THE PERINEURONAL TURN

A Theory of the Transition to Synaptic Collapse in Alzheimer's Disease — The Perineuronal Net as Protective Pivot, the Latent Casualty, and the Window of Rescue

The Protective Net · The Somatostatin Control · The Stripping
The Latent Casualty · The Excitatory Cascade · The Window of Rescue

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A structural theory of the Phase II–III transition: the perineuronal net read as a protective variable, its stripping as the proximate lesion, the silenced parvalbumin neuron as a casualty not yet arrived, and the interval between them as the disease's window of rescue.

Contents

Abstract

Between the failure of the brain's resident immune cells and the collapse of its synaptic architecture there lies a transition, and the transition — not either of the states it joins — is where Alzheimer's disease becomes irreversible. This paper proposes that the transition is governed by a single structure, the perineuronal net, and it reconceives that structure's role. The net is not one casualty among many in the late disease; it is the *protective pivot* on which the whole transition turns, and the disease crosses from a disorder of glial regulation to a disorder of cortical computation precisely by degrading it.

Three propositions organize the account. The first is that the perineuronal net is best read as a *protective variable*, and that the otherwise puzzling order in which the cortex's inhibitory neurons fail is its direct expression: the somatostatin interneuron, which carries no net, is an early casualty, while the parvalbumin interneuron, sheathed in aggrecan, is protected and falls late — the same lesion arriving at two cells on two timetables set by whether each was ever shielded. The somatostatin neuron is, in this sense, the disease's own control experiment, demonstrating what an unprotected fast-inhibitory cell does when no net stands between it and its environment. The second proposition is that the transition is a *two-step lesion separated in time*: the net is stripped first, and the cell it protected does not fail until much later, persisting through a long interval in a downregulated, electrically quiescent state that is not death but survival without a shield. This latent interval — the gap between the loss of the net and the loss of the neuron — is the disease's principal and most neglected window of rescue, for a silenced cell can be reawakened and a dead one cannot. The third proposition is that the consequences of stripping the net are not confined to the interneuron it surrounded. They cascade onto the excitatory population through three channels at once — the disinhibition that renders pyramidal neurons hyperexcitable and converts their own activity into a source of amyloid and tau; the direct loss of the matrix that had excluded tau from the excitatory neurons that bore nets of their own; and the biophysical destabilization of glutamatergic synapses stripped of the extracellular scaffold that disciplined their plasticity. Together these close a self-sustaining loop in which matrix loss begets excitatory injury and excitatory injury begets further matrix loss, which is why the transition, once crossed, does not spontaneously reverse.

We close by stating the proposition on which the theory stakes itself. The apparent disagreement in the literature over whether perineuronal nets are lost or preserved in the Alzheimer brain is, we argue, resolvable: the net is neither uniformly destroyed nor uniformly spared but *stage- and compartment-specifically stripped at its aggrecan core*, a remodeling visible to antibodies against the proteoglycan backbone but maskable to the lectin stains that report only its sugar coat. The theory's central, falsifiable claim is therefore precise — that in the human disease the aggrecan core of the parvalbumin net is degraded, that this degradation precedes and predicts the silencing of the cells it protected, and that intervention within the latent interval can preserve them. A transition named at this resolution is a transition that can be timed, measured at a

single structure, and interrupted.

I. The Problem of the Transition

A theory of Alzheimer's disease that resolves it into phases inherits a problem its predecessors could ignore: it must account not only for the states but for the passages between them. The disease's long middle — the decade in which a hippocampal disorder of microglial regulation becomes a cortical disorder of synaptic computation — has been the least specified interval in every staging scheme, because the field's instruments are better at photographing states than at filming the movement between them. One can see, at autopsy, a brain in which the resident immune cells have lost their homeostatic identity; one can see, at autopsy, a brain in which the synaptic architecture has collapsed; what one cannot see in a single section is the mechanism that carries the first condition into the second. That mechanism is the subject of this paper, and our central claim is that it has a structural address. The transition is not diffuse. It turns on the degradation of one identifiable extracellular structure, and the structure is the perineuronal net.

This is a stronger claim than the observation, now common, that perineuronal nets are altered in the Alzheimer cortex. It is a claim about *causal position*. We argue that the net is not a downstream casualty that happens to be damaged as the disease passes through; it is the load-bearing element whose loss *constitutes* the passage. To establish this requires three moves that the remainder of the paper makes in turn: to show that the net's role is fundamentally protective, so that its loss is the removal of a defense rather than the addition of an insult; to show that the cells it protects fail on a delay that reveals the net, and not the neuron, as the proximate lesion; and to show that the loss of the net injures not only the cell it wrapped but the excitatory population around it, so that a single structural event becomes a circuit-wide collapse. We begin with the structure itself.

