THE FIRST EMBER

How the Tangle Is Kindled in the Locus Coeruleus — the Self-Poisoning Nucleus that, with One Protease Roused by the Metabolite of Its Own Transmitter, Cleaves Tau into Seed and Silences Its Own Phosphatase, in the Single Neuron the Reelin Brake Was Never Staged to Guard

The Two Questions · The Unguarded Nucleus · The Withheld Brake
The Self-Poison · One Enzyme, Two Crimes · The First Fire

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The genesis volume to The Coerulean Pincer (the writer, glycogen-synthase-kinase-3β) and The Silenced Eraser (the eraser, protein-phosphatase-2A). Those volumes traced how tau's phosphorylation balance is deranged across the disease's long middle passage. This one descends beneath them to the first neuron in the brain to tangle — the locus coeruleus — and asks the prior question they assumed: how is the tangle kindled at all, and does the reelin brake have any part in its beginning? The answer is one protease, roused by the metabolite of the neuron's own norepinephrine, that cleaves tau into a seed and cleaves SET to silence tau's phosphatase — in the one nucleus whose want of a perineuronal net leaves the reelin brake with no surface to stand on.

"Look for the disease at its height and you will find a fire no water reaches. Look instead for its first ember — kindled decades early, in the dark, in one small nucleus that poisons itself with the very transmitter that keeps us awake — and you will find the only fire small enough to put out."

— ONS Methodology Working Notes, 2026

For those who asked not how Alzheimer's disease burns, but how it is lit — and who were willing to follow the answer down to the one neuron, the one metabolite, and the one enzyme that begins it, in the decades before the guard it never had is even missed.

THE COLLAPSE FRAMEWORK THE COERULEAN GENESIS

The Coerulean Pincer — norepinephrine's two arms drive the writer, glycogen-synthase-kinase-3β

The Silenced Eraser — the ungoverned microglion silences the eraser, protein-phosphatase-2A

The Architect's Reprieve / Scaffold / Handshake — reelin, the brake, and the sulfated surface that stages it

The First Ember (how the tangle is kindled in the locus coeruleus, before either enzyme's middle-passage work) — this volume

The companion volumes are volumes of the disease's middle passage — the long years in which tau's balance, already tipped, propagates and matures. Both assume an ignition they do not describe. This volume descends beneath them to the first neuron in the brain to bear abnormal tau — the locus coeruleus, the net-less blue nucleus that tangles from the third decade of life, alone, for decades — and asks how the very first ember catches. It answers with one protease. Norepinephrine that escapes its vesicle is metabolised to an aldehyde, DOPEGAL, made in no other cell; DOPEGAL activates asparagine endopeptidase; and that one enzyme commits two crimes at once — cleaving tau at asparagine-368 into an aggregation-prone seed, and cleaving the inhibitor SET, whose fragments silence the tau phosphatase. Writer and eraser, both deranged by one enzyme roused from within. And the reelin brake that might have held the kinase down was never posted here, for it must be staged on a sulfated surface the locus coeruleus does not possess: reelin is present at the ignition only by its absence — the guardian withheld, thinnest where the fire is first. An ember, unlike a conflagration, has a single source; and a single source can, in principle, be reached.

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Abstract

The earliest deposit of abnormal tau anywhere in the human brain is not cortical. It is a small cluster of hyperphosphorylated, truncated tau in the locus coeruleus — the brainstem's blue nucleus, the sole source of the cortex's norepinephrine — and it is present, in most people, decades before any symptom, from the third decade of life. Two questions follow from that fact, and this dissertation exists to answer them in the specific molecular detail the phenomenon demands. First: *how* does tau get started in this one nucleus, at the level of the enzyme and the residue — not merely that it does, but by what chemistry? And second, the question the corpus's reelin volumes raise but do not close: is the reelin brake — the signal whose failure the companion volumes blamed for the mid-disease surge of tau — *involved in the ignition itself*, or only in the conflagration that follows?

The answer to the first question is a single protease, roused by the neuron's own transmitter. Norepinephrine, metabolised by monoamine oxidase A inside the noradrenergic neuron, yields an aldehyde — 3,4-dihydroxyphenylglycolaldehyde, DOPEGAL — that is produced *exclusively* in noradrenergic cells and that activates the lysosomal cysteine protease asparagine endopeptidase (AEP, also called δ-secretase or legumain). This dissertation's central structural claim is that this one activated protease commits *two* crimes at once, and that their simultaneity in one cell is why the locus coeruleus is where the disease begins. Its first crime is against tau directly: AEP cleaves tau at asparagine-368 into a truncated species that can no longer hold the microtubule and that is primed to aggregate and to propagate — tau is not merely phosphorylated here but *cut into a seed*. Its second crime is against tau's eraser: the same AEP cleaves SET, the endogenous inhibitor of protein phosphatase 2A, whose cleaved fragments translocate to the cytoplasm, bind the phosphatase, and silence it — so that the phosphate the neuron's kinases lay down is no longer removed. One enzyme, roused by one metabolite of the neuron's own norepinephrine, writes the seed and gags the eraser in the same stroke.

The answer to the second question is more delicate, and this dissertation grades it with care. There is no study that has measured reelin signalling in the human locus coeruleus, and this volume does not pretend otherwise. What can be argued, from established facts, is structural and permissive rather than causal: reelin's brake on the tau kinase is not a free-floating signal but one *staged* on a surface of N-sulfated heparan sulfate — the same sulfated matrix, condensed into the perineuronal net, that the locus coeruleus constitutionally lacks. The blue nucleus is the archetype of the net-less neuron; and a neuron without the net is a neuron without the staging bed on which its own reelin brake would be presented. Reelin, that is, is not the arsonist. It is the guardian withheld — its protection is structurally weakest in precisely the nucleus where tau ignites, so that the writer it would have restrained runs least-braked exactly where the self-poison lights the fire. The reelin brake is absent at the ignition not because the disease has cut it, as in the mid-disease cortex the companion volume described, but because the locus coeruleus was never built with the surface on which to hold it.

The synthesis, then, is a nucleus triply disposed to kindle tau and to keep it lit. Its writer is *un-braked* from birth, for want of the sulfated surface that would stage the reelin signal. Its writer is *driven*, by the same noradrenergic excess the companion volume traced and by AEP's truncation of the substrate. And its eraser is *silenced*, by the SET the same AEP unleashes. The apolipoprotein-E receptor system that reelin shares with ApoE sharpens the picture from the genetic side: the ε4 allele, by inhibiting the vesicular transporter that would keep norepinephrine safely packaged, floods the cytosol with the substrate for DOPEGAL and so feeds the very protease that ignites the nucleus, while the two rarest human resiliences yet found — the Reelin-COLBOS and the APOE3-Christchurch variants — both act on this one receptor system. This dissertation sets the ignition down as an ordered sequence, grades every joint of it in a validity ledger that is candid about the reelin inference above all, states the predictions by which it can be falsified, and draws the therapeutic corollary the mechanism dictates: that the first ember, unlike the late fire, is reached by disarming one protease — before the seed it makes has spread beyond the nucleus that made it.

I. The First Neuron The Two Questions

Every account of Alzheimer's disease must eventually confront a fact of natural history that the amyloid-centred narrative long left to one side: the first abnormal protein deposit anywhere in the human brain is a tau lesion, and it does not appear in the cortex, or the hippocampus, or the amyloid-laden regions the imaging tracks. It appears in the locus coeruleus, a nucleus of a few thousand pigmented neurons in the floor of the fourth ventricle, and it appears astonishingly early — before plaques, before symptoms, before middle age. This dissertation begins where the disease begins, and it takes that starting point literally: if we wish to understand how Alzheimer's disease is kindled rather than how it burns, we must understand what happens, molecule by molecule, in this one small nucleus, in the decades before anything else in the brain has gone wrong.

