THE CELLULAR ARCHITECTURE OF COLLAPSE

Second, Expanded Edition

A Quantitative Census of the Neurons and Synapses Destroyed in Alzheimer's Disease — From the Coerulean Neuron to the Perisomatic Synapse

The Coerulean Neuron · The Raphé and the Nigra · The Cholinergic Forebrain
The Entorhinal Stellate Cell · The Hippocampal Pyramidal Neuron · The Great Projection Neurons
The Custodial Microglion · The Reactive Astrocyte · The Oligodendrocyte
The Parvalbumin Interneuron · The Dendritic Spine · The Perisomatic Synapse

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Dr. James Truchard & Benjamin Aaron Gustafsson

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The second, expanded edition roughly doubles the census — adding the aminergic chorus, the cholinergic forebrain, the great projection neurons, the reactive astrocyte, the dendritic spine, the molecular identity of the doomed, and the geometry of sparing — and counting the disease in three currencies: cells, synapses, and molecules.

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Abstract

Its companion paper, *The Temporal Architecture of Collapse*, resolved Alzheimer's disease in time: a three-phase front of failure crossing the brain over half a century, from a small nucleus in the pons in the third decade to the inhibitory scaffolding of the cortex in the eighth, joined by two mechanistically specified bridges. The first edition of the present work answered the questions *which* and *how many* — an enumeration, cell type by cell type and synapse class by synapse class, of what is destroyed across that arc. This second edition is not a revision but an extension: it roughly doubles the census, and in doing so it adds two new instruments that have, in the last decade, transformed a counting exercise into a precise science. The first is the single-nucleus transcriptomic atlas, which no longer merely counts the dying cell but *names* it by its molecular identity — RORB, SST, the supragranular long-range excitatory neuron — and so converts "selective vulnerability" from a phenomenon into a list of suspects with addresses. The second is in-vivo synaptic-density imaging, which counts synapses in the living brain and so turns the autopsy census into a clinical one.

The expanded list deepens every entry of the first and adds new ones. We follow the noradrenergic neuron of the locus coeruleus, the first cell in the brain to bear the disease's signature, and place beside it the rest of the aminergic chorus that the field long overlooked — the serotonergic neuron of the dorsal raphe, whose pretangle pathology is detectable before the transentorhinal cortex is touched; the dopaminergic neuron of the ventral tegmentum; the histaminergic neuron of the tuberomammillary nucleus. We give the cholinergic projection neuron of the basal forebrain the full chapter its >75% end-stage depletion has always deserved, and we resolve the long argument over whether it dies or merely falls silent. We follow the entorhinal stellate cell, ~60% lost before the disease is diagnosable, and now name its molecular sub-identity. We add the great corticocortical projection neurons of layers III and V — the large, neurofilament-rich cells whose long axons make them, by their very architecture, the disease's preferred target. We add the reactive astrocyte and the dendritic spine. And, crucially, we add the chapter the first edition lacked: an account of what does *not* die — the cerebellum, the primary sensory cortices, the calcium-buffering interneurons — because the geometry of sparing is the strongest proof that the geometry of destruction is a phenotype and not a fog.

Three principles now organize the count. The first, **selectivity with a signature**, the first edition argued; the new sparing and atlas data confirm it and sharpen it: the doomed neuron is large, long-projecting, fast-firing, oxidatively exposed, and dependent on a protective envelope, and the spared neuron is, point for point, its opposite. The second, **the primacy of the synapse over the soma**, is now measurable in life: synaptic density falls earliest and predicts cognition better than amyloid, tangle, or grey-matter volume, and at the disease's end the majority of neurons in the worst-hit fields are still, by the stereologists' own count, alive. The third is new to this edition — **the molecular legibility of vulnerability**: the cell that dies can now be identified, before it dies, by a transcriptional signature, which is the strongest

evidence yet that the casualty list is written in advance. We assemble these counts from the primary stereological, synaptic, and single-cell literature, state the confidence and the method-dependence of each, and decline to launder uncertainty into false precision. The result is the temporal architecture rendered in the currency of cells, synapses, and now molecules — a disease one can, at last, count three ways.

I. The Question of Number

What the field has counted, and what it has not

For four decades the quantitative energy of Alzheimer's research was spent counting two things: plaques and tangles. The neuritic plaque and the neurofibrillary tangle are countable, stainable, stageable; they are the substrate of Braak staging and of CERAD scoring and of the entire neuropathological apparatus by which the disease is confirmed at autopsy. They are also, as measures of the thing that matters, strangely disappointing. The correlation between plaque burden and the severity of dementia in life is weak; the correlation between tangle burden and dementia is better but imperfect; and the most consequential single finding in the quantitative neuropathology of the disease is that *neither* is the best predictor of how demented a patient was. The best predictor is the loss of synapses (Terry et al., 1991; DeKosky & Scheff, 1990). The field spent a generation counting the lesions that are easiest to see rather than the casualties that best explain the illness.

This paper counts the casualties. It takes as given the temporal architecture established in the companion synthesis — three phases, two bridges, one homeostatic system failing across the brain in sequence — and asks, at each station of that arc, a set of deliberately concrete questions. *Which* cell, defined by which molecular markers and which anatomical address? *How many* of them are there in a healthy brain, and by what method do we know? *What* does each connect to, and across how many synapses? *How many* are lost, at what stage of the disease, and with what confidence? And *by what mechanistic chain* — which named sequence of molecules — is each population brought down? The answers, assembled, constitute the cellular and synaptic census of the disease.

Three properties, and a new tractability

Three properties of the census make the exercise worth performing rather than a mere tabulation, and a fourth development has, in the last decade, made it newly tractable.

The disease is **selective**. It does not kill neurons at random. Of the roughly eighty-six billion neurons in the brain (Azevedo et al., 2009), the overwhelming majority — the granule cells of the cerebellum, the neurons of the primary sensory and motor cortices, the great mass of subcortical

grey — are spared until very late or entirely. The casualties are drawn from a short list of specific, nameable populations, and the membership of that list is itself a clue to mechanism. The second edition devotes a full chapter (§XVI) to the obverse of this fact — the populations that resist — because the controls prove the case.

The disease is **countable**. Each of those populations has been subjected, over the past thirty years, to design-based stereology — the unbiased counting methods that replaced the biased two-dimensional profile counts of the older literature and made absolute neuron numbers trustworthy for the first time. We therefore possess, for the load-bearing populations, real numbers and real loss fractions, not impressions.

The disease is **ordered**. The populations do not fall together. They fall in a sequence — the same rostro-limbic-cortical sequence that the temporal architecture describes — and the order is reproducible enough that the identity of the dying cell is itself a clock. To know which population is currently being lost is to know, within a decade, where on the arc a given brain has travelled.

What is new is that the census can now be taken in *life* and at *molecular resolution*. Synaptic-vesicle positron-emission tomography counts synapses in the living patient; single-nucleus RNA sequencing counts, and names, the vulnerable cell types in atlases now comprising millions of cells from hundreds of brains. The first edition's census was an autopsy census of cells and synapses; this edition's is a census of cells, synapses, *and molecular identities*, two of them measurable before death. After a chapter on the instruments by which all of this counting is done, we proceed station by station — from the first neuron to fall to the last synapse to be silenced — and then ask what the whole count means.

II. The Instruments of the Census

How a neuron is counted

A census is only as trustworthy as its method, and the history of neuron counting in Alzheimer's disease is in large part a history of correcting for method. The older literature counted *profiles* — neuronal cross-sections visible in a thin histological section — and converted them to densities. This is biased in ways that matter, and the bias is not small: profile counts deviate from true number by amounts that, across the review literature, range from roughly fifteen to sixty per cent depending on tissue and cell geometry (Coggeshall & Lekan, 1996), because a profile count over-represents large cells, and the correction Abercrombie proposed in 1946 only partially repairs a quantity — number — that is intrinsically three-dimensional and cannot be recovered from two-dimensional silhouettes without assumptions (Abercrombie, 1946).

The correction was the design-based, or unbiased, stereology developed across the 1980s and 1990s, whose validity is built into the geometry of the sampling rather than into assumptions about the tissue (Schmitz & Hof, 2005). Its elementary probe is the disector (Sterio, 1984): two parallel planes a known distance apart, in which one counts the particles that appear in a sampling section but not in a look-up section — a rule that yields a count independent of particle size, shape, and orientation. Built upon it, the optical fractionator samples a known fraction of a structure's volume with three-dimensional counting frames and counts whole cells under strict rules, returning an absolute number that is unaffected by lost caps, overprojection, and tissue shrinkage before, during, or after processing; in practice, counting on the order of one to two hundred cells per specimen suffices for adequate precision (West, Slomianka & Gundersen, 1991). The companion Cavalieri estimator measures a structure's total volume without assuming its shape, by point-counting on systematic sections (Gundersen & Jensen, 1987). The precision of any such estimate is captured by the coefficient of error, itself predictable from the sampling data (Gundersen & Jensen, 1987).

The deepest methodological lesson of this literature is the one most often ignored: **density is not number**, and in a disease that atrophies the brain the difference is decisive. Because a density is a number divided by a reference volume, and because atrophy, oedema, and differential shrinkage all change the reference volume, a density can rise, fall, or hold steady with no change whatever in the true number of cells — the "reference trap" (Braendgaard & Gundersen, 1986). A study that reports neuronal density in an atrophic Alzheimer cortex and infers cell loss from it may be measuring the shrinkage of the surrounding neuropil rather than the death of any neuron. Essentially every load-bearing count in this paper rests on absolute, design-based estimates for exactly this reason.

