THE COERULEAN SHEARS

Norepinephrine, MMP-9, and the Enzymatic Unstaging of Reelin — How the Locus Coeruleus Comes to Wield the Protease that Cuts the Sulfated Matrix Staging Reelin's Brake on Tau

The Unnamed Hand · The Shears in the Weave · The Sheared Receptor
The Antagonists at the Kinase · The Coerulean Paradox

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

Prepared under the Organic Network Synthesis methodology

AdultCognitiveDisease.com

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July 2026

The enzymatic sequel to The Architect's Scaffold. That volume proved reelin's brake on tau and the perineuronal net's shield to be two functions of one sulfated surface, and named its destroyer only as 'matrix-degrading proteases.' This one names the instrument — matrix metalloproteinase-9 — and the hand that guides it: the noradrenergic output of the locus coeruleus, the first structure in the brain to tangle. It grades, connection by connection, the cascade by which the earliest lesion of Alzheimer's disease comes to cut the matrix that stages reelin's protection.

"The nets are degraded. The matrix is digested. The weave is unpicked. Every synthesis that reached the perineuronal net reached, at its far edge, a verb it could not conjugate — a destruction with no named destroyer. This dissertation is written to conjugate the verb: to say what protease holds the shears, and whose hand is on the protease."

— ONS Methodology Working Notes, 2026

For the students of three literatures that scarcely cite one another — the reelin, the perineuronal net, and the locus coeruleus — who have been describing, in three vocabularies, the two ends and the middle of one cut.

THE COLLAPSE FRAMEWORK MATRIX & COERULEAN COMPANION

The Architect's Reprieve — reelin as an axis of resilience

The Architect's Scaffold — reelin & the perineuronal net, one sulfated surface

The Coerulean Interface — the locus coeruleus & the noradrenergic keystone

The Coerulean Shears (norepinephrine, MMP-9 & the cut matrix) — this volume

This volume welds two lines of the corpus that had run in parallel: the reelin/matrix line, which established a sulfated surface at the neuronal membrane that shields the neuron, stages reelin's signal through ApoER2 and VLDLR, and gates the entry of tau; and the coerulean line, which identified the locus coeruleus as the earliest structure to fail. It argues that a single enzyme — matrix metalloproteinase-9 — degrades all three offices of that surface, and that the dysregulated noradrenergic output of the failing coeruleus is what calls the enzyme up: the protease is the shears, norepinephrine the hand, and the reelin brake on tau the thread they cut. Because the coeruleus alone among the nuclei wears no net of its own, it tangles first — and so operates, in its dysregulation, the demolition of the very defense it exists to serve.

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Abstract

A companion dissertation, *The Architect's Scaffold*, argued that reelin's brake on tau and the perineuronal net's shield are two functions of one sulfated surface at the neuronal membrane: a single lattice that shields the neuron, stages the reelin signal through ApoER2 and VLDLR by presenting the N-sulfated heparan sulfate the receptors require, and gates the entry of pathological tau. That argument closed on a destruction — "when microglia unpick the weave, all three functions fail together" — but it left the instrument of destruction and the hand that guides it unnamed. It spoke only of "matrix-degrading proteases" in the abstract. This dissertation names them.

The instrument is matrix metalloproteinase-9. It is the gelatinase whose activation cleaves the aggrecan and brevican core proteins of the perineuronal net, sheds the ectodomains of the syndecan heparan-sulfate proteoglycans that carry reelin's obligatory co-receptor sugar, and strips the lipoprotein receptors of the low-density-lipoprotein-receptor family — the family to which ApoER2 and VLDLR belong — from the cell surface. One enzyme, that is, can degrade all three offices of the sulfated matrix at once: the shield, the reelin-staging bed, and, by shedding the receptors themselves, the reelin apparatus entire. The hand that guides the enzyme is norepinephrine. Catecholamine signalling through β-adrenergic receptors drives the transcription of MMP-9 through the cAMP–protein-kinase-A–AP-1 and NF-κB axes; the same neuromodulator, when chronically in excess, over-activates protein kinase A and glycogen-synthase-kinase-3β — the very kinase reelin's signal exists to suppress. Norepinephrine and reelin are therefore antagonists twice over: reelin brakes the tau kinase from inside the neuron while the noradrenergic drive releases it, and reelin's staging surface is dismantled by the protease that the noradrenergic drive calls up.

The synthesis exposes a tragedy of geometry that neither literature could see alone. The locus coeruleus — the sole cortical source of norepinephrine — is, by the same subcortical survey that first mapped the protective net, a nucleus *without* a perineuronal net of its own; it is therefore ground zero for tau, the first structure in the brain to accumulate the pretangle, and among the first to die. As it sickens and its firing becomes dysregulated, the noradrenergic supply to the cortex swings from a compensatory excess to a terminal collapse — and it is precisely the excess that drives the protease that unpicks reelin's protection everywhere the axons reach. The nucleus that should defend the cortex operates, in its dysregulation, the demolition of the cortex's defense. We assemble the cascade connection by connection, grade each in an explicit validity ledger — candid that the norepinephrine-to-MMP-9 step is proven in the periphery and inferred in the brain, that MMP-9's shedding of the reelin receptors is shown for their kin and not yet for ApoER2 itself, and that direct proteolysis of reelin by MMP-9 is not established — and close on the therapeutic knot the synthesis ties: that the protease is also a clearer of amyloid and a maker of memory, so that to still the shears is to risk the hand that also mends.

I. The Unnamed Hand

Every synthesis in this corpus that has reached the perineuronal net has reached, at its far edge, a verb it could not conjugate. The nets are *degraded*. The matrix is *digested*. The weave is *unpicked*. *The Architect's Scaffold* — the dissertation to which the present one is the mechanistic sequel — built its entire case on the destruction of the sulfated surface and then, at the decisive moment, named the destroyer only by its category. "Microglia," it wrote, "unpick the weave, through the matrix-degrading proteases their activation unleashes." The passive construction and the generic plural were honest: the Scaffold's argument did not depend on which protease, and to have named one without warrant would have been to smuggle a specificity the evidence had not yet earned.

But the verb has an agent, and the agent has a name, and the name matters — because a category cannot be inhibited, timed, or blamed, and a molecule can. This dissertation is written to conjugate the verb. It argues that the protease which discharges the destruction the Scaffold described is, in the main, a single well-characterized enzyme — matrix metalloproteinase-9, the 92-kilodalton gelatinase B — and that the enzyme is not an autonomous vandal but an effector, called into being and activity by an upstream signal that the reelin and perineuronal-net literatures have almost never thought to implicate: the noradrenergic output of the locus coeruleus. The hand on the shears, this dissertation contends, is norepinephrine.

The claim is worth stating plainly at the outset, because its shape is unusual. Most accounts of Alzheimer's disease that reach the extracellular matrix treat its degradation as a downstream consequence — amyloid rouses microglia, microglia degrade the net, and the matter ends there, the protease an anonymous instrument of a story whose protagonist is the plaque. The present account inverts the emphasis. It takes the protease seriously as a node in its own right, asks what governs its expression and activation in the brain, and finds at the controls a neuromodulatory system that the temporal architecture of this corpus has already identified as the earliest to fail. The result is not a new initiator of the disease — this dissertation is emphatic that it proposes no such thing — but the identification of a specific, druggable, and tragically self-defeating relay by which the earliest lesion of Alzheimer's disease, the pretangle in the locus coeruleus, is mechanically coupled to the dismantling of one of the cortex's principal resilience systems, the reelin-bearing sulfated matrix.

Three literatures must be introduced to one another for the argument to stand, and none of the three has been much in the habit of citing the other two. The first is the reelin axis: the secreted glycoprotein that signals through the lipoprotein receptors ApoER2 and VLDLR to the intracellular adaptor Disabled-1, restraining, by way of that cascade, the phosphorylation of tau. The second is the biology of the perineuronal net and its sulfated matrix — the condensed lattice of chondroitin- and heparan-sulfate proteoglycans that ensheaths vulnerable neurons and that the companion

dissertation identified as the physical staging ground of the reelin signal. The third is the neurochemistry of the locus coeruleus and its transmitter, norepinephrine, together with the metalloproteinase biology that connects catecholaminergic tone to matrix turnover. The reelin worker rarely reads the metalloproteinase literature; the locus-coeruleus neurologist rarely reads the perineuronal-net histology; and the matrix biologist rarely reaches for the adrenergic pharmacology. This dissertation reads all three at once and argues that they describe a single cut.

