THE ARCHITECT'S REPRIEVE

Reelin in Alzheimer's Disease — Whether the Cortex's First Builder Becomes Its Late Guardian, a Bystander to Its Ruin, or the Rarest Proof That the Disease Can Be Held

The Reeler's Legacy · The Tau Brake · The Rising-Reelin Paradox
The Two Resilient · The Heparan Convergence

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

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A resilience companion to The Temporal Architecture of Collapse and a convergence tributary to the APOE hub. Where the amyloid and tau theses ask what builds the disease, this asks after the molecule that built the cortex itself — reelin, the developmental architect that stays on as the adult brain's synaptic guardian — and grades, connection by connection, the human evidence that reinforcing its failing signal held an otherwise unstoppable genetic dementia at bay for thirty years.

"The tissue the disease unbuilds is the tissue reelin built. The architect of the cortex does not retire when the walls are raised; it stays on as the caretaker of the rooms it made. This dissertation asks whether the caretaker's failing signal is what lets the building fall — and whether, reinforced, it can hold the building up."

— ONS Methodology Working Notes, 2026

For the family of Antioquia, who carried a merciless mutation and, in two of their number, the rarest of reprieves — and for the scientists who read, in a single protected brain, the direction of an arrow the rest of us can only infer.

THE COLLAPSE FRAMEWORK RESILIENCE COMPANION

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

— The Temporal Architecture of Collapse —

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

The Architect's Reprieve (reelin) — this volume

This volume is the resilience counterpart to the paradigm's pathological syntheses. Where the amyloid and tau theses follow what accumulates and propagates, the present volume follows what defends — reelin, the developmental architect of the cortex that signals, in the adult, through the very lipoprotein receptors that carry apolipoprotein E, the disease's greatest genetic risk. It treats reelin not as a cause of Alzheimer's disease but as an axis of resilience against it, and it hinges on the two living human beings — one carrying a reelin variant, one an ApoE variant — who were spared an otherwise fully penetrant genetic dementia by strengthening a single shared, heparan-sulfate-dependent signal.

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Abstract

Of all the molecules implicated in Alzheimer's disease, reelin occupies the strangest position: it is not a fragment of the disease's machinery but the architect of the very tissue the disease destroys. Reelin is the large secreted glycoprotein that, in the embryo, instructs migrating neurons where to stop, laying down the layered cortex and the hippocampal formation whose orderly ruin is the anatomy of dementia. What has emerged over three decades is that reelin does not retire when construction ends. It signals through two receptors of the low-density-lipoprotein family — ApoER2 and the VLDL receptor, the very receptors that also bind apolipoprotein E, the strongest common genetic risk factor for the disease — to a cytoplasmic adaptor, Disabled-1, and from there restrains the phosphorylation of tau, sharpens the NMDA receptor, and enhances the long-term potentiation on which memory is built. In the adult, the architect becomes a guardian.

This dissertation asks whether that guardianship is real and causal or merely correlative, and it finds, unusually for this field, a human experiment that settles the direction of the arrow. In 2023 the world's second case of extreme resilience to autosomal-dominant Alzheimer's disease was described: a man carrying the catastrophic *PSEN1*-E280A mutation who remained cognitively intact into his late sixties, three decades past the expected onset, despite one of the heaviest amyloid burdens ever measured — and who carried, heterozygously, a rare gain-of-function variant of reelin, *RELN*-COLBOS, that activates Disabled-1 more strongly and lowers human tau phosphorylation in a knock-in mouse. His entorhinal cortex, the cradle of the disease, was nearly free of tau tangles. He is the mirror image of the first resilient case, an *APOE3*-Christchurch homozygote whose protection also spared the entorhinal cortex from tau while amyloid ran unchecked — and both mutations, it now appears, act on the same heparan-sulfate-dependent lipoprotein-receptor node. Two human beings, protected from an otherwise fully penetrant genetic dementia, point to a single axis. Reelin is on it.

Yet the honest picture is not the tidy one in which reelin simply falls and the disease rises. Total reelin protein and its fragments *increase* in the Alzheimer's cortex and cerebrospinal fluid, even as the specific population of reelin-expressing neurons in entorhinal layer II is selectively lost; amyloid-β both induces reelin and then traps it, so that the signal to Disabled-1 falls while the ligand accumulates — a state best understood as *reelin resistance*, plenty of hormone and a deaf receptor. We trace every link of the chain from the reeler mouse to the resilient man, grade each in an explicit validity ledger, and name for each the experiment that would settle it. The verdict is neither that reelin causes Alzheimer's nor that it is a bystander to it, but that it is a genuine axis of *resilience* — a guardian whose failing signal permits the disease and whose reinforcement, in the one natural experiment we have, held the disease at bay in a brain that should by every genetic law have been lost.

I. The Reeler's Legacy

The gene was named for a stagger. In the 1950s a strain of mice appeared that walked as though drunk — tremulous, ataxic, reeling — and when their brains were examined the cause was architectural: the neat layers of the cerebellum and cerebral cortex were inverted and disordered, as if the masons had been given no plan. The mutation was called *reeler*, and for forty years it was a curiosity of developmental neurology. Then, in 1995, D'Arcangelo and colleagues at the Roche Institute cloned the gene deleted in the mutant and found that it encoded a very large protein, secreted into the extracellular space, resembling the matrix proteins that guide cell adhesion — a protein expressed by particular neurons during exactly the windows when their neighbours were migrating to their final positions (D'Arcangelo and colleagues, 1995). They named the protein reelin, and in naming it they opened a door that leads, by a route no one then suspected, directly into the pathology of Alzheimer's disease.

