THE FIFTH SURFACE

Containment as a Substrate of the Convergent Collapse — How Microglial Restraint Enters the Homeostatic–Matrix–Synaptic–Propagation Architecture as Its Fifth Layer, and Why Joint Preservation Is a Threshold and Not a List

The Quarrel at the Centre · The Containment Substrate · One Effector, Two Addresses
The Net of Restraints · The Return Path

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience

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The cross-axis synthesis of The Gardener's Restraint with the Convergent Synaptic Collapse thesis and the HMS+P architecture raised upon it. It argues that the corpus's four-substrate model is missing a layer; that the missing layer is containment — the executed microglial mantle around the deposit; and that with it in place, resilience ceases to be a list of preserved layers and becomes a threshold on a five-substrate sum.

“Four theses found four layers and called their joint preservation resilience. A fifth volume found one cell that walls the plaque and called its discipline resilience. They were not describing different brains. They were describing the same brain from either side of a wall — and the wall, which neither had counted, is the layer that decides how much of the pathology the other four are ever asked to bear.”

— ONS Methodology Working Notes, 2026

For the reader who noticed that the corpus said microglial activation was the lesion and also that microglial activation was the barrier, and declined to let the contradiction pass.

THE COLLAPSE FRAMEWORK — CROSS-AXIS SYNTHESIS

Convergent Synaptic Collapse — eight frameworks, four convergence nexuses, one synapse

Homeostatic Microglial Collapse — the TGF-β-maintained state as the upstream variable

Perineuronal Net Integrity — the matrix as mechanical substrate and resilience anchor

Convergent Propagation Collapse — templated misfolding as the fourth substrate

Unified Collapse, Chapter 1 — the HMS+P architecture and the lipid/APOE gate

The Gardener's Restraint — microglial resilience and the uncoupling of amyloid from dementia

The Fifth Surface (containment as a substrate of the convergent collapse) — this volume

This volume performs the convergence operation on two documents that had reached the resilient brain from opposite directions. The unified architecture reads Alzheimer's disease as the failure of four co-extensive substrates — microglial homeostasis, perineuronal matrix, the parvalbumin perisomatic synapse, and templated propagation — and locates resilience in their joint preservation. *The Gardener's Restraint* located it in one cell's discipline: the microglion that does not clear the plaque but walls it, compacting the neurotoxic halo into an inert core so that the deposit stands and does nothing. The two accounts appear to quarrel, because one calls departure from the homeostatic state the lesion and the other calls it the cure. Settling that quarrel — by distinguishing the state from the excursion, and homeostatic collapse from the loss of the return path — does not repair the architecture but extends it. Containment satisfies the corpus's own criterion for substrate status, and the corrected statement is HMS+P+R: resilience becomes a threshold on a five-substrate sum, three separately named thresholds resolve into one, and the therapeutic instruction arrives in two halves that must be given together — push the gardener out to the plaque, and repave the road home.

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Abstract

The Organic Network Synthesis corpus has arrived, by two roads, at the same brain. The Convergent Synaptic Collapse thesis and its successors read Alzheimer's disease as the failure of a homeostatic architecture — four co-extensive substrates, the microglial homeostatic state, the perineuronal matrix, the parvalbumin-positive perisomatic synaptic zone, and the templated propagation step, held by a TGF-β/SMAD signalling loop and gated by an APOE/LRP1 lipid-availability axis — and it locates resilience in the joint preservation of all four. *The Gardener's Restraint* arrived at the same resilient brain from the opposite direction: from the clinical fact that a substantial minority of elderly people die with neocortical plaque burdens sufficient to diagnose Alzheimer's disease and with their minds intact, and from the mechanism that most economically explains them — that the disciplined microglion does not clear the plaque but *contains* it, wrapping the deposit in a tight cellular mantle, compacting its diffuse protofibrillar halo into an inert core, and thereby insulating the neurites and synapses the naked plaque would injure.

This dissertation asks what the two accounts jointly describe, and it finds that they describe one architecture with a missing layer. The missing layer is containment. We argue that microglial restraint is not a restatement of the homeostatic substrate H, not a sixth convergence of the kind the unified chapter enumerates, and not an upstream gate of the kind lipid availability turns out to be, but a substrate in the corpus's own technical sense: a layer whose failure produces a collapse pattern that no other substrate predicts, which possesses sufficient internal mechanistic density to be decomposed on its own terms, and whose preservation explains observations the four-substrate architecture leaves unexplained. We name it R, the containment substrate, and we argue that the correct statement of the architecture is HMS+P+R.

The argument turns on a quarrel that must be settled before the integration can proceed. The Homeostatic Microglial Collapse thesis identifies the departure from the Butovsky signature — the entry into the disease-associated state — as the upstream lesion. *The Gardener's Restraint* identifies that same entry, in its clean and timely form, as the protective program: the barrier-builder, the plaque-compactor, the state Keren-Shaul's group named for its association with *restricting* the development of Alzheimer's disease. Both cannot be simply true. We resolve the quarrel by distinguishing the state from the excursion. Homeostasis is not a resting place the healthy microglion never leaves; it is the place it can always return to. The disease-associated program is a licensed excursion from homeostasis, and restraint is the governance of that excursion — the capacity to enter it on demand, execute the containment work, and come

home. Homeostatic collapse, correctly stated, is not the loss of the resting state but the loss of the return path. On that reading the two theses are not in conflict: H is the disposition, R is the executed work, and the pathology of the microglion is the failure of either the departure or the return.

With the quarrel settled, the couplings can be drawn, and each is a mechanism rather than an analogy. R–M: the mantle around the plaque and the digestion of the net around the parvalbumin interneuron are the same proteolytic effector program delivered to two addresses; restraint is spatial targeting, and its failure is not more enzyme but enzyme sprayed into the perineuronal space. R–S: the mantle holds down the soluble, protofibrillar species that constitutes the complement tag on the synapse, so the containment substrate sits directly upstream of the neuroimmune interface that the Convergent Synaptic Collapse thesis identified as its terminal effector — the resilient brain's lower oligomer burden and its spared synapses are one fact, not two. R–P: the dystrophic, tau-filled neurites that form around unmantled plaques are the propagation substrate's seeding field, so containment sets the size of the seed reservoir the Braak march draws upon. R–Gate: the barrier is a lipid-handling feat performed by a lipid-sensing receptor around a deposit whose apolipoprotein-E shell is itself TREM2-dependent, which makes the mantle the place where the APOE/LRP1 gate becomes a structure one can see in tissue.

Three consequences follow. First, resilience is restated, and the restatement is forced by the human data rather than chosen for elegance. The de Vries and Carulli neuropathology — the field's closest look at matrix biology in cognitively resilient donors carrying Alzheimer-threshold pathology — reports perineuronal net *remodelling* in those donors, with net density and aggrecan immunoreactivity falling below controls, alongside microglia that lack the matrix-proteolytic transcriptional signature of symptomatic disease. Resilience therefore cannot be a list of layers held intact, because one of the layers is not intact. It can be a weighted sum, because a sum distinguishes a matrix reorganised toward plasticity from a matrix digested by unaimed proteolysis. The qualitative claim that the layers must hold together acquires the quantitative form *The Gardener's Restraint* supplied — resilience is the depth of the remaining margin, the sum of restraints still holding, and dementia is crossed when the net falls below what the pathology demands. Second, three thresholds named separately in the corpus — Rappoport's allostatic threshold, the HMS+P feed-forward self-sustaining threshold, and the coerulean net-of-brakes threshold — are one threshold described from three angles, and the first region to fall is the region where the net is thinnest, which is why the locus coeruleus, matrix-poor by native constitution, goes first. Third, the therapeutic instruction sharpens into a form neither parent thesis states: TREM2 agonism has been read as the right receptor at the wrong stage, but the one completed efficacy trial enrolled early symptomatic disease and failed anyway; the containment reading diagnoses

mode rather than stage, because agonism drives the excursion without restoring the return, and the rational combination is containment enhancement paired with homeostatic restoration — push the gardener out to the plaque and give it a road home — read out at a paired biomarker of mantle integrity and perineuronal net preservation rather than at amyloid burden.

Each load-bearing claim is graded in an explicit validity ledger. The containment mechanism is Tier I in human and animal tissue; the identification of containment as a substrate rather than a facet of H is a Tier III architectural claim; the spatial-targeting account of R–M is Tier III and is the most falsifiable proposition in the volume. The synthesis is offered in the corpus's standing spirit: the ledger, not the prose register, is the honest record of what this volume knows and what it infers.

I. The Quarrel at the Centre

Two documents in this corpus describe the resilient brain, and they do not, at first reading, describe it the same way.