The locus coeruleus tangles first, and it tangles alone for decades. The pretangle — soluble, hyperphosphorylated tau that has not yet assembled into the mature neurofibrillary tangle — is present in the locus coeruleus of the great majority of people by the third decade of life, decades before any possibility of dementia, and it is now widely recognised as the first detectable Alzheimer's-like neuropathology anywhere in the human brain (Mather and Harley, 2016; Weinshenker, 2018). From this nucleus the pathology later spreads, in the stereotyped order the neuropathology has mapped, along the coerulean projections to the other neuromodulatory nuclei and to the cortex (Ghosh and colleagues, 2019; Giorgi and colleagues, 2017). For a long latent interval, however, the locus coeruleus carries its lesion alone — a single nucleus bearing abnormal tau in a brain otherwise clean. That interval is the subject of this dissertation. It is the window in which the disease is a nucleus's private affair, and it is the window in which, if the disease is ever to

be caught before it becomes a conflagration, it must be caught.

The prior question the companion volumes assumed. The corpus of which this dissertation is a part has traced, in two companion volumes, how tau's phosphorylation is deranged across the disease. *The Coerulean Pincer* took the tau kinase glycogen-synthase-kinase-3β and showed the dysregulated locus coeruleus driving it from two sides — cutting the reelin brake that held it down and flooring the noradrenergic throttle that pushed it up. *The Silenced Eraser* took the tau phosphatase protein-phosphatase-2A and showed the ungoverned microglion silencing it. Both volumes are volumes of the disease's *middle passage* — the long years in which the pathology, already begun, propagates and matures. Both, that is, assume an ignition they do not describe. They begin with a locus coeruleus already dysregulated, already over-firing, already deranging its neighbours. This dissertation descends beneath them to ask the question they took for granted: before the coeruleus can derange the rest of the brain, something must first go wrong *in the coeruleus itself*. What is that something? How does the very first ember catch?

The two questions, stated precisely. Two questions organise everything that follows, and it is worth stating each in the strongest and most specific form, because the value of the answers depends on the precision of the questions. The first is mechanistic and local: *by what chemistry does tau become abnormal in the locus coeruleus?* Not "tau is hyperphosphorylated" — that is a description, not a mechanism — but which enzyme, acting on which residue, converts the ordinary tau of a healthy noradrenergic neuron into the truncated, hyperphosphorylated, aggregation-prone species that is the pretangle. The second is the question the reelin volumes of this corpus force upon us but do not resolve: *is reelin involved in the ignition?* The companion volumes made reelin's brake the guardian of the tau kinase and blamed its withdrawal for the mid-disease surge of tau. But those volumes located the withdrawal in the cortex, worked by a protease of the disease's middle passage. The locus coeruleus is a different neuron in a different phase, and the honest question is whether reelin has any part in the *first* lesion at all — whether the brake fails at the ignition, and if so, why, and whether its failure is cause or merely circumstance.

The shape of the answer. This dissertation will argue that the two questions have a single, joined answer, and that the joining is the reason the locus coeruleus is special. The chemistry of the first question turns out to be one protease — asparagine endopeptidase — roused by a metabolite the noradrenergic neuron alone produces, and doing double damage: cleaving tau into a seed and cleaving the inhibitor that silences tau's phosphatase. And the reelin of the second question turns out to be involved not as an agent of the ignition but as a guardian structurally absent from it: the locus coeruleus lacks the sulfated surface on which the reelin brake is staged, so the writer runs un-braked in the one nucleus where the self-poison drives it hardest. The ignition, in a phrase this dissertation will earn section by section, is a writer un-braked, a writer driven, and an eraser silenced, all converging in one net-less, self-poisoning neuron. We begin with the balance those three derangements move.

II. The Balance at the Residue Writer and Eraser

Because the whole argument concerns the phosphorylation state of one protein, that state must be understood first as what it is: not a static property but a running equilibrium between two opposed enzymatic activities. This dissertation imports the balance from its companion volumes rather than re-deriving it, and states it briefly, because the novelty here is not the balance but what tips it in this particular nucleus.

Tau's phosphorylation is a running score. Tau is a microtubule-associated protein whose job is to bind and stabilise the microtubule, and whose capacity to do so is governed by its phosphorylation: phosphate added at particular serine and threonine residues detaches tau from the microtubule and disposes it toward the paired helical filament and the tangle. The level of that phosphorylation at any moment is not set by a single enzyme but by the balance of two — the kinases that add phosphate and the phosphatases that remove it — and the balance is dynamic, written and erased continuously. To understand any derangement of tau, one must ask not "which enzyme is abnormal" but "which way has the balance tipped, and by what."

The writer: glycogen-synthase-kinase-3β, and the brake that guards it. The principal kinase that phosphorylates tau at the pathological residues is glycogen-synthase-kinase-3β, a constitutively active enzyme — on by default, and normally held down rather than switched on — whose over-activity gathers so many of the disease's features that it has been proposed as the disease's central hub (Hooper and colleagues, 2008). Because the kinase is on by default, the biological question is always how it is held off, and the answer the companion volume established is: by the reelin signal. Reelin, binding its receptors, phosphorylates the adaptor Disabled-1, which through phosphoinositide-3-kinase and Akt phosphorylates glycogen-synthase-kinase-3β on its inhibitory serine and holds it suppressed (Hiesberger and colleagues, 1999). A live reelin signal is a continuous inhibitory input to the tau kinase — a brake; withdraw it, and the default-on kinase drifts back toward activity and tau phosphorylation rises. This is the writer and its brake, and we shall need both when we come to the reelin question.

The eraser: protein phosphatase 2A, and the inhibitor that gags it. The principal phosphatase that removes phosphate from tau is protein phosphatase 2A, which by direct measurement accounts for the large majority — on the order of seventy per cent — of tau-directed phosphatase activity in human brain (Liu and colleagues, 2005), acting directly on the pathological residues to restore tau's microtubule binding (Sontag and colleagues, 1996). The eraser, like the writer, does not run unopposed: its activity is restrained by endogenous inhibitor proteins, chief

among them for tau a protein called SET, or inhibitor-2 of protein phosphatase 2A. In the healthy neuron SET is largely sequestered in the nucleus; unleashed into the cytoplasm, it binds the phosphatase and silences it, and tau accumulates phosphate (Tanimukai and colleagues, 2005). This is the eraser and its inhibitor, and we shall need both when we come to the second crime.

Why the balance matters here. The reason this brief recapitulation is necessary is that the ignition of tau in the locus coeruleus is not a single event but a coordinated tipping of this whole balance — and tipping it, moreover, from both sides at once. In the sections that follow, the writer will be shown to run un-braked in this nucleus (for want of the reelin-staging surface) and to be driven (by the neuron's own chemistry); and the eraser will be shown to be silenced (by an inhibitor the same chemistry unleashes). The pretangle is what a balance looks like when it is pushed toward phosphate from every available lever simultaneously. To see why the locus coeruleus, and not some other neuron, suffers this, we must first see what the locus coeruleus is.

III. The Unguarded Nucleus The Constitution of the Locus Coeruleus

The locus coeruleus tangles first not by accident but by constitution. It is, of all the brain's nuclei, among the most exposed, and its exposures are written into its anatomy and its chemistry long before the disease begins. This section assembles the nucleus's native vulnerabilities, because the ignition of the following sections is only intelligible as what happens when a self-poisoning chemistry meets a defenceless cell.