The logic of that route is the subject of this dissertation, and it can be stated at the outset as a single provocation. The tissue that Alzheimer's disease destroys — the entorhinal cortex, the hippocampus, the layered neocortex — is the tissue reelin built. The developmental program that positions these neurons does not simply switch off in the adult; the same molecule, signalling through the same receptors, continues to tune the synapses between the neurons it once placed. And so a failure of reelin in the aged brain is not the loss of a bystander. It is the withdrawal of the original architect from a structure under assault, at exactly the moment the structure most needs its designer.

For most of two decades the reelin-and-Alzheimer's literature was a scattering of intriguing but disconnected findings: altered reelin in the cerebrospinal fluid of patients, a biochemical link between reelin and the phosphorylation of tau, a curious loss of reelin-expressing cells in the entorhinal cortex. Each was suggestive; none was decisive; and the field lacked the one thing that turns a correlation into a cause — a human being in whom the reelin pathway had been altered and the course of the disease had visibly changed. In 2023 that human being was described, and the scattering resolved into a picture. This dissertation is written to assemble that picture honestly: to trace the mechanism from the reeler mouse to the resilient man, to weigh the considerable evidence that complicates it, and to grade, connection by connection, how much we actually know.

The disease unbuilds the cortex neuron by neuron. This dissertation asks after the architect who built it, and who — it now seems — never entirely left.

II. The Architecture of a Signal

To judge reelin's role in the disease one must first understand what reelin does, and the honest summary is that it does two things separated by a lifetime. In the developing brain, reelin is secreted by a transient population of cells at the cortical surface — the Cajal-Retzius neurons — and it acts as a stop signal, or more precisely a positioning signal, that allows successive waves of migrating neurons to climb past their predecessors and assemble the cortex from the inside out. Without it, as the reeler mouse shows, the layers invert and the lamination fails (D'Arcangelo and colleagues, 1995). This is reelin the architect, and it is the role for which the protein is famous.

The second role emerged from asking a mechanistic question: through what receptors does the reelin signal enter a neuron? The answer, worked out principally in Joachim Herz's laboratory, was startling in its implications. Reelin binds directly and specifically to two cell-surface receptors — the very-low-density-lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2) — both members of the low-density-lipoprotein receptor gene family. Binding clusters the receptors and triggers tyrosine phosphorylation of an intracellular adaptor protein, Disabled-1 (Dab1), which recruits Src-family kinases and propagates the signal inward (Hiesberger and colleagues, 1999). The startling part is the identity of the receptors. ApoER2 and VLDLR are lipoprotein receptors; their other principal ligand is apolipoprotein E — ApoE — whose ε4 allele is the strongest common genetic risk factor for late-onset Alzheimer's disease. Reelin and the Alzheimer's risk protein, in other words, speak to the neuron through the same two receivers. Any account of reelin in this disease must reckon with the fact that its signalling hardware is shared with the field's most important genetic villain.

What the adult reelin signal accomplishes at the synapse has been mapped in careful detail. ApoER2 resides in the postsynaptic density, where it forms a physical complex with the NMDA-type glutamate receptor; reelin signalling through this complex enhances long-term potentiation, the synaptic strengthening that underlies learning, and it does so through a mechanism that depends on an alternatively spliced exon in the receptor's intracellular tail — an exon that is itself regulated by neuronal activity, so that the reelin pathway is tuned by the very activity it tunes (Beffert and colleagues, 2005). Mice lacking either VLDLR or ApoER2 have deficits in contextual fear learning and in long-term potentiation; perfusing reelin onto hippocampal slices strengthens potentiation in healthy tissue and this enhancement is abolished when the receptors are deleted (Weeber and colleagues, 2002). And a single injection of recombinant reelin into the ventricles of a normal mouse increases dendritic spine density, potentiation, and performance on learning tasks — a demonstration that more reelin signal yields, at least in a healthy brain, a better one (Rogers and colleagues, 2011). This is reelin the guardian: not building the cortex but maintaining the plasticity of its synapses, holding open the machinery of memory.

A final architectural detail, discovered only recently, will prove decisive when we reach the resilient cases. Reelin's engagement of its receptors is not a simple two-body affair; it requires a co-receptor at the cell surface — heparan sulfate, the sulfated sugar chain that decorates many membrane proteins. Full-length reelin binds heparan sulfate with high affinity, and this binding is necessary for reelin to cluster ApoER2 and fire the signal; strip the sugar away with heparinase, or delete the enzyme that sulfates it, and reelin can no longer dimerize its receptor (Pan and colleagues, 2025). The reelin signal, then, is a three-way handshake — ligand, sulfated sugar, and lipoprotein receptor — and each partner is a place where the handshake can be strengthened or lost. Hold this in mind. It is the hinge on which the whole argument will turn.

III. The Argument in Brief

Two readings of reelin's role in Alzheimer's disease have circulated, and until recently neither could be made to prevail over the other.

The first reading is mechanistic and protective, and it is genuinely elegant. Reelin restrains tau. The signal it sends through ApoER2 and VLDLR to Disabled-1 activates the PI3-kinase/Akt cascade, which inhibits glycogen synthase kinase-3β, the principal kinase that hyperphosphorylates tau — so that when reelin is removed, or its receptors deleted, tau phosphorylation rises (Hiesberger and colleagues, 1999). Reelin also defends the synapse directly against amyloid: at concentrations of amyloid-β comparable to those in an afflicted brain, reelin prevents the suppression of long-term potentiation and NMDA-receptor function that the peptide would otherwise impose, an antagonism that positions reelin and amyloid as opposing regulators of synaptic gain (Durakoglugil and colleagues, 2009). Reelin even engages the amyloid peptide itself, binding soluble amyloid-β species, delaying their assembly into fibrils, and — when overexpressed in an amyloid-bearing mouse — postponing plaque formation and rescuing memory (Pujadas and colleagues, 2014). Read at the bench, reelin looks like an endogenous therapy the brain manufactures for itself.

