ACCSCIENCE PUBLISHING

Brain & Heart

REVIEW ARTICLE

The beat that clears the brain: Cardiac pulsatility as a driver of glymphatic flow during sleep

Gerardo Villalobos-Valdez[†], Karyme M. Alemán-Villa[†], David A. Armienta-Rojas, and Alberto K. De la Herrán-Arita*

Department of Neuroscience, Faculty of Medicine, Universidad Autónoma de Sinaloa, Culiacán, Sinaloa, México

Abstract

The brain, long considered an organ with limited means of waste disposal, is now understood to possess a highly efficient clearance network: the glymphatic system. This perivascular network facilitates the exchange of cerebrospinal fluid with interstitial fluid, clearing metabolic byproducts, including neurotoxic proteins such as amyloid-β and tau. The system's activity is not constant; it is overwhelmingly active during sleep, particularly the deep, slow-wave stages. A critical and often underappreciated driver of this process is the relentless, rhythmic pulsatility of cerebral arteries, powered by the cardiac cycle. This integrative review aims to synthesize evidence to build a wide-ranging picture of the heart–sleep–brain axis. We explored how the mechanical energy of the heartbeat is harnessed to propel cerebrospinal fluid through the brain's parenchyma and how this process is exquisitely modulated by sleep-dependent changes in autonomic tone and interstitial space. Furthermore, we detailed how common cardiovascular pathologies, including atrial fibrillation, heart failure, hypertension, and arterial stiffness, mechanistically disrupt this clearance pathway. Such disruptions provide a compelling, non-vascular explanation for the strong epidemiological link between heart disease and neurodegenerative disorders such as Alzheimer's disease. Finally, we discussed the diagnostic and therapeutic implications of this axis, from novel neuroimaging techniques to assess glymphatic function to the potential for cardiovascular and sleep-based interventions to preserve long-term brain health. This neurocardiology framework reframes the heart's role from a simple supplier of blood to an active custodian of the sleeping brain's integrity.

Keywords: Cardiac pulsatility; Cardiovascular; Glymphatic system; Sleep; Neurodegenerative diseases

[†]*These authors contributed equally to this work.*

***Corresponding author:**
Alberto K. De la Herrán-Arita (alberto.kousuke@uas.edu.mx)

Citation: Villalobos-Valdez G, Alemán-Villa KM, Armienta-Rojas DA, De la Herrán-Arita AK. The beat that clears the brain: Cardiac pulsatility as a driver of glymphatic flow during sleep. *Brain & Heart.* doi: 10.36922/BH025390057

Received: September 26, 2025

Revised: November 22, 2025

Accepted: December 17, 2025

Published online: June 23, 2026

1. Introduction

For nearly a century, the central nervous system (CNS) was conceptualized as an "immune-privileged" sanctuary, anatomically segregated from the body's peripheral lymphatic system. This paradigm, born from the absence of classical lymphatic vessels within the brain parenchyma, implied that the brain relied on slower, diffusion-based mechanisms for the removal of metabolic waste. This long-standing view was fundamentally challenged by the discovery of the glymphatic system, a term coined to

reflect its functional dependence on glial cells (specifically, astrocytes) and its analogous role to the peripheral lymphatic system.[1,2] This brain-wide perivascular network facilitates the convective bulk flow of cerebrospinal fluid (CSF) through the interstitial space, acting as a high-efficiency "dishwasher" that removes soluble proteins and other waste products accumulated during waking cellular activity.[2]

The functional significance of this discovery cannot be overstated, particularly in the context of the rising global burden of age-related neurodegenerative diseases. Disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are pathologically defined by the aggregation and deposition of misfolded proteins, amyloid-β (Aβ) and tau in AD, and α-synuclein in PD. A failure of clearance mechanisms is now considered a central pathogenic event, potentially preceding and driving the neurotoxic cascade that leads to cognitive decline.[3-5] The glymphatic system has emerged as a primary pathway for the removal of these very proteins, and its efficiency is profoundly state-dependent. Landmark studies revealed that glymphatic clearance is suppressed during wakefulness and dramatically enhanced during sleep, particularly the non-rapid eye movement (NREM) slow-wave stages.[4-6] This finding provided a compelling biological explanation for the universal, evolutionarily conserved need for sleep: it is the brain's dedicated time for housekeeping and restoration.

