THE ARCHITECT'S SCAFFOLD

Reelin and the Perineuronal Net — How the Cortex's Builder Comes to Dwell in the Matrix that Shields Its Neurons, and Why a Single Sulfated Lattice Governs Both the Reelin Signal and the Spread of Tau

The Net's Tenant · The Sulfation Code · The Doubly-Guarded Neuron
The Matrix that Admits Tau · The Three-Read Dial

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

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The matrix companion to The Architect's Reprieve. That volume argued reelin is an axis of resilience; this one locates the address at which the resilience is mounted — the sulfated perineuronal matrix into which reelin is secreted, which shields the neuron, stages the reelin signal, and gates the entry of pathological tau. It joins two literatures that scarcely cite one another, the reelin and the perineuronal-net, and argues that they describe one guarded surface — grading, connection by connection, how much of that unity the evidence yet sustains.

"The architect did not guard from nowhere. It was woven into the sulfated matrix at the neuron's surface — the same lattice that, condensed into the perineuronal net, walls the neuron against ruin and closes it against the tangle. Three defenses fall together in the disease because they were, all along, one surface."

— ONS Methodology Working Notes, 2026

For the two communities — the students of reelin and the students of the perineuronal net — who described the same guardian in different words, and for the resilient in whom the sulfated dial was set to spare the tau while the amyloid raged.

THE COLLAPSE FRAMEWORK RESILIENCE COMPANION

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

— The Temporal Architecture of Collapse —

Convergence line: the APOE hub · the lipoprotein-receptor axis shared by reelin and ApoE

The Architect's Scaffold (reelin & the perineuronal net) — this volume

This volume is the matrix companion to *The Architect's Reprieve*. That thesis argued that reelin is an axis of resilience whose signal restrains tau; the present one asks where that signal is staged, and answers: in the sulfated perineuronal matrix into which reelin is secreted. It shows that one sulfated lattice discharges three offices at once — it shields the neuron, it is the co-receptor bed the reelin signal requires, and it is the surface through which pathological tau is internalized and propagated — so that reelin's brake and the perineuronal net's shield are revealed as two functions of a single guarded surface, degraded together when microglia digest the weave.

Contents

Abstract

Two of the strongest resilience signals in the Alzheimer's literature have been developed, until now, as if they belonged to different diseases. The first is reelin: the secreted glycoprotein that builds the layered cortex in the embryo and, in the adult, signals through the lipoprotein receptors ApoER2 and VLDLR to the adaptor Disabled-1 to restrain the phosphorylation of tau. The second is the perineuronal net: the condensed lattice of chondroitin-sulfate proteoglycans that ensheaths vulnerable interneurons, and whose integrity tracks with cognitive resilience to Alzheimer's neuropathology. The reelin literature and the perineuronal-net literature scarcely cite one another. This dissertation argues that they are describing one thing.

The argument rests on a fact hidden in plain sight since 1999: reelin is not merely *near* the perineuronal net — it is secreted *into* it. A subset of cortical GABAergic interneurons exports reelin directly into the perineuronal matrix, where it acts extrasynaptically. Reelin, in other words, is a tenant of the net. And the material of that net — sulfated glycosaminoglycan — turns out to hold three offices at once. It is the structural scaffold that shields the neuron; it is the co-receptor bed that the reelin signal *requires* in order to fire, since reelin cannot cluster ApoER2 without N-sulfated heparan sulfate; and it is the very surface through which pathological tau is internalized and propagated from cell to cell, since tau seeds enter neurons by binding heparan-sulfate proteoglycans. One sulfated lattice therefore stages the protective reelin signal, physically repels the tangle, and — while it is intact — denies tau its route of entry. When microglia digest that lattice, as they do in the Alzheimer's cortex, all three functions are predicted to fail together.

We assemble the evidence connection by connection, grade each in an explicit validity ledger, and are candid about the seams: the reelin-secreting cell, the net-wearing cell, and the reelin-responding cell are frequently three different cells, so the unity we claim is a unity of the *matrix compartment*, not of a single neuron. We show that the two known human resilience variants and the human resilience-net data are three readings of a single sulfated dial — Christchurch loosening the ApoE grip that spreads tau, COLBOS tightening the reelin grip that brakes it, and perineuronal-net-bearing neurons carrying strikingly little phospho-tau in resilient human cortex. And we close on a therapeutic tension that only this synthesis exposes: a heparan-sulfate-blocking drug that stops tau from spreading may, by the same action, silence the reelin signal that protects. The matrix is the shared surface. It must be modulated, not merely blocked.