The first is the Convergent Synaptic Collapse thesis and the architecture that grew from it. That line of work resolved eight frameworks — Ramsden's lipid peroxidation, Small's retromer traffic jam, Gouras's inside-out intraneuronal amyloid, Moosmann's chronic excitatory insufficiency, Rappoport's allostatic load, Huang's monomer dose-response, Margolis's synaptic confinement, and the Shatz–Stevens complement axis — into four convergence nexuses and a four-phase trajectory in which sporadic Alzheimer's disease is the parallel, not serial, failure of endosomal, excitatory-homeostatic, cytoskeletal-proteostatic, and neuroimmune systems converging on the synapse. Three analyses then widened the frame: the TGF-β-maintained Butovsky signature identified as the upstream microglial variable whose loss is common to every pathological microglial state; the perineuronal matrix around the parvalbumin-positive interneuron identified as the mechanical substrate on which amyloid, microglia and inhibitory circuit failure jointly act; and templated misfolding with LRP1-mediated uptake identified as the mechanism by which pathology advances across the connectome. Subjecting those four analyses to the same convergence operation each had performed on its own inputs returned the HMS+P Collapse Model: four co-extensive substrates, one TGF-β/SMAD signalling loop, one APOE/LRP1 lipid gate, six bidirectional couplings, no privileged upstream entry point. On that architecture, cognitive resilience is the joint holding of the four layers, and its human anchor is the de Vries

and Carulli neuropathology of donors carrying Alzheimer-threshold amyloid and tau burden without dementia. Section IX takes that anchor up in detail, because what it actually reports constrains how the joint-holding claim can be stated.

The second document is *The Gardener's Restraint*. It begins not from the literature but from a fact: Katzman's 1988 subgroup, functioning in the top quintile of their cohort to the end, brains heavy and large-neuroned, carrying roughly four-fifths as many neocortical plaques as the demented and meeting the pathological criteria of mild Alzheimer's disease; and Perez-Nievas's dissection of matched-pathology resilient tissue, in which the resilient brain differed from the demented brain not in tangle count but in a set of linked findings — preserved synaptic markers, markedly lower fibrillar and plaque-associated oligomeric amyloid deposition, absence of the selective accumulation of soluble tau into the synaptic compartment, and *less glial activation*, in CD68-positive microglia and GFAP-positive astrocytes alike. From that fact it derives a mechanism with a physical core: the disciplined microglion does not, in the main, clear mature fibrillar amyloid; it contains it. Condello and Grutzendler's high-resolution imaging showed microglia forming a tight cellular mantle around the deposit, and showed that where the mantle is intact the plaque is compact and its diffuse protofibrillar hotspots are held off the surrounding neurites, while where the mantle is thin or breached the protofibrillar species leak outward and the neurites swell into the tau-filled dystrophic spheroids that are the plaque's true injury to the circuit. The mantle is built by a definite apparatus with TREM2 at its head — required for the early reach to the nascent plaque, required for the metabolic fitness the barrier programme consumes, and read in reverse by the R47H hypomorph that raises risk three- to four-and-a-half-fold and by the mild PLCG2 P522R hypermorph that lowers it. Resilience, on that reading, is not less amyloid. It is amyloid better walled.

The quarrel is now visible, and it should be stated in its sharpest form rather than smoothed over. The microglial thesis identifies the departure from homeostasis — the downregulation of the *P2RY12*, *CX3CR1*, *TMEM119* checkpoint and the entry into the disease-associated programme — as the upstream lesion from which every downstream microglial pathology follows. *The Gardener's Restraint* identifies that same departure, entered cleanly and in time, as the protective programme itself, and observes that the name Keren-Shaul's group chose was a rebuke to the reflex that reads all microglial activation as harm: a unique microglia type associated with *restricting* development of Alzheimer's disease. Worse, the two theses appear to make opposite predictions about the resilient brain. The microglial thesis, read naively, predicts that the resilient brain preserves the homeostatic signature — that its microglia have not activated. Perez-Nievas found exactly that, less activation at matched pathology, and the microglial thesis takes it as

confirmation. But *The Gardener's Restraint* requires that the resilient brain's microglia have gone to the plaque and built the mantle, which is to say that they have activated, in the specific and bounded sense the barrier programme requires. A theory cannot have it both ways.

This dissertation exists because settling that quarrel turns out not to be a repair but a discovery. When the two accounts are made compatible — and they are made compatible by one distinction, developed in Section IV — what falls out is not a reconciliation but a layer. The HMS+P architecture, we will argue, is missing a substrate, and the missing substrate is the one *The Gardener's Restraint* spent its length describing. We proceed by first stating the criterion the corpus uses to decide what counts as a substrate, because the argument stands or falls on whether containment meets it.

II. A Criterion for Substrate Status, and Its Application

The *Unified Collapse* chapter did something unusual when it added templated propagation to the trilayer, and its discipline there supplies the test we now owe the reader. It did not add propagation because propagation is important, or because the literature is large, or because the mechanism is fashionable. It added propagation because propagation satisfied three conditions that the chapter applied explicitly, and it declined to add lipid availability as a fifth substrate — despite lipid availability being, by its own account, upstream of all four layers — because lipid availability failed one of them. The chapter's exact words are worth holding in view: lipid availability "is not a fifth substrate in the substrate-inclusion sense (its dysfunction does not produce a substrate-irreducible collapse pattern of its own; it potentiates the collapse of the four existing substrates). It is an upstream gate." That is a real criterion, honestly applied against the author's own convenience, and it is the criterion we must now satisfy.

Extracted and stated generally, substrate status in this corpus requires three things.

The first is **irreducibility**: the layer's failure must produce a collapse pattern that the other substrates, jointly, do not predict. A gate potentiates; a substrate fails in its own manner, and that manner is recognisable in tissue.

The second is **mechanistic density**: the layer must have enough internal structure to be decomposed into components on its own terms, as the propagation substrate decomposes into templating, seeding, receptor-mediated uptake, strain fidelity, and trans-synaptic spread. A single molecular event is a node; a substrate is an architecture.

The third is **explanatory yield**: the layer's inclusion must resolve observations that the architecture without it leaves unexplained or explains only by assertion.

Containment satisfies all three, and the demonstration is not strained.

Irreducibility. Consider the tissue phenotype of TREM2 haplodeficiency, in mice and in human variant carriers. 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. Note carefully what does *not* change: the total plaque number. The composition shifts — compact thioflavin-S deposits fall modestly, filamentous deposits rise, individual plaque area grows — but the burden a pathologist would tally does not. This is the signature of a failure that is invisible to the pathologist's ruler and devastating to the neurite, and no other substrate in the architecture predicts it. The homeostatic substrate H predicts loss of the Butovsky signature and the downstream release of proteolytic and complement effectors — it does not predict that plaques become morphologically diffuse at unchanged burden. The matrix substrate M predicts the loss of aggrecan and tenascin-R around parvalbumin interneurons — it says nothing about the compaction state of a cortical deposit. The synaptic substrate S predicts the elimination of tagged synapses. The propagation substrate P predicts the connectomic advance of strain-faithful seeds. The specific, reproducible, measurable pattern — *same total plaque number, different plaque morphology, different neuritic injury* — is a collapse pattern of its own, and it is exactly the pattern that distinguishes the Katzman brain from the demented brain at matched burden. Containment is irreducible.

Mechanistic density. The containment substrate decomposes into five components with the same granularity the propagation substrate exhibits. There is *detection and reach*: the TREM2- and TAM-receptor-dependent recognition of the nascent deposit and the timely migration to it, which limits diffusion and toxicity from the outset. There is *envelopment*: the formation of the tight, sealed cellular mantle that constitutes the physical seawall. There is *compaction*: the conversion of diffuse, protofibrillar, neurotoxic species into a dense inert core, with the plaque-associated apolipoprotein-E shell that the mantle concentrates and that is itself TREM2-dependent. There is *metabolic sustainment*: the TREM2-maintained, mTOR-coupled energetic and biosynthetic state — chiefly glycolytic and trophic,

on Ulland's measurements, rather than a wholesale oxidative reprogramming — without which the cell collapses into the energy-starved, autophagy-stressed condition that cannot mount the response at all. And there is *termination and return*: the disengagement that prevents the containing cell from tipping into the chronic, complement-spraying, synaptotoxic dysregulation that harms more than the plaque it was summoned to. Five components, each with its own genetics, its own tissue readout, and its own failure mode. This is an architecture, not a node.

Explanatory yield. The architecture without R leaves at least four observations under-explained, and each is a load-bearing observation for the corpus.

First, the uncoupling of amyloid burden from dementia at the level of *morphology*. HMS+P explains why plaque count is a poor predictor of cognition — because the substrates that decide cognition are downstream of the deposit — but it does not explain why two brains with identical counts differ so completely in neuritic injury. Containment explains it precisely: the pathologist's ruler reads bulk, and the neurite reads halo.

