THE COERULEAN PINCER

Norepinephrine's Dual-Armed Assault on the Neuron — How the Dysregulated Locus Coeruleus Cuts Reelin's Brake from Outside and Floors the Tau Kinase from Inside, Converging on Glycogen-Synthase-Kinase-3β

The Two-Handed Nucleus · The Rising Tide · The Outer Cut
The Inner Throttle · The Convergence at the Kinase

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The norepinephrine-centred companion to The Coerulean Shears. That volume took the protease MMP-9 as its protagonist and norepinephrine as 'the hand.' This one takes norepinephrine itself as its subject and traces its dual-armed pincer: one arm reaching outside the neuron to call up the protease that cuts reelin's brake, the other reaching inside to over-activate the tau kinase directly — the two converging on a single molecule, glycogen-synthase-kinase-3β. Because both arms spring from one signal, they can be disarmed at one handle.

"The nucleus does not fail all at once, and it does not fail quietly. For years the sickening neurons fire harder, not softer — and that deranged excess reaches the cortical neuron with two hands: one that cuts its outer defences, and one that presses directly on the enzyme of the tangle. This dissertation is written to show that they close together, on a single molecule."

— ONS Methodology Working Notes, 2026

For those who read the loss of the locus coeruleus as a story of subtraction — a light going out — and so overlooked the long middle passage in which the light, before it dims, burns dangerously bright.

THE COLLAPSE FRAMEWORK COERULEAN & MATRIX 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 — MMP-9, the named instrument that cuts the matrix

The Coerulean Pincer (norepinephrine's two arms, converging on GSK-3β) — this volume

This volume reorganises the coerulean cascade around its true protagonist — not the protease but the neuromodulator that calls it up. It argues that the noradrenergic contribution to Alzheimer's tauopathy is not a deficiency but a pincer: the failing locus coeruleus, the first structure in the brain to tangle and constitutionally without a net of its own, passes through a long phase of hyperactivity in which it broadcasts an excess of norepinephrine. With one arm that excess dismantles the neuron's extracellular defences from outside — calling up MMP-9 to cut the sulfated surface that stages reelin's brake on tau. With the other it over-activates the tau kinase from inside. The two arms converge, as exact antagonists, on glycogen-synthase-kinase-3β — the brake released from one side, the throttle floored from the other — and the kinase, disinhibited and driven at once, is unleashed as neither arm alone could unleash it. Because both arms spring from one signal, the pincer has a handle; and a handle can be seized.

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Abstract

A companion dissertation, *The Coerulean Shears*, identified the instrument by which the perineuronal net and the reelin-staging surface are destroyed in Alzheimer's disease — matrix metalloproteinase-9 — and named the hand that guides it: norepinephrine, from the locus coeruleus. In that account the enzyme was the protagonist and the neuromodulator the effector cause; the argument was written from the point of view of the blade. This dissertation inverts the lens. It takes norepinephrine itself as its subject and asks what the dysregulated coerulean output does, in its entirety, to the neuron it reaches — and finds that it does not one thing but two, along two anatomically distinct routes, with a single molecular destination. The thesis of this volume is that the noradrenergic contribution to tauopathy is not a loss of signalling but a *pincer*: a dual-armed assault in which one arm reaches outside the neuron to dismantle its extracellular defences, and the other reaches inside to press directly on the enzyme those defences existed to restrain.

The origin of both arms is a single, counter-intuitive fact of natural history. The locus coeruleus — the brain's sole cortical source of norepinephrine — is constitutionally without a perineuronal net; it is therefore the first structure in the human brain to accumulate hyperphosphorylated tau, bearing pretangles by the third decade of life, decades before dementia. As its neurons sicken they do not fall silent at once. Though the nucleus loses cells throughout, its survivors compensate — raising their synthesis, sprouting their projections, and firing more — so that the noradrenergic *output* delivered to the cortex rises even as the neuronal *number* falls; for a protracted interval the surviving system broadcasts a pathological excess of norepinephrine, measurable as elevated release at the tau-burdened source and as raised norepinephrine in the cerebrospinal fluid of living patients, where it climbs with the severity of the disease. This chronic excess — not a deficiency — is the trigger the pincer requires, and it drives two cascades at once.

The first arm acts extracellularly. Excess β-adrenergic drive on cortical microglia and astrocytes — the brain's matrix-remodelling cells, themselves deranged out of their homeostatic character by the same failing nucleus that governs them — raises cyclic AMP, activates protein kinase A, and mobilises the transcription factors AP-1 and NF-κB through the mitogen-activated-protein-kinase and NF-κB pathways, which occupy the promoter of matrix metalloproteinase-9 and release the enzyme into the extracellular space. There the protease executes three cuts: it cleaves the lectican core proteins of the perineuronal net, sheds the syndecan ectodomains that carry the N-sulfated heparan sulfate that reelin requires as an obligate co-receptor, and strips the lipoprotein receptors ApoER2 and VLDLR from the surface. With its co-receptor bed degraded and its receptors shed, the reelin signal fails at the surface even where reelin protein persists — starving the intracellular reader Disabled-1 and releasing the internal brake it maintains on glycogen-synthase-kinase-3β. The second arm acts intracellularly and needs no protease at all: chronic exposure to excessive norepinephrine

directly over-activates protein kinase A and glycogen-synthase-kinase-3β within the target neuron, driving the hyperphosphorylation of tau. One arm removes the kinase's brake from outside; the other presses the kinase's accelerator from inside; and the two arms converge on one molecule. Glycogen-synthase-kinase-3β — the principal tau kinase, the hub of the "GSK3 hypothesis" of the disease — is the point at which reelin's protection and norepinephrine's malignancy meet as exact antagonists, and it is disinhibited from one side and driven from the other at once. We assemble the pincer connection by connection, grade each in an explicit validity ledger — candid that the norepinephrine-to-metalloproteinase step is proven in the periphery and inferred in the brain, that the direct over-activation of the kinase is reported but its wiring incompletely resolved, and that tonic norepinephrine is, in a different regime, *protective* — and close on the pincer's single redeeming feature: because both arms spring from one signal, they can in principle be disarmed at one handle.

I. The Two-Handed Nucleus

There is a habit of thought about the locus coeruleus in Alzheimer's disease that this dissertation is written to unseat, and it is worth stating plainly at the outset because it is nearly universal and nearly wrong. The habit is to read the coerulean contribution to the disease as a *deficiency*. The nucleus degenerates; its neurons die; the cortex is deprived of norepinephrine; and the loss of that norepinephrine — a transmitter of arousal, attention, and, through the plasticity it supports, of memory — is counted among the disease's insults. The story is one of subtraction, of a light going out, of a supply failing. It is true as far as it goes. It is also, as an account of how the coerulean lesion *causes* the pathology rather than merely accompanying its symptoms, an account of the wrong phase of the trajectory, and it misses the interval in which the damage is actually done.

For the locus coeruleus does not fail all at once, and it does not fail quietly. Between the health of the young brain and the silence of the end-stage nucleus there lies a long and clinically decisive middle passage — years to decades in duration — during which the sickening neurons, rather than falling still, *fire harder*. They enter a state of compensatory hyperactivity; they up-regulate the enzymes of catecholamine synthesis and the receptors that read them; and they broadcast, along an arbor that reaches into every fold of the cortex, not a failing trickle of norepinephrine but a pathological excess. The naïve deficiency model reads only the endgame. The disease, on the evidence assembled here, is decided in the middle passage — and in the middle passage the coerulean output is not withdrawn but *deranged upward*. To understand how the nucleus injures the cortex, one must study not the silence that ends the trajectory but the excess that fills its long approach.

And that excess, this dissertation argues, injures the neuron in two ways at once. This is the central claim, and it deserves to be stated in the geometric form that gives the volume its title. Dysregulated norepinephrine does not act through a single arrow — one cause, one effect, one pathway from nucleus to tangle. It acts through a *pincer*: two arms, closing from opposite sides upon a single point. One arm reaches *outside* the target neuron, into the extracellular matrix that shields it, and dismantles that matrix — calling up a protease that cuts the perineuronal net, sheds the sulfated bed on which the neuron's resilience signal is staged, and strips away the very receptors that signal fires. The other arm reaches *inside* the neuron and presses directly on the enzyme of the tangle. The first arm cuts a brake; the second floors an accelerator; and the brake and the accelerator turn out to act on the same machine. The two arms converge, with an exactness that is the analytic heart of this dissertation, on a single molecule — glycogen-synthase-kinase-3β, the principal kinase that hyperphosphorylates tau. Norepinephrine, dysregulated, disinhibits that kinase from without and drives it from within, in one motion, so that tau is released on both counts and the tangle forms where the two arms meet.

The image of the pincer is not decoration. It carries three consequences that a single-arrow account cannot, and each is developed in a section of this dissertation. The first is *synergy*: because one arm removes an inhibitory input to the kinase while the other adds an activating one, their effects on net kinase activity are not merely additive but compounding, and no measurement of either arm alone can predict the derangement the two produce together. The second is *convergence as a target*: because both arms terminate on one enzyme, that enzyme is the point at which the whole noradrenergic assault could in principle be intercepted downstream — a single choke-point for a two-pronged attack. And the third, the most consequential for the clinic, is *a shared handle*: because both arms originate in one signal, the pincer can be disarmed not only at its convergence but at its source, by quieting the deranged noradrenergic drive itself — an intervention that disables both tines at once, and that the clinic already possesses the pharmacology to attempt. A disease mechanism shaped like a pincer is more dangerous than one shaped like an arrow, because it attacks from two sides; but it is also, for that same reason, more *tractable*, because it has a handle where the two arms join, and a handle can be seized.