I. Two Guardians That Were Never Introduced

The companion to this dissertation, *The Architect's Reprieve*, made the case that reelin is a genuine axis of resilience in Alzheimer's disease — a guardian whose signal restrains tau, whose failure permits the disease, and whose reinforcement in a single fortunate man held an otherwise unstoppable genetic dementia at bay for three decades. That argument was built entirely from the reelin literature: the receptor biology, the Disabled-1 cascade, the resilient carriers. It never once mentioned the perineuronal net.

The perineuronal-net literature has, in parallel, assembled an argument of nearly identical shape. Perineuronal nets are condensed extracellular-matrix lattices — hyaluronan backbones hung with chondroitin-sulfate proteoglycans of the lectican family, cross-linked by tenascin-R and stabilized by link proteins — that ensheath the somata and proximal dendrites of predominantly parvalbumin-positive fast-spiking interneurons. They stabilize synapses, close critical periods of plasticity, buffer oxidative and ionic insult, and form a diffusion barrier at the neuronal surface. And their loss tracks the disease: perineuronal nets are extensively degraded in the Alzheimer's cortex, their aggrecan turns up inside dense-core plaques, and — decisively — their preservation is a substrate of *cognitive resilience*, the state in which a brain carries the neuropathology of Alzheimer's disease without carrying its dementia (Crapser and colleagues, 2020; de Vries and colleagues, 2024). This is a guardian too. It was simply described by a different community, in a different vocabulary, and filed under the extracellular matrix rather than under lipoprotein signalling.

Two guardians, then, each independently nominated for the same role — the protection of the same vulnerable cortical circuitry against the same tangle — and each developed in near-total ignorance of the other. This dissertation introduces them, and argues that the introduction is not a courtesy but a discovery: that reelin and the perineuronal net are not two protective systems that happen to coincide, but two faces of a single guardianship whose medium is the sulfated matrix they share.

II. The Net's Tenant

The connection begins with an anatomical fact that has been available, and largely unremarked in the Alzheimer's context, for a quarter of a century. It is worth recalling that reelin was, from its discovery, a molecule of the matrix: the protein deleted in the reeler mouse proved to be a large secreted glycoprotein structurally akin to the extracellular-matrix proteins that guide cell adhesion (D'Arcangelo and colleagues, 1995) — a pedigree that makes its residence in the perineuronal matrix less a surprise than a homecoming. Reelin does not simply diffuse through the adult brain. A defined population of cortical GABAergic interneurons — the bitufted, horizontal, and Martinotti

cells of the upper and deep layers — synthesizes reelin and *secretes it into the perineuronal net*, where it resides extrasynaptically and modulates the expression of genes in the neurons it surrounds (Pesold and colleagues, 1999). Reelin messenger RNA persists in the adult cortex and hippocampus long after the Cajal-Retzius cells that made it in the embryo have vanished, now expressed preferentially in GABAergic neurons (Pesold and colleagues, 1998). The architect did not only stay on after construction, as the companion dissertation argued; it took up residence in a specific structure — the perineuronal matrix — and works from within it.

This is the hinge of the present argument, and it must be stated with more care than enthusiasm invites, because the anatomy contains a genuine complication that a careless synthesis would paper over. The interneurons that *secrete* reelin are, by Pesold's own characterization, not the parvalbumin cells; they are the neuropeptide-Y-, somatostatin-, and calbindin-expressing subtypes. The interneurons that most conspicuously *wear* a perineuronal net are the parvalbumin cells. And the neurons in which reelin's signal is transduced — where Disabled-1 is expressed and phosphorylated — are predominantly the pyramidal, glutamatergic neurons (Pesold and colleagues, 1999). The reelin-secreting cell, the net-bearing cell, and the reelin-responding cell are therefore frequently three different cells. The unity this dissertation claims is accordingly not the unity of a single neuron carrying both systems, but the unity of the *extracellular compartment* they share: reelin is deposited into the sulfated matrix, diffuses and is held within it, and acts on the neurons embedded in it. The perineuronal net and the wider perineuronal matrix are the medium in which the reelin signal is staged. That is a weaker claim than "reelin is a parvalbumin-net protein," and it is the claim the evidence actually supports — but it is strong enough to carry everything that follows, because the argument turns on the matrix, not on the cell.

