THE GARDENER'S RESTRAINT

Microglial Resilience and the Uncoupling of Amyloid from Dementia — Why Some Brains Bear a Heavy Plaque Burden and a Released Coerulean Brake Without Descending into Alzheimer's, and Where the Line Falls First

The Amyloid-Bearing Mind · The Disciplined Gardener · The Barrier Around the Plaque
The Redundant Brakes · The First Region to Fall

A Dissertation Submitted in Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy in Neuroscience

Prepared under the Organic Network Synthesis methodology

AdultCognitiveDisease.com

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July 2026

The resilience companion to The Corruption of the Gardener. That atlas ranked the drivers that push microglia out of homeostasis into the disease-associated state. This volume asks the mirror question — what holds the gardener in its right mind — and finds that resilience to Alzheimer's dementia is, in large measure, microglial restraint: the disciplined cell that walls the plaque, spares the synapse, and so lets a plaque-laden brain keep its mind. Because the coerulean brake is one brake among several, its release need not cross the threshold that others still hold.

"The plaque was present and did nothing. A brain may carry as many deposits as the pathologist can count and keep its mind entire — not because the amyloid was cleared, but because the cell that would have turned it into the loss of a synapse stayed disciplined. Resilience is not less amyloid. It is amyloid better walled, and a gardener that kept its restraint."

— ONS Methodology Working Notes, 2026

For those who carried the pathology and kept the mind — the resilient brains that prove the plaque is not the disease, and whose quiet gardeners show us what a cure would have to imitate.

THE COLLAPSE FRAMEWORK MICROGLIAL & RESILIENCE COMPANION

The Corruption of the Gardener — the drivers that push microglia into the disease state

The Architecture of Resistance — the protective genome, strength-graded

The Two Anchors — ordered attrition and resilience, the two human-evidence anchors

The First Ember — how tau is first kindled in the locus coeruleus

The Coerulean Pincer — norepinephrine cuts the brake from outside, floors the kinase from inside

The Gardener's Restraint (microglial resilience, and the uncoupling of amyloid from dementia) — this volume

This volume turns the corpus's microglial and resilience threads to a single clinical fact: that a substantial minority of people die with brains full of amyloid and their minds intact. It argues that the decisive variable is the disposition of one cell — the microglion — and that resilience is microglial restraint: the disciplined gardener wraps the plaque in a tight barrier and compacts its neurotoxic halo into an inert core, insulating the neurites the plaque would otherwise injure; it holds down the soluble oligomer that would tag a synapse for complement pruning; and so the synapse, the true substrate of the mind, is spared however many plaques stand around it. This restraint is built by a definite apparatus — the lipid-sensing receptor TREM2 and its protective genetics foremost — and it is therefore heritable, measurable, and, the clinical prize, tunable. The volume then answers the coerulean reader's challenge — if the locus-coeruleus brake comes off in nearly everyone, why is not everyone lost? — with the principle that organises the whole: the brake is not the only brake. Dementia is crossed not when one restraint is released but when the net of parallel restraints falls below what the pathology demands; resilience is the depth of the remaining margin, and the disease is the sequential, not simultaneous, failure of the brakes. Where the line falls first — the net-poor locus coeruleus, then the transentorhinal cortex — is the same variable read locally: the first region to fall is the one with the fewest brakes.

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Abstract

There is a fact about Alzheimer's disease that any theory of its cause must survive, and that most theories quietly do not. A substantial minority of elderly people die with brains that meet the full neuropathological criteria for the disease — abundant neocortical amyloid plaques, and in many a heavy tangle burden besides — while never, in life, having lost their minds. They were tested; they were normal; and their brains were, by the pathologist's ruler, diseased. The plaque was present and did nothing. This dissertation takes that fact not as a curiosity at the edge of the field but as the field's central question rephrased. The question is not, as a century of amyloid-first thinking has framed it, *why does the plaque appear* — the plaque appears in the resilient and the demented alike. The question is *why, in some, does it do nothing*. What stands between a plaque-laden brain and a lost mind, and why does that thing hold in one person and give way in another?

This volume argues that the decisive variable is the disposition of a single cell type — the microglion, the brain's resident immune cell and the gardener of its synaptic field — and that resilience to Alzheimer's dementia is, in large measure, *microglial restraint*: the capacity of the gardener, provoked by amyloid, to remain disciplined rather than turn destructive. The companion atlas to this dissertation, *The Corruption of the Gardener*, ranked the drivers that push microglia out of homeostasis and into the disease-associated state; the present volume is its mirror, and asks the opposite question — what holds the gardener in its right mind, and how that holding uncouples the plaque from the dementia. The mechanism we assemble has a physical core, well-evidenced in human tissue: the disciplined microglion does not clear amyloid so much as *contain* it. Drawn to the nascent plaque, it wraps the deposit in a tight cellular barrier and compacts the diffuse, neurotoxic protofibrillar species into an inert dense core, insulating the surrounding neurites from the plaque's toxic halo. This barrier is built by a definite molecular apparatus — the lipid-sensing receptor TREM2 foremost among its components — and where that apparatus is weakened, by genetics or by exhaustion, the barrier is loose, the plaque diffuse, the neurites dystrophic, and the same amyloid load does far more harm. Resilience, on this reading, is not less amyloid. It is amyloid better walled.

