The Cage and the Clock

The perineuronal net, the parvalbumin interneuron and the forty-hertz rhythm in late Alzheimer's disease: what breaks when the last brake is digested

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The third and last of the short papers on the model's three stacked phases. A lattice is digested, the cell it protected loses the ability to keep time, and the cortex becomes noisy rather than quiet. At the synapse, four receptor systems deliver contradictory instructions. The series closes with what the three steps imply together.

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Abstract

This is the third and last of the short papers on the model's three stacked steps. The first described the base: brainstem and basal forebrain neurons whose supplies fade from the third decade, and which have been retarding amyloid all along. The second described the step above it: the brain's immune cell, released from nine restraints, which stops clearing amyloid and begins to secrete the enzymes that digest the only brake left. This paper is about what happens when they finish.

The last brake is physical. A condensed lattice of sugar and protein, the perineuronal net, wraps a particular kind of inhibitory neuron and keeps the microglion away from its surface. The cell inside is the parvalbumin interneuron, whose job is timing: it fires fast and precisely, inhibits its neighbours in rhythm, and generates the forty-hertz cortical oscillation on which coordinated cortical activity depends. For six decades it is the best-protected cell in the cortex. Then the net is digested, and it becomes the worst-affected one.

Four consequences follow, and the paper takes them in order. **The net goes**, by proteolysis, and with it the cell's protection against the oxidative cost of its own fast firing. **The parvalbumin cell fails**, which is a failure of inhibition rather than of excitation — and the counter-intuitive result is that removing a brake produces noise, not silence: the Alzheimer cortex is hyperexcitable, carries subclinical epileptiform activity in a substantial minority of patients, and declines faster when it does. **The clock stops**, and with it the mechanism that keeps assemblies of excitatory neurons in phase; the excitatory cells then fail for want of coordination rather than for want of drive. **And at the synapse itself**, amyloid acts through a set of named receptors — the restraint receptor LilrB2 with its complement ligand C4d, the exchange factor Ephexin5 below EphB2, and the reelin–ApoER2 clasp that normally antagonises amyloid at that very membrane — which together describe synapse loss as misdirection rather than damage: nothing is broken, and the instructions have changed.

The paper carries two honest difficulties on its face. The forty-hertz entrainment literature, which is the most visible therapeutic programme aimed at this step, has a failure to replicate at its centre. And the corpus's own analysis argues that preserving the net and driving the rhythm are not two halves of one therapy, because the intervention that preserves the net makes the rhythm worse. The series closes with what the three steps imply

together, and with the measurement that would settle the most important open question in all three.

How to read this paper

This paper follows *What the Brainstem Stops Sending* and *The Hands That Let Go*, and assumes their conclusions, which are summarised in Section 1. As in those papers, each section below condenses a longer corpus volume, and those volumes carry the full argument and their own ledgers.

The grades are the corpus's four. **Established** means replicated in human material by more than one group. **Probable** means good evidence with a gap. **Inference** means a conclusion drawn here, or in the corpus, from evidence gathered for another purpose. **Speculative** means coherent and untested.

Two cautions govern this paper in particular. First, the unit throughout the series is the **connection**, not the cell, because synapse loss is the structural change that tracks cognitive decline most closely — the finding that opened this literature and has never been overturned (Terry and colleagues, 1991; Selkoe, 2002). Second, this step contains the field's most active therapeutic programme and its sharpest replication dispute, and both are reported here in full.

1. Where the Series Has Got To

The first step begins in the third decade, in a handful of small nuclei that each supply one chemical messenger to the whole forebrain. Their axons fail long before their cell bodies, and their supplies fade with them. Three of those supplies hold amyloid back: serotonin brakes its production, somatostatin licenses the enzyme that disposes of it, noradrenaline enables both its cellular clearance and its drainage during sleep. Two of them — noradrenaline and acetylcholine — also hold the brain's immune cell at rest.

The second step begins around the sixth decade, on top of the first. The microglion is not switched on; it is let go, as nine restraints fail in a particular

order. Once released it stops clearing amyloid, assembles the NLRP3 inflammasome, which suppresses clearance further and seeds more amyloid, and secretes the proteases that digest the perineuronal net.

Neither step has ended. That is the point of drawing the model as stacked layers rather than a relay. A person in the eighth decade carries all three at once: the brainstem still failing underneath, the microglion still released, and now a third thing beginning on top of both.