III. The Net Repels Tau

If reelin is staged in the perineuronal matrix, and if reelin restrains tau, then one would predict that neurons embedded in an intact perineuronal net should bear less tau pathology than neurons without one. They do — and the observation was made, again, from the perineuronal-net side, without reference to reelin.

Morawski and colleagues (2010) examined the subcortical regions that Alzheimer's disease attacks and found a striking complementarity: the nuclei devastated early by tau — the locus coeruleus, the nucleus basalis of Meynert, the raphe, the dorsal thalamus — are precisely those *devoid* of an aggrecan-based perineuronal matrix, while neurons ensheathed by nets, even in regions where tangles form all around them, extremely rarely carry neurofibrillary tangles themselves. The

perineuronal net and the neurofibrillary tangle, in region after region, occupy complementary territory. The authors concluded, cautiously, that the aggrecan matrix is neuroprotective — and their map of net-poor vulnerability reads, uncannily, like the map of selective vulnerability that the companion reelin dissertation and the wider corpus have drawn from the opposite direction. The locus coeruleus, ground zero for tau and a hub of the entire temporal architecture, is a region without a net.

The decisive confirmation is recent, human, and comes from the study of resilience itself. de Vries and colleagues (2024), comparing the frontal cortex of Alzheimer's, resilient, and control subjects, reported that excitatory neurons still bearing a perineuronal net carried strikingly low levels of phospho-tau. Here the two guardians are seen in the same tissue at the same time: a net-bearing neuron is a low-tau neuron. And the same study administers the discipline that keeps this from becoming a fairy tale. Resilience was *not* simply a matter of more net. Aggrecan around parvalbumin neurons was reduced in both Alzheimer's and resilient brains, and the sulfated sugar chains of the net were reduced specifically in the resilient — a homeostatic *remodeling* of the matrix rather than its wholesale preservation, distinct from the destructive, protease-driven degradation of the disease (de Vries and colleagues, 2024). The protective relationship is therefore not "thicker nets, less disease"; it is subtler, a matter of which neurons retain a functional net and of how the matrix is remodeled rather than merely how much of it survives. This is the same caution the companion dissertation drew for reelin itself, where the quantity that protects is the *signal*, not the bulk protein. In both systems, abundance and function must not be confused — and in both, the honest reading is the one that survives.

One caveat is owed and paid here: these human observations are correlative. That net-bearing neurons carry less tau is consistent with the net protecting them, and consistent with tangle-prone neurons simply being the kind that never had a net. The complementarity cannot, by itself, fix the arrow — the same limitation the companion dissertation faced with the vanishing of reelin-expressing entorhinal neurons (Chin and colleagues, 2007). What fixes the arrow, in both cases, is mechanism, and to the mechanism the two systems share we now turn.

IV. One Sulfated Lattice, Three Offices

The load-bearing claim of this dissertation is that the perineuronal matrix is not merely the place where reelin and tau happen to meet, but a single material that discharges three distinct offices in the disease — and that this triple role is what binds reelin's fate to the net's.

The first office is structural and protective. The chondroitin-sulfate lattice is the scaffold itself: it stabilizes synapses onto the ensheathed neuron, buffers cations and restrains oxidative injury, and forms a diffusion barrier that limits the access of neurotoxic species to the neuronal surface. This is the office the perineuronal-net literature has always described, and it is the basis of the net's protection of parvalbumin interneurons.

The second office is that of a signalling address. The sulfation pattern of the matrix is not inert packing; it is a code that specific proteins read. Otx2, the homeoprotein that opens and closes cortical critical periods, is captured and concentrated on parvalbumin-cell perineuronal nets through a short glycosaminoglycan-binding motif that binds with high affinity to specific chondroitin-sulfate species — the doubly-sulfated CS-D and CS-E — and hydrolyzing the net with chondroitinase strips this bound Otx2 away (Beurdeley and colleagues, 2012). The matrix, that is, is a sulfation-addressed reservoir: it holds signalling proteins at the neuronal surface by the specific sulfation of its sugars. And reelin's own signal depends on exactly this kind of sulfated address. Reelin cannot fire through ApoER2 as a simple two-body ligand; it requires N-sulfated heparan sulfate as an obligate co-receptor to cluster the receptor and phosphorylate Disabled-1, and stripping or de-sulfating the sugar abolishes the signal (Pan and colleagues, 2025). The reelin signal is thus read from the sulfated matrix in the same grammar by which the net holds Otx2 — a ligand presented and clustered by the sulfation of the surrounding sugar. The staging ground for reelin's tau-brake *is* the sulfated matrix of which the net is the densest expression.

