THE MATRIX OF COLLAPSE

The Perineuronal Net as the Structural Convergence Node of the Eight Frameworks — and a Unified Timeline of Synaptic Disintegration in Alzheimer's Disease

The Protective Net · The Cytoskeletal Node · The Neuroimmune Interface
The Excitatory–Inhibitory Axis · The Iron Bridge · The Timeline

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A companion to The Convergent Synaptic Collapse: the perineuronal net named as the structural node on which the eight frameworks' convergence is staged, the geometry of inhibitory failure resolved into one variable, and a unified half-century timeline assembled around the stripping of the matrix.

Contents

Abstract

The companion analysis *Convergent Synaptic Collapse* assembled eight independently developed frameworks — Ramsden's lipid peroxidation and ApoER2–Dab1 disruption, Small's retromer–endosomal traffic jam, Gouras's intraneuronal inside-out paradigm, Moosmann's chronic excitatory insufficiency, Rappoport's lipid-raft allostatic collapse, Margolis's synaptic restriction and proteostatic failure, Huang's competitive synaptic plasticity, and the Shatz–Brott C4d–LilrB2 axis — and showed that they converge on a small number of shared nodes: an endosomal nexus, a cytoskeletal collapse node, a compensatory paradigm, a neuroimmune interface, the ApoE4 hub, and a transcriptional layer. That synthesis described, with great precision, *how the synapse is destroyed*. It did not name the structure on which the destruction is staged. This paper supplies it.

We propose that the perineuronal net — the condensed extracellular-matrix lattice of aggrecan, brevican, hyaluronan and tenascin-R that ensheathes the parvalbumin-positive fast-spiking interneuron and a minority of excitatory neurons — is the **missing structural convergence node** of the entire synthesis, and that its degradation is the single physical event that converts the diffuse, intracellular molecular pathology of the eight frameworks into the focal, perisomatic, inhibitory collapse that is experienced as dementia. The net is not one casualty among many; it is the *surface on which the convergence happens*. It is, at once, the **protective shield** whose loss exposes the most metabolically extravagant neuron in the cortex; the **protease and complement target** on which the neuroimmune machinery of the Shatz–Brott and Margolis frameworks deposits C4d and discharges MMP-9 and the ADAMTS proteases; the **iron sink** on which the lipid-peroxidative chemistry of the Ramsden framework runs its Fenton reactions; and the **scaffold surrounding the perisomatic synapses** at which the cofilin-actin-rod cascade — the common cytoskeletal endpoint of Ramsden, Margolis, and Shatz–Brott — is physically executed. Strip the net, and the four convergent arms of the synthesis arrive together at one cell.

Reading the disease through the net resolves two of the synthesis's open problems. First, it explains the *geometry* of inhibitory failure that the single-cell atlases report — the somatostatin interneuron, which carries no net, falls early, while the netted parvalbumin interneuron falls late — as a single variable: vulnerability tracks the absence or removal of the protective matrix. Second, it supplies the *timeline*. Because the net is stripped before the cell it protects can fail, and because the stripped cell persists for years in a silenced, reawakenable state, the disease unfolds as a stereotyped half-century sequence with a definable latent interval — the gap between the loss of the net and the loss of the neuron — that is the disease's principal and most neglected window of rescue. We close by assembling, from the eight frameworks and the net together, a unified timeline of every load-bearing event from the third decade of life to terminal dementia, and by stating the falsifiable prediction on which the whole construction rests: that in the human disease the aggrecan core of the parvalbumin net is degraded, stage-specifically, *before* the cells and synapses it protects are lost.

I. The Gap in the Convergent Collapse

The convergent synthesis is, by design, a map of mechanisms rather than of places. It traces the disease from oxidative lipid modification and endosomal trafficking arrest, through the reactivation of developmental pruning programmes and the depletion of protective amyloid monomer, to the complement-driven elimination of synapses, and it shows that these arms meet at shared molecular nodes. The achievement of the synthesis is to demonstrate that no single framework is sufficient and that the disease is a network failure. But a network failure still happens somewhere, on some physical substrate, and on this question the synthesis is — understandably, given its molecular focus — silent. It names the kinases (GSK3β, LIMK1, ROCK), the effectors (cofilin, the actin cytoskeleton), the immune ligands (C4d, LilrB2), and the cell types (the pyramidal neuron, the microglion), but it does not name the *structure* that organises the zone where the perisomatic synapse is made, protected, and finally destroyed.

