From Synapse Loss to Neuronal Death

The Tolerated Subtraction, and What Converts It — a mechanistic hypothesis for how the elimination of synapses in Alzheimer's disease becomes the death of the neurons that bore them

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Synapse loss predicts cognitive decline better than any other structural measure and precedes neuronal death by years. The programmes that remove synapses are identified; the step that joins them to cell death is not. This paper argues that the step is non-trivial — a cortical neuron tolerates the loss of roughly half its synapses — and proposes three couplings that convert a tolerated subtraction into a lethal one.

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Abstract

Synapse loss is the strongest structural correlate of cognitive impairment in Alzheimer's disease, exceeding both plaque and tangle burden, and it precedes neuronal death by years. The molecular programmes that remove synapses are increasingly well characterised: reactivation of a developmental spine-repression pathway following amyloid-driven EphB2 degradation; dysregulation of activity-dependent synaptic competition; complement-mediated tagging and microglial engulfment; and neuron-autonomous structural collapse driven by the complement fragment C4d acting at the neuronal receptor LilrB2. What remains unspecified is the step that joins this literature to the neuropathology of cell loss: by what mechanism does the elimination of synapses become the death of the neuron that bore them?

The question cannot be answered by asserting a proportionality, because the simple relation is contradicted on three independent grounds. Synaptic transmission and the ion pumping that restores it constitute the dominant metabolic expense of grey matter, so a partially pruned neuron carries a *smaller* energetic burden. Homeostatic synaptic scaling exists precisely to absorb changes in drive and restores firing rate by multiplicative adjustment of remaining synaptic weights. And the measured tolerance is very large: the CA1 stratum radiatum loses approximately fifty-five per cent of its synapses in mild Alzheimer's disease at a stage at which stereology detects no CA1 neuronal loss in preclinical disease, and at end-stage roughly three-quarters of entorhinal layer II and CA1 profiles remain viable neurons. A cortical neuron can lose half of its synapses and survive.

We propose that three couplings convert a tolerated subtraction into a lethal one. First, the neuron's activity-dependent survival programme — CREB-driven transcription, brain-derived neurotrophic factor, and the intrinsic antioxidant defences induced by synaptic NMDA-receptor activity — is transacted *per synapse and locally*. Homeostatic scaling therefore restores the neuron's firing rate without restoring its trophic settlement, and because the activity–BDNF–CREB loop carries positive gain, each contact lost reduces the capacity to maintain those remaining. The neuron appears compensated while decompensating. Second, the effectors of cell death are already active during the long presymptomatic phase, but they are *compartmentalised*: caspase-3 is activated within dendritic spines to produce long-term depression, spine loss and memory impairment without killing the cell, and the C4d–LilrB2 axis executes cofilin-dependent structural collapse inside individual spines. We propose that somatic death represents failure of this compartmentalisation — the escalation of a programme the healthy neuron executes thousands of times within a spine to the scale of the whole cell. This reading accounts for the long-standing scarcity of apoptotic profiles in Alzheimer tissue: caspase activation is not absent but local. Third, the subtraction propagates. Withdrawal of an afferent projection debits every downstream target by the same arithmetic, providing a mechanism for degeneration along connectional pathways that does not require network hyperactivity.

The point at which subtraction becomes lethal is set cell-autonomously by at least four lesions: tau-dependent targeting of Fyn to the postsynaptic density; depletion of calbindin-D28k from selectively vulnerable populations; upregulation of endoplasmic-reticulum-to-mitochondrion calcium transfer and lowered permeability-transition threshold; and APOE4-dependent derangement of the neuronal membrane proteasome that maintains the synaptic proteome. A population of neurons with a distribution of such thresholds, crossed sequentially, predicts a linear decline in neuron number under an exponentially accumulating lesion burden — the dissociation reported in large single-nucleus atlases and not expected under a dose–response model.

Two consequences follow. The persistent difficulty in identifying the modality of somatic death in human tissue reflects sampling: at plausible rates, roughly one neuron in six thousand is morphologically identifiable as dying at any moment, whereas the same cell is the site of order ten thousand elimination events, each individually sublethal and each accessible to array tomography, complement assay, and synaptic-vesicle-glycoprotein-2A positron emission tomography in living patients. And if a neuron that has lost most of its connections and fallen silent is functionally lost irrespective of whether it subsequently dies, then disconnection rather than death is the operative lesion, synaptic density is the appropriate trial endpoint, and interventions that block elimination should be prioritised over those that block execution.

1. Introduction

The neuropathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles, but neither predicts the clinical syndrome well. What predicts it is the loss of synapses. Terry and colleagues established in 1991 that synapse density in the neocortex is the major correlate of cognitive impairment, outperforming plaque and tangle counts; DeKosky and Scheff had reached the same conclusion the previous year from frontal-cortex biopsy material, in which fixation and post-mortem artefacts are minimal. Selkoe summarised the position in a title that has not required amendment: Alzheimer's disease is a synaptic failure.

The mechanisms by which synapses are removed have since been characterised in some detail. Amyloid-β oligomers bind and deplete EphB2, disinhibiting a guanine-nucleotide exchange factor whose developmental role is to suppress excitatory synapse formation, and thereby reactivating a spine-repression programme in the adult brain. Activity-dependent synaptic competition, normally a mechanism of circuit refinement, becomes indiscriminate. Complement components tag synapses for microglial engulfment through a developmental pathway that is re-expressed in disease. And the complement fragment C4d, acting on the neuronal receptor LilrB2, instructs the neuron to dismantle its own spines through the cofilin–actin axis. These are not speculative pathways: several have been tested by genetic ablation with rescue of the synaptic phenotype.

The neuropathology of cell loss is equally well described. Entorhinal cortex layer II loses approximately sixty per cent of its neurons by the threshold of clinically detectable impairment and up to ninety per cent in severe disease. The CA1 field loses roughly half to two-thirds of its pyramidal neurons in established disease. In prefrontal association cortex, more than ninety per cent of neurofilament-enriched layer III and V projection neurons are lost at end stage, and neuronal loss in association cortex accounts for the majority of the variance in cognitive score while amyloid burden is largely non-predictive.

Between these two literatures there is a gap that is usually crossed by assertion. It is widely and correctly stated that synaptic loss precedes neuronal loss. It is rarely asked how the first produces the second — whether it does so at all, by what mechanism, and how much subtraction is required. The purpose of this paper is to state that question precisely, to show that its naive answer is contradicted by the available data, and to propose a mechanism.

Section 2 summarises the elimination programmes. Section 3 assembles the quantitative relation between synapse loss and neuron loss in the same structures at the same stages, which turns out to be a dissociation rather than a proportionality. Section 4 sets out three reasons why synaptic subtraction should not, on its face, kill a neuron; any proposed bridge must survive them. Sections 5

to 7 propose three couplings that convert a tolerated loss into a lethal one, and Section 8 identifies what determines the point of conversion. Sections 9 and 10 draw two consequences — one for the interpretation of the cell-death literature, one for the choice of therapeutic endpoint. Sections 11 to 13 give testable predictions, therapeutic implications, and limitations.