How a synapse is counted

The synapse is harder to count than the soma, and the difficulty is worth respecting, because the synapse is the unit that matters most. Four methods underwrite the figures in this paper. Electron microscopy counts synapses directly, by their ultrastructure, applying the disector rule in the electron micrograph — the gold standard, laborious, and the basis of the biopsy counts of DeKosky and Scheff and the stereological synapse counts of the Scheff series. Immunohistochemical densitometry quantifies a presynaptic protein, classically synaptophysin or synapsin, as a proxy for synaptic density — the basis of the Terry correlations. Array tomography reconstructs synapses in three dimensions from ribbons of ultrathin sections subjected to repeated rounds of multi-antibody immunofluorescence; a panel of around seventeen antibodies can discriminate several glutamatergic synapse subtypes from GABAergic ones at scale, identifying immunopositive puncta as synaptic proxies (Micheva et al., 2010). And volume electron microscopy now reconstructs entire blocks of neuropil at nanometre resolution, itemizing every axon, dendrite, spine, synapse, and vesicle within them and refuting, along the way, the convenient assumption that connectivity can be inferred from proximity (Kasthuri et al., 2015).

The living census, and the molecular census

Two instruments postdate the first synapse counts and have changed what a census can be. The first images synapses in the living brain. Synaptic vesicle glycoprotein 2A (SV2A) is expressed at roughly five copies per synaptic vesicle across virtually all synapses, and the positron-emitting ligand [11C]UCB-J — validated against synaptophysin in primate and in resected human epileptic tissue — renders synaptic density visible in vivo (Finnema et al., 2016). For the first time the synaptic census can be taken in a patient who is still able to be asked how much they remember. The second instrument names the casualties. Single-nucleus RNA sequencing partitions a piece of cortex into its constituent transcriptomic cell types and counts the relative abundance of each; applied to the Alzheimer brain in atlases that now span millions of nuclei from hundreds of donors (Mathys et al., 2019, 2023; Gabitto et al., 2024), it has converted the question "which neuron dies" from a morphological guess into a molecular identification. The instruments are summarized below; the census proper then begins.

Instrument	What it counts	Principal strength	Principal caveat	Source
Optical fractionator	absolute neuron number	unbiased by size, shape, shrinkage	labour-intensive; needs whole region	West et al. 1991
Cavalieri estimator	absolute volume	shape-free; pairs with fractionator	section-interval dependent	Gundersen & Jensen 1987
Profile / density counts	density (number / volume)	fast, historical	the reference trap; ~15–60% bias	Coggeshall & Lekan 1996
EM disector	synapses (ultrastructural)	gold standard for synapses	tiny sampled volumes	DeKosky & Scheff 1990
Array tomography	synapse subtypes (proxy)	molecular subtyping at scale	puncta, not EM-confirmed contacts	Micheva et al. 2010
SV2A PET ([11C]UCB-J)	synaptic density, in vivo	living, longitudinal, clinical	reference-region & partial-volume dependent	Finnema et al. 2016
snRNA-seq atlas	cell-type relative abundance	names the vulnerable cell molecularly	abundance, not absolute count	Gabitto et al. 2024

Table 1. The instruments of the census — what each method counts, and cannot.

The ledger

The full census is summarized in the ledger below; the chapters that follow defend each line, giving for each population its molecular identity, its synaptic commerce, and the mechanistic chain that destroys it. The ledger is deliberately conservative — baselines are given as method-dependent ranges, and where a loss is contested the entry says so.

Population	Standing number	Documented loss	Earliest stage detected	Primary source
Locus coeruleus (noradrenergic)	~20–50k / side	~30% by MCI; ~60% in AD	Braak 0–I (pretangle, 3rd decade)	German 1992; Kelly 2017; Theofilas 2017
Dorsal raphe (serotonergic)	—	~39%; effect size d≈1.8	pretangle before transentorhinal	Aletrino 1992; Lyness 2003; Grinberg 2009
Nucleus basalis (Ch4, cholinergic)	~210,000 / hemisphere	>75% (end-stage)	preserved to MCI, then falls	Gilmor 1999; Whitehouse 1982
Entorhinal layer II (stellate)	~650,000	~60% (very mild) › ~90% (severe)	CDR 0.5 (very mild)	Gómez-Isla 1996
Hippocampal CA1 (pyramidal)	~14 million	~48–68%	symptomatic (spared preclinically)	West 1994 / 2004
Layer III/V projection pyramids	large (>350 µm2) cells	>90% of NF-rich subset (area 9)	with NFT, not plaque	Bussière 2003
Association cortex (sup. temporal sulcus)	—	>50%; exceeds tangle count manyfold	with disease duration	Gómez-Isla 1997
RORB+ entorhinal excitatory subtype	—	selective early depletion	Braak 2 (molecular)	Leng 2021
SST+ inhibitory subtypes	—	early supragranular loss	early pseudoprogression	Mathys 2023; Gabitto 2024
Parvalbumin interneuron	~40% of INs (Rudy 2011)	~60% immunoreactivity (hippocampal; neocortical soma spared; contested, functional)	late	Brady & Mufson 1997
Perineuronal net (aggrecan–brevican)	enwraps ~60–80% of PV	extensive, plaque-proportional	Phase III	Celio 1986; Crapser 2020
Neocortical synapse (the unit)	~150 trillion	~18% (MCI) › ~55% (CA1, mild AD); in vivo ~17–20% (hipp.)	MCI	Terry 1991; Scheff 2007; Chen 2018

Table 2. The census of the dying — the load-bearing cellular and synaptic casualties of Alzheimer's disease.

With the instruments stated, the census proper begins.

III. The First to Fall The Coerulean Neuron

Identity

The first neuron to show Alzheimer-type pathology is among the most distinctive in the brain. The noradrenergic neuron of the locus coeruleus is defined by its catecholaminergic enzymatic machinery — tyrosine hydroxylase and dopamine-β-hydroxylase, the synthetic enzymes for noradrenaline, and the noradrenaline transporter that recovers it — and by a feature visible to the naked eye: the dense blue-black pigment neuromelanin, the polymerized by-product of catecholamine metabolism, which accumulates across the lifespan and gives the nucleus its name. Many of these neurons co-express galanin. The cell is autonomously pacemaking, firing tonically at roughly one to three hertz throughout waking life and modulating that rate with arousal, and it is this ceaseless activity, sustained over decades, that sets the metabolic terms of its destruction.

The standing population

Counted as tyrosine-hydroxylase-positive, neuromelanin-bearing cells, each locus coeruleus holds on the order of twenty thousand neurons in young adulthood (Manaye et al., 1995); counted inclusively, nearer fifty thousand (Theofilas et al., 2017). It is, by either count, a tiny nucleus — a few tens of thousands of cells out of eighty-six billion, less than one neuron in a million — and yet from it long, thin, sparsely myelinated axons ascend, branching into varicose fibres that reach virtually the entire forebrain.

Synaptic commerce

The coerulean neuron's mode of connection is as distinctive as its chemistry. It signals very largely by *volume transmission*: its varicose boutons release noradrenaline not into discrete one-to-one synaptic clefts but diffusely into the parenchyma, bathing wide territories in noradrenergic tone. A single neuron thereby influences enormous numbers of downstream cells, including the microglia, which express the β2-adrenergic receptor and listen to coerulean tone as a standing brake on their own activation. The relevant "synapse," in other words, is partly a chemical atmosphere rather than a wire — which is exactly why the loss of these few thousand cells deregulates territories vastly larger than their number would suggest.

The toll, and the three curves

The coerulean census is the clearest demonstration in the disease that *volume loss, functional loss, and cell death are three different curves*. Stereology across Braak stages shows that the nucleus loses volume early and almost linearly — on the order of eight per cent per Braak stage, with roughly a quarter of its volume gone before clinical onset — while its actual *neuron number* is comparatively preserved through the early-to-middle stages and only declines significantly from Braak stage III onward, accelerating thereafter (Theofilas et al., 2017). Counted across the clinical continuum, the population falls by roughly thirty per cent already at the transition into mild cognitive impairment and by a further quarter into established disease (Kelly et al., 2017); disease-specific stereology places the loss in established Alzheimer's at around sixty per cent, concentrated in the rostral and middle thirds of the nucleus with relative caudal sparing (German et al., 1992). That the cell is sick, atrophic, and pathology-bearing for decades before it dies is precisely the "clinically silent ignition" the temporal architecture predicts — and it is quantified at the level of the single accumulating lesion: at Braak stage 0, fully **7.9 per cent** of locus-coeruleus neurons already bear hyperphosphorylated-tau pretangle inclusions (Ehrenberg et al., 2017), pathology smouldering in the cell for years before any decline in its number.

The mechanistic chain

Why this cell first? Because it lives perpetually at the ceiling of its metabolic capacity, with no reserve to spend on the slow accumulation of unrepaired damage. The destructive chain is the one detailed for Phase I in the companion work: hyperactivation of PARP-1 in response to accumulating DNA damage depletes NAD+, starving the sirtuins and crippling mitochondrial biogenesis; the obstruction of mitochondrial protein import as Aβ binds the import channel TOM40 (Devi et al., 2006) leaves damaged mitochondria unrepairable; and the PINK1/Parkin mitophagy that should clear them is itself defeated, both because PINK1 import depends on the channel that is now blocked and because the autophagy–lysosomal apparatus downstream is failing. The terminal morphology is the flower-like, autolysosome-swollen neuron named PANTHOS, and the plaque that forms where such a neuron ruptures is its gravestone, not its cause (Lee et al., 2022). The coerulean neuron is killed by the failure of its own quality control under a metabolic load no other cell sustains for so long.

IV. The Aminergic Chorus — The Raphé, the Nigra, and the Subcortical Pretangle

The brainstem as the true origin

The locus coeruleus does not begin the disease alone. The staging work that overturned the cortical-origin assumption — Braak and colleagues' survey of more than two thousand brains spanning the human lifespan — found Alzheimer-type tau beginning not in the entorhinal cortex but in the locus coeruleus and its brainstem neighbours, in subcortical stages that *precede* any cortical involvement, with the first neocortical plaques appearing only after this brainstem tauopathy is established and, in a minority of people, already in the fifth decade of life (Braak et al., 2011); in individuals under thirty, the pretangle tau that confines itself to subcortical sites lies overwhelmingly in the coeruleus/subcoeruleus complex, in brains almost entirely free of amyloid (Braak & Del Tredici, 2011). The disease's earliest countable lesion is therefore a subcortical, aminergic one, and the locus coeruleus is the first voice in a chorus.