A neuron built without a shield. The subcortical survey that first established the perineuronal net's protective role made an observation whose full weight has taken two decades to register: the nuclei attacked earliest and hardest by tau — the locus coeruleus foremost, with the nucleus basalis, the raphe, and the dorsal tegmentum — are precisely those *devoid* of an aggrecan-based perineuronal net, while net-ensheathed neurons even in the thick of the pathology rarely tangle (Morawski and colleagues, 2010). The perineuronal net is a condensed lattice of chondroitin- and heparan-sulfate proteoglycans that sheathes certain neurons, and its presence marks the neurons that resist the tangle; its absence marks those that succumb earliest. That association has since been sharpened into a marker of resilience: the specific configuration and integrity of perineuronal nets tracks with resistance to Alzheimer's disease across human cases (de Vries and colleagues, 2024). The locus coeruleus lives on the wrong side of that line. It is, by native constitution, an *unguarded* neuron — lacking the sulfated shield that resists the tangle, and, as the next section will insist, lacking the very surface on which its own molecular brake would be staged.

A neuron with an enormous exposed membrane. The coerulean neuron is anatomically extreme. Its axons are long, thin, and unmyelinated or only sparsely myelinated — a diffuse projection that reaches broadly across the forebrain — so that the cell exposes an enormous membrane surface to whatever the extracellular space contains, and bears an enormous metabolic burden that arises not from the extent of that projection but from what sustains it: ceaseless pacemaking, and the handling of a transmitter that oxidises (Giorgi and colleagues, 2017; Mather and Harley, 2016). A neuron of ordinary compact geometry can defend a small surface; the coerulean neuron cannot, and its very reach — the property that makes it the brain's master modulator — is the property that makes it the brain's most exposed cell and, later, the highway along which its pathology spreads.

A neuron that never rests. The locus coeruleus is an autonomously active, tonically firing nucleus; it pace-makes, and it is under near-constant demand, driving arousal, attention, and the stress response throughout waking life. Tonic activity is metabolically expensive and imposes a continuous calcium and bioenergetic load, and the nucleus's activity is not steady across the lifespan of the disease: as the earliest tau accumulates, the coerulean neuron becomes *hyperexcitable* — depolarised, more readily fired, discharging more spontaneous action potentials as its inhibitory tone weakens — and, by direct measurement, releases more norepinephrine than a healthy neuron (Wang and colleagues, 2025). This matters enormously for what follows, because the chemistry of the ignition is driven by the neuron's own activity: the harder the coerulean neuron fires, the more of its own transmitter it must handle, and the more of the toxic metabolite that handling produces.

A neuron that traffics a dangerous cargo. Above all, the locus coeruleus is defined by what it makes and moves: norepinephrine. Norepinephrine is a catecholamine, and catecholamines are chemically double-edged — indispensable as transmitters, hazardous as free molecules in the cytosol, where they are subject to oxidation into reactive species. The healthy noradrenergic neuron manages this hazard by keeping its norepinephrine packaged in synaptic vesicles, sequestered from the cytosolic enzymes that would oxidise it. But the packaging is imperfect and, as we shall see, defeasible: norepinephrine that escapes the vesicle into the cytosol is metabolised by monoamine oxidase A into an aldehyde that no other class of neuron produces. The nucleus's defining cargo is, in the wrong compartment, its defining poison. It is this — the self-poisoning that the coerulean neuron's own transmitter makes possible — that distinguishes the locus coeruleus from every other unguarded, exposed, tonically active neuron in the brain, and it is the engine of the ignition. But before the poison, the guardian that was never there: the reelin brake, and the answer to the second question.

IV. The Withheld Brake — Reelin and the Answer to the First Question of Reelin

Here this dissertation confronts, directly and with the candour the claim demands, the question the corpus's reelin volumes raise: is reelin involved in the ignition of tau in the locus coeruleus? The answer is yes, but not in the manner the question naïvely supposes — not as an agent of the ignition, but as a guardian constitutively absent from it. To reach that answer honestly, the reasoning must be laid out in full, and its most important step must be graded as the inference it is.

What reelin does, and where. Reelin is a large secreted glycoprotein, first identified as an architect of the layered cortex (D'Arcangelo and colleagues, 1995), that acts in the adult brain as a brake on the tau kinase. Signalling through the lipoprotein receptors ApoER2 and VLDLR, it phosphorylates Disabled-1 and, through phosphoinositide-3-kinase and Akt, holds glycogen-synthase-kinase-3β in its inhibited state (Hiesberger and colleagues, 1999) — so that reducing reelin accelerates tau pathology in the intact brain (Kocherhans and colleagues, 2010) and reelin signalling opposes the amyloid-driven derangement of the synapse (Durakoglugil and colleagues, 2009). A live reelin signal keeps the default-on tau kinase suppressed and tau unphosphorylated. This is the brake, and it is the most mechanistically secure of reelin's protective actions.

The brake is not free-floating; it is staged on a sulfated surface. The decisive fact for the locus coeruleus is that the reelin signal does not assemble in free solution. It requires a scaffold, and the scaffold is a chain of N-sulfated heparan sulfate, which acts as an obligate co-receptor: the sulfated sugar clusters ApoER2 and VLDLR into the configuration that permits Disabled-1 to be phosphorylated, and stripping or de-sulfating that sugar abolishes the signal even when reelin and its receptors are both present (Pan and colleagues, 2025). The functional reelin brake is therefore not a protein but a three-body complex — reelin, a lipoprotein receptor, and a chain of N-sulfated heparan sulfate presented on the cell surface — and one of its three components is a feature of the extracellular matrix. The brake needs a bed to be laid on, and the bed is sulfated sugar. Where the sulfated matrix is rich — condensed, in its most organised form, into the perineuronal net — the brake can be staged; where the matrix is absent, the brake has nowhere to assemble.

The locus coeruleus is the archetype of the net-less neuron. Now the two facts join. The locus coeruleus, as Section III established, constitutionally lacks an aggrecan-based perineuronal net (Morawski and colleagues, 2010) — it is the paradigm case of the net-less, matrix-poor neuron. And the reelin brake requires the sulfated matrix as its obligate staging bed (Pan and colleagues, 2025). It follows, as a structural inference, that the locus coeruleus is a nucleus in which the reelin brake is *structurally under-served* — not cut, as in the mid-disease cortex the companion volume described, but never well-staged in the first place, for want of the surface on

which to stage it. The writer glycogen-synthase-kinase-3β, which a well-staged reelin signal would hold suppressed, runs in the coerulean neuron with its principal brake structurally weak from the outset. Of all the brain's neurons, the one that tangles first is the one whose tau kinase is, by native constitution, least braked.

The candour the claim requires. This is the single most important place in the dissertation for honesty, and it will be graded accordingly in the ledger. There is *no* study that has directly measured reelin signalling, reelin-dependent Disabled-1 phosphorylation, or reelin receptor expression in the human locus coeruleus, and this dissertation does not claim one. Searches of the primary literature return no work on reelin in this nucleus at all. The argument above is therefore an *inference from two established facts* — that the locus coeruleus lacks the net, and that the reelin brake requires the sulfated surface the net provides — and not a measured finding. It is a strong inference, because both of its premises are secure and the logic connecting them is direct; but it is an inference, and a reader is owed the distinction plainly. What is measured is that net-bearing neurons resist tau and net-less nuclei succumb (Morawski and colleagues, 2010); what is inferred is that one reason the net-less nucleus succumbs is that it cannot stage the reelin brake. The inference makes a prediction, stated in Section XII, by which it can be tested and, if wrong, refuted.