The third step is the one in which the disease becomes visible to other people. It is also the one where almost every drug ever trialled has been given.

2. The Cage: What the Perineuronal Net Is and Does

The perineuronal net is a condensed lattice of extracellular matrix wrapped around the cell body and nearest dendrites of certain neurons. It is built of hyaluronan as a backbone, lecticans — aggrecan and brevican above all — as the load-bearing proteins, link proteins that fasten them to the backbone, and tenascin-R as a cross-link. It is not a shapeless coating. It is a structure, with holes left open at synaptic contacts, and it does several jobs at once (Fawcett and colleagues, 2019).

- **It excludes.** The net physically restricts access to the neuronal surface, which is the office that matters for this series: it is the brake that keeps the released microglion of the second step away from the cell it would otherwise strip.
- **It protects against the cell's own chemistry.** Fast-spiking neurons pay a high metabolic price, and that price is paid in oxidative stress. Nets protect these cells against it, and degrading the net makes them, and the fast rhythms they generate, more vulnerable (Cabungcal and colleagues, 2013). **Established.**
- **It protects against tau.** In subcortical regions of the Alzheimer brain, neurons wearing aggrecan-based nets are protected from tau pathology (Morawski and colleagues, 2010). **Established.**

- **It sets the cell's firing properties.** The net is not inert scaffolding: its brevican component gates the parvalbumin cell's function in an activity-dependent way, organising the ion channels and the inputs the cell needs to fire fast (Favuzzi and colleagues, 2017). **Established.**
- **It closes the critical period.** Nets assemble as juvenile plasticity ends, and removing them in an adult reopens it — in part by *decreasing* inhibition and increasing gamma activity (Lensjø and colleagues, 2017). That result is worth holding onto, because it is the clearest demonstration that what the net does to the network is not simply protective: it is regulatory.

And it is a brake its own target attacks. Microglia facilitate the loss of perineuronal nets in the Alzheimer brain, and chronic depletion of microglia prevents the loss, despite plaques persisting (Crapser and colleagues, 2020). **Established** in models. In human tissue, resilience to Alzheimer's disease — intact cognition despite the pathology — is associated with distinct alterations in these nets, and in people with the disease the genes for net-degrading enzymes are raised (de Vries and colleagues, 2025). **Probable**, from one well-designed human series.

3. How the Cage Is Opened

The corpus calls this transition the **proteolytic turn**, and its argument is that three chemically distinct arms converge on the same structure at the same time.

- **The protease arm.** The inflammasome of the second step matures interleukin-1β, and interleukin-1β is the principal inducer of the aggrecan-degrading enzymes — the ADAMTS aggrecanases and matrix metalloproteinases, MMP-9 chief among them — that cleave the net's core protein. This is the best-characterised route from a cytokine to a protease in matrix biology, but it was characterised in cartilage. The corpus grades it **established** in the joint and **conjecture** in the brain, where the intermediate steps have not been measured (*One Sensor, Two Collapses*).
- **The iron arm.** Iron liberated from failing oligodendrocytes catalyses oxidative damage to the same structure, which is already the cell's

defence against oxidative stress (*The Proteolytic Turn*).

- **The complement arm.** Complement proteins tag what is to be removed, and the tagging reaches the same neighbourhood.

Why three arms matter therapeutically. The corpus's conclusion from this is unusually practical and unusually firm: because three mechanistically distinct arms converge, interdicting any one of them produces partial protection while the other two continue. This window, on the corpus's reading, admits **no single-target intervention** (*The Proteolytic Turn*). **Inference**, and the strongest prediction the third step makes.

4. The Cell: Why the Parvalbumin Interneuron Is the One That Matters

Inside the cage is a particular cell, and its job explains the shape of the whole step.

What it does. The parvalbumin interneuron is a fast-spiking inhibitory cell that synapses on the cell bodies and initial segments of excitatory neurons — the places from which it can veto an output rather than merely shade it. It does not carry content. It supplies timing: it inhibits its neighbours in fast, precise rhythm, keeping cortical activity from running away with itself and holding assemblies of excitatory cells in phase.

Why it is protected for so long, and then is not. It wears the densest net in the cortex. On the model's accounting of connection loss, it is the best-protected of the five cell types counted for six decades — and then, when the lattice is digested, it becomes the worst-affected, losing some 84 per cent of its connections against 54 per cent for the excitatory cells around it. That crossing point is the model's explanation for why the last phase arrives so much faster than the first (*The Shape of the Disease*). **The curves are the model's own and are not a measurement**; the ordering, not the percentages, is the claim.

