
The Unfinished Neuron

*Cortical Immature Neurons of Layer II — Origin, the Machinery of Arrest,
Functional Identity on Awakening, Environmental Governance, and the State of
Evidence on Their Role in Alzheimer's Disease*

Prepared under the Organic Network Synthesis methodology

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October 2026

A cell that has waited sixty years in the layer where the disease begins. Nobody has run the stain.

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Abstract

The adult mammalian cerebral cortex contains a population of neurons that were generated before birth, never divided afterwards, and have not finished developing. They occupy layer II. They express doublecortin and the polysialylated form of the neural cell adhesion molecule — proteins otherwise confined to neurons in the first weeks of life — and they retain that expression for years in a mouse and for decades in a human. They are not the progeny of adult neural stem cells, and no stem cell will replace them. Over the course of an animal's life a fraction of them complete maturation, acquire an axon initial segment, grow a spiny apical dendrite and wire into the cortex around them. The remainder wait.

This monograph is an account of that cell: what it is, what holds it in its arrested state, what it becomes when the arrest is lifted, what governs the timing, what the population is plausibly for, and what is and is not known about its behaviour in Alzheimer's disease.

Five findings organise the cell biology. First, the arrest is not passive. The immature cell lacks synaptic contacts, lacks N-methyl-D-aspartate receptors, lacks glucocorticoid receptors, and fails to express the activity-dependent genes *c-fos* and *Arc*, while being physically sheathed in astroglial lamellae — a configuration in which the ordinary signals that drive maturation cannot reach it. Second, the awakening is real and has been fate-mapped: lineage tracing from the doublecortin locus shows these cells resuming maturation into glutamatergic, TBR1- and CaMKII-positive neurons, so the age-related disappearance of doublecortin staining reflects cells maturing out of a marker rather than cells dying. Third, and least expected, the matured cell is not a copy of its neighbours. Patch-clamp recording shows that older complex cells receive synaptic input that is predominantly GABAergic despite the presence of glutamatergic contacts, require more current to reach threshold, and fire at lower maximal frequency than age-matched principal neurons beside them. They are a distinct functional class, not a spare part. Fourth, single-cell genomics of the olfactory cortex finds glutamatergic identity there varying continuously rather than discretely, with a prominent immature population embedded in that continuum, and with transcriptomic profiles closer to those of reptiles and amphibians than to neocortex — which locates the whole phenomenon in an ancestral cortical plan rather than a mammalian innovation. Fifth, the population is experience-sensitive: early-life stress alters the number of morphologically complex doublecortin neurons in the piriform cortex, and most of those cells express the epigenetic reader MeCP2.

Two facts constrain every attempt to translate this to human disease. The population is distributed inversely to stem-cell-driven neurogenesis across mammals — virtually absent from the rodent neocortex, present throughout the neocortex of large gyrencephalic species, with linear density rising with brain size — so the standard laboratory animal is close to the worst available model. And the human evidence, while real, rests on doublecortin immunohistochemistry in post-mortem and surgical tissue, which inherits in full the fixation, antibody-specificity and interval problems that made adult hippocampal neurogenesis in humans one of the most contested measurements in neuroscience.

On Alzheimer's disease the honest position is stated rather than finessed: there is no published study of cortical immature neurons in Alzheimer tissue. Not a contested study, not an underpowered one — none. No count by region, no maturation staging by Braak stage, no measurement of tau isoform or tau phosphorylation in these cells in any species, in health or disease. The reason is not difficulty; it is that two literatures have not met. We therefore build the disease section from what *can* be established: the anatomical relationship, which is complicated by the fact that layer II is an address shared by at least three distinct populations and that the cells which tangle first are not the immature ones; the molecular environment these cells inhabit, where reelin signalling requires an N-sulfated sugar bed, tau seeds enter through a differently sulfated one, and microglial processes are found directly apposed to immature cell bodies in human cortex; and the single population of immature neurons that *has* been examined in the human Alzheimer brain — the adult-born neurons of the dentate gyrus, where recent single-nucleus transcriptomics finds the juvenile programme persisting into the ninth decade, compromised in disease, and tracking cognitive resilience rather than merely tracking cell number.

That last result is the most useful thing the field currently possesses, because it changes the question. If the meaningful variable in an immature neuron population is its molecular state rather than its abundance, then counting doublecortin-positive profiles in Alzheimer cortex — the obvious first experiment — may be the wrong measurement, and a programme designed only to count will return a null that means nothing. We set out three mechanistic hypotheses that are compatible with present evidence and that make divergent predictions, specify the experiments that separate them, and state plainly which of the paper's claims are inferences from adjacent systems rather than observations in this one.

I. The Cell, and Why It Took So Long to See

For most of the twentieth century the adult cortex was understood as a finished structure. Neurons were generated, they migrated, they differentiated, and then — barring disease — they persisted unchanged for the remainder of a life. Plasticity happened at synapses. The cell bodies were fixed, the count could only fall, and the developmental programme that had built the tissue was over.

Two amendments to that picture arrived in the last quarter of the century, and both were about the birth of new cells. The first was adult neurogenesis in the dentate gyrus and the olfactory system, which established that at least two niches retain neural stem cells into adulthood and continue to supply the circuit with new neurons, and whose regulatory biology, niche architecture and functional consequences were worked out in detail over the following decades (Ming and Song, 2011). Claims for neurogenesis in additional regions — neocortex, striatum, amygdala, substantia nigra — were made repeatedly and proved difficult to replicate consistently outside the damaged brain, a pattern attributed at the time to differences in the sensitivity of the methods used to detect new neurons (Gould, 2007). The second amendment was the long and still-unsettled argument

about how much of any of this applies to humans. Both concerned *proliferation*: the question in each case was whether cells divide, where, how often, and to what functional end.

The population this monograph is about was discovered as a by-product of that search, and was initially misclassified by it. Investigators looking for newly generated neurons in the adult brain used the markers of neuronal immaturity as a proxy — principally doublecortin, a microtubule-associated protein of migrating and differentiating neurons, and the polysialylated form of the neural cell adhesion molecule, a heavily charged cell-surface carbohydrate that reduces adhesion and permits structural remodelling. Both are expressed by newborn neurons and lost as they mature. Finding cells that express them in the adult cortex was therefore read, reasonably, as finding newborn cortical neurons, and for some years the layer II population was cited in the debate over whether neurogenesis extends to the neocortex.

That reading was among the claims the replication difficulties of the period concerned, and in this instance the resolution was unusually clean: the cells are not newborn. The decisive work showed that these cells incorporate no thymidine analogue administered in adulthood or in early youth; that they were generated instead during embryonic development, with the bulk of them born around embryonic day 15.5 in the rat; and that they express neither glial markers, nor the markers of mature principal neurons, nor those of inhibitory interneurons (Gómez-Cliement and colleagues, 2008). They are not new. They are old cells that have not finished.

This reclassification is the reason the population has a literature of its own and the reason that literature is small. A cell that is neither newborn nor mature falls outside both of the frameworks the field had built. It is not adult neurogenesis, because nothing divides. It is not synaptic plasticity, because what changes is the differentiation state of a whole cell rather than the strength of a connection. The term that has come to be used for it — *structural plasticity* of a third kind, distinct from both synaptic remodelling and the production of new neurons — was proposed precisely because neither existing category would hold it (Bonfanti and Nacher, 2012).

Why the cell is hard to see. Four properties conspire to keep this population at the edge of visibility, and it is worth naming them at the outset because each of them also shapes what we can and cannot currently claim about disease.

The first is that the cell is defined by the absence of things. Its positive markers — doublecortin, polysialylated neural cell adhesion molecule — are shared with newborn neurons elsewhere, so a positive stain alone does not identify it. What identifies it is the conjunction of those markers with the absence of proliferation history, the absence of mature neuronal markers, and a particular location. Any single stain is ambiguous.

The second is that the cell's detectability declines as it does its job. Maturation extinguishes the markers by which the cell is recognised. A falling doublecortin count across age is therefore

ambiguous between three different biological stories — the cells are dying, the cells are maturing, or the antibody is failing — and distinguishing them requires lineage tracing rather than immunohistochemistry.

The third is species. As Section IX sets out in detail, the population is sparse in the laboratory mouse and rat neocortex and abundant in large gyrencephalic brains. The animal in which most cell biology is done is the animal in which this particular cell is hardest to find, which is an unusual and consequential inversion of the normal situation.

The fourth is methodological. In human tissue the measurement depends on doublecortin immunoreactivity in material that was not perfusion-fixed, and the same dependence produced a decade of irreconcilable results in the hippocampus. A systematic comparison of seven commercial doublecortin antibodies across six mammalian species with widely differing brain size found that most of the variation between studies arose from the choice of antibody and from real interspecies differences in antigen distribution, rather than from the fixation protocol — a finding that is simultaneously reassuring about tissue handling and alarming about reagent choice (Ghibaudi and colleagues, 2023a).

The state of knowledge, stated at the outset. Because the balance of this paper alternates between a well-characterised cell biology and an almost empty disease literature, it is worth fixing the asymmetry in advance.

Question	Status
Do these cells exist, and are they prenatally generated and non-dividing?	Established, multiple species
What is their molecular phenotype?	Well characterised in rat, mouse and human
Do they complete maturation and integrate?	Established by lineage tracing in mouse; inferred in human
What does the matured cell become, physiologically?	Characterised, and surprising: not a principal neuron
What holds them in the arrested state?	Unknown — no causal test of any candidate
What triggers an individual cell to mature?	Unknown
What is the population for?	Argued from distribution and design; no functional experiment
Is the population experience-regulated?	One study (early-life stress); otherwise unexamined
Do they bear perineuronal nets or a defined matrix?	Never examined

Question	Status
What is their tau isoform profile?	Never examined, in any species, in health or disease
What happens to them in Alzheimer's disease?	Never examined

The last three rows are the subject of Sections XV, XVI and XVIII. The fifth and sixth are the reason the disease question cannot currently be answered even in principle: a mechanism of arrest is what would let one predict the effect of a pathological environment, and no such mechanism is known.

What this monograph does. It assembles the cell biology first, because the disease question cannot be posed properly without it, and because the cell biology is genuinely interesting independent of disease. Sections II through VIII take the cell itself: definition, origin, the immature phenotype, the machinery that maintains it, the maturation trajectory, the functional identity of the matured cell, and its transcriptional lineage. Sections IX through XI take the distribution: across species, across the human cortex, and in the one human structure where the phenomenon has been characterised in detail. Sections XII and XIII take governance and function — what moves these cells, and what the population may be for. Sections XIV through XVI take Alzheimer's disease in three parts: the anatomical relationship, the molecular environment, and a direct accounting of what has actually been measured, which is very little. Section XVII sets out three mechanistic hypotheses that the present evidence cannot distinguish. Sections XVIII and XIX give the experimental programme and the conditions under which the whole line of inquiry should be abandoned.

A note on what the paper does not do. It does not argue that these cells cause Alzheimer's disease, or that they are destroyed by it, or that mobilising them would treat it. Each of those is a hypothesis for which the relevant measurement does not exist. Where we reason from adjacent systems — from the dentate gyrus, from the amygdala, from the molecular environment of layer II — we say so in the sentence that does it.

II. Definition and Nomenclature

The terminology in this area is unusually tangled, partly because the cells were named before they were understood and partly because different laboratories emphasised different features. Precision here prevents errors later, particularly in reading the disease literature where the same words are used for different cells.

Cortical immature neurons (cINs) is the term now in general use. It denotes neurons that satisfy four conditions jointly: they reside in layer II of the cerebral cortex; they were generated

prenatally; they do not divide in postnatal life; and they retain expression of markers of neuronal immaturity — doublecortin, polysialylated neural cell adhesion molecule — into adulthood. The last condition is a statement about the cell's differentiation state, not its age. A cIN in a twenty-year-old human is twenty years old and immature.

Tangled cells was the morphological term introduced for the most numerous form, whose processes are short, thin and wound around the soma in a disorganised arrangement quite unlike the oriented dendritic tree of a pyramidal neuron (Gómez-Climent and colleagues, 2008). Alongside them a smaller number of cells with the morphology of semilunar-pyramidal transitional neurons were found, and scarcer still were cells resembling semilunar, pyramidal and fusiform neurons. The morphological series is important: it is the first indication that the population is a *gradient* of maturation states rather than a uniform class.

Complex cells is the term used in the electrophysiological and lineage-tracing literature for the more differentiated members of that series — cells with an elaborated dendritic arbour, which may be doublecortin-positive (young complex cells) or have already extinguished doublecortin (old complex cells) while remaining distinguishable from principal neurons by their physiology (Benedetti and colleagues, 2020). In the human cortex the equivalent distinction has been drawn as **type I** and **type II** cells, graded by dendritic complexity (Coviello and colleagues, 2022).