Second, the sign of the innate-immune genetics. The genome-wide architecture of Alzheimer's risk is dominated by microglial genes, and it has a consistent sign: variants that push the gardener *toward* the containing, debris-clearing programme protect, and variants that blunt that programme, or strand the cell in maladaptive activation, harm. *TREM2* R47H raises risk three- to four-and-a-half-fold by weakening the barrier; *PLCG2* P522R, a mild functional hypermorph acting immediately downstream in the same cascade — on Magno's measurements an enhancement of enzymatic activity of the order of 1.2-fold, far short of the pathogenic gain-of-function comparator — lowers it. The magnitude is modest and the argument should not be asked to carry more than the magnitude allows; what matters is the *sign*. An architecture whose only microglial layer is "homeostatic state, whose loss is the lesion" is embarrassed by a protective variant of any size that makes the cell more responsive rather than more quiescent. Containment absorbs it without strain.

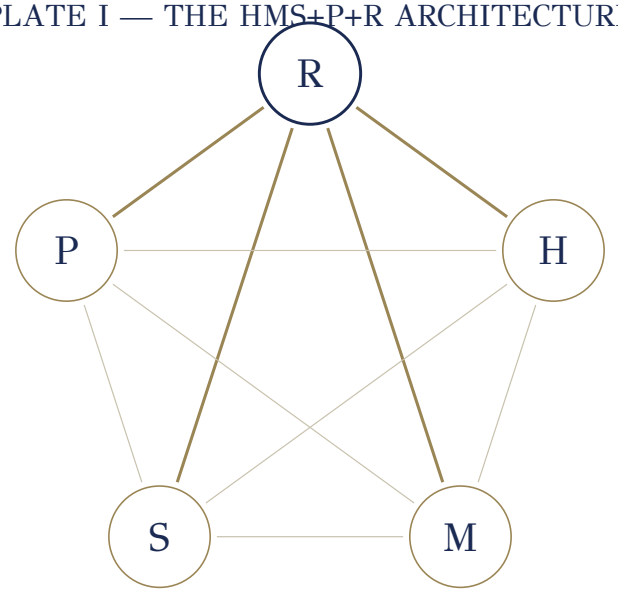
Third, the two experiments of nature. The *APOE3*-Christchurch homozygote and the *RELN*-COLBOS heterozygote each carried a *PSEN1* E280A mutation guaranteeing an autosomal-dominant plaque avalanche, and each held cognition for decades past the expected age of onset. HMS+P reads Christchurch through the lipid gate, and correctly. But the Christchurch brain's most striking neuropathological feature, on Sepúlveda-Falla's autopsy series, is not a low tau burden — the brain was Thal phase 5 and Braak VI — but an *atypically distributed* one: severe in occipital cortex, hippocampus and amygdala, negligible in the frontal cortex whose function was preserved. A pathology that is heavy in bulk and selectively spared where it

would have cost the most is a pathology whose local consequences were governed by something other than its quantity. Governing local consequence at fixed quantity is what containment does.

Fourth, the therapeutic history. The *Unified Collapse* chapter explains the failure of blanket anti-inflammatory strategies as intervention at the wrong layer. Containment explains it more sharply: blanket immunosuppression does not merely miss the target, it dismantles the seawall along with the flood, converting the disciplined gardener not into a quiet one but into the insufficient one — Streit's dystrophic, fragmented, senescent cell that lets the plaque spread its halo unchecked. The failure was not neutral. It was iatrogenic in mechanism, and only a containment layer makes that legible.

Containment therefore enters the architecture as a substrate. We designate it **R**, and we state the corrected architecture as **HMS+P+R**: five substrates, one signalling loop, one lipid gate. The remainder of this dissertation specifies R and draws its couplings.

PLATE I — THE HMS+P+R ARCHITECTURE



APOE / LRP1 lipid-availability gate — sets the threshold at every node

H homeostatic microglial state M perineuronal matrix S PV+ perisomatic synapse
P templated propagation R containment — the executed microglial mantle

Grey edges are the six bidirectional couplings of the four-substrate model. Gold edges are the four contributed by the containment substrate and specified in Sections V to VIII. The TGF-β/SMAD loop maintains the homeostatic identity of H, the latent reservoir sequestered in M, the complement restraint in S, and the return path of R; the propagation substrate P sits outside it in proximal causation and inside it in substrate dependency. With R admitted, the interaction graph is complete: every substrate is coupled to every other, and no privileged upstream entry point exists.

III. The Containment Substrate

Before the couplings, the substrate itself must be stated with enough precision that it can be measured, and measurement is where a substrate earns its keep.

R is defined as *the executed physical containment of deposited pathology by microglia, and the maintenance of that containment over time*. It is not a cell state, and this is the distinction on which the whole architecture turns. H, the homeostatic substrate, is a

disposition — a transcriptional identity, maintained by TGF-β/SMAD signalling from the parenchymal niche, readable in a cell taken in isolation. R is a *work product* — a structure in tissue, readable only in the relation between a cell and a deposit. One can in principle have a homeostatically competent microglial population that has not built a mantle, because it has not reached the plaque in time or because its lipid handling cannot sustain the effort; and one can have a mantle built by cells that have travelled far from the homeostatic signature, which is the ordinary case and the protective one. The two layers are correlated and distinct, exactly as the perineuronal matrix M is correlated with and distinct from the microglial state that digests it.

The natural readout of R is therefore geometric rather than transcriptional. We propose the **mantle coverage index**, and because the whole volume leans on it, it is worth specifying rather than naming.

The index is a triple, measured per deposit and aggregated per field. The first term is *coverage*: the fraction of a deposit's perimeter, in a confocal optical section through its widest plane, in direct contact with microglial process membrane. IBA1 supplies the process label with the most reliable post-mortem performance; P2RY12 supplies the homeostatic-checkpoint counter-stain, since plaque-associated cells characteristically lose it and the loss is itself informative. The denominator must be the deposit perimeter, not the field area, or the measure becomes a microgliosis score by another name. The second term is *compaction*: the ratio of dense-core to total deposit area, by thioflavin-S or an equivalent amyloid-conformation stain. The third is *halo extent*: the radial distance at which conformation-selective staining for protofibrillar and oligomeric species falls to background, measured outward from the compact core. Coverage without halo extent is uninterpretable, because the mechanistic claim is not that microglia surround plaques but that surrounding them shortens the toxic gradient.

The measurement is demanding but not novel. Its three components have each been made in mouse tissue, and its second and third in human tissue in the *TREM2* R47H autopsy series. What has not been done is to make all three in matched-pathology resilient and demented human brains and to regress them against antemortem cognition. The confounds are the ordinary ones of human neuropathology and they bear on this measure with particular force: agonal state and terminal illness alter microglial morphology; post-mortem interval degrades fine process detail before it degrades somata, which biases coverage downward in exactly the direction that would flatten a true effect; and fixation duration alters conformation-selective epitope retrieval, which bears on the halo term. A serious study must match these across groups and report them, and a null obtained without

matching them should not be read as a null.

This is the missing measurement in the resilience literature, and Section IX turns it into the volume's decisive test.

R's failure has two modes, and naming them separately matters because they have opposite therapeutic instructions. *Insufficiency* is the failure to build: the gardener too weak, too old, too metabolically starved, or too late to reach the deposit and wrap it. Streit's dystrophic microglion of the aged human brain — fragmented, beaded, senescent — is the histological portrait of insufficiency, and where the gardener is dystrophic, tau and its spread appear to follow. *Dysregulation* is the failure to stop: the cell that activates and cannot disengage, that overprunes the healthy synapse and floods the parenchyma with inflammatory mediators and matrix proteases. Between them lies a narrow disciplined band, and to remain in that band under the provocation of amyloid, for decades, is what the resilient brain does and the vulnerable brain fails to do.

That the band is narrow is not a rhetorical flourish; it is the structural fact that generates most of this volume's therapeutic content, and it is why R cannot be collapsed into H. The homeostatic substrate has one failure direction — collapse. The containment substrate has two, in opposition, and a therapy that corrects one without regard for the other will produce the opposite failure. That asymmetry is a property of R alone.

IV. The Bounded Excursion — Restraint as Governance, Not Quiescence

We may now settle the quarrel of Section I, and the settlement is a single distinction that repays the space.

The Homeostatic Microglial Collapse thesis is right that every pathological microglial state in the literature — disease-associated Stage 1 and Stage 2, lipid-droplet-accumulating, dystrophic, senescent — shares, as its most reproducible feature, the downregulation of the Butovsky signature. It is right that this signature is maintained by TGF-β/SMAD signalling from the parenchymal niche, and right that the age-dependent dysregulation of SMAD2/3 with accumulating SMAD7 inhibitory feedback is a specific and plausible route by which the maintenance fails. What the thesis does not say, and what the naive reading

supplies without warrant, is that the healthy microglion never leaves the homeostatic state.