The serotonergic neuron of the dorsal raphe

The second voice is serotonergic. The dorsal raphe nucleus, the brain's principal source of ascending serotonin, is among the most severely depleted nuclei in the disease: a meta-analysis of eleven studies places its neuron loss at an effect size of roughly 1.8 standard deviations — some three times that of the substantia nigra, and approaching that of the locus coeruleus itself (Lyness, Zarow & Chui, 2003). In absolute terms the loss is on the order of forty per cent (Aletrino et al., 1992). Two findings give it particular weight. First, the loss is not an artefact of the depression that so often accompanies Alzheimer's: patients with the disease have markedly fewer dorsal-raphe serotonergic neurons than controls whether or not they were depressed, while primary major depression alone produces no such loss (Hendricksen et al., 2004). Second, and remarkably, the dorsal raphe's tau pathology may be the earliest cortical-bound lesion of all: phospho-tau neurofibrillary changes appear in a subnucleus of the dorsal raphe in every brain at Braak stage I or above, and in more than a fifth of brains staged at Braak 0 — that is, before the transentorhinal cortex is involved (Grinberg et al., 2009). Quantified against the coeruleus, the raphe lags only slightly: at Braak 0, 2.6 per cent of dorsal-raphe neurons bear pretangle inclusions against the coeruleus's 7.9 per cent (Ehrenberg et al., 2017). The serotonergic neuron is, with the noradrenergic, a founding casualty.

The dopaminergic and histaminergic voices

The chorus extends further, though here the census must be careful to distinguish Alzheimer's from its neighbours. The substantia nigra, the dopaminergic nucleus whose collapse defines Parkinson's disease, is only mildly affected in Alzheimer's — an effect size of roughly 0.6, the smallest of the four great subcortical nuclei, such that a heavily depleted nigra in a demented brain points toward Lewy-body co-pathology rather than Alzheimer's itself (Lyness, Zarow & Chui, 2003). But the dopaminergic projection that matters for memory may be the other one: in a transgenic model, selective degeneration of the *ventral tegmental* dopaminergic neurons — not the nigral ones — appears at pre-plaque stages and reduces dopaminergic outflow to the hippocampus and the reward circuitry, with correlated deficits in CA1 plasticity, memory, and motivation (Nobili et al., 2017). In humans the evidence is volumetric rather than stereological — ventral-tegmental volume on magnetic-resonance imaging tracks hippocampal volume and episodic memory (De Marco & Venneri, 2018) — and a defensible post-mortem neuron count for the human ventral tegmentum in Alzheimer's does not yet exist; we flag the gap rather than paper over it. The histaminergic neurons of the tuberomammillary nucleus complete the chorus: they are reduced in number and laden with tangles in the Alzheimer brain where age-matched controls have none (Nakamura et al., 1993), though here too a precise loss fraction is not reportable, and the nucleus's wake-promoting neurons are in fact relatively *preserved* in Alzheimer's compared with progressive supranuclear palsy (Oh et al., 2022) — a caution against overstating its destruction.

The meaning of the chorus

The aminergic chorus matters out of all proportion to its numbers. These nuclei together contain a vanishing fraction of the brain's neurons, yet each broadcasts a single neurotransmitter across vast territories by volume transmission, so that the early, quiet loss of a few tens of thousands of cells withdraws noradrenaline, serotonin, dopamine, and histamine from the entire forebrain at once. The prodromal phenomenology of Alzheimer's — disturbed sleep, blunted arousal, depressed mood, autonomic instability, anhedonia — is, on this reading, the audible early failure of the chorus, decades before the cortex is counted among the dead. Whether this early subcortical tauopathy inevitably becomes Alzheimer's disease, or in some individuals represents a primary age-related tauopathy that never progresses, remains genuinely unresolved (the staging *order* is robust; the deterministic interpretation is not) — a caveat we carry forward honestly.

V. The Cholinergic Forebrain — The Nucleus Basalis and Its Cortical Reach

Identity and architecture

If the aminergic chorus sings from the brainstem, the cholinergic system answers from the base of the forebrain, and its destruction is the most severe of any single projection population in the disease. The cholinergic projection neurons of the basal forebrain are organized into four sectors in the scheme of Mesulam and colleagues: Ch1 in the medial septal nucleus and Ch2 in the vertical limb of the diagonal band, which together supply the hippocampus; Ch3 in the horizontal limb of the diagonal band, supplying the olfactory bulb; and Ch4, the great nucleus basalis of Meynert, a sheet of large, deeply staining magnocellular neurons in the substantia innominata that contains the large majority of the system's cells and projects acetylcholine across the entire cortical mantle and the amygdala (Mesulam et al., 1983; Mesulam & Geula, 1988; Liu et al., 2015). Like the aminergic neurons, the cholinergic projection cell is large, metabolically expensive, and diffusely broadcasting; like them, it depends for survival on trophic support — in its case, nerve growth factor retrogradely supplied from its cortical targets through the TrkA and p75 receptors.

The standing population and its toll

A defensible modern stereological baseline for the nucleus basalis is on the order of two hundred and ten thousand choline-acetyltransferase-positive neurons per hemisphere in the cognitively normal elderly (Gilmor et al., 1999) — a figure worth stating precisely, because the original demonstrations of cholinergic loss reported only the loss fraction, and because where the first edition of this census, following those founding studies, left the basal-forebrain baseline "not cleanly established," modern design-based stereology now lets us state it. That fraction is severe: the founding studies described a "profound and selective" degeneration of the nucleus basalis exceeding seventy-five per cent of its neurons in advanced disease (Whitehouse et al., 1982), and classical morphometry placed the loss at around seventy per cent in Alzheimer's (against seventy-seven per cent in Parkinson's and forty-seven per cent in Korsakoff's psychosis) (Arendt et al., 1983). This was the observation that launched the cholinergic hypothesis and, with it, the cholinesterase-inhibitor therapeutics that remain in clinical use four decades later.

Does the cell die, or fall silent?

The severity of those end-stage figures concealed, for years, a subtler and more hopeful truth that the census must now state. When the cholinergic neurons of the nucleus basalis are counted not at autopsy in advanced disease but across the early clinical continuum, their *number* is essentially preserved: there is no significant difference in choline-acetyltransferase- or vesicular-acetylcholine-transporter-positive neuron counts among the cognitively normal, the mildly impaired, and those with mild Alzheimer's disease — only a non-significant reduction of roughly fifteen per cent (Gilmor et al., 1999). The early cholinergic deficit is therefore not, in the main, a deficit of cells but a deficit of cholinergic *phenotype*: a progressive dedifferentiation driven by failing nerve-growth-factor signalling, in which the neuron survives but downregulates the machinery that made it cholinergic (Mufson et al., 2008). The point is sharpened by an apparent paradox — cortical and hippocampal choline-acetyltransferase activity is not reduced, and may even be transiently *up*-regulated, in mild cognitive impairment, falling only in established disease (DeKosky et al., 2002). The cholinergic system, in short, first falls silent and only later dies, and the magnitude and timing of the transition from atrophy to death remain genuinely unsettled. We record the honest tension rather than resolve it by fiat: the >75 per cent figure is real but end-stage; the cell is largely present, and partly recoverable, through the years in which the patient is merely impaired. The cholinergic neuron is not, however, clean proof that cell number is uncoupled from cognition: in the very cohort in which its number was preserved, that number still correlated with the Mini-Mental State Examination. Basal-forebrain atrophy is, accordingly, detectable on magnetic-resonance imaging from the earliest stages of impairment and most pronounced in the posterior nucleus basalis (Grothe et al., 2010, 2012), a volumetric shadow of a phenotypic withdrawal that precedes frank loss.

VI. The Cortical Bridgehead The Entorhinal Stellate Cell

Identity and the gateway it guards

When the disease crosses from brainstem to cortex — the transition the companion paper assigns to the first bridge, the coerulean projection carrying both the withdrawal of the noradrenergic brake and a stream of templated tau — it makes landfall at a specific and famous cell: the stellate (and pyramidal) projection neuron of layer II of the entorhinal cortex. This is the origin of the perforant path, the great fibre bundle that carries cortical information into the hippocampus, and it is therefore the literal gateway of memory: essentially everything the neocortex tells the hippocampus passes through these cells. Their position at the head of the hippocampal circuit makes them the single most consequential small population in the disease.

The standing population and its toll

Layer II of the entorhinal cortex holds roughly six hundred and fifty thousand neurons in the healthy aged brain; the whole entorhinal cortex holds on the order of seven million (Gómez-Isla et al., 1996; West & Slomianka, 1998). The figure that made this cell famous is its loss fraction in the *mildest* clinically detectable disease. In individuals at a Clinical Dementia Rating of 0.5 — the threshold of detectable impairment — layer-II entorhinal neurons are already reduced by about sixty per cent, the deeper layer IV by about forty per cent, and the entorhinal cortex as a whole by about thirty-two per cent; in severe disease the layer-II loss reaches roughly ninety per cent (Gómez-Isla et al., 1996). Sixty per cent of the gateway is gone before the disease is unambiguously diagnosable. No statistic in the cellular census more sharply contradicts the intuition that early Alzheimer's is a mild disease: at the level of this one critical population, "very mild" dementia is already a near-decimation.

The molecular identity of the gateway

The first edition could name this cell only by its layer and its projection; the single-cell era now names it by its transcriptome, and the identification is one of the most important results in the modern cellular pathology of the disease. Sequencing the entorhinal cortex across Braak stages, Leng and colleagues found that the selectively vulnerable excitatory neurons of the superficial entorhinal layers are marked by the transcription factor **RORB**, and that specific entorhinal excitatory subpopulations among them are substantially depleted — on the order of half — already by Braak stage 2, with little further loss thereafter, an early and sub-type-specific decimation, while phospho-tau accumulates preferentially in the RORB-positive cells (Leng et al., 2021). The gateway neuron, in other words, is not merely defined by where it sits but by a molecular identity that marks it for death in advance, and that identity is shared by a small number of related excitatory subtypes that fall together and early. This is the molecular legibility of vulnerability, made concrete at the disease's cortical point of entry.

