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The Borrowed Road

Templated Tau Misfolding Across the Three Phases of Alzheimer's Disease — How the Route Is Anatomy, the Vehicle Is Borrowed Physiology, and the Permission Changes Hands Three Times Between the Brainstem and the Neocortex

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Tau builds no road. It is carried on services the brain already runs — and what changes between the phases is not the route but who holds the key.

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Abstract

Abnormal tau appears in the human brain in a sequence so reproducible that it has been used as a staging scheme for thirty-five years, and the dominant explanation of that sequence is templated misfolding: a misfolded tau molecule leaves one neuron, enters the next, imposes its conformation on the native protein it finds there, and the lesion advances one connection at a time. The evidence that tau can do this is now very strong. The evidence that its doing so is what produces the human sequence is considerably weaker, and the gap between those two statements is the subject of this dissertation.

We argue that the standard framing conflates three separable variables, and that almost every unresolved dispute about tau propagation is a dispute about which of them is rate-limiting. The first is the **route** — which cells are anatomically able to hand material to which. The route is not a property of the disease: it is the wiring of a healthy brain, present at twenty, present in people who never become demented, and unchanged by the arrival of pathology except where it is destroyed by it. The second is the **vehicle** — the physical process that moves a seed-competent species from one cell's interior to another's. Tau has no vehicle of its own. It is carried on services the brain already runs for other purposes: activity-dependent release at the terminal, receptor-mediated endocytosis by way of low-density lipoprotein receptor-related protein 1 and heparan sulfate proteoglycans, vesicular traffic, phagocytosis by glia, bulk interstitial flow. The third is the **permission** — the set of conditions under which an arriving seed is amplified rather than degraded, and under which the recipient cell survives long enough to become a source in its turn.

The central claim of this volume is that the route is approximately constant across the disease, the vehicle changes with the tissue available to carry it, and the permission changes hands three times. In the brainstem decades, tau is seeded locally by a chemistry that only noradrenergic neurons possess, and its permission is neuronal firing in a cell that has no perineuronal net and no scheduled rest except rapid-eye-movement sleep; but the same firing that releases tau also condemns the axon that would carry it, so the earliest phase is a high-exposure, low-throughput regime, and this — not an absence of seeds — is our proposed explanation for the twenty-five-year interval between the first brainstem pretangles and the first cortical disease. At the entorhinal bridgehead, the route becomes a dense, point-to-point, reciprocally connected circuit, and the permission that arrives is amyloid: the human and animal evidence that plaque burden gates the conversion of medial temporal tau into neocortical tau is, we argue, the strongest single piece of support the gated-propagation model has, and the natural experiment that confirms it is primary age-related tauopathy, in which the route is intact, the seeds are present, and the permission never arrives. In the neocortex, the permission is the collapse of restraint: degradative failure in the recipient, which converts an exposed neuron into an amplifying one; matrix loss, which exposes uptake surfaces the perineuronal net had covered; and the recruitment of non-neuronal carriers — microglial vesicles, oligodendroglia, astrocytes — which means that the connectome model of spread is at its least complete exactly where the disease is at its most visible.

Three consequences follow. First, the rate-limiting step is phase-specific, so an anti-propagation therapy is not a single therapy; the antibody programme of the last decade tested the entorhinal lock in neocortical patients, and its results are better read as a statement about timing and compartment than as a refutation of templated spread. Second, transmission is not sufficient to explain staging, because the route exists in brains that never stage; the explanatory weight sits on permission, which is also where the tractable targets are. Third, the single-trajectory assumption is false in a measurable proportion of patients: when tau distribution is modelled without a prior, only about a third of individuals follow the classical medial-temporal sequence, and a phase architecture must therefore be stated as a modal trajectory rather than a law.

We grade every load-bearing step, and we are explicit that the most original of them are inferences rather than results. No study has demonstrated that tau reaches the human entorhinal cortex from the locus coeruleus; seeding activity measured in human tissue is greatest in the transentorhinal cortex and is not uniformly present in the coeruleus until later stages; and the most direct experimental test available — ablating the noradrenergic source in a tauopathy model — accelerated degeneration without reducing forebrain tau. We take those negatives seriously rather than around, and we conclude that the brainstem is where tau begins while the entorhinal cortex is where spread begins. We close with twelve predictions, each with the result that would falsify it, and with an argument about what a drug aimed at spread would have to do differently.

Part PART ONE

The Instrument

What a mechanism of spread would have to explain, and how to take it apart

I. The Question the Staging Map Does Not Answer

The neuropathology of Alzheimer's disease has one finding that everything else is arranged around, and it is not a mechanism. It is a map. Neurofibrillary pathology, examined across large unselected autopsy series, is not distributed at random and is not distributed according to the severity of dementia alone; it occupies a sequence of territories in an order so consistent that the order itself can be used to stage the disease. The transentorhinal region and entorhinal cortex first; then the hippocampus and the limbic belt; then the association neocortex; then, at the end, the primary sensory and motor fields that are affected only in the most advanced cases (Braak and Braak, 1991). The scheme was constructed from eighty-three autopsy brains, demented and non-demented, in which amyloid deposit density proved to be of limited staging value while the tangle sequence did not — and it has survived thirty-five years of attempts to improve it, which in a field with the recent history of this one is an unusual distinction.

What the map does not contain is an explanation. A reproducible spatial order is compatible with at least three mechanisms that differ in everything that matters therapeutically, and the staging data alone cannot separate them.

The first is **transmission**: the lesion appears in region B after region A because material passes from A to B. On this reading the order is a causal chain, the anatomy of connections is the substrate, and the correct intervention is to interrupt transit.

The second is **ordered vulnerability**: the lesion appears in region B after region A because the cells of A are intrinsically more susceptible to a pressure applied to the whole brain, and the cells of B are next in line. On this reading the order is a ranking, not a chain; nothing travels; and the correct intervention is to reduce the pressure or to fortify the cells. This is not a fringe position. It is the reading that the most careful recent audits of the sequence keep returning to, and it is compatible with essentially all of the human staging evidence.

The third is **ordered exposure**: the lesion appears in region B after region A because the *permissive condition* — not the seed — arrives in A before B. Amyloid deposition, for instance, has its own staging scheme, which runs in nearly the opposite direction, from the neocortex down toward the brainstem (Thal and colleagues, 2002), and within individual subjects the regional correspondence between amyloid and tau is weak: across thirty cortical regions in sixteen patients imaged for both, the within-subject correlation was 0.18 with a standard deviation of 0.09 — while tau's correlation with regional hypometabolism in the same subjects was -0.49 (Ossenkoppele and colleagues, 2016). Two pathologies with different spatial rules, interacting where they overlap, can generate an ordered sequence in which nothing is transmitted at all.

These three are usually presented as rivals to be adjudicated. We think that framing has cost the field a decade. All three are true of some part of the disease, and the useful question is not which one wins but **which one is rate-limiting, where, and when**. That question has an answer, the answer is different in the brainstem, the medial temporal lobe and the neocortex, and organising the evidence by phase makes the differences visible in a way that organising it by mechanism does not.

A note on what the staging literature is routinely made to say. Two misreadings are common enough to have become load-bearing in secondary accounts. The first is that Braak and Braak's later analysis of neocortical involvement explains why the entorhinal cortex is affected first; it does not make that claim, and it is a description of spread through the neocortex once the process is established, not an account of onset. The second is the assertion that the earliest-affected projection neurons tangle *because* they are unmyelinated. The correlation with thin or sparse myelination is real and was stated by its authors as a susceptibility criterion for "select types of projection cells that generate long, unmyelinated or sparsely myelinated axons" (Braak, Rüb, Schultz and Del Tredici, 2006), but the causal claim is an inference added later by readers, and we could find no source in which it is demonstrated. We use the criterion as a description of which cells are vulnerable, and not as a mechanism of vulnerability.

What a mechanism of spread would have to explain. If templated misfolding is the engine of the human sequence, then five facts are its burden of proof, and we will hold the argument to them throughout.

- 1. The interval.** Abnormal tau is present in the brainstem of most people by the fourth decade, and cortical disease does not appear for roughly twenty-five years. A propagating agent with a doubling time measured in weeks in the laboratory has to be reconciled with a clinical latency measured in decades.
- 2. The inefficiency.** In every model system in which it has been quantified, the overwhelming majority of neurons exposed to seed-competent tau never develop pathology. Propagation is not merely slow; it fails almost every time it is attempted.
- 3. The stall.** In a substantial fraction of the elderly, medial temporal tau is present, sometimes abundantly, and never reaches the neocortex in a lifetime. The route was available; the process stopped anyway.
- 4. The variability.** When the spatial pattern is modelled without assuming Braak's order, the population divides into several trajectories, of which the classical one accounts for roughly a third (Vogel and colleagues, 2021). A mechanism that is purely a function of fixed anatomy cannot generate a spread of trajectories.
- 5. The dissociation from dementia.** Tangles at Braak stages III and above are compatible with intact cognition in a measurable minority of the elderly, and the odds ratio linking

plaque burden to dementia falls from 8.63 at age seventy-five to a non-significant 2.48 at ninety-five (Savva and colleagues, 2009). Spread and disease are not the same variable.

None of these five refutes templated misfolding. Each of them refutes the *sufficiency* of templated misfolding as an account of the human sequence, and together they define the space that the rest of this dissertation tries to fill.

II. The Decomposition Route, Vehicle, Permission

We propose a three-variable decomposition of propagation, and then use it as the organising instrument of the volume. The decomposition is not a new mechanism. It is a way of separating claims that are usually bundled, so that the evidence for each can be graded independently and so that the rate-limiting step can be named for each phase rather than for the disease as a whole.

The route is the set of anatomical adjacencies across which material could pass: the axonal projections, the synaptic contacts, the glial and vascular contiguities, the interstitial and cerebrospinal fluid compartments that connect one territory to another. Three properties of the route are worth stating plainly, because each is routinely elided.

The route is *not a disease variable*. It is present in the healthy twenty-year-old and in the cognitively intact centenarian. If the route were sufficient, everyone with a brainstem pretangle would eventually develop a neocortical tauopathy, and they do not.

The route is *partly destroyed by the process that uses it*. This is not a subtlety; it is, we will argue, decisive for the earliest phase. A projection that is being pruned cannot deliver at increasing volume, and the noradrenergic projection on which the brainstem-origin model depends is already measurably thinned at the stage at which it is supposed to be seeding the cortex.

The route is *not exclusively synaptic*. The connectome model of spread treats the synapse as the unit of transfer, and for the medial temporal phase that is a defensible simplification. It becomes indefensible in the neocortical phase, where a substantial part of the tau lesion sits in and moves through cells that have no synapses at all.

The vehicle is the physical mechanism that moves a seed-competent tau species out of one cell and into another. The critical observation about the vehicle is that tau does not possess one. Every step of transit that has been characterised is a service the brain runs for another purpose and that tau is carried on: activity-dependent release from the presynaptic terminal, which exists to signal; receptor-mediated endocytosis through low-density lipoprotein receptor-related protein 1 and the sulfated glycosaminoglycan surface, which exists to take up ligands and lipoproteins; extracellular vesicle traffic, which exists for intercellular signalling; microglial phagocytosis, which exists to clear debris; and bulk flow through the interstitial space, which exists to remove solutes. This is what we

mean by a borrowed road. It has a direct therapeutic consequence: every candidate target on the transit path is a target that the healthy brain is using for something, and the therapeutic index of blocking it is set by that other function rather than by tau.

The permission is the set of conditions under which a seed that has arrived in a new cell is amplified rather than destroyed, and under which that cell survives to become a source. Permission has at least four components, and they fail at different times: the recipient's degradative capacity, which determines whether an internalised seed is degraded in the endolysosomal compartment or escapes it; the availability of native substrate in a conformation and phosphorylation state competent to be templated; the extracellular and matrix environment, which determines what fraction of released material reaches an uptake surface at all; and the cell's tolerance of the resulting burden.

The analytic payoff of separating these is that the *same* observation supports different conclusions depending on which variable it is assigned to. Consider the best-known therapeutic result in the field: antibodies that bind extracellular tau have repeatedly failed to slow symptomatic Alzheimer's disease. Assigned to the vehicle, that result reads as evidence against extracellular transit as the rate-limiting step. Assigned to permission, it reads as evidence that by the time a patient is symptomatic the rate-limiting step is no longer transit at all. Assigned to the route, it says nothing whatever. The trials cannot distinguish these readings, but the decomposition tells us which further measurement would.

