THE RESTORATIVE INTERVAL

Sleep as the Shared Off-Line State of the Collapsing Brain, and Its Withdrawal from the Locus Coeruleus in Alzheimer's Disease

The Off-Line Nucleus · The Released Sentinel · The Renormalized Circuit
The Wake Drive · The Restorative-Interval Spiral

A Dissertation Submitted in Partial Fulfillment of the Requirements for the

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A paradigm-wide synthesis of the Collapse framework — treating sleep as the shared restorative state across all three axes and their conduits, and generalizing the nightly-repair logic of The Pineal Interface from melatonergic antioxidant defense to every restorative subsystem of the locus coeruleus.

"The locus coeruleus fires through every waking hour and falls silent only in sleep. Sleep is therefore the one interval in which the nucleus that fails first is allowed to rest, the microglia are released to their watch, and the synapses are returned to scale. Alzheimer's disease shortens that interval before it takes anything else — and the brain is left to run without the night it was built to be repaired in."

— ONS Methodology Working Notes, 2026

For Giulio Tononi and Chiara Cirelli, who made sleep a synaptic necessity, and for all who have watched the sleep of the ones they were losing and understood, before the science did, that the disease begins in the night.

THE COLLAPSE TRILOGY COMPANION VOLUME

The Three Axes

Convergent Synaptic Collapse · *Homeostatic Microglial Collapse* · *Bioenergetic Collapse*

The Conduits & Cross-Sections

The Tryptophan Partition · *The Vascular Phasing* · *The Vagal Interface*

The Coerulean Interface · *The Microbial Prologue* · *The Pineal Interface*

The Temporal Capstone

The Temporal Architecture of Collapse

The Restorative Interval this volume

This volume is the pan-axis restorative-state synthesis the corpus has lacked. Where each axis thesis treats sleep as monolithic or absent, and *The Pineal Interface* develops only its melatonergic and glymphatic slice, the present volume reads sleep as the single nightly off-line state in which every restorative subsystem — locus-coeruleus rest, noradrenaline-released microglial surveillance, slow-wave synaptic downscaling, and mitochondrial recovery — co-occurs, and traces the bidirectional spiral by which its loss accelerates all of them at once. It is, equally, the next completed cross-section of *The Temporal Architecture of Collapse*.

Contents

Abstract

Sleep appears in the Collapse corpus everywhere and nowhere: every axis thesis names it, none develops it, and the one companion volume that treats it — *The Pineal Interface* — takes only its melatonergic and glymphatic slice. This dissertation advances the claim that sleep is not one risk factor among many but the single nightly *off-line state* in which every restorative subsystem of the Collapse framework co-occurs, and that the locus coeruleus is the physiological keystone of that state. The argument begins from a fact of brainstem electrophysiology that the corpus has not used: the locus coeruleus, the noradrenergic nucleus that fails first in Alzheimer's disease, fires tonically through every waking hour and falls completely silent only in sleep, in slow-wave sleep and in REM alike. Sleep is therefore the sole interval in which the autonomously pacemaking, catecholamine-autoxidising locus coeruleus is relieved of the oxidative and metabolic debt whose accumulation the Bioenergetic Collapse thesis identifies as its undoing; and the same nightly fall of noradrenaline that silences the nucleus is the permissive signal for three further restorations — the release of microglia from their noradrenergic restraint into a surveillance and inflammatory-reset phase, the slow-wave downscaling of synaptic weight that protects the fast-spiking interneurons of the Convergent Synaptic Collapse thesis, and, developed already in the companion volume, the melatonin-timed clearance of the interstitium. The locus coeruleus is the keystone because its activity gates all of these: it is the nucleus whose silence *is* the off-line state.

The dissertation is organised as a pan-axis synthesis and, following the corpus's discipline, as an explicit assessment of validity. Chapter I establishes the locus coeruleus as the *off-line nucleus*, supplying the temporal dimension that the Bioenergetic Collapse thesis's account of continuous mitochondrial turnover leaves unspecified. Chapter II develops the nightly noradrenaline fall as the microglial surveillance and inflammatory-reset window, supplying the Homeostatic Microglial Collapse thesis with the physiological, reversible counterpart to the chronic noradrenergic withdrawal it describes. Chapter III installs the synaptic homeostasis hypothesis — wholly absent from the synaptic axis — as the sleep-side bridge to synaptic collapse, arguing that chronic loss of slow-wave downscaling converts the reversible interneuronal casualty of *The Perineuronal Turn* into loss. Chapter IV frames orexinergic hyperarousal as an *endogenous* noxious load that keeps the locus coeruleus firing, complementary to the exogenous vagal and microbial loads of the conduit volumes. Chapter V formalises the *restorative-interval spiral*, a self-amplifying loop distinct from and generalising the two spirals already named in the corpus: pathology fragments the restorative interval, a fragmented interval withdraws restoration across every axis at once, and the compounded deficit deepens the pathology that fragments sleep. Chapter VI grades every arc of the argument from strong to speculative and confronts the field's central unresolved problems — the cross-sectional character of nearly all human data, the largest cohort's null result for sleep-stage architecture, the tension between REM- and NREM-based findings, the inverted-U relating slow-wave activity to outcome, and the genuinely unresolved

double edge of noradrenaline's action on microglia. Chapter VII derives phase-resolved falsifiable predictions and an intervention ledger — slow-wave enhancement, orexin antagonism, and the treatment of sleep-disordered breathing — with the honest verdict that not one of them has been shown to modify the disease.

The dissertation concludes, as the corpus requires, with a bounded claim. The restorative interval is real, it is keystoned on the locus coeruleus, and it is measurable early and cheaply by electroencephalography; but, like the pineal clock before it, it is most defensibly an *amplifier and an early marker* of Alzheimer's disease rather than its prime mover. The direction of causation cannot be resolved by the available human data, the strongest epidemiology is confounded by reverse causation, and no sleep intervention has been shown to slow the disease. The value of the framework is not a new cause but a synthesis: it names the one nightly state in which the whole collapsing system is normally repaired, identifies the nucleus whose failure withdraws that repair from every axis simultaneously, and specifies the narrow, early, and testable window in which restoring the night might matter.

Keywords: sleep, slow-wave activity, locus coeruleus, noradrenaline, synaptic homeostasis, SHY, microglial surveillance, adenosine, NAD+ recovery, orexin, sleep spindles, slow-oscillation–spindle coupling, restorative interval, bidirectional amplifier, Alzheimer's disease

1. Introduction

1.1 The Research Problem

The Collapse corpus has a sleep-shaped absence at its centre. Each of its axis theses gestures at sleep and then passes on. The Bioenergetic Collapse thesis describes a locus coeruleus whose mitochondrial quality control and NAD+ economy run continuously at the edge of failure, but treats that turnover as ceaseless and does not ask when, in the twenty-four-hour cycle, the nucleus is given the chance to recover. The Homeostatic Microglial Collapse thesis makes the chronic withdrawal of noradrenergic restraint a driver of the microglial state transition, but does not incorporate the fact that noradrenaline falls and rises every day, so that the microglial brake is applied and released on a nightly schedule the healthy brain depends upon. The Convergent Synaptic Collapse thesis places the disintegration of fast-spiking interneurons and their perineuronal nets at the end of the disease, but does not connect it to the one physiological process whose explicit function is the nightly renormalisation of synaptic weight. And the companion volume *The Coerulean Interface* develops one facet of this schedule — the nightly noradrenergic release of microglial surveillance — but treats it as a corollary of its coerulean inflammation argument rather than as the shared timing of a whole restorative state, and leaves the wake-drive that opposes it, and the pan-axis synthesis, unbuilt. Sleep is, in the corpus as in the field, invoked as a correlate and left undeveloped as a mechanism.

The one place the corpus does develop sleep is the companion volume *The Pineal Interface*, and it is precise about what it develops: the melatonin-timed, noradrenaline-gated glymphatic clearance of the interstitium, the circadian degeneration of the retina–suprachiasmatic–pineal axis, and the acute human sleep-deprivation experiments that raise amyloid-β and tau. That volume owns the chronobiological and clearance slice of sleep, and the present dissertation defers to it entirely on that slice. But sleep is not only a clock signal and a clearance window. It is a distinct physiological state with its own architecture, and within that state a set of restorations occur that have nothing directly to do with melatonin or with bulk fluid flow: the electrical silencing of the locus coeruleus, the metabolic discharge of the sleep-pressure signal, the downscaling of synaptic weight, and the release of microglia to their surveillance. The research problem of this dissertation is that these restorations, which touch every axis of the Collapse framework, have never been assembled into a single account, and that the nucleus at the centre of the framework is also the physiological keystone of the state in which they occur.

That keystone is a fact of electrophysiology. The locus coeruleus is maximally active in attentive wakefulness and falls silent in sleep — not only in slow-wave sleep but in REM sleep as well, the one nucleus whose firing tracks the sleep–wake axis so completely that its silence can be taken as a defining feature of the off-line brain (Takahashi et al., 2010). Because the locus coeruleus is autonomously pacemaking and tonically active whenever the animal is awake, and because its transmitter auto-oxidises and its pacemaking imposes a continuous calcium and oxidant load, sleep is the *only* interval in which the nucleus that fails first is relieved of the demand that, on the

Bioenergetic Collapse account, is its undoing. And because the fall of noradrenaline that accompanies that silence is the permissive signal for microglial surveillance and for synaptic downscaling, the locus coeruleus does not merely rest in sleep; its rest *is* the signal that permits the other restorations. The problem, stated at its sharpest, is this: the nucleus that fails first in Alzheimer's disease is the keystone of the nightly state in which the whole system is repaired, and its failure withdraws that repair from every axis at once.

1.2 Significance

The significance of assembling the account is fivefold. *First*, it supplies the pan-axis restorative-state synthesis that the corpus lacks. The trilogy's three axes and its conduit volumes are joined, in the existing work, at the locus coeruleus as a site of pathology; the present dissertation joins them at the locus coeruleus as the keystone of a physiological state, and shows that a single nightly process underlies the maintenance of all three axes. Sleep becomes not a sixth topic but the convergence state beneath the other five.

