THE PINEAL INTERFACE

Melatonergic Withdrawal, Circadian Disintegration, and the Undefended Locus Coeruleus in Alzheimer's Disease

The Failing Clock · The Melatonergic Withdrawal · The Undefended Nucleus
The Glymphatic Night · The Chronobiological Spiral

A Dissertation Submitted in Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy in Neuroscience

Prepared under the Organic Network Synthesis methodology

AdultCognitiveDisease.com

Benjamin Aaron Gustafsson

July 2026

Chronobiological companion to The Coerulean Interface and to the Bioenergetic Collapse thesis — the deep expansion of the melatonergic (pineal) branch of The Tryptophan Partition Node.

"The same nucleus that fails first is the one the night was built to protect. The pineal keeps the clock that darkens the brain so that the locus coeruleus may rest and the tide may run; when the clock fails, the nucleus is worked without relief and defended without its antioxidant — worn from both sides at once."

— ONS Methodology Working Notes, 2026

For Russel J. Reiter, who made melatonin a mitochondrial molecule, and for Dick Swaab, who showed that the human clock and its hormone fail in the Alzheimer brain.

THE COLLAPSE TRILOGY COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition · The Vascular Phasing · The Vagal Interface

V. The Coerulean Interface · The Microbial Prologue

VI. The Pineal Interface this volume

This volume is the chronobiological face of the coerulean cluster. Where *The Coerulean Interface* traces the afferent vagus as a chronic inflammatory *load* on the locus coeruleus, the present volume traces the failing pineal clock as the withdrawal of a chronic melatonergic *protection* from the same nucleus — two conduits onto one hub, one adding demand and one removing defense. It is, equally, the deep expansion of the pineal branch named in §7.4 of *The Tryptophan Partition Node*.

Contents

Abstract

The locus coeruleus is the earliest site of Alzheimer's disease pathology and the most oxidatively vulnerable nucleus in the brain. Hyperphosphorylated "pretangle" tau appears in this small pontine noradrenergic nucleus in the first decades of life, decades before cortical pathology and before any clinical sign; and the same nucleus that fails first is, on independent grounds, the one whose cellular economy is most exposed to oxidative injury — an autonomously pacemaking neuron that sustains dendritic calcium oscillations, carries long, thin, largely unmyelinated axons, and runs a catecholaminergic biochemistry that generates quinones, hydrogen peroxide, and the neuromelanin of chronic auto-oxidation. This dissertation asks what the pineal gland — the brain's melatonin-secreting clock organ — has to do with the fate of that nucleus, and advances a bounded, deliberately falsifiable answer: the failing pineal clock does not initiate Alzheimer's disease, but it *withdraws two chronic protections from the locus coeruleus at exactly the moment the nucleus can least afford to lose them.* Melatonin is the endogenous antioxidant best matched to the locus coeruleus's specific vulnerability — it concentrates in mitochondria, scavenges the superoxide of the respiratory chain at its source, and defends the permeability transition pore — and the nocturnal, melatonin-timed sleep state is the condition under which noradrenergic tone falls, microglial surveillance is released, and the interstitial clearance of amyloid-β and tau is permitted. The pineal is thus, in this framework, the organ that both *chemically defends* the locus coeruleus and *schedules its rest*; and its decline, which begins at the preclinical Braak I–II stage in lockstep with the earliest coerulean pathology, removes the defense and degrades the rest together.

The thesis is organised as a coupling argument and, unusually for the Collapse corpus, as an explicit assessment of validity. Chapter I establishes the locus coeruleus as the *undefended nucleus*: it recapitulates the intrinsic oxidative vulnerability characterised by the Bioenergetic Collapse thesis and shows that melatonin's antioxidant pharmacology is specifically matched to it. Chapter II documents the failing clock — the several-fold fall of cerebrospinal-fluid melatonin in Alzheimer's disease, its appearance at the preclinical stage, and the pineal calcification and volume loss that accompany it. Chapter III performs the load-bearing honest work of the dissertation: it dissects the anatomy of the pineal–coerulean linkage and finds that there is no direct neural projection from the pineal to the locus coeruleus, that the connection is instead humoral (melatonin acting on the MT1 receptors that locus coeruleus neurons demonstrably express) and shared-clock-mediated (both nuclei are downstream of the suprachiasmatic nucleus), and that native melatonin itself does not measurably alter locus coeruleus firing — a finding that constrains the framework and is stated rather than suppressed. Chapter IV develops the glymphatic night: the sleep- and noradrenaline-gated clearance of amyloid and tau, presented with its genuine mechanistic controversy intact. Chapter V formalises the *chronobiological–coerulean spiral*, the self-amplifying loop in which a failing clock worsens the locus coeruleus and a failing locus coeruleus worsens the clock. Chapter VI is an explicit grading of

every arc of the argument, from strong to speculative, and confronts the reverse-causation problem — the well-evidenced possibility that melatonin decline is a downstream *marker* of suprachiasmatic degeneration rather than a driver. Chapter VII derives therapeutic implications and falsifiable predictions and gives an unsparing account of the melatonin clinical-trial literature, which supports a modest sleep benefit at most and has produced a flatly negative result in its largest cognition trial.

The dissertation concludes that the pineal interface is real but subordinate: the locus coeruleus is worn from both sides at once — worked without its nightly relief and defended without its antioxidant — but the clock is more plausibly an amplifier and an early marker of the disease than its prime mover. The value of the framework is not a new cause of Alzheimer's disease but a precise account of *why the nucleus that fails first is the one the night was built to protect*, and of the narrow, early, and testable window in which restoring the protection might matter.

Keywords: pineal gland, melatonin, locus coeruleus, noradrenaline, Alzheimer's disease, MT1 receptor, suprachiasmatic nucleus, circadian disruption, glymphatic clearance, mitochondrial antioxidant, oxidative stress, neuromelanin, sleep, Braak staging, chronobiology

1. Introduction

1.1 The Research Problem

The locus coeruleus occupies a singular position in the natural history of Alzheimer's disease. The neuropathological evidence, developed over two decades by Braak and Del Tredici and independently confirmed, places the earliest abnormal, hyperphosphorylated "pretangle" tau not in the entorhinal cortex where cortical staging begins, but caudal to it, in the small bilateral pigmented noradrenergic nucleus of the dorsal pons; the material is present in individuals too young to have any cortical pathology and becomes essentially universal by middle age. The Bioenergetic Collapse thesis of the Collapse trilogy took up the question of *why* a brainstem nucleus rather than the cortex it supports should fail first, and answered in terms of intrinsic vulnerability: the locus coeruleus neuron is autonomously pacemaking, sustains dendritic calcium oscillations that impose a continuous mitochondrial oxidant load, projects long, thin, largely unmyelinated axons throughout the forebrain, and runs a catecholaminergic biochemistry whose auto-oxidation generates reactive quinones, hydrogen peroxide, and the neuromelanin that is the visible residue of a lifetime of oxidative stress. The locus coeruleus, on this account, is the brain's most oxidatively exposed neuron, poised at the edge of its bioenergetic ceiling.

This dissertation begins from an observation that the intrinsic account leaves untouched. The molecule whose pharmacology is most precisely matched to the locus coeruleus's specific

vulnerability — a small, amphiphilic, mitochondrially-concentrating antioxidant that scavenges the superoxide of the respiratory chain at the site of its production and defends the mitochondrial permeability transition pore — is melatonin, the principal secretory product of the pineal gland. And melatonin is not a static feature of the brain's chemistry but a rhythmic one: it is secreted at night, under the control of the suprachiasmatic clock, and it both marks and helps to consolidate the sleep state during which noradrenergic tone falls, microglial surveillance is released, and the interstitial clearance of metabolic waste — including amyloid-β and tau — is at its most efficient. The pineal gland is thus, at least in principle, an organ that performs two services for the locus coeruleus: it supplies the antioxidant best suited to the nucleus's chemistry, and it schedules the nightly state in which the nucleus rests and the brain is cleared.

The problem this dissertation takes up is that both services decline in Alzheimer's disease, and decline early. Cerebrospinal-fluid melatonin falls to roughly a fifth of control levels in Alzheimer's disease, and — critically — the decline is already present in cognitively intact individuals with only the earliest, Braak I–II neuropathology, the same preclinical window in which the locus coeruleus is the principal site of the disease. The pineal gland itself shows increased calcification and reduced parenchymal volume; its clock-gene rhythm is disturbed; and the circadian rest–activity rhythm fragments before symptoms appear. The coincidence is arresting: the nucleus that fails first loses, at the same early moment, the antioxidant defense and the scheduled rest that the pineal clock had supplied. The research problem is to determine whether this coincidence is mechanistically load-bearing — whether the withdrawal of melatonergic protection and the disintegration of the melatonin-timed sleep state actively condition the fate of the locus coeruleus — or whether it is an epiphenomenon, the pineal failing alongside the locus coeruleus as two followers of a common upstream lesion.

1.2 Significance

The significance of posing the problem in this way is fourfold. First, it supplies the Collapse corpus with the chronobiological complement to its inflammatory account of the same nucleus. The companion volume *The Coerulean Interface* traces the afferent vagus as a chronic inflammatory *load* on the locus coeruleus — an escalating demand delivered from the inflamed periphery. The present thesis traces a symmetrical but opposite process: the failing pineal clock as the *withdrawal of a chronic protection* from the same nucleus. The two conduits are complementary — one adds demand, the other removes defense — and together they convert the standing intrinsic vulnerability of the locus coeruleus into a progressive process from two directions at once.

Second, the framework connects a large and largely separate literature — the chronobiology of ageing and the melatonin-decline data of Alzheimer's disease — to the specific cellular vulnerability that the Collapse trilogy places at the origin of the disease. The melatonin-and-Alzheimer literature is dominated by sleep and by the suprachiasmatic clock; it has not, in general, been read against the

oxidative economy of the locus coeruleus, whose chemistry melatonin's antioxidant profile happens to fit. Drawing the two together makes a testable claim: that the benefit of melatonin, to the extent it has any, should be concentrated at the locus coeruleus and in the earliest, pre-amyloid phase of the disease.