The criterion we use for naming a phase's rate-limiting step. A step is rate-limiting in a phase if manipulating it in that phase changes the rate of tau accumulation, and manipulating the other two does not. Where such a manipulation exists we cite it; where it does not, we say so and name the experiment. This is a demanding criterion and it is met in full for exactly one of the three phases. We consider the honest statement of that asymmetry more useful than a uniform account that hides it.

The phases. We use a three-phase parsing of the course, following the subcortical-to-cortical sequence of the staging literature rather than a clinical one, and we define each phase by the territory in which the lesion is advancing rather than by the patient's symptoms.

	Phase I — brainstem	Phase II — medial temporal	Phase III — neocortical
Approximate decades	Third to fifth	Fifth to seventh	Seventh onward
Advancing territory	Locus coeruleus, raphe, subcortical nuclei	Transentorhinal and entorhinal cortex, hippocampus	Association neocortex
Route in use	Diffuse ascending projections	Dense reciprocal cortico-hippocampal circuitry	Long-range cortical networks plus non-neuronal contiguity
Dominant vehicle	Activity-dependent release from a degenerating projection	Point-to-point synaptic transfer with receptor-mediated uptake	Mixed: synaptic, vesicular, glial, interstitial
Proposed rate-limiting step	Throughput of a route being pruned as it is used	Arrival of permission (amyloid) and uptake capacity	Failure of restraint: degradation, matrix, glial recruitment
Best available instrument in living humans	None validated	Tau positron emission tomography	Tau positron emission tomography

The last row is the one we would ask a reader to hold onto. The phase in which our mechanistic claims are strongest is the phase that can be measured; the phase in which they are boldest cannot currently be measured in a living person at all.

III. What Is Actually Established About Templated Tau

Before arguing about what propagation explains, it is worth stating, without hedging, how much of it is secure. The experimental case that tau is a templating protein is one of the better-built bodies of evidence in neurodegeneration research, and the criticism developed later in this dissertation is not a criticism of it.

Aggregated tau, and not monomeric tau, is taken into cells and imposes its conformation on native protein. In the founding cell-culture demonstration, extracellular tau aggregates — but not monomer — were internalised, co-localised with markers of fluid-phase endocytosis, and induced fibrillisation of the cell's own full-length tau; the intracellular fibrils so produced were themselves competent to seed recombinant monomer, and newly aggregated tau transferred between co-cultured cells (Frost, Jacks and Diamond, 2009). Every element of the templating claim is present in that one experiment: uptake, conversion of native substrate, and onward transfer.

Human brain material transmits, and it transmits with strain fidelity. Brain extract from mutant P301S tau mice injected into mice expressing only wild-type human tau induced the assembly of that wild-type protein into filaments and the spread of pathology beyond the injection site — establishing that a mutation in the recipient is not required (Clavaguera and colleagues, 2009). Extended to human tissue, extracts from patients who died with Alzheimer's disease, tangle-only dementia, Pick disease, argyrophilic grain disease, progressive supranuclear palsy and corticobasal degeneration each induced argyrophilic tau inclusions, and each **recapitulated the hallmark lesions of the disease the extract came from**; inclusions also formed in non-transgenic mice, and the induced aggregates could be passaged between animals (Clavaguera and colleagues, 2013). Conformational information, not merely aggregated protein, is what is transferred.

The pattern of spread follows connectivity rather than physical proximity. This is the observation on which the connectome model of staging rests, and the cleanest demonstration is a unilateral infusion of aggregate-containing extract into human P301S transgenic mice: new tangle pathology appeared at two weeks and increased with time, and it appeared contralaterally and at a distance in nuclei with strong afferent or efferent connections to the infusion site, while spatially adjacent but unconnected regions were spared — with corroborating pathology in the interconnecting white-matter tracts (Ahmed and colleagues, 2014). The same logic holds when the seed is not injected but expressed: restricting human P301L tau to entorhinal layer II produced pathology first in transgene-expressing neurons, then in neighbouring neurons **without detectable transgene expression**, then in downstream synaptic targets, with human tau co-aggregating with endogenous mouse tau (de Calignon and colleagues, 2012); and in a second entorhinal model, axonal tau at the perforant-path terminal zones at ten to eleven months was followed by intense somatic immunoreactivity in the subiculum, CA1 and dentate granule cells beyond twenty-two months (Liu and colleagues, 2012). The most anatomically specific version of the experiment routes the pathology along the projection that matters clinically: wolframin-1-expressing entorhinal layer II pyramidal neurons, a population conserved in human entorhinal cortex and co-localising with abnormally phosphorylated tau in early disease, transferred tau to **CA1** pyramidal neurons, with reduced CA1 excitability, reduced CA1 firing on optogenetic stimulation of the entorhinal axons, and impaired trace and contextual fear memory (Delpech and colleagues, 2021).

It happens in a primate, from human tissue, with anatomical selectivity and a cognitive consequence. Mouse lemurs inoculated in posterior cingulate cortex and corpus callosum with Alzheimer brain extract developed widespread amyloid- β and tau pathology in all twelve animals after a twenty-one-month incubation, against none of six given control extract; tau pathology appeared in regions distant from the inoculation sites and free of amyloid deposits, including entorhinal cortex, while some adjacent but unconnected regions such as occipital cortex

were spared; and the inoculated animals developed cognitive deficits and cerebral atrophy, reproduced with two independent extract batches (Lam and colleagues, 2021).

The propagating species is small, and it is not necessarily a fibril. Assemblies of tau purified from Alzheimer brain and resolved by size showed that all assembly sizes bind cell-surface heparan sulfate proteoglycans, but only assemblies of three units or more were internalised, and only those spontaneously seeded intracellular aggregation (Mirbaha and colleagues, 2015). The lower bound has since moved further down: tau monomer exists in two stable forms, an inert form and a seed-competent form in which the aggregation motifs are exposed rather than buried, and the seed-competent form triggers intracellular aggregation and self-assembles (Mirbaha and colleagues, 2018); the monomer itself encodes strain information, with a single strain recovered from an Alzheimer brain and three sub-strains from a corticobasal degeneration brain, each reproducing the full set on passage (Sharma and colleagues, 2018). In a transgenic mouse, soluble seeding activity carried by purified monomer was detectable at four weeks — before any insoluble material and before larger assemblies — and no phosphorylation unique to the seed-competent form was found either in the mouse or in human Alzheimer brain (Mirbaha and colleagues, 2022). The initiating conversion is therefore a conformational event, and it is upstream of both aggregation and phosphorylation.

Uptake is receptor-mediated, and the receptor is a clearance receptor. Tau binding to the sulfated glycosaminoglycan surface is required for entry: uptake of tau fibrils is blocked by heparin, by chlorate, by heparinase and by knockdown of the glycosyltransferase *Ext1*, blocking the interaction prevents both intracellular aggregate induction and transcellular propagation, and a heparin mimetic blocked neuronal uptake of stereotactically injected fibrils in vivo — while the same route is used by α -synuclein and **not** by huntingtin, which is the specificity control that makes the finding a mechanism rather than a surface effect (Holmes and colleagues, 2013). Within that surface, the sulfation pattern matters: aggregated tau has higher affinity for 3-*O*-sulfated heparan sulfate, uptake falls in cells lacking 3-*O* sulfation or when the available 3-*O*-sulfated chains are competed away, and 3-*O*-sulfation-bearing chains are the more effective competitive inhibitor (Ferreira and colleagues, 2022). The protein receptor was identified as low-density lipoprotein receptor-related protein 1: knockdown reduced tau uptake in neuroglioma cells and in neurons derived from induced pluripotent stem cells, the interaction is mediated by lysines in the microtubule-binding repeat region, and receptor downregulation reduced neuron-to-neuron propagation in vivo (Rauch and colleagues, 2020).

Two qualifications of that last result are load-bearing for this dissertation and are, in our reading, not yet absorbed by the literature that cites it.

The first is that the receptor is a **degradative** receptor before it is a propagative one. Radiolabelled tau taken up by this receptor is efficiently delivered to the lysosome and degraded;

phosphorylated recombinant tau binds it weakly and is internalised less efficiently; and apolipoprotein E inhibits receptor-mediated tau uptake, with the $\epsilon 4$ isoform the most potent inhibitor. When the ligand is post-translationally modified tau purified from human Alzheimer brain, receptor-expressing cells promote cytosolic seeding and apolipoprotein E enhances it (Cooper and colleagues, 2021). The same receptor therefore clears tau or seeds with it depending on the species presented and the lipoprotein environment — which means that a therapeutic aimed at the receptor has two opposite possible effects, and which one it has is a function of disease stage.

The second is that a whole-genome loss-of-function screen in human excitatory neurons derived from induced pluripotent stem cells found that monomeric and fibrillar tau enter by **different** receptor-mediated routes: the receptor is the primary route for monomeric tau and contributes considerably less to fibrillar entry, and monomeric uptake additionally requires the kinase LRRK2, which fibrillar uptake does not (Evans and colleagues, 2025). The frequently repeated summary — that this receptor is *the* gateway for tau seeds — is therefore too strong. It is the gateway for the species that is most abundant, not necessarily for the species that is most seed-competent.

Seeding activity is measurable in human tissue, and it is present before the lesion. A fluorescence-resonance-energy-transfer biosensor detects tau seeds at femtomolar concentration and, in P301S mice, reported robust seeding at 1.5 months, more than a month before the earliest histological stain (Holmes and colleagues, 2014). Applied to human brain, the assay found widespread seeding at early Braak stages across 104 cases, including in regions predicted to be free of phospho-tau and in detergent-insoluble fractions in which tau was undetectable by immunoassay, with seeding correlating positively with Braak stage and negatively with cognitive score (Furman and colleagues, 2017). In a six-region series along the Braak pathway, substantial seeding was present in entorhinal cortex in cases with only very rare tangles, in the *next* and still pathology-free region along that pathway, and in white-matter tracts and optic nerve where somata are nearly absent — and seed-competent phosphorylated tau was significantly enriched in the synaptosome fraction of regions lacking extensive cellular pathology (DeVos and colleagues, 2018).

And it can now be measured in living people, with prognostic content. A cellular biosensor applied to cerebrospinal fluid stratified patients by seeding activity, and those with high or intermediate activity declined more rapidly than those with low activity; the same assay predicted which human brain lysates would induce aggregation on transmission into animals (Houzé and colleagues, 2025). This complements the tissue finding that seeding magnitude tracks clinical aggressiveness: across thirty-two patients, soluble oligomeric seed-competent tau varied strikingly between individuals, and seeding activity correlated with the aggressiveness of the clinical disease, with some post-translational modification sites associated with both greater seeding and worse outcome and others not (Dujardin and colleagues, 2020).

We note two honest limits on the assay literature, because they constrain what can be claimed for biomarkers later. Real-time quaking-induced conversion assays discriminate tau strains with great sensitivity — three-repeat seeds in Pick disease brain at dilutions to ten to the minus tenth, and four-repeat seeds in progressive supranuclear palsy and corticobasal degeneration at femtomolar sensitivity, with seeds detected in post-mortem cerebrospinal fluid from all confirmed cases and no controls (Saijo and colleagues, 2017; Saijo and colleagues, 2020) — but both papers state that the assays are **orders of magnitude less responsive to Alzheimer brain**, which carries both isoform classes. There is at present no validated seed-amplification assay for Alzheimer tau in antemortem cerebrospinal fluid with published diagnostic operating characteristics, and living-subject seeding responses are weaker than post-mortem ones.

