
THE DORMANT NEURON

*Prenatally Generated Immature Neurons of the Cerebral Cortex
and Amygdala, and the Question of Whether Alzheimer's Disease
Begins in Cells That Never Finished Developing*

*The Third Cellular Category, the Coincidence of Address,
the Molecular Vacancy, and the Therapeutic Collision*

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a third cellular category for the theory of Alzheimer's disease, and the experiment that would settle it

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Abstract

The cellular accounting of Alzheimer's disease has, for four decades, recognized two kinds of neuron in the adult human forebrain. The first is the fixed post-mitotic population, established before the end of adolescence, subject thereafter to attrition and never to renewal, and comprising essentially the whole of the cortex, the hippocampal pyramidal fields, the brainstem aminergic nuclei and the basal forebrain. The second is the renewing population of the dentate granule cell layer, supplied by neural stem cells of the subgranular zone, whose existence in adult humans has been the subject of a long methodological dispute and whose reduction in Alzheimer's disease is among the earliest cellular abnormalities the disease displays. Theories of the disease have been built on both categories: on the vulnerability of the fixed population, and on the failure of the renewing one. A third category exists, is quantitatively substantial in the human brain, occupies precisely the cortical layer in which the disease's earliest cortical lesions appear, and has never, to our knowledge, been examined in Alzheimer's disease at all. Its cells are generated before birth, do not divide, and remain for years or decades in a state of arrested maturation, expressing doublecortin and the polysialylated form of the neural cell adhesion molecule into adult life; they are capable of resuming maturation and integrating into circuits long after the developmental period has closed; and they are concentrated in layer two of the cerebral cortex and in the paralaminar nucleus of the amygdala. They are abundant in large gyrencephalic brains and nearly absent from the rodent neocortex, an inverse relationship to stem-cell-driven neurogenesis that has been interpreted as an evolutionary trade-off between two ways of keeping young neurons available. This paper assembles the case that these cells constitute a missing term in the cellular theory of Alzheimer's disease, and it does so without claiming that they cause it. We set out what is established about the cells themselves; we document the coincidence of address by which their distribution — cortical layer two, the amygdalar paralaminar nucleus, the piriform and olfactory cortices, and in the human a temporal-lobe residue in old age — reproduces with uncomfortable fidelity the topography in which tau pathology begins; we establish, by systematic search, that the molecular question on which everything turns has never been asked, since no study has measured tau isoform composition or tau phosphorylation in these cells, in any species, in health or in disease; we develop the inversion of frame that the cells make available, in which immaturity is not a resource the disease destroys but a state the disease exploits, and we trace that inversion through the existing theoretical literature in which it has been proposed for the neurogenic niche and never extended to the cortex; we analyse what would have to be true of a dormant cell for its awakening to be dangerous, and find three candidate mechanisms of which the most promising is the age-related failure of proteostasis in a cell attempting a developmental program in an aged tissue; we confront the addressing problem, which is the question of why one cortical territory and not another, and conclude that neither the reservoir account nor its rivals can presently answer it; we set out the collision between two active therapeutic programmes, one seeking to restore immature-neuron populations and one warning that their mobilization under amyloid

conditions would be dangerous, and show that the published evidence does not adjudicate between them; and we specify the experimental programme, largely consisting of stains that could be run on tissue that already exists in brain banks, that would convert this paper's conjecture into a result. The conclusion is that the reservoir hypothesis is unproven, unexamined, and cheap to test, and that the cheapness of the test is the strongest argument for performing it.

I. Introduction: The Third Category

1.1 What the Cellular Accounting Has Contained

Every theory of a neurodegenerative disease contains, whether or not it states it, an inventory of the cells available to become diseased. The inventory constrains the theory more tightly than the theory's authors usually notice. If the inventory contains only post-mitotic neurons fixed in number since adolescence, then the disease can only be a subtraction, and the theoretical questions become questions about which neurons are subtracted first and why. If the inventory also contains a renewing population, then the disease can be a failure of addition as well as an excess of subtraction, and a new class of question opens: what happens to a tissue when the supply of new cells stops.

The cellular inventory of Alzheimer's disease has, for most of its history, contained one entry. The cortex, the hippocampal pyramidal fields, the entorhinal projection neurons, the cholinergic basal forebrain, the locus coeruleus and the raphe are all populations established during development and never replaced, and the disease's cellular story in each of them is a story of loss. The great advances of the neuropathological era — the staging of neurofibrillary pathology through transentorhinal, limbic and isocortical territories (Braak and Braak, 1991), the demonstration that the disease isolates the hippocampal formation by destroying precisely the cells that connect it to the rest of the brain (Hyman et al., 1984), the finding that layer two of the entorhinal cortex has already lost some sixty percent of its neurons by the stage of very mild clinical impairment (Gómez-Isla et al., 1996) — were all achievements within that single-entry inventory. They described which fixed cells go, in what order.

The second entry arrived with the demonstration that the adult human dentate gyrus contains newly generated neurons (Eriksson et al., 1998), and with the carbon-dating work that put a rate on the process and a fraction on its cumulative contribution (Spalding et al., 2013). It has been contested ever since, in a dispute whose current state we take up in section 4.6; but the contest itself is evidence of how much was at stake, because a renewing population in the hippocampus changes what kind of thing the disease can be. Within two decades the second entry had generated its own literature: the demonstration that immature granule neurons decline in Alzheimer's disease from the

earliest stages and that the decline tracks disease progression (Moreno-Jiménez et al., 2019), the extension of that finding across neurodegenerative conditions (Terrerós-Roncal et al., 2021), the single-cell work finding immature granule cells across the lifespan and reduced in number in the disease (Zhou et al., 2022), and a therapeutic literature aimed at restoring what the disease removes.

The third entry has not arrived. It exists in the cell-biological literature, where it has been developed steadily for two decades, and it has not crossed into the literature of neurodegeneration. Its cells are neither fixed-and-mature nor newly-generated. They are old cells that never finished.

1.2 The Cells

The population was first characterized in the rodent paleocortex, where a set of cells in layer two express doublecortin, the polysialylated form of the neural cell adhesion molecule, and other markers of the immature neuronal state, while lacking the markers of mature neurons, of glia, and of the principal inhibitory and excitatory classes. They are mostly without synapses, they are ensheathed by astroglia, and — the finding that defines them — they are generated in embryonic life, principally around embryonic day fifteen, and not in adulthood (Gómez-Climent et al., 2008). They are therefore immature without being new. The distinction is not a technicality; it separates two entirely different cellular economies. A newly generated neuron is the output of a stem cell that can, in principle, produce more. A prenatally generated immature neuron is a fixed allocation, drawn down over a lifetime and never replenished.

Fate mapping established what becomes of them. In the adult murine piriform cortex they do not simply persist and die; they progressively resume maturation, acquiring the markers, the dendritic spines, the axon initial segment and the synaptic apparatus of glutamatergic neurons, so that the population functions as a non-renewable reservoir that is spent slowly across the lifespan (Rotheneichner et al., 2018). Electrophysiological work has shown that the cells which awaken do integrate, and that they can be driven to awaken by experience and by injury; it has also shown that cells awakening in the aged brain mature slowly and incompletely, retaining higher intrinsic excitability and higher input resistance and receiving less spontaneous synaptic input than their neighbours (Benedetti et al., 2023). The reservoir metaphor is therefore exact in a way metaphors usually are not: the population is a store of undifferentiated capacity, laid down once, drawn on continuously, and not refilled.

The comparative anatomy is where the population becomes interesting for human disease. In a systematic survey across twelve mammalian species using a single quantification method, these cortical immature neurons proved nearly absent from the rodent neocortex, confined there to the paleocortical piriform region, while in larger-brained species they extend across the entire neocortical mantle, with linear density in layer two rising with brain size (La Rosa et al., 2020). The relationship has since been confirmed in carnivores and ungulates (Pattaro et al., 2025) and in macaques (Pattaro et al., 2026). A homologous population occupies the amygdala, where the

paralamina nucleus holds immature excitatory neurons that mature during adolescence and persist into old age while local progenitor proliferation ceases in infancy (Sorrells et al., 2019), and this amygdalar population is markedly expanded in primates (Ghibaudi et al., 2025a). The pattern across the two populations is consistent and it runs opposite to the pattern for stem-cell-driven neurogenesis, which declines from small-brained, short-lived species to large-brained, long-lived ones. The interpretation offered by the field that discovered it is that mammalian evolution has traded one mechanism of neuronal youth for another: brains that cannot afford continuous cell division in an expanded and highly specified cortex instead lay down a reserve of young cells before birth and spend it slowly (Ghibaudi et al., 2025b; Riga et al., 2026). Whatever the evolutionary reading, the empirical consequence is direct. The species in which this reservoir is largest is the human. The species in which it is smallest is the mouse.

1.3 Why This Paper Exists

The argument of this paper begins from a conjunction that we have not seen stated in the literature, and that we state at the outset so that the reader can weigh everything that follows against it.

These cells sit in cortical layer two. Cortical tau pathology begins in layer two of the transentorhinal and entorhinal cortex. The homologous population sits in the amygdala, which is among the earliest regions to show tau and is the first region to show the TDP-43 pathology of primary age-related tauopathy (Zhang et al., 2018). In the human the cortical reservoir contracts with age into the temporal lobe surrounding the amygdala (Li et al., 2023), which is the territory of late-onset disease. In the adult rat, the embryonic three-repeat tau isoform persists in a specific set of regions — the piriform and olfactory cortex, the locus coeruleus, the raphe nuclei, the medial septum — in a distribution the authors explicitly note mirrors that of doublecortin and the polysialylated neural cell adhesion molecule (Bullmann et al., 2010). That list of regions is, almost item for item, the list of regions in which Alzheimer's disease begins.

None of this is evidence of causation, and we will spend a good part of this paper insisting on how far it falls short of evidence of causation. A coincidence of address is a reason to look, not a finding. But the reason to look is strong, the looking has not been done, and the cost of doing it is low. We were unable to find, by systematic search of the indexed literature, a single study measuring tau isoform composition or tau phosphorylation in cortical layer two immature neurons, in any species; a single study of tau in the amygdalar paralamina population; or a single study reporting the state of either population in Alzheimer's disease or in any tauopathy. A dedicated review of these cells published this year surveys their alteration in temporal lobe epilepsy, traumatic brain injury and stroke, and does not treat neurodegeneration (Riga et al., 2026). The cells have been characterized for two decades by developmental neurobiologists, and the neurodegeneration field has not looked at them.

There is a second reason this paper exists, and it concerns the direction in which the field's thinking about immature neurons runs. The literature treats immature neurons almost exclusively as a good thing to have: a substrate of plasticity, a reserve for repair, a resource whose loss in disease is part of what the disease does and whose restoration is therefore a therapeutic goal. That reading is well supported, and this paper does not dispute it. But it has a consequence for what gets tested. If immaturity is a resource, the experiment one runs is whether the disease depletes it. If immaturity is also a liability — if a cell holding a developmental program in an aged brain is a cell holding something dangerous — then the experiment one runs is whether the disease uses it. The second experiment has not been run on the cortical reservoir, and the theoretical proposal that would motivate it has been made only for the neurogenic niche. Extending that proposal to the third cellular category, stating it in falsifiable form, and specifying the experiments that would kill it are the tasks of this paper.