Bridging the fields of neurology and cardiology, a third crucial element has emerged: cardiovascular hemodynamics. The primary motive force driving CSF through the microscopic perivascular channels is the pulsatile energy generated by the heart.[6,7] Each heartbeat creates a pressure wave that propagates through the cerebral arterial tree, causing a minute expansion and recoil of the arterial walls. This mechanical action effectively "pumps" CSF along the outside of the arteries deep into the brain tissue. Consequently, the health of the cardiovascular system is inextricably linked to the efficacy of brain clearance. Conditions that alter the heart's rhythm (e.g., atrial fibrillation [AF]), reduce its output (e.g., heart failure [HF]), or stiffen the arteries (e.g., hypertension and aging) can directly sabotage this clearance mechanism.[7-11] This provides a powerful mechanistic link to explain the well-established, yet incompletely understood, epidemiological association between cardiovascular disease and the risk of dementia.[12]

This narrative review aims to provide an integrative synthesis of these interconnected domains based on a structured survey of the current literature. We first deconstruct the anatomy and physiology of the glymphatic system, detailing its cellular components and the multiple forces that govern its function. We then explore the profound modulatory role of sleep, focusing on the autonomic and electrophysiological changes that create an optimal window for clearance. The central thesis of this review is that various cardiovascular disorders mechanistically impair glymphatic function, thereby transforming systemic vascular pathology into a direct driver of neurodegenerative processes. Finally, we examine the translational horizon, discussing emerging diagnostic tools to visualize and quantify glymphatic flow in humans and exploring therapeutic strategies, from cardiovascular management to sleep optimization, that may be harnessed to preserve the integrity of this vital clearance system and promote lifelong brain health.

2. Methodology

To examine the mechanistic links within the heart–sleep–brain axis, we conducted a narrative review of the literature using the PubMed/MEDLINE, Scopus, and Google Scholar databases. The search strategy focused on identifying peer-reviewed articles published primarily between January 2012 (following the initial characterization of the glymphatic system) and March 2025. We also included seminal historical papers to provide a physiological context where necessary.

Regarding keywords and selection criteria, we employed combinations of the following Medical Subject Headings (MeSH) and keywords: "glymphatic system," "cerebrospinal fluid clearance," "perivascular space," "aquaporin-4," "cardiac pulsatility," "hemodynamics," "arterial stiffness," "atrial fibrillation," "sleep architecture," "slow-wave sleep," and "neurodegeneration." Boolean operators (AND, OR) were used to identify studies at the intersection of these fields (e.g., "cardiac pulsatility AND glymphatic flow" or "sleep AND amyloid clearance"). Articles were selected for inclusion based on their relevance to the physiological coupling of cardiovascular and neurological function. Priority was given to *in vivo* studies in mammalian models, human neuroimaging studies, and recent clinical trials. While this is not a systematic review, we prioritized high-impact original research and meta-analyses to ensure a representative synthesis of the current state of the field.

3. The glymphatic system: A primer on brain clearance

The glymphatic system represents a paradigm shift in our understanding of brain fluid dynamics. It is not a system of discrete vessels but rather a functional pathway composed of existing anatomical structures: the perivascular spaces, the brain's interstitial compartment, and the unique cellular architecture of astrocytes.

3.1. Anatomy and fluid pathways

The journey of fluid through the glymphatic circuit follows a defined trajectory. It begins with CSF, which is produced primarily by the choroid plexus within the brain's ventricles. From the ventricles, CSF flows into the subarachnoid space surrounding the brain. At the brain's surface, CSF enters the parenchyma by flowing into the Virchow–Robin spaces, annular tunnels surrounding the brain's penetrating arteries.[13,14] CSF enters the brain by flowing along the outside of penetrating arteries, moving in the same direction as arterial blood flow. Once in the periarterial space, the CSF convectively exchanges with interstitial fluid (ISF), the fluid bathing the neurons and glial cells of the parenchyma. This process allows for the collection of soluble waste products that have diffused out of the cells. The mixture of CSF and ISF, now laden with metabolites, continues its journey through the interstitial compartment toward the perivenous spaces surrounding the brain's draining veins.[15] From these perivenous tunnels, the fluid is cleared from the brain through several proposed exit routes (Figure 1). A major pathway involves drainage into the recently characterized meningeal lymphatic vessels, a true lymphatic network located in the dura mater that was overlooked for decades. These vessels then carry the fluid to the deep cervical lymph nodes in the neck, directly connecting brain clearance to the peripheral immune system. Other exit routes include drainage along cranial and spinal nerves and across the cribriform plate into the nasal lymphatics.[16]

To conceptualize this complex fluid dynamic for the non-specialist, the glymphatic system can be viewed as a macroscopic waste clearance service analogous to a municipal water system. In this framework, the Virchow–Robin spaces function as the high-pressure inlet pipes, utilizing the space around the arteries to drive fresh fluid deep into the brain. The parenchyma, the functional tissue of the brain containing neurons, is the neighborhood being serviced. Here, the process of convective exchange occurs; rather than relying on slow, passive diffusion, this is an active "wash cycle" where fresh fluid physically sweeps away metabolic debris. Finally, the perivenous spaces act as drainage canals, collecting the waste-laden fluid and flushing it into the lymphatic system to ensure the neural environment remains pristine.