Third, the framework is honest about a hard problem that the inflammatory account does not face as acutely — the problem of causal direction. The strongest human mechanistic work on the melatonin decline, from the very group that first documented it, attributes the decline to the *functional disconnection of the pineal from a degenerating suprachiasmatic nucleus*: the pineal, on this reading, is deafferented rather than diseased, a passive follower of a failing master clock. Any framework that assigns the pineal a causal role must confront this alternative directly, and the value of doing so is methodological as much as substantive: it forces the framework to state which of its arcs are load-bearing and which are speculative, and to grade them.

Fourth, the framework reorganises a therapeutic question that has been asked badly. Melatonin has been trialled in Alzheimer's disease for two decades with results that are, at best, modest and, at worst, flatly negative — and the framework explains why. The trials have used doses two orders of magnitude below the neuroprotective range identified in animal models, in patients whose disease was already established, at a stage at which the locus coeruleus the melatonin might have protected has already largely degenerated. The framework predicts, with the same timing logic that recurs throughout the Collapse corpus, that the intervention can only work early, while the nucleus it defends still exists.

1.3 Scope and Limitations

This dissertation is a synthetic review centred on Alzheimer's disease and on a single nucleus. It is narrower than a general treatment of chronobiology and neurodegeneration would be: it does not develop the melatonin literature of Parkinson's disease, the light-therapy and bright-light-intervention literature except where it bears on the mechanism, or the peripheral and oncological functions of melatonin. It concentrates on the locus coeruleus, on melatonin as an antioxidant and a sleep signal, and on the pineal clock as the source of both.

The thesis makes a bounded causal claim and states its limits at the outset. It does not claim that pineal decline or melatonin loss initiates Alzheimer's disease. The developmentally early pretangle tau of the locus coeruleus appears before any plausible pineal lesion and is most parsimoniously intrinsic; and the strongest evidence locates the primary chronobiological lesion upstream, in the suprachiasmatic nucleus, with the pineal as a follower. The thesis claims, more modestly, that the withdrawal of melatonergic protection and the disintegration of melatonin-timed sleep *condition and accelerate* a process whose seed is intrinsic — that they are amplifying and early-marking factors rather than initiating ones. Where the evidence for an arc is strong, the thesis says so; where it is contested, animal-only, or absent, the thesis says that instead. Chapter VI is given over entirely to

this grading, and Chapter VII states the conditions under which the framework would be falsified. The dissertation's ambition is not to add a cause to the long list of proposed causes of Alzheimer's disease, but to state precisely and falsifiably what the pineal clock does to the nucleus that fails first.

2. Literature Review

2.1 The Locus Coeruleus as the First and Most Oxidatively Vulnerable Site

The neuropathological priority of the locus coeruleus rests on the work of Braak and Del Tredici and has been independently confirmed. Their staging of subcortical tau pathology demonstrated that abnormal, non-argyrophilic pretangle tau accumulates in the locus coeruleus before it is detectable in the transentorhinal cortex, in individuals as young as children and adolescents, with a prevalence rising monotonically with age until it is essentially universal (Braak & Del Tredici, 2011; Braak et al., 2011). Streit and colleagues (2013), examining an independent series, confirmed the subcortical locus coeruleus pretangle stages. Whether or not one accepts the stronger interpretation that tau pathology spreads trans-synaptically from the locus coeruleus to its cortical targets — a claim supported experimentally in mice by Iba and colleagues (2015) but complicated by the observation that the murine spread pattern does not reproduce the human one — the descriptive priority of the locus coeruleus is among the most robust facts in Alzheimer neuropathology, and Weinshenker's (2018) synthesis placed noradrenergic dysfunction at the centre of the neurodegenerative process.

This descriptive priority is matched by a mechanistic account of *why* the locus coeruleus should be so vulnerable, developed most decisively by Surmeier and colleagues. Sanchez-Padilla and colleagues (2014) demonstrated that locus coeruleus neurons, like the dopaminergic neurons of the substantia nigra, are autonomously pacemaking and sustain dendritic calcium oscillations through L-type calcium channels, and that this calcium load drives a continuous mitochondrial oxidant stress that can be attenuated by inhibiting nitric oxide synthase. Surmeier and colleagues (2010) framed this "cell-specific phenotype" — autonomous pacemaking plus L-type calcium entry plus sustained mitochondrial oxidant stress — as the basis of the selective vulnerability of exactly these catecholaminergic populations. The catecholaminergic biochemistry compounds the load: the auto-oxidation of noradrenaline and dopamine generates reactive quinones and forms neuromelanin, whose iron-binding is protective when the pigment is intact but a source of oxidative stress and neuroinflammation when it is overloaded (Zucca et al., 2015). The neuromelanin that results is now measurable in living humans by neuromelanin-sensitive MRI, which exploits the

paramagnetism of the neuromelanin–iron complex (Sulzer et al., 2018); the locus coeruleus signal follows a quadratic trajectory across the lifespan, peaking near age sixty and declining thereafter (Liu et al., 2018), tracks memory and cognitive reserve in healthy adults (Clewett et al., 2015; Dahl et al., 2019), and is reduced in Alzheimer's disease in a manner that correlates with cognitive decline (Chen et al., 2022). The locus coeruleus is thus, on convergent neuropathological, electrophysiological, and imaging grounds, both the first-affected and the most oxidatively exposed nucleus in the brain — a neuron whose survival depends on the quality of its antioxidant defense.

2.2 The Pineal Clock and the Melatonin Rhythm: Synthesis and the Suprachiasmatic Relay

The pineal gland is the brain's melatonin-secreting organ, and its output is the principal humoral signal of biological night. Melatonin is synthesised from serotonin — itself the product of the tryptophan-to-5-hydroxytryptophan-to-serotonin pathway analysed at length in the companion volume *The Tryptophan Partition Node* — by two enzymatic steps: N-acetylation by arylalkylamine N-acetyltransferase (AANAT) and O-methylation by acetylserotonin O-methyltransferase. AANAT is the rate-limiting "timezyme," and in humans it is controlled largely post-translationally, through cyclic-AMP-dependent phosphorylation and 14-3-3 binding that protect the enzyme from proteasomal degradation (Klein, 2006; Ackermann & Stehle, 2006) — a species difference from the transcriptional control of rodents that qualifies the extrapolation of much rodent data to human disease.

The rhythm of melatonin synthesis is not intrinsic to the pineal but is imposed on it by a well-characterised neural relay from the master clock. The canonical pathway, established across independent groups, runs from the retina through the retinohypothalamic tract to the suprachiasmatic nucleus, thence to the paraventricular hypothalamic nucleus, down to the intermediolateral cell column of the upper thoracic spinal cord, out to the superior cervical ganglion, and finally through postganglionic sympathetic noradrenergic fibres to the pineal, where noradrenaline acting on β-adrenergic receptors drives AANAT and thus melatonin synthesis (Moore, 1996). Lesion and microdialysis studies confirm each node: suprachiasmatic and paraventricular lesions and ganglionectomy each abolish the melatonin rhythm, and the suprachiasmatic nucleus provides both a nighttime stimulatory and a daytime inhibitory drive (Perreau-Lenz et al., 2003, 2005; Garidou et al., 2001). Two features of this anatomy matter for the present thesis and are developed in Chapter III. First, the pineal is an *effector* organ: it receives a sympathetic noradrenergic input and secretes a hormone; it does not, on the available evidence, send axons of its own to other brain nuclei. Second, the noradrenergic drive to the pineal is sympathetic and peripheral, arising from the superior cervical ganglion, and is not supplied by the locus coeruleus — a fact that constrains any claim of a direct pineal–coerulean circuit.

2.3 Melatonin as a Mitochondrial Antioxidant

The pharmacological property of melatonin most relevant to the locus coeruleus is its antioxidant action, and specifically its mitochondrial antioxidant action. Melatonin is a broad-spectrum direct scavenger of reactive oxygen and nitrogen species — the hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, and peroxynitrite — and its scavenging is amplified by a metabolic cascade in which its oxidation products are themselves scavengers, so that a single molecule can neutralise several oxidants (Reiter et al., 1999; Tan et al., 2002). Unlike the classical lipophilic antioxidants, melatonin is amphiphilic and crosses all morphophysiological barriers, distributing to the cytosol, the nucleus, and — most importantly here — the mitochondrion, where it concentrates. Acuña-Castroviejo and colleagues (2001) and León and colleagues (2004) positioned melatonin as an intramitochondrial antioxidant that scavenges superoxide at its site of production, increases the efficiency of electron transport at complexes I and IV, limits electron leakage, raises the mitochondrial glutathione pool, and thereby preserves ATP synthesis; and León and colleagues (2005) described a direct action of melatonin to limit the fall in mitochondrial membrane potential that triggers opening of the permeability transition pore and the apoptotic cascade. This is precisely the profile of protection the locus coeruleus requires: its vulnerability, per §2.1, is a pacemaking-driven mitochondrial oxidant stress, and melatonin is an antioxidant that acts inside the mitochondrion on exactly that stress. The match is the mechanistic foundation of Chapter I. Its principal caveat, developed in Chapters VI and VII, is one of dose: nearly all of this mechanistic work uses micromolar concentrations in cells or high milligram-per-kilogram doses in animals, often one to two orders of magnitude above the concentrations that physiological nocturnal melatonin achieves in the human brain.

2.4 The Decline of Melatonin in Ageing and Alzheimer's Disease

The human data on melatonin in Alzheimer's disease are the empirical anchor of the thesis and are, in direction and magnitude, consistent and replicated. Liu and colleagues (1999), in a postmortem study of eighty-five Alzheimer cases and eighty-two age-matched controls from the Netherlands Brain Bank, found cerebrospinal-fluid melatonin in Alzheimer's disease reduced to roughly a fifth of control levels, with the lowest values in ApoE ε4/4 homozygotes. Zhou and colleagues (2003) extended the finding to the preclinical stage: cerebrospinal-fluid melatonin was negatively correlated with Braak stage and was already significantly decreased in cognitively normal individuals with only the earliest neuropathological changes, implying that the decline is an early event rather than a consequence of established dementia. Magri and colleagues (2004) reported that the nocturnal melatonin peak declines with age and is inversely correlated with the severity of cognitive impairment, while centenarians preserve their rhythm. Structurally, the pineal shows increased calcification in Alzheimer's disease on in-vivo computed tomography, in age-matched comparison (Mahlberg et al., 2008), and reduced parenchymal volume on volumetric MRI (Matsuoka et al., 2017). The circadian machinery upstream shows parallel disruption: the pineal clock-gene rhythm is lost in Alzheimer's disease, which Wu and colleagues (2006) attributed to a functional disconnection of the pineal from the suprachiasmatic nucleus; the suprachiasmatic MT1 receptor declines with age and disease (Wu et al., 2007); and Wu and Swaab (2005) synthesised the picture as a degeneration of the retina–suprachiasmatic–pineal axis beginning at the earliest disease stages. The consistency of these findings is a genuine strength; their limitations — cross-sectional and largely postmortem design, dominance by a single cohort, and above all the unresolved direction of causation — are taken up in §2.7 and graded in Chapter VI.