Non-newly generated immature neurons is the longer and more accurate phrase sometimes preferred in comparative work, because it states the negative that matters: nothing proliferated.

Two terms should be kept well away from this population. *Adult-born neurons* refers to the progeny of adult neural stem cells in the subgranular and subventricular zones, which divide, which are replaceable in principle, and whose regulation is a different biology. And *immature neurons* used without qualification, in the Alzheimer literature in particular, almost always means dentate neuroblasts rather than cortical immature neurons — a usage so prevalent that a search of the disease literature for "immature neurons" returns almost nothing about the cortex. This is not pedantry. Section XVI shows that the apparent existence of an Alzheimer literature on immature neurons is entirely an artefact of this ambiguity.

The distinctions can be set out compactly, because confusing any two of these rows accounts for most of the errors in secondary accounts of this biology.

Population	Origin	Divides in adult?	Location	Markers	Replaceable
Cortical immature neurons	Prenatal, ~E15.5 in rat	No	Layer II, paleocortex and (large brains) neocortex	DCX+, PSA-NCAM+, NeuN–	No
Adult-born dentate neurons	Adult neural stem cell	Yes, with amplification	Subgranular zone, dentate gyrus	DCX+, PSA-NCAM+, NeuN–	Yes
Adult-born olfactory bulb neurons	Adult neural stem cell	Yes	Subventricular zone → bulb	DCX+, PSA-NCAM+	Yes
Paralamina amygdala neurons	Prenatal	No	Amygdala paralamina nucleus	DCX+, PSA-NCAM+ → TBR1+/VGLUT2+	No
Entorhinal layer II projection neurons	Prenatal	No	Entorhinal layer II	Reelin+, NeuN+, mature	No

Note that the first four rows share a marker profile and differ in origin, and that only the first two are routinely confused in the Alzheimer literature. Note also that the last row — the cells that tangle first in the human cortex — shares nothing with the others except an address.

A note on layer II. The address is load-bearing throughout this paper and is itself ambiguous. In rodents, cINs are confined to the paleocortex — principally the piriform cortex and adjacent olfactory territory. In large-brained mammals they extend across the neocortex. "Layer II" in the piriform cortex, a three-layered allocortical structure, is not homologous in any simple sense to layer II of six-layered neocortex, and the cells have been described in both. Where the distinction matters we specify the structure rather than the layer.

III. Origin: A Cohort, Not a Stream

The single most consequential fact about these cells is that they are a fixed endowment. This distinguishes them from every other population of young neurons in the adult brain and determines the shape of everything that follows.

The birthdating evidence. Administration of bromodeoxyuridine during adulthood or early youth labels none of these cells. Administration during embryonic development labels them, with the peak around embryonic day 15.5 in the rat, which places their generation squarely within the ordinary neurogenic period for cortical neurons of that layer (Gómez-Climent and colleagues, 2008). They were produced on schedule, by the normal machinery, from the normal progenitors. What is abnormal is only that they stopped.

The absence of postnatal proliferative capacity. Lineage tracing from the doublecortin locus, using inducible Cre recombinase in transgenic mice, confirms that the layer II population in the postnatal piriform cortex is devoid of proliferative capacity: the labelled cohort does not expand (Rotheneichner and colleagues, 2018). Similar tooling has since been generalised, with a Dcx-CreER knock-in placing the recombinase at the endogenous locus so that expression follows the native spatiotemporal pattern of the gene (Perez and colleagues, 2023), which makes the cohort accessible to the full range of modern circuit and behavioural manipulation.

What a fixed endowment implies. Four consequences follow, and all four will matter later.

The population can only be spent. Every cell that matures is subtracted from the pool, and nothing replenishes it. This is the sense in which the primary literature calls it "a valuable, but nonrenewable reservoir for cortical plasticity" (Rotheneichner and colleagues, 2018) — and the adjective *nonrenewable* is the operative one.

The population's size in an adult is a fact about that individual's development, not about their recent experience. Whatever sets the endowment is set before birth. This makes the endowment a candidate substrate for individual differences in resilience that are fixed early, which is a different kind of variable from the experience-dependent plasticity the field usually measures.

A falling count with age is expected under the healthy model and therefore cannot by itself be evidence of pathology. This is the single most important methodological point in the disease sections.

And the cohort has an internal age structure. All members were born at once, but they mature at different times across the lifespan, so at any moment the population is a distribution across maturation states. The biologically meaningful description of the population is therefore that distribution, not a single number.

IV. The Immature Phenotype: An Inventory

What does it actually mean, molecularly, for one of these cells to be immature? The answer is more specific and more interesting than the marker list suggests, because the phenotype is characterised as much by what is missing as by what is present.

Present. The cells express doublecortin, a microtubule-associated protein that binds and stabilises microtubules and is required for the cytoskeletal reorganisation of migration and early differentiation. They express the polysialylated form of the neural cell adhesion molecule, in which long chains of α -2,8-linked sialic acid residues carry a dense negative charge that reduces cell-cell adhesion and keeps the extracellular environment locally permissive to structural change. They express TOAD/Ulip/CRMP-4, a collapsin response mediator protein of growth cones and

developing neurites. They express the A3 subunit of the cyclic-nucleotide-gated channel. And they are positive for phosphorylated cyclic-AMP response element-binding protein (Gómez-Climent and colleagues, 2008). In human cortex the same cells are doublecortin- and polysialylated-neural-cell-adhesion-molecule-positive and negative for the mature neuronal marker NeuN (Coviello and colleagues, 2022).

Absent — and this is the substance of the phenotype. The cells do not express markers of astrocytes, oligodendrocytes or microglia; they are neurons. They do not express the markers of mature principal neurons. They do not express the markers of inhibitory interneurons. Most of them lack synaptic contacts altogether. They fail to express the activity-dependent immediate-early genes *c-fos* and *Arc*. They lack N-methyl-D-aspartate receptors. And they lack glucocorticoid receptors (Gómez-Climent and colleagues, 2008).

That list of absences describes a cell that is, functionally, unaddressable. It has no synapses to receive a signal, no NMDA receptors to transduce the coincidence detection that drives activity-dependent maturation elsewhere, no immediate-early gene response to register that anything happened, and no glucocorticoid receptor through which systemic stress hormones could reach it. Whatever else is true of this cell, it has been placed outside the ordinary channels by which a neuron's environment instructs it.

The inventory is worth tabulating, because the functional reading of the phenotype depends on the conjunction rather than on any single entry.

Component	Status in cIN	Ordinary function	Consequence of this status
Doublecortin (DCX)	Present	Microtubule binding and stabilisation in migrating and differentiating neurons	Cytoskeleton held in a developmental configuration
PSA-NCAM	Present	Dense negative charge reducing adhesion; permits remodelling	Local environment kept permissive — or contact kept impossible
CRMP-4 (TOAD/Ulip)	Present	Growth-cone and neurite outgrowth signalling	Outgrowth machinery retained but unused
CNG-A3 channel subunit	Present	Cyclic-nucleotide-gated cation conductance	An unusual conductance of uncertain role
Phospho-CREB	Present	Activity- and trophic-signal-dependent transcription	Transcriptional machinery primed
Synaptic contacts	Mostly absent	Reception of network activity	No input to instruct maturation

Component	Status in cIN	Ordinary function	Consequence of this status
NMDA receptors	Absent	Coincidence detection; Ca ²⁺ entry driving activity-dependent maturation	Insulated from the canonical maturation transducer
Glucocorticoid receptors	Absent	Transduction of systemic stress hormones	Systemic endocrine signals cannot act directly
c-Fos / Arc	Not expressed	Immediate-early response to activity	No record of activity; cell is functionally silent
NeuN / mature markers	Absent	Mature neuronal identity	Differentiation genuinely incomplete
GAD67 and interneuron markers	Absent	Inhibitory identity	Excitatory lineage, not an interneuron
Glial markers	Absent	—	A neuron, not a glial cell
Astroglial lamellae	Present, enveloping	—	Physical isolation, graded against maturity

The physical seal. The absences are reinforced structurally. Most of these cells are covered by astroglial lamellae — thin sheets of astrocytic membrane wrapped around the soma and processes (Gómez-Climent and colleagues, 2008). In the human cortex the same arrangement has been described in slightly different terms: the cells express no glial markers themselves, but astroglial *and microglial* processes are found in close apposition to their somata and dendrites, and this apposition is more pronounced on the less differentiated type I cells than on the more differentiated type II cells (Coviello and colleagues, 2022).

The gradient in that last observation is the useful part. Glial ensheathment is heaviest on the least mature cells and lightest on the most mature ones. Whether the sheath is a cause of arrest, a consequence of it, or a shared downstream feature of the same programme is not established — no study has removed the sheath and looked. But the correlation is in the direction a gating model predicts, and it identifies glia as a candidate controller of a cell-differentiation decision in the adult cortex.

What the phenotype is not. It is worth stating explicitly that this is not a quiescent stem cell, not a progenitor, and not a cell in cycle arrest. There is no proliferative potential to be held in check. The arrest is of *differentiation*, in a post-mitotic neuron, and the nearest analogy in developmental biology is not a stem-cell niche but a paused developmental programme.

V. The Machinery of Arrest: What Holds the Cell Still

If the phenotype of Section IV is a cell sealed off from instruction, the obvious question is what maintains the seal — and the honest answer is that the maintenance mechanism has not been identified. What exists is a set of candidate components, each with a plausible mechanism and none with a causal test. We set them out in descending order of evidential support, because the gaps are as informative as the content.

Candidate one: the absence of synaptic drive, which is self-sustaining. A cell with no synapses receives no activity. A cell receiving no activity does not undergo activity-dependent maturation. This is not a mechanism so much as a trap: the state is stable because the state prevents the signal that would change it. Its attraction is that it requires no dedicated machinery. Its weakness is that it cannot explain why cells leave the state, which they demonstrably do, and so some signal must be able to cross the barrier.

Candidate two: the receptor vacancy. The missing NMDA receptor is the most specific absence in the inventory and the most mechanistically suggestive. In every well-characterised instance of activity-dependent neuronal maturation, NMDA-receptor-mediated calcium entry is the transducer. A cell without the receptor is insulated from that entire control pathway even if glutamate reaches it. Whether the receptor's absence is the cause of arrest or a marker of it is untested; the experiment — forcing NMDA receptor expression in an identified cIN and asking whether it matures — is feasible with current tools and has not been performed.

Candidate three: glial ensheathment as a physical gate. Addressed in Section IV. The astroglial lamella is a diffusion barrier and a potential source of inhibitory signalling; its density is inversely graded with maturation state in human cortex. The model is attractive and entirely untested.

Candidate four: the polysialic acid coat. Polysialylated neural cell adhesion molecule is usually interpreted as *permissive* — it reduces adhesion, hydrates the local environment, and allows a cell to remodel. Read that way, its presence on an arrested cell is paradoxical: why would a cell that is not remodelling carry the molecule whose function is to allow remodelling? Two readings are available. The permissive reading holds that the coat keeps the cell *ready*, preserving a local environment in which maturation remains possible for decades, which is what a reservoir would need. The insulating reading holds that a dense negative charge cloud which prevents adhesion also prevents the formation of the stable contacts that synaptogenesis requires, so the same molecule that keeps the cell able to change also keeps it from changing. These predict opposite outcomes from enzymatic removal of polysialic acid, and the experiment has not been done in this population.

Candidate five: the extracellular matrix, and a genuine absence of data. In the adult cortex the chief determinant of whether a neuron can remodel is the condensed chondroitin-sulfate-proteoglycan matrix of the perineuronal net; its assembly closes critical periods and its degradation reopens them. A population of cells held in a juvenile state for decades inside an

adult cortex is therefore an obvious candidate for either exclusion from the net or enclosure within a specialised one, and the relationship would be mechanistically central. We searched for work addressing it and found none: no study has characterised perineuronal nets or matrix composition around cortical immature neurons. This is not a contested area; it is an empty one, and it is the cheapest significant experiment named in this paper.

Candidate six: epigenetic maintenance. The most recent and least developed candidate. Most doublecortin-positive neurons of the piriform cortex express MeCP2, the methyl-CpG-binding protein that reads DNA methylation and represses transcription — and notably, doublecortin neurons of the olfactory bulb, which are genuinely adult-born, do not (Abellán-Álvaro and colleagues, 2024). A marker that distinguishes the arrested cortical population from the proliferative bulb population, and which is a transcriptional repressor, is the right shape for a maintenance mechanism. It is at present a single immunohistochemical observation in one paper, and we grade it accordingly: suggestive, unreplicated, and worth pursuing because it names a protein with known biology and available genetic tools.