One correction the corpus has already made, and keeps. A blind re-reading of the evidence found parvalbumin involvement to be late and

functional, with **somatostatin** interneurons failing earlier. The ordering claim survives; the identity of the terminal cell is held more loosely than it once was. The somatostatin cell, as the first paper described, largely has no net at all — which is consistent with it failing earlier and for a different reason.

The decisive causal experiment is from the other direction. Restoring Nav1.1 — the sodium channel the cell needs in order to fire fast — specifically in parvalbumin interneurons corrects network dysfunction and cognitive deficits in an amyloid model (Verret and colleagues, 2012). **Established** in models. That is the cleanest demonstration in the literature that the inhibitory cell's loss of *capacity*, rather than its death, is doing the damage.

5. The Clock: Forty Hertz, and What Stops

What the rhythm is. When parvalbumin cells fire in synchrony they impose a cortical oscillation at roughly forty cycles a second. Gamma rhythm is not an epiphenomenon of busy cortex; it is the mechanism by which populations of excitatory neurons are held in a common timeframe, so that signals arriving together are read together.

It falls early, before plaques. Driving fast-spiking parvalbumin interneurons at gamma frequency reduced amyloid in a mouse model, and the behaviourally driven rhythm was already reduced before plaques formed or cognition declined (Iaccarino and colleagues, 2016). **Probable**, in models.

What driving it appears to do. The programme that followed is the most ambitious therapeutic effort aimed at this step. Multisensory forty-hertz stimulation reduced pathology and improved cognition across models (Martorell and colleagues, 2019); it entrained the rhythm in deeper structures and preserved neurons and synapses in two models of neurodegeneration (Adaikkan and colleagues, 2019); and it promoted the glymphatic clearance of amyloid, the same drainage route the first paper's noradrenaline drives at night (Murdock and colleagues, 2024).

And the replication that the corpus insists on reporting. A separate laboratory, recording with multisite probes in the visual cortex, entorhinal

cortex and hippocampus of two amyloid models, found that forty-hertz flickering light **did not engage native gamma oscillations** in those regions and did not suppress amyloid (Soula and colleagues, 2023). The corpus's position is that this does not refute the clinical programme, which is being tested on its own endpoints, but that it bears directly on the mechanism the programme claims. **The dispute is live and should be presented as live.**

The corpus's own warning, which is sharper than either. It is tempting to pair the two interventions of this step: preserve the lattice, then exercise the cell it protects. *The Price of the Net* argues that this pairing does not survive the evidence. The manipulation that preserves the net — suppressing microglia — **worsens** gamma disruption, increases network hyperactivity, and increases epileptiform discharge in the same animals. Matrix integrity, the intrinsic excitability of the fast-spiking cell, and the network's excitatory–inhibitory set-point are three variables, and only the first is improved by removing microglia. The two interventions act on different variables with different signs, and were joined by an inference about shared substrate rather than by any experiment that ran them together. **Inference**, and the most useful negative result in this part of the corpus.

6. Noise, Not Silence: Why Losing a Brake Produces Hyperactivity

The intuitive picture of a failing brain is one that goes quiet. This step does the opposite, and the evidence is unusually direct.

What is observed. Clusters of hyperactive neurons appear near amyloid plaques in a mouse model, and the measured cause is a relative *decrease* in synaptic inhibition (Busche and colleagues, 2008). Aberrant excitatory activity, non-convulsive seizure activity and compensatory remodelling of inhibitory circuits are documented across amyloid models (Palop and colleagues, 2007), and interneuron dysfunction is the organising theme of the field's principal review of the subject (Palop and Mucke, 2016). **Established** in models.

In patients. Extended monitoring found subclinical epileptiform activity in 42.4 per cent of Alzheimer patients with no history of seizures, against 10.5 per cent of age-matched controls — and the patients with it declined roughly twice as fast on a global cognitive measure, 3.9 points a year against 1.6 (Vossel and colleagues, 2016). **Established**, in one well-conducted prospective series.

