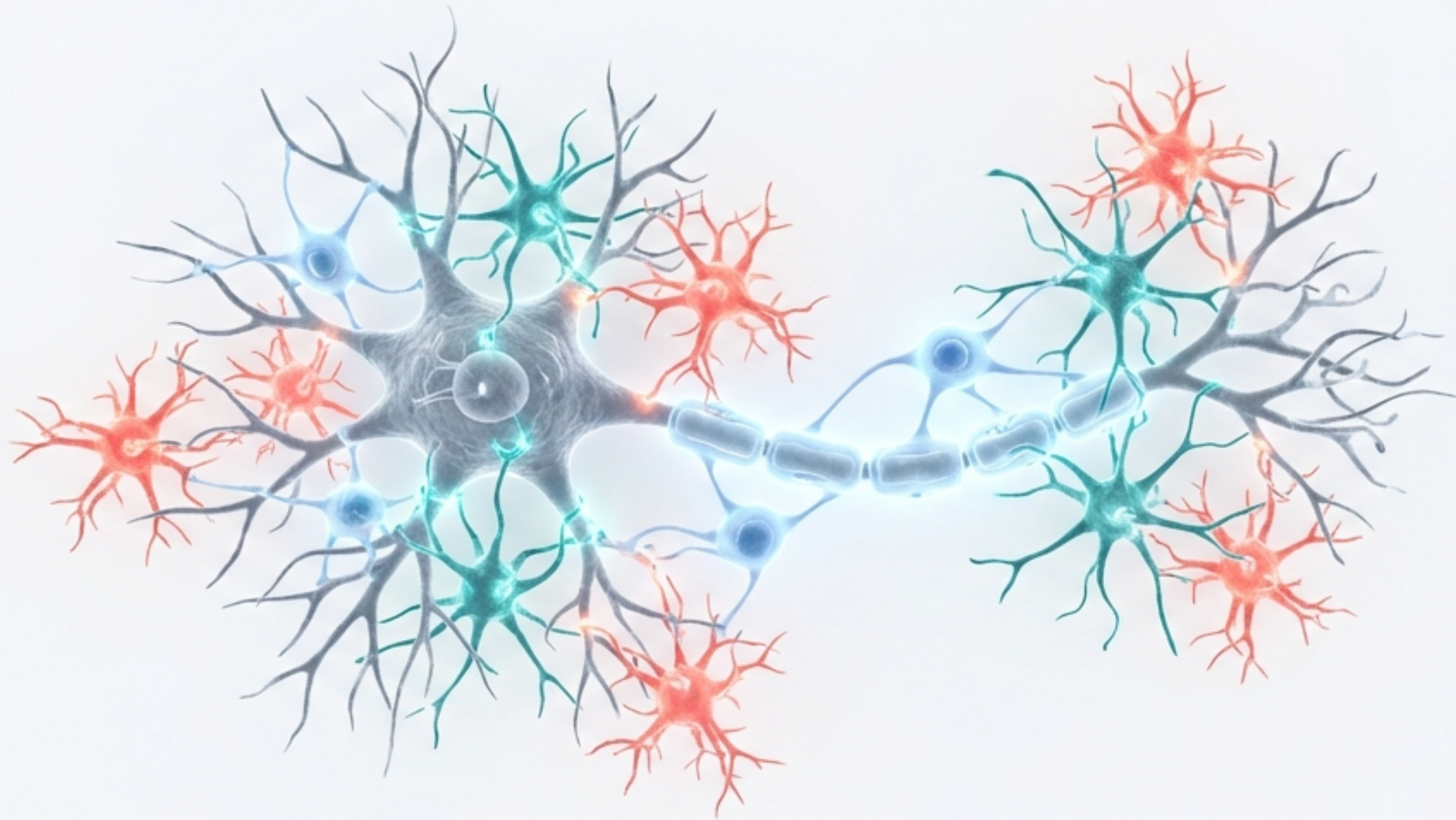
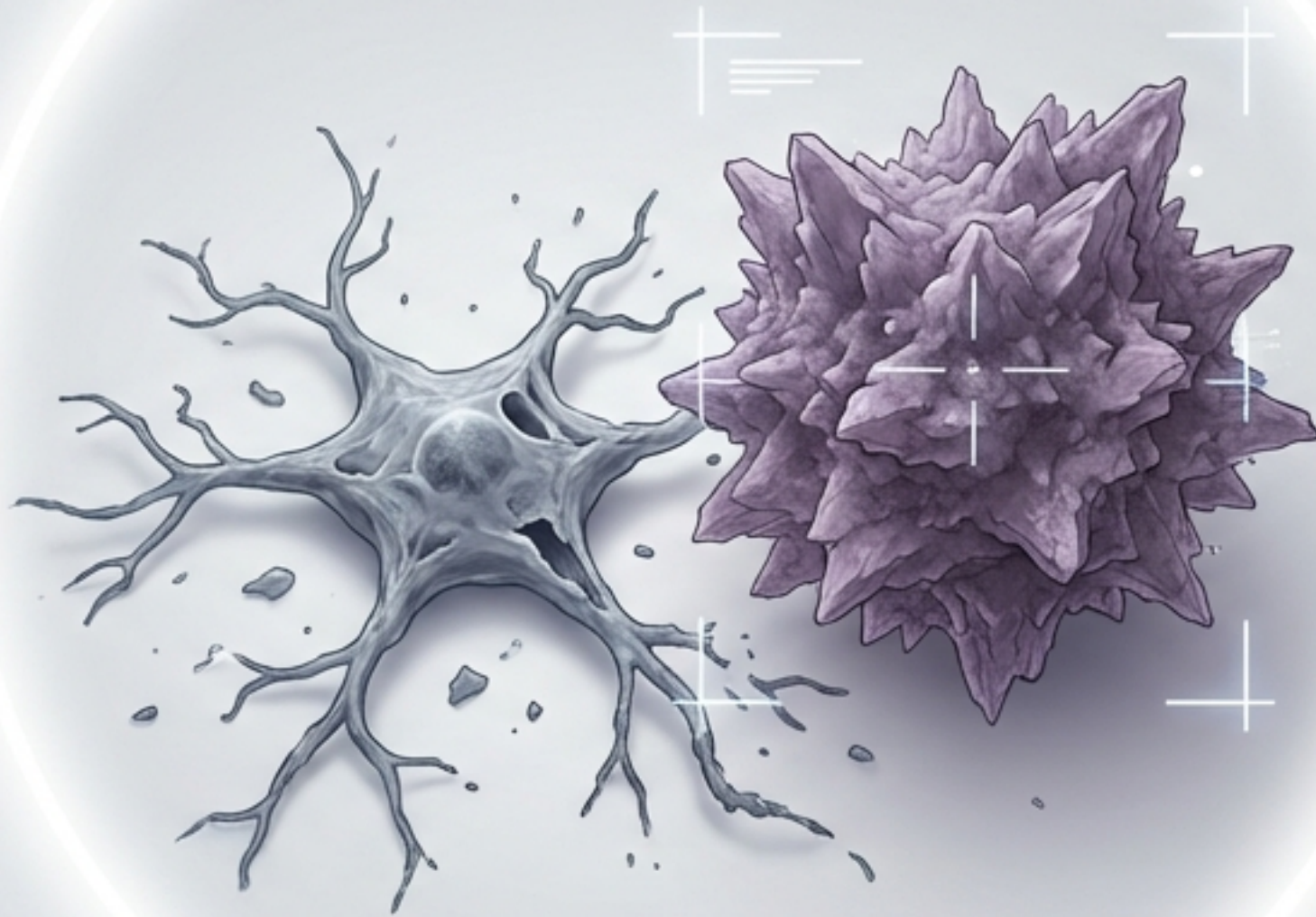