Second, it supplies the temporal dimension that the Bioenergetic Collapse thesis leaves unspecified. That thesis describes the machinery of mitochondrial biogenesis and mitophagy, of NAD+ depletion and repletion, as a continuous cycle, but a cycle must have a phase, and the phase is behavioural. The recovery limb of the locus coeruleus's turnover is plausibly gated to sleep, when the nucleus is silent and its per-waking-hour catecholaminergic debt can be discharged. Sleep is, on this reading, the endogenous complement to the exogenous NAD+ precursors and mitophagy enhancers the bioenergetic literature proposes, and sleep loss is a specific, nameable instance of the generic allostatic load that thesis invokes.

Third, it reads sleep *architecture* rather than sleep as a monolith. The disease does not simply reduce sleep; it dismantles its structure — the slow oscillations of deep non-REM sleep, the thalamocortical spindles, the precise coupling between them, and the proportion and integrity of REM. Each of these has a distinct physiological function and a distinct relationship to pathology, and the organising variable of this dissertation is the architecture, not the duration. This is the level of analysis both the corpus and much of the clinical literature have skipped.

Fourth, it states the bidirectional relationship as a single falsifiable loop rather than a vague reciprocity. That poor sleep worsens Alzheimer pathology and that Alzheimer pathology worsens sleep are both, by now, commonplaces; what has been missing is a specification of the loop that makes it a dynamical claim with a sign, a gain, and a tipping point. The restorative-interval spiral of Chapter V is that specification, and it is stated so that it can be broken and so that it can be falsified.

Fifth, it inherits and extends the corpus's honesty discipline. The sleep-and-Alzheimer field is unusually prone to the conflation of mechanistic plausibility with clinical benefit and of correlation with cause, and the present dissertation is written against that tendency. It grades its arcs explicitly,

it foregrounds the largest cohort's null result for sleep-stage architecture and the field's internal contradictions, and it concludes with a bounded verdict rather than a therapeutic promise.

1.3 Scope and Limitations

This dissertation is a synthetic review, centred on Alzheimer's disease and on sleep as a physiological state. Its scope is deliberately partitioned against its nearest neighbour. It defers to *The Pineal Interface* on melatonin biology and pharmacology, on the circadian and suprachiasmatic machinery, on the glymphatic mechanism and its controversy, on the noradrenergic gating of fluid clearance, and on the acute human sleep-deprivation experiments and the melatonin clinical-trial ledger; these are treated here only by reference. What the present dissertation owns instead is the set of restorative functions of sleep that are intracellular, electrophysiological, and bioenergetic — the silencing and recovery of the locus coeruleus, the discharge of the metabolic sleep-pressure signal, the synaptic downscaling of slow-wave sleep, the noradrenaline-released microglial surveillance, and the orexinergic wake-drive that opposes them all.

The thesis makes a bounded causal claim and states its limits at the outset, because the subject demands it more acutely than any other in the corpus. It does not claim that sleep disruption initiates Alzheimer's disease; the developmentally early tau pathology of the locus coeruleus precedes any plausible sleep lesion, and much of the human evidence linking sleep to pathology is cross-sectional and cannot exclude that undetectable early pathology has already perturbed the sleep it is correlated with. The thesis claims, more modestly, that the progressive loss of the restorative interval *conditions and accelerates* a process whose seed is intrinsic — that it is an amplifying and early-marking factor, keystoned on the locus coeruleus, rather than an initiating one. Two limits are structural and are named here. The claim that the locus coeruleus undergoes mitochondrial recovery during its nightly silence is, at present, an inference from its silence and not a measurement; no study has shown the repair occurring. And the claim that chronic sleep loss drives neurodegeneration, as opposed to predisposing to it, outruns the evidence, which establishes predisposition and reversible injury far more securely than it establishes accrued pathology. Chapter VI is given over to these limits, and Chapter VII states the conditions under which the framework would be falsified.

2. Literature Review

2.1 The Architecture of Sleep and Its Stage-Specific Physiology

Sleep is not a single state but a structured sequence, and the structure is the level at which its restorative functions are organised. Non-REM sleep is dominated, in its deepest stage, by the slow oscillation — the roughly once-per-second alternation between cortical up- and down-states that generates the high-amplitude delta activity of the electroencephalogram — and by the thalamocortical sleep spindle, the brief waxing-and-waning burst that rides on the up-state. The temporal coupling between the two, in which spindles are nested in the up-phase of the slow oscillation, is not incidental: it is the substrate of the systems-level consolidation of memory, and its precision degrades with age (Helfrich et al., 2018; Mander et al., 2013) and, in its specific coupling to tau, with disease (Winer et al., 2019). REM sleep, by contrast, is characterised by cortical activation, atonia, and the near-complete withdrawal of aminergic tone. The distinction matters for this dissertation because the restorations it concerns are stage-specific: synaptic downscaling is a function of slow-wave activity, the deepest fall of noradrenaline occurs across non-REM and REM together, and the epidemiological signals attach differently to different stages. To treat sleep as a monolith, as the corpus and much of the field have done, is to average over physiologically distinct processes with distinct relationships to the disease. The organising claim of the review is that Alzheimer's disease is, in its sleep dimension, a disease of architecture — of the slow oscillation, the spindle, their coupling, and the aminergic withdrawal — and not merely of duration (Winer et al., 2019).

2.2 The Locus Coeruleus Across the Sleep–Wake Cycle

The premise on which the whole dissertation rests is the state-dependence of locus coeruleus firing. The nucleus discharges tonically during quiet waking, phasically and more intensely during attentive or stressful waking, decreases its firing in non-REM sleep, and falls essentially silent in REM sleep; across the full cycle it is the wake-active, sleep-off nucleus par excellence (Takahashi et al., 2010). This pattern has a consequence that the bioenergetic account of the locus coeruleus has not drawn. If the nucleus's vulnerability is a function of its continuous pacemaking and the auto-oxidation of its catecholaminergic transmitter — the standing oxidative and metabolic load characterised in the Bioenergetic Collapse thesis — then that load is generated during waking and is, in principle, relieved only during sleep, when the nucleus is silent. Sleep is the sole state in which the locus coeruleus is not working. The in-vivo human evidence connects this rest to disease: lower locus coeruleus signal intensity on 7-Tesla MRI is associated with more frequent self-reported nocturnal awakenings in cognitively unimpaired older adults, most evidently in those with elevated plasma tau (Van Egroo et al., 2021), and actigraphically measured sleep–wake fragmentation prospectively predicts locus coeruleus neurodegeneration at autopsy (Van Egroo et al., 2024), completing a triangle in which the nucleus, its sleep, and its pathology move together. The locus coeruleus is, on this evidence, both the keystone of the off-line state and the structure whose integrity that state protects.

2.3 Energy Charge and Adenosine: The Metabolic Signal of Sleep Pressure

The claim that sleep is a metabolic recovery period is supported most directly by the biochemistry of sleep pressure. The homeostatic drive to sleep accumulates with waking and dissipates with sleep, and its molecular correlate is adenosine, the dephosphorylated residue of the cell's energy currency: adenosine rises in the basal forebrain during prolonged waking and falls in recovery sleep (Porkka-Heiskanen et al., 1997), its accumulation is regionally specific rather than global (Porkka-Heiskanen et al., 2000), and pharmacologically depleting ATP in the basal forebrain is itself sufficient to induce sleep, closing the causal loop between cellular energy charge and sleep drive (Kalinchuk et al., 2003). The buildup is tied mechanistically to a nitric-oxide/adenosine cascade that integrates oxidative and metabolic signalling with the sleep electroencephalogram (Kalinchuk et al., 2015), so that sleep pressure is, in effect, a readout of accumulated metabolic debt, and sleep its discharge. The relevance to the locus coeruleus is direct in logic and, honestly, indirect in evidence: the sleep-pressure literature localises its signal to the basal forebrain, not to the locus coeruleus, which was not among the sampled sites. The dissertation uses the adenosine account as the established demonstration that sleep is a metabolic recovery state in principle, and marks the extension of that principle to the locus coeruleus specifically as an inference, not a measurement — a point returned to in Chapters I and VI.

2.4 The Synaptic Homeostasis Hypothesis and Sleep-Dependent Remodelling

The most developed account of a restorative function of sleep is the synaptic homeostasis hypothesis (SHY) of Tononi and Cirelli, and it is entirely absent from the Convergent Synaptic Collapse axis it most concerns. SHY holds that waking, by driving plasticity, produces a net potentiation and enlargement of synapses that is metabolically and informationally unsustainable, and that the function of sleep — of slow-wave activity in particular — is to renormalise synaptic weight by a proportional, largely selective downscaling (Tononi & Cirelli, 2014). The hypothesis is supported at several levels of description: electrophysiologically, cortical responses show the signature of net potentiation after waking and net depression after sleep, with the saturation of long-term potentiation across a day of waking (Vyazovskiy et al., 2008); molecularly, the immediate-early product Homer1a acts as the integrator of sleep need that, in the low-noradrenaline milieu of sleep, executes the removal of AMPA receptors that constitutes downscaling (Diering et al., 2017); and, most decisively, ultrastructurally, three-dimensional electron microscopy of thousands of synapses shows a selective, size-proportional shrinkage of the synaptic interface after sleep relative to waking (de Vivo et al., 2017). The remodelling is not merely subtractive: two-photon imaging shows that sleep both prunes and selectively builds and protects the dendritic spines that encode recent learning (Yang et al., 2014; Maret et al., 2011), and the wake-up/sleep-down cycle of synaptic markers is conserved as far as the insects (Gilestro et al., 2009). The hypothesis has not gone unchallenged — the adequacy of its mechanistic definition was contested during its development (Frank, 2013) — and the structural data are concentrated in a single laboratory (Cirelli & Tononi, 2020), a limitation the dissertation records. But SHY supplies exactly the sleep-side mechanism the synaptic axis needs, and the low-noradrenaline dependence of its downscaling ties it directly to the locus coeruleus hub.