The direction of the effective drug tells you the direction of the lesion. Of a panel of antiepileptic drugs, only levetiracetam reduced abnormal spike activity in an amyloid model, and chronic treatment reversed the circuit remodelling, the synaptic deficits and the learning failure (Sanchez and colleagues, 2012). A low dose reduced hippocampal hyperactivation and improved memory in people with amnestic mild cognitive impairment (Bakker and colleagues, 2012). In a randomised crossover trial in Alzheimer's disease the drug did **not** improve the primary endpoint in the group as a whole, but improved performance on spatial memory and executive tasks in the prespecified subgroup with epileptiform activity (Vossel and colleagues, 2021). **Established** that the effect is confined to the hyperexcitable subgroup; **inference** that this is the correct dosing rather than a failed drug.

The rival account, taken seriously. The corpus's adjudication volume gives the opposite reading a fair hearing: that the disease is at bottom a failure of excitatory transmission, and the seizures are what an over-inhibited network does. That is not a fringe position — seizures genuinely can arise from too much inhibition, as in absence epilepsy. But in absence epilepsy the rational and demonstrated therapy is to *reduce* inhibition, and in Alzheimer's disease every intervention that works runs the other way. The adjudication goes to disinhibition (*Low Signal, High Noise*). **Inference**, with the rival's strongest leg conceded.

And the consequence for the excitatory neuron. On this reading the excitatory cell fails not for want of drive but for want of coordination. It is left firing without restraint, in a network whose timing has gone, which is both excitotoxic and uninformative. That is why the model counts connections rather than cells, and why the loss of an inhibitory cell shows up as a loss of excitatory function.

7. At the Synapse: Four Receptors and One Instruction

The preceding sections are about a circuit. This one is about a single synapse, and about what amyloid does there. The corpus's reading, assembled across two volumes, is that **nothing at the synapse is broken**. The molecules are present, often in normal amounts. What has changed is where they are, what covalent marks they carry, and therefore which instruction they are executing. The corpus's phrase is *misdirection, not damage* (*The Hand and the Address*).

Amyloid at the glutamate synapse

Soluble amyloid oligomers, rather than the deposit, are the species that act here. They alter the trafficking of NMDA-type glutamate receptors, promoting their removal from the surface (Snyder and colleagues, 2005). Oligomers extracted **directly from human Alzheimer cortex** inhibit long-term potentiation, enhance its reversal, and reduce dendritic spine density in normal rodent hippocampus — the demonstration that the agent in the human brain confers the deficit (Shankar and colleagues, 2008). **Established.** A receptor complex for this action has been identified: oligomers bound to cellular prion protein couple to Fyn kinase through metabotropic glutamate receptor 5 (Um and colleagues, 2013). **Probable.**

The restraint receptor: PirB, LilrB2, and C4d

This is the receptor set Dr. Truchard asked for, and it is the most developed account of how a synapse is instructed to disassemble.

What the receptor normally does. PirB in the mouse, LilrB2 in the human, is a neuronal receptor that *restrains* plasticity throughout life. Deleting it leaves ocular-dominance plasticity in the visual cortex unrestricted (Syken and colleagues, 2006), and it regulates dendritic spine density cell-autonomously (Vidal and colleagues, 2016). Animals lacking it form more spines and stabilise new ones. **Established.**

What amyloid does to it. PirB and LilrB2 are receptors for soluble amyloid oligomers, binding at nanomolar affinity through the same two domains that bind their normal ligands; engagement enhances cofilin signalling — the same

signalling seen in human Alzheimer brain — and deleting the receptor rescues both long-term potentiation and memory in an amyloid model (Kim and colleagues, 2013). **Established** in models; the human arm is a tissue measurement.

And the ligand that was found later. C4d, a durable cleavage fragment of complement component 4, binds LilrB2 and PirB with nanomolar affinity, colocalises with the receptor at excitatory synapses in human cortex, is elevated in Alzheimer's disease, and mediates synapse pruning (Brott and colleagues, 2025). **Probable**: a recent result from one laboratory. Its importance for this series is that it joins the complement arm of Section 3 to the receptor arm of this one — the same protein family that tags a synapse for a microglion also speaks directly to the neuron's own restraint receptor. The neuron, on this reading, disassembles its own spine.

The exchange factor: EphB2 and Ephexin5

A second account describes the machinery inside the spine rather than the receptor on its surface.