Human transmission, finally, is no longer hypothetical for amyloid- β , and is not yet demonstrated for tau. Four of eight recipients of cadaveric pituitary growth hormone who died of iatrogenic Creutzfeldt-Jakob disease at ages thirty-six to fifty-one carried moderate-to-severe parenchymal and vascular amyloid- β , without pathogenic mutations or risk alleles, against minimal or absent amyloid in 116 other prion-disease patients of similar or greater age (Jaunmuktane and colleagues, 2015); archived vials from the implicated batches contained amyloid- β and **tau**, and that material seeded plaques and amyloid angiopathy on inoculation into mice — though the readout tested was amyloid, not tau (Purro and colleagues, 2018). In a French series of twenty-four such patients, three had intracellular tau accumulation, and immunoassay of twenty-four hormone batches produced between 1974 and 1988 found amyloid- β contamination in seventeen and **tau contamination in six**, leading the authors to raise, as a hypothesis, that tauopathy might also be transmissible in humans (Duyckaerts and colleagues, 2018). Recipients who did not die of prion disease have since been described with dementia and biomarker changes within the Alzheimer spectrum (Banerjee and colleagues, 2024), and in the post-mortem follow-up of that series one patient with onset at forty-seven showed unequivocal Alzheimer neuropathology **including severe tauopathy** at autopsy at fifty-seven (Banerjee and colleagues, 2026). The correct statement of the human evidence is therefore precise and slightly awkward: tau seeds were present in the implicated inoculum; tau transmission from human brain extract is demonstrated in a primate; iatrogenic amyloid- β exposure in humans is now associated with severe downstream tauopathy; and a primary iatrogenic human tauopathy has never been shown.

That is the established core. It is substantial, and it is enough to make templated misfolding a real mechanism operating in real human brains. What it is not, as the next section argues, is an explanation of the staging map.

IV. What Templated Misfolding Cannot Explain By Itself

The five burdens set out in Section I are now taken in turn, using the evidence assembled in Section III. The purpose is not to embarrass the propagation model but to locate precisely where it needs a second variable, because that location is where the therapeutic opportunity is.

The seeds are not the limiting reagent. This is the most important single fact in the human seeding literature, and it is routinely reported as though it were support for the propagation model when it is in fact a constraint on it. Across 104 fresh-frozen brains spanning all Braak stages, seeding activity was widespread at early stages, including in regions predicted to be free of phospho-tau (Furman and colleagues, 2017). Along the Braak pathway in a six-region series, seeding was present in the next, still pathology-free region, and in white matter and optic nerve where cell bodies are nearly absent (DeVos and colleagues, 2018). In 247 individuals assayed in four regions each, seeding was detected in superior temporal gyrus and in primary visual cortex **before** tangles or immunoreactive tau appeared there (Kaufman and colleagues, 2018). Seed-competent tau is therefore present, in quantity, in territories that will not develop pathology for years and in some cases will not develop it at all. Whatever determines the lesion, it is not the arrival of the seed. It is what the tissue does with it.

The interval, and a correction to the direction of the earliest evidence. Abnormal phosphorylated tau is present in the brainstem in youth: of 42 individuals aged four to twenty-nine, 38 carried pretangle tau, 41 had no amyloid deposition at all, and among the 26 who lacked transentorhinal tau, 19 of the 22 with subcortical lesions had that material confined to the noradrenergic coeruleus–subcoeruleus complex (Braak and Del Tredici, 2011). In the companion series of 2,332 unselected brains aged one to a hundred, 58 cases carried subcortical tau predominantly in the locus coeruleus with **no** abnormal cortical tau, and the first amyloid plaques appeared only after brainstem tauopathy was already established (Braak, Thal, Ghebremedhin and Del Tredici, 2011). The brainstem is first. That is not in dispute. Nor is the slowness of what follows: modelling stage prevalences across 887 routine autopsy brains gives transit times of sixteen years or more from stage I to stage II, about fourteen years from II to III, thirteen from III to IV and five from IV to V — an inference from cross-sectional prevalence rather than serial observation, but one implying that the process can be traced back some fifty years and may begin in adolescence (Ohm and colleagues, 1995). No study has measured years per stage by serial autopsy or by longitudinal imaging of stage transitions, and the absence of that measurement is itself worth noting in a field that speaks confidently about disease duration.

What is in dispute — and what we think the field has not confronted — is whether being first makes it the source. The same human assay that found seeding in pathology-free neocortex reported that the earliest and most robust seeding activity was in the **transentorhinal and entorhinal cortex**, and that the locus coeruleus did not uniformly show seeding until later neurofibrillary stages (Kaufman and colleagues, 2018). Pretangle immunoreactivity and seeding competence are different measurements, and in the one study that made both in the same brains they dissociate in

the earliest structure. We take this seriously throughout, and it is the reason this dissertation distinguishes the site where tau *begins* from the site where *spread* begins.

The inefficiency, and the negative that is usually skipped. If the brainstem were the source and its projection the route, then removing the source should reduce the downstream lesion. The experiment has been done: noradrenergic lesioning in a P301S tauopathy model accelerated neuronal death and shortened survival **without profoundly affecting forebrain tau pathology** (Chalermpananupap and colleagues, 2018). The most natural reading is that the brainstem's contribution to the forebrain is trophic and immunological rather than proteopathic — that it withdraws a restraint rather than delivering a seed.

The route itself is also being dismantled at the moment it is supposed to deliver. In *A β* ^{NL-G-F} mice, noradrenergic fibre loss in a target field reached 14 per cent at two months, 27 per cent at three and 33 per cent at six, while locus coeruleus cell number remained indistinguishable from wild type at twelve months; in human tissue, pronounced degeneration of noradrenergic fibres was present at Braak stages 1–2 and did not further decline in more advanced disease (Meyer and colleagues, 2025). A projection that has lost a third of its terminals by the earliest cortical stage, and does not deteriorate further, is a poor candidate for a delivery system whose throughput must rise for decades.

The stall. Medial temporal tau without amyloid is not a rarity, and it does not usually become Alzheimer's disease. In a forensic series of 1,589 autopsies aged forty and over, primary age-related tauopathy was present in 719 — 45.2 per cent — and its prevalence peaked at 65.5 per cent in the seventh decade and **fell** to 21.5 per cent in the ninth, because in the oldest brains other pathology supervenes (Yoshida and colleagues, 2024). In seventy-seven autopsies at a mean age of 102, Alzheimer pathology was not universal, but some hippocampal tangles were observed in **every case** (Neltner and colleagues, 2015). And in the study that first put the two lesions side by side in the non-demented, tangles were found in all thirty-nine non-demented cases while plaques were absent in some brains up to the age of eighty-eight — with tangle number and the *rate* of tangle increase with age both jumping in the subgroup that had widespread plaques (Price and Morris, 1999).

That last observation, made in 1999, is the gated-propagation model in miniature, and it has a genetic echo: across 1,190 Alzheimer and 376 primary-age-related-tauopathy cases, apolipoprotein E ϵ 4 dosage tracked Braak stage in Alzheimer's disease and in probable primary age-related tauopathy but **not** in definite primary age-related tauopathy (McMillan and colleagues, 2018). The condition in which tau stays in the medial temporal lobe is the condition in which the amyloid-linked risk allele stops predicting how far it gets.

The variability. When the spatial pattern of tau is modelled without imposing Braak's order, the population does not resolve into one trajectory. In a discovery sample of 1,143 people imaged with flortaucipir, 700 — 61 per cent — had no abnormal signal; fitting four subtypes to the

remaining 443 gave a limbic-predominant trajectory with a Braak-like progression in 145 (32.7 per cent), a medial-temporal-sparing parietal trajectory in 79 (17.8 per cent), a posterior occipitotemporal trajectory in 135 (30.5 per cent) and a lateral temporal trajectory in 84 (19.0 per cent), with 12 per cent falling cleanly into none; three of the four reproduced in an independent 469-person sample imaged with a different tracer (Vogel and colleagues, 2021). Only one of the four is Braak-like, and it is a third of the tau-positive group. A model in which the route is fixed anatomy and nothing else cannot produce four trajectories from one connectome.

The dissociation from dementia. Tangle burden and dementia come apart in both directions. Across 456 brains aged sixty-nine to a hundred and three, the odds ratio linking neocortical neuritic plaques to dementia fell from 8.63 at age seventy-five to a non-significant 2.48 at ninety-five, while the association with neocortical atrophy held at both ages (Savva and colleagues, 2009). In 1,672 autopsies across four cohorts, 47 per cent of the cognitively normal had moderate or frequent neuritic plaques, and only 6 per cent of those also reached Braak stage V or VI (Sonnen and colleagues, 2011). Advanced tangle pathology without dementia is real but uncommon and rarely silent: 12 per cent of non-demented participants in one large series and 8 per cent in another reached Braak V–VI, and those individuals were often measurably memory-impaired despite not meeting dementia criteria (SantaCruz and colleagues, 2011).

The resilience cohorts sharpen the point. In eighty-five centenarian brains, pathology reached the highest levels of every scale in use — amyloid phase 5, Braak stage V, Lewy stage 6, limbic TDP-43 stage 3 — yet only tangle stage and limbic TDP-43 pathology were associated with cognitive performance at all, and some of the best performers carried the heaviest burdens (Zhang and colleagues, 2023); an earlier series from the same programme found amyloid and tau abundantly present in most or all cognitively healthy centenarians (Ganz and colleagues, 2018). At the other end of the vulnerable sequence, individuals with exceptional memory for their age had roughly three times fewer entorhinal tangles than age-matched controls, and about a hundred times fewer than typical amnesic cases, with **no difference in plaque density** (Gefen and colleagues, 2021). And in a post-mortem comparison of asymptomatic and symptomatic individuals matched for plaque burden, the asymptomatic brains showed more compact and fewer filamentous plaques, more plaque-associated microglia, less tau in dystrophic neurites, and — the finding that matters most here — **tau seeding activity comparable to healthy brains** despite Alzheimer-level amyloid (Jury-Garfe and colleagues, 2024). Resilience, measured this way, is not the absence of amyloid. It is the absence of permission.

Where this leaves the two explanations. The honest conclusion is not that connectivity fails and vulnerability wins, and the field's best recent work says so directly. Fitting a network-diffusion model to tau positron-emission tomography in 196 patients and then regressing out its prediction, many Alzheimer risk genes correlated more strongly with the **residual** tau than with raw regional tau; the genes sorted into network-aligned and network-independent classes with

different functional enrichment — cell death, stress and metabolism in the first, amyloid processing and immune response in the second (Anand and colleagues, 2025). Both kinds of vulnerability exist, in the same brains, on different genes. A recent analysis states the division of labour more sharply still, and we cite it as a preprint rather than as a result: whether tau is present in a region is consistent across people and largely explained by spread through white-matter networks, while how much accumulates there varies between people and is governed by regional amyloid, gene expression and blood flow (Xiao and colleagues, 2026, preprint).

Presence by route; load by permission. That is the thesis of this dissertation in nine words, and the next three parts test it phase by phase.

Part PART TWO

The Brainstem

Phase I — the seed that is made where it cannot travel

V. Phase I The Seed's Birthplace

The first phase is the one in which this dissertation departs most from the standard account, and it does so in both directions: we think the case that tau *originates* in the brainstem is stronger than the amyloid-first literature allows, and the case that brainstem tau *propagates* to the cortex is considerably weaker than the brainstem-first literature allows. Both claims rest on the same body of evidence.

Why this cell, and why so early. The locus coeruleus is the first structure in the human brain to carry abnormal tau, in the young, in the absence of amyloid (Braak and Del Tredici, 2011; Braak, Thal, Ghebremedhin and Del Tredici, 2011). The explanation that has emerged for that selectivity is metabolic and is specific to noradrenergic neurons. Norepinephrine escaping vesicular storage is metabolised by monoamine oxidase A to the aldehyde 3,4-dihydroxyphenylglycolaldehyde, which is produced exclusively in noradrenergic neurons, and which activates asparaginyl endopeptidase; that protease cleaves tau at asparagine 368 into aggregation- and propagation-prone forms, producing coerulean neurotoxicity and, in the authors' model, propagation of tau pathology to the forebrain (Kang and colleagues, 2020). The same aldehyde also reacts directly with tau at lysine 353 to form a covalent adduct that stimulates aggregation and spreading; mutating that lysine reduced adduct formation and reduced spread, and fibrils made from the mutant failed to trigger the propagation and cognitive impairment that wild-type fibrils produced (Kang and colleagues, 2022).

This is a genuinely local explanation of a locally selective lesion, and it has a property worth naming: the seed in the locus coeruleus is **manufactured in place**, by a chemistry no other cell possesses, rather than received from elsewhere. Phase I does not need a propagation mechanism to explain its own lesion. This matters for the argument, because it means the brainstem's priority in time is not evidence of its priority in a causal chain.