It leaves it constantly. Microglial homeostasis is not quiescence; the homeostatic cell is intensely active, surveying its territory, extending and retracting processes, contacting and pruning synapses, clearing debris. What the checkpoint genes enforce is not stillness but *return* — a surveilling, ramified, low-inflammatory attractor to which the cell comes back after each excursion. The disease-associated programme is an excursion of larger amplitude and longer duration than a debris-clearance event, but it is an excursion of the same kind: a licensed departure, executed for a purpose, from which the cell is meant to come home.

On that reading the correct statement of homeostatic collapse is not *the cell left homeostasis* but *the cell lost the road back*. And the correct statement of restraint is not *the cell stayed home* but *the cell governed its excursion*. Restraint is the governance of departure and return: the capacity to go out to the plaque when the plaque appears, to build and hold the mantle, and — this is the part the field has systematically underweighted — to stand down when the containment is achieved rather than escalating into a chronic, complement-spraying inflammation that consumes the synapses the containment was built to protect.

Three things follow immediately, and each is load-bearing.

First, the Perez-Nievas result stops being a problem and becomes a prediction. Resilient brains at matched pathology showed *less* glial activation — by CD68 and GFAP burden — than demented brains. Read through the excursion distinction, this is not evidence that resilient microglia stayed home; it is evidence that they were not *stuck out*. The markers by which neuroinflammation is conventionally scored in human tissue — CD68 and GFAP burden, HLA-DR, morphological activation indices — report chronic, generalised, parenchyma-wide activation, which is the signature of failed return. It is worth being exact here: the Perez-Nievas contrast was carried by CD68 and GFAP, both elevated in the demented brain and neither in the resilient one, which makes the effect glial rather than specifically microglial. They are poor reporters of the bounded, spatially restricted, plaque-focal barrier programme, which occupies a small tissue fraction and does not flood the parenchyma. The prediction, stated sharply because the volume must be falsifiable: in matched-pathology human tissue, the resilient brain will show *high* mantle coverage and *low* generalised activation, and these two measures will dissociate. The demented brain will show the inverse. If they do not dissociate — if mantle coverage and generalised activation prove to be one variable — the distinction developed in this section is empty and the reconciliation fails.

Second, TGF-β/SMAD acquires a second and more precise job. In the Homeostatic Collapse account, TGF-β maintains the homeostatic identity, and its loss permits departure. In the account developed here, TGF-β does something more specific and more useful: it holds the *return path*. It is the niche signal by which a cell that has gone out to do containment work is drawn back to the surveilling attractor when the work is done. This reframing matters therapeutically, and Section XI cashes it: a therapy that restores TGF-β tone is not sedating the gardener, it is repaving the road home, and it is therefore compatible with — indeed required by — a therapy that pushes the gardener out to the plaque.

Third, the two failure modes of R map onto the two halves of the excursion. Insufficiency is failed departure: the cell cannot go, or cannot sustain the going, and the plaque is never walled. Dysregulation is failed return: the cell went and cannot come back, and the containment programme degenerates into the chronic inflammation that the *Corruption of the Gardener* atlas anatomised. The Homeostatic Microglial Collapse thesis, in these terms, is a theory of failed return; *The Gardener's Restraint* is a theory of successful departure *and* return. They are two views of one governance function, and R is the layer at which that function is executed and can be observed.

V. One Effector, Two Addresses — Containment and the Matrix

The coupling between the containment substrate and the matrix substrate is the most interesting of the five, because it is not a coupling of the ordinary kind — one layer feeding another — but an identity of effector with a difference of address.

The Perineuronal Net thesis describes the matrix's destruction with precision: post-homeostatic microglia release MMP-2, MMP-9, ADAMTS-4, and cathepsin-S into the perineuronal space; these enzymes digest the aggrecan, versican, hyaluronic acid, tenascin-R and link-protein architecture that constitutes the net; the ensheathed parvalbumin interneuron loses its structural, ionic and oxidative protection; and inhibitory circuit failure follows, destabilising excitation–inhibition balance and further activating microglia through the downstream inflammatory consequences. The cycle is self-reinforcing and well drawn.

The containment substrate describes the mantle's construction with equal precision, and here is the observation this volume contributes: *the mantle is built with the same molecular toolkit*. The barrier-building programme is a phagocytic,

proteolytic, lipid-handling, metabolically expensive effort. It requires matrix metalloproteinase activity to remodel the extracellular space around the deposit, cathepsins for lysosomal processing of ingested material, and the TREM2–DAP12–SYK signalling axis to license and sustain the whole. These are not analogous mechanisms to those that dismantle the perineuronal net. They are, at the level of the enzymes involved, the same mechanisms.

The difference is not the toolkit. The difference is where the toolkit is pointed.

This yields a formulation with real content: **restraint is spatial targeting.** The disciplined gardener directs its proteolytic and phagocytic effort at the deposit, in a tight envelope, and the perineuronal space three hundred micrometres away is untouched. The dysregulated gardener performs the same programme without spatial confinement — enzyme released into the parenchyma at large rather than delivered into a sealed compartment — and the aggrecan around the nearest parvalbumin interneuron is digested as collateral. On this reading the matrix substrate M does not fail because microglia become *more* proteolytic; it fails because they become *less aimed*. And the phenotype the Perineuronal Net thesis catalogues — matrix loss around PV+ cells in the regions of highest amyloid exposure — is the shadow cast by a containment programme that has lost its confinement.

Two consequences follow that neither parent thesis generates.

The first is a resolution of the CSPG–TREM2 feedback loop the PNN thesis identifies. That thesis notes, correctly, that chondroitin-sulphate proteoglycan fragments released from the degrading matrix engage TREM2, amplifying microglial lipid-sensing and phagocytic programmes and driving further matrix degradation — a positive feedback that, read as written, makes TREM2 a straightforward accelerant of matrix loss. This sits uncomfortably beside TREM2 loss-of-function being a risk allele. The containment reading dissolves the discomfort. TREM2 engagement by CSPG fragments is not intrinsically destructive; it is a signal that *demands* an address. In a cell with intact spatial confinement, the amplified phagocytic programme is delivered to the deposit and the loop is damped, because the deposit is where the ligand density is highest and the barrier is where the effort goes. In a cell that has lost confinement, the same amplification is delivered indiscriminately and the loop runs away. The sign of TREM2 in the matrix literature is therefore conditional on R, and the paradox of a protective receptor in a destructive loop is a paradox only when R is missing from the architecture.

The second is a prediction about geography, and its form matters, because the between-subject version of the question has already been asked and returned an

answer that a simple "restraint preserves nets" account cannot accommodate. The de Vries and Carulli series found perineuronal net density *lower* in resilient donors than in either controls or demented cases — a result Section IX takes up in full. That is a comparison of global net counts across brains. The spatial-targeting claim is not a claim about global counts. It is a claim about *local* relationships within a single brain, and the two can differ without contradiction.

Stated properly: if the mantle and the matrix are competing addresses for one effort, then within any given cortical field the net integrity in the immediate neighbourhood of a well-mantled, compact deposit should exceed the net integrity in the neighbourhood of a poorly mantled, diffuse one — and the difference should be accompanied by the collateral markers of unaimed proteolysis, complement deposition and neuritic dystrophy around the second and not the first. A brain may remodel its nets globally for reasons that have nothing to do with plaques, which is what the resilient donors appear to have done; the prediction concerns the residual local gradient, measured with each brain as its own control. The relevant experiment is spatial, on human tissue, at matched global plaque burden, and it is stated as a formal prediction in Section XII. It is the most falsifiable claim in this dissertation and the one whose failure would most damage it.

VI. The Halo and the Tag — Containment and the Synapse

The coupling between containment and the synaptic substrate is the one that carries the volume's central clinical claim, because the synapse is the currency in which resilience is finally paid.

The Convergent Synaptic Collapse thesis established the terminal effector of its four-phase progression as the reactivated developmental pruning programme: the classical complement cascade, catalogued by Stevens and Barres, in which C1q is deposited onto vulnerable synapses, opsonised by C3, and engulfed by complement-receptor-bearing microglia; joined by the cell-autonomous C4d–LilrB2 pathway of Shatz and Brott, in which complement deposition on the synaptic structure triggers postsynaptic signalling, localised cytoskeletal collapse, and synapse withdrawal. The framework is right that this is the executioner arm. What it inherits from the amyloid literature, and does not itself interrogate, is the question of *what tags the synapse*.

