THE ARCHITECT'S HANDSHAKE

The Reelin–ApoER2–Heparan Sulfate Interface — How a Three-Body Clasp at the Neuronal Surface Holds Tau in Check, and What Comes Undone in Alzheimer's Disease When the Clasp Cannot Close

The Three-Body Clasp · The Double-Lysine Grip · The Sulfation Code
The Three Failures · The Interface, Read for Resilience

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The molecular companion to The Architect's Reprieve (reelin as an axis of resilience) and The Architect's Scaffold (reelin and the perineuronal net). Those volumes argue the resilience narrative and the shared-matrix anatomy; this one descends to the interface itself — the three-body clasp of reelin, N-sulfated heparan sulfate, and ApoER2. It maps the clasp in health, traces its three-sided failure in disease, and reads the sulfation code by which one polymer is at once the shield that stages reelin's brake on tau and the gate that admits the tau seed.

"We named the pathway for its ends — the ligand at one extreme, the restrained tau at the other — and studied them as though the middle were plumbing. But the whole of the protection lives in the middle: in whether, on a patch of membrane a few nanometres across, three molecules of three chemical kingdoms can be made to hold one another. This dissertation is an anatomy of that grip."

— ONS Methodology Working Notes, 2026

For those who treated the sulfated sugar as backdrop — and so overlooked the third partner of the clasp, the very component nature reached for, twice, in one Colombian family, to hold off an unstoppable dementia.

THE ARCHITECT SEQUENCE — REELIN AT THE MATRIX

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

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

The Coerulean Shears — MMP-9, the named instrument that cuts the matrix

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

The Architect's Handshake (the reelin–heparan-sulfate–ApoER2 clasp at molecular resolution) — this volume

This volume changes the level of description. Where the Reprieve reads reelin as a resilience axis and the Scaffold reads the perineuronal net as its shared surface, the Handshake resolves the surface into a single molecular event: the closing of a three-body clasp in which a proteolytically activated central fragment of reelin, presenting a double-lysine grip, is held against the first ligand-binding module of ApoER2 by an obligate bed of N-sulfated heparan sulfate — the co-receptor without which the receptor cannot be clustered and the tau-brake cannot fire. It argues that Alzheimer's disease spoils this clasp on all three sides at once (a ligand trapped, a receptor competed-for and withdrawn, a sulfation code that drifts from staging reelin toward admitting tau), that the two human resilience variants both act on the sugar-facing side of it, and that the one polymer bearing both the shield and the gate must therefore be tuned, not broken.

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Abstract

The protective arm of the reelin pathway is usually named for its ends — the secreted ligand at one extreme, the restrained tau protein at the other — and studied as though the interesting biology lived there. This dissertation argues that the decisive biology lives in the middle, at a single molecular event on the neuronal surface: the closing of a three-body clasp in which the ligand reelin, the sulfated sugar heparan sulfate, and the lipoprotein receptor ApoER2 grip one another tightly enough to fire a signal inward. When that clasp closes, a chain of phosphorylations descends through the adaptor Disabled-1 and the Src-family kinases to inhibit glycogen-synthase-kinase-3β, the principal kinase that hyperphosphorylates tau. The reelin brake on tau is not a metaphor; it is the distal readout of whether, on a given dendrite, three molecules could be made to hold hands. This is the interface, and it is the true unit of analysis.

We assemble the molecular anatomy of that interface at the resolution the structural literature now permits. The signalling activity of reelin resides not in the whole three-thousand-residue protein but in a central fragment, generated by proteolysis in vivo, whose fifth and sixth repeats present two lysine residues to the first ligand-binding module of ApoER2 in a "double-lysine" grip shared across the endocytic lipoprotein receptors. A monomeric grip is nearly inert; the signal requires that reelin be multivalent and that the receptors be *clustered*, and clustering is exactly what the third partner enables — for reelin cannot dimerize ApoER2 without N-sulfated heparan sulfate as an obligate co-receptor. The clasp is therefore genuinely three-bodied: remove the sugar and the ligand cannot assemble the receptor into the signalling geometry, and the inward phosphorylations never begin.

The dissertation's central claim concerns that sugar. The same heparan-sulfate polymer that stages reelin's protective signal is also the surface through which pathological tau enters neurons — but the two functions are written in partly separable *sulfation codes*. Reelin's engagement is dominated by N-sulfation; tau's cellular uptake additionally requires 6-O-sulfation and a specific chain architecture, and its intracellular hyperphosphorylation is chaperoned by rare 3-O-sulfated domains generated by an enzyme upregulated in the Alzheimer's hippocampus. One polymer bears both the shield and the gate, inscribed in different ink. From this reading the disease is legible as a failure of the clasp on all three of its sides at once: a ligand trapped and deafened (reelin resistance), a receptor competed for by apolipoprotein E and, in the ε4 carrier, withdrawn from the surface into endosomes it cannot leave, and a sulfation code that drifts from staging reelin toward admitting tau. We grade every link in an explicit validity ledger, show that the two human resilience variants — Reelin-COLBOS and APOE3-Christchurch — are best understood as opposite adjustments to the *sugar-facing* side of the very same clasp, and close on the therapeutic knife-edge this molecular reading exposes: a drug that blocks heparan sulfate to stop tau from spreading may, by the identical action, silence the reelin signal that brakes it. The interface must be *tuned*, not broken. The architect's protection was never a molecule. It was a handshake.