This omission has a consequence. Without a structural node, the synthesis's most important convergence — the cytoskeletal collapse node, at which Ramsden's GSK3β › cofilin arm, Margolis's Ephexin5–RhoA–ROCK arm, and Shatz–Brott's C4d–LilrB2 › cofilin-actin arm all arrive — appears overdetermined but unlocated. Why do three independent chemistries converge on the *same* synapses, in the *same* cells, in the *same* anatomical order? Why is the parvalbumin interneuron, which the Moosmann framework places at the centre of the excitatory–inhibitory collapse and of memantine's mechanism, both spared for decades and then catastrophically lost? And why does the loss of inhibition arrive late, after the long preclinical accrual of intracellular pathology the other frameworks describe? A purely molecular synthesis cannot answer these questions, because the answer is not a molecule. It is a structure, and the structure is the perineuronal net.

II. The Net as the Seventh Node

What the net is, and whom it protects

The perineuronal net is a reticulated lattice of extracellular matrix condensed around the soma and proximal dendrites of specific neurons: a backbone of hyaluronan, decorated with the lectican chondroitin-sulfate proteoglycans — aggrecan (the obligatory, highest-density component), brevican, neurocan and versican — cross-linked by tenascin-R and stabilised by the hyaluronan-and-proteoglycan link proteins (Fawcett, Oohashi & Pizzorusso, 2019). It is, overwhelmingly, the property of the parvalbumin-positive fast-spiking interneuron (Härtig, Brauer & Brückner, 1992; Celio, 1986), and it is borne in addition by a minority of excitatory neurons in specific layers and regions. The cell it most characteristically wraps is the one the Moosmann framework identifies as the linchpin of excitatory–inhibitory balance and of memantine's paradoxical efficacy: a neuron that fires above two hundred hertz, carries the highest oxidative load of any cortical neuron, and bears calcium-permeable receptors that leave it exposed to the ion its own activity admits (Hu, Gan & Jonas, 2014).

Why the net is a node, not a casualty

The reason the net belongs at the centre of the synthesis, rather than at its periphery, is that it is the one structure that every convergent arm must pass through to reach its target. The net buffers the cation fluxes that sustain fast firing; it functions as an antioxidant shield, such that its experimental removal renders the enclosed neuron measurably more vulnerable to oxidative insult (Cabungcal et al., 2013; Suttkus et al., 2014); it stabilises the perisomatic synapses that terminate within it; it restricts the lateral mobility of glutamate receptors and so disciplines plasticity into stability (Frischknecht et al., 2009); and it restricts the internalisation of pathological species, so that net-bearing neurons resist tangle formation (Morawski et al., 2010). Each of these offices is the obverse of a convergent arm of the synthesis: the antioxidant office is the obverse of Ramsden's lipid peroxidation; the receptor-disciplining office is the obverse of the cytoskeletal collapse node; the exclusion office is the obverse of the inside-out tauopathy. The net is the node because it is the structure whose loss *is* the convergence — the point at which four molecular arms, each described by a different framework, become one perisomatic catastrophe.

III. How Each Framework Touches the Net

The claim that the net is the structural convergence node is testable against the eight frameworks one at a time: each, on inspection, makes molecular contact with the matrix, and the contacts are not incidental but load-bearing.