1.4 What This Paper Claims and What It Does Not

We claim the following. That a third category of adult forebrain neuron exists, is substantial in humans, and has been absent from the cellular inventory on which theories of Alzheimer's disease are built. That its anatomical distribution corresponds, to a degree that warrants investigation, with the distribution of early tau pathology. That the molecular question which would make the correspondence meaningful or dismiss it as coincidence has not been asked. That the therapeutic programmes currently aimed at this substrate are proceeding without the information that question would supply. And that a small set of tractable experiments, most of them requiring only antibodies and tissue that already exist, would resolve the matter in either direction.

We do not claim that these cells cause Alzheimer's disease, that they are the source of its tau, that they migrate, that they are the reason for the disease's regional specificity, or that any therapeutic decision should presently be changed on the strength of the argument assembled here. Where the evidence is rodent, we say so. Where the evidence is absent, we say that too, and we have tried to make the absences as visible as the presences, since in a paper of this kind the absences are the load-bearing structures. A conjecture that has not been tested is not a weak finding; it is not a finding at all, and its only value lies in the precision with which it specifies what would make it one.

1.5 The Shape of the Argument

Section 2 sets out the cell biology: origin, markers, maturation trajectory, awakening, and the evidence that these cells are not newly generated. Section 3 develops the comparative architecture and the evolutionary trade-off, and draws the methodological consequence that a pathology running through this population would be systematically invisible in rodent models. Section 4 maps the human distribution across the lifespan, which is the most disease-relevant and the most fragile part of the evidence, and states the human neurogenesis controversy in its current form. Section 5 develops the coincidence of address in detail, region by region, and asks what would distinguish a mechanism from a coincidence. Section 6 documents the molecular vacancy, states exactly what searches were run and what they returned, and sets out what is known about tau in the immature state elsewhere, which is the nearest available evidence. Section 7 develops the inversion of frame — immaturity as liability rather than resource — and traces its existing statement for the neurogenic niche. Section 8 analyses the conversion problem: what would have to be true for the awakening of a dormant cell to be pathogenic, with three candidate mechanisms assessed. Section 9 confronts the addressing problem. Section 10 sets out the therapeutic collision and what the published evidence does and does not decide. Section 11 specifies the experimental programme. Section 12 sets out what the hypothesis would and would not explain. Section 13 states what would refute it. Section 14 gives the verdict, and section 15 the validity ledger in which every load-bearing claim of this paper is graded.



2. The Cell Biology of Arrested Maturation

2.1 Definition and Nomenclature

The population under discussion has accumulated an unhelpful number of names. In the rodent paleocortical literature its members were "tangled cells," after their morphology. In the comparative literature they are "cortical immature neurons," abbreviated cINs, with "subcortical immature neurons" for the amygdalar population. In the functional literature they are "dormant neuronal precursors" or "dormant neurons," which captures the awakening but overstates the precursor status, since these cells are post-mitotic and are not precursors in the stem-cell sense. In reviews they are sometimes described as the product of "neurogenesis without division," which is accurate and awkward. We use "immature neuron" where the anatomy is at issue and "dormant neuron" where the functional state is at issue, and we note that the nomenclatural confusion is itself a minor cause of the population's invisibility to adjacent fields: a neurodegeneration researcher searching for work on new neurons in the cortex will not find papers filed under arrested maturation.

The defining properties, on which the literature agrees, are four. The cells express markers of immaturity — doublecortin and the polysialylated form of the neural cell adhesion molecule chief among them — into adult and aged life. They are generated prenatally and do not divide thereafter. They are capable of resuming maturation, acquiring mature markers and functional integration, at any point across the lifespan. And they are anatomically restricted, being found principally in layer two of the cerebral cortex, with the paleocortical piriform region as their densest and phylogenetically oldest location, and in the paralamina nucleus of the amygdala.

2.2 Origin: Generated Before Birth

The claim that these cells are not newly generated is the one on which everything else depends, since a population of newly generated cortical neurons would simply be adult neurogenesis in a new location and would carry all the disputes that attach to that subject. The evidence is of three kinds.

The first is birth-dating. In the rat paleocortex, thymidine-analogue labelling places the birth of these cells in embryonic life, principally around embryonic day fifteen, with no appreciable adult addition (Gómez-Clement et al., 2008). The second is the absence of local proliferation. In the human amygdala, the paralamina nucleus contains abundant immature cells in children and adolescents, and its local progenitor proliferation drops sharply in infancy, which means the immature cells present in an adult cannot have been made recently (Sorrells et al., 2019). The third is fate mapping. Lineage tracing from a doublecortin-driven reporter in the adult mouse piriform cortex follows a cohort of labelled cells forward in time and finds them maturing into excitatory neurons, with no evidence of replenishment of the labelled pool (Rotheneichner et al., 2018).

The consequence is a cellular economy quite unlike that of the neurogenic niche. There is no stem cell to activate, no progenitor pool to expand, and no proliferative response to injury or stimulation. Whatever the population does, it does by spending itself. Interventions that "increase" it

can only do so by slowing its maturation or its death, not by making more of it; interventions that mobilize it are spending a finite endowment. This asymmetry will matter in section 10, where we consider what it means to aim a therapy at such a population.

2.3 The Immature Phenotype and Its Maintenance

What the cells express is well described. Doublecortin, a microtubule-associated protein required for migration and for the cytoskeletal dynamics of immature neurons; the polysialylated form of the neural cell adhesion molecule, which reduces adhesion between cells and permits structural remodelling; and, in the original rat characterization, the collapsin response mediator protein CRMP-4 and phosphorylated CREB, alongside a conspicuous absence of the markers of mature neurons, astroglia, oligodendroglia and the principal interneuron classes (Gómez-Climent et al., 2008). Morphologically the cells are small, with simple, sparsely branched processes, and they are frequently found in clusters, often ensheathed by astroglial processes, with few or no synaptic contacts.

What maintains the immature state is not known. This is stated plainly in the most recent dedicated review, which lists the molecular program sustaining immaturity, the triggers of differentiation, and the functional consequences of integration as the three critical gaps in the field (Riga et al., 2026). The gap matters for the present argument in a specific way: if we do not know what holds these cells in arrest, we cannot say what releases them, and the release is the event on which any pathological role would depend. A theory that proposes that awakening is dangerous must at some point say what causes the awakening, and the honest answer in 2026 is that the field does not know.

What is known is that the state is modifiable. The cells' immature phenotype responds to neurotransmitter systems, to stress, to sensory experience and to age (Riga et al., 2026). In the rat, olfactory bulbectomy sharply reduces the number of immature layer two cells while mature neuronal counts rise without matching cell death, which is the signature of induced maturation rather than of loss (Gómez-Climent et al., 2011). That single experiment is worth dwelling on, because it establishes the principle on which the pathological hypothesis rests: an injury at a distance, acting through changed input, can cause a population of dormant cells to convert. If a bulbectomy can do that, a chronic inflammatory milieu might do it too.

2.4 Awakening and Its Consequences

The awakening has been characterized functionally, and the characterization contains a fact that the disease-oriented reader should notice.

Dormant precursors that resume maturation do integrate. They develop spines, axon initial segments and synaptic contacts, and they acquire the electrophysiological properties of cortical excitatory neurons (Rotheneichner et al., 2018). But integration is not equivalent to normality. Cells

that awaken in the adult and aged brain mature slowly and incompletely: they retain higher intrinsic excitability and higher input resistance, and they receive less spontaneous synaptic input, than the neurons around them (Benedetti et al., 2023). Earlier work on cells matured in the adult piriform cortex found them differing from neighbouring principal neurons in their synaptic input, which was predominantly inhibitory, and in their rheobase and maximum firing rate, leading the authors to suggest they constitute a distinct neuronal type rather than a replacement for an existing one (Benedetti et al., 2020).

Two implications follow. The first is that the reservoir does not simply restore what was lost; it adds cells with different properties, and the functional consequence of a large awakening is therefore not predictable from the number of cells involved. The second, more relevant here, is that a cell attempting a developmental program late is a cell doing something difficult. Maturation involves a substantial biosynthetic and cytoskeletal undertaking — process extension, membrane synthesis, cytoskeletal reorganization, synapse formation — and the evidence says that this undertaking, attempted in an aged brain, is not completed properly. Incomplete maturation is the observed phenotype. Whether incomplete maturation in a diseased brain produces something worse than a functionally divergent neuron is exactly the question this paper is about.

2.5 The Distinction from Adult Neurogenesis, Stated Precisely

Because the two phenomena are persistently conflated, and because the conflation is one reason the reservoir has not entered disease thinking, it is worth stating the differences in a form that can be checked.

	Stem-cell-driven adult neurogenesis	The dormant reservoir
Cell of origin	Radial glia-like stem cell in a niche	None: cells generated prenatally
Division in adult life	Yes, progenitor amplification	No
Anatomical location	Subgranular zone of dentate gyrus; subventricular zone	Cortical layer two; amygdalar paralaminar nucleus
Replenishable	In principle yes, while the stem pool lasts	No: a fixed endowment
Species scaling	Declines with increasing brain size	Increases with increasing brain size
Response to injury	Proliferative expansion documented	Maturation of existing cells; no proliferation
Human adult status	Contested	Documented, with an age-dependent regional contraction
Studied in Alzheimer's disease	Extensively	Not at all

The final two rows are the ones that motivate this paper. The human status of the reservoir is, remarkably, less contested than the human status of adult hippocampal neurogenesis: the cells are large, the markers are robust, and the same laboratories that could not find new neurons in the adult human dentate gyrus report immature neurons in the human cortex and amygdala without difficulty. And the disease literature is empty.



3. The Comparative Architecture and the Rodent Blind Spot

3.1 The Phylogenetic Gradient

The comparative work on this population is unusually clean, because it was done deliberately as comparative work rather than assembled from studies with different methods in different species. A single quantification protocol was applied to twelve mammalian species spanning small lissencephalic to large gyrencephalic brains, and the result was a heterogeneous distribution with a clear axis: the cells are virtually absent from the rodent neocortex, present throughout the neocortex of many other species, and increasing in layer two linear density with brain size (La Rosa et al., 2020). Subsequent studies extended the sample. Dogs and horses, chosen to separate the effects of brain size from those of dietary and social ecology, confirmed the covariance with brain size and with neocortical surface (Pattaro et al., 2025). Rhesus macaques placed a standard translational primate on the same curve and confirmed a primate-specific elevation of the amygdalar population (Pattaro et al., 2026). The multispecies analysis of the amygdala, across eight species from naked mole rat to chimpanzee, found the immature cells concentrated in the basolateral complex, expanded in primates, and — in contrast to most forms of plasticity — stable in number through adulthood and old age (Ghibaudi et al., 2025a).

In aged nonhuman primates the cortical population persists into the fourth decade of life. Doublecortin-expressing cells with heterogeneous morphology were found in layers two and three, predominantly over associative cortex and in the amygdala, in rhesus monkeys at twelve, twenty-one and thirty-one years of age, declining in density with age but present in every group, including in two aged animals with cerebral amyloid pathology; in the same animals, dentate subgranular doublecortin cells diminished markedly in the middle-aged and aged groups (Zhang et al., 2009). The dissociation within a single set of brains is important: the niche population fell away with age while the cortical population persisted. Two systems with different rules.

