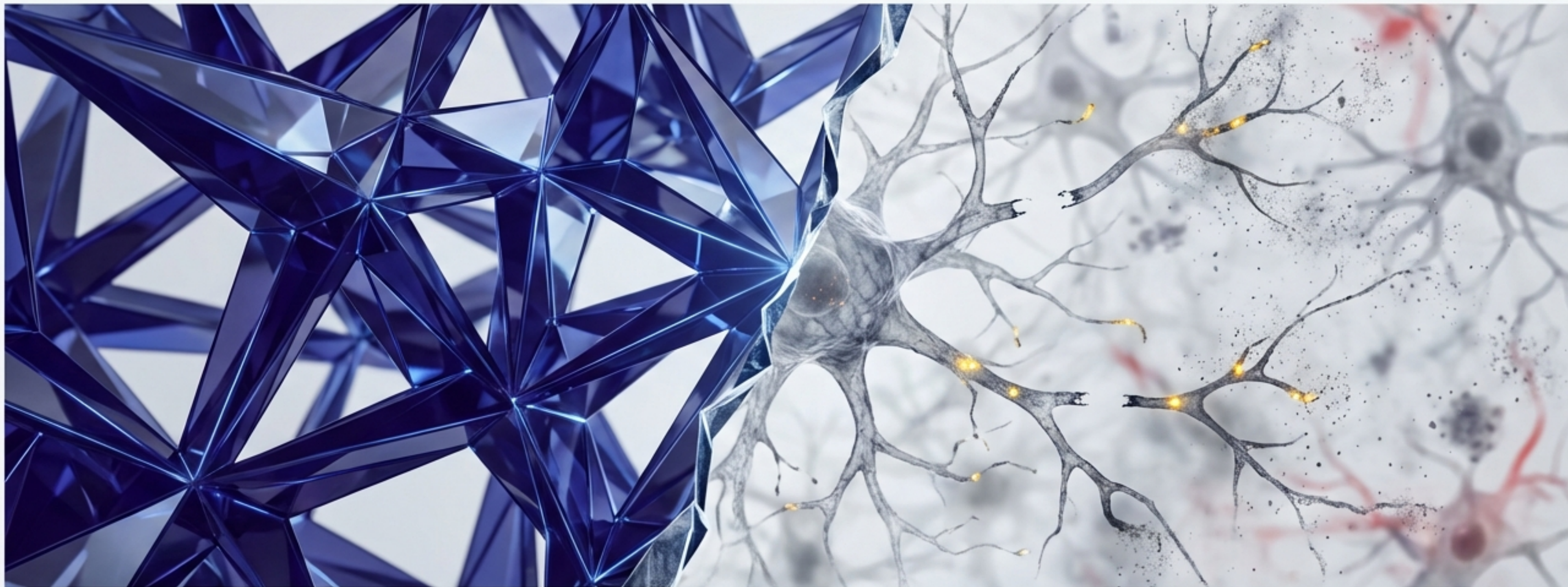


The Ontological Crisis of Alzheimer's Disease

From the Amyloid Cascade to the Synaptic Imperative

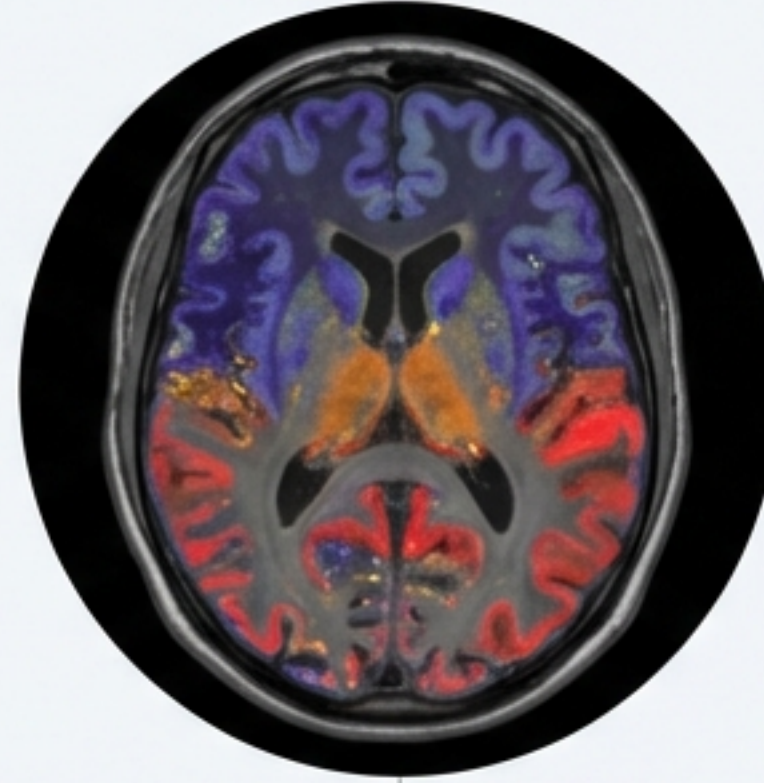


Based on a critical review of the 2018 NIA-AA Framework and the 2024 Revised Criteria.
Prepared for Dr. James F. Rudd and Benjamin Gustafson.
Drafted by Gemini3.0