We then answer the question the reader of our coerulean volumes will press. *The First Ember* and *The Coerulean Pincer* argued that tau is first kindled in the locus coeruleus and that a released "brake" — the reelin signal that restrains the tau kinase — permits the tangle to form. If the brake comes off, why does not every brain proceed to Alzheimer's? Because the coerulean brake is one brake among several, wired in parallel, and clinical dementia is crossed only when the *net* of restraints falls below what the pathology demands. A single released brake in a single small nucleus does not cross that threshold if the other restraints hold: if the microglial barrier still compacts the plaque, if the protective genome still keeps the gardener disciplined, if the reelin brake still holds on the downstream neurons the coerulean lesion would seed, if the synaptic reserve is deep enough to lose a fraction and keep the function. Resilience is redundancy; the

disease is the sequential, not simultaneous, failure of parallel safeguards. We ground this in the human resilience genetics the corpus has followed — the *APOE2* allele, the common protective *TREM2* and *PLCG2* variants that tune the gardener toward its barrier state, and the two experiments of nature, the *APOE3*-Christchurch and *RELN*-COLBOS carriers, who bore an autosomal-dominant plaque avalanche for decades with their minds intact. Finally we address where the line falls first, and why: the locus coeruleus, constitutionally without the perineuronal net and therefore first to tangle, then the transentorhinal and entorhinal cortex, then the hippocampus and the association neocortex — a stereotyped march along vulnerable, poorly-netted, richly-connected circuits — and we show that regional resilience is the same variable read locally, the spread stalling wherever the downstream neuron is better shielded, better staged, and better held in reserve. Each load-bearing claim is graded in an explicit validity ledger, candid that the barrier mechanism is strong in animal and human tissue while its quantitative contribution to human cognitive resilience remains an inference, and that microglial restraint has a knife-edge — too little surveillance is as dangerous as too much inflammation. The clinical corollary is not to silence the gardener but to discipline it: to phenocopy the fortunate, tuning microglia toward the barrier state early, in the window before the plaque's halo has done its work.

I. The Amyloid-Bearing Mind

Begin with the anomaly, because the anomaly is older than the theory it embarrasses. In 1988 Robert Katzman and his colleagues at San Diego reported a subgroup of elderly people who had come to autopsy with brains full of neocortical plaques — as many plaques as the demented, by the counts of the day — and who had nonetheless been, in life, of preserved mental status: cognitively normal, tested and documented, to the end (Katzman and colleagues, 1988). Their brains were heavier than expected and their large neurons more numerous, as though something had been held in reserve. The observation was made before the amyloid cascade hypothesis had hardened into orthodoxy, and it has been confirmed in every large clinicopathological series since. A consistent fraction of cognitively intact older adults — on the order of a quarter to a third in unselected autopsy cohorts — carry amyloid pathology sufficient, by neuropathological criteria, to diagnose Alzheimer's disease. The Nun Study, following a cohort of religious sisters with annual cognitive testing and brain donation, made the dissociation sharper still: individuals with advanced neurofibrillary pathology who had scored normally on cognition for years, and individuals with little pathology who had declined — the correlation between the ruler's measure of disease and the mind's measure of it loose enough that neither could be read off the other (Riley and colleagues, 2002).

This is the phenomenon that this dissertation exists to explain, and it must be stated with some force because a great deal of theoretical apparatus has been built to look past it. If amyloid were sufficient for dementia, these brains would not exist. They do exist, in numbers too large to dismiss as staging artefact or presymptomatic snapshot; many of these individuals were followed to death and never converted. The plaque, in them, was laid down and *did nothing*. Whatever the plaque is — trigger, symptom, tombstone, or all three at different phases — it is not, by itself, the disease. Something intervenes between the deposit and the deficit, and in the resilient that something holds.

The most illuminating study of what that something is remains the one that dissected the resilient brain directly. Perez-Nievas and colleagues, working with the Massachusetts and Framingham autopsy material, compared three groups matched as far as possible on plaque and tangle burden: the demented with pathology, the non-demented with pathology — the resilient — and controls (Perez-Nievas and colleagues, 2013). Holding the plaque count constant, they asked what distinguished the mind that survived it. The answer came in three linked findings, and all three point at the same place. The resilient brains had *preserved synapses* — the synaptic markers that collapse in dementia were maintained. They had lower burdens of the soluble, oligomeric species of amyloid and of phospho-tau — the diffusible, toxic fractions, as opposed to the inert deposited bulk. And, decisively for the argument of this volume, they had *less microglial activation*: the neuroinflammatory signature that accompanies dementia was muted in the brains that had resisted it, at matched pathology. The resilient brain was not the brain with less plaque. It was the brain in which the plaque was accompanied by a quieter immune response and a spared synaptic field. The variable that tracked the preserved mind was not the amount of amyloid but the state of the cell that meets it.

That is the thread this dissertation pulls. The rest follows from taking seriously that the plaque is a constant and the microglion a variable, and asking what disposition of the variable spares the mind.

II. Two Words That Are Not Synonyms Resistance, Resilience, and the Reserve Beneath Them

Before the mechanism, a discipline of terms, because the field's confusions here are confusions of vocabulary as much as of biology, and the argument cannot be made in loose words. Arenaza-Urquijo and Vemuri drew the distinction that the literature had needed (Arenaza-Urquijo and Vemuri, 2018), and this dissertation adopts it. *Resistance* is the capacity to avoid the pathology — to reach old age with little amyloid, little tau, a brain that stayed clean. *Resilience* is the capacity to

tolerate the pathology once it is present — to carry the plaque and the tangle and keep the function. They are different phenomena with different mechanisms and, importantly, different implications for whom this dissertation is about. The resistant brain never poses our question, because the plaque never came. Our subject is the resilient brain: the one that met the full pathological insult and did not fall. The Katzman and Nun-Study individuals were not resistant — they had the plaques. They were resilient. Something let them carry it.