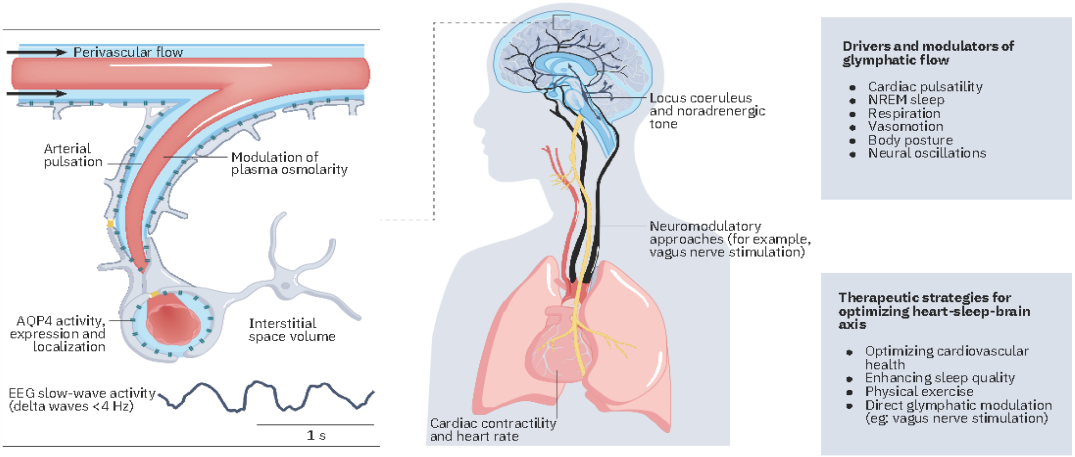

Figure 1. The heart–sleep–brain axis: mechanisms of glymphatic clearance and therapeutic targets. This schematic integrates the physiological drivers of glymphatic clearance with potential therapeutic interventions. (Left panel) The neurovascular unit acts as the functional site of clearance. The rhythmic pulsation of cerebral arteries (arterial pulsation) drives cerebrospinal fluid (CSF) into the perivascular space. This convective influx is facilitated by aquaporin-4 (AQP4) water channels localized on astrocytic endfeet. The process is highly sleep-dependent; during non-rapid eye movement (NREM) sleep, low-frequency delta waves (electroencephalography [EEG] slow-wave activity) are coupled with CSF flow, while a reduction in noradrenergic tone expands the interstitial space volume, reducing resistance to waste removal. (Right panel) The systemic regulation of this axis involves the interplay between cardiac contractility, respiration, and autonomic tone (mediated by the locus coeruleus [LC] and vagus nerve). The boxes summarize the primary physiological drivers (e.g., cardiac pulsatility, vasomotion) and outline translational therapeutic strategies, ranging from optimizing cardiovascular health and sleep quality to direct neuromodulatory approaches such as vagus nerve stimulation. Image created by the authors with Adobe Illustrator 2025.

3.2. The central role of astrocytes and aquaporin-4

The entire process of brain clearance is critically dependent on astrocytes. These star-shaped glial cells extend specialized processes known as "endfeet" that almost completely ensheathe the brain's entire vasculature, arteries, capillaries, and veins. This forms a structure called the glia limitans perivascularis, which acts as a crucial interface between the vascular and interstitial compartments.[17]

Embedded within these astrocytic endfeet at an extremely high density are aquaporin-4 (AQP4) water channels. AQP4 is a protein that facilitates the rapid movement of water across cell membranes. Its role in the glymphatic system is to expedite the exchange of fluid between the CSF in the periarterial space and the ISF of the parenchyma.[18] The localization of AQP4 is highly polarized; it is concentrated almost exclusively on the endfeet membranes facing the vasculature (Figure 1). This polarization is essential for creating a low-resistance pathway for water movement and maintaining the unidirectional, convective flow of the glymphatic circuit. In various disease states, such as after traumatic brain injury (TBI), stroke, or in the context of reactive gliosis associated with aging and neurodegeneration, this polarization is lost. AQP4 channels become diffusely expressed across the entire astrocyte membrane, severely impairing glymphatic fluid transport and leading to inefficient waste clearance.

In simpler terms, the astrocytes act as the "plumbing couplers" of the brain. Their endfeet form a tight sleeve around the blood vessels, creating a structural interface. The AQP4 channels function like high-speed sluice gates embedded specifically within this sleeve. The concept of polarization is critical here: it means these gates are installed exclusively on the side facing the fluid source (the vessel), ensuring that fluid is rapidly siphoned into the brain tissue in a unified direction. When pathology causes these gates to scatter randomly around the cell (loss of polarization), the directional pressure is lost. The system transforms from a high-flow pump into a passive, leaky sieve, resulting in stagnant fluid and the accumulation of toxic debris.