3.2 The Trade-Off Reading

The interpretation the field has put on this gradient is that it represents an evolutionary trade-off between two ways of making young neurons available to a mature brain (Ghibaudi et al., 2025b; Riga et al., 2026). Stem-cell-driven neurogenesis, which is abundant in small-brained, short-lived species, delivers genuinely new cells but requires a niche, a proliferative program, and a tolerance for the integration of cells into circuits whose specification is not finished. The reservoir strategy delivers cells that were made during development, under developmental control, and holds them in reserve; nothing has to divide, no niche has to be maintained, and the cells that integrate were specified at the same time as their neighbours.

The reading makes functional sense for the cortex of a large, long-lived, highly specified brain, and it has a corollary that is directly relevant to this paper: the reservoir is the strategy of exactly those brains in which Alzheimer's disease occurs. Whatever else may be said about the species distribution of the disease, it is a disease of long-lived large-brained mammals, and the reservoir is a feature of long-lived large-brained mammals. This is far too coarse an observation to support any inference on its own. We note it because the opposite observation — that the substrate is abundant in rodents and scarce in humans — would have been a reason to stop, and it is not what the data say.

3.3 The Rodent Blind Spot

The methodological consequence is sharper than the evolutionary one and deserves its own statement.

If a pathological process ran through cortical layer two immature neurons, it would be very difficult to observe in a mouse. The cells are nearly absent from the mouse neocortex, being confined to the paleocortical piriform region. A transgenic mouse model of amyloidopathy or tauopathy would therefore lack, across essentially the whole neocortical mantle, the cell population in which the process was supposed to occur. The model would not show a weakened version of the pathology; it would show a different pathology, driven by whatever other mechanisms the model does support, and it would show it in the cells the model does have.

This has three implications for how the hypothesis should be tested and how existing negative evidence should be read. First, the absence of any report of this population's involvement in mouse models of Alzheimer's disease is close to uninformative, since the population is not there to be involved. Second, any experimental test of the hypothesis in a rodent should use the piriform cortex, where the cells do exist in numbers, rather than the neocortex, where they do not; and the piriform cortex is, conveniently, among the earliest regions affected in human Alzheimer's disease and among those in which the embryonic tau isoform persists in the adult rat. Third, species with large gyrencephalic brains — the dog, the sheep, the macaque — become more attractive as models for

this specific question than they usually are, and the comparative work has now quantified the population in several of them, which means the denominator for such a study already exists.

We do not present the rodent blind spot as an explanation for the failure of translation in Alzheimer's therapeutics, which has many candidate causes and needs no new ones. We present it as a reason why a substrate of this size could have remained unexamined for twenty years: the dominant experimental system does not contain it.

4. The Human Map

4.1 What Is in the Human Cortex, and Where

The human data come principally from one systematic study that examined doublecortin-expressing neurons in cortical layer two and in the amygdala across the full postnatal age range, from infancy to one hundred years (Li et al., 2023). Its findings, which we will be leaning on throughout this paper, are these.

Layer two doublecortin-positive neurons occur throughout the cerebrum in infants and toddlers. In adolescents and adults they occur mainly in the temporal lobe. In the elderly they are found only in the temporal cortex surrounding the amygdala. Amygdalar doublecortin-positive neurons occur in all age groups, localized primarily to the paralaminar nucleus, and decline in number with age. The cells are small, unipolar or bipolar, and form migratory chains extending tangentially, obliquely and inwardly within layers one to three of the cortex, and from the paralaminar nucleus to other amygdalar nuclei. Cells with a more mature appearance have larger somata and weaker doublecortin reactivity, consistent with maturation rather than death as the exit route from the immature state. And, in the same sections processed in parallel, doublecortin-positive cells in the hippocampal dentate gyrus were detected only in the infant cases.

Four features of this map deserve comment before we use it.

4.2 The Age Gradient Is a Contraction, Not Merely a Decline

The population does not simply thin with age; it withdraws geographically. A pan-cortical distribution in early childhood becomes a temporal-lobe distribution by adolescence and a peri-amygdalar residue in old age. This is a different shape of change from the one the neurogenesis literature has accustomed the field to, in which a niche's output falls while its location stays fixed, and it has a consequence that we will return to in section 9: at any given age, the reservoir is present in some cortical territories and absent from others, which means that a pathology dependent on the reservoir would be anatomically constrained by the reservoir's map at the age of onset.

It also creates an immediate difficulty for any attempt to explain early-onset disease by this route, which we state here rather than burying it. The atypical variants of early-onset Alzheimer's disease affect posterior, frontal and left perisylvian territories in patients typically in their fifties and sixties. On the human map as reported, the extra-temporal reservoir is largely gone well before those ages. A reservoir-based account of the early-onset variants therefore requires either that the map be incomplete — that more cells persist in extra-temporal cortex than the doublecortin stain reveals — or that the relevant event occurred decades before the clinical presentation, or that the account simply does not extend to those variants. The third possibility should be held open. Not every theory has to explain everything, and a reservoir account that covered only the temporal-predominant, late-onset form of the disease would still be an account of the commonest form of it.

4.3 The Chains

The report of migratory chains extending tangentially, obliquely and inwardly through layers one to three (Li et al., 2023), together with the earlier description of long tangential chains in aged primate cortex and of apparently distorted cell clusters in the oldest animals (Zhang et al., 2009), establishes that these cells are not strictly stationary. They do not migrate from a ventricular germinal zone across the hemisphere; the claim being made here is much more modest. They move within and between adjacent cortical layers, over distances measured in hundreds of micrometres rather than centimetres.

That modest movement matters for two reasons. The first is mechanistic: any hypothesis that assigns pathogenic significance to the cytoskeletal demands of migration — and there is such a hypothesis in the literature on the neurogenic niche — need not be abandoned when the substrate is relocated to a resident cortical population, because the resident population moves too, only less. The second is interpretive: the presence of chains is a reminder that the immature state in the adult cortex is an active state, not a frozen one. These are cells doing something, in tissue whose extracellular matrix is not the matrix of a developing brain.

4.4 The Amygdalar Population

The human amygdalar population is better characterized than the cortical one and, for the purposes of this paper, is at least as interesting. The paralaminar nucleus develops adjacent to the caudal ganglionic eminence, yet most of its cells express excitatory rather than inhibitory markers; in children most are immature by marker profile, and across adolescence many transition to a mature excitatory phenotype, while immature cells persist into old age and local proliferation ceases in infancy (Sorrells et al., 2019). In humans the amygdalar population persists across all ages examined, declining in number, while the cortical population contracts geographically (Li et al., 2023). In the comparative series, the amygdalar population is expanded in primates, concentrated in the basolateral complex, and stable in number through adulthood and old age (Ghibaudi et al., 2025a).

The amygdala's position in the pathology of ageing and dementia is not marginal. It carries tau early in the limbic stages of the disease, and in primary age-related tauopathy it is the first region to show the associated TDP-43 pathology, with the reported staging running amygdala, then hippocampus, then neocortex, then basal ganglia and insula (Zhang et al., 2018). A region that holds a persistent population of immature excitatory neurons across the whole lifespan, and that is among the earliest regions to accumulate abnormal protein, is a place worth looking at with a double stain.

4.5 The Methodological Caveats

Three caveats attach to the human map, and they are serious enough that we state them before building on it rather than after.

The first is that doublecortin is not a perfect marker. The same protein is expressed in contexts other than immaturity, and a study comparing hippocampal and prefrontal expression of the canonical neurogenesis markers found doublecortin and several others present in both regions, with doublecortin higher in prefrontal cortex by digital PCR, concluding that these markers are not by themselves definitive indicators of adult neurogenesis (Cho et al., 2024). What identifies the reservoir is not a single stain but a conjunction: marker expression, morphology, laminar position, absence of mature markers, and birth-dating or fate-mapping evidence where species permit. Human work cannot supply the last of these, which means the human population is identified by analogy with animal populations that have been fate-mapped.

The second is post-mortem tissue quality, which has been the central methodological issue in the adjacent controversy about hippocampal neurogenesis and which applies here with equal force. Immature-neuron epitopes are sensitive to fixation conditions and post-mortem interval, and the methods that recover them have had to be developed deliberately.

The third is that the human map rests substantially on one laboratory's systematic series. It is a careful study with a wide age range and parallel processing across regions, and its findings are consistent with the primate and comparative work. It is nonetheless one series, and the field would be better served by an independent replication in a second cohort, which is among the recommendations in section 11.

4.6 The Adjacent Controversy, Stated Honestly

Because this paper repeatedly distinguishes the reservoir from stem-cell-driven neurogenesis, and because the latter's status in adult humans is genuinely unsettled, we state that status rather than assuming it.

On the side of persistence: carbon dating indicated the continuous addition of new neurons to the adult human dentate gyrus (Spalding et al., 2013); quantitative stereology found immature neurons across the adult lifespan (Boldrini et al., 2018); optimized post-mortem methodology found thousands of immature neurons in the healthy dentate gyrus into the ninth decade, with number and maturation declining as Alzheimer's disease advanced (Moreno-Jiménez et al., 2019); doublecortin-positive neuroblasts were found in aged and demented brains with high inter-individual variability, and more neuroblasts associated with better cognitive status (Tobin et al., 2019); single-nucleus sequencing identified immature granule cells across the lifespan and reduced in Alzheimer's disease (Zhou et al., 2022); and proliferating neural progenitors were identified in the adult human hippocampus by combining proliferation markers with machine-learning classification, and localized transcriptomically to the dentate gyrus (Dumitru et al., 2025).

On the side of absence or of caution: immature neurons and proliferating progenitors were undetectable in adult human dentate gyrus in a series spanning infancy to the eighth decade, with the sharp decline occurring in the first year of life (Sorrells et al., 2018); a transcriptomic taxonomy of adult hippocampal and entorhinal cells found neurogenic signatures in mouse, pig and macaque but not in human (Franjic et al., 2022); the canonical markers proved non-specific in a direct comparison across regions (Cho et al., 2024); and a systematic re-analysis of the published single-cell datasets concluded that the conflicting results are confounded by methodological, conceptual and biological factors and that these data cannot yet settle the question (Tosoni et al., 2023).

Our position is that the question is open, that the weight of recent evidence has moved toward persistence at low rates, and that no argument in this paper should depend on it. This is not a rhetorical hedge but a structural feature of what follows: the reservoir hypothesis developed here is, in an important sense, insulated from the hippocampal controversy, because the cells it concerns are not produced by a niche and their existence in the adult human cortex is not in dispute. A reader who believes that adult human hippocampal neurogenesis is negligible can still hold everything in this paper. That insulation is, we think, the reservoir's principal theoretical advantage over its

neurogenic cousin, and it is worth more than any single piece of evidence assembled here.



5. The Coincidence of Address

5.1 The Claim and Its Status

The observation that motivates this paper is that the anatomical distribution of the dormant reservoir and the anatomical distribution of early tau pathology are, to a first approximation, the same distribution. We set the correspondence out region by region, and then we do the thing that such correspondences usually do not receive, which is to ask seriously how much of it could be produced by coincidence, by shared dependence on a third factor, or by the ordinary anatomy of the temporal lobe.