1906

The Dualism:
Symptoms + Pathology
Inseparable



Present

The Decoupling:
Biomarker Dissociation

Cognitively unimpaired older adults harbor significant amyloid burdens, while individuals with clinical dementia often lack amyloid.

If you have pathology without symptoms, or symptoms without pathology, do you have the disease?

The Biological Turn: The ATN Framework



A

Amyloid

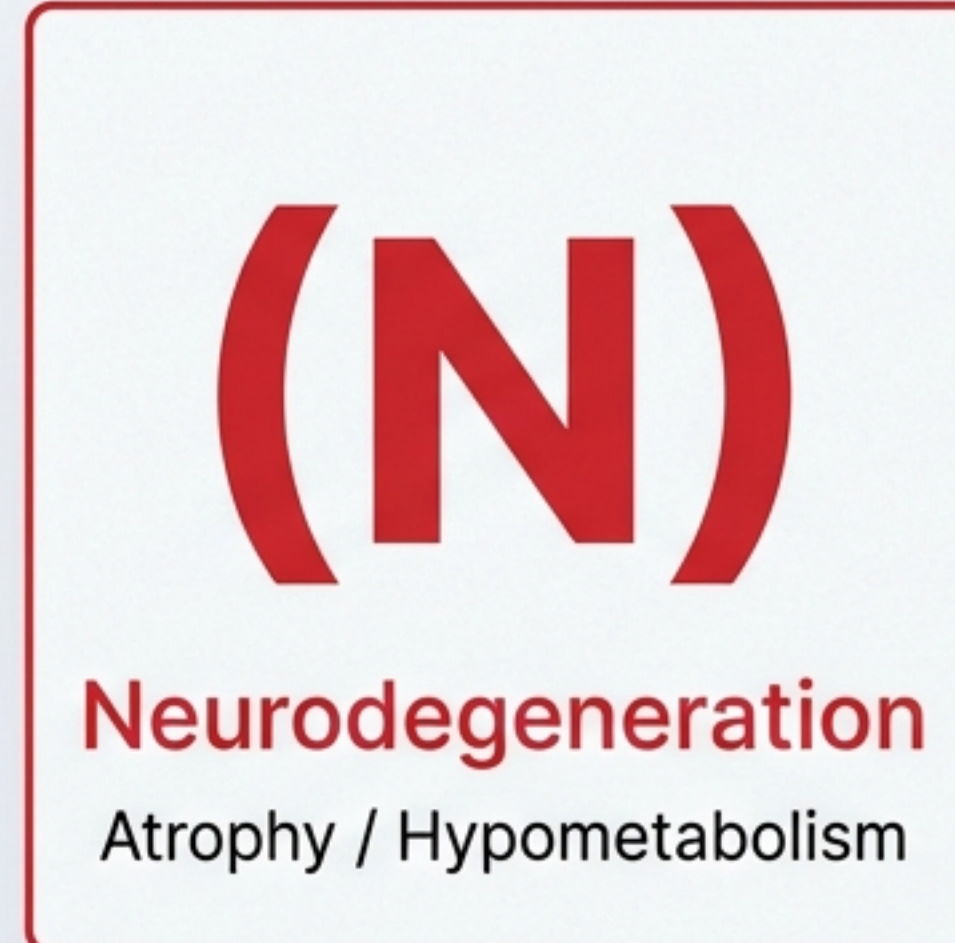
A β 42 / Amyloid PET



T

Tau

p-Tau / Tau PET



(N)