II. The Sulfated Staging Ground, Recalled

Because the argument that follows presupposes the conclusions of *The Architect's Reprieve* and *The Architect's Scaffold*, and because a dissertation should stand on its own feet, the shared foundation is recalled here in compressed form. The reader who knows those volumes may pass quickly; the reader who does not will find in this section the whole of what the present argument imports.

Reelin brakes tau from inside the neuron. Reelin binds the extracellular domains of two receptors of the low-density-lipoprotein-receptor family, apolipoprotein-E receptor 2 (ApoER2, the product of the *LRP8* gene) and the very-low-density-lipoprotein receptor (VLDLR). Receptor binding clusters the receptors and induces tyrosine phosphorylation of the cytoplasmic adaptor Disabled-1, which recruits and activates the phosphoinositide-3-kinase–Akt pathway and, through it, inhibits glycogen-synthase-kinase-3β — the principal kinase that hyperphosphorylates tau (Hiesberger and colleagues, 1999). A live reelin signal keeps that kinase suppressed; the withdrawal of the signal releases it. In transgenic Alzheimer models, reducing reelin expression accelerates both amyloid plaque formation and tau pathology (Kocherhans and colleagues, 2010), and reelin signalling antagonizes the amyloid-β-driven suppression of synaptic potentiation directly (Durakoglugil and colleagues, 2009). Reelin, from a molecule discovered as an architect of the layered cortex (D'Arcangelo and colleagues, 1995), is thus in the adult a guardian of the neuron against the tangle.

The reelin signal requires the sulfated matrix to fire. Reelin is not a simple two-body ligand for ApoER2. It requires N-sulfated heparan sulfate as an obligate co-receptor: the sulfated sugar clusters the receptor and permits the phosphorylation of Disabled-1, and stripping or de-sulfating the heparan sulfate abolishes the signal (Pan and colleagues, 2025). This is the hinge on which the companion dissertation turned, for it means that the reelin brake is not merely staged near the sulfated matrix but is chemically dependent upon it. The heparan sulfate is not scenery; it is a functional component of the receptor complex.

Reelin is a tenant of the perineuronal net. A defined subset of cortical GABAergic interneurons secretes reelin directly into the perineuronal matrix, where it acts extrasynaptically upon the neurons embedded there (Pesold and colleagues, 1998, 1999). The reelin-secreting cell, the net-bearing cell, and the reelin-responding cell are frequently three different cells, so the unity is one of a shared matrix compartment rather than of a single neuron — but the compartment is real, and it is sulfated, and it is the medium in which the reelin signal is presented.

The same sulfated surface gates the tangle. Pathological tau is internalized and propagated from neuron to neuron by binding heparan-sulfate proteoglycans on the cell surface; the uptake is blocked by heparin, by heparinase, by chlorate, and by knockdown of a heparan-sulfate synthetic enzyme (Holmes and colleagues, 2013). The class of sulfated sugar that reelin requires to signal is the class through which tau enters. And the matrix holds signalling proteins by their sulfation quite generally: the plasticity regulator Otx2 is captured on perineuronal nets through a defined chondroitin-sulfate-binding motif (Beurdeley and colleagues, 2012), establishing the matrix as a sulfation-addressed reservoir.

Net-bearing neurons resist the tangle; the net is degraded in the disease. Neurons ensheathed by an aggrecan-based perineuronal net rarely bear neurofibrillary tangles, while the nuclei devastated early by tau are precisely those devoid of such a net (Morawski and colleagues, 2010). In resilient human cortex, excitatory neurons that retain a perineuronal net carry strikingly low phospho-tau (de Vries and colleagues, 2024). And the net is actively destroyed in the Alzheimer brain: perineuronal nets are lost in proportion to plaque burden, microglia engulf them, and depleting microglia prevents the loss even where plaques persist (Crapser and colleagues, 2020).

This is the surface the present dissertation watches being cut. *The Architect's Scaffold* proved it was one surface discharging three offices. The task now is to identify the blade.

III. The Receptors and Their Reader — ApoER2, VLDLR, and Disabled-1

The cascade this dissertation traces cuts a signal, and a signal has parts that can each be cut. Before the enzyme is examined it is worth resolving the reelin apparatus into its components at higher magnification than the recap of Section II allowed, because the argument that MMP-9 *unstages* reelin depends on exactly which components are exposed to the protease at the neuronal surface — and three of them are: the two receptors, ApoER2 and VLDLR, and, indispensable to both, the sulfated sugar that clusters them. The fourth component, the intracellular adaptor Disabled-1, is the

one the protease cannot touch, and it is precisely for that reason that it makes the best read-out of whether the signal, upstream, still lives.

ApoER2. Apolipoprotein-E receptor 2, the product of the *LRP8* gene, is a member of the low-density-lipoprotein-receptor family: a single-pass transmembrane receptor with an ectodomain of ligand-binding complement-type repeats, epidermal-growth-factor precursor homology domains, and — in the isoforms relevant to the brain — a variably spliced insert, all sitting above a short cytoplasmic tail that carries the NPxY motif through which the intracellular machinery is engaged. Two features of ApoER2 make it the pivot of this dissertation's receptor arm. The first is that its ectodomain is *shed*: reelin binding induces the regulated proteolytic cleavage of ApoER2, releasing a soluble ectodomain fragment whose abundance in the cerebrospinal fluid reports on how much reelin signalling has occurred, and that read-out is deranged in Alzheimer's disease — reduced in sporadic disease, isoform-dependent in its relation to apolipoprotein-E genotype (López-Font and colleagues, 2018, 2022). A receptor whose ectodomain is already known to be cleavable is a receptor a gelatinase can, in principle, strip. The second feature is that ApoER2 is not merely a conduit for reelin but a structural participant in the synapse: its cytoplasmic tail couples, through scaffolding adaptors, to the machinery of the postsynaptic density and to the regulation of glutamatergic transmission, so that the loss of ApoER2 from the surface is not only the loss of a reelin dock but a disturbance of the synapse itself.

VLDLR. The very-low-density-lipoprotein receptor is ApoER2's partner and, in the reelin pathway, its complement. It shares the family architecture and the capacity to bind reelin and to transmit the signal inward, but the two receptors are not simple duplicates. The genetics of reelin signalling establish their relationship with unusual clarity: deleting reelin, or deleting the intracellular adaptor Disabled-1, reproduces the *reeler* phenotype of a disordered cortex; deleting *both* ApoER2 and VLDLR reproduces it as well; but deleting *either* receptor alone does not, each leaving a hypomorphic remnant of function the other can partly carry — a redundancy that flows directly from the shared step Hiesberger and colleagues (1999) established, in which reelin binding to *either* receptor drives the tyrosine phosphorylation of Disabled-1 and modulates tau. The two receptors thus back one another up, and the practical consequence for this dissertation is sobering: because the signal survives the loss of one receptor but not of both, a protease that thins *both* receptors from the surface — as an untargeted gelatinase would — is more dangerous to the reelin brake than one that removed a single receptor type. Redundancy protects against the loss of a gene; it does not protect against a blade that cuts the whole family at once.

The N-sulfated heparan sulfate, once more, as the third receptor leg. The two lipoprotein receptors do not fire on reelin alone. As Section II recalled and as the argument now leans upon, reelin requires N-sulfated heparan sulfate as an obligate co-receptor: the sulfated sugar clusters ApoER2 (and, by extension, VLDLR) into the configuration that permits Disabled-1 to be phosphorylated, and removing or de-sulfating the sugar abolishes the signal even with reelin and

receptor both present (Pan and colleagues, 2025). This is worth stating as a matter of stoichiometry, because it changes what counts as the signalling unit. The functional reelin receptor is not a protein but a *complex*: reelin, plus a lipoprotein receptor, plus a chain of N-sulfated heparan sulfate presented on the surface. The sulfation is not a modifier of an otherwise sufficient two-body reaction; it is a constituent of the three-body one. And the specificity is fine — it is the *N*-sulfation, the sulfate on the glucosamine nitrogen, that Pan and colleagues found to carry the co-receptor activity, so that the signal depends not merely on the presence of heparan sulfate but on a particular decoration of it, laid down by particular sulfotransferases and, in principle, removable by particular sulfatases. The reelin brake is staged on a sulfation code as exact as the one by which the perineuronal net holds the plasticity factor Otx2 (Beurdeley and colleagues, 2012).