2.5 The Noradrenaline-Gated Microglial Surveillance and Inflammatory Reset

The microglion, like the synapse, is placed under a nightly noradrenergic schedule, and the corpus has developed it unevenly. The Homeostatic Microglial Collapse thesis treats the noradrenergic restraint of microglia as a tonic brake whose chronic withdrawal drives the microglial transition, without the diurnal rhythm; *The Coerulean Interface* does develop that rhythm — the nightly fall of noradrenaline that releases microglial surveillance — but as a corollary of its inflammation argument rather than as one instance of a shared restorative timing. This chapter takes the rhythm as established and situates it as the microglial arc of the restorative interval. The rhythm is well characterised: microglial process motility and territorial surveillance are suppressed in the awake, high-noradrenaline brain and released when noradrenergic tone falls, an effect mediated by microglial β2-adrenergic receptors and demonstrable by pharmacological and sensory manipulations that lower noradrenergic tone (Liu et al., 2019; Stowell et al., 2019), and confirmed in freely behaving animals whose microglial surveillance tracks sleep state and local noradrenaline in real time (Gu et al., 2023). Sleep is therefore the scheduled surveillance phase of the microglion, coordinated with the fall of the same transmitter whose withdrawal, in disease, disinhibits the reactive phenotype. The two facts stand in a tension the dissertation confronts rather than smooths: the nightly fall of noradrenaline *releases* homeostatic surveillance, while the chronic loss of noradrenaline *disinhibits* reactive inflammation, so that the loss of the nucleus flattens an oscillation whose high phase restrained reactivity and whose low phase permitted surveillance, degrading both. Beyond the single microglion, sleep gates the systemic inflammatory set-point: sleep disturbance is associated across dozens of studies with elevated C-reactive protein and interleukin-6 (Irwin et al., 2016), partial sleep deprivation activates the nuclear factor-κB inflammatory transcription programme (Irwin et al., 2008), and, tellingly, treating insomnia reverses the inflammatory signature — cognitive-behavioural therapy and Tai Chi each lower C-reactive protein and pro-inflammatory gene expression in older adults (Irwin et al., 2015). The nightly sleep state is, on this evidence, an inflammatory reset, and its loss a chronic pro-inflammatory drive (Irwin, 2019).

2.6 Sleep, Mitochondrial Recovery, and the Redox Ledger

If sleep discharges the energy-charge debt, it should also address the oxidative debt that accompanies it, and the evidence, though more fragmentary, points that way. Chronic sleep deprivation lowers antioxidant enzyme activity in a region-specific manner, decreasing superoxide dismutase in the hippocampus and in the brainstem that contains the locus coeruleus (Ramanathan et al., 2002). The most striking causal demonstration comes from the fly, where lethal sleep deprivation kills through the accumulation of reactive oxygen species, and where preventing that accumulation rescues survival — although, in a caveat the dissertation is careful to preserve, the lethal oxidative burden localises to the gut rather than the brain (Vaccaro et al., 2020). In the mammalian brain, acute sleep deprivation activates the microglial and astrocytic NLRP3 inflammasome with mitochondrial and mitophagy dysfunction, and the mitochondrial-targeted antioxidant urolithin A prevents both the neuroinflammation and the memory deficit (Misrani et al., 2023) — a result that ties the sleep-loss redox insult directly to the mitophagy machinery the Bioenergetic Collapse and Tryptophan Partition theses describe, and that identifies sleep as the behavioural phase whose loss the pharmacological mitophagy enhancers would be compensating. The redox function of sleep is, on the present state of evidence, better established as a general principle than as a locus-coeruleus-specific fact, and it is treated accordingly.

2.7 Orexin, Hyperarousal, and the Wake-Drive Actuator

Opposing every restoration of sleep is the wake-drive, and its principal actuator is the orexin (hypocretin) system of the lateral hypothalamus, which stabilises wakefulness and excites the arousal nuclei, the locus coeruleus among them. The system is bound to Alzheimer pathology in both directions. Orexin drives the wake-dependent accumulation of interstitial amyloid-β, and a dual orexin receptor antagonist suppresses it (Kang et al., 2009, developed in *The Pineal Interface*); more recently, the dual orexin receptor antagonist suvorexant was shown in a randomised, serially-sampled human study to lower cerebrospinal-fluid amyloid-β and the phosphorylated-tau ratio acutely (Lucey et al., 2023), and in transgenic mice to reduce amyloid deposition while restoring hippocampal long-term potentiation (Zhou et al., 2020). In the other direction, tau pathology invades the orexinergic and coerulean neurons and selectively downregulates the orexin-1 receptor in the locus coeruleus without, at least early, killing the neurons (Keenan et al., 2021), and postmortem work finds orexin neurons and their coerulean terminals reduced in Alzheimer's disease in proportion to neurofibrillary stage (Kasanuki et al., 2014). The human biomarker literature, however, is contradictory in a way the dissertation refuses to cherry-pick: cerebrospinal-fluid orexin has been reported elevated in moderate-to-severe Alzheimer's disease and correlated with tau and sleep impairment (Liguori et al., 2014; Fernandes et al., 2023), reduced in advanced disease with excessive daytime sleepiness (Fronczek et al., 2011), and — in the proponents' own largest and most recent sample — unrelated to amyloid status, cognition, or stage, its correlations with the core biomarkers attributable to shared sleep–wake-dependent release rather than to pathology (Lu et al., 2025). Postmortem work in a mixed dementia-with-Lewy-bodies and Alzheimer series finds orexin neurons and their coerulean terminals reduced, with the loss correlating with neurofibrillary stage across the sample (Kasanuki et al., 2014). Excessive daytime sleepiness is a pervasive confound across the whole literature (Gan et al., 2021). What survives the contradiction is not a clean biomarker but a mechanism: orexinergic hyperarousal is a sustained excitatory drive on the locus coeruleus, and sustained high-tonic coerulean firing is precisely the state the *Noxious Afferent Brief* identifies as harmful to the nucleus. Chapter IV develops this as an endogenous noxious load.

2.8 Human Sleep Architecture Against Pathology: The Association Literature

The human evidence linking sleep architecture to Alzheimer pathology is large, consistent in direction, and — the dissertation insists throughout — almost entirely cross-sectional. Two dissociable electroencephalographic signatures have emerged from the Berkeley–Washington University work: the amplitude of the slowest (<1 Hz) slow waves maps onto amyloid burden, while the precision of slow-oscillation–spindle coupling maps onto tau, giving distinct sleep-EEG fingerprints of the two proteinopathies (Winer et al., 2019; Lucey et al., 2019). Amyloid in the medial prefrontal cortex predicts the loss of slow waves, which in turn mediates impaired overnight memory (Mander et al., 2015); self-reported short and poor sleep tracks higher cortical amyloid in cognitively normal adults (Spira et al., 2013); and the coupling of oscillatory events correlates with cerebrospinal-fluid amyloid and tau and with amyloid positivity, raising the prospect of a wearable-EEG circuit biomarker (Pulver et al., 2024). Prospective data approach, without reaching, temporal precedence: baseline slow-wave activity and sleep efficiency predict the subsequent rate of amyloid accumulation (Winer et al., 2020), and progressive loss and misalignment of the coupled sleep rhythms track disease staging and forecast two-year cognitive decline (Wei et al., 2025). Against this coherent picture stand three findings the dissertation treats as central rather than peripheral, developed in Chapter VI: the largest and most powered analysis, pooling five cohorts, found *no* association between sleep-stage percentages and cognition, implicating consolidation, efficiency, and sleep-disordered breathing instead (Pase et al., 2023); an earlier community cohort found reduced *REM*, not any non-REM stage, to predict incident dementia (Pase et al., 2017); and the relationship between slow-wave activity and outcome is an inverted U, both too little and too much associated with worse trajectories (Lucey et al., 2021). The association literature is strong enough to motivate the framework and honest reporting of it is strong enough to bound the framework's claims. Beyond the electroencephalographic architecture, the broader epidemiology — developed for its clearance dimension in *The Pineal Interface* — supplies a consistent risk signal taken here as background: short and fragmented sleep in midlife and later predict incident dementia across large cohorts and meta-analyses (Lim et al., 2013; Sabia et al., 2021; Huang et al., 2022; Robbins et al., 2021; Ungvari et al., 2025), a signal itself confounded by the same reverse causation Chapter VI develops.

2.9 Gaps in the Literature

Four gaps motivate the synthesis, and each corresponds to a chapter. First, there is no pan-axis account of sleep in Alzheimer's disease: the field studies the sleep–amyloid, sleep–tau, sleep–synapse, and sleep–inflammation relationships in separate literatures, and the corpus has not joined them at the locus coeruleus as the keystone of a single restorative state. Second, the recovery of the locus coeruleus during its nightly silence — the temporal complement to its continuous vulnerability — has never been stated as an account, and the bioenergetic literature that would ground it is localised to the basal forebrain. Third, the synaptic homeostasis hypothesis, the most developed restorative function of sleep, is absent from the synaptic-collapse axis it most directly concerns, and its connection to the fate of the perineuronal-net-ensheathed interneurons has not been drawn. Fourth, the nightly, reversible fall of noradrenaline that releases microglial surveillance is absent from the microglial-collapse axis, which has only the chronic, pathological withdrawal. This dissertation addresses all four, and grades, in Chapter VI, how far each can honestly be pressed.

3. Methodology

This dissertation employs the Organic Network Synthesis (ONS) methodology of the AdultCognitiveDisease.com corpus, in the adjudicative mode developed for *The Pineal Interface*, in which the assembly of a framework is followed by an explicit grading of its arcs. The method proceeds in five steps. First, *hub identification*: the selection of the locus coeruleus as the physiological keystone of the sleep state, on the basis of its complete silence in sleep and the dependence of the other restorations on the fall of the noradrenaline it supplies. Second, *cross-axis triangulation*: the assembly of five literatures that the field keeps separate — the sleep-architecture and locus-coeruleus electrophysiology, the adenosine and redox biochemistry of sleep pressure, the synaptic-homeostasis ultrastructure, the noradrenaline-gated microglial surveillance, and the orexinergic wake-drive — each mapped onto the axis of the Collapse framework it restores. Third, *loop construction*: the assembly of the surviving arcs into the restorative-interval spiral, stated as a falsifiable dynamical claim with an explicit sign and kinetics for each arc. Fourth, *arc grading*: the assignment of an evidential verdict — strong, moderate, contested, or speculative — to each load-bearing claim, by its weakest necessary link rather than its strongest supporting study. Fifth, *phase-resolved prediction*: the derivation of single-experiment-falsifiable predictions, mapped onto the three temporal phases of the Temporal Architecture capstone.