5.2 Layer Two

The single most striking correspondence is laminar rather than regional. Cortical immature neurons are a layer two population; the literature describes them as invariably so, across every species in which they have been quantified, with extension into layer three in some primate material (Zhang et al., 2009; La Rosa et al., 2020; Li et al., 2023). Cortical neurofibrillary pathology in Alzheimer's disease begins in layer two of the transentorhinal and entorhinal cortex — this is the content of the transentorhinal stages of the standard staging scheme (Braak and Braak, 1991) — and the same layer two population sustains the earliest and most severe neuronal loss, some sixty percent at the stage of very mild clinical impairment, against thirty-two percent for the entorhinal cortex as a whole (Gómez-Isla et al., 1996). The cells that connect the hippocampal formation to the association cortices, and whose destruction isolates the hippocampus functionally, are in layers two and four (Hyman et al., 1984).

Two populations, both defined by their occupancy of layer two, one the site where the disease starts and the other a reservoir of cells that never finished developing. The question is whether they are the same cells, overlapping cells, or merely co-resident cells.

They are certainly not entirely the same cells: entorhinal layer two contains large projection neurons — the stellate and fan cells of the perforant path — which are mature, are not doublecortin-positive, and are the cells whose loss Gómez-Isla and colleagues counted. A reservoir hypothesis cannot claim that the stellate cells of entorhinal layer two are dormant immature neurons. What it can claim, and what is worth testing, is that the immature population is also present in that layer, in the same neighbourhood, and that its state has not been examined in the

disease.

There is one piece of human evidence that bears directly on this and it is suggestive in both directions. Polysialylated neural cell adhesion molecule immunoreactivity is significantly reduced in the entorhinal cortex in Alzheimer's disease, and the reduction correlates inversely with hyperphosphorylated tau load (Murray et al., 2016). The follow-up study quantified which cells were lost, and found a significant decrease in the number of polysialylated-marker-positive cells per unit area in layers two and five of the entorhinal cortex, with the decrease driven by cells co-labelling for the mature neuronal marker and for parvalbumin, rather than by the immature population (Murray et al., 2018). The finding is therefore not the one a naive reservoir hypothesis would want: the polysialylated marker in the human entorhinal cortex belongs substantially to interneurons, and its loss in disease is a loss of interneurons. But the first study's inverse correlation with tau load is exactly the kind of relationship the hypothesis predicts, and neither study was designed to ask whether the layer two immature population specifically is altered. This is the closest the literature comes to the experiment this paper is asking for, and it comes close enough to make the experiment obviously worth doing.

5.3 The Amygdala

The amygdalar correspondence is the cleanest, because both facts are about the same nucleus rather than about the same layer. The paralaminar nucleus holds immature excitatory neurons through the whole human lifespan (Sorrells et al., 2019; Li et al., 2023), and the population is expanded in primates and stable through old age (Ghibaudi et al., 2025a). The amygdala takes tau in the limbic stages of Alzheimer's disease, and in primary age-related tauopathy it is the first region to show the associated TDP-43 pathology, ahead of the hippocampus and well ahead of the neocortex (Zhang et al., 2018). No study has examined the paralaminar population in either disease.

5.4 The Piriform and Olfactory Territory

The paleocortical piriform region is the phylogenetically oldest and densest location of the cortical reservoir, and the only cortical location where the rodent has an appreciable population at all (La Rosa et al., 2020). It is also among the regions affected early in human Alzheimer's disease, a point made in the mouse literature in passing (Carbonell et al., 2020) and reflected in the clinical observation that olfactory dysfunction is among the earliest detectable deficits in the disease. The olfactory territory is additionally the destination of the rodent rostral migratory stream, which is the reason it has been examined at all in the neurogenesis literature; and in the human, primary age-related tauopathy involves olfactory areas alongside medial temporal, basal forebrain and brainstem regions (Crary et al., 2014).

5.5 The Isoform Map

The most unexpected correspondence, and the one we had not anticipated when this work began, is not anatomical but biochemical.

In the adult rat central nervous system, the embryonic tau isoform — the shortest form, containing neither amino-terminal insert nor the second microtubule-binding repeat, designated 0N/3R — is not uniformly absent. It persists in a specific and restricted set of regions: the olfactory bulb and olfactory cortex, the locus coeruleus, the raphe nuclei, the medial septum, and related structures. The authors of that study noted explicitly that the distribution of persistent embryonic tau mirrors the distribution of doublecortin, the polysialylated neural cell adhesion molecule and CRMP-4, and interpreted the pattern as the retention of a juvenile phenotype in the adult brain (Bullmann et al., 2010).

Set that list beside the list of regions in which tau pathology begins in the human. The locus coeruleus carries pretangle tau in early adult life, before any cortical involvement, in the majority of brains examined (Braak and Del Tredici, 2011; Braak et al., 2011). The raphe nuclei carry it at the same early stages. The medial septum is part of the basal forebrain cholinergic system affected early in the disease. The olfactory territory is affected early, and is named in the definition of primary age-related tauopathy. The overlap between "regions retaining embryonic tau in the adult rat" and "regions in which human tau pathology begins" is close to complete.

We are conscious of how much weight this observation could be made to bear and how little it can actually carry. It is a rat study. It concerns mature neurons that retain an embryonic isoform, not the immature layer two population, although the authors themselves link the two distributions. The regional list is short enough that overlap by chance is not negligible, and several of the regions in question — brainstem aminergic nuclei especially — are separately distinguished by long unmyelinated axons, high metabolic load and catecholamine chemistry, any of which could independently explain early vulnerability. The correspondence is a hypothesis generator, not a result.

But it generates a specific and unusually clean hypothesis: that what these regions share is not a chemistry or a wiring pattern but a developmental status. On that reading, the reason tau pathology starts where it does is that it starts in the parts of the adult brain that never fully grew up — the regions that retain embryonic tau, the layers that retain immature cells, the nuclei that retain the capacity for structural plasticity into adult life. This is a strong claim, and we do not assert it. We say that it is testable, that the test is a double stain, and that nobody has done it.

5.6 How Much of This Could Be Coincidence

A responsible treatment of a correspondence like this has to consider the ways it could be spurious, and there are at least four.

The first is anatomical confounding. Many of the regions in both lists are medial temporal or paleocortical, and medial temporal structures are over-represented in every list of things that go wrong in ageing brains. A correspondence between two medial-temporal-weighted distributions is worth less than a correspondence between two distributions drawn from the whole brain.

The second is the plasticity confound, and it is the serious one. The regions that retain immature cells are, by definition, regions of high structural plasticity, and it has been argued for a long time — most explicitly by Arendt — that the regional pattern of neurofibrillary vulnerability follows the regional pattern of neuroplasticity, and inversely recapitulates the ontogenetic and phylogenetic order of cortical development (Arendt, 2012). If plasticity is the common cause of both distributions, then the presence of immature neurons in vulnerable regions is a marker of the vulnerability rather than its mechanism, and the reservoir is a passenger. This possibility cannot be excluded by any anatomical observation and can only be addressed by asking whether the immature cells themselves carry the pathology.

The third is marker non-specificity, treated in section 4.5: some of the apparent correspondence may reflect the behaviour of doublecortin and polysialylated adhesion molecule in contexts other than immaturity.

The fourth is the file-drawer of the obvious. Regions get studied because they are interesting, and both literatures have concentrated their effort on the temporal lobe. Correspondence between the well-studied parts of two fields is partly a correspondence between their funding histories.

Our assessment is that the plasticity confound is the one that matters, that it is not resolvable at the level of maps, and that its existence is precisely why this paper's central recommendation is a cellular experiment rather than a further anatomical argument. The question is not whether immature cells live where the disease starts. It is whether, in the brains where the disease has started, those particular cells contain the pathology.

5.7 A Natural Experiment: Trisomy 21

One human population develops Alzheimer's pathology with near certainty and on a compressed schedule, and it offers a probe of the reservoir hypothesis that requires no new theoretical commitment.

People with Down syndrome carry three copies of the amyloid precursor protein gene, accumulate amyloid from early adult life, and develop the neuropathology of Alzheimer's disease at rates approaching certainty by the sixth decade. If the reservoir is a substrate of the disease, then trisomy 21 offers a case in which the driving conditions are present early, are present in everyone, and are present against a developmental background that is itself abnormal.

The one relevant observation we could find is from the mouse. In the Ts65Dn model, the piriform cortex — the rodent's only substantial cortical reservoir — shows fewer immature neurons in layer two and a reduction in polysialylated adhesion molecule expression in the neuropil, alongside dendritic atrophy and a shifted balance of excitatory and inhibitory synapses (Carbonell et al., 2020). The authors frame the finding as impaired structural plasticity contributing to the olfactory processing deficits of the syndrome, and they note in passing that the piriform cortex is among the first regions affected in Alzheimer's disease.

We draw attention to it for a different reason. It establishes that the reservoir is modifiable by a genetic condition that also produces Alzheimer pathology, and it raises a question with three possible answers, each of which would be informative. If the reservoir is reduced in trisomy 21 before pathology develops, the population is a casualty of the genetic background and its depletion may contribute to the cognitive phenotype, which would make it a resource lost rather than a substrate used. If it is reduced in parallel with the accumulation of pathology, the cells may be being consumed by the process, which is what the reservoir hypothesis predicts. If it is preserved and tau-bearing, the hypothesis is directly supported.

Human material from Down syndrome brain banks, stained as described in section 11.1 and scored across the age range at which pathology accumulates, would discriminate among the three. The compressed timeline that makes trisomy 21 a natural experiment for the amyloid cascade makes it one here too, and the tissue exists.

6. The Molecular Vacancy

6.1 What We Looked For and What We Found

The argument of the preceding section converges on one question: what is the state of tau in these cells? We therefore attempted to establish what is known, and the answer is that nothing is known. Because a claim of absence is only as good as the search that produced it, we set out the search.

We queried the indexed biomedical literature for studies combining tau, the three-repeat and four-repeat isoforms, or phosphorylated tau, with each of the terms by which this population is known — cortical immature neurons, immature neurons, dormant precursors, late-maturing neurons, doublecortin, polysialylated neural cell adhesion molecule — and with each of its anatomical locations — cortical layer two, piriform cortex, paleocortex, paralaminar nucleus, amygdala. We queried separately for any study of these cells in Alzheimer's disease or in any

tauopathy. We queried separately for glycogen synthase kinase three beta, the principal tau kinase of the immature state, in this population.

The results were as follows. No study measures tau isoform composition or tau phosphorylation in cortical layer two immature neurons, in any species. No study examines tau in the amygdalar paralaminar population; the retrieved records combining that nucleus with tau or neurodegeneration are magnetic resonance volumetry studies, not cellular ones. No study reports the state of either population in Alzheimer's disease or in any tauopathy; the most recent dedicated review of these cells evaluates their alteration in temporal lobe epilepsy, traumatic brain injury and stroke, and does not treat neurodegeneration among the conditions with clinical evidence (Riga et al., 2026). No study examines glycogen synthase kinase three beta in this population.

A negative search is a weak instrument and we do not overstate it. Work may exist under terminology we did not anticipate, in figures rather than abstracts, or outside the indexed literature. But the consistency of the result across query formulations, and the confirmation from a current review whose authors had every reason to cite such work if it existed, makes us reasonably confident that the gap is real.

6.2 What Is Known About Tau in Immature Neurons Elsewhere

The vacancy is specific to the cortical and amygdalar reservoir. In the neurogenic niche, the corresponding questions have been asked and answered, and the answers are what make the vacancy worth filling.