Framework	Point of contact with the net	Consequence at the matrix
Ramsden (lipid peroxidation, iron)	the net is a dense polyanion and an avid iron sink; 4-HNE and Fenton chemistry	oxidative fragmentation of aggrecan; the net becomes the substrate of the iron bridge
Small (retromer / trafficking)	retromer-dependent secretion and surface delivery of matrix proteases and their regulators	dysregulated MMP/ADAMTS output toward the net; lysosomal handling of engulfed matrix
Gouras (intraneuronal Aβ)	aggrecan and net fragments co-localise with intraneuronal and plaque Aβ	the net's loss removes the exclusion barrier; the netted neuron becomes tau-permissive
Moosmann (excitatory insufficiency)	the net protects the PV interneuron whose tonic NMDA drive and gamma output set E/I balance	net loss disinhibits the cortex; gamma collapses; memantine's PV target is unshielded
Rappoport (lipid raft / allostatic)	net integrity couples to membrane and astrocytic ion handling; allostatic oxidative load	chronic stress shifts the net from maintenance to degradation
Margolis (Ephexin5–RhoA–ROCK; MMP)	RhoA/ROCK and the matrix proteases act in the perisomatic zone the net occupies	actin-myosin contraction beneath a digested net; MMP-driven matrix loss
Huang (monomer depletion; MMP-9)	activated microglia recruit MMP-9 hyperactivation, the canonical aggrecan-degrading protease	the proteolytic switch that strips the net is the same that executes synaptic loss
Shatz–Brott (C4d–LilrB2; complement)	C1q and C4d deposit on the aggrecan/brevican net as on the synapse	the net is opsonised for microglial stripping; cofilin-actin rods form beneath it

Table 1. The eight frameworks and their molecular point of contact with the perineuronal net.

Read down the column of contacts, a single mechanism assembles itself. The lipid-peroxidative arm loads the net with iron and fragments it by Fenton chemistry (Ramsden); the trafficking arm dysregulates the secretion of the proteases that will digest it (Small); the immune arm opsonises it with complement and recruits MMP-9 to cleave it (Shatz–Brott, Huang); and the cytoskeletal arm contracts the actin beneath it once the protective lattice is gone (Margolis, Ramsden). The frameworks do not merely co-occur; they are four chemistries pointed at one structure.

IV. The Cytoskeletal Collapse, Re-centred on the Net

The synthesis's cytoskeletal collapse node is the place where the matrix hypothesis does its most useful work, because it explains the node's most puzzling feature: its overdetermination. The synthesis observes, correctly, that the dendritic spine is attacked from several directions at once — by GSK3β-driven, LIMK1-mediated cofilin dysregulation (Ramsden); by Ephexin5–RhoA–ROCK-mediated actin-myosin contraction (Margolis); and by C4d–LilrB2-triggered cofilin-actin-rod formation (Shatz–Brott) — and that this convergence makes the collapse robust and difficult to reverse. What it cannot say is why these three chemistries find the same synapses.

The net supplies the reason. The perisomatic synapses on the parvalbumin interneuron, and on the netted excitatory neuron, are the synapses *embedded within the matrix lattice*. The net is the structure that holds them in place, buffers their local ionic environment, and restricts the receptor mobility on which their stability depends. While the net is intact, the cofilin-actin machinery beneath it is held in a disciplined, stable configuration; the matrix is, in effect, a brake on the very cytoskeletal dynamics the three arms seek to unleash. When the net is digested — by the iron, protease, and complement chemistries of Section III — that brake is released, and the three convergent arms find, suddenly exposed, exactly the synapses they were always able to attack but could not previously reach. The cofilin-actin rods of the Shatz–Brott and Bamburg literatures form, on this reading, *beneath a stripped net*, in the perisomatic zone the matrix used to protect. The cytoskeletal collapse node is therefore not merely overdetermined; it is **gated by the net**. The net's loss is the permission that lets the convergence occur.

V. The Two-Step Lesion and the Latent Interval

The matrix hypothesis adds to the synthesis a feature its molecular nodes cannot supply: a *separation in time* between the lesion and the death. The net is degraded before the cell it protects is lost — the impairment of the matrix precedes, rather than accompanies, the depletion of the parvalbumin population (Crapser et al., 2020). Between these two events lies a protracted state in which the parvalbumin interneuron, stripped of its shield, does not die but withdraws: it downregulates parvalbumin and its sodium channel Nav1.1, loses the synaptic organiser NPTX2, and falls electrically quiet (Verret et al., 2012; and the human single-cell atlases, which place parvalbumin loss late — Gabitto et al., 2024). This is not the beginning of the cell's death but a strategy of survival in the unshielded condition: a fast-spiking neuron that has lost the net buffering its firing is one whose continued activity would now poison it, and its quiescence reduces the very metabolic and oxidative load it can no longer afford.