2. Mechanisms of Synaptic Elimination

Four partly independent programmes remove synapses in Alzheimer's disease. They are summarised in Table 1 and described below. What matters for the present argument is not which predominates but that each is a regulated programme with identified effectors, rather than a passive consequence of neuronal injury.

2.1 Reactivation of a developmental spine-repression pathway

Ephexin5 is a guanine-nucleotide exchange factor for RhoA, the small GTPase that governs dendritic spine structure. During development, EphB receptor signalling drives the degradation of Ephexin5, and this degradation is what relieves a brake on excitatory synapse formation (Margolis et al., 2010). The disease-relevant claim is that the brake is re-applied in the adult brain. Amyloid-β oligomers bind EphB2 and drive its degradation; restoring EphB2 expression rescues cognitive function in an amyloid model (Cissé et al., 2011). With EphB2 depleted, Ephexin5 is disinhibited, RhoA activity rises, cofilin is dysregulated, actin is severed faster than it is nucleated, and the spine retracts.

Two features are relevant. The destructive mechanism is not a novel pathological invention but a physiological programme operating in an inappropriate context, which is why it is efficient and produces no inflammatory signature of its own. And Ephexin5 is pleiotropic — it also regulates Cdc42, which promotes spine growth — so non-selective inhibition would suppress both spine collapse and spine formation.

2.2 Dysregulated synaptic competition

Amyloid-β has a concentration-dependent, biphasic action. At physiological, largely monomeric concentrations it participates in activity-dependent axonal and synaptic competition; at oligomeric concentrations it becomes a signal for elimination (Huang, 2023, 2024). On this model, synaptic competition in the healthy brain uses fitness checkpoints that preferentially prune weakly active, metabolically compromised contacts. The proposed disease mechanism is that aggregation acts as a thermodynamic sink for soluble monomer, so that a rising total amyloid burden is accompanied by a *falling* concentration of the monomeric species that restrains microglial activation and supports competitive plasticity.

The consequence that matters here is a change in the character of pruning rather than its rate: a checkpoint that had been selecting against weak synapses begins removing strong ones. The distinction between more elimination and *less selective* elimination separates a circuit being refined

from one being dismantled, and it is the reason a physiological programme can produce a pathological outcome without any change in its machinery.

2.3 Complement: tagging, engulfment, and neuron-autonomous collapse

The complement pathway contributes through two mechanistically distinct arms.

The first is opsonisation and engulfment. C1q deposition marks synapses; C1q tagging triggers C3 cleavage, depositing opsonins; complement receptor 3 on microglia recognises them and initiates phagocytosis. In amyloid models, C1q is upregulated before plaque formation, binds amyloid-β oligomers, and knockout of C1q, C3 or CR3 each rescues synapse loss — critically, *independently of amyloid burden* (Hong et al., 2016). This last result establishes complement-mediated elimination as a proximate cause of the synaptic phenotype rather than a downstream consequence of deposition.

The second arm is neuron-autonomous. LilrB2 (murine PirB) is an amyloid-β receptor that regulates synaptic plasticity in an Alzheimer model (Kim et al., 2013). The complement fragment C4d is a high-affinity ligand for the same receptor, is elevated in Alzheimer's disease, and mediates synapse pruning; infusion of C4d reduces spine density in wild-type mice and has no effect in PirB-null animals (Brott et al., 2025). Here complement is not a tag awaiting a phagocyte but a ligand instructing the neuron to execute structural collapse through the LIMK–cofilin pathway. **This arm is important to the argument of Section 6, because it establishes that a destructive programme runs to completion inside a single spine, within the neuron, without the neuron dying.**

2.4 Oligomer signalling at the postsynaptic density

Amyloid-β dimers isolated directly from Alzheimer brain impair long-term potentiation, enhance long-term depression, reduce spine density and disrupt learned behaviour at low nanomolar concentrations (Shankar et al., 2008). Oligomeric amyloid-β localises to postsynaptic densities and correlates with excitatory synapse loss in the halo surrounding plaques (Koffie et al., 2009), where spine density falls by roughly half within twenty micrometres of a plaque edge (Spires et al., 2005) and fibrillar deposition breaks neuronal branches outright (Tsai et al., 2004). Receptor-level mediators have been identified, including cellular prion protein (Laurén et al., 2009) and its co-receptor metabotropic glutamate receptor 5 (Um et al., 2013); amyloid-β additionally promotes endocytosis of synaptic NMDA receptors (Snyder et al., 2005).

Table 1 — Programmes of synaptic elimination

Programme	Trigger	Effector	Causal evidence
Developmental spine repression	Aβ-driven EphB2 degradation	Ephexin5 → RhoA → cofilin; actin severing	EphB2 restoration rescues cognition (Cissé 2011)
Dysregulated competition	Monomer depletion into aggregate	Fitness checkpoints applied indiscriminately	Model-level; concentration-dependence established
Complement opsonisation	C1q binding to Aβ oligomers	C3 deposition; CR3-mediated microglial engulfment	C1q, C3 or CR3 knockout each rescues, amyloid-independently (Hong 2016)
Neuron-autonomous collapse	C4d binding neuronal LilrB2/PirB	LIMK → cofilin; spine retraction	C4d reduces spine density; no effect in PirB-null (Brott 2025)
Postsynaptic oligomer signalling	Aβ oligomers at the PSD	PrP^{C}/mGluR5; NMDA-receptor endocytosis	Human-derived dimers are synaptotoxic at low nM (Shankar 2008)

3. The Quantitative Relation Between Synapse Loss and Neuron Loss

The relation is usually described as temporal. Described quantitatively, in the same structures at the same stages, it is a dissociation, and the size of the dissociation is the central fact this paper attempts to explain.

Synapse loss. Stereological counts in the CA1 stratum radiatum show synapse number reduced by approximately eighteen per cent at mild cognitive impairment and fifty-five per cent in mild Alzheimer's disease (Scheff et al., 2007); the neocortical and hippocampal pattern has been reviewed across the series (Scheff and Price, 2006; Scheff et al., 2006). Synaptic-vesicle-glycoprotein-2A positron emission tomography detects reduced hippocampal synaptic density in early Alzheimer's disease in living patients (Chen et al., 2018), with widespread cortical involvement (Mecca et al., 2020). Synapse counts correlate with cognitive performance but show no relationship to Braak stage or APOE genotype (Scheff et al., 2006, 2007).