Disabled-1, the reader that cannot be cut. Downstream of the surface complex sits the one component of the apparatus that lies safely inside the membrane, beyond the reach of any extracellular protease: the cytoplasmic adaptor Disabled-1. It binds the NPxY motif of the receptor tails through its phosphotyrosine-binding domain and, when reelin clusters the receptors, is itself tyrosine-phosphorylated by Src-family kinases; phosphorylated Disabled-1 then recruits phosphoinositide-3-kinase, activating Akt and, through it, inhibiting glycogen-synthase-kinase-3β — the step that holds tau unphosphorylated (Hiesberger and colleagues, 1999). Disabled-1 is, in the strict sense, the *reader* of the reelin signal: its phosphorylation state integrates everything that has happened at the surface — whether reelin is present and untrapped, whether the receptors are on the membrane, whether the sulfated sugar is there to cluster them — into a single output, kinase-suppressed or kinase-released, that determines tau's fate. This is why the finding that matters most in the biomarker literature is not the level of any protein but the *phosphorylation of Disabled-1*, which is reduced in the Alzheimer brain even as reelin protein rises (Cuchillo-Ibáñez and colleagues, 2016). A protease at the surface cannot reach Disabled-1; but it does not need to. By stripping any leg of the surface complex it can drive the reader's output to the kinase-released state from outside, leaving the adaptor intact and simply unfed. The reelin brake fails not because its reader is destroyed but because its reader is starved of the signal the surface can no longer assemble.

Set these four components in a row — two shed-able receptors, one degradable and de-sulfatable sugar, one untouchable but signal-dependent reader — and the target the enzyme will attack comes into focus. Everything reelin needs to reach Disabled-1 is displayed on the outside of the membrane, in the extracellular space, on precisely the surface a secreted gelatinase patrols. The reader is safe; the apparatus that feeds it is not. To the enzyme that patrols that surface we now turn.

IV. The Shears in the Weave

Matrix metalloproteinase-9 is a zinc-dependent endopeptidase of the gelatinase subfamily, secreted as an inactive zymogen and activated at the cell surface by proteolytic removal of its pro-domain. In the healthy brain its expression is low and tightly disciplined; it is called up transiently by neuronal activity and by the machinery of inflammation, and it is held in check by its endogenous inhibitor, tissue inhibitor of metalloproteinases-1, and by the sequestration of the zymogen in the matrix itself. What makes it the protagonist of this dissertation is the breadth of its substrate list, which reads, uncannily, like an inventory of the three offices the sulfated matrix performs.

Before that list is read, the discipline of the enzyme must be described, because it is the failure of that discipline, and not the mere existence of the enzyme, that the disease exploits. MMP-9 is secreted as an inactive zymogen, pro-MMP-9, whose pro-domain occludes the catalytic zinc; it becomes dangerous only when that pro-domain is removed, a step performed at the cell surface by other proteases in an activation cascade, and it is restrained even then by its endogenous inhibitor, tissue inhibitor of metalloproteinases-1, which the same catecholamine stimuli that induce the enzyme also modulate (Speidl and colleagues, 2004). The healthy brain therefore holds three separate brakes on the enzyme's matrix-cutting: it transcribes little of it, activates little of what it transcribes, and inhibits much of what it activates. Alzheimer's disease loosens all three brakes at once — it raises the transcriptional drive, as this dissertation will argue, through the noradrenergic and inflammatory signals that converge on the MMP-9 promoter; it raises the activation, as in the apolipoprotein-E-ε4 brain where the cyclophilin-A pathway drives the gelatinase to activity at the vasculature (Montagne and colleagues, 2020); and it tips the inhibitor balance toward the enzyme. The result is not a new enzyme but an old one off its leash. The shears were always in the drawer; the disease is the hand that takes them out and forgets to put them back.

MMP-9 cleaves the core proteins of the perineuronal net. The lattice of the net is built of lecticans — aggrecan, brevican, neurocan, versican — hung on a hyaluronan backbone and cross-linked by tenascin-R. These chondroitin-sulfate proteoglycans are metalloproteinase substrates, and MMP-9 is among the proteases that degrade them: in a model of noise-induced cortical remodeling, elevated MMP-9 expression tracked with, and is inferred to have driven, the loss of brevican from the perineuronal nets of the auditory cortex (Park and colleagues, 2020). Where MMP-9 rises, the lectican scaffold thins. This is the first office — the structural shield — cut.

MMP-9 sheds the heparan-sulfate proteoglycans that carry reelin's co-receptor sugar. The N-sulfated heparan sulfate that reelin requires (Pan and colleagues, 2025) is not free in solution; it is carried on the core proteins of cell-surface proteoglycans — the syndecans and glypicans — and on secreted proteoglycans of the matrix. The ectodomains of syndecan-1 and syndecan-4 are cleaved by tumour-associated matrix metalloproteinases, and MMP-9 and its sister

gelatinase MMP-2 cut them at defined membrane-proximal sites, releasing the heparan-sulfate-bearing ectodomain into solution (Manon-Jensen and colleagues, 2013). To shed a syndecan ectodomain is to remove from the neuronal surface the very sulfated sugar on which reelin's clustering of ApoER2 depends — and, moreover, to convert a surface-anchored co-receptor into a soluble decoy that may bind reelin away from the membrane where it can do its work. This is the second office — the reelin-staging bed — cut.

MMP-9 strips the lipoprotein receptors from the surface. The receptors of the low-density-lipoprotein-receptor family are susceptible to proteolytic shedding of their ectodomains, and MMP-9 is an enzyme that performs it. At the blood–brain barrier, MMP-9 dose-dependently elevates the shedding of lipoprotein receptors from brain endothelial cells and isolated cerebral vessels, and inhibiting MMP-9 mitigates the amyloid-β-induced shedding of those receptors (Shackleton and colleagues, 2019). ApoER2 and VLDLR are members of that same family; ApoER2, indeed, is known to undergo regulated proteolytic cleavage that liberates a soluble ectodomain, and the abundance of that soluble ectodomain in cerebrospinal fluid serves as a read-out of reelin-signalling efficiency (López-Font and colleagues, 2018). An enzyme that sheds the family sheds, in principle, the reelin receptors — and if it does, it does not merely degrade the sugar that helps reelin fire; it removes the receptor that fires. This is the third office — the reelin apparatus itself — cut.

Set the three substrate classes together and the enzyme's reach is total. One protease can degrade the lectican shield, shed the heparan-sulfate co-receptor bed, and strip the lipoprotein receptors — the structural, the staging, and the signalling components of the guarded surface — because all three are proteins, and all three are within its catalogue. MMP-9 is not merely *a* matrix-degrading protease; it is, of the proteases the microglia unleash, the one whose substrate list maps most exactly onto the three offices *The Architect's Scaffold* proved the matrix to hold. It is the specific shears the general argument implied.

And yet the enzyme is not a villain by nature, and the dissertation is obliged to say so before it proceeds, because the fact will return to complicate every therapeutic inference. MMP-9 is *required* for the late phase of hippocampal long-term potentiation and for the consolidation of hippocampal-dependent memory: stimuli that induce late long-term potentiation rapidly raise MMP-9 activity, its pharmacological blockade selectively prevents that late potentiation, MMP-9-null mice are impaired in both the potentiation and the memory, and adding recombinant active enzyme to the null slices restores the deficit (Nagy and colleagues, 2006). The very capacity that makes MMP-9 dangerous — its remodeling of the matrix at the synapse — is the capacity that makes learning possible. The enzyme is a tool of plasticity turned, in the disease, into an instrument of ruin. It is the same shears that tailor the garment and cut it to rags; what changes is the hand, and the discipline, that guides them.

