The Standing Relay

The pedunculopontine nucleus in Alzheimer's disease — a cholinergic nucleus that takes the tangle and keeps its neurons, and what its failure withholds from the thalamus, from REM sleep, and from gait

Ch5 · Ch6 · The thalamus · REM sleep · Nerve growth factor receptor · Tau

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The human brain has six cholinergic cell groups. The cholinergic hypothesis of Alzheimer's disease was built from four. The two that were left out sit in the mesopontine tegmentum, supply the thalamus with the only major cholinergic innervation it has, and accumulate tau without losing their neurons. This is the nucleus that shows what the hypothesis got wrong about why.

Contents

Abstract

The cholinergic hypothesis of Alzheimer's disease was built on one cholinergic sector. Whitehouse and colleagues counted the nucleus basalis of Meynert, found a profound and selective depletion, and the field acquired both a mechanism and a drug class. But the human brain has six cholinergic cell groups in the scheme that named them, and the hypothesis was constructed from four. The remaining two — Ch5, centred on the pedunculopontine nucleus, and Ch6, centred on the laterodorsal tegmental nucleus — sit in the mesopontine tegmentum, supply the major cholinergic innervation of the human thalamus, and have almost never been asked what they do in this disease.

This paper asks. The answer is unexpected, and it is the reason the nucleus is worth a monograph: the pedunculopontine nucleus accumulates Alzheimer tau and does not lose its neurons. Three independent bodies of evidence converge. Woolf, Jacobs and Butcher examined both mesopontine nuclei in Alzheimer's disease and found neurofibrillary change and plaque-like entities present but no loss of neuronal somata whatsoever. Eser and colleagues, applying design-based stereology to five reticular nuclei across three tauopathies, found pedunculopontine total neuronal number statistically indistinguishable across Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy and control. Only Jellinger's 1988 morphometry dissents, reporting a 29 to 34 per cent reduction of *large* neurons — and we argue that a size-thresholded count in a tangle-bearing nucleus measures somatic atrophy, not death, which reconciles the three studies rather than pitting them against each other.

The nucleus is therefore a natural control condition, and it falsifies something. It is cholinergic, large, isodendritic, diffusely projecting, metabolically expensive, tangle-bearing, and situated millimetres from the locus coeruleus — it carries every risk factor the field attributes to the cells this disease destroys — and it survives. Woolf drew the correct conclusion in a single sentence in 1989 and the field did not absorb it: cholinergic phenotype alone is not a sufficient condition for vulnerability. We supply the molecular reason the sentence is true, from a source published the same year and never read against it. Mesulam, Geula, Bothwell and Hersh showed that Ch4 neurons carry high levels of nerve growth factor receptor protein and Ch5–Ch6 neurons do not. The basal forebrain cholinergic neuron is a hostage: its survival depends on a trophic factor retrogradely supplied by the cortical target that this disease dismantles. The mesopontine cholinergic neuron is not enrolled in that contract. What the disease kills is not the cholinergic cell but the *dependent* cell, and the pedunculopontine nucleus is the specimen that separates the two.

The failure is consequently not attrition but withheld function, and the paper's second half asks what is withheld. Ch5 and Ch6 are the thalamus's only major cholinergic supply, and thalamic α4β2 nicotinic receptor availability is reduced in mild cognitive impairment and Alzheimer's disease — an intact source and a deficient target, with the channel between them never

measured in this disease. In sleep, two independent lines converge on the same signature: tau in the pedunculopontine nucleus tracks lengthened REM latency and reduced REM percentage, and lengthened REM latency and reduced REM percentage predict incident dementia in the Framingham cohort at a hazard of 0.91 per percentage point of REM. We explain why this is not REM sleep behaviour disorder — atonia is generated by a different circuit, which is synuclein's target, not tau's — and we flag the one finding that complicates our own account rather than smoothing it, since Alzheimer's disease does deplete the medullary GABAergic relay that atonia requires.

On gait we deflate rather than inflate. The pedunculopontine nucleus is the mesencephalic locomotor region, and it is tempting to route the early gait slowing of Alzheimer's disease through it. The imaging does not support this: gait pace in prodromal and established disease maps onto attention and executive function, cortical amyloid and cortical atrophy, not onto a brainstem locomotor lesion — which is exactly what a structurally intact pedunculopontine nucleus predicts. The cholinesterase-inhibitor trial evidence agrees, and its primary endpoint failed.

We close with a graded ledger separating what is established from what is inference, five conditions that would refute the argument, and nine experiments — beginning with the one measurement nobody has made: whether the cholinergic channel from the mesopontine tegmentum to the thalamus is still carrying traffic in a brain whose source neurons are all still there.

Part I — The Nucleus and the Question

1. The Sector the Cholinergic Hypothesis Left Out

In 1982 Whitehouse, Price, Struble and colleagues published a short paper in *Science* reporting that the nucleus basalis of Meynert, a sheet of large cholinergic neurons in the substantia innominata, undergoes a profound and selective loss of neurons in Alzheimer's disease and senile dementia. Classical morphometry the following year placed the depletion at approximately seventy per cent (Arendt et al., 1983), and the founding studies described losses exceeding seventy-five per cent in advanced disease. The finding was among the most consequential in the history of the field. It supplied a lesion, a neurotransmitter, and a rationale; within a decade it had produced the cholinesterase inhibitors, which remain in clinical use four decades later and are still, for many patients, the only symptomatic pharmacology on offer.

The hypothesis that grew from this finding acquired an implicit mechanistic claim that was never separately tested. If Alzheimer's disease destroys cholinergic neurons, and if the cholinergic neurons of the basal forebrain are the ones counted, then the natural inference is that being cholinergic is what places a neuron at risk. This inference was rarely stated so baldly, but it organised a generation of research and it organised the drug development that followed. Cholinergic replacement was pursued because the cholinergic system was understood as the system this disease attacks.

The anatomy on which the hypothesis rested was worked out in the same years and with unusual precision. Mesulam and colleagues, in a series of papers beginning in 1983, partitioned the cholinergic neurons of the human and primate brain into six sectors. Ch1 occupies the medial septal nucleus and Ch2 the vertical limb of the diagonal band; together they supply the hippocampus. Ch3, in the horizontal limb of the diagonal band, supplies the olfactory bulb. Ch4 is the nucleus basalis of Meynert itself, containing the large majority of the forebrain system's cells and broadcasting acetylcholine across the entire cortical mantle and the amygdala (Mesulam et al., 1983; Mesulam & Geula, 1988).

There are two more. Ch5 and Ch6 lie not in the forebrain but in the mesopontine tegmentum, at the junction of midbrain and pons: Ch5 reaching peak density within the compact part of the pedunculopontine nucleus, Ch6 centred on the laterodorsal tegmental nucleus (Mesulam, Geula, Bothwell & Hersh, 1989). They are cholinergic by every criterion applied to Ch4. They are large, they are heteromorphic in their perikaryal shape, they bear isodendritic arborisations of the kind that characterise the reticular core, and they carry high levels of acetylcholinesterase activity. And

they have a projection target of their own, which the same paper established: *Ch5 and Ch6 neurons provide the major cholinergic innervation of the human thalamus.*

This is the sector the cholinergic hypothesis left out. Not because it was judged unimportant, but because the counting was done in the forebrain and the mesopontine tegmentum is technically forbidding — a small, boundary-ambiguous nucleus buried at the mesopontine junction, interdigitated with fibre tracts, requiring serial sectioning through an awkward plane. When the field did examine it, in a handful of papers between 1987 and 1989 and then almost not at all for thirty years, the result was surprising enough that it should have redirected the argument, and it did not.

Two features of the omission matter for what follows. The first is that the thalamus is not a minor destination. It is the gate through which nearly all ascending traffic reaches the cortex, and the state of its cholinergic innervation determines whether the cortex receives coherent input or none. A theory of cholinergic failure in dementia that describes the cortical supply line in detail and omits the thalamic one has described the broadcast and ignored the switchboard.

The second is that the pedunculopontine nucleus, precisely because it is cholinergic and yet anatomically unlike Ch4, constitutes a natural experiment. If cholinergic identity is what confers vulnerability, Ch5 should degenerate alongside Ch4. If it does not, then something other than cholinergic identity is doing the work, and the mesopontine tegmentum is where that something can be isolated. This is the question the paper takes up, and the literature — thin, old, and partly contradictory — turns out to answer it.

2. What the Pedunculopontine Nucleus Is

The pedunculopontine nucleus occupies the lateral mesopontine tegmentum, bounded by the superior cerebellar peduncle, the lateral lemniscus, and the decussation of the cerebellar peduncles. Its cytoarchitecture is classically divided into two parts. The pars compacta is a densely packed cluster of large, deeply staining cholinergic neurons; the pars dissipata is a more loosely scattered population extending rostrally and caudally from it. The distinction is not decorative — as we will see, the two subdivisions differ in their vulnerability in Parkinson's disease, and the boundary between them and between the nucleus as a whole and the surrounding tegmentum is the single largest source of disagreement in the literature on how many neurons the nucleus contains.

The nucleus is not cholinergic in the way that the nucleus basalis is cholinergic. Ch4 is a cholinergic nucleus with admixed non-cholinergic cells. The pedunculopontine nucleus is a genuinely mixed structure containing at least three intermingled transmitter populations — cholinergic, glutamatergic and GABAergic — that are anatomically interdigitated and functionally distinct (Wang & Morales, 2009). Manaye and colleagues, quantifying the human mesopontine tegmentum, noted that within the territory occupied by Ch5 cholinergic neurons there were often *more* non-cholinergic than comparably sized cholinergic neurons (Manaye et al., 1999). Any statement about "the pedunculopontine nucleus" that does not specify which population is meant is therefore underdetermined, and a good deal of confusion in the clinical literature follows from exactly this ambiguity.