Neurodegeneration

Atrophy / Hypometabolism

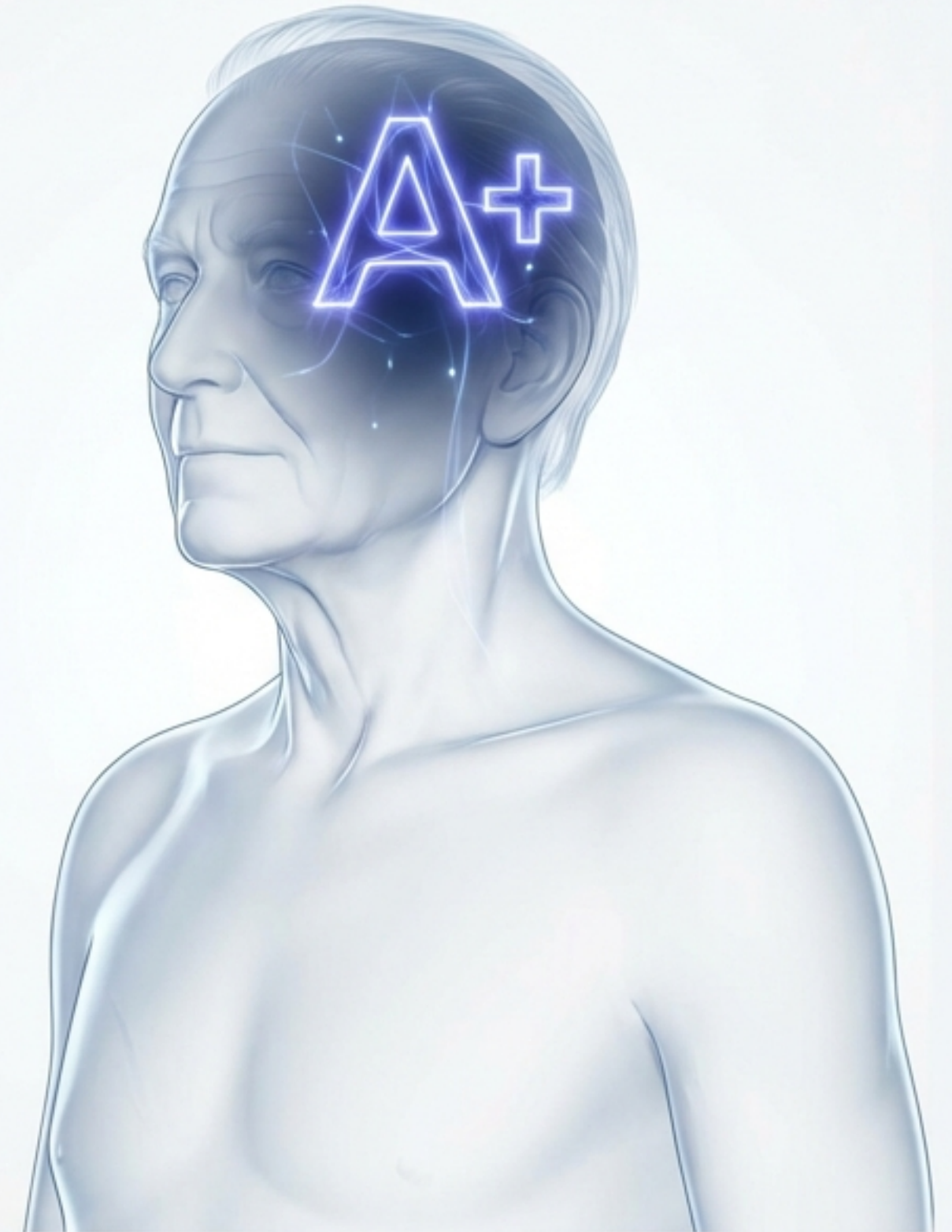
The Shift (2018): AD redefined purely as a Biological Construct regardless of symptoms.

The Codification (2024 Revised Criteria): Core 1 (Amyloid/p-Tau) allows for diagnosis without clinical impairment.

Diagnosis is not based on the clinical consequences of the disease. — Jack et al., 2018

The Danger of Reification: The Patient-in-Waiting

- The Concept: Confusing a risk factor (Amyloid) with the disease entity itself.
- The Consequence: Asymptomatic individuals are diagnosed as 'biologically sick' despite normal function.
- The Error: Defines non-conforming cases out of existence to insulate the theory.



The Hegemony of the Amyloid Cascade Hypothesis (ACH)



Proposed by Hardy & Higgins (1992). Posits a linear, deterministic cause-and-effect where Amyloid is the sufficient trigger for all pathology.