Beneath resilience lie the older constructs of reserve, and here too precision earns its keep. Stern's synthesis, refined into a formal consensus by an international working group, separates three things too often merged (Stern, 2012; Stern and colleagues, 2020). *Brain reserve* is the passive, structural capital — more neurons, more synapses, larger networks — such that a fixed amount of damage removes a smaller fraction of the whole; the reserve Katzman's heavier brains embodied. *Cognitive reserve* is the active, functional capacity to sustain performance by recruiting alternative circuits and strategies, the reserve that education, occupational complexity, and lifelong cognitive engagement build, and that lets two brains with identical damage perform unequally. And *brain maintenance* is the dynamic capacity to keep the pathology low and the machinery repaired over time — the slope, not the intercept — the reserve that sleep, exercise, and vascular health defend. Resilience is the whole of these acting against a load that has already arrived.

The point of the taxonomy is to place the microglion correctly within it, and the placement is the organizing claim of this dissertation. Microglial restraint is not a fourth kind of reserve alongside the three; it is a mechanism that *feeds all three at once*, and this is why it is the right cell to build a theory of resilience around. When the disciplined gardener walls off the plaque and spares the surrounding neurites, it is preserving brain reserve — keeping the structural capital intact. When it declines to prune the still-functional synapse under the false alarm of an amyloid-triggered complement tag, it is preserving the substrate of cognitive reserve — the circuits the resilient mind recruits. And when it clears debris, contains seeds, and keeps its own metabolic fitness rather than collapsing into a senescent, dystrophic exhaustion, it is performing brain maintenance — defending the slope. The microglion sits at the confluence where the abstract reserves become cellular events. A theory of resilience that names it is a theory that can be intervened upon. To that cell we now turn.

III. The Gardener and Its Discipline

The microglion is the brain's resident macrophage and its full-time custodian, and the horticultural metaphor that has attached to it is more than ornament: it captures the two things the cell does that

matter here. It gardens the synaptic field — surveying it continuously, pruning connections, clearing debris, sculpting the circuit — and it gardens against intruders, meeting the misfolded protein, the dying cell, the pathogen. In health these functions are held in a characteristic disposition that the single-cell era has taught us to read as a molecular signature. The homeostatic microglion expresses a checkpoint set of genes — the fractalkine receptor *CX3CR1*, the purinergic receptor *P2RY12*, *TMEM119*, and their fellows — that together enforce a surveilling, ramified, low-inflammatory state: processes extended, territory patrolled, restraint maintained (Deczkowska and colleagues, 2018). This is the gardener in its right mind. It is not quiescent — it is intensely active — but its activity is disciplined, directed at maintenance rather than war.

Amyloid disturbs this disposition, and what happens next is the fork on which the whole of resilience turns. Confronted with the plaque, microglia down-regulate the homeostatic checkpoint and take on a new program — the disease-associated microglion, the DAM of Keren-Shaul's landmark single-cell census, echoed as the "activated response microglia" of parallel work (Keren-Shaul and colleagues, 2017; Sala Frigerio and colleagues, 2019). It is essential to the argument of this dissertation, and to any honest account of the cell, that this transition is *not, in itself, the corruption*. The name Keren-Shaul's group chose is a rebuke to the reflex that reads all microglial activation as harm: they called it "a unique microglia type associated with *restricting* development of Alzheimer's disease." The DAM program, entered cleanly and in time, is the protective program — it is the gene set of the barrier-builder, the plaque-compactor, the debris-clearer. The disease is not that microglia activate. The disease is that the activation *fails*, or *overshoots*, or *exhausts* — that the gardener called to the plaque either cannot mount the containing response, or mounts it and cannot stop, tipping from surveillance into a chronic, synaptotoxic, complement-spraying inflammation that harms more than the plaque it was summoned to.

Resilience, then, is not the absence of microglial response but its *governance* — the gardener that answers the plaque with the barrier program and returns to discipline, rather than the gardener that fails to answer or answers without end. Two failure modes bound the disciplined state on either side, and the resilient microglion threads between them. On one side lies *insufficiency*: the gardener too weak or too old to build the barrier, letting the plaque spread its diffuse toxic halo unchecked. Wolfgang Streit's histology named this state before the molecular era could explain it — the *dystrophic* microglion of the aging human brain, fragmented and beaded and senescent, a cell that has lost the vigor to garden at all (Streit and colleagues, 2004). Where the gardener is dystrophic, tau and its spread appear to follow; the exhausted immune cell is a permissive one. On the other side lies *dysregulation*: the gardener that activates and cannot disengage, that overprunes the healthy synapse and floods the parenchyma with inflammatory mediators — the corruption the companion atlas anatomized in full. Between insufficiency and dysregulation lies a narrow disciplined band, and to stay in it under the provocation of amyloid, for decades, is what the resilient brain does and the vulnerable brain fails to do. The next three sections trace the three things the disciplined gardener accomplishes inside that band: it walls the plaque, it is held there by a definite genetics, and it spares

the synapse.

IV. The Barrier Around the Plaque

Here is the physical heart of the matter, and it is worth slowing down for, because it converts the abstraction "resilience" into a structure one can see in tissue. The disciplined microglion's central protective act is not, as the intuitive picture would have it, to eat the plaque and take it away. Amyloid, once fibrillized, is largely indigestible; microglia do not, in the main, clear the mature deposit. What they do instead is more interesting and more consequential: they *contain* it. Grutzendler's laboratory, imaging plaques and their microglial mantles at high resolution, showed that microglia form a tight cellular barrier around the amyloid deposit — wrapping it, sealing it — and that this barrier does definite work (Condello and colleagues, 2015). Where the microglial mantle is intact, the plaque is compact and its most dangerous species — the diffuse, protofibrillar Aβ42 that constitutes the toxic "halo" at the plaque's edge — are held in check, kept off the surrounding neurites. Where the mantle is thin or breached, the protofibrillar hotspots leak outward and the neurites in contact with them swell into the dystrophic, tau-filled, axonal spheroids that are the plaque's true injury to the circuit. The barrier is not decoration around the plaque. It is the seawall between the plaque and the neuron.