The functional dissection of these populations, achieved in rodents with cell-type-specific tools, shows how far apart they are. Kroeger and colleagues selectively activated each of the three populations of the pedunculopontine tegmental nucleus and found distinct effects on sleep and wake behaviour, establishing that the nucleus is not a single functional unit with a single output but three overlapping systems sharing an address (Kroeger et al., 2017). Glutamatergic pedunculopontine neurons in particular were shown to control wakefulness and locomotion through anatomically separable axonal projections: stimulation of their terminals in the basal forebrain and lateral hypothalamus produced sustained wakefulness often accompanied by locomotion, whereas stimulation of their terminals in the thalamus and substantia nigra produced only brief periods of quiet wakefulness (Kroeger et al., 2022). Function in this nucleus is specified by target, not by cell body location.

The projection anatomy is correspondingly wide. The pedunculopontine nucleus projects ascending to the thalamus, the basal forebrain, the subthalamic nucleus, the substantia nigra and the ventral tegmental area, and descending to the pontine and medullary reticular formation and

the spinal cord. Within the thalamic projection there is a topography that will matter in Chapter 10: cholinergic axons from the pedunculopontine nucleus preferentially innervate the relay thalamic nuclei, while those from the laterodorsal tegmental nucleus preferentially innervate the limbic thalamic nuclei. The two mesopontine sectors are not redundant. One serves sensory and motor throughput; the other serves the limbic thalamus, including the anterior and midline nuclei that carry memory-relevant traffic.

The nucleus belongs, in consequence, to three literatures that rarely cite one another. To the sleep field it is a component of the ascending reticular activating system and a principal source of the cholinergic drive that supports both waking and REM sleep. To the movement disorders field it is the core of the mesencephalic locomotor region, a stimulation target for freezing of gait, and a structure whose degeneration in Parkinson's disease correlates with postural instability and falls. To the consciousness literature it is a node in the ascending arousal network, and it appears as a labelled region of interest in the Harvard Ascending Arousal Network Atlas, the reference volume by which brainstem arousal nuclei are now segmented in living human brains (Edlow et al., 2023) — a technical development that, as Chapter 11 shows, is what finally made the nucleus measurable in vivo.

What holds these three functions together is a single physiological role: the pedunculopontine nucleus sets the *state* in which the rest of the brain operates. It does not carry the content of perception, movement or memory. It determines whether the thalamus is in a burst-firing mode incompatible with information relay or a tonic mode that permits it, and whether the spinal motor apparatus is enabled or suppressed. During wakefulness, acetylcholine facilitates thalamocortical signalling by directly exciting thalamocortical relay neurons while reducing activity in the inhibitory reticular nucleus of the thalamus. At the onset of non-REM sleep, reduced cholinergic drive has the opposite effect: thalamocortical neurons hyperpolarise into a burst-firing mode in which they cannot relay information to or from the cortex. The nucleus is a gate-keeper, and gate-keepers fail in a characteristic way — not by disappearing, but by ceasing to open the gate.

3. How Many Neurons, and Whose Count to Believe

Before one can ask whether a nucleus loses neurons in a disease, one must know how many it has, and here the pedunculopontine literature contains a discrepancy large enough to require its own chapter. It is not a trivial bookkeeping matter. The size of the disagreement about the healthy baseline sets the size of the loss that any study can detect, and it is the main reason the question addressed in Chapter 6 stayed open for three decades.

Manaye and colleagues quantified cholinergic and selected non-cholinergic mesopontine populations in six adult human brains aged twenty-eight to sixty, with less than seven per cent variation between subjects. They estimated the average number of cholinergic cells in the combined pedunculopontine and laterodorsal tegmental nuclei at approximately twenty thousand, distributed as thirty per cent in the pars compacta, fifty-seven per cent in the pars dissipata, and thirteen per cent in the laterodorsal tegmental nucleus (Manaye et al., 1999).

Sharma, Gentleman, Dexter and Pienaar, applying unbiased cerebro-bilateral three-dimensional stereology to control and Parkinson's disease cases, reported a mean of 72,458 ± 5,629 cholinergic neurons using a boundary drawn around the Ch5 cholinergic population — and approximately 35,842 ± 769 per unilateral nucleus when the boundary was drawn instead by the surrounding white matter fibre tracts (Sharma et al., 2025).

These numbers do not agree. Depending on which is taken, the human mesopontine cholinergic population is either about twenty thousand cells or about seventy-two thousand — a discrepancy of roughly three and a half fold. Some of it is method: Manaye's estimates predate the general adoption of design-based stereology, and cell-counting methodology changed substantially in the intervening quarter century. But the more instructive part of the discrepancy is internal to the newer study. Sharma and colleagues deliberately applied two boundary definitions to the same tissue and obtained counts differing roughly two-fold. The pedunculopontine nucleus has no crisp anatomical edge. Where one draws it determines how many neurons it contains, and reasonable anatomists draw it differently.

Table 1 — Reported neuron counts for the human mesopontine cholinergic complex.

Study	Method	Boundary definition	Reported count
Manaye et al. (1999)	Quantification, 6 brains aged 28–60, <7% inter-subject variation	Cytoarchitectonic; PPN + LDT combined	~20,000 cholinergic cells total (PPNc 30%, PPNd 57%, LDT 13%)
Sharma et al. (2025)	Unbiased 3-D stereology, bilateral, 4 controls (7 complete nuclei)	Ch5 cholinergic population extent	72,458 ± 5,629
Sharma et al. (2025)	Same tissue, same cases	Surrounding white matter fibre tracts	~35,842 ± 769 per unilateral nucleus

Three consequences follow, and they govern the interpretation of everything in Part II.

The first is a matter of statistical power. A nucleus whose healthy baseline is uncertain within a factor of two or three cannot support the detection of modest losses. A twenty per cent depletion of a structure counted with that much boundary variance will not reach significance in the small autopsy cohorts that brainstem work permits, and its absence from the record cannot be read as evidence of preservation. This cuts against the argument of this paper as much as for it, and we state it before making the argument rather than after.

The second is that the *within-study* comparison is far more trustworthy than the between-study one. When a single laboratory applies one boundary rule to both disease and control tissue, the boundary ambiguity largely cancels. This is why Sharma's Parkinson's disease result is credible despite the baseline disagreement: both boundary definitions gave essentially the same answer for the disease effect — a forty-eight per cent reduction using the Ch5 definition and a fifty per cent reduction using the white-matter definition, each at $p < 0.0001$. The absolute counts differed two-fold; the loss fraction did not move. A finding robust to the boundary rule that changes the denominator is a finding about the disease.

The third consequence is specific to Alzheimer's disease and becomes central in Chapter 7. If the counted object is defined by cell *size* rather than by cell *identity* — "large neurons," as in the morphometry of the 1980s — then a nucleus whose neurons atrophy will appear to lose cells whether or not any cell dies. In a nucleus that accumulates neurofibrillary tangles, this is not a hypothetical concern. It is the expected artefact.

4. What the Nucleus Does, and How One Would Know It Had Stopped

A nucleus that sets brain state rather than carrying content presents a particular diagnostic problem: its failure does not produce a deficit that can be localised by examination. There is no pedunculopontine sign. Damage to the nucleus does not abolish a movement, a percept or a memory; it degrades the conditions under which movements, percepts and memories are produced. The clinical signature is therefore distributed, fluctuating, and easy to attribute elsewhere — which is a substantial part of the reason its role in Alzheimer's disease has gone unexamined.

Three functional domains are well enough established to serve as read-outs, and each is measurable in living patients.

The first is thalamocortical gating. The cholinergic projection from Ch5 and Ch6 to the thalamus determines the firing mode of thalamocortical relay neurons. Cholinergic drive depolarises relay cells into tonic firing, in which they faithfully transmit, and simultaneously suppresses the GABAergic reticular nucleus that would otherwise gate them. Withdrawal of that drive returns relay cells to burst firing, a mode incompatible with information relay. This is the physiology of falling asleep, and it is also, if it occurs partially and chronically during waking, a plausible physiology of inattention. Steckler, Inglis, Winn and Sahgal reviewed the evidence that the pedunculopontine tegmental nucleus participates in cognitive processes and located its contribution in exactly this register — attentional and arousal-dependent rather than mnemonic (Steckler et al., 1994).

The second is REM sleep. The mesopontine cholinergic neurons are the classical REM-promoting population; the state is generated by their activity and terminated by its cessation, and the nucleus is central to the high-frequency cortical activity that waking and REM sleep share. Because REM architecture is quantifiable by polysomnography — latency to the first REM period, percentage of total sleep time spent in REM — this domain offers something rare in brainstem pathology: a continuous, sensitive, non-invasive read-out of the nucleus's output. Chapter 11 is built on it.

The third is locomotion and posture. The pedunculopontine nucleus is the principal component of the mesencephalic locomotor region, and its degeneration in Parkinson's disease is associated with the axial motor features that dopaminergic therapy does not touch — postural instability, freezing of gait, and falls. This is the domain in which the nucleus has received the most clinical attention, and the domain in which, as Chapter 13 argues, the temptation to over-read its role in Alzheimer's disease is strongest.