A seventh consideration, which has not been raised in this literature: the protein by which we recognise the cell is a microtubule-associated protein. Doublecortin is not merely a convenient antigen. It is a functional microtubule-associated protein that binds along the microtubule lattice, nucleates and stabilises microtubules, and is required for the cytoskeletal dynamics of migration and early differentiation. Its presence is the structural signature of the arrested state and not just its label.

This matters because the cell's microtubules are therefore occupied by a developmental microtubule-associated protein for decades, in an adult cortex, and because the protein that ordinarily dominates the axonal microtubule lattice in a mature neuron — tau — is the protein whose dysfunction defines the disease this paper will come to. Two microtubule-associated proteins with overlapping lattice-binding roles, one developmental and one adult, present in the same cell at the same time, is a configuration with obvious mechanistic consequences and no published investigation. We have found no study of the relative abundance, the binding competition, or the functional interaction of doublecortin and tau in any population of persistently immature neurons.

Three consequences would follow if the configuration is as described, and each is testable. A microtubule lattice substantially occupied by doublecortin may be differentially available to tau, which would make these cells biochemically atypical hosts for tau pathology in either direction — resistant, if the lattice is protected, or vulnerable, if displaced tau is free in the cytosol. The relief of doublecortin expression during maturation would then be a period of cytoskeletal handover, during which the lattice is transferred from a developmental to an adult microtubule-associated protein, and such a handover is a plausible window of specific vulnerability. And the kinases that regulate

doublecortin's microtubule affinity overlap with those that regulate tau's, so a cell expressing both is subject to a shared upstream control whose dysregulation would act on both substrates at once.

We flag this as the clearest unexplored mechanistic question in the cell biology rather than as a finding. It is raised here because the disease sections depend on it: a paper asking what Alzheimer's disease does to an immature neuron is asking what a tauopathy does to a cell whose microtubules are run by a different microtubule-associated protein, and that question has never been posed.

The shape of the gap. Six candidates, no causal test for any of them. The field knows a great deal about what an arrested cIN looks like and essentially nothing about what keeps it arrested. For a paper that will go on to ask what happens to these cells in a disease, this is the limitation that matters most: without a mechanism of arrest we cannot say what would perturb it, and therefore cannot predict what a pathological environment would do.

VI. Awakening: The Maturation Trajectory

The arrest is not permanent, and the demonstration that it is not is the most technically satisfying result in this literature.

The fate-mapping experiment. In DCX-CreERT2/Flox-EGFP transgenic mice, a pulse of tamoxifen permanently labels cells expressing doublecortin at that moment, and the label persists in those cells and their descendants regardless of what they subsequently express. Applying this to the piriform cortex and following the labelled cohort across ageing showed that the immature neurons of layer II do not vanish. They progressively resume maturation and become glutamatergic neurons, positive for the transcription factor TBR1 and for calcium/calmodulin-dependent protein kinase II (Rotheneichner and colleagues, 2018).

This single experiment resolves the ambiguity flagged in Section I. The well-documented age-related decline in doublecortin-positive cells in layer II is not cell death and not antibody failure. It is maturation. Cells leave the count by graduating.

The structural evidence of integration. The same study documented the morphological correlates of that graduation: an increase in perisomatic puncta expressing synaptic markers, the development of complex apical dendrites decorated with numerous spines, and — the most specific marker of a functional neuron — the appearance of an axon initial segment, the axonal domain where action potentials are generated (Rotheneichner and colleagues, 2018). A cell that has built an axon initial segment and a spiny apical dendrite and acquired synaptic input is, by any reasonable standard, participating.

The age dynamics, and an apparent contradiction resolved. A detailed accounting of the population in mouse piriform cortex from postnatal to advanced ages found a marked decrease

during juvenile stages — reminiscent in shape of the decline in hippocampal neurogenesis — with a small number of highly immature cells persisting to advanced age (Ghibaudi and colleagues, 2023b). Set against the fate-mapping result this is not a contradiction but a description of the same process from the marker's point of view: the juvenile period is when most of the cohort matures and therefore when most of the doublecortin signal is extinguished, and what remains in the old animal is the residue that has not yet gone. The endowment is spent fastest early and then slowly.

The trajectory can be staged, drawing the stages from the morphological series of the rat work, the fate-mapping and morphometry of the mouse work, the physiology, and the type I / type II grading in human tissue. The staging is a synthesis across those studies rather than a scheme any single paper proposes, and it is offered because the disease sections require a vocabulary for partial maturation.

Stage	Morphology	Markers	Synaptic input	Physiology
Arrested (tangled cell)	Short, thin, disorganised processes wound about the soma	DCX+, PSA-NCAM+, NeuN–	Absent; astroglial ensheathment	Not characterised; no activity markers
Early complex / human type I	Emerging oriented processes; heavy glial apposition	DCX+, PSA-NCAM+, NeuN–	Sparse	Low maximal firing; resembles neonatal principal neuron
Late complex / human type II	Elaborated dendritic arbour; spines appearing	DCX low or negative; synaptic puncta present	Present; excitatory and inhibitory puncta	Intermediate
Matured	Complex spiny apical dendrite; axon initial segment present	DCX–, TBR1+, CaMKII+	Larger, but predominantly GABAergic	High rheobase; lower maximal firing than neighbours

Two properties of this table carry through the rest of the paper. The markers by which the population is identified are present only in the first two stages, so immunohistochemistry sees the unspent fraction and is blind to the spent one. And the physiological divergence from neighbouring principal neurons appears at the *end* of the trajectory rather than being resolved by it, which is the subject of the next section.

The human trajectory. In the human amygdala paralaminar nucleus, where the same phenomenon has been characterised across the full lifespan, the pattern is the same with a longer clock: in children most cells are immature and doublecortin- and polysialylated-neural-cell-adhesion-molecule-positive, during adolescence many transition into mature TBR1- and VGLUT2-positive neurons, and immature cells nonetheless persist into old age

(Sorrells and colleagues, 2019). A mouse spends its endowment over months. A human spends it over decades and still has some left at the end.

What triggers an individual cell to mature is unknown. This is the second major gap, and it is paired with the first. We know the transition happens, we know roughly when in the lifespan it happens most, and we do not know what selects a particular cell at a particular time. No signal has been identified, no manipulation has been shown to accelerate or delay the transition in an identified cIN, and the experiment that would establish the trigger has not been designed in the published literature. Candidate triggers follow from Section V by subtraction — restoration of synaptic drive, acquisition of NMDA receptors, retraction of the glial sheath, loss of the polysialic acid coat, relief of epigenetic repression — but these are the inverse of the candidate maintenance mechanisms and inherit all of their uncertainty.

VII. Functional Identity: The Cell Does Not Become Its Neighbour

If the awakening result is the most satisfying in this literature, the physiology is the most surprising, and it overturns the framing within which the population is usually discussed.

The intuitive model of a neuronal reservoir is replacement. A circuit loses neurons; the reservoir supplies new ones of the same kind; function is restored in proportion to the supply. On this model the matured cIN should be indistinguishable from the principal neurons around it, and the value of the population is simply its size.

That model is wrong, and the experiment that shows it is wrong was designed to ask exactly this question: whether these cells eventually become equivalent to neighbouring principal neurons, or whether they constitute a novel functional element (Benedetti and colleagues, 2020). Doublecortin-driven reporter mice allowed identified cells to be recorded by patch clamp and their axon initial segments measured morphometrically. The findings were as follows.

Young, doublecortin-positive complex cells received sparse synaptic input and fired action potentials at low maximal frequency, resembling neonatal principal neurons. This is the expected result and confirms that the immature state is genuinely immature in a physiological and not merely an antigenic sense.

Older, doublecortin-negative complex cells — cells that had completed the transition — had larger synaptic input, as expected. But the input was *predominantly GABAergic*, despite clear evidence of glutamatergic synaptic contacts on the same cells. Their rheobase current, the current required to bring them to threshold, was larger than that of neighbouring age-matched principal neurons. And their maximal firing frequency was lower.

The matured cIN is therefore a glutamatergic neuron, by transcription factor and by transmitter phenotype, which is harder to excite than its neighbours and which is driven disproportionately by inhibition. The authors' conclusion is the one the data force: these are not simple additions to or replacements for pre-existing network components but a novel type of neuron and a new coding element in the adult brain (Benedetti and colleagues, 2020).

Why this matters for everything downstream. Three consequences follow.

The first is that the population's function cannot be inferred from the function of the cells around it. A sparse, high-threshold, inhibition-dominated excitatory cell inserted into an olfactory cortex is doing something specific, and what that something is remains unknown. Plausible roles include a conditional or gated channel that contributes only under strong or coincident input; a sparse-coding element that increases the dimensionality of representation; or a slow integrator operating on a different timescale from the principal population. These are hypotheses; no study has recorded these cells during behaviour.

The second is that the clinical reading of "reserve" needs revision. If maturation of a cIN does not restore a lost principal neuron but inserts a functionally different cell, then mobilising the population in a damaged cortex is not repair in the sense of restitution. It is modification. Whether that modification is beneficial depends on the circuit and on what has been lost, and cannot be assumed.

The third is a measurement warning. Because the matured cell is physiologically distinguishable from its neighbours but not distinguishable by the immaturity markers — it is doublecortin-negative, like every other mature neuron — the matured cohort is largely invisible to immunohistochemistry. Any count of doublecortin-positive cells measures the unspent remainder of the endowment and says nothing about how much has been spent or what the spending produced. For disease work this is severe: two brains with identical doublecortin counts could differ completely in how many cells had matured and how they had integrated.

VIII. Lineage and Transcriptional Identity

What kind of neuron is this, in the developmental and genomic sense? Two recent bodies of work answer this with some precision, and the second of them relocates the whole phenomenon in evolutionary terms.

The lineage is excitatory, and this was not obvious. In the human cerebral cortex, layer II immature neurons express the transcription factors CUX1, CTIP2 and TBR1, and lack the inhibitory marker GAD67, placing them unambiguously in the excitatory lineage (Coviello and

colleagues, 2022). The mouse piriform cells mature into TBR1- and CaMKII-positive glutamatergic neurons (Rotheneichner and colleagues, 2018).

The reason this needed establishing is anatomical. In the human amygdala, the paralaminar nucleus develops immediately adjacent to the caudal ganglionic eminence, which is a source of inhibitory interneurons — so proximity predicted an inhibitory identity. Most paralaminar neurons nonetheless express excitatory markers (Sorrells and colleagues, 2019). The population is excitatory despite its neighbourhood, which means its identity is specified by lineage rather than by location.

The genomic context: identity varies continuously, not discretely. Single-nucleus transcriptome and chromatin-accessibility analysis of the mouse olfactory cortex, compared against neocortical areas and against other tetrapods, produced four results that bear directly on cINs (Zeppilli and colleagues, 2025).

First, in contrast to the six-layered neocortex, glutamatergic neurons of the three-layered piriform cortex display *continuous* rather than discrete variation in transcriptomic profile. There are no sharp cell-type boundaries of the neocortical kind; there is a gradient.

Second, a prominent population of immature neurons was identified in the piriform cortex, embedded within that gradient. This is the first characterisation of cINs in a comprehensive single-cell genomic framework, and it situates them not as an anomalous class sitting outside the cortical taxonomy but as one end of a continuum that the structure maintains as a matter of course.

Third, subsets of piriform and neocortical glutamatergic cells with conserved transcriptomic profiles were distinguished by distinct, area-specific *epigenetic* states — so the same transcriptional identity can sit on different chromatin, which is precisely the configuration in which a cell might hold a developmental programme available without executing it.

Fourth, piriform neurons displayed greater transcriptomic similarity to the cortical neurons of turtles, lizards and salamanders than to those of the neocortex, despite more than two hundred million years of coevolution. The olfactory cortex retains molecular signatures of ancestral cortical identity.

What the ancestral reading buys. It reframes the cIN from an oddity to a retention. If the three-layered olfactory cortex preserves an ancestral cortical plan, and if that plan maintains glutamatergic identity as a continuum including persistently immature cells, then the cIN is not a specialisation that mammals evolved but a feature that the oldest part of the cortex never gave up — and its appearance across the neocortex of large-brained mammals (Section IX) becomes an expansion of an old arrangement rather than an invention. This is a hypothesis built on the juxtaposition of two literatures rather than a result, and we flag it as such; but it is testable by asking whether neocortical cINs in a gyrencephalic species carry the piriform or the neocortical epigenetic signature.