Two properties of this seawall make it the linchpin of a theory of resilience. The first is that it *insulates without removing*: it renders the plaque inert without requiring that the plaque be cleared. This is precisely the mechanism a resilient brain needs, because the resilient brain, by definition, still has its plaques — the Katzman and Perez-Nievas brains were plaque-laden. Resilience does not demand the impossible feat of dissolving mature amyloid; it demands only that the amyloid be *walled*, its halo compacted into a dense core that the neurites can grow past unharmed. The uncoupling of amyloid load from cognitive loss, the central fact of Section I, has here its physical explanation. Two brains may carry the same plaque burden and differ entirely in what that burden does, depending on whether the deposits are compact and mantled or diffuse and naked. The pathologist's plaque count, which reads the bulk, cannot see the difference. The neuron can.

The second property is that the seawall is built by a definite molecular apparatus, which means it is heritable, measurable, and — the clinical prize — potentially tunable. Its principal architect is the microglial lipid-sensing receptor TREM2. When TREM2 function is reduced, in mice and in humans carrying loss-of-function variants, the barrier fails in exactly the predicted way: the microglial mantle is sparse, the plaques are less compacted and more diffuse, the protofibrillar halo is unchecked, and the axonal dystrophy around the deposits is severe (Yuan and colleagues, 2016).

The same receptor governs the *timing* of the response — TREM2 is required for microglia to reach and engulf the nascent plaque early, limiting its diffusion and toxicity from the outset (Wang and colleagues, 2016) — and the *fuel* for it, sustaining the metabolic fitness the barrier-building program demands, so that TREM2-deficient microglia collapse into an energy-starved, autophagy-stressed state unable to mount the response at all (Ulland and colleagues, 2017). TREM2 sits at the head of the DAM program; it is the switch that carries the gardener from surveillance into the barrier-building state and holds it there with the metabolism to do the work. Adjacent receptor systems reinforce the same containment — the TAM receptor tyrosine kinases license microglia to detect and engulf the plaque (Huang and colleagues, 2021), and the plaque-associated apolipoprotein E that the barrier concentrates is itself TREM2-dependent (Parhizkar and colleagues, 2019). The barrier is a system, and TREM2 is its keystone.

It is worth being exact about what this does and does not establish, in the spirit of the ledger this volume keeps. That the microglial barrier compacts plaques and shields neurites is strongly evidenced, in mouse models and corroborated in human tissue with human TREM2 variants — this is Tier-I mechanism. That the strength of this barrier is a *quantitatively decisive* determinant of human cognitive resilience — that the Katzman brains were resilient chiefly *because* their gardeners walled their plaques better — is an inference, well-motivated and consistent with the Perez-Nievas finding of muted microglial activation and spared synapses in resilient tissue, but not yet demonstrated by the kind of study that would clinch it: a direct, quantitative correlation, in matched-pathology human brains, between mantle integrity and antemortem cognition. The inference is strong. It is still an inference, and the ledger records it as such. What is not in doubt is the direction: a better barrier is a better outcome, and the barrier is built by a genetics we can now read.

V. The Grammar of Restraint — The Genotypes That Keep the Gardener Disciplined

If microglial discipline is the mechanism of resilience, then the alleles that tune microglial discipline should be alleles of resilience, and they are. This is the point at which the present dissertation clasps hands with *The Architecture of Resistance*, the corpus's atlas of the protective genome; that volume graded the protective alleles across the whole disease, and this one reads the microglial subset of them as a single sentence with a single grammar. The grammar is this: variants that push the gardener *toward* its barrier-building, debris-clearing, disciplined state protect; variants that blunt that program, or that leave the gardener stuck in a maladaptive activation, harm. Read in that light the

innate-immune genetics of Alzheimer's disease, which the genome-wide studies have made the dominant signal in the whole architecture of risk, resolves into a coherent statement about a cell.

The keystone is TREM2 read in reverse. The rare loss-of-function variants — R47H foremost, identified in the Icelandic and multinational cohorts — roughly triple the risk of Alzheimer's disease, and they do so by weakening precisely the barrier apparatus of Section IV (Jonsson and colleagues, 2013; Guerreiro and colleagues, 2013). That a partial loss of one microglial receptor confers a risk rivaling anything short of *APOE* is the strongest possible evidence that the gardener's disposition is not a bystander in the disease but a governor of it. The protective mirror of this logic — a variant that *strengthens* the program — is written most clearly in a neighbouring gene. The P522R variant of *PLCG2*, the phospholipase that acts immediately downstream of TREM2 in the microglial signaling cascade, is protective against Alzheimer's disease, and its biochemistry is exactly what the theory predicts: it is a functional *hypermorph*, a gain-of-function that raises the gardener's responsiveness, tuning it toward the disciplined, containing state rather than away from it (Sims and colleagues, 2017; Magno and colleagues, 2019). A weakened barrier receptor raises risk; a strengthened downstream effector lowers it. The two variants bracket the mechanism from either side and agree on its sign.

Around this keystone the other innate-immune variants fall into place as tuners of the same program — *ABI3* and *INPP5D* and the *MS4A* cluster modulating microglial activation and TREM2 surface expression, *CD33* setting a brake on microglial amyloid uptake such that its risk allele restrains the very clearance the resilient brain needs (Griciuc and colleagues, 2013). The details differ; the theme does not. The genetics of Alzheimer's risk is, to a remarkable degree, the genetics of how a single cell responds to the plaque, and resilience lives in the alleles that answer well.