2.5 Melatonin Receptors and the Locus Coeruleus: What Is and Is Not Established

The question on which the anatomical plausibility of the thesis turns is whether the locus coeruleus is a target of melatonin, and here the literature has recently and decisively improved — though in a way that both enables and constrains the argument. López-Canul and colleagues (2024), in the single most important paper for this dissertation, demonstrated that locus coeruleus noradrenergic neurons express the MT1 melatonin receptor, that the selective MT1 partial agonist UCM871 dose-dependently inhibits locus coeruleus firing and increases REM sleep, and that both effects are abolished by MT1 antagonism and by adeno-associated-viral knockdown of MT1 selectively in locus coeruleus noradrenergic neurons. This is a rigorous, causal, receptor-specific demonstration that the locus coeruleus is wired to be modulated by MT1 signalling, and it is corroborated by the receptor-localisation review of Gobbi and Comai (2019), which places MT1 in the locus coeruleus and lateral hypothalamus as regulators of REM sleep.

The same literature, read honestly, constrains the claim in three ways, and the thesis states all three. First, the receptor is MT1, and there is no comparable evidence for MT2 in the locus coeruleus. Second, and more importantly, native melatonin itself does not measurably alter locus coeruleus firing at the doses tested: Chenu and colleagues (2013) found that repeated melatonin at forty milligrams per kilogram per day left locus coeruleus noradrenergic firing unaltered, and Millan and colleagues (2003) reported that melatonin has negligible activity on locus coeruleus adrenergic firing, the firing changes seen with the melatonergic antidepressant agomelatine being attributable to its 5-HT2C antagonism rather than to melatonin-receptor engagement. The robust modulation of the locus coeruleus required the high-potency synthetic agonist, not the endogenous hormone. Third, all of this is animal — rat — electrophysiology; there is no human locus coeruleus melatonin-receptor or firing data, and no study of MT1 or MT2 in the human locus coeruleus in Alzheimer's disease, a genuine gap given that the receptor changes documented in the disease are in the hippocampus, suprachiasmatic nucleus, and cortex (Savaskan et al., 2002, 2005; Brunner et al., 2006) and are themselves directionally inconsistent. What the receptor literature establishes, then, is that the locus coeruleus *can* be a melatonergic target through MT1; what it does not establish is that endogenous melatonin, at physiological concentrations, tonically modulates the human locus coeruleus. This distinction is the pivot of Chapter III and is graded explicitly in Chapter VI.

Separately from receptor-mediated modulation of firing, melatonin protects locus coeruleus tissue by its antioxidant action: Chen and colleagues (2003) showed that systemic melatonin attenuates iron-induced oxidative injury and the loss of tyrosine-hydroxylase neurons in the rat locus coeruleus, and Jameie and colleagues (2019) showed that melatonin protects locus coeruleus noradrenergic neurons after REM sleep deprivation, reducing caspase-3 activation and microglial migration and raising glutathione. These are protection experiments, not circuit experiments, and they are the more directly relevant to a thesis about the antioxidant defense of the nucleus.

2.6 The Sleep–Glymphatic–Amyloid Axis and Its Noradrenergic Gate

The second service the pineal clock performs for the brain — the scheduling of the nightly state in which waste is cleared — runs through a mechanism that is at once the strongest and the most contested part of the argument. That sleep loss raises the pathological proteins of Alzheimer's disease is, in humans, robust and partly causal: one night of sleep deprivation increases amyloid-β burden on PET in the hippocampus and thalamus (Shokri-Kojori et al., 2018); experimental disruption of slow-wave activity raises cerebrospinal-fluid amyloid-β (Ju et al., 2017); and sleep deprivation raises cerebrospinal-fluid tau in humans and interstitial tau in mice, with chronic sleep loss accelerating tau spread (Holth et al., 2019). These human findings stand on their own, independent of any particular clearance mechanism. Upstream, the sleep-wake control of amyloid was established by Kang and colleagues (2009), who showed that interstitial amyloid-β tracks wakefulness and is driven by orexin, and by Roh and colleagues (2012), who showed that the diurnal amyloid rhythm collapses once plaques form — closing a bidirectional loop in which pathology degrades the sleep that would clear it.

The *mechanism* most often invoked to explain the sleep-dependence of clearance is the glymphatic system: the sleep-associated expansion of the interstitial space and the convective exchange of cerebrospinal and interstitial fluid along perivascular routes, which accelerates amyloid clearance (Iliff et al., 2012; Xie et al., 2013), shows an endogenous circadian rhythm (Hablitz et al., 2020), and — of note for the present thesis — has cerebrospinal-fluid influx nodes at the pineal and pituitary recesses (Iliff et al., 2013). Critically, the state variable that gates glymphatic flow is noradrenergic tone: the fall of noradrenaline in sleep opens the pathway, and the failure of the infraslow noradrenaline oscillations of healthy NREM sleep coincides with amyloid accumulation in an Alzheimer model (Cankar et al., 2024; Hauglund & Nedergaard, 2026). This places the locus coeruleus at the centre of the clearance mechanism: it is the sole source of the noradrenaline whose nightly withdrawal permits clearance, so that its degeneration flattens the very oscillation the mechanism depends upon.

Intellectual honesty requires that the glymphatic mechanism be presented as contested rather than settled. Smith and colleagues (2017) and Smith and Verkman (2018) found parenchymal solute transport to be diffusive and aquaporin-4-independent, failing to replicate the core convective claims; Hladky and Barrand (2014), independently of either camp, concluded that net convective interstitial flow "remains to be established." The proponent laboratories have replied that the effect is real but fragile and highly sensitive to anaesthesia, age, and injection method (Mestre et al., 2018; Gomolka et al., 2023). The defensible position, adopted throughout this thesis, is that the sleep-dependence of amyloid and tau clearance is real and partly demonstrated in humans, that noradrenergic tone is its most plausible gate, and that the glymphatic convective account is the leading but unproven candidate mechanism — a distinction that matters because the thesis's clearance arc survives even if the glymphatic specifics do not.

2.7 The Reverse-Causation Problem: The Pineal as Follower of the Suprachiasmatic Nucleus

The most serious objection to the framework is not that its arcs are weak but that its causal arrow may point the wrong way, and the objection must be stated at full strength. The melatonin decline of Alzheimer's disease is real, but the strongest mechanistic account of it — from Wu, Swaab, and colleagues, the same group that documented the decline — attributes it not to a primary pineal lesion but to the *functional disconnection of the pineal from a degenerating suprachiasmatic nucleus*: the loss of suprachiasmatic vasopressin neurons and the uncoupling of the pineal clock-gene rhythm from its master, reproduced in suprachiasmatic-lesioned rats (Wu et al., 2006; Wu & Swaab, 2005). On this reading the pineal is deafferented rather than diseased, a passive follower whose falling melatonin is a downstream readout of upstream degeneration; and the human neuropathology supports suprachiasmatic involvement directly, with Harper and colleagues (2008) demonstrating loss of suprachiasmatic neurotensin and vasopressin neurons in dementia and Musiek and colleagues (2018) showing rest-activity fragmentation already in preclinical, amyloid-positive but cognitively normal individuals. A second and independent challenge questions whether the celebrated "age-related melatonin decline" is even robust in the first place: Zeitzer and colleagues (1999), studying healthy, medication-free older adults under constant-routine conditions, found no significant reduction in circadian melatonin amplitude relative to young men, implying that much of the reported decline reflects medication, comorbidity, and light exposure rather than pineal ageing per se. Taken together, these findings sustain a coherent alternative to the thesis: that melatonin decline is an early *marker* of the disease's circadian dimension, generated upstream in the suprachiasmatic nucleus and possibly confounded, rather than an independent driver acting on the locus coeruleus. The thesis does not dismiss this alternative; it incorporates it, and Chapter VI states precisely how much of the framework survives if it is true.

2.8 Gaps in the Literature

Four gaps motivate the synthesis. First, the chronobiology of Alzheimer's disease and the cellular biology of locus coeruleus vulnerability have developed independently; the melatonin-decline literature is read against the suprachiasmatic clock and sleep, almost never against the oxidative economy of the locus coeruleus that melatonin's antioxidant profile happens to fit. Second, the recent demonstration that the locus coeruleus expresses MT1 and can be modulated by an MT1 agonist has not been connected to the nucleus's pathological priority in Alzheimer's disease. Third, there is no human study of melatonin receptors in the locus coeruleus in ageing or disease — the receptor data stop at the hippocampus, cortex, and suprachiasmatic nucleus — leaving the humoral arc of the thesis inferential at its most important node. Fourth, the melatonin clinical-trial literature has never been designed around the timing and dose logic the mechanism implies, and has consequently tested the hypothesis in the population and at the dose least likely to reveal it. This dissertation addresses the first two gaps by synthesis, states the third as an explicit limit, and reframes the fourth as a set of design predictions in Chapter VII.

3. Methodology

This dissertation employs the Organic Network Synthesis (ONS) methodology of the AdultCognitiveDisease.com corpus, applied across the Collapse trilogy and its companion volumes. ONS treats the published literature as a network of mechanistic claims and seeks the convergence nodes at which independently developed frameworks make contact, on the premise that these nodes carry the explanatory leverage of a systems account. The present application differs from its companions in one respect: because the causal status of its central linkage is genuinely contested, the methodology is applied in an explicitly adjudicative mode, in which the assembly of the argument is followed by a formal grading of each of its arcs.

The method proceeds in five steps. First, *hub identification*: the selection of the locus coeruleus as the candidate hub, on the basis of its dual status as the earliest and most oxidatively vulnerable site of the disease. Second, *literature triangulation*: the assembly of four literatures that do not ordinarily cite one another — the Braak and Surmeier locus-coeruleus literature, the pineal chronobiology of Klein, Moore, and the Swaab group, the melatonin antioxidant pharmacology of Reiter and Acuña-Castroviejo, and the sleep-clearance literature of Nedergaard, Holtzman, and their critics. Third, *anatomical adjudication*: the honest reconstruction of the pineal–coerulean linkage from primary circuit and electrophysiology data, undertaken with a bias toward disconfirmation, so that the framework rests on what the anatomy supports rather than on what the coincidence suggests.