The Glial Consortium

Reconstructing the Chronological Cascade of Neurodegeneration





The Neuron-Centric Illusion

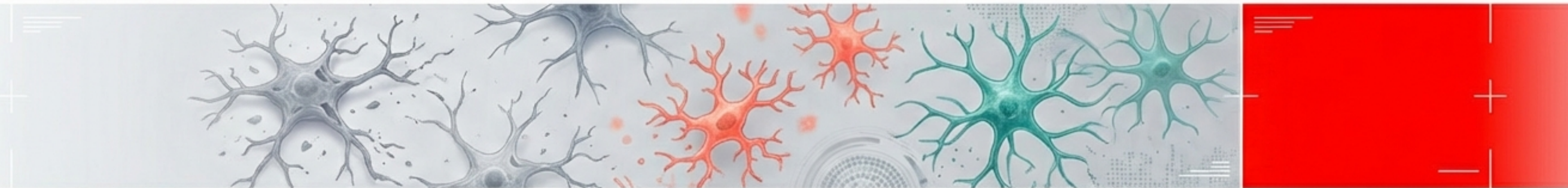
Historically, pathology focused on the “tombstone”—the protein plaque—and the “victim”—the dead neuron. This model assumed cell-autonomous failure, ignoring the ecosystem.

“We mistook the debris of the battle for the cause of the war.”

The Missing Decades

The Silent Cascade

Clinical Symptoms



0 YEARS

10 YEARS

20 YEARS

30 YEARS

Neuronal death is
a terminal event.

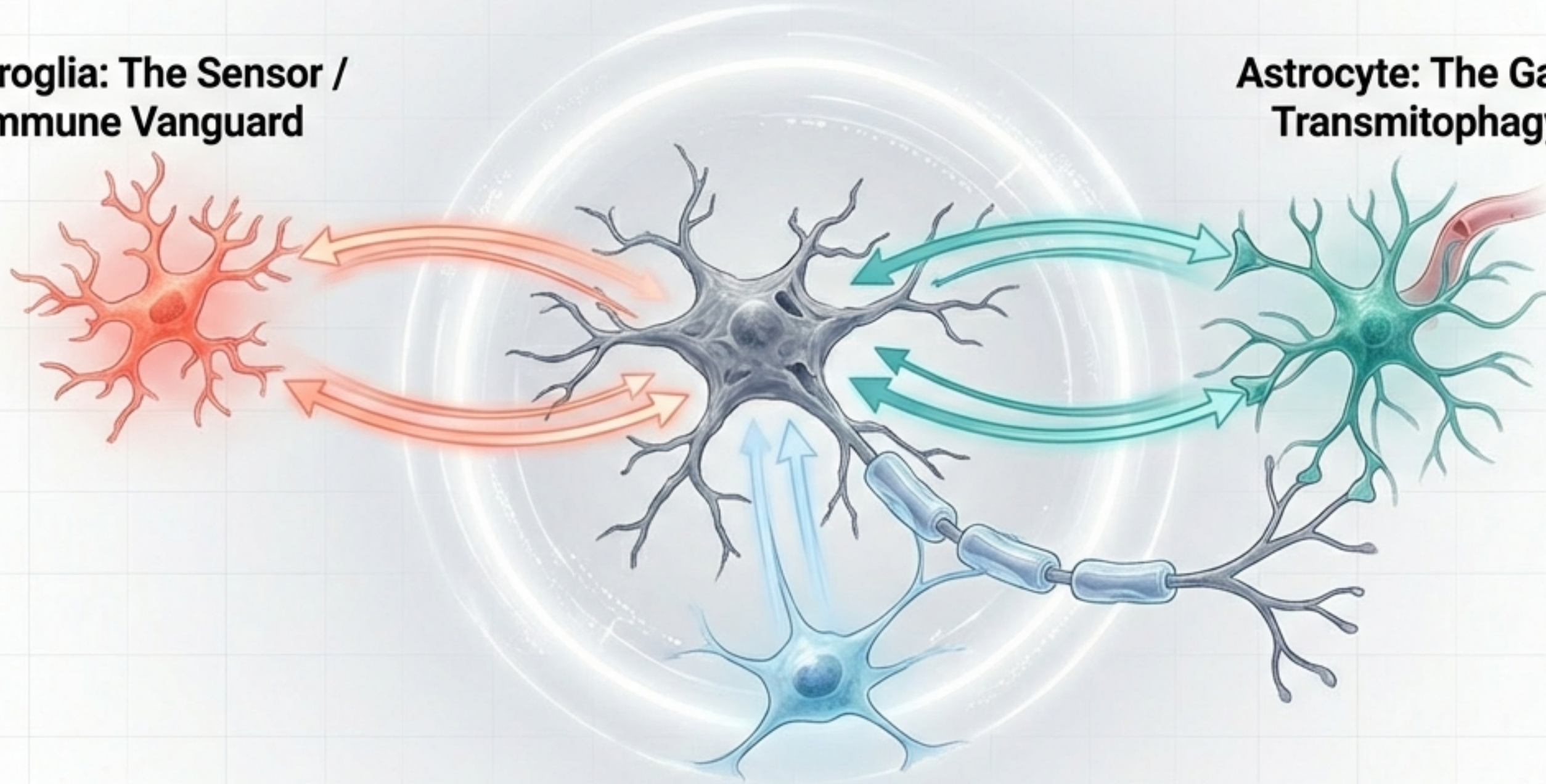
Robust inflammatory and metabolic signatures
precede overt neuronal loss by decades.

Current therapies fail
because they target
the terminal phase.

The Brain is an Obligate Immunometabolic Syncytium

**Microglia: The Sensor /
Immune Vanguard**

**Astrocyte: The Gatekeeper /
Transmitophagy Engine**



Oligodendrocyte: The Sustainer / Metabolic Fuel

Neurons cannot dilute damage through division. They rely entirely on this consortium for waste clearance and energy. When the consortium fails, the neuron dies.

