The Price and the Permission

The ventral tegmental area in Alzheimer's disease — how the mesolimbic dopamine neuron fails, why the nucleus Parkinson's disease spares is the one this disease is said to take, and what the withdrawal of a permission signal costs the hippocampus, the appetite and the will

Dopamine · The mesolimbic projection · Parvalbumin interneurons · Memory persistence · Apathy · Hippocampal hyperexcitability

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Alzheimer's disease has a census, and the ventral tegmental area is missing from it. The nucleus has an experimental literature, an imaging literature, and no autopsy count. This paper asks what is actually known about how these neurons fail, and what their failure costs.

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Abstract

The ventral tegmental area is a small collection of dopaminergic, GABAergic and glutamatergic neurons in the floor of the midbrain, and it is the source of the brain's mesolimbic and mesocortical dopamine. Over the last decade a body of experimental work has placed it among the earliest casualties of Alzheimer's disease — earlier than plaques, earlier than measurable cortical tau, earlier than the hippocampal deficits it is said to cause. This paper asks two questions of that literature. How does the ventral tegmental neuron fail? And what does its failure cost?

On the first question the evidence supports a more interesting answer than simple attrition. In amyloid-bearing mice the nucleus loses dopaminergic neurons from three months of age, before deposits form, and the loss is confined to the mesolimbic subnuclei while the neighbouring substantia nigra is untouched. The dying cells show swollen mitochondria and nuclear translocation of apoptosis-inducing factor; the survivors raise their calcium-binding proteins and lower their free cytosolic calcium, so that the classical protective buffer appears here as a response to injury rather than a shield against it. In a second, tau-and-amyloid model the same neurons do not die at all by twelve months but fire too fast, through a casein-kinase-2-dependent failure of the small-conductance calcium-activated potassium channel, while their axon terminals thin. Failure is therefore better described as a sequence — physiological derangement, then loss of terminals, then loss of cell bodies — than as a single event, and the sequence explains why studies disagree about whether the nucleus dies.

The nucleus's vulnerability is also paradoxical, and the paradox is diagnostic. Every classical explanation of dopaminergic vulnerability — the enormous unmyelinated axonal arbor, the reliance on CaV1.3 pacemaking, the absence of calbindin, the neuromelanin burden — predicts that the substantia nigra should fail first. In Parkinson's disease it does. The claim that Alzheimer's disease inverts this ranking is either wrong or it means that the operative insult is not the one those explanations describe.

On the second question the paper assembles six consequences, each tied to a projection. The loss of hippocampal dopamine removes both the initiation of a dopamine-gated form of long-term potentiation within a 200-millisecond window and the twelve-hour permission that converts a decaying memory into a persistent one. The loss of D2-like drive on parvalbumin interneurons removes inhibition, thins perineuronal nets, lowers NaV1.1, and leaves CA1 *hyper*excitable with degraded gamma — so that withdrawing a modulator produces noise rather than silence, which is what the early Alzheimer hippocampus actually shows. The loss of accumbal dopamine degrades effort-based decision making and food reward, offering a mechanism for the two commonest and least explained non-cognitive features of the prodrome: apathy, which roughly doubles the risk of conversion, and weight loss, which begins a decade before diagnosis. The loss of dopaminergic arousal bears on sleep–wake regulation. And midbrain lesioning itself amplifies

microglial and astrocytic reactivity, plaque burden and tau phosphorylation in target tissue — so the nucleus's failure is not only a consequence of the disease but a driver of it.

The human evidence is thinner than the mechanistic story it is asked to support, and the paper says so precisely. There is no published unbiased stereological count of ventral tegmental dopaminergic neurons in Alzheimer's brains. The human case rests on midbrain volumetry and resting-state connectivity from a small number of groups, on a 1988 case series of six demented brains with pigmented-cell loss, and on the negative constraint that dopamine-transporter imaging is normal in Alzheimer's disease and abnormal in dementia with Lewy bodies — a constraint that does not refute mesolimbic loss but bounds it, because the scan reads the nigrostriatal terminal field and not the mesolimbic one. The pharmacology is consistent with the lesion and modest in size: levodopa, selegiline, a c-Abl inhibitor, phasic optogenetic stimulation and prefrontal transcranial stimulation all restore plasticity and behaviour in mice; in patients, a dopamine agonist spared frontal function and daily activities without touching memory, and methylphenidate improved apathy. The paper closes with a graded ledger separating what is established from what is inferred, nine experiments that would settle the open questions, and the results that would refute the account.

1. Introduction: The Nucleus That Was Not Counted

Alzheimer's disease has a census. For four decades the field has counted what it destroys — pyramidal neurons in the entorhinal cortex, cholinergic projection neurons in the nucleus basalis, noradrenergic neurons in the locus coeruleus, serotonergic neurons in the dorsal raphe, and the synapses that vanish before any of these cell bodies do. The count is uneven in quality but it exists, and it is the empirical spine on which claims about the disease's anatomy rest.

The ventral tegmental area is missing from it.

This is not because the nucleus is unimportant. It is the origin of the mesolimbic and mesocortical dopamine systems: the source of the signal that determines which experiences are worth storing, how much effort a goal is worth, and whether the organism gets out of bed. Nor is it because nobody has looked. Between 2017 and 2025 a substantial experimental literature has appeared placing ventral tegmental degeneration among the earliest events in transgenic models of the disease — earlier than amyloid deposition, earlier than the hippocampal dysfunction it is said to cause — and a parallel human imaging literature has reported that midbrain volume and midbrain connectivity are reduced in mild cognitive impairment and predict conversion to dementia.

It is missing because the specific measurement that would put it in the census has not been made. There is, at the time of writing, no published unbiased stereological estimate of dopaminergic neuron number in the human ventral tegmental area in Alzheimer's disease compared with age-matched controls. The nucleus has an experimental literature and an imaging literature and no autopsy count. Every review of the subject, including those written by the investigators who built the experimental case, cites mouse stereology and human volumetry and then falls silent at exactly the point where the human number should be.

That gap is the reason this paper is organised the way it is. It would be easy — and it has been done — to write an account of the ventral tegmental area in Alzheimer's disease that runs from a mouse to a mechanism to a clinical syndrome without pausing. The mouse data are good, the mechanism is specific, and the clinical syndrome is real. But the chain has a weak link in the middle of it, and a paper that does not mark the link is not describing the evidence, it is advertising a hypothesis.

So this paper does three things in sequence. It asks what is actually known about how these neurons fail, distinguishing carefully between the several distinct failure modes the literature reports

and treating the disagreement between them as informative rather than embarrassing. It asks why a nucleus that every classical theory of dopaminergic vulnerability predicts should be *protected* would be the one this disease takes — a paradox that has been noticed but rarely pressed, and which turns out to constrain the mechanism sharply. And it asks what the failure costs, projection by projection, because a nucleus that broadcasts one transmitter to a dozen targets fails in a dozen ways at once, and the phenomenology of early Alzheimer's disease contains several features — apathy, weight loss, hippocampal hyperexcitability — that the field's dominant framework explains poorly and this one explains well.

The title names the two functions at stake. Dopamine sets the **price** an organism will pay for a goal: it is the currency of effort-based decision making, and its withdrawal is the best-characterised neurochemistry of amotivation. And dopamine grants the **permission** for a memory to persist: it does not carry the content of an experience but it decides, within a narrow window and again some hours later, whether the trace will be kept. A nucleus that supplies both is a nucleus whose silence should produce a person who remembers less and wants less. That is a recognisable description of the Alzheimer prodrome, and the burden of this paper is to say how much of it the evidence will actually bear.

2. The Nucleus: What It Is Made Of and Where It Goes

The anatomy

The ventral tegmental area occupies the floor of the midbrain, medial to the substantia nigra pars compacta and dorsal to the interpeduncular nucleus. In the classical catecholaminergic nomenclature it is cell group A10, distinguished from A9 (the substantia nigra pars compacta) laterally and A8 (the retrorubral field) caudally. Its principal subdivisions — the paranigral nucleus, the parabrachial pigmented nucleus, the interfascicular nucleus and the rostral linear nucleus — are not merely topographic conveniences: they differ in transmitter composition, in projection target, and, as the following sections will show, in vulnerability.

The boundary between A10 and A9 is a genuine source of quantitative confusion. The two cell groups are continuous, the criteria for dividing them have varied across laboratories and species, and published estimates of the human ventral tegmental dopaminergic population differ several-fold as a result. Reviews working specifically on Alzheimer's disease have cited a figure near sixty thousand dopaminergic neurons for the human nucleus. Unbiased stereology in the young male macaque, by contrast, yields roughly 110,000 tyrosine-hydroxylase-positive neurons per hemisphere for the whole A10 field, against roughly 87,000 for A9 and 12,500 for A8, with human counts generally reported at about twice the macaque figures. Nothing in this paper turns on resolving that discrepancy, but it is worth stating plainly at the outset: the nucleus whose loss is under discussion does not have an agreed size in our own species, which is a further symptom of the missing census.

The cell types

It is a mistake, though a common one, to treat the ventral tegmental area as a bag of dopamine neurons. Roughly three quarters of its neurons are dopaminergic and roughly a quarter are GABAergic; a smaller glutamatergic population exists, and a substantial fraction of cells co-release more than one transmitter — dopamine with GABA, or dopamine with glutamate — in a target-specific way. In the macaque the ratio of tyrosine-hydroxylase-positive to GAD67-positive neurons across the whole midbrain dopaminergic complex is about three to one, though it approaches unity in the retrorubral field.

This heterogeneity matters for a degeneration argument in two ways. First, a measurement of "neurons in the ventral tegmental area" is not a measurement of dopaminergic capacity, and a measurement of tyrosine hydroxylase is not a measurement of neurons — a point that becomes

decisive when studies disagree about whether cells die. Second, the local GABAergic population is the substrate of the nucleus's own inhibitory control; a disease process that removed dopaminergic neurons and spared GABAergic ones would not merely reduce output, it would change the pattern of what remains.

The projections

The functional geography of the nucleus is defined by where its axons go, and the targets are the ones this paper's second half is organised around.

To the nucleus accumbens — the mesolimbic projection proper, arising largely from the paranigral and parabrachial pigmented subnuclei, terminating in the shell and core. This is the pathway of reward, incentive salience and effort-based decision making.

To the prefrontal cortex — the mesocortical projection, sparser but functionally weighty, supplying the dopaminergic tone on which working memory and executive control depend.

