THE GLYMPHATIC COLLAPSE

The Sleeping Brain's Extracellular Clearance and Its Failure in Alzheimer's Disease — From the Noradrenergic Switch to the Perivascular Tide

Periarterial Influx · The AQP4 Endfoot · The Noradrenergic Switch
Perivenous Efflux · Meningeal Lymphatics

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Extracellular companion to The Clearance Collapse — tracing the perivascular–glymphatic clearance system through the three-phase architecture of Alzheimer's disease, with an honest grading of a contested mechanism.

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Abstract

A companion analysis, *The Clearance Collapse*, argued that Alzheimer's disease is at bottom a failure of clearance — but it confined itself to clearance *inside* the cell: autophagy, the machinery by which a neuron digests and renews its own contents. That account left a second clearance system untouched, one that operates not within the cell but around it, in the fluid-filled spaces that thread the brain along its blood vessels. This paper is about that second system — the glymphatic system, the brain's proposed route for washing metabolic waste, including amyloid-β and tau, out of the interstitial space and into the lymphatics of the neck — and about the specific, sleep-gated way it is thought to fail in Alzheimer's disease.

We do two things. First, we trace the mechanism as it is currently understood: cerebrospinal fluid enters the brain along the spaces surrounding penetrating arteries, exchanges with interstitial fluid across the aquaporin-4 (AQP4) water channels densely arrayed on astrocytic endfeet, sweeps solutes toward the perivenous spaces and the newly rediscovered meningeal lymphatics, and does most of this work during slow-wave sleep, when noradrenergic tone from the locus coeruleus falls and the interstitial space physically expands. Second — and this is the paper's methodological spine — we *weigh the validity* of these claims rather than asserting them, because the glymphatic hypothesis is among the most contested constructs in contemporary neuroscience. We separate what is well established (perivascular spaces are genuine conduits; sleep alters amyloid dynamics in humans; AQP4 loses its polarization in the Alzheimer brain; functional meningeal lymphatics exist) from what is genuinely disputed (whether transport through the dense neuropil is convective *bulk flow* or mere *diffusion*; whether AQP4 is strictly required; how much of total brain clearance the route actually carries) from what is under active challenge (a 2024 report that clearance *falls* rather than rises during sleep; the specificity of the human MRI markers now in wide use). A paper that assessed the connection honestly could not do otherwise.

The integrative claim, offered with its uncertainty attached, is this: the glymphatic system connects to Alzheimer's disease most defensibly not as an independent cause but through the *locus coeruleus* — the same small noradrenergic nucleus that the Organic Network Synthesis framework places at the ignition point of the disease. Noradrenaline is the glymphatic system's master switch; the locus coeruleus is the sole source of cortical noradrenaline and the governor of the sleep-wake states that open and close the clearance window. The nucleus that fails first in Alzheimer's disease is therefore also the nucleus whose failure degrades the sleep architecture on which extracellular clearance depends — the arsonist who also disables the sprinkler. On this reading the glymphatic collapse is not a separate disease mechanism bolted onto the temporal architecture but a downstream consequence of its first phase, one that then feeds forward to accelerate the accumulation the rest of the architecture describes. We defend this connection where the evidence supports it, flag it as provisional where it does not, and close with predictions sharp enough to be wrong.

I. The Question of the Second Clearance

Two systems, not one

The brain disposes of its waste twice over, by two systems that share a purpose and almost nothing else. The first is intracellular: autophagy and its lysosomal terminus, the machinery by which a cell engulfs and digests its own spent components. That system was the subject of a companion paper, *The Clearance Collapse*, which argued that its age-dependent failure runs beneath all three phases of Alzheimer's disease. The second system is extracellular. Whatever a cell cannot digest — and whatever it secretes, sheds, or extrudes at death — must still be removed from the narrow, tortuous fluid space between cells, and the brain has no obvious way to do this. It has no conventional lymphatic vessels threading its parenchyma; it sits behind a blood-brain barrier that guards what enters but explains little about what leaves. How, then, does the brain wash itself?

The glymphatic hypothesis is one answer, and for a decade it has been the dominant one. Proposed by Iliff, Nedergaard and colleagues in 2012, it holds that the brain co-opts its own vasculature as a plumbing scaffold: cerebrospinal fluid (CSF) is driven into the brain along the sleeve-like spaces that surround penetrating arteries, passes into the interstitial fluid (ISF) across the water channels of astrocytes, flushes through the tissue collecting solutes, and exits along perivenous routes to be carried, finally, out of the skull altogether. The name — a contraction of *glial* and *lymphatic* — advertises both its claim (that this is the brain's functional analogue of the lymphatic system) and its distinctive dependence on glia (astrocytes and their AQP4 channels). It is a beautiful idea, and it is a contested one, and both of those facts are essential to what follows.

Where the glymphatic system fits — and the honesty the question demands

To ask how the glymphatic system "affects Alzheimer's disease" is to ask a question that can be answered dishonestly with great ease. The temptation, in a field hungry for tractable mechanisms and clean therapeutic targets, is to state the strongest version of the hypothesis as settled fact: the brain washes itself during sleep, sleep declines with age, therefore poor sleep causes Alzheimer's by letting amyloid accumulate — a syllogism clean enough to print on a magazine cover and reductive enough to be, in its confidence, false. The glymphatic literature has suffered from exactly this over-reach, and a serious assessment must resist it.