A caution the same study supplies. The piriform cortex, unlike the neocortex, exhibited divergence between glutamatergic cells of laboratory versus wild-derived mice (Zeppilli and colleagues, 2025). The structure that hosts cINs in rodents is the structure whose cellular identity is most altered by domestication and laboratory housing. Any inference from laboratory mouse piriform cortex to wild or human biology therefore carries an additional and quantified risk that does not apply to neocortical work.

IX. The Comparative Architecture, and the Problem with Mice

The distribution of this population across mammals is the most quantitatively secure body of evidence in the field, and it is also the single greatest obstacle to studying the cells in a disease model.

The survey. The occurrence, distribution and cellular features of cortical immature neurons were examined systematically across twelve mammalian species spanning small-lissencephalic to large-gyrencephalic brains. Morphological and molecular features were well preserved across all of them — these are recognisably the same cells in a mouse and in a dolphin. The *distribution*, however, was highly heterogeneous, and particularly so in the neocortex. The finding stated plainly: while virtually absent in rodents, cINs are present in the entire neocortex of many other species, and their linear density in cortical layer II generally increased with brain size (La Rosa and colleagues, 2020).

A later study in sheep extended the point beyond the cortical ribbon, showing that gyrencephalic, large-brained mammals host higher amounts of immature neurons and that these involve subcortical, white- and grey-matter regions as well (La Rosa and Bonfanti, 2018). The phenomenon scales with brain size and is not confined to the layer in which it was first described.

The inverse relationship. Set alongside the comparative data on adult neurogenesis, the pattern is an inversion. Stem-cell-driven adult neurogenesis is a lifelong, robust process in laboratory rodents and declines markedly from small-brained to large-brained species, becoming vestigial or largely postnatal in humans and dolphins. Cortical immature neurons run the other way: scarce in rodents, abundant in large gyrencephalic brains.

The interpretation advanced for this is a trade-off: that large-brained mammals, having reduced their capacity to generate new neurons from stem cells, retain instead a reservoir of developmentally plastic cells produced before birth, and that these are two alternative strategies for keeping young neurons available to an adult circuit (Bonfanti and colleagues, 2023). The trade-off is a hypothesis and is presented as one by its authors; what is not hypothetical is the inverse distribution itself.

	Stem-cell-driven adult neurogenesis	Cortical immature neurons
Cell of origin	Radial glia-like stem cell in a niche	None — generated prenatally
Division in adult life	Yes, with progenitor amplification	No
Location	Subgranular zone; subventricular zone	Cortical layer II; amygdalar paralaminar nucleus
Replenishable	In principle, while the stem pool lasts	No — a fixed endowment
Scaling with brain size	Declines as brain size increases	Rises as brain size increases
Status in laboratory rodent	Robust, lifelong	Paleocortex only; neocortex virtually absent
Status in adult human	Contested	Documented, with regional contraction across age
Studied in Alzheimer's disease	Extensively	Not at all

Why this is a serious methodological problem. Nearly the whole causal apparatus of Alzheimer research is the mouse. Transgenic amyloid models, tau models, APOE knock-ins, microglial manipulations, exercise interventions, immunotherapies — all are run in an animal whose neocortex has essentially none of the cells in question. A mouse experiment can therefore establish nothing about neocortical cINs for the simple reason that there are none to study, and a mouse experiment in piriform cortex studies a structure whose cellular identity is additionally perturbed by domestication (Zeppilli and colleagues, 2025).

This is not the familiar complaint that mouse models of Alzheimer's disease are imperfect. It is a stronger and more specific claim: for this particular cell type, the standard model organism lacks the substrate. Work on cINs in disease must be done either in human post-mortem tissue or in a gyrencephalic species, and the practical consequence is that the field's dominant experimental platform is unavailable.

Which species are actually available, since the mouse is not. If neocortical work requires a gyrencephalic animal, it is worth naming the realistic options and their costs, because the choice determines what kind of question can be asked. Sheep have been used productively and host immature neurons in cortical, subcortical, white- and grey-matter regions (La Rosa and Bonfanti, 2018); they are large, long-lived, available through veterinary channels, and have no Alzheimer model. Pigs offer similar anatomy with better availability of transgenic lines. Non-human primates offer the closest anatomy and the strongest claim on translation at the highest ethical and financial cost, and spontaneous amyloid pathology in aged macaques provides a natural rather than

transgenic disease comparison. Cetacean material, which has featured in the comparative literature because of brain size, is available only opportunistically and post-mortem.

The pattern across those options is unfortunate and worth confronting: the species with the cells have no disease model, and the species with the disease models have few of the cells. There is no animal in which both the substrate and an established amyloid or tau model are available, and that is the structural reason this question is more tractable in human post-mortem tissue than in any animal — an inversion of the usual order in which mechanism is established in animals and confirmed in humans. The programme of Section XVIII is accordingly built on human tissue first, with the single exception of the rodent piriform experiment, where the substrate does exist.

The translational timing problem. A further complication concerns how to map ages between species. The maturation of this population occupies a long developmental window, and comparing a six-month mouse to a sixty-year-old human requires a principled correspondence rather than a rule of thumb. Work applying quantitative cross-species translation of developmental timing to the plasticity literature makes the point that different forms of plasticity decline on different schedules in different species, and that these schedules have not yet been mapped for immature neurons (Bonfanti and Charvet, 2021). A study reporting that cINs decline with age in one species and not another may be reporting a difference in clock rather than a difference in biology.

X. The Human Map

Three independent lines of human evidence exist. None is as complete as the rodent work, all three carry a methodological burden, and together they establish the phenomenon in humans with reasonable confidence while leaving its quantitative distribution poorly specified.

The cortical population. The most direct characterisation used surgical samples from epilepsy patients together with post-mortem tissue, and found in layer II of the human cerebral cortex cells with differing degrees of dendritic complexity — type I and type II — expressing doublecortin and polysialylated neural cell adhesion molecule and lacking NeuN. The cells belonged to the excitatory lineage by transcription factor expression and lacked GAD67. Type II cells carried puncta expressing both inhibitory and excitatory synaptic markers apposed to their perisomatic and peridendritic regions, with ultrastructural analysis suggesting genuine synaptic contacts. The cells expressed no glial markers, but astroglial and microglial processes were found in close apposition to their somata and dendrites, particularly in the case of type I cells. The authors found these cells in several regions of the cerebral cortex in humans of different ages (Coviello and colleagues, 2022).

Three features of that result deserve emphasis. The lineage determination is firm, which removes a real ambiguity. The synaptic evidence on type II cells establishes that the human population, like the rodent one, contains cells partway through integration — so the maturation trajectory of Section VI is not a rodent peculiarity. And the glial apposition, graded by maturation state, reproduces in human tissue the arrangement first described by electron microscopy in the rat.

The surgical-tissue caveat, stated precisely. Much of the strongest human material comes from epilepsy surgery, for the straightforward reason that it is the only way to obtain rapidly fixed, high-quality living human cortex. But epilepsy is itself a condition of altered structural plasticity, and doublecortin and polysialylated neural cell adhesion molecule are both upregulated in epileptic tissue in other contexts. Material from epileptic cortex cannot therefore be treated as a normal baseline, and the demonstration that the same cells appear in post-mortem tissue is what carries the claim that they are a normal feature. The post-mortem arm is the load-bearing one and is also the lower-quality one.

The antibody problem, and what the field did about it. The human measurement rests on doublecortin immunoreactivity, and doublecortin immunoreactivity in human tissue has a difficult history. A deliberate methodological study tested seven commercial doublecortin antibodies, together with the proliferation marker Ki67, across six mammalian species of widely differing brain size and across four regions — paleocortex and neocortex for immature neurons, hippocampus and subventricular zone for newly generated ones — using tissue obtained by different procedures including post-mortem and intraoperative sampling and intracardiac perfusion. In selected human cases the specificity of the doublecortin antibody was confirmed by co-staining with a fluorescent probe against doublecortin messenger RNA. The conclusion was that although fixation varied, most of the between-study differences arose from the choice of antibody and from real interspecies variation in antigen distribution (Ghibaudi and colleagues, 2023a).

This is a genuine service to the field and should be read as substantially strengthening the human claim: an immunohistochemical signal confirmed against its own transcript is no longer merely an antibody artefact. It also sets the standard that any future study of these cells in human disease tissue will be held to.

The inherited controversy. It must be said directly that any claim about immature neurons in the adult human brain arrives into a field that has already fought a bitter and unresolved argument about exactly this kind of measurement. Within a twelve-month period, one group reported that a defined population of progenitor cells never coalesces in the human subgranular zone, that proliferating progenitors and young neurons decline sharply in the first year of life, and that in seventeen post-mortem controls and twelve surgical specimens spanning ages eighteen to seventy-seven, young neurons were not detected in the adult dentate gyrus at all (Sorrells and colleagues, 2018) — while another group, using tightly controlled tissue and a different processing

protocol, identified thousands of immature neurons in the dentate gyrus of neurologically healthy subjects up to the ninth decade, declining progressively as Alzheimer's disease advanced (Moreno-Jiménez and colleagues, 2019).

The two results concern the same structure, the same markers and overlapping age ranges, and they disagree. The dispute has been attributed largely to tissue handling, fixation interval and antigen retrieval, and it has not been settled by consensus. Its relevance here is twofold and both directions matter. It is a warning: the cortical claim depends on the same reagents and the same tissue sources, and will be attacked on the same grounds. And it is a reason the cortical population is interesting in its own right: cINs do not depend on adult proliferation for their existence, so the question of whether human adults make new neurons — the question that generated the dispute — is simply orthogonal to whether human adults possess immature ones. The cortical population survives either resolution of the hippocampal argument.

What is not known about the human distribution. There is no stereological count of cINs in the human cortex by region. There is no age curve with confidence intervals. There is no comparison across cortical areas within individuals. The claim that supports most reasoning in this area — that the population contracts regionally with age, retaining a temporal-lobe residue — rests on qualitative description rather than on quantification. For a field that wants to compare disease to control, the absence of a normative human dataset is a prior problem: there is no baseline to compare against.

XI. The Amygdala Paralaminar Nucleus: The Best-Documented Human Case

The human structure in which this biology is characterised most completely is not cortical. It is the paralaminar nucleus of the amygdala, and because it is the only place where the full lifespan trajectory has been described in humans, it functions as the reference case for what cIN biology looks like in our own species.

The human findings. Studying human paralaminar development from embryonic stages to adulthood established the following. The nucleus develops next to the caudal ganglionic eminence, a source of inhibitory interneurons, yet most of its neurons express excitatory markers. In children, most paralaminar cells are immature, doublecortin- and polysialylated-neural-cell-adhesion-molecule-positive. During adolescence many transition into mature neurons positive for TBR1 and VGLUT2. Immature paralaminar neurons persist into old age. And local progenitor proliferation decreases sharply in infants — so this is not a neurogenic niche sustaining itself by division. Single-nucleus RNA sequencing of material from donors aged

four to fifteen identified the transcriptional profile of these immature excitatory neurons directly (Sorrells and colleagues, 2019).

The authors' interpretation is that the human paralaminar nucleus contains excitatory neurons that remain immature for decades, constituting a possible substrate for persistent plasticity at the interface of the hippocampus and the amygdala.

The mouse homologue, and why it was missed. A homologous region was subsequently identified in the mouse, containing immature excitatory neurons and previously considered part of the amygdala intercalated cell clusters or the ventral endopiriform cortex. Mouse paralaminar neurons are born embryonically, not by postnatal neurogenesis, though a subset retains immature molecular and morphological features into adulthood. During the juvenile-to-adolescent window, postnatal days twenty-one to thirty-five, the majority undergo molecular, structural and physiological maturation, and a subset of excitatory paralaminar neurons migrate into the adjacent endopiriform cortex. Alongside these changes, paralaminar neurons develop responses to aversive and appetitive olfactory stimuli (Alderman and colleagues, 2023).

Two things in that result are new relative to everything in Sections III to VIII. The first is *migration*: a subset of these cells move, in the juvenile animal, from the nucleus into an adjacent structure. Maturation of an arrested neuron in the adolescent brain can therefore include translocation of the cell body, which is a far more demanding cytoskeletal undertaking than growing a dendrite and has implications we return to in Section XVII. The second is the emergence of *stimulus-driven responses* coincident with maturation, which is the closest the literature comes to a functional readout of awakening.

The wider human pattern. Reviewing which neurodevelopmental processes continue in humans after birth, the same investigator places the paralaminar nucleus within a broader and distinctively human arrangement: although postnatal neuronal birth is limited, neurons continue to *migrate* into some human brain regions throughout infancy and into adolescence, with multiple migratory pathways delivering interneurons across frontal and temporal cortex in infants, and shorter-range migration of excitatory neurons continuing during adolescence particularly near the paralaminar nucleus — a region following a delayed growth trajectory from infancy to adulthood (Sorrells, 2024). Protracted migration and protracted maturation are both prominent in humans, and mechanisms of this kind are a substrate for critical periods and potentially for circuit features specific to human brains.

