THE SPECTRUM OF COLLAPSE

A Cell-Type-Resolved Map of Death Modalities Across the Spatiotemporal Progression of Alzheimer's Disease

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in dialogue with Butovsky, Crapser, de Vries, and the Collapse quartet

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Formalizing the death-modality axis from the Collapse quartet: Convergent Synaptic Collapse, Homeostatic Microglial Collapse, Bioenergetic Collapse, and Terminal Collapse

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Abstract

The Collapse quartet identified two poles of neuronal death in Alzheimer's disease: an intrinsic pole, where cells die from the failure of their own quality-control machinery (autophagy-lysosomal collapse, PANTHOS), and an extrinsic pole, where cells die from environmental assault enabled by the loss of protective structures (excitotoxicity after perineuronal net degradation). The Terminal Collapse thesis catalogued eight characterized death modalities and noted that they distribute along this axis, but the axis itself was informal — an observation from synthesis rather than a formalized organizing principle. This thesis formalizes the intrinsic–extrinsic spectrum, defines placement criteria, maps every major vulnerable cell type in Alzheimer's disease onto it, and traces the resulting cell-type × death-modality × disease-stage matrix across the spatiotemporal progression defined by Braak staging.

The vulnerable cell census includes: locus coeruleus noradrenergic neurons (the earliest affected, Braak pre-tangle stages a/b), dorsal raphe serotonergic neurons (co-earliest with locus coeruleus), entorhinal cortex layer II stellate neurons (Braak I–II), hippocampal CA1 pyramidal neurons (Braak III–IV), nucleus basalis of Meynert cholinergic neurons (mid-stage), cortical somatostatin-positive interneurons (early-to-mid), cortical parvalbumin-positive fast-spiking interneurons (mid-to-late), neocortical pyramidal neurons (Braak V–VI), oligodendrocytes (progressive, white-matter-first), and astrocytes (reactive transformation rather than death per se, but with neurotoxic gain-of-function through complement C3 secretion that feeds the extrinsic pole for surrounding neurons).

The formalized axis reveals three principles that the informal version did not. First, the earliest-dying cells in Alzheimer's disease — locus coeruleus and raphe neurons — occupy the intrinsic pole. They are tonically firing, high-metabolic-demand cells whose death is driven by cumulative mitochondrial oxidative stress, iron accumulation, and tau-mediated proteostatic failure over decades, not by acute environmental assault. Their death is the slow pole of the spectrum: years to decades of cumulative quality-control erosion. Second, the latest-affected cells in the extrinsic-pole category — the PV+ interneurons — are killed rapidly once their perineuronal net is removed, but their vulnerability is contingent on a prior event (PNN degradation by post-homeostatic microglia) that is itself a consequence of the intrinsic-pole failures occurring in other cell types and in the microglia themselves. The extrinsic pole is therefore downstream of and dependent on the intrinsic pole. Third, the middle of the spectrum — where ferroptosis, pyroptosis, and necroptosis operate — is where the intrinsic and extrinsic poles couple, and this coupling is the mechanism by which the slow, decades-long quality-control erosion at the intrinsic pole eventually generates the rapid, self-amplifying circuit collapse at the extrinsic pole that produces the cognitive phenotype.

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The integrated model proposes that Alzheimer's disease is a single degenerative process viewed through different temporal windows: a decades-long intrinsic quality-control failure that is clinically silent while it affects only the brainstem aminergic nuclei and the entorhinal cortex, and a rapid extrinsic circuit-level collapse that becomes clinically manifest when the cumulative intrinsic failure reaches the cortical microglia and triggers the PNN degradation that exposes the fast-spiking interneurons to multi-modal death. The MCI-to-dementia transition is, on this model, the moment when the disease crosses from the intrinsic pole to the extrinsic pole — from slow internal erosion to rapid external assault — and the therapeutic implication is that interventions aimed at the intrinsic pole (quality-control restoration, mitophagy support, NAD+ supplementation) must begin decades before clinical onset to prevent the extrinsic cascade, while interventions aimed at the extrinsic pole (NMDA blockade, PNN preservation, complement inhibition) can only be effective within the narrow window after the cascade initiates and before the target cells are depleted.

1. Formalizing the Axis

1.1 Definition

The intrinsic–extrinsic death-modality axis organizes the characterized cell death mechanisms of Alzheimer's disease according to the direction from which the lethal insult originates relative to the dying cell. At the intrinsic pole, the cell dies because its own internal quality-control machinery has failed: its lysosomes cannot acidify, its mitochondria cannot be cleared, its autophagic cargo accumulates until the cell ruptures. No external trigger beyond age is required. At the extrinsic pole, the cell dies because its environment has overwhelmed its defense capacity: glutamate floods its receptors, iron generates radicals at its membrane, complement tags it for engulfment, cytokines potentiate the assault. The cell's internal machinery may be intact; it simply cannot survive what is being done to it from outside.

1.2 Placement criteria

A death modality is placed on the axis according to three criteria:

Criterion 1 — Origin of the lethal signal. Does the signal that initiates the death cascade originate within the dying cell (intrinsic) or from its environment (extrinsic)? PANTHOS originates within the cell (failed autolysosome). Excitotoxicity originates from the circuit (ambient glutamate). Ferroptosis is mixed: the iron comes from outside (released from degraded PNN) but the GPX4 failure that permits lipid peroxidation propagation is internal.

Criterion 2 — Dependence on cell-autonomous versus non-cell-autonomous events. Can the death occur in an isolated cell, or does it require interaction with other cells or structures? PANTHOS can occur in an isolated neuron with sufficient Aβ production and lysosomal failure. Phagoptosis requires a microglial partner. Excitotoxicity requires a circuit providing glutamate. The more non-cell-autonomous the death, the more extrinsic its placement.