To the hippocampus — the mesohippocampal projection, the most contested of the three. Its existence is not in doubt; its density and its functional monopoly are. Optogenetic work in mice describes sparse tyrosine-hydroxylase-positive fibres in CA1 arising from dopamine-transporter-expressing midbrain neurons, and there is evidence for a denser innervation of the CA1 pyramidal layer from a cluster in the lateral ventral tegmental area. Against this, the locus coeruleus projects more profusely to the hippocampus than the ventral tegmental area does, and co-releases dopamine there. Section 8 takes this dispute seriously, because a large part of the ventral tegmental area's claimed importance in Alzheimer's disease is mnemonic, and if the hippocampus gets most of its dopamine from somewhere else then that claim needs restating.

To the amygdala, septum, bed nucleus and hypothalamus — the projections that carry the nucleus's contribution to affect, arousal and autonomic state.

Table 1 — The ventral tegmental area in numbers and in outline.

Property	Value or description	Source class
Cell group	A10 (paranigral, parabrachial pigmented, interfascicular, rostral linear)	Classical anatomy
Dopaminergic neurons, macaque A10	~110,300 ± 9,600 per hemisphere (TH+)	Unbiased stereology
GABAergic neurons, macaque A10	~33,700 ± 1,900 per hemisphere (GAD67+)	Unbiased stereology
Human dopaminergic population	Disputed; estimates from ~60,000 to several hundred thousand depending on boundary criteria	Review and stereology
Transmitter phenotypes	Dopamine, GABA, glutamate; extensive co-release	Circuit dissection
Principal outputs	Nucleus accumbens (shell, core); prefrontal cortex; hippocampus; amygdala; septum	Tract tracing
Firing modes	Tonic (pacemaker, ~1–5 Hz) and phasic burst	In vivo and slice recording
Functions attributed	Reward prediction, incentive salience, effort valuation, novelty coding, memory persistence, arousal	Behavioural neuroscience

Two firing modes, and why the distinction is not decorative

Dopaminergic neurons of the ventral tegmental area fire in two regimes: a slow, regular, autonomously generated tonic pacemaker rhythm, and brief high-frequency bursts driven by afferent input. The tonic mode sets ambient extracellular dopamine; the phasic mode delivers the transient, temporally precise signal that carries information about novelty, reward prediction error and salience.

The distinction matters here for a reason that only becomes visible in section 14. When these neurons are stimulated optogenetically in an Alzheimer model, *phasic* stimulation restores hippocampal plasticity and prolonged stimulation does not. A therapy that raises tonic dopamine is therefore not the same intervention as one that restores burst structure, and the difference predicts which clinical deficits a dopaminergic drug should and should not fix. That prediction is, as it happens, borne out in the two randomised trials the field has.

3. The Paradox of the Spared Nucleus

Before examining the evidence that the ventral tegmental area degenerates in Alzheimer's disease, it is worth stating precisely how surprising that claim ought to be.

What makes a dopamine neuron vulnerable

Parkinson's disease has given neuroscience its most complete account of why one dopaminergic population dies and another does not, and every element of that account ranks the substantia nigra above the ventral tegmental area.

Axonal arbor. Midbrain dopaminergic neurons maintain axonal arbors of extraordinary size, largely unmyelinated, with vast numbers of release sites. Computational modelling of action-potential propagation in these arbors shows that energy cost rises exponentially with the number of branch levels and as a power law of arbor size, and that the striatal arbor of a nigral dopaminergic neuron is at least an order of magnitude larger and more complex than that of less susceptible dopaminergic neurons. On this argument the nigral cell lives permanently at the edge of its energy budget and the ventral tegmental cell does not.

Pacemaking calcium load. Nigral dopaminergic neurons rely heavily on CaV1.3 L-type calcium channels for their autonomous pacemaking, admitting a continuous calcium load that must be pumped back out at metabolic cost. Ventral tegmental neurons lean more on sodium and HCN conductances for the same job, and so pace with less calcium entry.

Calcium buffering. The vulnerable ventral-tier nigral neurons largely lack calbindin-D28k; ventral tegmental neurons express it at high levels. The correlation between calbindin expression and survival in Parkinson's disease is one of the older and more robust observations in the field.

Neuromelanin. Nigral neurons carry the heavier pigment load, with the associated iron chemistry and oxidative liability.

Put together, these give a clean prediction: whatever generic insult is applied to the midbrain, A9 should fail before A10. In Parkinson's disease it does, conspicuously, and in Alzheimer's disease the substantia nigra is only mildly affected — sufficiently so that heavy nigral depletion in a demented brain is read as evidence of Lewy body co-pathology rather than of Alzheimer's disease itself.

The inversion

The experimental claim under examination is the exact opposite. In the Tg2576 mouse, dopaminergic neurons of the ventral tegmental area are lost from three months of age while the neighbouring substantia nigra pars compacta remains intact. The nucleus that Parkinson's disease spares is the nucleus that this model takes, and the nucleus Parkinson's disease destroys is the one this model leaves alone.

Table 2 — Predictors of dopaminergic vulnerability, and what they predict.

Feature	Substantia nigra pars compacta	Ventral tegmental area	Ranking implied
Axonal arbor size and branch complexity	Largest in the brain; order of magnitude above less susceptible dopamine cells	Substantially smaller	SNc first
Pacemaking calcium source	CaV1.3 L-type prominent	More NaV/HCN dependent	SNc first
Calbindin-D28k	Largely absent in vulnerable ventral tier	Highly expressed in many cells	SNc first
Neuromelanin burden	Higher	Lower	SNc first
Observed vulnerability in Parkinson's disease	Severe	Relatively spared	Consistent
Claimed vulnerability in Alzheimer's models	Spared	Severe	**Inverted**

What the inversion means

There are only three ways to read Table 2, and each is a substantive commitment.

The first is that the claim is an artefact — of the model, of the counting, or of the boundary between A9 and A10. This possibility cannot be dismissed and section 7 gives it the weight it deserves.

The second is that the insult in Alzheimer's disease is not a generic metabolic stressor at all. The classical predictors rank neurons by how hard it is to keep them alive under an unspecified burden. If the actual insult is specific — a particular protein expressed in a particular cell, a particular kinase, a particular afferent — then the ranking it produces need not follow the metabolic one. In Tg2576 the transgene is human amyloid precursor protein, expressed under a prion promoter, and the degeneration precedes plaque deposition; whatever is killing these cells is acting intracellularly or

as a soluble species, in a cell-autonomous or near-cell-autonomous way, and there is no reason such an insult should respect the nigral ranking.

The third is that the protective features are not protective in the way assumed. This turns out to be the most interesting reading, because it is the one the data support. When calcium-binding proteins were examined in the Tg2576 ventral tegmental area, the neurons expressing calbindin-D28k and calretinin were themselves lost in an age-dependent way — and the neurons that survived had *raised* their calcium-binding protein levels and *lowered* their free cytosolic calcium. The buffer is not standing between these cells and the disease. The buffer is going up because the cells are in trouble. A shield that appears only after the blow has landed is a symptom, and reading it as a defence inverts the causal arrow.

That reframing dissolves the paradox without weakening it: calbindin correlates with survival in Parkinson's disease not because it neutralises the Alzheimer insult but because the Parkinson insult is a calcium insult and this one is not. The inversion in Table 2 is therefore not an anomaly to be explained away. It is the single strongest piece of evidence that the mechanism operating on the ventral tegmental area in Alzheimer's disease is not the mechanism operating on the substantia nigra in Parkinson's disease — and any account that treats "dopaminergic vulnerability" as one phenomenon will get this wrong.

4. What Degenerates, and When: The Animal Evidence

The founding observation

The modern case begins with a 2017 report in Tg2576 mice, which carry the Swedish mutation of human amyloid precursor protein. Tyrosine-hydroxylase-positive neurons in the ventral tegmental area were reduced from three months of age — a stage at which the model has no amyloid plaques. The neighbouring substantia nigra pars compacta was intact by the same measurement in the same animals. Microdialysis showed reduced basal dopamine outflow in both the hippocampus and the nucleus accumbens shell. The progression of dopaminergic cell loss tracked, in the same cohorts, with impairments in CA1 synaptic plasticity, with memory performance, and with the processing of food reward. Sub-chronic treatment with levodopa or with the monoamine-oxidase-B inhibitor selegiline rescued the synaptic and behavioural deficits.

Four features of that result deserve emphasis, because the subsequent literature turns on them.

It is **early** — before plaques, and before the target-region pathology it is proposed to cause. It is **selective** — within the midbrain, and thereby resistant to the objection that the transgene is simply toxic to catecholaminergic cells. It is **correlated with function**, not merely with time. And it is **pharmacologically reversible** at the level of behaviour, which means that at the age tested the deficit is a deficit of transmission rather than an irrecoverable loss of tissue.

Which cells, and which projection

A 2022 study localised the loss. Degeneration in Tg2576 fell on mesolimbic dopaminergic neurons of the paranigral and parabrachial pigmented subnuclei — the population projecting to the nucleus accumbens medial shell and core. Neuron numbers were strongly reduced at three months and more strongly at six. Electron microscopy of the vulnerable population at three months showed accumulation of swollen and vacuolated mitochondria, with a significantly raised ratio of damaged to normal organelles, and apoptosis-inducing factor was found translocating from mitochondria to the nucleus — a caspase-independent death pathway. The calcium-binding protein result described in section 3 came from the same work.

The localisation is important and slightly awkward. The projection identified as vulnerable is the accumbal one; the 2017 study reported reduced dopamine outflow in hippocampus as well. These are reconcilable — a general reduction in nucleus output will reduce hippocampal dopamine

whether or not the hippocampus-projecting cells are the ones dying, and dying-back of terminals can precede somatic loss in a population whose cell bodies are still being counted as present — but they are not the same claim, and the field has tended to blur them. The honest statement is that the somatic degeneration is best documented for the accumbens-projecting population, and that the hippocampal dopamine deficit is documented as an outflow measurement whose cellular origin has not been separately established.

The consequences within the circuit

A 2018 study followed the deficit forward through the circuit rather than backward to the cell. In Tg2576, reduced dopaminergic innervation of the hippocampus produced reduced synaptic plasticity and reduced excitability of dorsal subiculum pyramidal neurons, and the glutamatergic transmission from hippocampus to nucleus accumbens core was itself impaired. Both chemogenetic activation of subicular neurons and levodopa administration restored the impaired transmission. The loop, in other words, does not merely lose its modulator; the loss of the modulator degrades the excitatory transmission running through it.