There is a fourth read-out worth naming because it is the only one that directly interrogates the nucleus rather than its consequences. Low-frequency deep brain stimulation of the pedunculopontine nucleus in Parkinson's disease has been reported to ameliorate night-time sleep disturbance and daytime sleepiness, with low-frequency stimulation at around twenty-five hertz producing better effects on alertness than high-frequency stimulation at sixty to eighty hertz. The evidence is genuinely weak — a systematic review of the deep brain stimulation literature concluded that pedunculopontine stimulation remains experimental, with heterogeneity between and within surgical centres in targeting, stimulation parameters and experimental method, and with the available studies limited by small sample sizes and short follow-up. We cite it not as established therapeutics but as an existence proof: the human pedunculopontine nucleus can be driven from outside, and driving it changes arousal and sleep. A nucleus whose neurons survive is a nucleus that can, in principle, be driven.

What would it look like if this nucleus stopped working while remaining structurally present? It would look like lengthened REM latency and reduced REM sleep; like a thalamus receiving less cholinergic support than it should; like attentional and dual-task performance degrading faster than single-task performance; and like none of these being attributable, on structural imaging, to any visible lesion. That list is a prediction, and the second half of this paper tests it against the record.

Part II — The Failure

5. The Tangle Arrives

That the pedunculopontine nucleus is touched by Alzheimer pathology is not in dispute and has not been since the earliest examinations. What is remarkable is how consistently it was reported and how little was made of it.

Jellinger's 1988 morphometric study found neurofibrillary tangles in nine to thirty-eight per cent of the remaining pedunculopontine neurons in Alzheimer's disease and senile dementia of Alzheimer type (Jellinger, 1988). Woolf, Jacobs and Butcher, examining the pedunculopontine and laterodorsal tegmental nuclei together as the pontomesencephalotegmental complex, observed neurofibrillary changes and plaque-like entities in both nuclei in Alzheimer's disease and in Parkinsonian dementia — and, importantly for specificity, found that these pathological indices were not seen consistently in control individuals or in patients with multi-infarct dementia (Woolf, Jacobs & Butcher, 1989). The finding is disease-related, not an artefact of age or of dementia in general.

Modern work confirms it with better methods. Rüb and colleagues, in a synthesis of the brainstem tau cytoskeletal pathology of Alzheimer's disease, identify tau pathology in the raphe nuclei, the locus coeruleus, and the compact parts of the substantia nigra and the pedunculopontine nucleus, and note that these alterations plausibly underlie a range of clinical features including parkinsonian extrapyramidal motor signs, depression, hallucinations and dysfunctions of the sleep–wake cycle (Rüb et al., 2016). Dugger, Tu, Murray and Dickson quantified phospho-tau burden by immunohistochemistry and image analysis in twenty-six Alzheimer cases, thirty-seven progressive supranuclear palsy cases and eleven controls, using the substantia nigra and the pedunculopontine nucleus as comparison nuclei against the visual and auditory structures that were their primary interest (Dugger et al., 2011). Their principal result is itself a lesson in regional specificity: tau burden was greater in the superior colliculus in progressive supranuclear palsy than in Alzheimer's disease or controls, and greater in the inferior colliculus in Alzheimer's disease than in progressive supranuclear palsy or controls — a disease selectivity that parallels the visual reflex deficits of the one condition and the auditory deficits of the other. Tau does not fall on the brainstem as a fog. It selects.

Where the pedunculopontine nucleus falls in the temporal sequence is less settled than one would like. The staging of Alzheimer tau begins subcortically: the locus coeruleus is the first nucleus in which pretangle material appears, detectable in young adults decades before cortical involvement (Braak & Del Tredici, 2011), and quantitative work has traced the accretion of hyperphosphorylated tau in the locus coeruleus and dorsal raphe as the pathological building blocks of early disease

(Ehrenberg et al., 2017). The pedunculopontine nucleus is named among the involved brainstem structures in the synthesis literature, and neurofibrillary pathology in pontine nuclei including the locus coeruleus and the pedunculopontine nucleus has been described as accumulating progressively with increasing Braak stage. But we could not find a study that assigns the pedunculopontine nucleus a stage of first involvement with the rigour that has been applied to the locus coeruleus and the dorsal raphe. We record this as a gap rather than filling it by inference. The honest statement is that the nucleus is tau-bearing in established Alzheimer's disease, that its involvement appears to increase with stage, and that whether it is an early or a middle event in the subcortical sequence is not currently answerable from the published record.

What can be said, and what the next chapter is about, is that the tangle arrives and the neuron stays.

6. The Neurons Stay

Three studies have asked whether the pedunculopontine nucleus loses neurons in Alzheimer's disease. Two say no. One says yes, by a modest amount, and its method is the one that would produce a false positive.

Woolf, Jacobs and Butcher (1989). The most direct statement in the literature comes from the paper whose title says it: *The pontomesencephalotegmental cholinergic system does not degenerate in Alzheimer's disease*. Examining the pedunculopontine and laterodorsal tegmental nuclei in Alzheimer's disease and senile dementia, Parkinsonian dementia and multi-infarct dementia, the authors found the pathology described in the previous chapter — and reported that "in none of the diagnostic categories was loss of neuronal somata found in the PMT cholinergic complex." Their conclusion is the sentence this paper is built around: because appreciable degeneration of cholinergic neurons does occur in the basal forebrain in the same patients, "it is concluded that cholinergic phenotype alone is not a sufficient condition indicating predilection for neuronal loss in that dementing illness."

Eser and colleagues (2018). Thirty years later the question was reopened with modern quantitative methods and a comparative design. Eser, Ehrenberg, Petersen and colleagues applied multidimensional quantitative analysis to five reticular formation nuclei — the locus coeruleus, substantia nigra, gigantocellular nucleus, pedunculopontine nucleus and dorsal raphe nucleus — in fourteen Alzheimer cases, fourteen corticobasal degeneration cases, ten progressive supranuclear palsy cases and three controls (Eser et al., 2018). For the pedunculopontine nucleus, total neuronal numbers were similar across all groups. The nucleus accrued tau, and in the four-repeat tauopathies it accrued more of it, and its glutamatergic population was reduced in corticobasal degeneration and progressive supranuclear palsy relative to Alzheimer's disease — but in Alzheimer's disease the neurons were there.

The same study is worth reading for what it found elsewhere, because it establishes that the method was capable of detecting loss when loss was present. In the locus coeruleus, neuronal loss in Alzheimer's disease was severe — so severe that the authors noted the paradox that few neurons remained to develop aggregates, which is why progressive supranuclear palsy and corticobasal degeneration showed *more* tau-bearing noradrenergic neurons than Alzheimer's disease did. In the gigantocellular nucleus, Alzheimer's disease showed dramatic depletion of GABAergic neurons while these cells remained present in progressive supranuclear palsy and corticobasal degeneration. Two nuclei in the same sections, in the same cases, by the same method, showed severe Alzheimer-specific depletion. The pedunculopontine nucleus did not. This is the strongest single piece of evidence in the paper, because it is internally controlled: the failure to find loss in the

pedunculopontine nucleus cannot be attributed to an insensitive method that failed to find loss anywhere.

Jellinger (1988). The dissenting study reported that in Alzheimer's disease and senile dementia of Alzheimer type, large neurons of the pedunculopontine nucleus pars compacta were reduced by twenty-nine and thirty-three point eight per cent respectively (Jellinger, 1988). Taken at face value this is a real depletion, and it is regularly cited as such.

Two features of the paper argue against taking it at face value. The first is that the author did not himself present it as a positive finding. The opening sentence of his own abstract states that significant loss of neurons in the pedunculopontine pars compacta "has been demonstrated in progressive supranuclear palsy (PSP) and Parkinson's disease but not in Alzheimer's disease" — and in reporting his results he attaches the word *significant* to the progressive supranuclear palsy figure (a sixty per cent loss) and to the Parkinson's disease figures (fifty-three per cent by cell number and fifty-one per cent by density), but not to the Alzheimer figures. The study was framed, by the person who did it, as finding loss in two diseases and not in the third.

The second is the counted object, and it is the crux. Jellinger counted *large* neurons. A count of cells above a size criterion is not a count of cells. In a nucleus in which nine to thirty-eight per cent of surviving neurons bear neurofibrillary tangles — Jellinger's own figure — and in which the expected somatic response to tangle-bearing is atrophy, a size-thresholded count will register every neuron that has shrunk below the threshold as a neuron that has vanished. The artefact runs in exactly the direction of the reported result, and its expected magnitude is of the same order.

Table 2 — The pedunculopontine nucleus in Alzheimer's disease: three studies.

Study	Cohort	Counted object	Result in AD	Reads as
Jellinger (1988)	AD and SDAT vs age-matched controls; 2 PSP, PD cohort	"Large neurons" of PPN pars compacta, morphometry	−29% (AD), −33.8% (SDAT); significance not asserted for AD	Loss, or somatic atrophy below a size threshold
Woolf, Jacobs & Butcher (1989)	AD-SDAT, Parkinsonian dementia, multi-infarct dementia, controls	Neuronal somata, PPN + LDT	No loss of neuronal somata in any diagnostic category	No loss
Eser et al. (2018)	14 AD, 14 CBD, 10 PSP, 3 controls	Total neuronal number, design-based quantification	Total neuronal numbers similar across all groups	No loss

Our reading is that the three studies do not in fact conflict. Jellinger measured a reduction in the number of neurons large enough to count as large; Woolf and Eser measured the number of neurons. In a tangle-bearing nucleus these are different quantities, and the difference between them

is the somatic atrophy that tangle-bearing produces. On this reading all three studies observed the same thing — a nucleus full of shrunken, tau-laden, living neurons — and described it in the vocabulary each method made available.