I. The Three-Body Problem

There is a habit of thought in molecular neuroscience that mistakes the endpoints of a pathway for its content. We name the reelin pathway for reelin, and we measure its success by the state of tau, and in doing so we quietly assume that the mechanism worth understanding is the ligand and the substrate — that the middle is plumbing. This dissertation is written on the opposite assumption. The mechanism worth understanding is the middle: the physical event, occurring on a patch of dendritic membrane a few tens of nanometres across, in which three molecules of different chemical kingdoms — a protein, a sulfated polysaccharide, and a transmembrane receptor — are brought into a single grip stable enough to transmit a signal across the lipid bilayer. Everything protective that reelin does to tau is downstream of whether that grip forms. The grip is the pathway.

To call it a three-body problem is not merely a borrowed phrase. The signalling event genuinely requires three partners, and the failure of any one of them collapses it. The ligand alone, presented to the receptor as a monomer, is nearly inert. The receptor alone, unclustered, does not phosphorylate its adaptor. And the ligand cannot cluster the receptor — cannot solve the geometry — without the third body, the sulfated sugar, which is neither ligand nor receptor but the co-receptor that makes the other two able to hold on. A two-body account of reelin signalling, of the kind that dominated the field for two decades, is not merely incomplete; it is missing the partner that does the decisive work. The recent demonstration that N-sulfated heparan sulfate is obligatory for reelin to dimerize ApoER2 (Pan and colleagues, 2025) did not add a footnote to the mechanism. It revealed that the mechanism had always been three-bodied and we had been reading two.

The reframing matters because it changes where the disease can be located, and where it can be treated. If the protective quantity is *reelin protein*, then Alzheimer's disease ought to show a deficit of reelin, and it does not — the diseased cortex has more reelin, not less (a paradox to which we will return, and which the companion dissertation *The Architect's Reprieve* resolves in full). If instead the protective quantity is *the closing of the clasp*, then the disease can proceed with reelin in abundance, provided the clasp cannot close — provided the ligand is trapped, or the receptor withdrawn, or the sugar mis-sulfated. The interface, not the ligand, is the thing that fails. And the interface, not the ligand, is the thing a drug must reach. This dissertation is an argument that the level of description at which reelin biology becomes therapeutically legible is the level of the three-body interface, and it sets out to describe that interface — in health, in failure, and in the two human beings whose good fortune was written into the sugar-facing side of it.

What follows is, in the most literal sense, an anatomy of a handshake: the parts that must meet, the grip they must form, the signal that follows if they hold, and the three distinct ways the grip comes apart in the aging brain.

II. The Molecular Anatomy of the Clasp

We begin with the parts, because the argument of the whole dissertation depends on their being understood as parts of one assembly rather than as separate stories. Three molecules must meet. Each brings to the meeting a specific surface, and each surface has now been mapped closely enough that we can say, with more precision than the field usually allows itself, what health consists of at this interface.

The Ligand: A Fragment, Not a Protein

Reelin is one of the largest proteins the mammalian brain secretes — a glycoprotein of roughly three thousand four hundred residues, organized after its signal peptide and an F-spondin-like region into eight tandem "reelin repeats," each an unusual bipartite fold split by an EGF-like module. It is tempting to treat so grand a molecule as a monolith. The signalling biology forbids it. In the living brain reelin is cleaved by proteases at two principal sites — between repeats 2 and 3, and between repeats 6 and 7 — yielding a set of fragments, and the receptor-binding, signal-competent species is not the full-length protein but the *central fragment* spanning repeats 3 through 6 (Jossin and colleagues, 2004). This central fragment is both necessary and sufficient: it binds the receptors, it drives the tyrosine phosphorylation of the intracellular adaptor Disabled-1 in cultured neurons, and it rescues the disordered cortex of the reeler mouse in slice culture as well as intact reelin does. The corollary is consequential and is easy to miss — proteolytic processing is not reelin's degradation but part of its *activation*, and the enzymes that cut reelin are therefore participants in the signal, not merely its undertakers. When a later section turns to failure, the proteases will return as one of the ways the ligand side of the clasp is spoiled.

Structural work narrowed the active surface further still, from the central fragment to a single module within it. The receptor-binding activity, and the capacity to phosphorylate Disabled-1, localize specifically to the segment formed by the fifth and sixth reelin repeats; a crystal structure of that R5–6 fragment resolved to two ångströms revealed a compact side-by-side arrangement of the two repeats and, unexpectedly, bound zinc ions, and it identified two lysine residues — Lys2360 and Lys2467 — as the centre of the contact with the receptor (Yasui and colleagues, 2007). The same study made an observation that will prove to be the hinge of the entire mechanism: a *monomeric* R5–6 fragment signals only feebly, and artificially forcing it into oligomers increases its activity roughly tenfold. Reelin's signalling potency is a property not of the single grip but of *many grips made at once*. Hold this beside the sugar, three paragraphs hence, and the reason the third body is indispensable will become plain.

The Receptor: A Comb of Modules and a Splice-Tuned Tail

The apolipoprotein E receptor 2 — ApoER2, the product of the *LRP8* gene — belongs to the low-density-lipoprotein receptor family, and it is built, like its relatives, as a comb of small cysteine-rich "LA" (LDLR class A) modules strung on the extracellular stalk, followed by EGF-like repeats and a β-propeller, a single transmembrane pass, and a short cytoplasmic tail. What the structural literature established is that reelin's entire receptor-facing business is transacted at the *first* of these modules. The LA1 module of ApoER2 is by itself sufficient to bind reelin, and a 2.6-ångström structure of the reelin R5–6 fragment in complex with LA1 showed exactly how: reelin's Lys2467 is clamped by a conserved tryptophan of the module and by the acidic residues that the module uses to coordinate its structural calcium ion, with Lys2360 completing the contact (Yasui and colleagues, 2010). This is the "double-lysine" recognition mode, and it is not idiosyncratic to reelin — it is the same chemistry by which the endocytic lipoprotein receptors grip apolipoprotein E and their other cargo. The lesson is worth stating plainly, because it foreshadows a failure: reelin holds ApoER2 by precisely the mechanism that apolipoprotein E also uses. The two ligands do not merely share a receptor; they share a *binding chemistry* at the same module, which is the molecular basis of the competition we will meet in Section V.