Replication, and its limits

Reduced tyrosine-hydroxylase-positive cell counts in the ventral tegmental area, or reduced midbrain dopaminergic output, have now been reported in 3×Tg-AD, APPswe/PS1dE9 and 5xFAD models, and goal-directed behaviour is impaired early in the TgF344-AD rat. That breadth is worth something: it means the finding is not an idiosyncrasy of one transgene.

It is worth less than it appears, for two reasons that must be stated. First, a large share of the primary work — the founding observation, the subcellular localisation, the circuit consequences, the pharmacological rescues and the neuroinflammatory extension — comes from a single research programme. That is not a criticism of the work, which is careful and internally consistent; it is a statement about the independence of the evidence, and independence is what converts a body of results into a fact. Second, the effect has not been detected in all strains, and there is a live alternative reading in which changes in terminal neurotransmitter levels reflect local axonal degeneration rather than the death of cell bodies. That alternative is not a footnote. It is a different disease mechanism, and section 5 is about what happens when it is tested directly.

Table 3 — Reported midbrain dopaminergic findings across Alzheimer models.

Model	Principal finding	Earliest age reported	Nigra	Notes
Tg2576 (APPswe)	Loss of TH+ VTA neurons; reduced DA outflow to hippocampus and NAc shell	3 months	Spared	Pre-plaque; correlates with CA1 plasticity, memory, food reward
Tg2576	Loss localised to paranigral and parabrachial pigmented subnuclei, NAc-projecting; damaged mitochondria; AIF nuclear translocation	3 months	Spared	Survivors upregulate Ca^{2+}-binding proteins, lower cytosolic Ca^{2+}
Tg2576	Reduced subicular plasticity and excitability; impaired hippocampus→NAc core transmission	6 months	—	Restored by levodopa and by chemogenetic subicular activation
Tg2576	Reduced dopaminergic contacts on parvalbumin interneurons; CA1 hyperexcitability; gamma loss	3 and 7 months	—	Rescued by levodopa and D2-like agonists
3×Tg-AD	VTA dopamine neurons hyperexcitable; **no** loss of TH+ cell number at 12 months; reduced TH and DAT staining in ventral striatum	12 months (peak)	—	CK2-dependent SK channel dysfunction; inverted-U time course
APPswe/PS1dE9, 5xFAD	Reduced TH+ midbrain neurons / reduced dopaminergic input reported	Early	Variably reported	Not detected in all strains
TgF344-AD rat	Impaired goal-directed behaviour early	Early	—	Behavioural rather than anatomical evidence

5. Failure Without Death: The Second Mode

A study that found the opposite

In 2024 an independent laboratory recorded from ventral tegmental dopaminergic neurons in the 3×Tg-AD mouse, which carries amyloid precursor protein, presenilin-1 and tau mutations. It found the neurons **hyperexcitable**. Spontaneous firing frequency rose with age along an inverted-U curve, peaking at twelve months. At that peak there was no decline in the total number of tyrosine-hydroxylase-positive cells — but tyrosine hydroxylase staining within the nucleus was reduced, and tyrosine hydroxylase and dopamine transporter staining in the ventral striatum were reduced, consistent with loss of neurites rather than loss of neurons.

The mechanism was specific. Casein kinase 2 became hyperactive and phosphorylated the calmodulin bound to small-conductance calcium-activated potassium (SK) channels, lowering calmodulin's calcium-binding affinity. Because SK-channel activation depends on calmodulin sensing calcium, the channel's afterhyperpolarising brake failed and the neuron fired faster and less regularly. Pharmacological inhibition of casein kinase 2 restored both basal firing rate and firing regularity.

Why the disagreement is the finding

At first sight this contradicts section 4. One model loses these neurons early; another keeps them and merely deranges their physiology late. It is tempting to adjudicate — to decide that one model is the right one. That would be a mistake, because the two results are describing different points on one trajectory, and the trajectory is the more informative object.

Consider what "failure" can mean for a projection neuron with a vast, thinly myelinated arbor and a modulatory job. It can mean:

1. **Physiological derangement** — the cell is present, its terminals are present, but the code it emits is wrong. Firing rate rises or falls; burst structure degrades; the phasic signal that carries information is corrupted while the tonic signal that sets ambient tone persists or even increases.
2. **Terminal and axonal loss** — the cell body survives and is counted, but its arbor retracts. Transmitter delivery to target falls in proportion to lost release sites, not lost somata. Any

measurement made at the terminal (transporter density, tyrosine hydroxylase fibre density, microdialysis) records a large deficit; any measurement made at the soma records none.

3. **Somatic death** — the cell is gone and stereology finds it gone.

These are ordered. Terminal loss without somatic loss is the classic dying-back pattern of long-projection neurons, and it is precisely what the 3×Tg result shows: preserved cell number, thinned terminals, deranged firing. The Tg2576 result shows the next stage. Both models can be right about their own animals and the disagreement then carries a substantive message: **the ventral tegmental neuron's failure begins in its code and its terminals, and the cell body is the last thing to go.**

That message has three consequences that run through the rest of this paper.

It explains why hyperexcitability and loss are both reported without either being wrong. A neuron whose SK brake has failed fires faster; a population thinning at its terminals delivers less transmitter to target despite firing more. Output and activity can move in opposite directions, and a study measuring one will contradict a study measuring the other.

It predicts that human post-mortem stereology, when it is finally done, may find *less* cell loss than the functional literature implies — and that a negative stereological result would therefore not refute the account. This is an uncomfortable but necessary implication: the hypothesis as stated is harder to falsify by cell counting than it first appears, which is exactly why section 16 specifies falsifiers at the level of terminals and transmission rather than somata.

And it identifies the therapeutic window. A cell that is present but miscoding is a cell that can be corrected. Section 14 shows that the interventions which work in these models — phasic optogenetic stimulation, casein kinase 2 inhibition, levodopa, D2-like agonists — are all interventions on transmission rather than on survival, and that they work at ages when transmission is deranged.

6. Why the Neuron Fails: Candidate Mechanisms

No single mechanism accounts for the observations above, and the literature does not claim one. What follows separates the candidates by the class of evidence supporting each, and grades them, because they are not equally well founded and the differences matter for what should be tested next.

6.1 Intracellular amyloid precursor protein and soluble amyloid species

In Tg2576 the degeneration precedes plaque deposition, which excludes extracellular fibrillar amyloid as the proximate cause and points toward the transgene product acting within or immediately around the cell. Transcranial stimulation work in the same model found intracellular amyloid unchanged in younger animals while plaque burden fell in older ones, which suggests the intracellular pool is not simply tracking the extracellular one. What is missing is a demonstration that ventral tegmental dopaminergic neurons are unusually sensitive to a defined soluble species relative to nigral neurons under matched exposure — the experiment that would convert this from a correlation with model genotype into a mechanism. **Grade: supported in model, mechanism unresolved.**

6.2 c-Abl activation and autophagic failure

Chronic treatment of Tg2576 mice with nilotinib, a c-Abl kinase inhibitor, reduced c-Abl phosphorylation, improved autophagy, reduced amyloid-β levels, and prevented both the degeneration and the functional and morphological alterations of ventral tegmental dopaminergic neurons, while preventing the fall in hippocampal dopamine outflow and improving hippocampus-dependent cognition. A parallel line of work framed the same result as autophagy-targeting.

This is the strongest *causal* mechanistic evidence in the set, because it is an intervention rather than an observation, and because the intervention was applied upstream of the cell death and prevented it. Its limitation is that c-Abl inhibition is not a selective probe: nilotinib alters amyloid handling as well as dopaminergic survival, so the rescue of the neurons and the rescue of cognition could in principle run through separate arms. **Grade: causal in model; specificity unresolved.**

6.3 Mitochondrial injury and caspase-independent death

Vulnerable Tg2576 ventral tegmental neurons at three months accumulate swollen and vacuolated mitochondria, and apoptosis-inducing factor translocates from mitochondria to the nucleus. This describes a specific death route — caspase-independent, AIF-mediated — rather than generic apoptosis, and it dates the organelle injury to the onset of loss rather than its aftermath. What it does not do is explain why these mitochondria and not nigral ones. **Grade: well described; upstream cause unidentified.**

6.4 Calcium handling — as response, not shield

Section 3 set this out: calbindin-D28k- and calretinin-expressing neurons are lost with age in the model, while surviving neurons upregulate calcium-binding proteins and show significantly reduced free cytosolic calcium. The natural reading is homeostatic compensation — cells increasing buffering capacity in an attempt to survive.

This is worth dwelling on because it inverts a standard inference. In the Parkinson's literature calbindin marks the survivors and is read as protective. Here it rises *in* the survivors, in a population that was calbindin-rich to begin with, and the marker of protection has become a marker of stress. The corollary is that calcium-buffer expression cannot be used as a vulnerability index across diseases, and that a therapeutic strategy of raising buffering capacity would be reinforcing a compensation that is already maximal rather than supplying one that is missing. **Grade: well described; interpretation as compensation is inference.**

6.5 Channel and kinase dysfunction: the CK2–calmodulin–SK axis

The 3×Tg finding described in section 5 supplies the best-specified molecular lesion in the whole set: hyperactive casein kinase 2 phosphorylates SK-bound calmodulin, calcium affinity falls, the afterhyperpolarisation weakens, and firing becomes fast and irregular; inhibiting the kinase restores both. It is specific, it is reversible, and it is an account of *dysfunction* rather than death, which makes it the natural mechanism for the earliest phase of the trajectory in section 5. Its limitation is that it has been shown in one model, and that the link from a firing abnormality to terminal loss has not been demonstrated. **Grade: well specified; single model; downstream link untested.**

6.6 Catecholaldehyde autotoxicity — an inference, flagged as such

Catecholaminergic neurons carry a chemical liability that non-catecholaminergic neurons do not. Cytoplasmic dopamine that escapes vesicular storage is oxidatively deaminated by monoamine oxidase to 3,4-dihydroxyphenylacetaldehyde (DOPAL), a highly reactive aldehyde normally detoxified by aldehyde dehydrogenase. Manipulations that impair that detoxification and allow DOPAL to accumulate promote catecholaminergic neurodegeneration; DOPAL forms quinone adducts with many proteins and drives α-synuclein oligomerisation, generating self-reinforcing cycles in which vesicular and mitochondrial dysfunction shift more dopamine into the cytoplasm and thence into more aldehyde.