3.3. Major contributing forces of glymphatic flow

While the glymphatic pathway provides the anatomical route, fluid movement requires energy. Several physiological forces contribute to this process, acting in concert (Table 1):

- Cardiac pulsatility: The dominant force is widely considered to be the pulsatile wave generated by the cardiac cycle. With each systole, the elastic walls of cerebral arteries expand and recoil. This creates a peristaltic-like pumping motion within the rigid confines of the skull, which propels the surrounding perivascular CSF inward.[6] The importance of this mechanism has been demonstrated experimentally; stopping the heart or pharmacologically dampening

Table 1. Key drivers and modulators of glymphatic flow

Driver/Modulator	Mechanism of action	References
Cardiac pulsatility	The relentless expansion and recoil of cerebral arterial walls, driven by the heartbeat, creates a peristaltic-like wave that "pumps" cerebrospinal fluid (CSF) into the brain's perivascular spaces. This is considered the dominant driving force.	20
Respiration	Rhythmic changes in intrathoracic pressure during breathing are transmitted to the intracranial compartment. The slower, deeper breathing characteristic of sleep creates low-frequency pressure oscillations that help propel CSF.	21-23
Sleep state (non-rapid eye movement [NREM])	The transition to deep, slow-wave sleep causes a profound (~60%) expansion of the brain's interstitial space. This is triggered by a drop in norepinephrine from the locus coeruleus, causing astrocytes to shrink and drastically reducing resistance to fluid flow.	24
Vasomotion	Slow, spontaneous oscillations (~0.1 Hz) in the diameter of cerebral arterioles, independent of heart rate or breathing, are thought to help mix fluids in the deeper parenchyma, facilitating the movement of waste toward perivenous exit routes.	24,25
Neuronal oscillations	The large-amplitude delta waves of deep sleep are coupled to CSF flow. The "down-state" of the wave reduces local cerebral blood volume, triggering a compensatory influx of CSF to maintain intracranial pressure, thus actively driving fluid into the brain.	25
Body posture	Clearance has been shown to be most efficient in the lateral (side-sleeping) position compared to prone or supine postures. This may be because prone or supine positions can compress major venous outflow tracts, creating back-pressure that impedes drainage.	26

arterial pulsations brings glymphatic influx to a near-complete halt.[7-10] The regularity, amplitude, and frequency of these pulsations are therefore critical determinants of clearance efficiency.[18-20]

- Respiration: Respiratory cycles also contribute significantly. The rhythmic changes in intrathoracic pressure during inhalation[21] and exhalation[22] are transmitted to the intracranial compartment, creating slower, lower-frequency oscillations in CSF pressure.[23] Deeper, slower breathing, such as that occurring during sleep, is thought to be more effective at promoting CSF movement than the rapid, shallow breathing typical of an awake, active state. Respiration may act synergistically with cardiac pulsatility to drive fluid through the system.
- Vasomotion: Independent of both the cardiac and respiratory cycles, the smooth muscle walls of cerebral arterioles exhibit spontaneous, slow oscillations in diameter, occurring at a frequency of approximately 0.1 Hz. This phenomenon, known as vasomotion, is thought to contribute to the mixing of fluids within the deeper interstitial spaces, helping shuttle waste from parenchymal "dead-ends" toward the main perivenous outflow tracks.[24,25]
- Body posture: Recent research suggests that body posture also influences glymphatic efficiency. Studies in rodents have shown that clearance is more efficient in the lateral (side-sleeping) position compared to the supine (on the back) or prone (on the stomach) positions.[26] The proposed mechanism is that supine and prone postures may cause partial compression of major venous outflow tracts, such as the internal jugular veins, creating a slight "back-pressure" that impedes the final drainage step of the glymphatic circuit.

For the general clinician, it is helpful to visualize these forces not as isolated events but as a synchronized hydraulic system responsible for a "wash cycle." The cardiac pulse acts as the primary pump, providing the high-energy propulsive force that drives cleansing fluid into the brain with every beat. Respiration functions as a secondary bellows, creating a slower, tidal pressure gradient that supports this flow. Vasomotion adds a layer of local agitation, similar to the tumbling action of a washing machine, ensuring that fluid mixes thoroughly within the deep tissues rather than just bypassing them. Finally, body posture acts as a gravity-dependent valve; the correct position ensures the venous "drain pipes" remain open and uncompressed, preventing back-pressure from stalling the entire clearance process.

4. Sleep: The prime time for brain clearance

The discovery that glymphatic function is predominantly a nocturnal, sleep-dependent process has revolutionized our understanding of sleep's fundamental purpose. It is during sleep that the brain transitions into a unique physiological state optimized for waste removal.

4.1. The sleep-wake cycle and interstitial space dynamics

The most dramatic change that occurs in the brain upon transitioning from wakefulness to sleep is a physical restructuring of the brain's microarchitecture. Using two-photon microscopy in live, behaving mice, a landmark study by Xie *et al.* [5] demonstrated that the volume of the brain's interstitial space increases by up to 60% during natural sleep or under anesthesia. This expansion is profound; it drastically reduces the resistance to fluid flow, allowing CSF to penetrate deeper and more freely throughout the parenchyma. Upon waking, the interstitial space rapidly constricts again, effectively closing the floodgates and suppressing bulk fluid flow.[27] This dynamic expansion and contraction of the brain's extracellular compartment is the primary reason why glymphatic clearance is orders of magnitude more efficient during sleep.[28-31]

4.2. Autonomic control and neuromodulation

The mechanism controlling this dynamic change in interstitial volume is tied to the brain's major neuromodulatory systems, particularly the noradrenergic system originating from the LC. During wakefulness, the LC is highly active, releasing norepinephrine (NE) throughout the brain to promote arousal and alertness. One effect of high NE tone is to maintain astrocytes in a relatively "swollen" state, thereby keeping interstitial volume small[32-34] (Table 1).