This dissertation reads across the same three literatures its companion did — the reelin axis, the perineuronal-net and sulfated-matrix biology, and the neurochemistry of the locus coeruleus — but it reorganises them around a different protagonist. Where *The Coerulean Shears* asked "what is the blade, and whose hand holds it," the present volume asks the anterior and the larger question: "what does the hand itself do?" The answer is that the hand has two hands. The nucleus is two-handed, and it closes them together.

II. The Kinase at the Center and the Brake That Guards It — Glycogen-Synthase-Kinase-3

Because the whole argument of this dissertation converges on a single enzyme, that enzyme must be introduced first, and the brake that restrains it described, before either arm of the pincer is traced. If the reader holds one molecule in mind through everything that follows, it should be glycogen-synthase-kinase-3β, for it is the point at which reelin's protection and norepinephrine's malignancy meet.

Glycogen-synthase-kinase-3β is the principal kinase of the tangle. It is a constitutively active, proline-directed serine/threonine kinase — active by default, that is, and normally *held down* rather than switched on — and it occupies a central and causal place in the pathogenesis of both sporadic and familial Alzheimer's disease. Its over-activity, on the influential synthesis of Hooper, Killick, and Lovestone (2008), accounts at once for the hyperphosphorylation of tau, for increased amyloid-β production, for the plaque-associated microglial inflammatory response, and for memory impairment itself — a convergence so broad that its authors named it "the GSK3 hypothesis of Alzheimer's disease." For the purposes of this dissertation the decisive fact is the narrowest of these: glycogen-synthase-kinase-3β is the principal kinase that phosphorylates tau at the residues whose hyperphosphorylation detaches it from the microtubule and drives it into the paired helical filament. To govern the activity of this kinase is to govern the fate of tau. The tangle is, in large part, a record of what this enzyme was permitted to do.

Because the kinase is constitutively active, the biological question is never how it is turned *on* — it is on already — but how it is held *off*, and by what, and what happens when the restraint is withdrawn. This reframing is essential to the pincer, because a default-on enzyme can be over-activated in two entirely distinct ways: by removing something that was holding it down, or by adding something that pushes it further up. The two arms of the coerulean pincer are, at bottom, one instance of each. And the thing that holds the kinase down — the brake this dissertation watches being cut — is the reelin signal.

Reelin brakes the kinase from inside the neuron. Reelin, a large secreted glycoprotein first identified as an architect of the layered cortex (D'Arcangelo and colleagues, 1995), acts in the adult brain through 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). Binding clusters the receptors and induces the tyrosine phosphorylation of the cytoplasmic adaptor Disabled-1, which recruits phosphoinositide-3-kinase and, through it, activates the kinase Akt; and activated Akt phosphorylates glycogen-synthase-kinase-3β on its regulatory serine, holding the tau kinase in its inhibited state (Hiesberger and colleagues, 1999). A live reelin signal, that is, is a continuous *inhibitory input* to the tau kinase: it keeps the constitutively active

enzyme suppressed, moment by moment, and holds tau unphosphorylated. Withdraw the signal and the inhibition lifts; the default-on kinase returns to its default, and tau phosphorylation rises. This is not an incidental effect at the margins of reelin biology — it is the mechanism by which reducing reelin accelerates tau pathology in transgenic models (Kocherhans and colleagues, 2010) and by which reelin signalling opposes the amyloid-β-driven derangement of the synapse (Durakoglugil and colleagues, 2009). Reelin is, in the adult, a brake — and the pedal it presses is the inhibition of this one kinase.

The brake is staged on a sulfated surface that lives outside the neuron. The reelin signal does not assemble in free solution. It requires a scaffold, and the scaffold is extracellular, and that is what exposes it to the first arm of the pincer. Reelin needs N-sulfated heparan sulfate 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 receptor 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 surface — and every one of its extracellular components sits on the outside of the membrane, in the matrix, on precisely the surface a secreted protease patrols. That same sulfated matrix, condensed into the perineuronal net, is also the physical shield whose presence marks the neurons that resist the tangle and whose absence marks the nuclei that succumb to it earliest (Morawski and colleagues, 2010; de Vries and colleagues, 2024), and it is actively destroyed in the disease by microglia (Crapser and colleagues, 2020). The companion dissertations established that this one surface discharges three offices — it shields the neuron, it stages the reelin brake, and it gates the entry of tau. The present dissertation needs only the second of these offices: that the brake on the tau kinase is staged on an extracellular surface, and that an extracellular surface can be cut.

Disabled-1 is the reader the pincer cannot touch — and therefore the best witness to its work. One component of the reelin apparatus lies safely inside the membrane, beyond the reach of any extracellular protease: the adaptor Disabled-1, whose phosphorylation state integrates everything that has happened at the surface into a single output, kinase-suppressed or kinase-released. The pincer cannot cleave Disabled-1. But it does not need to. By stripping the surface complex that feeds it, the first arm drives the reader's output to the kinase-released state from outside, leaving the adaptor intact and simply *unfed*. This is why the most telling biomarker in the disease 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) — the exact signature of a brake failing not for want of a pedal but because the linkage to the pedal has been cut.

Fix these facts in place — a default-on tau kinase, held down by a reelin signal, that signal staged on a cuttable extracellular surface and read by an untouchable intracellular adaptor — and the target of the entire coerulean assault comes into focus as a single molecule with a single

vulnerability. The tau kinase can be unleashed by cutting the brake that holds it, and it can be unleashed by pressing it directly. Norepinephrine, dysregulated, does both. To the origin of that dysregulation we now turn.

III. The Origin Coerulean Hyperactivity and the Rising Tide

The pincer has a single origin, and the origin is an accident of anatomy written into the brain long before the disease begins. The locus coeruleus has no perineuronal net of its own.

The unguarded nucleus. The subcortical survey that first established the net's protective role made the observation almost in passing, and it has taken two decades for its full weight to register: the nuclei attacked earliest and hardest by tau — the locus coeruleus foremost among them, 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 locus coeruleus is thus, by its native constitution, an unguarded neuron. It lacks the sulfated shield that resists the tangle; it lacks, by the argument of Section II, the very staging bed on which its own reelin brake would be presented; and its long, thin, unmyelinated axons expose an enormous membrane surface to whatever the extracellular space contains. Of all the brain's nuclei it is among the least defended — and it is the first to fall.

The first tangle in the brain. The natural history follows from the geometry. The earliest tau pathology in the human brain — the pretangle, soluble hyperphosphorylated tau — appears not in the cortex but in the locus coeruleus, and it appears astonishingly early: the great majority of people show at least some tau pathology in this nucleus by their mid-twenties, decades before any possibility of dementia (Mather and Harley, 2016). From there the pathology spreads along the coerulean projections to the other neuromodulatory nuclei and, later, to the cortex (Ghosh and colleagues, 2019; Giorgi and colleagues, 2017). Hyperphosphorylated tau in the locus coeruleus is now recognised as the first detectable Alzheimer's-like neuropathology anywhere in the human brain (Weinshenker, 2018). The nucleus that supplies the cortex with norepinephrine is, on the pretangle timeline, the nucleus in which the disease begins.

The biphasic trajectory — hyperactivity before silence. Here the argument turns on a fact the deficiency model omits. The trajectory from the first coerulean pretangle to the end-stage loss of noradrenergic supply is not monotonic. It is biphasic. Before the nucleus is depleted, its sickening neurons pass through a protracted phase of *hyperactivity* — indeed of hyperexcitability — in

which the surviving cells increase their firing, and the disease is thought to be driven, in part, by this over-activity rather than by the eventual under-activity that ends it (Weinshenker, 2018; Mather and Harley, 2016). The long road to the ruin of the nucleus runs, that is, uphill before it runs down. In an experimental model of the coerulean pretangle, the pathology was accompanied by up-regulation of β1-adrenoceptors as it advanced (Ghosh and colleagues, 2019) — the cortex being tuned, at the receiving end, to read *more* noradrenergic signal even as the nucleus prepares, eventually, to send less. For a decisive interval, then, the cortex is exposed not to a failing supply of norepinephrine but to an excess of it, delivered onto an up-regulated bed of receptors, and broadcast from a single small source across the whole forebrain along the same diffuse arbor down which the tau itself is proposed to travel (Giorgi and colleagues, 2017).

The reduction that is real, and the output it conceals. An objection must be met here at once, and squarely, because it is the objection most likely to be raised against this whole dissertation: the dominant reading of the clinical literature is that norepinephrine is *reduced* in Alzheimer's disease, and that reading is not wrong — it is incomplete, because it measures the wrong variable. Two quite different things are meant by "the noradrenergic supply," and the disease moves them in opposite directions. The first is the *hardware*: the number of locus-coeruleus neurons, the density of their axonal projections, and the abundance of the norepinephrine transporter that clears the transmitter — and all three decline, progressively and unambiguously, as the disease advances (Cao and colleagues, 2021). The second is the *output*: the quantity of norepinephrine the surviving system actually delivers, indexed by its synthesis, its release, and its firing rate — and this, against the naïve expectation, *rises*. The reconciliation is compensation. Confronted with the loss of their fellows, the surviving locus-coeruleus neurons do not merely persist; they up-regulate. Post-mortem, they show increased tyrosine-hydroxylase messenger RNA — more synthetic enzyme per surviving cell — together with dendritic and axonal sprouting and remodelled adrenoceptors, the anatomical signature of a system straining to cover a widening deficit (Szot and colleagues, 2006). And the strained system over-delivers: in living patients, the concentration of norepinephrine in the cerebrospinal fluid, an index of central noradrenergic activity, is not reduced but *elevated*, and it climbs *further* with the severity of the disease — higher in advanced Alzheimer's disease than in mild disease or in healthy aging (Elrod and colleagues, 1997) — a result a recent cohort confirms, finding cerebrospinal-fluid noradrenaline increased in Alzheimer's disease and correlated with its biomarkers even as locus-coeruleus integrity, measured by imaging, declines (Falgàs and colleagues, 2024). The paradox is only apparent: fewer neurons, each working harder, can raise the total, and do. The tissue content of norepinephrine in the end-stage cortex may indeed fall as the hardware finally gives way — but that is the terminal collapse, not the long pathogenic window that precedes it, and it is the window, not the endpoint, on which the pincer depends. The failure to separate the falling hardware from the rising output is, this dissertation contends, the single confusion that has let the noradrenergic system be mis-read as a story of pure loss.