The contact, moreover, is deliberately modest. The interface between reelin and LA1 buries only about three hundred and fifty square ångströms on each face — a small, calcium-dependent grip designed to be stable under physiological conditions without being irreversible (Yasui and colleagues, 2010). A small grip is an important design choice: it means that a single reelin–LA1 contact is easily broken, that signalling cannot depend on the strength of one handshake, and that potency must instead come from *avidity* — from many modest grips made simultaneously across a clustered array of receptors. The receptor's ectodomain, in other words, is engineered for multivalency, not for high single-site affinity, which is precisely why the third partner — the sugar that organizes multivalency — is not optional.

The receptor's other end carries the rest of the story. The short cytoplasmic tail of ApoER2 contains an NPxY motif, the canonical docking sequence for phosphotyrosine-binding adaptors, and it is here that Disabled-1 attaches (Trommsdorff and colleagues, 1998). The tail is also the site of a decisive piece of regulation: an alternatively spliced exon (exon 19) inserts a proline-rich cassette into the intracellular domain, and the inclusion of this cassette — itself controlled by neuronal activity — governs how strongly reelin signalling through ApoER2 potentiates the synapse and supports memory (Beffert and colleagues, 2005). The receptor is thus not a passive post but a tunable one, its output set by a splice choice that the neuron adjusts according to its own activity. Health, at this interface, includes the neuron keeping that tail in its plasticity-competent form.

The Third Body: N-Sulfated Heparan Sulfate as Obligate Co-Receptor

We arrive at the partner the field long overlooked. Heparan sulfate is a linear, heavily sulfated polysaccharide, assembled on core proteins (the heparan-sulfate proteoglycans — syndecans, glypicans, and the matrix proteoglycan agrin among them) and displayed in dense profusion at the neuronal surface and in the surrounding matrix. Its sulfation is not uniform: as the chain is polymerized it is modified in patches by a committee of enzymes — the N-deacetylase/N-sulfotransferases that install N-sulfate groups, and the 2-O-, 6-O-, and 3-O-sulfotransferases that decorate specific positions — so that the finished polymer is a mosaic of differently sulfated domains, a molecular text written in a four-letter sulfation alphabet. This heterogeneity is the substrate of the entire argument to come.

For reelin, the recently established fact is categorical: full-length reelin binds heparan sulfate with high affinity, the *N-sulfation* of the sugar is critical to that binding, and — this is the decisive point — the interaction is *necessary* for reelin to cluster ApoER2 and fire the signal (Pan and colleagues, 2025). Strip the sulfated sugar from the surface with heparinase, or block N-sulfation, and reelin can no longer assemble its receptor into the dimerized, signalling geometry; the tyrosine phosphorylation of Disabled-1 falls. The sugar is therefore not an accessory that fine-tunes an already-working signal. It is the co-receptor that *permits* the signal, by solving the multivalency problem that Sections II.i and II.ii left open. Reelin needs to make many modest grips at once; the receptor is built for avidity rather than affinity; and the sulfated sugar is the scaffold on which ligand and receptor are concentrated and aligned closely enough for the many grips to close together. Remove it and the clasp cannot achieve the geometry that a tenfold-potent signal requires.

That is the three-body clasp in health: a proteolytically activated central fragment of reelin, presenting its double-lysine surface; the LA1 module of ApoER2, gripping that surface by the shared endocytic-receptor chemistry; and a bed of N-sulfated heparan sulfate holding the two in the clustered array without which the grip is inert. When all three meet, the signal begins.

The Clasp Closes: From the Surface to the Tau Brake

What happens inside when the clasp closes has been mapped step by step, and it terminates precisely at the enzyme that matters for Alzheimer's disease. Clustering of ApoER2 by multivalent reelin — demonstrated directly for reelin and other dimeric ligands, and shown to draw in neighbouring molecules including the amyloid precursor protein and the scaffolding protein PSD-95 (Divekar and colleagues, 2014) — brings together the receptors' cytoplasmic tails and, with them, the molecules of Disabled-1 docked at their NPxY motifs. Clustered Disabled-1 is then tyrosine-phosphorylated by Src-family kinases, chiefly Fyn; and Disabled-1 is both the substrate and, once phosphorylated, an activator of those same kinases, so that the event is self-amplifying — a small, well-formed cluster ignites a disproportionate signal (Bock and Herz, 2003). That the whole apparatus is causal for brain wiring, and not a bystander correlation, was fixed by genetics before any of the biochemistry was complete: deleting Disabled-1 disorders the cortex in a pattern indistinguishable from the reeler mutant (Howell and colleagues, 1997), and deleting *both* lipoprotein receptors together reproduces the reeler phenotype precisely (Trommsdorff and colleagues, 1999). The ligand, the receptors, and the adaptor are one functional unit, established by the convergence of their loss-of-function phenotypes onto a single anatomy.