The answer is not the plaque. Hong and colleagues showed that soluble oligomeric amyloid is the species that drives early complement-dependent synapse loss in Alzheimer models, and that the loss precedes plaque deposition. The trigger is the diffusible fraction, not the deposited bulk — and this is precisely the fraction the mantle controls. Condello's containment work is, read in this light, a paper about the synapse: the microglial barrier holds the neurotoxic protofibrillar Aβ42 hotspots in check at the plaque edge, and where the mantle is breached those hotspots leak into the surrounding neuropil. The barrier does not merely protect the neurites it physically shields. It sets the concentration of the very species that tags synapses for elimination across the surrounding volume.

The coupling R–S is therefore direct and mechanistically specific: **containment sets the tag density, and the tag density sets the pruning rate.** The Convergent Synaptic Collapse thesis identified the executioner; the containment substrate identifies what loads the gun.

This resolves the Perez-Nievas findings into a single causal chain rather than a set of correlations, and it does so in a way that requires the reader to attend to exactly *which* amyloid pool the study measured — because that study's most instructive result is a null, and the null is on our side.

Perez-Nievas measured two things and found them to differ in opposite ways. In situ, the resilient brain carried far less fibrillar thioflavin-S amyloid and far less NAB61-positive, plaque-associated oligomeric deposition than the demented brain. In bulk biochemistry — soluble monomers, dimers and higher-molecular-weight species in whole-brain homogenate and in synaptoneurosomal preparation — no significant difference was found. Total soluble tau likewise did not differ; what differed was its *compartmental distribution*, with preferential accumulation into the synaptic fraction in the demented cases alone.

A theory predicting a uniformly lower soluble amyloid burden in the resilient brain would be embarrassed by that null. The containment substrate predicts it. Containment is *spatial*: the mantle governs the concentration of diffusible species in the neuropil immediately around the deposit, not the total quantity of soluble amyloid dissolved in a homogenate of a whole cortical block. A mechanism that flattens a steep local gradient while leaving a bulk average intact is precisely a mechanism that appears in an in-situ, plaque-associated measure and vanishes in a homogenate. The measurement that reports it is the one made in tissue, and it is the one this volume proposes in Section III.

Read through R, the chain runs: the mantle held, so the plaque-associated oligomeric field stayed small and the fibrillar deposit stayed compact; the local field

stayed small, so the complement tag was sparse on the synapses within diffusion range and the microglion was not driven into the chronic pruning dysregulation that generalised glial markers report; and because the tag was sparse and the cell disciplined, tau did not redistribute into the synaptic compartment and the synapse — the strongest structural correlate of antemortem cognition in the whole of Alzheimer neuropathology, on Terry's and DeKosky and Scheff's evidence — survived. One mechanism, one direction of causation, and a bulk-homogenate null that the mechanism requires rather than merely tolerates.

It also supplies the missing quantitative link in the CSC four-phase model. That model's Phase 2 — synaptic failure and local tau hyperphosphorylation, five to fifteen years before symptoms — is precisely the window in which the containment substrate is doing its decisive work, because it is the window in which deposits are nascent and mantles are either built or not. The CSC framework describes what happens when the pruning programme reactivates; it does not specify what determines whether the reactivation reaches threshold in a given brain. R specifies it. Phase 2, in the corrected architecture, is the containment window, and its outcome is written by whether the barrier was built early, held, and terminated.

VII. The Mantle and the Seed — Containment and Propagation

The propagation substrate P was the addition that turned the trilayer into HMS+P, and it earned its place by explaining the Braak sequence, strain fidelity, and the lecanemab–donanemab progression gap. Its coupling to containment is the least explored of the five and, we will argue, the most consequential for interpreting the amyloid-immunotherapy era.

The propagation cascade requires seeds — extracellular assemblies of misfolded tau, in a conformation competent to template — and it requires receptor access at the recipient membrane, chiefly LRP1 with heparan-sulphate proteoglycan co-receptor handoff. Where do the seeds come from? The propagation literature answers, correctly, that they are released from affected neurons and travel trans-synaptically along the connectome. The corpus's own coupling S–P adds an important refinement: complement-mediated synaptic engulfment is a controlled release of synaptic content, and therefore constitutes the next round of seeds. What neither says is where, anatomically, the tau that is competent to seed is concentrated.

It is concentrated in the dystrophic neurites. The swollen, tau-filled axonal spheroids that form around amyloid deposits — the structures that make a plaque *neuritic*, and that constitute, on Condello's evidence, the direct consequence of a breached or absent microglial mantle — are among the densest local accumulations of hyperphosphorylated tau in the Alzheimer cortex. This is not a peripheral observation. The plaque-associated dystrophic neurite is a seed factory, and containment determines whether it forms.

The coupling R–P is therefore: **the mantle sets the size of the local seeding reservoir that the propagation cascade draws upon.** A well-mantled plaque is a compact, inert deposit with comparatively few dystrophic neurites around it and a correspondingly small local seed field. A poorly mantled plaque is a diffuse deposit with a wide halo, extensive neuritic dystrophy, and a large seed field sitting in exactly the neuropil where the propagation substrate's uptake receptors are exposed.

Two implications follow.

The first is a reading of the immunotherapy result that is sharper than the corpus has yet stated. The *Unified Collapse* chapter explains the lecanemab–donanemab progression gap — robust amyloid removal, modest clinical slowing — by noting that anti-amyloid antibodies engage no HMS substrate and do not block the propagation cascade. True, but incomplete. The containment reading adds that plaque removal by antibody-mediated microglial phagocytosis is *not the same event* as plaque containment by microglial mantling, and may in some respects be its opposite: the antibody drives an Fc-receptor-mediated engulfment programme that is neither spatially confined in the way the native barrier is nor self-terminating, which is the mechanistic neighbourhood in which ARIA lives. On this reading, the disappointing arithmetic of amyloid clearance versus clinical benefit is not merely a matter of layer but of *mode*: the field has been removing the bulk that the pathologist counts while leaving unaddressed — and possibly disturbing — the containment that the neurite experiences. The prediction is uncomfortable and therefore worth stating: clinical benefit in anti-amyloid trials should correlate better with reduction in the diffuse and protofibrillar fraction and with preservation of neuritic architecture than with reduction in total plaque load, and should be modulated by *TREM2* and *PLCG2* genotype.

The second is a completion of the corpus's Braak account. The First Ember and the coerulean volumes established that tau is first kindled in the locus coeruleus, and the Perineuronal Net work established that net-poor neurons tangle first while net-bearing neurons resist even in the thick of the pathology. The containment substrate adds the amyloid-side term to the same geography: the march advances not only where the receiving neuron is least defended but where the local seed field

is largest, and the local seed field is largest where mantles are thinnest. Regional vulnerability, in the corrected architecture, is a two-variable map — receiver defence and sender load — and both variables are read off substrates in the same model.

VIII. The Lipid Gate Made Visible

The APOE/LRP1 lipid-availability gate is, in the *Unified Collapse* architecture, an upstream variable that sets the threshold at which each substrate's collapse becomes self-sustaining. It is a gate rather than a substrate because its dysfunction potentiates rather than producing an irreducible pattern. That judgement stands. What the containment substrate adds is that the gate, which has until now been an inference from binding kinetics and knockout phenotypes, becomes in R a structure one can photograph.

The barrier programme is, mechanically, a lipid-handling feat. It is initiated by a lipid-sensing receptor. It is sustained by a metabolic state — TREM2-maintained and mTOR-coupled, glycolytic and trophic in its measured components — that fails into the energy-starved, autophagy-stressed condition when the receptor is lost. It concentrates, at the deposit, an apolipoprotein-E shell whose accumulation is itself TREM2-dependent, on Parhizkar's evidence, with the paradoxical and instructive consequence that loss of TREM2 increases amyloid seeding while reducing plaque-associated apoE. And it fails, when lipid handling fails, into the lipid-droplet-accumulating state that Marschallinger described — a cell full of lipid it cannot process, which is insufficiency with a specific biochemical cause.

The gate and the substrate therefore meet at a single visible object. APOE genotype sets the lipid chemistry with which the gardener meets the plaque; the mantle is the record of how that meeting went. The *APOE* ε2 allele, the strongest common protective variant and associated with an exceptionally low likelihood of Alzheimer's dementia in the rare homozygote, is on this account, among other things, the allele whose microglia meet the deposit with a more favourable lipid load. The ε4 allele, which saturates LRP1 and degrades lipid-delivery throughput simultaneously, is the allele whose microglia meet it with a worse one.