The synaptic consequence, and the count that indicts the tangle

The death of the entorhinal stellate cell is experienced by the hippocampus as deafferentation: the perforant-path synapses onto the granule cells of the dentate gyrus, which terminate in the outer molecular layer, are withdrawn as their presynaptic partners die. The Scheff series quantified this directly: synapse numbers in the dentate outer molecular layer are significantly reduced in early Alzheimer's, and even at the mild-cognitive-impairment stage three-quarters of individuals already sit below the unimpaired group mean (Scheff et al., 2006). The first synaptic casualty of the cortical disease is the very connection that lets experience enter memory. And the entorhinal census supplies the disease's most important quantitative argument *against* the sufficiency of the tangle as the proximate cause of death: in high-order association cortex, more than half the neurons are lost, and the amount of neuronal loss *exceeds, by manyfold, the number of neurofibrillary tangles ever accumulated* (Gómez-Isla et al., 1997). If neurons died only by becoming tangles, the two counts would track; instead the dead outnumber the tangled many times over. Indeed, even at the disease's end, stereology finds that on the order of seventy-three per cent of the profiles in entorhinal layer II — and seventy-seven per cent in CA1 — remain viable neurons (Hof et al., 2003): the tangle marks a process that kills by other means and on a longer timetable than tangle formation itself.

VII. The Limbic Resident The Hippocampal Pyramidal Neuron

Identity and selectivity within the hippocampus

The hippocampus is not lost as a whole; it is lost subfield by subfield, and the selectivity is itself informative. The principal casualty is the pyramidal neuron of the CA1 field — a glutamatergic projection neuron receiving the Schaffer-collateral input from CA3 and supplying the chief hippocampal output to the subiculum and entorhinal cortex. CA1 is the hippocampal subfield most specifically vulnerable to Alzheimer's disease, and its vulnerability is disease-specific rather than age-related: in normal ageing CA1 is largely spared, so that CA1 loss is a signature of the disease and not of the years (West et al., 1994). Its neighbours fall on a steep gradient — a fact we develop fully in the chapter on sparing (§XVI), but preview here because the gradient is part of CA1's own census.

The standing population and its toll

The healthy CA1 field holds on the order of fourteen million pyramidal neurons (West et al., 1994). In Alzheimer's disease that population is reduced by roughly half to two-thirds — a final CA1 count near 4.4 million against some 14 million in normal ageing in the original Lancet series (a deficit of about sixty-eight per cent), and a loss of about forty-eight per cent against matched controls in the same group's later, refined stereology, in which the subiculum lost about twenty-four per cent and the hilus about fourteen, while the dentate granule layer and the CA3–CA2 fields were not significantly reduced at all (West et al., 1994, 2004). The defensible statement is that CA1 loses on the order of half to two-thirds of its pyramidal neurons in established disease, more than any other hippocampal subfield, and the range — 48 to 68 per cent across two cohorts — should be stated openly rather than averaged into false precision. Critically, the same group found *no* significant CA1 loss in preclinical disease — brains bearing Alzheimer pathology without cognitive decline — which places CA1 death on the symptomatic, not the silent, side of the arc (West et al., 2004): the neuron dies as the patient declines, not decades before.

Synaptic commerce and its loss

Before the CA1 pyramidal soma dies, its synapses are stripped, and they are stripped earliest at the input the disease attacks first. Stereological synapse counts in the CA1 stratum radiatum — the Schaffer-collateral field — show that synapse number falls by roughly fifty-five per cent in mild Alzheimer's disease relative to unimpaired controls, with the mild-cognitive-impairment stage already down by some eighteen per cent (Scheff et al., 2007). The ordering matters: synapse number in these counts correlates with cognitive performance but shows *no* relationship to Braak stage or APOE genotype (Scheff et al., 2006, 2007), a recurring signature of the census — the synaptic casualty tracks the symptom, not the stainable lesion.

The chain

The chain that kills the CA1 pyramidal neuron is the quality-control collapse of Phase I now playing out in a second cell population, compounded by the immune attack of Phase II. The endosomal–lysosomal trafficking apparatus jams — the retromer hub fails, intraneuronal Aβ accumulates in late endosomes and multivesicular bodies — even as the disinhibited, post-homeostatic microglia of the surrounding tissue begin to tag and strip the cell's synapses by the complement and C4d pathways detailed in §X. The pyramidal neuron is caught between an intrinsic failure of its own housekeeping and an extrinsic withdrawal of synaptic support, and it is the conjunction, not either alone, that brings it down.

VIII. The Great Projection Neurons Layer III and V Pyramidal Cells

A vulnerability written in axonal length

The entorhinal stellate cell and the CA1 pyramid are limbic neurons; but Alzheimer's is, finally, a disease of the association cortex, and there the census identifies a population whose vulnerability follows from its very architecture. The large pyramidal neurons of cortical layers III and V that furnish the long corticocortical association pathways — the wiring that binds distant cortical regions into the distributed networks of cognition — are selectively and severely lost. These are big cells: the loss concentrates on those with perikaryal cross-sectional areas above roughly three hundred and fifty square micrometres, and it falls on layers III and V specifically (Hof, Cox & Morrison, 1990). They are distinguished by a molecular marker, the non-phosphorylated neurofilament protein recognized by the antibody SMI-32, and the magnitude of their loss is extreme: in the prefrontal association cortex (area 9) of end-stage disease, more than ninety per cent of the neurofilament-rich subset is gone, with layer Va more severely affected than layer IIIc, and these neurons are far more likely than their neighbours to develop neurofibrillary tangles and to shrink as they do (Bussière et al., 2003). Their loss, like that of the great projection neurons generally, correlates with tangle counts and not with neuritic-plaque burden — the same dissociation seen throughout the census.

The principle of selective connectivity

Why these cells? Because the feature that makes a neuron useful to a distributed cognitive network — a long, energetically costly axon projecting across the cortical mantle — is the feature that makes it vulnerable. Morrison and Hof drew the general principle: Alzheimer's disease preferentially targets the large, long-axon, corticocortically projecting pyramidal neurons, while locally projecting interneurons and the neurons of primary sensory and motor cortex are relatively spared, and ageing itself causes little of this neuronal death (Morrison & Hof, 1997). The neurofilament enrichment that marks the vulnerable cells is itself a correlate of long-range projection: in the macaque, the long ipsilateral association pathways are heavily neurofilament-enriched while short corticocortical, callosal, and limbic projections are much less so (Hof, Nimchinsky & Morrison, 1995) — a relationship inferred for the human cortex by homology rather than measured directly, a caveat worth keeping. The consequence is that the disease does not merely kill cells; it *disconnects networks*, severing the long-range association fibres on which distributed cognition depends, which is why the superior temporal sulcus — a high-order association region — loses more than half its neurons in the disease, again by an amount that exceeds the tangles formed there manyfold (Gómez-Isla et al., 1997). When neuron and tangle counts are set against the clinical record, neuron loss in these association regions explains, in that cross-sectional cohort, on the order of eighty per cent of the variance in the Mini-Mental State Examination, while amyloid burden is, with one regional exception, non-predictive (Giannakopoulos et al., 2003).

A disambiguation

One population must be excluded by name, because it is easy to assume it belongs. The von Economo neurons — the large, distinctive projection cells of the anterior cingulate and frontoinsular cortex — are a target of behavioural-variant *frontotemporal* dementia, in which they are lost by some three-quarters, but they are *not* selectively lost in Alzheimer's disease, which leaves their number and morphology essentially normal even amid extensive local tangle pathology (Seeley et al., 2006; Kim et al., 2011). The contrast is instructive: selective vulnerability is disease-specific as well as cell-specific, and the same neuron may be a casualty in one dementia and a bystander in another.

IX. The Molecular Identity of the Doomed

From morphology to transcriptome

For most of the disease's history the question "which neuron dies" could be answered only by morphology and location — a large pyramidal cell here, a stellate cell there. In the last decade the single-nucleus transcriptomic atlas has made it possible to answer the question in the cell's own molecular language, and the answer it returns is the strongest evidence the census can offer that the casualty list is written in advance. This chapter assembles that evidence, because it does not belong to any single anatomical station: it is a cross-cutting account of *what kind* of cell the disease selects, read across the whole cortex.

What the atlases found

The atlases are large and recent. The first single-nucleus survey of the Alzheimer prefrontal cortex profiled some eighty thousand nuclei from forty-eight individuals and established that the disease's transcriptomic changes are early and highly cell-type-specific, with a recurrent perturbation of myelination programmes (Mathys et al., 2019). It was followed by an atlas of 2.3 million cells from 427 individuals — the largest single-region survey of the aged human cortex assembled — which identified specific inhibitory neuron subtypes, belonging to the somatostatin (SST) class, that are selectively depleted as pathology rises and are correspondingly over-represented in individuals who remained cognitively resilient (Mathys et al., 2023). And the Seattle Alzheimer's Disease Atlas reconstructed the middle temporal gyrus from 3.4 million nuclei across eighty-four donors at the resolution of a hundred and thirty-nine cell "supertypes," with replication and external validation in millions more (Gabitto et al., 2024). Sorting tangle-bearing from tangle-free neurons directly, a further study sequenced more than sixty thousand single somata from end-stage cortex and resolved twenty neocortical subtypes, finding that neurofibrillary tangles are present in only about six per cent of all neurons at end-stage and that the most tangle-prone excitatory subtypes are specific layer II–V corticocortical cells, with deeper layer IV and layer VI subtypes relatively resistant (Otero-Garcia et al., 2022).

The shape of the molecular census

Three results from this body of work reshape the cellular census. First, the atlases confirm and refine the morphological story: the predominantly vulnerable excitatory neurons are supragranular and long-range — the layer II–III intratelencephalic cells and the RORB-marked entorhinal neurons of §VI — exactly the population the neurofilament and stereological work of §VIII identified by other means. Second, the atlases reveal a vulnerability the morphological census had missed: specific *inhibitory* subtypes, of the SST class, are lost early. The Seattle atlas resolves the disease into two epochs along a pseudoprogression score — an early phase marked by inflammatory microglia, reactive astrocytes, and the loss of SST interneurons, and a late phase marked by the loss of excitatory neurons together with parvalbumin and VIP interneurons — and finds that the SST loss precedes the loss of the very layer II–III excitatory neurons that bear the highest tangle burden (Gabitto et al., 2024). Of the hundred and thirty-nine supertypes, about a quarter are significantly affected, and the affected neurons are overwhelmingly supragranular. Third — and most telling for the census's central thesis — the atlas finds that as the disease advances, the number of NeuN-positive neurons declines *linearly* while tangle-bearing neurons and amyloid plaques accumulate *exponentially* (Gabitto et al., 2024): cell death and lesion burden run on different curves, exactly as the tangle-exceeds-loss arithmetic of §VI predicted from autopsy counts alone.