As an individual falls asleep and enters the deep, slow-wave stages, the LC becomes virtually silent. The resulting dramatic drop in brain-wide NE levels is the key trigger that allows astrocytes to shrink in volume, thereby causing the interstitial space to expand.[35] This shift in autonomic control from sympathetic (high NE) dominance during wake to parasympathetic dominance during sleep also has critical vascular effects. Reduced sympathetic tone promotes mild vasodilation and increased arterial compliance, which may allow the cardiac pulse wave to propagate more effectively through the perivascular spaces, further enhancing the efficiency of the glymphatic pump. Therefore, sleep orchestrates a "perfect storm" for brain clearance: it quiets the LC to open the interstitial floodgates while simultaneously optimizing vascular conditions for pulsatile flow.

4.3. Brain oscillations and cerebrospinal fluid flow

More recent and technologically advanced studies have revealed an even deeper level of integration between sleep physiology and fluid dynamics. It appears that the characteristic electrophysiological signature of deep sleep, the large-amplitude, low-frequency delta waves, is directly coupled to CSF movement. Using simultaneous functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in sleeping humans, researchers have shown that large-scale neuronal silencing during the "down-state" of a delta wave reduces the brain's metabolic demand and, consequently, local cerebral blood volume.[35] To maintain constant intracranial pressure, this reduction in blood volume is met with a compensatory, pulsatile influx of CSF. This creates a macroscopic fluid wave that is time-locked with the neuronal oscillations of deep sleep. This finding suggests that delta waves do more than just facilitate memory consolidation; they actively participate in driving CSF through the sleeping brain, coupling the brain's electrical activity directly to its physiological maintenance. Any condition that suppresses delta wave activity, therefore, is likely to impair glymphatic clearance.

Essentially, the brain operates like a high-functioning corporate office that requires a nightly deep clean. During the day (wakefulness), the office is in "production mode": the building is packed with staff (high neuronal activity) and the manager, the LC, keeps the environment high-stress and tight (NE release), leaving no physical room for janitorial equipment to pass. At night (sleep), the manager leaves, and the staff clears out. The furniture effectively shrinks, widening the hallways by 60% (interstitial expansion). In this open environment, the delta waves of deep sleep act as the rhythmic swish of a mop, mechanically driving the cleaning fluid through the building in time with the electrical "down-state" of the facility, ensuring the workspace is pristine for the next day's production.

5. Cardiovascular disorders and their impact on glymphatic function

Given that cardiac pulsatility is the primary engine of the glymphatic system, it logically follows that any pathology affecting the heart or vasculature will have direct, deleterious consequences on brain clearance. This section explores the specific mechanisms by which common cardiovascular disorders degrade glymphatic function (Table 2).

5.1. Hypertension and arterial stiffness

Chronic hypertension is a leading risk factor for cognitive

Table 2. Impact of cardiovascular pathologies on glymphatic function

Cardiovascular pathology	Primary hemodynamic disruption	Consequence for the glymphatic system	References
Atrial fibrillation	The heartbeat becomes chaotic and irregular. The extreme beat-to-beat variability in stroke volume and blood pressure eliminates the rhythmic, predictable pulse needed for efficient pumping.	The chaotic pulsations fail to generate a coherent, propulsive wave, leading to stagnant or turbulent flow within the perivascular spaces and inefficient clearance of waste. This contributes to cognitive decline independent of stroke risk.	10,11
Hypertension & arterial stiffness	Arterial walls become stiff and less compliant. This dampens the pulse pressure amplitude in small arterioles and increases pulse wave velocity, losing the slow, peristaltic quality of the pressure wave.	The perivascular "pump" is severely weakened, reducing the mechanical energy available to drive cerebrospinal fluid (CSF) into the brain. Chronic inflammation also leads to a loss of aquaporin 4 (AQP4) polarization, impairing fluid transport.	36,37
Heart failure	(i) Low cardiac output: A weakened ventricle ejects less blood, resulting in a low-amplitude arterial pressure wave with diminished energy. (ii) Venous congestion: Elevated central venous pressure propagates to the brain, increasing intracranial pressure.	A "double blow" to the system: (i) The driving force is weakened at its source, leading to feeble CSF influx. (ii) Downstream obstruction is created in the perivenous outflow paths, hindering the final removal of waste.	38,39
Small vessel disease	Pathologies such as cerebral amyloid angiopathy and lipohyalinosis physically thicken, stiffen, and obstruct the small penetrating arteries and arterioles that form the core of the glymphatic pathway.	Creates a physical "roadblock" for glymphatic flow. It impairs the initial influx of CSF and also traps waste products within the vessel walls, creating a destructive feedback loop that damages the neurovascular unit.	40-44

decline and dementia. While much of this risk has been attributed to ischemic damage from strokes and microbleeds, its impact on the glymphatic system provides a complementary, non-ischemic mechanism. Chronic high blood pressure accelerates the process of arteriosclerosis, or the stiffening of arterial walls, through the degradation of elastic fibers and deposition of collagen.[36] Stiff arteries are less compliant; they are less able to expand and recoil with each heartbeat.