We grade the central claim as **probable rather than established**, and we are explicit about why. The cohorts are small; Eser's three control brains are a thin comparison base; and, as Chapter 3 established, a nucleus with this much boundary ambiguity cannot exclude a modest depletion. What the evidence supports is that the pedunculopontine nucleus does not undergo anything resembling the catastrophic loss seen in the nucleus basalis in the same disease or in the same nucleus in progressive supranuclear palsy and Parkinson's disease. What it cannot exclude is a loss of, say, fifteen per cent. The argument of this paper does not require the stronger claim.

7. Why the Distinction Between Silence, Shrinkage and Death Matters

The preceding chapter's reconciliation is not a technicality. The three-way distinction between a neuron that has fallen silent, a neuron that has shrunk, and a neuron that has died is the distinction on which the therapeutic prospects of a nucleus depend, and Alzheimer's disease research has a specific history of collapsing it.

The history is instructive because it happened in the nucleus basalis first. The founding studies reported end-stage losses exceeding seventy-five per cent, and for years this was understood as the natural history of the cholinergic lesion. Then Gilmor and colleagues counted the nucleus basalis not at autopsy in advanced disease but across the early clinical continuum, and found that neuron *number* was essentially preserved: there was no significant difference in choline-acetyltransferase- or vesicular-acetylcholine-transporter-positive neuron counts among the cognitively normal, the mildly impaired, and those with mild Alzheimer's disease, only a non-significant reduction of roughly fifteen per cent (Gilmor et al., 1999). The early cholinergic deficit turned out to be, in the main, not a deficit of cells but a deficit of cholinergic *phenotype* — a progressive dedifferentiation in which the neuron survives while downregulating the machinery that made it cholinergic (Mufson et al., 2008). The point was sharpened by an apparent paradox: cortical and hippocampal choline acetyltransferase activity is not reduced, and may be transiently upregulated, in mild cognitive impairment, falling only in established disease (DeKosky et al., 2002).

So the nucleus basalis first falls silent and only later dies. The end-stage figure was real and the inference from it was wrong: for the years in which the patient is merely impaired, the cell is largely present.

The pedunculopontine nucleus extends this lesson by one step, and it is a step with different consequences. In the nucleus basalis, silence is a prelude to death; the trajectory ends in the seventy-five per cent figure. In the pedunculopontine nucleus, on the evidence of Chapter 6, the trajectory does not appear to end there at all. The nucleus receives the pathology, its neurons shrink, and they go on standing. If that is right, the pedunculopontine nucleus is not a slow version of the nucleus basalis. It is a different outcome of the same disease, and the difference is the subject of the next chapter.

Three consequences follow for how the nucleus should be studied and treated.

First, atrophy-based measurement will mislead. If the neurons shrink without dying, then any measure sensitive to tissue volume — structural magnetic resonance imaging, nuclear area morphometry, size-thresholded cell counts — will report degeneration where there is dysfunction. This is not a small matter for a nucleus that is now segmentable in vivo. A volumetric finding of pedunculopontine atrophy in Alzheimer's disease, should one be reported, would be entirely compatible with a full complement of living neurons, and would not license the language of cell loss.

Second, function-based measurement is the only measurement that can settle the question. What one wants to know about a standing relay is whether it is relaying. That means the output side: terminal markers in the target, receptor availability in the target, and the physiological consequences of the transmission. Chapters 10 and 11 pursue exactly these.

Third, and most consequentially, a surviving neuron is a therapeutic target of a different kind. A nucleus that has lost three-quarters of its cells cannot be restored by modulating the cells that remain. A nucleus that retains its full complement of shrunken, tau-bearing, electrically competent neurons is, in principle, a nucleus that can be driven — pharmacologically, or, as the deep brain stimulation literature suggests, electrically. The distinction between silence and death is the distinction between a target and a ruin.

8. Why This Nucleus Survives: The Trophic Contract

If cholinergic identity does not confer vulnerability — Woolf's conclusion, now supported by better methods — then what distinguishes the cholinergic neurons that die from the cholinergic neurons that do not? The answer is available in the literature and, as far as we can determine, has never been placed alongside Woolf's conclusion, although the two papers were published within months of each other.

Mesulam, Geula, Bothwell and Hersh characterised the cytochemistry of the human Ch5 and Ch6 neurons and compared them directly with the forebrain cholinergic neurons of Ch4 (Mesulam et al., 1989). The similarities are extensive, and they are the similarities that would predict shared vulnerability: both populations show perikaryal heteromorphism, both bear isodendritic arborisations, both carry high levels of acetylcholinesterase activity. On the criteria by which one would sort neurons into risk classes — size, transmitter, dendritic geometry, membership in the reticular core — Ch4 and Ch5–Ch6 belong together.

Two differences emerged. The Ch5–Ch6 neurons displayed high levels of NADPH-diaphorase activity, which the Ch4 neurons lacked. And, in the other direction, the Ch4 neurons possessed high levels of nerve growth factor receptor protein, which the Ch5–Ch6 neurons did not.

The second of these differences is, we propose, the explanation for the divergence in survival, and it is not a speculative mechanism but a restatement of the best-established fact about basal forebrain cholinergic neurons. The Ch4 neuron does not manufacture its own survival signal. It depends for survival on nerve growth factor retrogradely supplied from its cortical targets, taken up at its terminals and transported to its soma through the TrkA and p75 receptors. This dependence is the organising principle of basal forebrain neurobiology, it is the basis of the nerve growth factor pathobiology that has been mapped in detail across the progression of Alzheimer's disease (Mufson et al., 2002), and it is the reason the Ch4 neuron's fate is coupled to the fate of the cortex it innervates.

That coupling is a liability of a very specific kind. It means the Ch4 neuron is a hostage. Its survival is contingent on the integrity of a target that this disease dismantles, and on the integrity of a retrograde transport apparatus that this disease disrupts. Cortical synapses are lost; the retrograde supply of trophic support diminishes; the neuron dedifferentiates, atrophies, and eventually dies. The cholinergic phenotype is incidental to this sequence. What kills the Ch4 neuron is the termination of a contract.

The Ch5 and Ch6 neurons are not party to that contract. Lacking nerve growth factor receptor protein, they are not dependent on retrograde trophic supply from a cortical target — and their principal target is not the cortex but the thalamus, which in Alzheimer's disease is not dismantled in the way the association cortex is. They are cholinergic without being trophically enrolled, and on this account that is precisely why they survive.

Table 3 — The vulnerability asymmetry between the two cholinergic divisions.

Feature	Ch4 (nucleus basalis)	Ch5–Ch6 (PPN, LDT)	Source
Transmitter	Cholinergic	Cholinergic	Mesulam et al. (1983, 1989)
Perikaryal heteromorphism	Present	Present	Mesulam et al. (1989)
Isodendritic arborisation	Present	Present	Mesulam et al. (1989)
Acetylcholinesterase activity	High	High	Mesulam et al. (1989)
NADPH-diaphorase activity	Absent	High	Mesulam et al. (1989)
Nerve growth factor receptor protein	**High**	**Absent**	Mesulam et al. (1989)
Principal projection target	Cortical mantle, amygdala	Thalamus (PPN → relay nuclei; LDT → limbic nuclei)	Mesulam et al. (1983, 1989)
Neuronal loss in AD	~70–75% end-stage; number preserved early	Not detected	Whitehouse et al. (1982); Arendt et al. (1983); Gilmor et al. (1999); Woolf et al. (1989); Eser et al. (2018)

We grade this mechanism as **inference**. Both of its premises are established — the receptor asymmetry is a published observation, and the trophic dependence of Ch4 is among the best-supported facts in the field — but the causal link between them and the survival differential has not been tested, and Chapter 16 specifies the experiment that would test it. We also note the honest alternative: the second cytochemical difference, the high NADPH-diaphorase activity of Ch5–Ch6, marks these cells as nitric-oxide-producing, and it is at least arguable that this is protective rather than the receptor difference being decisive. We prefer the trophic account because it connects to an established disease mechanism rather than a hypothetical one, but we do not claim the alternative is excluded.

There is a broader implication, and it reaches past this nucleus. Recent transcriptomic work on the differential vulnerability of brainstem nuclei to Alzheimer's disease compared the locus coeruleus with the substantia nigra at early Braak stages by bulk RNA sequencing and concluded that cholesterol homeostasis, rather than neuroinflammation or oxidative stress, most plausibly explains why one nucleus is destroyed and its neighbour is not. That result and ours point the same way: selective vulnerability in the brainstem is not a function of transmitter class, and neurons that look alike by the classical criteria can be sorted into survivors and casualties by features — a receptor here, a lipid pathway there — that the classical criteria do not see. The pedunculopontine nucleus is the clearest available demonstration, because it holds every classical risk factor constant and comes out on the other side.

9. The Comparison Cases: What Three Diseases Do to One Nucleus

The strongest evidence that the preservation of the pedunculopontine nucleus in Alzheimer's disease is a fact about Alzheimer's disease, rather than a fact about the difficulty of counting the nucleus, is that other diseases destroy it — measurably, reproducibly, and in the same laboratories using the same methods.

Progressive supranuclear palsy. Zweig and colleagues reported the loss of pedunculopontine neurons in progressive supranuclear palsy in 1987 (Zweig et al., 1987). Jellinger's morphometry found a significant sixty per cent neuronal loss in the pars compacta, with neurofibrillary tangles in forty to sixty-four per cent of the remaining neurons (Jellinger, 1988). This is a nucleus being destroyed, and the tangle burden in the survivors is two to four times the Alzheimer figure from the same study.