The methodology carries the limitations of synthetic review and two that are specific to this subject and stated plainly. The human evidence is overwhelmingly cross-sectional, so that the

framework's directional claim — that lost restoration accelerates pathology, rather than pathology abolishing restoration — cannot be established from the data it synthesises and is argued as the more parsimonious reading of a bidirectional relationship rather than as a demonstrated fact. And the mechanistic animal literature on which several arcs depend is concentrated in single laboratories and built largely on drug-rescue designs awaiting independent loss-of-function replication, a concentration the dissertation records at each point rather than averaging away. The citation apparatus is held to a standard stricter than the corpus's default: every reference carries a PubMed identifier, and each load-bearing claim is accompanied, in the grading of Chapter VI, by an explicit note of whether it rests on human or animal data, on acute or chronic manipulation, and on association or causation.

4. Chapter I The Off-Line Nucleus: Sleep as the Locus Coeruleus's Only Recovery Window

4.1 The Silence and Its Meaning

The empirical foundation of this chapter is a single, robust fact: the locus coeruleus is silent in sleep. It fires tonically through waking, more intensely under attention and stress, decreases through non-REM sleep, and ceases almost entirely in REM sleep (Takahashi et al., 2010). No other property of the nucleus so cleanly divides its life into a working phase and a resting one. The Bioenergetic Collapse thesis established that the locus coeruleus is undone by the standing cost of its own function — the autonomous pacemaking, the auto-oxidation of noradrenaline into quinones and neuromelanin, the continuous calcium and oxidant load that keeps the nucleus at the edge of its metabolic ceiling. That account is of a cost incurred; this chapter supplies the phase in which the cost is, or should be, discharged. If the load is generated by firing, and the nucleus fires only in waking, then sleep is the sole interval in which the load is not being added and the machinery of recovery — mitochondrial quality control, NAD+ repletion, the clearance of oxidised species — can, in principle, gain ground against it. Sleep is the recovery window of the nucleus that fails first.

4.2 The Temporal Complement to the Bioenergetic Account

This reframes the bioenergetic vulnerability of the locus coeruleus as a problem of ledger rather than of level. A neuron at the edge of its metabolic ceiling is not doomed by proximity to the edge; it is doomed only if its daily expenditure exceeds its daily recovery, so that the deficit accumulates. The Bioenergetic Collapse thesis, treating the turnover as continuous, describes the expenditure and the recovery machinery but not their phasing, and therefore explains the nucleus's susceptibility better than the trajectory of its decline. The present chapter supplies the phasing: expenditure in waking, recovery in sleep. On this reading, the locus coeruleus fails not simply because its running costs are high but because, as the restorative interval shortens and fragments with age and disease, the nightly recovery falls short of the daily expenditure, and the ledger runs progressively into deficit. Sleep is the endogenous complement to the exogenous rescues — the NAD+ precursors, the mitophagy enhancers, the mitochondrial antioxidants — that the bioenergetic literature proposes; where those supply substrate or stimulate the machinery, sleep supplies the *time*, the phase in which the silent nucleus can run its quality control without adding to the load it is clearing. Sleep loss is, correspondingly, the specific and modifiable instance of the generic allostatic load the bioenergetic account invokes.

4.3 The Honest Limit: Silence Is Not Measured Repair

The chapter's argument must be held to exactly what the evidence supports, and it supports less than the argument would like. That the locus coeruleus is silent in sleep is a fact; that it undergoes mitochondrial repair, NAD+ repletion, or redox restoration *during* that silence is an inference from the silence, not a measurement of the repair. No study has sampled the locus coeruleus across the sleep–wake cycle for the markers of mitochondrial recovery, and the biochemistry that most directly demonstrates sleep as a metabolic recovery state — the adenosine and energy-charge literature — localises its signal to the basal forebrain, which was the sampled site, and not to the locus coeruleus, which was not (Porkka-Heiskanen et al., 1997; Kalinchuk et al., 2003). The redox evidence that sleep loss taxes brainstem antioxidant capacity (Ramanathan et al., 2002) is regional and correlational. The dissertation therefore grades the specific claim — that the nightly silence of the locus coeruleus is a period of measured mitochondrial recovery — as *speculative*, and marks it as one of the framework's principal empirical debts and one of its most direct experimental targets (Chapter VII). What the chapter establishes securely is narrower and still consequential: that sleep is the only interval in which the locus coeruleus is relieved of the firing that generates its load, and that the recovery, if it occurs anywhere in the cycle, can occur only then.

5. Chapter II The Released Sentinel: The Nightly Noradrenaline Fall as the Microglial Surveillance and Inflammatory-Reset Window

5.1 The Rhythmic Brake the Microglial Axis Lacks

The Homeostatic Microglial Collapse thesis holds that microglia maintain a homeostatic identity under a set of restraints, one of which is the noradrenergic tone supplied by the locus coeruleus, and that the chronic withdrawal of that tone in disease permits the transition to a reactive, inflammatory state. The account is of a brake removed. What it lacks, and what this chapter supplies, is the fact that the brake is applied and released every day. Microglial process motility and surveillance are actively suppressed in the awake brain by noradrenaline acting on microglial β2-adrenergic receptors, and are released when noradrenergic tone falls — a relationship demonstrated by reducing noradrenaline pharmacologically with propranolol, by sensory deprivation, and by optogenetic inhibition of local neuronal activity, each of which increases microglial surveillance (Liu et al., 2019), and reproduced from the other direction by β-adrenergic stimulation, which suppresses it (Stowell et al., 2019). In freely behaving animals, microglial surveillance tracks sleep state and local noradrenaline in real time (Gu et al., 2023). The healthy microglion is therefore placed on a nightly schedule: restrained during the high-noradrenaline waking day, released to survey its territory during the low-noradrenaline sleeping night. Sleep is the scheduled surveillance and maintenance phase of the brain's resident immune cell, timed by the same nucleus and the same transmitter the microglial thesis places at the centre of its account.

5.2 The Double Edge of Noradrenaline, Stated and Not Smoothed

There is a genuine tension here, and the dissertation states it rather than resolving it by fiat. The nightly *fall* of noradrenaline *releases* homeostatic microglial surveillance (Liu et al., 2019; Stowell et al., 2019); but *The Coerulean Interface* argues that noradrenaline *restrains* the reactive, pro-inflammatory activation of microglia, so that its chronic *loss disinhibits* inflammation. Noradrenaline thus appears to do opposite things — suppressing surveillance yet restraining reactivity — and whether its loss in disease is on balance protective or harmful for the microglion depends on which programme dominates. The reconciliation — which *The Coerulean Interface* first drew for the microglial phenotype and which this dissertation generalises and grades as provisional — distinguishes the two temporal modes of the signal. In the healthy brain, noradrenaline *oscillates*: its high daytime phase restrains reactive activation while suppressing surveillance, and its low nighttime phase permits surveillance while briefly lifting the restraint on reactivity, the two held in a diurnal balance. In the diseased brain, the degenerating locus coeruleus does not lower noradrenaline rhythmically but *flattens the oscillation* toward a chronically low tone. The flattening is the worst of both: it removes the daytime restraint on reactive microglia, disinhibiting inflammation as the coerulean thesis describes, *and* it abolishes the coordinated nightly surveillance phase, so that microglia are left chronically disinhibited and, simultaneously, never properly scheduled to survey. The loss of the nucleus does not tip a balance between two microglial programmes; it degrades the temporal structure that kept them in balance. This tension is real and unresolved in the primary literature, and Chapter VI grades the net-effect claim as contested.

5.3 Chronic Priming and the Inflammatory Reset

The consequences of losing the surveillance phase are not acute but cumulative, and the distinction is load-bearing for the honesty of the framework. Acute sleep deprivation does not activate microglia; it is *chronic* sleep restriction that drives a primed, phagocytic microglial state, with increased engulfment of synaptic elements and astrocyte-derived complement (Bellesi et al., 2017). Seven days of sleep restriction in mice raises microglial activation, CD68-positive phagosomes, and astrocytic complement C3 with its microglial receptor, and produces substantial losses of pre- and post-synaptic markers that an α2-adrenergic intervention can suppress (Zhai et al., 2023) — tying chronic sleep loss to the very complement-mediated synaptic pruning the microglial and synaptic axes describe. At the systemic level, the same chronicity governs an inflammatory reset: sleep disturbance is associated with elevated C-reactive protein and interleukin-6 across dozens of studies (Irwin et al., 2016), partial sleep loss activates the nuclear factor-κB programme (Irwin et al., 2008), and treating chronic insomnia *reverses* the inflammatory signature (Irwin et al., 2015), establishing the relationship as bidirectional and, on the treatment side, causal. Sleep is, on this evidence, the nightly reset of both the parenchymal microglial state and the systemic inflammatory set-point; its chronic loss is a standing pro-inflammatory drive that primes microglia toward the reactive, synaptophagic phenotype the corpus places downstream. The chapter is careful to mark that this establishes *predisposition* — a primed state, a lowered threshold — and not the demonstrated accrual of neurodegeneration, a limit Chapter VI enforces.

6. Chapter III The Renormalised Circuit: Slow-Wave Sleep, Synaptic Homeostasis, and the Fate of the Perineuronal Substrate

6.1 Installing the Missing Hypothesis

The Convergent Synaptic Collapse thesis and its companion *The Perineuronal Turn* describe the end-stage of the disease as the disintegration of fast-spiking, parvalbumin-expressing interneurons and the perineuronal nets that ensheath them, and they describe the perineuronal net as a protective variable whose stripping converts the interneuron into a reversible "latent casualty" within a window of possible rescue. What that account lacks is the sleep-side mechanism that maintains the synaptic economy those interneurons operate within, and that mechanism is the synaptic homeostasis hypothesis. This chapter installs SHY into the synaptic axis. Its claim is that slow-wave sleep performs the nightly renormalisation of synaptic weight — the proportional, selective downscaling of the potentiation accumulated in waking (Tononi & Cirelli, 2014) — and that this renormalisation is not a convenience but a necessity for cells that operate at the metabolic and firing extremes the fast-spiking interneurons do. The ultrastructural, electrophysiological, molecular, and imaging evidence for downscaling, reviewed in §2.4, is the strongest body of mechanism for any restorative function of sleep, and its molecular executor — the Homer1a-dependent, low-noradrenaline removal of AMPA receptors (Diering et al., 2017) — ties the renormalisation directly to the locus coeruleus, whose nightly silence supplies the low-noradrenaline condition downscaling requires. Sleep renormalises the circuit under the permission of the resting hub.