And the *APOE3*-Christchurch case acquires a second reading that complements the corpus's first. The *Unified Collapse* chapter reads Christchurch as the in-vivo experiment confirming the gate: a mutation that reduces APOE binding to LRP1

dampens the lipid-availability axis enough to reduce intracellular lipid peroxidation without crossing into lipid starvation. Correct, and this volume does not displace it. The containment reading attends instead to what the autopsy actually showed, and it is important to state this precisely because the case is easily over-claimed. The Christchurch homozygote was not a brain that stayed clean. It was, on Sepúlveda-Falla's autopsy analysis, Thal phase 5 and Braak VI — a full pathological load — with an unusual regional distribution in which the frontal cortex, whose function was clinically preserved for decades, carried very little tangle pathology while occipital, hippocampal and amygdalar regions carried a great deal. The *RELN*-COLBOS proband is the same shape of result: CERAD C and Braak VI at autopsy, with entorhinal sparing against a heavier inferior-temporal burden. Neither brain resisted pathology. Both brains *tolerated* it unevenly, and the unevenness fell in the regions that mattered.

That is the phenotype containment predicts, and it is not the phenotype a lipid gate alone predicts, because a systemic gate acts systemically. A gate sets the global threshold; something local decides where the load is borne. On the combined reading, a partially dampened lipid gate left the microglion competent enough to contain what it met, and the containment held, regionally, in the places where the mantle was intact. Christchurch is therefore not evidence that R can prevent an autosomal-dominant plaque load — it plainly cannot — but evidence that R can decouple that load from its consequence, region by region, for decades.

IX. Resilience Restated — The Net of Restraints

We can now state resilience in the corrected architecture, and the statement is a genuine advance on either parent because it marries a list to a threshold.

The HMS+P architecture holds that no single preservation suffices and that the four layers must hold together. The human evidence that bears most directly on that claim is the de Vries and Carulli neuropathology, and it must be read carefully, because what it reports is more interesting than a simple confirmation and it constrains the form the claim can take.

The study compared cognitively resilient donors carrying Alzheimer-threshold amyloid and tau against demented donors and non-pathological controls. Its microglial result is what the architecture expects: bulk transcriptomic enrichment showed the matrix-proteolytic programme elevated in the demented group and not

in the resilient one. Its matrix result is not. Aggrecan immunoreactivity around parvalbumin neurons was *decreased* in the resilient donors as well as in the demented; peridendritic net complexity was reduced; and *Wisteria floribunda* agglutinin-positive net density was lower in the resilient group specifically, falling significantly below both the control and the demented groups. Tenascin-R was not measured. Synaptic contacts onto ensheathed neurons in the resilient donors were a statistical null lying between the two comparison groups rather than a demonstration of intactness. The authors' own reading of their headline result is that resilience is associated with net *remodelling* — plausibly a reorganisation permitting greater plasticity — rather than with net preservation.

This matters for the form of the resilience claim, and the constraint is sharp. Resilience cannot be a list of layers held intact, because the layer most directly measured in resilient human tissue was not intact. It can be a weighted sum, and only a weighted sum, because a sum can distinguish two routes to the same reduced net count: a matrix reorganised in a brain whose gardeners are still delivering their proteolytic effort to the deposit, and a matrix digested by a gardener that has lost its address. The first is compatible with the absent proteolytic signature the same study found in the resilient group. The second is what the demented group shows. A list cannot tell them apart, because a list counts nets. A sum can, because it grades what accompanies the loss. *The Gardener's Restraint* states resilience differently: not as a list of things preserved but as a *depth of margin* — the coerulean brake is one brake among several wired in parallel, dementia is crossed not when one restraint is released but when the net of restraints falls below what the pathology demands, and resilience is the sum of the brakes still holding.

These are not competing statements. They are the qualitative and quantitative forms of one claim, and each supplies what the other lacks.

Joint preservation, stated as a list, has a known weakness: it cannot say what happens in the ordinary case, which is partial preservation. Real brains do not present as four intact layers or four collapsed ones. They present as a locus coeruleus that lost its brake at fifty, a perineuronal matrix that is thinning in the entorhinal cortex and intact in the calcarine, a microglial population half of which has drifted post-homeostatic, and a mantle coverage index somewhere between the Katzman brain and the demented one. A list cannot grade that. A threshold can.

The net-of-restraints formulation, stated alone, has the mirror weakness: it is a quantitative intuition without an enumeration. It says the brakes must be counted but does not say which brakes there are.

Put together, the statement becomes precise. **Resilience is the margin between the total restraint the brain currently exerts — summed across five substrates, weighted by region — and the load the pathology currently imposes.** The five substrates are the enumeration the net formulation lacked. The threshold is the grading the list lacked. Dementia is the crossing, and it is a crossing of a sum, which is why single-layer preservation is insufficient, why single-target therapy fails, and why the natural history of the disease is sequential rather than simultaneous failure: the brakes come off in order, and the clinical event is the moment the running total falls short.

Two predictions follow directly, and both are sharper than the categorical form permits. The first concerns what a resilience cohort should show. The containment substrate is the discriminating layer, because it is the only one whose state is not already partly implied by the others and the only one whose measurement has not been made: **resilient brains at matched pathology will show high mantle coverage and low protofibrillar-halo extent, and this containment measure will separate resilient from demented tissue more sharply than any transcriptional microglial measure taken alone.** The second concerns partial preservation, which is the ordinary case. Preservation of a single layer against the collapse of the others will confer *partial* protection proportional to that layer's weight in the sum — not the categorical failure a list predicts — and the reason isolated preservation nonetheless looks like failure in practice is that the feed-forward couplings drag the preserved layer down once the others have gone.

Remodelling and Digestion — Distinguishing Two Routes to Fewer Nets

The distinction the previous paragraphs lean on deserves to be stated as something a pathologist could test, because it is now carrying the weight of the resilience argument and because, at present, its evidence is thin and should be described as such.

The claim is that a perineuronal net can be lost in two ways with opposite consequences. In *digestion*, the proteolytic effector programme of Section V is delivered without spatial confinement: matrix metalloproteinases and cathepsin-S enter the perineuronal space as parenchymal spill from a containment effort that has lost its address. The net is degraded as collateral, and the degradation arrives in the company of everything else that unconfined effort produces — complement deposition on nearby synapses, dystrophic neurites around poorly mantled deposits, and the chronic glial activation that generalised markers report. In *remodelling*, the net is reduced by regulated turnover — the ordinary aggrecanase-mediated plasticity mechanism that operates throughout adult life and is upregulated by activity — in a brain whose containment effort is still being

delivered to the deposit. The net count falls; the collateral does not appear.

Five observable differences follow, and they are the criteria a study would score. *First*, the accompanying transcriptional signature: digestion should carry the MMP-2, MMP-9, ADAMTS-4 and cathepsin-S upregulation of symptomatic disease, and remodelling should not. *Second*, the cleavage products: aggrecanase and metalloproteinase cleavage of aggrecan generate distinguishable neo-epitopes, and the ratio between them is in principle a direct readout of which route was taken. *Third*, the spatial relationship to deposits: digestion should be steepest near poorly mantled plaques and remodelling should be indifferent to plaque proximity. *Fourth*, the synaptic consequence: digestion should be accompanied by loss of perisomatic synaptic contacts onto the affected interneuron, remodelling by their maintenance or redistribution. *Fifth*, the complement burden on those contacts, which should track digestion and not remodelling.

The evidence currently available speaks to the first criterion only. The de Vries series reports the matrix-proteolytic programme elevated in demented donors and absent in resilient ones, at reduced net density in both — which is the pattern the two-route account predicts, and is the reason the account is worth stating. It is a single bulk-transcriptomic contrast, and it is not a demonstration. The remaining four criteria have not been scored in human tissue, and until they are, the two-route distinction is a hypothesis that rescues the resilience claim rather than a finding that supports it. It is graded accordingly in Section XIII.

X. One Threshold, Three Names — and Where the Line Falls First

Three thresholds appear in this corpus under three names, derived in three literatures, and the integration's cleanest result is that they are one.

Rappoport's **allostatic threshold**, inherited by the Convergent Synaptic Collapse thesis, is the point at which compensation itself becomes limiting — the transition from a brain that is paying to hold its function to a brain that can no longer afford the payment. It is a threshold in the economics of compensation.

The *Unified Collapse* chapter's **feed-forward self-sustaining threshold** is the point at which the couplings between substrates close into a loop that no longer requires the original stressor — the point past which removing the upstream insult does not return the system to the homeostatic attractor. It is a threshold in

dynamical systems.

The Gardener's Restraint's **net-of-brakes threshold** is the point at which the sum of parallel restraints falls below the load the pathology imposes. It is a threshold in redundancy.

These are the same event described from the economics, the dynamics, and the redundancy. When the net of restraints falls below the load, the compensatory mechanisms must work at a rate they cannot sustain, which is the allostatic crossing; and a system compensating beyond its sustainable rate generates the very stressors — oxidative, inflammatory, proteostatic — that degrade the remaining restraints, which is the feed-forward closure. One crossing, three vocabularies. Naming them as one is not a semantic tidying: it means that a measurement made in any one of the three registers is a measurement of the others, which is why the corpus's biomarker recommendations from different volumes have converged without coordination.