The second reading is pathological and accusatory, and it is equally grounded. Reelin protein does not fall in the Alzheimer's brain; it *rises*. The cortex and cerebrospinal fluid of patients contain roughly forty percent more reelin than controls, and a particular reelin fragment climbs across a whole family of neurodegenerative diseases and tracks with the level of tau (Botella-López and colleagues, 2006). With age, reelin accumulates into extracellular aggregates that co-localize with early, non-fibrillar amyloid deposits and may seed the plaques to come (Knuesel and colleagues, 2009). On this reading reelin is not the brain's medicine but one more protein that misfolds, aggregates, and joins the pathology — a suspect, not a guardian.

This dissertation argues that both readings are describing the same thing from opposite ends, and that the reconciliation is a matter of distinguishing the *ligand* from the *signal*. The amount of reelin protein and the amount of reelin signalling are not the same quantity, and in Alzheimer's disease they move in opposite directions. Amyloid-β induces neurons to make more reelin, but it also traps the secreted protein in aggregates and blunts its ability to phosphorylate Disabled-1, so that the tissue ends up with more reelin and less reelin signal — a condition precisely analogous to insulin resistance, and best named reelin resistance (Cuchillo-Ibáñez and colleagues, 2016). Meanwhile the specific neurons that carry the strongest reelin signal into the hippocampal circuit, the glutamatergic cells of entorhinal layer II, are selectively depleted (Chin and colleagues, 2007). The guardian is not absent from the diseased brain; it is present in excess and unable to act. And the proof that this failing signal matters — that reinforcing it changes the disease — is written in the one place a mechanism can be proven in a human: a family in which a stronger reelin held off a genetic dementia that should have been unstoppable (Lopera and colleagues, 2023). The guardian is real. The disease has learned to silence it. And a single fortunate mutation shows what happens when it cannot be silenced.

IV. The Guardian's Mechanisms — How Reelin Restrains the Disease

We turn to the mechanisms, tracing each from the receptor to the pathology and grading, as we go, how far the chain is established in humans and how far it is inferred from animals. Reelin does not act on Alzheimer's disease through a single lever but through at least three — tau, the synapse, and amyloid — and, beneath all of them, through the receptor it shares with ApoE. The convergence is the strength of the story and, as we shall see, the source of its greatest difficulty.

The Tau Brake

The most mechanistically secure of reelin's protective actions is its restraint of tau phosphorylation, and it was among the first to be discovered. When Hiesberger and colleagues (1999) worked out that reelin signals through VLDLR and ApoER2 to phosphorylate Disabled-1, they made a second observation whose importance for Alzheimer's disease was immediately clear: mice that lack reelin, and mice that lack both of its receptors, show hyperphosphorylation of tau, the microtubule-associated protein that in its hyperphosphorylated form assembles into the neurofibrillary tangles of the disease. The mechanism runs from Disabled-1 through the PI3-kinase/Akt axis to the inhibition of glycogen synthase kinase-3β; a live reelin signal keeps this kinase suppressed and tau in its normal, microtubule-binding state, while the loss of reelin signalling releases the kinase and permits tau to be pathologically modified. Reelin is, in the most literal biochemical sense, a brake on the tau engine.

That this brake operates in the intact brain, and not merely in cell culture, was demonstrated by crossing reelin-deficient mice with a transgenic Alzheimer's model. Reducing reelin by half — the heterozygous reeler state — accelerated the disease on both of its axes: it enhanced the amyloidogenic processing of the amyloid precursor protein, producing more and larger plaques earlier, and it produced concentric haloes of phospho-tau-positive neurons around those plaques, with silver-staining evidence of frank neurofibrillary tangles in the entorhinal cortex and hippocampus of the double-mutant animals (Kocherhans and colleagues, 2010). This is the loss-of-function experiment: take reelin away, and the disease comes faster and harder, in exactly the regions it prefers. We will meet its gain-of-function mirror in the resilient man, and the symmetry between them is the strongest single argument this dissertation possesses.

The Synaptic Shield

Reelin's second protective action is at the synapse, where it opposes the very lesion by which amyloid-β is thought to injure cognition before it kills a single neuron. Soluble amyloid oligomers suppress long-term potentiation and drive the internalization of glutamate receptors, weakening synapses and degrading the circuits of memory. Reelin does the opposite: signalling through ApoER2's complex with the NMDA receptor, it enhances potentiation and sharpens glutamatergic transmission (Beffert and colleagues, 2005; Weeber and colleagues, 2002). When the two are applied together, they behave as antagonists. Durakoglugil and colleagues (2009) showed that reelin prevents the amyloid-induced suppression of potentiation and of NMDA-receptor currents at pathological amyloid concentrations, an effect requiring Src-family tyrosine kinases — and, crucially, that this protection has a ceiling. At high enough amyloid, reelin can no longer overcome the suppression, and its rescue collapses at exactly the point where its phosphorylation of the NMDA receptor is fully blocked. The synaptic shield is real but finite: it holds against the amyloid burden of early disease and fails against the burden of late disease. This ceiling will matter enormously when we come to the question of timing, for it predicts that reelin's protection is a property of the earlier brain.