The signature, and an honest dispute

What makes a cell doomed? The atlases suggest the answer is partly transcriptional: the vulnerable SST supertypes are nearly indistinguishable from their spared siblings except in specific programmes — among them an early downregulation of nerve-growth-factor signalling (*NGF*) and of the membrane metalloendopeptidase *MME* (neprilysin, an amyloid-degrading enzyme) (Gabitto et al., 2024) — which begins to make "vulnerability" a measurable molecular state rather than a fate inferred after the fact. But the census must record a genuine dispute at the heart of this literature. The single-soma study found that tangle-bearing and tangle-free neurons of the dominant excitatory subtypes showed *highly similar* susceptibility to death, sharing a common stress signature centred on the synaptic-vesicle cycle, and concluded that the tangle is more nearly a marker of cellular stress than its executioner (Otero-Garcia et al., 2022). The empirical findings are solid; the causal inference is the uncertain part — the study's own data show a small but significant excess death-susceptibility among certain interneurons, and its cross-sectional, end-stage design cannot exclude the survivor bias inherent in counting only the cells that remain. We present the molecular census, in short, as the most powerful new instrument of the casualty count and as a field still arguing, productively, about what its own numbers mean.

X. The Custodian Turned The Microglion

A different kind of census entry

The microglion requires a different accounting, because it is not, in the main, *destroyed*: it is *converted*. The pathology of the microglion is a change of state, not a change of number, and so its census entry quantifies a transformation rather than a loss. But it belongs at the centre of the cellular architecture for a reason the temporal companion makes plain: the microglion is the agent by which most of the disease's *synaptic* casualties are actually inflicted. If the neurons are the victims of the census, the microglion is, in large part, its executioner — and the single-cell atlases now place its activation, alongside reactive astrogliosis, at the very *start* of the disease's molecular timeline (Gabitto et al., 2024).

Identity — the homeostatic signature

The healthy microglion is defined by a transcriptional signature maintained by TGF-β/SMAD signalling: P2RY12, TMEM119, CX3CR1, SALL1, HEXB, and a larger companion ensemble (Butovsky et al., 2014). This signature is a behavioural programme, not a label — it specifies a cell that surveys, supports, and prunes with restraint. P2RY12 couples the cell to extracellular ATP and ADP gradients; CX3CR1, ligated by neuronal fractalkine, carries a tonic anti-inflammatory signal. The loss of this signature *is* the Phase II lesion, and it is the loss of a state, measurable as the down-regulation of these markers, that the census records here rather than a fall in cell count.

The post-homeostatic trajectories

Having exited homeostasis, the microglion enters one of a family of post-homeostatic states, each defined by its own markers. The disease-associated microglia (DAM) of Keren-Shaul and Amit pass from a TREM2-independent first stage into a TREM2-dependent second stage marked by APOE, CST7, the cathepsins CTSB and CTSD, LPL, SPP1, ITGAX, CLEC7A, and TYROBP (Keren-Shaul et al., 2017). The lipid-droplet-accumulating microglia (LDAM) of Marschallinger up-regulate PLIN2, DGAT2, and ACSL1 as their cytoplasm gridlocks with lipid, becoming at once metabolically senescent and primed for inflammasome assembly (Marschallinger et al., 2020). The dystrophic microglia of Streit, driven by iron and ferritin accumulation, show cytoplasmic beading, process fragmentation, and spheroid formation as they fragment toward terminal senescence in the company of pretangle tau (Streit et al., 2009). The receptor TREM2 sits at the collision point of these trajectories, coupling lipid and apolipoprotein sensing to phagocytic and metabolic competence (Ulland et al., 2017) — which is why it recurs at every level of the disease.

Synaptic commerce — the executioner's arms

The microglion's relevant commerce, for this census, is its capacity to remove synapses, and the effector arms are quantified and causal. Post-homeostatic microglia deposit complement C1q on vulnerable synapses, activating the classical cascade through C4 to the C3 and C4d "eat-me" opsonins that license CR3-mediated engulfment; genetic removal of C1q or C3 is protective, and complement-mediated synapse loss is demonstrable in Alzheimer models *before* and independently of plaque deposition (Stevens et al., 2007; Hong et al., 2016). A parallel, cell-autonomous arm requires no engulfment at all: C4d, a high-affinity ligand for the postsynaptic LilrB2 receptor, drives synaptic withdrawal directly (Werneburg et al., 2025). These are the same arms that, deployed with restraint in the homeostatic state, *maintain* the very synapses they now dismantle. Phase II is therefore not the acquisition of a harmful cell type but the loss of the governor on a cell the brain has always possessed — and the cost of that loss is paid, synapse by synapse, by the neurons of the preceding census entries.

XI. The Reactive Astrocyte The Tripartite Partner Withdrawn

A second custodian, a second transformation

The microglion is not the only glial custodian whose conversion the census must record. The astrocyte — the most numerous glial partner of the synapse, the third element of the "tripartite synapse" and the brain's principal buffer of extracellular glutamate and potassium — undergoes its own state-change in Alzheimer's disease, and like the microglion it is transformed rather than destroyed. The transformation is consequential because the healthy astrocyte is a synaptic life-support system, and its withdrawal removes a service on which the most active neurons most depend.

The toxic conversion and its trigger

The decisive mechanistic finding is that the reactive astrocyte of neurodegeneration is *induced by the activated microglion*. Liddelow, Barres, and colleagues showed that a trio of microglial signals — interleukin-1α, tumour necrosis factor, and the complement component C1q — is together necessary and sufficient to convert resting astrocytes into a neurotoxic reactive state that loses its homeostatic functions (the support of synaptogenesis, of phagocytosis, and of neuronal survival) and actively kills neurons and oligodendrocytes; such astrocytes are abundant in Alzheimer's and the other major neurodegenerations (Liddelow et al., 2017). The census must add two honest qualifications. First, the once-popular binary of "A1" toxic versus "A2" protective astrocytes has been formally deprecated by the field as too simple, and no clean quantitative measure of the abundance of toxic astrocytes in the human Alzheimer brain exists (Escartin et al., 2021); we therefore report the mechanism, not a percentage. Second, whether Alzheimer astrocytes predominantly *hypertrophy* (as the plaque-associated, GFAP-bright astrocyte does) or *atrophy* (as distal astrocytes withdrawing their synaptic coverage appear to, with reductions of a third to a half in astrocytic surface area in a transgenic model) is genuinely region-, stage-, and marker-dependent, complicated by the fact that the standard marker, GFAP, labels only about fifteen per cent of an astrocyte's volume (Kulijewicz-Nawrot et al., 2012). The census records a transformation with two faces, not a single trajectory. That the transformation is, on either face, among the earliest events of the disease is now visible in life: plasma glial fibrillary acidic protein (GFAP) rises with amyloid burden before tau and predicts amyloid-positron-emission-tomography positivity better than several cerebrospinal-fluid markers (Pereira et al., 2021), so that the astrocyte's turning can be read from a tube of blood years before the cortex is counted among the dead.

What is lost when the astrocyte turns

Two losses are quantifiable and matter for the synaptic census downstream. The first is glutamate clearance. The astrocytic glutamate transporter EAAT2 (GLT-1), which performs the bulk of synaptic glutamate uptake and so protects neurons from excitotoxicity, is selectively reduced in the Alzheimer cortex — a post-transcriptional loss specific to EAAT2, with the related transporters EAAT1 and EAAT3 spared and EAAT2 messenger RNA unchanged (Li et al., 1997; Jacob et al., 2007). The withdrawal of glutamate buffering — and, with it, of the potassium buffering on which sustained fast firing depends — exposes exactly the fast-firing, calcium-permeable parvalbumin neuron of §XIII, leaving it to face its own metabolism unbuffered: the astrocytic counterpart to the loss of its perineuronal coat, the same cell stripped of two protective envelopes at once. The second loss is synaptic coverage itself. Even in the healthy brain, astrocytic processes appose only about fifty-seven per cent of hippocampal synapses, and where they do they cover only some forty-three per cent of the synaptic interface (Ventura & Harris, 1999) — a baseline that makes the further withdrawal of coverage in disease a removal of an already-partial protection from the synapses that retain it.

A note on number

The astrocyte also corrects a textbook figure worth stating, because it bears on how we imagine the brain's composition. The human brain holds roughly equal numbers of neuronal and non-neuronal cells overall (Azevedo et al., 2009); within the neocortex specifically, glia outnumber neurons, but only modestly — at a ratio on the order of 1.3 to 1.5 to one, not the tenfold excess of legend — and of those neocortical glia the astrocytes are a minority (around a fifth), the oligodendrocytes the large majority (around three-quarters), and the microglia a few per cent (Pelvig et al., 2008). The custodial cells of the brain are, in number, comparable to the neurons they serve; their pathology is not a matter of how many there are but of what they are doing.

XII. The Iron-Bearer The Oligodendrocyte

Identity and its dangerous cargo

The oligodendrocyte enters the census not for its number — though, as the previous chapter noted, it is in fact the most numerous glial cell of the cortex — but for its chemistry. It is the myelinating glial cell of the central nervous system, and it carries the highest iron concentration of any brain cell type, iron it requires for the lipid synthesis of myelin, and which makes it both metabolically distinctive and, in death, dangerous to its neighbours. The human neocortex contains on the order of one hundred and fifty to one hundred and eighty thousand kilometres of myelinated fibre (Pakkenberg et al., 2003), an immense surface of iron-laden membrane threading the very territory the disease attacks — and the single-cell atlases' recurrent finding of disturbed myelination programmes, present from the earliest transcriptomic changes (Mathys et al., 2019), suggests the oligodendrocyte lineage is perturbed early as well as dangerous late.