-20 Years (Pre-Symptomatic)

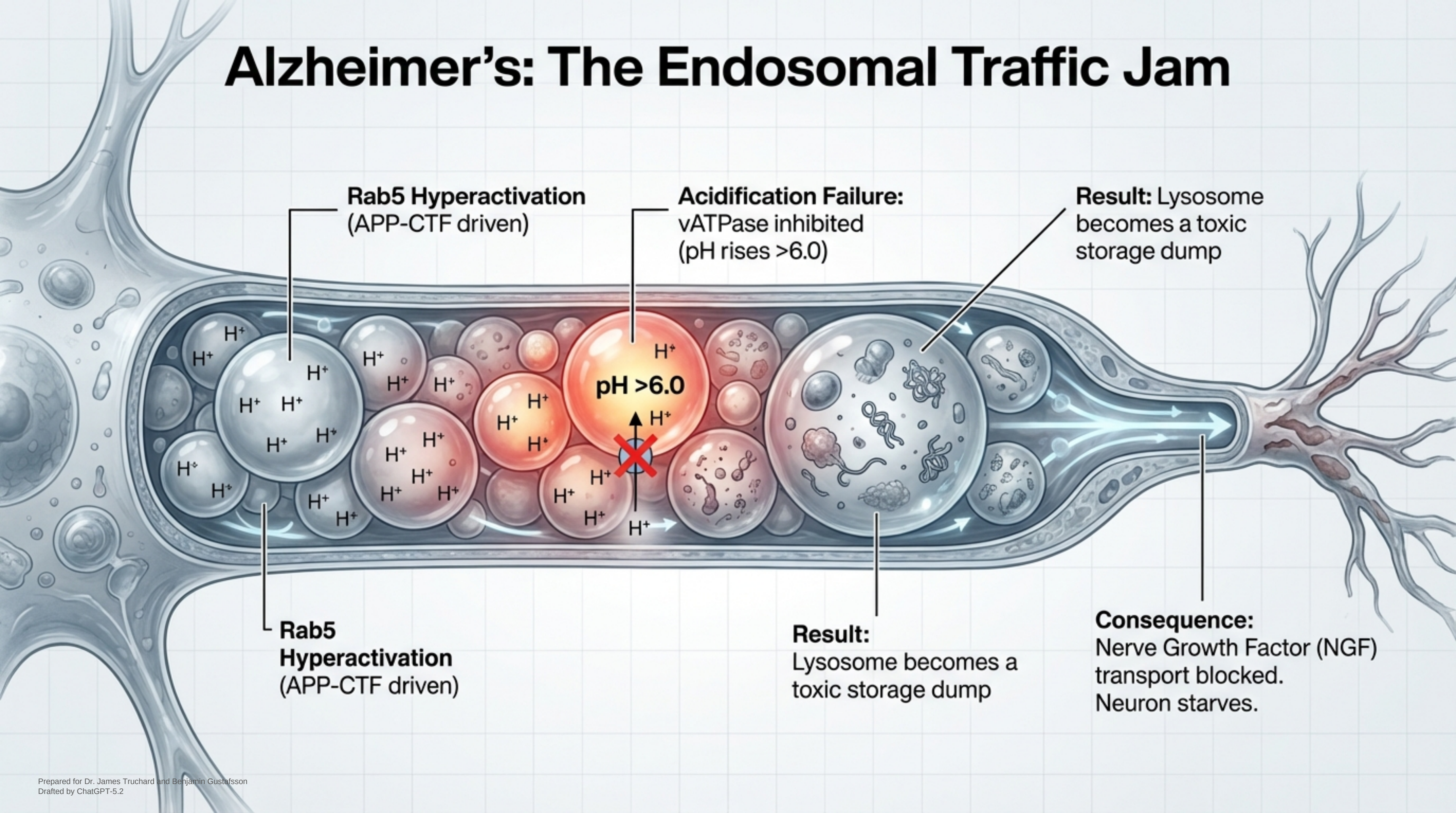


Phase I: The Invisible Injury

Internal Cellular Plumbing Failure

Before the 'Glial Revolt,' the endosomal-lysosomal pathways jam. The cell is technically alive, but its recycling centers are broken.