II. The Net as a Protective Variable

What the net is

The perineuronal net is a condensed lattice of extracellular matrix that encloses the soma and proximal dendrites of certain neurons in a reticulated sheath. Its architecture is well established: a backbone of hyaluronan, synthesized at and tethered to the membrane, is decorated with the lectican family of chondroitin-sulfate proteoglycans — aggrecan, the obligatory and highest-density component, together with brevican, neurocan, and versican — which are cross-linked by tenascin-R and stabilized by the hyaluronan-and-proteoglycan link proteins (Fawcett, Oohashi & Pizzorusso, 2019). The chondroitin-sulfate chains carry a position-specific pattern of sulfation that tunes the net's binding properties, and it is the sulfated glycan that the lectin *Wisteria floribunda* agglutinin recognizes — a point of method to which we will return, because the distinction between the glycan coat and the protein core is the key to reconciling an apparent contradiction in the disease literature.

The historical association of the net is with the parvalbumin-positive, fast-spiking interneuron. The majority of net-bearing neurons in the neocortex and hippocampus are of this class (Härtig, Brauer & Brückner, 1992; Celio, 1986), and the relationship is not incidental but functional, which is the point this section develops. The net is not a passive cast around a cell. It is a working organ of that cell's survival.

What the net does

The offices the net performs for the neuron it surrounds are, on inspection, exactly the offices a metabolically extravagant, fast-firing, oxidatively exposed cell most requires. The parvalbumin interneuron sustains firing rates an order of magnitude above those of the pyramidal cells it inhibits; it carries the highest oxidative metabolism of any neuron in its territory; and it bears calcium-permeable receptors that leave it exposed to the very ion its activity admits (Hu, Gan & Jonas, 2014). A cell of this design lives at the edge of its own tolerance, and the net is the structure that holds it there. It buffers the cation fluxes that high-frequency firing demands, maintaining the local ionic microenvironment against the cell's own throughput. It functions as an antioxidant shield, and the experimental removal of the net renders the enclosed neuron measurably more vulnerable to oxidative insult (Cabungcal et al., 2013; Suttkus et al., 2014). It stabilizes the perisomatic synapses that terminate within it, fixing the wiring that the cell's inhibitory function requires. It restricts the lateral mobility and turnover of synaptic components, disciplining plasticity into stability. And it restricts the internalization of pathological species into the cell it encloses — a property of particular consequence in a tauopathy, and one we take up in detail below.

The net's protective office	Molecular basis	Consequence of its loss
Cation buffering for fast firing	fixed polyanionic charge of sulfated glycosaminoglycans	ionic dysregulation under the cell's own throughput
Antioxidant shielding	matrix sequestration; redox buffering	heightened vulnerability to oxidative insult
Perisomatic synapse stabilization	matrix anchoring of presynaptic terminals	withdrawal and instability of inhibitory contacts
Restraint of plasticity	limitation of receptor mobility and turnover	destabilized, labile synaptic state
Exclusion of pathological uptake	barrier to internalization of extracellular species	permissiveness to tau seeding and propagation

Table 1. The protective offices of the perineuronal net, and what is lost with each.

The unifying reading is that the net is a *protective variable*: a structure whose presence is protection and whose absence is exposure. This reframing is the paper's first proposition, and everything that follows is its consequence. If the net is protection, then to ask why a neuron fails is, in part, to ask whether it had a net and whether it kept it — and that question, posed across the cortex's inhibitory neurons, answers a puzzle the disease has long presented.

III. The Somatostatin Control

A puzzle of order

The inhibitory neurons of the cortex do not fail together. The somatostatin-expressing interneuron is among the earliest neuronal casualties of the disease, depleted as the molecular pathology begins to rise and before the principal excitatory populations are lost; the parvalbumin interneuron, by contrast, is a late casualty, its loss concentrated in the disease's final epoch (Gabitto et al., 2024). On the surface this ordering is a difficulty for any account that places the parvalbumin cell at the centre of the disease, for it appears to demote that cell from protagonist to afterthought and to promote a different interneuron to primacy. We argue the opposite: that the ordering is not a difficulty but a demonstration, and that it follows directly from the protective-variable reading of the net.