The normal arrangement. Ephexin5 is a RhoA exchange factor that acts as a brake on excitatory synapse formation; EphB receptor signalling degrades it, and that degradation is what permits a synapse to be built (Margolis and colleagues, 2010). **Established.**

What fails. Amyloid oligomers bind EphB2 and trigger its degradation; reducing EphB2 impairs NMDA currents and potentiation, and restoring it in an amyloid model reverses both the plasticity deficit and the memory impairment (Cissé and colleagues, 2011). **Established** in models. With EphB2 gone, the brake is no longer removed: Ephexin5 accumulates, and reducing its expression ameliorates the Alzheimer-like impairment in mice (Sell and colleagues, 2017). **Probable.**

So the spine is not demolished. It is forbidden to rebuild — which is why the corpus describes this limb as a ratchet rather than a weapon.

The clasp: reelin and ApoER2

The fourth receptor system is the one that normally opposes all of this at the same membrane.

What it is. Reelin, secreted in the adult cortex by inhibitory interneurons, binds the lipoprotein receptors ApoER2 and VLDLR, which phosphorylate the adaptor Disabled-1 — and mice lacking either the ligand or both receptors show hyperphosphorylation of tau (Hiesberger and colleagues, 1999). **Established.** The same signal enhances synaptic strength: ApoER2 sits in the postsynaptic density in a complex with the NMDA receptor, reelin markedly enhances long-term potentiation through it, and the enhancement is abolished when the receptors are deleted (Weeber and colleagues, 2002; Beffert and colleagues, 2005). **Established.**

Why it belongs in this paper. Reelin signalling **antagonises amyloid at the synapse**. It prevents the suppression of potentiation and of NMDA-receptor function caused by amyloid at concentrations comparable to the diseased brain — but at high amyloid concentrations the protection is overwhelmed and the reelin-dependent phosphorylation is completely blocked (Durakoglugil and colleagues, 2009). **Established** in slices. The clasp is a brake on this step in the same sense that serotonin is a brake on amyloid production in the first: real, measurable, and finite.

And the genotype term. ApoE4 selectively impairs the recycling of ApoER2, sequestering it along with glutamate receptors inside the cell, so that reelin can no longer enhance synaptic function — and the ability of reelin to protect slices against human Alzheimer brain extract is severely impaired in mice carrying the human ApoE4 isoform (Chen and colleagues, 2010). **Probable.** This is one of the few places in the series where the strongest common genetic risk factor acts on a named mechanism at a named membrane.

Why this is called misdirection rather than damage

Two features of the receptor account deserve stating separately, because they change what kind of lesion this is.

The receptor's own working limb has never been pointed at its assigned targets. The cytoplasmic tail of LilrB2 carries inhibitory motifs that recruit the phosphatases SHP-1 and SHP-2 — the machinery by which the receptor would actually deliver its instruction inside the cell. That was reported in a single clause of the founding paper, and it has one demonstrated neuronal consequence, on a third-party receptor kinase in the same membrane. Searching the indexed literature for the receptor or its phosphatases paired with EphB2, with Ephexin5 or with Disabled-1 returns nothing on point (*The*

Hand and the Address). The hand is described; what it grips is not. **Inference**, from an absence, and stated as such.

And the field's standard measurement cannot see the lesion. If the disease-relevant change is where a molecule sits and what covalent mark it carries, rather than how much of it there is, then homogenising a piece of cortex and reporting a mean is systematically blind to it. The corpus's address claim survives in three of four regulators examined and fails in the fourth — and the failure is informative, because in the two cases where abundance was never measured, the method used could not have seen what moved. **Inference**, and the reason the corpus asks for single-synapse measurements rather than better blots.

What the four accounts say together, and where they collide

Read side by side, the four describe one synapse receiving several instructions at once: a restraint receptor engaged by amyloid and by complement, an exchange-factor brake that can no longer be lifted, and a clasp that would oppose both but is overwhelmed and, in ApoE4 carriers, mislocated.

The corpus does not pretend they agree. *The Hand and the Address* shows that where the receptor account and the exchange-factor account are joined, they **predict opposite signs at the same two residues**, and that the single measurement which would separate them — the phosphorylated fraction of Ephexin5 and of Tiam1, reported jointly across single synapses — has not been attempted in disease tissue although the reagent has existed for sixteen years. That is the most specific unperformed experiment in this series. **Inference**, and the corpus's own.

A supply question runs underneath all four of these receptors and is taken up in the fourth paper. Each is held at the membrane only as long as it is returned there faster than it is removed, which makes a synapse a balance rather than a stock; *The Long Way Back* argues that the return side of that balance is where this disease does its damage, and marks the extension to these four receptors as untested.