Fourth, *loop construction*: the assembly of the surviving arcs into the chronobiological–coerulean spiral, with explicit attention to the sign and strength of each arc. Fifth, *grading and prediction*: the assignment of an evidential verdict to each arc (Chapter VI) and the derivation of falsifiable predictions weighted toward those that discriminate the framework from the reverse-causation alternative (Chapter VII).

The methodology has the limitations inherent to synthetic review — it cannot establish causation, and the spiral in particular is a hypothesised feedback loop inferred from its separately evidenced arcs rather than demonstrated as a whole. It carries two further limitations specific to this subject and stated plainly. The mechanistic melatonin literature is dominated by supraphysiological doses, so that mechanistic plausibility and physiological relevance must be kept separate throughout; and the human melatonin-and-Alzheimer data are cross-sectional and cannot, by their design, resolve the direction of causation that the framework most needs resolved. The thesis foregrounds these limitations rather than suppressing them, and treats the reverse-causation alternative of §2.7 not as an objection to be rebutted but as a hypothesis to be weighed.

4. Chapter I The Undefended Nucleus: Melatonin and the Oxidative Vulnerability of the Locus Coeruleus

4.1 The Match Between the Vulnerability and the Defense

The argument of this chapter is a claim of fit. The locus coeruleus fails first, per the Bioenergetic Collapse thesis and §2.1, because of a specific and unusual vulnerability: an autonomous pacemaking that drives dendritic calcium oscillations and, through them, a continuous mitochondrial oxidant stress, compounded by the auto-oxidation of its own catecholaminergic transmitter into quinones and neuromelanin. This is not a generic vulnerability to be met by a generic antioxidant. It is a vulnerability located inside the mitochondrion, at the respiratory chain and the permeability transition pore, and generated continuously by the neuron's normal function. The molecule whose antioxidant pharmacology matches this vulnerability most precisely is melatonin: amphiphilic, mitochondrially-concentrating, a scavenger of superoxide at its site of production, an enhancer of complex-I and complex-IV efficiency that limits electron leakage, a restorer of the mitochondrial glutathione pool, and a stabiliser of the membrane potential that governs the permeability transition pore (§2.3). The defense is matched to the vulnerability not in general but in its specifics — same compartment, same chemistry, same pore.

The claim of fit is strengthened by the two locus-coeruleus-specific protection experiments in the literature. When the rat locus coeruleus is subjected to iron-induced oxidative injury — a reasonable model of the neuromelanin–iron oxidative stress of §2.1 — systemic melatonin attenuates the loss of noradrenergic neurons (Chen et al., 2003); and when the locus coeruleus is stressed by REM sleep deprivation, melatonin protects its noradrenergic neurons, reducing apoptotic signalling and microglial recruitment and raising glutathione (Jameie et al., 2019). These are the two experiments one would design to test the claim of this chapter, and both are positive. Their limitation is the recurring one: they use pharmacological melatonin, not the withdrawal of physiological melatonin, and they establish that melatonin *can* protect the locus coeruleus, not that the nightly loss of endogenous melatonin *un*protects it.

4.2 The Antioxidant as a Nightly, Rhythmic Defense

What makes the melatonin defense distinctive, and what ties it to the disease's chronobiology, is that it is not constant but rhythmic. Melatonin is secreted at night; its antioxidant defense of the locus coeruleus is therefore delivered on a daily schedule, concentrated in the same nocturnal window in which the nucleus's firing demands are lowest and its opportunity for mitochondrial recovery is greatest. The healthy locus coeruleus thus operates a daily cycle of stress and repair: high tonic firing and oxidant generation by day, and by night a fall in firing, a rise in melatonin, and a window of antioxidant-supported mitochondrial recovery. This coupling of the antioxidant to the rest phase is the reason a chronobiological lesion, and not only a chemical one, bears on the locus coeruleus: to disrupt the melatonin rhythm is not merely to lower an antioxidant level but to abolish a scheduled repair phase, and to do so for the neuron least able to tolerate its loss.

4.3 The Bioenergetic Reading and Its Extension

The Bioenergetic Collapse thesis explained the *susceptibility* of the locus coeruleus but, as its own analysis conceded, explained susceptibility better than progression: a standing vulnerability is not yet a disease, and to convert one into the other requires an escalating demand or a diminishing defense. *The Coerulean Interface* supplied one escalating demand, the afferent vagal inflammatory load. The present thesis supplies a diminishing defense: the age- and disease-related withdrawal of the melatonergic antioxidant that had defended the nucleus's mitochondria, and the disintegration of the rest phase in which that defense was delivered. Where the vagal account adds work, the pineal account removes protection; and the two are not alternatives but complements, acting on the same nucleus from opposite directions. The locus coeruleus, on the combined account, is driven harder by the inflamed periphery and defended less by the failing clock — worn from both sides at once. This is the sense in which the pineal interface is the chronobiological face of the coerulean cluster, and it is developed as a formal loop in Chapter V.

5. Chapter II The Failing Clock: Pineal Melatonin Decline as an Early Event

5.1 The Magnitude and the Timing

The empirical core of this chapter is that the melatonin decline of Alzheimer's disease is large and early. It is large: cerebrospinal-fluid melatonin falls to roughly a fifth of control levels (Liu et al., 1999), a reduction of a magnitude unusual among the biochemical changes of the disease. It is early: the decline is present in cognitively intact individuals with only Braak I–II neuropathology (Zhou et al., 2003), the same preclinical window in which the locus coeruleus is the principal site of pathology. The temporal coincidence is the chapter's central fact. In the decades-long preclinical phase of Alzheimer's disease, two processes are demonstrably under way at once: the locus coeruleus is accumulating pretangle tau and beginning its slow attrition, and the melatonin that would have defended it is falling. Whether these two early processes are causally linked or merely concurrent is the question of Chapter VI; that they are concurrent, and early, is established.

5.2 The Structural Correlates

The functional decline is accompanied by structural change in the pineal itself. Pineal calcification is increased in Alzheimer's disease relative to age-matched controls on in-vivo computed tomography (Mahlberg et al., 2008), and pineal parenchymal volume — the uncalcified, melatonin-producing tissue — is reduced on volumetric MRI (Matsuoka et al., 2017). These findings must be read with care, and their principal confound is stated here rather than deferred: pineal calcification rises steeply with normal ageing, so that any disease-associated difference is heavily confounded by age unless controls are tightly matched, and the interpretation of calcification as a melatonin-deficit marker is inferential rather than a direct measurement of the hormone. The age-matched design of the Mahlberg study partly mitigates the confound but cannot, in a cross-sectional comparison, establish that calcification precedes or drives disease. The structural data corroborate the functional decline; they do not, on their own, establish its cause.

5.3 The Upstream Machinery

The decline does not begin at the pineal. The retina–suprachiasmatic–pineal axis shows disruption at each level in Alzheimer's disease: the pineal clock-gene rhythm is lost and functionally disconnected from the suprachiasmatic nucleus (Wu et al., 2006); the suprachiasmatic MT1 receptor declines with age and disease (Wu et al., 2007); and the suprachiasmatic nucleus itself loses the vasopressin and neurotensin neurons that carry its rhythm (Harper et al., 2008), with the downstream consequence of rest-activity fragmentation appearing already in preclinical, amyloid-positive individuals (Musiek et al., 2018). This upstream disruption is, as §2.7 anticipated and Chapter VI will weigh, the strongest evidence *against* a primary pineal role and *for* a picture in which the pineal is deafferented by a failing master clock. The present chapter states the machinery neutrally: the melatonin signal fails, and the failure is distributed across the whole retina–suprachiasmatic–pineal axis, not localised to the pineal. Whether the locus coeruleus is affected by the melatonin loss regardless of where in that axis it originates is the question that makes the site of the primary lesion, for the purposes of this thesis, less decisive than it first appears — a point developed in §6.5.

6. Chapter III The Two Conduits: The Honest Anatomy of the Pineal Coerulean Linkage

6.1 The Absence of a Direct Projection

This chapter performs the dissertation's central act of intellectual discipline, and it begins with a negative result. There is no evidence of a direct monosynaptic neural projection from the pineal gland to the locus coeruleus. The pineal, as §2.2 established, is an effector organ: it receives a sympathetic noradrenergic input from the superior cervical ganglion and secretes melatonin into the cerebrospinal fluid and blood; it does not send axons to the brainstem. Any influence of the pineal on the locus coeruleus must therefore be indirect, and the honest reconstruction of the linkage yields exactly two conduits — a humoral conduit and a shared-clock conduit — of unequal strength, neither of which is the hardwired pineal-to-coeruleus tract that the framing "pineal locus coeruleus" might naively suggest. Naming this absence at the outset is what distinguishes a defensible chronobiological account from a speculative one.

6.2 The Humoral Conduit: Melatonin and the MT1 Receptor of the Locus Coeruleus

The first conduit is humoral: melatonin, secreted by the pineal, circulates and acts on receptors expressed by the locus coeruleus. The strength of this conduit rests on the demonstration by López-Canul and colleagues (2024) that locus coeruleus noradrenergic neurons express MT1 and that a selective MT1 agonist inhibits their firing, with both the receptor and the effect confirmed by selective knockdown (§2.5). This is the load-bearing datum of the humoral conduit, and it is strong on its own terms: rigorous, causal, receptor-specific. But its interpretation for the present thesis is bounded by the finding that native melatonin does not, at the doses tested, measurably alter locus coeruleus firing (Chenu et al., 2013; Millan et al., 2003). The reconciliation the thesis adopts is that the humoral conduit operates through two distinguishable channels of different strength. The first is *receptor-mediated modulation of firing*, which is demonstrated for the synthetic MT1 agonist but not for endogenous melatonin, and which the thesis therefore treats as a pharmacological possibility rather than an established physiological tonic input. The second is *receptor-independent antioxidant protection*, in which circulating melatonin defends locus coeruleus mitochondria by the chemistry of §2.3 and §4.1, which does not require the hormone to change the neuron's firing and which is supported by the two locus-coeruleus protection experiments (Chen et al., 2003; Jameie et al., 2019). The humoral conduit, in short, is real but its physiological weight falls on the antioxidant channel, not on the firing-modulation channel — a distinction that the naive reading of the López-Canul result would miss and that Chapter VI grades accordingly.