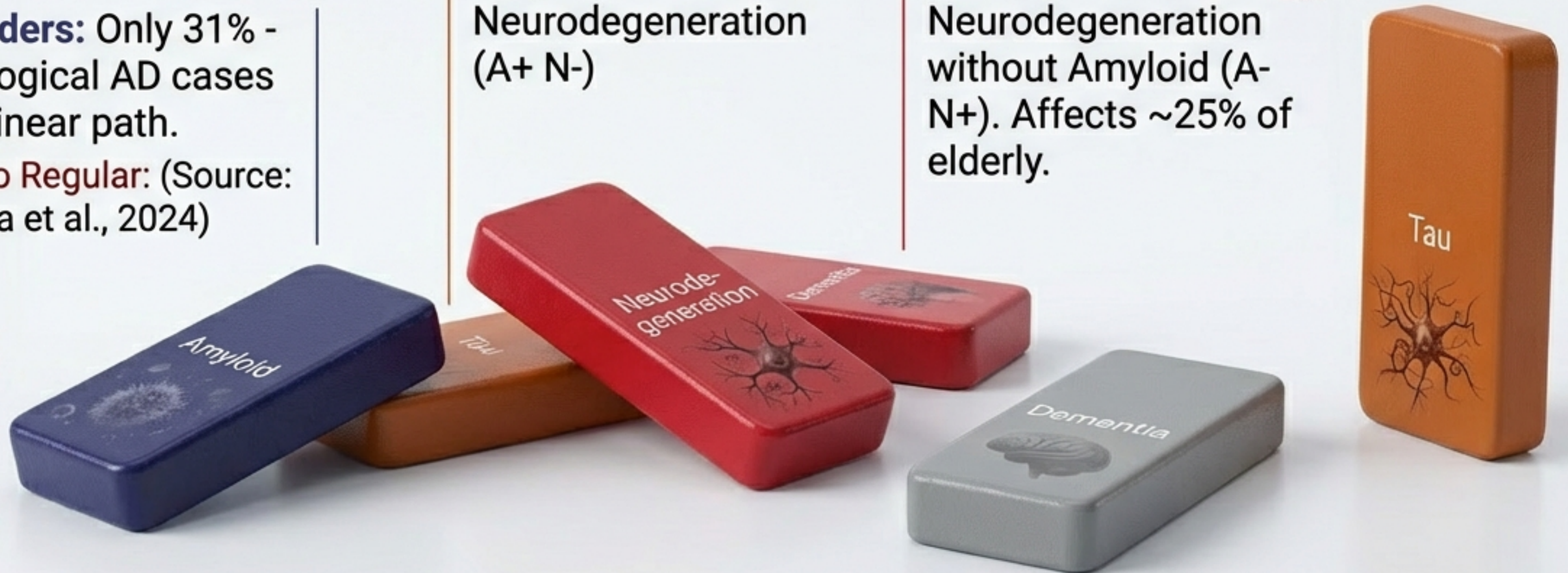
Falsification by Data

Non-Cascaders: Only 31% - 36% of biological AD cases follow the linear path.

(Crimson Pro Regular: (Source: Ferrari-Souza et al., 2024)

Resilience: High Amyloid without Neurodegeneration (A+ N-)

SNAP (Suspected Non-Alzheimer's Pathology): Neurodegeneration without Amyloid (A- N+). Affects ~25% of elderly.



Amyloid is neither necessary (SNAP) nor sufficient (Resilience) for neurodegeneration.

The "N" Exclusion and the No True Scotsman Fallacy' — in Inter Bold, tight tracking

2024 Revised Criteria



The 2024 criteria removed Neurodegeneration (N) from the core definition to protect the amyloid theory.

If a patient has dementia and atrophy but no amyloid, they are excluded from the AD diagnosis.
Neurodegeneration is reclassified as a consequence, not a definition.