The catecholaldehyde hypothesis is well developed for Parkinson's disease. Its application to the ventral tegmental area in Alzheimer's disease is, at present, an argument from shared chemistry: these are dopamine neurons, they run the same metabolic route, and any lesion that destabilises vesicular storage or mitochondrial function should raise their aldehyde burden. That is a reasonable prediction and it is testable — DOPAL and its adducts can be measured — but it has not been tested in this context, and it should not be presented as part of the evidence. It is stated here because it is the most obvious untested mechanism in the field, and because section 16 turns it into an experiment. **Grade: inference from adjacent literature; untested here.**

6.7 Neuroinflammation as amplifier

Lesioning the midbrain monoaminergic nuclei — dopaminergic ventral tegmental area and substantia nigra pars compacta, serotonergic interpeduncular nucleus — in otherwise normal mice produced pronounced microglial activation through the NLRP3 inflammasome pathway, reversible with dopaminergic or serotonergic drugs. Superimposed on amyloid pathology, the same lesions markedly amplified the phenotype: heightened microglial reactivity, a robust astrocyte response, earlier plaque burden, and induction of pathological tau hyperphosphorylation. Levodopa or fluoxetine significantly attenuated both the astrocyte reactivity and the tau hyperphosphorylation.

This is not a mechanism of the nucleus's own failure. It is the mechanism by which the nucleus's failure becomes a driver of the wider disease, and section 13 treats it in that role. It belongs in this list only to mark the loop: monoamine loss provokes glial reactivity, and glial reactivity is not kind to the cells that remain.

6.8 Dying back from the target

The pattern in section 5 — preserved somata, thinned terminals, reduced striatal transporter and tyrosine hydroxylase staining — is the signature of axon-first degeneration. For a neuron sustaining an arbor of this size, the axon is the expensive, exposed and repair-limited compartment, and its loss is both the earliest structural failure and the one that determines transmitter delivery. This is less a distinct mechanism than a statement about *where* any of the mechanisms above will express themselves first, and it is the reason that terminal-level measurements should be preferred to somatic ones when testing this account in humans. **Grade: strong inference from the model data; direct longitudinal demonstration lacking.**

7. The Human Evidence and Its Limits

This is the section on which the paper's credibility rests, and it is the shortest on positive findings.

7.1 What post-mortem work exists

In 1988 a series of six demented brains was reported under the heading of mesolimbic pathology. The clinical syndrome was parkinsonism, progressive dementia and behavioural disturbance, generally depression. The histopathology uniformly included loss of pigmented neurons in the ventral tegmental area, with additional loss in the adjacent substantia nigra and locus coeruleus, and neurofibrillary tangles and cell loss in entorhinal cortex and the hippocampal pyramidal layer. The authors noted that tangles appeared in the perforant path in the absence of senile plaques and raised the possibility that this was linked to reduced dopaminergic input from the damaged ventral tegmental area.

That series is nearly four decades old, it is six cases, it is not stereological, its cases are clinically heterogeneous by modern criteria, and its co-involvement of the substantia nigra and locus coeruleus means it does not isolate the ventral tegmental area. It is nonetheless the closest thing the field has to a human neuropathological observation of this nucleus in dementia, and the fact that it remains so is the point.

Brainstem tau pathology in Alzheimer's disease has since been characterised across Braak stages in midbrain and pontine sections, with neurofibrillary tangles and neuropil threads whose three-repeat tau content rises as in the hippocampus. But the systematic staging work that established the early involvement of the locus coeruleus and dorsal raphe — the work that lets one say what fraction of neurons in a nucleus bear pretangle inclusions at a given Braak stage — has no published equivalent for the ventral tegmental area.

There is no published unbiased stereological count of dopaminergic neurons in the human ventral tegmental area in Alzheimer's disease against age-matched controls. Everything else in this section is imaging.

7.2 Structural imaging

Ventral tegmental volume measured on structural magnetic resonance imaging has been related to the clinical markers of Alzheimer's disease in a cohort of 51 healthy adults, 30 patients with mild cognitive impairment and 29 with Alzheimer dementia, with ventral tegmental volume associated with hippocampal volume and with memory performance.

An independent and more recent study, in 160 participants (79 healthy controls, 54 with subjective cognitive decline, 17 with mild cognitive impairment, 10 with Alzheimer dementia), measured substantia nigra volume and neuromelanin-sensitive contrast. Substantia nigra volume was 23% lower in Alzheimer dementia than in healthy controls ($p = 0.016$, Hedges' $g = 1.4$) and 28% lower than in subjective cognitive decline ($p = 0.004$); contrast showed no group difference. Higher substantia nigra volume predicted better recognition memory ($R^2 = 0.071$, $p = 0.004$) and better global cognition ($R^2 = 0.096$, $p < 0.001$), with associations across five cognitive domains.

That second study is genuinely independent corroboration that the midbrain dopaminergic complex is structurally smaller in Alzheimer's disease and that its size tracks cognition. It is also, by the authors' own statement, unable to separate the ventral tegmental area from the substantia nigra — they name this as a limitation. So it supports "the midbrain dopaminergic region is affected and it matters for cognition" and does not support "the ventral tegmental area specifically is affected and the substantia nigra is not," which is the claim the animal work makes. The two human structural results point in the same direction as the animal work at low anatomical resolution and are silent at the resolution where the interesting claim lives.

7.3 Functional connectivity, and the prospective result

Resting-state functional connectivity offers the only prospective human evidence. In a cohort of 35 patients with mild cognitive impairment due to Alzheimer's disease followed for 24 months, of whom 16 converted to dementia, ventral tegmental connectivity measured at baseline contributed to correctly classifying the converters. Related work describes a pattern of disconnection between the ventral tegmental area and the thalamus, medial temporal regions and parietal lobe from the mild cognitive impairment stage, progressing across disease severity, and reports that behavioural symptoms — aggression, irritability, sleep and eating disturbance — are associated with the degree of that disconnection.

A prospective design with a hard endpoint is worth more than a cross-sectional correlation, and this is the strongest human result the field has. It should be read with its size in view: 35 patients, 16 events, one centre, one analytic pipeline, and a measure — seed-based resting-state connectivity of a small deep nucleus — with known susceptibility to physiological noise and registration error at conventional field strengths.

7.4 The negative constraint that must be answered

Dopamine-transporter imaging is normal in Alzheimer's disease. This is not an incidental observation; it is the basis of an established clinical differential. In dementia with Lewy bodies there is 40–70% loss of striatal dopamine with corresponding loss of the transporter, and reduced tracer uptake is a diagnostic indicator; a normal scan supports a diagnosis of a condition without nigrostriatal degeneration, such as Alzheimer's disease. A minority of Alzheimer patients show minimal alteration of presynaptic dopaminergic transport, always significantly higher than in Lewy body dementia.

Any claim that the dopaminergic system degenerates early in Alzheimer's disease has to be compatible with that fact, and this one is — but only in a specific way that constrains it usefully. Dopamine-transporter single-photon imaging measures the **nigrostriatal** terminal field in the dorsal striatum. The claimed lesion is **mesolimbic** and **mesocortical**: cell bodies in the paranigral and parabrachial pigmented subnuclei, terminals in the accumbens shell and core, prefrontal cortex and hippocampus. A normal dorsal-striatal scan is exactly what the animal model predicts, since the model spares the substantia nigra.

So the normal scan does not refute the hypothesis. But it does two things. It bounds the magnitude: whatever is happening cannot be extending appreciably into the nigrostriatal system, or the clinical differential would fail. And it supplies a sharp, cheap test — quantitative ventral-striatal-to-dorsal-striatal transporter ratios in Alzheimer's disease, which the hypothesis predicts should be reduced even where the dorsal measurement is normal. To the author's knowledge this ratio has not been reported as a test of this hypothesis, and it should be.

7.5 The state of the human case, stated plainly

Table 4 — Human evidence on the midbrain dopaminergic system in Alzheimer's disease.

Modality	Cohort	Finding	What it does not establish
Post-mortem histopathology (1988)	6 demented brains	Uniform loss of pigmented VTA neurons; entorhinal and hippocampal tangles; perforant-path tangles without plaques	Not stereological; nigra and locus coeruleus also involved; clinically heterogeneous
Structural MRI	51 control / 30 MCI / 29 AD	VTA volume associated with hippocampal volume and memory	Cross-sectional; volume is not neuron number
Structural MRI, neuromelanin contrast	79 HC / 54 SCD / 17 MCI / 10 ADD	SN volume 23% lower in ADD vs HC (g = 1.4); volume predicts recognition memory and global cognition; contrast unchanged	VTA not separated from SN — stated by the authors as a limitation
Resting-state fMRI, prospective	35 MCI, 16 converters over 24 months	Baseline VTA disconnection contributes to classifying converters	Single centre; small; connectivity of a small deep nucleus is noise-prone
Resting-state fMRI, cross-sectional	AD cohorts across stages	Progressive VTA disconnection; association with apathy, irritability, sleep and eating disturbance	Association, not direction
DAT-SPECT	Clinical populations	**Normal in AD**, reduced in DLB	Measures nigrostriatal terminals only; ventral-striatal ratio untested
Unbiased stereology of human VTA in AD	—	**Does not exist**	—

The honest summary is this. The human midbrain dopaminergic complex is smaller in Alzheimer's disease, and its size and connectivity track cognition and predict conversion. Whether the ventral tegmental area is affected disproportionately to the substantia nigra in humans, and whether the change is neuronal loss rather than neuropil or terminal loss, are both open. The mechanistic literature is a mouse literature with a specific, well-supported story; the human literature is a volumetric and connectivity literature that is consistent with it and cannot yet confirm it at the resolution that matters.

8. Effect I: The Permission to Consolidate

Everything from here forward assumes the lesion and asks what it costs. This section takes the mnemonic cost, which is the most-claimed and the most contested.

8.1 Two jobs, at two timescales

Dopamine does two separable things for a hippocampal memory.

It permits persistence. In rats, a long-lasting fear memory vanished when a D1 antagonist was injected into dorsal hippocampus **12 hours** after training — not immediately, and not at 9 hours. Conversely, a D1 agonist at that same critical post-training time converted a rapidly decaying memory into a persistent one. The effect was mediated by brain-derived neurotrophic factor and regulated by the ventral tegmental area. This is a late, slow, permissive function: the trace exists, and dopamine at a specific delayed moment determines whether it is kept.