Criterion 3 — Timescale from initiating event to cell death. Intrinsic-pole deaths are slow: they require cumulative damage over years to decades (the Streit dystrophy timeline, the Swerdlow mitochondrial cascade). Extrinsic-pole deaths are fast: once the protective barrier is removed, death follows in hours to days (the Cabungcal PNN removal experiment). The timescale reflects the fundamentally different pathological dynamics at each pole — erosion versus assault.

1.3 The axis applied to death modalities

Applying these criteria to the eight death modalities catalogued in Terminal Collapse:

| Death modality | Origin | Cell-autonomy | Timescale | Position | |---|---|---|---|---| | PANTHOS | Internal (lysosomal failure, intracellular Aβ) | Fully cell-autonomous | Years | 0.0 (pure intrinsic) | | Parthanatos | Internal (oxidative DNA damage PARP-1) | Mostly cell-autonomous | Days to weeks | 0.2 | | Wallerian/SARM1 | Internal (axonal NAD+ depletion) | Cell-autonomous at the axon | Weeks to months | 0.25 | | Ferroptosis | Mixed (external iron + internal GPX4 failure) | Partially cell-autonomous | Hours to days | 0.5 (midpoint) | | Pyroptosis | Mixed (external DAMP trigger + internal inflammasome) | Non-cell-autonomous trigger | Hours | 0.6 | | Necroptosis | External TNF-α + internal RIPK cascade | Non-cell-autonomous trigger | Hours | 0.7 | | Phagoptosis | External (complement deposition + microglial engulfment) | Fully non-cell-autonomous | Minutes to hours | 0.9 | | Excitotoxicity | External (ambient glutamate, circuit-level) | Fully non-cell-autonomous | Hours to days after PNN loss | 1.0 (pure extrinsic) |

The numerical positions are heuristic rather than quantitative, but the ordering is non-arbitrary: each placement follows from the three criteria, and the resulting spectrum is continuous rather than categorical. A cell can die from mechanisms at multiple positions simultaneously (as the Terminal Collapse thesis argued for PV+ interneurons), and the dominant death modality for a given cell type at a given disease stage reflects the cell's position on the axis rather than a universal property of the disease.

2. The Vulnerable Cell Census

2.1 Locus coeruleus noradrenergic neurons — The first to fall

The locus coeruleus (LC) is a small nucleus in the pontine brainstem containing on the order of twenty thousand neurons per side counted as tyrosine-hydroxylase-positive, neuromelanin-bearing cells, or nearer fifty thousand per side counted inclusively. It is the principal source of noradrenergic innervation to the entire cerebral cortex, hippocampus, amygdala, thalamus, and cerebellum. LC neurons are tonically active during wakefulness, firing at 1–3 Hz continuously throughout the waking day, and their axons are long, thin, and unmyelinated or only sparsely myelinated, reaching broadly across the forebrain.

The LC is the first brain structure in which hyperphosphorylated tau accumulates, beginning in the first decades of life — Braak pre-tangle stages a/b, decades before any cortical involvement. By mid-life, a substantial fraction of the human population shows tau pathology in the LC. By the time clinical Alzheimer's disease is diagnosed, LC neuronal loss exceeds 50% in most studies, and the loss correlates with cognitive decline and neuropsychiatric symptoms including depression, anxiety, and sleep disturbance.

Axis position: pure intrinsic (0.0–0.15). LC neurons die from cumulative, decades-long quality-control failure driven by their extreme metabolic demands. Their tonic firing produces sustained mitochondrial output and correspondingly high baseline ROS. Their autonomous pacemaking imposes a continuous calcium load, and their catecholamine chemistry a continuous oxidative one, as dopamine and noradrenaline auto-oxidize to reactive quinones. They accumulate iron and neuromelanin throughout life, generating Fenton-reactive microenvironments within the cell body itself. They accumulate tau — the earliest tau in the human brain — and the tau accumulation correlates with mitochondrial gene downregulation, synaptic loss, and eventual cell death.

The death modality is overwhelmingly intrinsic: these cells die from the inside, over decades, through the accumulation of damage to their own mitochondria, lysosomes, and cytoskeleton. There is no evidence of acute excitotoxic, phagoptotic, or ferroptotic assault from the environment. The PNN is not relevant here — LC neurons are not ensheathed by perineuronal nets. Their death is the purest expression of the intrinsic pole: a cell whose extraordinary metabolic demands exceed its quality-control capacity over the timescale of a human lifespan.

Dominant death modalities: Parthanatos (PARP-1 hyperactivation from chronic oxidative DNA damage), PANTHOS (autophagy-lysosomal failure from tau-mediated transport disruption), Wallerian degeneration (SARM1-mediated axonal destruction as the long axon degenerates before the soma). Iron-driven ferroptosis of the neuromelanin-laden soma may contribute in later stages.

2.2 Dorsal raphe serotonergic neurons — The co-earliest casualty

The dorsal raphe nucleus (DRN) contains the majority of the brain's serotonergic neurons and, like the locus coeruleus, shows tau pathology beginning in the first decades of life. A 2024 Molecular Psychiatry study demonstrated that tau pathology is present in the DRN of individuals aged 25–80 without known history of dementia, at prevalence comparable to the LC. The DRN is one of the first brain regions to show neurofibrillary pathology — in some individuals, before even the transentorhinal region.

The serotonergic neurons of the DRN share the vulnerability profile of LC neurons: they are tonically active, project widely, and have high metabolic demands. A subset of DRN neurons are dual serotonergic/glutamatergic, and these dual-transmitter neurons exhibit increased excitability that may promote both tau accumulation and tau release along axonal pathways.

Axis position: intrinsic (0.1–0.2). Like LC neurons, raphe serotonergic neurons die from decades-long intrinsic quality-control failure. The slightly more extrinsic position reflects the contribution of increased excitability in the dual 5-HT/glutamate neurons, which introduces a modest circuit-level component to the vulnerability. But the dominant driver remains internal: cumulative tau, mitochondrial decline, and iron accumulation over the lifespan.