This has two critical hemodynamic consequences for the glymphatic system. First, the pulse wave velocity increases dramatically, and the pressure wave travels too quickly along the stiffened arterial wall, losing its slow, peristaltic quality. Second, the pulse pressure amplitude (the difference between systolic and diastolic pressure) is dampened in the smaller downstream arterioles that form the core of the glymphatic influx pathway.[36,37] Together, these changes severely weaken the perivascular pumping mechanism, reducing the energy available to drive CSF into the brain. This was demonstrated directly in a study by Li *et al.*[9], which used *in vivo* imaging to show that hypertensive mice had significantly reduced glymphatic influx and impaired clearance of interstitial solutes compared to normotensive controls. Furthermore, chronic hypertension promotes a low-grade inflammatory state in the brain, leading to reactive gliosis and a loss of AQP4 polarization, dealing a "double blow" to the glymphatic system by impairing both its engine and its plumbing.[38]

5.2. Atrial fibrillation and arrhythmias

Atrial fibrillation is the most common cardiac arrhythmia and a major independent risk factor for dementia, even in patients who never suffer an overt stroke. The hemodynamic signature of AF is chaos. The loss of a coordinated atrial contraction (the "atrial kick") and, more importantly, the irregular, chaotic ventricular response lead to extreme beat-to-beat variability in stroke volume and blood pressure.[39]

This irregularity is profoundly disruptive to the glymphatic system, which relies on a rhythmic, predictable pulse to establish an efficient pumping wave. The chaotic pulsations in AF fail to generate a coherent, propulsive force, leading to stagnant or turbulent flow within the perivascular spaces. The result is inefficient mixing and clearance of interstitial waste. This provides a compelling hypothesis for the non-thromboembolic component of AF-related cognitive decline. It suggests that years of inefficient brain cleaning, driven by an irregular heartbeat, could lead to a slow but steady accumulation of neurotoxic proteins, culminating in dementia. Studies have indeed found that AF is associated with higher burdens of cerebral microbleeds and white matter hyperintensities, which may be markers of underlying perivascular damage and glymphatic failure.[40]

5.3. Heart failure and low cardiac output

Heart failure, a condition of impaired cardiac pump function, impacts the glymphatic system through two distinct but synergistic mechanisms.

First, in systolic dysfunction (HF with reduced ejection fraction), the weakened ventricle ejects less blood with each beat. This results in a low-amplitude arterial pressure wave with diminished energy.[40] The initial force driving the entire system is weakened at its source, leading to a feeble perivascular pump and reduced CSF influx. The engine is not powerful enough to drive the clearance effectively.

Second, in both systolic and diastolic dysfunction, HF often leads to systemic venous congestion. This elevates central venous pressure, which propagates backward through the jugular veins into the cerebral venous system.[40,41] This creates a state of increased intracranial pressure and a "back-log" in the brain's venous outflow tracts. Since the glymphatic system ultimately drains via these perivenous pathways, this elevated venous pressure creates a downstream obstruction, reducing the overall pressure gradient across the brain and hindering the final, crucial step of waste removal. HF thus attacks the glymphatic system from both ends: it weakens the inflow pressure while simultaneously blocking the outflow path, creating a potent recipe for interstitial stagnation and metabolite accumulation.

5.4. Small vessel disease and microvascular pathology

The macrovascular diseases described above often lead to pathology at the level of the brain's smallest vessels, where the core function of glymphatic exchange takes place. Conditions such as cerebral amyloid angiopathy, where Aβ is deposited within the walls of cerebral arteries and arterioles, can physically stiffen and obstruct the perivascular spaces, creating "roadblocks" for glymphatic flow.[42] Similarly, hypertensive lipohyalinosis thickens and damages the walls of small penetrating arteries, compromising the integrity of the entire neurovascular unit, including the surrounding astrocytic endfeet. These microvascular pathologies not only impair the initial influx of CSF but also trap waste products within the vessel walls themselves, further accelerating vascular damage and disrupting blood-brain barrier function in a destructive feedback loop.[42-44]

To synthesize the impact of these pathologies for the clinician, we can extend the hydraulic analogy. If the

healthy heart acts as a precision pump ensuring a steady wash cycle, hypertension transforms the flexible supply hoses into rigid pipes; the fluid shoots through too rapidly, losing the gentle, peristaltic squeeze necessary to flush the tissue. AF represents a pump misfiring; the erratic rhythm causes the fluid to merely agitate or "slosh" in place rather than flow forward in a coherent wave. HF presents a catastrophic "double failure" of the plumbing: it combines low water pressure at the intake with a backed-up main sewer line (venous congestion), halting flow entirely. Finally, small vessel disease acts as the physical corrosion or scaling of the pipes themselves, narrowing the conduits and physically trapping debris within the system.