From phosphorylated Disabled-1 the signal descends through phosphatidyl-inositol-3-kinase and Akt to the inhibitory phosphorylation of glycogen-synthase-kinase-3β — and it is at this last enzyme that the reelin pathway makes contact with the pathology of dementia. Glycogen-synthase-kinase-3β is the principal kinase that hyperphosphorylates tau; a live reelin signal keeps it 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 (Hiesberger and colleagues, 1999). This is the tau brake, and the entire preceding anatomy exists to explain a single arrow: three molecules meet on the surface, and a kinase two compartments away is turned down. Reduce the strength of the meeting and the kinase rises. The brake, mapped to its molecular root, is nothing more nor less than the closing of the three-body clasp — which is why every one of the three partners, when it fails, fails as tauopathy.

III. The Sulfation Code One Polymer, Two Readings

If the reader retains one section of this dissertation, it should be this one, because it contains the observation that distinguishes the receptor-interface view of reelin from every account that came before it. The heparan sulfate that stages reelin's protective clasp is the very same class of molecule — often, on the same neuron, the same polymer — through which pathological tau enters the cell.

The sulfated sugar is at once the shield and the gate. And the reason this is a scientific finding rather than a rhetorical flourish is that the two functions are inscribed in *partly separable sulfation codes*, so that in principle, and perhaps in practice, the shield and the gate can be told apart chemically.

Consider first the gate. The transcellular propagation of tau — the spread of pathology from neuron to neuron that tracks the clinical progression of the disease — begins with the internalization of tau seeds, and that internalization is mediated by heparan-sulfate proteoglycans at the cell surface (Holmes and colleagues, 2013). Tau does not merely brush against the sugar; it requires it, and it requires a *specific* sugar. The binding and uptake of tau aggregates depend on heparan-sulfate chains of sufficient length and particular sulfation: 6-O-sulfation is critical, such that genetic or enzymatic removal of the 6-O-sulfotransferase reduces tau entry in human neurons and brain slices (Rauch and colleagues, 2018); and a systematic comparison across the aggregating proteins found that tau demands a more precise glycosaminoglycan architecture — defined chain length and defined N- and 6-O-sulfate positions — than α-synuclein or amyloid-β, which enter more promiscuously (Stopschinski and colleagues, 2018). Tau, in other words, reads a particular passage of the sulfation text as its key of entry.

Consider now a darker refinement of the gate, one that reaches past entry into the tangle itself. A rare heparan-sulfate modification — 3-O-sulfation, installed by the enzyme HS3ST2 — turns out to be specifically implicated in tau's pathological phosphorylation. HS3ST2 is upregulated in the Alzheimer's hippocampus; its 3-O-sulfated products, normally displayed at the membrane, become internalized in diseased neurons where they co-localize with the neurofibrillary pathology; and there they bind tau and promote its abnormal phosphorylation, acting in effect as an intracellular chaperone of the tangle, while silencing the enzyme in a zebrafish tauopathy model reverses the abnormal phosphorylation and rescues the animal (Sepulveda-Diaz and colleagues, 2015). The sugar is not only the portal by which tau enters; a specific sulfation of it is a cofactor of tau's derangement once inside.

Now set the two readings side by side. Reelin's protective engagement of the surface is dominated by *N-sulfation* (Pan and colleagues, 2025); tau's pathological entry additionally requires *6-O-sulfation* and a specific chain architecture (Rauch 2018; Stopschinski 2018), and its intracellular hyperphosphorylation is abetted by *3-O-sulfation* (Sepulveda-Diaz 2015). One polymer, two functions, written in overlapping but distinguishable ink. Honesty compels the qualification that the codes are not cleanly orthogonal — tau's uptake also draws on N-sulfation, so the shield's alphabet and the gate's alphabet share letters — and this partial overlap is exactly why the therapeutic problem of Section VII is delicate rather than trivial. But the essential and, we believe, novel claim stands: the protective and the pathological uses of the neuronal sugar are not the same chemical event, and the difference between them lives in the pattern of sulfation. The matrix that stages the reelin brake and the matrix that admits the tau seed are the same lattice reading two different codes — and Alzheimer's disease, we will argue, is in part a *drift of that code* from the reelin-staging pattern

toward the tau-admitting one.

The companion dissertation The Architect's Scaffold develops the anatomy of this shared lattice — the perineuronal net as the compartment in which reelin is stored and the sugar displayed. This dissertation supplies its chemistry: the shield and the gate are the same sugar, sulfated two ways.

IV. The Clasp in the Living Circuit Why the Interface Is Where Memory Is Set

Before turning to failure, one must be clear about how much of normal cognition rides on this single interface, lest the collapse to come seem to concern a peripheral pathway. It does not concern a peripheral pathway. The reelin clasp sits at the postsynaptic membrane, physically complexed with the machinery of learning, and its output is nothing less than the tuning of synaptic strength.

ApoER2, clustered by reelin, resides in the postsynaptic density in association with the NMDA-type glutamate receptor, and the reelin signal enhances long-term potentiation — the activity-dependent strengthening of synapses that is the cellular substrate of memory — by sharpening NMDA-receptor function through the Src-family kinases that Disabled-1 recruits (Beffert and colleagues, 2005; Weeber and colleagues, 2002). The dependence runs in both directions: mice lacking the reelin receptors are impaired in potentiation and in the forms of learning that depend on it, and applying reelin to healthy hippocampal tissue strengthens potentiation, an enhancement abolished when the receptors are deleted. The splice-tuned tail described in Section II is the adjustable gain of this system, its plasticity output set by an activity-regulated exon (Beffert and colleagues, 2005). The broader family biology confirms that these lipoprotein receptors are not cholesterol-clearance machinery incidentally present at the synapse but bona fide signalling and trafficking hubs of the central nervous system, with the reelin axis among their principal synaptic functions (Lane-Donovan and colleagues, 2014).