The third office is the one that makes the disease. The same sulfated glycosaminoglycan chemistry that stages the reelin signal is the route by which pathological tau enters neurons and spreads. Holmes and colleagues (2013) showed that tau fibrils are taken up into cells by binding heparan-sulfate proteoglycans on the cell surface, that this uptake and the transcellular propagation of tau seeding are blocked by heparin, by heparinase, by chlorate, and by genetic knockdown of a key heparan-sulfate synthetic enzyme, and that a heparin mimetic blocks neuronal uptake of injected tau fibrils in vivo. Proteoglycan sulfation is the doorway through which tau propagates from neuron to neuron. It is the same doorway — the same class of sulfated sugar on the same neuronal surface — that the reelin signal requires to enter, and it is embedded in the same matrix the perineuronal net is built from.

Set the three offices side by side and the architecture of the whole disease compartment appears. One sulfated lattice at the neuronal surface *shields* the neuron, *stages* the protective reelin signal, and *gates* the entry of pathological tau. While the lattice is intact and properly sulfated, the neuron is defended on all three counts: physically buffered, reelin-guarded, and — this is the underappreciated point — able to hold tau seeds at a surface that has not yet been remodeled into a propagation-competent state. The net-bearing, reelin-staged, low-tau neuron of the resilient cortex is a neuron whose matrix still performs all three offices. This is why reelin and the perineuronal net cannot be understood apart: they are not two guardians standing side by side, but two functions of

one guarded surface.

V. Two Routes to One Restraint

That reelin and the net converge on the matrix does not make them redundant. They restrain tau by different routes, and the difference is the reason a neuron possessing both is protected more completely than a neuron possessing either.

Reelin restrains tau from *inside* the neuron. Its signal runs from ApoER2 and VLDLR through Disabled-1 to the PI3-kinase/Akt axis and the inhibition of glycogen synthase kinase-3β, the principal kinase that hyperphosphorylates tau; a live reelin signal keeps the kinase suppressed, and the withdrawal of the signal — by loss of reelin or of its receptors — releases the kinase and permits tau to be pathologically modified (Hiesberger and colleagues, 1999). The same intracellular signal also stiffens the synapse against amyloid directly, opposing the amyloid-β-driven suppression of long-term potentiation up to a concentration ceiling (Durakoglugil and colleagues, 2009). This is a biochemical brake on the enzyme that makes the tangle, cell-autonomous and intracellular.

The perineuronal net restrains tau from *outside* the neuron. It does not touch the kinase; it guards the surroundings — buffering the oxidative and ionic stress that drives tau pathology, stabilizing the synapses whose failure precedes it, and, in light of the third office above, occupying the sulfated surface through which tau seeds would otherwise enter. The net's protection is extracellular, structural, and — in the propagation dimension — a matter of controlling the doorway rather than the engine.

The two are therefore complementary in the strict sense: reelin keeps a neuron from generating hyperphosphorylated tau, while the net keeps the neuron's environment survivable and its surface closed to tau seeds arriving from elsewhere. A neuron staged in an intact, reelin-bearing net has its tau kinase suppressed *and* its tangle-seeding entry route defended; lose the net and it loses both the external defense and — because the same sulfated sugar is reelin's co-receptor — the staging of the internal one. The doubly-guarded neuron is not protected twice over by chance. It is protected twice over because one matrix serves both defenses.

VI. When Microglia Unpick the Weave

If the matrix discharges all three offices while intact, then its destruction should collapse all three at once, and the destruction is exactly what the disease performs. Crapser and colleagues (2020) established that perineuronal nets are lost in the Alzheimer's brain in proportion to plaque burden, that activated microglia associate with and engulf the nets, that inclusions of net material appear inside microglia in both mouse and human tissue, and — the causal step — that chronic pharmacological depletion of microglia prevents the net loss even though the plaques persist. The net is unpicked by microglia, through the matrix-degrading proteases their activation unleashes; aggrecan is cleaved, the lattice thins, and the parvalbumin interneurons it protected are lost after their nets are already impaired (Crapser and colleagues, 2020; de Vries and colleagues, 2024).