V. The Enzyme That Unstages Reelin

The claim on which this dissertation turns can now be stated in its strong form. If reelin's brake on tau is chemically dependent on the sulfated matrix — if the heparan sulfate is an obligate co-receptor and the receptors are shed-able — then the activation of MMP-9 does not merely thin the structural net. It *unstages the reelin signal*: it degrades the co-receptor bed the signal requires and sheds the receptors the signal fires, silencing the tau-brake at its source. The withdrawal of reelin's protection in Alzheimer's disease, on this reading, need not await the loss of reelin protein. It can be accomplished by the destruction of the surface on which reelin acts, with the reelin molecule still present and simply unable to signal.

This prediction has an unexpected confirmation waiting for it in the cerebrospinal-fluid biomarker literature, developed by a community — the group of Sáez-Valero and colleagues in Alicante — working on reelin proteolysis in complete independence of the perineuronal-net field. Their data draw, from the fluid, precisely the picture the matrix argument predicts.

Reelin protein rises in the Alzheimer brain even as the reelin signal falls. Reelin messenger RNA and both soluble and insoluble reelin protein increase with advancing Braak stage in the frontal cortex, while the expression of ApoER2 does not change — and yet reelin-dependent phosphorylation of Disabled-1 is *reduced* in the disease (Cuchillo-Ibáñez and colleagues, 2016). More reelin, less reelin signal. The mechanism the Alicante group identifies is that amyloid-β co-aggregates with reelin and traps it, and reduces reelin's capacity to induce the internalization and processing of ApoER2. This is the "rising-reelin paradox" that *The Architect's Reprieve* named from the genetics; here it is measured biochemically. It is the exact signature of a signal failing not for want of ligand but for want of a functional surface on which the ligand can act — and the destruction of that surface is what MMP-9 accomplishes.

The receptor's own cleavage is a read-out of the signal, and it is deranged in disease. Reelin binding to ApoER2 induces the proteolytic cleavage of the receptor, liberating a soluble ectodomain fragment into the cerebrospinal fluid; the abundance of that fragment reports on how much reelin signalling is occurring. In sporadic Alzheimer's disease the soluble ectoApoER2 fragment is reduced by roughly a third and the reelin-to-fragment ratio is raised — reelin present, receptor cleavage diminished, signal impaired (López-Font and colleagues, 2018). And the balance of reelin's own proteolytic fragments is disturbed: full-length reelin falls, the pattern of its N- and C-terminal cleavage products shifts, and an aberrant high-molecular-weight reelin species appears in the fluid of Alzheimer patients that is absent from controls; the ApoER2 fragments, moreover,

are lower in apolipoprotein-E ε4 carriers than in ε3 homozygotes (López-Font and colleagues, 2022). The detectability of altered reelin fragments in the fluid of neurodegeneration is not new — a 180-kilodalton reelin fragment was found raised in the cerebrospinal fluid of Alzheimer's and frontotemporal dementia two decades ago (Sáez-Valero and colleagues, 2003) — but the recent resolution of the fragment pattern shows a system in which both the ligand and the receptor are being proteolytically remodeled in the disease, and remodeled in the direction of a weaker signal.

The matrix argument supplies the connective tissue these biomarker studies do not claim. The Alicante group attributes the impaired signalling chiefly to amyloid's trapping of reelin, and that mechanism is real. But the same disease that traps reelin also activates the protease that degrades the co-receptor bed and sheds the receptors — and a signal can be extinguished from either end. If MMP-9 sheds ApoER2, then the soluble ectoApoER2 in the fluid has two possible parentages: the *signalling* cleavage that follows reelin binding, which reports protection at work, and a *destructive* shedding by the metalloproteinase, which reports the receptor being stripped from the surface. That the total soluble fragment falls in sporadic disease while reelin cannot induce its own receptor's processing suggests that the signalling cleavage collapses faster than any destructive shedding can compensate — the surface, in other words, is failing. This dissertation does not claim to have separated the two parentages; it claims that the matrix perspective predicts their entanglement, and that the resolution of destructive from signalling ectoApoER2 in the cerebrospinal fluid is a decisive experiment the two literatures, read together, now demand.

One complication must be faced squarely, because it is the kind of objection an honest synthesis raises against itself, and because facing it sharpens rather than blunts the argument. The very sulfated surface whose degradation silences reelin is *also* the surface through which tau enters the neuron: pathological tau is internalized by binding heparan-sulfate proteoglycans (Holmes and colleagues, 2013), the same class of sugar that reelin's clustering of ApoER2 requires (Pan and colleagues, 2025). If MMP-9 sheds that heparan sulfate from the surface, then by the identical action it should not only unstage reelin but *remove tau's doorway* — degrading the co-receptor bed ought, on its face, to protect against tau uptake even as it disables the reelin brake. Does the cascade therefore contain its own antidote?

It does not, and the reasons it does not are instructive. First, the two effects are not symmetrical in permanence: reelin's brake is a continuous, cell-autonomous suppression of a kinase that must be held down at every moment, so that any interruption of the signal releases tau phosphorylation *within* the neuron immediately and indefinitely, whereas the surface's gating of tau *entry* matters only at the moments a seed happens to arrive from outside. To trade a permanent internal brake for an intermittent external barrier is a bad bargain. Second, the shedding of syndecan ectodomains does not abolish surface heparan sulfate so much as *solubilize* it, converting a membrane-anchored, receptor-clustering co-receptor into a diffusible fragment that may still bind tau — and may even ferry it — while no longer serving reelin (Manon-Jensen and colleagues, 2013). Third, and

decisively, the internal generation of hyperphosphorylated tau that follows reelin's silencing does not depend on any doorway at all: a neuron whose glycogen-synthase-kinase-3β is disinhibited makes its own tangle from its own tau, seeded from within, and then becomes a *source* of seeds for its neighbours rather than merely a target of theirs. The cut that opens the door also lights the fire inside the room; closing the door does not help once the fire is lit. The double-edge is real, and it is the reason the net effect still runs toward pathology — a subtlety the synthesis exposes precisely because it holds the reelin and the tau-propagation literatures in the same hand.

There is, finally, a caution this section must state and not bury, because it is the load-bearing honesty of the whole enzymatic argument. It is not established that MMP-9 cleaves reelin *itself*. The proteases identified in the direct processing of reelin are serine proteases and members of the ADAMTS family, not the gelatinases; the reelin fragments in the cerebrospinal fluid are the work, so far as the evidence shows, of enzymes other than MMP-9. The dissertation's claim is therefore precise and bounded: MMP-9 unstages reelin by degrading the *surface on which reelin acts* — the sulfated bed and the shed-able receptors — and not, on present evidence, by cutting the reelin molecule. Whether MMP-9 also contributes to the direct proteolysis of reelin is an open question the ledger will mark as unproven. The strength of the argument does not require it. To silence a signal it suffices to dismantle its receiver; one need not also destroy the transmitter.

VI. The Hand on the Shears

An enzyme is only as dangerous as the signal that calls it up. MMP-9 is transcriptionally quiet in the resting brain; its danger in Alzheimer's disease is a danger of *induction*, and the question this dissertation was written to answer is what does the inducing. The conventional answer — amyloid, through microglial activation — is true and incomplete. It is incomplete because it treats the protease as the terminus of a one-way street from the plaque, and thereby misses a controller that acts upstream of, and in parallel to, the amyloid signal, and that fails earlier than amyloid in the natural history of the disease: the noradrenergic output of the locus coeruleus.

Norepinephrine drives the transcription of MMP-9. The catecholamines are inducers of gelatinase B. In human monocytes and macrophages, epinephrine and norepinephrine up-regulate matrix metalloproteinases and potentiate their inflammatory induction, acting through β-adrenergic receptors and raising the enzyme's messenger RNA, antigen, and activity by enhancing the DNA binding of the transcription factor AP-1 (Speidl and colleagues, 2004). Noradrenaline induces MMP-9 gene expression through the β2-adrenergic receptor by way of the cyclic-AMP–protein-kinase-A, mitogen-activated-protein-kinase, and NF-κB pathways, and

blocking any of those relays abolishes the induction (Yamazaki and colleagues, 2014). The signalling logic is canonical and generalizable: β-adrenergic engagement raises cyclic AMP, activates protein kinase A, and mobilizes the AP-1 and NF-κB transcription factors that occupy the MMP-9 promoter. Wherever a cell bears β-adrenergic receptors and the capacity to make MMP-9, norepinephrine is, in principle, a switch upon the enzyme.