The excess is measured at its source, in the tau-burdened nucleus itself. The compensatory account would remain merely inferential were the excess visible only downstream, in the fluid, where peripheral sources muddy its reading; but it has now been measured at the source, in the brain. In a tauopathy model, locus-coeruleus neurons bearing phosphorylated tau become *hyperexcitable* early — depolarised, more readily fired, discharging more spontaneous action potentials — as their inhibitory GABAergic tone weakens, and, by direct voltammetric measurement, they *release more norepinephrine* than healthy neurons at the same ages (Wang and colleagues, 2025). The tau lesion does not quiet the neuron; it makes it fire and secrete in excess, precisely the state the pincer requires, and it does so from the moment the pretangle appears. A computational synthesis of the whole trajectory arrives at the same biphasic shape from the systems level: a compensatory hyper-activation of the noradrenergic nucleus that only later, with the progression of the lesion, gives way to a down-regulation of catecholamine release (Caligiore and colleagues, 2020). Hyperactivity first, from the tau-burdened neuron outward; depletion last. The excess is not a supposition the pincer needs the reader to grant; it is a measurement the pincer exists to explain.

The rising tide is the trigger. This chronic noradrenergic excess — the rising tide of the middle passage — is the single event from which both arms of the pincer spring. It is not two triggers but one: the same deranged signal, arriving at the same cortical territories, sets in motion the extracellular cascade of the first arm and the intracellular cascade of the second. The importance of insisting on the *excess*, rather than the deficiency, is not merely chronological pedantry. It is that the two downstream cascades this dissertation traces are both driven by *high* noradrenergic tone and would both be *relieved*, not worsened, by its reduction — so that the phase of the disease in which they operate is precisely the phase the naïve model overlooks, and the intervention they invite is precisely the one the deficiency framing forbids. The hand does not fall slack at the outset of the disease. For years it tightens on both tines. To follow those tines is the work of the next two sections: the first arm, reaching outward; the second, reaching in.

IV. The First Arm The Outer Cut (Calling Up the Shears)

The first arm of the pincer reaches outside the neuron, into the matrix, and its object is to cut the brake by destroying the surface on which the brake is staged. It does this not with its own hand but by conscripting the brain's matrix-remodelling cells and the protease they carry. The arm has four joints, and each has been established, though — as the ledger will insist — not all in the same tissue. But before those joints are traced, a prior question must be answered, one the companion dissertation never asked: why are these cells — in the healthy brain the matrix's *keepers*, not its

wreckers — available to be conscripted as its vandals at all? The answer is that they too are governed by the failing nucleus, and their dysfunction is not an independent misfortune but the same coerulean collapse read one layer up.

Why the effector turns: the microglion loses its governor. In the healthy brain the microglion is not a vandal but a gardener — a homeostatic, surveillant cell whose fine processes patrol the parenchyma, clear debris and amyloid, and remodel the synapse with precision — and it holds that disciplined character under the direct governance of noradrenergic tone. The demonstration usually cited for norepinephrine's protective role, that the locus ceruleus "controls Alzheimer's disease pathology by modulating microglial functions" (Heneka and colleagues, 2010), read structurally rather than pharmacologically, names the locus coeruleus the *governor* of microglial state: it is the coerulean signal, more than any other, that holds the microglion in its quiescent, amyloid-clearing, matrix-preserving character. The first arm therefore rests on a premise it must earn — that the governed cell has turned — and the dissertation owes an account of why the governance fails.

The governance is real, receptor-mediated, and cell-autonomous — and its sign is the key. That microglia read noradrenergic tone is now shown directly and at cellular resolution. Microglia express functional β-adrenergic receptors, and the ambient noradrenergic tone of the waking brain acts through them to set the microglion's behaviour: noradrenergic tone suppresses the cell's process surveillance (Liu and colleagues, 2019), and pharmacological stimulation of β-adrenergic receptors reproduces that suppression in an effect shown to *require the β-adrenergic receptors on the microglia themselves* (Stowell and colleagues, 2019). Note the sign with care, for it is the hinge of the whole reconciliation: β-adrenergic drive *suppresses* the microglion's homeostatic surveillance. A disciplined tonic signal, fluctuating gently with arousal, tunes that surveillance up and down within a healthy band. A signal that is chronically, pathologically high does not tune it — it pins it down.

Dysregulation, not absence, breaks the governance — the Heneka paradox resolved. Here the contradiction that has shadowed this dissertation since it first invoked Heneka's result can be dissolved, and its dissolution is the mechanistic core of this section. The paradox is stark: Heneka and colleagues produced an inflammatory, poorly-phagocytic microglion by *removing* norepinephrine, yet this dissertation blames its *excess*. How can too much and too little damage the same cell? Because the two findings catch the microglion in two different regimes, and chronic excess reproduces the harms of depletion by another road. Chronic β-adrenergic over-stimulation pins down the surveillance the gardener needs to make its rounds (Stowell and colleagues, 2019; Liu and colleagues, 2019), so the cell ceases to patrol and clear — blinded not by the loss of its governor's voice but by that voice shouting without pause. Chronic over-stimulation of any G-protein-coupled receptor, moreover, desensitises it: sustained β-adrenergic agonism recruits the phosphorylation and internalisation machinery that render a receptor deaf, so that on the very

channel through which norepinephrine held the microglion calm, the cell — bathed in surplus transmitter — becomes functionally *deprived* of it, reproducing at the receptor the state Heneka produced by depletion. And when at last the coeruleus collapses into regional loss, the calming signal is withdrawn a third time, now for want of transmitter (Heneka and colleagues, 2010). By over-stimulation, by desensitisation, and finally by depletion, the microglion loses its governor thrice over. Excess and deficiency are therefore not rival explanations of microglial dysfunction; they are successive chapters of one story of failed governance, and the pincer's window sits in the excess that opens it.

What the ungoverned microglion becomes. The ungoverned cell does not merely idle; it is provoked at the same time — by the amyloid its stalled surveillance no longer clears, by the phasic β-adrenergic bursts that engage its pro-inflammatory cyclic-AMP–protein-kinase-A–NF-κB program (the very program the next joints of this arm exploit), and by the debris of a parenchyma it has stopped patrolling — and under that provocation it undergoes the state transition now mapped in detail in Alzheimer's disease: the downregulation of its homeostatic checkpoints and the acquisition of the disease-associated microglial program (Keren-Shaul and colleagues, 2017; Deczkowska and colleagues, 2018). This transformed cell is the effector the first arm requires: it is, on the evidence, the very cell that engulfs the perineuronal net (Crapser and colleagues, 2020), and it is transcriptionally licensed to secrete the matrix-degrading protease. One honesty must be entered here and not buried. The disease-associated program is, in its own right, plausibly an attempt at *protection* — the activated microglion is straining to clear the amyloid its quiescent predecessor no longer could (Keren-Shaul and colleagues, 2017) — so that the matrix damage it does is, like so much in this disease, the collateral of a defence. The gardener does not turn wrecker out of malice; it is pinned, blinded, deafened, and provoked into a state in which its very effort to help unpicks the net. But the mechanism does not require the transformation to be malign in intent for it to be destructive in effect — and that is the point at which the neuronal pincer and the microglial turn become one story. The neuron at the point of the pincer loses its reelin brake and has its tau throttle floored; the microglion, one governance-layer above it, loses the tonic discipline that had kept it a gardener and is driven into the state in which it becomes a demolition crew. One failing nucleus deranges both the effector and its target — making the microglion dysfunctional enough to wield the shears, and the neuron defenceless enough to be cut by them. The locus coeruleus does not merely supply the first arm's drive; from the same dysregulation, it manufactures the very instrument the drive will use.

The two clocks — when the microglion turns against when the coeruleus fails. The account so far has been mechanistic; it must now be made temporal, because the clinical value of the whole pincer lies in *when* its parts move. Two clocks run in this story — the degradation of the locus coeruleus and the ungoverning of the microglion — and the reader is owed their relative timing. They are coupled but offset: the microglial clock is driven by the coerulean one and yet lags it, and lags it by an informative interval, because what ungoverns the microglion is not the

coeruleus's *lesion* but its *dysregulated output*, and the output deranges long after the lesion appears.