The synthesis of Section IV converts this familiar chain into a wider prediction. If the sulfated matrix stages the reelin signal, then microglial digestion of that matrix should not only strip the neuron of its structural net but degrade the sulfated co-receptor bed on which reelin depends — silencing the tau-brake at the very moment the structural defense falls. This coupled failure is, at present, a prediction rather than a demonstrated fact: no study has yet measured reelin signalling before and after perineuronal-net degradation. But it is a prediction with three independent supports already in hand — that reelin requires N-sulfated heparan sulfate to signal (Pan and colleagues, 2025), that microglial proteases remodel and degrade the sulfated matrix (Crapser and colleagues, 2020), and that reducing reelin accelerates both amyloid and tau pathology in vivo (Kocherhans and colleagues, 2010). It also closes a feed-forward loop that the corpus has drawn twice from opposite ends. On the reelin side, amyloid reduces reelin expression and traps the reelin that is made, weakening the signal (Chin and colleagues, 2007). On the net side, amyloid activates the microglia that digest the matrix (Crapser and colleagues, 2020). If the matrix is reelin's staging ground, these are not two loops but one: amyloid drives the microglial digestion of the sulfated surface, which simultaneously removes the net and unstages reelin, which lifts the brake on tau, whose propagation the same degraded surface now admits more freely. There is no single origin to such a loop, but there is a single leverage point, and it is the sulfation of the matrix.

VII. The Resilient, Re-read Through the Matrix

The companion dissertation rested its causal weight on two human beings — the *APOE3*-Christchurch homozygote and the *RELN*-COLBOS heterozygote — who each escaped an autosomal-dominant dementia for three decades with heavy amyloid but spared entorhinal tau, and

it argued that both variants act on the shared heparan-sulfate-dependent lipoprotein-receptor node: Christchurch loosening apolipoprotein E's binding to heparan sulfate (Arboleda-Velasquez and colleagues, 2019), COLBOS tightening reelin's (Lopera and colleagues, 2023; Pan and colleagues, 2025). The present dissertation adds a third reading of the same dial, and it comes from the perineuronal net.

Consider what the three human data sets have in common once the matrix is placed at the centre. The Christchurch variant dials down a heparan-sulfate interaction that, left alone, *spreads tau* — for the heparan-sulfate engagement that apolipoprotein E competes at is the same class of sulfated sugar through which tau seeds are internalized (Holmes and colleagues, 2013). The COLBOS variant dials up a heparan-sulfate interaction that *brakes tau*, tightening the reelin–sugar handshake that fires Disabled-1 (Pan and colleagues, 2025). And the resilient human cortex, examined directly, shows perineuronal-net-bearing neurons carrying little phospho-tau, with the matrix homeostatically remodeled rather than destructively degraded (de Vries and colleagues, 2024). Three windows onto resilience — a genetic loosening of a tau-spreading grip, a genetic tightening of a tau-braking grip, and a histological preservation of a functional matrix — and all three are readings of the sulfation state of the perineuronal surface. The resilient are not protected by three separate mechanisms that happen to co-occur. They are protected by three settings of one sulfated dial.

This re-reading also honors the de Vries paradox rather than burying it. That resilience was associated, in bulk, with *less* aggrecan and *less* sulfated sugar is not an embarrassment to the matrix thesis; it is its refinement. What protects is not the quantity of the matrix but its *state* — a remodeled, homeostatically maintained sulfation that continues to stage reelin, hold signalling factors, and resist protease-driven destruction, as against the pathological degradation that dumps aggrecan into plaques and unstages every function the surface performed. Bulk matrix and functional matrix are as different as bulk reelin and reelin signal, and the disease, characteristically, raises the misleading quantity while lowering the one that matters.

VIII. The Validity Ledger

The discipline that separates synthesis from speculation is the graded ledger, each connection assigned a tier and the experiment that would settle it named alongside.