The brain's matrix-remodeling cells bear exactly those receptors. Microglia and astrocytes — the cellular sources of MMP-9 in the inflamed brain, and the very microglia that *The Architect's Scaffold* and Crapser and colleagues (2020) showed engulfing the perineuronal net — express β-adrenergic receptors and are transcriptionally responsive to noradrenergic tone. This is where the dissertation must be scrupulous, and is: the direct demonstration that norepinephrine induces MMP-9 has been made in peripheral cells — monocytes, macrophages, tumour lines — and not, to the resolution the argument would like, in brain microglia in situ. The step from the periphery to the parenchyma is an inference from shared receptor biology and shared promoter architecture, not a proven identity, and the ledger will grade it as such. But the inference is not idle. It predicts that the noradrenergic state of the cortex is a determinant of the matrix-degrading load upon it, and that prediction is testable.

A paradox of sign, and its resolution. An objection presents itself here, and it must be met, because the noradrenergic literature is famous for a result that seems to point the opposite way: tonic norepinephrine is broadly *anti*-inflammatory in the brain, restraining microglial activation, and it is the *loss* of coerulean norepinephrine — not its excess — that is classically held to disinhibit neuroinflammation as the locus coeruleus degenerates. How can the same transmitter both restrain microglia and drive their matrix-degrading protease? The resolution is that norepinephrine's sign is not fixed; it is a function of concentration, of receptor subtype, and of temporal pattern. Steady, moderate tone acting through the higher-affinity α- and β-receptor complement holds glia quiescent; but the pathological coerulean state is not steady moderate tone. It is dysregulation — bursts and troughs, the compensatory hyperactivity and adrenoceptor up-regulation documented in the pretangle model (Ghosh and colleagues, 2019), superimposed on a background of failing supply — and it is exactly such excess, and such β-receptor engagement, that the metalloproteinase literature shows to *potentiate* the inflammatory induction of MMP-9 rather than to suppress it (Speidl and colleagues, 2004). The tonic-anti-inflammatory and the phasic-pro-proteolytic roles are therefore not contradictory but sequential and dose-dependent: the healthy nucleus, firing in disciplined patterns, keeps the glia calm; the sickening nucleus, firing in deranged excess before it falls silent, drives the very protease the calm had prevented. This dissertation's claim attaches specifically to the deranged phase, and the objection, correctly stated, becomes one of its predictions — that it is dysregulated and not physiological noradrenergic signalling that raises cortical MMP-9.

The noradrenergic supply in Alzheimer's disease is not merely lost; it is, for a long interval, dysregulated upward. The naïve expectation — that because the locus

coeruleus degenerates, cortical norepinephrine simply declines — is only the endgame of a more complicated trajectory. Before the nucleus is lost, its surviving neurons and their terminals pass through a phase of compensatory hyperactivity: as coerulean neurons drop out, the survivors increase their firing and their synthetic enzymes, and the remaining terminals sprout and up-regulate their machinery, so that for a protracted preclinical and early-clinical interval the cortex may be exposed to *excess* noradrenergic drive and to up-regulated adrenoceptors. In a rat model of the coerulean pretangle, the expression of β1-adrenoceptors was up-regulated as the pathology advanced (Ghosh and colleagues, 2019). The disease thus opens a window in which noradrenergic signalling is not withdrawn but deranged and, in places, amplified — and it is amplification, not withdrawal, that the MMP-9 promoter reads. The hand does not fall slack at the outset. For years it tightens on the shears.

The same excess drives the tau kinase directly. Here the two arms of norepinephrine's malignancy converge on a single molecule, and the convergence is the analytic heart of this dissertation. Chronic exposure of the brain to excessive norepinephrine — produced experimentally by blocking its reuptake — induces tau aggregation, hippocampal neuronal death, and cognitive deficits in tau-transgenic mice, and it does so by *over-activating protein kinase A and glycogen-synthase-kinase-3β*, driving the hyperphosphorylation of tau; human brain organoids exposed to higher norepinephrine concentrations reproduce the elevated phospho-tau and the same kinase activation (Jeong and colleagues, 2024). Read that result beside the reelin cascade of Section II and the antagonism is exact. Reelin signals through Disabled-1 and Akt to *inhibit* glycogen-synthase-kinase-3β and hold tau unphosphorylated; excessive norepinephrine *activates* the same kinase and drives tau into the tangle. Norepinephrine and reelin are opponents at one enzyme. The neuromodulator whose dysregulated excess switches on the protease that dismantles reelin's staging surface is the same neuromodulator whose excess, at the kinase, pushes the reaction reelin was restraining.

The hand on the shears, in other words, does two things with the one motion. It calls up the enzyme that cuts the surface staging reelin's brake, and it directly presses on the accelerator reelin's brake was resisting. Whether it cuts the brake or floors the throttle, the result at the tangle is the same, and the two effects are additive. This is why the noradrenergic contribution to the reelin axis cannot be read as a single arrow. It is a pincer.

VII. The Coerulean Paradox

If the hand that guides the shears belongs to the locus coeruleus, then the deepest irony of the whole cascade is anatomical, and it was written into the brain long before the disease began. The locus coeruleus has no perineuronal net.

The subcortical survey that first established the net's protection made the point in passing, and it has waited two decades for its full significance to be read. The nuclei attacked earliest and hardest by tau — the locus coeruleus, the nucleus basalis of Meynert, the raphe, the dorsal tegmentum — are precisely the nuclei *devoid* of an aggrecan-based perineuronal matrix, while net-ensheathed neurons even in the thick of the pathology rarely tangle (Morawski and colleagues, 2010). The locus coeruleus is thus, by its native constitution, an unguarded neuron: it lacks the sulfated shield that Section II showed to resist the tangle, it lacks the reelin-staging bed, and its long, thin, unmyelinated, massively arborizing axons expose an enormous membrane surface to whatever the extracellular space contains. It is, of all the brain's nuclei, among the least defended — and it is the first to fall.

The natural history follows from the geometry. The earliest tau pathology in the human brain — the pretangle, hyperphosphorylated soluble tau — appears in the locus coeruleus, in young adults, decades before dementia, and spreads from there along the coerulean projections to the other neuromodulatory nuclei and, later, to the cortex (Ghosh and colleagues, 2019; Giorgi and colleagues, 2017). The nucleus that supplies the cortex with norepinephrine is the nucleus in which Alzheimer's disease, on the pretangle timeline, begins. Its degeneration is an early and underappreciated feature of the pathology, and the loss of its noradrenergic supply has functional consequences across every cortical and subcortical territory its axons reach (Weinshenker, 2008). Because those axons spread norepinephrine over the whole forebrain from a single small source, the dysregulation of that source is not a local event; it is broadcast, along the same arbor down which the tau itself is proposed to travel (Giorgi and colleagues, 2017).

Assemble the pieces and the paradox is complete. The locus coeruleus, unprotected because it never wore a net, tangles first. As it sickens, its output is dysregulated — amplified for years before it collapses — and that amplified noradrenergic drive, broadcast across the cortex, switches on MMP-9 in the microglia and astrocytes of the very territories the reelin-bearing net protects. The protease unpicks the sulfated surface, shedding the co-receptor bed and the receptors, unstaging reelin's brake on tau; and the same noradrenergic excess, arriving at the same neurons, over-activates the kinase reelin was restraining. Tau, released on both counts, tangles in the cortex — and the cortical tangling further compromises the network feedback that might have disciplined the failing locus coeruleus, which sickens further, and dysregulates further, and drives the shears harder. The nucleus that ought to be the cortex's defender becomes, through the enzyme it calls up and the kinase it drives, the operator of the cortex's undoing.