The geography follows from the same principle, and here the two parent theses agree so exactly that the agreement is itself evidence. *The Gardener's Restraint* states it as a slogan with a mechanism behind it: the first region to fall is the one with the fewest brakes. The locus coeruleus falls first because it is, by native constitution, the least defended neuron in the brain — no aggrecan-based perineuronal net to shield it or stage its reelin brake, long thin unmyelinated axons exposing an enormous membrane, and Morawski's demonstration that the subcortical nuclei preferentially affected by tau — the nucleus basalis, dorsal thalamus, hypothalamic nuclei, raphe and locus coeruleus among them — are precisely those devoid of the aggrecan-based net, while net-ensheathed neurons resist even amid heavy pathology. Morawski's series establishes the association across nuclei; the temporal claim that these nuclei are affected *first* is Braak's, and the two lines are here read together. The transentorhinal and entorhinal cortices fall next because they are richly and 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.

The corrected architecture adds the containment term to that map, and the addition is not decorative. Regional vulnerability is a function of receiver defence — matrix, reelin staging, synaptic reserve — *and* of sender load, which is set by the local seed field, which is set by mantle integrity. A region with thin nets and well-mantled deposits is safer than the net variable alone predicts. A region with adequate nets and diffuse, unmantled deposits is more dangerous than it predicts. This is a testable refinement of Braak's geography, and it says that the map of where

the disease goes is the negative image not of one defence but of the summed five, read locally.

Regional resilience and individual resilience are therefore one variable at two scales, exactly as *The Gardener's Restraint* argued — and the corrected architecture specifies what the variable is summing.

XI. Therapeutic Corollary — Discipline, and the Return Path

The therapeutic content of this integration is a single instruction with two halves, and the halves must be given together or the instruction inverts.

Begin with TREM2 agonism, because it is the intervention this architecture most obviously recommends and because it has already disappointed once.

The natural explanation of that disappointment is a stage explanation, and it is the one the field has reached for: agonism of a receptor whose downstream execution depends on a metabolically competent, homeostatically intact cell cannot rescue a population whose microglia have already collapsed, whose matrices are already degraded, and whose synaptic endosomes have already entered proteostatic gridlock. Right receptor, wrong stage. The logic is sound, and if the trials had enrolled advanced disease it would be sufficient. They did not.

There is, at the time of writing, exactly one completed efficacy readout of a TREM2 agonist in Alzheimer's disease. It enrolled early symptomatic disease: roughly two-thirds mild cognitive impairment due to Alzheimer's and one-third mild dementia, Clinical Dementia Rating 0.5 to 1.0. It missed its primary endpoint, with no supportive secondary or biomarker signal. A second programme was discontinued for a haematological toxicity arising from its brain-delivery vehicle rather than for any efficacy result, and a third is in mid-stage trials in a comparable early population. The stage explanation is therefore under-determined by the evidence it was offered to explain. The population was not advanced, and the agent failed anyway.

The containment substrate supplies a second and more actionable diagnosis of that same failure, and it concerns *mode* rather than *stage*. Restraint, as Section IV established, is the governance of an excursion — departure and return. A TREM2 agonist is a departure signal. Given alone, it pushes the gardener out toward the

plaque and supplies nothing to bring it back. In a cell whose return path is intact, that may be sufficient and beneficial; the barrier is built, held, and terminated. In a cell whose TGF-β/SMAD tone has already decayed — and by the early symptomatic stage that the completed trial enrolled, a substantial fraction of the parenchymal population has drifted post-homeostatic even where the clinical picture is mild — a departure signal without a return path is precisely the intervention that converts insufficiency into dysregulation. It does not fail neutrally. It risks driving the cell past the disciplined barrier state into the chronic, complement-spraying condition that prunes the very synapses resilience exists to spare. Over-restraint and over-activation are both failures, and a monotherapy that addresses only one of R's two failure modes will produce the other.

The rational instruction is therefore paired. **Push the gardener out, and repave the road home.** Containment enhancement — TREM2 agonism, or any agent that strengthens the barrier-building programme — combined with homeostatic restoration — SMAD7 inhibition, enhanced TGF-β receptor signalling in the microglial compartment, oxidative-stress reduction targeted to the microglial cytoplasm, restoration of the niche inputs that sustain the Butovsky signature. The corpus has argued for the second class on its own merits and identified it as the most systematically neglected therapeutic direction in the field. This volume argues that the two classes are not alternatives and not merely additive: they are the two halves of one governance function, and each is dangerous alone. Homeostatic restoration alone risks the quiet, insufficient gardener that lets the halo spread. Containment enhancement alone risks the gardener that cannot stop. Together they are the pharmacological description of restraint.

The window follows from the substrate, and it is earlier than the completed trial reached. Containment is decided when deposits are nascent and mantles are either built or not — the corpus's Phase 1 and Phase 2, the CSC framework's preclinical decades, which lie years before the Clinical Dementia Rating of 0.5 at which that programme began. A mantle not built around a young plaque cannot be retrofitted around an old one that has already spent a decade injuring the neurites around it. This is the same conclusion the *Unified Collapse* chapter reaches from the feed-forward argument, arrived at independently from the structure of the containment substrate, and the convergence of two independent derivations on the same window is the strongest reason to trust it.

The biomarker recommendation is where this integration is most immediately usable. The corpus's standing recommendation is perineuronal net integrity around parvalbumin interneurons — the readout at which the four substrates meet, and the human resilience signature. This volume proposes that it be *paired*, not replaced.

Mantle integrity and matrix integrity are the two ends of the spatial-targeting account of Section V: the first says the effort was made, the second says it was aimed. A therapy that raises mantle coverage while matrix integrity falls is driving dysregulation and should be stopped. A therapy that preserves matrix while mantle coverage falls is sedating the gardener and will fail into insufficiency. A therapy that raises the first and holds the second is doing what resilience does. No amyloid or tau measure distinguishes these three cases, and the difference between them is the difference between benefit and harm.

Finally, stratification. The *Unified Collapse* chapter argues that *APOE* genotype is a structural feature of trial design rather than a covariate, because it sets when the lipid gate saturates and therefore when a given individual enters the trajectory. The containment substrate adds a second stratifier of the same structural kind: the microglial innate-immune genotype — *TREM2* R47H, *PLCG2* P522R, and the *MS4A* and *CD33* variants that tune the same programme — sets the native strength of R, and therefore both the baseline margin and the expected response to containment enhancement. A trial of a barrier-strengthening agent that does not stratify on the genotype of the barrier is a trial that has left its own effect size to chance.

XII. What Would Falsify This

A theory that cannot be broken is not a theory, and this volume's load-bearing propositions are each attached to an observation that would break them.

The substrate claim — that containment is a fifth substrate rather than a facet of the homeostatic state — would be falsified by a demonstration that mantle integrity and homeostatic-signature preservation are one variable: that in matched-pathology human tissue, plaque compaction and protofibrillar-halo extent are fully predicted by the transcriptional state of the surrounding microglia, with no residual variance. If R adds nothing to H, R is not a substrate and this volume's architecture is an unnecessary complication.

The bounded-excursion claim of Section IV would be falsified by a failure of the predicted dissociation: if, in matched-pathology human tissue, mantle coverage and generalised activation markers (CD68, GFAP, HLA-DR) prove to be positively and tightly correlated rather than dissociable, then the distinction between bounded and chronic activation has no tissue correlate, the reconciliation of Perez-Nievas with the barrier literature fails, and the quarrel of Section I must be settled the other

way.

The spatial-targeting claim of Section V is the volume's most exposed proposition, and deliberately so. It predicts that in human tissue, with each brain serving as its own control, perineuronal net integrity in the immediate neighbourhood of a well-mantled compact deposit will exceed net integrity in the neighbourhood of a poorly mantled diffuse one, and that the markers of unaimed proteolysis will track the second and not the first. If the local relationship is absent — if net degradation is indifferent to the mantling state of nearby plaques — then the identity of effector with difference of address is wrong, the R–M coupling reduces to a generic inflammatory correlation, and Section V should be struck. The claim is deliberately stated within-brain, because the between-subject version has already returned a result that does not support the naive form.

The R–S claim would be falsified by a demonstration that soluble oligomeric burden in the neuropil is independent of local mantle integrity — that walling a plaque does not lower the diffusible fraction around it. The mechanism requires that the barrier control the tag, and if it does not, the containment substrate has no route to the synapse and the volume's central clinical claim collapses.