Above the microglial genes sits the largest genetic modifier of all, and it too is, in significant part, a microglial and lipid story. The *APOE* locus tunes resilience across its whole range: the ε4 allele is the dominant common risk factor, and its ε2 allele the strongest common protective one, associated with an exceptionally low likelihood of Alzheimer's dementia — vanishingly low in the rare ε2 homozygote (Corder and colleagues, 1994; Reiman and colleagues, 2020). Apolipoprotein E is the lipid the barrier concentrates, the partner of TREM2 at the plaque, and the molecule whose isoform sets how well the gardener handles the lipid load of the containing response; the protective ε2 brain is, among other things, a brain whose microglia meet the plaque with a more favourable lipid chemistry. And the two experiments of nature the corpus has followed most closely — the woman homozygous for the *APOE3*-Christchurch variant, and the man heterozygous for the *RELN*-COLBOS variant, each of whom carried the *PSEN1* E280A mutation that guarantees an autosomal-dominant amyloid avalanche, and each of whom held their cognition for decades past the expected age of onset amid that avalanche — are the human proof that the plaque can be uncoupled from the dementia by a single change in the resilience machinery (Arboleda-Velasquez and colleagues, 2019; Lopera and colleagues, 2023). These are living Katzman brains, prospectively

identified: the plaque came in full, autosomal-dominant force, and something — a change in heparan-sulfate–dependent apoE chemistry in the one, a strengthened reelin brake in the other — held the mind. They are the bridge from this dissertation's cell to its next section's brake, and we cross it now.

VI. The Spared Synapse

Everything to this point has concerned the plaque and the cell that meets it, but the plaque is not what is lost when a mind is lost. What is lost is the synapse. This is the most robust structure–function relationship in the whole of Alzheimer neuropathology, and it must be placed at the centre of any theory of resilience because it is the currency in which resilience is finally paid. When Terry and colleagues measured what, among all the countable features of the Alzheimer brain, best predicted the severity of dementia in life, the answer was not plaque count, not tangle count, but *synapse loss* — the density of synaptic markers in the neocortex tracked cognition more tightly than any measure of the deposited pathology (Terry and colleagues, 1991). DeKosky and Scheff had found the same in biopsy tissue, where synaptic density in the frontal cortex graded with cognitive impairment (DeKosky and Scheff, 1990). The plaque and the tangle are the disease's signature; the synapse is its substrate. A brain keeps its mind for exactly as long as it keeps its synapses, however many plaques accumulate around them. Resilience, reduced to its final term, *is* synaptic preservation under pathological load — and this is precisely what Perez-Nievas found distinguished the resilient brain: spared synaptic markers at matched plaque burden (Perez-Nievas and colleagues, 2013).

The synapse returns us to the gardener, because in Alzheimer's disease the gardener is the agent of synaptic loss, and its restraint is the agent of synaptic preservation. Stevens and Barres and their colleagues showed that early synapse elimination in Alzheimer models is executed by microglia through the complement system: the complement protein C1q is deposited onto vulnerable synapses, which are then opsonized by C3 and engulfed by complement-receptor-bearing microglia — the developmental synaptic-pruning program, aberrantly reawakened by amyloid and turned against the mature circuit (Hong and colleagues, 2016). Soluble oligomeric amyloid is the trigger that tags the synapse for the complement mark; the microglion is the executioner that reads the mark and prunes. This is the mechanism by which a plaque, or more precisely the diffusible oligomer that a poorly-walled plaque releases, is transduced into the loss of a synapse and thence into the loss of a memory. And it is the mechanism whose *restraint* is resilience. The disciplined gardener that walls the plaque holds down the oligomer that would tag the synapse; the disciplined gardener that has not tipped into a chronic complement-spraying activation does not over-read the

tags it does receive; and so the synapse is spared, and the mind with it. The muted microglial activation and the preserved synapses that Perez-Nievas found in the resilient brain are not two independent facts. They are cause and effect. The quiet gardener is why the synapse survived.

This closes the circle of the first half of the dissertation. Resilience is microglial restraint; microglial restraint walls the plaque and holds down the oligomer and declines the false pruning; and the synapse, spared, keeps the mind. The plaque may stand in the tissue, as many as the pathologist can count, and do nothing — because the cell that would have turned it into synapse loss stayed disciplined. We turn now to the question the coerulean reader has been holding, and to the region where the whole process begins.

VII. The Brake Is Not the Only Brake

The reader who has followed the corpus's coerulean volumes will now press the question this dissertation was, in part, written to answer. *The First Ember* argued that tau is first kindled in the locus coeruleus — that the brain's sole cortical source of norepinephrine, constitutionally without a perineuronal net, is the first neuron to accumulate hyperphosphorylated tau, decades before dementia. *The Coerulean Pincer* argued that a released "brake" — the reelin signal that, staged on a sulfated extracellular surface, holds down the tau kinase glycogen-synthase-kinase-3β — permits the tangle to form, and that dysregulated norepinephrine cuts that brake from outside while flooring the kinase from inside. The natural inference, and the reader's honest challenge, is this: if the brake comes off in the locus coeruleus of essentially every aging human — for the coerulean pretangle is very nearly universal by midlife — then why does not every human proceed to Alzheimer's disease? Why are there resilient brains at all, if the first domino falls in everyone?

The answer is the organizing principle of this entire dissertation, and it can be stated as a single correction to the intuition behind the question. The intuition treats the brake as *the* brake — one restraint, whose release starts an unstoppable cascade. But the coerulean brake is *one brake among several*, wired in parallel, and no single one of them is the disease. Clinical dementia is not crossed when a brake is released; it is crossed when the *net of restraints* falls below what the pathology demands. This is a threshold, and it has many contributors, and the release of one small nucleus's reelin brake moves the system toward the threshold without, by itself, crossing it. Resilience is the depth of the remaining margin — the sum of the brakes still holding when one has let go.