It initiates plasticity. More recently, optogenetic stimulation of midbrain dopamine terminals in dorsal CA1 delivered simultaneously with Schaffer collateral stimulation and for the next **200 milliseconds** triggered long-term potentiation at glutamatergic synapses; earlier or later dopamine release produced no potentiation. The effect required D1/D5 receptors and was abolished by SCH23390. Stimulating the pathway facilitated contextual learning in awake behaving mice; inhibiting it impaired learning. This challenges the older view that dopamine only maintains potentiation already induced: within a narrow window it can act as a teaching signal that triggers plasticity.

These findings frame the older synaptic-tagging-and-capture account, in which a weakly stimulated synapse sets a tag and captures plasticity-related proteins made available by strong stimulation elsewhere, and they specify what dopamine contributes to it: a temporally precise trigger and a delayed licence.

8.2 The loop, and novelty as its input

The hippocampal–ventral tegmental loop was proposed as the circuit that decides what enters long-term memory. The hippocampus detects that arriving information is not already stored; the resulting novelty signal reaches the ventral tegmental area via subiculum, accumbens and ventral pallidum, contributing along with salience and goal information to novelty-dependent firing; dopamine released back into the hippocampus enhances long-term potentiation and learning.

In humans, functional imaging of the substantia nigra/ventral tegmental complex shows responses driven by stimulus novelty rather than by rareness, negative valence or target status, with hippocampal responses less selective — and, notably, the midbrain response scales with *absolute* novelty rather than novelty relative to the current context.

That last detail is worth pausing on. A system coding absolute novelty is a system that answers "have I ever seen this?" rather than "is this the odd one here?" It is precisely the signal an organism needs to decide whether an experience deserves the metabolic expense of consolidation. Its degradation would not produce amnesia. It would produce a person who encodes indiscriminately or not at all — whose memory system has lost its editor rather than its recorder.

8.3 The complication: whose dopamine is it?

The claim that the ventral tegmental area's degeneration causes the hippocampal memory deficit of Alzheimer's disease has a serious problem, and it should be met head-on rather than buried.

Dopamine acting on hippocampal D1/D5 receptors is not necessarily ventral tegmental dopamine. Locus coeruleus neurons are catecholaminergic; they synthesise dopamine as the immediate precursor of noradrenaline; and they co-release it. Two 2016 studies established this. In one, locus coeruleus firing was found especially sensitive to environmental novelty, and locus coeruleus tyrosine-hydroxylase-positive neurons were shown to project **more profusely** to the hippocampus than ventral tegmental tyrosine-hydroxylase-positive neurons do; photoactivation of locus coeruleus tyrosine-hydroxylase-positive neurons enhanced memory and produced long-lasting potentiation of CA1 transmission, and both effects were blocked by hippocampal D1/D5 antagonism and were resistant to adrenoceptor blockade. In the other, dopamine release from locus coeruleus to dorsal hippocampus was shown to promote spatial learning and memory.

This matters enormously in the present context, because the locus coeruleus is the nucleus with the best-documented early tau pathology in the human Alzheimer brain. If hippocampal dopamine is substantially coerulean, then the hippocampal dopamine deficit in Alzheimer's disease may be a coerulean deficit that a ventral tegmental account has annexed.

The current resolution is a division of labour rather than a winner. The authors of the 2024 optogenetic study, who demonstrated the ventral tegmental CA1 projection directly and confirmed that the labelled fibres co-express tyrosine hydroxylase, propose that dopamine released in the hippocampus by ventral tegmental terminals serves the learning of new contexts and the forging of new memories, while dopamine from the locus coeruleus serves the updating and linking of memories already established. That is a specific, testable proposal, and it is the right shape of answer: two catecholaminergic nuclei converging on one receptor population in one subfield, with different afferent triggers and different behavioural roles.

For this paper the consequence is a discipline. Any observed hippocampal dopaminergic deficit in Alzheimer's disease has at least two possible sources, and attributing it to the ventral tegmental area requires either source-specific measurement or a behavioural dissociation along the lines the division-of-labour hypothesis predicts. Section 16 specifies both.

8.4 What the memory phenotype should look like

If the ventral tegmental contribution is degraded, the predicted memory phenotype is not global amnesia. It is:

- **Normal or near-normal immediate encoding**, since the trace is formed by glutamatergic transmission that dopamine modulates rather than carries;
- **Disproportionate failure of persistence** at delays beyond several hours, since the late permissive window is the one that fails;
- **Loss of the novelty benefit** — the enhancement of retention that normally follows exploration of a novel environment shortly before or after encoding;
- **Preserved procedural and nigrostriatal-dependent learning**, since that system is spared.

Each of these is measurable in patients, and the third is the most specific: the novelty-induced memory enhancement is a well-characterised paradigm, it depends on exactly the signal in question, and its selective loss in early Alzheimer's disease — with preserved baseline encoding — would be strong evidence that this system is failing.

9. Effect II: The Disinhibited Hippocampus

This is the least intuitive consequence and, on the current evidence, the best specified.

9.1 The finding

In Tg2576 mice, reduced dopaminergic innervation impairs D2-like receptor activation on parvalbumin-expressing interneurons in the hippocampus. Dopaminergic contact density on parvalbumin interneurons is reduced ($p = 0.028$) and tyrosine-hydroxylase-positive fibre density is substantially decreased at both 3 and 7 months ($p < 0.0001$). Within the parvalbumin interneurons, phosphorylated CREB and c-Fos fall. NaV1.1 — the sodium channel subunit on which fast-spiking interneurons depend to sustain high firing rates — is significantly reduced ($p = 0.009$). Perineuronal net density around these interneurons falls. The interneuron population itself is reduced by roughly 15–30% by 7 months.

The functional consequence is a failure of inhibition. Spontaneous inhibitory postsynaptic current total charge transfer and instantaneous frequency are reduced at 3 and 7 months. CA1 population spike amplitude is increased at 3 months at maximal stimulation and across multiple stimulation intensities by 7 months. Bicuculline-induced multiple population spikes — an index of epileptiform predisposition — are enhanced at 7 months. Carbachol-induced gamma oscillation power and peak frequency are reduced at 7 months.

And the causal direction was tested pharmacologically in both directions. Sub-chronic levodopa enhanced inhibitory charge transfer and frequency and reduced population spike amplitudes in 7-month-old mice. The D2-like agonists quinpirole and sumanirole restored phosphorylated CREB and c-Fos in parvalbumin interneurons to wild-type levels, and sumanirole restored gamma oscillations. Conversely, the D2-like antagonist sulpiride reduced phosphorylated CREB in wild-type parvalbumin interneurons, **mimicking the transgenic phenotype in a normal animal**.

That last experiment is the load-bearing one. Blocking D2-like receptors in a healthy mouse reproduces the interneuron molecular phenotype of the disease model. It converts the account from "dopamine loss correlates with disinhibition" to "removing D2-like drive is sufficient to produce it."

9.2 Why this inverts the intuitive expectation

The intuition about a lost modulatory nucleus is that its target goes quiet. Less dopamine, less drive, less activity. What actually happens here is the opposite, and the reason is that the dopamine in question was driving an **inhibitory** cell.

The chain is: ventral tegmental dopamine → D2-like receptors on parvalbumin fast-spiking interneurons → CREB phosphorylation and activity-dependent gene expression → maintained NaV1.1 and maintained perineuronal net → sustained high-frequency inhibitory output onto pyramidal cells → controlled pyramidal firing and coherent gamma. Break the first link and the last two fail: pyramidal neurons lose their brake, and the gamma rhythm that the parvalbumin network generates degrades.

So the withdrawal of a modulator produces **noise, not silence**. The hippocampus does not fall quiet when it loses its dopamine; it becomes hyperexcitable and rhythmically incoherent.

9.3 Why that matters clinically

Because that is what the early human Alzheimer hippocampus does.

Elevated hippocampal activation is observed in conditions conferring risk for Alzheimer's disease. In amnestic mild cognitive impairment, dentate gyrus/CA3 activation is elevated relative to healthy controls; a low dose of levetiracetam reduced that activation to a level indistinguishable from controls, and memory performance in the scanning task improved significantly relative to placebo. Increased hippocampal activation in this population is, on that evidence, dysfunctional rather than compensatory, and reducing it is therapeutically useful.

Hippocampal hyperactivity has been a durable puzzle for accounts of Alzheimer's disease centred on protein deposition, which supply no natural reason for a network to become *more* active as it degenerates. The dopaminergic account supplies one: the hyperactivity is disinhibition, the disinhibition follows the failure of parvalbumin interneurons, and the interneurons fail in part because they have lost a D2-mediated trophic and excitatory drive from a nucleus that degenerates before the plaques arrive.

Three cautions are owed. This chain has been demonstrated in one model, by one programme. Parvalbumin interneuron dysfunction in Alzheimer's disease has many proposed causes and dopaminergic withdrawal is one candidate among several. And the human hyperactivity literature has not tested a dopaminergic contribution at all. What the account offers is not a settled explanation but an unusually specific and testable one — and it makes a prediction that no other account of hippocampal hyperactivity makes, which section 16 states.

Table 5 — Consequences of ventral tegmental failure, by projection.

Target	Signal withdrawn	Immediate consequence	Clinical correlate
Dorsal CA1 (pyramidal)	D1/D5-dependent trigger and late permissive signal	Failure to initiate dopamine-gated LTP; failure of memory persistence at long delay	Episodic memory loss with relatively preserved immediate encoding
Dorsal CA1 (PV interneurons)	D2-like drive → pCREB, NaV1.1, perineuronal net	Loss of inhibition; CA1 hyperexcitability; degraded gamma	Hippocampal hyperactivity in aMCI; seizure risk; rhythm disruption
Dorsal subiculum	Dopaminergic innervation	Reduced plasticity and excitability; impaired hippocampus→NAc core transmission	Failure to convert memory into action
Nucleus accumbens shell and core	Mesolimbic dopamine	Degraded reward processing and effort valuation	Apathy; anhedonia; reduced food reward
Prefrontal cortex	Mesocortical dopamine	Reduced prefrontal cortical activity	Executive and frontal-lobe dysfunction; loss of daily function
Arousal network	Dopaminergic wake drive	Reduced wakefulness and salience-induced arousal	Sleep–wake disturbance
Glia in target fields	Monoaminergic tone	NLRP3-mediated microglial activation; astrocyte reactivity; tau phosphorylation; plaque burden	Faster progression with midbrain deficit

10. Effect III: The Price of Effort

10.1 Apathy is not a footnote

Apathy is among the most common neuropsychiatric features of Alzheimer's disease and among the least well explained by the field's dominant framework. It is also prognostically heavy. In a meta-analysis of cognitively normal populations, apathy was associated with more than a doubling of the risk of progression to cognitive impairment, with odds ratios of 3.38 for progression to mild cognitive impairment and 2.12 for progression to dementia. In mild cognitive impairment, 36.1% of patients with apathy converted to Alzheimer's disease against 14.2% of those without, and median time to conversion was 3.79 years with apathy against 6.83 years without. A separate meta-analysis of longitudinal studies gives a hazard ratio of 1.54 for conversion.