The R–P claim would be falsified by a demonstration that plaque-associated dystrophic neurites are not a material contributor to the local seeding-competent tau reservoir — for example, by seeding assays showing that neuropil remote from deposits carries equivalent seeding activity per unit tau. The coupling requires that the mantle set the size of a reservoir that matters.

The therapeutic pairing claim of Section XI makes the sharpest prediction of all, and it is the one the ongoing TREM2-agonist programmes will test whether or not they intend to. It predicts that containment enhancement given without homeostatic support will produce a dysregulation signature — rising complement deposition, rising matrix proteolysis, falling perineuronal net integrity — even where it demonstrably strengthens the barrier, and that the same agent given with homeostatic support will not. If a TREM2 agonist given alone, early, to preclinical carriers strengthens the mantle and preserves both cognition and matrix integrity without any accompanying restoration of TGF-β tone, then the return path is not rate-limiting, the pairing argument is wrong, and the therapeutic core of this volume should be abandoned.

The threshold-identity claim of Section X would be falsified by the discovery of a genuine single point of failure — a restraint whose release, alone, reliably produces dementia regardless of the state of every other layer. The architecture predicts that no such restraint exists, that all are contributors to a sum, and that none is the

disease by itself.

XIII. Validity Ledger

The claims of this dissertation 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 data 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

- *TREM2* R47H carriers show, at unchanged plaque burden, markedly increased peri-plaque axonal dystrophy and phospho-tau — the human demonstration that the same amyloid load can differ entirely in what it does to the neurite (Yuan).
- Microglia form a physical barrier that compacts amyloid deposits, holds protofibrillar Aβ42 hotspots off surrounding neurites, and whose disruption produces diffuse deposits with unchecked halos; the barrier is TREM2-dependent and is required early, when the deposit is nascent (Condello; Yuan; Wang; Ulland). Demonstrated in mouse tissue and in *TREM2*-variant human autopsy material; the generalisation of the barrier mechanism to sporadic human disease is graded Tier II.
- The uncoupling of amyloid burden from dementia: a substantial fraction of cognitively intact elders carry Alzheimer-defining plaque pathology (Katzman; Perez-Nievas; and the community-based autopsy series that have replicated it).
- 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 tangle burden, shows preserved synaptic markers, markedly lower fibrillar and plaque-associated oligomeric amyloid deposition in situ, no selective accumulation of soluble tau into the synaptic compartment, and less CD68- and GFAP-scored glial activation than the demented brain. Bulk soluble amyloid species did not differ — a null that the

containment reading of Section VI requires (Perez-Nievas).

- The innate-immune genetics of Alzheimer's risk are largely microglial and sign-consistent: *TREM2* R47H raises risk roughly three- to four-and-a-half-fold, *PLCG2* P522R (a mild functional hypermorph, of the order of 1.2-fold) lowers it, *APOE* ε2 is strongly protective and ε4 the dominant common risk allele (Guerreiro; Jonsson; Sims; Magno; Corder; Reiman).
- The homeostatic microglial signature is TGF-β-dependent, and its downregulation is common to every catalogued pathological microglial state (Butovsky; Keren-Shaul; Deczkowska; Sala Frigerio).
- Perineuronal net material is found within microglia in Alzheimer human tissue, and net architecture around parvalbumin interneurons is altered in both dementia and resilience (Crapser; de Vries and Carulli). In resilient donors the alteration is a reduction in net density and aggrecan immunoreactivity accompanied by an absent matrix-proteolytic transcriptional signature; in demented donors the reduction carries that signature (de Vries and Carulli). The human arm of Crapser is descriptive; the causal demonstration is murine and is graded Tier II below.
- Complement-mediated microglial engulfment drives early synapse loss in Alzheimer models, and soluble oligomeric amyloid is the upstream trigger (Hong; Stevens).
- The locus coeruleus and subcortical aminergic nuclei bear the earliest hyperphosphorylated tau, decades pre-symptom (Braak and Del Tredici); the subcortical nuclei preferentially affected by tau are those devoid of the aggrecan-based perineuronal net, while net-bearing neurons resist (Morawski). The temporal ordering and the matrix association come from different series and are here read together.
- Human resilience to autosomal-dominant Alzheimer's disease exists and can turn on a single locus (*APOE3*-Christchurch; *RELN*-COLBOS). Both probands reached Braak VI at autopsy with atypical regional distribution and clinical sparing — tolerance of a full pathological load, not resistance to its accumulation (Sepúlveda-Falla; Lopera).

Tier II — Well-supported inference

- Containment failure has two distinct modes — insufficiency (dystrophic, senescent, metabolically starved microglia) and dysregulation (chronic, complement-spraying activation) — with opposite therapeutic instructions (Streit; Bussian; Marschallinger).

- Plaque-associated apoE accumulation is TREM2-dependent, and loss of TREM2 function increases amyloid seeding while reducing that shell (Parhizkar — an induced-seeding paradigm whose PET effect reverses with age, and whose apoE reduction spans several *TREM2* variants rather than R47H alone). That the barrier is more generally a lipid-handling programme gated by APOE isoform is an inference across this result and the lipid-droplet literature (Marschallinger), not a single demonstrated finding.
- Microglia causally drive perineuronal net loss: depletion by CSF1R inhibition preserves nets in 5xFAD and 3xTg-AD models, and lipopolysaccharide degrades them in wild-type mice. The human tissue supplies descriptive support only, and the field is not fully settled — lectin-binding artefact has been proposed as a confound in the human measurement (Crapser).
- Plaque-associated dystrophic neurites are a major local reservoir of hyperphosphorylated tau and therefore a plausible seeding field for the propagation substrate (Condello; Braak staging data; propagation-substrate literature).
- TREM2 agonism can push microglia toward the barrier state and reduce pathology in models; the disposition of the gardener is a therapeutic lever, not only a marker (Wang 2020).
- The correct statement of homeostatic collapse is the loss of the return path rather than the loss of the resting state; TGF-β/SMAD tone is the signal that draws the excursion home (Butovsky; von Bernhardi; Deczkowska).

Tier III — Synthesis and inference

- **The substrate claim.** That containment (R) is a fifth substrate of the HMS+P architecture rather than a facet of the homeostatic substrate H is an architectural inference. It satisfies the corpus's own three-part criterion — irreducible collapse pattern, internal mechanistic density, explanatory yield — but the criterion is itself a methodological convention, and the decisive human measurement (mantle integrity versus antemortem cognition at matched pathology) has not been made.
- **The two-route account of net loss** — that remodelling and digestion are distinguishable routes to a reduced net count, with opposite synaptic consequences — currently rests on a single bulk-transcriptomic contrast. Four of the five criteria set out in Section IX have not been scored in human tissue. It is the hypothesis on which the resilience argument of Section IX depends, and it is the weakest link in that argument.

- **The spatial-targeting account** of R–M — that the mantle and the perineuronal net are competing addresses for one proteolytic effector programme, and that restraint is therefore spatial confinement — is the most novel and least demonstrated claim in this volume. It is consistent with the shared enzymology and with the PNN thesis's CSPG–TREM2 loop, and it makes a sharp local prediction, but it has not been tested.
- **The quantitative reading of resilience** as a weighted five-substrate sum crossed at a threshold is an interpretive unification of the corpus's joint-preservation claim with the net-of-restraints claim. It is well-motivated by the natural history but is not itself a measured quantity, and no weighting has been estimated.
- **The identity of the three thresholds** — allostatic, feed-forward, net-of-brakes — is a synthesis across volumes, coherent with each but not directly measured as a single formal threshold.
- **The immunotherapy reading** of Section VII — that antibody-mediated plaque removal is a different and possibly opposed event to native containment — is an inference from mechanism, not from a trial result, and the genotype-modulated prediction it generates has not been tested.
- **The therapeutic pairing** of containment enhancement with homeostatic restoration is a rational combination derived from the two-failure-mode structure of R. It has not been attempted, and the combination's superadditivity is predicted rather than observed.

A Note on Provenance and Verification

This dissertation was assembled under the Organic Network Synthesis methodology as a cross-axis synthesis of two prior documents in the corpus — *The Gardener's Restraint*, the microglial-resilience volume, and Chapter 1 of the *Unified Collapse*, which established the HMS+P architecture on the foundation of the Convergent Synaptic Collapse thesis and its three successors. It introduces no new primary data. Every reference was confirmed against PubMed, and every claim in the body attributed to a named study was checked against that study's own reported result rather than against a secondary characterisation of it. Where the primary source reports something narrower than the claim it is customarily cited for — the bulk-soluble-amyloid null in Perez-Nievas, the direction of the perineuronal net

finding in de Vries and Carulli, the disease stage of the completed TREM2-agonist trial, the plaque-count ratio in Katzman, the glycolytic rather than oxidative character of the TREM2 metabolic deficit in Ulland — the narrower statement is the one used here, and the argument is built on it. 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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