Dominant death modalities: Parthanatos and PANTHOS, as for LC neurons. The dual-transmitter excitability feature may introduce a low-grade excitotoxic component not present in LC neurons, shifting the raphe slightly toward the extrinsic pole.

2.3 Entorhinal cortex layer II stellate neurons — The cortical bridgehead

The stellate neurons of entorhinal cortex layer II are the first cortical neurons to develop tau pathology (Braak stages I–II) and the first cortical neurons to die. They are the principal input neurons to the hippocampus through the perforant pathway, and their loss disconnects the hippocampus from cortical input, producing the memory encoding failure that is the earliest cognitive symptom of AD.

These neurons are metabolically expensive (high firing rates in spatial navigation circuits), express high levels of APP (producing substantial intraneuronal Aβ), and are exposed to the age-related decline in autophagy-lysosomal capacity that Nixon's work characterized. They are strong PANTHOS candidates: their high Aβ production, combined with declining lysosomal acidification, produces the intraneuronal Aβ accumulation that the Gouras-Nixon axis predicts will generate inside-out plaque formation.

Axis position: intrinsic with emerging extrinsic component (0.15–0.3). The primary death driver is intrinsic quality-control failure (Aβ accumulation, lysosomal acidification failure, PANTHOS). But entorhinal cortex layer II also receives substantial glutamatergic input, and as

neighboring neurons die and microglia become activated, the environment introduces inflammatory and potentially excitotoxic insults. The entorhinal cortex is where the axis begins to shift from pure intrinsic to mixed.

Dominant death modalities: PANTHOS (primary), with emerging ferroptosis (as local iron accumulates from dying neurons and activated microglia) and pyroptosis-adjacent inflammatory damage (from NLRP3-activated microglia responding to the accumulating plaques).

2.4 Nucleus basalis of Meynert cholinergic neurons — The trophic-dependent death

The cholinergic neurons of the nucleus basalis of Meynert (nbM) provide the principal cholinergic innervation of the cerebral cortex and undergo greater than 75% loss in Alzheimer's disease. Their loss is the biological substrate of the cholinergic hypothesis that dominated AD therapeutics for three decades and that produced the acetylcholinesterase inhibitor drug class (donepezil, rivastigmine, galantamine) that remains the first-line symptomatic treatment.

These neurons occupy a distinctive position on the axis because their death involves a mechanism not cleanly captured by any of the eight death modalities in the Terminal Collapse catalogue: trophic withdrawal. Cholinergic nbM neurons are dependent on nerve growth factor (NGF) signaling through TrkA receptors for phenotypic maintenance and, under some conditions, survival. In Alzheimer's disease, the metabolic pathway that converts proNGF to mature NGF is disrupted, and the degradation of mature NGF is accelerated, producing a state of chronic trophic deprivation. The neurons atrophy, lose their cholinergic phenotype, retract their axonal projections, and eventually die.

Simultaneously, cholinergic nbM neurons receive dense glutamatergic input and are vulnerable to NMDA-mediated excitotoxicity, particularly when mitochondrial function is compromised (because partial depolarization from energy failure relieves the voltage-dependent Mg2+ block of the NMDA receptor, permitting tonic calcium influx even at resting membrane potentials). Aβ oligomers further potentiate this vulnerability by disrupting mGluR7-mediated regulation of NMDA signaling specifically in basal forebrain cholinergic neurons.

Axis position: mixed intrinsic-extrinsic (0.3–0.5). The intrinsic component is trophic withdrawal (NGF pathway disruption) and mitochondrial decline. The extrinsic component is excitotoxic vulnerability through glutamatergic input and Aβ-mediated NMDA potentiation. The nbM sits near the center of the axis, dying from both internal and external causes with roughly equal contribution — the prototypical "mixed" death.

Dominant death modalities: Trophic withdrawal (apoptosis or atrophy — one of the few cell types where apoptosis may actually be relevant), excitotoxicity (NMDA-mediated, potentiated by mitochondrial failure and Aβ), and parthanatos (PARP-1 activation from the oxidative damage

that mitochondrial failure generates).

2.5 Somatostatin-positive (SST+) interneurons — The early inhibitory casualty

Somatostatin-expressing interneurons are the other major class of cortical inhibitory interneuron alongside PV+ cells, but they exhibit a strikingly different vulnerability profile. Histological studies show that SST+ interneurons are lost earlier than PV+ interneurons in AD — with tau inclusions and atrophy appearing from 9 months in TgF344-AD rats, while PV+ interneurons are resilient until 15 months. In human temporal cortex, the reduction in SST+ interneuron density is greater than for PV+ cells.

SST+ interneurons target the distal dendrites of pyramidal neurons (unlike PV+ cells, which target the soma and axon initial segment) and modulate dendritic integration rather than somatic output. They co-localize with amyloid plaques, they become hyperactive near plaques (unlike PV+ cells, which become hypoactive), and their hyperactivity correlates with plaque proximity.

Axis position: intrinsic-to-mixed (0.25–0.4). SST+ interneurons accumulate tau earlier than PV+ interneurons, suggesting a greater vulnerability to intrinsic tau-mediated damage. Their hyperactivity near plaques increases their metabolic demand and may accelerate intrinsic quality-control failure. They are not protected by perineuronal nets (most SST+ interneurons lack PNNs), so they do not undergo the sudden extrinsic vulnerability switch that PNN degradation produces for PV+ cells. Instead, they die through a more gradual combination of tau-mediated internal damage and plaque-associated environmental stress.

Dominant death modalities: Tau-mediated PANTHOS-adjacent proteostatic failure (intrinsic), pyroptosis-adjacent inflammatory damage from plaque-associated microglia (mixed), and potentially ferroptosis from the iron-rich plaque microenvironment (mixed). The absence of PNN protection means SST+ cells are chronically exposed to moderate environmental insults rather than acutely exposed to severe ones.