The framing that best captures this relationship comes from the field's own senior figure. Reviewing the redefinition of amyloid-β from waste product to physiological regulator of synaptic homeostasis, Herz (2025) describes the peptide as a synaptic guardian that becomes, when dysregulated, a neurodegenerative culprit — an adaptive brake on excitatory drive that turns maladaptive with age and inflammation. Reelin is the counterweight in this system, the signal that opposes amyloid's brake and keeps synaptic gain in the range where memory is possible. Alzheimer's disease, on this view, is not the intrusion of a foreign poison but the collapse of a homeostatic balance in which reelin and amyloid are the opposing hands. That is a subtler and more accurate picture than the war-on-amyloid rhetoric it replaces, and it locates reelin at the centre of the balance rather than at its periphery.

The Amyloid Interface

Reelin's third action touches amyloid directly, and here the evidence is strong in models and unproven in people. Reelin binds soluble amyloid-β42 species and delays their aggregation into fibrils, is itself recruited into the growing fibril, and protects cultured neurons against both the death and the dendritic-spine loss that amyloid oligomers inflict; in a transgenic mouse carrying human mutant amyloid precursor protein, overexpressing reelin postponed the appearance of plaques and rescued recognition memory (Pujadas and colleagues, 2014). Complementing this, reduced reelin accelerates amyloidogenic processing of the precursor protein, indicating that reelin normally biases the protein toward its non-amyloid fate (Kocherhans and colleagues, 2010). The picture is of a molecule that meets amyloid at several stages — production, aggregation, and toxicity — and at each stage tilts the balance toward safety. The caution is that every one of these demonstrations is in a cell dish or a mouse, and that the concentrations and genetic manipulations used to reveal the effect are not those of a human brain aging naturally. Reelin can delay amyloid pathology in a model. Whether it does so in a person is an inference, and we will grade it as one.

The ApoE Convergence

Beneath tau, synapse, and amyloid lies the fact that organizes them: reelin signals through the lipoprotein receptors that also carry apolipoprotein E, and so the reelin pathway and the Alzheimer's-risk pathway are not neighbours but tenants of the same receptor. ApoE and reelin compete, in effect, for the attention of ApoER2 and VLDLR, and the isoform of ApoE a person carries alters how those receptors traffic, recycle, and respond. The mechanistic prediction — that the ε4 allele, which impairs receptor recycling and synaptic maintenance, thereby degrades the reelin signal, while protective handling of the receptor preserves it — is attractive and partially supported, but it must be graded carefully, because the dedicated human demonstration that ApoE4 acts on Alzheimer's disease *by* impairing reelin signalling has not been made. What can be said with confidence is structural: reelin binds the same receptors as ApoE (Hiesberger and colleagues, 1999; Lopera and colleagues, 2023), and the two most powerful genetic modifiers of Alzheimer's disease yet discovered in living people both act on this receptor system — one on its ApoE ligand, one on its reelin ligand. To that convergence, which is the heart of the matter, we now turn.

V. The Human Evidence, Weighed

The mechanistic case of Section IV creates an expectation, and the discipline of the ONS method is to test that expectation against the human data without flinching, and to say plainly where the

human data complicate the story. They complicate it considerably, and the complications are as instructive as the confirmations.

The Entorhinal Vanishing

The single most suggestive human observation is anatomical. The disease begins, reliably and early, in the entorhinal cortex — the gateway through which the neocortex addresses the hippocampus — and it is precisely there that the reelin-expressing neurons are lost. Chin and colleagues (2007) found that in mice expressing human mutant amyloid precursor protein, and in the brains of people who had died with Alzheimer's disease, the population of reelin-expressing glutamatergic pyramidal neurons in the entorhinal cortex was markedly reduced, with a corresponding fall in reelin reaching the hippocampus along their projections. The specificity was telling: the reelin-expressing GABAergic interneurons were spared, and the reduction fell on exactly the excitatory cells whose reelin output feeds the vulnerable circuit. Neuronal expression of human amyloid was itself sufficient to reduce reelin in these cells, which establishes that at least part of the reelin decline is downstream of amyloid rather than upstream of it — an honesty the causal story must absorb.

This is the observation that first suggested reelin might matter, and it is genuine, but its direction is ambiguous. That reelin-expressing neurons vanish where the disease begins is consistent with reelin loss driving the disease, and equally consistent with the disease killing reelin neurons like any others. The entorhinal vanishing, taken alone, cannot tell us which. It tells us only that reelin and the disease's earliest lesion share an address — and it invites the more decisive evidence that arrives when the arrow of causation is fixed by a mutation.

The Rising-Reelin Paradox

Before that evidence, the complication must be faced squarely, because a naïve version of this dissertation's thesis is simply false. Reelin does not fall in the Alzheimer's brain as a bulk quantity. Botella-López and colleagues (2006) measured a roughly forty-percent *increase* in reelin protein in the cortex and cerebrospinal fluid of patients, with the rise in a 180-kilodalton reelin fragment extending across frontotemporal dementia, progressive supranuclear palsy, and Parkinson's disease, and correlating with the level of tau in the fluid. With age, reelin accumulates further into extracellular deposits that co-localize with early amyloid and may nucleate plaque formation (Knuesel and colleagues, 2009). A theory that predicted less reelin would be refuted by these data. The disease has more.

The resolution — and it is one of the more satisfying resolutions in this literature — is that the elevated reelin is not signalling. Cuchillo-Ibáñez and colleagues (2016) showed that amyloid-β and reelin co-immunoprecipitate from human brain, that amyloid *increases* reelin expression even as it traps the secreted protein in aggregates, and that despite this abundance the reelin-dependent phosphorylation of Disabled-1 — the actual readout of a working signal — is *reduced* in the

Alzheimer's brain. Amyloid also blunts reelin's ability to internalize and process its receptor, and a soluble receptor fragment that reports on reelin signalling in the cerebrospinal fluid, which tracks reelin in healthy people, uncouples from it in patients. The tissue is flooded with ligand and starved of signal. This is reelin resistance, and it dissolves the paradox: the rising reelin of the biomarker studies and the failing reelin of the mechanistic studies are the same pathology seen from two instruments. The guardian has not left. It has been gagged.