The chronology is three clocks, not one, and only one of them is fast. Tau comes first and kills nothing for a long time: pretangles are present in the locus coeruleus from the third decade, and in one series 7.9 per cent of its neurons bore phosphorylated tau at Braak stage 0 (Ehrenberg and colleagues, 2017), while the nucleus loses 8.4 per cent of its *volume* for each one-unit increase in Braak stage and its neuronal loss begins only midway through the progression, ageing alone sparing it (Theofilas and colleagues, 2017). Volume and cell number are not the same measurement, and the two can dissociate — cell counts remain stable despite volume loss in cognitively impaired aged macaques (McDermott and Barnes, 2025) — so the cell-loss figures should be taken from the studies that counted cells: about 30 per cent of noradrenergic neurons lost across the transition to amnesic mild cognitive impairment, with a further 25 per cent in mild to moderate disease (Kelly and colleagues, 2017). The axon, however, goes early — and the best-characterised instance of that comes with a restriction that must be stated. In an amyloid

knock-in model, noradrenergic axon degeneration began between one and two months **exclusively in the olfactory bulb**: density was unaltered at one month, 14 per cent lost at two months, 27 per cent at three and 33 per cent at six, while axons in hippocampus, piriform and medial prefrontal cortex did not begin to degenerate until between six and twelve months. In human olfactory bulb from early cases staged at Thal phase 1–2 and Braak stage 1–2, degeneration of noradrenergic transporter-positive fibres was pronounced against age-matched controls and **did not decline further in progressive disease** (Meyer and colleagues, 2025).

Phase I's permission is firing, and firing is also its self-destruction. Tau release is activity-dependent. Stimulation or glutamate-receptor activation induces release of endogenous tau from healthy neurons; the released protein is less phosphorylated than the intracellular pool; and release is calcium-dependent and blocked by presynaptic vesicle-release inhibition (Pooler and colleagues, 2013). In vivo microdialysis showed that raising neuronal activity rapidly increases interstitial tau and that presynaptic glutamate release alone suffices, while elimination of tau from the brain compartment is slow, with a half-life near eleven days (Yamada and colleagues, 2014). Optogenetic and chemogenetic stimulation increase release in vitro and worsen tau pathology in vivo (Wu and colleagues, 2016), and the converse holds: chronic chemogenetic silencing of entorhinal neurons reduced amyloid accumulation and reduced pathological tau spread downstream (Rodriguez and colleagues, 2020).

Now place the locus coeruleus in that framework. It is a tonically active nucleus whose discharge is highest in waking, lower in slow-wave sleep and virtually absent in rapid-eye-movement sleep (Aston-Jones and Bloom, 1981) — which makes it, on the activity-release relationship, a structure that releases tau through most of the day and is granted one scheduled reprieve. And the same activity that releases tau is implicated in the destruction of the axon that would carry it: microglia recognise externalised phosphatidylserine on noradrenergic axons — the ligand read by the vitronectin-receptor bridging protein milk fat globule-EGF factor 8 and by the triggering receptor expressed on myeloid cells 2 — and phagocytose them, with bulb microglia showing 33 per cent higher phagocytic capacity within twelve hours and with genetic reduction of phagocytosis preserving both the axons and the behaviour they support (Meyer and colleagues, 2025).

The consequence we draw, and its stated limit. Phase I is a high-exposure, low-throughput regime. The seed is made continuously in a cell that cannot stop releasing it, and at least one of its terminal fields is being pruned by microglia at the same time. We propose this as the explanation of the interval — the twenty-five years between the first brainstem pretangles and the first cortical disease — and we prefer it to the two alternatives on offer. It is not that seeds are absent, because they are demonstrably present. It is not that the cortex is not yet connected, because it always was. It is that the route out of the brainstem is narrow, partly self-consuming, and unaccompanied by the amplifying conditions that arrive later.

The limit is that the axonal evidence is olfactory. The early, steep degeneration was found in the olfactory bulb and not in the hippocampus or the cortex, where loss began only at six to twelve months; and the human confirmation was also in olfactory tissue. Whether the projection to the medial temporal lobe — the one a brainstem-origin model actually requires — is pruned on the same schedule has not been measured. If it is not, then the self-consuming-route argument is a claim about olfaction, and the interval needs a different explanation. We name that measurement in Section XV because it is the cheapest decisive test in this dissertation.

The case on the other side, which we do not think can be dismissed. Injecting synthetic tau fibrils directly into the mouse locus coeruleus produced tau pathology distributed according to the nucleus's own afferent and efferent connections (Iba and colleagues, 2015). Expressing pseudo-hyperphosphorylated human tau in the rat locus coeruleus was built explicitly to test whether coerulean pretangles generate downstream pathology and preclinical change (Ghosh and colleagues, 2019). And the proposal itself was made carefully by the authors of the staging work, who observed abnormal tau developing within the *proximal axons* of coerulean projection neurons before any transentorhinal tau or cortical amyloid, and asked in terms whether neuron-to-neuron propagation follows (Braak and Del Tredici, 2011b).

So the mouse experiment says seeds placed in this nucleus travel along its connections; the human assay says that, in the human brain, this nucleus is not where the seeding activity is greatest early; and the ablation experiment says removing the nucleus does not reduce forebrain tau. Our reading, which Section XVI grades as inference, is that the coeruleus is genuinely the first site of the lesion and is *not* the principal source of the cortical seed load — that it contributes a small early seed burden and, more importantly, the withdrawal of a restraint. A further observation supports demoting the single-nucleus account: in 118 brains, the dorsal raphe carried phosphorylated-tau cytoskeletal changes before the transentorhinal region as well (Grinberg and colleagues, 2009). Whatever begins this disease acts on more than one brainstem nucleus at once, which is easier to reconcile with a shared vulnerability than with a point source.

What we decline to claim. Three things, each of which the brainstem-origin literature tends to assert.

We do not claim that the noradrenergic projection is an ideal distributor by virtue of its size. The most commonly cited figure for the axonal extent of these neurons — a cumulative arbor of several metres — belongs to human substantia nigra dopamine neurons, not to noradrenergic ones (Pissadaki and Bolam, 2013), and we could find no published estimate of total axonal length per human locus coeruleus neuron. The susceptibility criterion that is actually supported is the one its authors stated: select projection neurons with long, unmyelinated or sparsely myelinated axons are particularly vulnerable (Braak, Rüb, Schultz and Del Tredici, 2006).

We do not claim that brainstem tau is the principal source of the cortical seed load, for the reasons just given.

And we do not claim that Phase I is measurable in a living person. We could find no study that quantifies tau positron-emission-tomography signal within a locus coeruleus region of interest, which is unsurprising: the structure is a few millimetres across, automated segmentation work reports voxel dimensions of 0.69 millimetres as the relevant scale (Sibahi and colleagues, 2023), and harmonised tau tracer resolution is several times coarser. The human literature reaches this nucleus only through structural or neurochemical surrogates, and reads tau out of the cortex.

What the human surrogates do show — and it is more than we expected. Lower locus coeruleus integrity on high-resolution magnetic resonance imaging identified elevated entorhinal tau in 188 asymptomatic individuals better than amyloid imaging did, with an area under the curve of 85 per cent against 77 per cent for amyloid and 76 per cent for hippocampal volume, and low integrity carried a two-fold increase in clinical progression over six years (Engels-Domínguez and colleagues, 2024). In autosomal-dominant disease, lower rostral locus coeruleus integrity correlated with tau burden and memory decline, with post-mortem confirmation of neuronal loss in carriers of the same mutation (Dahl and colleagues, 2021). And the conduit itself has now been measured: in presenilin-1 E280A carriers, lower integrity of the white-matter tract between locus coeruleus and entorhinal cortex was associated with higher entorhinal tau and poorer memory, with tau mediating the relationship between tract integrity and memory (Koops and colleagues, 2026).

We are careful about what that last study establishes. It is thirty carriers and thirty-three non-carriers; it is a correlation between a tract measure and a target-region tau measure; and a degenerating tract is equally compatible with tau having travelled along it and with both structures failing under a shared pressure. It is, however, the first human measurement of the anatomical link that the brainstem-origin model requires, and it points the right way.

Part PART THREE

The Bridgehead

Phase II — where spread begins, and what unlocks it

VI. The Route Becomes a Circuit

If the brainstem is where tau begins and the neocortex is where it is finally counted, the entorhinal cortex is where the disease acquires the property that makes it a progressive disease. That is a strong claim and the evidence for it is unusually direct: the earliest and most robust seeding activity in the human brain, measured as seeding activity rather than inferred from immunostaining, is in the transentorhinal and entorhinal cortex (Kaufman and colleagues, 2018). Whatever the brainstem contributes, the amplification begins here.

What changes at the entorhinal station is the character of the route. The noradrenergic projection is a broadcast system: neurons projecting to one target also project to every other target examined, and neurons serving different outputs receive largely the same inputs, so the system has limited sub-circuit specificity (Schwarz and colleagues, 2015). Its terminals are a mixed population — ultrastructurally, thin unmyelinated intervaricose segments and varicosities of which somewhat over half form specialised axodendritic synapses (Olschowka and colleagues, 1981) — and its cortical fibre density is comparatively uniform across limbic areas rather than topographically targeted (Gaspar and colleagues, 1989). That is an efficient architecture for distributing a diffusible signal across a wide territory, and an unselective one for handing a particle to a specific partner.

The entorhinal-hippocampal system is the opposite: dense, laminated, topographically organised, reciprocal and point-to-point. If templated misfolding requires close apposition and receptor-mediated capture — and the uptake literature says it does — then the perforant path is the first place in the ascending sequence where the anatomy matches the mechanism.

And the target population is the most vulnerable in the cortex. Entorhinal layer II is where the human lesion begins: Braak's stages I and II are defined by alteration of its pre- α cell islands. The cost is measurable early and it is specific to that layer. Against controls carrying roughly 650,000 layer II neurons and about seven million in the entorhinal cortex as a whole — numbers that are stable between sixty and ninety years of age — individuals at the earliest clinical stage had lost 32 per cent of entorhinal neurons overall, 60 per cent of layer II and 40 per cent of layer IV; by severe disease, layer II was down about 90 per cent (Gómez-Isla and colleagues, 1996). An independent stereological series found layer II stellate neurons reduced by 63.5 per cent in mild cognitive impairment, already indistinguishable from established disease (Kordower and colleagues, 2001). We note the counterweight in the same literature: a series examining preclinical cases found little or no loss in ageing or in preclinical disease, with the decline appearing at symptom onset (Price and colleagues, 2001) — which places the neuronal loss at the transition rather than before it, and is consistent with tau arriving well ahead of the cell death it eventually causes.

Why this population is a bridgehead rather than merely a waypoint is a question about the cells and not the wiring. The layer II neurons that carry intracellular amyloid at the pre-plaque stage are the reelin-immunoreactive ones (Kobro-Flatmoen and colleagues, 2016); the selectively vulnerable excitatory population in the entorhinal cortex can be identified molecularly by the transcription factor RORB (Leng and colleagues, 2021); and the tau-accumulating neurons across regions share a tau-homeostasis expression signature whose hub, BAG3, modulates accumulation bidirectionally in primary neurons (Fu and colleagues, 2019).

Where in the entorhinal cortex it starts has now been localised in living people.

Across 443 adults, with two-year follow-up in 104, the initial cortical tau signal emerged near the rhinal sulcus in clinically normal individuals, and the subsequent spread went first to nearby temporal neocortex and then beyond it, with the rate of spread associated with baseline global amyloid burden and baseline medial temporal tau (Sanchez and colleagues, 2021).

The model evidence is unambiguous about direction and specificity. Restricting pathological human tau to entorhinal layer II produces pathology in downstream synaptic targets that never expressed the transgene (de Calignon and colleagues, 2012; Liu and colleagues, 2012), and when the expressing population is defined more precisely — wolframin-1-positive entorhinal layer II pyramidal neurons, a population conserved in the human entorhinal cortex and carrying abnormal phosphorylated tau in early disease — the pathology travels to CA1 and takes function with it: reduced CA1 excitability, reduced firing on optogenetic stimulation of the entorhinal axons, and impaired trace and contextual fear memory (Delpech and colleagues, 2021). Injected seeds obey connections rather than distance, appearing contralaterally and in connected nuclei while sparing adjacent unconnected tissue (Ahmed and colleagues, 2014). And when the experiment is scaled — seeding Alzheimer-derived tau in non-transgenic mice and quantifying pathology across 134 regions over nine months — diffusion through the connectome was the best predictor of the observed pattern, with the residuals mapping onto regional vulnerability and its gene expression (Cornblath and colleagues, 2021).