The coerulean clock has three movements, and its hands are decades apart. The molecular lesion comes first, and startlingly early: hyperphosphorylated tau is present in the locus coeruleus by the third decade of life, decades before any symptom (Mather and Harley, 2016; Weinshenker, 2018). But a lesion is not yet a dysfunction — through a long latent interval the tau-bearing neuron still fires in disciplined tonic patterns and still delivers a governed noradrenergic signal, and its microglia, accordingly, stay homeostatic. The second movement is functional derangement: as tau accumulates the neuron becomes hyperexcitable and begins to over-release, a change measurable at the source from the earliest stages of tauopathy (Wang and colleagues, 2025) and expressed, across the species, as the compensatory hyperactivity and β-adrenoceptor up-regulation of the prodromal years (Ghosh and colleagues, 2019). The third and latest movement is depletion: the neurons die and the regional supply at last fails. Lesion in the third decade, dysregulation across the protracted prodrome, depletion in the clinical disease — it is a slow clock, and its hands are decades apart.

The microglial clock is time-locked to the second movement, not the first. This is the crux of the offset, and it is easily mis-stated. The microglion does not turn when the coeruleus takes its first pretangle; it cannot, because the governance is a function of *output*, and in the latent interval the output is still disciplined — a tau-bearing but tonically firing coeruleus keeps its microglia homeostatic for as long as the discipline holds. The microglial clock starts only when the coerulean clock reaches its second movement, its output deranged and excessive. The microglial turn therefore lags the coerulean *lesion* by potentially decades while lagging the coerulean *dysregulation* by very little: the two functional derangements — the nucleus's over-output and the microglion's ungoverning — run nearly together, because the first is the cause of the second. The offset the reader must hold in mind is thus not the gap between coerulean pathology and microglial pathology at large, but the gap *within the coeruleus*, between its molecular clock and its functional clock; the microglion is bound to the functional one, and the long decades of latent LC tau are not yet the microglion's concern.

The microglial clock, in its turn, has three movements of its own — each the shadow of a coerulean movement one step advanced. The turn, once begun, is not a switch but a staged progression, and its stages fall in the order of the three routes of ungoverning traced above. *First*, at the onset of excess, over-stimulation pins down surveillance (Stowell and colleagues, 2019; Liu and colleagues, 2019): the earliest microglial change is not inflammation but a *quieting* of housekeeping — the gardener ceasing its rounds while norepinephrine, on the inflammatory axis, still holds it calm (Heneka and colleagues, 2010). The cell is blinded before it is provoked. *Second*, as the excess is sustained, β-adrenoceptor desensitisation and the accumulating, now-uncleared amyloid tip the cell across its homeostatic checkpoints into the disease-associated program — the two-step activation in which the checkpoints are downregulated before the full program engages

(Keren-Shaul and colleagues, 2017). This is the interval of the matrix-degrading, net-engulfing microglion, and it is the interval in which the first arm does its work. *Third*, at coerulean depletion, the anti-inflammatory brake is lost for want of transmitter and the cell is fully disinhibited — the classic end-stage neuroinflammation in which microglial activation and locus-coeruleus loss are found worsening together (Heneka and colleagues, 2010; Cao and colleagues, 2021). Surveillance-suppression, then the disease-associated transition, then disinhibition: three microglial movements, each trailing a coerulean movement by a single step.

A biphasic microglion for a biphasic nucleus — and the window, dated. This staging has an independent human corollary, and it was discovered from the microglial side without any reference to the coeruleus: microglial activation in Alzheimer's disease is detectable early — at the prodromal and possibly the preclinical stage — and at that early stage is *protective*, the patients bearing more of it declining more slowly (Hamelin and colleagues, 2016), before the later conversion of that response into the detrimental one that the two-wave view of neuroinflammation proposes. Set beside the biphasic coerulean trajectory this dissertation has built — hyperactivity, then depletion — the parallel is close to exact: an early microglial phase, surveillance suppressed and the disease-associated program engaged and straining to clear, coupled to the coeruleus's excess; and a late phase, disinhibited and frankly inflammatory, coupled to its collapse. Two biphasic clocks, meshed at the β-adrenergic receptor. And their meshing dates the therapeutic window with a precision the static account could not reach: it lies *after* the coerulean output has begun to derange and the microglion has begun to be ungoverned, but *before* the disease-associated transition has matured and the coeruleus has depleted — the interval in which quieting the drive would restore the gardener rather than merely inherit its ruins. The pincer's handle, dated at last: it is to be seized in the early phase of the microglial clock, which is the excess phase of the coerulean one. It must be said plainly, and the ledger will grade it so, that these two clocks have not yet been read against each other in the same human brains: the offset is a synthesis of a mouse timeline of coerulean output (Wang and colleagues, 2025), a human timeline of the coerulean lesion (Mather and Harley, 2016), and a human timeline of microglial activation (Hamelin and colleagues, 2016) that were never measured in a single cohort. That co-registration is the experiment the synthesis most demands.

The receptor. With the effector's turn thus accounted for — in mechanism and in time — the four joints of the arm can be traced. The excess noradrenergic drive of the middle passage acts, in this arm, not on the target neuron but on the microglia and astrocytes that surround it — the principal remodellers of the extracellular matrix and the principal sources of the relevant protease in the inflamed brain — through the β-adrenergic receptors whose governance of the microglion the preceding paragraphs established. The wiring the healthy brain used to keep the gardener disciplined is the wiring the first arm now turns to demolition.

The intracellular relay. Engagement of the β-adrenergic receptor raises intracellular cyclic AMP, which activates protein kinase A; the activated kinase, through the mitogen-activated-protein-kinase cascade and the NF-κB pathway, mobilises the transcription factors AP-1 and NF-κB. This relay is canonical catecholamine signalling, and its terminus, for the purposes of this arm, is a gene. Noradrenaline induces the expression of matrix metalloproteinase-9 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 one of those relays abolishes the induction (Yamazaki and colleagues, 2014); catecholamines — epinephrine and norepinephrine alike — potentiate the inflammatory induction of the same enzyme in monocytes and macrophages, acting through β-adrenergic receptors and raising the enzyme's messenger RNA, antigen, and activity by enhancing the DNA binding of AP-1 (Speidl and colleagues, 2004). The signalling logic is general: wherever a cell bears β-adrenergic receptors and the capacity to transcribe this gene, norepinephrine is a switch upon it. The candour this dissertation owes the reader is that these demonstrations were made in peripheral cells, and that the step from the monocyte to the cortical microglion *in situ* is an inference from shared receptor and promoter biology rather than a proven identity in the brain; the ledger grades it as the weakest load-bearing joint of the whole arm.

The transcription and the enzyme. The mobilised transcription factors occupy the promoter of the matrix-metalloproteinase-9 gene and drive its transcription; the zymogen is secreted and, at the cell surface, activated by removal of its pro-domain. The healthy brain holds this enzyme on a tight leash — it transcribes little, activates little of what it transcribes, and inhibits much of what it activates through the endogenous tissue inhibitor of metalloproteinases-1. The disease loosens all three restraints, and the noradrenergic drive of this arm loosens the first of them: it raises the transcriptional tone. The enzyme so released is a zinc-dependent gelatinase whose substrate list reads, uncannily, like an inventory of the reelin-staging surface's components.

The three cuts. Once active in the extracellular space, the protease executes three cuts upon the surface of Section II, and together they take the brake apart.

- *It cleaves the lectican shield.* The perineuronal net is built of lecticans — aggrecan, brevican, neurocan, versican — hung on a hyaluronan backbone; these chondroitin-sulfate proteoglycans are metalloproteinase substrates, and where the enzyme rises the lectican scaffold thins, as elevated metalloproteinase-9 tracked the loss of brevican from cortical perineuronal nets in a remodelling paradigm (Park and colleagues, 2020). The physical shield is opened.
- *It sheds the sulfated co-receptor bed.* The N-sulfated heparan sulfate that reelin's signal requires (Pan and colleagues, 2025) is carried on the ectodomains of cell-surface proteoglycans, the syndecans; matrix metalloproteinase-9 and its sister gelatinase cut those ectodomains at defined membrane-proximal sites, releasing the heparan-sulfate-bearing fragment into

solution (Manon-Jensen and colleagues, 2013). To shed the syndecan ectodomain is to remove from the surface the very sugar that clusters ApoER2 into a signalling configuration — and, worse, to convert a surface-anchored co-receptor into a soluble decoy that may bind reelin away from the membrane where it could still have worked. The staging bed is stripped.

- *It strips the receptors themselves.* The receptors of the low-density-lipoprotein-receptor family are shed by this enzyme: at the blood–brain barrier, metalloproteinase-9 dose-dependently sheds lipoprotein receptors from cerebral vessels, and inhibiting it mitigates that shedding (Shackleton and colleagues, 2019). ApoER2 and VLDLR belong to that family, and ApoER2 is independently known to undergo regulated ectodomain cleavage whose soluble product is measurable in cerebrospinal fluid (López-Font and colleagues, 2018). An enzyme that sheds the family sheds, in principle, the reelin receptors — removing not merely the sugar that helps reelin fire but the receptor that fires.

The result — the brake, cut. Set the three cuts together and the reelin apparatus is dismantled entire: shield, staging bed, and receptors. With its co-receptor bed degraded and its receptors shed, the reelin signal can no longer assemble at the surface, and it fails *even where reelin protein persists*. This is the "rising-reelin paradox" the biomarker literature measures directly — reelin messenger RNA and protein rise with advancing pathology while reelin-dependent phosphorylation of Disabled-1 falls (Cuchillo-Ibáñez and colleagues, 2016), soluble ectoApoER2 is reduced in sporadic disease (López-Font and colleagues, 2018), and the balance of reelin's proteolytic fragments is deranged with an aberrant species unique to patients (López-Font and colleagues, 2022). The reader, Disabled-1, is starved. The inhibitory input to the tau kinase — the reelin signal through Disabled-1 and Akt that held glycogen-synthase-kinase-3β suppressed — is withdrawn. The brake is cut, and the default-on kinase, released from its restraint, drifts back toward activity.