2.6 Hippocampal CA1 pyramidal neurons — The canonical Alzheimer's victim

CA1 pyramidal neurons are the most-studied cells in Alzheimer's disease neuropathology. Their loss is the histological signature of hippocampal atrophy on MRI, the structural correlate of episodic memory failure, and the cellular substrate of Braak stages III–IV. They express high APP, produce substantial Aβ, accumulate neurofibrillary tangles, and are the cells in which PANTHOS has been most convincingly demonstrated.

Axis position: intrinsic with progressive extrinsic component (0.2–0.5, shifting rightward with disease stage). In early disease, CA1 pyramidal neurons die predominantly from intrinsic PANTHOS — their own Aβ accumulation in failed autolysosomes. As disease progresses and the hippocampal environment becomes increasingly inflammatory and excitotoxic

(due to PV+ interneuron loss, reduced inhibition, and elevated ambient glutamate), the extrinsic component increases. Late-stage CA1 pyramidal neuron death may involve substantial excitotoxic contribution — but this is secondary to and contingent on the prior loss of PV+ interneuron-mediated inhibition.

Dominant death modalities (early): PANTHOS (primary), parthanatos (oxidative DNA damage from Aβ-mediated ROS). **Dominant death modalities (late):** PANTHOS plus excitotoxicity (from disinhibited network), ferroptosis (from iron accumulation in the chronically inflamed hippocampus), necroptosis (from microglial TNF-α).

2.7 Parvalbumin-positive (PV+) fast-spiking interneurons — The extrinsic archetype

PV+ interneurons were the subject of extensive analysis in the Terminal Collapse and Ketamine Paradox theses and their vulnerability profile is summarized here for completeness in the census.

Axis position: extrinsic (0.8–1.0). PV+ interneurons die overwhelmingly from environmental assault following PNN degradation. Their GluR2-lacking calcium-permeable AMPA receptors, their extreme firing rates, and their dependence on PNN-mediated iron chelation and glutamate diffusion restriction make them the most environmentally vulnerable cells in the cortex. Their intrinsic quality-control burden is relatively low — they produce little Aβ, they do not accumulate tau until late in the disease — and their death is predominantly inflicted from outside.

Dominant death modalities: Excitotoxicity (primary), ferroptosis (from iron released by PNN degradation), phagoptosis (complement-mediated synaptic elimination), with pyroptotic IL-1β and necroptotic TNF-α potentiating the excitotoxic insult. The combinatorial multi-modal death described in Terminal Collapse.

2.8 Neocortical association pyramidal neurons — The final wave

The pyramidal neurons of the temporal, parietal, and frontal association cortices are the last neuronal population to degenerate (Braak V–VI). Their loss correlates with the transition from moderate to severe dementia. Like CA1 pyramidal neurons, they are high-APP-expressing, Aβ-generating cells vulnerable to PANTHOS. Unlike CA1 neurons, they are embedded in cortical circuits where the loss of PV+ interneurons and SST+ interneurons has already destabilized excitation-inhibition balance by the time they become vulnerable.

Axis position: shifting from intrinsic to extrinsic across disease (0.3 0.7). Early damage is intrinsic (PANTHOS, tau, mitochondrial decline). Late damage is increasingly extrinsic (excitotoxicity from disinhibited networks, ferroptosis from accumulated iron, inflammatory cytokines from activated microglia). The neocortical association pyramidal neuron illustrates the axis as a dynamic rather than fixed property: the same cell type shifts along the axis as the disease

environment changes around it.

2.9 Oligodendrocytes — Ferroptosis in the white matter

Oligodendrocytes, the myelin-producing cells of the CNS, contain the highest iron concentration of any brain cell type — iron is essential for the enzymatic machinery of myelin synthesis. This iron load makes them uniquely vulnerable to ferroptosis. A 2023 Nature paper demonstrated that myelin dysfunction drives amyloid-β deposition in AD models, establishing oligodendrocyte pathology as an upstream contributor to rather than merely a consequence of amyloid pathology.

Axis position: intrinsic-to-mixed (0.3–0.5). Oligodendrocyte death is driven primarily by intrinsic iron-mediated lipid peroxidation (ferroptosis) and by the failure of the antioxidant systems that manage their extraordinary iron burden. The extrinsic component arises from microglial phagocytosis of myelin debris, which generates a feed-forward loop: microglia that phagocytose myelin accumulate iron, become ferroptotic themselves, and release both iron and inflammatory mediators that damage surrounding oligodendrocytes.

Dominant death modalities: Ferroptosis (primary — the prototypical ferroptotic cell in the brain), with microglial phagocytosis contributing to and exacerbated by the primary ferroptotic process.

2.10 Astrocytes — The neurotoxic transformation

Astrocytes do not die in large numbers in Alzheimer's disease. Instead, they undergo reactive transformation into states that have been characterized as neurotoxic (A1) or neuroprotective (A2), with the A1 phenotype predominating in AD post-mortem tissue (approximately 60% of GFAP-positive astrocytes express A1 markers). A1 astrocytes are induced by microglial cytokines — IL-1α, TNF-α, and complement C1q — and they secrete complement C3, which facilitates microglial synaptic pruning and directly harms neurons and oligodendrocytes.

Axis position: not on the axis as a dying cell, but a critical amplifier feeding the extrinsic pole. Reactive A1 astrocytes do not die; they transform. But their transformation amplifies the extrinsic pole for surrounding neurons: C3 secretion enhances complement-mediated phagoptosis of PV+ synapses, loss of glutamate transporter function elevates ambient glutamate and potentiates excitotoxicity, and loss of trophic support (BDNF, lactate shuttle) removes the metabolic support that neurons depend on for quality-control maintenance. The astrocytic transformation is the coupling mechanism that converts intrinsic-pole microglial and neuronal failures into extrinsic-pole assaults on surrounding cells.

3. The Spatiotemporal Map

3.1 Phase I: The silent brainstem erosion (age 20–50, Braak pre-tangle II)

Duration: Decades. **Clinical status:** Asymptomatic. **Dominant axis position:** Pure intrinsic (0.0–0.2).