The Missing Core: The Synaptic Imperative

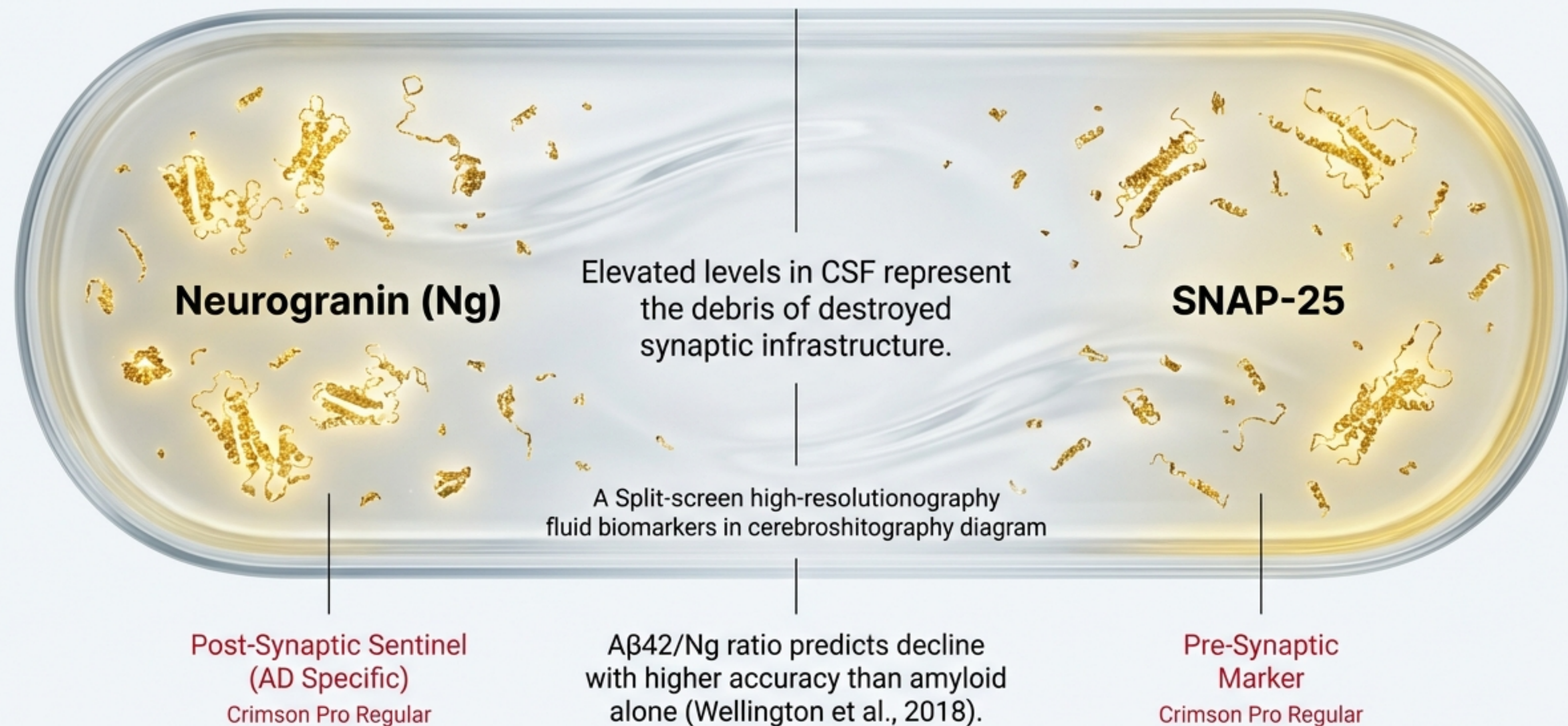
**The Architects
(Risk)**
Amyloid & Tau



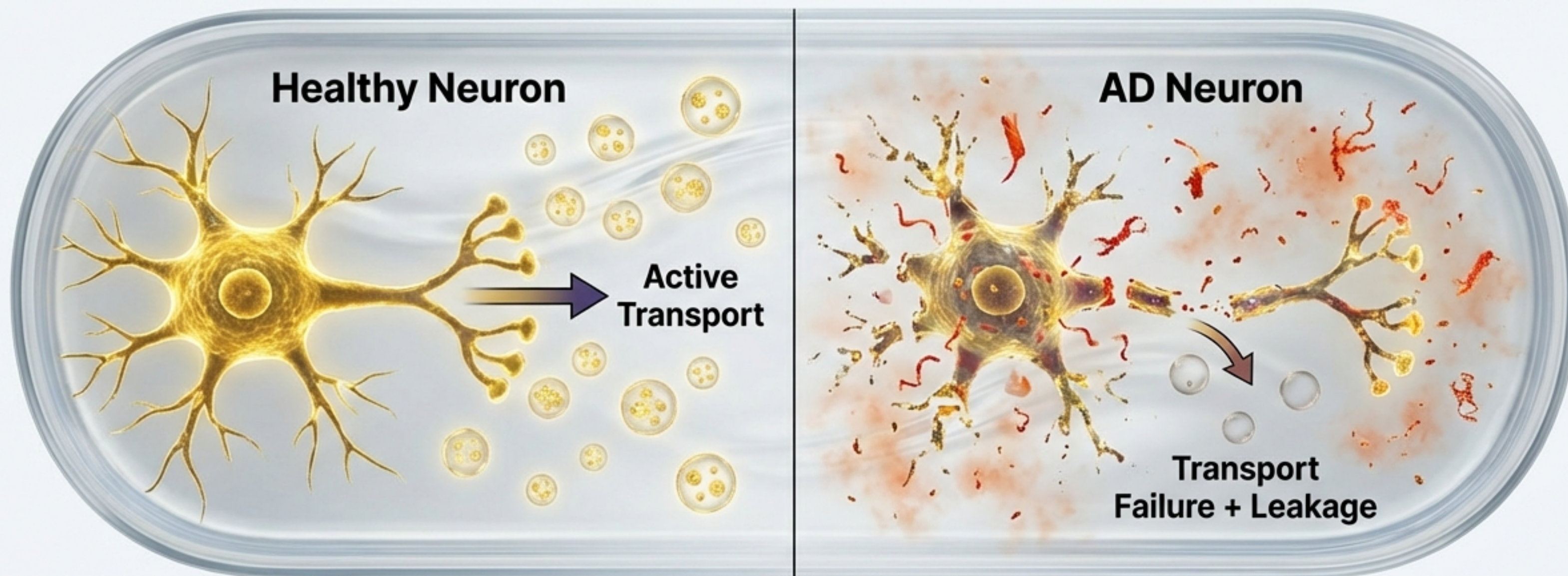
**The Structural
Integrity**
The Synapse

Synaptic loss is the strongest biological correlate of cognitive decline,
yet is absent from the core ATN definition.