This paper therefore adopts a discipline it will hold throughout: every link in the chain from glymphatic function to Alzheimer pathology is graded, not asserted. Some links are strong — the anatomy of perivascular conduits, the human evidence that sleep alters amyloid dynamics, the loss

of AQP4 polarization in the diseased brain. Some are contested at the level of basic physics — whether solute moves through the neuropil by convective flow or by diffusion is a live argument among people who model the hydrodynamics for a living. And at least one central claim, the sleep-dependence of clearance itself, has been directly challenged in the most recent literature. A PhD-quality treatment of "how the glymphatic system affects Alzheimer's disease" is, in 2026, largely a treatment of *how confident we are entitled to be* — and it is the honest grading of that confidence, not the assertion of a mechanism, that this paper offers as its contribution.

Thesis

The argument proceeds in three moves. First, that the glymphatic system, understood as perivascular CSF-ISF exchange terminating in meningeal lymphatic drainage, is a real and consequential clearance route whose sleep-dependence and age-related decline are supported by convergent — though not unanimous — human and animal evidence. Second, that its most defensible connection to Alzheimer's disease runs through the locus coeruleus: the noradrenergic nucleus that the temporal architecture names as the disease's origin is also the switch that gates glymphatic clearance, so that the first lesion of the disease is, simultaneously and by the same stroke, a lesion of its extracellular waste disposal. Third, that the glymphatic collapse is best read not as a competitor to the intracellular clearance failure of the companion paper but as its extracellular twin — the two together describing a brain that can neither digest its waste within its cells nor wash away what those cells extrude. Each move is stated with the strength the evidence licenses, and no more.

II. The Machinery of the Perivascular Tide

Before the disease, the system in working order. The glymphatic model assembles a small number of anatomical and physiological components into a directional circuit; the disease, on this account, is the failure of nameable steps within it, and the components must be set out before their failures can be located.

Periarterial influx: the vasculature as scaffold

Every artery that dives from the brain's surface into its depths carries with it a sleeve of the space it came from — the perivascular, or Virchow-Robin, space, a fluid-filled annulus between the vessel wall and the surrounding brain, bounded on its outer face by the endfeet of astrocytes. The glymphatic model proposes that CSF from the subarachnoid space is driven *into* the brain along these periarterial sleeves, penetrating deep into the tissue before it ever crosses into the interstitium. The perivascular space is thus not a passive gap but the system's inflow manifold: a low-resistance channel that distributes CSF throughout the parenchyma using the arterial tree as its delivery scaffold. This much — that perivascular spaces exist and conduct CSF-borne tracer into the brain — is among the least disputed elements of the model, visible in tracer studies across species and, increasingly, in human MRI.

The driving forces: pulsation, vasomotion, respiration

A fluid does not flow without a pump, and the glymphatic system's proposed pumps are the vessels themselves. The dominant force, on the original account, is *arterial pulsatility*: each cardiac systole expands the penetrating artery, and the rhythmic squeeze of the vessel against its perivascular sleeve drives CSF inward — a peristalsis powered by the heartbeat, demonstrated when Iliff and colleagues showed that dampening the pulse slowed paravascular influx and augmenting it sped it up. Later work added slower rhythms: *vasomotion*, the spontaneous low-frequency oscillation of arterial smooth muscle, and *respiration*, whose thoracic pressure swings modulate the intracranial fluid compartments. Most recently, Jiang-Xie and colleagues reported that synchronized neuronal activity itself generates rhythmic ionic waves in the interstitial fluid that potentiate CSF perfusion and clearance — an *active* driver, suppressible and enhanceable, that supplies a mechanism by which the brain's own electrical state, including the slow oscillations of deep sleep, could drive its washing. The multiplicity matters for the disease, because it means the pump has several failure modes — a stiffened artery loses its pulsatile stroke, an arteriosclerotic vessel loses its vasomotion, a hypoactive or seizure-prone cortex loses its neuronal drive — and because it locates one of the system's vulnerabilities squarely in the vascular aging that accompanies Alzheimer's disease.

The AQP4 endfoot: the glial gate

Here is the component that gives the system its *g*. To exchange with interstitial fluid, CSF in the perivascular space must cross the wall of astrocytic endfeet that encases the vasculature — and that wall is studded, with extraordinary density and polarization, with aquaporin-4, the principal water channel of the central nervous system. AQP4 is not distributed evenly over the astrocyte; it is concentrated, anchored by the dystrophin-associated complex and α-syntrophin, precisely on the endfoot membrane facing the vessel, where it is positioned to facilitate the movement of water — and, the model proposes, the convective exchange of CSF into the interstitial space. The strong form of the hypothesis holds that this polarized AQP4 array is *required* for efficient glymphatic exchange: knock out AQP4, or scatter its polarization, and clearance falls. This claim is central, and it is contested; we return to the dispute in Section III. What is not in dispute is the anatomy — AQP4 is real, it is polarized to the perivascular endfoot, and in the Alzheimer brain that polarization is lost.

Interstitial transit and perivenous efflux

Having entered the interstitium, CSF mixes with ISF and, on the glymphatic account, moves *convectively* through the tissue — a directed bulk flow, not merely a random diffusion — sweeping dissolved solutes ahead of it toward the low-pressure spaces surrounding veins. Whether this interstitial transit is truly convective is the single most disputed point in the entire model, and the reader should hold the word "sweeps" in suspicion until Section III; but the model's logic requires it, because diffusion alone is famously too slow to clear large solutes across the distances involved. The solutes carried include the disease's own proteins: soluble amyloid-β, which the original 2012 work showed is cleared in part by this route, and, later, tau, whose interstitial clearance Iliff and colleagues found impaired after the perivascular disruption of traumatic brain injury. The efflux collects along perivenous channels and departs the parenchyma — and where it goes next reopened a question the textbooks had considered closed.