6.3 The Shared-Clock Conduit

The second conduit is architectural rather than humoral: the locus coeruleus and the pineal are both downstream of the suprachiasmatic nucleus, and their coupling is largely the coupling of two followers of a common master. The suprachiasmatic nucleus drives the locus coeruleus indirectly, through a relay to the dorsomedial hypothalamus and thence to the locus coeruleus, with orexin as the neurochemical carrier; lesions of the dorsomedial hypothalamus abolish the circadian variation of locus coeruleus firing, and an orexin antagonist in the locus coeruleus attenuates its active-phase firing increase (Aston-Jones et al., 2001; Gompf & Aston-Jones, 2008). The same suprachiasmatic nucleus drives the pineal through the sympathetic relay of §2.2 (Garidou et al., 2001). The locus coeruleus and the pineal are therefore *siblings under the clock*: their rhythms are correlated not because one drives the other but because both are driven by the suprachiasmatic nucleus. This shared-clock architecture is, paradoxically, both a weakening and a strengthening of the thesis. It weakens the direct causal claim — much of the pineal–coerulean correlation is confounded by the common upstream driver — but it strengthens the systems claim, because a lesion of the shared master clock degrades both the melatonin defense and the circadian regulation of the locus coeruleus simultaneously, which is precisely the concurrent early failure that §5.1 documents.

6.4 The Reconciliation

The honest anatomy therefore yields a linkage that is real, indirect, and dominated by two channels: the receptor-independent antioxidant protection of the locus coeruleus by circulating melatonin, and the shared suprachiasmatic control of both the melatonin rhythm and the circadian regulation of the locus coeruleus. The firing-modulation channel through MT1 is a demonstrated capacity of the nucleus but not an established physiological input of endogenous melatonin, and the thesis does not rest weight on it beyond noting its therapeutic implication (Chapter VII). What survives this reconstruction is enough to support the framework's central claim — that the failing clock withdraws antioxidant protection from, and degrades the circadian regulation of, the nucleus that fails first — without requiring the direct projection that does not exist or the physiological firing input that the electrophysiology denies. It is a smaller claim than the framing suggests, and it is the one the anatomy will bear.

7. Chapter IV The Glymphatic Night: Sleep, Noradrenergic Gating, and Clearance

7.1 The Second Service

The pineal clock's second service to the brain is the scheduling of sleep, and specifically of the nocturnal state in which the interstitial clearance of amyloid-β and tau is most efficient. This service is, unlike the antioxidant defense, not delivered to the locus coeruleus alone but to the whole brain; but it is gated by the locus coeruleus, and its failure feeds back on the locus coeruleus, which makes it part of the same loop. The chapter develops the service and its gate, and — because the mechanism is contested — states its evidential status at each step.

7.2 The Human Evidence, Which Stands Alone

The strongest and most decision-relevant facts are the human ones, and they do not depend on any particular clearance mechanism. One night of sleep deprivation raises amyloid-β on PET (Shokri-Kojori et al., 2018); disruption of slow-wave activity raises cerebrospinal-fluid amyloid-β (Ju et al., 2017); sleep deprivation raises cerebrospinal-fluid tau (Holth et al., 2019); and short sleep in midlife predicts incident dementia over twenty-five years of follow-up (Sabia et al., 2021), with sleep-disordered breathing and its attendant hypoxia predicting incident cognitive impairment (Yaffe et al., 2011). These findings establish, in humans, that the loss of sleep raises the pathological proteins of Alzheimer's disease and that chronic poor sleep predicts the disease. They are the empirical floor of the chapter, and they survive whatever becomes of the glymphatic hypothesis.

7.3 The Noradrenergic Gate

The mechanism that links sleep to clearance is gated by noradrenergic tone, and this is what draws the locus coeruleus into the account. In sleep, noradrenergic tone falls; the fall opens the interstitial space and permits convective fluid exchange; and the infraslow oscillation of noradrenaline across the sleep cycle is itself the rhythm that drives the clearance. Cankar and colleagues (2024) showed that the failure of these infraslow noradrenaline oscillations coincides with amyloid accumulation in an Alzheimer model, and Hauglund and Nedergaard (2026) synthesised the noradrenaline-gated account of restorative sleep. The locus coeruleus is the sole source of the noradrenaline whose nightly withdrawal permits clearance; its degeneration therefore flattens the oscillation the mechanism depends upon, so that the same nucleus whose loss withdraws the microglial and vascular brakes (the argument of *The Coerulean Interface*) also, by the argument of this chapter, degrades the nocturnal clearance rhythm. The noradrenergic gate is the point at which the sleep-clearance axis and the coerulean axis are the same axis.

7.4 The Contested Mechanism, Stated as Contested

The convective glymphatic account of how sleep clears waste — perivascular cerebrospinal-fluid influx, aquaporin-4-dependent exchange, and the sleep-associated expansion of the interstitial space (Iliff et al., 2012; Xie et al., 2013; Hablitz et al., 2020) — is the leading candidate mechanism, and it carries a detail of incidental relevance to this thesis in that its cerebrospinal-fluid influx nodes include the pineal recess (Iliff et al., 2013). But it is genuinely contested. Smith and colleagues (2017) and Smith and Verkman (2018) found solute transport to be diffusive and aquaporin-4-independent and failed to replicate the convective claims; Hladky and Barrand (2014) concluded that net convective interstitial flow remains unestablished; and the proponent laboratories concede that the effect, where present, is fragile and highly sensitive to anaesthesia, age, and method (Mestre et al., 2018; Gomolka et al., 2023). The thesis therefore adopts the minimal position that the chapter's argument requires and no more: that the sleep- and noradrenaline-dependence of amyloid and tau accumulation is real and partly demonstrated in humans, and that the locus coeruleus gates it through noradrenergic tone — a position that holds whether the clearance is convective-glymphatic or diffusive, and that does not stake the framework on the outcome of an unresolved dispute in fluid physiology. There is, additionally, a cell-autonomous route to the same conclusion: the core clock protein BMAL1 governs autophagy and endolysosomal proteostasis in astrocytes (McKee et al., 2023), so that circadian disruption may impair protein clearance intracellularly and independently of any bulk-flow mechanism at all.

8. Chapter V The Chronobiological Coerulean Spiral

8.1 The Loop Stated

The preceding chapters supply the arcs of a loop, which this chapter states as a falsifiable dynamical claim rather than a metaphor. The loop has four arcs. First, the failing pineal clock withdraws melatonergic antioxidant protection from the locus coeruleus (Chapters I–III), accelerating the oxidative attrition of a nucleus already at its bioenergetic ceiling. Second, the same failing clock degrades the melatonin-timed sleep state, and with it the nocturnal, noradrenaline-gated clearance of amyloid and tau (Chapter IV). Third, the resulting attrition of the locus coeruleus removes the source of the noradrenaline whose nightly oscillation gates clearance and whose tone stabilises arousal state — so that a degraded locus coeruleus produces a more fragmented sleep–wake cycle and a flatter clearance rhythm. Fourth, the degraded sleep–wake cycle and the loss of locus coeruleus input to the circadian system feed back to worsen the very rhythm whose failure began the loop. The result is a self-amplifying spiral: a failing clock injures the locus coeruleus, and an injured locus coeruleus further degrades the clock.

8.2 The Asymmetry of the Arcs

The loop's arcs are not of equal strength, and the honest statement of the loop is the statement of its asymmetry. The first two arcs — clock-to-coeruleus, by withdrawal of antioxidant and of rest — are the better supported: the antioxidant match is mechanistically strong (Chapter I), the melatonin decline is documented and early (Chapter II), and the sleep-clearance floor is human and robust (Chapter IV). The fourth arc — coeruleus-to-clock — is the weakest closure of the loop, because there is no strong direct projection from the locus coeruleus to the suprachiasmatic nucleus; the locus coeruleus feeds back on the clock indirectly, through its degradation of sleep architecture and arousal stability rather than through a hardwired coeruleus-to-suprachiasmatic tract. The loop therefore closes, but it closes through behaviour and state rather than through a dedicated circuit, and the thesis says so. This asymmetry matters for intervention: the loop is more readily broken on its strong arcs (protect the locus coeruleus; restore the clock and the rest phase) than on its weak one.

8.3 The Kinetics and the Tipping Point

The spiral, like the coerulean–microglial spiral of the companion volume, is a slow positive-feedback loop with a long subclinical phase and a threshold. In the preclinical decades, the arcs turn slowly: melatonin falls gradually, the locus coeruleus attrites gradually, sleep fragments gradually, and each increment of one worsens the others by a small amount. The system is buffered by redundancy — the antioxidant defense of the locus coeruleus is not melatonin alone, the clearance of amyloid is not the nocturnal glymphatic route alone, and the circadian regulation of the locus coeruleus is not the pineal alone — so that for a long time the loop's gain is below one and the decline is slow and compensated. The tipping point is the moment at which enough locus coeruleus neurons have been lost that the noradrenergic gate and the arousal-stabilising output fail together, the loop's gain crosses one, and the slow compensated decline becomes a fast uncompensated one. This kinetic structure predicts, as the corpus repeatedly predicts, that intervention is effective before the tipping point and ineffective after it — the theme of Chapter VII.

9. Chapter VI An Assessment of Validity: Grading the Arcs

9.1 The Purpose of an Explicit Grading

The user of a synthetic framework is entitled to know not only what it claims but how much to believe each claim, and this chapter supplies that accounting. It grades every load-bearing arc of the framework on a five-level scale — *strong*, *moderate*, *contested*, *speculative*, and *unsupported* — with the evidence and its limitations stated for each. The grading is deliberately conservative: an arc is graded by the weakest link that the framework requires it to bear, not by the strongest study that can be found in its favour. The purpose is not to defend the framework but to locate precisely where it is secure and where it is not.