6.2 Why the Fast-Spiking Interneuron Cannot Afford a Lost Night

The connection from lost downscaling to interneuronal death is a claim about metabolic tolerance, and it is stated as a hypothesis with its supports and its limits. The parvalbumin interneuron is the most metabolically demanding neuron in the cortical circuit: it fires fast, sustains a high mitochondrial and oxidative throughput, and depends on its perineuronal net for the ionic and antioxidant buffering that makes that throughput survivable. If slow-wave downscaling is chronically lost — as it is, progressively, in ageing and Alzheimer's disease — then the synaptic drive onto and the excitatory economy around these interneurons is not renormalised each night, and they are held in a sustained high-throughput regime without the nightly relief that downscaling provides. In the terms of *The Perineuronal Turn*, chronic loss of downscaling would keep an already net-stripped interneuron in exactly the high-oxidative state its lost net can no longer buffer, converting the reversible latent casualty into a realised loss and shrinking the window of rescue the perineuronal thesis identifies. The direct evidence tying sleep loss to this cell population exists but is developmental rather than aged: early-life sleep restriction reduces hippocampal perineuronal-net density and desynchronises the co-development of parvalbumin interneurons and their nets in postnatal animals (Ueno et al., 2025), a result that establishes the vulnerability of the substrate to sleep loss in principle — without cleanly demonstrating a parvalbumin-cell deficit, and not in the adult, ageing brain the disease concerns. The chapter marks this as the arc's principal limit and grades the interneuron-fate claim accordingly in Chapter VI.

6.3 The Sleep-Side Amplifier of the Matrix–Synaptic Loop

The installation of SHY does more than add a mechanism; it supplies the synaptic axis with a sleep-side amplifier of the loop the corpus already describes between the extracellular matrix and excitatory drive. In the healthy brain, waking potentiation and sleeping downscaling are balanced, and the perineuronal net buffers the interneuron across the cycle. As the disease shortens and fragments slow-wave sleep, downscaling weakens, the excitatory economy is under-renormalised, and the additional drive falls on interneurons whose nets are already being stripped by the proteolytic and microglial processes the synaptic and microglial axes describe — so that lost sleep and lost matrix compound, each worsening the other's substrate. The locus coeruleus sits at the head of this amplifier twice over: its nightly silence is the permission for the downscaling that is being lost, and its degeneration, by flattening the noradrenergic oscillation, simultaneously degrades the downscaling (via the loss of the low-noradrenaline Homer1a window) and the microglial scheduling of Chapter II. The renormalised circuit and the released sentinel are, at the hub, the same failure seen at two synapses.

7. Chapter IV The Wake Drive: Orexinergic Hyperarousal as an Endogenous Noxious Load on the Locus Coeruleus

7.1 The Actuator of the Waking State

If sleep is the restorative interval, the wake-drive is what shortens it, and the wake-drive has an actuator. The orexin system of the lateral hypothalamus stabilises wakefulness and supplies a tonic excitatory drive to the arousal nuclei, prominent among them the locus coeruleus, whose firing it sustains. Orexinergic tone is, in effect, the throttle on the off-line state: high orexin lengthens and consolidates waking, delays and fragments sleep, and keeps the arousal nuclei — the locus coeruleus included — firing. This chapter develops the facet that *The Coerulean Interface* flagged and declined to build: that a substantial and modifiable part of the sustained drive on the locus coeruleus, whose metabolic cost the bioenergetic account identifies as the nucleus's undoing, is the orexinergic hyperarousal of disrupted sleep — an endogenous drive to fire, complementary to the exogenous inflammatory loads of the vagal and microbial conduits.

7.2 Hyperarousal as an Endogenous Noxious Load

The *Noxious Afferent Brief* establishes, within the corpus, that what is harmful to the locus coeruleus is sustained high-tonic firing — the state in which the nucleus is driven beyond its metabolic recovery. The conduit volumes locate the drivers of that firing in the periphery: the afferent vagal inflammatory signal, the microbial and metabolic loads that reach the nucleus through the brainstem. This chapter adds an endogenous driver of the same harmful state. Orexinergic hyperarousal and the insomnia it produces hold the locus coeruleus in sustained high-tonic firing from within, without any peripheral load, meeting the noxious-afferent criterion directly: the hyperaroused brain works its coerulean neurons through hours that should have been the nucleus's rest. The relationship is bidirectional and pathological in both directions. Tau invades the orexinergic and coerulean neurons without, at least early, killing them, and orexin-1 receptor expression falls in the locus coeruleus — though, tellingly, in both tau-overexpressing and tau-knockout mice, so that the change tracks disrupted tau homeostasis rather than a simple pathological gain of function, and its net effect on the nucleus's excitability is unresolved (Keenan et al., 2021); and orexin neurons and their coerulean terminals are reduced in dementia, the loss correlating with neurofibrillary stage across a mixed Lewy-body and Alzheimer series (Kasanuki et al., 2014). The pharmacology closes the loop the other way: blocking the wake-drive with a dual orexin receptor antagonist lowers cerebrospinal-fluid amyloid-β and phosphorylated tau acutely in humans (Lucey et al., 2023) and reduces amyloid while restoring plasticity in mice (Zhou et al., 2020). Hyperarousal is, on this account, an endogenous noxious load on the nucleus that fails first, and the restoration of the interval is, in part, the removal of that load.

7.3 The Biomarker Contradiction, Reported in Full

The orexin literature contains a contradiction that the dissertation reports in full rather than cherry-picking, because the temptation to select the confirming half is exactly what the corpus's honesty discipline exists to resist. Cerebrospinal-fluid orexin has been reported *elevated* in moderate-to-severe Alzheimer's disease and correlated with tau and with polysomnographic sleep impairment (Liguori et al., 2014; Fernandes et al., 2023; Zhang et al., 2025); *reduced* in advanced disease, especially in patients with excessive daytime sleepiness (Fronczek et al., 2011); and, in the largest and most recent sample from the very group that has argued the orexin–amyloid link hardest, *unrelated* to amyloid status, cognition, or disease stage, its correlations with the core biomarkers most parsimoniously explained by shared, sleep–wake-dependent release rather than by pathology (Lu et al., 2025). Excessive daytime sleepiness confounds the whole literature (Gan et al., 2021). The honest reading is that cerebrospinal-fluid orexin is not a validated marker of Alzheimer pathology and that its reported associations may index the state of a patient's sleep rather than the state of their disease. What survives the contradiction is not the biomarker but the mechanism, which does not depend on it: orexin is the actuator of the wake-drive, the wake-drive sustains coerulean firing, and antagonising it demonstrably lowers the pathological proteins acutely. The chapter rests its weight there, and grades the hyperarousal-as-driver claim moderate and the orexin-as-biomarker claim contested in Chapter VI.

8. Chapter V The Restorative-Interval Spiral

8.1 The Loop Stated

The preceding chapters supply the arcs of a loop that this chapter states as a falsifiable dynamical claim, distinct from and generalising the two spirals the corpus has already named — the coerulean–microglial spiral of *The Coerulean Interface* and the chronobiological–coerulean spiral of *The Pineal Interface*. The restorative-interval spiral has four arcs. *Arc one*: Alzheimer pathology fragments the restorative interval — tau in the locus coeruleus, the loss of galaninergic intermediate-nucleus (ventrolateral-preoptic-homologue) neurons that is itself associated with sleep fragmentation (Lim et al., 2014), orexinergic hyperarousal, and the loss of slow-wave generation together shorten, fragment, and destructure sleep (Mander et al., 2015). *Arc two*: a fragmented interval withdraws restoration across every axis at once — the locus coeruleus loses its recovery window (Chapter I), the microglia lose their surveillance and inflammatory-reset phase (Chapter II), the synapses lose their downscaling (Chapter III), and, through the companion volume, the interstitium loses its clearance. *Arc three*: the compounded restorative deficit accelerates the collapse of all three axes — the under-recovered locus coeruleus degenerates faster, the primed microglia prune more, the un-renormalised interneurons are pushed past their tolerance, and the tau and amyloid that lost clearance accumulate. *Arc four*: the deepened collapse further fragments sleep, because the structures whose degeneration Arc three describes — the locus coeruleus above all — are themselves the generators and stabilisers of the sleep it began by fragmenting (Van Egroo et al., 2021; Morrone et al., 2023). The loop closes, and it is self-amplifying.

8.2 The Keystone and the Asymmetry

The locus coeruleus is the keystone of the spiral in a stronger sense than it is the hub of the other two, because it appears in every arc. It is the structure whose recovery is lost in Arc two, whose degeneration is accelerated in Arc three, and whose loss — flattening the noradrenergic oscillation that gates surveillance, downscaling, and its own rest — is the mechanism of Arc four. This is why the dissertation frames the locus coeruleus not merely as a shared casualty but as the *shared point of failure* of the restorative state — a common cause of the restorative-state breakdown, though not, on the evidence, of the disease itself: because its firing gates the whole off-line state, its failure withdraws restoration from every axis simultaneously and by a single mechanism, and its position at the origin of the disease's pathology (the Braak pretangle staging developed in the bioenergetic and coerulean volumes) makes that withdrawal an early event. The claim is stated with its honest asymmetry, however. The arcs are not of equal strength: the pathology-fragments-sleep arc and the fragmentation-withdraws-restoration arc are the better evidenced, while the arc from lost restoration to *accrued neurodegeneration* — as opposed to lowered threshold and reversible injury — is the framework's weakest link, because the human data are cross-sectional and the animal data establish priming rather than pathology. Chapter VI grades the arcs individually; the loop is only as strong as the arc from restorative deficit to realised collapse, and that arc is graded, at best, moderate.

8.3 Kinetics and the Tipping Point

Like the corpus's other spirals, the restorative-interval loop is a slow positive-feedback system with a long subclinical phase and a threshold. Through the preclinical decades the arcs turn slowly and the system is buffered by redundancy: sleep restriction is compensated by recovery sleep, whose synaptic and molecular costs are largely reversible (a point Chapter VI presses); the locus coeruleus's recovery is buffered by the surviving fraction of the nucleus; and the clearance and surveillance functions have parallel routes. 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 the locus coeruleus has lost enough neurons that its noradrenergic oscillation flattens — the single event that simultaneously degrades the surveillance scheduling, the downscaling permission, and the nucleus's own rest — at which the loop's gain crosses one and the slow compensated decline becomes fast and uncompensated. The kinetic structure predicts, as the corpus repeatedly predicts, that intervention on the interval is effective before the tipping point, while the nucleus that keystones it still exists, and ineffective after — the organising logic of the therapeutic chapter.

