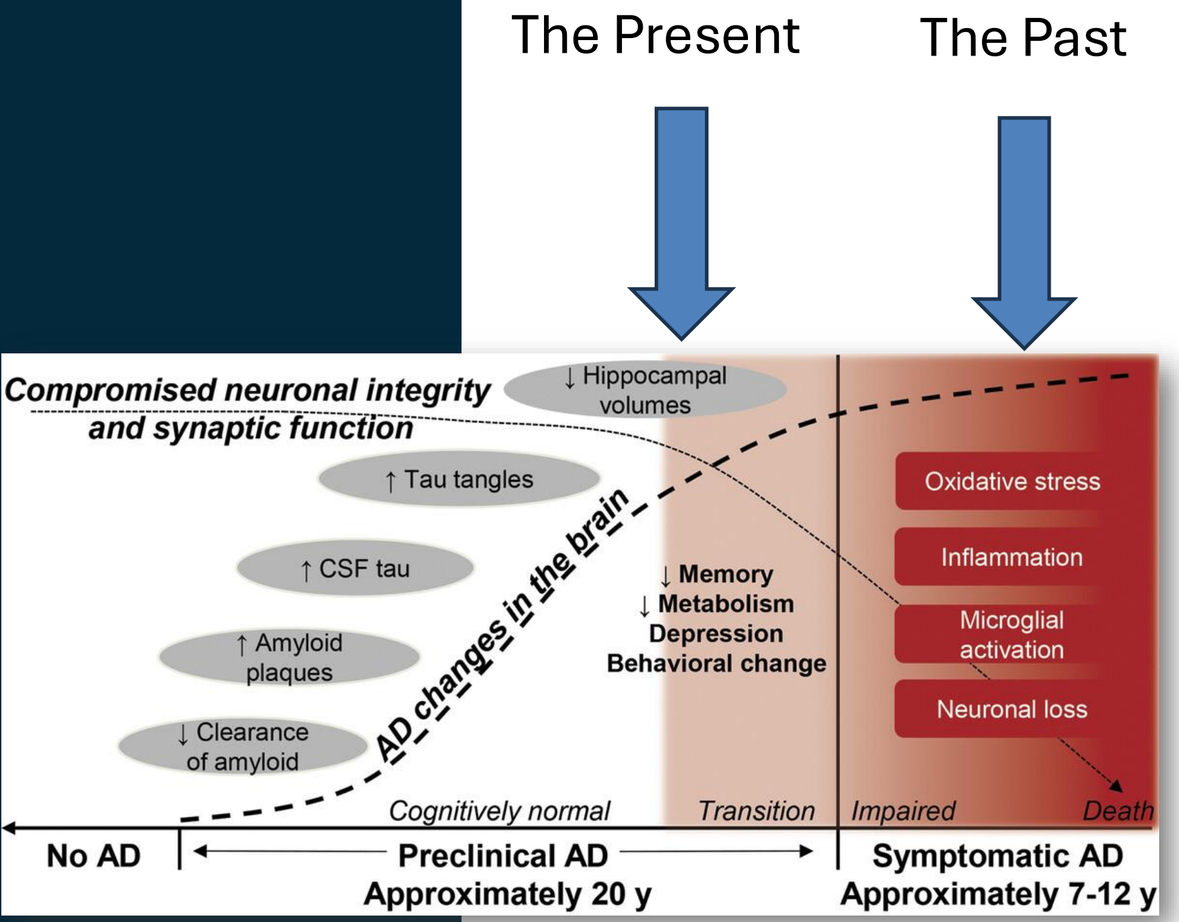
Different proteins → different vulnerable networks → different symptoms

- TDP43 builds up in motor networks→ ALS/PLS
- TDP43 builds up in language/behavioral networks→ FTLD

Pievani et al., 2014;
Gan et al., 2018


Disease
Pathology
Gene
Alzheimer disease
Lewy body dementia
Frontotemporal dementia
amyloid-β
tau
α-synuclein
TDP-43
tau
APP
PSEN1
PSEN2
GBA
SNCA
GRN
C9orf72
MAPT


Compromised neuronal integrity and synaptic function
↓ Hippocampal volumes
↑ Tau tangles
↑ CSF tau
↑ Amyloid plaques
↓ Clearance of amyloid
AD changes in the brain
↓ Memory
↓ Metabolism
Depression
Behavioral change
Oxidative stress
Inflammation
Microglial activation
Neuronal loss
Cognitively normal
Transition
Impaired
Death
No AD
Preclinical AD
Approximately 20 y
Symptomatic AD
Approximately 7-12 y



Why Biomarkers Matter

- Neurodegeneration does not start suddenly; it **builds over decades** before symptoms appear.
- In the past, neurologists waited for symptoms to become clinically manifest—however at this point, the disease is already quite progressed
- Biomarkers are **helpful** in
  - earlier detection of disease
  - clarification of what the underlying cause is,
  - may guide treatment
  - Early enrollment in clinical trials

Huang et al., 2020;
Hadjichrysanthou et al., 2020;
Mattason-Cargren et al., 2020;
Cummings et al., 2021;
Hansson., 2021

Proteins shape networks—and networks shape symptoms.

Why This Matters Now

Understanding the protein biology now matters in real-world care because it influences

- Diagnosis
- Prognosis
- Treatment selection
- Research enrollment

If you are concerned, talk with your doctor about early screening.

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Brain Restoration

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  This is the citation most often associated with the "functional amyloid/biofilm" point in reviews, but the PubMed match I could confirm directly from your shorthand was also this related paper:
  Dueholm, M. S., Søndergaard, M. T., Nilsson, M., Christiansen, G., Stensballe, A., Overgaard, M. T., Givskov, M., Tolker-Nielsen, T., Otzen, D. E., & Nielsen, P. H. (2013). Expression of Fap amyloids in *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, and *Pseudomonas putida* results in aggregation and increased biofilm formation. *MicrobiologyOpen, 2*(3), 365–382. https://doi.org/10.1002/mbo3.81
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  I'm less certain on this exact match from the slide shorthand and would verify before finalizing.
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  Your slide says "Lovestone et al., 1997," but the tau/GSK-3 landmark paper commonly cited is 1994. This one needs checking against the original deck source note.
- Luna-Muñoz, J., Chávez-Macías, L., García-Sierra, F., & Mena, R. (2007). Earliest stages of tau conformational changes are related to the appearance of a sequence of specific phospho-dependent tau epitopes in Alzheimer's disease. *Journal of Alzheimer's Disease, 12*(4), 365–375.
  Your slide says 2013, but Luna-Muñoz has several tau papers and the shorthand is not enough to lock one without seeing the source notes. Needs verification.

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THANK YOU