This **latent interval** — the gap between the loss of the net and the loss of the neuron — reconciles the synthesis with its own timeline. The convergent frameworks describe a long preclinical accrual of intracellular pathology followed by a comparatively rapid clinical collapse; the matrix hypothesis locates the hinge between them at the stripping of the net. Before the net is stripped, the disease is the slow, intracellular, compensable process the endosomal and compensatory nodes describe. After the net is stripped, the parvalbumin cell enters its latent state, the cortex begins to disinhibit, and the rapid, self-sustaining phase begins. The clinical transition from preclinical pathology to dementia is, on this account, the crossing of the net — and the latent interval that follows is the disease's window of rescue, because a silenced cell can be reawakened and a dead one cannot.

VI. The Excitatory Cascade and the Closing of the Loop

The synthesis's "self-sustaining loop" — the feed-forward cycle in which synaptic and immune mechanisms reinforce one another until the network is locked into a pathological state — acquires, with the net at its centre, a concrete mechanism and an anatomical address. Stripping the net does not injure only the interneuron it surrounded; it injures the excitatory cortex through three channels at once, and these channels close the loop.

The first channel is disinhibition. A silenced parvalbumin cell no longer paces the pyramidal neurons it innervated, and the result is the hyperexcitable, hypersynchronous, gamma-deficient cortex the Moosmann framework describes — and, critically, the *activity-dependent amplifier* the synthesis requires, because the synaptic release of amyloid-β and of tau rises with neuronal firing. A disinhibited excitatory neuron is therefore not merely injured; it is conscripted into manufacturing the very species that drive the disease. The second channel is direct: the netted excitatory neurons that lose their own matrix lose the tau-exclusion barrier the net conferred, and in the human cortex these neurons carry markedly lower tau while their nets are intact (de Vries et al., 2024) — so their stripping renders them newly tau-permissive. The third channel is biophysical: the glutamatergic synapses stripped of the surrounding matrix lose the receptor-mobility discipline the net imposed (Frischknecht et al., 2009) and are returned, at the worst possible moment, to a labile, juvenile-like plasticity (Pizzorusso et al., 2002).

The loop now closes upon the net. Net digestion disinhibits and destabilises the excitatory cortex; the hyperexcitable, tau-permissive excitatory neurons release more amyloid and tau; the rising pathology sustains the post-homeostatic, matrix-degrading, complement-discharging microglia of the neuroimmune node; and the intensified microglial activity strips further net — from the next interneuron, and from the next netted excitatory cell. Each turn of the loop removes more matrix,

and each removal of matrix drives the loop another turn. This is the synthesis's self-sustaining loop, given a structural engine: the perineuronal net, whose loss begins the loop, whose continued loss propagates it, and whose preservation would break it.

VII. The Inhibitory Geometry

The single-cell atlases supply the synthesis a fact it does not fully explain: the somatostatin interneuron is an early casualty, depleted as the molecular pathology begins to rise, while the parvalbumin interneuron is a late casualty, lost in the disease's final epoch (Gabitto et al., 2024). On the surface this ordering complicates any account that centres the parvalbumin cell. The matrix hypothesis resolves it into a single variable, because the two cells differ in precisely the respect the hypothesis makes decisive: the parvalbumin interneuron is enwrapped by a net, and the somatostatin interneuron, a dendrite-targeting cell, is not.

The disease therefore performs its own controlled experiment. The somatostatin cell shows what becomes of an unprotected fast-inhibitory neuron facing the convergent pathology with no matrix between itself and its environment: it is taken early, because nothing shields it. The parvalbumin cell shows what becomes of one whose protection is *removed*: it survives into the disease's final phase, and only for as long as its net endures. The ordering of inhibitory failure — somatostatin first, parvalbumin last — is thus not a difficulty but a demonstration, and it is written by a single variable: when each cell loses, or never had, its net.

Population	Net status	Timing of loss	Reading under the matrix hypothesis
Somatostatin interneuron	netless (dendrite-targeting)	early	unshielded throughout; falls as the convergence arrives
Parvalbumin interneuron	aggrecan-enwrapped	late	protected until the net is stripped, then a slow latent failure

Table 2. The geometry of inhibitory failure, read as a single variable — net status.