Tau isoform composition is developmentally regulated: the six human isoforms arise by alternative splicing, and the four-repeat and amino-terminal-insert-containing forms are adult-specific while the three-repeat transcripts are expressed throughout life including in fetal brain (Goedert et al., 1989). Fetal tau is phosphorylated in a manner recognized by the antibodies raised against paired helical filaments, which is the foundational observation of the entire developmental-tau literature and the one on which every subsequent argument of this kind rests (Brion et al., 1993).

In the adult rodent hippocampus, the embryonic isoform persists in the immature cells of the neurogenic lineage: zero-insert three-repeat tau is present in proliferating progenitors beneath the granule cell layer, co-labelling with the polysialylated adhesion molecule and doublecortin, while mature granule cells express the adult form (Bullmann et al., 2007). The three-repeat isoform marks the new axons generated from the subgranular zone in the adult dentate gyrus (Llorens-Martín et al., 2012). Doublecortin-positive immature neurons are immunoreactive for phosphorylated tau and not for non-phosphorylated tau, in the adult rat and — importantly for the present argument — in human Alzheimer's disease tissue; and hippocampal neurogenesis is impaired in tau-knockout mice, which establishes that the relationship is functional rather than incidental (Hong et al., 2010).

The picture in the niche is therefore coherent and well evidenced: immature neurons carry the embryonic isoform and carry it phosphorylated, and tau phosphorylation is required for their normal development. What is entirely unknown is whether the same is true of a cell that has held the immature state for fifty years in the cortex.

6.3 Why the Answer Is Not Obvious

It would be easy to assume that a cell expressing doublecortin and the polysialylated adhesion molecule must also express embryonic tau, since all three are markers of the same developmental state, and the assumption is a reasonable prior. It is not, however, safe, and the reasons are worth stating because they determine what the experiment would mean.

First, arrested maturation is not the same state as active maturation. A cell frozen for decades may maintain some components of the immature program and not others; the program that holds it in arrest is unknown (Riga et al., 2026), and a maintenance program is not obliged to maintain everything. The tau isoform ratio is set by splicing, and splicing regulation in a cell that is neither dividing nor extending processes need not resemble that of a migrating neuroblast.

Second, the functional logic that makes three-repeat tau appropriate for an immature neuron is a logic of dynamics. The isoform confers lower microtubule affinity and greater cytoskeletal lability, which is what a cell extending and retracting processes requires. A dormant cell is not doing that. It is plausible that the dormant state involves a more stable cytoskeleton than the migrating state, and therefore a more adult isoform ratio, with the embryonic profile returning only on awakening. That possibility, if true, would be the more interesting result, because it would make the isoform switch an event with a trigger rather than a standing condition — and events with triggers can be dated, blocked and measured.

Third, the rat evidence that persistent embryonic tau occurs in regions rich in immature markers (Bullmann et al., 2010) is regional, not cellular. The two markers occupy the same territories; nobody has shown them in the same cells.

6.4 The Experiment

The experiment that would fill this vacancy is neither expensive nor technically demanding, which is the strongest argument for doing it. It is a double or triple immunofluorescence stain on human post-mortem cortex, entorhinal cortex and amygdala, using an antibody against doublecortin or the polysialylated adhesion molecule to identify the cells, and isoform-specific antibodies against three-repeat and four-repeat tau, together with the standard phospho-tau antibodies, to characterize their tau. The tissue exists in brain banks. The antibodies exist and have been used in exactly this combination to characterize tangle evolution in human tissue (Uchihara et al., 2011; Hara et al., 2013). The age range required is wide but the sample size is not large, because the question at this stage is qualitative.

Four outcomes are possible and all four are informative. If the cells carry three-repeat tau and phospho-tau epitopes, the reservoir becomes a candidate substrate for tau pathology and the topographic correspondence acquires a mechanism. If they carry three-repeat tau without phosphorylation, the reservoir is a substrate awaiting a kinase, and the relevant question becomes what activates it. If they carry the adult isoform profile, the developmental-tau reading of the reservoir is dead, which would be a clean and valuable negative result. And if their tau profile changes on awakening — detectable by staining cells at different points along the maturation gradient, which the morphology permits — then the awakening becomes the pathogenically interesting event, which is a different and more tractable theory than the one this paper started with.

6.5 The Pretangle Complication

One piece of evidence bears against the developmental-tau reading in general, and it should be stated here rather than left to the discussion, because it is the strongest single objection to the whole family of theories to which this paper belongs.

If pathological tau in Alzheimer's disease arose in cells carrying the embryonic three-repeat isoform, the earliest lesions should be three-repeat-enriched. They are not. Double-labelling of tangle evolution finds pretangles — the earliest, still non-fibrillar accumulations — labelling for four-repeat tau and not for three-repeat tau; mature tangles labelling for both; and ghost tangles, the extracellular remnants of dead neurons, labelling for three-repeat and not four-repeat (Uchihara et al., 2011). The transition from four-repeat to three-repeat has been described as underlying the dendrosomatic and regional progression of the pathology, with dendritic four-repeat immunoreactivity retracting first (Hara et al., 2013). The three-repeat signature that a developmental theory reads as the signature of origin appears, on this evidence, at the end.

Three responses are available. The first is that these studies examined the pyramidal populations of the entorhinal-hippocampal system, which is where tangles are counted, and not immature neurons in layer two or the paralaminar nucleus; a distinct lesion sequence in a distinct population has not been excluded because it has not been looked for. The second is that epitope accessibility in early lesions is not equivalent to isoform absence. The third is that a theory of this kind does not strictly require the first lesion to be three-repeat, only that the immature cell's tau be aggregation-prone — but this concedes a great deal, since the isoform argument is the principal reason for thinking that immature cells are aggregation-prone in the first place.

We regard the first response as legitimate and the other two as weak. The pretangle data are a genuine problem for developmental-tau theories, and the reservoir hypothesis inherits the problem. What the reservoir hypothesis adds is a population in which the question has not been asked, so that the problem is at least addressable rather than settled against it.



7. The Inversion: Immaturity as Liability

7.1 Two Ways to Read a Young Cell in an Old Brain

The literature on immature neurons in the adult brain is, with near unanimity, a literature about a resource. New or young neurons are the substrate of pattern separation, of structural plasticity, of cognitive reserve and of endogenous repair; their decline with age is a loss; their reduction in disease is part of the disease; and their restoration is a therapeutic ambition. That reading is not wrong. It is supported by ablation and enhancement experiments, by the correspondence between neurogenic decline and cognitive decline, and by the intuitive proposition that a brain with more young cells has more capacity to reorganize.

There is a second reading, and it is not the negation of the first. A cell in an immature state is a cell running a developmental program. Developmental programs have properties that are adaptive in a developing brain and are not obviously adaptive anywhere else: labile cytoskeletons, high kinase activity, high rates of membrane and protein synthesis, motility, low thresholds for structural change, and — in the case that concerns us — a tau configuration that is heavily phosphorylated and poorly bound to microtubules. In a developing brain these properties are held in a system built to contain them, with matched extracellular matrix, matched metabolic supply, matched trophic support and matched timing. In an eighty-year-old brain none of those conditions obtains.

The inversion is the proposal that the same properties that make immature cells valuable make them dangerous under the wrong conditions, and that Alzheimer's disease is a condition under which they become dangerous. Stated at that level of generality it is unfalsifiable and not worth much. What makes it a scientific proposal is the specification of which properties, under which conditions, with which consequences, and it is that specification which the present section and the next attempt.

7.2 Where the Inversion Already Exists

The inversion is not new, but it has been developed only for the neurogenic niche.

The most complete statement is Abbate's adult neurogenesis theory, which holds that the tau pathology of Alzheimer's disease originates in the neural stem cells and immature neurons of the adult neurogenic niches, where the developmental tau configuration — three-repeat isoform, heavily phosphorylated by glycogen synthase kinase three beta — is physiologically present, and that this configuration is pushed past the aggregation threshold by conditions in the diseased brain, with the immature cell then carrying the resulting seeds into the tissue it enters (Abbate, 2023). The

theory is explicit that the amyloid pathology of the disease acts on tau indirectly, through chronic microglial activation that shifts the niche toward reactive production, and it assigns different conversion mechanisms to the early-onset and late-onset forms: the demands of migration in the first case, and the age-related decline of autophagic clearance in the niche in the second.

Adjacent inversions exist in other conditions and are better evidenced than the Alzheimer version. Aberrant neurogenesis after seizures produces ectopic granule cells that integrate into excitatory loops and contribute to epileptogenesis, and ablating neurogenesis before an epileptogenic insult reduces chronic seizure frequency and normalizes the associated cognitive deficits (Cho et al., 2015). Increasing neurogenesis after a memory has been encoded is sufficient to induce forgetting in normal adult mice, which is a demonstration that the addition of young cells to a circuit can degrade its contents (Akers et al., 2014). Driving stem cell activation through neuronal hyperexcitability converts radial stem cells into astrocytes and depletes the pool, so that stimulation costs the reservoir it draws on (Sierra et al., 2015). And reviews of the cortical reservoir itself note that its cells have been implicated in pathological circuit remodelling as well as in repair (Riga et al., 2026).

What has not been done is to apply the inversion to the third cellular category. The reason is straightforward: the category has not been in the disease inventory, so there has been nothing to invert.

7.3 What the Reservoir Changes in the Argument

Moving the inversion from the niche to the reservoir changes four things, and on balance it strengthens the argument rather than merely relocating it.

It removes the dependence on contested biology. A theory that requires adult human hippocampal neurogenesis at a substantial rate inherits a dispute it cannot settle. A theory that requires only the existence of immature neurons in the adult human cortex and amygdala does not: those cells are reported by multiple groups, including groups sceptical about hippocampal neurogenesis, and their presence is not seriously contested.

It removes the dependence on migration. A theory that requires immature cells to travel from a germinal zone to a cortical destination in the adult human brain is in difficulty, because the human rostral migratory stream is substantially closed after infancy (Sanai et al., 2011) and the extensive migration into frontal cortex that does occur is an infant phenomenon (Paredes et al., 2016). A theory whose cells are already in the cortex requires no such journey. It requires, at most, the local movement within layers one to three that has been described in human and primate cortex (Zhang et al., 2009; Li et al., 2023).

It changes the shape of the therapeutic implication, which we take up in section 10: an endowment that cannot be replenished behaves differently under stimulation than a niche that can.

And it makes the theory harder to confirm and easier to kill, which is the property a theory should want. The niche version has a persistent problem of testability, because the niche is small, deep, and difficult to sample, and because its principal predictions concern events decades before death. The reservoir version concerns cells that sit in the outer layers of accessible cortex, in tissue that brain banks hold in quantity, and its central prediction is a stain.

7.4 The Form of the Hypothesis

We state the hypothesis in the form in which we think it should be tested, with its components separated so that they can fail independently.

The substrate claim. The adult human cerebral cortex and amygdala contain a population of prenatally generated neurons in arrested maturation, concentrated in cortical layer two and the amygdalar paralaminar nucleus, whose regional distribution changes across the lifespan.

The molecular claim. These cells carry, or acquire on awakening, the tau configuration characteristic of the immature neuronal state: three-repeat-predominant isoform composition and phosphorylation at epitopes shared with the pathological tau of Alzheimer's disease.