CSF Biomarkers: The Debris of Synaptic Destruction



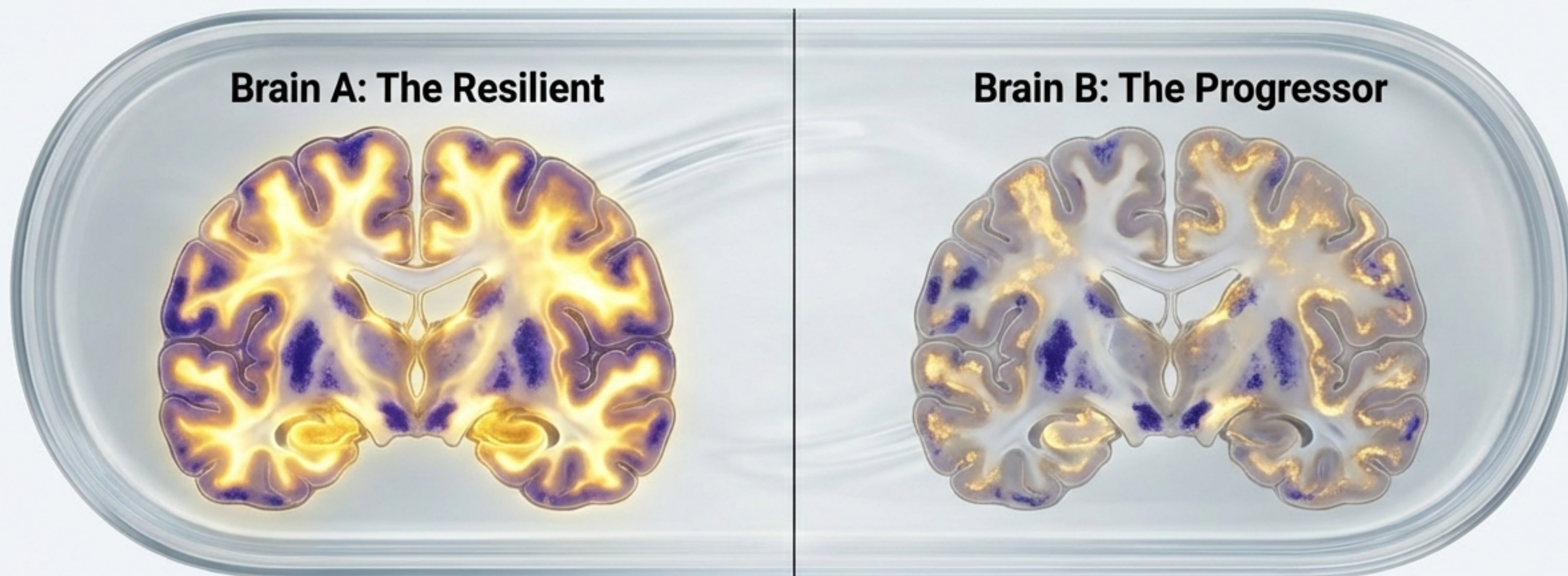
The Exosomal Paradox



High CSF Levels + Low Plasma Exosomal Levels = Synaptic Maintenance Failure

Plasma exosomal panels predict disease 5-7 years before symptoms (Jia et al., 2021).

Visualizing Resilience (SV2A PET)



Brain A: The Resilient

Brain B: The Progressor

Brain A: The Resilient

High Amyloid, High Synaptic Density (SV2A). Cognitively Normal.

Brain B: The Progressor

High Amyloid, Low Synaptic Density (SV2A). Cognitive Decline.