That last study deserves emphasis because it is the experimental analogue of the human analysis quoted in Section IV: connectome first, vulnerability in the residual. The two literatures, working on different species with different instruments, have converged on the same division of labour.

In living humans, the connectome predicts where tau is and how fast it arrives.

An epidemic-spreading model constrained by the human connectome explained up to 70 per cent of the variance in the spatial pattern of tau across 312 individuals spanning the disease continuum (Vogel and colleagues, 2020). Functional connectivity between region pairs predicted the covariance of tau signal, in normal ageing, in Alzheimer's disease and in vascular cognitive impairment alike (Franzmeier and colleagues, 2019). Longitudinally, connectivity between regions predicted correlated tau *accumulation*, and baseline connectivity plus baseline tau predicted future

accumulation in two independent samples (Franzmeier and colleagues, 2020a); when the analysis is centred on each patient's own tau epicentre, connectivity to that epicentre predicts the subsequent spreading sequence and accumulation rate, and outperforms Braak staging as a trial outcome, cutting simulated sample sizes by about 40 per cent (Franzmeier and colleagues, 2020b). Tau in globally connected fronto-parietal hub regions predicts faster subsequent accumulation and mediates the relationship between earlier disease onset and faster cognitive decline (Frontzkowski and colleagues, 2022).

And the structural conduit behaves as a conduit should. In 256 cognitively healthy older adults, lower baseline hippocampal volume predicted higher mean diffusivity of the hippocampal cingulum bundle, and that tract measure predicted tau accumulation in the downstream-connected posterior cingulate — **only in amyloid-positive individuals** (Jacobs and colleagues, 2018). The conditional is the finding. The route did its work where permission had been granted and not elsewhere, in the same cohort, measured the same way.

One qualification, stated because the modelling literature tends to bury it. These models are fitted to cross-sectional or short-interval longitudinal data and they predict *distributions*, not trajectories of individual molecules. A connectome-weighted diffusion model will fit any process whose spatial statistics follow the network — including a process of ordered vulnerability in which connected regions are similar because connected regions are made of similar cells. The one recent analysis that tries to separate these reports that whether tau is present in a region is largely explained by network spread, while how much accumulates there is governed by regional amyloid, gene expression and blood flow (Xiao and colleagues, 2026, preprint). We cite it as the cleanest available statement of the division and as a preprint, not a result.

VII. The Vehicle Release, Capture, Entry, and the Step Nobody Can See

The transit path has four steps. Three are well characterised. The fourth is where the mechanism is actually decided, and it has been described in the literature as the obscure step for a decade.

Release. Tau leaves healthy neurons as a function of activity, calcium and presynaptic vesicle machinery (Pooler and colleagues, 2013), rises in the interstitial fluid when activity rises in vivo (Yamada and colleagues, 2014), and is cleared from that compartment slowly, with a half-life near eleven days — so the extracellular pool integrates activity over days rather than tracking it. Release is also vesicular in part: neuron-derived exosomal tau is hypophosphorylated relative to the cytosolic pool, depolarisation promotes its release, and transfer between neurons in three-chamber microfluidic devices depends on synaptic connectivity (Wang and colleagues, 2017). A second, non-exclusive route is direct cytoplasmic continuity: tau is a constituent of tunnelling nanotubes,

and exogenous tau assemblies increase the number of nanotubes between primary neurons and are transferred through them (Tardivel and colleagues, 2016).

The vesicular route is not a minor one, and the quantity required is remarkably small. Extracellular vesicles isolated from Alzheimer brain are enriched in oligomeric tau relative to vesicles from prodromal or control brain, and inoculating **300 picograms** of vesicle-borne tau into the dentate molecular layer of aged mice produced hippocampus-wide phosphorylated tau within four and a half months — while the same mass of tau delivered as control-brain vesicles, or as isolated oligomers or fibrils from the *same donor*, produced little pathology. The material accumulated preferentially in inhibitory interneurons, with a measurable fall in CA1 inhibitory postsynaptic current amplitude (Ruan and colleagues, 2021). Packaging, not merely quantity, determines what a given amount of tau can do.

The pool that matters is at the synapse. In control human brain, tau is present at pre- and post-synaptic terminals; in Alzheimer's disease it becomes hyperphosphorylated, misfolded, ubiquitinated and enriched in synaptoneurosome as stable oligomers, alongside evidence of proteasomal insufficiency (Tai and colleagues, 2012). Sub-diffraction imaging of human temporal and occipital cortex finds oligomeric tau in both pre- and post-synaptic terminals **even in regions without abundant fibrillar tau**, and a higher proportion of oligomeric than phosphorylated or misfolded tau at terminals (Colom-Cadena and colleagues, 2023). The species positioned at the point of transfer is the species that seeds, and it is there before the lesion is visible.

Capture. The sulfated glycosaminoglycan surface concentrates tau before internalisation, and the chemistry has become specific enough to be a drug target rather than a description. A screen of 3,200 genes identified heparan sulfate biosynthesis as the principal modifier of tau uptake, with 6-*O* sulfation critical to the interaction in human cell lines, stem-cell-derived neurons and brain slice culture (Rauch and colleagues, 2018). The 3-*O* position carries additional specificity: aggregated tau prefers 3-*O*-sulfated chains, and uptake falls when those chains are absent or competed away (Ferreira and colleagues, 2022). And the human tissue has the corresponding abnormality — a specific 3-*O*-sulfated species is increased about sevenfold in Alzheimer brain relative to controls, attributable to the sulfotransferase encoded by an Alzheimer risk gene, with a synthetic fourteen-sugar chain carrying that domain inhibiting tau internalisation more strongly than one without it (Wang and colleagues, 2023). The matrix is therefore not a passive surface: its sulfation pattern is altered in the disease, in the direction that favours capture, at a locus the genetics already implicated. The chondroitin sulfate arm shows the same logic with the opposite sign of enzyme regulation — an enzyme whose expression falls in healthy ageing but is maintained or raised in Alzheimer brain increases non-sulfated chondroitin units and enhances tau seed uptake (Nadanaka and colleagues, 2026).

Entry. Receptor-mediated endocytosis by way of low-density lipoprotein receptor-related protein 1 is the best-characterised route, and Section III set out both its demonstration (Rauch and colleagues, 2020) and the two qualifications that matter: the receptor is a degradative route whose product depends on the tau species and the apolipoprotein E environment (Cooper and colleagues, 2021), and in human neurons it is principally the route for monomeric tau, contributing considerably less to fibrillar entry (Evans and colleagues, 2025). A monograph that wanted a tidy mechanism would omit the second. We think it is the single most important recent correction in the uptake literature, because the therapeutic programme implied by "block the receptor and stop the spread" is aimed at whichever species the receptor actually carries.

Escape — and the possibility that there is nothing to escape from. An internalised seed is in a vesicle. To template the cytosolic tau pool it must reach the cytosol, and this step is where the mechanism has been weakest. It is now being resolved, and not in the direction most accounts assumed.

Loss of endosomal sorting complex function promotes propagation: knockdown of *CHMP6*, or of *CHMP2A* together with *CHMP2B* — the latter linked to familial frontotemporal dementia — increased propagation and caused endolysosomal membrane damage, with leakiness enhancing prion-like propagation (Chen and colleagues, 2019). An unbiased screen in a whole-organism spreading model identified 59 genes required for endolysosomal integrity, enriched for sorting-complex, proteasomal, splicing and fatty-acid metabolic functions, with the conserved hits worsening seeded aggregation in human cortical neurons derived from stem cells (Sandhof and colleagues, 2025). The lipid arm of that result has been followed up directly: silencing sphingolipid-metabolism genes rigidified endolysosomal membranes and increased rupture, aggregated tau inside the vesicles aggravated the rigidification, and supplementation with unsaturated fatty acids restored fluidity, suppressed rupture and suppressed seeded aggregation (Tittelmeier and colleagues, 2026).

But the imaging evidence complicates the rupture model in a way that is worth stating plainly. In primary astrocytes and neurons, endocytosed tau fibrils caused lysosomal swelling and deacidification and recruited sorting-complex proteins **without recruiting galectin-3**, the canonical sensor of a ruptured lysosome — consistent with nanoscale damage rather than wholesale rupture — and nucleation of cytosolic tau occurred primarily *at the lysosomal membrane*, beginning as soon as fibril ends emerged (Rose and colleagues, 2024). A recent report goes further, and we flag it as an unrefereed preprint: in live human neurons derived from stem cells, seeded aggregation occurred *inside* intact acidic endolysosomes, with no galectin-3 or sorting-complex recruitment and no membrane discontinuities on volume electron microscopy, and with evidence of recurrent self-limited access events rather than persistent rupture (Sanyal and colleagues, 2025, preprint).

If that reading holds, the geometry of the rate-limiting step changes: templated conversion would begin at or within the vesicle, and the therapeutic question becomes one of vesicle chemistry — acidification, membrane lipid composition, sorting-complex sufficiency — rather than one of interception in the extracellular space. That is a testable difference, and Section XV makes it a prediction.

A note on what the vehicle is not. There is no evidence that tau spreads through the interstitial or cerebrospinal compartment as a bulk-flow process. What the glymphatic literature demonstrates is the opposite direction of traffic: impaired cerebrospinal-interstitial exchange and loss of aquaporin-4 polarisation in a tauopathy model reduce tau **clearance**, and pharmacological aquaporin-4 inhibition impairs that clearance further (Harrison and colleagues, 2020). Bulk flow removes tau; it has not been shown to distribute it. We note, for symmetry, that the corresponding analysis for amyloid- β reaches the opposite conclusion about that protein — spatial proximity fits the amyloid data better than connectivity does (Mezias and Raj, 2017) — which is a useful reminder that "proteopathic spread" is not one phenomenon with one geometry.

VIII. The Permission Amyloid Holds the Key

The observation that organises this section was made in 1999, before any of the mechanisms in it existed. Among thirty-nine non-demented individuals, tangles were found in **all** of them, concentrated in hippocampal and parahippocampal regions and rising exponentially with age, while plaques were absent in some brains up to age eighty-eight; and in the subgroup that did have widespread plaques, both tangle number and the rate of tangle increase with age jumped (Price and Morris, 1999). Medial temporal tau is close to universal. What is not universal is its escape.

The experimental evidence that amyloid licenses the escape is consistent across four designs. Crossing an entorhinal tau model to an amyloid model produced a dramatic increase in the speed of tau propagation, an extraordinary increase in spread to distal regions, and significantly increased tau-induced neuronal loss (Pooler and colleagues, 2015). Human Alzheimer-derived tau injected into plaque-bearing mice that do not overexpress tau was rapidly amplified in the plaque environment, forming neuritic-plaque tau first and then tangles and threads by secondary seeding (He and colleagues, 2018). Human tissue at Braak stage II with plaques seeded more aggregation in a biosensor than tissue at the same stage without them, and an amyloid-bearing tau model showed a **threefold** increase in seeding activity with no change in tau production or extracellular release — and the increase appeared *before* overt amyloid deposition (Bennett and colleagues, 2017). That last detail matters: the permission is granted by something about the amyloid process that precedes the plaque, which is why plaque counts and tau maps correspond so poorly in space.

In living humans the interaction has now been localised, and it is of two kinds.

The lateral entorhinal cortex is subject to a *remote*, connectivity-mediated amyloid-tau interaction associated with the initiation of spreading, while the inferior temporal gyrus shows the strongest *local* interaction together with a connectivity profile suited to accelerating it (Lee and colleagues, 2022). This dissolves the old objection that amyloid cannot gate tau because their distributions do not match: the gate does not have to sit where the tau is. A region can be unlocked from a distance.

The clearest single human datum is a staging observation. In 159 individuals with follow-up tau imaging, progression beyond positron-emission-tomography Braak stage III occurred **uniquely in the presence of amyloid positivity** (Therriault and colleagues, 2022). Stage III is, approximately, the limbic boundary. Below it, tau advances without amyloid; above it, in that series, it did not.