This corpus has met the shape of this tragedy once before. In *The Glymphatic Collapse* the locus coeruleus was named the arsonist that also operates the sprinkler — the noradrenergic switch that governs the clearance system whose failure it causes. The present dissertation finds the same nucleus at the same double station in a different building. Here it is not the sprinkler but the loom: the locus coeruleus operates the shears that cut the weave it should have helped to keep whole. That one small blue nucleus should sit at the control point of two distinct resilience systems — the glymphatic clearance of the interstitium and the reelin-staging of the perineuronal matrix — and should, in its dysregulation, disable both, is either a coincidence of two independent accidents or a sign that the noradrenergic system is a master regulator of the brain's protective housekeeping whose early failure has been systematically underweighted. This dissertation takes the second view, and offers the reelin-matrix cut as its second instance.

VIII. One Cascade, Assembled

It is time to set the whole chain down as a single sequence, so that its structure and its seams are both visible at once. The cascade runs in seven steps, from the earliest lesion to the tangle, and each step has been given its evidence above.

First, the locus coeruleus, constitutionally without a perineuronal net (Morawski and colleagues, 2010), accumulates the pretangle earliest of any structure in the brain and begins to degenerate (Ghosh and colleagues, 2019; Giorgi and colleagues, 2017; Weinshenker, 2008).

Second, the sickening nucleus dysregulates its noradrenergic output — for a protracted interval upward, with compensatory hyperactivity and adrenoceptor up-regulation (Ghosh and colleagues, 2019) — and broadcasts that deranged signal across the cortex along its diffuse arbor.

Third, the excess noradrenergic tone, acting through β-adrenergic receptors on cortical microglia and astrocytes by the cyclic-AMP–protein-kinase-A–AP-1 and NF-κB pathways, induces the transcription and activation of MMP-9 (Speidl and colleagues, 2004; Yamazaki and colleagues, 2014).

Fourth, activated MMP-9 degrades the three offices of the sulfated surface: it cleaves the lectican core proteins of the perineuronal net (Park and colleagues, 2020), sheds the heparan-sulfate-bearing syndecan ectodomains that carry reelin's obligate co-receptor sugar (Manon-Jensen and colleagues, 2013; Pan and colleagues, 2025), and strips lipoprotein receptors of the ApoER2/VLDLR family from the surface (Shackleton and colleagues, 2019).

Fifth, with its co-receptor bed degraded and its receptors shed, the reelin signal fails at the surface even where reelin protein persists — the biochemical rising-reelin paradox, with reduced Disabled-1 phosphorylation and deranged ectoApoER2 in the fluid (Cuchillo-Ibáñez and colleagues, 2016; López-Font and colleagues, 2018, 2022).

Sixth, the failure of the reelin signal releases glycogen-synthase-kinase-3β from inhibition (Hiesberger and colleagues, 1999; Kocherhans and colleagues, 2010) — and the same noradrenergic excess, arriving at the same neurons, over-activates that kinase directly (Jeong and colleagues, 2024), so that the tau kinase is disinhibited from one side and pressed from the other.

Seventh, tau is hyperphosphorylated and aggregates, and the tangle propagates from neuron to neuron across the sulfated surface whose degradation has stripped away the last barrier to its uptake (Holmes and colleagues, 2013) — and the cortical pathology so produced feeds back upon the failing coeruleus, closing the loop.

Two amplifiers run alongside this spine and must be entered into the account, because they connect the cascade to the disease's dominant genetic and cellular drivers and show that the noradrenergic relay is not an isolated curiosity but a convergence point.

The amyloid–microglial amplifier. Amyloid-β activates the microglia that engulf the net (Crapser and colleagues, 2020) and traps reelin directly (Cuchillo-Ibáñez and colleagues, 2016), so that the plaque and the noradrenergic drive push the same protease and the same surface in the same direction. The two inputs are additive upon MMP-9 and upon the failure of reelin, and neither excludes the other. Amyloid is the amplifier the field already knows; norepinephrine is the amplifier it has overlooked, and the earlier of the two.

The apolipoprotein-E amplifier. The genetic engine of sporadic Alzheimer's disease enters the cascade at the metalloproteinase. In apolipoprotein-E ε4 carriers, breakdown of the blood–brain barrier proceeds through an accelerated cyclophilin-A–MMP-9 pathway and predicts cognitive decline independently of amyloid and tau (Montagne and colleagues, 2020); and the amyloid-induced shedding of lipoprotein receptors by MMP-9 is itself apolipoprotein-E-isoform-dependent, strongest in the ε4 background (Shackleton and colleagues, 2019). The reelin biomarker data close the ring: soluble ectoApoER2 is lower in ε4 carriers than in ε3 homozygotes (López-Font and colleagues, 2022). The ε4 allele, that is, raises the MMP-9 tone that unstages reelin — which is why the resilience conferred by the two famous protective variants, the *APOE3*-Christchurch and the *RELN*-COLBOS, both read on this same surface. Christchurch loosens the apolipoprotein-E grip on heparan sulfate that would otherwise spread tau (Arboleda-Velasquez and colleagues, 2019); COLBOS tightens the reelin grip on heparan sulfate that brakes it (Lopera and colleagues, 2023; Pan and colleagues, 2025). Both act on the sulfated surface this cascade dismantles. The protective genotypes defend the weave; the ε4 genotype hands the shears an extra measure of drive.

The order of events, and why it matters. The distinctive claim of this cascade is not only mechanistic but *chronological*, and the chronology is what makes it worth stating separately from the amyloid account. The lesions it strings together are not simultaneous; they are ordered, and the order runs from the earliest detectable pathology in the human brain to the clinical disease. The coerulean pretangle appears first — in young adults, decades before dementia, at Braak's pretangle stages that precede the cortical tangles entirely (Ghosh and colleagues, 2019; Giorgi and colleagues, 2017). The noradrenergic dysregulation it produces, and the compensatory hyperactivity that raises the adrenergic drive, belong to the long preclinical and prodromal interval — the same interval in which, by every account in this corpus's temporal architecture, the disease is being *decided* rather than merely expressed. The MMP-9 induction, the matrix degradation, and the unstaging of reelin therefore fall into the window before dementia, upstream of the frank cortical tangle and of the amyloid plaque's maturation, at a time when the surface is still mostly whole and the intervention still mostly possible. This is why the cascade cannot be dismissed as a late epiphenomenon of end-stage neurodegeneration: its first two steps are, on the pretangle timeline, among the earliest events in the entire disease, and its middle steps fall in the resilience window that the *APOE3*-Christchurch and *RELN*-COLBOS carriers survived. The synthesis places a druggable enzymatic relay precisely where the disease is still contestable — and dates it, which the anonymous "matrix degradation" of the earlier accounts never could.

The cascade, assembled, is therefore not a rival to the amyloid and apolipoprotein-E accounts of Alzheimer's disease but a mechanism that threads through them — locating, between the earliest lesion and the tangle, a specific enzymatic relay under noradrenergic and genetic control, acting on a surface whose protective offices the companion dissertations had already established. Its distinctive contribution is to make the destruction of that surface a named, timed, and in principle interruptible event rather than an anonymous consequence.

IX. 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. The cascade of Section VIII is only as strong as its weakest load-bearing link, and the reader is owed an explicit accounting of where the argument stands on the ground and where it stands on inference.

Strong (imported, established) — reelin restrains tau through ApoER2/VLDLR, Disabled-1, and glycogen-synthase-kinase-3β, and requires N-sulfated heparan sulfate to signal. Biochemically and genetically secure (Hiesberger and colleagues, 1999;

Kocherhans and colleagues, 2010; Pan and colleagues, 2025), and imported intact from the companion dissertations. This is the receiver whose dismantling the cascade describes.

Strong (imported, established) — pathological tau is internalized and propagated via heparan-sulfate proteoglycans, and net-poor nuclei tangle earliest. Reproducible across systems (Holmes and colleagues, 2013) and consistent with the subcortical vulnerability map (Morawski and colleagues, 2010). The locus coeruleus's want of a net is a matter of record, not of inference.