The answer to the reelin question, stated carefully. With the inference graded, the answer to the corpus's reelin question can be given precisely. *Is reelin involved in the ignition of tau in the locus coeruleus?* Yes — but as the guardian withheld, not as the arsonist. Reelin does not cause the pretangle; nothing in reelin's biology drives tau toward phosphate or aggregation, and reelin's every action opposes the tangle. Reelin's involvement is that its protection is *structurally weakest in precisely the nucleus where tau ignites* — the writer it would have restrained runs least-braked exactly where the self-poison of the next sections drives it hardest. The reelin brake is absent at the ignition not because the disease has cut it but because the locus coeruleus was never built with the surface to hold it. This is a different and more permissive role than the one the companion volume assigned reelin in the cortex, and the difference is exactly the difference between ignition and conflagration: in the cortex of the middle passage, the disease *cuts* a brake that had been working; in the locus coeruleus at the ignition, the brake was structurally faint all along, and the fire catches where the guard was always thinnest. The withheld brake is the permissive condition. The self-poison is the spark. To the spark we now turn.

V. The Self-Poison DOPEGAL, the Metabolite of the Neuron's Own Transmitter

If the withheld reelin brake is why the coerulean neuron cannot resist tau, the self-poison is why tau starts there and nowhere else. This is the answer to the first question — the chemistry of the ignition — and its first step is a molecule the noradrenergic neuron alone produces from the very transmitter that defines it.

Norepinephrine, in the wrong compartment, becomes a poison. Norepinephrine is synthesised and stored in synaptic vesicles, where it is safe. The hazard begins when norepinephrine escapes the vesicle into the cytosol, for the cytosol contains monoamine oxidase A, the enzyme that degrades catecholamines, and the product of that degradation is not inert. When monoamine oxidase A acts on norepinephrine, it yields an aldehyde intermediate — 3,4-dihydroxyphenylglycolaldehyde, abbreviated DOPEGAL — and this aldehyde is reactive, toxic, and, crucially, *produced exclusively in noradrenergic neurons*, because only they metabolise norepinephrine (Kang and colleagues, 2020). Here is the first molecular reason the locus coeruleus is unique: it is the only population of neurons in the brain that manufactures this particular poison, because it is the only population that handles this particular transmitter in this particular way. Every other neuron, whatever its exposures, cannot make DOPEGAL, for it has no norepinephrine to make it from. The self-poison is a coerulean monopoly.

How norepinephrine reaches the cytosol: the leak that feeds the poison. The poison is only produced if norepinephrine escapes into the cytosol, so the mechanisms that cause that escape are the mechanisms that load the ignition, and two have been resolved. The first is activity-dependent. The tonically firing, and in early disease *hyperexcitable*, coerulean neuron must repeatedly take back up the norepinephrine it releases; a recent electrophysiological study shows that chronic stress internalises the α2A-adrenergic autoreceptors and their coupled potassium channels that normally restrain the neuron's firing, so that the cell over-excites, over-releases, and over-reuptakes its own transmitter, driving norepinephrine into the somatodendritic cytosol where monoamine oxidase A converts it to DOPEGAL — and the same study measured the downstream consequence directly, finding increased monoamine oxidase A, increased DOPEGAL-induced protease activity, and increased truncated tau in the stressed nucleus (Toyoda and colleagues, 2025). The neuron's own over-activity feeds its own poisoning: the harder it fires, the more transmitter it must recycle, the more escapes to the cytosol, the more DOPEGAL it makes. This closes a loop with Section III's hyperexcitability and with the companion volume's account of coerulean over-firing — the excess that the *Pincer* traced from outside is here traced to its self-poisoning consequence within.

The genetic leak: apolipoprotein E4 and the vesicle that fails to hold. The second mechanism of cytosolic escape is genetic, and it links the ignition to the single greatest genetic risk factor for the disease. The vesicular monoamine transporter 2 is the pump that loads norepinephrine into the synaptic vesicle and so keeps it out of the cytosol; and the ε4 isoform of apolipoprotein E — ApoE4 — selectively binds this transporter and inhibits it, so that norepinephrine is excluded from the vesicle, accumulates in the cytosol, and is there oxidised to

DOPEGAL, which activates the protease and cleaves tau, driving locus-coeruleus neurodegeneration (Kang and colleagues, 2021). The same work found the protective mirror: ApoE3 binds tau directly and shields it from the protease's cut. Here the ApoE risk allele is not a distant modifier of amyloid but a *proximate accelerant of the coerulean ignition* — it pries open the vesicle that holds the transmitter, floods the cytosol with the substrate for the poison, and so feeds the very protease that lights the fire. This dissertation returns to the ApoE convergence, and to what it means that reelin shares ApoE's receptors, in Section IX; for now it is enough to mark that both the activity-dependent leak and the genetic leak converge on one outcome — cytosolic norepinephrine, and therefore DOPEGAL.

The poison's single target. DOPEGAL is reactive and could, in principle, injure the neuron by many routes — and doubtless contributes to the oxidative burden the coerulean neuron labours under. But its decisive action, for the genesis of tau, is specific and named: DOPEGAL activates a protease. It is not a diffuse toxin whose harms are the sum of a hundred small oxidations; it is, for the purposes of tau, a switch that turns on one enzyme. And that enzyme, once turned on, is the hinge of the whole dissertation, because it does not do one thing to tau but two. To the protease, and to its first crime, we now turn.

VI. The First Crime — One Protease Cleaves Tau into a Seed

The poison's target is asparagine endopeptidase — a lysosomal cysteine protease also called δ-secretase or legumain, abbreviated AEP — and the first thing this dissertation must establish is that AEP does to tau something categorically different from, and worse than, phosphorylation. It does not merely mark tau; it *cuts* it, and the cut converts an ordinary protein into a seed.

The protease, and how it is switched on in the coeruleus. AEP is normally a quiescent lysosomal enzyme, but it is activated during aging, and it is activated in the Alzheimer brain (Zhang and colleagues, 2014). In the locus coeruleus it has a specific and local activator: DOPEGAL. The keystone demonstration of this dissertation's first question showed that DOPEGAL, produced by monoamine oxidase A metabolism of norepinephrine in the noradrenergic neuron, activates asparagine endopeptidase in the locus coeruleus (Kang and colleagues, 2020). The chain from the neuron's chemistry to the protease is therefore complete and local: norepinephrine escapes the vesicle, monoamine oxidase A makes DOPEGAL, DOPEGAL activates AEP — every step inside a single coerulean neuron, driven by that neuron's own transmitter. The protease is not roused by some distant inflammatory signal, as the eraser-silencing of the mid-disease cortex was in the companion volume; at the ignition it is roused from *within*, by the self-poison the neuron

manufactures. This is what makes the coerulean ignition cell-autonomous — a nucleus setting fire to itself, needing nothing from outside.

The cut, and the residue. Once activated, AEP cleaves tau, and it cleaves it at a defined site: asparagine-368. The truncated tau species that results — tau ending at residue 368 — has lost the portion required to bind and stabilise the microtubule, so that AEP cleavage *abolishes tau's microtubule-assembly function*, and, worse, the truncated fragment is *aggregation-prone and propagation-prone*, disposed to assemble into the pathological filament and to template its shape onto other tau molecules (Zhang and colleagues, 2014; Kang and colleagues, 2020). This is the crux of the answer to how tau "gets started," and it corrects a common oversimplification: the first lesion of the disease is not merely *phosphorylated* tau but *truncated* tau — tau that has been cut into a shorter, self-templating species. Phosphorylation detaches tau from the microtubule and disposes it toward aggregation; truncation at N368 removes the microtubule-binding capacity outright and yields a fragment that is itself a seed. The pretangle is the product of both marks, and AEP is the enzyme of the second.