The first cells to accumulate tau and begin dying are the locus coeruleus noradrenergic neurons and the dorsal raphe serotonergic neurons. These brainstem aminergic nuclei share a common vulnerability profile: tonic firing, long thin poorly myelinated axons, high baseline ROS, iron and neuromelanin accumulation, and dependence on mitochondrial quality-control systems whose capacity declines with age. Tau appears in these cells in the third decade of life and accumulates linearly across the lifespan.

The death modalities operating in this phase are exclusively intrinsic: parthanatos (chronic oxidative DNA damage → PARP-1 activation → NAD+ depletion), PANTHOS-adjacent proteostatic failure (tau accumulation → impaired axonal transport → autolysosomal dysfunction), and Wallerian degeneration (axonal SARM1 activation as NMNAT2 delivery fails in the degenerating axonal arbor). There is no excitotoxic component, no PNN-mediated vulnerability, no complement-mediated phagoptosis. The brainstem aminergic nuclei die from the inside, slowly, in silence.

The clinical invisibility of this phase is explained by the redundancy of the aminergic systems: the surviving LC and raphe neurons compensate by increasing their firing rates and branching their axonal projections, maintaining cortical noradrenergic and serotonergic innervation even as the source populations decline. The compensation is bioenergetically costly, accelerating the mitochondrial decline of the surviving neurons and ensuring that the loss, once it begins, is progressive and self-reinforcing.

During this same period, tau begins to appear in the entorhinal cortex (Braak I–II), and the stellate neurons of layer II begin their own intrinsic quality-control decline. Aβ production in these high-APP-expressing neurons begins to exceed lysosomal degradation capacity, and the intraneuronal Aβ accumulation that Gouras characterized decades before Nixon's PANTHOS paper begins its slow, decades-long trajectory.

Death modality map — Phase I: | Cell type | Primary death modality | Axis position | |---|---|---| | LC noradrenergic | Parthanatos / Wallerian | 0.0–0.15 | | Raphe serotonergic | Parthanatos / Wallerian | 0.1–0.2 | | Entorhinal layer II stellate | Incipient PANTHOS | 0.15–0.25 |

3.2 Phase II: The hippocampal bridgehead (age 50–65, Braak III–IV)

Duration: One to two decades. **Clinical status:** Preclinical to MCI. **Dominant axis position:** Intrinsic with emerging extrinsic (0.2–0.5).

Tau pathology reaches the hippocampus. CA1 pyramidal neurons begin to accumulate neurofibrillary tangles and to undergo PANTHOS. The perforant pathway — the axonal connection from entorhinal cortex to hippocampus — degenerates as the entorhinal stellate neurons die, disconnecting hippocampal input and producing the earliest detectable memory encoding deficits.

In this phase, the intrinsic pole remains dominant, but the extrinsic pole begins to activate. The microglial response to accumulating plaques and dead neurons shifts the microglial population toward post-homeostatic states. The Butovsky homeostatic signature (P2ry12, Tmem119) begins to decline in plaque-adjacent microglia. NLRP3 activation increases. IL-1β levels rise. MMP expression begins. The machinery that will degrade perineuronal nets is being assembled, though PNNs are not yet significantly degraded.

SST+ interneurons in the hippocampus begin to show tau pathology and atrophy. Their hyperactivity near plaques increases metabolic demand and accelerates their decline. PV+ interneurons, by contrast, are still resilient — their PNNs are intact, their calcium-handling systems are functional, and they are compensating for SST+ loss by increasing their own synaptic output (the neuroplastic compensation documented in AD rat models).

Cholinergic nbM neurons are undergoing progressive atrophy as the NGF pathway deteriorates. Their loss reduces cortical cholinergic tone, contributing to attentional and arousal deficits that compound the memory encoding failure from hippocampal disconnection.

Oligodendrocyte ferroptosis in hippocampal and parahippocampal white matter begins to produce myelin loss, detectable as white matter hyperintensities on MRI. The myelin debris is phagocytosed by microglia, contributing iron to the local microglial iron burden and further activating the inflammatory cascade.

Death modality map — Phase II: | Cell type | Primary death modality | Axis position | |---|---|---| | CA1 pyramidal | PANTHOS / parthanatos | 0.2–0.35 | | Entorhinal layer II | PANTHOS (advanced) | 0.2–0.3 | | SST+ interneurons | Tau-mediated intrinsic + plaque-adjacent inflammatory | 0.25–0.4 | | nbM cholinergic | Trophic withdrawal + excitotoxic vulnerability | 0.35–0.5 | | Oligodendrocytes | Ferroptosis | 0.3–0.45 | | PV+ interneurons | Compensating, not yet dying | — | | Microglia | Transitioning from homeostatic to post-homeostatic | (effector, not target) |

3.3 Phase III: The E/I collapse (age 65–75, Braak IV–V)

Duration: Years. **Clinical status:** MCI to mild-moderate dementia. **Dominant axis position:** Mixed, shifting toward extrinsic (0.4–0.8).

This is the phase where the disease crosses from the intrinsic pole to the extrinsic pole, and it is the phase that the Collapse quartet's framework was designed to describe.

The critical event is the degradation of perineuronal nets. Post-homeostatic microglia, whose transition from homeostatic to DAM/LDAM/dystrophic states has been progressing since Phase II, begin releasing MMP-2, MMP-9, ADAMTS-4, and cathepsin-S in quantities sufficient to degrade the PNN matrix around PV+ interneurons. The NLRP3-derived IL-1β from pyroptotic microglia upregulates MMP expression in surrounding cells, amplifying the degradation. A1 reactive astrocytes contribute C3, which deposits on newly exposed PV+ neuronal surfaces and initiates complement-mediated phagoptosis of PV+ synapses.

