THE UNIFIED ARCHITECTURE OF COLLAPSE

A Graded, Multiscale Synthesis of the Temporal, Cellular, and Ecological Mechanisms of Alzheimer's Disease

The Ecological Entry · *The Vago-Coerulean Conduit* · *The Bioenergetic Ignition*
The Microglial Bridgehead · *The Proteolytic Turn* · *The Silenced Synapse*

A Doctoral Synthesis Prepared in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience

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The convergence capstone of the Collapse corpus, and the graded second edition of the unified synthesis. Where The Temporal Architecture of Collapse arranged the disease by time, this volume arranges it by time and evidentiary weight together — every load-bearing claim tiered as established, bridging, or conjectural, so that the architecture may be tested at its joints rather than believed at its edges.

“A theory assembled from findings drawn across organisms, tissues, and diseases lives or dies not by the plausibility of its parts but by the validity of the joints between them. The honest way to hold such a theory is not to defend it whole, but to grade it joint by joint — and to say, at each one, exactly how much weight the evidence will bear.”

— ONS Methodology Working Notes, 2026

For the reader who asks not only what might be true but how well it is known — and for a field that has too often let the confidence of its best module vouch for the weakness of its worst bridge.

THE COLLAPSE CORPUS CONVERGENCE CAPSTONE

The Temporal Architecture of Collapse (the temporal spine)

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

Cross-sections: The Vascular Phasing · The Genetic Architecture · The Senescent Front · The Fading Score

The Unified Architecture of Collapse ← this volume

This volume stands to the corpus as its convergence capstone: where the component theses each drew one lens through the disease, and *The Temporal Architecture* arranged them along a single fifty-year front, this synthesis asks how the several *upstream entry lanes* — amyloid-driven, vascular-first, glia-first, and the ecological gut-to-brainstem route — converge on one downstream architecture, and grades each junction of that convergence on an explicit scale of evidence. It is the corpus's answer to the question a hostile examiner asks last: *not whether the story is elegant, but how much of it is known.*

Contents

Abstract

Alzheimer's disease is not an event but a process that occupies the better part of a human life. It begins, in most people who develop the sporadic form, decades before memory fails; it advances along anatomically constrained routes rather than diffusing at random; and it terminates in a functional disconnection of cortical circuits that correlates far better with synaptic and inhibitory failure than with the gross counting of plaques and tangles. Any theory equal to the disease must therefore explain three things that single-molecule cascades treat separately: its half-century latency, its stereotyped spatial order, and the loose coupling between protein burden and dementia. This thesis assembles such a theory — a temporal, cellular, and ecological architecture that traces the disease from an upstream ecological perturbation, through a brainstem bioenergetic crisis, into a collapse of microglial homeostasis, and finally into the demolition of the perineuronal net that shields the brain's fast-spiking inhibitory interneurons.

This second edition differs from the first in a way that is central to its claim to seriousness. The first edition presented the architecture as a near-total replacement for protein-first thinking and assigned uniform confidence across a long causal chain whose links are not, in fact, equally well evidenced. Here we do the opposite. We present the architecture as a **hybrid, multiscale convergence model** rather than a monocausal grand theory, and we grade every load-bearing claim on an explicit three-tier scale — established, bridging, and conjectural — so that the reader can see, at each junction, exactly how much weight the evidence will bear. We reposition amyloid-β not as an eliminated error but as a validated node that remains causally active throughout the architecture, and we concede that in autosomal-dominant disease amyloid is genuinely the initiating trigger — while qualifying even that concession, since deterministic-mutation carriers who resisted dementia for three decades (the Reelin-COLBOS and APOE3-Christchurch cases) prove that amyloid initiation does not, by itself, author the outcome. We segregate four distinct senses in which the locus coeruleus is "first," conceding only the ones the neuropathology supports. We treat the gut-to-brainstem route as one upstream entry lane — dominant, we argue, in an inflammatory, gut-affected sporadic subtype — rather than as the universal origin of all Alzheimer's disease, and we place it alongside the amyloid-driven, vascular-first, and glia-first lanes that a complete model must also accommodate. We recast the perineuronal net not as *the* sole terminal substrate but as a high-value final common bottleneck at which several upstream routes cash out into cognitive failure. And we acknowledge the price of this scope: a serial model of many contingencies is less parsimonious than a cascade, and buys its explanatory reach only by submitting each contingency to independent evidentiary grading.

What survives this discipline is, we contend, stronger than what preceded it: not a claim that the field's existing theories are wrong, but a claim that time, anatomy, glial state, extracellular matrix, and systemic metabolism can be arranged into one convergent architecture, with named transitions and falsifiable, mechanistically discriminating predictions — an integrative program for expert readers rather than a settled master theory.

A Note on Evidentiary Grading

The most common and most fatal error in integrative disease theory is to let the confidence earned by a model's best-supported module silently transfer to its weakest bridging inference. A theory assembled from findings drawn across organisms, tissues, timescales, and even diseases lives or dies not by the plausibility of its individual parts but by the validity of the joints between them. This thesis therefore adopts, and applies without exception, an explicit three-tier grading of every load-bearing claim. The grades are stated in the running text as short italic verdicts at the close of each mechanistic module, and are consolidated in the Validity Ledger that closes the work.

Tier I — Established. Directly supported by primary evidence in human Alzheimer's tissue or in well-validated Alzheimer's models. These are claims the field would broadly accept as facts, whatever theory it holds. Example: pretangle tau appears in the locus coeruleus before it appears in the cortex.

Tier II — Bridging inference. Plausible and mechanistically constrained, but resting on cross-domain, cross-species, or cross-disease extrapolation, or on the linkage of two established facts by an inferred connection that has not itself been directly measured in Alzheimer's disease. These are the architecture's structural joints, and they are where honest disagreement will concentrate. Example: that the vagal relay carries a *chronic, Alzheimer-specific* excitatory load to the locus coeruleus.

Tier III — Conjectural. Internally coherent and generative, but not yet directly evidenced; offered as hypotheses with the discriminating tests that would confirm or refute them. Marking a claim Tier III is not a concession that it is unlikely — several Tier III claims are the most original in the work — but a refusal to present it as settled. Example: that bacterial amyloids cross-seed *tau*, as opposed to α-synuclein, in the human gut.

A reader who wishes to know only "what is proven" may read the Tier I spine alone. A reader interested in the theory qua theory should attend to the Tier II joints, for it is there that the architecture is genuinely at risk.

I. The Problem and the Frame

What a systems model must explain

For nearly four decades the intellectual energy of the field has been spent adjudicating a question of priority — which molecule is primary, amyloid or tau, the activated microglion or the failing mitochondrion — and arranging the answer as a cascade in which a first insult begets a second, terminating in the death of neurons and the loss of mind. The amyloid cascade hypothesis is the most influential instance, but it is not unusual in form; every major framework in the field is a cascade, and they differ mainly in what they place at the top (Selkoe & Hardy, 2016; Karran & De Strooper, 2016).