The exit: meningeal lymphatics and the cervical nodes

For a century, anatomy taught that the brain has no lymphatic vessels. In 2015 two groups — Louveau and colleagues, and Aspelund and colleagues — showed otherwise: the dural meninges contain functional lymphatic vessels that carry fluid, macromolecules, and immune cells from the CSF toward the deep cervical lymph nodes of the neck. This rediscovery supplied the glymphatic circuit with an exit it had lacked. Efflux from the parenchyma reaches the CSF; the CSF drains, in part, through these meningeal lymphatics (and through older-known routes across the cribriform plate to the nasal mucosa) to the cervical nodes and thence to the systemic circulation. Da Mesquita and colleagues then closed the loop to disease: ablating the meningeal lymphatics in mice impaired paravascular influx and worsened amyloid-β pathology, and the vessels themselves decline with age. The meningeal lymphatic is, in this picture, the system's drain — and a drain that ages is a drain that backs up. The precise anatomy of the exit remains, however, an open question and a moving target: Yoon and colleagues identified in 2024 a nasopharyngeal lymphatic plexus that serves as a major hub for CSF outflow to the deep cervical nodes and that atrophies with age, a finding that complicates any tidy claim that the dural meningeal vessels are the dominant route out. The drain is real; which pipe carries most of the flow is not yet settled.

The noradrenergic switch and the primacy of sleep

The glymphatic system's most striking and most consequential claim is that it runs chiefly during *sleep*. Xie and colleagues reported in 2013 that the interstitial space of the mouse brain expands markedly in the transition from wakefulness to sleep — the interstitial volume fraction rising from roughly fourteen to roughly twenty-three percent, an increase near sixty percent — and that this expansion, by lowering the resistance to fluid movement, roughly doubles the clearance of injected amyloid-β. The proposed governor of this switch is *noradrenaline*. Noradrenergic tone, high in waking and low in sleep, was shown to control the interstitial volume: suppressing noradrenaline reproduced the sleep-like open state even in a waking animal, and noradrenaline is supplied to the entire forebrain by a single source — the locus coeruleus. Sleep, on this account, is not merely when the glymphatic system happens to work; sleep is a state the brain enters, in part, *in order to* clear itself, and the locus coeruleus, by falling silent, throws the switch. Hablitz and colleagues later added a circadian layer, reporting that glymphatic influx and AQP4 polarization themselves oscillate with the daily clock, peaking during the rest phase. This coupling — of clearance to sleep, and of sleep to the noradrenergic nucleus that Alzheimer's disease attacks first — is the hinge on which this paper's integrative claim turns, and we develop it fully in Section IV. It is also, as the next section must acknowledge, the claim that the most recent literature has most sharply challenged.

III. The Evidence, Weighed

The glymphatic hypothesis is not one claim but a stack of them, and they do not stand or fall together. A responsible assessment grades each tier separately, because the practice of citing the well-established anatomy to lend borrowed credibility to the contested physics is precisely the rhetorical move that has inflated the field. What follows sorts the evidence into three registers: established, contested, and under active challenge.

What is well established

Several elements of the model rest on evidence strong enough that their denial would be perverse.

Perivascular spaces are genuine conduits. That CSF-borne tracer enters the brain along periarterial spaces has been shown in rodents by multiple independent groups and, increasingly, in humans: intrathecally administered contrast agents distribute through the brain in a pattern consistent with perivascular influx, and enlarged perivascular spaces are visible on routine MRI and associate with age and small-vessel disease. The existence and permeability of the inflow conduit is not seriously disputed.

Sleep alters amyloid dynamics in humans. Independent of any particular hydrodynamic model, the human evidence that sleep and amyloid interact is robust. Interstitial and CSF amyloid-β follow a diurnal rhythm, rising with wakefulness and falling with sleep, as Kang and colleagues first showed in mice and as human CSF sampling confirmed. A single night of sleep deprivation measurably raises amyloid-β burden in the human brain on PET, as Shokri-Kojori and colleagues demonstrated. Reduced slow-wave sleep predicts higher amyloid and tau in cognitively normal adults, in the work of Ju, Lucey, Holtzman and colleagues. Whatever the mechanism, sleep and Alzheimer proteins are coupled in humans — and the coupling runs at least partly in the direction of sleep loss preceding and predicting pathology.

AQP4 loses its polarization in the Alzheimer brain. In human post-mortem tissue, Zeppenfeld and colleagues found that the tight perivascular polarization of AQP4 is degraded in Alzheimer's disease, with the channel redistributing away from the endfoot — and that the degree of depolarization tracks pathological stage. This is a structural lesion of the glymphatic gate, observed in human disease, not merely inferred from mouse models.

Functional meningeal lymphatics exist and matter. The 2015 rediscovery of dural lymphatic vessels has been replicated and extended; that these vessels drain CSF-derived macromolecules to cervical nodes, decline with age, and — when experimentally impaired — worsen amyloid pathology and blunt the response to anti-amyloid immunotherapy in mice is now well supported by the work of Louveau, Aspelund, Da Mesquita, Kipnis and colleagues. The brain's lymphatic exit is real.