Parkinson's disease. Jellinger found a significant decrease in cell number and density of fifty-three and fifty-one per cent respectively, with Lewy bodies involving six to thirty-nine per cent of neurons. Sharma and colleagues, with unbiased three-dimensional stereology, confirmed and refined this: a forty-eight per cent reduction of cholinergic neurons using the Ch5 boundary definition and a fifty per cent reduction using the white matter definition, each at $p < 0.0001$, with the pars dissipata more vulnerable than the pars compacta (fifty-five versus thirty-seven per cent) (Sharma et al., 2025). The subnuclear gradient is a detail worth carrying forward: it is the opposite of what the Alzheimer literature has examined, since Jellinger's Alzheimer figures are for the pars compacta alone.

Corticobasal degeneration. Eser and colleagues found the pedunculopontine glutamatergic population reduced in corticobasal degeneration and progressive supranuclear palsy relative to Alzheimer's disease, with higher tau burden in the four-repeat tauopathies (Eser et al., 2018).

Table 4 — The pedunculopontine nucleus across four diseases.

Disease	Neuronal loss reported	Inclusion burden in survivors	Population affected	Source
Progressive supranuclear palsy	60% (pars compacta), significant	NFT in 40–64%	Cholinergic; glutamatergic reduced	Zweig et al. (1987); Jellinger (1988); Eser et al. (2018)
Parkinson's disease	53% by number, 51% by density; 48–50% by stereology (PPNd 55%, PPNc 37%)	Lewy bodies in 6–39%	Cholinergic	Jellinger (1988); Sharma et al. (2025)
Corticobasal degeneration	Glutamatergic reduced vs AD	Higher tau than AD	Glutamatergic	Eser et al. (2018)
Alzheimer's disease	None detected by somata count or total neuronal number; −29 to −34% of *large* neurons	NFT in 9–38%	—	Jellinger (1988); Woolf et al. (1989); Eser et al. (2018)

Read across, the table makes three points that no single row makes.

The first is methodological and decisive. The pedunculopontine nucleus is countable. A structure in which two independent laboratories, four decades apart, using morphometry and then unbiased stereology, can detect a fifty to sixty per cent depletion at high significance is not a structure so refractory to measurement that real loss would escape notice. The absence of an Alzheimer signal is therefore informative, within the power limits stated in Chapter 6.

The second is that tangle-bearing and dying are dissociable in this nucleus, and the dissociation runs in both directions. In progressive supranuclear palsy the nucleus bears heavy tau and dies. In Alzheimer's disease it bears lighter tau and lives. But the four-repeat tauopathies also deposit more tau here in general, so the comparison does not isolate quantity from species. What Eser's dataset does isolate is more interesting: within Alzheimer's disease, the locus coeruleus is destroyed while bearing *less* tau than progressive supranuclear palsy deposits there, for the arithmetic reason that its neurons died before they could accumulate aggregates. Tau burden at autopsy is a measure of what surviving neurons have accumulated, not of what the disease did. The pedunculopontine nucleus in Alzheimer's disease has a moderate tangle burden because its neurons are alive to display one.

The third point is the one that bears on the paper's central argument. Alzheimer's disease is not gentler on this region of the brainstem than progressive supranuclear palsy is. Two millimetres away, in the same sections, it annihilates the locus coeruleus — a loss that Eser and colleagues found

so extreme that few neurons remained to bear aggregates, consistent with the stereological trajectory established for that nucleus across the course of the disease (Theofilas et al., 2017). And in the same study it dramatically depleted the GABAergic neurons of the gigantocellular nucleus, which progressive supranuclear palsy and corticobasal degeneration largely spared. The disease reaches the mesopontine and medullary tegmentum, empties two nuclei there, and leaves the cholinergic one standing. That is selectivity of a very high order, and it needs an explanation of the kind Chapter 8 proposed.

Part III — What the Failure Withholds

10. The Thalamic Channel

If the pedunculopontine neurons survive, the question becomes whether their projection works. This is the measurement that matters, and it is the measurement nobody has made.

The architecture makes the stakes clear. Ch5 and Ch6 provide the major cholinergic innervation of the human thalamus (Mesulam et al., 1989), and the projection is topographically ordered: pedunculopontine axons preferentially innervate the relay thalamic nuclei, laterodorsal tegmental axons the limbic thalamic nuclei. The basal forebrain, whose cholinergic projection dominates the cortical mantle, contributes to the thalamus only to a lesser extent. These are two separate cholinergic axes with two separate sources and two separate targets, and the cholinergic hypothesis of Alzheimer's disease was constructed almost entirely from the first.

The functional significance of the thalamic axis is not in doubt. Cholinergic input determines whether thalamocortical relay neurons fire tonically, and so transmit, or in bursts, and so do not; it simultaneously suppresses the inhibitory reticular nucleus that gates them. Whatever the cortex's own cholinergic supply is doing, the traffic reaching the cortex from everywhere else passes a gate whose position is set from the mesopontine tegmentum. A cortex with an intact cholinergic innervation and an unsupported thalamus is a cortex being modulated but not informed.

What is known about the state of that axis in Alzheimer's disease amounts to one indirect measure, and it points toward deficiency. Radioligand imaging of α4β2 nicotinic acetylcholine receptors shows widespread reductions in mild cognitive impairment and Alzheimer's disease, and the thalamus is among the affected regions — indeed the thalamus and midbrain are the regions in which the 2-fluoro-A-85380 ligand reliably measures this receptor at all, cortical measurement being limited by low signal-to-noise ratio. Reduced subcortical α4β2 availability was associated with worse global cognition (Kendziorra et al., 2011). Reduced α4β2 binding in Alzheimer brain tissue is corroborated post mortem.

This is suggestive and it is not sufficient, and the reasons are worth stating precisely because they define the experiment that is needed. A nicotinic receptor is postsynaptic. Its availability can fall because the thalamic neurons expressing it are lost, because those neurons downregulate it, or because the presynaptic cholinergic supply has changed — and the direction of the last of these is not even determinable a priori, since receptor number responds to transmitter availability in ways that can go either way. A reduction in thalamic α4β2 binding is a finding about the target, not about the channel.

The channel itself has, as far as we can establish, never been assessed in Alzheimer's disease. The measurements that would assess it are unglamorous and entirely feasible on existing tissue: vesicular acetylcholine transporter immunoreactivity and acetylcholinesterase histochemistry in thalamic relay nuclei and limbic nuclei separately, across Braak stages, with the mesopontine source nuclei counted in the same brains. The relevant regional biochemistry that does exist is not adequate to the question — the classical choline acetyltransferase surveys sampled cortex, hippocampus and cerebellum rather than resolving thalamic nuclei (Bird et al., 1983) — and modern post-mortem magnetic resonance work on cholinergic pathways has concentrated on the forebrain projection routes.

So the state of the evidence is this. The source neurons are present. The target's cholinergic receptors are reduced. Between them lies an unmeasured projection, and the whole functional claim of this paper turns on it. We therefore state the claim as a **proposal**, not a finding: that in Alzheimer's disease the mesopontine cholinergic innervation of the thalamus is functionally deficient despite a preserved source population, and that this deficiency — not pedunculopontine cell loss — is the nucleus's contribution to the disease. Chapter 15 grades it accordingly and Chapter 16 specifies how it would be tested and what result would abandon it.

One anatomical prediction is worth recording now, because it is testable on the same tissue and would discriminate our proposal from a generic thalamic degeneration. Because the pedunculopontine and laterodorsal tegmental projections have different thalamic destinations, a source-side lesion should produce a *patterned* deficit — relay nuclei and limbic nuclei affected differently, according to which mesopontine sector is more involved. A target-side degeneration should not respect that boundary. The topography is the signature.

11. The REM Signature

The most direct evidence that the pedunculopontine nucleus fails functionally in Alzheimer's disease comes from sleep, and it arrives as a convergence of two literatures that were not written with each other in mind.

The first is a tau imaging study. Jeon, Yi, Byun and colleagues, working in the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease, measured tau deposition in the pedunculopontine nucleus in twenty-two non-demented older adults using [18F]AV-1451 positron emission tomography, with amyloid status established by [11C]Pittsburgh compound B, and defined the nucleus with participant-specific regions of interest prepared in native space from the Harvard arousal network atlas. Sleep was measured by nocturnal polysomnography over two consecutive nights. Controlling for age, sex, education and apolipoprotein E ε4 status, pedunculopontine tau was associated with increased REM latency ($p < 0.001$) and, at trend level, with decreased REM percentage ($p = 0.079$). Stratified by amyloid status, the associations were present in amyloid-positive participants — increased REM latency ($p = 0.001$) and decreased REM percentage ($p = 0.011$) — and absent in amyloid-negative participants (Jeon et al., 2025).

We must be explicit about the weight this can bear. It is a conference abstract, not a peer-reviewed full report. The sample is twenty-two. The tau tracer has known off-target binding, and the brainstem is a demanding region for a tracer with any off-target signal at all; an atlas-derived region of interest in a nucleus of this size, at the spatial resolution of positron emission tomography, will contain substantial signal from neighbouring structures. The amyloid stratification, on a sample of twenty-two, rests on subgroups small enough that the contrast between positive and negative strata should not be over-interpreted. This is a preliminary result and we grade it as one.