Cascades of this shape have three recurring difficulties, and a systems model earns its keep only if it addresses them. The first is *latency*: the disease unfolds over roughly half a century, and a theory that names only its endpoints has nothing to say about the decades between the first molecular lesion and the first symptom. The second is *spatial order*: the pathology is not diffuse but follows a stereotyped, anatomically constrained progression, sparing some populations almost entirely while decimating others — a geography no purely chemical account predicts. The third is the *burden–dementia gap*: amyloid and tau burden correlate only loosely with cognitive state, and a substantial fraction of cognitively intact elderly people carry pathology fully in the Alzheimer range (de Vries et al., 2024). These are not marginal anomalies; they are the disease's most distinctive structural features, and they motivate a model organized by time, anatomy, and cellular state rather than by molecular species alone.

What this thesis does and does not claim

It is important to state at the outset, against the polemical framing of the first edition, what is and is not being asserted. This thesis does **not** claim that amyloid, tau, vascular, or glial theories are wrong, nor that the gut is the universal origin of Alzheimer's disease, nor that the perineuronal net is the single mechanism of dementia. It claims something more modest and, we think, more defensible: that a neglected brainstem-glia-matrix axis, running along anatomically real conduits and governed by the cell biology of senescence, is a major organizing structure in at least some — and plausibly many — forms of the disease; that this structure can be specified mechanistically, phase by phase, with named transitions; and that when the existing single-substrate theories are read as describing different *phases and lanes* of one convergent architecture rather than rival primary causes, most of their apparent contradictions dissolve. The contribution is integrative and generative, not eliminative.

The shape of the argument

The architecture has three parts. An **upstream ecological lane** (Part II) describes how a peripheral perturbation — dysbiosis, barrier failure, microbial amyloid, chronic afferent drive — can load the brainstem in a specific sporadic subtype. A **temporal core** (Part III) describes the disease's advance through the brain in three mechanistically bridged phases: bioenergetic ignition in the locus coeruleus, the collapse of homeostatic microglia in the limbic system, and the proteolytic demolition of the perineuronal net in the cortex. An **integrative synthesis** (Part IV) shows how multiple entry lanes converge on the same downstream architecture, why the disease nonetheless takes its specific anatomical form, what the model predicts that its rivals do not, and what it would cost to be wrong. Before any of this, however, the model must situate itself with respect to the two facts its predecessors are strongest on: the genetics of amyloid, and the biology of the vessel.

II. The Place of Amyloid, and the Boundary Conditions

Amyloid is repositioned, not eliminated

A recurring and fair criticism of ecological, LC-first accounts is that they position themselves rhetorically against amyloid while continuing to rely on amyloid-β at every load-bearing step. This thesis takes the criticism seriously and resolves it by repositioning amyloid honestly rather than by pretending to do without it. Amyloid-β remains causally active across the entire architecture proposed here. The butyrate–cathelicidin checkpoint of Part II is, in its mechanism, an *anti-amyloid* defense: LL-37 is invoked precisely because it binds and retards Aβ fibrillation. The bioenergetic crisis of Phase I is intensified by intraneuronal Aβ obstructing the mitochondrial import channel TOM40. The terminal disinhibition of Phase III accelerates because activity-dependent synaptic release of Aβ and tau rises when inhibitory control is lost. A model this dependent on amyloid cannot honestly call itself anti-amyloid.

What the model does claim is a change of *role*, not of *reality*. In the dominant reading of the amyloid cascade, Aβ is the singular upstream initiator from which all else follows. Here, Aβ is repositioned as one validated node within a broader systems architecture: a genuine driver and amplifier, load-bearing in several phases, but not the universal point of origin and not the substrate on which cognition most directly depends. This is a weaker claim about amyloid's *primacy* and a fully compatible claim about amyloid's *importance* — and it is the claim the human data actually support, since anti-amyloid monotherapy removes the protein without reliably restoring cognition, exactly as a "necessary node, insufficient endpoint" reading predicts.

> *Evidentiary grade — Tier I that amyloid is mechanistically active at multiple points in the architecture; Tier II that its correct systemic role is amplifier-and-node rather than sole initiator.*

The genetic anchor and the qualified autosomal-dominant concession

The amyloid tradition's deepest foundation is human genetics: mutations in APP and the presenilins cause early-onset familial Alzheimer's disease with essentially complete penetrance, and the protective A673T variant in APP lowers lifetime risk (Goate et al., 1991; Jonsson et al., 2012). Any model that treats amyloid as merely permissive must explain why disturbing Aβ production or clearance is, in these families, sufficient to cause the disease. This thesis does not attempt to explain that away. It concedes directly that **in autosomal-dominant Alzheimer's disease, amyloid-β is the initiating trigger** — necessary and sufficient to set the disease in motion — and that the ecological entry lane of Part II is bypassed. What the temporal architecture contributes to these families is not an alternative origin but a downstream *itinerary*: the same progression through LC, microglia, and matrix, telescoped into a shorter and more amyloid-driven course.

The concession must nonetheless be qualified, and qualified in exactly the way the rest of the architecture predicts, because *initiating* is a claim about triggering the sequence, not about authoring its outcome — and the most decisive evidence for the difference comes from the autosomal-dominant families themselves. Within the Colombian PSEN1-E280A kindred, whose carriers face a fully penetrant, deterministic dementia by their mid-forties, two individuals resisted for roughly three further decades despite carrying the mutation and despite some of the highest amyloid burdens ever measured: a homozygous APOE3-Christchurch carrier (Arboleda-Velasquez et al., 2019) and, in the same kindred, a Reelin-COLBOS heterozygote (Lopera et al., 2023). In both, amyloid arrived on schedule, but tau was held out of the entorhinal cortex, and dementia did not come. These are the sharpest human demonstrations available that amyloid initiation, even under a deterministic amyloid-driving mutation, does not by itself dictate the disease: the outcome still runs through a downstream architecture — tau propagation, the extracellular matrix, the reelin brake — that a single resilience factor can hold. Amyloid is the trigger of autosomal-dominant disease; it is not, even there, the sole author of dementia. That distinction is the whole of the model's claim, made in the one setting where amyloid's causal priority is least in doubt — and the mechanism by which the downstream architecture holds is developed, as a resilience story, in Part IX.

> *Evidentiary grade — Tier I that autosomal-dominant AD is amyloid-initiated; Tier I too that deterministic carriers can nonetheless resist dementia (the COLBOS cases), which qualifies "initiating cause" to "initiating trigger, not sole author of the outcome."*

APOE4 as a multi-module threshold modifier

The great majority of Alzheimer's disease is sporadic, and there the strongest common genetic signal is APOE4. The model treats APOE4 not as an entry lane of its own but as a modifier that lowers thresholds across *several* modules of the architecture at once: it impairs lipid handling and endosomal recycling in stressed neurons; it biases microglia toward the disease-associated, lipid-laden states of Phase II; it degrades blood–brain-barrier integrity through a cyclophilin-A–MMP-9 pathway in pericytes (Montagne et al., 2020); and it shifts the complement-mediated matrix attack of Phase III. A single allele that lowers the threshold of four different modules is exactly the kind of pleiotropic risk factor a convergence model predicts, and exactly the kind that a single-substrate cascade struggles to place.