These four pillars establish that the *ingredients* of the glymphatic model — perivascular conduits, a sleep-amyloid coupling, an AQP4 gate that fails in disease, a lymphatic drain that ages — are genuine. They do not, by themselves, establish that the ingredients assemble into the specific convective circuit the model proposes.

What is genuinely contested

Between the established anatomy and the disputed physics lies the crux of the scientific argument.

Convection versus diffusion. The glymphatic model requires that solute move through the interstitium by *convective bulk flow* — a directed current — because diffusion is too slow to account for the observed clearance of large molecules over the relevant distances. But whether such bulk flow actually occurs within the dense neuropil, as opposed to within the perivascular spaces, is precisely what critics deny. Computational and experimental analyses — Holter and colleagues' modeling of solute transport in reconstructed neuropil, the sustained critiques of Hladky and Barrand, the work of Asgari and colleagues — argue that the interstitial matrix is too resistive for meaningful bulk flow through the tissue, and that transport across the parenchyma is dominated by diffusion, perhaps enhanced ("dispersed") by the mixing that perivascular pulsation induces near vessels. On this view the perivascular spaces are indeed rapid convective channels, but the tissue between them clears by diffusion, and the word "flow" has been over-applied. This is not a fringe objection; it is a serious, quantitative disagreement about the physics, and it remains unresolved. Its consequence for Alzheimer's disease is real: if deep-parenchymal clearance is diffusive, then interventions premised on "increasing flow" through the tissue may do less than hoped, and the defensible therapeutic targets narrow to the perivascular conduit and the lymphatic exit.

The AQP4 requirement. The strong claim that AQP4 is *necessary* for glymphatic exchange was directly challenged when Smith and colleagues, in 2017, reported that they could not reproduce AQP4-dependent solute clearance and argued the data were better explained by diffusion. The reply, when it came, was unusually structured: Mestre and colleagues in 2018 assembled a coordinated five-laboratory replication and meta-analysis, tested four independent AQP4-knockout lines, and found that AQP4 deletion does impair perivascular CSF influx, attributing the original discrepancy chiefly to differences in anesthesia and tracer delivery. That it took a multi-laboratory consortium to settle the point is itself the point: the effect is real but method-sensitive, and a finding that requires five laboratories to stabilize is not a finding one should describe as robust without qualification. The honest summary is that AQP4 *matters* — the human depolarization data make this hard to dismiss — but that the magnitude of its contribution is sensitive to experimental conditions in a way that should temper any claim that it is a simple, indispensable valve.

The fractional contribution to clearance. Even granting that the glymphatic route works, it is one of several. Amyloid-β leaves the brain by receptor-mediated transcytosis across the blood-brain barrier (chiefly via LRP1), by enzymatic degradation in the interstitium (neprilysin, insulin-degrading

enzyme), by cellular uptake and by direct efflux to CSF. In the classical rodent literature it is the blood-brain-barrier transcytosis and the enzymatic-degradation routes that are quantitatively dominant, with barrier transport often credited with a large share of amyloid export and peripheral degradation with much of the remainder; the glymphatic contribution, by contrast, is described qualitatively as "substantial" but has never been fixed to a defensible number. How much of the total the glymphatic route actually carries is genuinely uncertain, and published estimates vary widely with method, species, and assumption; there is no agreed figure. A claim that "the glymphatic system contributes to amyloid clearance" is defensible; a claim that it is *the* clearance route, or carries a specific large fraction, is not.

What is under active challenge

The most important recent development for this assessment is that the sleep-dependence claim itself — the very heart of the Alzheimer connection — has been directly contradicted in the primary literature. In 2024 Miao and colleagues, in the laboratory of Franks and Wisden, published in *Nature Neuroscience* a study titled, without hedging, "Brain clearance is reduced during sleep and anesthesia": using a different method to measure the movement of a fluorescent tracer, they reported that clearance was markedly *reduced*, not enhanced, during sleep and under anesthesia — the exact inversion of Xie and colleagues' foundational 2013 result. The finding, if it holds, would upend the field's central therapeutic intuition. The dispute that followed was aired in full and in public: the Nedergaard group published a formal rebuttal (Plá and colleagues, "A curious concept of CNS clearance," 2025) arguing that cortical dye injection raises intracranial pressure and damages tissue and that the controls were inadequate, and the original authors replied in the same issue, characterizing the objections as misunderstandings. As of this writing the exchange is unresolved, with both sides holding their positions and the matter openly acknowledged in the field's news pages as a live debate. Two things follow. First, no honest 2026 treatment can present "the brain clears itself during sleep" as established fact; it is a leading hypothesis under live challenge. Second — and this is why the present paper routes its integrative claim through the locus coeruleus and the human sleep-amyloid data rather than through the mouse clearance-during-sleep result — the *human* coupling of sleep loss to amyloid accumulation stands on its own evidentiary legs (PET, CSF, epidemiology) independent of the disputed rodent clearance kinetics. The connection between sleep and Alzheimer's disease is more secure than the specific glymphatic mechanism proposed to explain it.