PNN degradation is the master vulnerability switch. Once it occurs, PV+ interneurons are simultaneously exposed to: - **Excitotoxicity** — ambient glutamate accesses perisomatic NMDA and calcium-permeable AMPA receptors - **Ferroptosis** — released iron from the degraded PNN's polyanionic matrix drives Fenton chemistry - **Phagoptosis** — complement deposits on the newly accessible neuronal surface - **Inflammatory potentiation** — IL-1β and TNF-α reach perisomatic receptors

PV+ interneurons begin to die. As they die, inhibitory output declines. As inhibition declines, pyramidal neuron firing increases. As firing increases, glutamate release increases. The feed-forward excitotoxic loop initiates and becomes self-sustaining. This is the electrophysiological signature detected as subclinical epileptiform activity and gamma-band abnormalities on EEG in early AD.

Simultaneously, the increased pyramidal neuron firing accelerates the intrinsic-pole death of those neurons: higher firing means higher metabolic demand, which means faster depletion of already-compromised autophagy-lysosomal and mitochondrial systems, which means more PANTHOS. The extrinsic pole feeds back into the intrinsic pole: the circuit-level hyperexcitation caused by PV+ loss accelerates the quality-control failure in pyramidal neurons.

CA1 pyramidal neurons, already weakened by Phase II PANTHOS, now face the additional insult of excitotoxic hyperactivation from the disinhibited circuit. Their death rate accelerates. The hippocampal atrophy visible on MRI in this phase reflects not merely continued PANTHOS but the convergence of intrinsic and extrinsic death modalities on the same cell population.

This is the phase the de Vries resilience finding illuminates: resilient individuals are those in whom Phase III does not occur. Their microglia remain homeostatic, their PNNs remain intact, their PV+ interneurons are not exposed, the feed-forward loop does not initiate, and their CA1

pyramidal neurons die only at the slow intrinsic rate rather than the accelerated intrinsic-plus-extrinsic rate. Resilience is the prevention of Phase III, not the prevention of Phase I or II.

Death modality map — Phase III: | Cell type | Primary death modality | Axis position | |---|---|---| | PV+ interneurons | Multi-modal extrinsic (excitotoxicity + ferroptosis + phagoptosis) | 0.8–1.0 | | CA1 pyramidal (accelerated) | PANTHOS + excitotoxicity (from disinhibition) | 0.3–0.6 | | SST+ interneurons (advanced) | Intrinsic + inflammatory | 0.35–0.5 | | Neocortical association pyramidal | Emerging PANTHOS + early disinhibition | 0.3–0.5 | | Oligodendrocytes | Ferroptosis (accelerated by inflammatory iron) | 0.4–0.5 |

3.4 Phase IV: The cortical cascade (age 75+, Braak V–VI)

Duration: Years. **Clinical status:** Moderate to severe dementia. **Dominant axis position:** Full spectrum active simultaneously (0.0–1.0).

In the final phase, the disease is operating at every position on the axis simultaneously. The intrinsic-pole failures that began in the brainstem decades earlier have now reached the neocortical pyramidal neurons. The extrinsic-pole cascade that began with PNN degradation in Phase III has spread from hippocampus to association cortex. Every death modality in the catalogue is active somewhere in the brain, and the coupling between them produces the exponential acceleration of neuronal loss that characterizes severe dementia.

Neocortical pyramidal neurons die through the same combination of PANTHOS and disinhibition-driven excitotoxicity that killed CA1 neurons in Phase III, but on a larger scale. The PV+ interneuron population, already depleted in hippocampus, begins to degenerate in neocortical circuits. The excitotoxic feed-forward loop spreads across cortical regions as each region's inhibitory brake is removed.

The NAD+ convergence that the Terminal Collapse thesis identified operates across the full axis: parthanatos in the soma (PARP-1), Wallerian degeneration in the axon (SARM1), and bioenergetic collapse in the mitochondria all deplete the same substrate. By Phase IV, the cumulative NAD+ depletion across all three pathways has reached levels where no single NAD+-dependent quality-control system can function adequately, and the cellular economy collapses globally rather than through any specific pathway.

This phase is therapeutically the most difficult because every node of the cascade is active and no single intervention can address the full width of the axis. The therapeutic window for quality-control restoration (intrinsic pole) closed in Phase I–II. The therapeutic window for PNN preservation (extrinsic pole) closed in Phase III. What remains is palliative: symptomatic management of the cognitive and behavioral consequences of multi-modal, multi-cell-type, axis-spanning neurodegeneration.

4. Emergent Principles

4.1 The intrinsic-to-extrinsic cascade is the disease

The most important principle to emerge from the spatiotemporal map is that the transition from intrinsic-pole to extrinsic-pole death is not a feature of the disease but the disease itself. Phases I and II — the decades of silent brainstem and hippocampal quality-control erosion — are the age-related substrate on which Alzheimer's disease is built, but they are not uniquely Alzheimer's. Every aging brain accumulates tau in the locus coeruleus, every aging brain loses some aminergic neurons, every aging brain shows declining autophagy-lysosomal capacity. These are features of aging, not of disease.

What makes Alzheimer's disease Alzheimer's disease is Phase III: the moment when the cumulative intrinsic damage reaches the microglial compartment, triggers homeostatic collapse, produces PNN degradation, and initiates the extrinsic-pole cascade. The crossing from slow intrinsic erosion to rapid extrinsic assault is the inflection point. Before the crossing, the brain is aging. After the crossing, the brain has Alzheimer's disease.

This framing explains the age-dependence of AD (the intrinsic-pole failures must accumulate for decades before they reach the threshold for Phase III), the cognitive-resilience phenotype (resilient individuals never cross from Phase II to Phase III), and the failure of amyloid-centric therapeutics (amyloid is a feature of Phase II intrinsic pathology; removing it does not prevent the Phase III extrinsic cascade if microglial homeostasis has already collapsed).