Neuron loss in the same structures. There is no significant CA1 neuronal loss in preclinical disease — brains bearing Alzheimer pathology in the absence of cognitive decline (West et al., 2004) — and roughly forty-eight to sixty-eight per cent loss in established disease (West et al., 1994, 2004). At end stage, approximately seventy-three per cent of entorhinal layer II profiles and seventy-seven per cent of CA1 profiles remain viable neurons (Hof et al., 2003). Neurons may persist for decades bearing neurofibrillary tangles (Morsch et al., 1999). Neuronal loss exceeds tangle number manyfold in association cortex (Gómez-Isla et al., 1997).

The dissociation. *In the CA1 field, roughly half the synapses are absent at a stage at which essentially none of the neurons are.*

A second dissociation, in the shape of the curves. Across the pathological axis of a large multimodal single-nucleus atlas, neuron number declines approximately linearly while tangle-bearing neurons and plaques accumulate exponentially (Gabitto et al., 2024). A death rate that is linear under an exponentially rising insult is not the signature of a dose–response relation. Section 8 returns to this.

Scale. An average cortical neuron carries on the order of several thousand synapses (Drachman, 2005), with human pyramidal cells substantially higher, against a neocortical total on the order of 10^{14} (Pakkenberg et al., 2003). A neuron losing half its complement over a decade is therefore the site of order 10^{4} elimination events. This figure is used in Section 9.

4. Why Synaptic Subtraction Should Not, By Itself, Kill

Three arguments contradict the simple proportional relation. A proposed bridge must meet all three, and the failure to state them is why the step from synapse loss to cell death has generally been assumed rather than argued.

The metabolic argument. Synaptic transmission and the sodium–potassium pumping that restores the gradients it dissipates constitute the dominant energetic expense of grey matter (Harris et al., 2012). A neuron that has lost half of its synapses has lost, to a first approximation, half of its principal cost. If metabolic burden were the lethal variable — and the vulnerable phenotype in this disease is precisely the cell with the largest connectivity load and the longest axon — then pruning should be protective. On this argument alone, a partially eliminated neuron ought to be safer than an intact one.

The homeostatic argument. Cortical neurons possess machinery whose function is to hold firing near a set point despite changes in drive. Synaptic scaling multiplicatively adjusts the weights of remaining excitatory synapses, restoring average firing rate while preserving relative weights (Turrigiano, 2008); intrinsic excitability adjusts in the same direction. Partial loss of input is among the canonical perturbations this system corrects, and compensatory circuit remodelling is directly observed in amyloid models (Palop et al., 2007). The first-order consequence of losing synapses is therefore not a silenced neuron but a renormalised one.

The empirical argument, which is the strongest. The tolerance is measured and it is large. Approximately half the CA1 synaptic population is absent at a stage with no detectable CA1 neuronal loss (Scheff et al., 2007; West et al., 2004). Three-quarters of entorhinal layer II profiles remain viable at end stage (Hof et al., 2003). Outside this disease, experimental deafferentation of adult central targets characteristically produces atrophy, dendritic remodelling and functional impairment rather than prompt death of the target population.

A cortical neuron can lose half its synapses and live. Subtraction is necessary and it is not sufficient. What follows is an account of what converts it.

5. First Coupling: Trophic Support Is Settled Per Synapse, and the Loop Has Gain

5.1 What synaptic activity purchases

The survival programme of a cortical neuron is not constitutive; it is purchased continuously with the neuron's own patterned synaptic transmission, and the purchasing mechanism is specific.

Synaptic NMDA-receptor activity — phasic, coincidence-gated, occurring within the postsynaptic density — drives CREB phosphorylation and a pro-survival transcriptional programme, whereas extrasynaptic NMDA-receptor activation driven by ambient glutamate triggers CREB shut-off and death signalling (Hardingham et al., 2002; Hardingham and Bading, 2010; Bading, 2017). Among the products of the synaptic arm are the neuron's intrinsic antioxidant defences: synaptic NMDA-receptor activity boosts the thioredoxin–peroxiredoxin system and confers resistance to oxidative insults the cell would not otherwise survive (Papadia et al., 2008).

Brain-derived neurotrophic factor is the principal trophic component of the same programme. Calcium influx regulates *BDNF* transcription through CREB-family factors (Tao et al., 1998); the protein is packaged into dense-core vesicles and secreted in an activity-dependent manner concentrated at active contacts, where it engages TrkB and signals back onto CREB. The loop is closed and its gain is positive: activity produces trophic support, and trophic support sustains the machinery of activity. BDNF messenger RNA is reduced in the Alzheimer hippocampus (Phillips et al., 1991), and the reduction is present early.

5.2 The proposal

Homeostatic scaling stabilises firing rate. It does not stabilise the trophic account, because that account is settled per contact and locally.

The subsidy is not delivered to the cell in bulk in proportion to its output. It is delivered at the synapse, to the synapse, by machinery localised there — BDNF secreted at active contacts, acting on TrkB at those contacts, maintaining the spines that house them. A synapse that has been eliminated cannot be subsidised by the increased weight of a surviving one. When scaling doubles the strength of the remaining contacts, the neuron recovers its firing rate and its computational role; what it does not recover is the *number of independently subsidised sites*, and it is sites rather than rate in

which the maintenance economy is denominated.

Because the loop carries positive gain, this converts a step change into a slope. Each eliminated synapse lowers the total activity-dependent trophic output of the cell, which lowers the maintenance available to those remaining, which raises their probability of subsequent elimination — both by fitness checkpoints that select against weak and metabolically compromised contacts (Section 2.2) and by complement, which tags them (Section 2.3). The neuron's trajectory under elimination is therefore not a step down to a new stable state but a descent whose rate increases as it proceeds, concealed beneath a firing rate that homeostasis holds approximately constant. **The cell appears compensated while decompensating.**

5.3 Status of the claim

Every component is established: the synaptic/extrasynaptic dichotomy, the antioxidant induction, the activity-dependence and local secretion of BDNF, the reduction of BDNF in Alzheimer tissue, and multiplicative synaptic scaling. The assembly into a per-contact, positive-gain trophic model of the Alzheimer principal neuron is a hypothesis. No study has measured trophic signalling and synapse number in the same neurons across the disease course, and the causal direction within the loop is not separable in principle — falling BDNF reflects fewer active synapses and also produces them. That circularity is the claim rather than an objection to it, but it means the model must be tested interventionally rather than correlatively; Section 11 states how.

6. Second Coupling: Compartmentalised Execution and the Failure of Containment

6.1 The death machinery is already running, and it is local

Caspase-3 — the canonical executioner of apoptosis — is activated within dendritic spines early in an amyloid model, where it drives calcineurin-dependent long-term depression, spine loss and memory impairment **without killing the neuron** (D'Amelio et al., 2011). The machinery of cellular execution is being used as an instrument of local structural editing.