The toll and the chain — fuel for the second bridge

The oligodendrocyte's role in the cellular architecture is to supply the inorganic arm of the second bridge, the Proteolytic Turn. When oligodendrocytes die by ferroptosis — the iron-dependent, lipid-peroxidation-driven death modality — they do not die cleanly: their membranes dismantle and release redox-active ferrous iron (Fe2+, liberated from ferritin, from heme, from iron–sulfur clusters) into the surrounding parenchyma. The perineuronal net of the nearby parvalbumin interneuron is an avid iron sink, its sulfate and carboxylate groups binding iron tightly, and an iron-loaded net is a substrate for Fenton chemistry: Fe2+ and hydrogen peroxide generate the hydroxyl radical, a species so reactive that its diffusion radius is on the order of a nanometre, so that it damages whatever holds the iron that made it. The radical fragments the matrix, the fragmentation is self-amplifying, and the oligodendrocyte's death is thereby converted into the chemical demolition of the next, and final, casualty. The oligodendrocyte is not the disease's victim so much as its accelerant.

XIII. The Final Substrate and Its Net — The Parvalbumin Interneuron

Identity — the metronome of the cortex

Every thread of the architecture converges on one cell and the structure that protects it. The parvalbumin-positive (PV) fast-spiking interneuron is the metronome of cortical computation: a GABAergic interneuron that provides the perisomatic inhibition pacing pyramidal-cell firing and that generates the gamma-frequency rhythms (conventionally 30–80 Hz) on which working memory and attention depend. It is built for speed — capable of sustained firing above two hundred hertz (Hu et al., 2014) — and it constitutes roughly forty per cent of all cortical GABAergic interneurons (Rudy et al., 2011). It is also, by virtue of that firing rate, among the most metabolically demanding and oxidatively exposed neurons in the cortex, and it bears, uniquely, calcium-permeable AMPA receptors lacking the GluA2 subunit, which leave it exposed to calcium overload. These features make it the cortical analogue of the coerulean neuron: extravagant, fast, exposed — and dependent for survival on a protective envelope.

The perineuronal net — a census of a structure

That envelope is the perineuronal net, and it deserves its own enumeration, because it, rather than the cell, is the proximate casualty of Phase III. The net is a lattice of extracellular matrix condensed around the soma and proximal dendrites: a backbone of hyaluronan (synthesized by hyaluronan synthases and tethered at the membrane), decorated with the lectican chondroitin-sulfate proteoglycans — aggrecan (the obligatory, highest-density component), brevican, neurocan, and versican — cross-linked by tenascin-R and stabilized by the hyaluronan-and-proteoglycan link proteins HAPLN1 and HAPLN4 (Fawcett et al., 2019). Its chondroitin-sulfate chains carry a position-specific "sulfation code" (4-O, 6-O, and the 4,6-disulfated CS-E) that tunes its function. The majority of cortical PV interneurons are enwrapped by such a net — commonly cited at sixty to eighty per cent, and higher in some regions (Celio, 1986; Härtig et al., 1992) — and the net is at once a structural scaffold, an ion-exchange buffer for the cation fluxes of fast firing, and an antioxidant shield. Strip it, and the cell's own activity begins to poison it.

Synaptic commerce — the arithmetic of pacing

The PV interneuron's power lies in a startling divergence. A single hippocampal PV basket cell innervates on the order of fifteen hundred to twenty-five hundred pyramidal cells, placing a handful of GABAergic boutons on the perisomatic region of each; conversely, a single pyramidal soma receives on the order of sixty perisomatic terminals, of which roughly sixty per cent are of PV origin (Freund & Buzsáki, 1996; Freund & Katona, 2007). This is the anatomical basis of the metronome: a small population of fast cells, each broadcasting inhibition to thousands of principal neurons, can synchronize enormous ensembles into the gamma rhythm. It is also the reason the disease's terminal lesion is so cognitively catastrophic out of proportion to the number of cells involved — to silence one PV basket cell is to release thousands of pyramidal neurons from the timing signal that made their collective computation coherent.

The toll — an honest reconciliation

Here the census must be most careful, because the literature is genuinely divided, and the division — once a simple disagreement — has become, in the single-cell era, a reconciliation worth setting out in full. Three bodies of evidence appear to conflict. The classical neocortical immunohistochemistry of Hof, Morrison, and colleagues found the parvalbumin interneurons of the neocortex *resistant* — no change in their number or size in the prefrontal or inferior temporal cortex (Hof et al., 1991), corroborated by others (Ferrer et al., 1991). The hippocampal immunohistochemistry of Brady and Mufson found an apparent *sixty per cent* reduction of parvalbumin-immunoreactive neurons in the dentate/CA4 and CA1–CA2 fields (Brady & Mufson, 1997). And the single-cell atlas places parvalbumin-interneuron loss firmly among the *late* casualties, in the second epoch of the disease, as a genuine depletion of specific PV supertypes (Gabitto et al., 2024). The reconciliation is threefold. First, region matters: the neocortical PV cell is more resistant than the hippocampal one, so Hof and Brady-Mufson are not in simple contradiction. Second, *what is counted* matters: the hippocampal "loss" is a loss of parvalbumin *immunoreactivity*, and a substantial literature now holds that much of the apparent deficit is a downregulation of parvalbumin expression and a dysregulation of the perineuronal net — a functional silencing — rather than frank death, with PV somata relatively preserved in several models (La Barbera et al., 2024). Third, *timing* matters: the atlas shows PV loss is late, consistent with its being a terminal rather than an initiating event. The honest census therefore records a strong claim and a weak one. *The net* is lost: in Alzheimer's disease and its models, perineuronal nets are extensively degraded in proportion to plaque burden, microglia engulf the damaged matrix, aggrecan appears within human plaques, and the impairment of net integrity *precedes* any loss of the PV cells themselves (Crapser et al., 2020). *The cell* falls late, partly by genuine depletion and partly by functional silencing — and the distinction is the therapeutic crux, because a cell that is silenced may be reawakened, while a cell that is dead cannot.

The functional readout — gamma, and the proof of concept

What the net's loss costs, measurably, is the gamma rhythm. Causal optogenetic work established that driving PV interneurons is sufficient to generate gamma and that silencing them abolishes it (Sohal et al., 2009; Cardin et al., 2009); Alzheimer models show gamma deficits emerging early, before major plaque accumulation, in the modulation of hippocampal firing (Iaccarino et al., 2016). And the same line of work supplies the census's most striking proof that this final lesion is, for a window, functional and reversible: restoring forty-hertz activity — by optogenetic drive of PV interneurons or by non-invasive sensory flicker — reduces amyloid markedly (Aβ40 down some fifty-three per cent and Aβ42 by some forty-five per cent after a single hour of optogenetic gamma in one model) and recruits microglia to the cleared material (Iaccarino et al., 2016). That a rhythm generated by the disease's final-target cell can, when restored, reach back up the chain and clear the pathology of earlier phases is the strongest possible evidence that the parvalbumin–net system is the load-bearing node of the entire architecture.

The chain

The chain that digests the net is the three-armed Proteolytic Turn, converging on the aggrecan–brevican coat: the lipid-driven proteolytic switch (NLRP3 › IL-1β › MMP-9 and the ADAMTS proteases), the iron-catalysed Fenton chemistry supplied by the dying oligodendrocyte, and the complement priming (C1q › C4 › C4d › CR3) that marks the matrix for phagocytic stripping. Three chemistries, one structure — and when that structure is gone, the most exposed neuron in the cortex is left to face its own metabolism unbuffered.

XIV. The Dendritic Spine The Census at the Finest Grain

The unit beneath the synapse

Beneath the synapse counted as a presynaptic punctum lies a still finer and more dynamic structure: the dendritic spine, the tiny postsynaptic protrusion that receives most excitatory input and whose appearance and disappearance constitute the physical substrate of learning. The spine is the finest grain at which the census can be taken, and it is also the grain at which the disease's earliest, most reversible damage is visible. A human cortical pyramidal neuron carries spines at a density on the order of 1.25 per micrometre of dendrite on its most-spined segments — somewhat higher than the mouse, with larger and longer individual spines, and these are explicit underestimates, counting only laterally-protruding spines (Benavides-Piccione et al., 2002). Across the dendritic arbor this amounts to many thousands of spines per neuron, each a candidate synapse, and it is their attrition that the synaptic loss of the coarser census ultimately comprises.

The halo around the plaque

The most vivid quantification of spine loss comes from imaging the living cortex around amyloid plaques. In transgenic mice imaged by intravital multiphoton microscopy, spine density falls by roughly half within about twenty micrometres of a plaque's edge, with a robust decrement of around a quarter persisting even on dendrites not associated with any plaque (Spires et al., 2005). Array-tomographic reconstruction of more than fourteen thousand synapses refined the picture: excitatory synapses are lost by some sixty per cent in the immediate halo around a plaque, with the density recovering approximately linearly to control values by about fifty micrometres out, and oligomeric amyloid-β colocalizing with the postsynaptic densities in the halo (Koffie et al., 2009). The plaque, on this evidence, is surrounded by a zone of synaptic devastation whose radius is measurable and whose agent is the soluble oligomer that haloes it.

The soluble culprit and the reversible lesion

The agent of spine loss is not the insoluble plaque core but the soluble oligomer. Picomolar concentrations of amyloid-β dimers and trimers — not monomers — reduce spine density through an NMDA-receptor-dependent pathway engaging cofilin and calcineurin, and the loss is *reversible* and blocked by amyloid antibodies (Shankar et al., 2007); dimers isolated directly from human Alzheimer brain reduce spine density in healthy rodent hippocampus and impair synaptic plasticity and memory, while insoluble plaque cores are inert until solubilized, and the spine loss specifically requires NMDA receptors (Shankar et al., 2008). That the finest unit of the census is lost by a soluble, antibody-neutralizable, receptor-mediated, reversible mechanism is among the most hopeful facts in the whole count.