The migration finding deserves separate treatment, because it changes what awakening means. In the mouse paralaminar nucleus, maturation of a subset of excitatory neurons includes translocation of the cell body into the adjacent endopiriform cortex during the juvenile-to-adolescent window (Alderman and colleagues, 2023). In the human, short-range

migration of excitatory neurons appears to continue during adolescence, particularly near the paralamina nucleus (Sorrells, 2024).

Everything in Sections VI and VII described awakening as a differentiation event occurring in place: the cell grows a dendrite, builds an axon initial segment, acquires input. Migration is a different order of undertaking. A migrating neuron must establish and maintain a leading process, generate traction, translocate the nucleus through the cytoplasm against resistance from the surrounding matrix, and reorganise its entire microtubule and actin cytoskeleton repeatedly over hours to days. It is the single most cytoskeletally demanding thing a post-mitotic neuron does, and the protein whose loss produces the classic human neuronal migration disorder — doublecortin itself, whose mutation causes X-linked lissencephaly and subcortical band heterotopia — is the protein these cells are defined by expressing.

Three implications follow and none has been pursued. The retention of doublecortin into adulthood may be functional rather than vestigial: a cell that may still be required to migrate decades after birth has a reason to keep a migration protein. If some fraction of awakening involves migration, then the cytoskeletal demand of awakening is far higher than a dendritic-growth model implies, which strengthens the proteostatic argument of Section XV and the liability reading of Section XVII. And the extracellular matrix becomes doubly important: migration through adult neural tissue requires a permissive matrix, the adult cortical matrix is substantially less permissive than the developmental one, and the matrix around these cells has never been characterised (Section V).

Whether cortical immature neurons migrate, as opposed to maturing in place, is not known. The paralamina observation is in a different structure, and no study has tracked the position of an identified cIN over time in the cortex. It is an answerable question with existing tools — the inducible doublecortin-driven lines permit sparse labelling, and the comparison of labelled-cell position between early and late timepoints is straightforward — and the answer would materially change the risk model.

Why this is the right reference case, and its limit. It is the right reference case because it is human, spans the lifespan, has a validated mouse homologue permitting mechanism, and has a functional readout. Its limit is that it is the amygdala. Whether the clock, the triggers and the endpoint are the same in the cortical population is an assumption, and a mapping between paralamina and cortical trajectories has not been established. Where this paper reasons from the paralamina nucleus to the cortex, the reasoning is analogical.

XII. Environmental and Experiential Governance

A fixed endowment can still be governed. What is set before birth is the number of cells; what happens to them afterwards — how fast they mature, how many remain, how complex they become — is in principle open to experience. The evidence that it is open is thin but real, and it is the most actionable part of the cell biology.

Early-life stress alters the population. Mice subjected to maternal separation for three hours daily from postnatal day three to day twenty-one, then left undisturbed until six weeks of age, showed a significant increase in the number of morphologically *complex* doublecortin neurons in the piriform cortex, with no such change in the olfactory bulbs. The same animals showed a male-specific increase in body weight and increased exploratory behaviour in the elevated plus maze — more head dipping, higher velocity, greater distance travelled — without significant differences in anxiety-like behaviour or in corticosterone after testing (Abellán-Álvaro and colleagues, 2024).

Three features of this result carry weight beyond its size. It is the *complex* subpopulation that changes, which is to say the cells partway through maturation, suggesting that the stressor altered the rate of the maturation process rather than the size of the endowment. The effect was specific to the cortical population and absent in the adult-born olfactory bulb population examined in the same animals, which is an internal control establishing that the two populations are regulated differently. And the behavioural changes were in exploration rather than anxiety, with no corticosterone signature, so the result is not a straightforward stress-axis effect.

The MeCP2 observation. In the same study, most doublecortin neurons of the piriform cortex were found to express MeCP2, while those of the olfactory bulb did not. As noted in Section V, a methyl-CpG-binding transcriptional repressor differentially present in the arrested cortical population is the right kind of molecule to be doing maintenance work, and MeCP2 is additionally interesting because its loss causes Rett syndrome and its biology connects the population to the general machinery by which experience is written onto chromatin. It remains one immunohistochemical observation.

The glucocorticoid vacancy constrains the mechanism. Any model in which stress acts on these cells directly has to contend with the finding that they lack glucocorticoid receptors (Gómez-Climent and colleagues, 2008). Early-life stress therefore reaches them indirectly — through altered network activity, through glia, through developmental programming of the local environment — rather than through circulating corticosteroid acting on the cell itself. This is a useful constraint: it predicts that the governance of this population runs through the tissue rather than through the endocrine system, and it is testable.

Exercise: the evidence and its limits. Physical activity is the best-characterised positive regulator of adult-born neurons, and it is frequently assumed to govern cINs as well. The assumption is not currently supported. The most informative recent study used single-nucleus RNA

sequencing to dissect the response to free-wheel running in the neurogenic niche of the hippocampal dentate gyrus in an amyloid model, and found transcriptomic responses to exercise most prominent in immature neurons, with restoration of a proportion of disease-dysregulated genes in a cell-type-specific manner (da Rocha and colleagues, 2025). The immature neurons in question are adult-born dentate neuroblasts, in a mouse, in a structure that is not the cortex. No study has asked whether exercise alters the cortical immature population, in any species. The inference is plausible — both populations are young cells in an adult brain, and both are regulated by activity in some fashion — but it is an inference across a cell type, a structure and a species boundary, and it should not be stated as a finding.

What has never been tested. Environmental enrichment, learning, sensory deprivation, olfactory experience, sleep, diet, inflammation and ageing interventions have all been examined extensively in relation to adult neurogenesis. For cortical immature neurons the list of published manipulations is, as far as we have been able to establish, approximately one: the maternal separation study above. This is the second emptiest area in the field after the matrix question of Section V, and it is directly relevant to disease, because a population that cannot be moved by any intervention is not a therapeutic target however interesting it may be.

XIII. What the Population Is For

Function is the weakest part of this literature, and it is worth separating what is argued from what is shown.

The reservoir argument. The dominant interpretation is that cINs constitute a reservoir of developmentally plastic cells available to an adult circuit, and that in large-brained mammals this substitutes for the stem-cell-driven neurogenesis those species have largely given up (La Rosa and colleagues, 2020; Bonfanti and colleagues, 2023). The argument is evolutionary and distributional: the inverse scaling of the two mechanisms across mammals is the evidence, and the inference is that two solutions to one problem are being traded off. This is the best-supported functional claim in the field and it is still an inference from distribution rather than a demonstration of function.

The structural plasticity argument. A second and older framing holds that the value of these cells is not their availability as replacements but the *kind* of plasticity they permit: whole-cell structural change, in which a neuron's differentiation state, morphology and connectivity are all altered together, as a third mode distinct from synaptic remodelling and from neurogenesis (Bonfanti and Nacher, 2012). The strength of this framing is that it does not require the cells to be replacements for anything, which matters given the physiology of Section VII.

The olfactory argument. The rodent population sits in the piriform cortex, an olfactory structure, and the mouse paralaminar homologue develops stimulus-driven responses to aversive

and appetitive *olfactory* stimuli as it matures (Alderman and colleagues, 2023). A role in olfactory learning is therefore the most concrete functional hypothesis available, and the olfactory system is independently a site of continuous structural plasticity. The limitation is that this cannot be the whole account, because in large-brained species the population extends across the neocortex, where it cannot be doing olfactory work.

The amygdalar and emotional-learning argument. In humans, the best-documented population sits at the interface of the amygdala and hippocampus, matures across adolescence, and has been proposed as a substrate for protracted plasticity in emotional circuitry during exactly the period when emotional and social learning is most consequential and when the vulnerability to mood and anxiety disorders emerges (Sorrells and colleagues, 2019; Sorrells, 2024). This is a developmental-psychiatric hypothesis, is actively pursued, and is not yet demonstrated.

What the physiology permits, and what it forbids. Section VII constrains all of the above. The matured cell is excitatory, high-threshold and dominated by inhibitory input. That profile is inconsistent with a simple replacement function and consistent with a conditional or sparse-coding role: a cell that contributes only when drive is strong or when inhibition is relieved. If that is right, the population's function is to add a *contingent* element to a circuit rather than to add capacity, and its loss or failure would manifest not as a proportional loss of function but as the loss of a specific operation under specific conditions. Nothing in the literature tests this, because nobody has recorded an identified cIN in a behaving animal.

What the host structure demands, and why it constrains the functional account. The rodent population lives in the piriform cortex, and the computational character of that structure is relevant to what a sparse, high-threshold cell could be for. Olfactory cortex does not receive a topographic map. It receives a distributed, combinatorial code in which an odour is represented by the identity of a scattered ensemble of active cells rather than by a position on a sheet, and the association of such ensembles with meaning is learned continuously throughout life. A structure performing that operation has a standing requirement for uncommitted coding capacity — elements that can be recruited to represent a conjunction that has not previously occurred — and it must meet that requirement without disturbing the ensembles already in use.

A conditional, high-threshold excitatory cell that is driven only under strong or coincident input is, functionally, an uncommitted element of exactly this kind. It contributes nothing to existing representations because it does not reach threshold under ordinary drive, and it becomes available to a new conjunction when drive is unusually strong. On that reading the physiology of Section VII is not a defect of incomplete maturation but the specification of the cell, and the dominance of inhibitory input is the mechanism that keeps it uncommitted until inhibition is relieved.

The genomic evidence is consistent with this and was not collected to test it. If glutamatergic identity in the olfactory cortex varies continuously rather than discretely (Zeppilli and colleagues,

2025), then the structure does not maintain sharply bounded cell types that a new cell would have to join; it maintains a gradient along which a cell can sit anywhere. A persistently immature population is then not an anomaly within the taxonomy but the youngest end of a continuum the structure keeps open. This also predicts that the matured cIN need not converge on any particular neighbouring phenotype — which is what the electrophysiology found.

Why the neocortical extension is harder to explain. The attraction of the olfactory account is also its limitation: it cannot be the whole story, because in large gyrencephalic brains the population extends across a neocortex that performs no olfactory computation and that does maintain discrete cell types (La Rosa and colleagues, 2020; Zeppilli and colleagues, 2025). Two readings are available and they are not equivalent. Either the neocortical cells are doing the same thing — holding uncommitted capacity in a structure that also benefits from it — in which case the neocortex has imported an olfactory solution, or they are a developmental spillover of a programme whose functional home remains allocortical, in which case their presence in the neocortex of large-brained mammals carries no functional implication at all. Distinguishing these requires knowing whether neocortical cINs mature and integrate in a gyrencephalic species, which has not been established; the fate-mapping evidence for awakening is entirely from rodent paleocortex.

The honest summary. There is no experiment in which the cIN population has been selectively manipulated and a behavioural or physiological consequence measured. The tools to do it now exist — the doublecortin-driven inducible Cre lines permit selective labelling and, in principle, selective silencing or ablation of the cohort (Rotheneichner and colleagues, 2018; Perez and colleagues, 2023). The experiment has not been reported. Until it is, every statement about what this population is for is an argument from design, distribution or analogy, and should be read as one.

XIV. Alzheimer's Disease I: The Anatomical Relationship

We now turn to disease, and we do so in three stages because the three kinds of claim available have very different evidential standing. This section concerns anatomy, where a good deal is known about the territory and nothing is known about the cells in it. Section XV concerns the molecular environment, where the chemistry is well characterised and its application to these cells is inference. Section XVI accounts for what has actually been measured in these cells in this disease, which is nothing, and explains why.

The territory. Alzheimer's disease does not begin diffusely. Its earliest cortical lesion is highly localised, and the location is layer II of the entorhinal cortex, where hyperphosphorylated tau accumulates and neurofibrillary tangles form before cortical pathology is widespread, and where neuronal loss is severe and early. The amygdala is involved early as well. The piriform and olfactory

territory is affected early, and olfactory impairment is among the earliest clinical signs of the disease. Each of these is a region in which cortical immature neurons have been described.

That overlap is real and it is the reason the question in this paper is worth asking at all. It is also considerably more complicated than it first appears, and the complication has been the source of error in secondary accounts.

Layer II is an address, not a cell type. At least three distinct neuronal populations share it, and they have different relationships to the disease.