Amyloid at two concentrations, and the receptor we have left out

Everything above describes what amyloid does to a synapse. It says nothing about what the molecule is *for*, and the omission distorts the picture — it makes the account read as a list of poisonings rather than as a regulator pushed past its range.

The peptide is required, not merely tolerated. Healthy brains make amyloid-β continuously, in proportion to how hard their neurons are working. At low picomolar concentrations a preparation of amyloid-β42 markedly *increases* long-term potentiation and enhances both reference and contextual fear memory, while high nanomolar concentrations produce the familiar reduction (Puzzo and colleagues, 2008). The dose-response is biphasic.

The stronger version of the result is a subtraction rather than an addition. Removing the animal's *own* peptide — with an antibody against rodent amyloid-β, or by silencing murine precursor protein — **impairs** plasticity and memory in a healthy brain, and adding human amyloid-β42 back rescues the deficit (Puzzo and Arancio, 2013). A molecule whose removal breaks memory in a normal animal is not waste. **Established** in rodent preparations; no human equivalent exists and none is likely.

Where the useful effect happens, and through what. It is not a gentler version of the damage described above. At 200 picomolar, oligomeric amyloid-β acts **presynaptically**: it raises the frequency of miniature excitatory currents, reduces paired-pulse facilitation and increases the number of docked vesicles, which is to say it augments neurotransmitter release. Postsynaptically it lengthens the postsynaptic density and raises the plasticity proteins — phosphorylated CREB and CaMKII, and brain-derived neurotrophic factor — converting early potentiation into late potentiation and short-term memory into long-term. The effects require the peptide to be outside the cell, and they require **α7 nicotinic acetylcholine receptors** (Gulisano and colleagues, 2019). **Established** in models.

That receptor is not one of the four this section is about. It is a fifth, and it is cholinergic.

The four receptors, asked the same question. Setting the positive literature against this section's four produces an asymmetry worth stating plainly rather than smoothing.

Receptor system	What amyloid does at disease concentrations	Is a physiological role known here?
NMDA-type glutamate receptors	Removed from the surface; potentiation suppressed	No. The beneficial effect is presynaptic and α7-dependent, and reaches this receptor only downstream
PirB / LilrB2, with C4d	Bound at nanomolar affinity; cofilin signalling enhanced	No physiological-concentration role reported
EphB2 with Ephexin5	EphB2 degraded; the brake on rebuilding is never lifted	No physiological-concentration role reported
Reelin with ApoER2	Protection against amyloid, overwhelmed at high concentration	**The concentration axis is already here** — reelin preserves potentiation at disease-comparable amyloid and is completely blocked above it (Durakoglugil and colleagues, 2009)
α7 nicotinic receptors	Not characterised as a damage route in this section	**Yes** — this is where the useful effect acts

So the positive role is documented at one receptor, absent from the literature at two, and already implicit at a third without having been named as such. That is a statement about where the field has looked, not a claim that the other three have no physiological arm.

What this implies for the stack, and it is ours. The useful arm of amyloid runs through an acetylcholine receptor. Acetylcholine is what the nucleus basalis supplies, and its withdrawal is a Phase I event — the first paper in this series. The harmful arms run through four postsynaptic receptors that have nothing to do with it, and they are engaged at Phase III concentrations.

Read across the stack, that is a two-stroke failure of a single molecule. **Phase I removes the channel through which amyloid does its useful work; Phase III raises amyloid to the concentrations at which it does harm.** The beneficial arm is lost first and the harmful arms are gained second, in the order the steps occur.

Inference, and ours. No study has measured the α7 arm and the four-receptor arm in the same preparation, and the cholinergic loss and the amyloid rise have never been staged against each other in one animal. It is stated here because it is the kind of claim the series was built to make visible,

and because it names an experiment: raise amyloid to picomolar levels in a preparation with cholinergic input intact and again with it removed, and see whether the benefit survives.

8. What the Third Step Adds Up To

Table 1. The third step, element by element.