And the natural experiment runs the other way. Primary age-related tauopathy is medial temporal tau in an amyloid-free brain, and it is common — 719 of 1,589 forensic autopsies aged forty and over, or 45.2 per cent, with prevalence peaking at 65.5 per cent in the seventh decade (Yoshida and colleagues, 2024). In extreme old age, hippocampal tangles were found in every one of seventy-seven brains at a mean age of 102, while Alzheimer-level plaque pathology was not universal (Neltner and colleagues, 2015). The route in these brains is intact; the seeds, by the seeding-assay evidence, are present — the same assay that mapped seeding onset to the transentorhinal region did so in Alzheimer's disease **and** in primary age-related tauopathy (Kaufman and colleagues, 2018). What is missing is the permission, and the genetics agrees: apolipoprotein E ϵ 4 dosage tracks Braak stage in Alzheimer's disease and probable primary age-related tauopathy, but not in definite primary age-related tauopathy (McMillan and colleagues, 2018).

The interventional test exists, and it is the strongest evidence in this dissertation that permission is causal rather than correlated. Removing amyloid in living patients slowed tau accumulation. In a placebo-controlled trial of an anti-amyloid antibody with a tau-imaging endpoint, treatment slowed tau accumulation in a region-dependent manner, with the slowing more pronounced in participants achieving complete amyloid clearance and **in regions appearing later in the pathologic sequence** (Shcherbinin and colleagues, 2022). The regional pattern is exactly what a gating model predicts and is difficult to explain on any account in which amyloid and tau are merely correlated markers of severity. In the same programme, plasma phosphorylated tau fell significantly against placebo by twelve weeks, and the fall tracked the magnitude of amyloid removal (Pontecorvo and colleagues, 2022); across the phase 3 population, lower residual amyloid correlated with slower clinical progression and with reductions in phosphorylated tau species, while showing **no** correlation with neurofilament light, the marker of axonal injury (Lu and colleagues, 2025).

That last dissociation is the honest limit of the result. Amyloid removal moves the tau phosphorylation markers and the clinical rate; it does not move the marker of neuroaxonal damage. Unlocking the gate later is not the same as closing it earlier.

What amyloid does not do. It does not create the route: the connectome model predicted tau patterns irrespective of amyloid status, with amyloid-rich regions simply carrying more tau than connectivity alone would predict (Vogel and colleagues, 2020), and connectivity predicted tau covariance in amyloid-negative normal ageing as well as in disease (Franzmeier and colleagues, 2019). Nor is it the only permission, as the next part argues at length. It is the permission that governs the medial-temporal-to-neocortical transition specifically, and it is the one we can currently manipulate in people.

IX. Four Routes, Not One

A phase architecture implies a single sequence. The best available human data say that a single sequence describes a minority.

Modelling tau positron-emission-tomography images without imposing Braak's order, in a discovery sample of 1,143 individuals, produced four trajectories fitted to the 443 with abnormal signal: limbic-predominant with a Braak-like progression in 145 (32.7 per cent); medial-temporal-sparing and parietal-dominant in 79 (17.8 per cent); posterior occipitotemporal in 135 (30.5 per cent); and lateral temporal in 84 (19.0 per cent), with 12 per cent assignable to none and three of the four reproducing in an independent 469-person sample using a different tracer (Vogel and colleagues, 2021). The classical trajectory is the largest single group and it is not a majority.

Three readings are available and only one of them is tenable.

The first is that the subtypes are measurement artefact. This is hard to sustain across two tracers and two cohorts, and the neuropathological literature independently describes hippocampal-sparing and limbic-predominant distributions at autopsy.

The second is that the phase sequence is simply wrong. We do not think the data support this either: the limbic trajectory is the largest, it is the one that matches the autopsy staging on which the whole scheme was built, and the remaining three are not random — each has a coherent epicentre and a coherent spreading pattern from it.

The third, which we adopt, is that **the phase sequence is a modal trajectory rather than a law**, and that what varies between individuals is the location of the epicentre rather than the mechanism of spread from it. This reading is supported by the observation that patient-specific epicentre connectivity predicts subsequent spread better than population staging does (Franzmeier

and colleagues, 2020b): the machinery is the same in all four groups; the starting point differs. It has an immediate methodological consequence, which is that a trial or a biomarker built on the assumption of a single anatomical sequence will misclassify roughly two-thirds of tau-positive patients at some point in their course.

Why the epicentre might differ is the open question, and the evidence points at the recipient rather than the route. Fitting a network-diffusion model to 196 patients and then examining the residual found that many Alzheimer risk genes correlated more strongly with residual tau than with total regional tau, and that the genes divided into network-aligned and network-independent classes with different functional enrichment — cell death, stress and metabolism in the first; amyloid processing and immune response in the second (Anand and colleagues, 2025). In the mouse, the same structure appears: connectome diffusion is the best predictor of the pattern, and the deviations from it define regional vulnerability whose gene-expression correlates can be recovered (Cornblath and colleagues, 2021). In two independent cognitively normal cohorts, connectomic and genetic gradients both run along the tau-spreading network, with 577 genes whose expression is associated with the spatial spread and with apolipoprotein E and glutamatergic synaptic genes central among them (Montal and colleagues, 2022). The additional variance that local molecular phenotype contributes has even been quantified: adding the regional densities of nine neurotransmitter receptors to an epicentre-connectivity model increased explained variance by 3 to 7 per cent at group level and 3 to 8 per cent individually (Nabizadeh, 2025) — modest, non-zero, and a reasonable estimate of how much of the pattern connectivity alone leaves on the table.

The strongest demonstration that a destination can generate the lesion without receiving it comes from manipulating the recipient directly. Silencing the chromatin factor DEK in entorhinal layer II neurons *in vivo* altered activity-induced transcription and excitability and produced somatodendritic tau accumulation in those neurons, with microglial reactivity and microglia-mediated neuron loss following (Rodriguez-Rodriguez and colleagues, 2024). No seed was introduced. A cell-intrinsic perturbation of the bridgehead population reproduced the early lesion on its own, which is the cleanest available evidence that arrival is not the only way for tau pathology to appear somewhere.

We therefore state the position of this dissertation on the oldest dispute in the field as follows. Connectivity and selective vulnerability are not competing explanations of the staging map. Connectivity supplies the *set of destinations*; vulnerability and permission determine *which destinations are realised, in what order, and to what degree*. The subtypes are what that division of labour looks like when it is measured across a population rather than asserted for an average patient.

Part PART FOUR

The Neocortex

Phase III — when restraint fails and the carriers stop being neurons

X. When the Recipient Stops Refusing

Everything in Part Three concerns delivery. This part concerns the recipient, and the argument is that in the neocortical phase the recipient is what changes. A neuron that degrades what it takes up is a sink; a neuron that cannot is a relay. The conversion of sinks into relays, at scale, is what turns a slow limbic process into a rapid cortical one — and it is a degradative failure before it is a proteopathic one.

The evidence that degradative capacity sets seeding competence is now direct. Interfering with the endosomal sorting complex required for transport increases propagation and produces endolysosomal membrane damage, with the leakiness itself enhancing prion-like propagation (Chen and colleagues, 2019). An unbiased genome-wide screen found 59 genes required for endolysosomal integrity whose silencing worsened seeded aggregation in human cortical neurons (Sandhof and colleagues, 2025). Membrane lipid composition sets the same threshold: rigidified endolysosomal membranes rupture more readily and seed more, and restoring fluidity with unsaturated fatty acids suppresses both (Tittelmeier and colleagues, 2026). Conversely, driving the lysosomal biogenesis programme in astrocytes increases uptake and lysosomal activity and **reduces** hippocampal pathology and ipsilateral-to-contralateral spreading in a tauopathy model (Martini-Stoica and colleagues, 2018).

There is a caution in this literature that should not be skipped, because it shows the arithmetic is not simply "more degradation, less spread". Deleting cathepsin B in an in vivo tau-spreading model reduced tau **release from donor neurons** without changing uptake by recipients, and decreased propagation despite impairing lysosomal acidification — apparently through a compensatory shift to proteasomal degradation that depleted the secretable pool (Zhao and colleagues, 2026). Degradation determines both how much a cell emits and how much it amplifies, and the two effects can run in opposite directions for the same intervention.

Where the templating actually happens is being revised as we write, and it matters for therapy. The standard model has the seed rupturing its vesicle and converting cytosolic tau. The best current imaging supports something narrower: tau fibrils cause nanoscale damage — swelling, deacidification, sorting-complex recruitment **without** galectin-3 recruitment — and cytosolic tau nucleates *at the lysosomal membrane*, as soon as fibril ends emerge (Rose and colleagues, 2024). An unrefereed report goes further, placing the seeded aggregation inside intact acidic endolysosomes with no detectable membrane discontinuity and describing recurrent, self-limited access rather than persistent rupture (Sanyal and colleagues, 2025, preprint).

We draw a specific consequence. If conversion begins at or within the vesicle membrane, then the compartment in which an anti-propagation agent must act is not the synaptic cleft and not the

cytosol, but the lumen and membrane of the recipient's endolysosomal system — a compartment that antibodies do not reach and that lipid, acidification and sorting-complex manipulations do.

XI. The Carriers That Are Not Neurons

The connectome model of spread assumes that the units of transfer are neurons and that the edges are synapses. In the neocortical phase, that assumption fails in three directions at once, and the failures are not marginal.

Microglia are vehicles as well as sweepers, and the same cell does both. Depleting microglia suppressed propagation from entorhinal cortex to dentate gyrus, with phosphorylated tau in the granule cell layer reduced by 72 per cent after liposomal depletion and 86 per cent after colony-stimulating-factor-1-receptor inhibition; in a tauopathy model, depletion reduced phosphorylated tau by 47 per cent in entorhinal cortex and 70 per cent in dentate gyrus. Blocking exosome synthesis reproduced the effect — neutral sphingomyelinase-2 knockdown and pharmacological inhibition each cut tau transduction into neurons to about 36 per cent of control, and in vivo inhibition reduced labelled cells in the granule layer by 75 per cent and oligomeric tau in hippocampus by 44 per cent (Asai and colleagues, 2015). Human and mouse microglia isolated from tauopathy brain stably contain seed-competent tau despite synthesising none, and release seeds into their medium; they reduce but do not eliminate seeding activity (Hopp and colleagues, 2018). The mechanism by which a phagocyte becomes a distributor has since been described: microglia that phagocytose living neurons bearing tau aggregates — drawn in by aggregate-induced phosphatidylserine exposure — become hypophagocytic while releasing seed-competent insoluble tau, and adopt a senescence-like state with matrix-metalloproteinase-3 maturation replicated in human tauopathy tissue (Brelstaff and colleagues, 2021).

The opposite behaviour is equally well documented. Microglia internalise and degrade hyperphosphorylated tau from Alzheimer brain, clear tangles from tissue sections, and do so more efficiently in the presence of an anti-tau antibody (Luo and colleagues, 2015); they internalise both soluble and insoluble human tau in vitro and in vivo (Bolós and colleagues, 2016). What tips the balance is, in part, the modification state of the ligand: tau engages the fractalkine receptor to trigger internalisation, and phosphorylation at serine 396 **decreases** its affinity for that receptor (Bolós and colleagues, 2017). The disease-modified species is the one the sweeper grips least well — and recognition through the toll-like receptor route, which does engage oligomeric tau, drives activation and neuronal uptake rather than disposal, with antibody blockade reducing spread and memory loss in a tauopathy model (Kim and colleagues, 2024).

This is the cleanest example in the dissertation of a borrowed service becoming a vehicle. Phagocytosis exists to remove debris. Applied to a templating protein by a cell whose degradative

capacity is exceeded, it becomes a distribution system with a wider anatomical reach than any axon, because microglia are mobile and are not constrained by the connectome at all.

Astrocytes amplify what they fail to digest. Human astrocytes engulf dead tau-bearing neurons, synthetic fibrils and Alzheimer-brain-derived aggregates, fail to degrade them fully, and re-release the material by secretion and by tunnelling nanotubes, inducing pathology directly in healthy human neurons in co-culture. The finding that matters is quantitative: the tau proteoforms secreted by the astrocyte had **exceptional seeding capacity compared with the species originally engulfed** (Mothes and colleagues, 2023). The astrocyte is not a sink that leaks. It is an amplifier that changes the species.