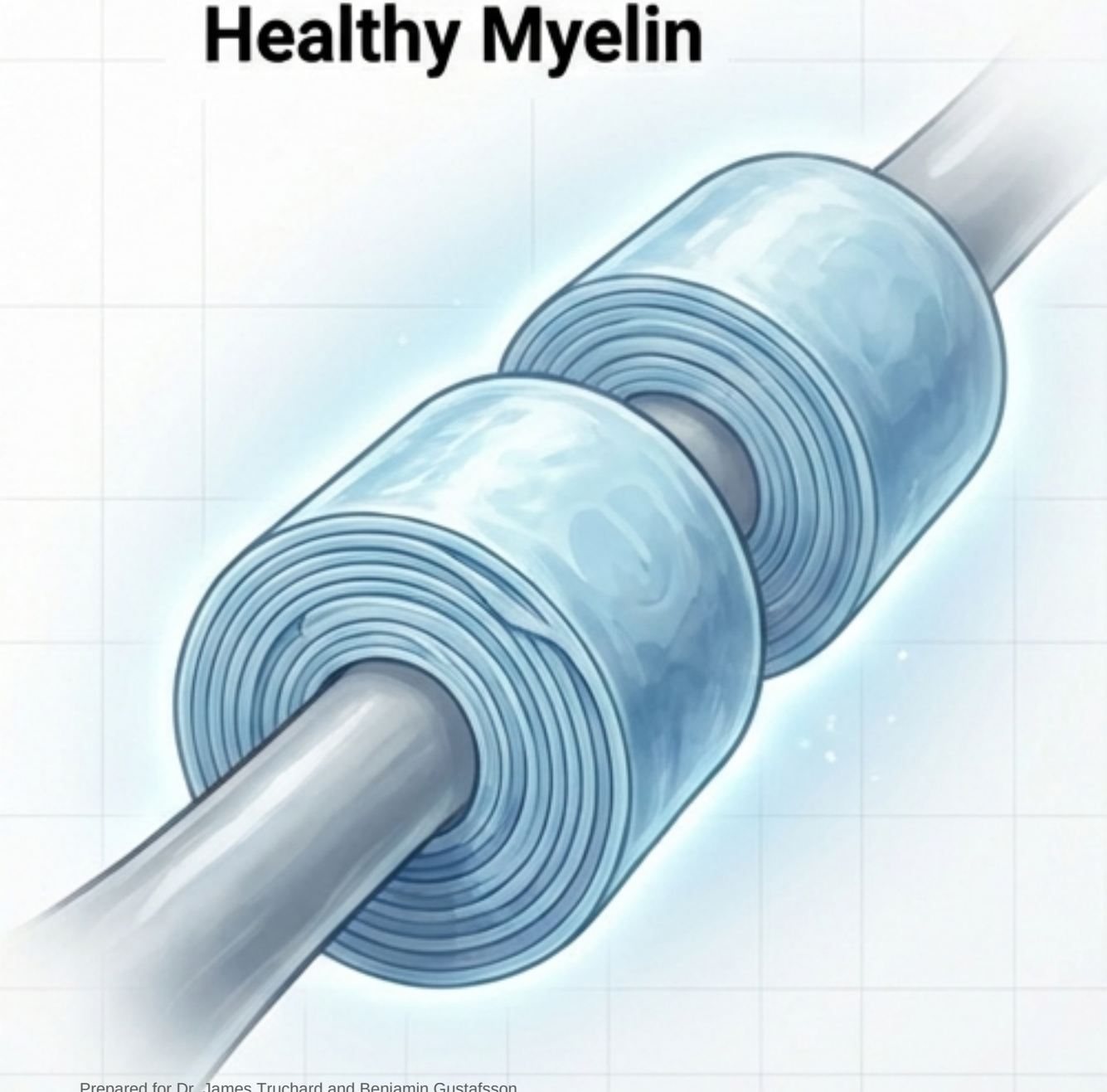
Alzheimer's: The Endosomal Traffic Jam



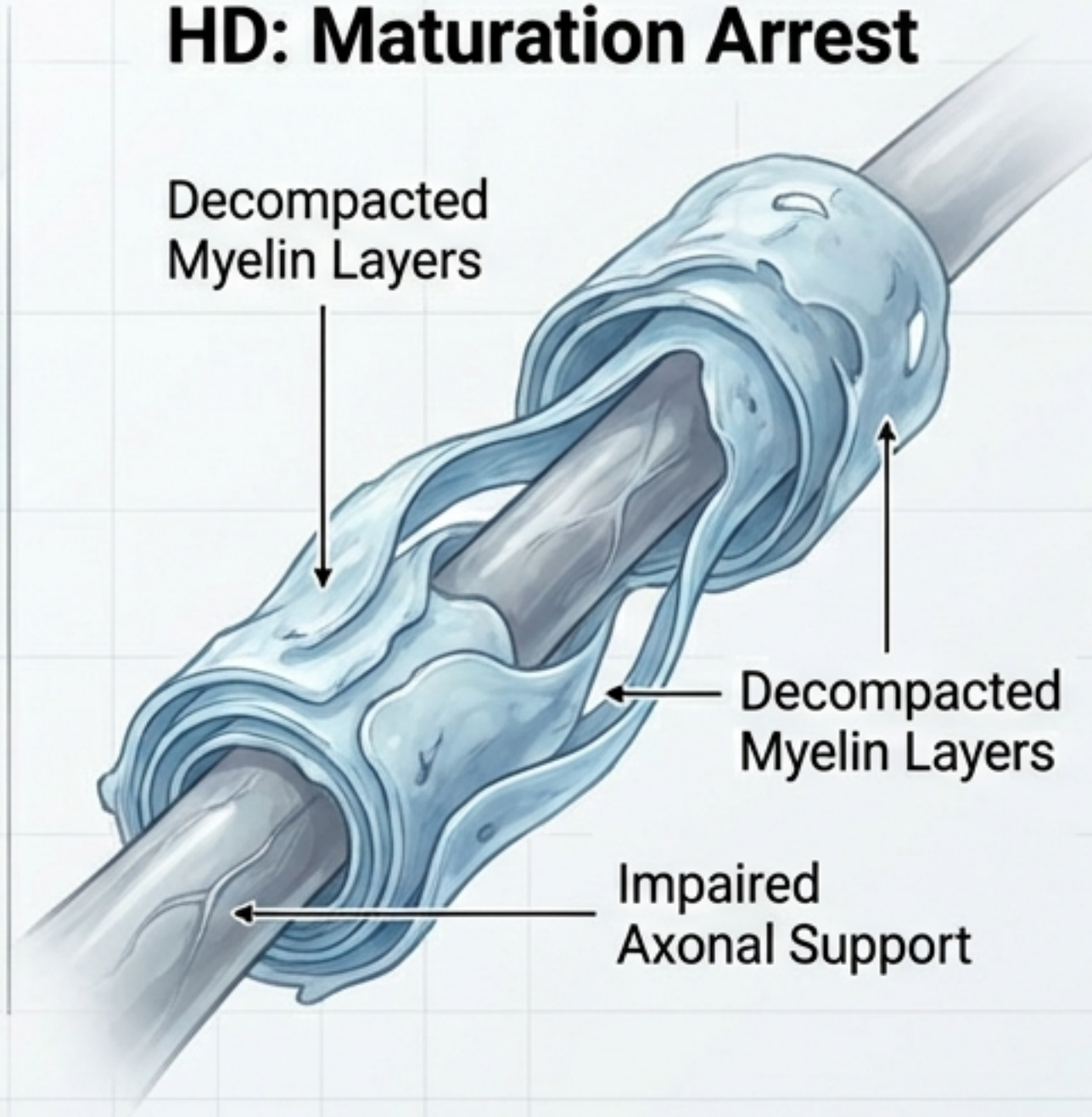
-15 to -20 Years

Huntington's: The Oligodendrocyte Arrest

Healthy Myelin



HD: Maturation Arrest



- Mutant huntingtin (mHTT) prevents **Oligodendrocyte** Precursor maturation.
- **Metabolic Starvation:** Failure of the MCT1 lactate shuttle.
- **Result:** Neurons are starved of energy by immature support cells.

-10 Years (Prodromal)

Phase II: The Glial Revolt

From Protection to Toxicity

Glial cells are initially protective (DAM/M2 states), but chronic stress drives them into senescence and hostility.