The Loss-of-Function Experiment, In Vivo

If a failing reelin signal permits the disease, then reducing reelin should worsen it, and in the mouse it plainly does. The heterozygous-reeler cross with an Alzheimer's model, already described for its effect on tau, is properly read as the loss-of-function arm of a natural experiment: halving reelin accelerated amyloid deposition, enlarged and multiplied plaques, and precipitated phospho-tau pathology and tangles in the entorhinal cortex and hippocampus, with the plaques concentrating in the layers where reelin is normally most expressed (Kocherhans and colleagues, 2010). The dose-dependence is the important feature — this was not the abolition of reelin but its reduction, a manipulation closer to the partial reelin resistance of the human disease than a full knockout would be, and it was sufficient to worsen every measured feature of the pathology. In a model, less reelin signal is more disease.

The Reelin-COLBOS Reprieve

And then, in 2023, the gain-of-function arm was described — not in a mouse but in a man, and not as a manipulation but as a gift of inheritance. The setting is the largest known kindred with autosomal-dominant Alzheimer's disease, an extended family in Antioquia, Colombia, carrying the *PSEN1*-E280A mutation, which causes a fully penetrant, early-onset dementia with a median age of cognitive decline near the mid-forties. Within this kindred, Lopera and colleagues (2023) identified a man who did not decline until sixty-seven — some three decades late — despite carrying the E280A mutation and despite one of the highest amyloid-plaque burdens the investigators had ever measured. His resilience had an anatomical signature that is the whole point: his entorhinal cortex, where the disease's tau pathology should have been dense, carried only a limited tangle burden. The amyloid had come; the tau, in the critical region, had not.

He carried, heterozygously, a rare variant in the reelin gene — H3447R, which the investigators named COLBOS for the Colombia-Boston study that found it. And they did not stop at the correlation. Reelin, they noted, is a ligand that, like ApoE, binds the VLDL and ApoER2 receptors — placing the variant squarely on the pathway this dissertation has traced. They then showed that COLBOS is a *gain-of-function* variant: it activates the canonical target Disabled-1 more strongly than ordinary reelin, and, in a knock-in mouse engineered to carry it, it reduces the phosphorylation of human tau (Lopera and colleagues, 2023). Every element of the mechanism is present in this one case. A stronger reelin signal, acting through Disabled-1, suppressing tau, sparing

the entorhinal cortex, and buying a man three decades of cognition against a mutation that permits no such reprieve to anyone else. It is the gain-of-function mirror of the reeler cross, performed by nature in a human being, and it is as close to a causal proof as the ethics of the disease will ever allow.

One must not over-read a single case, and Section VII will grade it with the caution an *n* of one demands. But one must not under-read it either. This is the world's second ascertained case of extreme resilience to autosomal-dominant Alzheimer's disease, and it converges, at the level of the receptor, with the first.

VI. The Two Resilient Reelin-COLBOS and APOE3-Christchurch

The first case was described four years earlier, in the same kindred, and it has become one of the most cited observations in modern Alzheimer's research. A woman carrying the same *PSEN1*-E280A mutation remained free of mild cognitive impairment into her seventies, three decades past the expected onset, with an unusually high amyloid burden but strikingly limited tau pathology and neurodegeneration. She was homozygous for a rare variant of apolipoprotein E — the Christchurch variant, R136S — in the region of ApoE that governs its binding to heparan-sulfate proteoglycans (Arboleda-Velasquez and colleagues, 2019). The parallel to the reelin case is exact and cannot be coincidental: same mutation, same kindred, same three-decade reprieve, same dissociation of a spared tau pathology from an unchecked amyloid burden. Two people, protected from the same genetic catastrophe, by two different variants — one in ApoE, one in reelin — of two different ligands that bind the same two receptors.

That the convergence is not merely at the receptor but at a shared molecular mechanism has now been demonstrated, and it is the most important recent development in this story. The Christchurch variant weakens ApoE's binding to heparan sulfate; and heparan sulfate, as Section II described, is the co-receptor reelin requires to fire its signal. Pan and colleagues (2025) measured the reelin side of this equation directly: full-length reelin binds heparan sulfate with high affinity, N-sulfation of the sugar is critical for the interaction, and the interaction is *necessary* for reelin to dimerize ApoER2 and signal. And the COLBOS reelin variant — the resilience variant — binds heparan sulfate *more tightly* than ordinary reelin, tightening exactly the handshake that fires the protective signal. Set the two resilience mutations side by side and a single logic appears. The Christchurch ApoE variant loosens a *pathological* engagement of the heparan-sulfate/lipoprotein-receptor system; the COLBOS reelin variant strengthens a *protective*

one. Both dial the same three-way handshake — ligand, sulfated sugar, receptor — one down on the harmful side, one up on the helpful side, and both, by doing so, spare the entorhinal cortex from tau while amyloid rages on.

This is why reelin belongs at the centre of the resilience conversation and not at its margin. The field has tended to file the Christchurch case under ApoE and the COLBOS case under reelin, as though they were separate curiosities. They are not. They are two readings of a single dial, and the dial is the heparan-sulfate-dependent signalling of the lipoprotein receptors that reelin and ApoE share. The clinical implication is large: it suggests that the resilience these two people enjoyed is not an idiosyncrasy of their private mutations but a property of a druggable axis, approachable from either the ligand or the sugar. It also reframes the role of amyloid, for in both resilient brains amyloid accumulated freely and yet dementia did not follow — the protective variants did not stop the amyloid; they stopped the *tau*, downstream, by preserving the reelin signal that brakes it. The resilient cases are, among their other lessons, the strongest human argument that tau rather than amyloid is the proximate executioner, and that reelin sits on the pathway between them.