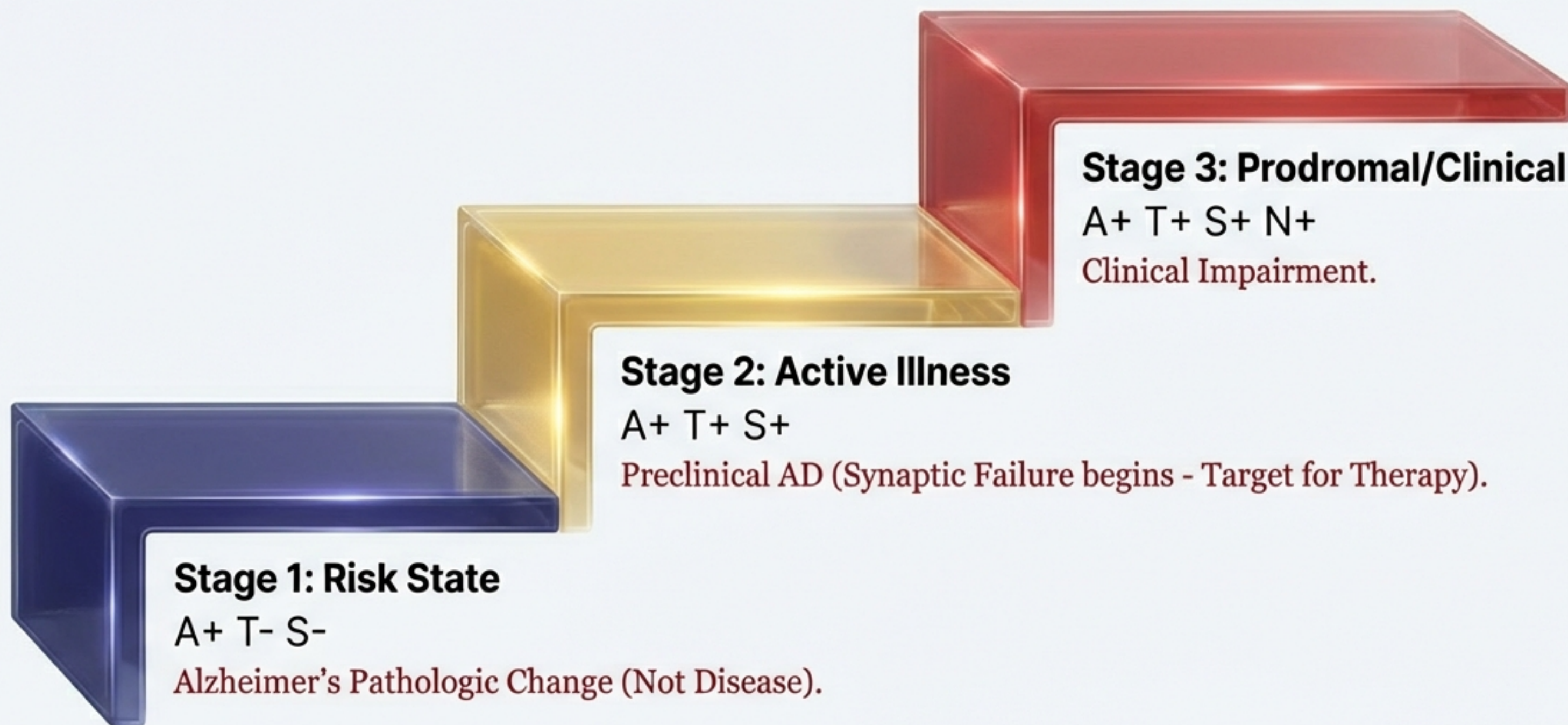
Synaptic maintenance differentiates benign proteinopathy from malignant disease.

Proposal: The AT(S)N Framework

Synaptic dysfunction (S) serves as the obligate marker of active disease, bridging proteinopathy and neurodegeneration.