The control the disease performs

The somatostatin interneuron and the parvalbumin interneuron differ in a respect that the protective-variable hypothesis predicts to be decisive: the parvalbumin cell is enwrapped by a perineuronal net, and the somatostatin cell, as a rule, is not. The somatostatin neuron is largely a dendrite-targeting cell, and it is largely netless; it faces its metabolic and oxidative environment without the sheath that the parvalbumin cell wears throughout adult life. The disease therefore presents, in these two populations, something close to a controlled experiment of its own devising. Here are two classes of inhibitory neuron, both implicated in the illness, distinguished above all by the presence or absence of the protective structure — and they fail in exactly the order the structure predicts. The unprotected cell falls early; the protected cell falls late.

Read this way, the somatostatin interneuron is the disease's natural control, and its early loss is not a rival hypothesis to the parvalbumin account but its corroboration. It shows what becomes of a fast-inhibitory neuron that must face the Alzheimer environment with no net between itself and that environment: it is taken early, because nothing shields it. The parvalbumin cell's lateness is then not evidence of its irrelevance but evidence of its protection — it survives into the disease's final phase precisely because, and only for as long as, its net endures. The contrast resolves the order of inhibitory failure into a single variable. What differs between the two cells is not, at bottom, their identity but their armour, and the timetable of the cortex's inhibitory collapse is written by when each cell loses, or never had, its own.

Population	Net status	Protected?	Timing of loss	Mode of loss
Somatostatin interneuron	netless (dendrite-targeting)	no	early	unshielded throughout; falls as the environment turns
Parvalbumin interneuron	aggrecan-enwrapped	yes, until stripped	late	protected until its net is degraded, then slow failure

Table 2. The geometry of inhibitory failure — why the somatostatin neuron falls early and the parvalbumin neuron falls late.

This is the bridge between the two halves of the theory. If the somatostatin cell shows what an unprotected inhibitory neuron suffers, the parvalbumin cell shows what happens when protection is *removed* from one that had it — and that removal is the transition this paper is about.

IV. The Stripping

The agent and the mechanism

The structure that protects the parvalbumin interneuron is, in the transition, dismantled, and the agent of its dismantling is the microglion that has, in the preceding phase, lost its homeostatic restraint. A post-homeostatic microglion is a cell whose secretory and phagocytic programmes have been redirected, and the perineuronal net — a large, accessible, proteinaceous structure studded with epitopes the cell can recognize — is among the substrates it turns upon. The degradation proceeds along converging chemistries rather than a single enzyme, which is the expected signature of an attack on a structure as compositionally heterogeneous as the aggrecan–brevican sheath.

The first chemistry is proteolytic. The lipid-burdened, inflammasome-primed microglion of the late immune phase shifts its secretory output from cytokines toward matrix-degrading enzymes, elaborating the matrix metalloproteinases and the aggrecan-specific ADAMTS proteases that cleave the proteoglycan core directly; this proteolytic redirection is the proximate microglial cause of net loss in disease models (Crapser et al., 2020). The second chemistry is oxidative. The same degenerating environment liberates redox-active iron, and the net — a dense polyanion — is an avid binder of it; an iron-loaded matrix is a substrate for Fenton chemistry, whose hydroxyl radicals fragment the proteoglycan backbone and render it, in turn, a better substrate for the proteases, so that the enzymatic and oxidative arms are not parallel but multiplicative. The third chemistry marks the structure for removal: complement components deposited on the net opsonize it for the phagocytic stripping that the classical cascade licenses elsewhere in the synaptic compartment (Stevens et al., 2007; Hong et al., 2016). Three chemistries, one structure. What they accomplish in concert is the removal of the parvalbumin cell's only defense against its own metabolism.

The order that matters

The single feature of the stripping that organizes everything downstream is its *timing relative to the cell*. The net is degraded before the neuron it protects is lost; impairment of the net precedes, rather than accompanies, the depletion of the parvalbumin population (Crapser et al., 2020). This is the empirical anchor of the theory's second proposition, and it transforms the interpretation of every subsequent observation. If the net falls first and the cell falls later, then the proximate lesion of the transition is the *matrix*, not the neuron — and the neuron's fate, in the interval between, is the subject of the next section.