The conversion claim. Under the conditions of the ageing or diseased brain — which we specify in section 8 — that configuration is converted into an aggregation-competent species within these cells, rather than merely resembling one.

The topographic claim. The regional distribution of the resulting pathology is constrained by the regional distribution of the reservoir at the age at which conversion occurs.

The clinical claim. Interventions that mobilize the reservoir in a brain where conversion conditions obtain will accelerate the process, and interventions that mobilize it where they do not obtain will not.

The substrate claim is established. The molecular claim is untested. The conversion claim is untested and currently unspecified. The topographic claim is testable against existing tau-imaging and post-mortem data. The clinical claim is the one that matters and the one furthest from evidence. A reader who wishes to be economical can take the position that only the first two are worth anyone's time at present, and we would not argue with them.



8. The Conversion Problem

8.1 Why a Dormant Cell Is Not Automatically Dangerous

Every theory of this family faces the same difficulty, and it is fatal to the loose versions. Immature neurons carrying phosphorylated embryonic tau exist in every healthy brain that has been examined, throughout life. If that configuration were sufficient for pathology, every brain would be diseased. Fetal tau is heavily phosphorylated at epitopes shared with paired helical filaments and does not polymerize (Brion et al., 1993); the immature cells of the adult niche carry phosphorylated tau as a normal condition (Hong et al., 2010); and the dormant reservoir sits in the cortex for decades without producing tangles in most people.

What a theory of this kind must supply, therefore, is not a resemblance but a conversion: some factor, present in the diseased brain and absent in the healthy one, that turns a physiological configuration into a pathological one. The theory is only as good as the conversion mechanism it names, and the strength of that mechanism is what distinguishes a hypothesis from an analogy. Three candidate mechanisms are available for the reservoir. We assess each.

8.2 Candidate One: The Failure of Disposal

The first candidate does not require anything to change in the cell's tau at all. It requires only that the machinery which disposes of the products of a normal process should slow down while the process continues.

The proteostatic argument in Alzheimer's disease has become considerably stronger over the last five years, and it is now specific at the molecular level. The autophagic-lysosomal system fails early: autolysosome de-acidification precedes extracellular amyloid deposition, undigested material accumulates in enlarged autolysosomes that form perikaryal rosettes, and the individual neurons displaying that morphology are the principal source of senile plaques (Lee et al., 2022). The proximate cause of the de-acidification has been identified as a direct molecular inhibition: the phosphorylated carboxy-terminal fragment of the amyloid precursor protein binds the V0a1 subunit of the vacuolar ATPase and competitively blocks assembly of the proton pump, and reducing that phosphorylation restores pump activity (Im et al., 2023). The general framework has been set out in review (Nixon and Rubinsztein, 2024; Nixon, 2024).

Apply this to a dormant cell. Such a cell contains, on the molecular claim, tau in a labile, heavily phosphorylated configuration — a species that in a young brain is continuously produced, used and cleared. Clearance requires a functioning autophagic-lysosomal system. In an aged brain, and much more so in a brain where amyloid precursor protein fragments are inhibiting the lysosomal proton pump, that system is compromised. The result is not a new pathological process but the accumulation of the products of an old physiological one. No kinase has to be activated, no isoform has to switch, and no stress has to be applied. The cell simply stops being able to take out the rubbish while continuing to produce it.

This mechanism has three attractions. It is molecularly specific and experimentally tractable. It explains why the pathology is a disease of old age without requiring anything to go wrong until old age. And it unifies the reservoir account with the account of the neurogenic niche, since exactly the same argument has been made there — the decline of autophagy in aged stem cells, allowing accumulation of the byproducts of a tau phosphorylation that is itself physiological (Abbate, 2023). One mechanism, two substrates.

Its weakness is that it is generic. A failure of clearance affecting all cells does not obviously explain why these cells should be affected first, and the topographic claim of section 7.4 therefore requires something additional: either that immature cells produce more of the relevant substrate, and so reach the threshold earlier, or that they have less clearance capacity to begin with. The first is plausible and testable. The second is unknown.

8.3 Candidate Two: The Difficulty of Late Maturation

The second candidate locates the danger not in the dormant state but in the exit from it.

Maturation is the most demanding thing a neuron ever does. It involves the extension of processes over substantial distances, the synthesis of large quantities of membrane, a wholesale reorganization of the cytoskeleton, the establishment and pruning of synapses, and the switching of transmitter-receptor configurations — all under precise temporal control and all requiring energy and raw material in quantity. In development it occurs in a tissue configured to support it: permissive extracellular matrix, abundant trophic factor, immature inhibitory architecture, and neighbours doing the same thing at the same time.

A dormant cell awakening at eighty attempts the same program in a tissue that is configured for stability rather than growth: an adult extracellular matrix rich in chondroitin sulphate proteoglycans, a mature inhibitory architecture, reduced trophic support, and a metabolic environment constrained by declining mitochondrial and vascular function. The evidence says the attempt does not go well even in normal ageing: late-awakened neurons mature slowly and incompletely, and remain functionally divergent from their neighbours (Benedetti et al., 2023).

The pathological version of this argument is that incomplete maturation in a hostile tissue is a state of sustained cytoskeletal and proteostatic strain, and that a cell held in such a state for a long period is a cell in which a labile, hyperphosphorylated tau species is continuously produced under conditions of impaired disposal. The two candidates therefore combine naturally: awakening supplies the production, ageing supplies the failure of clearance, and the conjunction supplies the accumulation.

This candidate has a property the first lacks: it names an event. Dormant cells awaken, the awakening can in principle be dated by the maturation gradient visible in the tissue, and the hypothesis predicts that cells caught mid-awakening should be the ones carrying pathology. That is

a stain, on one section, with three antibodies.

Its weakness is that we do not know what triggers awakening, and therefore cannot say whether the disease increases it. The literature establishes that awakening is modulated by experience, by sensory input, by stress and by age (Gómez-Climent et al., 2011; Riga et al., 2026), and that it proceeds continuously across the lifespan in the absence of any insult (Rotheneichner et al., 2018). Whether chronic neuroinflammation accelerates it is unknown and is among the experiments proposed in section 11.

8.4 Candidate Three: The Cytoskeletal Demand of Local Movement

The third candidate is the one inherited from the niche theories, and it survives the move to the cortex in reduced form.

The proposal in the niche literature is that the cytoskeletal demands of migration through an inhibitory adult parenchyma drive tau phosphorylation beyond the physiological level, because the migrating cell must continuously destabilize and rebuild its microtubule array (Abbate, 2023). Applied to the reservoir, the proposal appears at first to fail, since these cells do not migrate. But the human and primate material describes chains of immature cells extending tangentially, obliquely and inwardly through layers one to three, and clusters that appear distorted in the oldest animals (Zhang et al., 2009; Li et al., 2023). The cells move, over short distances, through an adult cortical matrix.

Whether a few hundred micrometres of movement through adult neuropil imposes enough cytoskeletal demand to matter is unknown, and we suspect this is the weakest of the three candidates. We include it because it is the one that preserves continuity with the existing theoretical literature, and because the chains are a real observation that a complete account has to accommodate.

8.5 What the Three Candidates Share, and the Test That Separates Them

All three candidates predict that the pathology should be found in immature or recently awakened cells, which is the prediction that matters and which the stain in section 6.4 addresses. They differ in what they predict about timing and about the cells' state at the time of involvement.

The disposal mechanism predicts that dormant cells carrying accumulated tau should be found in the dormant state, since nothing has to happen to them beyond the passage of time. The late-maturation mechanism predicts that the affected cells should be caught in transition, showing intermediate marker profiles, larger somata and weaker doublecortin reactivity — a morphological gradient the human material already describes (Li et al., 2023). The movement mechanism predicts that affected cells should be found in chains and clusters rather than singly.

These are distinguishable on the same sections, by the same investigator, in the same afternoon. That is the practical case for the programme in section 11: the three mechanistic alternatives are separated not by three experiments but by three ways of scoring one.

8.6 The Missing Kinase

One component of every version of this argument is currently unsupported and should be flagged as the largest hole in the mechanism.

Glycogen synthase kinase three beta is the kinase that carries the developmental-tau argument. Its activity is elevated in immature neurons, it phosphorylates tau at several of the epitopes that characterize paired helical filaments, and it is the principal tau kinase implicated in the niche versions of this theory, where tau phosphorylation has been shown to be required for the normal development of adult-born neurons (Hong et al., 2010). Whether it is active in cortical layer two immature neurons is unknown; our searches returned no study of this kinase in this population. Without it, the conversion mechanisms above describe a substrate and a disposal failure but leave the phosphorylation itself unaccounted for in these specific cells.

This is not a fatal gap, since the phosphorylation may simply be inherited from the cell's developmental history and maintained, and since other kinases are available. It is, however, an honest statement of where the mechanism is thin: we are proposing that cells carry a kinase-dependent modification without having established that the kinase is there.



9. The Addressing Problem

9.1 The Phenomenon That Needs Explaining

Alzheimer's disease is not anatomically vague. Its clinical variants respect territories with a precision that is easy to underestimate because it is so familiar. Posterior cortical atrophy takes posterior parietal and occipital cortex, in patient after patient, and produces a visual syndrome. The logopenic variant takes left temporoparietal cortex and produces a language syndrome. The behavioural and dysexecutive variants take frontal territory. Tau imaging tracks these distinctions directly: the topography of tracer binding mirrors clinical phenotype and neuroanatomical variability, while amyloid binding is diffuse and does not (Ossenkoppele et al., 2016). And the topography is prospective rather than merely descriptive, since baseline tau imaging predicts the location of subsequent atrophy at the level of the individual patient (La Joie et al., 2020).

A disease that behaved as a diffuse metabolic or proteostatic failure would not do this. Something in the disease knows where it is going.

9.2 Why the Reservoir Does Not Solve It

It would be convenient for this paper if the reservoir explained the addressing, and it does not. We say so plainly because the temptation to overclaim is strongest exactly here.

The reservoir constrains the addressing without determining it. If pathology can only begin where immature cells are, then the map of immature cells is a map of possible starting points, and that is a real constraint: on the human data it would predict a temporal-predominant disease in old age, which is what the common form of the disease is. But within the reservoir's territory, nothing in the reservoir hypothesis says why this patient's posterior pool and that patient's left perisylvian pool. The pools are, on the human map, present in the same places in everyone of the same age.

The problem is general and it is not created by this paper. Any account that locates the disease's origin in a cell type distributed across many regions inherits it. Accounts that locate the origin in a migration inherit it in a different grammar — what steers the migration? — and accounts that locate it in intrinsic vulnerability inherit it as the question of why one region's cells are more vulnerable than another's. The addressing problem is the field's, not the reservoir's.

9.3 The Candidate Answers and Their Status

Four kinds of answer have been offered and none is presently adequate.

The first is intrinsic vulnerability: the affected populations differ in some measurable property — metabolic demand, axonal length, calcium handling, gene expression — that makes them fail first. This has explanatory successes, notably for the locus coeruleus, and it has a structural weakness: it predicts a stereotyped topography, since the intrinsic properties of cortical regions do not differ between patients, and the atypical variants are precisely the cases where topography is not stereotyped.

The second is connectional: pathology spreads along axonal connections from a common origin, so topography is a function of network position, and variant syndromes reflect variation in where the process happened to start. This is well supported as an account of spread and it pushes the addressing problem back one step, to the question of what determined the initial focus.