Why the cut is causal, not incidental. That AEP's cleavage of tau is a genuine driver of pathology, and not a mere epiphenomenon of a dying cell, is shown by the cleanest experiment the question admits: removing the enzyme. Tau-P301S transgenic mice bred to lack the gene encoding AEP show substantially reduced tau hyperphosphorylation, less synapse loss, and rescue of impaired synaptic function and cognition; and mice given an *uncleavable* tau mutant — tau engineered so that AEP cannot cut it — are protected relative to mice given cleavable tau (Zhang and colleagues, 2014). Delete the protease, or make its substrate uncuttable, and the pathology abates. In the locus coeruleus specifically, activating AEP-cleaved tau aggregation with DOPEGAL produced coerulean neurotoxicity and propagation of the pathology to the forebrain, while the corresponding genetic protections blocked it (Kang and colleagues, 2020). The cut is upstream and causal: it is not that dying neurons happen to contain cleaved tau, but that cleaving tau helps kill the neurons and seeds the spread.

The seed that leaves the nucleus. One further property of the AEP-cut tau closes the loop with the disease's natural history. The truncated, aggregation-prone species is also *propagation*-prone — it is a transmissible seed, and the locus coeruleus, with its projections reaching broadly across the forebrain, is ideally built to broadcast it. The same delta-secretase activity that ignites tau in the coeruleus thereby mediates the spread of tau pathology to the rest of the brain (Kang and colleagues, 2020; Kang and colleagues, 2020b), and the sulfated surfaces that receive proteopathic tau seeds in recipient neurons — heparan-sulfate proteoglycans — are the established gateway for tau's transcellular propagation (Holmes and colleagues, 2013). The first ember, in other words, is not merely lit; it throws sparks. The coerulean neuron that cuts its own tau into a seed becomes a source, exporting that seed along the very projections by which it modulates the forebrain. But the first crime — cutting tau into a seed — is only half of what the activated protease does. Its second

crime is against the enzyme that would have kept the neuron's remaining tau clean.

VII. The Second Crime The Same Protease Silences the Eraser

Here is the structural discovery at the centre of this dissertation, and the reason it was worth writing as a separate volume rather than a footnote to the companions: the very protease that DOPEGAL activates to cleave tau is *also* the protease that silences tau's phosphatase. AEP does not merely make the seed. It disables the enzyme that would erase the phosphate from all the tau the seed does not consume. One activated protease, two crimes, and the two crimes are the writer-side and eraser-side halves of the balance of Section II — both committed, in the coerulean neuron, by one enzyme roused by one metabolite.

SET is the eraser's enemy, and AEP unleashes it. Recall from Section II that protein phosphatase 2A, the principal tau eraser, is restrained by an endogenous inhibitor, SET, which is safe so long as it stays in the nucleus and dangerous once it reaches the cytoplasm. The mechanism by which SET is moved and armed is proteolytic, and the protease is AEP. In the Alzheimer neuron, asparaginyl endopeptidase is activated and cleaves SET at an asparagine residue; the cleaved fragments, which retain and even concentrate their inhibitory power, translocate with the enzyme from the nucleus into the cytoplasm, where they bind and inhibit protein phosphatase 2A — and the phosphatase so gagged permits the hyperphosphorylation of tau (Basurto-Islas and colleagues, 2013). This is the same enzyme, by the same name and the same catalytic chemistry — asparagine endopeptidase, δ-secretase, legumain — that Section VI showed cleaving tau at N368. The protease that cuts tau into a seed and the protease that cleaves SET to silence the eraser are not two enzymes that happen to co-occur; they are one enzyme with two substrates, and in the coerulean neuron both substrates are cut by the one activation.

The eraser is measurably down, and its inhibitor measurably up. That the eraser is in fact silenced in the Alzheimer brain is among the more secure quantitative facts of the disease's biochemistry: the tau-directed activity of protein phosphatase 2A is reduced relative to the aged control brain, on the order of a third of its activity (Gong and colleagues, 1995; Gong and colleagues, 1993). And that its endogenous inhibitors are correspondingly up-regulated is equally established: the inhibitors of protein phosphatase 2A, SET among them, are elevated in the disease, and their up-regulation is associated with the reduced phosphatase activity and the tau hyperphosphorylation that define it (Tanimukai and colleagues, 2005). The measured fall of the eraser and the measured rise of its inhibitor are the empirical anchors of the second crime; the AEP

cleavage of SET (Basurto-Islas and colleagues, 2013) is the mechanism that ties the rise of the inhibitor to the activation of the protease — the same protease the coerulean self-poison switches on.

Why the second crime completes the first. Consider what the two crimes do together to the balance of Section II. The first crime attacks tau on the writer side, but in a manner deeper than phosphorylation: it removes tau's microtubule-binding function by truncation and yields a self-templating seed. The second crime attacks the eraser side: it silences the phosphatase that would strip phosphate from the tau that has *not* been cut, so that the neuron's remaining tau — driven toward phosphate by the un-braked, self-poisoned kinase — accumulates the mark rather than shedding it. A neuron subject only to the first crime would make some cut seed but might still keep the rest of its tau clean by an active eraser; a neuron subject only to the second would hyperphosphorylate its tau but might not truncate it into the most transmissible seed. The coerulean neuron suffers both, from one enzyme, at once. Its tau is cut into seeds it cannot help making, and the phosphate on the tau that remains cannot be erased because the eraser has been gagged by a fragment the same enzyme released. The first crime makes the seed; the second ensures the field around it stays phosphorylated and primed. Together they are the pretangle.

A protease that also feeds the amyloid fire. It should be recorded, as an honesty and not a digression, that AEP's substrate list extends beyond tau and SET: the same enzyme cleaves the amyloid precursor protein, contributing to amyloidogenic processing, so that AEP sits at a junction where the tau and amyloid pathologies of the disease share a single protease (Kang and colleagues, 2020b; Zhang and colleagues, 2014). This dissertation does not need the amyloid arm for its argument, which concerns the genesis of tau; but it marks the breadth of the enzyme because it bears on the therapeutic reading of Section XIII. A protease that ignites tau, silences tau's eraser, and feeds amyloid production is a protease whose inhibition would reach three of the disease's processes at their common root — and it is roused, in the first neuron to fall, by a metabolite of that neuron's own transmitter.

VIII. One Enzyme, Two Crimes The Convergence in the Blue Nucleus

This section is where the dissertation's parts close into a single mechanism, and it earns the word "convergence" the way the companion volumes earned theirs: by showing that several roads to tau meet not loosely but at one enzyme, in one nucleus, from one spark. The convergence here is tighter than in either companion, because where the *Pincer* converged two arms on one kinase and the

Eraser converged two routes on one phosphatase, this volume converges the writer side and the eraser side of the whole balance on *one protease* — and locates that protease in the one neuron that manufactures its activator.

The ignition, stated as a convergence. Set the three findings of the middle sections side by side. First, the writer is *un-braked* in this nucleus: the locus coeruleus lacks the sulfated surface that stages the reelin brake (Morawski and colleagues, 2010; Pan and colleagues, 2025), so glycogen-synthase-kinase-3β runs least-restrained here of anywhere (Hiesberger and colleagues, 1999). Second, the writer is *driven* and, more than driven, the substrate is *cut*: the self-poison DOPEGAL activates AEP (Kang and colleagues, 2020), which truncates tau into an aggregation-prone seed (Zhang and colleagues, 2014), while chronic noradrenergic excess independently raises the tau kinase's activity (Jeong and colleagues, 2024). Third, the eraser is *silenced*: the same AEP cleaves SET, which gags protein phosphatase 2A (Basurto-Islas and colleagues, 2013; Tanimukai and colleagues, 2005), so the phosphate is not removed (Gong and colleagues, 1995). A writer un-braked, a writer driven and its substrate cut, an eraser silenced — three derangements of one balance, and two of the three are the work of a single enzyme roused by a single metabolite of the neuron's own norepinephrine.