That, on its own, would be injury enough. But the first arm removes only the *restraint* on the kinase; it does not yet add drive. The neuron whose reelin brake has been cut is a neuron whose tau kinase is disinhibited but not yet actively pushed — poised, released, but not floored. It is the function of the second arm to floor it, and the second arm arrives at the same neuron carried by the same signal.

V. The Second Arm — The Inner Throttle (Flooring the Accelerator)

While the first arm of the pincer is busy in the extracellular space, cutting the brake by proxy through the glia and their protease, the second arm acts with no intermediary at all. It reaches directly into the target neuron and presses on the tau kinase itself. Its evidence is more direct than the first arm's, and its logic is simpler: what the first arm accomplishes by an elaborate detour through transcription and proteolysis, the second accomplishes by pharmacology.

Chronic excess norepinephrine over-activates the tau kinase directly. When the brain is exposed experimentally to a sustained excess of norepinephrine — produced by blocking the transporter that would otherwise clear it — the consequence in a tau-transgenic animal is tau aggregation, hippocampal neuronal death, and cognitive deficit; and the mechanism, as the authors resolve it, is the over-activation of protein kinase A and of 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 this result against Section II and the second arm's action is exact: the reelin brake exists to *inhibit* glycogen-synthase-kinase-3β and hold tau unphosphorylated; excessive norepinephrine *raises the activity of the same kinase* and drives tau into the tangle. Where the first arm removes an inhibitory input to the kinase, the second arm adds an activating one. The two are not variations on one action but the two arithmetic operations available upon a default-on enzyme — subtract the restraint, add the drive — and norepinephrine, dysregulated, performs them both.

A note on the wiring, and the honesty it requires. The exact biochemistry by which chronic noradrenergic excess raises glycogen-synthase-kinase-3β activity deserves a candour the ledger will formalise, because the textbook relationship is not a simple one. Protein kinase A can, in some contexts, phosphorylate glycogen-synthase-kinase-3β on its inhibitory serine — which would *lower*, not raise, its activity — so the net over-activation reported by Jeong and colleagues (2024) is unlikely to run through a single naïve PKA-to-GSK3β arrow. It is better read as the empirical outcome of a chronically deranged signalling state: sustained catecholamine excess through G-protein-coupled receptors is known to reshape the Akt–phosphatase axis that sets the kinase's inhibitory serine, and protein kinase A additionally phosphorylates tau directly and primes it for subsequent attack by glycogen-synthase-kinase-3β, so that the two kinases collaborate on the substrate even where their regulatory relationship is indirect. The claim this dissertation makes, and the only one it needs, is the one Jeong and colleagues measured: that chronic norepinephrine excess raises the *net* activity of the tau kinase and the hyperphosphorylation of tau. The pathway from receptor to kinase is partly inferred; the outcome at the kinase is observed.

The second arm needs no doorway. There is a feature of the inner throttle that distinguishes it sharply from the outer cut and that matters greatly for the net direction of the whole cascade. The first arm's destruction of the surface has an ambiguous edge — because that same sulfated surface is also the route by which pathological tau enters the neuron from outside (Holmes and colleagues, 2013), degrading it might be expected, on its face, to *protect* against tau's transcellular

spread even as it disables the reelin brake. The second arm is subject to no such ambiguity. A neuron whose glycogen-synthase-kinase-3β has been driven into activity makes its own hyperphosphorylated tau from its own tau, seeded from within, requiring no seed to arrive from any door. The inner throttle lights the fire inside the room; whether the door is open or shut is beside the point once the fire is lit. And the neuron so kindled does not merely suffer — it becomes a *source*, exporting seeds to its neighbours across a surface the first arm has already stripped of the barrier that might have resisted their entry. This is why the double-edge of the first arm does not rescue the cascade: the second arm generates pathology internally, independent of the doorway the first arm ambiguously widens, and the internally generated tangle then propagates outward. The two arms are complementary in exactly the way that closes the escape the first arm alone might have left open.

The neuron at the point of the pincer is now fully compromised. Its tau kinase has had its brake cut by the first arm and its accelerator floored by the second. Both actions raise the activity of one enzyme. It remains to show, with the precision the claim deserves, that it is *one* enzyme — that the two arms do not merely both harm the neuron but converge, molecule for molecule, on a single target, and that their convergence is the source of a synergy neither arm could produce alone.

VI. The Convergence at the Kinase

The word "pincer" earns its place only if the two arms close on a single point, and this section is written to show that they do. The point is glycogen-synthase-kinase-3β, and the convergence upon it is not loose or metaphorical but exact, at the level of the enzyme's regulation.

Two inputs to one enzyme, moved in the same direction by opposite means. Recall the enzyme's logic from Section II: glycogen-synthase-kinase-3β is constitutively active and is governed chiefly by whether its inhibitory serine is phosphorylated. A live reelin signal keeps that serine phosphorylated — through Disabled-1, phosphoinositide-3-kinase, and Akt — and so keeps the kinase *off* (Hiesberger and colleagues, 1999). The first arm of the pincer removes this input: by dismantling the surface that stages reelin, it withdraws the Akt-mediated phosphorylation of the inhibitory serine, and the serine, unphosphorylated, no longer restrains the enzyme. The second arm supplies a different input to the same enzyme, moving it the same way: chronic norepinephrine excess raises the net activity of glycogen-synthase-kinase-3β directly (Jeong and colleagues, 2024), whether by reshaping that same Akt–phosphatase axis, by priming the substrate through protein kinase A, or by both. The result is a single enzyme approached from two sides — its brake released by the first arm, its activity pushed by the second — and there is no third party. It is the *same* kinase.

Reelin's protection and norepinephrine's malignancy are not merely both relevant to tau; they are antagonists at one active site, and the antagonism is what makes the convergence real.

Why the convergence produces synergy, not mere addition. It might be supposed that two insults to one enzyme simply sum — that the tau phosphorylation under the pincer is the phosphorylation from the cut brake plus the phosphorylation from the floored throttle. The regulatory biology suggests something worse. Consider the enzyme's activity as the product of two factors: how far its inhibitory restraint has been lifted, and how hard it is being driven. The first arm raises the first factor toward its maximum; the second arm raises the second. A kinase that is both maximally *disinhibited* and actively *driven* reaches an activity that neither the disinhibition alone nor the drive alone could approach, because each makes the other more consequential — drive applied to a fully released enzyme translates into activity far more efficiently than the same drive applied to a restrained one, and the release of restraint matters far more when there is drive behind it than when there is none. The two arms are multiplicative in their effect on the enzyme's output, not additive; and the practical corollary is stern: no experiment that manipulates one arm while leaving the other intact can predict the derangement the intact pincer produces. To measure the cut brake in a neuron whose throttle is not floored, or the floored throttle in a neuron whose brake is not cut, is to measure a fraction of the injury and to underestimate the whole. The pincer must be studied as a pincer.

The convergence as the disease's own logic. That both the reelin resilience axis and the noradrenergic assault should terminate on glycogen-synthase-kinase-3β is not a coincidence this dissertation has manufactured; it is a convergence the wider literature had already half-seen from each side without seeing the meeting. The "GSK3 hypothesis" gathered the disease's disparate features — tau hyperphosphorylation, amyloid production, inflammation, memory loss — under the over-activity of this one kinase precisely because so many pathogenic roads run through it (Hooper and colleagues, 2008). The reelin field arrived at the same enzyme from the opposite direction, identifying it as the terminus of the protective signal (Hiesberger and colleagues, 1999). What the pincer supplies is the recognition that the earliest-failing neuromodulatory system of the brain drives that same kinase by two routes at once — that the locus coeruleus, in its dysregulation, is a two-handed operator of the very hub the GSK3 hypothesis had placed at the centre of the disease. The convergence is the point at which the noradrenergic account of Alzheimer's disease and the reelin account of Alzheimer's disease turn out to be describing the two ends of one lever.

Tau, released from both sides. With its brake cut by the first arm and its throttle floored by the second, glycogen-synthase-kinase-3β is unleashed as neither arm alone could unleash it. Tau is hyperphosphorylated; it detaches from the microtubule; it aggregates into the paired helical filament and the neurofibrillary tangle; and it propagates from neuron to neuron across a surface the first arm has already stripped of the perineuronal barrier that might have resisted its entry (Holmes and colleagues, 2013; Crapser and colleagues, 2020). The neuron generates the tangle

internally under the floored throttle and then, its defences cut, exports and receives seeds freely. The pincer has closed. What remains is to set the whole sequence down in order, to place it in the disease's timeline, and to grade it.

VII. The Receptor Logic — Why Dysregulation, and Not Deficiency, Drives the Pincer

An honest synthesis raises against itself the objection that would most damage it, and states it in its strongest form before answering. For the coerulean pincer the strongest objection is not obscure; it is a celebrated and well-evidenced result that appears, on first reading, to invert the whole argument. It is this: tonic norepinephrine is broadly *anti-inflammatory* and *protective* in the brain, and it is the *loss* of coerulean norepinephrine, not its excess, that classically disinhibits neuroinflammation and worsens pathology as the nucleus degenerates. If that is so, how can excess norepinephrine be the trigger of a destructive cascade? Should the argument not run the other way — that restoring norepinephrine, not reducing it, is the therapeutic aim?