Strong (anatomy) — reelin is secreted into the perineuronal matrix. Directly demonstrated: a defined subset of adult cortical GABAergic interneurons expresses reelin and

secretes it into perineuronal nets, where it acts extrasynaptically (Pesold and colleagues, 1998, 1999). The load-bearing caveat is the cell-type mismatch — reelin-secreting, net-bearing, and reelin-responding cells are often distinct — so the claim is one of a shared matrix compartment, not a shared cell. *Settling experiment: none needed for the deposition itself; what remains is to quantify how much of the perineuronal reelin pool is signalling-competent.*

Strong (mechanism) — reelin restrains tau phosphorylation through Disabled-1 and GSK-3β. Established biochemically and in vivo, and imported intact from the companion dissertation (Hiesberger 1999; Kocherhans 2010; Lopera 2023).

Strong (mechanism) — tau is internalized and propagated via heparan-sulfate proteoglycans. Reproducibly demonstrated across cell, primary-neuron, and in vivo systems, with multiple orthogonal blockades (Holmes and colleagues, 2013). This is the third office and it is secure.

Strong (mechanism) — reelin requires N-sulfated heparan sulfate as an obligate co-receptor. Directly shown biochemically (Pan and colleagues, 2025). Together with the previous entry, this establishes that reelin signalling and tau propagation read the same class of sulfated sugar.

Moderate — perineuronal-net-ensheathed neurons are relatively protected from tau pathology. Consistent across a subcortical survey (Morawski and colleagues, 2010) and confirmed in resilient human frontal cortex, where net-bearing excitatory neurons carry low phospho-tau (de Vries and colleagues, 2024); but the human data are cross-sectional and cannot alone exclude that tangle-prone neurons are simply those that never bore a net. *Settling experiment: staged post-mortem or lineage series establishing whether net loss precedes local tangle onset in a given neuron.*

Moderate — perineuronal nets are degraded by activated microglia in Alzheimer's disease. A clean, causal model result with human corroboration; microglial depletion prevents net loss despite persistent plaques (Crapser and colleagues, 2020).

Moderate — the perineuronal matrix functions as a sulfation-addressed reservoir for surface-signalling proteins. Demonstrated for Otx2 via a defined chondroitin-sulfate-binding motif (Beurdeley and colleagues, 2012); generalized to reelin here by mechanistic analogy with its heparan-sulfate dependence (Pan 2025), not yet by direct demonstration that perineuronal sulfation stages the reelin signal. *Settling experiment: show that chondroitinase or sulfotransferase manipulation of the perineuronal matrix alters reelin-dependent Disabled-1 phosphorylation in situ.*

Plausible / predicted — microglial degradation of the sulfated matrix silences reelin signalling as it removes the net, collapsing structural and signalling defense together. Mechanistically coherent from three established facts (Pan 2025; Crapser 2020; Kocherhans 2010) but not directly measured. This is the central novel prediction of the dissertation.

Settling experiment: measure reelin-dependent Disabled-1 phosphorylation before and after perineuronal-net degradation in the same tissue.

Plausible — an intact perineuronal matrix limits transcellular tau propagation by controlling the sulfated surface tau requires for uptake. Follows from the third office (Holmes 2013) but not directly tested for perineuronal nets specifically. *Settling experiment: compare tau-seed uptake in net-bearing versus net-stripped neurons.*

Rejected as stated — the perineuronal net protects simply by being abundant. The resilience data show reduced bulk aggrecan and sulfated sugar in protected brains; what protects is the functional, remodeled state of the matrix, not its quantity (de Vries and colleagues, 2024). The naïve "more net is better" model is not supported; the functional-matrix model is.

IX. Predictions and Falsification

The matrix-guardianship thesis risks several specific predictions, each falsifiable.

- Reelin-dependent Disabled-1 phosphorylation will fall when the perineuronal matrix is degraded — by chondroitinase, by sulfotransferase deletion, or by microglial activation — even where total reelin protein is unchanged. A demonstration that matrix degradation leaves reelin signalling intact would sever the staging claim on which the dissertation turns.
- Neurons bearing an intact perineuronal net will take up and propagate exogenous tau seeds less efficiently than net-stripped neurons, and the difference will depend on the sulfation of the surface. If net-bearing and net-stripped neurons take up tau equally, the third office is wrong.
- Across brain regions, the density and functional sulfation of the perineuronal matrix will predict resistance to tau pathology better than neuronal identity alone, extending the Morawski complementarity quantitatively. A region rich in functional nets that nonetheless tangles early would weaken the thesis.
- Interventions that strengthen matrix sulfation, or that deliver reelin-pathway agonism, will spare tau while leaving amyloid largely intact, mirroring the resilient brains; and they will do so more effectively before the microglial digestion of the matrix has advanced. A matrix- or reelin-directed agent that clears amyloid but does not touch tau would overturn the placement of this axis downstream of amyloid and upstream of the tangle.