The second literature is prospective and epidemiological, and it is strong. Pase, Himali, Grima and colleagues followed 321 Framingham Heart Study Offspring participants aged sixty and over — mean age sixty-seven, half male — who had undergone polysomnography, for a mean of twelve years and up to nineteen, during which thirty-two developed dementia, twenty-four of them Alzheimer dementia. Lower REM sleep percentage and longer REM sleep latency were each associated with a higher risk of incident dementia. Each percentage point of REM sleep carried a hazard ratio of 0.91 (95% CI 0.86–0.97); for REM latency, the lowest tertile compared with the highest gave a hazard ratio of 0.37 (95% CI 0.14–0.97) in the age- and sex-adjusted model and 0.26 (95% CI 0.08–0.85) in the fully adjusted model. Effect sizes for Alzheimer dementia specifically were similar (Pase et al., 2017).

The convergence is exact, and it is exact in a way that a coincidence would have difficulty reproducing. Two parameters, two directions, two independent designs:

Table 5 — Two literatures, one REM signature.

Parameter	Association with PPN tau (Jeon et al., 2025; n = 22, conference abstract)	Association with incident dementia (Pase et al., 2017; n = 321, 12 yr)
REM latency	Increased ($p < 0.001$; amyloid-positive $p = 0.001$)	Longer latency → higher risk; lowest vs highest tertile HR 0.26–0.37
REM percentage	Decreased (trend, $p = 0.079$; amyloid-positive $p = 0.011$)	Lower percentage → higher risk; HR 0.91 per percentage point

Neither study alone supports a mechanism. Jeon and colleagues establish a cross-sectional correlation in a small sample; Pase and colleagues establish that the same two parameters, moving in the same directions, predict the disease over a decade. Together they license a specific and falsifiable proposal: that the REM abnormality which precedes Alzheimer dementia is generated in the mesopontine cholinergic tegmentum, by tau, in neurons that are still alive.

This proposal has a virtue that deserves emphasis. It predicts the *right kind* of abnormality. A nucleus that had lost its REM-promoting neurons should produce a REM deficit that worsens monotonically toward abolition. A nucleus whose REM-promoting neurons are present but under-driven should produce a REM period that is *late* and *short* — delayed in its onset because the drive required to initiate the state takes longer to assemble, and curtailed because the drive is insufficient to sustain it. Increased latency with decreased percentage is the signature of a weakened generator, not an absent one. It is what a standing relay looks like on a polysomnogram.

It also supplies something the field has wanted: a mechanistic account of why sleep measures predict dementia at all. The dominant explanation has been clearance — that sleep disruption impairs the removal of pathological protein, making poor sleep a cause of accumulation. Our proposal is not a rival to that account but a complement with the arrow reversed: tau in the arousal nuclei degrades sleep architecture, so the sleep measure is an early *read-out* of subcortical pathology rather than only a *driver* of it. Both can be true, and if both are true the loop closes, which would explain why the association is as robust as it is. What distinguishes the two arrows empirically is timing and specificity, and Chapter 16 proposes the study that would separate them.

12. Why It Is Not REM Sleep Behaviour Disorder

An obvious objection arrives at this point, and answering it properly strengthens the account rather than merely defending it. If Alzheimer tau impairs the mesopontine cholinergic nuclei that generate REM sleep, why is REM sleep behaviour disorder not a feature of Alzheimer's disease? The disorder is the best-known clinical consequence of brainstem REM circuit failure, and its association with neurodegeneration is among the strongest in clinical neurology — but the neurodegeneration it predicts is the wrong kind. More than eighty per cent of patients with isolated REM sleep behaviour disorder go on to develop Parkinson's disease, dementia with Lewy bodies or, less commonly, multiple system atrophy: the α-synucleinopathies. Alzheimer's disease appears in these cohorts only in a minority of cases and with acknowledged uncertainty about diagnostic accuracy (Postuma et al., 2019), and the specificity of the disorder for synuclein pathology rather than tau has been examined directly and repeatedly (Galbiati et al., 2018).

The answer is that REM sleep behaviour disorder is not a disorder of REM sleep generation. It is a disorder of REM sleep *atonia*, and atonia is produced by a different circuit.

The atonia circuit has been mapped with precision. Glutamatergic neurons of the sublaterodorsal nucleus, also called the subcoeruleus, are REM-active; they project to GABA- and glycine-releasing reticulospinal neurons of the rostromedial and ventromedial medulla and to inhibitory interneurons of the spinal ventral horn. Activation of this descending chain releases GABA and glycine onto skeletal motoneurons and produces the paralysis of REM sleep. A glycinergic population in the ventral medulla receiving direct input from the sublaterodorsal nucleus and projecting almost exclusively to brainstem and spinal motoneurons has been identified as a specific inducer of REM atonia.

Krenzer and colleagues made the crucial separation explicit, and it is the anatomical foundation of this chapter. Dissecting the circuitry, they found that glutamatergic sublaterodorsal neurons and spinal glycinergic and GABAergic interneurons contribute to REM *atonia*, whereas a *separate* population of glutamatergic neurons in the caudal laterodorsal tegmental nucleus and sublaterodorsal nucleus is important for REM sleep *generation* (Krenzer et al., 2011). Generation and atonia are dissociable in the brainstem by experiment, not merely in principle — and the generation limb sits in the caudal laterodorsal tegmental territory, which is Ch6's address.

This chain is anatomically adjacent to the pedunculopontine and laterodorsal tegmental nuclei and functionally separate from them. The mesopontine cholinergic neurons set the timing and the

quantity of REM sleep — when the state begins and how much of it there is. The sublaterodorsal glutamatergic neurons and their medullary targets set whether the state is accompanied by paralysis. Damage the first system and REM comes late and sparse. Damage the second and REM comes with movement.

The dissociation therefore predicts precisely the clinical pattern observed. Tau in the pedunculopontine nucleus should produce lengthened REM latency and reduced REM percentage without behavioural release — which is what Jeon and colleagues measured, and what Pase and colleagues found to predict dementia. Synuclein in the sublaterodorsal and medullary circuits should produce behavioural release, which is REM sleep behaviour disorder, and is why the disorder marks synucleinopathy. The absence of REM sleep behaviour disorder in Alzheimer's disease is not evidence against mesopontine cholinergic failure. It is evidence that the failure is confined to the sector our account assigns it to.

Intellectual honesty requires that we now state the finding that complicates this, rather than leaving it for a reader to discover. Eser and colleagues, in the same study that found the pedunculopontine nucleus preserved, found that the GABAergic neurons of the gigantocellular nucleus were *dramatically depleted in Alzheimer's disease*, while remaining present in progressive supranuclear palsy and corticobasal degeneration (Eser et al., 2018). The gigantocellular region of the medullary reticular formation is part of the territory through which the descending atonia pathway runs. On the face of it, an Alzheimer-specific depletion of medullary GABAergic neurons should predict impaired atonia — that is, it should predict REM sleep behaviour disorder in Alzheimer's disease, which is not observed.

We do not think this refutes the chapter, and we can say why, but the reasons are arguments rather than data. The gigantocellular nucleus as delineated for a comparative study of reticular nuclei is not coextensive with the specific ventromedial glycinergic and GABAergic populations that the atonia work identifies; the relevant cells are a subset, defined by projection target, and their depletion is not established by a nucleus-level count. Loss of a descending inhibitory population would in any case produce a different phenotype from disinhibition of an intact one, and severe motor release requires that REM sleep occur in quantity — which, on this paper's own account, is exactly what Alzheimer's disease reduces. A patient with little REM sleep has little opportunity to enact it.

But these are reconciliations, not evidence, and the finding stands as the most substantial internal tension in the account offered here. We list it in the ledger as an open problem and, in Chapter 16, as an experiment: the atonia circuit in Alzheimer's disease has not been characterised at the resolution of its projection-defined cell types, and until it has, the clean dissociation this chapter draws is a well-motivated hypothesis rather than a demonstrated fact.

13. Gait, Falls, and the Discipline of Not Over-Reading

The pedunculopontine nucleus is the principal component of the mesencephalic locomotor region. Its degeneration in Parkinson's disease is associated with postural instability, freezing of gait and falls; it is a deep brain stimulation target chosen for exactly those indications. Meanwhile, gait slowing is an early and well-replicated feature of Alzheimer's disease, appearing before diagnosis and predicting progression. The inference is nearly irresistible: the pedunculopontine nucleus is the locomotor nucleus, Alzheimer's disease impairs gait, therefore the pedunculopontine nucleus is where Alzheimer gait impairment comes from.

We think this inference is wrong, and we think the discipline of rejecting it is what makes the rest of the paper credible. An argument that the pedunculopontine nucleus matters in Alzheimer's disease should not annex every symptom the nucleus could conceivably produce. It should annex the ones the evidence assigns to it.

The evidence does not assign gait. The most direct test available compared gait parameters against cognitive scores, amyloid deposition and cortical atrophy in forty-eight patients with Alzheimer dementia, twenty-seven with prodromal Alzheimer's disease and forty-one cognitively unimpaired individuals. Prodromal and demented patients walked significantly more slowly than unimpaired individuals — and the slowing was linked to attention and executive function, to widespread cortical amyloid-β deposition, and to cortical atrophy in the inferior parietal lobule, middle temporal gyrus, precuneus and insula (Kim et al., 2025). The correlates of gait slowing in Alzheimer's disease are cortical, attentional and executive. They are not the correlates of a brainstem locomotor lesion.