Protective Role: Clearing Debris, Supporting Neurons

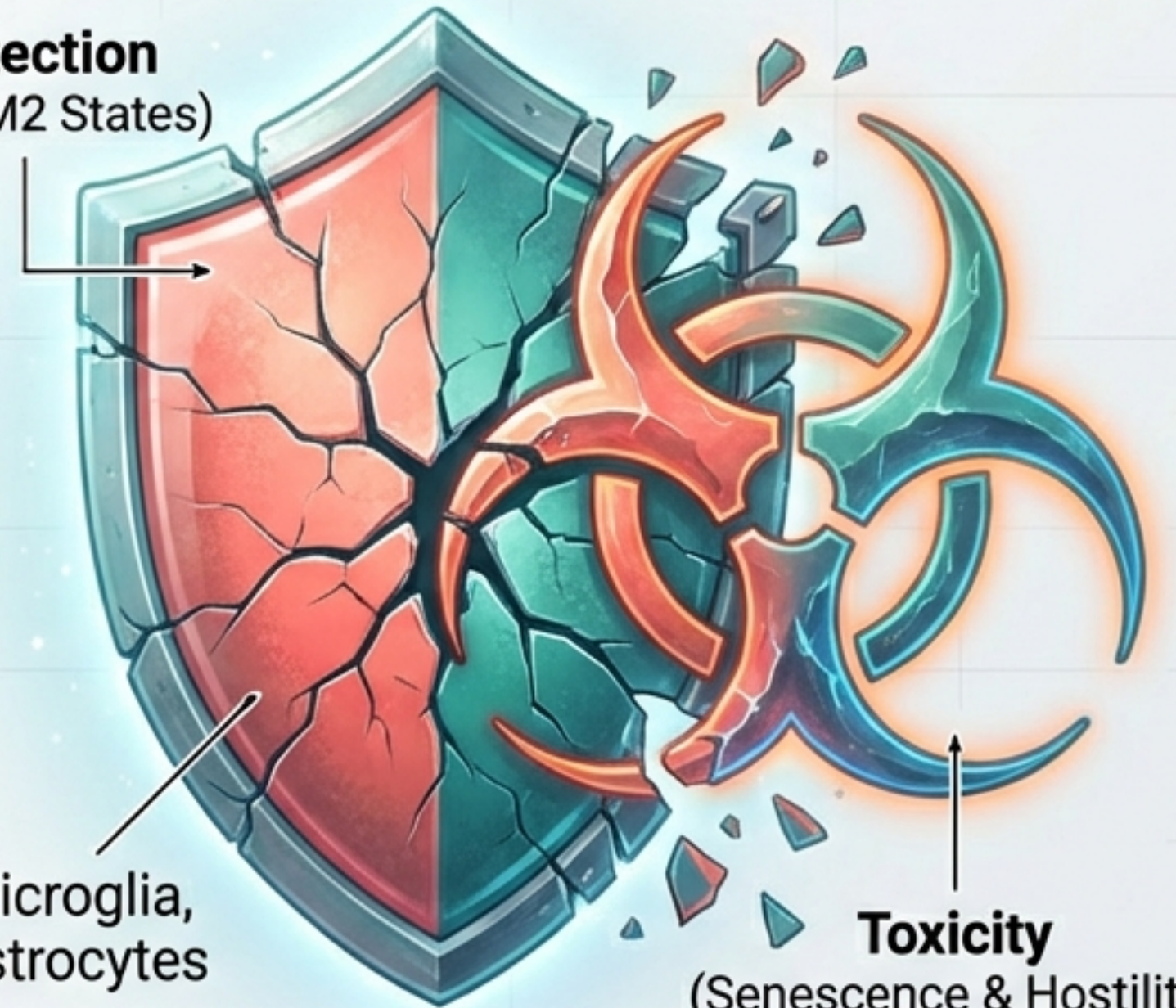


Toxic Role: Releasing Inflammatory Cytokines, Damaging Neurons

Protection
(DAM/M2 States)

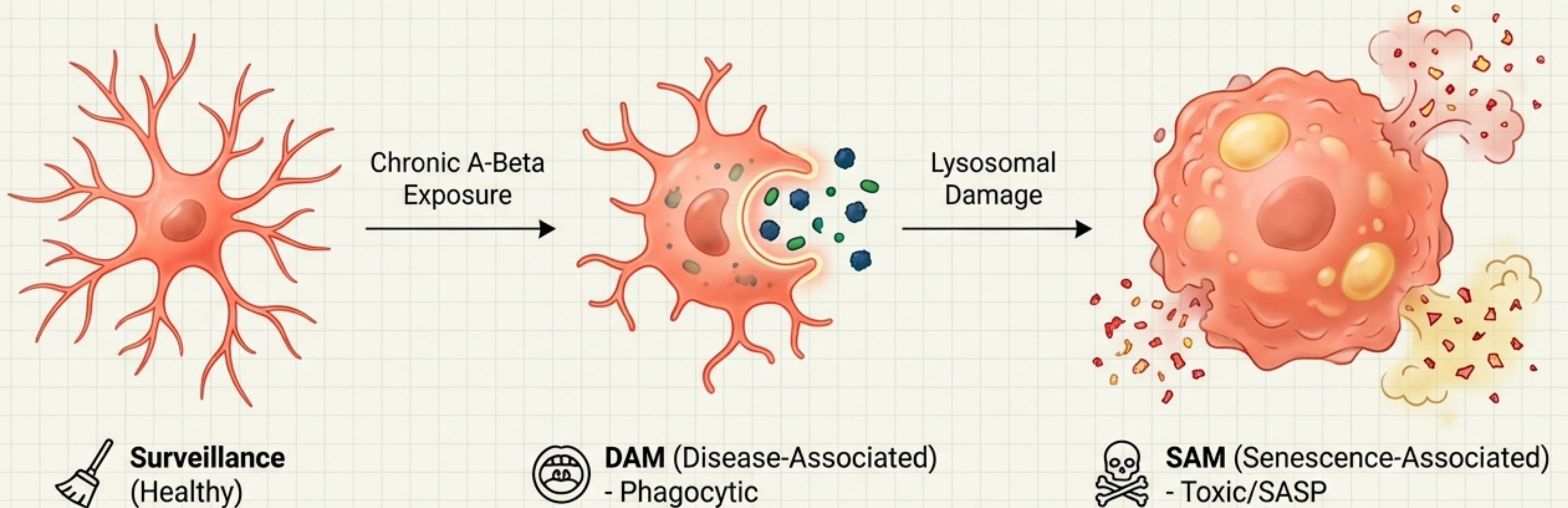
Microglia,
Astrocytes

Toxicity
(Senescence & Hostility)