Oligodendrocytes propagate tau without neurons, and the human epigenome says they are not a footnote. In mice in which neuronal tau was knocked down, oligodendroglial tau pathology propagated across the brain in the absence of neuronal tau pathology and caused oligodendrocyte loss, whereas astrocytic pathology did not propagate (Narasimhan and colleagues, 2020). Inoculating sarkosyl-insoluble fractions from a range of human tauopathies directly into the corpus callosum produced seeding in ipsilateral and contralateral white matter as coiled-body-like oligodendroglial deposits and threads, with myelin disruption at six months (Ferrer and colleagues, 2019). And in the largest human molecular dataset bearing on the question, an epigenome-wide analysis of 472 Alzheimer brains found 5,478 significant associations of which **99.7 per cent were with tau** rather than amyloid measures, with transcriptome-methylome integration enriched for oligodendrocyte and myelination genes — *MYRF*, *MBP*, *MAG*, the risk gene *BIN1*, and a novel locus — rather than for neuronal genes (Oatman and colleagues, 2026).

We do not claim that oligodendroglial transmission drives the human neocortical phase; the direct evidence is a mouse knockdown model and a white-matter inoculation series. We claim something weaker and, we think, unavoidable: a propagation model whose only edges are synapses cannot accommodate a lesion that travels along white matter in the absence of neuronal tau, and the cell type most enriched in the human tau-associated epigenomic signal is not the neuron.

What this does to the connectome model. It does not refute it — the model fits, and fits well, in the phases where it has been tested. It bounds it. The synaptic connectome is the right description of the route while neurons are the carriers, which is Phase II and the early part of Phase III. As glial carriage becomes significant, the effective network acquires edges that no tractography will show, and this is one plausible reason why connectome-based models fit the early distribution better than the late one.

XII. The Matrix as Gatekeeper

There is a structure that decides how much of the extracellular pool ever reaches an uptake surface, and it has been in the neuropathological literature since long before the propagation era. The perineuronal net is a condensed, aggrecan-based extracellular matrix that ensheathes a minority of neurons, most conspicuously parvalbumin-expressing interneurons, leaving holes at synaptic contacts.

The anatomical correlation is remarkable and is rarely cited in propagation papers. Examining aggrecan-based matrix and neurofibrillary degeneration together across human Alzheimer brain, the regions preferentially affected by tau — the basal nucleus of Meynert, dorsal thalamic nuclei, hypothalamic nuclei, the raphe nuclei and **the locus coeruleus** — were found to be devoid of characteristic aggrecan-based extracellular matrix, and in the amygdala, thalamus and oculomotor complex the distributions of tangles and nets were largely complementary; tangles in net-ensheathed neurons were extremely rare (Morawski and colleagues, 2010). The structure that fails first in this disease is a structure that has no net.

The mechanism is not merely correlative. In organotypic slice culture, perineuronal nets restricted both the distribution and the internalisation of exogenous aggregated tau; net-ensheathed neurons were less frequently affected than neurons without nets; and cultures from mice lacking aggrecan, hyaluronan-and-proteoglycan-link-protein-1 or tenascin-R each showed independent modulation of distribution and uptake (Suttkus and colleagues, 2015). The net is a diffusion barrier and a capture barrier at once.

And the net is dismantled by the innate immune process that dominates the neocortical phase. In an amyloid model, net area fell in the subiculum at every timepoint examined and in visual cortex from eight months, inversely correlated with plaque number, and net loss **preceded** loss of the parvalbumin neurons themselves; human middle frontal gyrus from twelve Alzheimer cases versus nine controls showed fewer aggrecan-positive nets, with aggrecan detected inside plaque cores and inside microglia. Systemic inflammatory challenge alone reproduced the net loss in wild-type animals, and microglial depletion completely prevented it despite plaques persisting (Crapser and colleagues, 2020). A comparable disruption in hippocampal CA2, where matrix-cleaving metalloproteinases are upregulated, is sufficient to reproduce a specific memory deficit, and chronic metalloproteinase inhibition retains the nets and delays it (Chaunsali and colleagues, 2025).

Assembled, these give a coherent Phase III permission: microglial activation degrades the matrix; matrix loss exposes uptake surfaces and removes a diffusion barrier; exposed neurons take up more of an extracellular pool that is itself larger because degradation has failed and because glia are now releasing seeds. Restraint fails in three places at once, and they are the same event seen from three angles.

Two honest complications, both of which cut against the tidy version.

The first is that the matrix arrow has been shown to run the other way for amyloid. Conditional deletion of aggrecan in an amyloid model, which abolishes perineuronal nets, produced *more* plaque, less spherical deposits, impaired microglia-plaque association and an enhanced disease-associated microglial signature — with, notably, decreased dystrophic neurite formation (Barahona and colleagues, 2025). We note precisely what that study measured: amyloid plaques and microglial state. It contains no tau measurement, and it cannot be cited for a claim about tau uptake. But it establishes that the net is an upstream regulator of the microglial response and not only a casualty of it, and any therapeutic programme aimed at preserving nets has to reckon with the possibility of worsening plaque handling.

The second is that matrix is not uniformly protective, because sulfation decides. The same chemistry that makes heparan sulfate a capture surface applies to chondroitin sulfate: an enzyme whose expression is maintained or raised in Alzheimer brain increases non-sulfated chondroitin units and **enhances** tau seed uptake, and chondroitin sulfate binds both seeds and monomer with high affinity and promotes aggregation in vitro (Nadanaka and colleagues, 2026). A net with one sulfation pattern excludes tau; a matrix with another concentrates it. "Preserve the net" is therefore not yet a therapeutic instruction, and stating it as one would be the kind of simplification this dissertation is arguing against.

XIII. Throughput Why the Last Phase Is the Fast One

The final element of Phase III permission is the one that connects it back to Phase I, because it is the same variable: neuronal activity.

The relationship is established in both directions. Raising activity optogenetically or chemogenetically increases tau release and worsens pathology in vivo (Wu and colleagues, 2016); lowering it chronically in the entorhinal cortex reduces amyloid accumulation and reduces downstream tau spread (Rodriguez and colleagues, 2020); interstitial tau tracks activity in vivo with presynaptic glutamate release sufficient to drive it (Yamada and colleagues, 2014). In humans, a structural-connectivity model weighted by regional metabolic activity or by amyloid identified the entorhinal cortex as the primary tau seeding region, and the model-derived seeding predicted measured entorhinal tau after adjustment for age, sex and genotype; we note the honest half of that paper, which is that the amyloid-weighted associations replicated in a second cohort and the activity-weighted ones did not (Alexandersen and colleagues, 2026).

Host state matters as much as host activity. Viral entorhinal tau spread **more** in old mice than in young ones, with more misfolded tau — and produced no misfolding at any age in the striatum, a region normally spared (Wegmann and colleagues, 2019). Age and regional identity gate propagation independently of the seed.

The clinical corollary is uncomfortable and we state it rather than avoid it. If throughput is activity, then network hyperexcitability in symptomatic Alzheimer's disease is not only a symptom but a propagation variable, and suppressing it should slow accumulation. That inference does not license sedation as therapy: the same activity carries cognition, the entorhinal silencing experiment was chronic and chemogenetic rather than pharmacological, and there is a directly relevant contradiction in the adjacent literature. Treating an amyloid model with a colony-stimulating-factor-1-receptor inhibitor — the manipulation that preserves perineuronal nets — reduced microglial proliferation, attenuated the disease-associated microglial phenotype, lowered lysosomal marker expression and synaptic engulfment, and partially rescued synaptic loss; but in slices from those animals it had no significant effect on plaque burden or cognition and **exacerbated** network hyperactivity and the incidence and complexity of epileptiform activity, in a preparation that already showed reduced gamma amplitude, increased beta power and loss of parvalbumin- and somatostatin-positive interneurons (Delaney and colleagues, 2026). A strategy that preserves the matrix by removing microglia and then finds it has worsened the rhythm has traded one lesion for another. We flag this as an internal tension in the Phase III argument rather than resolving it, and Section XV names the experiment that would.

Part PART FIVE

The Test

What the clinic has already said, and what would settle the rest

XIV. The Experiment the Field Has Already Run

Between 2015 and 2026 the propagation hypothesis received the most expensive test any biological hypothesis in this field has had: a decade of antibodies designed to intercept tau in the extracellular space, on the explicit rationale that intercepting transit would interrupt spread. The programme failed. What that failure means is the most consequential interpretive question in the subject, and we think the standard readings — "tau is not a prion" on one side, "the trials were too late" on the other — are both premature.

The record. An N-terminal antibody in progressive supranuclear palsy reduced unbound N-terminal cerebrospinal tau by 98 per cent against an 11 per cent rise on placebo, and produced adjusted mean changes on the primary rating scale of 10.4 against 10.6 — a difference with a p-value of 0.85 — with all secondary endpoints negative and the extension discontinued (Dam and colleagues, 2021). The same antibody in early Alzheimer's disease, across 654 randomised patients at four dose levels for 78 weeks, again reduced the target analyte at every dose and produced no favourable change on the clinical dementia rating at any dose (Shulman and colleagues, 2023). A second N-terminal antibody in progressive supranuclear palsy was terminated for futility at the second interim analysis, with a treatment effect on the primary scale of 0.0 points and an effect size of 0.000 at the lower dose (Höglinger and colleagues, 2021). An antibody binding all full-length tau isoforms showed no effect across 422 patients with prodromal-to-mild disease (Teng and colleagues, 2022); in mild-to-moderate disease the same antibody produced a 42.2 per cent reduction in decline on one cognitive co-primary — a 2.89-point difference with a p-value of 0.0008 — while the functional co-primary was null at −0.83 points, and the trial was declared negative on its prespecified endpoints (Monteiro and colleagues, 2023). An antibody against misfolded extracellular tau showed no benefit across 360 patients over 100 weeks, no effect on tau imaging, volumetric imaging or neurofilament light, and a dose-related **rise** in plasma tau species (Fleisher and colleagues, 2024). An active vaccine generating high antibody titres produced a clinical dementia rating difference of −0.360 with a confidence interval spanning zero (Novak and colleagues, 2021). Two network meta-analyses of the pooled programme report that placebo holds the best rank on the principal clinical endpoints (Cai and colleagues, 2025; Huang and Guo, 2026).

The pharmacological explanation is quantitative, and it is devastating to the strong reading of the failure. A quantitative systems pharmacology model of these antibodies estimated maximal target engagement of monomeric tau at 45 to 99 per cent in cerebrospinal fluid and 30 to 99 per cent in interstitial fluid — but **1 to 3 per cent in the synaptic cleft**, yielding less than a 1 per cent reduction in neuronal uptake of oligomeric tau (Geerts and colleagues, 2023). On this analysis the trials did not test the spread hypothesis. They tested whether saturating a compartment adjacent to the one where transfer occurs is sufficient, and the answer was no.

The human neuropathology agrees. Post-mortem tissue from three recipients of an N-terminal antibody showed **no clearance of inclusions**, alongside novel perivascular vesicular astrocytes containing tau in lysosomes, bushy astrocytosis and rod microglia (Kim and colleagues, 2021). Engagement occurred. It did not touch the aggregates.

Two results in the same programme point at where the compartment problem is solvable. Lowering tau production rather than intercepting it in transit does change seeding: antisense reduction of tau in a tauopathy model reduced inclusions, reversed pre-existing pathology, prevented neuronal loss and hippocampal volume loss, extended survival, and **reversed pathological tau seeding**, with the approach reproduced in non-human primates (DeVos and colleagues, 2017). In humans, an intrathecal tau antisense oligonucleotide reduced cerebrospinal total tau by 56 per cent and phosphorylated tau by 51 per cent at the higher doses, with reduced tau accumulation on imaging against placebo and reductions from baseline in all regions at 100 weeks (Edwards and colleagues, 2023); exploratory clinical outcomes in that small cohort trended in the favourable direction but are unpowered and must not be read as efficacy (Shulman and colleagues, 2026). The phase 2 result is not published, and any figure circulating for it is a company or conference disclosure rather than a peer-reviewed result. An antibody directed at the microtubule-binding region — the epitope that the uptake chemistry implicates — reduced cerebrospinal phosphorylated tau by 30 to 58 per cent and the microtubule-binding-region fragment by up to 72 per cent, with tau imaging stable at 108 weeks, in an open-label study of **eight** patients with no control group (Andreozzi and colleagues, 2026).