V. The Latent Casualty

Two events, separated in time

The parvalbumin interneuron, stripped of its net, does not die. It enters instead a protracted state that the theory names the *latent interval*: a downregulated, electrically quiescent condition in which the cell persists, sometimes for a long time, between the loss of its protection and the loss of itself. The outward sign of this state is the decline of the very protein by which the cell is identified — the cell ceases to express parvalbumin at its former level and ceases to fire at its former rate — and the decline has, for this reason, been read as the cell's disappearance. We read it instead as the cell's adaptation. Parvalbumin expression is activity-dependent; a fast-spiking neuron that has lost the net which buffered its firing is a neuron whose continued high-frequency activity would now poison it, and its withdrawal into quiescence is, on this view, not the beginning of its death but a strategy of survival in the unshielded condition — a turning-down of the metabolic and oxidative load it can no longer afford to carry. The silenced parvalbumin cell is therefore neither healthy nor lost. It is a casualty in waiting, alive in the interval, failing only when the cumulative, now-unbuffered damage finally exceeds what even quiescence can withstand.

This two-step structure — net lost, then, much later, cell lost — is the resolution of an apparent paradox in the disease's phenomenology. It has been observed that the loss of parvalbumin neurons in the human disease is late, and that it is in substantial part a loss of the parvalbumin *phenotype* rather than a frank death of the cell. Far from contradicting the theory, this is precisely what the theory predicts: lateness is the signature of the latent interval, and the phenotypic, non-fatal character of the loss is the signature of the cell surviving in it. The transition's proximate lesion is the stripping of the net; the silencing of the cell is the lengthening shadow that the stripping casts; and frank loss, when it comes, comes last of all.

Why the interval is the point

The latent interval is not a curiosity of timing. It is the disease's most consequential and most neglected therapeutic asset, because a cell that is silenced is a cell that can be reawakened, and a cell that is dead is not. For as long as the parvalbumin neuron persists in its quiescent state, the lesion that defines the transition is, in principle, reversible: restore the protection the cell has lost, and the cell that withdrew under exposure may return under shelter. The window of rescue, developed in Section VIII, is exactly this interval, and its existence is the strongest practical reason to identify the net rather than the neuron as the lesion to be measured and the structure to be preserved. The disease gives a span of time between removing the guard and taking the cell. The theory's clinical claim is that the span is usable.

VI. The Excitatory Cascade

The error of confining the consequences of net loss to the interneuron it surrounded is the error of treating an inhibitory cell as if it acted only on itself. The parvalbumin neuron exists to govern the excitatory population, and its perisomatic net sits at the junction where that governance is exercised. To strip the net is therefore to injure the excitatory cortex, and it does so through three channels that operate at once.

Channel one — disinhibition and the activity-driven amplifier

The first and most immediate consequence is the withdrawal of inhibition. A silenced parvalbumin cell no longer paces the pyramidal neurons it innervated, and the result is a disinhibited, hyperexcitable excitatory population, prone to the network hypersynchrony and subclinical epileptiform activity that accompany the disease, and stripped of the gamma-frequency timing that perisomatic inhibition generates and on which the coordination of pyramidal ensembles depends (Sohal et al., 2009; Cardin et al., 2009; Verret et al., 2012). The hyperexcitable pyramidal neuron suffers a calcium-mediated excitotoxic burden it would not otherwise carry; but the channel's deeper significance is that it makes the excitatory neuron an *engine of pathology*. The synaptic release of amyloid-β, and of tau, is activity-dependent — a more active neuron releases more of both (Cirrito et al., 2005; Wu et al., 2016) — so that disinhibition does not merely injure the excitatory cell but conscripts it into manufacturing and disseminating the very species that drive the disease. The matrix lesion, through this channel, becomes a pathology accelerant.

Channel two — the loss of tau exclusion

The second channel is direct, and it depends on a fact about the net that is too often forgotten: the perineuronal net is not the exclusive property of the parvalbumin interneuron. Subsets of excitatory neurons bear nets of their own, and where they do, the net confers on them the same exclusionary protection it confers elsewhere — the matrix is a barrier to the internalization of pathological species, and net-bearing neurons resist the formation of tangles (Morawski et al., 2010). In the human cortex this protection is measurable in the currency of the disease itself: excitatory neurons that retain a perineuronal net carry a markedly lower burden of hyperphosphorylated tau than their unnetted neighbours (de Vries et al., 2024). To strip the net from such a neuron, therefore, is to remove its tau-exclusion barrier and to render it newly *permissive* to the seeding and accumulation of the pathology it had been resisting. This is a route by which net loss accelerates tau pathology not through the interneuron at all, but directly in the excitatory compartment — and it is, of the three channels, the one with the firmest anchor in human tissue.