A feature that halves the time to dementia is not a complication of the disease. It is a marker of something the disease is doing, and it is doing it early.

10.2 What apathy is, mechanistically

Apathy is best understood not as sadness or as inertia but as a disorder of **effort-based decision making**: a reduced willingness to expend effort for reward. The framework locates normal motivated behaviour in an interconnected group of regions with the dorsal anterior cingulate cortex and ventral striatum at its core, and it decomposes motivation into the willingness to work, the ability to keep working, and the capacity to learn what is worth working for, with deficits in any component producing the clinical syndrome.

Dopamine is the transmitter of that computation. In Parkinson's disease, both apathy and dopaminergic drugs alter effort-based decision making, though — importantly — in different sectors of the cost–benefit space, which the investigators read as evidence that dopamine is necessary but not sufficient to account for apathy and that other transmitters contribute.

That nuance should be carried forward. The claim available here is not "apathy is dopamine deficiency." It is that apathy is the behavioural signature of a degraded valuation system, that mesolimbic dopamine is the best-characterised substrate of that system, and that a disease which degenerates the mesolimbic projection early should produce apathy early. It does.

10.3 The convergence

Three independent lines meet here.

The **anatomical** line: the ventral tegmental neurons documented as vulnerable in the model are specifically the paranigral and parabrachial pigmented cells projecting to the nucleus accumbens shell and core — the effort-valuation pathway, not the memory pathway.

The **human imaging** line: patients with apathy, depression or anxiety show stronger ventral tegmental disconnection from default-mode networks, and behavioural symptoms including irritability and disturbances of sleep and eating have been reported as directly associated with the degree of ventral tegmental disconnection.

The **pharmacological** line: in a phase III, placebo-controlled, six-month, multicentre randomised trial, 200 patients with Alzheimer's disease and apathy received methylphenidate 20 mg daily or placebo. Methylphenidate produced significant improvement in two of three efficacy outcomes with a trend toward improved global cognition and minimal adverse events. The investigators describe a modest but potentially clinically significant benefit, with small-to-medium effect sizes and no effect on activities of daily living.

A catecholamine reuptake inhibitor improves apathy in Alzheimer's disease in a properly powered randomised trial. This is not decisive about aetiology — methylphenidate raises noradrenaline as well as dopamine, and a symptomatic response does not establish where the lesion is — but it is a rare instance of the pharmacology, the anatomy and the epidemiology all pointing at the same system.

10.4 The reverse-causation trap

One caution belongs here explicitly. Apathy predicts conversion, and it is tempting to read that as apathy revealing a lesion that is also driving the cognitive decline. The alternative is that apathy is an early *consequence* of the same pathology that will later cause dementia, with no special mechanistic priority. The two readings are hard to separate in observational data.

They are separable in principle. If apathy in Alzheimer's disease is mesolimbic, it should carry the specific signature of degraded effort-based decision making — a leftward shift in the acceptance of effort for a given reward, particularly at low reward magnitudes — rather than a generic reduction in behaviour. That signature is measurable with existing paradigms. To the author's knowledge it has not been characterised in a prospectively followed Alzheimer cohort against midbrain imaging, and it should be.

11. Effect IV: Appetite, Reward, and the Weight That Falls First

Weight loss in Alzheimer's disease has been treated for decades as a late complication of dementia — a consequence of forgetting to eat, of institutional diet, of swallowing difficulty. The epidemiology does not support that reading.

Weight loss precedes the onset of dementia by a decade or more and accelerates toward diagnosis; estimates of the interval range from six to twenty years. Dementia cases show faster decline in body mass index and waist circumference up to eleven years before diagnosis than matched controls. Weight loss may precede mild cognitive impairment itself, and it has been associated with Alzheimer biomarkers in cognitively healthy individuals, with baseline cortical thinning and with accelerated brain atrophy. The evidence increasingly supports weight loss as a prodromal feature rather than a risk factor.

A prodromal feature requires a prodromal mechanism, and the mesolimbic account supplies a candidate that the "forgetting to eat" account does not. In Tg2576, deficits in the processing and consumption of palatable food reward accompany ventral tegmental dopamine neuron death and attenuated accumbal dopamine release by six months, and the progression of dopaminergic cell death correlates with impaired food reward processing. The cells shown to die are the accumbens-projecting ones. Degrading the shell and core projection degrades the hedonic and incentive evaluation of food specifically, and a person whose food has become less rewarding eats less long before a person who has forgotten to eat.

The prediction that separates the two accounts is straightforward and testable: prodromal weight loss driven by mesolimbic failure should be accompanied by reduced hedonic response to palatable food and reduced willingness to work for food reward, in individuals whose memory is still normal, and should correlate with midbrain rather than medial temporal measures. Loss driven by amnesia should not.

Anhedonia belongs in the same frame. It is a core feature of the depressive syndrome that so often precedes an Alzheimer diagnosis, its principal substrate is the mesolimbic system, and an account that has the mesolimbic system degenerating in the prodrome has a mechanism for it. This paper does not develop the depression link further, but it notes that the pre-diagnostic depressive syndrome of Alzheimer's disease is anhedonic and amotivational more often than it is classically melancholic, and that this is the phenotype a mesolimbic lesion predicts.

12. Effect V: Arousal and the Salience Gate

Ventral tegmental dopaminergic neurons bidirectionally regulate sleep–wake state and sleep-related nesting behaviour. Chemogenetic and optogenetic manipulation with polysomnographic recording showed these neurons are necessary for arousal, and that their inhibition suppresses wakefulness **even in the face of ethologically relevant salient stimuli** — an animal whose ventral tegmental dopaminergic neurons are silenced does not wake for things that should wake it. Fibre photometry showed arousal-state-dependent activity in these neurons, and the authors positioned them as the link between motivational processes and sleep–wake regulation and as mediators of salience-induced arousal.

The relevance to Alzheimer's disease is that sleep–wake disturbance is an early and near-universal feature of the disease, and that it is not simply insomnia: it is a degradation of the boundary between states, with fragmented nocturnal sleep and daytime somnolence. Reports that behavioural symptoms including sleep and eating disturbance are directly associated with the degree of ventral tegmental disconnection in patients are consistent with a dopaminergic contribution to that degradation.

Two qualifications keep this section short. The sleep–wake regulation of the Alzheimer brain has several failing inputs — the noradrenergic, histaminergic, orexinergic and circadian systems are all implicated, and several of them fail earlier and more severely than the evidence places the ventral tegmental area. And the specific claim that ventral tegmental dysfunction contributes to human Alzheimer sleep disturbance rests on a connectivity association rather than on any interventional or physiological test. The defensible statement is that the nucleus is a component of the arousal system, that the arousal system fails early in this disease, and that the nucleus's contribution has not been isolated.

The salience finding is more interesting than the sleep finding, and it deserves the emphasis. A system that fails to produce arousal *in response to what matters* is a system that has lost the gate between the world's events and the organism's engagement with them. That is a description not of sleepiness but of the flattening — the failure of things to register as worth responding to — that families describe long before they describe forgetting.

13. Effect VI: The Damage That Returns

The consequences described so far run outward from a failing nucleus to its targets. The final consequence runs back.

Smaller midbrain volumes predict Alzheimer's disease progression and faster conversion from mild cognitive impairment to dementia; the concomitance of neuroinflammation, amyloid-β and tau is a strong predictor of that conversion. To test whether midbrain damage is a cause of that acceleration rather than a marker of it, a mouse model was generated carrying lesions in three midbrain nuclei — the dopaminergic ventral tegmental area and substantia nigra pars compacta, and the serotonergic interpeduncular nucleus — to isolate the consequences of dopamine and serotonin deprivation in target territory.

In otherwise normal mice, this monoamine depletion produced pronounced microglial activation through the NLRP3 inflammasome pathway, reversible with dopaminergic or serotonergic drugs. Superimposed on amyloid pathology, the same lesions markedly amplified the phenotype: exacerbated microglial reactivity, a robust astrocyte response, precocious amyloid plaque burden, and induction of pathological tau hyperphosphorylation. Administration of levodopa or fluoxetine significantly attenuated both the astrocyte reactivity and the tau hyperphosphorylation.

Three things follow.

The nucleus's failure is a driver, not only a consequence. A lesion placed in the midbrain makes downstream amyloid and tau pathology worse. Whatever caused the midbrain lesion in the first place, its existence accelerates the disease in territory it innervates.

The mechanism runs through glia. Monoamines exert tonic restraint on microglial and astrocytic activation; withdrawing them releases that restraint, and the released inflammatory state is permissive for both amyloid deposition and tau phosphorylation. The specification of the NLRP3 inflammasome as the pathway is unusually precise for a claim of this shape.

The loop closes pharmacologically. Levodopa and fluoxetine — restoring the withdrawn monoamines — attenuate the glial and tau consequences. This is the clearest demonstration available that the pathological amplification is a consequence of the missing transmitter rather than of the lesion's collateral damage.

It also reframes the therapeutic proposition. If dopaminergic replacement in Alzheimer's disease were purely symptomatic, one would expect it to improve function without touching

pathology. This result says otherwise in mice: restoring the transmitter attenuates tau hyperphosphorylation and astrocyte reactivity. Whether anything comparable happens in humans is entirely unknown, and the caveat in section 14 about the size of the human effects should be read alongside this.

One further note of caution: the lesion model deliberately damages the substantia nigra and a serotonergic nucleus alongside the ventral tegmental area, so it establishes that *midbrain monoaminergic loss* amplifies pathology, not that ventral tegmental dopaminergic loss alone does. That is a meaningful difference, and it means this result supports the general claim of section 13 more strongly than it supports the specific claim of section 4.

14. What the Pharmacology Says About the Lesion

A useful discipline in evaluating a proposed lesion is to ask what direction of drug helps. If the proposed lesion is a loss of dopaminergic transmission, then agents that raise dopaminergic transmission should improve the functions attributed to it, and agents that block it should reproduce the deficit. The literature permits this test in both species and in both directions.