> *Evidentiary grade — Tier II. Each individual APOE4 effect is Tier I; the claim that its importance lies in simultaneous multi-module threshold-lowering is a bridging synthesis.*

The vascular lane, restored to the model

The first edition's most costly omission was the neurovascular tradition. Zlokovic's two-hit and neurovascular-unit frameworks marshal strong evidence that blood–brain-barrier breakdown, cerebral hypoperfusion, and impaired perivascular clearance frequently precede cognitive decline and gross atrophy (Zlokovic, 2011; Montagne et al., 2020). A model that invokes microglial priming, oxidative stress, complement activation, and matrix degradation cannot sidestep a competitor that derives several of the same mechanisms from vascular injury. This thesis therefore restores the vessel explicitly, and specifies the relationship rather than eliding it. Vascular dysfunction is treated as a **parallel entry lane and threshold-setter**: it is *primary* in vascular and mixed dementias and in a demonstrable share of sporadic disease; it runs *parallel* to the ecological and amyloid lanes in others, setting the tissue's clearance capacity and inflammatory reserve; and it is *secondary*, an amplifier, where the parenchymal lesion leads. Which of these obtains in a given patient is, we argue, a subtype question to be settled empirically, not a matter for theory to decree.

> *Evidentiary grade — Tier I that vascular injury frequently antecedes decline; Tier II that its correct place is a subtype-variable lane whose primacy is patient-specific.*

The convergence model in one figure

Read together, these boundary conditions yield the thesis's central structural claim. Alzheimer's disease has several **upstream entry lanes** — amyloid-driven (familial and APOE-loaded), vascular-first, glia-first, and the ecological gut-to-brainstem lane this work foregrounds — that converge on a shared **downstream architecture** of bioenergetic, microglial, and matrix collapse, and finally on a common substrate of synaptic and inhibitory circuit failure. The lanes are not mutually exclusive; most patients likely travel more than one. The value of naming them is that it converts an unwinnable argument about which theory is *the* theory into a tractable empirical question about which lane is load-bearing in which subtype.

Entry lane	Putative initiating driver	Where it is strongest	Relation to this architecture
Amyloid-driven (familial)	APP / presenilin mutation; Aβ dyshomeostasis	Autosomal-dominant early-onset AD	Initiating; enters the same itinerary, telescoped
Amyloid-modified (sporadic)	APOE4-loaded Aβ mishandling	Late-onset sporadic AD	Multi-module threshold modifier
Vascular / neurovascular	BBB breakdown, hypoperfusion, failed clearance	Vascular and mixed dementia; a share of sporadic AD	Parallel lane and threshold-setter
Glia-first	Primary microglial / complement dysregulation	Inflammatory and TREM2-variant subtypes	Enters at Phase II directly
Ecological (this work)	Dysbiosis → afferent drive → LC load	An inflammatory, gut-affected sporadic subtype	Upstream lane loading Phase I

III. The Ecological Entry Lane

The subtype claim, stated plainly

The chapters that follow describe a route by which a peripheral, ecological perturbation could load the brainstem and initiate the temporal architecture. The first edition presented this route as the origin of Alzheimer's disease. This edition presents it as **one entry lane, dominant in a specific subtype** — inflammatory, gut-affected, high-senescence, and more likely sporadic than familial — and probably a modulating contributor, rather than an origin, in others. The distinction matters because it is testable: if the ecological lane is a universal origin, gut and LC markers should outrun canonical cortical markers in *all* preclinical sporadic disease; if it is subtype-specific, they should do so preferentially in the gut-affected, inflammatory subgroup and not elsewhere. The subtype framing is not a retreat; it is what makes the lane falsifiable.

The ecological drift and the butyrate–cathelicidin checkpoint

In health, the adult microbiome, dominated by Firmicutes and Bacteroidetes, ferments dietary fiber into short-chain fatty acids, of which butyrate is the most consequential: it is the primary fuel of the colonocyte and the principal signal maintaining the tight-junction integrity of the epithelial barrier. Age-associated dysbiosis reproducibly reduces microbial diversity, depletes fiber-fermenting butyrate producers, and expands pro-inflammatory Proteobacteria — a drift that alters the chemical exports of the gut. That much is Tier I and not specific to Alzheimer's disease.

The model then proposes a specific neuroprotective consequence of butyrate loss. Butyrate is a histone-deacetylase inhibitor that upregulates the host CAMP gene encoding cathelicidin (LL-37); LL-37, beyond its antimicrobial role, binds and retards the fibrillation of amyloid-β. On this reading, dysbiotic butyrate depletion withdraws a standing anti-amyloid defense and, together with the barrier failure that admits lipopolysaccharide into the circulation, establishes a permissive, low-grade inflammatory tone. The individual biochemical steps are real; their assembly into a load-bearing "anti-amyloid checkpoint" whose failure helps initiate Alzheimer's disease is an inference that has not been directly demonstrated in human disease.

> *Evidentiary grade — Tier I that age-related dysbiosis depletes butyrate and weakens the barrier; Tier II that the butyrate–LL-37 axis constitutes an Alzheimer-relevant anti-amyloid checkpoint. The move from "microbiome ageing" to "Alzheimer initiation" is not unique to AD and must not be assumed.*

Bacterial amyloids and the cross-seeding question

The dysbiotic expansion of Enterobacteriaceae introduces functional bacterial amyloids into the gut. The best-characterized, curli (major subunit CsgA, produced by E. coli and Salmonella), polymerizes into a cross-β structure biophysically similar to human neurodegenerative amyloids. The cross-seeding hypothesis holds that exposure to such templates in the gut lowers the kinetic barrier to aggregation of host proteins. Here the evidence must be graded with unusual care, because it is exactly the kind of cross-disease extrapolation that inflates confidence illegitimately. Gnotobiotic experiments demonstrate that colonization with curli-producing E. coli, and administration of purified CsgA, accelerate the aggregation and pathology of α**-synuclein**, with intestinal and motor phenotypes (Sampson et al., 2020). This is a Tier I result — for synucleinopathy. The inference that analogous microbial amyloids cross-seed **tau**, the protein relevant to Alzheimer's disease, is biologically plausible but has not been established; the cross-seeding literature is markedly stronger for α-synuclein than for tau.

> *Evidentiary grade — Tier I that bacterial curli cross-seeds α-synuclein; Tier III that it cross-seeds tau in a manner relevant to Alzheimer initiation. A theory that leans on this bridge must predict route-specific, tau-relevant templating, not merely inflammatory plausibility.*

Transduction and the vago-coerulean conduit

For the gut's ecological state to influence the brainstem, physical conduits must exist, and two do. The humoral route runs through the area postrema, a circumventricular organ lacking a blood–brain barrier and positioned adjacent to the brainstem nuclei, where circulating cytokines and lipopolysaccharide are directly sampled. The high-speed neural route runs through the vagus. Enteroendocrine neuropod cells, residing in the gut epithelium, form structurally complete, fast glutamatergic synapses with vagal afferents and transduce luminal signals to the brainstem in milliseconds — a hardwired neuroepithelial circuit connecting the intestinal lumen to the brainstem in a single synapse (Kaelberer et al., 2018). This is a genuine and elegant Tier I anatomical fact.

What the model builds on it is more speculative. The vagal afferents terminate in the nucleus tractus solitarius, which relays to the locus coeruleus not directly but through a dual medullary circuit: an excitatory glutamatergic arm via the nucleus paragigantocellularis and an inhibitory GABAergic arm via the nucleus prepositus hypoglossi. The proposal is that a chronically inflamed, dysbiotic gut biases this relay toward sustained excitation, imposing a relentless noxious afferent load on the locus coeruleus. The relay anatomy is established; the claim that Alzheimer's disease involves a *chronic, disease-specific* excitatory drive along it has not been directly demonstrated, and it is one of the architecture's most exposed joints.