A parallel caution applies to the human MRI markers now proliferating in the clinical literature. The DTI-ALPS index — diffusion tensor imaging "along the perivascular space" — is widely reported as a "glymphatic" biomarker and correlates with cognition and age, but it is an indirect proxy that measures water diffusivity in a particular geometric relation to deep medullary veins, not glymphatic flow itself, and its specificity has been questioned. Human intrathecal-tracer studies (Ringstad, Eide and colleagues) provide more direct evidence that CSF solutes enter the

parenchyma and that clearance is delayed in conditions such as idiopathic normal-pressure hydrocephalus, but they are invasive, low-throughput, and cross-sectional — unable, by design, to establish whether impaired clearance *causes* dementia or merely accompanies its pathology and atrophy. The direction of causality in humans remains, at present, unproven.

An honest interim verdict

Weighing all of this: the glymphatic system is best regarded as a real perivascular CSF-ISF exchange and drainage system whose inflow conduits, glial gate, and lymphatic exit are well documented, whose parenchymal hydrodynamics and AQP4-dependence are genuinely contested, and whose signature claim of sleep-enhanced clearance is under active empirical challenge. Its connection to Alzheimer's disease is strongest at the two ends where the human evidence is independent of the disputed physics — the sleep-amyloid coupling at the front and the AQP4-depolarization and lymphatic-decline findings at the back — and weakest in the middle, where the convective-flow model does its heaviest and most disputed lifting. This is the verdict the rest of the paper builds on: a system worth taking seriously, integrated into the disease with its uncertainties intact, not a settled mechanism to be asserted.

IV. The Noradrenergic Switch Where the Glymphatic System Meets the Locus Coeruleus

The preceding section counsels humility about the glymphatic mechanism in general. This section makes the paper's positive claim, and it is deliberately narrow: whatever the ultimate resolution of the convection debate, the glymphatic system's regulatory switch and the disease's point of origin are the *same structure*, and that coincidence is the most defensible bridge between the two literatures.

The locus coeruleus governs both arousal and clearance

The locus coeruleus is a nucleus of a few thousand neurons in the pons, and it is the sole source of noradrenaline for the cortex and hippocampus. Two of its functions matter here, and they are usually studied apart. First, it is the principal engine of arousal: its firing rate sets the sleep-wake state, high in waking and vigilance, phasically silent in the transitions to and depths of non-REM sleep. Second — and this is the fact the glymphatic literature supplies — its neurotransmitter, noradrenaline, is the switch that controls interstitial volume and, through it, glymphatic clearance. These two functions are not merely both housed in the same nucleus; they are the same lever seen from two sides. When the locus coeruleus falls silent for sleep, it simultaneously *is* the descent into the sleep state and *throws* the glymphatic switch, because the noradrenaline whose withdrawal defines the sleep transition is the same noradrenaline whose withdrawal opens the interstitial space. The locus coeruleus is thus the single node at which the temporal architecture's account of the disease's origin and the glymphatic account of its clearance meet.

The origin lesion is a clearance lesion

The temporal architecture places the disease's ignition in the locus coeruleus: hyperphosphorylated "pretangle" tau appears there in early adulthood, decades before cortical pathology, in the brain's most metabolically extravagant and oxidatively exposed neurons. The companion papers of this program — *The Coerulean Interface*, *The Pineal Interface*, *The Restorative Interval* — trace how the failing nucleus disinhibits microglia, loses its melatonergic protection, and degrades the sleep it is supposed to schedule. The glymphatic account adds a further consequence, and it is a grave one. If the locus coeruleus is the switch that opens the clearance window during sleep, then the progressive dysfunction of the locus coeruleus is, by the same mechanism, a progressive failure of that switch. A nucleus that fires erratically cannot fall cleanly silent; a nucleus that has lost neurons cannot deliver the orderly nightly withdrawal of noradrenaline on which the open, low-resistance interstitial state depends; and the fragmented, slow-wave-poor sleep that locus-coeruleus pathology produces is precisely the sleep in which the glymphatic window fails to open. The disease's first lesion and its extracellular-clearance lesion are, on this account, one lesion described twice.

The arsonist and the sprinkler

The image is worth stating plainly because it captures the peculiar cruelty of the arrangement. The locus coeruleus, in the temporal architecture, is the arsonist — the site of bioenergetic ignition, the neuron whose oxidative failure begins the cascade. The glymphatic account reveals that the same nucleus also operates the sprinkler: the noradrenergic withdrawal that would, each night, open the interstitial space and permit the washing-away of the very amyloid and tau the disease generates. A disease that damaged only the arsonist would still leave the sprinkler intact; a disease that damaged only the sprinkler would leave the fire un-lit. Alzheimer's disease, on this reading, does both with a single lesion, because the arsonist *is* the sprinkler's operator. This is not merely rhetorical. It predicts that locus-coeruleus integrity should track glymphatic function and sleep quality together, that interventions preserving the nucleus should preserve clearance, and that the noradrenergic dysregulation of early disease should be detectable as a clearance deficit before structural pathology is widespread — predictions we sharpen in Section VIII.

A caution on the direction of the arrow

Consistency requires applying to this claim the same skepticism Section III applied to the field. The locus-coeruleus-to-glymphatic bridge inherits the uncertainties of both its ends: the glymphatic switch is established chiefly in rodents and by the very noradrenaline manipulations the 2024 challenge calls into question, and the human sleep-amyloid coupling, though robust, does not by itself prove that the coupling runs *through* glymphatic clearance rather than through some other consequence of sleep (synaptic downscaling, altered production, metabolic rate). The honest position is that the locus coeruleus offers the most *mechanistically coherent* bridge available — it unifies the disease's origin, its sleep pathology, and its clearance deficit under one structure — but that coherence is not proof, and the bridge is offered as the framework's most testable conjecture rather than its most secure conclusion.