Strong — MMP-9 is required for synaptic plasticity and remodels the matrix at the synapse. Directly demonstrated with pharmacology, genetics, and rescue (Nagy and colleagues, 2006). This establishes both the enzyme's competence at the neuronal surface and the double-edge that complicates its inhibition.

Strong — MMP-9 and MMP-2 shed the ectodomains of heparan-sulfate proteoglycans and of lipoprotein receptors. Shown at defined cleavage sites for syndecan-1 and -4 (Manon-Jensen and colleagues, 2013) and for lipoprotein-receptor-family members at the blood–brain barrier (Shackleton and colleagues, 2019). The enzyme's competence against the reelin-staging surface's components is established; the specific competence against ApoER2 and VLDLR is inferred from family membership (see below).

Strong (biomarker) — reelin signalling is impaired in Alzheimer's disease despite preserved or elevated reelin protein. Measured directly: reduced Disabled-1 phosphorylation with rising reelin (Cuchillo-Ibáñez and colleagues, 2016), reduced soluble ectoApoER2 in sporadic disease (López-Font and colleagues, 2018), and a deranged reelin-fragment balance with an aberrant species unique to patients (López-Font and colleagues, 2022; Sáez-Valero and colleagues, 2003). The signature of a signal failing at the surface is present in the fluid.

Moderate — MMP-9 degrades the lectican core proteins of the perineuronal net in the brain. Supported by the association of elevated MMP-9 with brevican loss from cortical nets (Park and colleagues, 2020), and consistent with the microglial net-degradation model (Crapser and colleagues, 2020); but the Park demonstration is a non-disease remodeling paradigm, and a direct demonstration that MMP-9 cleaves the aggrecan of the Alzheimer net remains to be made. *Settling experiment: quantify perineuronal-net integrity and reelin-dependent Disabled-1 phosphorylation in the Alzheimer cortex under genetic or pharmacological MMP-9 loss.*

Moderate — the apolipoprotein-E ε4 allele raises the MMP-9 tone that unstages reelin. Supported convergently by the cyclophilin-A–MMP-9 barrier pathway (Montagne and colleagues, 2020), the ε4-dependence of MMP-9 receptor shedding (Shackleton and colleagues, 2019), and the lower ectoApoER2 in ε4 carriers (López-Font and colleagues, 2022). The three lines agree; none was designed to test the reelin-staging claim directly.

Moderate-to-plausible — norepinephrine induces MMP-9 in the brain through β-adrenergic receptors on microglia and astrocytes. The induction is directly shown in peripheral cells (Speidl and colleagues, 2004; Yamazaki and colleagues, 2014) and the receptor and promoter biology are shared by brain glia, but the in-situ demonstration in cortical microglia is not yet in hand. This is the single most important step to nail. *Settling experiment: measure cortical MMP-9 expression and perineuronal-net integrity under chronic β-adrenergic agonism and antagonism, and in locus-coeruleus-lesioned versus intact animals.*

Plausible — dysregulated (transiently elevated) noradrenergic tone in early Alzheimer's disease supplies that induction. The compensatory-hyperactivity phase and adrenoceptor up-regulation are documented (Ghosh and colleagues, 2019), and excessive norepinephrine drives tau via protein kinase A and glycogen-synthase-kinase-3β (Jeong and colleagues, 2024); the linkage of that excess specifically to cortical MMP-9 and net loss is the cascade's central prediction, not yet a measured fact.

Plausible — MMP-9 sheds ApoER2 and VLDLR specifically, contributing a destructive parentage to the soluble ectoApoER2 pool. Inferred from lipoprotein-receptor-family shedding (Shackleton and colleagues, 2019) and the established shed-ability of ApoER2 (López-Font and colleagues, 2018); not yet demonstrated for these two receptors by this enzyme. *Settling experiment: resolve signalling from destructive ectoApoER2 fragments in cerebrospinal fluid, and test MMP-9 cleavage of ApoER2/VLDLR directly.*

Plausible (net direction) — degrading the sulfated surface harms more than it helps, despite removing tau's entry route. Because tau enters neurons via heparan-sulfate proteoglycans (Holmes and colleagues, 2013), shedding that sugar might be expected to protect; the cascade argues the net effect runs the other way, because reelin's brake is a continuous cell-autonomous suppression whose loss releases tau from within, whereas the surface's gating of entry is intermittent, and because shed heparan sulfate is solubilized rather than abolished (Manon-Jensen and colleagues, 2013). The balance of these opposing effects has not been measured directly. *Settling experiment: quantify both reelin-dependent Disabled-1 phosphorylation and transcellular tau uptake in the same neurons across a graded degradation of the surface.*

Not established (and not required) — MMP-9 cleaves reelin itself. The proteases known to process reelin are serine proteases and ADAMTS-family metalloproteinases, not the gelatinases; no evidence places MMP-9 on the reelin molecule. The cascade explicitly does not depend on this: it silences reelin by dismantling the receiving surface, not the ligand. The claim is entered here as a boundary, so that the argument is not credited with more than it asserts.

Rejected as stated — norepinephrine loss alone explains the noradrenergic contribution. The simple "coeruleus degenerates, norepinephrine falls, protection lost" model does not fit the promoter biology, which reads amplification, not withdrawal; the pathogenic

window is one of noradrenergic *excess and derangement*, with terminal depletion a late event (Ghosh and colleagues, 2019; Jeong and colleagues, 2024). The naïve deficiency model is not supported; the dysregulation model is.

X. Predictions and Falsification

The cascade risks a series of specific predictions, each of which could be shown false, and the willingness to name them is the price of proposing the synthesis at all.

- Lesioning or silencing the locus coeruleus, or blocking β-adrenergic signalling, will *reduce* cortical MMP-9 expression, spare the perineuronal net, and preserve reelin-dependent Disabled-1 phosphorylation in a tauopathy model; conversely, chronic β-adrenergic agonism or norepinephrine-reuptake blockade will raise cortical MMP-9, degrade the net, and depress reelin signalling. Should noradrenergic manipulation leave cortical MMP-9 and net integrity unchanged, the hand-on-the-shears claim is severed at its most important joint.
- Genetic or pharmacological loss of MMP-9 will preserve reelin-dependent Disabled-1 phosphorylation and reduce tau pathology in the face of an intact amyloid burden, mirroring the resilient brains. If MMP-9 loss thins tau pathology only by clearing amyloid, and not by preserving reelin signalling on a spared surface, the "unstaging" mechanism is wrong and the enzyme's relevance is confined to amyloid catabolism.
- The soluble ectoApoER2 pool of the cerebrospinal fluid will resolve into a signalling-derived fraction (reelin-binding-dependent, reporting protection) and a destructive fraction (metalloproteinase-derived, reporting surface stripping), and the destructive fraction will rise with MMP-9 activity while the signalling fraction falls with disease. A single-parentage ectoApoER2 that tracks only reelin binding would refute the destructive-shedding limb.
- Across brain regions and across individuals, cortical MMP-9 tone will predict perineuronal-net loss and reelin-signalling failure better than local amyloid burden alone, and the noradrenergic innervation density of a region will modulate that relationship. A region of high amyloid, high net integrity, and preserved reelin signal despite high MMP-9 would bound the cascade.
- The protective variants will continue to read on the sulfated surface, and the ε4 allele will continue to read on the MMP-9 tone: any newly discovered resilience factor in the *PSEN1*-E280A kindred will act on matrix sulfation, on a ligand that reads it, or on the protease that degrades it, rather than elsewhere. A resilience mechanism wholly independent

of this surface and this enzyme would mark the edge of the synthesis's reach.