This is precisely what a structurally intact pedunculopontine nucleus predicts, and the concordance is worth pausing on. If the nucleus retains its neurons, Alzheimer gait impairment should *not* look like Parkinsonian axial motor failure, and it does not. Parkinson's disease, which halves the nucleus's cholinergic population, produces freezing, festination and postural instability. Alzheimer's disease, which does not deplete it, produces a slower walk that tracks attention and dual-task load. Two diseases, one nucleus, two phenotypes, and the phenotypes align with the pathology rather than with the anatomy's potential.

The pharmacological evidence agrees, and it agrees in the disciplined direction of a negative result. Montero-Odasso and colleagues conducted a randomised controlled trial of donepezil for gait and falls in mild cognitive impairment, with gait speed under single- and dual-task conditions as

the primary outcome. The primary outcome was not met: dual-task gait speed improved by four to eleven centimetres per second, and this was not statistically significant. Two dual-task cost measures did improve significantly in the intention-to-treat analysis — counting backwards by one, 10.25 per cent versus 1.75 per cent on placebo ($p = 0.048$); counting backwards by seven, 21.38 per cent versus 14.64 per cent ($p = 0.037$) — and the per-protocol analysis showed a non-significant reduction in the rate of falls (Montero-Odasso et al., 2019). An earlier phase II study reported improved gait velocity in mild Alzheimer's disease, from 108.4 to 113.3 centimetres per second over four months (Montero-Odasso et al., 2014).

The honest summary is that cholinergic augmentation in this population produces small effects on the *motor–cognitive interface* — the dual-task cost, which is an attentional measure expressed in a motor variable — and does not convincingly improve gait speed or reduce falls. That pattern fits a cortical-attentional lesion modulated by cholinergic drug, not a brainstem locomotor lesion corrected by cholinergic replacement.

Two narrower claims survive this deflation, and we make only these. First, the mesopontine contribution to Alzheimer gait impairment, if any, should be sought in the attentional pathway — through the thalamic gate of Chapter 10 — rather than in the descending locomotor pathway; a dual-task cost is exactly the sort of measure a failing thalamic gate would degrade. Second, the subnuclear question is genuinely open: Sharma and colleagues found the pars dissipata more vulnerable than the pars compacta in Parkinson's disease, whereas the Alzheimer figures that exist are for the pars compacta alone (Jellinger, 1988). Nobody has counted the pars dissipata in Alzheimer's disease. Since it holds the majority of the mesopontine cholinergic population, the preservation established in Chapter 6 is, strictly, established for the minority subdivision. We flag that as a limitation of our own claim and as experiment eight.

14. What a Standing Relay Costs

It remains to state what the failure described in this paper actually costs a patient, and to keep the statement within the evidence.

The cost is not a symptom. It is a change in the conditions under which every other system operates, and the reason it has gone unnoticed for four decades is that such changes do not present as deficits with names. Three consequences can be stated with reasonable confidence, in descending order of evidential support.

The first is the sleep architecture itself, and it is not merely a marker. If REM sleep is late and sparse because its mesopontine generator is under-driven, then whatever REM sleep does is being done less. The convergence in Chapter 11 establishes that this abnormality is associated with tau in the nucleus and predicts incident dementia at a hazard ratio of 0.91 per percentage point of REM sleep over twelve years. Whether the reduced REM sleep contributes causally to the progression or merely reports the pathology is not settled by these data, and the loop may run in both directions. But the quantity being lost is not nothing: it is a nightly physiological state, reduced across years, in a brain that is concurrently accumulating pathology.

The second is thalamocortical gating, and here the reasoning is architectural and the measurement is missing. If the mesopontine cholinergic supply to the thalamus is deficient — the proposal of Chapter 10, graded as a proposal — then relay neurons sit closer to their burst-firing mode than they should, and the inhibitory reticular nucleus is less suppressed than it should be. The functional consequence would be a gate that opens less readily: not an absent percept or an abolished memory, but a raised threshold for the traffic that carries them. Clinically this would appear as fluctuating attention, degraded performance under divided-attention load, and a discrepancy between what a patient can do when engaged and what they can do when not. Those features are conspicuous in Alzheimer's disease and are conventionally attributed entirely to cortical network failure. We are proposing that a fraction of them is generated two millimetres from the locus coeruleus, in a nucleus with all its cells.

The third is the one we deliberately do not claim. Gait, on the evidence of Chapter 13, belongs to the cortical-attentional account, and the reader should hold us to that.

There is a fourth consequence, which is conceptual rather than clinical, and it is the reason this nucleus deserves attention out of proportion to the certainty of any single finding here. The dominant model of Alzheimer's disease is subtractive: cells are lost, and function is lost with them, in proportion. That model has organised the field's outcome measures — volumetry, cell counts,

atrophy rates — and its therapeutic logic, which is to prevent loss. The pedunculopontine nucleus does not fit it. Here is a nucleus with a full complement of neurons whose output is, on the evidence assembled here, degraded; whose degradation predicts the disease years in advance; and which no atrophy measure will detect, because there is no atrophy of the relevant kind to measure.

If that is right, it has one clear practical implication. A nucleus that has lost three-quarters of its cells offers little to work with. A nucleus that retains its cells, and whose cells can be driven — pharmacologically, or electrically, as the deep brain stimulation literature demonstrates in another disease — is a different sort of object. It is the rare thing in this field: an intact substrate. Whether it can be usefully driven in Alzheimer's disease is unknown and we do not assert it. But the question is worth asking, and it cannot be asked at all under a model in which the only thing that matters is how many neurons are left.

Part IV — Ledger and Tests

15. A Graded Ledger

The argument of this paper mixes well-established anatomy, a contested and small post-mortem literature, one conference abstract, and two mechanistic inferences of our own. Presenting these at a uniform level of confidence would misrepresent all of them. The following ledger separates them. **Established** means supported by multiple independent studies with adequate method. **Probable** means supported by the best available evidence with acknowledged limitations of power or replication. **Inference** means a claim we derive from established premises but which has not been tested. **Proposal** means a claim we advance for testing, with the test specified in Chapter 16.

Table 6 — Graded ledger of claims.

#	Claim	Grade	Basis and limitation
1	Ch5 and Ch6, centred on the PPN and LDT, provide the major cholinergic innervation of the human thalamus	Established	Mesulam et al. (1989); topography corroborated in tract-tracing work
2	The PPN contains intermingled cholinergic, glutamatergic and GABAergic populations with distinct functions	Established	Wang & Morales (2009); Kroeger et al. (2017, 2022)
3	The PPN accumulates tau in Alzheimer's disease	Established	Jellinger (1988); Woolf et al. (1989); Dugger et al. (2011); Rüb et al. (2016)
4	The PPN cholinergic population is severely depleted in PSP (~60%) and PD (~48–53%)	Established	Zweig et al. (1987); Jellinger (1988); Sharma et al. (2025)
5	Ch4 carries high nerve growth factor receptor protein; Ch5–Ch6 do not	Established	Mesulam et al. (1989)
6	Lower REM percentage and longer REM latency predict incident dementia	Established	Pase et al. (2017), 321 participants, 12-year mean follow-up
7	Thalamic α4β2 nicotinic receptor availability is reduced in MCI and AD	Established	Kendziorra et al. (2011); post-mortem corroboration

#	Claim	Grade	Basis and limitation
8	PPN total neuron number is not appreciably reduced in Alzheimer's disease	**Probable**	Woolf et al. (1989); Eser et al. (2018), internally controlled by severe loss in LC and GCN in the same sections. Small cohorts (3 controls in Eser); cannot exclude ~15% loss; Jellinger (1988) dissents
9	Jellinger's 29–34% reduction of "large neurons" reflects somatic atrophy, not death	**Probable**	Reconciles all three studies; size-thresholded counting in a tangle-bearing nucleus predicts this artefact; significance not asserted for AD in the source. Not directly demonstrated
10	Alzheimer gait slowing is cortical-attentional, not a PPN locomotor lesion	**Probable**	Kim et al. (2025): gait pace tracks attention/executive function, cortical amyloid, cortical atrophy. Montero-Odasso et al. (2019): primary gait-speed endpoint not met
11	PPN tau is associated with longer REM latency and lower REM percentage	**Inference from preliminary data**	Jeon et al. (2025) — conference abstract, n = 22, tracer off-target binding, small ROI at PET resolution. Direction concordant with claim 6
12	The absence of NGF receptor on Ch5–Ch6 explains their survival where Ch4 dies	**Inference**	Both premises established (claim 5; NGF dependence of Ch4, Mufson et al. 2002). Causal link untested. Alternative candidate: high NADPH-diaphorase activity of Ch5–Ch6
13	The mesopontine cholinergic innervation of the thalamus is functionally deficient in AD despite a preserved source	**Proposal**	Source preserved (claim 8) and target receptors reduced (claim 7), but the projection itself has never been assessed in AD
14	Alzheimer's REM abnormality is generated in the mesopontine tegmentum by tau in living neurons	**Proposal**	Convergence of claims 6 and 11; predicts the observed *pattern* (late and short, not absent). Requires powered replication
15	The absence of RBD in AD is explained by sparing of the sublaterodorsal–medullary atonia circuit	**Proposal, with a stated tension**	Circuit anatomy established (Krenzer et al., 2011); RBD's synuclein specificity established (Postuma et al., 2019; Galbiati et al., 2018). **But** Eser et al. (2018) found AD-specific depletion of gigantocellular GABAergic neurons, which our account does not comfortably accommodate
16	Whether the PPN is early or middle in the subcortical tau sequence	**Open**	No study assigns the PPN a stage of first involvement with the rigour applied to LC and DRN

#	Claim	Grade	Basis and limitation
17	Whether the pars dissipata is preserved in AD	**Open**	Jellinger's AD figures are for pars compacta only; the dissipata holds the majority of the cholinergic population and has not been counted in AD

Two entries deserve comment because they are the ones on which a critical reader should press.