V. Glymphatic Failure Across the Three Phases

If the glymphatic system fails in Alzheimer's disease, it does not fail all at once or in one way. Like the intracellular clearance failure of the companion paper, it can be traced across the temporal architecture's three phases, failing first functionally, then structurally, then hydraulically — a different lesion of the same circuit in each decade.

Phase I — the functional deficit: a window that opens less often

In the third to sixth decades, in the silent phase the temporal architecture locates in the locus coeruleus, the glymphatic lesion is *functional*, not structural. The conduits are patent, the AQP4 gate is still polarized, the lymphatics still drain — but the switch is failing. As locus-coeruleus dysfunction fragments sleep and erodes slow-wave activity, the nightly window during which noradrenaline withdraws and the interstitial space opens becomes shorter, shallower, and less reliable. Nothing is yet broken; the system is simply used less. The consequence is a slow, sub-clinical accrual: interstitial amyloid-β, which the human data show rises with wakefulness, is cleared incompletely night after night, and the resulting small nightly surplus compounds across decades. This is the phase in which the glymphatic contribution is at once least visible and most preventable — a deficit of *use* rather than of *machinery*, and therefore, in principle, the phase most responsive to the restoration of sleep.

Phase II — the structural deficit: the gate loses its polarization

When the disease reaches the hippocampus and the microglial phase begins, the glymphatic lesion becomes structural. Reactive astrogliosis — the astrocytic activation that accompanies neuroinflammation — is associated with the redistribution of AQP4 away from its tight perivascular polarization, the very depolarization Zeppenfeld and colleagues documented in the human Alzheimer brain and found to track pathological stage. The gate that admits CSF to the interstitium is now degraded at the level of its molecular architecture, not merely under-used. This couples the glymphatic collapse to the inflammatory machinery of the companion papers: the reactive, post-homeostatic astrocyte of the microglial phase is also a glymphatically incompetent astrocyte, its endfoot channels scattered, its contribution to perivascular exchange diminished. Extracellular clearance and neuroinflammation thus fail together, through the same cellular transition, in the same phase.

Phase III — the hydraulic deficit: the pump stiffens and the drain clogs

In the eighth decade, in the vascular and cortical phase, the glymphatic system fails on its hydraulic side — at the pump and at the drain. The arterial pulsatility that drives periarterial influx depends on compliant vessels; arteriosclerosis and arterial stiffening, the near-universal companions of aging and of Alzheimer's disease, blunt the pulse-driven stroke and abolish the vasomotion on which inflow depends. Simultaneously the efflux side clogs. Cerebral amyloid angiopathy (CAA) — the deposition of amyloid-β within and around the walls of cortical and leptomeningeal arteries, present in the large majority of Alzheimer brains — is, on one influential reading, a *disease of perivascular drainage itself*: the intramural periarterial drainage (IPAD) pathway described by Carare, Weller and colleagues proposes that solutes leave the brain along arterial basement membranes, and that amyloid-β deposits in vessel walls precisely because this drainage route jams. Whether efflux is chiefly perivenous (the glymphatic model) or intramural-periarterial (the IPAD model) is itself an unsettled and partly competing question — but both models agree that the vessel wall is where late clearance fails, and CAA is the visible residue of that failure. And the meningeal lymphatic drain, already declining with age, offers progressively less exit capacity. The late glymphatic lesion is therefore a hydraulic one: a weakened pump pushing against a clogged drain, in a brain whose vessels have become both the conduit and the graveyard of the protein they can no longer clear.

A feed-forward trap

The three phases compound. The functional deficit of Phase I raises the baseline burden that the structural deficit of Phase II must clear with a degraded gate, which raises the burden that the hydraulic deficit of Phase III must clear with a failing pump — and the amyloid that accumulates in vessel walls in CAA further stiffens and occludes the very conduits on which clearance depends, so that impaired drainage begets the deposits that further impair drainage. This is the extracellular counterpart of the self-sustaining loop the companion paper located inside the cell: there, oxidative aldehydes poisoned the lysosomal pump that would have cleared them; here, the amyloid that failed clearance deposits in the walls that would have carried it away. In both compartments the disease's late self-sufficiency is the same structural fact — a clearance failure that manufactures the obstacle to its own repair.

VI. Two Clearances, One Failure

The intracellular and the extracellular twin

The Clearance Collapse argued that autophagy — clearance *within* the cell — is the quality-control spine of the disease. This paper has argued that the glymphatic system — clearance *around* the cell — fails in a parallel, phase-staged way. The two are not rivals for the title of "the" clearance failure; they are two tiers of a single waste-management architecture, and their relationship is mechanical. What the neuron cannot digest internally, and what it extrudes when it dies — the dense amyloid of the PANTHOS gravestone in the companion account — becomes extracellular cargo that only the glymphatic tier can remove. And when the glymphatic tier fails, the rising extracellular concentration of amyloid-β and tau raises the load pressing back on the cell, seeding further intracellular uptake and aggregation. Intracellular failure feeds the extracellular burden; extracellular failure back-pressures the cell. The brain that cannot clear itself fails at both tiers, and the tiers accelerate each other.