Consider what must hold, downstream of the released coerulean brake, for the ember to become a fire. The tau kindled in the locus coeruleus must *spread* — trans-synaptically, along the

connectome, into the transentorhinal cortex and beyond — and whether it spreads depends on the state of the neurons it seeds and the microglia that surround them. Here the two halves of this dissertation meet. If the downstream neurons retain their perineuronal nets and their intact reelin staging, their own tau brake is *not* released, and the seed lands on defended ground; this is the resilience the COLBOS carrier's strengthened reelin brake supplied, holding the tangle in check across the cortex even as the coerulean ember burned and the plaque avalanche fell (Lopera and colleagues, 2023). If the microglia surrounding the seed are disciplined — walling the co-deposited plaque, clearing rather than propagating the tau seed, declining the inflammatory amplification that accelerates spread — the ember is contained rather than fanned; this is the barrier resilience of Sections IV and V. If the synaptic reserve is deep, the trans-synaptic route is longer and the functional cost of any given loss is smaller; this is the reserve of Section II. Each of these is a brake in parallel with the coerulean one. The locus coeruleus can lose its brake, and tangle, and even seed its targets, and the brain can still hold — for years, for decades, for a whole remaining lifetime — if the parallel brakes hold. The coerulean lesion is necessary to the earliest kindling and is nearly universal; it is nowhere near sufficient for the disease.

This is why the natural history of Alzheimer's is a natural history of *sequential* failure, not simultaneous collapse. The corpus's temporal architecture reads the disease as phases in time precisely because the brakes fail in order, not at once: the coerulean brake early and in nearly everyone, then — in those who will progress — the perineuronal and reelin brakes on the downstream neurons, the microglial barrier as the gardener exhausts or dysregulates, the synaptic reserve as it is drawn down, the vascular and glymphatic clearance as it silts. The resilient brain is the one in which the later brakes never fail, or fail so slowly that death arrives first. There is no single moment at which the resilient brain "resists"; there is a long succession of restraints, most of them holding most of the time, and resilience is the statistical fact of the succession holding. The demented brain is not the brain that lost a brake. It is the brain that lost enough of them, in enough of the wrong places, in the wrong order. And that phrasing — *the wrong places* — is the last question, and the one we take up now.

VIII. Where the Line Falls First

The disease has a stereotyped geography, and the geography is the clearest evidence that vulnerability and resilience are regional properties before they are global ones. Braak and Braak established the staging that bears their name: neurofibrillary tau pathology does not appear everywhere at once but marches in a fixed sequence, from a transentorhinal origin through the entorhinal cortex and hippocampus into the temporal, then the association, then finally the primary

neocortex — a progression so regular that a brain can be staged from where its tangles have and have not reached (Braak and Braak, 1991). The order is not arbitrary. It follows the connectome along a gradient of selective vulnerability, seeding the regions that are most heavily connected to the already-affected, most plastic, and — this is the thread that ties the geography to the mechanism — least defended.

But the true origin sits earlier and lower than the transentorhinal cortex, and identifying it is where the corpus's coerulean work revised the classical staging. Braak's own later work, examining young brains, found the first hyperphosphorylated tau not in the cortex at all but in the *locus coeruleus* and the other subcortical aminergic nuclei — pretangle material present in the coerulean neurons of children and adolescents, decades before any cortical involvement, decades before any symptom (Braak and Del Tredici, 2011; Braak and colleagues, 2011). The locus coeruleus is, on this evidence, the first region to fall, and *The First Ember* explained why in terms this dissertation has now completed: the locus coeruleus is constitutionally without a perineuronal net, and the net-poor neuron is the vulnerable neuron. Morawski and colleagues had shown the rule directly — the subcortical nuclei attacked earliest by tau are precisely those devoid of the aggrecan-based perineuronal net, while net-ensheathed neurons even in the thick of the pathology resist the tangle (Morawski and colleagues, 2010). The locus coeruleus lacks the net that would shield it and stage its reelin brake; its long, thin, unmyelinated axons expose an enormous membrane; it is, by native constitution, the least defended neuron in the brain, and it is the first to go. The first region to fall is the region with the fewest brakes.

This is the deep unity of the dissertation's two questions — *what confers resilience* and *where does the line fall first* — for they are the same question read at two scales. Vulnerability is the local poverty of brakes; resilience is their local abundance; and the disease's geography is simply the map of where the brakes are thin. The locus coeruleus falls first because it has no net. The transentorhinal and entorhinal cortex fall next because they are richly, plastically connected to the coerulean and olfactory inputs and comparatively lightly netted. The primary sensory and motor cortices fall last, or never, because they are heavily myelinated, heavily netted, and less plastic — better braked. And the same logic runs *within* a stage as between stages: in the resilient brain, the spread stalls wherever the downstream neuron is better shielded, better staged, and held in deeper reserve. Regional resilience and individual resilience are one variable. The COLBOS carrier's strengthened reelin brake was a *systemic* enrichment of the very defence the locus coeruleus natively lacks, applied to the neurons the coerulean ember would seed — which is why the ember, in that brain, did not spread along its usual geography despite an autosomal-dominant plaque load. The map of where the disease goes is the negative image of the map of where the brakes hold. To ask which region falls first is to ask which region is least defended; to ask what makes a person resilient is to ask whether their defences, region by region, are deep enough to stall the march before it reaches the cortex that carries the mind.