Tangle maturity and the dendrite

The relationship between the spine and tau pathology is, by contrast, a graded one, and it sharpens the census's recurring theme that the lesion and the loss run on different curves. Reconstructing more than nineteen thousand spines from human Alzheimer cortex, Merino-Serrais and colleagues found that diffuse, pre-tangle phospho-tau does *not* alter the dendrite at all, while mature, intraneuronal neurofibrillary tangles are associated with progressive spine loss, altered spine morphology, and dendritic atrophy in proportion to the tangle's maturation (Merino-Serrais et al., 2013). The dendrite is spared by the early lesion and damaged by the late one — which is to say that for much of the disease the neuron's synaptic apparatus is failing by mechanisms the tangle has not yet joined. At the coarsest end of the same spectrum the dendritic arbor itself simplifies: Golgi studies of the Alzheimer cortex describe marked spine loss, tortuous and distorted apical dendrites, and a severe reduction of horizontal arborization (Mavroudis et al., 2011) — the visible ruin of the tree on which the spines once grew.

XV. The Unit of Cognition The Synapse Itself

The true currency of the disease

Beneath every cellular casualty in this census lies a smaller and more numerous one: the synapse. The human neocortex contains on the order of one hundred and fifty trillion synapses (Pakkenberg et al., 2003); an average cortical neuron carries some thousands of them — the textbook figure of roughly seven thousand per neuron (Drachman, 2005), with human pyramidal cells running several-fold higher. It is at this scale, not the scale of the soma, that the disease is best measured, for the synapse is the unit of cognition and, as it turns out, the unit of decline.

The single strongest correlate

The cornerstone finding of the entire quantitative neuropathology of Alzheimer's disease is that synapse loss, not plaque or tangle burden, is the strongest structural correlate of dementia severity. In the canonical series, neocortical synaptic density correlated powerfully with every cognitive measure tested, and a model combining synaptic density with regional plaque counts reached a correlation with the Dementia Rating Scale of about 0.96 — within which plaque density contributed only about a quarter of the explanatory power, the rest carried by synapse loss (Terry et al., 1991). Independently, electron-microscopic synapse counts from frontal-cortex biopsies of living patients fell with cognitive severity and tracked the Mini-Mental State Examination, with a telling compensatory signature: as synaptic density fell, the mean size of the remaining synaptic contacts *rose*, the cortex enlarging its surviving synapses in a doomed attempt to hold total contact area constant (DeKosky & Scheff, 1990). The brain, in early disease, is visibly trying to compensate for a loss it cannot outrun.

The living census

What the autopsy established, synaptic-vesicle PET now measures in life — and the living census confirms the dead one. The first such study found hippocampal synaptic density reduced in Alzheimer's disease; after correction for the partial-volume effect of atrophy the reduction is on the order of twenty per cent (Chen et al., 2018) — and here the census must enforce its own discipline, for the headline forty-one per cent sometimes quoted is the small-sample, uncorrected figure and should not be used without its qualifications. Extended across the brain, synaptic loss in early Alzheimer's is widespread — significant in the hippocampus (around seventeen per cent on a cerebellar reference), entorhinal cortex (around sixteen), and across neocortical regions (seven to eleven per cent) — and, critically, the synaptic reductions *exceed the loss of grey-matter volume* in the same regions, so that the synapse is being lost faster than the tissue that holds it (Mecca et al., 2020). The clinical pay-off is the decisive one: within early Alzheimer's, the composite cortical synaptic density predicts global cognition better than grey-matter volume does (Mecca et al., 2022), and across the spectrum the relationship between amyloid and synaptic loss *decouples* as the disease advances — amyloid and hippocampal synaptic density are inversely related at the amnestic-MCI stage but unrelated by the mild-dementia stage (O'Dell et al., 2021) — exactly the pattern the census predicts if amyloid is an early driver that hands off, and the synapse is the quantity that keeps falling. (The in-vivo magnitudes are reference-region- and method-dependent, and at least one post-mortem binding study finds the cortical loss more regionally restricted than the in-vivo picture suggests (Mikkelsen et al., 2023) — a caution we carry rather than suppress.)

The order of synaptic loss

The synaptic census, like the cellular one, is ordered — and the synaptic order is nested inside the cellular order, each cell's input failing as its presynaptic partner up the chain succumbs.

Synapse class	Afferent pathway	Documented change	Stage of first loss	Source
Perforant-path › dentate	entorhinal layer II › dentate outer molecular layer	most MCI brains below normal mean; reduced in early AD	MCI	Scheff 2006
Schaffer collateral › CA1	CA3 › CA1 stratum radiatum	~18% (MCI) › ~55% (mild AD)	MCI	Scheff 2007
Peri-plaque excitatory	local cortical, around amyloid	~60% within ~20 µm; recovers by ~50 µm	with plaques	Koffie 2009
Perisomatic inhibition › pyramidal	PV interneuron › pyramidal soma	net digestion; gamma collapse; functional silencing	Phase III	Crapser 2020; Iaccarino 2016

Table 3. The order of synaptic loss — disconnection marching through the memory circuit.

The disease, read at the synapse, is a sequence of disconnections marching through the memory circuit in the order the temporal architecture predicts — input gateway, internal relay, the haloes around each plaque, and finally the inhibitory timing — until the network that was a brain is a set of disconnected parts.

XVI. The Geometry of Sparing What Does Not Die, and Why

The controls for selectivity

A census of the dead is incomplete without a census of the survivors, because the strongest proof that destruction is selective is the catalogue of what is spared. If Alzheimer's were a diffuse process — a fog dimming the whole brain — there would be no survivors to catalogue. There are many, and their identities, set against the casualties, resolve selective vulnerability from a mystery into a phenotype.

The catalogue of the spared

The cerebellum is the great control. It accumulates only diffuse amyloid deposits — never the neuritic plaques, never the neurofibrillary tangles, that define the disease elsewhere (Joachim et al., 1989) — and the strongest stereological study finds *no* significant loss of either Purkinje cells or granule cells in even severe Alzheimer's disease, with only a modest (around thirteen per cent) reduction of total cerebellar volume (Andersen et al., 2012) — though earlier, non-stereological work had reported losses on the order of thirty per cent of Purkinje and granule cells (Wegiel et al., 1999), a claim the design-based count supersedes without entirely silencing. A structure holding the majority of the brain's neurons is, by the most rigorous count, very largely spared at the level of its neurons. The primary sensory cortices are nearly as resistant: the primary visual cortex (area 17) carries tangle densities roughly twenty-fold lower than the adjacent visual association cortex (area 18), which in turn carries about half the density of the higher-order area 20 (Lewis et al., 1987) — the disease respecting, with precision, the hierarchy of cortical processing, sparing the primary and consuming the associative, exactly as Braak staging finds the primary motor and sensory isocortex affected last, at the very end of the disease (Braak & Braak, 1991). Within the hippocampus the gradient is equally sharp: against CA1's loss of half to two-thirds, the CA3–CA2 fields and the dentate granule layer are not significantly depleted (West et al., 2004), and they carry among the lowest tangle and plaque burdens of any hippocampal subfield (Furcila et al., 2019). And among the interneurons, the calcium-buffering populations are conspicuously spared: the calretinin-immunoreactive neocortical interneurons are unaffected, with no change in density or morphology (Hof et al., 1993), and the neocortical parvalbumin interneurons are resistant to frank loss (Hof et al., 1991) — though here the census must be exact, because calbindin protects only the interneurons that express it: the calbindin-containing *interneurons* of the superficial layers are spared, but the calbindin-containing layer-III *pyramidal* neurons are severely depleted in proportion to tangle density (Hof & Morrison, 1991). "Calbindin equals protection" is true of the interneuron and false of the pyramid.

Population	Status in AD	Magnitude	Proposed basis of resistance	Source
Cerebellar Purkinje & granule cells	spared	no significant neuron loss	no tangles; short local circuits	Andersen 2012; Joachim 1989
Primary visual cortex (area 17)	spared	tangles ~20× below assoc. cortex	low in processing hierarchy	Lewis 1987
Primary motor/sensory isocortex	spared till last	affected end of Braak VI	hierarchy; short projections	Braak & Braak 1991
Hippocampal CA3–CA2, dentate granule	relatively spared	not significantly reduced	low tangle/plaque burden	West 2004; Furcila 2019
Calretinin+ interneurons	spared	no density/morphology change	calcium buffering	Hof 1993
Neocortical parvalbumin+ interneurons	resistant (soma)	no frank loss (cf. hippocampus)	local circuit; calcium buffering	Hof 1991

Table 4. The geometry of sparing — what does not die, and why.

Selectivity is a phenotype

Set the spared beside the doomed and the principle declares itself as a clean opposition. The casualties are *large* (the coerulean and cholinergic projection neurons, the >350-square-micrometre layer III/V pyramids); the survivors are *small* (granule cells, local interneurons). The casualties are *long-projecting* (corticocortical association fibres, brain-wide aminergic projections); the survivors are *locally projecting* (cerebellar circuits, primary-cortex neurons, interneurons). The casualties are *high in the processing hierarchy* (association cortex, entorhinal gateway); the survivors are *low* (primary sensory cortex). The casualties are *fast-firing and oxidatively exposed*; the survivors are, disproportionately, equipped with *calcium-buffering proteins* (calretinin, calbindin) that the casualties lack. Selective vulnerability is not a riddle: it is the systematic failure of the cells that are largest, longest, fastest, most associative, and least buffered — and the systematic survival of their opposites. Morrison and Hof drew the connectivity half of this principle from the casualties alone (Morrison & Hof, 1997, 2002); the geometry of sparing supplies the proof from the other direction.