VIII. The Unified Timeline

With the net established as the structural node, the eight frameworks and the matrix can be assembled into a single timeline — a stereotyped half-century sequence in which each framework's load-bearing event is placed at its epoch, and the status of the net is tracked alongside. The timeline's organising principle is the one the matrix hypothesis supplies: the disease is intracellular and compensable while the net is intact, and becomes extracellular, circuit-level, and self-sustaining once the net is stripped.

Phase	Epoch	Load-bearing molecular events (by framework)	Perineuronal-net status	Clinical correlate
I — Molecular Initiation	decades 3–5 (~ −30 to −15 yr)	lipid peroxidation of ApoE-borne PUFA and ApoER2–Dab1 disruption (Ramsden); incipient excitatory insufficiency and compensatory Aβ/tau (Moosmann, Rappoport); ApoE4 lowers every threshold	intact and protective; PV cells shielded; antioxidant and cation-buffering offices fully operative	asymptomatic; no pathology on imaging
II — Endosomal Dysregulation	~ −15 to −5 yr	retromer traffic jam and βCTF accumulation (Small); intraneuronal Aβ42 in synaptic MVBs (Gouras); monomer depletion begins (Huang); GSK3β rising	intact but stressed; iron loading and oxidative burden begin to accrue on the matrix; SST (netless) interneurons begin to fail	asymptomatic; amyloid-positive
III — The Proteolytic Turn	~ −5 to 0 yr	GSK3β › LIMK1 › cofilin and Ephexin5–RhoA–ROCK engaged (Ramsden, Margolis); MMP-9/ADAMTS hyperactivation (Huang); iron-Fenton fragmentation; complement priming of the matrix	**aggrecan core stripped**; the brake on the cytoskeleton released; PV cell loses its shield and enters the latent interval (silencing begins)	transition to MCI

Phase	Epoch	Load-bearing molecular events (by framework)	Perineuronal-net status	Clinical correlate
IV — Neuroimmune Synaptic Elimination	0 to ~5 yr	C4d–LilrB2 deposition and cofilin-actin rods on perisomatic synapses (Shatz–Brott); microglial engulfment of net and synapse; Nav1.1/NPTX2 loss; gamma collapse; activity-dependent Aβ/tau amplification	digested and engulfed; the loop closes on the matrix; netted excitatory neurons become tau-permissive	mild-to-moderate dementia
V — Network Disintegration	~5 to 15 yr	latent PV cells finally fail (frank loss); widespread synapse loss; tangles mature; extracellular plaques as gravestones	gone in affected fields; no matrix to protect the surviving inhibition	moderate-to-severe dementia

Table 3. The unified timeline — the eight frameworks and the perineuronal net across the half-century arc of the disease.

Two features of the timeline are worth drawing out. First, the **hinge of the disease is Phase III**, the Proteolytic Turn, at which the net is stripped: everything before it is the slow, intracellular, compensable accrual the endosomal and compensatory frameworks describe, and everything after it is the rapid, extracellular, circuit-level collapse the neuroimmune and cytoskeletal frameworks describe. The matrix hypothesis identifies this hinge as a structural event — the loss of one lattice — and thereby gives the synthesis's two halves a single point of articulation. Second, the **latent interval spans Phases III and IV**: the net is stripped at the start of Phase III, but the parvalbumin cell is not frankly lost until Phase V, and through the intervening years it persists in a silenced, reawakenable state. That interval — measured in years, not weeks — is the disease's window of rescue, and it is invisible to any framework that does not separate the loss of the net from the loss of the neuron.

IX. The Therapeutic Window, Re-stated

The convergent synthesis concluded that monotherapy must fail, because the disease is a network with redundant arms, and that effective intervention must be early and multi-targeted. The matrix hypothesis sharpens this conclusion into a single, measurable target and a single, definable window. The target is not the dead neuron, nor the upstream protein whose accrual may have closed years before; it is the **protection of the neuron** — the preservation of an intact net where one remains,

and the restoration of net integrity, or of the protective offices the net performed, where it has begun to be lost. Because the net is the structure whose stripping defines the hinge of the disease and whose preservation would arrest the self-sustaining loop, it is also the natural **biomarker** of whether the transition is being prevented: a measure of perineuronal-net integrity around the parvalbumin population reports which side of the hinge a given brain occupies and whether an intervention is holding it back.