9.2 The Strong Arcs

Three claims are graded *strong*. The first is the pathological and oxidative priority of the locus coeruleus: that it is the earliest site of Alzheimer tau and the most oxidatively vulnerable nucleus, supported by large human neuropathological series (Braak & Del Tredici, 2011; Braak et al., 2011; Streit et al., 2013), by direct electrophysiological demonstration of the pacemaking-driven mitochondrial oxidant stress (Sanchez-Padilla et al., 2014; Surmeier et al., 2010), and by convergent neuromelanin-MRI evidence (Dahl et al., 2019; Chen et al., 2022). The second is the early and substantial decline of cerebrospinal-fluid melatonin in Alzheimer's disease, including at the preclinical stage, replicated within a large cohort (Liu et al., 1999; Zhou et al., 2003). The third is the human sleep-clearance floor: that the loss of sleep raises amyloid-β and tau in humans and that chronic poor sleep predicts dementia (Shokri-Kojori et al., 2018; Ju et al., 2017; Holth et al., 2019; Sabia et al., 2021). These three arcs are the framework's foundation and they are secure.

9.3 The Moderate Arcs

Two claims are graded *moderate*. The first is the antioxidant match: that melatonin's mitochondrial antioxidant pharmacology is specifically suited to the locus coeruleus's vulnerability, and that melatonin protects the locus coeruleus. The mechanistic pharmacology is strong (Reiter et al., 1999; Acuña-Castroviejo et al., 2001; León et al., 2005) and the two locus-coeruleus protection experiments are positive (Chen et al., 2003; Jameie et al., 2019); the grade is held to moderate rather than strong by the dose problem — the protection is demonstrated at pharmacological, not physiological, melatonin concentrations — and by the fact that the experiments show melatonin *can* protect the nucleus, not that endogenous melatonin's withdrawal *un*protects it. The second moderate arc is the noradrenergic gating of clearance: that locus coeruleus noradrenaline gates the nocturnal clearance of amyloid and tau (Cankar et al., 2024; Hauglund & Nedergaard, 2026). The mechanism is coherent and the human sleep-clearance floor supports its consequence, but the gating itself is demonstrated in rodents and inferred in humans, and it inherits some of the uncertainty of the contested clearance mechanism.

9.4 The Contested and Speculative Arcs

One arc is graded *contested* and one *speculative*. The contested arc is the glymphatic convective mechanism of clearance, whose status is discussed at length in §7.4: it is the leading candidate but has failed direct replication and is disputed on physiological grounds (Smith & Verkman, 2018; Hladky & Barrand, 2014; against Mestre et al., 2018). The framework is explicitly constructed not to depend on it. The speculative arc is the receptor-mediated melatonergic modulation of locus coeruleus firing as a *physiological* input: the MT1 receptor is present and a synthetic agonist engages it (López-Canul et al., 2024), but endogenous melatonin does not measurably modulate locus coeruleus firing (Chenu et al., 2013; Millan et al., 2003), so the claim that physiological nocturnal melatonin tonically restrains the locus coeruleus through MT1 is, at present, speculative. The framework accordingly rests its humoral conduit on antioxidant protection, not on firing modulation (§6.2).

9.5 The Unsupported Claims and the Reverse-Causation Problem

Two things must be graded *unsupported*, and naming them is the chapter's most important work. First, there is no direct neural projection from the pineal to the locus coeruleus; the framing "pineal locus coeruleus" is a shorthand for an indirect, humoral-and-shared-clock linkage, not a tract, and any reading that supposes a hardwired pineal-to-coeruleus circuit is unsupported (§6.1). Second, there is no human evidence on melatonin receptors in the locus coeruleus in ageing or disease; the receptor data stop at the hippocampus, cortex, and suprachiasmatic nucleus, so the humoral conduit's most important node is, in humans, inferential.

Above these specific gaps stands the general problem of causal direction, and the framework's honesty is measured by how it treats it. The reverse-causation alternative of §2.7 — that melatonin decline is a downstream marker of suprachiasmatic degeneration rather than a driver, with the pineal deafferented rather than diseased (Wu et al., 2006; Wu & Swaab, 2005), and with the very existence of an age-related melatonin decline questioned in medication-free subjects (Zeitzer et al., 1999) — is well evidenced and cannot be excluded. The framework's response is not to rebut it but to establish how much survives if it is true, which is the subject of §6.6.

9.6 What Survives If the Pineal Is Only a Follower

Suppose the reverse-causation alternative is correct in full: the primary chronobiological lesion is in the suprachiasmatic nucleus, the pineal is a passive follower, and the falling melatonin is a readout rather than a cause. How much of the framework survives? The answer is: most of the part that matters clinically, and this is the resolution that the shared-clock conduit of §6.3 makes possible. If the suprachiasmatic nucleus is the primary lesion, then the melatonin it once timed still falls, the antioxidant defense of the locus coeruleus is still withdrawn, and the nocturnal clearance is still degraded — the *consequences* for the locus coeruleus are identical regardless of whether the melatonin loss originates in the pineal or upstream of it. What the reverse-causation alternative changes is the *locus of the primary lesion*, not the *fact of the withdrawn protection*. The framework's claim is about the locus coeruleus as the recipient of a withdrawn protection, and that claim is agnostic to where in the retina–suprachiasmatic–pineal axis the withdrawal originates. This is why the thesis insists, in §5.3, that the site of the primary lesion is less decisive than it first appears: the locus coeruleus is undefended whether the pineal fails or is merely deafferented. What the reverse-causation alternative does defeat is the strong therapeutic inference that treating the pineal, or replacing melatonin, addresses a primary cause; if the pineal is a follower, melatonin replacement is a downstream patch, and its modest and inconsistent clinical results (Chapter VII) are exactly what one would then predict. The framework survives as an account of the locus coeruleus's undefending; it does not survive as a claim that the pineal is a prime mover, and it does not assert that it is.

10. Chapter VII Therapeutic Implications and Falsifiable Predictions

10.1 The Therapeutic Surface and Its Timing

The framework generates a therapeutic surface organised around the arcs of the spiral: protect the locus coeruleus with the antioxidant it is losing, restore the melatonin-timed rest phase and its clearance, and — the recurring theme of the corpus — do both early, while the nucleus the intervention would protect still largely exists. The timing logic is the framework's sharpest therapeutic prediction and its readiest explanation of past failure: an intervention that supports the melatonergic defense of the locus coeruleus can work only while the locus coeruleus survives to be defended, and must fail once the nucleus has degenerated. This predicts a benefit concentrated in the preclinical and prodromal phases and absent in established dementia — which is precisely the pattern the trial literature shows.

10.2 The Melatonin Trial Literature, Without Euphemism

The clinical evidence for melatonin in Alzheimer's disease must be reported as it is, because it is the framework's most immediate empirical test, and it is not encouraging for any strong therapeutic claim. The best evidence supports a modest sleep benefit at most: a meta-analysis found that melatonin prolongs nocturnal sleep but does not improve cognition (Wang et al., 2016), and the Cochrane review found no reliable benefit of melatonin on any major sleep outcome in moderate-to-severe Alzheimer's disease, and none for the MT1/MT2 agonist ramelteon (McCleery et al., 2014). On cognition the literature is contradictory: a prolonged-release melatonin trial reported benefit on secondary cognitive and functional measures but with a null result on its ADAS-Cog cognitive scale and in a small, industry-sponsored sample (Wade et al., 2014); one meta-analysis found a small MMSE gain confined to mild-stage disease with long treatment (Sumsuzzman et al., 2021) while another found no cognitive benefit at all (Wang et al., 2016); and the largest and best-powered melatonergic cognition trial, of the MT1/MT2/5-HT agonist piromelatine, was flatly negative on its primary and secondary endpoints (Schneider et al., 2022). The framework does not explain this away; it predicts much of it. The completed trials used doses around two milligrams — roughly two orders of magnitude below the neuroprotective range identified in animal models (Cardinali et al., 2014) — in patients whose disease was already established and whose locus coeruleus had already substantially degenerated. On the framework's own logic, these are the dose and the stage least likely to reveal a locus-coeruleus-protective effect, and the modest, sleep-limited, early-disease-weighted signal that the trials do show is consistent with the framework without confirming it.

10.3 The Design the Framework Implies

The framework's therapeutic contribution is therefore less a recommendation than a redesign. It predicts that a fair test of melatonergic protection of the locus coeruleus would differ from every completed trial in three respects: it would enrol individuals in the preclinical or prodromal phase, identified by reduced locus coeruleus neuromelanin-MRI signal and by circadian and cerebrospinal-fluid-melatonin markers, rather than patients with established dementia; it would use a dose informed by the neuroprotective, not the hypnotic, range, with the attendant safety work that implies; and it would take as its primary endpoint the preservation of locus coeruleus integrity on neuromelanin-MRI, not a global cognitive scale, so that the mechanism is tested where it is proposed to act. The framework also notes, without resting weight on it, that the demonstrated MT1-agonist inhibition of locus coeruleus firing (López-Canul et al., 2024) raises the distinct possibility of a selective MT1 agonist as a locus-coeruleus-directed agent — a possibility the crude endogenous hormone, which does not modulate locus coeruleus firing, cannot realise.

10.4 Falsifiable Predictions

The framework makes the following predictions, ordered from most to least readily testable.

First, locus coeruleus neuromelanin-MRI integrity and cerebrospinal-fluid or salivary melatonin should be positively correlated within individuals and should decline together across ageing and disease; a dissociation, in which locus coeruleus integrity declines independently of melatonin, would weaken the coupling that Chapters I–III propose.

Second, the rate of locus coeruleus decline on neuromelanin-MRI should be predicted by circadian and melatonin measures in prospective cohorts, and this prediction should hold after adjustment for suprachiasmatic and sleep measures; if melatonin adds no predictive power beyond a general circadian-degeneration index, the framework reduces to the reverse-causation alternative and its specific melatonergic claim is falsified.

Third, melatonergic intervention should preserve locus coeruleus integrity in proportion to residual integrity at baseline, having its largest effect early and diminishing as the nucleus degenerates; a uniform or late-predominant effect would contradict the timing logic of §10.1.

Fourth, a fair-dose, early-stage, locus-coeruleus-endpoint trial should show an effect where the completed low-dose, late-stage, cognition-endpoint trials did not; a null result in such a trial would be strong evidence against the therapeutic arm of the framework, and is the cleanest available falsification.