It is not alone in this. The C4d–LilrB2 axis executes structural collapse within a spine through LIMK and cofilin, severing actin faster than it can be nucleated (Brott et al., 2025). The Ephexin5–RhoA pathway does the same through a different GTPase (Margolis et al., 2010; Cissé et al., 2011). In each case a destructive programme runs to completion and the unit it destroys is a compartment, not a cell.

6.2 The proposal

Somatic death represents the failure of compartmentalisation.

Containment is an active achievement, not a default. It requires that activated caspase be inhibited and cleared before it diffuses beyond the spine; that calcium transients be buffered within the spine head; that cofilin activation be spatially restricted; and that the local proteostatic and energetic capacity to repair after each event remain available. Each of these capacities is degraded in the Alzheimer neuron — by loss of calcium-buffering protein, by proteasomal derangement, by lysosomal acidification failure, and by bioenergetic deficit. On this model the disease does not recruit a new executioner. It removes the walls around one the cell has been using all along.

Four features recommend the reading.

It accounts for the timing. The long presymptomatic phase is the phase during which local execution runs and is contained. Clinical progression begins as containment fails at the margins; somatic death is the point of general failure. Nothing new need be recruited at any stage.

It accounts for the stochasticity. Neuronal death in this disease is not synchronised: neighbouring cells of the same subtype under the same pathology die years apart, and tangle-bearing and tangle-free neurons of the dominant vulnerable subtypes show similar susceptibility (Otero-Garcia et al., 2022). Containment failure is a per-cell probabilistic event whose hazard rises as local capacity

falls, which is that pattern.

It resolves a long-standing negative result. Definitive apoptotic morphology is famously scarce in Alzheimer tissue, and this has been widely taken as evidence against apoptosis as the mechanism. On the present reading apoptotic signalling is not absent but local: caspase-3 is active, in spines, for years. A search conducted at the level of the soma would record a null against a hypothesis about the compartment.

It makes the effector question tractable. Section 9 develops this.

6.3 What would refute it

If the caspase-3 pool that produces spine loss were shown to be constitutively incapable of somatic execution — spatially restricted by a mechanism that does not fail, or differing in substrate profile — then local and global programmes are two programmes rather than one at two scales, and the escalation model fails.

7. Third Coupling: Propagation of the Subtraction

The first two couplings are intracellular. The third concerns why the disease follows connections.

When a neuron dies, or merely loses its axon, the synapses it made upon its targets are withdrawn. The canonical instance is entorhinal: the death of layer II projection neurons is experienced by the hippocampus as deafferentation, with perforant-path synapses in the dentate outer molecular layer significantly reduced in early disease (Scheff et al., 2006).

On the account of Section 5, an afferent synapse is not only a channel of information but a unit of the target neuron's trophic settlement. **Deafferentation therefore debits the downstream cell's survival account by the same arithmetic that debited the upstream one**, placing it on the same trajectory one synaptic generation later.

This supplies a mechanism for connectional degeneration that does not require the target population to be hyperactive. Neurodegenerative diseases target large-scale networks (Seeley et al., 2009); amyloid deposition overlaps the cortical hubs defined by intrinsic functional connectivity (Buckner et al., 2009); and models in which damage accumulates with activity reproduce hub vulnerability (de Haan et al., 2012). Under the present model, hubs are vulnerable because they possess the largest number of afferents to lose and the largest number of efferent targets to debit — that is, because connection is the quantity being subtracted. It also predicts spread along anatomical pathways without invoking transfer of a templated protein, and is therefore complementary to, rather than competing with, propagation models.

8. Determinants of the Lethal Threshold

Elimination determines the magnitude of the withdrawal. It does not determine the point at which withdrawal becomes fatal, which differs between neighbouring cells under identical pathology. At least four lesions lower it.

Tau-dependent coupling at the postsynaptic density. Reducing endogenous tau prevents amyloid-induced deficits without altering amyloid burden and protects both transgenic and non-transgenic animals against excitotoxic insult (Roberson et al., 2007); the effect generalises across models and is Fyn-dependent (Roberson et al., 2011). The mechanism is dendritic: tau targets Fyn to the postsynaptic density, where it phosphorylates GluN2B and stabilises the NMDA-receptor–PSD-95 complex that couples the receptor to downstream death signalling (Ittner et al., 2010). Tau reduction also prevents amyloid-induced impairment of axonal transport (Vossel et al., 2010) and prevents neuronal loss in tauopathy models (DeVos et al., 2017). This lesion is postsynaptic, and its effect is to render an ordinary glutamatergic load capable of killing.

Depletion of calcium buffering. Calcium-dependent proteins including calbindin-D28k are depleted from dentate granule neurons in amyloid models in tight linkage with cognitive deficit (Palop et al., 2003), and calcium-buffering capacity is lost with age and disease specifically from selectively vulnerable human populations (Riascos et al., 2011). A buffer does not alter how much calcium enters; it alters how much free calcium a given entry produces. Its most relevant consequence here is local: buffering is what confines a spine's calcium transient to the spine, so its loss is a direct attack on the containment described in Section 6.

Enhanced ER-to-mitochondrion calcium transfer. Ryanodine-receptor-mediated calcium release is exaggerated presymptomatically in a familial model, with the network resetting synaptic homeostasis around the aberrant signal (Chakroborty et al., 2009); mitochondria-associated endoplasmic-reticulum membrane function is upregulated in Alzheimer tissue (Area-Gómez et al., 2012); and deletion of the permeability-transition regulator cyclophilin D attenuates mitochondrial and neuronal perturbation and improves cognition in an amyloid model (Du et al., 2008). Calcium mishandling has long been proposed as an upstream feature of the disease (Bezprozvanny and Mattson, 2008); its role here is to lower the load at which mitochondrial permeability transition occurs.

APOE4-dependent derangement of the synaptic proteome. A nervous-system-specific plasma-membrane proteasome degrades activity-induced nascent protein at the neuronal surface (Ramachandran and Margolis, 2017), and neuroproteasome function regulates endogenous tau paired-helical-filament formation in an APOE-genotype- and age-dependent manner (Paradise et

al., 2026). This is a threshold lesion of a distinctive kind: it impairs the cell's capacity to *rebuild* what elimination removes, and it does so as a function of the principal genetic risk factor for late-onset disease. The model therefore predicts that APOE4 carriers cross into neuronal loss at a smaller fraction of synapses lost.

8.1 Why a threshold model rather than a dose–response

Section 3 recorded that neuron number falls approximately linearly across the pathological axis while lesion burden accumulates exponentially (Gabitto et al., 2024). Under a dose–response relation the two curves would share a shape; they do not.