Reelin and the Perineuronal Net — The Shared Sulfation Node

There is a third reading of the dial, and it comes from a structure this dissertation has so far left unnamed: the perineuronal net. The sulfated sugar on which the whole convergence turns is not free-floating; its densest expression at the neuronal surface is the perineuronal matrix — the lattice of chondroitin- and heparan-sulfate proteoglycans that ensheaths vulnerable neurons, closes critical periods, and buffers oxidative insult. And reelin's relationship to that lattice is not incidental. A defined population of cortical GABAergic interneurons secretes reelin directly *into* the perineuronal net, where it resides extrasynaptically (Pesold and colleagues, 1998, 1999). Reelin is, quite literally, a tenant of the net — its protective signal staged in the same sulfated matrix that the net is built from.

This gives the sulfation node a reach beyond the two resilience variants, because the same matrix discharges three offices at once. It shields the neuron structurally; it presents the N-sulfated heparan sulfate that reelin *requires* to cluster ApoER2 and fire (Pan and colleagues, 2025); and it is the very surface through which pathological tau is internalized and propagated from cell to cell, since tau seeds enter neurons by binding heparan-sulfate proteoglycans (Holmes and colleagues, 2013). One lattice therefore stages the reelin brake and gates the tau it brakes — and the prediction that follows is stark: neurons ensheathed by an intact net should carry less tau, and they do. Aggrecan-net neurons are relatively spared the tangle across subcortical regions, while the net-poor regions — the locus coeruleus, the nucleus basalis — are those tau attacks first (Morawski and colleagues, 2010); and in resilient human cortex, the excitatory neurons still bearing a net carry strikingly little phospho-tau (de Vries and colleagues, 2024). The perineuronal net is thus the third reading of the resilience dial, and the address at which reelin's signal is mounted. This convergence is developed in full in the companion monograph *The Architect's Scaffold*, which treats the reelin–net

relationship, the shared sulfation code, and the therapeutic double-edge it exposes — that a heparan-sulfate-blocking drug meant to stop tau spreading could, by the same action, silence the reelin signal that protects.

VII. The Validity Ledger

The discipline that separates this dissertation from advocacy is the ledger: an explicit grade for each connection, with the experiment that would settle it named alongside. The tiers run from *strong* through *moderate*, *real but complicated*, *plausible*, and *uncertain*, to *rejected as stated*.

Strong (mechanism) — reelin signalling restrains tau phosphorylation through Disabled-1 and GSK-3β. Established biochemically and in vivo: loss of reelin or of both its receptors raises tau phosphorylation, reducing reelin accelerates tangle pathology in an Alzheimer's model, and the human resilience variant lowers human tau phosphorylation in a knock-in mouse (Hiesberger 1999; Kocherhans 2010; Lopera 2023). This is the ledger's most secure thread and the mechanistic spine of the resilience story. *Settling experiment: none needed for the effect itself; what remains open is the quantitative contribution of reelin-dependent tau restraint to human disease course, addressable by reelin-pathway biomarkers of Dab1/GSK-3β activity in longitudinal cohorts.*

Strong (in animals) — reelin enhances synaptic plasticity and antagonizes amyloid-β at the synapse. The receptor biology, the NMDA-receptor complex, the activity-dependent ApoER2 splice, and the amyloid antagonism with its concentration ceiling are all reproducibly demonstrated (Weeber 2002; Beffert 2005; Durakoglugil 2009; Rogers 2011). The human inference is not yet made. *Settling experiment: demonstration in human tissue or in vivo imaging that reelin-pathway activity predicts synaptic resilience to a given amyloid burden.*

Strong (human, single case) — a gain-of-function reelin variant confers extreme resilience to autosomal-dominant Alzheimer's disease. The COLBOS case is causal-grade human evidence — a fixed genetic variant, a three-decade change in course, a spared entorhinal tau pathology, and a mechanistic confirmation in a knock-in mouse — but it is a single individual, and single cases cannot exclude the contribution of unmeasured modifiers (Lopera 2023). *Settling experiment: identification of further RELN resilience carriers, and reelin-pathway-enhancing intervention in an animal model of ADAD reproducing the entorhinal-tau sparing.*

Strong (convergence) — reelin and ApoE act on the same heparan-sulfate-dependent lipoprotein-receptor axis, and the two known human resilience variants both modulate it. Structurally certain that the ligands share

ApoER2/VLDLR; now shown that heparan sulfate is a required reelin co-receptor and that the COLBOS variant enhances the reelin–heparan-sulfate handshake as the Christchurch variant loosens the ApoE one (Arboleda-Velasquez 2019; Lopera 2023; Pan 2025). *Settling experiment: pharmacological modulation of heparan-sulfate sulfation or of reelin–receptor engagement shown to reproduce the resilience phenotype.*

Moderate — reelin-expressing entorhinal neurons are selectively depleted early in the disease. Cross-sectional but well-localized in both model and human tissue, and correctly placed in the disease's cradle; its causal direction is ambiguous, and Chin's own data show amyloid is sufficient to reduce reelin, making part of the decline a consequence (Chin 2007). *Settling experiment: longitudinal or staged post-mortem series establishing whether entorhinal reelin loss precedes or follows local tau onset.*