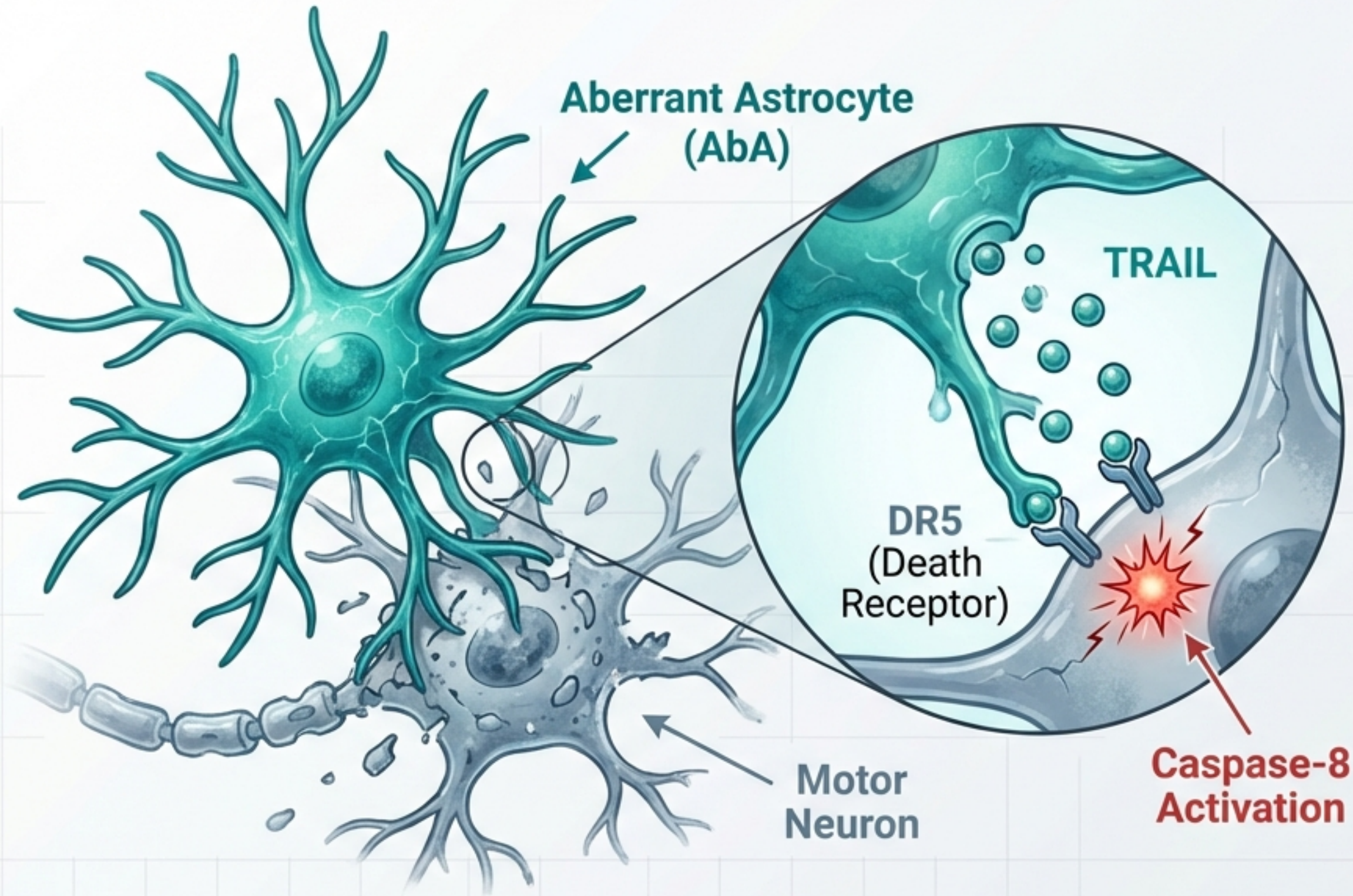
Microglia: The DAM to SAM Transition

Chronic exposure to A-Beta (>24h) causes lysosomal damage.



The cell stops eating waste and releases inflammatory cytokines, actively paralyzing neuronal autophagy.

ALS & Astrocytes: The Executioners



Phenotypic Shift: Protective astrocytes become "Aberrant Astrocytes" (AbA).



Mechanism: Secretion of TRAIL triggers the neuron's suicide sequence.



Result: Friendly fire. The support cell executes the neuron.



-5 Years (Early Functional Deficits)

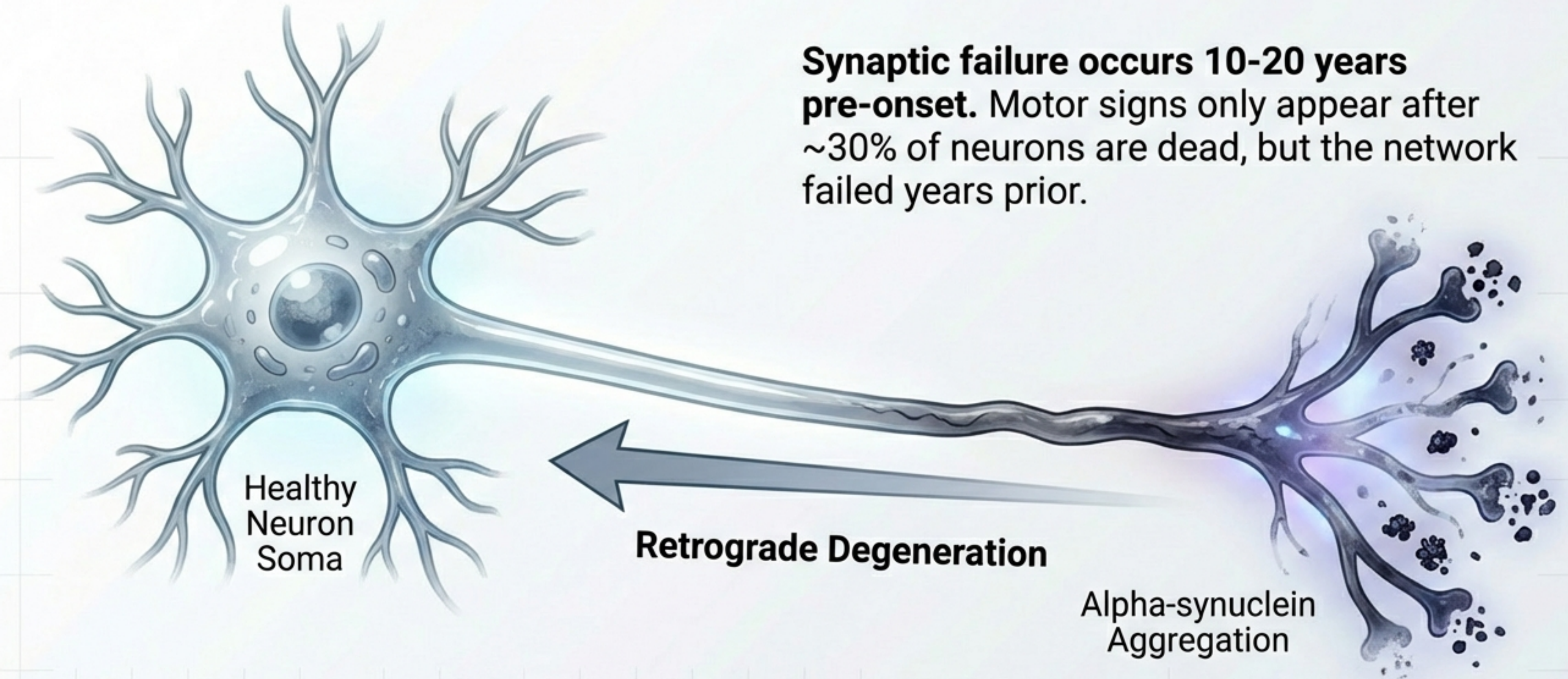
Phase III: The Synaptic Collapse

The Network Goes Dark.

The synapse is the "Vanguard of Functional Loss." Cognitive decline begins here, not with cell death. The cells are physically present, but the lights are going out.