Why the coupling matters for interpretation

The coupling dissolves a false choice. The amyloid cascade hypothesis, autophagic-failure accounts, and glymphatic accounts have often been posed as competitors — is Alzheimer's a disease of too much amyloid production, of failed intracellular digestion, or of failed extracellular washout? The two-tier clearance view answers: these are not competing causes but sequential stations of one process. Amyloid accumulates because it is produced, yes, but chiefly because it is *not removed* — and it is not removed because both the intracellular digestion that would degrade it and the extracellular tide that would wash it away have failed, in a stereotyped temporal order, under the governance of a nucleus that fails first. The proteins that a century of pathology has read as causes are, on this synthesis, the visible residue of a two-tier clearance collapse.

The honest weight of the glymphatic tier

Consistency demands a final calibration. This paper has argued that the glymphatic tier is real and consequential, but Section III established that it is one clearance route among several and that its parenchymal mechanism is contested. It would betray the paper's method to now inflate it into the master lesion. The defensible claim is bounded: the glymphatic tier is a *significant, sleep-gated, aging-vulnerable contributor* to extracellular clearance whose failure is coupled, through the locus coeruleus, to the disease's origin and, through AQP4 and vascular pathology, to its later phases — a genuine and integrable part of the architecture, not its foundation and not its whole. Its value to the framework is precisely that it names the extracellular half of a clearance story whose intracellular half the companion paper told, and that it does so through the same nucleus, giving the temporal architecture a unified account of why the brain, across half a century, becomes progressively unable to remove what is killing it.

VII. The Therapeutic Logic of Restored Clearance

A clearance failure invites, as its therapeutic corollary, the restoration of clearance — but the glymphatic account, like its intracellular twin, insists that the restoration be matched to the phase and step where the lesion actually lies, and that it be pursued with the humility Section III demands. Several strategies follow, arranged from the best supported to the most speculative.

Protect and restore sleep — the strongest and earliest lever

If the Phase I lesion is a functional under-use of the clearance window, the first-line intervention is the protection of slow-wave sleep, and this is also the strategy with the most independent human support, because its rationale does not depend on winning the convection argument: the human sleep-amyloid coupling stands on PET and CSF evidence regardless of the precise mechanism. The practical program is the one the companion sleep papers develop — preserving sleep architecture, treating sleep apnea and fragmentation, respecting circadian timing, and, where the melatonergic account of *The Pineal Interface* applies, supporting the nocturnal state chemically. Pharmacological slow-wave enhancement and the enhancement of slow oscillations by non-invasive means are plausible adjuncts, though the dual-orexin-receptor antagonists that improve sleep continuity have shown only preliminary and mixed effects on amyloid markers and cannot yet be called disease-modifying. The claim here is deliberately conservative: restoring sleep is the best-supported way to act on the clearance deficit early, and it is worth doing on the human sleep-amyloid evidence alone.

Preserve the noradrenergic switch

If the locus coeruleus is the switch, then preserving the nucleus preserves the switch — and the geroneuroprotective and anti-inflammatory strategies the ONS program has developed to protect the locus coeruleus in Phase I are, on this account, also glymphatic strategies. This is an integrative rather than a novel prescription: the same interventions that defend the bioenergetically imperiled nucleus (the NAD+ restoration and mitophagy support of the companion pharmacology series, the melatonergic protection of the pineal account) should, if the bridge of Section IV holds, preserve the orderly noradrenergic rhythm on which the clearance window depends. The prediction is testable and is stated in Section VIII; the therapeutic point is that locus-coeruleus protection and glymphatic protection may be the same intervention.

Support the exit: the meningeal lymphatics

The efflux side offers a target less entangled in the convection dispute, because lymphatic drainage of CSF-borne macromolecules is well documented. Da Mesquita and colleagues showed that enhancing meningeal lymphatic function — by delivery of the lymphangiogenic factor VEGF-C — improved paravascular influx and, in later work, augmented the clearance of amyloid and the efficacy of anti-amyloid immunotherapy in mice. Restoring or protecting the aging lymphatic drain is thus a mechanistically defensible strategy, and one whose combination with existing immunotherapies is a concrete, near-term experimental program rather than a distant hope. It remains, at present, pre-clinical.

Maintain the pump: vascular health

Because periarterial influx is driven by arterial pulsatility and vasomotion, the maintenance of vascular compliance is a glymphatic intervention. The management of hypertension and arterial stiffening, and the promotion of the physical activity that has been shown to augment glymphatic flow in animal models, act on the Phase III hydraulic lesion — preserving the pump and slowing the vascular deposition that clogs the drain. This overlaps entirely with conventional cardiovascular prevention, which is a strength: it means the glymphatic account reinforces, rather than competes with, an already well-evidenced dementia-prevention strategy.

The AQP4 gate — a target, not yet a therapy

Repolarizing or stabilizing AQP4 is mechanistically attractive given the human depolarization data, but it is the least mature target. The available AQP4 modulators are research tools (the inhibitor TGN-020, for instance) rather than therapeutics, and because AQP4 has roles in edema and in normal water homeostasis, its manipulation carries risks that make it a target for careful development rather than immediate translation. It is listed here for completeness and flagged as speculative.