Why one enzyme doing two things is worse than two enzymes doing one each. The economy of the mechanism is also its severity. Because AEP commits both crimes, the two arms of the tau balance are not merely both deranged in the coerulean neuron but *deranged together, in fixed proportion, by one activation* — there is no state of the neuron in which the seed is made but the eraser is spared, or the eraser silenced but the seed unmade, because the same enzyme does both and the same DOPEGAL switches it on. A neuron whose writer and eraser were attacked by separate, independently regulated enzymes might, by chance or by therapy, have one arm restored while the other failed; the coerulean neuron has no such luck, for its two derangements are welded to one catalytic event. This is the mechanistic form of the clinical observation that the pretangle, once it appears, is stubborn: it is stubborn because it is not a single lesion but a coordinated tipping of a two-sided balance by one master enzyme, and half-measures against one side leave the other, driven by the same activation, untouched.

Why the convergence explains the selectivity. The convergence also answers the question that has haunted the field since the pretangle's early appearance was first appreciated: *why the locus coeruleus, and not some other neuron?* Many neurons are exposed; many lack perineuronal nets; many are tonically active; many age. But only the noradrenergic neuron makes DOPEGAL, because only it metabolises norepinephrine — and DOPEGAL is the specific activator that switches on the two-crime protease. The selectivity of the first lesion is therefore not a mystery to be waved at with talk of "vulnerable neurons" but a consequence of a specific chemistry: the one nucleus that manufactures the activator of AEP is the one nucleus in which AEP is switched on early and from within, and AEP is the enzyme that both seeds tau and silences its eraser. The locus coeruleus

tangles first because it is the only neuron that can poison itself into rousing the protease that does both halves of the damage. The withheld reelin brake ensures the driven kinase meets no resistance; the self-poison and its protease do the rest. That is why the first ember catches here.

The convergence as the corpus's own logic, folded back to its origin. The companion volumes will recognise their own enzymes in this account, folded back to the point before either had begun its middle-passage work. The *Pincer*'s kinase, glycogen-synthase-kinase-3β, is here the writer that runs un-braked and driven; the *Eraser*'s phosphatase, protein phosphatase 2A, is here the eraser that AEP's cleavage of SET silences. What those volumes traced across the cortex of the disease's long middle passage, this volume finds already present, in miniature and from a single self-poisoning source, in the locus coeruleus at the very start. The corpus's account of tau, read from ignition to conflagration, is one story: a balance tipped first in one net-less, self-poisoning nucleus by one protease, and later tipped again across the cortex by the dysregulated broadcast of that same nucleus and the ungoverned microglia it fails to restrain. The first ember and the later fire are lit by the same chemistry, one cell at first and then a whole cortex. To see why the genetics point to the same place, we turn to the receptor reelin shares with ApoE.

IX. The ApoE Turn The Shared Receptor and the Two Resilient

The genetics of Alzheimer's disease, read against this dissertation's mechanism, point with unusual directness to the locus coeruleus and to the receptor system that reelin and apolipoprotein E hold in common. This section draws that convergence together, because it shows that the two rarest human resiliences yet discovered and the commonest human risk factor all act on one system — and that system is the one whose brake the coerulean neuron cannot stage.

ApoE4 accelerates the coerulean ignition directly. Section V established the mechanism, and it deserves restating here as a genetic fact: the ε4 allele of apolipoprotein E, the single greatest genetic risk factor for sporadic Alzheimer's disease, inhibits the vesicular monoamine transporter and so floods the coerulean cytosol with the norepinephrine that becomes DOPEGAL, feeding the protease that cleaves tau — while ApoE3 binds tau and protects it from that cleavage (Kang and colleagues, 2021). This is a startling relocation of ApoE4's action: not a distant effect on amyloid clearance but a *proximate accelerant of the first lesion in the brain*, acting inside the locus coeruleus to increase the very self-poison this dissertation places at the ignition. The commonest risk allele and the earliest lesion meet in the blue nucleus, and they meet through the vesicle that fails to hold the transmitter.

Reelin and ApoE share the receptor — and so share the axis of resilience. The receptors through which reelin brakes the tau kinase — ApoER2 and VLDLR — are the same lipoprotein receptors through which apolipoprotein E acts (Hiesberger and colleagues, 1999). Reelin and ApoE are, in effect, competing ligands for one receptor system, and the isoform of ApoE a person carries shapes how that system traffics and responds. This is why the two most powerful genetic modifiers of Alzheimer's disease yet found in living people both act on this one axis. The APOE3-Christchurch homozygote, who resisted autosomal-dominant Alzheimer's disease for decades despite a massive amyloid burden, carried a variant of ApoE itself (Arboleda-Velasquez and colleagues, 2019); and the Reelin-COLBOS heterozygote, who showed comparable resilience, carried a gain-of-function variant of reelin, the other ligand of the same receptors (Lopera and colleagues, 2023). Two individuals, two rare variants, one receptor system — one acting on its ApoE ligand, one on its reelin ligand — and both conferring extraordinary resistance to the disease. The axis on which resilience is written is the axis whose brake the locus coeruleus cannot stage.

The two resilient read backward onto the coeruleus. The resilience cases sharpen this dissertation's reading of the ignition in a way worth making explicit. If a gain-of-function in reelin (COLBOS) protects, and reelin's protective brake is one the coerulean neuron cannot well stage for want of the sulfated surface, then the coerulean neuron is the neuron least able to benefit from the very protection that, enhanced, confers resilience — a further sense in which the blue nucleus is the disease's weakest point. And if a protective ApoE variant (Christchurch) resists the disease while the risk ApoE4 accelerates the coerulean self-poison (Kang and colleagues, 2021), then the ApoE axis modifies the disease at least partly *through* the mechanism this dissertation traces at the ignition. The genetics do not merely co-locate with the mechanism; they press upon it from both directions — risk feeding the self-poison, resilience enhancing the brake the coeruleus cannot stage. The receptor system reelin shares with ApoE is, on this reading, the master dial of both the ignition and its resistance.

A boundary, honestly marked. The dissertation must not overstate the tidiness of this convergence. That reelin and ApoE share receptors is structural and secure; that the Christchurch and COLBOS variants confer resilience is established in the reported cases; that ApoE4 inhibits the vesicular transporter to feed DOPEGAL is shown in model systems (Kang and colleagues, 2021). But the claim that the ApoE axis modifies the *human coerulean ignition specifically* — as opposed to the disease at large — is an inference that joins these findings, not a single measured result, and the resilience cases are individually rare. The convergence is real and it is pointed; it is not yet a closed proof that the coeruleus is where ApoE and reelin do their most consequential work. The ledger grades it accordingly.

X. The Ignition, Assembled

It is time to set the whole mechanism down as one ordered sequence, so that its structure and its seams are visible at once. The ignition runs in eight steps, from the constitution of the nucleus to the seed that leaves it, and each has been given its evidence above.

First, the locus coeruleus is constitutionally unguarded: it lacks the aggrecan-based perineuronal net (Morawski and colleagues, 2010), exposes an enormous unmyelinated membrane along its long, thin axons (Giorgi and colleagues, 2017), fires tonically and becomes hyperexcitable as tau begins (Wang and colleagues, 2025), and — alone among the brain's neurons — traffics norepinephrine.