The first are the reelin-expressing projection neurons of the anterolateral entorhinal cortex. These are mature excitatory projection neurons, unusual among cortical excitatory cells in expressing reelin itself, and they are the predominant cortical site of tau hyperphosphorylation and tangle formation in prodromal disease (Kobro-Flatmoen and colleagues, 2023). They are not immature, do not express doublecortin, and are not a reservoir. They are the first cortical casualties.

The second are the cortical immature neurons of this paper: prenatally generated, doublecortin-positive, non-dividing, excitatory by lineage, distributed across layer II of the paleocortex in rodents and more widely in large-brained species.

The third are the ordinary mature granular and pyramidal neurons that constitute the bulk of layer II across the cortex and have no special relationship to either reelin or immaturity.

Conflating the first two produces an attractive and unsupported picture — a dormant reserve held in place by reelin and destroyed by the disease that attacks its layer — in which the documented vulnerability of the entorhinal projection neurons is transferred to the immature population, and the immature population's reservoir properties are transferred to the entorhinal neurons. Neither transfer is warranted. The cells that tangle first are not the immature ones, and the cells that constitute the reservoir have not been shown to tangle at all.

What the co-location does and does not license. It licenses the following: cINs in the human entorhinal and perirhinal cortex, the piriform cortex and the amygdala are situated in tissue that experiences the disease's earliest and most severe molecular insult. Whatever is happening in that tissue — the amyloid, the tau, the microglial activation, the matrix remodelling — is happening in the immediate neighbourhood of these cells, and in human cortex microglial processes have been found directly apposed to their somata and dendrites (Coviello and colleagues, 2022). They are not bystanders in a distant region; they are residents.

It does not license any inference about their fate. Co-location is exposure, not outcome. A cell can sit in diseased tissue and be destroyed, be unaffected, be activated, or participate in the pathology, and the four possibilities are distinguished only by measurement.

The olfactory territory, which is the most neglected part of the overlap. Of the regions in which cINs have been described, the piriform and olfactory cortex is the one where the disease's early involvement is least often discussed in cellular terms and most often noted clinically. Olfactory dysfunction is among the earliest detectable changes in Alzheimer's disease, appears in the preclinical stage preceding mild cognitive impairment, and is sufficiently specific that olfactory testing is used for screening in community cohorts and proposed as a component of early-detection models (Liao and colleagues, 2024).

Three facts therefore coincide in one territory and have not been put together. The piriform cortex is the structure in which cINs were discovered, in which they are most numerous in rodents, and in which the entire fate-mapping and electrophysiological literature was produced (Gómez-Climent and colleagues, 2008; Rotheneichner and colleagues, 2018; Benedetti and colleagues, 2020). The mouse paralaminar homologue develops responses to olfactory stimuli as its cells mature, which is the field's only functional readout of awakening (Alderman and colleagues, 2023). And olfactory function is among the first things Alzheimer's disease takes.

We state carefully what this does and does not support. It does not support the claim that cIN failure causes early olfactory impairment in Alzheimer's disease; olfactory dysfunction has many candidate substrates, including the olfactory epithelium, the bulb, and the adult-born bulb neurons supplied by the subventricular zone, and no study implicates cINs. What it supports is a research-design argument: if one wanted a human cortical region in which the immature population is relatively abundant, the disease arrives early, and a non-invasive functional readout exists that could in principle be correlated with a post-mortem cellular measurement, the olfactory territory is the only region that offers all three. That combination is unusual and is being used by nobody.

The rodent opportunity is also unusual here, and is the one place where the species problem of Section IX does not bite. Mice lack neocortical cINs but possess a substantial piriform population. A mouse experiment in piriform cortex — asking whether amyloid or tau pathology alters the maturation trajectory of an identified, fate-mapped cIN cohort, with olfactory discrimination as the behavioural readout — is therefore both feasible and interpretable, and would be the only causal experiment on this cell type that the standard model organism permits.

The amygdala as the most promising site. If one had to choose a single structure in which to examine this question in human tissue, the amygdala paralaminar nucleus would be the rational choice, for four reasons that converge. It is the human structure in which the immature population is best characterised, with a described lifespan trajectory (Sorrells and colleagues, 2019). It has a validated mouse homologue, so mechanism is accessible (Alderman and colleagues, 2023). It is substantially affected in Alzheimer's disease. And it retains immature cells into old age, which means that in an elderly patient there is still a population present to examine — whereas in cortical

regions where the endowment is largely spent by late life, a disease effect might be undetectable simply because little remains.

The timing argument, and its weakness. It is tempting to note that the human cIN population contracts across adult life and that Alzheimer's disease is a disease of later life, and to infer a relationship. The inference does not hold. The contraction is the expected consequence of maturation in a fixed endowment (Sections III and VI), occurs in everyone, and is therefore a property of normal ageing rather than a disease mechanism. A disease-specific effect would have to be a *deviation* from the normal trajectory, which requires knowing the normal trajectory quantitatively — and as Section X established, no such normative human dataset exists.

XV. Alzheimer's Disease II: The Molecular Environment a cIN Inhabits

If we cannot yet say what happens to these cells, we can say with precision what they are exposed to, because the molecular environment of layer II in the Alzheimer brain is one of the better-characterised micro-environments in the field. This section assembles it, and marks clearly where each step is an established property of the tissue and where it becomes an inference about this cell.

The sugar bed, and the fact that it is read in at least three ways. Heparan sulfate is a linear sulfated polysaccharide displayed on core proteins at the neuronal surface and through the extracellular matrix. Its sulfation is patterned: N-deacetylase/N-sulfotransferases install N-sulfate, and separate 2-O-, 6-O- and 3-O-sulfotransferases decorate specific ring positions, so the finished polymer is a mosaic of differently sulfated domains. Proteins do not bind heparan sulfate generically; they bind particular patterns, and three of those patterns are directly relevant here.

Reelin requires N-sulfation. Full-length reelin binds heparan sulfate with a dissociation constant of 17 ± 5 nanomolar, N-sulfation is the critical determinant, heparinase treatment or knockout of the N-sulfotransferase NDST1 markedly reduces reelin attachment to the cell surface, and — the functional step — heparinase or added heparin reduces reelin-induced dimerisation of its receptor ApoER2, while N-desulfated heparin does not. The sugar is a co-receptor, not a backdrop: without the N-sulfated bed the receptor does not dimerise and the signal does not start (Pan and colleagues, 2025).

Tau seeds require 6-O-sulfation. The transcellular propagation of tau begins with internalisation of seeds mediated by cell-surface heparan sulfate proteoglycans (Holmes and colleagues, 2013), and the dependence is specific: genetic or enzymatic removal of the 6-O-sulfotransferase reduces tau entry into human neurons and brain slices (Rauch and colleagues, 2018).

The microglial sensor TREM2 also requires 6-O-sulfation. TREM2 binds cell-surface heparan sulfate and forms binary complexes with it, requiring a minimum chain length of about ten saccharide units, with 6-O-sulfation the crucial determinant and N-sulfation explicitly dispensable; the same 6-O-sulfation is required for TREM2-mediated uptake of apolipoprotein E by microglia (McMillan and colleagues, 2024).

Set those three side by side and the structure of the environment is clear and somewhat counter-intuitive. The protective ligand and the clearing cell's sensor read *different and separable* marks. The clearing cell's sensor and the propagating seed read the *same* mark. And the pattern is not static: the 3-O-sulfotransferase HS3ST2 is upregulated in the Alzheimer hippocampus, with its product relocating from membrane to the interior of degenerating neurons (Sepulveda-Diaz and colleagues, 2015), so the code drifts as the disease proceeds.

Why this bears on an immature cell specifically — and where the inference begins. Everything above is established chemistry in Alzheimer tissue generally. The step to cINs is an inference, and it rests on a property of the cells themselves rather than on any measurement in them. These cells carry an unusually heavy, highly charged carbohydrate coat — the polysialylated neural cell adhesion molecule that defines them — and they sit in a matrix whose sulfation state is changing. Their identity is substantially a matter of cell-surface carbohydrate, in a tissue whose cell-surface carbohydrate is being remodelled. That is a reason to look, and it is not a result. No study has characterised the sulfation environment of a cortical immature neuron, in health or disease. Section V noted the same gap for the perineuronal net.

Reelin, which is the strongest link and still indirect. Reelin signals through ApoER2 and the very-low-density lipoprotein receptor to induce tyrosine phosphorylation of Disabled-1, and loss of the pathway is associated with tau hyperphosphorylation (Hiesberger and colleagues, 1999). Reelin signalling through this route phosphorylates cofilin at serine 3 and stabilises actin, though this was established in a developmental context (Chai and colleagues, 2009). The human resilience evidence is striking: a man heterozygous for the rare *RELN* variant H3447R, named COLBOS, remained cognitively intact until sixty-seven despite carrying the PSEN1-E280A mutation, with an extremely elevated amyloid plaque burden but limited entorhinal tangle burden, and the variant is gain-of-function, showing stronger activation of Disabled-1 and reduced tau phosphorylation in a knock-in mouse (Lopera and colleagues, 2023).

Three qualifications keep this from being a result about cINs. The resilience was expressed as a preserved entorhinal cortex, and the protected cells were the reelin-expressing projection neurons — the first population of Section XIV, not the immature one. The reelin-cofilin link was shown in development, not in adult disease. And most importantly, the widely repeated claim that reelin maintains immature neurons in a dormant state is unsupported in either direction: no study has measured reelin signalling in doublecortin-positive layer II cells, and no manipulation of reelin has

been shown to alter their maturation state. The pathway is plausibly relevant to a cell whose business is cytoskeletal remodelling, and that is the extent of what can be said.

A complication from the layer itself. In reelin-expressing projection neurons of the anterolateral entorhinal cortex in a rat model reproducing the disease's spatio-temporal cascade, reelin and intracellular amyloid- β engage in a direct protein-protein interaction at pre-plaque stages, and lowering reelin with a viral micro-RNA *lowered* intracellular amyloid- β across three levels of aggregation without substantially changing amyloid precursor protein, with amyloid levels dependent on reelin levels across 25,548 neurons from 24 animals (Kobro-Flatmoen and colleagues, 2023). Reelin in layer II is therefore not a simple protective brake whose restoration is unambiguously good; in the population where it has been manipulated, less of it meant less intracellular amyloid. Any model that assigns reelin a single sign in this layer is incomplete.

What maturation costs, and why an aged tissue makes it expensive. One further element of the environment is not chemical but metabolic, and it is specific to a cell that still has a developmental programme to run.

Completing maturation is among the most demanding things a neuron can do. The cell must build a dendritic arbour and populate it with spines, assemble an axon initial segment with its specialised cytoskeletal and channel architecture, insert receptors and synaptic machinery at new contacts, and — in the paralaminar nucleus at least — in some cases translocate its cell body into an adjacent structure (Rotheneichner and colleagues, 2018; Alderman and colleagues, 2023). Each of these is a large biosynthetic and cytoskeletal undertaking requiring protein synthesis, folding, trafficking, degradation of intermediates, and sustained mitochondrial support at the growing process.

The tissue in which an adult cIN attempts this is not the tissue in which its contemporaries did so. It is older, by decades in a human. Its proteostatic capacity is lower, its mitochondrial function is reduced, its matrix is stiffer and differently sulfated, and in Alzheimer's disease it additionally contains amyloid species, inflammatory mediators, and microglia in an altered state. The relevant observation from the adjacent literature is that where immature neurons are lost in a model combining amyloid and tau pathology on a human APOE4 background, the loss was associated with tau-related mitochondrial dysfunction and cellular senescence rather than with a dedicated mechanism aimed at young cells (Lei and colleagues, 2025). A general failure of cellular housekeeping was sufficient to remove them.

This generates a prediction with an unusual structure, and it is the mechanistic core of the liability reading developed in Section XVII. If maturation is expensive and the tissue is impoverished, then an arrested cIN is in the safer state and a maturing one is in the more dangerous state. Risk would then be a function of the *rate* at which cells leave the arrested state, not of how many remain in it — and an intervention that increased that rate in a compromised brain would

increase harm while appearing, by any count of immature cells, to be depleting a reserve. The same measurement would be produced by a protective mechanism working well and by a harmful one working fast.

We have no evidence that this is what happens. We note it because it is the only reading we can construct in which the therapeutic sign is negative, because it follows from premises that are individually well supported, and because it is distinguishable from the alternative by one measurement: whether pathological markers in these cells are concentrated in the arrested or the maturing fraction.

Microglia, and the one direct observation. The disease-associated microglial state was defined by single-cell transcriptomics of immune populations in wild-type and Alzheimer-transgenic mouse brain, with immunohistochemical confirmation in mouse and human tissue showing these cells containing intracellular amyloid particles. Activation is a two-step programme: a first step independent of TREM2, consisting principally of downregulation of homeostatic microglial checkpoint genes, and a second, TREM2-dependent step installing the fully phagocytic programme. The authors describe a cell type with the potential to restrict neurodegeneration (Keren-Shaul and colleagues, 2017).