6. Neurodegenerative consequences

The failure of the glymphatic system, driven by the convergence of cardiovascular disease and sleep disruption, provides a direct mechanistic route to the protein aggregation that defines the major neurodegenerative disorders.

6.1. Alzheimer's disease and amyloid-β

Alzheimer's disease is characterized by the extracellular deposition of Aβ plaques and the intracellular accumulation of hyperphosphorylated tau tangles. The glymphatic system has been shown to be a major clearance pathway for soluble Aβ, the monomeric precursor to plaques.[45-47] Impairment of this clearance is a central tenet of the amyloid cascade hypothesis. The cardiovascular pathologies discussed above, by weakening pulsatility, disrupting rhythm, and impeding outflow, all contribute to a chronic reduction in Aβ clearance.

This can initiate a devastating vicious cycle. The initial accumulation of Aβ, resulting from impaired clearance, is itself toxic to sleep architecture. Higher Aβ burdens are strongly associated with reduced NREM slow-wave sleep and suppressed delta wave activity.[48,49] This Aβ-induced poor sleep further impairs glymphatic function, which in turn leads to even more Aβ accumulation. Genetic risk factors such as the apolipoprotein E (ApoE4) allele, the strongest genetic predictor of late-onset AD, may contribute to this cycle, as some evidence suggests that the ApoE4 protein is less efficient at chaperoning Aβ through the interstitial space for clearance.[50,51] Furthermore, as tau is also cleared via this pathway, glymphatic failure could contribute to the accumulation and subsequent trans-synaptic spread of tau pathology throughout the brain.

6.2. Parkinson's disease and *α-synuclein*

While less studied than Aβ, evidence is mounting that α-synuclein, the protein that aggregates to form Lewy bodies in PD, is also cleared by the glymphatic system.[52] Its clearance has been shown to be sleep-dependent and is impaired when glymphatic function is compromised in animal models. The clinical picture of PD provides strong correlative evidence. A vast majority of PD patients suffer from profound sleep disturbances, most notably rapid eye movement (REM) sleep behavior disorder (RBD), which can predate motor symptoms by years. While RBD is a different sleep stage from slow-wave sleep, it is part of a broader pattern of sleep fragmentation that reduces overall sleep quality and efficiency.[53,54] Furthermore, autonomic dysfunction is a core feature of PD and can directly affect vascular tone and compliance, which are necessary for efficient glymphatic transport. The synergistic burden of a primary sleep disorder, autonomic dysregulation, and often co-morbid cardiovascular disease could create a perfect storm for α-synuclein accumulation.

6.3. Broader implications: Traumatic brain injury, stroke, and chronic traumatic encephalopathy

The relevance of glymphatic function extends beyond primary neurodegenerative diseases. Following an acute injury such as a TBI or stroke, the glymphatic system is acutely impaired due to local cell death, reactive gliosis, and loss of AQP4 polarization.[4] This acute failure contributes to the development of cerebral edema and the accumulation of toxic debris in the days following the injury.[55] Chronically, a persistent impairment of glymphatic function after TBI may underlie the increased long-term risk of developing dementia and chronic traumatic encephalopathy, a tauopathy associated with repetitive head trauma. The failure to adequately clear pathological proteins in the months and years following injury may allow the neurodegenerative process to take root.

7. Diagnostic and therapeutic implications

The recognition of the heart–sleep–brain axis as a critical determinant of neurological health opens a new frontier for diagnostics, prevention, and therapy. The focus shifts from reacting to established neurodegeneration to proactively maintaining the systems that keep the brain clean.

7.1. Advances in human imaging

A major challenge has been the visualization and quantification of glymphatic function in living humans. While invasive tracer studies are possible in animals, noninvasive methods are required for clinical use. Several promising techniques are emerging:

- Diffusion tensor imaging along the perivascular space (DTI-ALPS): This MRI technique measures the diffusivity of water specifically within the perivascular

spaces. The "ALPS index" is a quantitative measure of this diffusivity, which serves as an indirect proxy for glymphatic function. A lower ALPS index, suggesting restricted water movement, has been correlated with cognitive decline and has been observed in patients with AD, PD, and sleep disorders.[56,57] While powerful, it remains an indirect measure of flow.