Second, the reelin brake that would restrain its tau kinase is structurally under-served, because the brake requires the sulfated surface (Pan and colleagues, 2025) that the net-less nucleus does not present — so the writer glycogen-synthase-kinase-3β runs least-braked here (Hiesberger and colleagues, 1999). (Inference; graded in the ledger.)

Third, norepinephrine escapes the synaptic vesicle into the cytosol — driven there by activity-dependent over-reuptake as α2A-autoreceptors internalise (Toyoda and colleagues, 2025) and, in ApoE4 carriers, by inhibition of the vesicular monoamine transporter (Kang and colleagues, 2021).

Fourth, cytosolic norepinephrine is metabolised by monoamine oxidase A into DOPEGAL — the toxic aldehyde produced exclusively in noradrenergic neurons (Kang and colleagues, 2020).

Fifth, DOPEGAL activates the protease asparagine endopeptidase within the neuron (Kang and colleagues, 2020) — a protease independently activated by aging and in the Alzheimer brain (Zhang and colleagues, 2014).

Sixth — the first crime — the activated protease cleaves tau at asparagine-368, abolishing its microtubule binding and yielding an aggregation- and propagation-prone seed (Zhang and colleagues, 2014; Kang and colleagues, 2020).

Seventh — the second crime — the same protease cleaves SET, whose fragments translocate to the cytoplasm and silence protein phosphatase 2A (Basurto-Islas and colleagues, 2013), so the phosphate on the neuron's remaining tau is no longer erased (Gong and colleagues, 1995; Tanimukai and colleagues, 2005) — while the noradrenergic excess independently drives the kinase (Jeong and colleagues, 2024).

Eighth, the truncated, hyperphosphorylated tau assembles into the pretangle and, being propagation-prone, is exported along the coerulean arbor as a transmissible seed, received by downstream neurons through their heparan-sulfate surfaces (Holmes and colleagues, 2013), beginning the spread the companion volumes trace to the cortex (Kang and colleagues, 2020).

The sequence is a single line from a nucleus's native constitution to the first transmissible seed in the brain, and every step but the second is a measured finding; the second is a graded inference. This is the ignition, assembled — the first ember, and how it catches.

XI. 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 relay of this dissertation is only as strong as its weakest load-bearing joint, and the reader is owed an explicit accounting of where the argument stands on measured ground and where it stands on inference.

Strong (imported, established) — the locus coeruleus bears the earliest tau pathology in the human brain and lacks a perineuronal net. Securely established: pretangle tau appears in the locus coeruleus from the third decade, decades before symptoms, and is the first detectable Alzheimer's-like neuropathology anywhere in the brain (Mather and Harley, 2016; Weinshenker, 2018); and the nucleus is constitutionally devoid of the aggrecan-based net whose presence marks tau-resistant neurons (Morawski and colleagues, 2010; de Vries and colleagues, 2024). The starting point of the whole argument is not in doubt.

Strong (established) — DOPEGAL is produced exclusively in noradrenergic neurons and activates asparagine endopeptidase in the locus coeruleus. Directly demonstrated: norepinephrine metabolism by monoamine oxidase A yields DOPEGAL only in noradrenergic cells, and DOPEGAL activates AEP, providing the molecular basis for the selective vulnerability of the nucleus (Kang and colleagues, 2020). This is the keystone of the first question, and it stands on primary experiment.

Strong (established) — asparagine endopeptidase cleaves tau at N368 into an aggregation- and propagation-prone seed, and the cleavage is causal. Directly demonstrated: AEP is activated in aging and Alzheimer brain, cleaves tau, abolishes its microtubule-assembly function, and induces aggregation; AEP deletion and uncleavable-tau mutants rescue pathology and cognition (Zhang and colleagues, 2014), and the coerulean, DOPEGAL-driven version drives neurotoxicity and forebrain spread (Kang and colleagues, 2020). The first crime stands on the cleanest available loss-of-function evidence.

Strong (established) — the same protease cleaves SET to inhibit protein phosphatase 2A, and the eraser is measurably down in the disease. Directly demonstrated: AEP cleaves SET, whose fragments translocate and inhibit the phosphatase, driving

tau hyperphosphorylation (Basurto-Islas and colleagues, 2013); the endogenous inhibitors are up-regulated in the disease (Tanimukai and colleagues, 2005); and PP2A tau-directed activity is reduced by roughly a third (Gong and colleagues, 1995; Gong and colleagues, 1993). The second crime stands on established biochemistry. *What this dissertation adds by synthesis is the recognition that the SET-cleaving protease and the tau-cleaving protease are the one enzyme, so that in the DOPEGAL-activated coerulean neuron both crimes issue from one activation — a joining that is a strong inference from the shared identity of the enzyme, not yet a single experiment measuring both cuts in the same coerulean cells.*

Strong (established) — apolipoprotein E4 feeds the coerulean self-poison by inhibiting the vesicular monoamine transporter. Directly demonstrated in model systems: ApoE4 binds and inhibits the transporter, excluding norepinephrine from the vesicle and increasing cytosolic DOPEGAL and AEP-mediated tau cleavage, while ApoE3 protects tau (Kang and colleagues, 2021). The genetic accelerant of the ignition stands on primary experiment; its extrapolation to the human coerulean ignition at large is the inference below.

Moderate (mechanistic, partly inferred) — norepinephrine reaches the cytosol through activity-dependent over-reuptake as autoreceptors internalise. Shown in a stress model: chronic stress internalises α2A-autoreceptors and coupled potassium channels, over-exciting the neuron and increasing monoamine oxidase A, DOPEGAL-induced protease activity, and truncated tau (Toyoda and colleagues, 2025). The mechanism is demonstrated in rodent under a stress paradigm; its identity with the human sporadic ignition is a strong but not proven extrapolation.

Inference (the reelin claim — the dissertation's most-graded joint) — the reelin brake is structurally under-served in the locus coeruleus because the nucleus lacks the sulfated surface that stages it. This is an *inference from two established facts* — that the locus coeruleus lacks the net (Morawski and colleagues, 2010) and that the reelin brake requires N-sulfated heparan sulfate as an obligate co-receptor (Pan and colleagues, 2025) — joined to the established reelin-to-GSK-3β brake (Hiesberger and colleagues, 1999; Kocherhans and colleagues, 2010). It is *not* a measured finding: no study has assessed reelin signalling, Disabled-1 phosphorylation, or reelin-receptor expression in the human locus coeruleus, and the primary literature contains no work on reelin in this nucleus. The inference is strong because both premises are secure and the connecting logic is direct, but it is offered as inference, and the answer to the corpus's reelin question — reelin as guardian withheld, not arsonist — rests on it. Section XII states the experiment that would confirm or refute it.

Inference (the genetic convergence) — the ApoE/reelin receptor axis modifies the coerulean ignition specifically. That reelin and ApoE share receptors is structural; that Christchurch and COLBOS confer resilience is established in the reported cases; that ApoE4 feeds the self-poison is shown in models. That these act *through the coerulean ignition specifically*, as opposed to

the disease at large, is a synthesis of the findings, not a single result, and the resilience cases are rare. Pointed, but not closed.

XII. Predictions and Falsification

A synthesis earns its keep by exposing itself to refutation, and this dissertation makes several commitments specific enough to be wrong. Each is stated so that a definite experimental outcome would overturn it.