A threshold model predicts the dissociation. If each cell dies when its remaining trophic settlement crosses an individual threshold, and thresholds are distributed across the population by the lesions above, then the death rate at any moment is the number of cells whose thresholds lie in the interval the subtraction has just swept. Across the middle of a broad distribution that rate is approximately constant — a linear cumulative loss — irrespective of how steeply the driving lesion rises. The linearity is thus evidence for a distribution of thresholds. The inference is indirect: it argues from curve shape, assumes a broad and roughly uniform distribution, and other models can be fitted to the same two curves.

9. Implications for the Cell-Death-Modality Literature

Considerable effort has gone into identifying which regulated cell-death programme executes neurons in Alzheimer's disease — apoptosis, necroptosis, ferroptosis, pyroptosis, parthanatos — with no settled answer. The present model suggests the difficulty is partly one of sampling, and the arithmetic is worth stating.

Entorhinal layer II contains on the order of 6.5 × 10^5 neurons, and approximately sixty per cent are lost by a Clinical Dementia Rating of 0.5 (Gómez-Isla et al., 1996). Distributed over a decade, that is roughly one hundred neurons per day, or about 0.016 per cent of the population daily. A dying cell is morphologically identifiable only between the appearance of a recognisable death morphology and its clearance. If that window is twenty-four hours, approximately **one neuron in six thousand** is identifiable at any instant; at six hours, one in twenty-four thousand. Necroptosis and ferroptosis leave no distinctive light-microscopic morphology at all. The scarcity of apoptotic profiles is therefore only weakly informative, and morphological surveys are poorly powered to discriminate among modalities regardless of which operates.

The same calculation one level down runs the other way. If the cell carries several thousand synapses and loses half over a decade, it is the site of order 10^4 elimination events — each executed by an identified programme, each leaving a measurable trace, and the population of them accessible to instruments already in use: array tomography, which reconstructed some fourteen thousand synapses to define the plaque halo (Koffie et al., 2009); complement assay and genetic ablation, which established causality independently of amyloid burden (Hong et al., 2016); receptor blockade, which showed PirB-dependence of C4d-driven spine loss (Brott et al., 2025); and SV2A positron emission tomography, which measures synaptic density in living patients (Chen et al., 2018; Mecca et al., 2020).

Where molecular rather than morphological assays have been applied to human tissue, they have been informative. Necroptotic machinery is activated in post-mortem Alzheimer brain, correlating positively with Braak stage and inversely with brain weight and cognitive score, with RIPK1-regulated genes overlapping independent disease transcriptomic signatures and reduced necroptotic activation lowering cell loss in a mouse model (Caccamo et al., 2017). This is the appropriate form of evidence given the arithmetic above.

The general point is methodological: a process distributed across 10^4 sublethal events per cell over ten years is nearly invisible when observed as its single terminal event and readily visible at the

site of the events.

10. Disconnection as the Operative Lesion

A final consequence follows from the preceding sections rather than being asserted alongside them.

What is lost clinically is connections. Synapse loss is the major correlate of cognitive impairment (Terry et al., 1991; DeKosky and Scheff, 1990); synapse counts track cognitive performance while showing no relation to Braak stage or genotype (Scheff et al., 2006, 2007); synaptic density falls measurably in living patients before atrophy is measurable (Chen et al., 2018); and at the end of the disease most vulnerable somata are still present (Hof et al., 2003).

A neuron that has lost most of its contacts is therefore functionally lost irrespective of whether it subsequently dies. A silent, atrophic, disconnected pyramidal cell contributes nothing to cognition and is not recovered by an intervention that merely keeps it alive. Its eventual death alters the histology and not the patient.

Three consequences. Interventions should be ranked by how much subtraction they prevent rather than how much death — which moves anti-elimination strategies above neuroprotective ones, and predicts that a neuroprotectant preserving disconnected somata will produce a clean histological result and no clinical one. Trial endpoints should be synaptic rather than volumetric, which is now feasible in vivo. And cognitive resilience in the presence of Alzheimer-threshold pathology should be sought in preserved connectivity rather than preserved cell number — a testable distinction.

None of this implies that somatic death is unimportant. It is irreversible, it defines the end state, and it bounds what any future restorative therapy can achieve. The claim is that for the cortical principal neuron, the event that constitutes the illness is disconnection, and death is its epilogue.

11. The Proposed Sequence, and Testable Predictions

Table 2 — Proposed sequence, with evidence status

Step	Event	Status
1	Four programmes eliminate synapses: spine repression after EphB2 depletion; indiscriminate competitive pruning; complement opsonisation and engulfment; C4d–LilrB2 neuron-autonomous collapse	Established; two arms causally demonstrated by genetic ablation
2	The loss is tolerated; firing rate is restored by scaling; ~50% of CA1 synapses are lost with no CA1 neuronal loss	Established (human counts; scaling mechanism)
3	Trophic settlement is per contact and local, so scaling restores rate but not account; the loop's positive gain accelerates the descent	**Hypothesis**; components established
4	Local execution programmes run continuously and are contained by buffering, proteostasis and local energetic capacity	Established that they run locally without killing
5	Four lesions lower both the lethal set-point and the capacity to contain	Established individually; their action on containment is inferred
6	Containment fails; the programme run 10^4 times in a compartment runs once in the cell	**Hypothesis**; not directly demonstrated
7	Efferent withdrawal debits downstream targets by the same arithmetic; degeneration follows connections	Deafferentation established; the trophic reading is inferred

Steps 1–5 are concurrent and span years. What is claimed as ordered is that elimination precedes entry into the descending state, and that somatic death is last.

Predictions

On the subsidy. In neurons subjected to partial synaptic elimination sufficient to trigger homeostatic scaling, firing rate will recover while CREB-dependent transcriptional output and BDNF/TrkB signalling remain depressed in proportion to contacts lost rather than to restored rate. *If the trophic programme recovers with the firing rate, the subsidy is a bulk quantity and Section 5 fails.*

On the tolerated fraction. Measured in the same human tissue across the staging series, synapse counts and stereological neuron counts will show a region of substantial synaptic loss

without neuronal loss, followed by a neuronal-loss phase beginning at a reproducible synaptic fraction. *If neuronal loss begins immediately and proportionally, there is no tolerated region and the relation is a dose–response.*

On containment. Driving local caspase-3 activation at spines with somatic caspase inhibition intact will produce spine loss without death; degrading containment capacity — calbindin knockdown, proteasome inhibition, cyclophilin D manipulation — will convert equivalent local activation into somatic death. *If degrading containment does not convert local execution into somatic death, Section 6 is refuted.*

On genotype. APOE4 carriers will enter neuronal loss at a smaller fraction of synapses lost than non-carriers. *If the fraction is genotype-invariant, the neuroproteasome lesion is not acting as a threshold on synaptic subtraction.*

On direction of travel. After selective ablation of an upstream population, downstream targets will show falling CREB output and BDNF in proportion to afferent loss, before any pathology of their own. *If deafferented targets show no trophic decrement, Section 7 fails.*

On therapy. An agent blocking C1q or C3 will preserve synaptic density measured by SV2A PET, and preservation will precede and predict any effect on atrophy or cognition. *If synaptic density is preserved without cognitive benefit, synapse number is a marker rather than the operative lesion and Section 10 is wrong.*

12. Therapeutic Implications

The target is elimination. Each of the four programmes has a therapeutic handle. Complement is the most advanced, with anti-C1q and anti-C3 agents in clinical development, and the amyloid-independence of the rescue in preclinical models (Hong et al., 2016) argues that benefit need not wait on amyloid removal. The C4d–LilrB2 axis is druggable at the receptor and has an unusual property: because LilrB2 is inhibitory on microglia as well as instructive on neurons, blockade is predicted both to prevent neuron-autonomous spine collapse and to relieve a brake on microglial clearance. The Ephexin5–RhoA and LIMK–cofilin axes are druggable in principle but pleiotropic, since the same exchange factor supports spine growth through Cdc42.