Element	What it normally does	What fails	How firm
Perineuronal net	Excludes microglia; protects against oxidative stress and tau; sets fast-firing properties	Digested by proteases, iron and complement acting together	Net loss in AD: established. The three-arm convergence: inference
Parvalbumin interneuron	Perisomatic inhibition; generates the forty-hertz rhythm	Loses the capacity to fire fast, before it dies	Restoring Nav1.1 rescues the network: established in models
Forty-hertz rhythm	Holds excitatory assemblies in a common timeframe	Falls before plaques; driving it is therapeutic in some hands and inert in others	Disputed; the replication failure is live
Excitatory neurons	Carry the content	Fire without restraint, in a network whose timing has gone	Hyperexcitability established in models and in patients
The synapse	Builds, strengthens and prunes under instruction	Receives contradictory instructions through LilrB2, EphB2–Ephexin5 and reelin–ApoER2	Each limb probable or established; their joint reading is inference

Three things follow.

Function goes before the cell, again. This has been true at every step of the series. The brainstem axon is removed while its cell body lives; the nucleus basalis surrenders its receptor before its transmitter; the microglion loses its badge set before it does harm; and here the parvalbumin cell loses its capacity to fire fast before it is lost, while the synapse receives wrong

instructions rather than suffering breakage. **That is the series' single most consistent finding, and it is the ground of whatever hope the model carries.**

The step is a convergence, not a chain. Three proteolytic arms meet on one structure, and four receptor systems meet at one membrane. Single-target intervention is predicted to fail here specifically, and the record of single-target immune and anti-amyloid therapy in late disease is consistent with that.

And almost every drug ever trialled has been given here. If the model is even approximately right, the third step is the last few years of a forty-year process, and the target lies further left.

9. What This Step Implies for Treatment

Four things follow for therapy, and they are unusually specific.

No single-target drug in the turn window. Three arms converge on the net. Interdicting one leaves two running. The corpus states this as a flat prediction (*The Proteolytic Turn*).

Anti-excitability treatment belongs to the subgroup that has the excitability. Levetiracetam helped where epileptiform activity was documented and not otherwise, across an animal model, a mild-cognitive-impairment study and a randomised trial (Sanchez and colleagues, 2012; Bakker and colleagues, 2012; Vossel and colleagues, 2021). That is a dosing instruction, not a failure.

Do not assume the net and the rhythm are one therapy. They act on different variables with opposite signs on excitability, and the experiment that would settle it — microglial suppression against forty-hertz entrainment in one cohort, with net integrity, fast-spiking excitability, gamma power and epileptiform burden as four separate endpoints — has not been run (*The Price of the Net*).

And the target is capacity, not survival. The Nav1.1 result says that restoring the inhibitory cell's ability to fire corrects the network while the cell is still there (Verret and colleagues, 2012). Every step in this series has the

same shape, and this is where it is most directly testable.

10. Graded Ledger

Table 2. Each claim in this paper, with its grade and the evidence it rests on.

#	Claim	Grade	Basis
1	Synapse loss is the structural change that tracks cognition most closely	Established	Terry et al. 1991; Selkoe 2002
2	The perineuronal net protects fast-spiking cells against oxidative stress	Established	Cabungcal et al. 2013
3	Net-bearing neurons are protected against tau	Established	Morawski et al. 2010
4	The net gates parvalbumin-cell function; removing it reopens plasticity and raises gamma	Established	Favuzzi et al. 2017; Lensjø et al. 2017; Fawcett et al. 2019
5	Microglia digest the net; depleting them preserves it	Established (models)	Crapser et al. 2020
6	Human resilience is associated with altered nets	Probable	de Vries et al. 2025
7	Three arms converge on the net, so no single-target drug can work in this window	Inference	*The Proteolytic Turn*; *One Sensor, Two Collapses*
8	The parvalbumin cell is best protected for six decades, then worst affected	Inference; the curves are the model's own	*The Shape of the Disease*
9	Somatostatin interneurons fail earlier; the terminal cell's identity is held loosely	Probable	Blind re-reading recorded in the corpus; Gabitto et al. 2024
10	Restoring Nav1.1 in parvalbumin cells rescues network and cognition	Established (models)	Verret et al. 2012