> *Evidentiary grade — Tier I that the neuropod–vagus–NTS conduit exists and can transmit gut signals rapidly; Tier II/III that a chronic Alzheimer-specific excitatory bias of the NTS→PGi→LC relay is a genuine disease mechanism. This is a place the theory should be actively trying to falsify.*

IV. The Locus Coeruleus and the Four Senses of "First"

Before describing Phase I, the architecture must discharge a debt its first edition left unpaid. It repeatedly called the locus coeruleus the site where Alzheimer's disease "begins" and treated that as settled. But "first" has at least four distinct meanings, and the neuropathology supports them very unequally. Conflating them is the single largest source of overclaim in LC-centric models, and disentangling them is the single most useful clarification this edition can offer.

First in the sense of earliest detectable vulnerability. Braak and Del Tredici's staging places the earliest pretangle tau not in the entorhinal cortex but in the locus coeruleus and brainstem aminergic nuclei, in individuals in their third and fourth decades, free of amyloid and asymptomatic (Braak & Del Tredici, 2011, 2015). That the LC shows the earliest *detectable* tau-related change is **Tier I** — as well established as anything in the disease's natural history.

First in the sense of earliest major relay hub. Because the LC projects, through long and diffusely branching unmyelinated fibres, to virtually the entire forebrain, it is positioned to broadcast both regulation and pathology widely. That the LC is an unusually powerful *relay and amplifier* is **Tier II** — a strong inference from its anatomy, though its causal weight in propagation has not been fully quantified in humans.

First in the sense of canonical staging anchor. Staging schemes must begin their count somewhere, and locating the origin of the tau count in the LC is an *operational* convention with real utility. That the LC is a legitimate staging anchor is **Tier I as an operational matter** — but a staging anchor is a place to start counting, not a demonstrated first cause, and the two must not be equated.

First in the sense of earliest necessary causal initiator. This is the strong claim — that LC pathology is *upstream, necessary, and decisive*, such that without it the disease does not start. It is also the claim the evidence does **not** license. LC vulnerability being early and real does not make it the irreplaceable ignition of every case; the "irrefutable first event" language of the first edition overreached. That the LC is the necessary causal initiator of Alzheimer's disease is **Tier III** — a hypothesis, and one the discriminating predictions of Part IV are designed to test.

The architecture claims the first three senses and explicitly flags the fourth as conjectural. This is not a weakening of the theory but a sharpening of it: a model that knows the difference between "earliest visible" and "necessary first cause" is a model that can be tested, whereas one that fuses

them can only be believed or disbelieved.

V. Phase I — Bioenergetic Ignition and Amitosenescence

Why the locus coeruleus fails first

Granting the Tier I fact that the LC shows the earliest pathology, the model asks *why there*, and answers in the language of bioenergetics. The locus-coeruleus neuron is among the most metabolically extravagant cells in the brain: autonomously pacemaking and firing throughout waking life; sustaining long, thin, unmyelinated varicose fibres that project across the forebrain; and synthesizing catecholamines, a chemistry that is itself a source of oxidative load. The extravagance is established; its *derivation* is worth stating precisely, because the corpus has previously rested it on arbor size. The quantified arbor-burden calculation in the literature is for substantia nigra dopamine neurons and has no coerulean equivalent — no estimate of total axon length per human locus-coeruleus neuron exists — whereas the pacemaking and catecholamine-oxidation mechanisms are demonstrated in this cell directly. The bioenergetic account rests on the latter (**Tier I** for the mechanisms, **Tier II** for their sufficiency to explain selective vulnerability). See [[lc-morphology-what-is-established]]. A cell of this profile lives perpetually near the ceiling of its mitochondrial capacity, with little reserve to spend on repair — and so it is the cell in which the universal, age-dependent erosion of quality control first crosses from compensated to decompensated. This account is well aligned with the mitochondrial-cascade tradition and is Tier II: strongly motivated, partially demonstrated.

The NAD+ sink

Sustained oxidative load produces DNA double-strand breaks; the repair enzyme PARP-1 hyperactivates in response and consumes NAD+ prodigiously to synthesize poly-ADP-ribose. Because NAD+ is the central currency of mitochondrial metabolism, its depletion starves the sirtuins, cripples mitochondrial biogenesis, and disables the PINK1/Parkin mitophagy that clears depolarized mitochondria. The failure of quality control is compounded when intraneuronal amyloid-β binds the import channel TOM40, obstructing the entry of nuclear-encoded proteins needed for mitochondrial repair — a mechanism paralleled by α-synuclein's obstruction of TOM20 in Parkinson's disease. The pieces of this bioenergetic-collapse module are individually well evidenced; their assembly into the specific Phase I sequence is a Tier II synthesis.

> *Evidentiary grade — Tier I for age-related NAD+ decline and PARP-1 consumption; Tier II for the specific PARP→NAD+→mitophagy→TOM40 sequence as the Phase I lesion of the LC.*

Amitosenescence, and the disease-specificity problem it raises

The model's most distinctive Phase I claim is that the failing LC neuron does not simply die but enters a senescence-like state. Post-mitotic neurons cannot undergo classical replicative senescence, but they can enter a parallel state — *amitosenescence* — of stable dysfunction with a secretory phenotype. The strongest experimental anchor is the demonstration that loss of the chromatin organizer SATB1 induces a p21-dependent senescence program in post-mitotic dopaminergic neurons (Riessland et al., 2019). This is genuinely important, and it must be graded with scrupulous honesty, because it exposes a problem the first edition ignored: the SATB1 result is a **Parkinson's-disease and dopaminergic-neuron** finding, and neuronal amitosenescence, like the CD38/NAD loop discussed in Phase III, is a **generic mechanism of ageing**, not an Alzheimer-specific ignition.

This raises the disease-specificity problem squarely. If the engine of the architecture is a largely generic aging pathway — senescence, NAD+ decline, quality-control failure — then why does Alzheimer's disease take the specific anatomical and cellular form it does, rather than presenting as diffuse brain ageing? The model's answer, which it now states explicitly rather than assuming, is that **disease specificity comes not from the engine but from the substrate**: selective cellular vulnerability (the intrinsic phenotype of particular neurons) multiplied by anatomical wiring (which populations are connected to which) multiplied by regional threshold (where reserve is thinnest). The generic engine of ageing, applied to a non-generic map of vulnerability, produces a specific disease. This is a coherent answer, but it is a Tier II claim that must be argued, and the burden it places on the selective-vulnerability chapter is correspondingly heavy.

> *Evidentiary grade — Tier I that post-mitotic neurons can enter SATB1/p21-dependent senescence (in dopaminergic neurons); Tier III that LC amitosenescence is the specific ignition of Alzheimer's disease; Tier II that anatomical selectivity, not the senescence engine, supplies disease specificity.*

Why ignition is silent

Phase I produces no dementia. For two to three decades the LC and its aminergic neighbours degrade in near-silence, their only outward signs the prodromal disturbances of sleep, mood, and arousal that epidemiology has long linked to later dementia. The silence is the point: by the time memory fails, the disease is entering its third act, and the therapeutic window for the upstream lesion opened decades earlier. But a silent brainstem lesion becoming a forebrain disease requires its own mechanism — the first bridge.