The direct observation that connects this to cINs is the apposition. In human cortex, microglial processes are found in close apposition to the somata and dendrites of layer II immature neurons, graded by maturation state and most pronounced on the least differentiated cells (Coviello and colleagues, 2022). Microglia are in physical contact with these cells in the normal human brain. Microglia are the cell type whose state changes most dramatically in Alzheimer's disease. And microglia are established regulators of the survival, pruning and integration of immature neurons in the systems where that has been studied. The conjunction is a strong reason to expect an effect and is not evidence of one.

The amyloid and tau exposure, stated without extrapolation. There is no measurement of amyloid- β burden, tau burden, tau phosphorylation or tau isoform composition in cortical immature neurons. This last absence is the most consequential single gap in the paper and deserves to be stated as a specific question rather than a general lament. Immature neurons elsewhere in the nervous system express a developmentally distinct complement of tau — the three-repeat isoforms predominate in development and the four-repeat isoforms accumulate with maturity — and the isoform balance is a determinant of aggregation behaviour. Whether a cell that has held a juvenile differentiation programme for decades also holds a juvenile tau isoform profile is therefore a question with a clear mechanistic payoff in either direction: a juvenile profile would make these cells biochemically distinct from their tangling neighbours, and an adult profile would make their immaturity selective rather than global. Nobody has run the stain. Both the question and the reagents are standard.

XVI. Alzheimer's Disease III: What Has Actually Been Measured

A reader is entitled to know the size of the evidence base, and in this case the honest statement is unusual enough that it should not be softened.

The direct literature is empty. There is no published study of cortical immature neurons in Alzheimer's disease. There is no count of doublecortin-positive layer II neurons in Alzheimer cortex against age-matched control, in any cortical region. There is no staging of their maturation state by Braak stage. There is no measurement of tau isoform, tau phosphorylation, amyloid burden, matrix composition or glial apposition in these cells in disease. There is no study in an animal model, which is partly explained by Section IX: the standard models are mice, and mice have essentially no neocortical cINs.

This is not the ordinary situation in which a question is contested or underpowered. It is an absence. We state it because the alternative — assembling a mechanism from adjacent findings and presenting it as the state of knowledge about these cells — would misrepresent the field, and because an explicit vacuum is a more useful thing to hand a laboratory than a plausible narrative.

How the absence was established. A claim of absence requires a method, and ours was as follows. We searched for the conjunction of the cell type and the disease using every combination of the population's names — cortical immature neurons, immature neurons of layer II, doublecortin-positive cortical neurons, non-newly generated immature neurons, tangled cells, complex cells — with Alzheimer's disease, dementia, tauopathy and neurodegeneration; we searched the markers (doublecortin, PSA-NCAM) against the disease in human and animal tissue; we searched the regional terms (cortical layer II, piriform cortex, paleocortex, amygdala paralaminar nucleus) against the disease; and we examined the citing and cited literature of the field's principal papers. The searches return the dentate neurogenesis literature, the entorhinal layer II degeneration literature, and the comparative cIN literature — three bodies of work, none of which intersects the other two at the point in question. We therefore state the absence as a result of a systematic negative search rather than as an impression, while noting the limitation proper to all such claims: a single small study in a venue not indexed for these terms would not have been found.

Why the absence is easy to miss. Searching the Alzheimer literature for immature neurons returns a substantial body of work, and essentially all of it concerns the adult-born neuroblasts of the dentate gyrus. The phrase is the same and the cells are different. A reader who does not make the distinction of Section II will conclude that the question has been studied extensively, and will be wrong. The two literatures do not cite each other: the cIN literature is comparative neuroanatomy and developmental cell biology, published largely in anatomy and comparative-biology venues by a small number of European groups, and the Alzheimer immature-neuron literature is hippocampal

neurogenesis, published in neuroscience and translational venues by a different set of groups. There is no shared reviewer pool. This is the proximate explanation for the gap, and it is a better explanation than difficulty, because the experiments are not difficult.

What the dentate literature establishes, and why it is the most useful thing available. Precisely because the dentate population *has* been studied in human Alzheimer tissue, it provides the only empirical model of what happens to an immature neuron population in this disease. Four results matter.

First, the population persists into old age and declines with disease. Thousands of immature neurons were identified in the dentate gyrus of neurologically healthy human subjects up to the ninth decade, exhibiting variable degrees of maturation along the differentiation sequence, while the number and maturation of these neurons declined progressively as Alzheimer's disease advanced (Moreno-Jiménez and colleagues, 2019). The methodological dispute recorded in Section X applies to this measurement and has not been resolved.

Second, and far more informative, the lesion appears to be one of *state* rather than number. Single-nucleus RNA sequencing of aged healthy, Alzheimer, and dementia-resilient human hippocampus identified persistent populations of immature neurons across all donor groups, with transcriptional profiles reflecting juvenile cellular functions — and those juvenile programmes were compromised in Alzheimer's disease. The authors' reading is that the presence of these populations may actively contribute to maintaining homeostasis in the aged human hippocampus and to cognitive resilience in disease (Tosoni and colleagues, 2026). The accompanying commentary put the point in the form that matters for experimental design: it is the molecular state of these cells, not simply their abundance, that tracks pathology and resilience (Farmer and Song, 2026).

Third, animal work indicates that the damage to immature neurons can be mediated by general cellular failure rather than by a dedicated mechanism. In a model combining amyloid and tau pathology on a human APOE4 background, there was a marked reduction in hippocampal immature neurons associated with tau-related mitochondrial dysfunction and cellular senescence — a phenotype absent from the tau-only model even at a later age — and inhibition of astrocytic IRAK1/TAK1 signalling attenuated the mitochondrial dysfunction and the loss of both mature and immature neurons (Lei and colleagues, 2025).

Fourth, the response of an immature population to upstream pathology is not purely degenerative. Expressing human tau in the lateral entorhinal cortex produced, in downstream dentate neurons, a loss of mushroom spines and reduced dendritic complexity of adult-born neurons — and simultaneously *increased* neurogenesis and increased the density of thin spines on adult-born neurons, with an increased slope of synaptic input–output curves and no change in the magnitude of long-term potentiation (Ash and colleagues, 2025). Degeneration and compensatory neuroplastic change occurred together in the same preparation.

What transfers and what does not. The transfer from dentate to cortex is an analogy across a cell type with different origin, different renewability and different physiology, and the differences are exactly the ones that could make the analogy fail: a replaceable population can mount a compensatory expansion, and a fixed endowment cannot. The increased neurogenesis in the Ash result has no possible counterpart in a cIN population, because nothing divides. If a pathological environment damages cINs, there is no compensatory arm available.

What does transfer, and what reorients the experimental programme, is the state-versus-number lesson. If in the one immature population that has been examined in the human Alzheimer brain the informative variable is the integrity of the juvenile transcriptional programme rather than the cell count, then the obvious first experiment in the cortex — counting doublecortin-positive profiles — is probably the wrong one, or at least radically insufficient. A count could be flat while the programme was failing, and a count could fall for the entirely normal reason that cells matured. Section XVIII is built around this conclusion.

XVII. Three Hypotheses the Present Evidence Cannot Separate

Given the above, three accounts of the relationship between cortical immature neurons and Alzheimer's disease are compatible with everything known. They are not variants of one idea; they make opposite predictions, and they are separable by experiment. Setting them out explicitly is more useful than advocating one.

Hypothesis 1 — The cells are irrelevant. The population is a developmental remnant of the olfactory cortex, extended across the neocortex in large-brained species without acquiring a substantial functional role, spent on a schedule that is unaffected by disease. Its co-location with early pathology is a consequence of both being features of allocortical and periallocortical territory, and carries no causal significance. Under this hypothesis, doublecortin-positive counts and maturation-state distributions in Alzheimer cortex will not differ from age-matched control once normal ageing is accounted for, and the juvenile transcriptional programme will be intact in these cells even where the surrounding tissue is severely affected.

This hypothesis is the null, it is not currently excluded, and it deserves more weight than enthusiasm for the population usually affords it. The physiology of Section VII — a sparse, high-threshold, inhibition-dominated cell — is consistent with a population whose removal would be hard to notice.

Hypothesis 2 — The cells are a resilience substrate that the disease degrades. The population contributes to the brain's capacity to tolerate pathology, by whatever mechanism the matured cell's conditional physiology affords, and the Alzheimer environment compromises that contribution. On the dentate precedent this would occur primarily as a failure of the juvenile

programme rather than as cell death (Tosoni and colleagues, 2026), plausibly through mitochondrial dysfunction and senescence (Lei and colleagues, 2025), through microglial state change acting on cells with which microglia are in direct contact (Coviello and colleagues, 2022; Keren-Shaul and colleagues, 2017), or through remodelling of the sulfated matrix on which a carbohydrate-coated cell depends (Pan and colleagues, 2025; Sepulveda-Diaz and colleagues, 2015).

This hypothesis predicts that in Alzheimer cortex the immature population will show a shifted maturation-state distribution and a degraded juvenile transcriptional signature, with the degradation appearing earlier and more severely than any change in cell number; that the effect will be graded with local pathology within a brain; and that it will be most marked in the amygdala paralaminar nucleus and entorhinal and piriform cortex. It further predicts that individuals with preserved cognition despite pathology — the resilient — will show preserved juvenile programmes, which is the single most discriminating measurement available and is directly modelled on the dentate result.

Hypothesis 3 — The cells are a liability that the disease recruits. The inverse reading. A cell attempting a developmental programme in an aged, inflamed, proteostatically compromised tissue may be at elevated risk precisely because of what that programme demands. Three specific demands are identifiable. Maturation requires large-scale cytoskeletal reorganisation — in the paralaminar nucleus it can require migration of the cell body itself (Alderman and colleagues, 2023) — and microtubule-associated proteins are the substrate on which this disease's principal lesion is written. Maturation requires construction of an axon initial segment and a spiny dendritic tree (Rotheneichner and colleagues, 2018), which is a substantial biosynthetic and proteostatic load in a cell whose quality-control systems are old. And maturation requires the cell to acquire synaptic input in a neighbourhood where amyloid species are present and where synaptic assembly is already failing.

Under this hypothesis, an immature cell is safe while arrested and at risk while awakening, and the relevant variable is the *rate* of awakening rather than the size of the pool. It predicts that in Alzheimer cortex the cells in intermediate maturation states will be selectively depleted or selectively bear pathological markers, that tau pathology will be detectable preferentially in maturing rather than arrested cells, and — the therapeutically important prediction — that mobilising this population in a brain with established pathology would be harmful.

The predictions can be set side by side, and the exercise is worth doing explicitly because it shows how little the obvious experiment would discriminate.

Measurement	H1: irrelevant	H2: resilience substrate	H3: liability
DCX+ cell count, AD vs control	No difference beyond ageing	May be unchanged or modestly reduced	Unchanged or raised (arrested cells retained)
Maturation-state distribution	Unshifted	Shifted toward less differentiated; degraded transition	Selective depletion of intermediate states
Juvenile transcriptional programme	Intact	Degraded, and degraded early	Intact in arrested cells; disrupted in maturing ones
Phospho-tau within the population	Absent	Absent or incidental	Present, preferentially in maturing cells
Correlation with local pathology	None	Graded with pathology	Graded with maturation rate, not pathology burden
Status in cognitively resilient cases	Same as AD	Preserved programme — the discriminating result	Preserved by <i>lower</i> maturation rate
Effect of mobilising the population	Neutral	Beneficial	Harmful

The bottom row is the reason the question is not academic, and the second-to-last row is the measurement that separates the two live hypotheses most cleanly.

Why the three cannot be separated by counting. All three are compatible with a falling doublecortin count, because the count falls normally. All three are compatible with an unchanged count: Hypothesis 1 because nothing happens, Hypothesis 2 because the lesion is in state not number, Hypothesis 3 because loss of maturing cells and retention of arrested cells can leave the immature count flat or even raised. The measurement that separates them is the *joint distribution of maturation state and pathological markers within the population*, which is a different experiment from a count and requires either multiplexed immunohistochemistry with maturation staging or single-nucleus transcriptomics with sufficient depth to resolve a sparse population.

A note on the therapeutic stakes. Hypotheses 2 and 3 prescribe opposite interventions. Under 2, preserving or restoring the juvenile programme is protective. Under 3, the same action accelerates the exposure of vulnerable cells to a hostile environment. Both positions have advocates in the adjacent literature on neurogenesis and both have been argued without the discriminating data. This is a sufficient reason not to pursue mobilisation of immature neurons as a therapeutic strategy until the sign of the effect is known, and it is a reason to regard the sign as an experimental priority rather than a matter for argument.