XVII. The Shape of the Demolition

Selectivity with a signature, confirmed three ways

The first edition argued that the dying cells share a phenotype; the second edition can now demonstrate it from three independent directions that agree. The morphological census (the large, neurofilament-rich, long-projecting pyramids of §VIII) and the geometry of sparing (§XVI) bracket the phenotype from the two sides of vulnerability and resistance. The molecular census (§IX) names it in the cell's own transcriptional language — supragranular, long-range, marked by RORB or by specific SST programmes, downregulating *NGF* and *MME* before they fall. And the in-vivo and synaptic censuses (§§XIV–XV) show the phenotype expressed first at the synapse. Four physical features recur across all three accounts: an **extreme and sustained metabolic demand** (the tonic pacemaking of the coeruleus, the two-hundred-hertz firing of the PV cell, the relentless throughput of the entorhinal gateway); an **extensive axonal arbor or outsized connectivity load** (the brain-wide aminergic and cholinergic projections, the long corticocortical association fibres, the thousands of targets of a single basket cell); **high oxidative exposure** with poor calcium buffering (catecholamine chemistry, iron, GluA2-lacking receptors, the absence of calretinin or calbindin); and **dependence on a protective envelope** (the neuromelanin of the coeruleus, the perineuronal net of the interneuron) whose loss removes the last buffer between the cell and its own activity.

The primacy of the synapse over the soma, now measured in life

The second pattern is the consistent precedence of synaptic over somatic loss, and the second edition can now state it in life and at every grain. At the coarsest grain, the in-vivo synaptic census shows synaptic density falling faster than grey-matter volume and predicting cognition better than it (Mecca et al., 2020, 2022). At the finest grain, the spine census shows excitatory synapses lost in measurable haloes around plaques by a soluble, reversible mechanism before any neuron dies (Koffie et al., 2009; Shankar et al., 2008). In between, the stereological synapse counts fall in mild cognitive impairment, before the somata are significantly depleted; the count of dead neurons in association cortex exceeds the count of tangles manyfold; the perineuronal net is digested before the PV cell falls; the single-cell atlas measured the divergent curves of cell loss and lesion burden directly; and at the disease's end roughly three-quarters of the neurons in the worst-hit fields are, by the stereologists' own count, still alive (Hof et al., 2003). The disease is, in its mechanism and its arithmetic, a disease of *disconnection* punctuated by death, not a disease of death that incidentally severs connections.

The molecular legibility of vulnerability

The third pattern is new to this edition and follows from the molecular census. The cell that will die can now be identified, before it dies, by a transcriptional state — a state nearly identical to that of its surviving siblings except in a handful of specific programmes. That vulnerability is *legible in advance*, written in the cell's expression of RORB or of *NGF* and *MME*, is the strongest evidence the census can offer that the casualty list is not assembled by chance as the disease proceeds but is, in some measure, specified from the outset by what kind of cell each neuron is. The demolition has a blueprint, and we are beginning to be able to read it.

The convergence, counted

All three patterns point to the same address. The cellular architecture, assembled from independent stereological, molecular, in-vivo, and sparing literatures that never set out to agree, converges on the perisomatic zone of the parvalbumin interneuron exactly as the temporal architecture and the homeostatic–matrix–synaptic synthesis do — the coerulean, cholinergic, and aminergic projections that fail first are the systems that regulate it; the entorhinal and CA1 circuits that fall next are the ones that feed it; the microglion, astrocyte, and oligodendrocyte that turn in mid-disease are the agents that digest its net and withdraw its support; and the gamma rhythm it generates is the function whose loss is dementia. One address, reached from every direction, counted in every currency.

XVIII. The Arithmetic of Resilience

What the resilient brain keeps

The census makes resilience legible as a set of preserved counts. There exist individuals who carry amyloid and tau burdens fully in the Alzheimer range and yet die cognitively intact, and what distinguishes their brains is not less pathology but *preserved cellular and synaptic architecture*: homeostatic microglia still bearing the Butovsky signature, perineuronal nets still intact around their parvalbumin interneurons, and perisomatic synapses still in place (de Vries et al., 2024). The single-cell atlases add a molecular dimension to this resilience: the cognitively resilient are *over-represented* in the very SST interneuron subtypes that the disease depletes (Mathys et al., 2023), and preserved cortical synaptic density on SV2A imaging marks those who retain cognition despite atrophy (Giorgio et al., 2025). Resilience, in the currency of this paper, is the maintenance of the counts that matter — microglial state, net integrity, synapse number, vulnerable-subtype abundance — in the face of a plaque-and-tangle burden that, on the old census, should have guaranteed dementia. It is the clearest confirmation that the field counted the wrong things: the resilient brain proves that one can have the lesions without the disease, provided the cells and synapses survive.

Resilience is joint, not single

And the preservation is *joint*. Because the homeostatic system fails as a unit — one upstream signal (TGF-β/SMAD), one molecular pivot (TREM2), one anatomical address (the PV perisomatic zone) — no single preserved layer suffices. Resilience requires homeostatic microglia *and* intact matrix *and* competent synapses together, which is why it behaves like the survival of a structure rather than the sparing of a part, and why the transition from mild cognitive impairment to dementia behaves like the crossing of a threshold rather than the descent of a slope: it is the point at which the feed-forward loop among the layers becomes self-sustaining. Reversible by restoration before the crossing, irreversible after — and the perineuronal net around the parvalbumin interneuron, measurable in life, is the single most compact biomarker of which side of that line a given brain is on.

XIX. Falsifiable Predictions in the Currency of Number

The cellular architecture, being quantitative, generates predictions that are quantitative — about counts, ratios, orders, and rates — and the second edition's new instruments make several of them newly testable in life.

On the order of synaptic loss. Longitudinal synaptic-density PET will find synapse loss in the fixed order the census predicts — perforant-path/dentate first, Schaffer/CA1 second,

perisomatic/PV last — and the order will not vary with plaque or tangle distribution, because it is set by circuit position, not by lesion load.

On synapse before soma. Within each vulnerable population, quantified synaptic loss will reliably precede and exceed somatic loss at every stage, in-vivo synaptic density will fall faster than grey-matter volume, and the ratio of lost neurons to accumulated tangles will remain greater than one throughout.

On the net before the cell. In resilience and early-disease cohorts, perineuronal-net integrity around parvalbumin interneurons will predict gamma-band function and cognition *better* than parvalbumin cell counts do, because the load-bearing lesion is the digestion of the net and the silencing of the synapse, not the death of the soma.

On molecular legibility. The vulnerable transcriptomic subtypes will be found to be depleted in a fixed order — RORB-marked entorhinal excitatory neurons and SST interneurons early, parvalbumin and VIP interneurons and deep excitatory neurons late — and the early-vulnerable subtypes will show their distinguishing programmes (downregulated *NGF*, *MME*) *before* their abundance falls.

On the LC dissociation. The locus coeruleus will continue to show the volume/number dissociation — early, near-linear volume loss with neuron number preserved until mid-Braak — and interventions that restore quality control will rescue volume and function before the number begins to fall, but not after.

On the cholinergic phenotype. The early cholinergic deficit will be shown to be predominantly a loss of cholinergic *phenotype* with the neurons surviving, such that trophic (NGF-pathway) restoration in mild disease will recover cholinergic function, whereas the same intervention in late disease, after frank cell loss, will not.

On sparing. The resistant populations — cerebellar neurons, primary-cortex neurons, calcium-buffering interneurons — will be found to retain their homeostatic and synaptic counts even in brains with high cortical pathology, and experimentally conferring calcium-buffering capacity on a vulnerable neuron will reduce its loss.

On reversibility. Restoration of forty-hertz parvalbumin-driven activity, or of the upstream TGF-β/SMAD signal, will rescue synaptic counts and cognition in the window before the feed-forward loop becomes self-sustaining, and will fail after it — a discontinuity in outcome at a definable cellular threshold, not a continuum.

Each prediction is a number, an order, or a rate that a single well-designed quantification could overturn. That is the dividend of counting the right things: the casualty list becomes a set of hypotheses.

XX. Conclusion A Disease One Can Count

The history of Alzheimer's quantification was a history of counting what is easy to see. Plaques and tangles are stainable, stageable, and reassuringly objective, and the field built its diagnostic apparatus around them — only to discover, again and again, that they are not the measures that best explain the illness. The thing that best explains the illness is the loss of specific neurons and, above all, of specific synapses, in a specific order, by specific chains, in cells of a specific molecular kind. This census, in its second and expanded edition, has tried to count all of these.

The count yields a disease of startling precision. Out of eighty-six billion neurons and a hundred and fifty trillion synapses, Alzheimer's destroys a minute, exquisitely selected set — the coerulean, serotonergic, and cholinergic projection neurons that fail first; the entorhinal layer-II gateway that is sixty per cent gone before diagnosis and is marked, molecularly, by RORB; the great corticocortical pyramids whose long axons are their undoing; the SST and then the parvalbumin interneurons; the perineuronal net digested before its cell can die — and it destroys them in the rostro-limbic-cortical order that the temporal architecture independently derived from time, while leaving the cerebellum, the primary cortices, and the calcium-buffering interneurons almost untouched. The cellular architecture and the temporal architecture are the same structure read in different currencies: the order of the casualties *is* the chronology of the disease. And the casualties share a face — the large, long-projecting, fast-firing, oxidatively exposed, unbuffered, envelope-dependent neuron — so that selective vulnerability resolves, on counting, into a phenotype, and now into a molecular signature legible before death.

Three consequences follow. The first is conceptual: the disease is a *targeted demolition*, not a diffuse decline, and its target is, at the end, not even a cell but a synapse and the matrix that protects it — which is why cognition can be lost, and for a window regained, with the neurons still alive. The second is methodological: the census can now be taken in life. Synaptic-vesicle PET counts the synapse in the living patient; single-cell sequencing names the doomed cell before it dies; and the two together convert a post-mortem casualty list into a clinical instrument for staging, for selecting trial participants by where they sit on the arc, and for measuring whether a therapy preserves the counts that matter. The third is strategic: if the load-bearing casualty is the perisomatic synapse of the parvalbumin interneuron beneath its perineuronal net, then that is what trials should measure, that is the threshold whose crossing they should aim to prevent, and a restoration of the homeostatic signal — the one intervention with a claim on every phase — is what they should test, with the perineuronal net as the readout. The disease has always been a process one could count. The opportunity has always been to count the right things, early enough, in the one place where all the

chains converge — and we can now do so, at last, in three currencies and while the patient is still alive to be helped.

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