VI. The First Bridge — The Locus Coeruleus Projection

The transition from a private brainstem affair to a forebrain disease is executed, the model proposes, by the LC's own ascending axons, which carry two cargoes to the same destinations along the same substrate.

Arm one — withdrawal of the noradrenergic brake. The LC supplies noradrenaline to the forebrain by volume transmission. Microglia express the β2-adrenergic receptor, through which noradrenaline drives a Gs–cAMP–PKA program that tonically suppresses NF-κB and pro-inflammatory transcription. Noradrenergic tone is, in effect, a standing brake on microglial activation. As the LC degenerates, the brake is withdrawn brain-wide, raising the inflammatory set-point preferentially where LC innervation is densest — including the hippocampus. Heneka and colleagues demonstrated the principle directly: LC lesioning accelerates amyloid pathology and exaggerates neuroinflammation in models (Heneka et al., 2010). Tier I as a mechanism; Tier II as the specific first-bridge event in human disease.

Arm two — trans-synaptic tau seeding. The pretangle tau accrued in LC neurons is competent to seed: released presynaptically, internalized postsynaptically via LRP1 and heparan-sulfate proteoglycans, it templates native tau in a prion-like manner (Holmes et al., 2013; Rauch et al., 2020). The LC's vast efferent tree makes it a near-ideal distributor, and the hippocampus a near-ideal recipient. Tier I as a mechanism of tau spread.

One projection, two failures. The two arms are not independent processes that happen to co-occur; they are carried by one anatomical substrate to one destination and arrive together — the cessation of the microglial brake and a stream of tau seeds converging on the hippocampus in the same epoch. That convergence, more than either arm alone, is what converts a brainstem metabolic disease into a limbic immune disease. The dual-cargo synthesis is the bridge's signature claim and is Tier II.

Evidentiary grade — Tier I for each arm as a biological mechanism; Tier II for their simultaneous, same-substrate convergence as the operative Phase I→II transition.

VII. Phase II — The Microglial Bridgehead, as a Branched State-Space

Collapse of the homeostatic signature

The healthy microglion is defined by a TGF-β/SMAD-maintained transcriptional signature — P2RY12, TMEM119, CX3CR1, SALL1 — that is not a label but a behavioural program of surveillance and restrained pruning (Butovsky et al., 2014). Phase II begins when chronic oxidative and inflammatory stress, arriving with the withdrawn noradrenergic brake and the incoming tau seeds, dysregulates SMAD signalling and the homeostatic markers are lost. The decisive ordering evidence comes from resilience: de Vries and colleagues documented cognitively intact individuals carrying Alzheimer-range amyloid and tau whose brains are distinguished not by less pathology but by *preserved homeostatic microglia and intact perineuronal nets* (de Vries et al., 2024). This places microglial state, not protein burden, on the critical path to cognitive failure — a Tier I finding of unusual leverage.

Against the single downhill slope

Here the first edition committed its most consequential oversimplification, and this edition corrects it. It is not the case that all departures from microglial homeostasis are steps down one senescent slope. The disease-associated-microglia (DAM) literature explicitly describes a *branched state-space*, and several of its branches are protective or pathology-restricting rather than uniformly degenerative. The canonical DAM program of Keren-Shaul and colleagues was characterized as *restricting* the development of Alzheimer's pathology, its second stage gated by TREM2 (Keren-Shaul et al., 2017); TREM2 loss-of-function *increases* disease risk, which is the opposite of what a "all activation is harmful" model predicts. The correct picture is a state-space with at least three distinguishable trajectories that the first edition collapsed into one: **adaptive activation** (often protective, clearance-competent), **maladaptive pruning** (complement-driven synapse and matrix removal), and **true cellular senescence** (dystrophic, secretory, clearance-incompetent). These overlap but are not identical, and a serious model must specify the *state transitions, thresholds, and branch points* between them rather than treating every deviation from homeostasis as the same senescent act.

What the model retains, as a genuine insight, is narrower and more defensible: that in the *terminal, maladaptive* attractor of this state-space — the dystrophic, senescent microglion of Streit's descriptions, gorged with lipid (Marschallinger et al., 2020) and iron — clearance-incompetence (failure) and secretory matrix attack (harm) become, at the perineuronal net, two faces of the same

cellular act. The unification of "attack versus failure" is true *of the terminal state*, not of the whole activated repertoire. This is the corrected claim, and it is Tier II.

> *Evidentiary grade — Tier I that microglial state, not burden, gates resilience, and that DAM includes protective programs; Tier II that a terminal senescent-dystrophic attractor unifies attack and failure at the matrix; Tier III any claim that all post-homeostatic microglia are on a single degenerative trajectory — this the model now rejects.*

TREM2 at the collision point

TREM2 recurs at every level because it sits at the collision point of the branches: it gates the protective DAM transition, couples lipid and apolipoprotein sensing through DAP12–SYK–PI3K–AKT–mTOR to phagocytic and metabolic competence, and its variants are among the strongest single-gene risk factors after APOE (Guerreiro et al., 2013). That the same receptor can be protective (enabling clearance) and permissive (enabling lipid-gridlocked, inflammasome-primed states) depending on context is precisely why the state-space, not any single state, is the right unit of analysis.

VIII. The Second Bridge — The Proteolytic Turn

The transition from microglial collapse to synaptic loss was, before its specification, the least-described boundary in the architecture. The model fills it with three converging arms that meet on one structure — the aggrecan–brevican perineuronal net of the parvalbumin interneuron — because a chemically heterogeneous target can be attacked along several chemistries at once.

Arm one — the proteolytic switch. The lipid-laden terminal microglion uses lipid droplets as platforms for NLRP3 inflammasome assembly; activated NLRP3 licenses caspase-1 to mature IL-1β, which drives transcription of MMP-2/3/9 and ADAMTS proteases. The cell that spent Phase II secreting cytokines becomes one that secretes matrix proteases — the proximate microglial cause of perineuronal-net loss documented by Crapser and colleagues (Crapser et al., 2020). Tier I–II.

Arm two — iron liberation and Fenton catalysis. Oligodendrocytes dying by ferroptosis release redox-active Fe2+ into the parenchyma; the sulfated glycosaminoglycans of the net bind it avidly, making an iron-loaded net a substrate for Fenton chemistry, whose hydroxyl radicals fragment the proteoglycan core and render it more susceptible to enzymatic cleavage. Enzymatic and inorganic degradation are thus multiplicative, not merely additive. The iron biology is Tier I; its specific multiplicative coupling to matrix loss is Tier II.

Arm three — complement priming. Terminal microglia deposit C1q on the net and synapses; the classical cascade lays down C4d "eat-me" opsonins recognized by microglial receptors, licensing phagocytic stripping. Crucially, Hong, Stevens, and colleagues showed that complement and microglia mediate early synapse loss in Alzheimer models *independently of plaque burden*, and that removing C1q or C3 is protective — the clearest demonstration that this arm is causal rather than reactive (Hong et al., 2016; Stevens et al., 2007). Tier I.

The three arms meet on the parvalbumin interneuron's coat. The convergence — three independent chemistries on one structure, following the geography of prior Phase II damage — is the bridge's signature claim, and is Tier II.