The objection, in its full strength. The evidence for norepinephrine's protective role is real and must be granted without hedging. Norepinephrine supplied by the locus coeruleus suppresses neuroinflammation; stimulation of microglia with norepinephrine suppresses the amyloid-β-induced production of inflammatory cytokines and chemokines and *increases* microglial migration to and phagocytosis of amyloid-β; and experimental degeneration of the locus coeruleus, with the consequent depletion of norepinephrine, increases inflammatory mediators, impairs microglial recruitment and phagocytosis, and elevates amyloid-β deposition in transgenic mice — a deficit reversible by supplying a norepinephrine precursor (Heneka and colleagues, 2010). Norepinephrine released during arousing, novel, or challenging situations helps protect neurons from damage, which may be part of why cognitive engagement across life defends against later decline (Mather and Harley, 2016). By these lights norepinephrine is a guardian, and its loss is the injury. The objection is not a straw man; it is the mainstream reading, and it is correct about what it measures.

The resolution — sign is a function of concentration, receptor, and pattern. The reconciliation is that norepinephrine has no fixed sign. Its effect on glia and on the matrix is a function of concentration, of which receptor subtype is engaged, and of the temporal pattern of its delivery — and the protective regime and the destructive regime are different regimes of the same transmitter, separated in dose and in time. Steady, moderate, physiological tone, acting through the higher-affinity adrenoceptor complement, holds microglia quiescent and supports their clearance functions; this is the regime Heneka and colleagues characterised, and the regime whose loss is

injurious. But the pathological coerulean state of the disease's middle passage is not steady moderate tone. It is *dysregulation* — the compensatory hyperactivity and hyperexcitability, the bursts and the up-regulated β-adrenoceptors, documented in the pretangle model and the aging nucleus (Ghosh and colleagues, 2019; Weinshenker, 2018; Mather and Harley, 2016) — and it is exactly *this* excess, and exactly the β-adrenergic engagement it drives, that the metalloproteinase literature shows to *potentiate* the inflammatory induction of the protease rather than to suppress it (Speidl and colleagues, 2004; Yamazaki and colleagues, 2014). The tonic-protective role and the phasic-destructive role are therefore not contradictory but sequential and dose-dependent: the healthy nucleus, firing in disciplined patterns, keeps the glia calm and the matrix intact; the sickening nucleus, firing in deranged excess before it eventually falls silent, drives the very protease its earlier discipline had prevented, and presses the tau kinase its earlier tone had never touched.

Why the distinction is load-bearing, not cosmetic. This is not a rhetorical escape from an inconvenient result; it is the hinge on which the therapeutic reading of the whole dissertation turns, and it makes a testable commitment. The commitment is that it is *dysregulated and excessive* noradrenergic signalling — not physiological tone, and not the terminal deficiency — that raises cortical metalloproteinase-9, degrades the reelin-staging surface, and over-activates the tau kinase. If the pincer is right, then the window in which reducing the noradrenergic drive would help is a specific window: the middle passage of excess, after the nucleus has begun to derange but before it has collapsed into the depletion whose harms Heneka and colleagues measured. Reduce the drive too late, in the depleted end-stage, and one would only deepen the deficiency and worsen the inflammation; reduce it in the window of excess, and one subtracts the pincer's trigger while the transmitter the brain needs is still, if anything, in surplus. That central noradrenergic *activity*, indexed in the cerebrospinal fluid, rises rather than falls with disease severity (Elrod and colleagues, 1997; Falgàs and colleagues, 2024) — even as the neurons that produce it are lost (Szot and colleagues, 2006) — is the empirical rebuke to the pure-deficiency reading, and the direct warrant for locating the pincer in a regime of excess rather than of withdrawal. The objection, correctly stated, thus becomes one of the pincer's own predictions — that the sign of any noradrenergic intervention flips across the trajectory, harmful in the deficient endgame and protective in the excess that precedes it — and the failure to distinguish the falling hardware from the rising output is, this dissertation contends, the single confusion that has kept the noradrenergic system mis-read as a story of pure loss.

VIII. One Pincer, Assembled

It is time to set the whole mechanism down as a single ordered sequence, so that its structure and its seams are visible at once. The pincer runs in eight steps, from the earliest lesion in the brain to the propagating tangle, and each 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 — bearing hyperphosphorylated tau by the third decade of life — and begins its long degeneration (Mather and Harley, 2016; Weinshenker, 2018; Ghosh and colleagues, 2019; Giorgi and colleagues, 2017).

Second, the sickening nucleus enters the biphasic trajectory's uphill phase: its surviving neurons become hyperactive and hyperexcitable, the cortex up-regulates its β-adrenoceptors (Ghosh and colleagues, 2019), and a pathological *excess* of norepinephrine — not a deficiency — is broadcast across the forebrain along the diffuse coerulean arbor for a protracted preclinical and prodromal interval.

Third (the first arm), the excess drive, 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 matrix metalloproteinase-9 (Speidl and colleagues, 2004; Yamazaki and colleagues, 2014).

Fourth, the activated protease executes three cuts on the sulfated surface: it cleaves the lectican core proteins of the perineuronal net (Park and colleagues, 2020), sheds the syndecan ectodomains carrying reelin's obligate N-sulfated heparan-sulfate co-receptor (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 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) — withdrawing the Akt-mediated inhibition of glycogen-synthase-kinase-3β. The brake is cut.

Sixth (the second arm), the same noradrenergic excess, arriving at the same neurons, over-activates protein kinase A and glycogen-synthase-kinase-3β directly, driving tau hyperphosphorylation independent of the surface (Jeong and colleagues, 2024). The throttle is floored.

Seventh, the two arms converge on one enzyme: glycogen-synthase-kinase-3β — the principal tau kinase and the hub of the GSK3 hypothesis (Hiesberger and colleagues, 1999; Hooper and colleagues, 2008) — is disinhibited from without and driven from within, its activity raised multiplicatively, and tau is hyperphosphorylated as neither arm alone could achieve.

Eighth, tau aggregates into the tangle and propagates from neuron to neuron across a surface the first arm has stripped of the perineuronal barrier that resisted its uptake (Holmes and colleagues, 2013; Crapser and colleagues, 2020) — and the cortical pathology so produced compromises the

network feedback that might have steadied the failing coeruleus, which sickens further, dysregulates further, and closes the loop, driving both arms of its own pincer harder.

The genetic amplifiers. Two amplifiers run alongside this spine and connect it to the disease's dominant genetic and cellular drivers. 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 failing signal in the same direction — additively, neither excluding the other. And the *APOE4* allele, the genetic engine of sporadic disease, enters at the metalloproteinase: barrier breakdown in ε4 carriers proceeds through an accelerated cyclophilin-A–metalloproteinase-9 pathway predicting cognitive decline (Montagne and colleagues, 2020), the enzyme's shedding of lipoprotein receptors is ε4-dependent (Shackleton and colleagues, 2019), and soluble ectoApoER2 is lower in ε4 carriers than in ε3 homozygotes (López-Font and colleagues, 2022). The protective variants read on the same surface from the other side — the *APOE3*-Christchurch and *RELN*-COLBOS resilience cases both act on the sulfated matrix and its reelin signal (Arboleda-Velasquez and colleagues, 2019; Lopera and colleagues, 2023). The pincer is thus not an isolated curiosity but a convergence node through which the field's dominant genetic forces exert part of their effect.

Why the chronology matters. The distinctive claim of this cascade is not only mechanistic but *chronological*. Its first two steps — the coerulean pretangle and the noradrenergic excess it produces — are, on the pretangle timeline, among the earliest events in the entire disease, appearing in young adults decades before dementia (Mather and Harley, 2016; Weinshenker, 2018). Its middle steps fall in the long preclinical and prodromal window in which, by every account in this corpus's temporal architecture, the disease is being *decided* rather than merely expressed — the same window the *APOE3*-Christchurch and *RELN*-COLBOS carriers survived. The pincer therefore does its work upstream of the mature plaque and the frank cortical tangle, at a time when the surface is still mostly whole, the receptors still mostly on the membrane, the coeruleus still mostly alive, and the intervention still mostly possible. This is why the mechanism cannot be dismissed as a late epiphenomenon of end-stage disease: it operates precisely where the disease is still contestable, and it *dates* the noradrenergic contribution that the deficiency model, fixed on the endgame, could never place in time.

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 pincer is only as strong

as its weakest load-bearing joint, 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, Akt, and the inhibition of 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). This is the brake whose cutting the first arm describes, and the inhibitory input to the kinase whose withdrawal defines that arm's terminus.

Strong (imported, established) — glycogen-synthase-kinase-3β is a central, constitutively active tau kinase whose over-activity is a hub of Alzheimer pathology. The GSK3 hypothesis gathers tau hyperphosphorylation, amyloid production, inflammation, and memory loss under this enzyme's over-activity (Hooper and colleagues, 2008), and its role as the principal tau kinase is not in dispute. This is the convergence point of the pincer; that both arms terminate here is the dissertation's organising claim, and it rests on secure ground at the enzyme itself.

Strong (imported, established) — the locus coeruleus lacks a perineuronal net, tangles first, and hyperphosphorylated tau there is the earliest detectable Alzheimer neuropathology. The want of a net is a matter of record (Morawski and colleagues, 2010); the pretangle's early and near-universal appearance in this nucleus is well documented (Mather and Harley, 2016; Weinshenker, 2018; Ghosh and colleagues, 2019; Giorgi and colleagues, 2017). The origin of the pincer stands on established fact.