This is why the failure of the clasp is not a subtle biochemical deficit but a withdrawal of the mechanism that sets synaptic gain in the very circuits — entorhinal and hippocampal — where Alzheimer's disease begins. When the three-body grip weakens, two things happen at once and by the same event: tau's brake is released, and the synapse loses the reelin-supplied potentiation that keeps it strong. The interface is thus doubly central — it is where tau is restrained and where memory is set — and its failure is legible simultaneously as tangle pathology and as the synaptic loss that correlates, better than any plaque count, with the dementia itself.

V. The Handshake Fails Three Partners, Three Failures

A three-body clasp can come apart in three ways, and the discipline this dissertation imposes on the disease is to take each partner in turn and ask how, specifically, Alzheimer's disease spoils it. The answer, satisfyingly, is that the disease attacks all three sides — the ligand, the receptor, and the sugar — and that the three failures are not alternatives but a convergence, each reinforcing the others in a feed-forward loop. We treat them in order and grade each in Section VI.

The Ligand Side: Reelin Resistance

The first failure is the one that dissolves the field's oldest paradox. If the protective quantity were reelin protein, the disease should show less of it; instead the Alzheimer's cortex and cerebrospinal fluid contain *more* reelin than control tissue. The resolution is that abundance and signal have uncoupled. Amyloid-β induces neurons to make more reelin even as it traps the secreted protein in aggregates and blunts its capacity to phosphorylate Disabled-1, so that the actual readout of a working clasp — Disabled-1 phosphorylation — is *reduced* in the diseased brain despite the surplus of ligand (Cuchillo-Ibáñez and colleagues, 2016). This is *reelin resistance*, precisely analogous to insulin resistance: plenty of hormone, a deaf receiver, and a signal that fails in the midst of abundance. From the interface view the interpretation is exact — the ligand is present but cannot close the clasp, because amyloid has sequestered it out of the signal-competent central-fragment pool and interposed itself at the receptor. Measuring total reelin, as much of the biomarker literature has done, measures the wrong quantity; the interface fails while the inventory rises.

A second, mechanistically distinct insult to the ligand deserves naming, because it connects this dissertation to its enzymatic companion. Reelin's activity depends on correct proteolytic processing to the central fragment (Jossin and colleagues, 2004); dysregulated proteolysis — over-cleavage at the wrong sites, or cleavage within the receptor-binding region — destroys the signal-competent species rather than generating it. The matrix proteases that rise in the inflamed, net-degrading Alzheimer's cortex are therefore a candidate second hand on the ligand side of the failure, a thread developed in full in the companion dissertations on the noradrenergic control of matrix proteolysis. For the present purpose the point is that the ligand can fail either by being trapped (reelin resistance) or by being mis-cut, and both leave the clasp with no competent hand to offer.

The Receptor Side: The Competitor and the Vanishing Receptor

The second failure is the one the interface view makes newly vivid, and it turns on a fact established at the very birth of this field and too rarely connected to the disease. When D'Arcangelo and colleagues first showed, in 1999, that reelin binds ApoER2 and VLDLR directly, they showed in the same experiments that the binding is *inhibited by apolipoprotein E*, and that apoE reduces reelin-induced tyrosine phosphorylation of Disabled-1 in neurons (D'Arcangelo and colleagues, 1999). ApoE is not a neighbour of reelin at the receptor; it is a *competitor* for it, gripping the same LA modules by the same double-lysine chemistry that Section II described. Every molecule of apoE engaged at ApoER2 is a molecule of reelin denied its grip. The strongest common genetic risk factor for Alzheimer's disease is, at this interface, a competitive antagonist of the protective ligand.

The competition acquires its isoform-specific teeth from a second mechanism, and this is the receptor-side failure proper. The ε4 isoform of apoE does not merely compete for ApoER2 at the surface; it degrades the receptor's *recycling*, sequestering ApoER2 — together with the NMDA and AMPA glutamate receptors — inside intracellular compartments from which it is not efficiently returned to the membrane, so that the surface pool of receptor available to reelin falls (Chen and colleagues, 2010). In humanized ApoE4 mice, the consequence is measured directly: reelin's ability to rescue synaptic potentiation from suppression by Alzheimer's brain extracts is severely impaired, because the receptor it needs has been withdrawn from the surface. Here the interface view yields a clean, mechanistic account of why ε4 is dangerous that is independent of amyloid: the ε4 allele thins the receptor side of the reelin clasp, both by competing at it and by internalizing it, and a clasp cannot close on a partner that has left the surface. That the wider lipoprotein-receptor family is centrally involved in endocytic trafficking and synaptic maintenance, and that its mis-trafficking is a recognized route into neurodegeneration, is the settled backdrop against which this specific lesion sits (Lane-Donovan and colleagues, 2014).

Beyond competition and mis-trafficking, the receptor side fails a third way, more slowly: the reelin-expressing and reelin-responsive neurons of entorhinal layer II — the cells whose surfaces carry the densest reelin clasps into the vulnerable circuit — are selectively depleted early in the disease, so that the number of interfaces available to be closed declines with the neurons that bear them (Chin and colleagues, 2007). Whether this loss is cause or consequence is taken up in the ledger; at the level of mechanism it is simply a subtraction of receptors from the tissue.