- Interventions that protect the sulfated surface — matrix-sparing MMP-9 modulation, sulfation-directed agents, or reelin-pathway agonism — will spare tau while leaving amyloid largely intact, and will do so more effectively when applied before the locus coeruleus has collapsed and the noradrenergic drive has passed from excess into depletion. A benefit that appears only after coerulean collapse, or that clears amyloid without touching tau, would overturn the placement of this axis.
- The soluble, MMP-shed heparan-sulfate ectodomains predicted by the cascade will be detectable in the cerebrospinal fluid and will rise with disease and with MMP-9 activity, tracking net loss rather than net preservation; and the ratio of soluble to surface-bound heparan sulfate will correlate inversely with reelin-dependent Disabled-1 phosphorylation. Should surface heparan sulfate be preserved where reelin signalling has already failed, the co-receptor-stripping limb would be weakened relative to the receptor-shedding and ligand-trapping limbs.
- Because ApoER2 and VLDLR are partially redundant, animals lacking one receptor will show a reelin signal more easily extinguished by MMP-9 activation than wild-type animals, and doubly vulnerable where both are already reduced; conversely, reinforcing surface receptor density should buffer the signal against a given metalloproteinase load. A reelin signal indifferent to receptor gene dosage under protease stress would argue that surface receptor availability is not the limiting variable the cascade assumes it to be.

XI. Therapeutic Corollaries — Stilling the Shears Without Staying the Hand That Mends

If the destruction of reelin's staging surface is the work of a named enzyme under a named drive, then targets present themselves that the anonymous "matrix-degrading protease" of the earlier synthesis could not offer: the protease, the drive that calls it up, and the inhibitor balance that should have held it in check. Each is real, and each is booby-trapped, and the value of naming them is as much in the traps exposed as in the targets gained.

The protease. MMP-9 inhibition is a rational aspiration: to still the shears is to spare the sulfated surface, preserve the co-receptor bed and the receptors, and keep reelin's brake staged. The barrier-protective and receptor-sparing benefits of MMP-9 inhibition are already demonstrated — SB-3CT, an MMP-9 inhibitor, mitigates the amyloid-induced shedding of lipoprotein receptors and improves amyloid clearance in the ε4 background (Shackleton and colleagues, 2019), and the

cyclophilin-A–MMP-9 pathway is an explicit therapeutic target in ε4 carriers (Montagne and colleagues, 2020). But the same enzyme is required for the late phase of long-term potentiation and for memory consolidation (Nagy and colleagues, 2006), and it is one of the brain's degraders of amyloid-β itself (Hernandez-Guillamon and colleagues, 2015). To abolish MMP-9 is thus to risk abolishing a mechanism of learning and a route of amyloid clearance in order to save a mechanism of resilience. The design constraint the synthesis exposes is therefore not blockade but *discipline*: an agent, or a dosing, or a localization that suppresses the pathological, sustained, glia-driven MMP-9 that unpicks the net without silencing the transient, activity-driven, synaptic MMP-9 that consolidates memory. Whether the two pools are separable — by cell of origin, by kinetics, by compartment — is unknown, and is exactly the question the synthesis makes urgent.

The drive. Because the enzyme is downstream of a neuromodulatory signal, there is a target upstream of the enzyme, and it is one the clinic already possesses the tools to reach: the β-adrenergic receptor. If dysregulated noradrenergic excess drives cortical MMP-9, then attenuating that excess — with a centrally acting β-blocker, or by stabilizing rather than depleting the failing coeruleus — should reduce the protease's induction, spare the net, and preserve reelin's brake, while at the same time removing the direct noradrenergic over-activation of glycogen-synthase-kinase-3β (Jeong and colleagues, 2024). The pincer, attacked at its handle, is disarmed on both tines at once. But the same trap recurs in a new key. Norepinephrine is not only a driver of pathology; it is indispensable to arousal, attention, mood, and — through the very long-term potentiation MMP-9 subserves — to memory itself, and its terminal depletion is a documented contributor to the cognitive and neuropsychiatric burden of the disease (Weinshenker, 2008). To blunt the noradrenergic signal is to risk hastening the deficiency state that lies at the end of the same trajectory. The therapeutic window is therefore not merely a target but a *time*: the interval of noradrenergic excess, after the coeruleus has begun to derange but before it has collapsed, in which reducing the drive subtracts pathology without yet subtracting the transmitter the brain still needs. The synthesis converts a molecular target into a chronological one.

A third target sits between the two, and it is the one the synthesis most distinctively nominates: the *inhibitor balance* rather than the enzyme or its driver. Because MMP-9's danger is a danger of disinhibition — too little tissue inhibitor of metalloproteinases-1 restraining too much activated enzyme (Speidl and colleagues, 2004) — an agent that restores the endogenous brake, rather than one that poisons the enzyme outright, would spare the constitutive, activity-coupled MMP-9 that memory requires (Nagy and colleagues, 2006) while blunting the pathological surplus. This is a subtler pharmacology than blockade, and a safer one in principle, because it works with the brain's own regulation instead of overriding it; whether the inhibitor pool can be raised selectively at the sites and times that matter is unknown, and is the medicinal-chemistry question the cascade makes worth asking. The same logic recommends caution about the crude instruments already to hand: broad-spectrum metalloproteinase inhibitors failed in oncology precisely because they could not distinguish the pathological protease from the physiological one, and the lesson transfers intact to

the brain, where the physiological MMP-9 is not incidental but is the maker of long-term potentiation.

The three targets share a single strategic reading, and it is the reading this whole corpus has arrived at from many directions: the reelin-matrix axis is a system of the *earlier* brain, to be defended in the preclinical and prodromal window and not rescued in the ruins. The locus coeruleus tangles first; the noradrenergic dysregulation it broadcasts is among the first cortical insults; and the protease it drives does its damage before the plaque has finished accumulating. An intervention aimed at the shears or the hand belongs, if the cascade is right, to that early window — administered while the weave is still mostly whole, the receptors still mostly on the surface, and the coeruleus still mostly alive. It is a strategy for keeping the wall standing, not for rebuilding it once fallen; and the clinical instruments it would require — a disciplined metalloproteinase modulator, a timed and centrally selective adrenergic agent, a reelin-pathway agonist — are close enough to existing pharmacology that the chief obstacle is not chemistry but knowing when, and in whom, to reach for them.

XII. Coda The Blue Nucleus and the Cut Weave

The companion dissertations ended on the image of a weaver in a wall: reelin, the architect of the cortex, staying on after construction to dwell in the sulfated matrix at the neuron's surface, guarding from within the structure it had raised. *The Architect's Scaffold* watched that wall come down and named the process only as an unpicking. The present work has tried to say who holds the shears.

The answer is a small nucleus the colour of slate, no larger than a grain of rice, seated in the floor of the fourth ventricle — the locus coeruleus, the blue place, the brain's single wellspring of norepinephrine. It was never given a net of its own, and so it tangles before anything else, and as it sickens it does not fall silent all at once but for years pours out a deranged and amplified signal along axons that reach into every fold of the cortex. That signal, arriving at the microglia and astrocytes of the guarded surface, calls up the enzyme; the enzyme cuts the lectican shield, sheds the sulfated bed, and strips the receptors; and reelin, still present, still secreted, finds nothing left to signal through. The same signal, arriving at the same neurons, presses directly on the kinase that reelin's whole existence was arranged to restrain. The tangle, freed from within and admitted from without, spreads across a surface that no longer closes against it — and its spreading sickens the cortex that might have steadied the failing coeruleus, which frays further, and drives the shears harder. The blue nucleus operates the demolition of the very defense it exists to serve.

There is a bitter economy in it. One neuromodulator, dysregulated, disarms a resilience system twice — once by dismantling its apparatus and once by overpowering its effect — and the corpus has now caught the same small nucleus at the controls of a second such demolition, having found it once before operating the sprinkler it had set the fire beneath. Two protective systems, the clearance of the interstitium and the staging of the reelin brake, both governed at their upstream valve by the noradrenergic output of a nucleus that fails first. If that is not coincidence — and the geometry argues it is not — then the earliest and least defended cell in the Alzheimer brain is also, through the signal it broadcasts, among the most consequential, and the field's long focus on the plaque has kept it looking at the wrong end of the cascade.

The clinician cannot yet still the shears without staying the hand that also mends, nor quiet the hand without hastening the silence that follows. But the task is now legible in a way it was not when the protease had no name and the drive had no face: to find the discipline, and the hour, in which the pathological cutting can be stopped while the healing cutting is spared — to reach the blue nucleus in the years when its signal is merely deranged and not yet gone, and to keep the weave whole long enough for the weaver still dwelling in it to matter. The architect is in the wall. The shears are in the blue nucleus's hand. The work is to loosen the grip before the wall comes down.

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