Fifth, and least readily testable, experimental restoration of the noradrenaline-gated nocturnal clearance rhythm — whether by supporting the locus coeruleus or by pharmacologically restoring the rest-phase noradrenergic fall — should slow amyloid and tau accumulation more than either sleep consolidation or antioxidant supplementation alone, reflecting the convergence of the two services the pineal clock provides; confirmation would support the spiral of Chapter V, and its absence would suggest the two arcs act independently rather than as a loop.

11. Conclusion

This dissertation has asked what the pineal gland has to do with the nucleus that fails first in Alzheimer's disease, and has given a bounded and, it hopes, honest answer. The locus coeruleus is the earliest and most oxidatively vulnerable site of the disease, a pacemaking neuron whose mitochondria are stressed by its own function and whose survival depends on the quality of its antioxidant defense and the sufficiency of its rest. The pineal clock supplies both: melatonin, the mitochondrial antioxidant whose chemistry is specifically matched to the locus coeruleus's vulnerability, and the nocturnal, melatonin-timed sleep state in which noradrenergic tone falls and the brain is cleared. Both decline in Alzheimer's disease, and both decline early — at the preclinical

Braak I–II stage, in step with the earliest coerulean pathology. The framework's claim is that this concurrence is mechanistically real: the failing clock withdraws the antioxidant defense of the locus coeruleus and degrades the rest in which that defense was delivered, so that the nucleus is worn from both sides at once — worked without relief by the inflamed periphery of the companion volume, and defended without its antioxidant by the failing clock of this one.

The dissertation has been unusually explicit about the limits of this claim, because the subject demands it. There is no direct neural projection from the pineal to the locus coeruleus; the linkage is humoral and shared-clock-mediated, and its physiological weight falls on the antioxidant protection of the nucleus rather than on any melatonergic modulation of its firing, which endogenous melatonin does not perform. The glymphatic mechanism most often invoked for the clearance arc is contested, and the framework is built not to depend on it. And the direction of causation — whether the pineal is diseased or merely deafferented by a failing suprachiasmatic nucleus — cannot be resolved by the available cross-sectional human data, and may well favour the pineal-as-follower reading. The framework's response to that last and deepest uncertainty is its central methodological move: because its claim is about the locus coeruleus as the recipient of a withdrawn protection, it is agnostic to where in the retina–suprachiasmatic–pineal axis the withdrawal originates. The locus coeruleus is undefended whether the pineal fails or is deafferented, and the clinically load-bearing part of the framework survives the reverse-causation alternative even as its claim to have found a prime mover does not.

The value of the pineal interface is therefore not a new cause of Alzheimer's disease. It is a precise, graded, and falsifiable account of *why the nucleus that fails first is the one the night was built to protect* — of how the daily rhythm of antioxidant defense and cleared rest is matched to the vulnerability of the locus coeruleus, and of what is lost, and when, and with what consequence, as the clock that keeps that rhythm fails. It locates a narrow, early, and testable window in which restoring the protection might matter, and it states plainly the doses, the stages, and the endpoints at which the past melatonin trials looked for a benefit where the framework predicts none could be found. To protect the locus coeruleus, and to keep the antioxidant and the rest of the biological night while the nucleus still exists to receive them, is — on the bounded argument of this dissertation — to intervene not at the cause of the disease but at one of the conditions of its acceleration, and to do so at the hinge of time where the corpus locates the disease's long, silent beginning.

12. References

Ackermann, K., & Stehle, J. H. (2006). Melatonin synthesis in the human pineal gland: advantages, implications, and difficulties. *Chronobiology International*, 23(1–2), 369–379.

Acuña-Castroviejo, D., Martín, M., Macías, M., Escames, G., León, J., Khaldy, H., & Reiter, R. J. (2001). Melatonin, mitochondria, and cellular bioenergetics. *Journal of Pineal Research*, 30(2), 65–74.

Aston-Jones, G., Chen, S., Zhu, Y., & Oshinsky, M. L. (2001). A neural circuit for circadian regulation of arousal. *Nature Neuroscience*, 4(7), 732–738.

Braak, H., & Del Tredici, K. (2011). The pathological process underlying Alzheimer's disease in individuals under thirty. *Acta Neuropathologica*, 121(2), 171–181.

Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *Journal of Neuropathology & Experimental Neurology*, 70(11), 960–969.

Brunner, P., Sözer-Topcular, N., Jockers, R., Ravid, R., Angeloni, D., Fraschini, F., Eckert, A., Müller-Spahn, F., & Savaskan, E. (2006). Pineal and cortical melatonin receptors MT1 and MT2 are decreased in Alzheimer's disease. *European Journal of Histochemistry*, 50(4), 311–316.

Cankar, N., Beschorner, N., Tsopanidou, A., Nedergaard, M., et al. (2024). Sleep deprivation leads to non-adaptive alterations in sleep microarchitecture and amyloid-β accumulation in a murine Alzheimer model. *Cell Reports*, 43(11), 114977.

Cardinali, D. P., Vigo, D. E., Olivar, N., Vidal, M. F., & Brusco, L. I. (2014). Melatonin therapy in patients with Alzheimer's disease. *Antioxidants*, 3(2), 245–277.

Chen, K. B., Lin, A. M., & Chiu, T. H. (2003). Systemic vitamin C administration attenuates and melatonin protects against iron-induced neurotoxicity in rat locus coeruleus. *Journal of Pineal Research*, 35(2), 109–117.

Chen, Y., Chen, T., & Hou, R. (2022). Locus coeruleus in the pathogenesis of Alzheimer's disease: a systematic review. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 8(1), e12257.

Chenu, F., Shim, S., El Mansari, M., & Blier, P. (2013). Role of melatonin, serotonin 2B, and serotonin 2C receptors in modulating the firing activity of rat dopamine and noradrenergic neurons. *Journal of Psychopharmacology*, 28(2), 162–167.

Clewett, D. V., Lee, T. H., Greening, S., Ponzio, A., Margalit, E., & Mather, M. (2016). Neuromelanin marks the spot: identifying a locus coeruleus biomarker of cognitive reserve in healthy aging. *Neurobiology of Aging*, 37, 117–126.

Dahl, M. J., Mather, M., Düzel, S., Bodammer, N. C., Lindenberger, U., Kühn, S., & Werkle-Bergner, M. (2019). Rostral locus coeruleus integrity is associated with better memory performance in older adults. *Nature Human Behaviour*, 3(11), 1203–1214.

Garidou, M. L., Bartol, I., Calgari, C., Pévet, P., & Simonneaux, V. (2001). In vivo observation of a non-noradrenergic regulation of arylalkylamine N-acetyltransferase gene expression in the rat pineal gland. *Neuroscience*, 105(3), 721–729.

Gobbi, G., & Comai, S. (2019). Differential function of melatonin MT1 and MT2 receptors in REM and NREM sleep. *Frontiers in Endocrinology*, 10, 87.

Gomolka, R. S., Hablitz, L. M., Mestre, H., Giannetto, M., Du, T., Hauglund, N. L., et al. (2023). Loss of aquaporin-4 results in glymphatic system dysfunction via brain-wide interstitial fluid stagnation. *eLife*, 12, e82232.

Gompf, H. S., & Aston-Jones, G. (2008). Role of orexin input in the diurnal rhythm of locus coeruleus impulse activity. *Brain Research*, 1224, 43–52.

Hablitz, L. M., Plá, V., Giannetto, M., Vinitsky, H. S., Stæger, F. F., Metcalfe, T., et al. (2020). Circadian control of brain glymphatic and lymphatic fluid flow. *Nature Communications*, 11(1), 4411.

Harper, D. G., Stopa, E. G., Kuo-Leblanc, V., McKee, A. C., Asayama, K., Volicer, L., Kowall, N., & Satlin, A. (2008). Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. *Brain*, 131(6), 1609–1617.

Hauglund, N. L., & Nedergaard, M. (2026). Is glymphatic clearance the secret to restorative sleep? *Brain*, 149(6), 1819–1831.

Hladky, S. B., & Barrand, M. A. (2014). Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence. *Fluids and Barriers of the CNS*, 11(1), 26.

Holth, J. K., Fritschi, S. K., Wang, C., Pedersen, N. P., Cirrito, J. R., Mahan, T. E., et al. (2019). The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science*, 363(6429), 880–884.

Iba, M., McBride, J. D., Guo, J. L., Zhang, B., Trojanowski, J. Q., & Lee, V. M. Y. (2015). Tau pathology spread in PS19 tau transgenic mice following locus coeruleus (LC) injections of synthetic tau fibrils is determined by the LC's afferent and efferent connections. *Acta Neuropathologica*, 130(3), 349–362.

Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Science Translational Medicine*, 4(147), 147ra111.

Iliff, J. J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M., & Benveniste, H. (2013). Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *Journal of Clinical Investigation*, 123(3), 1299–1309.

Jameie, S. B., Mesgar, S., Aliaghaei, A., Raoofi, A., Abdollahifar, M. A., Ebrahimi, M. J., et al. (2019). Neuroprotective effect of exogenous melatonin on the noradrenergic neurons of adult male rats' locus coeruleus nucleus following REM sleep deprivation. *Journal of Chemical Neuroanatomy*, 100, 101656.

Ju, Y. S., Ooms, S. J., Sutphen, C., Macauley, S. L., Zangrilli, M. A., Jerome, G., et al. (2017). Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain*, 140(8), 2104–2111.

Kang, J. E., Lim, M. M., Bateman, R. J., Lee, J. J., Smyth, L. P., Cirrito, J. R., et al. (2009). Amyloid-β dynamics are regulated by orexin and the sleep-wake cycle. *Science*, 326(5955), 1005–1007.

Klein, D. C. (2007). Arylalkylamine N-acetyltransferase: "the Timezyme." *Journal of Biological Chemistry*, 282(7), 4233–4237.

León, J., Acuña-Castroviejo, D., Sainz, R. M., Mayo, J. C., Tan, D. X., & Reiter, R. J. (2004). Melatonin and mitochondrial function. *Life Sciences*, 75(7), 765–790.

León, J., Acuña-Castroviejo, D., Escames, G., Tan, D. X., & Reiter, R. J. (2005). Melatonin mitigates mitochondrial malfunction. *Journal of Pineal Research*, 38(1), 1–9.

Leng, Y., Musiek, E. S., Hu, K., Cappuccio, F. P., & Yaffe, K. (2019). Association between circadian rhythms and neurodegenerative diseases. *The Lancet Neurology*, 18(3), 307–318.