Channel three — the destabilization of excitatory synapses

The third channel concerns the glutamatergic synapse itself. The extracellular matrix that the net comprises is not inert scaffolding around the synapse; it is an active regulator of the synapse's biophysics. The matrix restricts the lateral diffusion of glutamate receptors in the membrane and thereby disciplines short-term plasticity (Frischknecht et al., 2009); it restrains the structural turnover of dendritic spines; and, as the structure whose maturation closes the critical periods of development, it holds the adult synapse in a consolidated, stable state, such that its experimental removal reopens a juvenile-like plasticity (Pizzorusso et al., 2002). In a developing brain such reopening is rejuvenation. In a degenerating one it is the opposite — a destabilization of consolidated circuits, an increase in the lability and turnover of the very synapses whose stability constitutes memory. The excitatory synapse stripped of its surrounding matrix is a synapse returned, at the worst possible moment, to a state it had been right to leave behind.

Channel of excitatory injury	Mechanism	Consequence	Firmest evidence
Disinhibition + activity amplifier	loss of perisomatic inhibition; gamma collapse; activity-dependent Aβ/tau release	hyperexcitability, excitotoxicity, accelerated pathology and spread	network and release data, models
Loss of tau exclusion	removal of the matrix barrier to internalization on netted excitatory neurons	tau-permissiveness; rising tangle burden	human tissue (netted excitatory neurons carry low tau)
Synaptic destabilization	increased receptor mobility, spine turnover, reopened plasticity	labile, unstable glutamatergic synapses	basic matrix-plasticity literature

Table 3. The excitatory cascade — three channels of injury opened by stripping the net.

VII. The Self-Sustaining Loop

The three channels do not act in isolation, and their interaction is what makes the transition, once begun, complete itself. Consider the loop they close. The stripping of the net disinhibits the excitatory population and renders it hyperexcitable; the hyperexcitable, activity-driven excitatory neuron releases more amyloid and more tau; the rising pathology sustains and intensifies the post-homeostatic, matrix-degrading activity of the microglia; and the intensified microglial activity strips further net — from the next parvalbumin cell, and from the netted excitatory neurons whose

tau exclusion then fails in turn, feeding the pathology again. Each turn of the loop removes more protection, and each removal of protection drives the loop another turn.

This feed-forward structure is the reason the transition behaves as a threshold rather than a slope. Before the loop becomes self-sustaining, the disease advances only as fast as its upstream drivers push it, and the removal of a driver can slow or arrest it; after the loop closes upon itself, the disease supplies its own forward pressure, and removing any single upstream input no longer stops a process that has become its own cause. The crossing of this threshold is, on the present account, the event that separates the long, modifiable prodrome of the disease from its short, refractory clinical phase — and it is centred, in every term of the loop, on the perineuronal net: the structure whose loss begins the loop, whose continued loss propagates it, and whose preservation would break it.

VIII. The Window of Rescue

The therapeutic consequence of the theory follows from the latent interval and the loop together, and it is specific. Because the net is stripped before the cell it protects is lost, and because the stripped-but-silenced cell persists in a reversible state, there exists a defined interval — opening when the net is degraded and closing when the parvalbumin neuron finally fails — within which the lesion of the transition can be undone. The clinical task is to act within it.

This reframes both the target and the readout of intervention. The target is not the dead neuron, which cannot be the object of rescue, 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 functions the net performed, where it has begun to be lost. And because the net is the structure whose loss defines the transition and whose preservation would arrest it, the net is also the natural *biomarker* of whether the transition is being prevented: a measure of perineuronal-net integrity around the parvalbumin population is a measure of which side of the threshold a given brain occupies and whether an intervention is holding it back. The theory thus nominates, from a single structure, both what to preserve and how to know whether one is succeeding. The window is real because the cell survives its stripping; the window is usable because the structure that defines it can be measured; and the window is the disease's, not the patient's, to keep open, for it is set by the interval between the loss of the net and the loss of the neuron — an interval the theory holds to be, for now, longer than the clinic has appreciated.

IX. Reconciling Loss and Preservation

A theory that stakes itself on the degradation of the perineuronal net must meet directly the body of work reporting that the net is, on the contrary, *preserved* in the Alzheimer cortex — that its distribution and number appear unchanged, and that net-bearing neurons remain conspicuously free of tangles. We regard this not as a refutation but as the most informative constraint the theory must satisfy, and we hold that the discrepancy is resolvable along three axes, each of which the theory specifies and each of which yields an experiment.