IX. The Individual Ledger of Resilience

Gather the threads into the single object the question asked for: a ledger of what, in a given person, sets the threshold — the depth of margin between a released coerulean brake and a lost mind. The ledger has a heritable column and a modifiable column, and every entry in both acts, in the end, on the same cellular substrate this dissertation has kept in view: the disposition of the gardener and the depth of the synaptic reserve it protects.

The heritable column we have largely written. *APOE* genotype sets the baseline — ε2 deepening the margin, ε4 shallowing it — through the lipid chemistry with which microglia meet the plaque (Corder and colleagues, 1994; Reiman and colleagues, 2020). The microglial innate-immune variants tune the gardener directly — protective *PLCG2* P522R strengthening the disciplined response, risk-conferring *TREM2* R47H weakening the barrier (Sims and colleagues, 2017; Guerreiro and colleagues, 2013). Brain reserve — the structural capital of neuron and synapse number, partly heritable, partly built — sets how large a fraction a fixed loss removes (Stern and colleagues, 2020). And the rare resilience variants, *APOE3*-Christchurch and *RELN*-COLBOS, mark the extreme of the heritable column: single changes that deepened the margin so far that an autosomal-dominant plaque avalanche could not cross it for decades (Arboleda-Velasquez and colleagues, 2019; Lopera and colleagues, 2023).

The modifiable column is where the ledger becomes actionable, and the corpus has devoted a volume to each of its principal entries, so this dissertation need only place them and name the cell they act on. *Sleep* defends the margin by two routes the corpus has traced — the glymphatic clearance that flushes the soluble amyloid and tau the microglial barrier would otherwise have to contain, and the coerulean rest that lets the locus coeruleus stand down from the hyperactive broadcasting that fans the ember; the sleeping brain is the brain that lowers the load the gardener must meet and quiets the nucleus that first kindles. *Physical exercise* defends it through, among other mediators, the muscle-derived hormone irisin, which crosses into the brain and supports cognitive function and a favourable microglial and synaptic milieu (Islam and colleagues, 2021) — the "exercise-in-a-pill" the corpus's muscle volume followed. *Cognitive reserve* — education, occupational complexity, lifelong engagement — deepens the functional margin, letting the mind recruit alternative circuits as the pathology draws down the primary ones (Stern, 2012). *Vascular and metabolic health* defends the clearance and the energy supply the barrier-building gardener demands. And running beneath all of them is the state of the gardener itself, which each entry nudges toward discipline: the well-slept, well-exercised, well-perfused brain is a brain whose microglia keep their metabolic fitness and their homeostatic checkpoint and do not tip, prematurely, into the dystrophic

exhaustion or the chronic dysregulation that would let the plaque do its worst. The individual's resilience is the sum of this ledger — the heritable baseline plus the modifiable margin — measured against the load the pathology brings. Two people with identical plaques differ in outcome by the difference in their ledgers, and the second column of the ledger is one a person can, in part, write.

X. Therapeutic Corollary Phenocopying the Disciplined Gardener

The therapeutic reading of this dissertation is a single, disciplined instruction that cuts against a long reflex, and stating it precisely matters because the reflex has cost the field a generation of failed anti-inflammatory trials. The instruction is *not* to silence the gardener. It is to *discipline* it — to phenocopy, by intervention, the restrained microglial state that the fortunate inherit. The distinction is the whole of the matter. Blanket immunosuppression, the non-steroidal anti-inflammatory strategy pursued for years, treats microglial activation as uniformly harmful and suppresses it wholesale; it has largely failed, and this dissertation explains why it had to. The barrier program is microglial activation. To suppress activation indiscriminately is to dismantle the seawall along with the flood — to convert the disciplined gardener not into a quiet one but into the *insufficient* one of Section III, the dystrophic cell that lets the plaque spread its halo unchecked. The goal is not less gardener. It is a better-governed gardener.

The rational target, on the mechanism assembled here, is to strengthen the barrier-building program early — to tune microglia toward the containing, compacting, debris-clearing state that resilient genetics confers natively. The clearest embodiment of this logic is TREM2 agonism: an antibody or small molecule that pushes the gardener into and holds it in the disciplined DAM state, phenocopying the protective *PLCG2* hypermorph and reversing the risk-conferring *TREM2* hypomorph (Wang and colleagues, 2020). Agonist anti-TREM2 antibodies reduce pathology and strengthen the microglial response in models, and the approach has moved into human trials — the proof of principle that the gardener's disposition is not merely a marker of resilience but a lever on it. But the mechanism also draws a knife-edge that any such therapy must respect, and the ledger insists on it. Microglial restraint is a *narrow band*, bounded by insufficiency on one side and dysregulation on the other. A TREM2 agonist that pushes too hard, or too late, risks driving the gardener past the disciplined barrier state into the chronic, synaptotoxic, complement-spraying dysregulation that prunes the very synapses resilience exists to spare (Hong and colleagues, 2016). Over-restraint and over-activation are both failures. The therapeutic window is the disciplined middle, and it is almost certainly an *early* window — before the plaque's halo has done its work,

before the gardener has exhausted into dystrophy, in the long preclinical decades when the resilient brain is quietly doing what a drug would seek to imitate. The instruction, in full, is to phenocopy the fortunate: to give the vulnerable brain, early and in measure, the disciplined gardener the resilient brain was born with.

XI. What Would Falsify This

A theory that cannot be broken is not a theory, and the corpus's discipline is to name the observations that would break each of its claims. This dissertation's load-bearing propositions are falsifiable, and here are the tests.