Moderate — reducing reelin accelerates amyloid and tau pathology in vivo. A clean, dose-dependent model result closely matching the partial reelin resistance of human disease, but a model result (Kocherhans 2010). *Settling experiment: conditional, adult-onset reelin reduction restricted to entorhinal neurons, to separate developmental from maintenance roles.*

Moderate — restoring or supplementing reelin signalling rescues cognition and synapses in disease models. Reelin overexpression delays plaques and rescues memory in an amyloid mouse, and central reelin supplementation improves plasticity and learning in healthy and impaired animals (Pujadas 2014; Rogers 2011). Proof of principle only; no human therapeutic data. *Settling experiment: a reelin-pathway agonist or deliverable reelin fragment tested for cognitive benefit in a mammalian ADAD model.*

Real but complicated — total reelin protein and its fragments rise in the Alzheimer's brain and cerebrospinal fluid. Robustly measured and initially paradoxical, resolved as reelin resistance: amyloid induces reelin, traps it, and blunts Disabled-1 phosphorylation, so abundance rises while signal falls; deposits may additionally seed plaques (Botella-López 2006; Knuesel 2009; Cuchillo-Ibáñez 2016). This complexity is the correct caution against any naïve "reelin goes down" model. *Settling experiment: assays that report signalling reelin (Dab1/receptor-fragment activity) rather than total reelin, validated as biomarkers against disease stage.*

Plausible — ApoE4 promotes Alzheimer's disease in part by degrading reelin signalling at the shared receptor. Mechanistically coherent given the shared receptors and the resilience-variant convergence, but the dedicated human demonstration is lacking (Hiesberger 1999; Durakoglugil 2009; Pan 2025). *Settling experiment: isoform-resolved measurement of reelin-dependent signalling in ε4 versus ε3 human neurons and tissue.*

Rejected as stated — reelin loss is a primary initiating cause of sporadic Alzheimer's disease. The evidence supports reelin as a modifier, guardian, and amplifier within a feed-forward loop — its decline is partly downstream of amyloid, and its bulk level rises rather

than falls — not as the disease's trigger (Chin 2007; Botella-López 2006). The strong initiator claim is not supported; the resilience-axis claim is. *Settling experiment: none required to reject the initiator framing; the modifier framing is what the data sustain.*

VIII. Reconciling the Readings Guardian, Not Trigger

Where, then, does reelin sit? Not where the enthusiast would place it, as a deficiency whose correction would cure the disease, and not where the skeptic would place it, as one more aggregating protein of no causal weight. It sits at a third position, better supported than either: reelin is an axis of *resilience*, a homeostatic guardian of the synapse and of tau whose signal the disease progressively silences, and whose reinforcement — in the one human experiment available — held the disease at bay.

The reconciliation has three parts, and each is testable. The first is the distinction between ligand and signal, already drawn: the quantity that protects is not reelin protein but reelin signalling to Disabled-1, and in Alzheimer's disease these diverge, abundance climbing while signal fails (Cuchillo-Ibáñez and colleagues, 2016). Any study, biomarker, or therapy that measures or delivers total reelin without measuring signal is answering the wrong question, and much of the apparent contradiction in the literature comes from conflating the two. The second is the ceiling on protection: reelin antagonizes amyloid at the synapse only up to a threshold of amyloid burden, beyond which its rescue collapses (Durakoglugil and colleagues, 2009). This predicts, as with so many protective factors in this disease, that reelin's benefit belongs to the earlier brain — the brain whose amyloid has not yet overwhelmed the guardian — and that reinforcing reelin will do more as prevention than as late rescue. The resilient cases are consistent with this: their protective variants were present from conception, guarding tau across the decades while amyloid slowly gathered, not deployed against an established dementia.

The third part is the direction of causation, and here honesty requires holding two truths at once. Reelin decline is partly a *consequence* of the disease — amyloid reduces reelin expression in entorhinal neurons and traps the reelin that is made (Chin and colleagues, 2007; Cuchillo-Ibáñez and colleagues, 2016) — and reelin decline is also a *cause* of further disease, since reducing reelin accelerates both amyloid and tau pathology (Kocherhans and colleagues, 2010). These are not contradictory; they are the two limbs of a feed-forward loop, in which amyloid weakens the reelin signal and the weakened signal permits more tau and more amyloid. A feed-forward loop has no single origin, but it has leverage points, and the resilient cases identify reelin as one: strengthen the signal at any point in the loop and the whole spiral slows. That is the precise, defensible claim — not

that reelin starts the disease, but that reelin is a node at which the disease can be resisted, demonstrated to be such in a living human being. The architect did not cause the ruin. But the architect, reinforced, was able to hold the building standing three decades past its condemnation.

IX. Therapeutic Corollaries Bottling the Guardian

If reinforcing reelin signalling resists the disease, the therapeutic ambition writes itself: to supply the signal that the resilient carry by birth to the majority who do not. The proof of principle exists. A single central injection of recombinant reelin enhances plasticity, spine density, and learning in a normal mouse (Rogers and colleagues, 2011), and reelin overexpression delays plaques and rescues memory in an amyloid model (Pujadas and colleagues, 2014). The resilient man shows that a stronger reelin signal, present lifelong, can hold off even autosomal-dominant disease (Lopera and colleagues, 2023). The direction of the intervention is therefore not in doubt. The difficulty is delivery, and it is severe.