Evidentiary grade — Tier I that complement-microglia mediate early, plaque-independent synapse loss; Tier II that the three arms act multiplicatively and converge specifically on the PV net as the operative Phase II→III transition.

IX. Phase III — Synaptic Disintegration, and the Final Common Bottleneck

The parvalbumin interneuron and its net

The perineuronal net is a dense lattice of hyaluronan, chondroitin-sulfate proteoglycans (aggrecan, brevican, neurocan, versican), and tenascin-R, condensed around the soma and proximal dendrites of specific neurons — in cortex and hippocampus, almost exclusively the parvalbumin-positive fast-spiking interneuron. These cells are the metronomes of cortical computation: through vast arborizations, a single basket cell paces thousands of pyramidal neurons and generates the gamma rhythms (30–80 Hz) underlying working memory and attention. Firing above 200 Hz and expressing calcium-permeable, GluA2-lacking AMPA receptors, they are extraordinarily exposed to oxidative and ionic stress, and depend on the net as a structural scaffold, an ion-exchange buffer, and an antioxidant shield. To strip the net is to leave the cell exposed to the toxicity of its own metabolism.

The latent interval and disinhibition

When the Proteolytic Turn digests the sheath, the denuded interneuron does not immediately die. It enters a *latent interval*, downregulating parvalbumin, Nav1.1, and NPTX2, and falling electrically silent. The consequence for the network is immediate: loss of perisomatic inhibition disinhibits pyramidal neurons, collapsing gamma rhythms and producing the hyperexcitability and hypersynchrony that characterize the Alzheimer cortex — and, because synaptic Aβ and tau release is activity-dependent, the disinhibited network accelerates its own pathology in a feed-forward loop. The convergence of senescent astrocytes (withdrawing EAAT2/GLT-1 glutamate clearance) and senescent oligodendrocyte progenitors (failing myelin maintenance) compounds the exposure. This cellular account of Phase III is Tier II, well grounded in the interneuron and gamma literatures.

The net as *a* final common bottleneck, not *the* terminal mechanism

The first edition claimed perineuronal-net demolition as the exclusive terminal substrate of dementia. This edition makes the weaker and more defensible claim the evidence supports. Necessity and sufficiency of PNN/PV failure across the whole disease spectrum remain unproven, and a monocausal terminal mechanism sits uneasily with the heterogeneity of Alzheimer phenotypes. The model therefore recasts the perineuronal net as **a high-value final common bottleneck of decompensation** — one convergence point, among several possible, at which multiple upstream routes cash out into cognitive failure, and a particularly instructive one because its integrity so cleanly separates the resilient from the demented. It is one bottleneck of great leverage, not the single gate through which all dementia must pass. This reframing fits both the resilience data and the phenotypic heterogeneity better than the exclusive claim did.

Resilience as the model's strongest evidence

The resilience finding is where the architecture is most persuasive, and it survives the reframing intact — indeed it motivates it. De Vries and colleagues found that cognitively intact, high-pathology individuals are distinguished by preservation of the perineuronal net, with the aggrecan core wrapping the parvalbumin interneuron remaining largely intact even where the sugar decorations are reduced (de Vries et al., 2024). Because the matrix survives, the interneuron keeps its shield, averts excitotoxic overload, and continues to pace the gamma rhythms cognition requires. The clean prediction this yields — that resilient high-pathology brains segregate more by preserved inhibitory-matrix architecture than by aggregate burden — is one of the model's most powerful and distinctive, precisely because it offers a mechanistic alternative to lesion-count explanations of dementia. It is Tier I as an association and Tier II as a causal claim.

The reelin brake and the matrix that stages it

The preserved net of the resilient brain is not merely an inert shield; it is also the staging ground for an active molecular brake on the disease, and naming that brake turns the resilience association into a mechanism. The guardian is reelin — the extracellular glycoprotein that, binding the ApoER2 and VLDL receptors, drives Dab1 phosphorylation to restrain tau hyperphosphorylation and to antagonize amyloid-β at the synapse (Hiesberger et al., 1999; Durakoglugil et al., 2009). Reelin is not incidental to the perineuronal net: in the adult cortex it is secreted directly *into* it (Pesold et al., 1999), so that the same lattice de Vries found preserved in resilient brains is the lattice that holds the reelin brake in place. This is why the autosomal-dominant resilience cases of Part II converge on this axis rather than on amyloid. The Reelin-COLBOS variant is a gain of function in the guardian itself (Lopera et al., 2023), and the APOE3-Christchurch variant acts on the same lipoprotein-receptor–heparan-sulfate system (Arboleda-Velasquez et al., 2019); both spared the entorhinal cortex from tau while amyloid ran on. The brake, strengthened, held the outcome open even under a deterministic amyloid-driving mutation — which is the mechanism behind the qualification the genetic concession required.

The deepest form of the finding is that shield, brake, and doorway are one structure. The sulfated glycosaminoglycan chemistry of the perineuronal matrix performs three offices at once: it shields the parvalbumin interneuron mechanically and antioxidatively; it stages the reelin signal, because N-sulfated heparan sulfate is the co-receptor reelin requires to dimerize ApoER2 and fire (Pan et al., 2025); and it is the very doorway through which pathological tau is internalized and propagated, since tau uptake proceeds by binding cell-surface heparan-sulfate proteoglycans (Holmes et al., 2013). One matrix, three functions — and the map confirms it from the opposite direction: neurons ensheathed by aggrecan nets rarely bear tangles, while the net-poor nuclei, the locus coeruleus first among them, are ground zero for tau (Morawski et al., 2010), closing the architecture's loop back onto Phase I. Two consequences follow. First, the shared node explains the resilience mutations economically: Christchurch loosens a *pathological* engagement of the heparan-sulfate/lipoprotein system while COLBOS tightens a *protective* one — the same three-way handshake of ligand, sulfated sugar, and receptor, dialed down on the harmful side and up on the helpful. Second, it issues a therapeutic warning only this convergence can see: a heparan-sulfate-blocking agent designed to jam the tau doorway would, by the identical action, risk silencing the reelin brake that requires the same sugar — so that the rational anti-tau strategy of occluding the sulfated surface and the rational pro-resilience strategy of preserving it are, unless the drug can discriminate the tau-uptake configuration from the reelin-signalling one, the same molecule pulled two ways. That the resilient brain often shows *rising* reelin expression even as its signalling falls — a reelin resistance rather than a reelin deficiency — only sharpens the point: the target is the functioning handshake, not the ligand's abundance.

Evidentiary grade — Tier I that reelin brakes tau and antagonizes Aβ and is secreted into the PNN, and that net-bearing neurons resist tangles (Morawski); Tier I that the COLBOS and Christchurch carriers resisted dementia; Tier II that reelin-staging, tau-uptake, and mechanical shielding are three offices of one sulfated node, and that this predicts the heparan-sulfate therapeutic double-edge.