- The two human resilience variants and the resilience-net histology will continue to co-localize on the sulfated surface: any further resilience factor discovered in the *PSEN1*-E280A kindred will, the thesis predicts, act on matrix sulfation or on a ligand that reads it. A resilience mechanism wholly independent of the sulfated matrix would bound the reach of this synthesis.

X. Therapeutic Corollaries The Shared Surface, and Its Double Edge

If reelin's brake and the net's shield are two functions of one sulfated surface, then that surface is the therapeutic target, and the synthesis both widens the target and issues a warning that neither literature could have issued alone.

The widening is straightforward. Three approaches that have been pursued separately — reelin-pathway agonism, perineuronal-net stabilization against protease degradation, and modulation of the matrix sulfation code — are revealed as three ways of acting on one substrate. An agent that preserves the functional sulfation of the perineuronal matrix would, if the staging claim holds, defend the structural net and the reelin signal at once; an agent that reinforces the reelin–heparan-sulfate handshake, modelled on the COLBOS variant, would strengthen the brake that the resilient carry by birth (Pan and colleagues, 2025; Lopera and colleagues, 2023). And the timing corollary of the companion dissertation applies with new force: because the microglial digestion of the matrix is a feature of established disease, matrix- and reelin-directed intervention belongs to the earlier brain, before the surface has been unpicked — a strategy for prevention and the prodromal window, not for late rescue.

The warning is the contribution only this synthesis can make, and it falls directly out of the third office. Holmes and colleagues (2013) proposed heparan-sulfate mimetics precisely because they *block* tau uptake — a heparin analogue prevented neuronal internalization of tau fibrils in vivo, and the strategy of jamming the sulfated doorway to stop tau propagation is a rational one. But the same sulfated sugar that admits tau is the sugar reelin *requires* to signal (Pan and colleagues, 2025). A blunt agent that occupies or removes heparan sulfate to stop tau spreading would, by the identical action, risk silencing the protective reelin brake — closing the doorway to the intruder and to the guardian alike. The two literatures, pursued in isolation, would each have prescribed a heparan-sulfate-directed drug in confident ignorance of the other's stake in the same molecule. Read together, they demand a subtler pharmacology: not the blockade of the sulfated surface but the selective tuning of it — an agent, or a sulfation pattern, that discriminates the tau-uptake

configuration from the reelin-signalling one. Whether such selectivity exists is unknown. That it is the design constraint is the practical fruit of seeing the two guardians as one.

XI. Coda The Weaver and the Wall

The cortex is built by a protein that told each neuron where to stand, and then, this dissertation and its companion have argued, stayed on to defend the structure it raised. What the present work adds is the address at which the defense is mounted. Reelin does not guard from nowhere; it is woven into the sulfated matrix at the neuron's surface — the same matrix that, condensed into the perineuronal net, walls the vulnerable interneuron against oxidative ruin, holds the signalling proteins that govern plasticity, and closes the surface against the tangle-seed that would otherwise walk in. The architect took up residence in the wall it helped to build, and from within it kept tau from tangling.

The disease attacks the wall. Amyloid rouses the microglia, and the microglia unpick the weave, and as the sulfated matrix is digested the neuron loses at a single stroke its physical shield, the staging of its reelin brake, and the closure of its tau-admitting surface. Three defenses fall because they were, all along, one surface. And the proof that this surface is worth defending is written where the companion dissertation left it — in the resilient, whose sulfated dial was set, by inheritance or by preservation, to spare the tau while the amyloid raged: a loosened grip that would have spread the tangle, a tightened grip that braked it, a matrix remodeled rather than destroyed. They are three readings of one weave.

The clinician cannot yet re-thread it. But the task is now legible in a way it was not when reelin and the net were studied apart: to keep the sulfated matrix functional in the window before the microglia reach it, and to learn the difference — at the level of a single sulfation — between the surface that admits the disease and the surface that stages the defense. The weaver is still in the wall. The work is to keep the wall standing long enough for the weaver to matter.

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