#	Claim	Grade	Basis
11	Gamma falls before plaques, and driving it reduces pathology	Probable, and disputed	Iaccarino et al. 2016; Martorell et al. 2019; Adaikkan et al. 2019; Murdock et al. 2024
12	Forty-hertz light does not entrain native gamma in two models	Established, as a negative result	Soula et al. 2023
13	Preserving the net and driving the rhythm are not complementary	Inference	*The Price of the Net*
14	The Alzheimer cortex is hyperexcitable, from reduced inhibition	Established (models)	Busche et al. 2008; Palop et al. 2007; Palop and Mucke 2016
15	Subclinical epileptiform activity affects ~42% of patients and doubles the rate of decline	Established, one series	Vossel et al. 2016
16	Anti-excitability treatment helps where hyperexcitability is documented, and not otherwise	Established	Sanchez et al. 2012; Bakker et al. 2012; Vossel et al. 2021
17	Human-brain-derived amyloid oligomers impair plasticity and spine density	Established	Shankar et al. 2008; Snyder et al. 2005; Um et al. 2013
18	LilrB2/PirB restrains plasticity and is a nanomolar amyloid receptor	Established	Syken et al. 2006; Kim et al. 2013; Vidal et al. 2016
19	C4d is a high-affinity LilrB2 ligand, elevated in AD, and prunes synapses	Probable; one laboratory	Brott et al. 2025
20	Amyloid degrades EphB2; Ephexin5 then accumulates and forbids rebuilding	Established (EphB2); probable (Ephexin5)	Cissé et al. 2011; Margolis et al. 2010; Sell et al. 2017
21	Reelin–ApoER2 signalling antagonises amyloid at the synapse and is overwhelmed at high concentrations	Established (slices)	Durakoglugil et al. 2009; Weeber et al. 2002; Beffert et al. 2005; Hiesberger et al. 1999

#	Claim	Grade	Basis
22	ApoE4 impairs ApoER2 recycling and disables the reelin protection	Probable	Chen et al. 2010
23	The receptor and exchange-factor accounts predict opposite signs at the same residues	Inference	*The Hand and the Address*

11. What Would Change This Account

- A human series showing the perineuronal net intact in late Alzheimer cortex. The whole step would need rebuilding.
- A single-target intervention at one of the three proteolytic arms that fully preserves the net. The convergence argument of Section 3 would fail.
- Evidence that the parvalbumin cell dies before it loses its fast-firing capacity. The therapeutic case for acting on capacity rather than survival would go.
- A properly powered trial of forty-hertz entrainment that succeeds on a clinical endpoint while the replication failure stands. The mechanism would then need an account that does not depend on native entrainment.
- A joint measurement of the Ephexin5 and Tiam1 phosphorylation marks across single synapses showing both rising together. One of the two synaptic accounts would be eliminated.
- Levetiracetam helping a whole unselected Alzheimer population. Hyperexcitability would be general rather than a subgroup property.

12. The Three Steps Together

This series has described a disease that begins in the third decade in a handful of brainstem neurons, loosens a braking system on the brain's immune cell in the sixth, and digests a protective lattice in the eighth — with no step ending when the next begins.

Three conclusions hold across all three papers.

Function fails before cells die, everywhere. At every step the measurable loss is of capacity, connection or instruction, and not of the cell. A neuron that has lost its inputs is in a different condition from a dead one, and the model's claim is that much of what is lost in the late step is the former.

The brakes are the story. Amyloid production is braked by serotonin, its disposal licensed by somatostatin, its clearance enabled by noradrenaline; the microglion is restrained by nine separate mechanisms; the parvalbumin cell is caged; the synapse is held by a reelin clasp. The disease is better described as the sequential failure of restraints than as the accumulation of a toxin.

And the target lies further left than the trials have gone. That is the practical conclusion the three papers share, and the one most worth attacking.

The measurement that would settle the most. Whether a silenced neuron can be recovered is the open question on which the hopeful reading of this whole model rests. It has not been answered, and nothing in these three papers answers it.

Corpus papers drawn on

The Shape of the Disease. *The Proteolytic Turn*. *One Sensor, Two Collapses* and *The Net and the Speck*. *The Price of the Net*. *Low Signal, High Noise*: Excitation and Inhibition in Alzheimer's Disease. *The Hand and the Address*: LilrB2, C4d, Ephexin5 and Reelin in Alzheimer's Disease — Misdirection, Not Damage. *No Switch but the Endosome*. *The Architect's Handshake*: The Reelin–ApoER2–Heparan Sulfate Interface. *The Matrix of Collapse* and *The Perineuronal Turn*. *Convergent Synaptic Collapse*. *The Unnetted Governor*. Papers one and two of this series, *What the Brainstem Stops Sending* and *The Hands That Let Go*. All are available in full at AdultCognitiveDisease.com.

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