The systemic CD38/NAD+ loop, graded honestly

Beneath the local synaptic destruction, the model proposes a systemic metabolic loop closing the architecture back on its origin: accumulating senescent cells across brain and periphery secrete a SASP that upregulates CD38 on macrophages; CD38, a potent NADase, degrades NAD+ regionally and systemically, mirroring on a large scale the NAD+ scarcity that drove the LC into amitosenescence in Phase I (Covarrubias et al., 2020). This is an elegant closure, and it must be graded honestly: the CD38/NAD+ loop is a **robust mechanism of systemic ageing**, not an Alzheimer-specific ignition. Its place in the architecture is that of a generic amplifier that lowers reserve everywhere and thereby accelerates whichever lane is load-bearing — not a disease-specific cause. Presented as the former it is Tier I; presented as the latter it would be Tier III and is not asserted here.

Evidentiary grade — Tier I that PNN preservation associates with resilience and that the CD38/NAD+ loop drives systemic NAD+ decline; Tier II that PNN failure is a high-value final common bottleneck; the exclusive-terminal-substrate and AD-specific-CD38-ignition claims are withdrawn.

X. The Arithmetic of Attrition and the Geometry of Resilience

Selective vulnerability supplies the disease specificity

The disease-specificity problem raised in Phase I is answered here, empirically. Alzheimer's destruction is highly non-random, and the populations it targets share a phenotype: they are physically large, maintain long-range projection axons, fire at high sustained rates, endure chronic oxidative exposure, and depend on specialized protective envelopes such as the perineuronal net or intense astrocytic buffering. Unbiased stereology — the optical fractionator and Cavalieri estimator, which yield absolute counts immune to the shrinkage artefacts of density-based profile counting — documents catastrophic, phenotype-selective loss in exactly these populations, while sparing populations that lack the phenotype.

Neuronal population	Structural / functional identity	Documented stereological loss in AD
Locus coeruleus	Brainstem; noradrenergic pacemakers	~60% in established AD; early volume loss
Entorhinal layer II	Stellate cortical gateway (RORB+)	~60% by very mild AD (CDR 0.5); ~90% in severe AD
Nucleus basalis (Ch4)	Basal-forebrain cholinergic projection	>75% end-stage; early phenotypic silencing
Hippocampal CA1	Pyramidal; primary limbic output	~48–68% in established AD
Layer III/V pyramids	Corticocortical association fibers	>90% loss of neurofilament-rich subsets

By contrast, the cerebellum accumulates diffuse amyloid yet loses essentially no Purkinje or granule cells; primary sensory and motor cortices are largely spared; and interneurons equipped with endogenous calcium-buffering proteins such as calretinin remain untouched. The geometry of sparing proves the point: Alzheimer's is not a diffuse neurotoxic fog but a precise, phenotype-driven demolition. And it is this map of vulnerability — not the generic senescence engine that drives destruction along it — that gives the disease its specific form. The arithmetic is Tier I; the interpretation, that selective vulnerability multiplied by wiring supplies disease specificity, is the Tier II synthesis on which the whole architecture's answer to "why this disease?" rests.

Synaptic loss precedes somatic death

In-vivo SV2A PET shows hippocampal synaptic-density reductions approaching 20% before measurable grey-matter loss, and synaptic degradation predicts cognitive decline better than atrophy. The disease severs connections through senescent pruning long before it kills cell bodies — which is why dementia tracks disconnection, not lesion count, and why the resilience data cohere.

XI. Integration, Parsimony, and Discriminating Predictions

The convergence beneath the sequence

The three phases are not three diseases but three expressions of the age-dependent collapse of one homeostatic system, maintained throughout by TGF-β/SMAD signalling, pivoting at each phase through TREM2, and converging on one anatomical address — the perisomatic zone of the parvalbumin interneuron. This is why resilience, when it occurs, requires the *joint* preservation of homeostatic microglia, intact matrix, and competent inhibitory synapses, and is never bought by preserving any single layer. The multiple entry lanes of Part II feed into this shared downstream system; the disease's specificity comes from the vulnerability map of Part X; and its terminal expression converges on the bottleneck of Part IX. That is the architecture, whole.

On parsimony and its price

Intellectual honesty requires stating plainly what this scope costs. A model that traces a fifty-year, multi-lane, phase-resolved architecture is far less parsimonious than a single-molecule cascade. It requires many serial contingencies — a specific microbial drift, a butyrate-linked checkpoint, an afferent bias, a bioenergetic threshold, a senescence program, a dual-cargo bridge, a branched glial state-space, a three-armed proteolytic turn, a matrix bottleneck, and a systemic metabolic loop — few of them absurd individually, but long in aggregate. This loss of parsimony is not free, and it is not hidden: it is the price paid for explaining latency, topology, cell-type specificity, resilience, and terminal disconnection at once, where single-substrate theories explain one or two and leave the rest as anomalies. The model does not ask to be believed because it is simple; it asks to be tested because it is graded. Every junction above carries its own tier, and the Validity Ledger collects them so that the reader can see precisely where the chain is strong iron and where it is inference.

Discriminating predictions

A theory earns its name by exposing itself to refutation. The following predictions are stated to *discriminate* this architecture from amyloid-first and vascular-first alternatives — not merely to be confirmable, but to come out differently depending on which model is right.

1. **If the ecological lane is a genuine origin in the gut-affected subtype, gut and LC markers should outrun canonical cortical markers in preclinical individuals of that subtype specifically.** Preclinical members of the inflammatory, gut-affected

subgroup should show coordinated dysbiosis, reduced butyrate-linked protective signalling, and early LC stress and senescence markers *before* transentorhinal-cortical progression signatures dominate. If instead amyloid or vascular markers lead uniformly across subtypes, the ecological lane is not an origin but a modifier.

2. **If bacterial amyloids are upstream of Alzheimer pathogenesis, the evidence must extend from α-synuclein to tau-relevant, route-specific templating.** The cross-seeding case is strong for synucleinopathy and unproven for tauopathy; a theory that depends on this bridge should predict direct, tau-relevant seeding or route-specific propagation, not merely inflammatory plausibility. Failure to demonstrate tau-relevant templating weakens the ecological lane's claim to *initiate* Alzheimer's specifically.

3. **If LC amitosenescence is the decisive conversion point, LC neuronal senescence markers should temporally precede sustained forebrain microglial-state collapse in the same disease trajectory.** If microglial or vascular pathology instead precedes or occurs independently of LC senescence, the LC is an early participant but not the necessary initiator — and the Tier III fourth sense of "first" is refuted.

4. **If the Proteolytic Turn is the core Phase II→III bridge, regions of perineuronal-net loss should show tightly coupled IL-1β / MMP / complement signatures and nearby parvalbumin dysfunction.** Spatial decoupling of these markers from PNN loss would weaken the model's strongest proposed bridge.

5. **If perineuronal-net integrity is central to resilience, resilient high-pathology brains should segregate more by preserved inhibitory-matrix architecture than by aggregate amyloid or tau burden.** This is the model's most distinctive prediction, because it yields a clean mechanistic alternative to lesion-count explanations of dementia. Its partial confirmation by de Vries and colleagues is encouraging; its full test requires single-cell and spatial resolution across resilience cohorts.

6. **If the architecture is subtype-limited rather than universal, it should perform best in sporadic, inflammatory, gut-affected, high-senescence phenotypes and worse in genetically driven early-onset APP/presenilin disease.** This prediction would not refute the model; it would delimit its proper explanatory domain — and a theory that knows its own boundaries is stronger, not weaker, for the knowledge.

Each prediction is stated so that a single well-designed study could move it. That is the dividend of grading a theory rather than merely asserting it: the joints, once named, become hypotheses.