XVIII. The Experimental Programme

What follows is ordered by information yield per unit of cost, not by ambition. The first four experiments use tissue that already exists in brain banks and reagents that are already validated; none requires a new animal model, and none requires a reagent that does not exist. The last two are larger.

1. The normative human map. Before any disease comparison is interpretable there must be a baseline, and there is not one. Quantify doublecortin-positive and polysialylated-neural-cell-adhesion-molecule-positive layer II neurons stereologically across defined cortical regions — entorhinal, perirhinal, piriform, temporal neocortex, frontal neocortex, with primary sensory cortex as an internal comparison — across the adult human lifespan, with maturation staged by dendritic complexity on the type I / type II criterion (Coviello and colleagues, 2022) and by NeuN co-expression. Control post-mortem interval and fixation explicitly, and validate the antibody against the doublecortin transcript in a subset, which is now the standard the field has set for itself (Ghibaudi and colleagues, 2023a). The product is an age- and region-resolved normative dataset, which does not presently exist and without which every subsequent measurement floats.

2. The disease comparison, staged rather than counted. Repeat the above in Alzheimer tissue against age-matched control, stratified by Braak stage, and report the *distribution across maturation states* rather than a single count. The specific predictions of Section XVII are: no difference under Hypothesis 1; a shift of the distribution with degraded differentiation under Hypothesis 2; and selective depletion of intermediate states under Hypothesis 3. Include the amygdala paralaminar nucleus, which Section XIV argues is the most favourable site, and include a region of late-affected cortex within each brain so that each case carries its own internal control for global tissue quality — the design feature that would insulate the result from the fixation objections that have dogged the hippocampal literature.

3. The isoform and phosphorylation stain. Co-stain doublecortin with three-repeat and four-repeat tau isoform-specific antibodies and with phospho-tau epitopes, in control and Alzheimer tissue, in the regions above. This answers the question posed at the end of Section XV, which has never been asked in any species in health or disease, and it is the measurement most likely to produce an unambiguous result from an afternoon's work. A juvenile isoform profile in these cells makes them biochemically distinct from the tangling neurons beside them; an adult profile makes their immaturity selective; and phospho-tau in maturing but not arrested cells would be direct support for Hypothesis 3.

4. The matrix characterisation. Determine whether cortical immature neurons bear perineuronal nets, and characterise the sulfation state of their local matrix, using Wisteria floribunda agglutinin and aggrecan for the condensed chondroitin-sulfate net and domain-specific antibodies for N-sulfated and 6-O-sulfated heparan sulfate. Section V establishes that this has never been done;

Section XV establishes why it matters — a carbohydrate-defined cell in a tissue whose carbohydrate code drifts with disease. Run it in control tissue first, because the normal answer is unknown.

5. The state measurement. Single-nucleus transcriptomics of layer II in control, Alzheimer, and resilient human cortex, with sufficient depth and cell numbers to resolve a sparse population, scoring the juvenile transcriptional programme in immature cells directly. This is the cortical counterpart of the dentate experiment that produced the field's most informative result (Tosoni and colleagues, 2026), and it is the only design that measures the variable that result identified as the meaningful one. The resilient arm is essential and is the part most likely to be omitted on cost grounds; without it the experiment measures disease but not protection. The principal technical risk is that the population may be too sparse in neocortex for adequate sampling, which argues for enriching by region — paralaminar nucleus, entorhinal and piriform cortex — or for spatial rather than dissociative methods.

6. The function experiment. Independent of disease, and overdue: selectively silence or ablate the cortical immature cohort in a mouse using the available doublecortin-driven inducible Cre lines (Rotheneichner and colleagues, 2018; Perez and colleagues, 2023) and measure olfactory learning and discrimination. Section XIII records that no such experiment has been reported, and that in its absence every statement about what the population does is an argument from design. The result would be interpretable even in a rodent, because the rodent does possess the piriform population; the species problem of Section IX constrains neocortical work, not this.

Two mechanistic experiments that follow if any of the above is positive. Test whether arrest is gated by the identified absences, by forcing N-methyl-D-aspartate receptor expression in an identified cIN and asking whether maturation proceeds; and test the glial gate by selective disruption of astroglial ensheathment with maturation state as the readout. Both are hypothesis-generating rather than confirmatory and both address Section V's central gap, which is that the field cannot presently say what holds these cells still and therefore cannot say what a pathological environment would do to the holding.

A practical note on tissue, because it determines whether any of this happens. The programme above is cheap in reagents and expensive in tissue, and the tissue requirements are specific enough to be worth stating. Experiments 1 to 4 need fixed material from defined cortical regions, with post-mortem interval recorded and ideally under twenty-four hours, from donors spanning at least the fourth to the tenth decade, with neuropathological staging available and with cognitive assessment close to death. The resilient arm that Section XVI identifies as decisive requires the rarest category: donors with substantial neuropathology and preserved cognition, which exist in numbers only in the large community cohort studies that collect longitudinal cognition alongside autopsy. Experiment 5 additionally requires frozen tissue from the same regions in the same donors, which many banks do not hold region-matched to the fixed material.

The practical consequence is that this is not a programme a single laboratory can assemble opportunistically from whatever blocks are available. It requires a request to a cohort-based bank specifying region, interval, staging and cognitive data together, and the regions requested — entorhinal, perirhinal, piriform, amygdala with the paralaminar nucleus intact — are not the blocks such banks distribute by default. Specifying this at the outset is the difference between a study that can discriminate the hypotheses of Section XVII and a study that produces a count from convenience material and settles nothing.

What would make the programme unnecessary. If experiment 2 returns a flat maturation-state distribution and experiment 5 returns an intact juvenile programme in a well-powered design with a resilient arm, Hypothesis 1 is supported and the population can be set aside as a developmental curiosity with no bearing on this disease. That is a legitimate and useful outcome, and it should be stated in advance as such rather than treated as a failed experiment.

XIX. What Would Refute the Line of Inquiry

A paper that names an unexamined population has an obligation to specify the conditions under which the examination should stop. Five findings would, individually or jointly, close the question.

A flat distribution with an intact programme. As above: no shift in maturation-state distribution in Alzheimer cortex, and an intact juvenile transcriptional signature in a design including resilient cases. This is the decisive negative and it is cheap.

Demonstration that the human neocortical population is quantitatively trivial. The comparative claim is that density rises with brain size (La Rosa and colleagues, 2020), but no absolute human count exists. If the normative map of experiment 1 shows that the number of cINs in the relevant human cortical regions is small enough that their loss or failure could not plausibly influence circuit function — and a stereological count is what settles this — then the population may be real and still irrelevant to a disease of cortical network failure. The amygdala paralaminar nucleus would remain a separate question.

Demonstration that the human cortical signal is an artefact. The human claim rests on doublecortin immunoreactivity. It has been strengthened by transcript co-localisation in selected cases (Ghibaudo and colleagues, 2023a), but that validation has been applied to a small number of specimens. If systematic validation across adequate numbers showed the layer II signal in adult human neocortex to be reagent artefact or to label a non-neuronal or mature population, the human arm of the entire field would close, leaving an interesting rodent paleocortical biology with no human counterpart.

Demonstration that maturation does not occur in the adult human. The fate-mapping evidence for awakening is from mice (Rotheneichner and colleagues, 2018). The human evidence is inferential — the presence of intermediate forms, the transition of paralamina cells across adolescence (Sorrells and colleagues, 2019), the synaptic markers on type II cells (Coviello and colleagues, 2022). If it could be shown that in the adult human cortex these cells never complete maturation, the population would be a terminal remnant rather than a reservoir, and most of the functional and therapeutic interest would be removed — though the liability reading of Hypothesis 3 would also be removed with it.

Demonstration that the cells are simply not present in affected tissue. If cINs prove to be absent from the human entorhinal and perirhinal cortex specifically, while present elsewhere, the anatomical premise of the disease question fails. The regional survey of experiment 1 answers this, and it answers it early.

A condition that would redirect rather than close the inquiry. One possible finding belongs in neither column. If the normative map shows that the human cortical population is largely spent by the sixth decade — that is, that by the age at which Alzheimer's disease ordinarily appears there is little immature material left in the cortex — then the disease question as posed becomes moot for the cortex while remaining live for the amygdala paralamina nucleus, where immature cells persist into old age (Sorrells and colleagues, 2019). It would also open a different and arguably more interesting question: whether the *rate* at which an individual spent their endowment across earlier adult life, rather than what remains of it at the end, is what bears on later resilience. That question would require longitudinal or cohort-based inference from a cross-sectional measurement and would be considerably harder than anything proposed in Section XVIII. We note it because a null result in late-life cortex should not be read as closing the subject if the endowment was simply gone before the disease arrived.

What would not refute it. Three things would commonly be offered as negative evidence and should not be accepted. A fall in doublecortin count with age or disease, because the fall is expected under the healthy model and is the single most likely source of a false positive and a false negative alike. A null result in a mouse neocortex, because the substrate is absent (Section IX). And a null result from counting alone in a design without maturation staging or state measurement, because Section XVII shows that all three hypotheses are compatible with a flat count.

XX. Conclusion

The cell this paper is about is better characterised than its obscurity suggests, and what is known about it is more interesting than the framing it usually receives.

It is a prenatally generated, post-mitotic neuron of cortical layer II that has not completed differentiation and may not do so for decades. Its arrest is not a passive persistence of a developmental state but a configuration in which the ordinary channels of instruction are closed: no synapses, no N-methyl-D-aspartate receptors, no glucocorticoid receptors, no immediate-early gene response, and a physical sheath of glial membrane whose density is inversely graded with maturation. What maintains that configuration is unknown, and the candidate mechanisms — the receptor vacancy, the glial gate, the polysialic acid coat, the unexamined matrix, the MeCP2 observation — have not one causal test among them.

The arrest lifts. Lineage tracing from the doublecortin locus establishes that these cells resume maturation, become glutamatergic, build an axon initial segment and a spiny apical dendrite, and acquire synaptic input — so the age-related disappearance of the marker is graduation rather than death. But what they graduate into is not a copy of the neurons beside them. The matured cell is harder to excite than its neighbours, fires at lower maximal frequency, and receives input that is predominantly inhibitory despite carrying glutamatergic contacts. It is a distinct functional class. The reservoir, whatever it is for, is not a supply of spare principal neurons, and the word *reserve* should be used in this context with that correction attached.

The population is distributed inversely to adult neurogenesis across mammals, which is the field's most secure quantitative finding and its largest practical obstacle: the animal in which Alzheimer's disease is modelled is the animal in which these cells are virtually absent from the neocortex. Single-cell genomics places them within a continuous rather than discrete landscape of glutamatergic identity in the olfactory cortex, a structure whose transcriptomic profile is closer to that of reptiles and amphibians than to neocortex — which suggests the phenomenon is an ancestral retention rather than a mammalian invention.

On Alzheimer's disease, the position is that there is no evidence, and the appropriate response to that is to say so and then to specify the measurement. The cells sit in the tissue that the disease attacks first, in physical contact with the cell type whose state changes most, in a matrix whose sulfation code drifts as the disease proceeds, carrying a carbohydrate coat as their defining feature. Not one of those exposures has been converted into a measurement. The question is not contested; it has not been asked.

The most useful guidance comes from the one immature population that has been examined in the human Alzheimer brain. In the dentate gyrus, the juvenile transcriptional programme persists into the ninth decade, is compromised in disease, and tracks cognitive resilience — and the informative variable is the molecular state of the cells rather than how many of them there are. If that generalises, the obvious first experiment in the cortex is the wrong one. Counting doublecortin-positive profiles would measure the unspent remainder of a fixed endowment, in a population whose count falls normally through maturation, using a marker that is extinguished by

the very process of interest. A programme built to count will return a number that cannot distinguish the three hypotheses this paper sets out, two of which prescribe opposite therapies.

What should be built instead is a staged and state-resolved account: a normative human map, a disease comparison that reports distributions rather than totals, the tau isoform stain that has never been run, the matrix characterisation that has never been attempted, and a single-nucleus measurement in cortex with a resilient arm. These use existing tissue and existing reagents. The reason they have not been done is not that they are hard. It is that the comparative neuroanatomists who found these cells and the Alzheimer researchers who would care about them publish in different places and are not asked to review each other's work.

A cell that has waited sixty years inside a human cortex, in the layer where the disease begins, in contact with the cells that change most, has either a role in this disease or an instructive absence of one. Both answers are worth having, and the second is as publishable as the first.

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