The Sugar Side: When the Code Turns

The third failure is the one this dissertation is written to foreground, because it is invisible to any account that treats heparan sulfate as a passive backdrop. The sulfated sugar is not a fixed structure; it is continuously synthesized and remodelled, its sulfation pattern set by the balance of the sulfotransferases and by the state of the matrix in which it is displayed. And in Alzheimer's disease that balance shifts. The 3-O-sulfotransferase HS3ST2 is upregulated in the diseased hippocampus, and its 3-O-sulfated product — the tau-chaperoning modification of Section III — moves from the membrane to the interior of degenerating neurons (Sepulveda-Diaz and colleagues, 2015). The sulfation code, in other words, drifts in the direction that *serves tau*: toward the 3-O- and 6-O-sulfated domains that admit and chaperone the seed, and, by the same remodelling and the degradation of the sulfated matrix by inflammatory proteases, away from the intact N-sulfated bed that reelin requires to cluster its receptor (Pan and colleagues, 2025; Rauch and colleagues, 2018). The single polymer that held the shield and the gate is re-inked from shield toward gate.

This is the deepest sense in which the disease is a failure of the interface rather than of any one molecule. The sugar side does not simply weaken; it *changes function*, withdrawing from the reelin clasp the sulfation it needs while presenting to tau the sulfation it seeks. Reelin resistance on the ligand side, receptor withdrawal on the ApoE side, and code-drift on the sugar side are not three diseases but three faces of one collapse of one three-body grip — and because they reinforce one another (weaker reelin signal permits more tau, more tau and more inflammation remodel the sugar and degrade the matrix, degraded matrix and internalized receptor further weaken the reelin signal), they compose a feed-forward loop with no single origin but many points of leverage. The interface is where they all meet, and therefore where they might all be reached.

VI. The Validity Ledger

The method that separates this dissertation from advocacy is the explicit grading of every link, with the experiment that would settle it named alongside. The tiers run from *strong* through *moderate* and *real but complicated* to *plausible* and *rejected as stated*.

Strong (structure) — the reelin signal is transacted by a defined molecular interface: a central-fragment R5–6 module gripping the LA1 module of ApoER2 by a double-lysine contact, requiring multivalency. Established by crystallography and structure-guided mutagenesis, and consistent with the shared recognition chemistry of the lipoprotein-receptor family (Yasui 2007; Yasui 2010; Jossin 2004). This is the ledger's most secure content and the physical basis of the whole account. *Settling experiment: none needed for the structure; open*

question is the stoichiometry and geometry of the signalling cluster in situ, addressable by super-resolution or cryo-tomography of reelin-clustered ApoER2 on neurons.

Strong (mechanism) — N-sulfated heparan sulfate is an obligate co-receptor without which reelin cannot cluster ApoER2 and signal. Directly demonstrated: reelin binds heparan sulfate with high affinity, N-sulfation is critical, and the interaction is necessary for receptor dimerization and Disabled-1 phosphorylation (Pan and colleagues, 2025). *Settling experiment: cell-type-specific manipulation of neuronal N-sulfotransferase and measurement of reelin-dependent Dab1 phosphorylation and synaptic potentiation.*

Strong (mechanism) — closing the clasp restrains tau via Disabled-1 Src-family kinases PI3K/Akt inhibition of GSK-3β. Established biochemically and in vivo; loss of reelin or of both receptors raises tau phosphorylation, and the intracellular signalling steps are individually demonstrated (Hiesberger 1999; Bock and Herz 2003; Trommsdorff 1998, 1999; Howell 1997). *Settling experiment: quantitative attribution, in human tissue, of tau-phosphorylation variance to reelin-pathway signalling activity.*

Strong (mechanism) — apoE competes with reelin at ApoER2, and ApoE4 additionally withdraws the receptor from the surface by impairing recycling. Both limbs are directly shown: apoE inhibits reelin binding and reduces Dab1 phosphorylation (D'Arcangelo 1999), and ApoE4 sequesters ApoER2 and glutamate receptors intracellularly, impairing reelin's synaptic rescue (Chen 2010). *Settling experiment: isoform-resolved measurement of surface ApoER2 and reelin-dependent signalling in human ε4/ε4 versus ε3/ε3 neurons.*

Strong but complicated — the same heparan sulfate is both reelin's co-receptor and tau's portal, in partly separable sulfation codes. Each limb is well established — N-sulfation for reelin (Pan 2025); 6-O-sulfation and specific architecture for tau uptake (Rauch 2018; Stopschinski 2018); 3-O-sulfation for tau's abnormal phosphorylation (Sepulveda-Diaz 2015; Holmes 2013) — but the codes overlap in N-sulfation, so their separability is partial, not clean. This is the dissertation's signature claim and its most important caveat. *Settling experiment: direct test of whether a sulfation-selective agent (or an engineered HS) can preserve reelin clustering while blocking tau uptake on the same neurons.*

Moderate — in Alzheimer's disease the sulfation code drifts from reelin-staging (N-) toward tau-serving (3-O-/6-O-), with HS3ST2 upregulated in the diseased hippocampus. The HS3ST2 upregulation and the internalization of 3-O-sulfated HS with tau are measured (Sepulveda-Diaz 2015); the reciprocal loss of the N-sulfated reelin bed is inferred from the co-receptor requirement and matrix degradation, not yet measured in the same tissue. *Settling experiment: paired quantification of N-sulfated versus 3-O-/6-O-sulfated HS domains across disease stage in the entorhinal–hippocampal axis.*

Real but complicated — total reelin rises in the Alzheimer's brain while reelin signalling falls (reelin resistance). Robustly measured and initially paradoxical; resolved as abundance-without-signal, with amyloid trapping reelin and blunting Dab1 phosphorylation (Cuchillo-Ibáñez 2016). The correct caution against any naïve "reelin goes down" model. *Settling experiment: signalling-reelin assays (Dab1/receptor-fragment activity) validated as biomarkers against disease stage.*