Liu, K. Y., Acosta-Cabronero, J., Cardenas-Blanco, A., Loane, C., Berry, A. J., Betts, M. J., et al. (2018). In vivo visualization of age-related differences in the locus coeruleus. *Neurobiology of Aging*, 74, 101–111.

Liu, R. Y., Zhou, J. N., van Heerikhuize, J., Hofman, M. A., & Swaab, D. F. (1999). Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-ε4/4 genotype. *Journal of Clinical Endocrinology & Metabolism*, 84(1), 323–327.

López-Canul, M., He, Q., Sasson, T., Ettaoussi, M., Gregorio, D. D., Ochoa-Sanchez, R., et al. (2024). Selective enhancement of REM sleep through MT1 melatonin receptors expressed in locus coeruleus neurons. *Journal of Neuroscience*, 44(29), e0914232024.

Magri, F., Sarra, S., Cinchetti, W., Guazzoni, V., Fioravanti, M., Cravello, L., & Ferrari, E. (2004). Qualitative and quantitative changes of melatonin levels in physiological and pathological aging and in centenarians. *Journal of Pineal Research*, 36(4), 256–261.

Mahlberg, R., Walther, S., Kalus, P., Bohner, G., Haedel, S., Reischies, F. M., et al. (2008). Pineal calcification in Alzheimer's disease: an in vivo study using computed tomography. *Neurobiology of Aging*, 29(2), 203–209.

Matsuoka, T., Imai, A., Fujimoto, H., Kato, Y., Shibata, K., Nakamura, K., et al. (2018). Reduced pineal volume in Alzheimer disease: a retrospective cross-sectional MR imaging study. *Radiology*, 286(1), 239–248.

Mather, M., & Harley, C. W. (2016). The locus coeruleus: essential for maintaining cognitive function and the aging brain. *Trends in Cognitive Sciences*, 20(3), 214–226.

McCleery, J., Cohen, D. A., & Sharpley, A. L. (2014). Pharmacotherapies for sleep disturbances in Alzheimer's disease. *Cochrane Database of Systematic Reviews*, (3), CD009178.

McKee, C. A., Polino, A. J., King, M. W., & Musiek, E. S. (2023). Circadian clock protein BMAL1 broadly influences autophagy and endolysosomal function in astrocytes. *Proceedings of the National Academy of Sciences*, 120(20), e2220551120.

Mestre, H., Hablitz, L. M., Xavier, A. L., Feng, W., Zou, W., Pu, T., et al. (2018). Aquaporin-4-dependent glymphatic solute transport in the rodent brain. *eLife*, 7, e40070.

Millan, M. J., Gobert, A., Lejeune, F., Dekeyne, A., Newman-Tancredi, A., Pasteau, V., et al. (2003). The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *Journal of Pharmacology and Experimental Therapeutics*, 306(3), 954–964.

Moore, R. Y. (1996). Neural control of the pineal gland. *Behavioural Brain Research*, 73(1–2), 125–130.

Musiek, E. S., & Holtzman, D. M. (2016). Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science*, 354(6315), 1004–1008.

Musiek, E. S., Bhattacharya, T., Fabbri, M., Kang, P., Roby, D. A., Fagan, A. M., et al. (2018). Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurology*, 75(5), 582–590.

Perreau-Lenz, S., Kalsbeek, A., Garidou, M. L., Wortel, J., van der Vliet, J., van Heijningen, C., et al. (2003). Suprachiasmatic control of melatonin synthesis in rats: inhibitory and stimulatory mechanisms. *European Journal of Neuroscience*, 17(2), 221–228.

Perreau-Lenz, S., Kalsbeek, A., Pévet, P., & Buijs, R. M. (2005). Glutamatergic clock output stimulates melatonin synthesis at night. *European Journal of Neuroscience*, 22(10), 2531–2540.

Pappolla, M., Bozner, P., Soto, C., Shao, H., Robakis, N. K., Zagorski, M., Frangione, B., & Ghiso, J. (1998). Inhibition of Alzheimer β-fibrillogenesis by melatonin. *Journal of Biological Chemistry*, 273(13), 7185–7188.

Reiter, R. J., Tan, D. X., Cabrera, J., D'Arpa, D., Sainz, R. M., Mayo, J. C., & Ramos, S. (1999). The oxidant/antioxidant network: role of melatonin. *Biological Signals and Receptors*, 8(1–2), 56–63.

Roh, J. H., Huang, Y., Bero, A. W., Kasten, T., Stewart, F. R., Bateman, R. J., & Holtzman, D. M. (2012). Disruption of the sleep-wake cycle and diurnal fluctuation of β-amyloid in mice with Alzheimer's disease pathology. *Science Translational Medicine*, 4(150), 150ra122.

Sabia, S., Fayosse, A., Dumurgier, J., van Hees, V. T., Paquet, C., Sommerlad, A., et al. (2021). Association of sleep duration in middle and old age with incidence of dementia. *Nature Communications*, 12(1), 2289.

Sanchez-Padilla, J., Guzman, J. N., Ilijic, E., Kondapalli, J., Galtieri, D. J., Yang, B., et al. (2014). Mitochondrial oxidant stress in locus coeruleus is regulated by activity and nitric oxide synthase. *Nature Neuroscience*, 17(6), 832–840.

Savaskan, E., Olivieri, G., Meier, F., Brydon, L., Jockers, R., Ravid, R., Wirz-Justice, A., & Müller-Spahn, F. (2002). Increased melatonin 1a-receptor immunoreactivity in the hippocampus of Alzheimer's disease patients. *Journal of Pineal Research*, 32(1), 59–62.

Savaskan, E., Ayoub, M. A., Ravid, R., Angeloni, D., Fraschini, F., Meier, F., et al. (2005). Reduced hippocampal MT2 melatonin receptor expression in Alzheimer's disease. *Journal of Pineal Research*, 38(1), 10–16.

Schneider, L. S., Laudon, M., Nir, T., Caceres, J., Ianniciello, G., Capulli, M., & Zisapel, N. (2022). A polymorphism cluster at the 2q12 locus may predict response to piromelatine in patients with mild Alzheimer's disease. *Journal of Prevention of Alzheimer's Disease*, 9(2), 247–254.

Shokri-Kojori, E., Wang, G. J., Wiers, C. E., Demiral, S. B., Guo, M., Kim, S. W., et al. (2018). β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proceedings of the National Academy of Sciences*, 115(17), 4483–4488.

Smith, A. J., Yao, X., Dix, J. A., Jin, B. J., & Verkman, A. S. (2017). Test of the "glymphatic" hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma. *eLife*, 6, e27679.

Smith, A. J., & Verkman, A. S. (2018). The "glymphatic" mechanism for solute clearance in Alzheimer's disease: game changer or unproven speculation? *FASEB Journal*, 32(2), 543–551.

Streit, W. J., Xue, Q. S., Braak, H., & del Tredici, K. (2014). Presence of severe neuroinflammation does not intensify neurofibrillary degeneration in human brain. *Glia*, 62(1), 96–105.

Sulzer, D., Cassidy, C., Horga, G., Kang, U. J., Fahn, S., Casella, L., et al. (2018). Neuromelanin detection by magnetic resonance imaging (MRI) and its promise as a biomarker for Parkinson's disease. *npj Parkinson's Disease*, 4, 11.

Sumsuzzman, D. M., Choi, J., Jin, Y., & Hong, Y. (2021). Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: a systematic review and meta-analysis of randomized controlled trials. *Neuroscience & Biobehavioral Reviews*, 127, 459–473.

Surmeier, D. J., Guzman, J. N., Sanchez-Padilla, J., & Goldberg, J. A. (2010). What causes the death of dopaminergic neurons in Parkinson's disease? *Progress in Brain Research*, 183, 59–77.

Tan, D. X., Reiter, R. J., Manchester, L. C., Yan, M. T., El-Sawi, M., Sainz, R. M., et al. (2002). Chemical and physical properties and potential mechanisms: melatonin as a broad-spectrum antioxidant and free radical scavenger. *Current Topics in Medicinal Chemistry*, 2(2), 181–197.

Wade, A. G., Farmer, M., Harari, G., Fund, N., Laudon, M., Nir, T., Frydman-Marom, A., & Zisapel, N. (2014). Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a

6-month, randomized, placebo-controlled, multicenter trial. *Clinical Interventions in Aging*, 9, 947–961.

Wang, Y. Y., Zheng, W., Ng, C. H., Ungvari, G. S., Wei, W., & Xiang, Y. T. (2017). Meta-analysis of randomized, double-blind, placebo-controlled trials of melatonin in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 32(1), 50–57.

Weinshenker, D. (2018). Long road to ruin: noradrenergic dysfunction in neurodegenerative disease. *Trends in Neurosciences*, 41(4), 211–223.

Wu, Y. H., & Swaab, D. F. (2005). The human pineal gland and melatonin in aging and Alzheimer's disease. *Journal of Pineal Research*, 38(3), 145–152.

Wu, Y. H., Fischer, D. F., Kalsbeek, A., Garidou-Boof, M. L., van der Vliet, J., van Heijningen, C., et al. (2006). Pineal clock gene oscillation is disturbed in Alzheimer's disease, due to functional disconnection from the "master clock." *FASEB Journal*, 20(11), 1874–1876.

Wu, Y. H., Zhou, J. N., Van Heerikhuize, J., Jockers, R., & Swaab, D. F. (2007). Decreased MT1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer's disease. *Neurobiology of Aging*, 28(8), 1239–1247.

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, 342(6156), 373–377.

Yaffe, K., Laffan, A. M., Harrison, S. L., Redline, S., Spira, A. P., Ensrud, K. E., Ancoli-Israel, S., & Stone, K. L. (2011). Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*, 306(6), 613–619.

Zeitzer, J. M., Daniels, J. E., Duffy, J. F., Klerman, E. B., Shanahan, T. L., Dijk, D. J., & Czeisler, C. A. (1999). Do plasma melatonin concentrations decline with age? *American Journal of Medicine*, 107(5), 432–436.

Zhou, J. N., Liu, R. Y., Kamphorst, W., Hofman, M. A., & Swaab, D. F. (2003). Early neuropathological Alzheimer's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. *Journal of Pineal Research*, 35(2), 125–130.

Zucca, F. A., Segura-Aguilar, J., Ferrari, E., Muñoz, P., Paris, I., Sulzer, D., et al. (2017). Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Progress in Neurobiology*, 155, 96–119.