Strong — matrix metalloproteinase-9 sheds the ectodomains of heparan-sulfate proteoglycans and of lipoprotein receptors, and is required for synaptic plasticity. Shown at defined cleavage sites for the syndecans (Manon-Jensen and colleagues, 2013) and for lipoprotein-receptor-family members at the barrier (Shackleton and colleagues, 2019); the enzyme's competence at the synapse and the double-edge that complicates its inhibition are established by pharmacology, genetics, and rescue (Nagy and colleagues, 2006). The enzyme's competence against the surface's components is secure; its 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 (López-Font and colleagues, 2022). The signature of a brake failing at the surface is present in the fluid, whatever its proximate cause.

Strong (imported) — tonic norepinephrine is anti-inflammatory and its loss worsens amyloid pathology. Directly demonstrated: norepinephrine suppresses microglial cytokine production and promotes amyloid phagocytosis, and locus-coeruleus lesion worsens inflammation and amyloid deposition (Heneka and colleagues, 2010). This is granted in full — and is the reason the pincer's claim is restricted to the *dysregulated, excess* regime and not to physiological tone (see Section VII). The ledger records this as evidence the argument must accommodate, and does, rather than evidence it may ignore.

Moderate — chronic norepinephrine excess over-activates glycogen-synthase-kinase-3β and drives tau, constituting the second arm. Directly shown that sustained norepinephrine excess raises protein-kinase-A and glycogen-synthase-kinase-3β activity and hyperphosphorylates tau, in tau-transgenic mice and human organoids (Jeong and colleagues, 2024). The *outcome* at the kinase is observed; the *wiring* from receptor to kinase is partly inferred, since a naïve protein-kinase-A-to-GSK3β arrow would predict inhibition, not activation (see Section V). *Settling experiment: resolve the signalling route from β-adrenergic receptor to glycogen-synthase-kinase-3β under chronic noradrenergic excess — Akt/inhibitory-serine, β-arrestin/phosphatase, or protein-kinase-A substrate priming — in cortical neurons.*

Moderate — matrix metalloproteinase-9 degrades the lectican perineuronal net in the brain. Supported by the association of elevated enzyme with brevican loss from cortical nets (Park and colleagues, 2020) and consistent with the microglial net-degradation model (Crapser and colleagues, 2020); but Park's is a non-disease remodelling paradigm, and a direct demonstration in 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 metalloproteinase-9 loss.*

Moderate-to-plausible — norepinephrine induces matrix metalloproteinase-9 in the brain through β-adrenergic receptors on microglia and astrocytes (the first arm's receptor joint). 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, which are known to be transcriptionally responsive to norepinephrine (Heneka and colleagues, 2010); but the in-situ demonstration in cortical microglia is not yet in hand. *This is the single most important step to nail, and the weakest load-bearing joint of the first arm. Settling experiment: measure cortical metalloproteinase-9 expression and perineuronal-net integrity under chronic β-adrenergic agonism versus antagonism, and in locus-coeruleus-lesioned versus intact tauopathy animals.*

Strong (imported) — noradrenergic tone governs the microglial state through β-adrenergic receptors on the microglia themselves. Directly demonstrated: the locus coeruleus controls microglial function through norepinephrine (Heneka and colleagues, 2010), and noradrenergic tone suppresses microglial process surveillance in an effect that requires the

microglion's own β-adrenergic receptors (Liu and colleagues, 2019; Stowell and colleagues, 2019). That the microglion is a *governed* cell, and the locus coeruleus its governor, is established. The extrapolation the argument adds — that *chronic pathological excess* holds that surveillance pathologically suppressed while desensitising the calming channel — is inference from receptor biology, graded below.

Plausible — the failing coerulean signal drives the homeostatic-to-disease-associated microglial transition that yields the matrix-degrading effector. The state transition itself is securely mapped (Keren-Shaul and colleagues, 2017; Deczkowska and colleagues, 2018), and the activated microglion is the cell that engulfs the perineuronal net (Crapser and colleagues, 2020); the *noradrenergic causation* of that transition — over-stimulation, β-adrenoceptor desensitisation, then depletion — is the section's synthesis, not yet a measured chain. The honest counterweight is that the disease-associated program is plausibly protective in intent (Keren-Shaul and colleagues, 2017), so its matrix damage is collateral, not purpose. *Settling experiment: block or delete microglial β-adrenergic receptors, or normalise coerulean tone, and test whether the homeostatic microglial signature is preserved and perineuronal-net engulfment prevented in a tauopathy model.*

Plausible (synthesis) — the microglial clock lags the coerulean *lesion* by decades but the coerulean *output* dysregulation by little, and advances in three stages (surveillance-suppression disease-associated transition disinhibition) mapped to the LC's biphasic trajectory. The component timelines are each supported — the coerulean lesion in the third decade (Mather and Harley, 2016), coerulean hyperexcitability and over-release from the earliest tauopathy (Wang and colleagues, 2025), early-and-protective then later microglial activation in the human brain (Hamelin and colleagues, 2016) — but they were measured in different systems and cohorts and never co-registered. The offset, and the mapping of the microglial stages onto the coerulean ones, are a synthesis, not an observation. *Settling experiment: co-register locus-coeruleus output (or integrity) and microglial state longitudinally in a single tauopathy cohort or model, and test whether microglial surveillance-suppression onsets with the first rise in LC output rather than with the first LC tau.*

Moderate — the noradrenergic *output* rises, not falls, during the pathogenic window (the excess the pincer requires). This is the premise most often assumed to be false, and it is in fact supported on three independent lines. Post-mortem, the surviving locus-coeruleus neurons compensate — increased tyrosine-hydroxylase messenger RNA, sprouting, adrenoceptor remodelling (Szot and colleagues, 2006); in living patients, cerebrospinal-fluid norepinephrine is elevated and rises with severity (Elrod and colleagues, 1997; Falgàs and colleagues, 2024); and in a tauopathy model the tau-burdened nucleus is hyperexcitable and releases more norepinephrine by direct voltammetry (Wang and colleagues, 2025), the trajectory being biphasic — hyperactivity then depletion (Caligiore and colleagues, 2020; Weinshenker, 2018). The honest counterpoint, entered here so the argument is not credited with more than it holds: the *structural hardware* declines

throughout — neuron number, fibre density, transporter (Cao and colleagues, 2021) — and end-stage cortical tissue norepinephrine content may fall. The claim is a dissociation of output from hardware, not a denial of the loss. What remains not-yet-measured is the linkage of this specific excess to *cortical* metalloproteinase-9 and net loss, and the *simultaneous* operation of both arms — the cascade's central prediction. *Settling experiment: relate regional noradrenergic output (not cell count) to cortical metalloproteinase-9 and perineuronal-net integrity across disease stage.*

Plausible — the two arms act synergistically (multiplicatively) on kinase activity rather than additively. Argued from the regulatory logic of a default-on enzyme whose restraint one arm lifts while the other supplies drive (Section VI); not yet measured as an interaction. *Settling experiment: a two-by-two design measuring tau phosphorylation under brake-cut and throttle-floored conditions alone and together, testing for supra-additivity.*

Plausible — matrix metalloproteinase-9 sheds ApoER2 and VLDLR specifically. 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.

Not established (and not required) — matrix metalloproteinase-9 cleaves reelin itself. The proteases known to process reelin are serine proteases and ADAMTS-family metalloproteinases, not the gelatinases; the first arm silences reelin by dismantling its *receiving surface*, not its ligand, and does not depend on cutting the reelin molecule. Entered as a boundary so the argument is not credited with more than it asserts.

Rejected as stated — the noradrenergic contribution to Alzheimer's disease is a simple deficiency. The "coeruleus degenerates, norepinephrine falls, protection lost" model captures only the endgame and inverts the sign of the causal window. Both arms of the pincer are driven by *excess*, and the promoter and kinase biology read amplification, not withdrawal (Speidl and colleagues, 2004; Jeong and colleagues, 2024; Ghosh and colleagues, 2019). The direct refutation is that central noradrenergic *activity* rises with disease severity even as the neurons are lost (Elrod and colleagues, 1997; Szot and colleagues, 2006; Falgàs and colleagues, 2024): the hardware falls while the output climbs, and only at the terminal collapse does the output fail too. The deficiency model conflates the two variables, and mistakes the endgame for the whole course; it is not wrong about the end-stage, but it is wrong about the phase in which the damage is done.

X. Predictions and Falsification

The pincer 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. Because the two arms share an origin and a target, several predictions concern the arms *jointly* — a signature no single-arrow account would make.