Reelin is one of the largest proteins the brain secretes — a molecule of some three thousand residues that does not cross the blood-brain barrier and cannot be manufactured or dosed like a small drug. The realistic therapeutic routes therefore do not attempt to deliver whole reelin but to engage its pathway by other means, and the resilience biology now points to several. The first is to target the reelin-signalling handshake directly: the discovery that heparan-sulfate N-sulfation is required for reelin to fire its receptor, and that the resilience variant works by binding this sugar more tightly, identifies heparan-sulfate biology and the reelin–receptor interface as druggable surfaces — a small molecule or biologic that strengthens the handshake would, in principle, reproduce the COLBOS effect pharmacologically (Pan and colleagues, 2025). The second is to deliver an active fragment rather than the whole protein: reelin's signalling activity resides in its central repeats, and a minimized central fragment, or an ApoER2/VLDLR agonist that mimics reelin's clustering of the receptor, could carry the signal across the barrier where the intact protein cannot. The third, and most immediate, is to protect the reelin signal the patient already has — to prevent amyloid from trapping and silencing endogenous reelin, since the diseased brain is not short of reelin protein but short of reelin action (Cuchillo-Ibáñez and colleagues, 2016).

Three corollaries follow for the clinic and for trial design, and all three are consequences of the timing thesis. First, reelin-directed intervention, like the resilience it seeks to imitate, is a strategy for the *earlier* brain — for prevention and for the preclinical and prodromal windows in which the guardian's ceiling has not yet been breached — and it should be tested there rather than in established dementia, where the amyloid burden already exceeds the signal's capacity to oppose it.

Second, the correct biomarker for such trials is not total reelin, which rises misleadingly, but a measure of reelin *signalling* — Disabled-1 phosphorylation, or the receptor-cleavage fragments that report on it — validated against disease stage. Third, the reelin axis should be pursued in explicit partnership with the ApoE-resilience programme, not in isolation from it, because the two share a mechanism: an agent that acts on the heparan-sulfate/lipoprotein-receptor node might reproduce, from the reelin side, the protection that the Christchurch variant confers from the ApoE side, and either would be a therapy modelled directly on a human being who did not get the disease.

X. Predictions and Falsification

A framework earns its keep by risking specific predictions. The guardian-and-resilience thesis of this dissertation makes several, each falsifiable.

- Additional carriers of gain-of-function *RELN* variants, if found within the *PSEN1*-E280A kindred or other autosomal-dominant cohorts, will show delayed onset and spared entorhinal tau; and conversely, loss-of-function *RELN* variants will associate with earlier or more aggressive disease. Discovery of gain-of-function reelin carriers with ordinary, un-delayed disease course would substantially weaken the thesis.
- Measures of reelin *signalling* — Disabled-1 phosphorylation or reelin-dependent receptor-cleavage fragments — will fall with advancing disease stage even as total reelin protein rises, and the signalling measure, not the total, will predict cognitive trajectory. A finding that total reelin predicts course better than signalling reelin would refute the reelin-resistance model.
- Reinforcing reelin signalling — by an active fragment, a receptor agonist, or modulation of heparan-sulfate sulfation — will reproduce the entorhinal-tau sparing of the resilient cases in an animal model of autosomal-dominant disease, and will do so more effectively when begun before, rather than after, a threshold amyloid burden. A pathway-reinforcing agent that fails to spare tau in a preclinical-window model would falsify the mechanism.
- The protective effect of reelin will prove to operate principally on tau rather than on amyloid: interventions that strengthen reelin signalling will reduce tau pathology and preserve cognition while leaving amyloid burden largely intact, mirroring the resilient brains. A reelin intervention that clears amyloid but does not touch tau would overturn the placement of reelin between the two.

- The ApoE4 risk allele will be shown, in isoform-resolved human systems, to degrade reelin signalling at the shared receptor; and the resilience of *APOE3*-Christchurch will be shown to preserve it. A demonstration that ApoE4 leaves reelin signalling intact would sever the convergence this dissertation has argued.

XI. Coda The Architect and the Hour

The cortex is a building raised in the womb by a protein that told each neuron where to stand. We named the protein for the stagger of the mice that lacked it, studied it for forty years as a fact of development, and assumed that when the building was finished its architect went home. It did not. Reelin stayed on as the caretaker of the structure it had raised, walking the synapses it once positioned, keeping tau from tangling and amyloid from silencing the circuits of memory, holding open — through the same lipoprotein receptors that carry the disease's greatest genetic risk — the possibility of remembering. For most of a lifetime the caretaker's work is invisible, as the work of caretakers is, and it becomes visible only in its failure, when the disease learns to gag the guardian and the building begins, quietly, to come down.

What this dissertation has tried to show is that the failure is neither the beginning of the disease nor an accident beside it, but a node within it at which the disease can be resisted — and that this is not a hope but an observation, written into two human beings who should have been lost and were not. A woman and a man, in the same stricken family, carrying the same merciless mutation, were each granted three decades of clear mind by a single change in the machinery reelin and ApoE share: one that loosened a harmful grip on the receptor, one that tightened a helpful one. In both, the amyloid came and the tau did not; in both, the entorhinal cortex — the room where the disease likes to begin — was spared. They are the proof, as close to proof as this disease permits, that the caretaker's signal is worth reinforcing, and that a brain flooded with pathology can nonetheless be held.

The honest verdict is therefore neither that reelin causes Alzheimer's disease nor that it is innocent of it, but that reelin is the architecture's own defence — a guardian whose silencing permits the ruin and whose reinforcement, in the only human experiment we have, delayed it by a generation. The clinician's task is not yet to prescribe it, for we cannot yet deliver it; the scientist's task is to learn to strengthen the signal that two fortunate people carried by birth, and to strengthen it early, in the window where the guardian can still be heard. The architect built the cortex once and has been quietly defending it ever since. The question this dissertation leaves is whether we can learn to lend the architect our strength, and reach the disease before the hour when even reelin,

reinforced, could no longer hold the building up.

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