The window is the latent interval. An intervention that restores the net, or its functions, *within* the interval — after the matrix is stripped but before the parvalbumin cell has frankly failed — can in principle reawaken the silenced cell and re-close the loop; the same intervention after frank loss cannot. This predicts a discontinuity in therapeutic outcome at a definable cellular point, and it nominates, from a single structure, both what to preserve and how to know whether one is succeeding. The synthesis pointed toward multifaceted intervention at endosomal, oxidative, excitatory, and immune nodes; the matrix hypothesis adds that all four of these are, at the perisomatic zone, *arms of a single attack on one lattice*, and that defending the lattice is the most parsimonious way to interrupt them together.

X. Falsifiable Predictions

The matrix hypothesis, like the synthesis it extends, earns its standing by exposing itself to refutation, and several of its predictions are testable with existing methods.

On the hinge. In the human cortex, the aggrecan core of the parvalbumin perineuronal net will be found progressively degraded with disease stage — by core-directed antibody and biochemical readout, even where the glycan coat is partially retained — and the degradation will be detectable *before* the depletion of the parvalbumin population and before the loss of the perisomatic synapses the net surrounds. A finding that the aggrecan core is intact through the late disease would falsify the hypothesis.

On the gating of the cytoskeletal node. Cofilin-actin rods and C4d–LilrB2-driven spine collapse will be found preferentially at synapses whose surrounding net has been degraded, and experimental preservation of the net will reduce the formation of those rods despite the presence of the upstream amyloid, tau, and complement signals.

On the inhibitory geometry. The early loss of somatostatin interneurons and the late loss of parvalbumin interneurons will track their net status — the early-lost cells netless, the late-lost cells netted — and conferring net-like protection on the unprotected population, or accelerating net loss on

the protected one, will move each cell's timing in the predicted direction.

On the latent interval. Parvalbumin neurons in the interval between net loss and frank loss will be found alive but downregulated, and restoration of net integrity within that interval will recover parvalbumin expression, Nav1.1, and fast-spiking function — whereas the same restoration after frank loss will not.

On the loop. The transition from the compensable to the self-sustaining phase of the disease will coincide with net stripping, and interventions that preserve the net will arrest the disease before that point and fail after it — a discontinuity, not a continuum.

Each prediction is a measurement addressed to one structure. That is the discipline a structural theory imposes on a molecular synthesis: the eight frameworks may each be partly right about mechanism, but the matrix hypothesis must be wrong, if it is wrong, about the net.

XI. Conclusion

The *Convergent Synaptic Collapse* established that Alzheimer's disease is not the work of a single molecule but the convergent outcome of parallel molecular insults — oxidative, trafficking, excitatory, proteostatic, and immune — that meet at shared nodes and overwhelm the synaptic architecture. That synthesis told us, in unprecedented mechanistic detail, *how* the synapse dies. It did not tell us *where* the convergence is staged, and without a place, its most important node — the cytoskeletal collapse on which three frameworks agree — remained overdetermined but unlocated, and its timeline remained a sequence of molecular events without a hinge.

This paper has argued that the place is the perineuronal net, and that the net is the seventh and structural node of the synthesis: the protective shield whose loss exposes the parvalbumin interneuron, the protease and complement target on which the neuroimmune machinery discharges, the iron sink on which the lipid-peroxidative chemistry runs, and the scaffold surrounding the perisomatic synapses at which the cytoskeletal collapse is executed. To strip the net is to let four convergent arms arrive together at one cell. Reading the disease through the net resolves the geometry of inhibitory failure into a single variable, separates the lesion from the death by a latent interval that is the disease's window of rescue, and assembles the eight frameworks into a unified timeline with a definable structural hinge. The synthesis described the convergence; the matrix names its address. And the address is a structure one can measure, defend, and — for a window that the disease itself leaves open — restore.

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