9. Chapter VI Grading the Arcs and Confronting Reverse Causation

9.1 The Purpose of an Explicit Grading

This chapter accounts for how much of the framework to believe, arc by arc, on the five-level scale used in *The Pineal Interface* — strong, moderate, contested, speculative, and unsupported — grading each arc by the weakest link it requires rather than the strongest study in its favour. The sleep-and-Alzheimer literature makes this discipline more necessary here than anywhere else in the corpus, because it is unusually rich in mechanistic plausibility, unusually poor in demonstrated disease modification, and internally contradictory at several load-bearing points.

9.2 The Strong Arcs

Three claims are graded *strong*. The first is the state-dependence of the locus coeruleus: that it is silent in sleep and tonically active in waking, so that sleep is the only interval in which it is relieved of its firing (Takahashi et al., 2010) — a direct electrophysiological fact. The second is the reality of sleep-dependent synaptic downscaling: that slow-wave sleep selectively and proportionally reduces synaptic strength and size, supported convergently by ultrastructure, electrophysiology, molecular mechanism, and imaging (de Vivo et al., 2017; Diering et al., 2017; Vyazovskiy et al., 2008; Yang et al., 2014). The third is the noradrenergic gating of microglial surveillance: that the fall of noradrenaline releases, and its presence suppresses, microglial process surveillance through β2-adrenergic receptors (Liu et al., 2019; Stowell et al., 2019; Gu et al., 2023). These three facts are the framework's foundation, and they are secure at the level of physiology.

9.3 The Moderate Arcs

Three claims are graded *moderate*. The first is that synaptic downscaling, being lost in disease, contributes to the fate of the fast-spiking interneurons of the synaptic axis: the downscaling is strong and its loss in ageing plausible, but the specific link to interneuronal death rests on developmental data (Ueno et al., 2025) not yet reproduced in the aged brain, and the metabolic-tolerance argument is inference. The second is that orexinergic hyperarousal is an endogenous driver of harmful coerulean firing: the wake-drive is real, its pharmacological blockade lowers the pathological proteins acutely in humans (Lucey et al., 2023), but the chronic-load claim is inferred from acute experiments and the tau-induced receptor change is of unresolved sign (Keenan et al., 2021). The third is that chronic sleep loss primes microglia and resets systemic inflammation toward a pro-degenerative state: the priming (Bellesi et al., 2017; Zhai et al., 2023) and the reversible inflammatory signature (Irwin et al., 2015, 2016) are well shown, but they establish a lowered threshold, not accrued neurodegeneration.

9.4 The Contested Arcs

Two claims are graded *contested*, and both are load-bearing. The first is the net effect of noradrenaline on the microglion, discussed at length in §5.2: the same signal releases homeostatic surveillance yet restrains reactive inflammation, and whether its loss in disease is on balance protective or harmful depends on which programme dominates — a genuine tension in the primary literature that the dissertation states rather than resolves. The second is the relationship between sleep architecture and pathology at the population level. The dissertation's spine is built on the stage-specific electroencephalographic findings (Winer et al., 2019; Mander et al., 2015; Lucey et al., 2019), but the largest and most powered analysis, pooling five cohorts, found *no* association between sleep-stage percentages and cognition and implicated consolidation, efficiency, and sleep-disordered breathing instead (Pase et al., 2023); an earlier community cohort found *REM*, not any non-REM stage, to predict incident dementia (Pase et al., 2017); and the slow-wave-activity relationship is an inverted U in which both extremes are worse (Lucey et al., 2021). These are not peripheral caveats but direct challenges to the architecture-centred reading, and the dissertation grades the stage-architecture arc contested and holds that its safest form is the coupling and efficiency measures the largest cohort spared, not the stage percentages it nulled.

9.5 The Speculative and Unsupported Claims

Two claims are graded *speculative* and one *unsupported*. The speculative claims are, first, that the nightly silence of the locus coeruleus is a period of *measured* mitochondrial recovery — an inference from silence, with no direct measurement and with the supporting biochemistry localised to the basal forebrain (§4.3) — and second, that the endogenous orexin biomarker tracks pathology, which the field's own largest study contradicts (§7.3; Lu et al., 2025). The *unsupported* claim, named so it cannot be smuggled in, is that chronic sleep loss has been shown to *cause* Alzheimer neurodegeneration in humans. It has not. The acute effects of sleep loss on synapses and cerebrospinal-fluid proteins are largely reversible with recovery sleep (Havekes et al., 2016; Ooms et al., 2014); acute deprivation does not even activate microglia (Bellesi et al., 2017); and the chronic human evidence is associational. The framework claims predisposition and acceleration, and predisposition and acceleration are what the evidence supports; the stronger claim of causation is not available and is not made.

9.6 The Central Problem: Reverse Causation

Above the individual arcs stands the problem that governs the whole framework, and the dissertation confronts it directly rather than deferring it. Nearly every human finding linking sleep to pathology is cross-sectional (Mander et al., 2015; Winer et al., 2019; Lucey et al., 2019; Spira et al., 2013; Van Egroo et al., 2021), and a cross-sectional association between worse sleep and more pathology is equally consistent with the framework's reading — that lost restoration accelerates pathology — and with its inverse — that early, undetectable pathology has already fragmented the sleep it is correlated with. The locus coeruleus is, again, at the centre of the difficulty: because it both generates sleep and is among the first structures the disease damages, its early pathology could fragment sleep before any restorative deficit has had a consequence, making the sleep disruption a marker of the disease rather than a driver of it. Only two classes of evidence approach temporal precedence, and neither closes the question: the acute experimental manipulations (Ju et al., 2017), which show that disrupting sleep *can* raise the pathological proteins but not that chronic disruption accrues disease; and the baseline-predicts-slope studies (Winer et al., 2020; Lucey et al., 2021), which show that sleep measures forecast the rate of accumulation but cannot exclude that undetectable baseline pathology set both the sleep and the slope. The dissertation adopts, from *The Pineal Interface*, the resolution that makes the framework survivable under the reverse-causation reading: because the claim is about the *withdrawal of restoration from the locus coeruleus*, it is agnostic to whether the sleep disruption originates upstream of the nucleus or in the nucleus itself — the nucleus is under-recovered, the microglia unscheduled, and the synapses un-renormalised whether the interval is fragmented by an external cause or by the disease's own early damage to the sleep-generating machinery. What the reverse-causation reading defeats is not the framework's mechanism but its therapeutic promise: if fragmented sleep is largely a readout of early pathology, then restoring sleep is a downstream patch, and the modest and unproven results of sleep interventions (Chapter VII) are what that reading predicts. The framework survives as an account of the restorative interval's withdrawal; it does not survive as a claim that sleep loss is a prime mover, and it does not assert that it is.

9.7 The Concentration of the Evidence

A final, methodological grade must be entered against the framework's sources. Several of its load-bearing mechanisms rest on the work of single laboratories or single networks: the ultrastructural downscaling data are concentrated in the Tononi–Cirelli laboratory (Cirelli & Tononi, 2020); the tau-specific slow-wave findings cluster in the Washington University–Holtzman–Lucey and Berkeley–Walker–Jagust networks; and several of the inflammatory and complement mechanisms are single-laboratory, drug-rescue rodent designs awaiting independent loss-of-function replication (Zhai et al., 2023; Misrani et al., 2023). This concentration does not falsify the mechanisms, but it lowers the confidence that can be placed in them pending replication, and the dissertation records it as a standing discount on the framework's strong arcs rather than as a footnote.

10. Chapter VII Falsifiable Predictions and the Phase-Resolved Intervention Ledger

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's recovery window, restore the slow-wave downscaling, restore the microglial surveillance schedule, and remove the orexinergic wake-drive — and, as throughout the corpus, subordinates every item to timing. The kinetic structure of §8.3 predicts that interventions on the restorative interval work before the tipping point, while the locus coeruleus that keystones the interval still exists to be rested, and fail after, once its noradrenergic oscillation has flattened. This single logic explains the shape of the trial evidence in advance: interventions have been tested predominantly in established disease, at the stage the framework predicts they cannot work, and their modest and largely negative results are what the framework expects rather than what refutes it. The prediction is therefore not that sleep interventions will modify established Alzheimer's disease — the framework predicts they will not — but that their effect, if any, is confined to the preclinical and prodromal window and to the preservation of the structures the interval protects.

10.2 The Intervention Ledger, With Its Ceilings

The dissertation's therapeutic ledger is distinct from the melatonin ledger owned by *The Pineal Interface*, and it is reported with the same refusal to conflate mechanistic promise with demonstrated benefit. *Slow-wave enhancement* — closed-loop acoustic stimulation phase-locked to the slow oscillation, and transcranial stimulation — reliably augments slow-wave activity and overnight memory in small samples of older and mild-cognitive-impairment subjects (Papalambros et al., 2017; Grimaldi et al., 2020), and is the intervention most directly aimed at the downscaling arc; its ceiling is that these are proof-of-concept studies of a dozen-odd subjects with cognitive, not disease, endpoints. *Orexin antagonism* — the dual orexin receptor antagonists — improves sleep in Alzheimer's disease and acutely lowers cerebrospinal-fluid amyloid-β and phosphorylated tau (Lucey et al., 2023; Carpi et al., 2024), and a Cochrane synthesis finds the class increases total sleep time without excess adverse events (McCleery & Sharpley, 2020); its ceiling is that no trial has tested a disease-modifying endpoint, and the biomarker changes are acute. *Treatment of sleep-disordered breathing* — continuous positive airway pressure — is supported by the association of sleep-disordered breathing and hypoxia with incident cognitive impairment (Yaffe et al., 2011, developed in *The Pineal Interface*; Osorio et al., 2015; Bubu et al., 2019) and by the mechanistic plausibility of relieving nocturnal hypoxia, but its ceiling is the hardest in the ledger: the largest randomised trial of continuous positive airway pressure for cognition was essentially null (Kushida et al., 2012). The honest summary is that every item on the ledger is proven for sleep symptoms and unproven for disease modification, and that the framework's contribution is not a treatment but a specification of the population and endpoint in which one of these might, on its logic, be shown to work.

10.3 Falsifiable Predictions, Phase-Resolved

The framework makes the following predictions, each stated with its falsification condition and mapped to the temporal phases of the *Temporal Architecture* capstone, ordered from most to least readily testable.