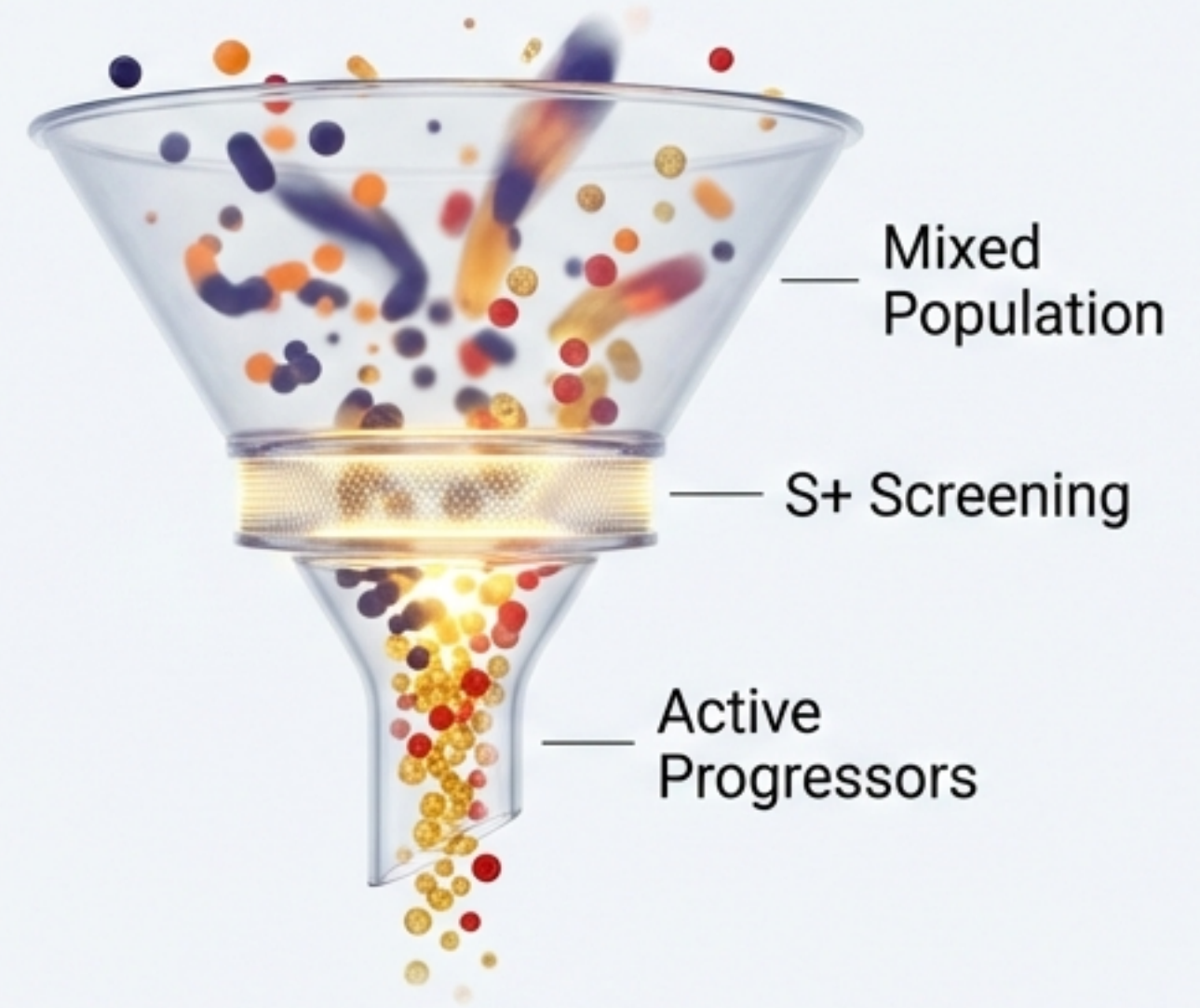
Redefining Preclinical Staging



Ethical & Clinical Implications



Ethical: Stops diagnosing healthy people with fatal diseases.



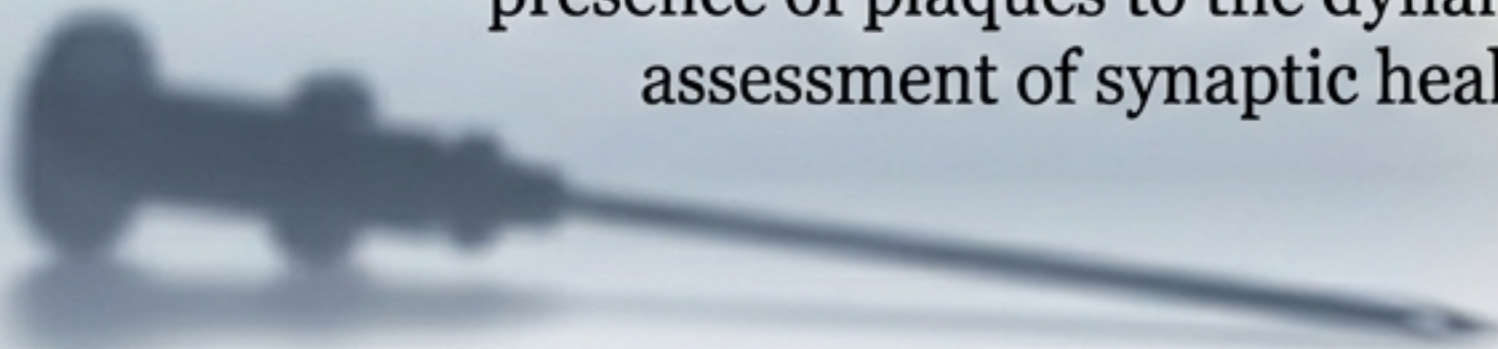
Clinical: Enriches trials with patients who are biologically progressing.

Aligns diagnosis with the biological reality of harm.

The Future is Synaptic

Plasma exosomal assays will replace CSF as the primary screen.

We must move beyond the static presence of plaques to the dynamic assessment of synaptic health.



**The era of the linear cascade is over.
The future is multivariate and synaptic.**