The first axis is *detection*. The lectin stains by which nets are most commonly visualized report the sulfated-glycan coat of the structure, whereas antibodies against aggrecan report its proteoglycan core, and the two need not change together. A net whose core is being cleaved by the ADAMTS proteases may retain enough glycan to remain lectin-positive while having lost the structural integrity that protection requires; conversely, the glycan coat may be remodeled while the core endures. A literature that reports "preservation" by one method and "loss" by another is not necessarily contradictory; it may be reporting the dissociation of the net's two readouts, which is itself a prediction of progressive core-directed degradation. The second axis is *compartment*. The net is not a single population: the dense parvalbumin perisomatic net and the nets borne by subsets of excitatory neurons are distinct structures with distinct vulnerabilities, and a study that pools them, or that samples chiefly one, may average a real loss in one compartment against a real preservation in another. The third axis is *stage*. The transition is, by hypothesis, an event of the disease's middle and late course; a structure that is intact early and stripped late will read as "preserved" in any cohort weighted toward the early disease and as "lost" in any cohort weighted toward the terminal disease, and the disagreement collapses once the axis of disease stage is held fixed.

The theory's resolution is therefore that the net is *neither* uniformly destroyed *nor* uniformly spared, but stage- and compartment-specifically remodeled at its aggrecan core — and this resolution is not a hedge but a sharpening, because it specifies exactly the measurement that would confirm or refute it: an aggrecan-core readout of the parvalbumin perineuronal net, resolved by disease stage, in human tissue. That measurement is the experiment on which the theory consents to be judged.

X. Falsifiable Predictions

The transition, named at the resolution of a single structure, generates predictions that are correspondingly sharp.

On the central claim. In the human Alzheimer 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 it protects. A finding that the aggrecan core is intact through the late disease would falsify the theory.

On the order of inhibitory loss. The early loss of somatostatin interneurons and the late loss of parvalbumin interneurons will be found to 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, or of its protective functions, within that interval will recover parvalbumin expression and fast-spiking function — whereas the same restoration after frank loss will not. The interval's existence predicts a discontinuity in therapeutic outcome at a definable cellular point, not a continuum.

On the excitatory cascade. Net-bearing excitatory neurons will retain low tau and will acquire tau pathology upon losing their nets; disinhibition consequent on parvalbumin silencing will be accompanied by activity-dependent increases in amyloid and tau release; and matrix integrity around excitatory synapses will predict their stability.

On the loop and the threshold. The transition from the modifiable to the refractory phase of the disease will coincide with the point at which net loss, excitatory injury, and microglial matrix degradation become mutually reinforcing, and interruption of any single term will arrest the disease before that point and fail after it.

Each prediction is a measurement that a single well-designed study could overturn, and each is addressed to the same structure. That is the discipline a structural theory of the transition imposes: it must be wrong, if it is wrong, about the net.

XI. Conclusion

The transition from the immune phase of Alzheimer's disease to its synaptic phase has been the field's least specified passage, and a theory of the disease is only as strong as its account of where the

disease becomes irreversible. We have argued that the passage turns on one structure, the perineuronal net, and that the net's role is best understood not as a casualty but as a protection — so that the disease crosses from a disorder of regulation to a disorder of computation precisely by stripping the cortex of a defense it had quietly maintained for half a century. The order in which the inhibitory neurons fail, long read as a complication, becomes on this account a demonstration: the unprotected somatostatin cell falls early because nothing shields it, and the protected parvalbumin cell falls late because its net does, until the net is taken. The lateness and the silence of the parvalbumin loss, read as evidence against its centrality, are revealed as the signatures of a latent interval in which the stripped cell survives — and that interval, the gap between the loss of the net and the loss of the neuron, is the disease's window of rescue. The stripping reaches beyond the interneuron to the excitatory cortex, disinhibiting it, exposing its netted members to the tau they had excluded, and destabilizing its synapses, until the three injuries close a self-sustaining loop and the transition completes itself.

The theory consents to be judged on a single measurement, and names it: the aggrecan core of the parvalbumin net, resolved by stage, in the human brain. If it is intact through the late disease, the theory is wrong. If it is progressively stripped, before the cells it protects are lost, then the transition has a structure, a clock, and a target — and the most consequential interval in the disease is one in which something can still be done. The disease has always had a middle. The claim of this paper is that the middle has an address, that the address is a structure one can measure, and that the structure is, for a while, a casualty that has not yet happened.

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