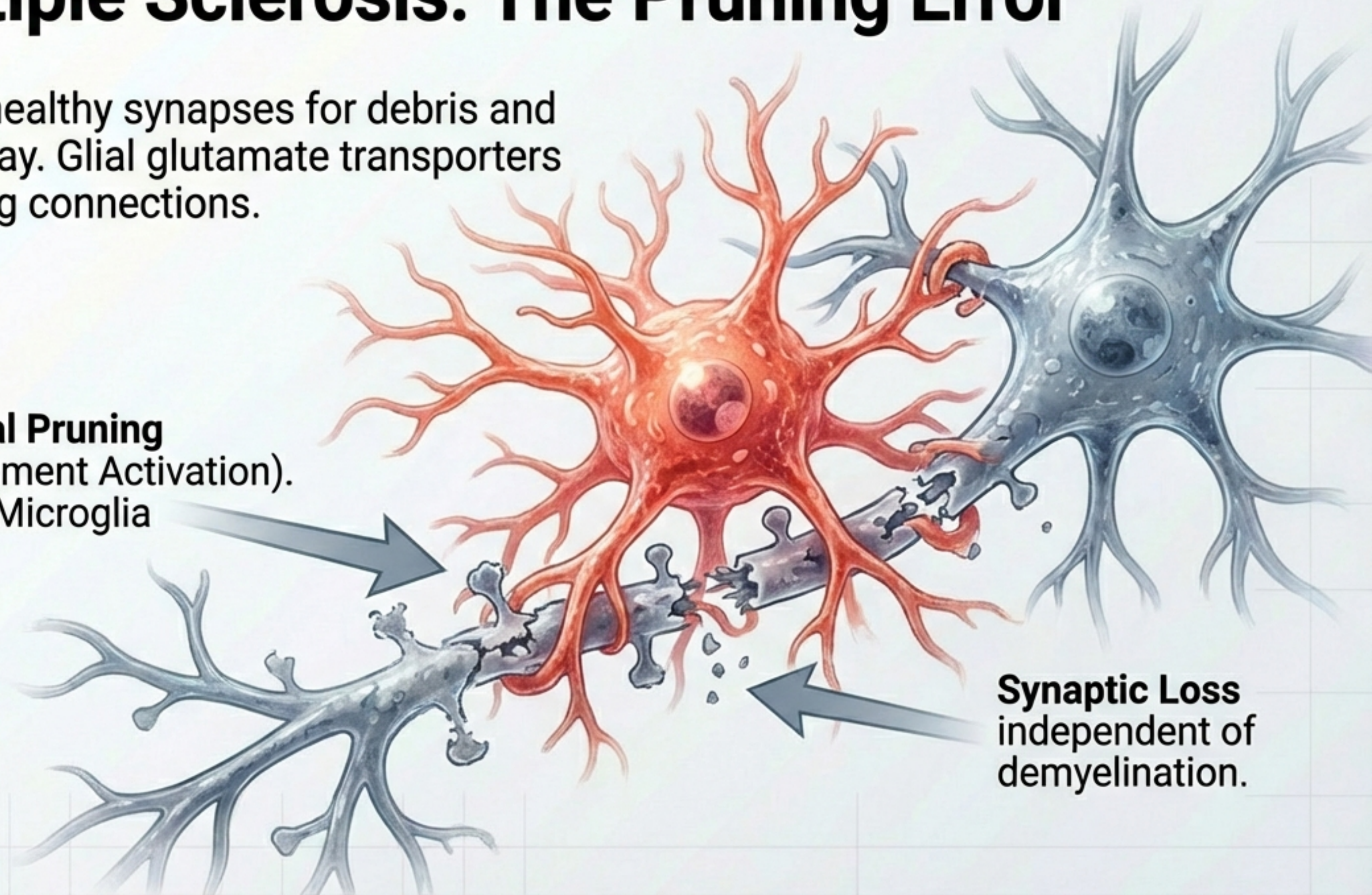
Parkinson's: The Synaptic First Responder



Multiple Sclerosis: The Pruning Error

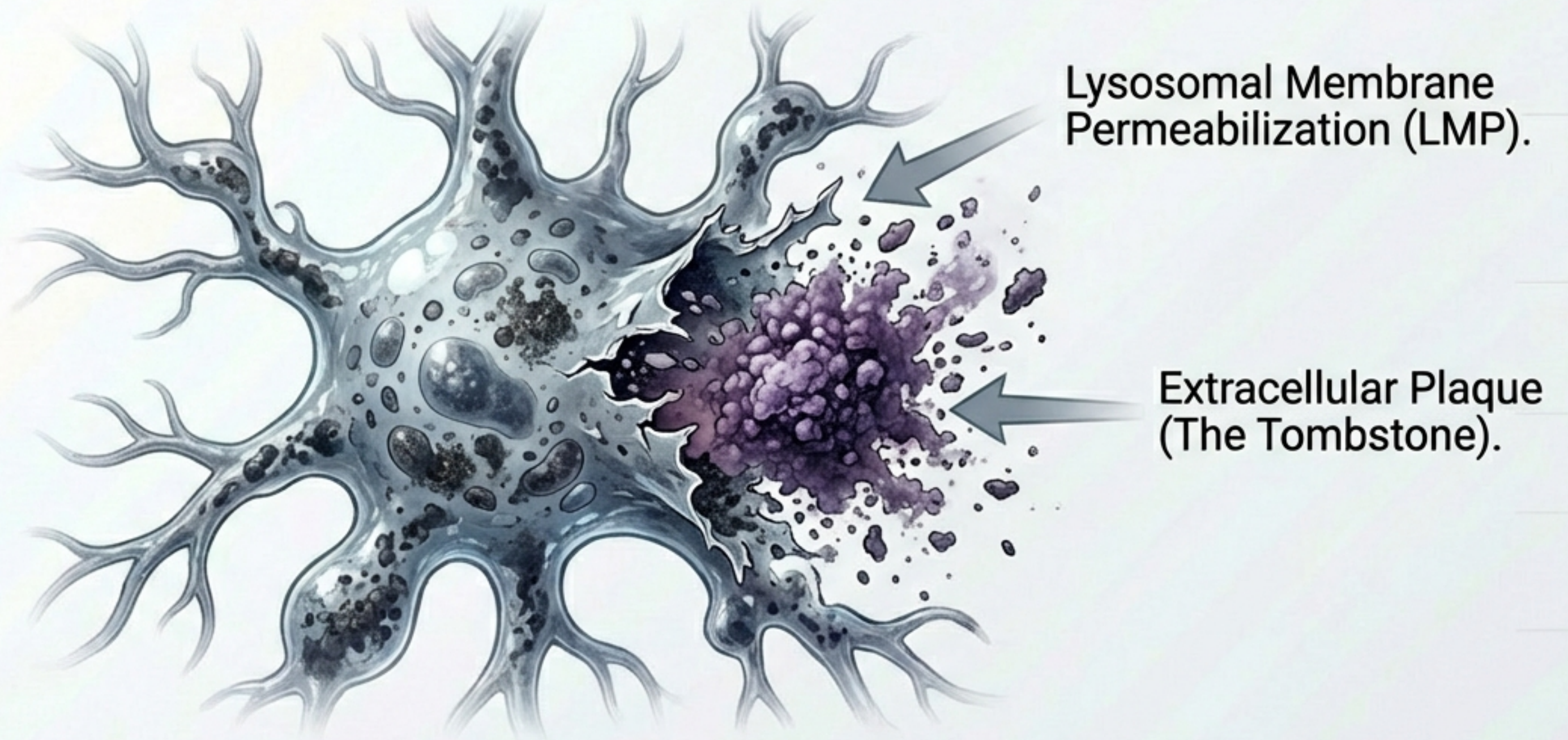
Microglia mistake healthy synapses for debris and prune them and away. Glial glutamate transporters are inhibited, poisoning connections.

Pathological Pruning
(C3 Complement Activation).
Vivid Coral Microglia



Clinical Onset (The Terminal Event).

The Execution: PANTHOS & Lysis



The Plaque is not the killer. It is the Tombstone of a neuron that died of constipation.