The third is developmental: the same positional information that specified cortical areas during development is reactivated, or persists, and directs the adult process to particular territories. This is the boldest answer and the one with the least evidence; the cortical arealization program is understood to be complete in embryonic life, and no reactivation in adult neurodegeneration has been demonstrated.

The fourth is plasticity-historical: the regions affected are those that have been most structurally plastic across life, with vulnerability inversely recapitulating the order of development (Arendt, 2012). This has the attraction of connecting the addressing problem to the same variable — developmental status — that this paper has been circling, and it shares the weakness of the developmental answer, in that the mechanism by which plasticity history becomes anatomical specificity in an individual patient is unspecified.

9.4 What Would Make This Tractable

We think the addressing problem is more tractable than its history suggests, and that the reason it has resisted is that it has been posed at the level of regions rather than of cells.

Posed at the level of regions, the question is why one territory and not another, and the available variables are the coarse ones: connectivity, metabolic rate, developmental origin. Posed at the level of cells, the question becomes what the first affected cells in a given brain have in common with each other and not with their neighbours, and that is a question spatial methods can now answer directly. Spatial transcriptomics on affected and unaffected cortex from the same brain, sampled with reference to a cellular marker rather than to a regional atlas, would establish whether the earliest affected sites differ in the persistence of positional or developmental gene expression, in the composition of the extracellular matrix, or in the density of the reservoir itself.

That is the form in which the arealization proposal could be tested without requiring anyone to believe it first: not "is the developmental program reactivated," which is difficult to operationalize, but "do the cortical territories differ, in the adult, in the persistence of the transcriptional signatures that specified them," which is a measurement. Existing atlases may already contain the answer.

9.5 An Honest Assessment

Our position is that the reservoir hypothesis constrains the topography of the disease to the territory where immature cells are, that this constraint is consistent with the temporal predominance of common late-onset disease, that it is in tension with the extra-temporal topographies of early-onset variants for the reasons set out in section 4.2, and that it does not explain individual variation in address at all. A theory that constrains without explaining is doing less than its proponents would like and more than nothing. The addressing problem remains open, and anyone who tells you their theory has solved it should be asked what determines the address in an individual patient, and then asked again.



10. The Therapeutic Collision

10.1 Two Programmes Aimed at One Substrate

Two active research programmes are aimed at immature neurons in the adult brain, and they point in opposite directions.

The first seeks to increase them. Its rationale is the well-documented reduction of immature neurons in Alzheimer's disease and the correlation of that reduction with cognitive status. It includes direct pharmacological approaches — allopregnanolone has completed a randomized, double-blind, placebo-controlled phase 1b/2a trial in early Alzheimer's disease as an explicitly regenerative therapeutic, with exploratory imaging suggesting slowed or reversed hippocampal atrophy and with advancement to a phase 2 proof-of-concept trial (Hernandez et al., 2020; Raikes et al., 2022); plasma-fraction approaches premised on pro-neurogenic activity, taken through placebo-controlled phase 2 in severe disease (Hannestad et al., 2021); the combination approach in which neurogenesis induction plus brain-derived neurotrophic factor elevation reproduces the cognitive benefit of exercise in a mouse model (Choi et al., 2018); and the epigenetic approach, in which cyclic expression of reprogramming factors rejuvenates the dentate gyrus and improves memory in aged mice (Rodríguez-Matellán et al., 2020), reduces tau pathology and astrogliosis in a tauopathy model (Antón-Fernández et al., 2025), restores neural progenitors in the aged niche (Xu et al., 2024), and reverses disease hallmarks when targeted to engram cells in Alzheimer models (Berdugo-Vega et al., 2026).

The second warns against increasing them. Its rationale is that the immature state is the state in which developmental tau is physiologically present, and that mobilizing immature cells in a brain with established amyloid pathology manufactures substrate for a pathological process rather than replacing what the process destroyed (Abbate, 2023).

Both programmes are serious, both have adherents, and they cannot both be right in the same patient at the same time.

10.2 What the Evidence Actually Decides

Very little, and the honest statement of that is the most useful contribution this section can make.

We searched deliberately for experiments in which stimulating neurogenesis worsened pathology or cognition in an Alzheimer model, and found none. The closest evidence in that direction lies outside Alzheimer models: increasing neurogenesis after encoding induces forgetting in normal mice (Akers et al., 2014); neurogenesis triggered by an epileptogenic insult is net harmful, since ablating it reduces subsequent seizures and normalizes cognition (Cho et al., 2015); and

forcing stem-cell activation depletes the pool by converting stem cells to astrocytes (Sierra et al., 2015). Inside Alzheimer models the relevant result is a null with a twist: inducing neurogenesis alone in a transgenic amyloid model produced no cognitive benefit and no reported harm, benefit required co-elevation of a trophic factor, and it was suppression of neurogenesis that worsened outcomes and caused loss of pre-existing dentate neurons (Choi et al., 2018). And in a tauopathy model, partial reprogramming — which acts on the same substrate from the epigenetic direction — reduced tau pathology rather than increasing it (Antón-Fernández et al., 2025).

The balance of published evidence therefore does not support the hazard claim and does not refute it. It does not support it because no Alzheimer-model experiment has produced the predicted harm. It does not refute it because the experiments that would test it directly — stimulation in the presence of established amyloid pathology, with tau pathology and topography as outcomes, in a system that possesses the relevant cell population — have not been done, and because the rodent systems in which such experiments are usually run lack the cortical reservoir entirely, as set out in section 3.3.

10.3 The Asymmetry That Changes the Calculation

There is one consideration that applies to the reservoir and not to the niche, and it changes the risk calculus in a way neither programme has accounted for.

A niche can, in principle, make more cells. A reservoir cannot. The cells are laid down before birth and are spent by maturation across the lifespan, without replenishment (Gómez-Climent et al., 2008; Rotheneichner et al., 2018). Any intervention that mobilizes them is therefore drawing down a finite endowment, and the drawdown is irreversible.

This matters in both directions. For the restoration programme, it means that a therapy which appears to increase immature-neuron-dependent plasticity by accelerating awakening is not adding anything; it is spending capital, and the appearance of benefit could be followed by exhaustion. The analogous phenomenon has been demonstrated in the niche, where driving activation depletes the stem pool (Sierra et al., 2015), and the reservoir has less margin, because it has no capacity for self-renewal at all. For the hazard programme, it means that the quantity of potentially dangerous substrate is bounded and declining with age, which limits the magnitude of any harm and predicts that the hazard, if real, would be greatest in younger brains with fuller reservoirs.

Neither programme currently measures the endowment. If the reservoir is a finite resource being spent, then the relevant clinical variable is not the rate of neurogenesis but the remaining reserve, and nobody is measuring it because no method exists to measure it in a living person. That is a tractable methodological target and we name it in section 11.

10.4 What Should Be Done Now

We are reluctant to draw clinical recommendations from an unconfirmed hypothesis, and the recommendations that follow are correspondingly modest.

Trials of neurogenesis-directed and regenerative therapies should stratify by amyloid biomarker status and should report outcomes by stratum. This costs nothing beyond analysis, is good practice regardless of the hypothesis, and would convert an ongoing programme into a test of the hazard claim. A differential outcome by baseline amyloid status is the signature that would distinguish the two programmes, and its absence would be evidence against the hazard.

Trials should include tau outcome measures where feasible, not only cognitive and volumetric ones, since the hazard claim is specifically about tau and would be invisible to a cognitive endpoint over a short horizon.

Post-mortem material from participants in such trials, where it becomes available, should be examined with the immature-neuron stains described in section 6.4 — which would make the most informative possible use of a resource that is otherwise rarely analysed for this purpose.

And the cellular experiment should be done before the clinical argument is pressed any further in either direction. The hazard claim and the restoration claim both rest on assumptions about what these cells contain, and nobody has looked.

II. The Experimental Programme

The value of a hypothesis of this kind lies in the experiments it makes obvious. We set out seven, ordered by tractability, with what each would establish and what would count as a negative result.

11.1 The Isoform Stain

Triple immunofluorescence on human post-mortem cortex, entorhinal cortex and amygdala: doublecortin or polysialylated neural cell adhesion molecule to identify the cells; isoform-specific three-repeat and four-repeat tau antibodies of the kind used to establish the tangle-evolution sequence (Uchihara et al., 2011; Hara et al., 2013); and standard phospho-tau antibodies. Cases across the adult age range, with and without disease.

This establishes whether the reservoir carries the developmental tau configuration. A negative — adult isoform profile, no phospho-tau — would remove the molecular basis of the hypothesis and should be published as such. This is the single experiment that most needs doing, and it needs one

investigator, one microscope and existing tissue.

11.2 The Disease Comparison

The same stains applied systematically across Braak stages, scoring immature-cell density, maturation-stage distribution, and tau content per cell in entorhinal layer two, temporal neocortex and the amygdalar paralaminar nucleus.

This establishes whether the population is altered in the disease and whether it carries pathology. Three distinguishable outcomes: the population is depleted in disease, which would make it a casualty and align it with the niche literature; the population is preserved but tau-bearing, which would make it a substrate; or the population is unchanged and tau-free, which would remove it from the disease picture entirely. Any of the three is publishable and the third is the cleanest refutation available.

11.3 The Maturation-Gradient Analysis

Within the same material, scoring tau content against maturation state, using the morphological gradient the human tissue already displays — small soma with strong doublecortin reactivity at one end, larger soma with weak reactivity at the other (Li et al., 2023).

This separates the three conversion mechanisms of section 8. Pathology concentrated in fully dormant cells supports the disposal-failure account; pathology concentrated in cells caught mid-maturation supports the late-maturation account; pathology concentrated in chained or clustered cells supports the movement account.

11.4 The Piriform Rodent Experiment

Because the rodent neocortex lacks the population but the piriform cortex has it, the piriform cortex is the correct site for any rodent work. Crossing an amyloid or tau model onto a doublecortin-lineage reporter would permit fate mapping of the reservoir under disease conditions: whether awakening accelerates, whether awakened cells acquire pathological tau, and whether the pool is depleted faster than in controls. The persistence of a small highly immature pool into advanced age in the mouse (Ghibaudi et al., 2023) makes the experiment feasible across a normal model lifespan.

11.5 The Awakening-Trigger Experiment

What releases these cells from arrest is unknown, and the question is answerable. Chronic inflammatory challenge, amyloid exposure, and microglial manipulation, each applied to a lineage-reporter animal with scoring of maturation rate in the piriform cortex, would establish whether the conditions of the diseased brain accelerate awakening. This is the experiment on which the conversion claim most depends, because a hypothesis in which the disease mobilizes the reservoir requires that the disease be capable of mobilizing it.

11.6 The Spatial-Transcriptomic Address Test

Spatial transcriptomics on affected and unaffected cortex from the same brain, sampled by reference to cellular markers rather than regional atlases, asking whether territories differ in the adult persistence of the positional and developmental transcriptional signatures that specified them, and whether those differences align with the topography of pathology in that individual.

This is the tractable form of the arealization question set out in section 9.4, and it does not require anyone to assume the developmental account is correct in order to test it.