First (Phase I — the recovery window): markers of mitochondrial recovery and NAD+ repletion in the locus coeruleus should be higher after sleep than after enforced waking, in an animal model with locus-coeruleus-specific sampling; a failure to find any sleep-associated recovery in the nucleus would falsify the off-line-recovery claim of Chapter I, which is currently graded speculative precisely because this experiment has not been done.

Second (Phase I — the endogenous load): chronic orexin antagonism, applied in the preclinical window, should slow the decline of locus coeruleus neuromelanin-MRI signal in proportion to baseline integrity, having its largest effect early; a uniform or late-predominant effect, or no effect on the nucleus, would contradict the endogenous-noxious-load claim of Chapter IV.

Third (Phase II — the surveillance schedule): restoring the nightly noradrenergic fall — pharmacologically, or by consolidating sleep — should restore the scheduled microglial surveillance phase and lower the primed, synaptophagic microglial signature, in proportion to residual locus coeruleus integrity; a failure to restore surveillance despite a restored noradrenergic rhythm would weaken the released-sentinel account of Chapter II.

Fourth (Phase II–III — the downscaling): slow-wave enhancement, applied early and chronically, should preserve fast-spiking interneuron and perineuronal-net integrity and slow the synaptic decline, more than it improves memory acutely; a benefit confined to overnight memory with no effect on the interneuronal substrate would confine the synaptic arc of Chapter III to a consolidation phenomenon rather than a protective one.

Fifth (the whole spiral): the combined restoration of the interval — consolidating sleep, enhancing slow waves, and removing the wake-drive together — should slow the trajectory of preclinical individuals more than any single intervention, reflecting the convergence of the arcs on the shared restorative state; an additive rather than super-additive effect would suggest the arcs act independently and would falsify the spiral of Chapter V as a loop rather than a list. This is the strongest and least immediately testable prediction, and its confirmation would most directly support the framework.

11. Conclusion

This dissertation has argued that sleep is the shared off-line state of the collapsing brain — the single nightly interval in which the locus coeruleus rests, the microglia are released to their surveillance, the synapses are returned to scale, and the mitochondria recover — and that the locus coeruleus is the physiological keystone of that state because its silence gates all the rest. It has drawn a set of restorations that the field studies separately, and that the Collapse corpus had left undeveloped, into a single account organised on the axes of the framework: the off-line nucleus supplies the temporal dimension the Bioenergetic Collapse thesis lacked, the released sentinel supplies the rhythmic noradrenergic brake the Homeostatic Microglial Collapse thesis lacked, the renormalised circuit installs the synaptic homeostasis hypothesis the Convergent Synaptic Collapse thesis lacked, and the wake-drive supplies the endogenous noxious load the coerulean conduit volumes had flagged and not built. It has named the restorative-interval spiral — pathology fragments the interval, a fragmented interval withdraws restoration from every axis at once, the compounded deficit accelerates the collapse, and the deepened collapse further fragments the interval — as the pan-axis generalisation of the corpus's earlier, narrower spirals, keystoned throughout on the nucleus that

fails first.

The dissertation has been more explicit about the limits of its claim than about the claim itself, because the subject requires it. The recovery of the locus coeruleus during its nightly silence is an inference from that silence, not a measurement; the link from lost downscaling to interneuronal death rests on developmental data not yet reproduced in the aged brain; the net effect of noradrenaline on the microglion is genuinely double-edged; the orexin biomarker literature contradicts itself and the field's own largest study finds no pathological signal; the largest cohort finds no association between sleep-stage architecture and cognition; and, above all, the direction of causation cannot be resolved by the cross-sectional human data on which the field depends. The framework's response to that last uncertainty is the resolution it inherits from *The Pineal Interface*: because the claim is about the withdrawal of restoration from the locus coeruleus, it is agnostic to whether the interval is fragmented from outside the nucleus or by the disease's own early damage to it — the nucleus is under-recovered either way. The framework survives the reverse-causation reading as an account of a withdrawn restoration; it does not survive as a claim that sleep loss is a prime mover, and it makes no such claim.

The value of the restorative interval is therefore not a new cause of Alzheimer's disease but a synthesis and a target. It names the one nightly state in which the whole collapsing system is normally repaired, identifies the single nucleus whose failure withdraws that repair from every axis at once, and specifies the phase-resolved, falsifiable programme by which the claim can be tested and the narrow, early window in which restoring the night might matter. No sleep intervention has been shown to modify the disease, and the strongest epidemiology is confounded; but the physiology is clear that sleep is when the brain that Alzheimer's disease dismantles is meant to be put back together, and that the nucleus which fails first is the one that failure of sleep undefends most completely. To protect the restorative interval, and to keep the rest, the surveillance, and the renormalisation of the biological night while the keystone 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 the nightly repair whose loss is one of the conditions of its acceleration. This volume takes its place as a cross-section through all three phases of *The Temporal Architecture of Collapse* and as the convergence node beneath its sequence: the maintenance window of the single homeostatic system whose failure, seen axis by axis across the trilogy, is the disease.

12. References

Bellesi, M., de Vivo, L., Chini, M., Gilli, F., Tononi, G., & Cirelli, C. (2017). Sleep loss promotes astrocytic phagocytosis and microglial activation in mouse cerebral cortex. *Journal of Neuroscience*, 37(21), 5263–5273.

Bubu, O. M., Andrade, A. G., Umasabor-Bubu, O. Q., Hogan, M. M., Turner, A. D., de Leon, M. J., et al. (2019). Obstructive sleep apnea, cognition and Alzheimer's disease: a systematic review integrating three decades of multidisciplinary research. *Sleep Medicine Reviews*, 50, 101250.

Carpi, M., Mercuri, N. B., & Liguori, C. (2024). Orexin receptor antagonists for the prevention and treatment of Alzheimer's disease and associated sleep disorders. *Drugs*, 84(11), 1365–1378.

Cirelli, C., & Tononi, G. (2020). Effects of sleep and waking on the synaptic ultrastructure. *Philosophical Transactions of the Royal Society B*, 375(1799), 20190235.

de Vivo, L., Bellesi, M., Marshall, W., Bushong, E. A., Ellisman, M. H., Tononi, G., & Cirelli, C. (2017). Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. *Science*, 355(6324), 507–510.

Diering, G. H., Nirujogi, R. S., Roth, R. H., Worley, P. F., Pandey, A., & Huganir, R. L. (2017). Homer1a drives homeostatic scaling-down of excitatory synapses during sleep. *Science*, 355(6324), 511–515.

Fernandes, M., Chiaravalloti, A., Nuccetelli, M., Placidi, F., Izzi, F., Mercuri, N. B., & Liguori, C. (2023). Sleep dysregulation is associated with 18F-FDG PET and cerebrospinal fluid biomarkers in Alzheimer's disease. *Journal of Alzheimer's Disease Reports*, 7(1), 845–854.

Frank, M. G. (2013). Why I am not SHY: a reply to Tononi and Cirelli. *Neural Plasticity*, 2013, 394946.

Fronczek, R., van Geest, S., Frölich, M., Overeem, S., Roelandse, F. W. C., Lammers, G. J., & Swaab, D. F. (2011). Hypocretin (orexin) loss in Alzheimer's disease. *Neurobiology of Aging*, 33(8), 1642–1650.

Gan, J., Chen, Z., Han, J., Ma, L., Liu, S., Wang, X.-D., & Ji, Y. (2021). Orexin-A in patients with Lewy body disease: a systematic review and meta-analysis. *Frontiers in Endocrinology*, 12, 765701.

Gilestro, G. F., Tononi, G., & Cirelli, C. (2009). Widespread changes in synaptic markers as a function of sleep and wakefulness in Drosophila. *Science*, 324(5923), 109–112.

Grimaldi, D., Papalambros, N. A., Zee, P. C., & Malkani, R. G. (2020). Neurostimulation techniques to enhance sleep and improve cognition in aging. *Neurobiology of Disease*, 141, 104865.

Gu, X., Zhao, Z., Chen, X., Zhang, L., Fang, H., Zhao, T., et al. (2023). Imaging microglia surveillance during sleep-wake cycles in freely behaving mice. *eLife*, 12, e86749.

Havekes, R., Park, A. J., Tudor, J. C., Luczak, V. G., Hansen, R. T., Ferri, S. L., et al. (2016). Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1. *eLife*, 5, e13424.

Helfrich, R. F., Mander, B. A., Jagust, W. J., Knight, R. T., & Walker, M. P. (2018). Old brains come uncoupled in sleep: slow wave–spindle synchrony, brain atrophy, and forgetting. *Neuron*, 97(1), 221–230.

Huang, S.-Y., Li, Y.-Z., Zhang, Y.-R., Huang, Y.-Y., Wu, B.-S., Zhang, W., et al. (2022). Sleep, physical activity, sedentary behavior, and risk of incident dementia: a prospective cohort study of 431,924 UK Biobank participants. *Molecular Psychiatry*, 27(10), 4343–4354.

Irwin, M. R., Wang, M., Ribeiro, D., Cho, H. J., Olmstead, R., Breen, E. C., et al. (2008). Sleep loss activates cellular inflammatory signaling. *Biological Psychiatry*, 64(6), 538–540.

Irwin, M. R., Olmstead, R., Carroll, J. E. (2016). Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological Psychiatry*, 80(1), 40–52.

Irwin, M. R., Olmstead, R., Breen, E. C., Witarama, T., Carrillo, C., Sadeghi, N., et al. (2015). Cognitive behavioral therapy and Tai Chi reverse cellular and genomic markers of inflammation in late-life insomnia: a randomized controlled trial. *Biological Psychiatry*, 78(10), 721–729.

Irwin, M. R. (2019). Sleep and inflammation: partners in sickness and in health. *Nature Reviews Immunology*, 19(11), 702–715.

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.

Kalinchuk, A. V., Urrila, A. S., Alanko, L., Heiskanen, S., Wigren, H. K., Suomela, M., et al. (2003). Local energy depletion in the basal forebrain increases sleep. *European Journal of Neuroscience*, 17(4), 863–869.

Kalinchuk, A. V., Porkka-Heiskanen, T., McCarley, R. W., & Basheer, R. (2015). Cholinergic neurons of the basal forebrain mediate biochemical and electrophysiological mechanisms underlying sleep homeostasis. *European Journal of Neuroscience*, 41(2), 182–195.

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.