And there is a negative from the model literature that the field has never satisfactorily absorbed. Human P301L tau expressed in the entorhinal cortex propagated to recipient neurons and accumulated there **equivalently in mice completely lacking endogenous tau**; the tau-null background left the numbers of recipient inclusions similar while protecting against neurotoxicity, leading the authors to conclude that tau does not strictly classify as a prion protein (Wegmann and colleagues, 2015). If transferred tau accumulates in a recipient that has no substrate to template, then in that model the transfer is a transfer of material, not of conformation — and the templating step, which is the whole content of the prion analogy, was not required for the spatial spread that is usually taken as evidence of it.

What we conclude. The trial record constrains the spread hypothesis in a specific and limited way. It shows that the extracellular soluble pool of tau outside the synapse is not rate-limiting for clinical progression in symptomatic disease. It does not show that transfer is unimportant, that templating does not occur, or that anti-propagation strategies cannot work — because the compartment the mechanism specifies was never reached. The reading that survives all of the evidence in this dissertation is that the field aimed at the vehicle, in the phase where the rate-limiting step is permission, using an agent that could not enter the compartment where transfer happens.

The one anti-propagation result that is positive in humans was obtained by attacking permission rather than transit, and it came from an amyloid programme: removing amyloid slowed tau accumulation, more so with complete clearance and more so in regions later in the sequence (Shcherbinin and colleagues, 2022).

Programme	Target compartment	Best biomarker effect	Clinical result
N-terminal antibody, supranuclear palsy	Extracellular, N-terminal	Unbound CSF tau -98%	Null (P=0.85); extension stopped
N-terminal antibody, Alzheimer's	Extracellular, N-terminal	Target reduced at all doses	Null at every dose, 78 weeks
Second N-terminal antibody, palsy	Extracellular, N-terminal	Not reported here	Futility; effect size 0.000
Full-length antibody, prodromal-mild	Extracellular, all isoforms	—	Null across 422 patients
Full-length antibody, mild-moderate	Extracellular, all isoforms	—	One cognitive co-primary positive; functional co-primary null
Misfolded-tau antibody	Extracellular, aggregated	No imaging change	Null; plasma tau rose
Active vaccine	Extracellular, humoral	High titres	Null on clinical endpoints
Antisense oligonucleotide	Intracellular production	CSF total tau -56%, p-tau -51%	Phase 1b; exploratory only
Microtubule-binding-region antibody	Seeding-competent species	MTBR fragment up to -72%	Open-label, n=8, no control
Anti-amyloid antibody	Permission, not transit	Tau accumulation slowed	Clinical benefit; tau-PET effect region-dependent

XV. Predictions and Falsification

Each prediction below is followed by the result that would falsify it. They are ordered from cheapest to most demanding.

1. **Seeding activity in the human locus coeruleus will be low relative to transentorhinal cortex at the stages when coerulean pretangle immunoreactivity is already established.** *Falsified if* a seeding assay applied to staged brainstem tissue finds coerulean seeding activity equal to or greater than transentorhinal activity at subcortical stages — which would restore the brainstem as the source and not merely the origin.
2. **The noradrenergic projection to the medial temporal lobe is pruned on the same early schedule as the olfactory projection.** Noradrenergic fibre density in human entorhinal cortex and hippocampus at Braak stages 1–2 will be reduced against age-matched controls, with locus coeruleus cell number preserved. *Falsified if* medial temporal noradrenergic fibre density at those stages is normal — in which case the early axonal loss is a fact about olfaction, the self-consuming-route explanation of the interval fails, and the interval requires a different account.
3. **The extracellular tau pool in Phase I is activity-limited and route-limited, not production-limited.** *Falsified if* suppressing noradrenergic firing in a tauopathy model reduces cortical tau seeding without reducing coerulean tau burden.
4. **Perineuronal-net-bearing neurons will show lower tau seeding competence than net-free neurons in the same human tissue section.** *Falsified if* single-cell seeding measurement finds no difference, or finds net-bearing neurons more affected.
5. **Sulfation state, not matrix quantity, predicts uptake.** Matrix enzymatically stripped of 3-*O*- and 6-*O*-sulfated epitopes will be less permissive than intact matrix of the same bulk density. *Falsified if* bulk matrix density predicts uptake independently of sulfation pattern.
6. **Templated conversion begins at or within the endolysosomal membrane rather than in the bulk cytosol.** *Falsified if* high-resolution live imaging in human neurons localises the first conversion events to the cytosol with intact vesicles elsewhere in the same cell.
7. **An agent that raises endolysosomal membrane fluidity or restores acidification will reduce seeding in human neurons more than an equivalently dosed extracellular antibody.** *Falsified if* the two are equivalent, which would restore the extracellular pool as rate-limiting.
8. **Glial carriage contributes measurably to human neocortical spread.** In a large series, the proportion of tau-bearing oligodendrocytes and microglia will predict neocortical progression rate independently of neuronal tau burden. *Falsified if* glial tau adds nothing once neuronal burden is in the model.

- 9. Tau epicentre location, not spreading mechanism, distinguishes the four human trajectories.** Connectivity from each patient's own epicentre will predict subsequent accumulation equally well in all four subtypes. *Falsified if* predictive accuracy differs systematically by subtype, which would imply different mechanisms rather than different starting points.
- 10. Amyloid gates the limbic-to-neocortical transition specifically, and not the earlier transitions.** In longitudinal imaging, amyloid status will predict progression across the limbic boundary and not progression within medial temporal stages. *Falsified if* amyloid predicts medial temporal progression equally.
- 11. An antibody that reaches the synaptic cleft will outperform one that does not, at equal affinity for the same epitope.** *Falsified if* a synapse-penetrant agent with demonstrated cleft engagement produces the same null as the current programme — which would move the rate-limiting step decisively out of the vehicle.
- 12. Microglial depletion trades pathology for rhythm.** In the same preparation, depletion sufficient to preserve perineuronal nets will degrade gamma-band network activity. *Falsified if* net preservation and rhythm preservation can be obtained together, which would remove the central objection to matrix-directed immunomodulation.

XVI. Strength of Evidence

Claims are graded by what was measured, in which species, and in which compartment — not by how well they serve the argument. Two of this dissertation's own load-bearing claims are graded as inference, and one of its background assumptions is graded as contradicted.

Claim	Strength	Basis
Aggregated tau is internalised and templates native tau	Established	Cells, mice, primate, human tissue
Human tauopathy brain transmits with strain fidelity	Established	Human-to-mouse, six diseases, passaged
Spread follows connectivity rather than proximity	Strong	Mouse, 134 regions; human connectome models
Seed-competent tau is present before the lesion, widely	Established (human)	104 and 247 brains, two assays
Uptake requires sulfated glycosaminoglycan capture	Strong	Genetic and chemical, multiple systems

Claim	Strength	Basis
The canonical receptor is the main route for fibrillar seeds	Contradicted as stated	Human neuron screen; principally monomeric tau
Amyloid gates the limbic-to-neocortical transition	Strong	Four model designs, human imaging, one interventional result
Tau spread is activity-dependent	Strong	Bidirectional manipulation in vivo
Perineuronal nets restrict tau uptake	Moderate	Slice culture and human distribution; no human causal test
Microglia act as vehicles	Moderate	Depletion and exosome-block in mice; human cells carry seeds
Oligodendroglial tau propagates without neuronal tau	Moderate	One knockdown model, one inoculation series
The human epigenomic tau signal is oligodendroglial	Strong (human, associative)	472 brains, 99.7% of associations with tau
The brainstem is the first site of abnormal tau	Established (human)	2,332 and 42 brains
The brainstem is the source of cortical tau seeds	Inference, partly contradicted	Seeding not uniform there until later; ablation did not reduce forebrain tau
Templating is required for spatial spread	Contradicted as stated	Propagation equivalent in tau-null recipients
Conversion begins at the endolysosomal membrane	Inference	Two imaging studies, one a preprint
The extracellular pool is rate-limiting in symptomatic disease	Refuted	Seven negative programmes; 1–3% cleft engagement
Single anatomical trajectory	Refuted	Four trajectories; the classical one is 32.7%

XVII. Limitations

The most important limitation is that the central organising claim of this dissertation — that permission rather than transit is rate-limiting, and that the identity of the permission changes by phase — is an interpretive framework rather than a measurement. It is constructed to be testable, and Section XV is the list, but no single experiment in the literature was designed to test it.

The phase assignments are coarse. The boundaries between them are defined by the territory in which the lesion is advancing, and in a real brain those territories overlap for years. The age ranges are population approximations and should not be read as applying to an individual.

Phase I is not measurable in living humans by the instrument that measures the other two. We could find no study quantifying tau positron-emission-tomography signal within a locus coeruleus region of interest, and the structure is at or below the effective resolution of the available tracers. Every human statement about Phase I in this dissertation is therefore either post-mortem or a structural or neurochemical surrogate read against cortical tau.

Several key mechanisms rest on rodent work in models that overexpress mutant tau, sometimes at supraphysiological levels, and in which the seeding inoculum is delivered at concentrations and by routes with no natural equivalent. The transfer efficiencies measured in those systems should not be transferred to the human brain, and the kinetic mismatch between mouse and human disease is orders of magnitude.

Two claims in Part Four rest on single studies or preprints: the intraluminal conversion model, and the specific contribution of oligodendroglial carriage to human neocortical spread. They are graded accordingly in Section XVI and named in Section XV as tests rather than assets.

We have treated amyloid as the Phase II permission and have not given the same treatment to the other candidate permissions of that phase — inflammation, vascular integrity, sleep and clearance — each of which has a literature of its own and each of which would modify the account. Their omission is a choice of scope and not a judgement of importance.

Finally, this dissertation says little about what determines the epicentre, which the subtype data suggest is the variable that actually differs between patients. That is the question we would take up next, and Section XV frames it as a prediction rather than answering it.

XVIII. Conclusion The Road and the Key

The hypothesis that Alzheimer's disease advances by templated misfolding has been argued for thirty years as though its truth would settle what to do. The evidence assembled here suggests that it is true and that it settles almost nothing on its own, because the mechanism has three components with three different biologies, and the component that limits the process is not the same one at the beginning of the disease as at the end.

The route is anatomy. It is the same anatomy in the person who will develop dementia and the person who will not, and it is the one component that no therapy will ever change. Its importance in the argument is negative: because the route is constant and the disease is not, the route cannot be the explanation.

The vehicle is borrowed. Every step of transit that has been characterised is a service the brain runs for another purpose — synaptic release, receptor-mediated uptake, vesicular traffic, phagocytosis, matrix capture. This is why the transit path has been such poor therapeutic ground: each target on it is load-bearing for something else, and the one compartment where transfer actually happens has proved to be the one compartment that circulating antibodies do not reach.

The permission changes hands. In the brainstem decades it is the firing of a cell that cannot stop firing and has no matrix to shield it, in a regime where the route out is being pruned as fast as it is used — which is why the earliest phase is also the slowest, and why twenty-five years can pass between the first pretangle and the first cortical lesion. At the entorhinal bridgehead it is amyloid, and the evidence for that is now strong enough to include an interventional result in humans: remove the amyloid and tau accumulates more slowly, most clearly in the regions that come later. In the neocortex it is the failure of restraint — degradation that no longer destroys what it takes in, a matrix that no longer covers the surfaces that take it, and glial cells that carry the material along routes the connectome does not contain.

If that is right, then the therapeutic question is not whether to block spread but **which lock to pick, and when**. Before the amyloid gate opens, the tractable variable is the seed's manufacture and the activity that releases it. At the gate, it is amyloid, and that lock has been picked. Beyond it, the tractable variable is the recipient's competence to destroy what it has taken up — the endolysosomal chemistry that the last three years of work have moved from an obscure step to a measurable one.

There is one more consequence, and it is the one we would most like to see tested. The measurement that predicts a patient's future is not the amount of tau but its seeding activity — the property that distinguishes a person whose pathology is a tombstone from a person whose pathology is an engine. That measurement already exists, it already tracks the aggressiveness of the disease in brain tissue, it is already detectable in living cerebrospinal fluid with prognostic content, and it is not yet a clinical endpoint. A field that has spent a decade measuring how much tau is present might learn more from measuring what that tau can still do.

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