XII. Therapeutic Implications — Phase- and Subtype-Matched Intervention

The architecture's most consequential implication is also its most uncomfortable. If the load-bearing lesion changes with the decade — metabolic in Phase I, immunological in Phase II, structural in Phase III — and if the operative *lane* varies by subtype, then a drug aimed at any one phase's molecule in an unselected population is useful only to the fraction of patients who are, at that moment, in that phase and that lane. The repeated failure of single-target monotherapies is, on this reading, not bad luck awaiting a better molecule but the structural consequence of treating a substrate-shifting, multi-lane process with a static, unselected tool.

The corollary is constructive and specific. **Phase I** is a metabolic-and-custodial problem whose rational interventions are upstream and presymptomatic — NAD+ restoration, PARP-1 restraint, support of mitophagy — administered decades early, in individuals identified by genetic and biomarker risk, and, in the gut-affected subtype specifically, by ecological measures (butyrate restoration, barrier repair, targeting of curli-producing Enterobacteriaceae). **Phase II** is a problem of microglial *identity*, whose rational target is the homeostatic state itself (restoration of TGF-β/SMAD signalling and noradrenergic tone) rather than the blunt depletion or activation of microglia wholesale — a distinction the branched state-space makes essential, since indiscriminate microglial clearance would remove protective DAM programs along with harmful ones. **Phase III** is a structural-and-electrical problem whose narrow window lies between the initiation of net loss and the depletion of the parvalbumin cells the net protects; there the logic is matrix preservation (MMP and complement inhibition) and metabolic rescue, and clearing microglia after the matrix is destroyed is structurally futile. Across all phases, the perineuronal net around the parvalbumin interneuron is the single most compact biomarker of whether a homeostatic intervention is succeeding.

Phase- and subtype-matched intervention, begun early, measured at the net, and aimed where possible at the shared homeostatic signal, is neither single-target nor indiscriminately combinatorial. It is the therapeutic grammar a graded, convergent architecture implies.

XIII. Conclusion

The history of Alzheimer's theory has been a long argument about substance conducted in the absence of time and in the absence of grading. Each generation has nominated its primary molecule and arranged the rest as sequelae, and each nomination has captured a real part of the disease while failing to fit the whole — because the whole is not a substance but a graded, multi-lane trajectory. The contribution of this thesis is to assemble time, anatomy, glial state, extracellular matrix, and systemic metabolism into one convergent architecture with named transitions, and to do so without the overreach that would make it merely another cascade wearing more boxes.

What that discipline requires, this edition has tried to supply: amyloid repositioned as a validated node rather than an eliminated error, and conceded as the initiator in familial disease; the vascular tradition restored as a parallel lane whose primacy is a subtype question; the locus coeruleus's four senses of "first" disentangled, with only the supported ones claimed; the microglial state recast as a branched space with protective as well as harmful branches; the perineuronal net named as a high-value bottleneck rather than the sole terminal gate; the generic engines of ageing distinguished from the anatomical map that gives the disease its specific form; and the whole submitted to an explicit tiering that lets the reader weigh each junction for themselves. The cost — a real loss of parsimony — is stated rather than hidden, and is the honest price of a model that tries to explain latency, topology, specificity, resilience, and disconnection together.

In its present form the thesis is best read not as a settled master theory but as an integrative mechanistic program: high in originality, explicit about its evidentiary balance, and, above all, testable at its joints. The disease has always been a process in time, entered through more than one door, converging on a shared architecture, and gated at the end by the survival of a fragile inhibitory scaffold. The opportunity to meet it has always been earlier, and broader, than we were looking — provided medicine learns to see the front while it is still upstream, to measure it at the net, and to match its tools to the phase, the lane, and the patient in front of it.

Validity Ledger

The architecture's major claims, each graded and paired with its principal caution. Tier I — established; Tier II — bridging inference; Tier III — conjectural.

Claim	Tier	Principal caution
Age-related dysbiosis depletes butyrate and weakens the gut barrier	I	Not specific to AD
Butyrate–LL-37 axis is an AD-relevant anti-amyloid checkpoint	II	Cross-domain extrapolation; not shown in human AD
Bacterial curli cross-seeds α-synuclein	I	Synucleinopathy, not tauopathy
Bacterial amyloids cross-seed tau relevant to AD	III	Weaker than the α-synuclein case; unproven
Neuropod–vagus–NTS conduit transmits gut signals rapidly	I	Anatomy established
Chronic AD-specific excitatory bias of the NTS→PGi→LC relay	II/III	Not directly demonstrated in AD
Amyloid-β is causally active at multiple points in the architecture	I	The model is not anti-amyloid
Amyloid is the initiating *trigger* in autosomal-dominant AD	I	Necessary to set the disease in motion; but the COLBOS carriers show it is not the sole author of dementia
APOE4 lowers thresholds across several modules simultaneously	II	Each effect Tier I; the synthesis is inferential
Vascular injury frequently antecedes decline	I	Primacy is subtype-variable
LC shows the earliest detectable tau-related pathology	I	Braak–Del Tredici staging
LC is the earliest major relay/amplifier hub	II	Anatomically strong; causal weight unquantified
LC is the necessary causal initiator of all AD	III	The strong claim; explicitly not licensed
PARP→NAD+→mitophagy→TOM40 is the Phase I LC lesion	II	Pieces Tier I; the sequence is a synthesis
Neurons can enter SATB1/p21-dependent senescence	I	Shown in dopaminergic neurons (PD)

Claim	Tier	Principal caution
LC amitosenescence is the specific ignition of AD	III	Generic ageing mechanism; specificity unproven
Disease specificity comes from selective vulnerability × wiring	II	The model's answer to "why this disease?"
Noradrenergic-brake withdrawal + tau seeding converge via one LC projection	II	Each arm Tier I; the convergence is inferred
Microglial state, not burden, gates resilience	I	de Vries resilience cohort
DAM state-space includes protective branches	I	Not all activation is harmful
A terminal senescent-dystrophic attractor unifies attack and failure	II	True of the terminal state, not all activation
Complement–microglia mediate early, plaque-independent synapse loss	I	Hong/Stevens; causal via C1q/C3 removal
The three proteolytic arms act multiplicatively on the PV net	II	Convergence inferred from separate literatures
PNN failure is a high-value final common bottleneck	II	Not the sole/necessary terminal mechanism
PNN preservation associates with cognitive resilience	I	Association Tier I; causal claim Tier II
Deterministic-AD carriers resist dementia via a downstream brake (RELN-COLBOS, APOE3-Christchurch)	I	Amyloid initiation ≠ destiny even in ADAD
Reelin (→ApoER2/VLDLR→Dab1) brakes tau, antagonizes Aβ, and is secreted into the PNN	I	Durakoglugil; Hiesberger; Pesold
Reelin-staging, tau-uptake, and shielding are three offices of one sulfated matrix node	II	Pan 2025 + Holmes 2013; predicts the HS therapeutic double-edge
Phenotype-selective stereological attrition (LC, EC-II, CA1…)	I	Unbiased stereology
CD38/NAD+ loop drives systemic NAD+ decline	I	Generic ageing amplifier, not AD-specific ignition
Single-target monotherapy fails because the lesion shifts by phase/lane	II	Therapeutic corollary of the architecture

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