14.1 In animals: five interventions, one direction

Levodopa and selegiline. Sub-chronic treatment of Tg2576 mice rescued synaptic plasticity, pyramidal neuron excitability and memory deficits. Levodopa also restored inhibitory charge transfer and reduced CA1 population spike amplitude at seven months, restored impaired hippocampus-to-accumbens transmission, and attenuated astrocyte reactivity and tau hyperphosphorylation in the midbrain-lesion model.

D2-like agonists. Quinpirole restored phosphorylated CREB and c-Fos in parvalbumin interneurons to wild-type levels; sumanirole raised phosphorylated CREB and restored gamma oscillations.

D2-like antagonism. Sulpiride reduced phosphorylated CREB in wild-type parvalbumin interneurons, mimicking the transgenic phenotype — the reverse-direction test, in a normal animal.

c-Abl inhibition. Chronic nilotinib prevented dopaminergic degeneration and its functional and morphological consequences, preserved hippocampal dopamine outflow, and improved hippocampus-dependent cognition.

Phasic optogenetic stimulation. In Tg2576, dopamine depletion disrupted long-term potentiation at hippocampal synapses; **phasic, but not prolonged**, optogenetic stimulation of midbrain dopaminergic neurons restored hippocampal function, acting through D1/D5 receptors.

Non-invasive stimulation. Repetitive prefrontal transcranial direct-current stimulation in Tg2576 enhanced ventral tegmental dopaminergic neuron activity, increased hippocampal dopamine release and improved synaptic function, with improvement in recognition memory and motivational responses, reduced microglial activation and reduced plaque burden in older animals.

Every arrow points the same way. Raising dopaminergic transmission — by precursor, by reuptake and degradation inhibition, by receptor agonism, by preventing the degeneration, by

stimulating the cells directly, or by driving them through a top-down cortical route — improves the deficits. Blocking it in a healthy animal reproduces them.

The phasic-versus-prolonged result deserves particular weight. It says that what the hippocampus needs is not more ambient dopamine but *correctly structured* dopamine, and it therefore predicts that a drug producing steady tonic elevation should be a poor substitute for the burst signal — which is exactly the pattern the human trials show.

14.2 In humans: two randomised trials, and what they did and did not move

Rotigotine. A dopamine agonist delivered by transdermal patch was tested against placebo in 94 patients with mild-to-moderate Alzheimer's disease (mean age 73.9) for 24 weeks, as add-on to a cholinesterase inhibitor. The primary outcome — global cognition on ADAS-Cog-11 — was **negative**: 2.92 points of decline on rotigotine against 2.66 on placebo. Secondary outcomes told a different story. The Frontal Assessment Battery improved by 0.48 points on rotigotine and declined by 0.66 on placebo. Activities of daily living declined less on drug (−3.32) than on placebo (−7.24). Neurophysiological recording showed prefrontal cortical activity increased in the rotigotine group and not in placebo. Adverse events and dropouts were more frequent on drug.

Methylphenidate. As described in section 10, a catecholamine reuptake inhibitor improved apathy in 200 patients over six months, with significant improvement in two of three efficacy outcomes and no effect on activities of daily living.

14.3 Reading the human results honestly

It would be easy to present the rotigotine trial as a success and easier still to present it as a failure. Neither is right.

It failed its primary endpoint, and a trial that fails its primary endpoint has not demonstrated efficacy. That must be stated first and without hedging.

But the pattern of the secondary outcomes is not random with respect to the hypothesis. A tonic dopaminergic agonist improved frontal executive function and daily function, raised prefrontal cortical activity, and did nothing for episodic memory. Section 8 predicted that the mesocortical projection subserves executive function and section 14.1 predicted that tonic elevation is a poor substitute for the phasic signal that hippocampal plasticity requires. A drug that produces continuous receptor occupancy should therefore help the frontal deficit and not the mnemonic one — and it did.

That is a post-hoc reading of secondary endpoints in a single trial and it is offered as consistency, not as evidence. What it earns is a specific design recommendation: the trial that would test this hypothesis properly is not another agonist trial powered on ADAS-Cog. It is a trial in the

prodromal population, powered on apathy and on frontal-executive and daily-function measures, with midbrain imaging as a stratifier — and, if the phasic/tonic distinction is real, using an intervention capable of restoring burst structure rather than ambient tone.

The wider caution is the one the field's own reviewers state: prospective randomised trials of dopaminergic drugs targeting conversion from mild cognitive impairment to Alzheimer's disease do not exist, and there are no approved medications for the neuropsychiatric symptoms this system is proposed to generate.

15. Strength of Evidence

Grading is the only honest way to present a literature in which some claims rest on interventional experiments and others on a single small cross-sectional cohort. The scheme below is deliberately coarse.

- **Established** — replicated across independent groups, with converging methods, and with a causal or interventional demonstration where the claim is causal.
- **Supported** — demonstrated with adequate method, but in one model, one programme, or without independent replication.
- **Inferred** — a reasonable extrapolation from adjacent literature, not tested in this context.
- **Open** — the measurement that would settle it has not been made.

Table 6 — Graded ledger of the claims in this paper.

#	Claim	Grade	Basis and principal limitation
1	Ventral tegmental dopaminergic neurons are lost early and pre-plaque in Tg2576, sparing the substantia nigra	Supported	Multiple papers, largely one programme; replicated in direction across other models but not in all strains
2	The vulnerable population is the accumbens-projecting paranigral/parabrachial pigmented group	Supported	Single localisation study; hippocampal-projecting population not separately resolved
3	Vulnerable neurons show mitochondrial injury and AIF-mediated, caspase-independent death	Supported	Ultrastructure and immunolocalisation in one model; upstream cause unidentified
4	Surviving neurons upregulate calcium-binding proteins and lower cytosolic calcium	Supported	Single study; interpretation as compensation is inference
5	Ventral tegmental neurons can fail physiologically without dying, via CK2-dependent SK channel dysfunction	Supported	Independent laboratory, one model, one age series; link to terminal loss untested

#	Claim	Grade	Basis and principal limitation
6	Failure proceeds code → terminals → soma	Inferred	Synthesis of claims 1 and 5; no longitudinal within-animal demonstration
7	Catecholaldehyde (DOPAL) autotoxicity contributes	Inferred	Strong in the Parkinson literature; never measured in this context
8	Human ventral tegmental dopaminergic neuron number is reduced in Alzheimer's disease	**Open**	No unbiased stereology exists
9	Human midbrain dopaminergic volume is reduced in Alzheimer's disease and tracks cognition	Established	Two independent cohorts; the larger cannot separate VTA from SN
10	Ventral tegmental disconnection precedes and predicts conversion from MCI	Supported	Prospective but small (35 patients, 16 events), single centre
11	The nigrostriatal terminal field is spared in Alzheimer's disease	Established	Clinical DAT-SPECT differential against DLB
12	Ventral-striatal dopamine terminals are reduced in Alzheimer's disease	**Open**	The ratio measurement has not been reported as a test of this hypothesis
13	Hippocampal dopamine gates memory persistence at a late post-encoding window	Established	Bidirectional pharmacology in rats; independent replication
14	Ventral tegmental dopamine can trigger CA1 LTP within a 200 ms window via D1/D5	Supported	Optogenetic, one laboratory; effect specific and well controlled
15	The locus coeruleus is a major source of hippocampal dopamine	Established	Two independent 2016 studies; anatomically and pharmacologically demonstrated
16	Hippocampal dopamine deficits in Alzheimer's disease are attributable to the VTA rather than the LC	**Open**	Source-specific measurement not performed
17	Loss of D2-like drive on PV interneurons disinhibits CA1 and degrades gamma	Supported	Demonstrated bidirectionally including antagonist phenocopy in wild-type; one programme, one model
18	Hippocampal hyperactivity in human aMCI is dysfunctional and reducible	Established	Randomised crossover with levetiracetam; cognition improved
19	Human hippocampal hyperactivity has a dopaminergic component	**Open**	Never tested

#	Claim	Grade	Basis and principal limitation
20	Apathy predicts conversion and shortens time to dementia	Established	Multiple meta-analyses
21	Apathy in Alzheimer's disease is mesolimbic in origin	Inferred	Consistent anatomy, imaging association and drug response; effort-based signature not characterised
22	Methylphenidate improves apathy in Alzheimer's disease	Established	Phase III randomised trial, n = 200
23	Weight loss precedes Alzheimer diagnosis by a decade or more	Established	Multiple longitudinal cohorts
24	Prodromal weight loss is mesolimbic in origin	Inferred	Food-reward deficits in model; untested in humans
25	Midbrain monoaminergic lesion amplifies plaque burden, astrocyte reactivity and tau phosphorylation	Supported	Interventional, and reversible with L-DOPA/fluoxetine; lesion includes SNc and a serotonergic nucleus
26	Raising dopaminergic transmission improves function in Alzheimer models	Established (in models)	Six independent interventions, consistent direction
27	Dopaminergic agonism improves global cognition in Alzheimer's disease	**Refuted at tested dose and duration**	Primary endpoint negative in randomised trial
28	Dopaminergic agonism improves frontal function and daily activities	Supported	Secondary endpoints, one trial, post-hoc reading

16. Predictions and Refutation Conditions

A hypothesis that cannot specify what would count against it is not doing work. The following nine experiments are ordered by how decisively they would settle the account, and each is paired with the result that would refute it.

1. Unbiased stereology of the human ventral tegmental area in Alzheimer's disease. Count tyrosine-hydroxylase-positive and total neurons in A10 subnuclei against A9, in Braak-staged Alzheimer cases and age-matched controls, with explicit and pre-registered A9/A10 boundary criteria and exclusion of Lewy body co-pathology. *Prediction:* reduced A10 dopaminergic number with preserved A9, with the deficit concentrated in the paranigral and parabrachial pigmented subnuclei. *Refutation:* A10 number preserved **and** terminal markers in ventral striatum preserved. Note carefully that preserved somatic number *with* reduced terminal markers would support rather than refute the account, per section 5 — which is why this experiment must be paired with the next.

2. Ventral-to-dorsal striatal dopamine transporter ratio in Alzheimer's disease. Quantitative reanalysis of existing DAT-SPECT or PET datasets in clinically diagnosed, biomarker-confirmed Alzheimer patients with normal visual reads. *Prediction:* reduced ventral-striatal binding relative to dorsal, i.e. a reduced ventral/dorsal ratio, in the presence of a normal absolute dorsal measurement. *Refutation:* a flat ratio. This is the cheapest decisive experiment in the list, because the data already exist.