The endpoint should be synaptic density. This is the most immediately actionable implication. SV2A PET measures the operative lesion in living patients, is closer to cognition than atrophy, and is closer to the mechanism than amyloid or tau burden. A trial of an anti-complement agent powered on synaptic density would test the therapy and the model together.

Restoring trophic support is a distinct and largely unbuilt category. No agent is designed to restore per-contact trophic settlement to a partially eliminated dendritic tree. Approaches exist in preclinical form — BDNF gene delivery, TrkB agonism — and the present model predicts that their benefit should be superadditive with anti-elimination therapy and limited without it, since raising the subsidy while contacts continue to be removed refills a leaking account.

Threshold interventions are preventive rather than restorative. Tau reduction raises the threshold at which subtraction becomes lethal, and human tools exist: a tau-targeting antisense oligonucleotide produced dose-dependent reductions in cerebrospinal-fluid tau in a phase 1b trial (Mummery et al., 2023). But the model predicts, and the data support, that raising a threshold does nothing for contacts already lost. Consistent with this, suppressing tau expression rapidly rescued neuronal impairment in tau-only animals but was substantially less effective in animals carrying both amyloid and tau (Busche et al., 2019). Inhibition of Fyn, the kinase implicated by the tau mechanism, did not slow cerebral metabolic decline in a randomised trial (van Dyck et al., 2019) — a result that should be weighed against the mechanism rather than set aside.

Timing. Every implication above is a statement about the presymptomatic period. The tolerated phase — during which the neuron is neither healthy nor dying, holds its firing rate, and remains structurally present — is both the largest therapeutic window in the disease and the one for which no clinical trial currently selects.

13. Strength of Evidence, and Limitations

Table 3 — Strength of evidence for the principal claims

Claim	Status
Synapse loss is the major correlate of cognitive impairment	Established (Terry 1991; DeKosky and Scheff 1990)
~55% of CA1 synapses are lost in mild AD; no CA1 neuronal loss preclinically; ~3/4 of vulnerable profiles viable at end stage	Established (Scheff 2007; West 2004; Hof 2003)
Complement mediates early synapse loss, amyloid-independently	Established (Hong 2016)
C4d–LilrB2 drives neuron-autonomous spine loss	Established (Brott 2025; Kim 2013)
Caspase-3 executes locally in spines without killing the cell	Established (D'Amelio 2011)
Synaptic and extrasynaptic NMDA-receptor activity are oppositely coupled	Established (Hardingham 2002; Papadia 2008)
Tau reduction protects against excitotoxicity via dendritic Fyn targeting	Established (Roberson 2007, 2011; Ittner 2010)
A cortical neuron tolerates loss of ~half its synapses	Supported inference; cross-study, not measured in one tissue set
The lethal threshold is set cell-autonomously by the four lesions	Supported inference; each lesion established, threshold role inferred
Trophic settlement is per contact, and scaling cannot restore it	**Hypothesis**; the paper's most falsifiable claim
Somatic death is failure of compartmentalisation	**Hypothesis**; not demonstrated in any system
Deafferentation debits the downstream trophic account	**Hypothesis**; deafferentation itself established
Threshold distribution explains the linear/exponential dissociation	**Hypothesis**; argues from curve shape; other models fit

Limitations. The tolerated-fraction estimate is assembled across cohorts, regions and methods; no single study has measured synapse number and neuron number in the same tissue across the staging series, so the paper's central quantity is inferred rather than observed. The compartmentalisation model has not been tested in any system and is stated as a hypothesis throughout. The sampling

arithmetic of Section 9 assumes a loss distributed over roughly a decade and a morphological window of six to twenty-four hours; the conclusion is robust across plausible variation in both, but neither is measured. Several of the elimination mechanisms are established principally in mouse models, and the transfer to sporadic human disease is an extrapolation — strongest for complement, where human tissue evidence for C4d elevation exists, and weakest for the competition model, which is at present largely theoretical. Finally, the account addresses the cortical principal neuron; the subcortical nuclei that degenerate early in this disease are small, densely projecting populations whose arithmetic may differ.

14. Conclusions

Synapse loss precedes neuronal death in Alzheimer's disease by years and predicts the clinical syndrome better than any other structural measure. The programmes that remove synapses are identified and, in several cases, causally demonstrated. What has been missing is the step that joins them to cell death, and the step is not trivial, because a cortical neuron tolerates the loss of approximately half its synapses without dying — a fact that follows from the metabolic economics of the cell, from homeostatic scaling, and from direct measurement.

We propose that three couplings convert the tolerated subtraction. The neuron's activity-dependent survival programme is settled per contact and locally, so homeostatic scaling restores what the cell computes without restoring what it is paid, and the positive gain of the activity–trophic loop turns a subtraction into an accelerating descent. The effectors of cell death are already running during this phase, confined to individual spines; somatic death represents the escalation of that programme when containment fails. And the withdrawal of efferent connections transfers the same arithmetic to downstream targets, so degeneration follows connections without requiring hyperactivity or protein transfer.

The point of conversion is set cell-autonomously by tau-dependent postsynaptic coupling, calcium-buffer depletion, enhanced ER-to-mitochondrion calcium transfer, and APOE4-dependent derangement of the proteasome that maintains the synaptic proteome — a distribution of thresholds that predicts the observed linear decline in neuron number beneath an exponentially rising lesion burden.

Two practical consequences follow. The persistent irresolution of the cell-death-modality question reflects the fact that a process distributed over 10^4 sublethal events per cell is nearly undetectable when observed as its terminal event; the evidence lies one compartment down, where it is already accessible in living patients. And if the disconnected neuron is functionally lost whether or not it dies, then the operative lesion is disconnection, the appropriate endpoint is synaptic density, and the interventions worth prioritising are those that stop the subtraction rather than those that prevent the execution.