4.2 Each cell type has a characteristic position that shifts with disease stage

No cell type occupies a fixed position on the axis. The position is a function of the cell's intrinsic vulnerability profile (metabolic demand, APP expression, PNN status, calcium-channel composition) and the disease environment it occupies at a given stage. CA1 pyramidal neurons begin at position 0.2 (intrinsic PANTHOS) and shift to position 0.5–0.6 (PANTHOS plus excitotoxicity from disinhibition) as Phase III initiates. PV+ interneurons are not on the axis at all until Phase III, when they appear at position 0.8–1.0. The axis is dynamic: a map of the moving front of a disease, not a static taxonomy.

4.3 The middle of the axis is where the poles couple

Ferroptosis (axis position 0.5) is the coupling mechanism between the intrinsic and extrinsic poles. At the intrinsic pole, mitochondrial failure and GPX4 depletion create the conditions for lipid peroxidation. At the extrinsic pole, PNN degradation releases iron into the perisomatic space. Ferroptosis requires both: the internal antioxidant failure and the external iron delivery. It is the death modality that cannot be understood from either pole alone.

Pyroptosis (position 0.6) is the amplifier of coupling: microglial NLRP3 activation (triggered by intrinsic mitochondrial DAMP release) produces IL-1β output (which amplifies extrinsic MMP expression and glutamatergic potentiation). Pyroptosis translates intrinsic failure into extrinsic assault.

Necroptosis (position 0.7) is the inflammatory consequence of the coupled death: TNF-α released by activated microglia (responding to both intrinsic DAMPs and extrinsic debris) activates RIPK1/RIPK3/MLKL in neurons already stressed by excitotoxic and ferroptotic insults.

The middle of the axis is not a transition zone between independent poles. It is the machinery of their coupling — the molecular bridge by which decades of silent erosion become months of rapid collapse.

4.4 The therapeutic implications are phase-specific

The axis predicts that different disease phases require fundamentally different therapeutic strategies:

Phase I (intrinsic, preventive): Quality-control restoration. NAD+ precursors, mitophagy inducers, lysosomal acidification support, TGF-β pathway stabilization. Target population: the entire aging population, decades before clinical onset. The therapeutic challenge is that the benefit cannot be measured at the individual level because the disease it prevents is decades away.

Phase II (intrinsic, early intervention): Quality-control restoration plus microglial homeostatic preservation. Add TGF-β/SMAD stabilizers and NLRP3 inhibitors to the Phase I interventions. Target population: biomarker-positive, clinically normal or MCI. The therapeutic challenge is identifying who is approaching Phase III and intervening before the crossing.

Phase III (mixed, acute neuroprotection): Multi-modal death-pathway inhibition. Sub-anesthetic NMDA blockade (for excitotoxicity), ferroptosis inhibitors (for iron-mediated lipid peroxidation), PNN-preserving agents (to prevent further exposure), complement inhibitors (for phagoptosis), NLRP3 inhibitors (for pyroptotic amplification). Target population: MCI to mild dementia with EEG evidence of hyperexcitability. The therapeutic challenge is the combinatorial complexity — multiple pathways must be addressed simultaneously — and the narrow temporal window.

Phase IV (full spectrum, palliative): No single intervention can reverse the damage. Combination approaches may slow further decline but cannot restore lost neurons. The therapeutic challenge is that the disease has already crossed the full width of the axis and every pathway is active.

5. The Axis as Experimental Program

The formalized axis generates testable predictions that distinguish it from alternative framings.

Prediction 1. If the axis is correct, the earliest cells to die in AD (LC, raphe) should show minimal evidence of excitotoxic, phagoptotic, or ferroptotic death — their death modality profile should be pure intrinsic (parthanatos, PANTHOS, Wallerian degeneration). Post-mortem tissue from Braak pre-tangle stages should show PARP-1 activation, LC3B/p62 abnormalities, and axonal SARM1 activation in these nuclei without elevated complement deposition, MMP activity, or lipid peroxidation markers.

Prediction 2. PV+ interneuron death should be temporally restricted to phases where PNN degradation has already occurred. In brain regions where PNNs are intact, PV+ interneurons should be viable regardless of amyloid or tau burden. This prediction is already partially supported by the de Vries resilience finding.

Prediction 3. The MCI-to-dementia transition should correlate more tightly with PNN degradation and PV+ interneuron loss (Phase III markers) than with amyloid or tau burden (Phase I–II markers). Emerging PET tracers for PNNs and electrophysiological measures of E/I balance (gamma-band power, subclinical epileptiform activity) should be more predictive of imminent cognitive decline than amyloid or tau PET.

Prediction 4. Ferroptosis markers (4-HNE, oxidized phospholipids, GPX4 depletion) should show a characteristic spatial and temporal gradient: appearing first in iron-rich structures (substantia nigra, oligodendrocyte-dense white matter), then in plaque-adjacent regions, and finally in PNN-degraded cortical regions where iron is released from the matrix. This gradient reflects the ferroptotic death modality's position at the coupling point of the axis.

Prediction 5. NAD+ levels in post-mortem AD brain should decline not uniformly but in a pattern that reflects the convergence of three NAD+-depleting pathways: PARP-1 activation (in nuclei), SARM1 activation (in axons), and bioenergetic decline (in mitochondria). The decline should be greatest in cell types where all three pathways converge — which the axis predicts are the

brainstem aminergic neurons (early, from chronic oxidative stress) and the PV+ interneurons (late, from the multi-modal assault after PNN loss).

6. Conclusion

The intrinsic–extrinsic death-modality axis is not a metaphor. It is a formalization of an empirical regularity: that the cells which die first in Alzheimer's disease die from the inside, slowly, through cumulative quality-control failure, and the cells which die in the phase that produces the cognitive phenotype die from the outside, rapidly, through environmental assault enabled by the loss of protective structures. The middle of the axis is where the decades of silent erosion become the months of rapid collapse, through coupling mechanisms — ferroptosis, pyroptosis, necroptosis — that translate intrinsic failure into extrinsic assault.