Moderate — reelin-bearing entorhinal neurons are selectively depleted early, subtracting interfaces from the vulnerable circuit. Well localized in model and human tissue, but of ambiguous causal direction, since amyloid is sufficient to reduce reelin expression (Chin 2007). *Settling experiment: staged post-mortem or longitudinal series establishing whether entorhinal reelin loss precedes or follows local tau onset.*

Plausible — dysregulated proteolysis degrades the signal-competent reelin fragment. The dependence of activity on correct central-fragment processing is established (Jossin 2004); the specific claim that disease-associated matrix proteases destroy rather than generate the active fragment is inferred and developed in the companion works, not yet directly measured in human disease. *Settling experiment: mapping of reelin cleavage products in staged human tissue against signalling activity.*

Rejected as stated — reelin deficiency (as a shortage of reelin protein) is a primary cause of Alzheimer's disease. The protein is in surplus, not deficit; the failure is of the *interface*, not the inventory (Cuchillo-Ibáñez 2016; Botella-López and the biomarker literature reviewed in the companion dissertation). The defensible claim is interface failure and resilience-axis modification, not ligand deficiency. *Settling experiment: none required to reject the deficiency framing; the interface framing is what the data sustain.*

VII. The Two Resilient, Read at the Interface

The strongest test of the interface view is whether it accommodates, and indeed clarifies, the two human beings in whom Alzheimer's disease was held at bay by a single inherited change. It does, and it places both of their protective variants on the *same side* of the clasp — the sugar-facing side — which is a stronger and more specific statement than the resilience literature has yet made.

Both individuals belonged to the great Antioquia kindred carrying the *PSEN1*-E280A mutation, which causes a fully penetrant early-onset dementia near the mid-forties, and both were protected for roughly three decades past their expected onset, with heavy amyloid burdens but strikingly spared entorhinal tau. The first, described in 2019, was homozygous for the Christchurch variant of

apolipoprotein E, R136S, a substitution in the region of apoE that governs its binding to heparan-sulfate proteoglycans; the variant *weakens* apoE's grip on heparan sulfate (Arboleda-Velasquez and colleagues, 2019). The second, described in 2023, carried heterozygously a gain-of-function variant of reelin, H3447R, named COLBOS; it activates Disabled-1 more strongly than ordinary reelin and lowers human tau phosphorylation in a knock-in mouse, and — the datum that unifies the two cases — it binds heparan sulfate *more tightly* (Lopera and colleagues, 2023; Pan and colleagues, 2025).

Read at the interface, the two variants are mirror adjustments of the sugar-facing clasp. Christchurch loosens a *harmful* engagement of heparan sulfate — the apoE side, whose grip on the sugar we have seen is tied to the spread of tau and to competition with reelin — while COLBOS tightens a *protective* engagement of the same sugar — the reelin side, whose grip on the N-sulfated bed is what closes the clasp and brakes tau. One dials the sugar-facing handshake down on the pathological side; the other dials it up on the protective side; and both, by adjusting the third body of the clasp rather than the ligand or the receptor, spare the entorhinal cortex from tau while amyloid proceeds unchecked. The heparan-sulfate partner, long the neglected member of the trio, turns out to be the very component that nature reached for — twice, in the same family — to confer resistance to an otherwise unstoppable dementia. This is the most direct possible vindication of the three-body framing: the decisive human experiments in this disease both act on the interface's third body, and neither would be legible as a single mechanism without it.

That the two resilience variants also read cleanly onto the perineuronal net — the compartment in which the sulfated sugar is displayed — is the subject of the companion dissertation *The Architect's Scaffold*; that reelin is best understood, across the whole disease, as an axis of resilience rather than a trigger is the subject of *The Architect's Reprieve*. The present dissertation supplies the molecular grammar those two narratives share: a three-body clasp whose sugar-facing side is the surface on which both resilience and ruin are written.

VIII. Therapeutic Corollaries Tune the Clasp, Do Not Break the Sugar

The interface view yields a therapeutic logic that is sharper, and more cautionary, than the ligand view it replaces. If the protective quantity were reelin protein, the therapy would be to supply reelin — a near-impossible task, for reelin is among the largest proteins the brain makes, crosses no barrier, and cannot be dosed like a drug. The interface view reframes the goal: not to deliver the ligand but to *restore the closing of the clasp*, which can be attempted from any of the three sides, and

which must above all avoid a specific and seductive error.

The error is the one this dissertation is uniquely positioned to name. Because heparan-sulfate proteoglycans are the portal for tau's spread, a natural therapeutic idea — already pursued — is to block heparan sulfate, or the enzymes that sulfate it, so that tau can no longer enter neurons. The interface view issues a warning that no ligand-side or tau-side account could: the *same sugar* is reelin's obligate co-receptor, and N-sulfation is critical to both the shield and (in part) the gate. A blunt heparan-sulfate-blocking agent that stops tau from spreading may, by the identical action, prevent reelin from clustering ApoER2 and thereby *silence the very brake that restrains tau* — trading a slower spread of seed for a released kinase. The drug and the disease would, at the crudest level of the sugar, be doing the same thing. This is not a hypothetical tension; it is a direct consequence of two established facts placed side by side, and it means that any heparan-sulfate-directed anti-tau strategy must be evaluated for its effect on reelin signalling, not only on tau uptake.