The barrier claim would be falsified by a demonstration, in matched-pathology human brains, that microglial mantle integrity and plaque compaction are *uncorrelated* with antemortem cognition — that resilient and demented brains at equal plaque burden do not differ in how well their plaques are walled. The theory predicts the correlation; its absence would sink the mechanism. The restraint claim would be falsified if resilient brains, examined at matched pathology, showed *more* microglial activation than demented brains rather than less — the reverse of the Perez-Nievas finding; a robust reversal in independent cohorts would overturn the identification of resilience with restraint. The redundancy claim of Section VII would be falsified by the discovery of a genuine single point of failure — a brake whose release, alone, reliably produces dementia regardless of the state of every other restraint; the theory predicts no such brake exists, that all are contributors to a threshold and none is the disease by itself. The genetic-grammar claim would be falsified by a protective microglial variant that *weakens* the barrier program, or a risk variant that *strengthens* it — a reversal of the sign that unites the innate-immune genetics; the theory predicts the sign holds. And the geographic claim would be falsified by a well-documented, reproducible Alzheimer's natural history that *inverts* the vulnerability gradient — that begins in the heavily-netted primary cortex and spares the net-poor locus coeruleus and transentorhinal cortex; the theory predicts the first region to fall is always the least defended.

The therapeutic corollary makes the sharpest prediction of all, and it is the one the ongoing TREM2-agonist trials will test: that tuning the gardener toward the disciplined barrier state, *early*, will spare cognition, and that pushing it too hard or too late will not — that the benefit will be found in the narrow band and the early window and nowhere else. If a TREM2 agonist given early to preclinical carriers fails to preserve cognition despite demonstrably strengthening the microglial barrier, the central mechanism of this dissertation is wrong. It is a real risk, honestly stated, and the theory is written to bear it.

XII. Validity Ledger

The dissertation's claims are not of one evidentiary weight, and the corpus's practice is to grade them explicitly rather than let a confident prose register launder an inference into a fact. Three tiers are used: **Tier I** — established, directly evidenced in human tissue or by convergent human and animal data; **Tier II** — well-supported by strong animal and partial human data, reasonably inferred to the human case; **Tier III** — plausible synthesis or inference, consistent with the evidence but not yet directly demonstrated.

Tier I — Established

- The uncoupling of amyloid burden from dementia: a substantial fraction of cognitively intact elders carry Alzheimer-defining plaque pathology (Katzman; Riley/Snowdon; Perez-Nievas).
- Synapse loss, not plaque or tangle count, is the strongest neuropathological correlate of antemortem cognitive severity (Terry; DeKosky and Scheff).
- The resilient brain, at matched pathology, shows preserved synapses, lower soluble oligomer/phospho-tau, and less microglial activation than the demented brain (Perez-Nievas).
- Microglia form a barrier that compacts plaques and shields neurites; the barrier is TREM2-dependent, and its failure produces diffuse plaques and severe axonal dystrophy in mouse and human-variant tissue (Condello; Yuan; Wang; Ulland).
- The innate-immune genetics of Alzheimer's risk is largely microglial: TREM2 R47H raises risk; PLCG2 P522R (a functional hypermorph) lowers it; APOE2 is strongly protective, APOE4 the dominant common risk allele (Guerreiro; Jonsson; Sims; Magno; Corder; Reiman).
- The locus coeruleus and subcortical aminergic nuclei bear the earliest hyperphosphorylated tau, decades pre-symptom; net-poor neurons tangle first, net-bearing neurons resist (Braak and Del Tredici; Braak 2011; Morawski).
- Human resilience to autosomal-dominant AD exists and can turn on a single locus (APOE3-Christchurch; RELN-COLBOS).

Tier II — Well-supported inference

- Early microglial complement tagging drives synapse loss in AD models; its restraint is the plausible mechanism of the spared synapse in human resilience (Hong; Perez-Nievas).
- Microglial dystrophy/senescence is a permissive, insufficiency state that lets pathology spread; its avoidance is part of resilience (Streit; and senescent-glia clearance data, Bussian).
- Modifiable exposures (sleep/glymphatic clearance, exercise/irisin, cognitive reserve, vascular health) deepen the resilience margin, acting in part through microglial state and load reduction (Stern; Islam).
- TREM2 agonism can push microglia toward the disciplined barrier state and reduce pathology; the disposition of the gardener is a therapeutic lever, not only a marker (Wang 2020).

Tier III — Synthesis and inference

- That microglial barrier integrity is a *quantitatively decisive* determinant of human cognitive resilience — that the Katzman brains were resilient chiefly because their gardeners walled their plaques better — is a strong but undemonstrated inference; the clinching matched-pathology mantle-versus-cognition study has not been done.
- The redundancy/threshold reading of Section VII — that clinical AD is the sequential failure of parallel brakes and that no single released brake is sufficient — is a synthesis across the corpus's volumes, coherent with the natural history but not directly measured as a formal threshold.
- The identification of regional and individual resilience as one variable read at two scales is an interpretive unification, well-motivated by the net/vulnerability data but not itself an experimental result.

A Note on Provenance and Verification

This dissertation was assembled under the Organic Network Synthesis methodology as a synthesis across the existing corpus — the microglial-dysfunction atlas *The Corruption of the Gardener*, the protective-genome atlas *The Architecture of Resistance*, the reelin-resilience series, *The First Ember*, *The Coerulean Pincer*, *The Two Anchors*, and *The Denominator* — and the primary literature they rest on. Its references are drawn from established, widely-cited primary sources selected for high confidence; the reader and any downstream editor should re-confirm each citation's identifiers against PubMed

before formal publication, as the corpus's standing practice requires and as this session's tooling did not permit in-line. Where a claim could not be anchored to Tier-I human evidence it is graded down in the ledger above rather than asserted; the ledger, not the prose register, is the honest record of what this volume knows and what it infers.

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