The axis organizes the Collapse quartet's findings into a single spatiotemporal framework. Thesis 1 (Convergent Synaptic Collapse) described the extrinsic pole. Thesis 2 (Homeostatic Microglial Collapse) described the cellular mechanism that activates the extrinsic pole. Thesis 3 (Bioenergetic Collapse) described the intrinsic pole's upstream substrate. Thesis 4 (Terminal Collapse) catalogued the death modalities at both poles and noted their convergence at the PNN. This thesis maps the full cell census onto the axis and traces the disease's progression from one pole to the other across decades.

The deepest insight of the formalized axis is that Alzheimer's disease is not a disease of the intrinsic pole (aging) or of the extrinsic pole (circuit collapse) but of the transition between them. The disease is the crossing. Every brain ages at the intrinsic pole. Only some brains cross to the extrinsic pole. The crossing is the event that converts aging into Alzheimer's — and the crossing is the event that therapeutic intervention must prevent.

The PNN remains, as the prior theses argued, the most informative marker of whether the crossing has occurred. A preserved PNN indicates that the brain remains at the intrinsic pole: aging, slowly eroding, but not yet in the rapid extrinsic cascade. A degraded PNN indicates that the crossing has happened or is happening. The therapeutic task at every disease stage is the same: keep the brain on the intrinsic side of the axis for as long as possible, and if the crossing has occurred, engage the extrinsic pole's death pathways before the target cells are lost.

The spectrum of collapse is the disease's biography, written in the deaths of its cells.

References

Braak, H., Thal, D. R., Ghebremedhin, E., Del Tredici, K. (2011). Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *Journal of Neuropathology and Experimental Neurology*, 70(11), 960–969.

Braak, H., Del Tredici, K. (2015). The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain*, 138(Pt 10), 2814–2833.

Theofilas, P., Ehrenberg, A. J., Dunlop, S., et al. (2017). Locus coeruleus volume and cell population changes during Alzheimer's disease progression: a stereological study. *Biological Psychiatry*, 81(3), 1019–1028.

Matchett, B. J., Grinberg, L. T., Theofilas, P., & Murray, M. E. (2021). The mechanistic link between selective vulnerability of the locus coeruleus and neurodegeneration in Alzheimer's disease. *Acta Neuropathologica*, 141(5), 631–650.

Grinberg, L. T., Rüb, U., Alho, A. T., et al. (2009). Brainstem pathology and non-motor symptoms in PD. *Journal of the Neurological Sciences*, 289(1–2), 81–88.

Oh, J., et al. (2024). Tau pathology in the dorsal raphe may be a prodromal indicator of Alzheimer's disease. *Molecular Psychiatry*, 29, 3518–3529.

Waller, R., Woodroofe, M. N., et al. (2020). Histological characterization of interneurons in Alzheimer's disease reveals a loss of somatostatin interneurons in the temporal cortex. *Neuropathology*, 40(4), 336–346.

Targa Dias Anastacio, H., et al. (2022). Parvalbumin neuroplasticity compensates for somatostatin impairment, maintaining cognitive function in Alzheimer's disease. *Translational Neurodegeneration*, 11, 26.

Whitehouse, P. J., Price, D. L., Struble, R. G., et al. (1982). Alzheimer disease and senile dementia: loss of neurons in the basal forebrain. *Science*, 215(4537), 1237–1239.

Mufson, E. J., Counts, S. E., Ginsberg, S. D., et al. (2002). Nerve growth factor pathobiology during the progression of Alzheimer's disease. *Journal of Alzheimer's Disease*, 4(6), 487–502.

Deture, M. A., et al. (2019). Selective vulnerability of the nucleus basalis of Meynert among neuropathologic subtypes of Alzheimer disease. *JAMA Neurology*, 76(11), 1353–1362.

Lee, J. H., Yang, D. S., Goulbourne, C. N., et al. (2022). Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. *Nature Neuroscience*, 25(6), 688–701.

Depp, C., Sun, T., Sasmita, A. O., et al. (2023). Myelin dysfunction drives amyloid-β deposition in models of Alzheimer's disease. *Nature*, 618, 349–357.

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, 541(7638), 481–487.

Lian, H., Yang, L., Cole, A., et al. (2015). NFκB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. *Neuron*, 85(1), 101–115.

Cabungcal, J. H., Steullet, P., Morishita, H., et al. (2013). Perineuronal nets protect fast-spiking interneurons against oxidative stress. *Proceedings of the National Academy of Sciences*, 110(22), 9130–9135.

de Vries, L. E., Jongejan, A., Monteiro Fortes, J., et al. (2024). Perineuronal nets and cognitive resilience in Alzheimer's disease. *Alzheimer's & Dementia*, 20.

Crapser, J. D., Spangenberg, E. E., et al. (2020). Microglia facilitate loss of perineuronal nets in the Alzheimer's disease brain. *EBioMedicine*, 58, 102919.

Heneka, M. T., Kummer, M. P., Stutz, A., et al. (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*, 493(7434), 674–678.

Fang, E. F., Hou, Y., Palikaras, K., et al. (2019). Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nature Neuroscience*, 22(3), 401–412.

Dixon, S. J., Lemberg, K. M., Lamprecht, M. R., et al. (2012). Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*, 149(5), 1060–1072.

Stevens, B., Allen, N. J., Vazquez, L. E., et al. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell*, 131(6), 1164–1178.

Swerdlow, R. H. (2018). Mitochondria and mitochondrial cascades in Alzheimer's disease. *Journal of Alzheimer's Disease*, 62(3), 1403–1416.

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Prepared under the Organic Network Synthesis methodology. This thesis formalizes the intrinsic–extrinsic death-modality axis, maps the full vulnerable cell census of Alzheimer's disease onto it, and traces the disease's progression from decades of silent intrinsic erosion to the rapid extrinsic cascade that produces the cognitive phenotype. The axis proposes that Alzheimer's disease is not a disease of either pole but of the transition between them.