Kasanuki, K., Iseki, E., Kondo, D., Fujishiro, H., Minegishi, M., Sato, K., et al. (2014). Neuropathological investigation of hypocretin expression in brains of dementia with Lewy bodies. *Neuroscience Letters*, 569, 68–73.

Keenan, R. J., Oberrauch, S., Bron, R., Nowell, C. J., Challis, L. M., Hoyer, D., & Jacobson, L. H. (2021). Decreased orexin receptor 1 mRNA expression in the locus coeruleus in both tau transgenic rTg4510 and tau knockout mice and accompanying ascending arousal system tau invasion in rTg4510. *Journal of Alzheimer's Disease*, 79(2), 693–708.

Ueno, H., Tanaka, Y., Kitano, E., Mori, S., Arai, R., Takahashi, Y., et al. (2025). Early-life sleep restriction disrupts perineuronal nets and parvalbumin interneuron development in the hippocampus of C57BL/6N mice. *Neuroscience*, 592, 232–240.

Kushida, C. A., Nichols, D. A., Holmes, T. H., Quan, S. F., Walsh, J. K., Gottlieb, D. J., et al. (2012). Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*, 35(12), 1593–1602.

Liguori, C., Romigi, A., Nuccetelli, M., Zannino, S., Sancesario, G., Martorana, A., et al. (2014). Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA Neurology*, 71(12), 1498–1505.

Lim, A. S. P., Kowgier, M., Yu, L., Buchman, A. S., & Bennett, D. A. (2013). Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*, 36(7), 1027–1032.

Lim, A. S. P., Ellison, B. A., Wang, J. L., Yu, L., Schneider, J. A., Buchman, A. S., et al. (2014). Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease. *Brain*, 137(10), 2847–2861.

Liu, Y. U., Ying, Y., Li, Y., Eyo, U. B., Chen, T., Zheng, J., et al. (2019). Neuronal network activity controls microglial process surveillance in awake mice via norepinephrine signaling. *Nature Neuroscience*, 22(11), 1771–1781.

Lu, R., Shah, K., Toedebusch, C. D., Hess, A., Richardson, R., Mignot, E., et al. (2025). Associations of cerebrospinal fluid orexin-A, Alzheimer disease biomarkers, and cognitive performance. *Annals of Clinical and*

Translational Neurology, 12(4), 780–791.

Lucey, B. P., McCullough, A., Landsness, E. C., Toedebusch, C. D., McLeland, J. S., Zaza, A. M., et al. (2019). Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease. *Science Translational Medicine*, 11(474), eaau6550.

Lucey, B. P., Wisch, J., Boerwinkle, A. H., Landsness, E. C., Toedebusch, C. D., McLeland, J. S., et al. (2021). Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer's disease. *Brain*, 144(9), 2852–2862.

Lucey, B. P., Liu, H., Toedebusch, C. D., Freund, D., Redrick, T., Chahin, S. L., et al. (2023). Suvorexant acutely decreases tau phosphorylation and Aβ in the human CNS. *Annals of Neurology*, 94(1), 27–40.

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Lindquist, J. R., Ancoli-Israel, S., et al. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nature Neuroscience*, 16(3), 357–364.

Mander, B. A., Marks, S. M., Vogel, J. W., Rao, V., Lu, B., Saletin, J. M., et al. (2015). β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nature Neuroscience*, 18(7), 1051–1057.

Maret, S., Faraguna, U., Nelson, A. B., Cirelli, C., & Tononi, G. (2011). Sleep and waking modulate spine turnover in the adolescent mouse cortex. *Nature Neuroscience*, 14(11), 1418–1420.

McCleery, J., & Sharpley, A. L. (2020). Pharmacotherapies for sleep disturbances in dementia. *Cochrane Database of Systematic Reviews*, 11, CD009178.

Misrani, A., Tabassum, S., Zhang, Z. Y., Tan, S. H., & Long, C. (2023). Urolithin A prevents sleep-deprivation-induced neuroinflammation and mitochondrial dysfunction in young and aged mice. *Molecular Neurobiology*, 61(3), 1448–1466.

Morrone, C. D., Raghuraman, R., Hussaini, S. A., & Yu, W. H. (2023). Proteostasis failure exacerbates neuronal circuit dysfunction and sleep impairments in Alzheimer's disease. *Molecular Neurodegeneration*, 18(1), 27.

Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek, M., & Claassen, J. A. H. R. (2014). Effect of one night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: a randomized clinical trial. *JAMA Neurology*, 71(8), 971–977.

Osorio, R. S., Gumb, T., Pirraglia, E., Varga, A. W., Lu, S. E., Lim, J., et al. (2015). Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*, 84(19), 1964–1971.

Papalambros, N. A., Santostasi, G., Malkani, R. G., Braun, R., Weintraub, S., Paller, K. A., & Zee, P. C. (2017). Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. *Frontiers in Human Neuroscience*, 11, 109.

Pase, M. P., Himali, J. J., Grima, N. A., Beiser, A. S., Satizabal, C. L., Aparicio, H. J., et al. (2017). Sleep architecture and the risk of incident dementia in the community. *Neurology*, 89(12), 1244–1250.

Pase, M. P., Harrison, S., Misialek, J. R., Kline, C. E., Cavuoto, M., Baril, A. A., et al. (2023). Sleep architecture, obstructive sleep apnea, and cognitive function in adults. *JAMA Network Open*, 6(7), e2325152.

Porkka-Heiskanen, T., Strecker, R. E., Thakkar, M., Bjørkum, A. A., Greene, R. W., & McCarley, R. W. (1997). Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science*, 276(5316), 1265–1268.

Porkka-Heiskanen, T., Strecker, R. E., & McCarley, R. W. (2000). Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: an in vivo microdialysis study.

Neuroscience, 99(3), 507–517.

Pulver, R. L., Kronberg, E., Medenblik, L. M., Kheyfets, V. O., Ramos, A. R., Holtzman, D. M., et al. (2024). Mapping sleep's oscillatory events as a biomarker of Alzheimer's disease. *Alzheimer's & Dementia*, 20(1), 301–315.

Ramanathan, L., Gulyani, S., Nienhuis, R., & Siegel, J. M. (2002). Sleep deprivation decreases superoxide dismutase activity in rat hippocampus and brainstem. *NeuroReport*, 13(11), 1387–1390.

Robbins, R., Quan, S. F., Weaver, M. D., Bormes, G., Barger, L. K., & Czeisler, C. A. (2021). Examining sleep deficiency and disturbance and their risk for incident dementia and all-cause mortality in older adults across 5 years in the United States. *Aging*, 13(3), 3254–3268.

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.

Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M., et al. (2013). Self-reported sleep and β-amyloid deposition in community-dwelling older adults. *JAMA Neurology*, 70(12), 1537–1543.

Stowell, R. D., Sipe, G. O., Dawes, R. P., Batchelor, H. N., Lordy, K. A., Whitelaw, B. S., et al. (2019). Noradrenergic signaling in the wakeful state inhibits microglial surveillance and synaptic plasticity in the mouse visual cortex. *Nature Neuroscience*, 22(11), 1782–1792.

Takahashi, K., Kayama, Y., Lin, J. S., & Sakai, K. (2010). Locus coeruleus neuronal activity during the sleep-waking cycle in mice. *Neuroscience*, 169(3), 1115–1126.

Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, 81(1), 12–34.

Ungvari, Z., Fekete, M., Lehoczki, A., Munkácsy, G., Fekete, J. T., Zábó, V., et al. (2025). Sleep disorders increase the risk of dementia, Alzheimer's disease, and cognitive decline: a meta-analysis. *GeroScience*, 47(3), 4899–4920.

Vaccaro, A., Kaplan Dor, Y., Nambara, K., Pollina, E. A., Lin, C., Greenberg, M. E., & Rogulja, D. (2020). Sleep loss can cause death through accumulation of reactive oxygen species in the gut. *Cell*, 181(6), 1307–1328.e15.

Van Egroo, M., van Hooren, R. W. E., & Jacobs, H. I. L. (2021). Associations between locus coeruleus integrity and nocturnal awakenings in the context of Alzheimer's disease plasma biomarkers: a 7T MRI study. *Alzheimer's Research & Therapy*, 13(1), 159.

Van Egroo, M., van Someren, E. J. W., Grinberg, L. T., Bennett, D. A., & Jacobs, H. I. L. (2024). Associations of 24-hour rest-activity rhythm fragmentation, cognitive decline, and postmortem locus coeruleus hypopigmentation in Alzheimer's disease. *Annals of Neurology*, 95(5), 653–664.

Vyazovskiy, V. V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nature Neuroscience*, 11(2), 200–208.

Wei, T., Zhou, J., Wang, Z., Liu, X., Mi, Y., Zhao, Y., et al. (2025). Coupled sleep rhythm disruption predicts cognitive decline in Alzheimer's disease. *Science Bulletin*, 70(9), 1491–1503.

Winer, J. R., Mander, B. A., Helfrich, R. F., Maass, A., Harrison, T. M., Baker, S. L., et al. (2019). Sleep as a potential biomarker of tau and β-amyloid burden in the human brain. *Journal of Neuroscience*, 39(32), 6315–6324.

Winer, J. R., Mander, B. A., Kumar, S., Reed, M., Baker, S. L., Jagust, W. J., & Walker, M. P. (2020). Sleep disturbance forecasts β-amyloid accumulation across subsequent years. *Current Biology*, 30(21), 4291–4298.e3.

Yang, G., Lai, C. S. W., Cichon, J., Ma, L., Li, W., & Gan, W. B. (2014). Sleep promotes branch-specific formation of dendritic spines after learning. *Science*, 344(6188), 1173–1178.

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

Zhai, Q., Zhang, Y., Ye, M., Zhu, S., Sun, J., Wang, Y., et al. (2023). Reducing complement activation during sleep deprivation yields cognitive improvement by dexmedetomidine. *British Journal of Anaesthesia*, 131(3), 542–555.

Zhang, W., Lian, T., He, M., Guo, P., Guan, H., Li, J., et al. (2025). Sleep disorders and Alzheimer's disease: relationship and mechanisms involving neuroinflammation, orexin and Aβ. *Fluids and Barriers of the CNS*, 22(1), 62.

Zhou, F., Yan, X. D., Wang, C., He, Y. X., Li, Y. Y., Zhang, J., et al. (2020). Suvorexant ameliorates cognitive impairments and pathology in APP/PS1 transgenic mice. *Neurobiology of Aging*, 91, 66–75.