Claim 8 is the load-bearing empirical claim, and it rests on two studies, one of which is thirty-seven years old and one of which has three control brains. Its strength does not come from the size of those cohorts but from the internal control: in Eser's sections, the same method that found no pedunculopontine loss found severe locus coeruleus loss and dramatic gigantocellular GABAergic depletion in the same cases. A method that detects loss in two nuclei and not in a third is reporting something about the third nucleus. That is a genuine argument, and it is still not the same as a well-powered stereological series, which is experiment one.

Claim 15 is the entry where we have argued against our own convenience. The gigantocellular finding is a real problem for the clean dissociation of Chapter 12, our reconciliations of it are arguments rather than data, and we would rather have it visible in the ledger than buried in a paragraph.

16. What Would Refute This, and What Should Be Done

Conditions of refutation. The following results would falsify specific claims, and we name them in advance.

1. **Design-based stereology of choline-acetyltransferase-positive neurons in the pedunculopontine and laterodorsal tegmental nuclei, in an adequately powered Alzheimer series, showing loss greater than about twenty-five per cent.** This would refute claim 8 and with it the central argument. The threshold is set deliberately above the fifteen per cent that Chapter 6 concedes cannot be excluded, and below the fifty per cent that Parkinson's disease produces.

2. **Demonstration that Ch5–Ch6 neurons express TrkA or p75 at levels comparable to Ch4 in human tissue.** This would refute the mechanism of claim 12 and leave the survival differential unexplained, returning attention to the NADPH-diaphorase alternative.

3. **Normal vesicular acetylcholine transporter immunoreactivity and acetylcholinesterase histochemistry in thalamic relay and limbic nuclei across Braak stages.** This would refute the proposal of claim 13, and with it the paper's central functional claim: an intact source and an intact channel would locate the reduced thalamic receptor availability entirely on the target side.

4. **An adequately powered tau-PET-plus-polysomnography study showing no association between pedunculopontine tau and REM latency.** This would refute claim 11 and undercut claim 14. Given the size of Jeon's sample, this is a live possibility and we say so.

5. **Demonstration that REM sleep behaviour disorder occurs in Alzheimer's disease at rates approaching those in synucleinopathy when patients are properly polysomnographed.** This would refute the dissociation of Chapter 12 and convert the gigantocellular finding from a tension into a contradiction.

Experiments, in order of what they would settle per unit of effort.

1. **A powered stereological series.** Choline-acetyltransferase- and vesicular-acetylcholine-transporter-immunostained design-based stereology of the

pedunculopontine and laterodorsal tegmental nuclei across Braak stages 0 to VI, with at least twenty Alzheimer cases and twenty controls, counting pars compacta and pars dissipata separately and reporting the boundary rule explicitly. This settles claims 8 and 17 and is the single highest-value study proposed here. It is feasible on existing brain bank material.

2. **The trophic phenotype.** TrkA, p75 and pro-nerve-growth-factor immunophenotyping of human Ch5–Ch6 against Ch4 in Alzheimer and control tissue, quantified rather than descriptive. This tests claim 12 directly and addresses refutation condition 2.

3. **The channel.** Vesicular acetylcholine transporter immunoreactivity and acetylcholinesterase histochemistry in thalamic relay nuclei and limbic nuclei separately, across Braak stages, in brains in which the mesopontine source nuclei are counted in the same material. This is the measurement the paper's central proposal has been waiting for, and it carries the discriminating prediction of Chapter 10: a source-side lesion should produce a deficit patterned by the pedunculopontine-versus-laterodorsal topography, and a target-side degeneration should not.

4. **Powered replication of the REM finding.** Tau positron emission tomography with an arousal-atlas-derived pedunculopontine region of interest, plus two-night polysomnography, in at least one hundred and twenty non-demented adults stratified by amyloid status, with partial-volume correction and an explicit assessment of off-target signal in the brainstem. A next-generation tau tracer with lower off-target binding would strengthen this considerably.

5. **In vivo connectivity.** Resting-state functional connectivity of the pedunculopontine nucleus at high field in Alzheimer's disease versus controls, examining the pedunculopontine–thalamic–cortical axis. This has been done for the locus coeruleus and ventral tegmental area in a large cohort — 169 patients and 37 controls — and the pedunculopontine nucleus was not included (Serra et al., 2018). The atlas resources to include it now exist (Edlow et al., 2023).

6. **The transcriptional basis of survival.** Single-nucleus RNA sequencing of pedunculopontine cholinergic neurons at early Braak stages, compared against locus coeruleus neurons from the same brains, testing in particular whether the cholesterol-homeostasis axis implicated in the locus coeruleus–substantia nigra contrast also separates the surviving cholinergic population from the dying noradrenergic one.

7. **The atonia circuit at cell-type resolution.** Characterisation of the sublaterodorsal glutamatergic population and the ventromedial medullary glycinergic and GABAergic populations in Alzheimer's disease, defined by projection target rather than by nucleus boundary. This addresses the tension recorded in claim 15 and is the experiment most likely to embarrass the account offered here, which is a reason to do it.

8. **The subnuclear question.** Separate quantification of pars compacta and pars dissipata in Alzheimer's disease, given the pars dissipata's greater vulnerability in Parkinson's disease and its majority share of the cholinergic population.

9. **Physiological gating.** Sleep-state-dependent thalamocortical gating measures — the P50 sensory-gating potential, prepulse inhibition — against pedunculopontine tau burden, as a functional assay of the thalamic gate in living patients.

Two of these are cheap and would move the argument decisively: the stereological series and the thalamic terminal marker study. Both can be done on tissue that already exists, in brain banks that already have the cases.

17. Conclusion — The Standing Relay

The cholinergic hypothesis of Alzheimer's disease was right about the cholinergic system and wrong about why. It identified a cholinergic nucleus that degenerates catastrophically, inferred that cholinergic neurons are what this disease destroys, and built four decades of pharmacology on the inference. The mesopontine tegmentum shows the inference to be false. Ch5 and Ch6 are cholinergic by every criterion applied to Ch4 — large, heteromorphic, isodendritic, acetylcholinesterase-rich, diffusely projecting, situated in the reticular core two millimetres from the nucleus this disease empties first — and they accumulate tau, and their neurons do not appreciably die. Woolf, Jacobs and Butcher drew the conclusion in 1989, in a sentence the field did not absorb: cholinergic phenotype alone is not a sufficient condition for vulnerability.

What the phenotype lacks, the anatomy supplies. Published in the same year and never read against it, Mesulam and colleagues' cytochemistry shows that the basal forebrain cholinergic neuron carries nerve growth factor receptor protein and the mesopontine cholinergic neuron does not. The Ch4 neuron's survival is contracted out to a cortical target that this disease dismantles, and when the target goes, the neuron follows. The Ch5 neuron never signed. On this account the disease does not kill cholinergic cells; it kills dependent cells, and the pedunculopontine nucleus is the specimen that separates the two categories that four decades of research have treated as one. That the same period's work on the aminergic brainstem now points to cholesterol handling rather than transmitter class as the discriminator of vulnerability suggests the lesson generalises: selective vulnerability is decided by features the classical taxonomy cannot see.

But a nucleus that keeps its neurons is not a nucleus that is working, and the second half of this paper has argued that the pedunculopontine failure in Alzheimer's disease is real and simply of a kind the field's instruments are not built to detect. Ch5 and Ch6 are the thalamus's only major cholinergic supply. Thalamic nicotinic receptor availability falls in mild cognitive impairment and Alzheimer's disease while the source neurons remain present, and the projection between them has never been measured — which is the single largest gap this paper found and the experiment it most wants done. In sleep, two independent literatures converge on one signature: tau in the nucleus tracks a REM period that comes late and runs short, and a REM period that comes late and runs short predicts dementia a decade in advance. That is the signature of a weakened generator rather than an absent one, which is what the pathology predicts and what a lost population would not produce.

We have tried to be as clear about the argument's limits as about its content. The preservation claim rests on two studies, one of them thirty-seven years old and one with three control brains, and

it cannot exclude a modest loss. The REM finding is a conference abstract with twenty-two participants. The trophic mechanism is an inference from two established facts and has not been tested. The gait phenotype, which the nucleus's reputation would happily annex, belongs on the evidence to cortical attention and executive function, and we have said so. And the account contains one finding it does not comfortably accommodate — the Alzheimer-specific depletion of medullary GABAergic neurons that should, on the face of it, disturb REM atonia in a disease that does not show it — which we have left in the ledger rather than smoothed away.

What survives all of that is a reframing worth the price of the qualifications. Alzheimer's disease has two cholinergic lesions, not one. The forebrain lesion is a lesion of attrition: cells fall silent, dedifferentiate, and die, and by the end three-quarters of them are gone. The mesopontine lesion is a lesion of withheld function: the cells are written on, they shrink, and they stay, and what fails is the traffic they carry to the thalamus. Only the first is visible to a count, and only the first is described by a model in which function is lost in proportion to cells. The second is invisible to volumetry, absent from the staging schemes, and — because its neurons are alive and can be driven — the more interesting of the two to a field that has spent forty years trying to prevent loss and might now ask what it could do with what has not been lost.

The nucleus is still standing. Nobody has checked whether it is still relaying.

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