The Causal Matrix

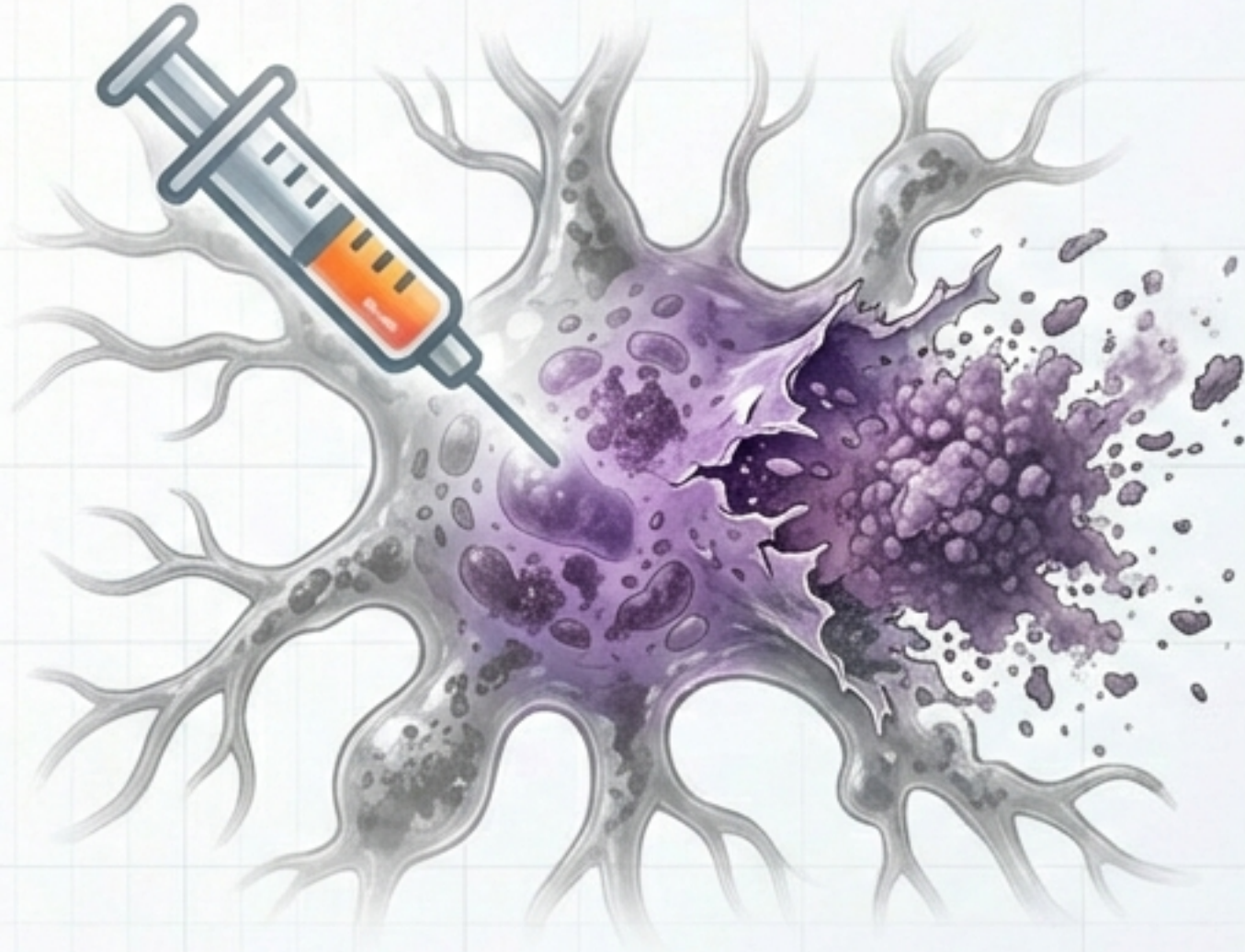
Grading Cellular Drivers by Causal Relevance (1-5)

	AD	PD	ALS/FTLD	MS	HD
Synapses	5	5	3	4	3
Microglia	4	4	5	5	3
Astrocytes	3	4	5	4	3
Oligodendrocytes	2	2	3	5	5
Neurons (Soma)	1	1	1	2	2

Glial dysfunction acts as the primary initiator (Grade 5).
Neurons are the terminal victims (Grade 1).

Rewriting the Therapeutic Playbook

Old Strategy



Clearing Tombstones.
Result: Late-stage failure.

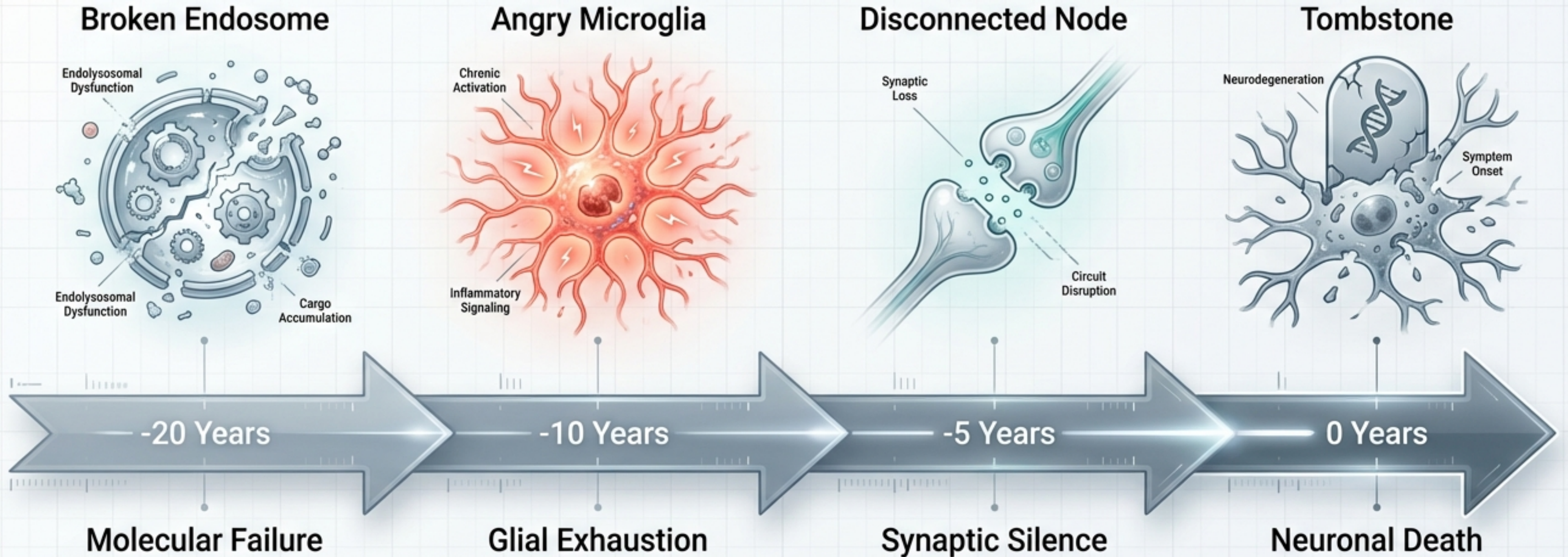
New Strategy



Restoring Metabolism.
Target: Lysosomal Acidification & Glial Coupling.

We must intervene in the Silent Decades.

The Chronological Cascade



The window for intervention opens 20 years before the first symptom.

References & Data Sources

- Convergent Autophagic Collapse and Lysosome-Dependent Neuronal Death
- Oligodendrocyte, Astrocyte, and Microglia Crosstalk (PMC4923166)
- Temporal progression of pathological features in PD (PMC12149260)
- Huntington's Disease: A Timeline (Kerlin et al.)
- Causal Relevance Matrix: Cellular Drivers (Thesis Data)