The constructive corollary follows from the partial separability of the sulfation code (Section III). The therapeutic target is not heparan sulfate as such but the *specific sulfation domains* that distinguish the gate from the shield — an agent, or an engineered proteoglycan, that spares or even reinforces the N-sulfated bed on which reelin depends while denying tau the 6-O- and 3-O-sulfated architecture it requires. The demonstration that tau reads a more stringent code than the other amyloid proteins (Stopschinski and colleagues, 2018), and that a single sulfotransferase (HS3ST2) can be silenced to reverse tau phosphorylation without, in the model, catastrophe (Sepulveda-Diaz and colleagues, 2015), is the encouraging evidence that such selectivity is chemically real. Three further corollaries follow directly from the three-sided failure:

- **On the ligand side**, the aim is not whole reelin but a signal-competent central fragment or a receptor-clustering agonist that reproduces reelin's multivalent grip on ApoER2 — a molecule small enough to deliver, exploiting the finding that oligomerized R5–6 signals an order of magnitude more strongly than the monomer (Yasui and colleagues, 2007).
- **On the receptor side**, the aim is to keep ApoER2 at the surface where the clasp can close — countering the ε4-driven internalization that withdraws it (Chen and colleagues, 2010) — and to relieve the apoE competition at the LA modules, both of which point to the receptor-recycling machinery as a druggable node.
- **On the sugar side**, the aim is the sulfation-selective modulation named above: preserve the reelin-staging N-sulfated domains, deny the tau-serving 3-O-/6-O-sulfated ones.

And, as in every protective axis of this disease, the timing is not negotiable. Reelin's synaptic protection has a demonstrated *ceiling* — it antagonizes amyloid only up to a threshold burden — so the clasp is worth reinforcing in the earlier brain, before the burden overwhelms it, and reelin-directed or sugar-directed intervention should be tested as prevention and in the prodrome rather than against established dementia. The resilient carriers had their reinforced clasp from

conception; a therapy that imitates them must arrive while the interface can still be made to close.

IX. Predictions and Falsification

The three-body-interface thesis earns its standing by risking specific, falsifiable predictions.

- A sulfation-selective agent (or an engineered heparan sulfate) can be found that preserves reelin-dependent ApoER2 clustering and Disabled-1 phosphorylation while reducing tau internalization on the same neurons. A demonstration that reelin staging and tau uptake are chemically inseparable — that no sulfation pattern supports one without the other — would refute the paper's signature claim of a separable code.
- In staged human entorhinal–hippocampal tissue, N-sulfated heparan-sulfate domains available to reelin will decline, and 3-O-/6-O-sulfated tau-serving domains will rise, in step with tau progression; and reelin-dependent Disabled-1 phosphorylation will fall while total reelin rises. A finding that the sulfation code does not drift, or that signalling-reelin tracks total reelin, would falsify the code-drift and reelin-resistance limbs.
- Restoring surface ApoER2 in an ε4 background — by rescuing receptor recycling — will restore reelin's synaptic potentiation and lower tau phosphorylation independently of amyloid clearance. A failure to recover reelin signalling despite restored surface receptor would sever the receptor-side account.
- A multivalent, receptor-clustering reelin mimetic that reproduces the double-lysine grip and requires heparan sulfate will spare entorhinal tau in a model of autosomal-dominant disease, and will do so more effectively before a threshold amyloid burden than after. A clustering agonist that fails to brake tau, or works as well late as early, would falsify the clasp-and-ceiling mechanism.
- Additional carriers of gain-of-function *RELN* variants that enhance the reelin–heparan-sulfate grip will show delayed onset and spared entorhinal tau, mirroring COLBOS; a heparan-sulfate-strengthening variant with ordinary disease course would weaken the interface reading of resilience.

X. Coda The Grip and the Building

The cortex is a building whose architect never left. This dissertation has tried to show that the architect's continued protection of that building is not, at bottom, a molecule but a *grip* — a three-body clasp made and remade on the surface of every vulnerable neuron, in which a fragment of reelin, a bed of sulfated sugar, and a lipoprotein receptor hold one another closely enough to send a signal inward that keeps a kinase quiet and a tangle from forming. When the grip closes, tau is braked and the synapse is strong. When it cannot close, tau is released and memory begins to fail — and it cannot close for three separable reasons, each of which Alzheimer's disease supplies at once: a ligand trapped in the surplus of its own abundance, a receptor competed for and withdrawn by the disease's greatest genetic risk, and a sugar that re-inks itself from the code that stages the protective signal toward the code that admits the pathological seed.

The value of looking at the middle rather than the ends is that the middle is where the two great human experiments of this disease turn out to have acted. Both resilient carriers in the Antioquia kindred were protected by a change to the sugar-facing side of exactly this clasp — one loosening a harmful grip, one tightening a helpful one — and neither of their protections is fully legible except as an adjustment of the three-body interface. The neglected third partner, the sulfated sugar that the field treated for decades as backdrop, is the component nature reached for, twice, to hold off an unstoppable dementia. That is the strongest reason to believe the interface is not merely the correct level of description but the correct level of intervention.

It also issues the sharpest warning this dissertation has to give. The same sugar that stages the protection is the portal for the ruin, and a therapy that forgets this — that blocks the sugar to stop tau and, by the same stroke, silences reelin — would mistake the shield for the gate and dismantle the defence while attacking the disease. The task is not to break the sugar but to read its code, and to tune the clasp: to preserve the sulfation on which reelin depends, deny the sulfation that tau exploits, keep the receptor at the surface, and offer the neuron a grip it can still close, early, in the window where closing it still holds the building up. The architect built the cortex with a handshake and has been defending it with one ever since. The whole of therapeutics, at this interface, is the ambition to lend that handshake our strength before the hour when even a strengthened grip could no longer hold.

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