Why timing and honesty decide everything

Two disciplines govern this program. The first is timing, as with the intracellular account: the functional deficit of Phase I is addressed by restoring sleep and protecting the switch, while the structural and hydraulic deficits of Phases II and III demand the harder targets of the gate, the drain, and the vessel — and an intervention matched to the wrong phase will disappoint. The second is honesty about the mechanism's contested core: if parenchymal transport proves largely diffusive, strategies premised on "increasing flow" through the deep tissue may underperform, and the robust bets are those that act where the evidence is strongest — the sleep window at the front, the lymphatic exit at the back, and the vascular pump throughout. The therapeutic logic of the glymphatic collapse is therefore not a promise but a rank-ordered set of conjectures, strongest where it touches the human sleep and lymphatic data and weakest where it depends on the convective model that remains, in 2026, unsettled.

VIII. Falsifiable Predictions

The glymphatic account, integrated through the locus coeruleus, generates predictions sharp enough to be refuted — and, in keeping with the paper's method, several of them are predictions that would refute the framework itself if they failed.

On the locus coeruleus as switch. Measures of locus-coeruleus integrity (neuromelanin-sensitive MRI, noradrenergic markers) will correlate with independent measures of glymphatic function and slow-wave sleep within individuals, and the correlation will be present in the preclinical phase, before widespread cortical pathology — because the switch fails before the tissue does. If locus-coeruleus integrity and clearance are found to be uncoupled, the paper's central bridge is wrong.

On the sequence of glymphatic failure. The glymphatic lesion will be found to progress from functional (a shortened, shallower clearance window with preserved machinery) in the earliest phase, to structural (AQP4 depolarization) in the inflammatory phase, to hydraulic (impaired pulsatility and CAA-clogged efflux) in the vascular phase — and interventions will be effective only when matched to the operative lesion, sleep restoration failing to help once the gate and pump have structurally failed.

On sleep versus mechanism. The human coupling of slow-wave sleep loss to amyloid and tau accumulation will remain robust even if the rodent claim of sleep-*enhanced* clearance is overturned — because the coupling is carried by multiple mechanisms, of which glymphatic

clearance is one contributor and not the whole. A demonstration that restoring slow-wave sleep reduces amyloid accumulation in humans would support the clinical claim; a demonstration that it does so *without* any change in perivascular clearance measures would falsify the specifically glymphatic interpretation while sparing the sleep-therapy conclusion.

On the efflux target. Enhancing meningeal lymphatic drainage (e.g., by VEGF-C) will augment amyloid clearance and the efficacy of anti-amyloid immunotherapy in models, and combined lymphatic-plus-immunotherapy strategies will outperform immunotherapy alone — a prediction already partly borne out and extendable to human trials.

On cerebral amyloid angiopathy as failed drainage. If CAA is the residue of failed perivascular efflux, then the anatomical distribution of vascular amyloid will follow the drainage pathways rather than the sites of neuronal production, and interventions that improve perivascular drainage will reduce vascular amyloid deposition — whereas if CAA is simply local overproduction, drainage interventions will leave it unchanged.

On the convection question, honestly stated. If high-resolution human and animal measurement ultimately establishes that deep-parenchymal transport is diffusive rather than convective, the paper's mechanistic claims about interstitial "flow" will require revision — but its integrative claim, which is anchored at the perivascular conduit, the sleep switch, and the lymphatic exit rather than in the neuropil, will survive. The framework is constructed so that the contested middle can fail without collapsing the supported ends.

IX. Conclusion The Brain That Could Not Wash Itself

The companion paper ended with the cell that could not clear itself. This one ends with the brain that could not wash itself — the same disease, one tier out. Between them they describe a waste-management architecture that fails at both levels: the neuron unable to digest its own contents, and the extracellular tide unable to carry away what the neuron extrudes, the two failures coupled and mutually accelerating across half a century.

The glymphatic system's place in that story must be stated with the honesty its contested science demands. It is not the cause of Alzheimer's disease, and this paper has refused every temptation to make it one. Its parenchymal hydrodynamics are genuinely disputed; its signature sleep-dependence has been directly challenged in the most recent literature; its fractional contribution to total clearance is unknown. What survives that scrutiny is narrower but real: the brain possesses a perivascular CSF-ISF exchange and lymphatic drainage system whose inflow conduits, glial gate,

and lymphatic exit are well documented, whose function is coupled — in humans, on independent evidence — to sleep and to amyloid dynamics, and whose regulatory switch is the noradrenaline of the locus coeruleus.

That last fact is the paper's contribution, and it is why the glymphatic collapse belongs in this program rather than beside it. The temporal architecture names the locus coeruleus as the disease's origin. The glymphatic literature names noradrenaline as clearance's switch. These are the same molecule from the same nucleus, and their identity means the disease's first lesion is also, and by the same stroke, the failure of the switch that would open the nightly window in which the brain washes itself. The arsonist operates the sprinkler. A framework that had located the fire's ignition had, without knowing it, also located the failure of the fire suppression — and naming that coincidence, with its uncertainties carried openly, is what a temporal theory of clearance can offer the study of the sleeping, and no longer self-cleaning, brain.

Where the glymphatic system fits, then, is at the extracellular end of a two-tier clearance failure, hinged to the disease's origin through a single nucleus, strongest as an explanation exactly where the human evidence is strongest and weakest exactly where the physics is unsettled. To restore the brain's ability to wash itself — by protecting the sleep that opens the window, the nucleus that throws the switch, the lymphatics that drain the effluent, and the vessels that pump the tide — is a therapeutic program that a temporal theory of clearance makes not certain, but specific, testable, and honest about the reach of its own claims.

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