On the reelin inference — the load-bearing test. If the locus coeruleus is under-served by the reelin brake for want of the sulfated staging surface, then the coerulean neuron should show low reelin-dependent Disabled-1 phosphorylation and sparse or poorly-clustered ApoER2/VLDLR relative to net-bearing, tau-resistant neurons, *even in the young, pre-pathological brain*. The direct test is to measure reelin-pathway signalling and receptor staging in the human locus coeruleus across age, against a net-rich control nucleus. Should the coerulean neuron prove to carry a robust, well-staged reelin signal after all, the dissertation's answer to the reelin question is wrong, and reelin's structural absence must be struck from the account of the ignition. This is the prediction the dissertation most wishes tested.

On the one-enzyme-two-crimes claim. If one activated protease commits both crimes in the coerulean neuron, then in the DOPEGAL-exposed or early-pretangle locus coeruleus, AEP-cleaved tau (the N368 fragment) and AEP-cleaved SET (with cytoplasmic SET translocation and reduced PP2A activity) should appear *together, in the same neurons, on the same timeline*, and AEP inhibition should abolish both. Finding truncated tau without SET cleavage, or SET cleavage without truncated tau, in the same DOPEGAL-driven cells would falsify the claim that the two crimes issue from one activation.

On selectivity. If the self-poison explains the selectivity of the first lesion, then blocking DOPEGAL production — by inhibiting monoamine oxidase A, or by restoring vesicular sequestration of norepinephrine — should reduce AEP activation and tau cleavage *specifically in noradrenergic neurons*, and non-noradrenergic neurons (which cannot make DOPEGAL) should not be rescued by the same intervention because they were never ignited by this route. A monoamine-oxidase-A intervention that rescued non-noradrenergic tau ignition would indicate the DOPEGAL route is not the selective mechanism.

On the ApoE accelerant. If ApoE4 accelerates the ignition by feeding the self-poison, then coerulean cytosolic norepinephrine, DOPEGAL, AEP activity, and N368-tau should be higher in

ApoE4 carriers than in non-carriers, *early*, before cortical pathology — and restoring vesicular monoamine transport should normalise them. Absence of any ApoE4 effect on coerulean DOPEGAL or AEP would sever the genetic accelerant from the mechanism.

On timing. If the ignition is cell-autonomous and self-poisoning, it should precede, not follow, the microglial and noradrenergic-broadcast derangements the companion volumes trace — the coerulean neuron should cut its own tau before its dysregulated output has begun to derange the cortex. Finding the microglial turn or cortical tau to precede coerulean AEP activation would invert the corpus's ignition-before-conflagration ordering.

XIII. Therapeutic Corollaries Reaching the Ember Before the Fire

The mechanism dictates its own therapeutics, and the dictation is unusually specific because the ignition, unlike the mature disease, runs through a small number of named, druggable steps in a single nucleus. The governing principle is one of *timing*: the first ember is reachable in a way the later fire is not, because at the ignition the pathology is still local, still cell-autonomous, and still dependent on the chain this dissertation has traced.

Disarm the one protease. The most direct corollary is that asparagine endopeptidase is a target of unusual leverage, because inhibiting it would reach both crimes at once and the amyloid arm besides: an AEP inhibitor would spare tau from truncation into a seed (Zhang and colleagues, 2014; Kang and colleagues, 2020), spare SET from the cleavage that silences the eraser (Basurto-Islas and colleagues, 2013), and reduce amyloidogenic processing (Kang and colleagues, 2020b) — three of the disease's processes disarmed at their common enzyme. That a single protease sits at the convergence of the writer-side and eraser-side crimes is not merely an explanatory economy but a therapeutic one.

Cut off the self-poison upstream. If the protease is roused by DOPEGAL, then reducing DOPEGAL is an equally rational aim, and it has two handles. The first is monoamine oxidase A, the enzyme that makes DOPEGAL from cytosolic norepinephrine; inhibiting it would starve the protease of its activator specifically in noradrenergic neurons (Kang and colleagues, 2020). The second is vesicular sequestration: restoring or protecting vesicular monoamine transport would keep norepinephrine packaged and out of the cytosol, and is the rational counter to the ApoE4 mechanism that empties the vesicle (Kang and colleagues, 2021). Both handles act *before* the protease, and both are specific to the self-poisoning nucleus.

Quiet the over-firing that feeds the leak. Because activity-dependent over-reuptake drives norepinephrine into the cytosol (Toyoda and colleagues, 2025), and because the companion *Pincer* volume located a window of coerulean *excess* before the terminal depletion, quieting the hyperexcitable nucleus in that early window — restoring the α2A-autoreceptor tone that normally restrains it — would reduce the self-poisoning leak at its source. The companion volume's caution applies with full force: this is an intervention for the window of excess, not for the depleted endgame, and its sign flips across the trajectory.

Restore the withheld brake — and un-silence the eraser. The two graded, structural derangements suggest two more distal aims. If the reelin brake is under-served for want of the sulfated staging surface, then interventions that restore matrix sulfation or enhance reelin signalling — the axis the COLBOS resilience variant strengthens (Lopera and colleagues, 2023) — would, in principle, restore restraint to the un-braked coerulean kinase; but this dissertation grades the reelin claim as inference and marks this corollary as the most speculative. And because the eraser is silenced rather than destroyed, lifting SET from the phosphatase would restore erasing capacity to a neuron whose tau is not yet fibrillar — the same logic of a paused-not-dead enzyme the companion *Eraser* volume urged.

The timing is the therapy. The single most important corollary is temporal. The ignition is reachable precisely because it precedes the self-sustaining loops the companion volumes describe — the tau-inflammasome cycle, the propagating seed, the cortical spread. Reach the coerulean neuron in the decades-long window when its pathology is still local and still dependent on its own self-poison, and one is arresting a fire of a single ember; reach it after the seed has spread and the loops have closed, and one inherits a conflagration that no longer needs its spark. The corollary the whole corpus has pressed toward finds here its earliest possible application: the first ember is the first, and best, place to put the fire out.

XIV. Coda The Ember and the Guard

There is a particular poignancy to the way Alzheimer's disease begins, and this dissertation has tried to render it in mechanism without losing it in mechanism. The disease begins in the one nucleus that gives the waking brain its vigilance — the small blue cluster that makes us alert, that fixes our attention, that answers to novelty and stress — and it begins there because that nucleus, to do its work, must handle a transmitter that becomes, in the wrong compartment, a poison. The locus coeruleus is undone by the chemistry of its own vocation. It tangles first because it alone can poison itself into rousing the protease that both seeds its tau and silences the enzyme that would keep tau

clean, and it does this in the decades before anything else has gone wrong, alone, from within, needing nothing from outside to light the first ember.

And the guard that might have held the fire down was never posted. The reelin brake that restrains the tau kinase is one a neuron must stage on a sulfated surface, and the locus coeruleus was built without that surface — so the writer runs un-braked in exactly the nucleus where the self-poison drives it hardest. This is the answer to the question the corpus's reelin volumes raised: reelin is present at the ignition only by its absence. It is not the arsonist; it is the guardian withheld, thinnest where the fire is first. That the two rarest human resiliences yet found both strengthen the very receptor axis the coeruleus cannot stage is the disease's own commentary on where its weak point lies — and where, perhaps, it might be defended.

To say that the tangle begins as one protease's double crime in one self-poisoning, unguarded neuron is not to make the disease smaller. It is to locate its beginning precisely enough to be reached. The mature disease is a conflagration across the cortex, fed by loops that outlive their spark, and it has defeated every therapy aimed at its height. But a conflagration has a first ember, and this dissertation's whole argument is that the first ember is knowable, nameable, and — in the long window before it throws its sparks — reachable. The blue nucleus poisons itself in the dark, decades early, with the metabolite of the transmitter that keeps us awake. To catch it there, before the guard it never had is even missed, is the earliest hope the mechanism allows.

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