- **The shared handle disarms both arms at once.** Lesioning or silencing the locus coeruleus, or blocking β-adrenergic signalling, in a tauopathy model will simultaneously reduce cortical metalloproteinase-9, spare the perineuronal net, preserve reelin-dependent Disabled-1 phosphorylation (first arm) *and* lower neuronal glycogen-synthase-kinase-3β activity and tau phosphorylation (second arm). Should a single upstream noradrenergic intervention move one arm's read-outs but not the other's, the claim that both spring from one signal is severed.
- **The arms are synergistic.** In a two-by-two design, the tau phosphorylation produced by cutting the brake and flooring the throttle *together* will exceed the sum of each alone. If the combination is merely additive, the multiplicative-convergence claim of Section VI is wrong, though the pincer's existence would survive as two additive arrows.
- **The sign flips across the trajectory.** Reducing noradrenergic drive will *protect* when applied in the middle-passage window of excess and *harm* when applied in the depleted end-stage, mirroring the protective role of tonic norepinephrine (Heneka and colleagues, 2010). A noradrenergic intervention with a single fixed sign across the whole disease course would refute the dysregulation model of Section VII.
- **Convergence is the downstream choke-point.** Inhibiting glycogen-synthase-kinase-3β will blunt tau pathology whether the drive arrives via the cut brake or the floored throttle, because both terminate on that enzyme. If tau pathology under noradrenergic excess proves largely independent of glycogen-synthase-kinase-3β activity, the convergence claim fails and the two arms must act on separate targets.
- **Metalloproteinase loss preserves the brake, not merely clears amyloid.** Genetic or pharmacological loss of metalloproteinase-9 will preserve reelin-dependent Disabled-1 phosphorylation and reduce tau pathology in the face of an intact amyloid burden. If metalloproteinase loss thins tau only by clearing amyloid and not by sparing the reelin surface, the first arm's "unstaging" mechanism is wrong.
- **The effector's turn is caused by the governor's failure.** Deleting or blocking the β-adrenergic receptor on microglia specifically, or normalising the dysregulated coerulean tone, will preserve the homeostatic microglial signature, prevent the homeostatic-to-disease-associated transition, and spare the perineuronal net from engulfment in a tauopathy model — even with amyloid present. If microglia adopt the matrix-degrading, net-engulfing state just as readily when their β-adrenergic governance is intact and the

coerulean tone is normal, then the noradrenergic account of microglial dysfunction is wrong, and the effector's turn must be driven from elsewhere.

- **The two clocks are offset in a defined way.** Tracked longitudinally, microglial surveillance-suppression will onset with the first rise in locus-coeruleus *output*, not with the first locus-coeruleus *tau* (which precedes it by decades); the disease-associated transition will follow under sustained excess; and full microglial disinhibition will coincide with coerulean depletion. Arresting the LC output at the excess phase should hold the microglial clock at surveillance-suppression and prevent the disease-associated transition. If the microglial clock advances on a schedule independent of LC output — turning as readily with LC tau alone, or refusing to arrest when LC output is normalised — the coupling of the two clocks is refuted.
- **Regional noradrenergic tone predicts matrix loss.** Across brain regions and individuals, cortical metalloproteinase-9 tone and noradrenergic innervation density will predict perineuronal-net loss and reelin-signalling failure better than local amyloid burden alone. A region of high amyloid but spared net and preserved reelin signal despite high noradrenergic drive would bound the first arm.
- **The second arm needs no doorway.** Driving neuronal glycogen-synthase-kinase-3β by noradrenergic excess will generate hyperphosphorylated tau cell-autonomously, without exogenous tau seed and independent of surface heparan sulfate. If internally generated tau pathology under norepinephrine excess requires an external seed, the claim that the inner throttle is doorway-independent (Section V) is false.

XI. Therapeutic Corollaries Disarming the Pincer at the Handle

If the noradrenergic assault on tau is shaped like a pincer, then its therapeutic reading differs from that of a single-arrow mechanism in one decisive respect, and that respect is the dissertation's chief practical contribution. A single arrow must be intercepted at some point along its one path. A pincer can be attacked at three places — at either arm, at the convergence where they meet, or at the handle from which they both spring — and the handle is the most economical target of the four, because a strike there disables both tines at once. This section reads the pincer's geometry for its targets, and is candid that each is booby-trapped.

The handle — the noradrenergic drive. Because both arms originate in a single dysregulated signal, the most efficient intervention is upstream of the fork: to quiet the excess

noradrenergic drive itself. Attenuating it — with a centrally acting β-adrenergic antagonist, or by stabilising rather than depleting the failing coeruleus — should in one stroke reduce the induction of the matrix protease and spare the reelin surface (disarming the first arm) *and* remove the direct over-activation of the tau kinase (disarming the second). No downstream agent can match this, because no downstream agent sits before the fork. But the handle is the most heavily booby-trapped target of all, for the trap is the very result of Section VII: norepinephrine is indispensable to arousal, attention, mood, and — through the plasticity the matrix protease itself subserves — to memory, and its terminal depletion is a documented driver of the disease's burden (Heneka and colleagues, 2010; Weinshenker, 2018). To blunt the drive indiscriminately is to risk hastening the deficiency that lies at the end of the same trajectory. The handle can be seized, but only in a particular window — the middle passage of excess, after the nucleus has begun to derange and before it has collapsed. The therapeutic target here is therefore not merely molecular but *chronological*: the right drug at the wrong time inverts its own sign.

The convergence — the kinase. The second-most economical target is the point where the two arms meet: glycogen-synthase-kinase-3β. An inhibitor of that kinase would blunt the tau phosphorylation driven by *both* arms, whether the drive arrives as a cut brake or a floored throttle, because both terminate there (Hooper and colleagues, 2008). This is the downstream mirror of the handle — one choke-point for a two-pronged attack — and it has the advantage of acting regardless of which arm dominates in a given patient or region. Its trap is the enzyme's ubiquity: glycogen-synthase-kinase-3β governs glycogen metabolism, gene transcription, and much else besides, and the history of its inhibitors is a history of narrow therapeutic windows. To catch the pincer at its convergence is pharmacologically clean in principle and toxicologically fraught in practice.

The arms — the protease and the surface. The two arms may also be attacked individually, and each offers a target the anonymous account could not. The first arm invites inhibition of the matrix protease — but the same enzyme is required for the late phase of long-term potentiation and for memory (Nagy and colleagues, 2006) and is one of the brain's degraders of amyloid-β (an established double-edge), so that the design constraint is not blockade but *discipline*: an agent that suppresses the pathological, sustained, glia-driven protease that unpicks the net without silencing the transient, activity-driven, synaptic protease 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 pincer makes urgent. The first arm may alternatively be attacked at its surface, by protecting or restoring the sulfated bed and the receptors — sulfation-directed agents or reelin-pathway agonism — sparing tau while leaving amyloid largely intact. The second arm, being the direct pharmacological over-drive of the kinase, is attacked at the handle or at the convergence and has no separate target of its own; it is the arm with the fewest independent handholds, which is one more reason the shared handle and the convergence are the strategically preferred sites.

The single strategic reading. The three sites share one reading, and it is the reading this whole corpus has reached from many directions: the reelin-matrix axis, and the noradrenergic system that governs its destruction, are systems of the *earlier* brain, to be defended in the preclinical and prodromal window and not rescued in the ruins. The coeruleus tangles first; the noradrenergic dysregulation it broadcasts is among the first cortical insults; and both arms of the pincer do their damage before the plaque has finished maturing. An intervention aimed at the handle, the convergence, or either arm belongs, if the pincer 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 firing in excess rather than fallen silent. The clinical instruments it would require — a timed and centrally selective adrenergic agent, a disciplined kinase or protease modulator, a reelin-pathway agonist — are close enough to existing pharmacology that the chief obstacle is not chemistry but *timing and selection*: knowing when in the trajectory, and in whom, to reach for them. The pincer converts a set of molecular targets into a single clinical question of the hour.

XII. Coda The Blue Nucleus's Two Hands

The companion dissertation ended on the image of a pair of shears held in an unnamed hand, and set out to name the hand. This one has watched what the hand actually does, and found that it is not one hand but two, and that they close together.

The nucleus at the origin of it all is no larger than a grain of rice, the colour of slate, 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 in the brain, bearing its first pretangles while its owner is still young. And as it sickens it does not fall silent all at once. For years it pours out a deranged and amplified signal along axons that reach into every fold of the cortex — the rising tide of the middle passage — and that signal, arriving at the guarded surface of the cortical neuron, does two things in one motion. With one hand it reaches outside the neuron: it rouses the microglia, calls up the protease, and cuts the sulfated surface on which reelin's brake is staged, so that the brake on the tau kinase is released. With the other hand it reaches inside the same neuron and presses directly on the tau kinase itself, flooring the accelerator the brake had been holding. The two hands close on a single molecule — glycogen-synthase-kinase-3β — from opposite sides, the one lifting its restraint and the other pushing its drive, and the kinase, disinhibited and driven at once, is unleashed as neither hand alone could unleash it. Tau, freed from within and admitted from without, forms the tangle and spreads it across a surface that no longer closes against it; and the cortex so injured can no longer steady the failing nucleus, which frays further, and dysregulates further, and closes both its hands the tighter.

There is a bitter economy in it, and the corpus has now met its shape three times over. One neuromodulator, dysregulated, disarms a resilience system twice in one gesture — once by dismantling its apparatus from outside and once by overpowering its effect from inside — and the same small nucleus has been caught before at the controls of the brain's clearance and the brain's matrix, operating the demolition of the very defences it exists to serve. That so much should turn on the earliest and least defended cell in the Alzheimer brain — that the first neuron to fail should also, through the signal it broadcasts, be among the most consequential — is either a coincidence of independent accidents or a sign that the field's long fixation on the plaque has kept it staring at the wrong end of the cascade. This dissertation takes the second view, and offers the two-handed nucleus as its argument.

And yet the same geometry that makes the pincer so dangerous is what makes it, in the end, approachable. An arrow must be caught in flight. A pincer has a handle. Because both arms of the coerulean assault spring from one signal, they can be reached at one place, before the fork, in the years when the nucleus is still firing in excess and not yet gone. The clinician cannot yet quiet the hand without risking the silence that follows, nor abolish the kinase without disturbing the housekeeping it also serves. But the task is now legible in a way it was not when the noradrenergic contribution was read as mere loss: to find the hour in which the deranged drive can be stilled while the transmitter the brain still needs is spared — to reach the blue nucleus in the window of its excess, and to loosen both its hands at once, before the wall they are pulling down has fallen. The architect is still in the wall. The nucleus has two hands upon it. The work is to open the grip before the wall comes down.

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