References

Area-Gómez E, Del Carmen Lara Castillo M, Tambini MD, Guardia-Laguarta C, de Groof AJW, Madra M, Ikenouchi J, Umeda M, Bird TD, Sturley SL, Schon EA. Upregulated function of mitochondria-associated ER membranes in Alzheimer disease. *EMBO Journal*. 2012;31(21):4106–4123. PMID 22892566.

Bading H. Therapeutic targeting of the pathological triad of extrasynaptic NMDA receptor signaling in neurodegenerations. *Journal of Experimental Medicine*. 2017;214(3):569–578. PMID 28209726.

Bezprozvanny I, Mattson MP. Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. *Trends in Neurosciences*. 2008;31(9):454–463. PMID 18675468.

Brott BK, Raissi AJ, Micheva KD, Vielmetter J, Mendes MS, Baccus CJ, Huang J, Shatz CJ. C4d, a high-affinity LilrB2 ligand, is elevated in Alzheimer's disease and mediates synapse pruning. *Proceedings of the National Academy of Sciences USA*. 2025;122(38):e2519253122. PMID 40966293.

Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*. 2009;29(6):1860–1873. PMID 19211893.

Busche MA, Wegmann S, Dujardin S, Commins C, Schiantarelli J, Klickstein N, Kamath TV, Carlson GA, Nelken I, Hyman BT. Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models in vivo. *Nature Neuroscience*. 2019;22(1):57–64. PMID 30559471.

Caccamo A, Branca C, Piras IS, Ferreira E, Huentelman MJ, Liang WS, Readhead B, Dudley JT, Spangenberg EE, Green KN, Belfiore R, Winslow W, Oddo S. Necroptosis activation in Alzheimer's disease. *Nature Neuroscience*. 2017;20(9):1236–1246. PMID 28758999.

Chakroborty S, Goussakov I, Miller MB, Stutzmann GE. Deviant ryanodine receptor-mediated calcium release resets synaptic homeostasis in presymptomatic 3xTg-AD mice. *Journal of Neuroscience*. 2009;29(30):9458–9470. PMID 19641109.

Chen MK, Mecca AP, Naganawa M, Finnema SJ, Toyonaga T, Lin SF, Najafzadeh S, Ropchan J, Lu Y, McDonald JW, Michalak HR, Nabulsi NB, Arnsten AFT, Huang Y, Carson RE, van Dyck CH. Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomographic imaging. *JAMA Neurology*. 2018;75(10):1215–1224. PMID 30014145.

Cissé M, Halabisky B, Harris J, Devidze N, Dubal DB, Sun B, Orr A, Lotz G, Kim DH, Hamto P, Ho K, Yu GQ, Mucke L. Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. *Nature*. 2011;469(7328):47–52. PMID 21113149.

D'Amelio M, Cavallucci V, Middei S, Marchetti C, Pacioni S, Ferri A, Diamantini A, De Zio D, Carrara P, Battistini L, Moreno S, Bacci A, Ammassari-Teule M, Marie H, Cecconi F. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease. *Nature Neuroscience*. 2011;14(1):69–76. PMID 21151119.

de Haan W, Mott K, van Straaten ECW, Scheltens P, Stam CJ. Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. *PLoS Computational Biology*. 2012;8(8):e1002582. PMID 22915996.

DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Annals of Neurology*. 1990;27(5):457–464. PMID 2360787.

DeVos SL, Miller RL, Schoch KM, Holmes BB, Kebodeaux CS, Wegener AJ, Chen G, Shen T, Tran H, Nichols B, Zanardi TA, Kordasiewicz HB, Swayze EE, Bennett CF, Diamond MI, Miller TM. Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. *Science Translational Medicine*. 2017;9(374):eaag0481. PMID 28123067.

Drachman DA. Do we have brain to spare? *Neurology*. 2005;64(12):2004–2005. PMID 15985565.

Du H, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD, Gunn-Moore FJ, Vonsattel JP, Arancio O, Chen JX, Yan SD. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. *Nature Medicine*. 2008;14(10):1097–1105. PMID 18806802.

Gabitto MI, Travaglini KJ, Rachleff VM, et al. Integrated multimodal cell atlas of Alzheimer's disease. *Nature Neuroscience*. 2024;27(12):2366–2383. PMID 39402379.

Gómez-Isla T, Price JL, McKeel DW Jr, Morris JC, Growdon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *Journal of Neuroscience*. 1996;16(14):4491–4500. PMID 8699259.

Gómez-Isla T, Hollister R, West H, Mui S, Growdon JH, Petersen RC, Parisi JE, Hyman BT. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. *Annals of Neurology*. 1997;41(1):17–24. PMID 9005861.

Hardingham GE, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nature Neuroscience*. 2002;5(5):405–414. PMID 11953750.

Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nature Reviews Neuroscience*. 2010;11(10):682–696. PMID 20842175.

Harris JJ, Jolivet R, Attwell D. Synaptic energy use and supply. *Neuron*. 2012;75(5):762–777. PMID 22958818.

Hof PR, Bussière T, Gold G, Kövari E, Giannakopoulos P, Bouras C, Perl DP, Morrison JH. Stereologic evidence for persistence of viable neurons in layer II of the entorhinal cortex and the CA1 field in Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*. 2003;62(1):55–67. PMID 12528818.

Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, Merry KM, Shi Q, Rosenthal A, Barres BA, Lemere CA, Selkoe DJ, Stevens B. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*. 2016;352(6286):712–716. PMID 27033548.

Huang Z. A function of amyloid-β in mediating activity-dependent axon/synapse competition may unify its roles in brain physiology and pathology. *Journal of Alzheimer's Disease*. 2023;92(1):29–57. PMID 36710681.

Huang Z. Evidence that Alzheimer's disease is a disease of competitive synaptic plasticity gone awry. *Journal of Alzheimer's Disease*. 2024;99(2):447–470. PMID 38669548.

Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J, Wölfing H, Chieng BC, Christie MJ, Napier IA, Eckert A, Staufenbiel M, Hardeman E, Götz J. Dendritic function of tau mediates amyloid-β toxicity in Alzheimer's disease mouse models. *Cell*. 2010;142(3):387–397. PMID 20655099.

Kim T, Vidal GS, Djurisic M, William CM, Birnbaum ME, Garcia KC, Hyman BT, Shatz CJ. Human LilrB2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science*. 2013;341(6152):1399–1404. PMID 24052308.

Koffie RM, Meyer-Luehmann M, Hashimoto T, Adams KW, Mielke ML, Garcia-Alloza M, Micheva KD, Smith SJ, Kim ML, Lee VM, Hyman BT, Spires-Jones TL. Oligomeric amyloid-β associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. *Proceedings of the National Academy of*

Sciences USA. 2009;106(10):4012–4017. PMID 19228947.

Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers. *Nature*. 2009;457(7233):1128–1132. PMID 19242475.

Margolis SS, Salogiannis J, Lipton DM, Mandel-Brehm C, Wills ZP, Mardinly AR, Hu L, Greer PL, Bikoff JB, Ho HY, Soskis MJ, Sahin M, Greenberg ME. EphB-mediated degradation of the RhoA GEF Ephexin5 relieves a developmental brake on excitatory synapse formation. *Cell*. 2010;143(3):442–455. PMID 21029865.

Mecca AP, Chen MK, O'Dell RS, Naganawa M, Toyonaga T, Godek TA, Harris JE, Bartlett HH, Zhao W, Nabulsi NB, Vander Wyk BC, Varma P, Arnsten AFT, Huang Y, Carson RE, van Dyck CH. In vivo measurement of widespread synaptic loss in Alzheimer's disease with SV2A PET. *Alzheimer's & Dementia*. 2020;16(7):974–982. PMID 32400950.

Morsch R, Simon W, Coleman PD. Neurons may live for decades with neurofibrillary tangles. *Journal of Neuropathology and Experimental Neurology*. 1999;58(2):188–197. PMID 10029101.

Mummery CJ, Börjesson-Hanson A, Blackburn DJ, et al. Tau-targeting antisense oligonucleotide MAPT_Rx in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. *Nature Medicine*. 2023;29(6):1437–1447. PMID 37095250.

Otero-Garcia M, Mahajani SU, Wakhloo D, et al. Molecular signatures underlying neurofibrillary tangle susceptibility in Alzheimer's disease. *Neuron*. 2022;110(18):2929–2948.e8. PMID 35882228.

Pakkenberg B, Pelvig D, Marner L, Bundgaard MJ, Gundersen HJ, Nyengaard JR, Regeur L. Aging and the human neocortex. *Experimental Gerontology*. 2003;38(1–2):95–99. PMID 12543266.

Palop JJ, Jones B, Kekonius L, Chin J, Yu GQ, Raber J, Masliah E, Mucke L. Neuronal depletion of calcium-dependent proteins in the dentate gyrus is tightly linked to Alzheimer's disease-related cognitive deficits. *Proceedings of the National Academy of Sciences USA*. 2003;100(16):9572–9577. PMID 12881482.

Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, Yoo J, Ho KO, Yu GQ, Kreitzer A, Finkbeiner S, Noebels JL, Mucke L. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron*. 2007;55(5):697–711. DOI: 10.1016/j.neuron.2007.07.025

Papadia S, Soriano FX, Léveillé F, Martel MA, Dakin KA, Hansen HH, Kaindl A, Sifringer M, Fowler J, Stefovska V, McKenzie G, Craigon M, Corriveau R, Ghazal P, Horsburgh K, Yankner BA, Wyllie DJA, Ikonomidou C, Hardingham GE. Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. *Nature Neuroscience*. 2008;11(4):476–487. PMID 18344994.

Paradise V, Konrad-Vicario KD, Nguyen C, et al. Neuroproteasomes regulate endogenous tau paired helical filament formation in an APOE genotype- and age-dependent manner. *Nature Neuroscience*. 2026. PMID 42215643.

Phillips HS, Hains JM, Armanini M, Laramee GR, Johnson SA, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. *Neuron*. 1991;7(5):695–702. PMID 1742020.

Ramachandran KV, Margolis SS. A mammalian nervous-system-specific plasma membrane proteasome complex that modulates neuronal function. *Nature Structural & Molecular Biology*. 2017;24(4):419–430. PMID 28287632.

Riascos D, de Leon D, Baker-Nigh A, Nicholas A, Yukhananov R, Bu J, Wu CK, Geula C. Age-related loss of calcium buffering and selective neuronal vulnerability in Alzheimer's disease. *Acta Neuropathologica*. 2011;122(5):565–576. PMID 21874328.

Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L. Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. *Science*. 2007;316(5825):750–754. PMID 17478722.

Roberson ED, Halabisky B, Yoo JW, Yao J, Chin J, Yan F, Wu T, Hamto P, Devidze N, Yu GQ, Palop JJ, Noebels JL, Mucke L. Amyloid-β/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. *Journal of Neuroscience*. 2011;31(2):700–711. PMID 21228179.

Scheff SW, Price DA. Alzheimer's disease-related alterations in synaptic density: neocortex and hippocampus. *Journal of Alzheimer's Disease*. 2006;9(3 Suppl):101–115. PMID 16914849.

Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*. 2006;27(10):1372–1384. PMID 16289476.

Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology*. 2007;68(18):1501–1508. PMID 17470753.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 2009;62(1):42–52. PMID 19376066.

Selkoe DJ. Alzheimer's disease is a synaptic failure. *Science*. 2002;298(5594):789–791. PMID 12399581.

Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nature Medicine*. 2008;14(8):837–842. PMID 18568035.

Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P. Regulation of NMDA receptor trafficking by amyloid-β. *Nature Neuroscience*. 2005;8(8):1051–1058. PMID 16025111.

Spires TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, Bacskai BJ, Hyman BT. Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *Journal of Neuroscience*. 2005;25(31):7278–7287. PMID 16079410.

Tao X, Finkbeiner S, Arnold DB, Shaywitz AJ, Greenberg ME. Ca2+ influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron*. 1998;20(4):709–726. PMID 9581763.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Annals of Neurology*. 1991;30(4):572–580. PMID 1789684.

Tsai J, Grutzendler J, Duff K, Gan WB. Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. *Nature Neuroscience*. 2004;7(11):1181–1183. PMID 15475950.

Turrigiano GG. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell*. 2008;135(3):422–435. PMID 18984155.

Um JW, Kaufman AC, Kostylev M, Heiss JK, Stagi M, Takahashi H, Kerrisk ME, Vortmeyer A, Wisniewski T, Koleske AJ, Gunther EC, Nygaard HB, Strittmatter SM. Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer Aβ oligomer bound to cellular prion protein. *Neuron*. 2013;79(5):887–902. PMID 24012003.

van Dyck CH, Nygaard HB, Chen K, et al. Effect of AZD0530 on cerebral metabolic decline in Alzheimer disease: a randomized clinical trial. *JAMA Neurology*. 2019;76(10):1219–1229. PMID 31329216.

Vossel KA, Zhang K, Brodbeck J, Daub AC, Sharma P, Finkbeiner S, Cui B, Mucke L. Tau reduction prevents Aβ-induced defects in axonal transport. *Science*. 2010;330(6001):198. PMID 20829454.

West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet*. 1994;344(8925):769–772. PMID 7916070.

West MJ, Kawas CH, Stewart WF, Rudow GL, Troncoso JC. Hippocampal neurons in pre-clinical Alzheimer's disease. *Neurobiology of Aging*. 2004;25(9):1205–1212. PMID 15312966.