11.7 A Measure of the Endowment

No method currently exists to estimate a living person's remaining reservoir. Developing one — whether by imaging ligand, by a molecular signature in cerebrospinal fluid, or by some proxy yet to be identified — would convert the reservoir from a post-mortem curiosity into a clinical variable, and would be necessary before any therapy that mobilizes it could be dosed rationally. We flag this as the hardest item on the list and the one with the largest consequences if it succeeded.

12. What the Reservoir Would and Would Not Explain

A hypothesis earns its place by what it accounts for that its rivals do not, and by admitting what it leaves untouched. We set the balance out directly.

12.1 What It Would Account For

The laminar specificity of the earliest cortical lesion. The standard accounts of why tau pathology begins in layer two of the transentorhinal and entorhinal cortex are connectional and metabolic: these are the cells that project to the hippocampus, they have long unmyelinated axons, and they carry a heavy functional load. Those accounts are plausible and they have a gap, which is that other projection populations with similar properties are affected much later. A reservoir account adds a property that is specific to that layer across the whole cortical mantle, and that is present in no other layer.

The species distribution of the disease. Alzheimer's disease in its full form is a disease of humans, and the failure of rodent models to reproduce it has been attributed to lifespan, to amyloid sequence differences, to the artificiality of transgenic overexpression and to several other causes. If a substantial part of the disease process ran through a cell population that is abundant in the human neocortex and nearly absent from the rodent neocortex, that would constitute a structural rather than a quantitative difference between the systems: not a smaller version of the same thing, but a missing component.

The temporal-predominance of the common form. In humans the cortical reservoir contracts into the temporal lobe by adulthood and into peri-amygdalar temporal cortex in old age (Li et al., 2023). Late-onset Alzheimer's disease is a temporal-predominant disease. On the reservoir account this is not a coincidence but a constraint: the disease begins where the cells are, and in old age the cells are in the temporal lobe.

The involvement of the amygdala. The amygdala's early involvement in tau pathology, and its position as the first region affected in the TDP-43 staging of primary age-related tauopathy (Zhang et al., 2018), sit awkwardly in accounts organized around the entorhinal-hippocampal circuit, since the amygdala is not on the perforant path. It is, however, the one subcortical structure holding a large immature-neuron population across the entire human lifespan.

The coexistence of pathology with preserved cognition. A pathology that begins in a population of cells that are not yet part of any circuit would, at its outset, produce no functional deficit whatever. The dissociation between pathological burden and clinical state in early disease is usually explained by reserve or by compensation. A reservoir account supplies a simpler version: the first cells affected are cells whose loss costs nothing, because they were not doing anything yet.

12.2 What It Would Not Account For

The addressing problem, as set out in section 9: the account constrains where the disease can begin and says nothing about why a particular patient's disease begins where it does.

The early-onset variants, for the reason given in section 4.2: on the reported human map, the extra-temporal reservoir is largely gone before those syndromes present.

The amyloid relationship. Nothing in the reservoir hypothesis explains why amyloid should be present, why it should precede tau by a decade, or why the genetic forms of the disease run through amyloid processing. The hypothesis is compatible with several accounts of that relationship and entails none of them.

The pretangle isoform sequence, which runs the wrong way for a developmental-tau origin and is the strongest evidence against this family of theories (section 6.5).

The bulk of the disease's course. Even on the most favourable reading, the reservoir could only be the origin of the process. The propagation of tau pathology through connected regions, the eventual death of mature projection neurons, and the clinical dementia that follows are not reservoir phenomena and require the established accounts of trans-cellular spread and neuronal death.

12.3 The Net Position

The hypothesis would explain a set of anatomical and comparative facts that are currently explained either loosely or not at all, and it would leave the central mechanistic questions of the disease where it found them. That is a modest offer. It is worth making because the facts it would explain are facts about where and in what the disease begins, and because the cost of testing it is a stain.



13. What Would Refute This

A hypothesis should specify its own defeat conditions, and this one has several, all reachable.

If the cells carry an adult tau isoform profile and no developmental phospho-epitopes, the molecular claim fails and the hypothesis is dead in its present form. The topographic correspondence would then be a coincidence, or a marker of something else — most likely of regional plasticity, which is the competing account set out in section 5.6.

If the reservoir is depleted in the disease in the same pattern and to the same degree as the niche population, without carrying pathology, the cells are a casualty and not a source, and the hypothesis converts into a redundant restatement of the existing neurogenic literature.

If the population in the disease is quantitatively unchanged against age-matched controls and contains no tau, it is irrelevant to the disease and should be dropped from the inventory.

If the earliest tau-bearing cells in well-staged early cases are shown to be mature projection neurons, with immature cells unaffected until late, the sequence runs the wrong way for a reservoir

origin, and the hypothesis is reduced to a claim about a late passenger population.

And if awakening cannot be shown to respond to any condition characteristic of the diseased brain, the conversion claim has no trigger, and the hypothesis has a substrate and a mechanism but no event.

We note that each of these is a result, not merely a refutation. The cellular question is unasked, and the answer is worth having whichever way it falls; the hypothesis's main function is to make the question conspicuous enough to be asked.

14. Verdict

The cellular inventory on which theories of Alzheimer's disease are built has two entries and needs three. The third entry — neurons generated before birth, held in arrested maturation for decades, concentrated in cortical layer two and in the amygdalar paralaminar nucleus, spent slowly across the lifespan and never replenished — is not a marginal population. It is abundant in exactly the brains that get the disease, scarce in exactly the model organism in which the disease is studied, and distributed in a pattern that reproduces the topography in which the disease's earliest lesions appear. It has been characterized for two decades by developmental neurobiologists who have asked, reasonably, why a brain would need dormant precursors at all (Benedetti and Couillard-Despres, 2022). The neurodegeneration literature has not engaged with it.

What we can assert is modest. The cells exist, in humans, in the relevant places, at the relevant ages. The correspondence between their distribution and the distribution of early tau pathology is close, is not obviously explained by the standard accounts, and is not evidence of anything by itself. The molecular question that would make the correspondence meaningful — what tau these cells contain — has not been asked in any species, and the kinase argument on which the developmental-tau family of theories rests has not been tested in these cells either. The mechanism by which a dormant cell could become a pathological one is available in at least three forms, of which the failure of proteostatic disposal in an aged tissue is the best evidenced and the most economical, since it requires nothing to go wrong except that clearance should slow while production continues. The strongest single objection to the whole family of arguments is the pretangle isoform sequence, which finds the earliest lesions four-repeat and the three-repeat signature arriving at the end; and the only legitimate answer to that objection is that the sequence was established in a population other than the one at issue here.

What we cannot assert is most of what would matter. We do not know that these cells carry developmental tau. We do not know that they are altered in the disease. We do not know what wakes them, whether the disease wakes them, or whether a woken cell in an aged cortex is dangerous or merely inefficient. We do not know why one patient's posterior cortex and another's left perisylvian cortex, and neither does anyone else. The therapeutic collision between the programme that seeks to mobilize immature neurons and the programme that warns against mobilizing them is unresolved, and the published evidence — no demonstrated harm in any Alzheimer model, no test in a system that contains the relevant cells — does not resolve it in either direction.

The case for taking the reservoir seriously is therefore not that it is likely to be the origin of Alzheimer's disease. It is that a substantial population of cells, sitting in the right layer, in the right regions, in the right species, in a developmental state whose biochemistry is the biochemistry the disease displays, has never been looked at in the disease; that the looking requires a stain rather than a programme; and that both of the therapeutic programmes now aimed at this class of cell are proceeding on assumptions about its contents that nobody has checked. The most useful thing this paper can do is to make that omission visible enough that someone corrects it.

15. The Validity Ledger

The argument above is only as strong as its weakest load-bearing joint, and the reader is owed an explicit accounting of where it stands on the ground and where it stands on inference.

``ledger - tier: strong basis: "primary literature, multiple independent groups" claim: "A population of prenatally generated, non-dividing neurons persists in an immature state in cortical layer II and the amygdalar paralaminar nucleus into adult life, and can resume maturation." why: "Established by birth-dating, by absence of local proliferation, and by lineage tracing, in several species including primates, with a consistent comparative gradient. Not seriously contested."

- tier: strong basis: "comparative quantification with a single method" claim: "The population increases with brain size and neocortical expansion and is nearly absent from the rodent neocortex." why: "Twelve-species survey plus subsequent carnivore, ungulate and macaque studies. The methodological consequence — that rodent models cannot display a pathology running through this population — follows directly."

- tier: moderate basis: "one systematic human series" claim: "In humans the cortical reservoir contracts from pan-cortical in infancy to temporal in adulthood and peri-amygdalar in old age,

while the amygdalar population persists across the lifespan." why: "A careful study with parallel regional processing across a full age range, consistent with primate data. It is one laboratory's series and needs independent replication; the doublecortin marker is not by itself definitive." settles: "Replication in a second cohort with a multi-marker panel."

- tier: weak basis: "inference from two distributions" claim: "The anatomical correspondence between the reservoir and the sites of earliest tau pathology is evidence that the two are related." why: "It is a coincidence of address and nothing more. Both distributions are medial-temporal-weighted; both may be explained by regional plasticity, which is an established competing account; and the isoform correspondence that strengthens it is a rat study of mature neurons, not of the reservoir."

- tier: absent basis: "systematic search returning nothing" claim: "The tau isoform composition and phosphorylation state of cortical and amygdalar immature neurons is unknown, in any species, in health or disease." why: "Multiple query formulations across markers, regions and diseases returned no study, and a dedicated 2026 review of these cells treats epilepsy, trauma and stroke but not neurodegeneration. A negative search is weak evidence of absence, but the consistency and the review's silence make the gap likely real. This is the paper's central claim and it is a claim about a vacancy." settles: "The stain described in section 11.1."

- tier: contested basis: "evidence running the other way" claim: "A developmental tau configuration is the origin of the pathological species." why: "Pretangles label for four-repeat and not three-repeat tau, with three-repeat accumulating as lesions mature and dominating ghost tangles. This is a serious objection to the whole family of developmental-tau theories. The only legitimate defence is that the sequence was established in pyramidal populations, not in immature cells, and has not been examined in the latter."

- tier: weak basis: "unsupported in this population" claim: "Glycogen synthase kinase three beta supplies the phosphorylation in these cells." why: "The kinase carries the developmental-tau argument elsewhere, and no study has examined it in the cortical reservoir. The mechanism currently proposes a kinase-dependent modification without establishing the kinase."

- tier: moderate basis: "inference from established proteostatic biology" claim: "Failure of autophagic-lysosomal disposal could convert a physiological tau species into an accumulating one without any change in its production." why: "The lysosomal failure itself is well evidenced and molecularly specific in Alzheimer's disease. Its application to this cell population is inference, and the mechanism is generic: it does not by itself explain why these cells would be affected first."

- tier: weak basis: "no test in a relevant system" claim: "Mobilizing immature neurons under amyloid conditions would accelerate the disease." why: "No published experiment demonstrates harm from stimulating neurogenesis in any Alzheimer model; the nearest harmful results are in

epilepsy and normal memory, and partial reprogramming reduced tau pathology in a tauopathy model. The claim is neither supported nor refuted, and the systems used to test it lack the cortical reservoir."

- tier: absent basis: "acknowledged failure" claim: "The reservoir explains why one cortical territory is affected and not another." why: "It does not. It constrains the possible sites to where the cells are and says nothing about individual variation in address. The addressing problem is unsolved by this account and by its rivals." ``

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