3. Source-specific attribution of hippocampal dopamine. In an amyloid model, chemogenetically silence ventral tegmental dopaminergic and locus coeruleus tyrosine-hydroxylase-positive projections to CA1 separately and together, with dopamine sensor imaging. *Prediction:* if the memory deficit is ventral tegmental, silencing the ventral tegmental projection in a wild-type animal phenocopies the model's contextual-learning deficit, while silencing the coerulean projection phenocopies a memory-updating deficit. *Refutation:* coerulean silencing accounts for the whole hippocampal dopamine deficit — in which case claim 16 of Table 6 resolves against the ventral tegmental area and section 8's mnemonic argument transfers to the locus coeruleus.

4. The novelty-benefit paradigm in prodromal Alzheimer's disease. Test whether exploring a novel environment shortly before or after encoding enhances retention, in biomarker-positive individuals with normal baseline memory, against midbrain volumetry. *Prediction:* selective loss of the novelty benefit with preserved baseline encoding, correlating with midbrain measures and not with hippocampal volume. *Refutation:* the novelty benefit is intact, or its loss tracks

hippocampal rather than midbrain measures.

5. Dopaminergic contribution to human hippocampal hyperactivity. In amnestic mild cognitive impairment with documented dentate/CA3 hyperactivation, administer a D2-like agonist and re-image. *Prediction:* reduced hippocampal hyperactivation, on the model of the levodopa and D2-agonist effects in mice. *Refutation:* no change, or an increase — which would sever the mouse chain from the human phenomenon and remove section 9's clinical claim.

6. Effort-based decision making against midbrain integrity. Characterise the effort–reward acceptance surface in a prospectively followed prodromal cohort with midbrain imaging. *Prediction:* a specific reduction in willingness to accept effort for low-magnitude rewards, correlating with midbrain measures, appearing before episodic memory decline. *Refutation:* apathy in this population shows a generic reduction in responding without the effort-specific signature, or does not track midbrain measures.

7. Catecholaldehyde burden in the Alzheimer midbrain. Measure DOPAL and DOPAL–protein adducts in post-mortem A10 and A9 tissue from Alzheimer cases and controls. *Prediction:* if section 6.6 is right, raised aldehyde burden in A10 in Alzheimer's disease. *Refutation:* no difference — which would retire the most attractive untested mechanism in the field.

8. Longitudinal within-animal ordering of code, terminal and soma. In a single cohort, serially measure firing properties in vivo, terminal density, and somatic number across the age range in which each has been separately reported. *Prediction:* firing derangement precedes terminal loss, which precedes somatic loss. *Refutation:* somatic loss precedes terminal loss, or the three are simultaneous — which would collapse the trajectory model of section 5.

9. A properly targeted clinical trial. A randomised trial in prodromal, biomarker-confirmed Alzheimer's disease, stratified by midbrain volume, powered on apathy and frontal-executive and daily-function endpoints rather than on global cognition. *Prediction:* benefit concentrated in the stratum with reduced midbrain volume, and in the motivational and frontal domains rather than the mnemonic one. *Refutation:* no interaction with midbrain stratum — which would indicate that whatever these drugs do, they are not acting on the lesion this paper describes.

Table 7 — Directional commitments. The account is wrong if any of these signs is reversed.

Measurement	Direction predicted in early Alzheimer's disease
A10 dopaminergic terminal density in ventral striatum	↓ reduced
A9 dopaminergic terminal density in dorsal striatum	→ unchanged

Measurement	Direction predicted in early Alzheimer's disease
Hippocampal extracellular dopamine	↓ reduced
CA1 pyramidal excitability	↑ increased
CA1 parvalbumin interneuron output	↓ reduced
Perineuronal net density around hippocampal PV cells	↓ reduced
Carbachol- or task-evoked gamma power	↓ reduced
Memory persistence at long delay, with normal immediate encoding	↓ reduced
Novelty-induced memory enhancement	↓ reduced
Effort accepted for low-magnitude reward	↓ reduced
Hedonic response to palatable food	↓ reduced
Response to D2-like agonism, in frontal and motivational domains	↑ increased
Response to tonic dopaminergic agonism, in episodic memory	→ unchanged

17. Limitations

The human anchor is missing. The central limitation is stated in section 7 and repeated here because no amount of mechanistic detail substitutes for it: there is no unbiased stereological count of human ventral tegmental dopaminergic neurons in Alzheimer's disease. Until that exists, the strongest human statements available are that the midbrain dopaminergic complex is volumetrically smaller and functionally disconnected, and that these measures track cognition and predict conversion.

Programme concentration. A large share of the mechanistic literature — the founding degeneration result, the subcellular localisation, the circuit consequences, the interneuron mechanism, the pharmacological rescues, the neuroinflammatory extension and the stimulation work — originates from one research programme. The work is careful and internally consistent, and its consistency is not the same thing as independent corroboration. The two genuinely independent contributions in this paper's evidence base — the hyperexcitability/SK finding and the substantia nigra volumetric study — both complicate the simple picture rather than confirming it.

Model dependence. Tg2576 overexpresses a mutant human protein under a non-native promoter and does not develop the tau pathology that defines the human disease's staging. That a nucleus degenerates in such an animal is evidence about that animal. The direction has been reproduced in other models; it has not been reproduced in all strains, and the one model carrying tau as well as amyloid gave a different answer.

Conflation of a region with a cell type. Measurements of "ventral tegmental" volume, connectivity or tyrosine hydroxylase are not measurements of dopaminergic neuron number. A quarter of the nucleus is GABAergic; tyrosine hydroxylase is regulated and can fall in living cells; volume includes neuropil. The distinction between losing cells, losing terminals and losing phenotype is not resolved by any human measurement currently available.

The locus coeruleus problem. The mnemonic argument of section 8 is weakened, though not eliminated, by the demonstration that the locus coeruleus projects more profusely to the hippocampus than the ventral tegmental area does and co-releases dopamine there. Since the locus coeruleus is also the nucleus with the best-documented early tau pathology in humans, a hippocampal dopamine deficit in Alzheimer's disease has a strong alternative explanation that this paper cannot exclude.

Symptomatic benefit does not localise a lesion. Methylphenidate improves apathy; this does not establish that apathy in Alzheimer's disease is mesolimbic, since the drug raises

noradrenaline as well as dopamine and since symptomatic improvement can arise from compensation in intact circuitry.

The trial evidence is thin and partly negative. Two randomised trials bear on this system. One improved apathy. The other failed its primary cognitive endpoint, and its supportive findings are secondary endpoints read post hoc.

Scope. This paper is confined to the ventral tegmental area. It does not attempt to weigh that nucleus against the cholinergic, noradrenergic or serotonergic systems, nor to place it in a sequence with them. Several of those systems have earlier and better-documented human pathology, and nothing here should be read as a claim of primacy.

18. Conclusions

The ventral tegmental area is the best-argued and least-counted nucleus in the anatomy of Alzheimer's disease. This paper's conclusions divide into what the evidence supports, what it complicates, and what it leaves open.

What it supports. In amyloid-bearing mice, mesolimbic dopaminergic neurons of the paranigral and parabrachial pigmented subnuclei are lost from three months of age, before plaques, while the substantia nigra is spared; the dying cells show mitochondrial injury and caspase-independent death; the survivors raise their calcium buffers and lower their cytosolic calcium. Their loss reduces dopamine delivery to hippocampus and accumbens, degrades CA1 plasticity, degrades the excitability and output of the subiculum, impairs food-reward processing and impairs memory. In humans, the midbrain dopaminergic complex is volumetrically smaller in Alzheimer's disease, its size tracks cognition across five domains, and its functional disconnection at the stage of mild cognitive impairment contributes to identifying who will convert.

What it complicates. Every classical predictor of dopaminergic vulnerability ranks the substantia nigra above the ventral tegmental area, and the claim under examination inverts that ranking. The resolution offered here is that the insult in this disease is not the metabolic-calcium insult of Parkinson's disease, and the strongest evidence for that resolution is that the calcium buffer which marks survival in Parkinson's disease appears here as a stress response — rising in the cells that are in trouble.

The second complication is that failure is not one event. One model loses these neurons early; another keeps every one of them at twelve months and instead finds them firing too fast through a casein-kinase-2-dependent failure of the SK channel, with their terminals thinning. Read as a contradiction this is an embarrassment. Read as a trajectory — code, then terminals, then soma — it is the most useful thing in the literature, because it explains why measurements disagree, it identifies the terminal rather than the cell body as the right place to look in humans, and it locates the therapeutic window in the phase when the cell is present and miscoding.

What it costs. The consequences follow the projections. From the hippocampal projection: the loss of a 200-millisecond trigger for dopamine-gated potentiation and of a twelve-hour permission for a memory to persist — a phenotype of failed persistence and lost novelty benefit rather than of failed encoding. From the same projection onto a different cell: the loss of D2-like drive on parvalbumin interneurons, and with it NaV1.1, the perineuronal net, inhibition and gamma — so that the hippocampus deprived of dopamine becomes *hyperexcitable*, which is what the early human Alzheimer hippocampus actually does and what protein-deposition accounts explain

least well. From the accumbal projection: the degradation of effort valuation and food reward, which supplies mechanisms for the two commonest unexplained features of the prodrome — an apathy that halves the time to dementia, and a weight loss that begins a decade before diagnosis. From the arousal function: a failure to wake for what matters. And returning inward: monoamine withdrawal releases NLRP3-mediated microglial activation and astrocyte reactivity, amplifies plaque burden and induces tau hyperphosphorylation, so that the nucleus's failure feeds the pathology that is destroying it.

What it leaves open. Whether any of this is true of human beings at the resolution that matters. The measurements that would decide it are specified in section 16, and two of them are cheap: a quantitative ventral-to-dorsal striatal transporter ratio, which can be extracted from scans already acquired; and an unbiased stereological count of A10 against A9 in Braak-staged brains, which requires only tissue and the decision to do it.

The system this paper describes does not carry the content of experience. It carries the endorsement of it: the signal that says *this is worth keeping* and *this is worth doing*. A disease that takes the endorsement first would produce a person who is not yet forgetful but is already uninterested — who eats less, wakes less readily to what matters, works less hard for what they used to want, and whose new memories, correctly formed, are not marked for retention. That is a recognisable description of the years before an Alzheimer diagnosis. Whether it is the right description is now an empirical question with a short list of answerable parts.

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