- Contrast-enhanced MRI: This research method involves injecting a gadolinium-based contrast agent intrathecally (into the spinal canal) and tracking its influx into the brain over many hours using MRI. This provides the most direct visualization of glymphatic transport in humans and has confirmed that CSF influx is greater during sleep.[58,59] However, due to the invasive nature and potential toxicity of intrathecal gadolinium, its use is currently restricted to specific clinical and research settings.
- fMRI-based methods: Newer analytic techniques are being applied to resting-state fMRI data. By analyzing the propagation of very low-frequency oscillations in the blood-oxygen-level-dependent (BOLD) signal, researchers can infer patterns of fluid flow.[60,61] One such study correlated a widespread, propagating fluid wave with the delta waves of NREM sleep, providing a completely noninvasive correlate of glymphatic activity.[24]

7.2. Therapeutic strategies: A multi-pronged approach

Therapeutically, the goal is to optimize the components of the heart–sleep–brain axis:

- Cardiovascular health optimization: This goes beyond traditional goals such as preventing stroke. Aggressive management of hypertension with drugs known to improve vascular compliance (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]) may have the added benefit of preserving the glymphatic pump. In AF, the question arises whether a rhythm-control strategy (e.g., catheter ablation), which restores a regular pulse, is superior to a rate-control strategy for preserving long-term cognitive function. Some retrospective studies suggest it might be.[62] For HF, therapies that improve cardiac output and reduce venous congestion could have profound downstream benefits for brain clearance.
- Sleep quality enhancement: Given the centrality of sleep, interventions aimed at improving it are paramount. For patients with obstructive sleep apnea, continuous positive airway pressure (CPAP) therapy not only improves sleep quality but also reduces CSF biomarkers of Aβ accumulation.[63,64] For insomnia, non-pharmacological approaches such as cognitive behavioral therapy for insomnia (CBT-I) are highly effective. In the future, pharmacological agents designed specifically to enhance the amplitude or duration of slow-wave sleep could be developed as "glymphatic enhancers."
- Lifestyle interventions: Simple, accessible interventions hold great promise. Physical exercise has been shown in animal models to significantly increase glymphatic flow, potentially by improving cardiovascular health and promoting trophic factor release. Dietary interventions, such as those rich in omega-3 fatty acids, may also be beneficial by reducing inflammation and improving vascular compliance. Additionally, it has been shown that slow-paced breathing via heart rate variability (HRV) biofeedback stimulates vagus-nerve pathways that counter noradrenergic stress and arousal pathways that can influence production and clearance of AD-related proteins.[65-68]
- Direct glymphatic modulation (future directions): More speculative but exciting avenues include direct modulation of the system. Vagus nerve stimulation, which is approved for epilepsy and depression, promotes a parasympathetic state and may enhance glymphatic flow. Pharmacological targets, such as drugs that can preserve or restore AQP4 polarization on astrocytic endfeet, are a major area of preclinical research[63-68] (Figure 1). Finally, neuromodulatory techniques such as transcranial focused ultrasound or transcranial direct current stimulation (tDCS) are being explored for their ability to noninvasively enhance slow-wave activity during sleep, potentially boosting clearance.

8. Conclusion

The discovery of the glymphatic system has fundamentally reshaped our understanding of brain physiology, revealing a sophisticated, high-speed clearance system that is critically dependent on the synergistic interaction between the heart and brain, primarily during sleep. The traditional view of the heart's role in brain health, limited to ensuring adequate perfusion, is now clearly insufficient. The heart's mechanical, pulsatile energy is actively harnessed as the engine for a system that maintains the brain's proteostatic balance.

The heart–sleep–brain axis provides a unifying framework that mechanistically links two of the most significant public health crises of our time: cardiovascular disease and neurodegenerative dementia. It posits that the path to a diseased brain can begin with a failing heart or fragmented sleep, which impedes the brain's ability to cleanse itself night after night. This cumulative failure of

clearance allows neurotoxic proteins to accumulate over decades, silently paving the way for cognitive decline.

This new perspective offers immense hope. It shifts the focus of dementia research from a near-exclusive concentration on neuronal pathology to a more holistic, systemic view. It suggests that a significant portion of dementia risk may be modifiable not only by treating established vascular pathology but by actively optimizing the physiological drivers of clearance.[68] This includes leveraging therapies we already have, such as better blood pressure control, effective rhythm management for AF, and treatment for sleep apnea, while also exploring novel interventions. Emerging evidence suggests that HRV biofeedback strategies can enhance the amplitude and stability of specific cardiovascular rhythms, particularly the 0.1 Hz and very low-frequency oscillations, that are essential for efficient glymphatic transport.

Looking forward, the complexity of these fluid dynamics presents a significant challenge that will likely require the integration of advanced computational modeling. Developing *in silico* models of the heart–sleep–brain interface will allow researchers to simulate interventions and test hypotheses regarding pulse wave propagation and fluid exchange in ways that are currently impossible *in vivo*. Ultimately, the future of preventive neurology may lie in the cardiology and sleep clinics of today. By preserving the heart's rhythmic beat and optimizing its oscillatory stability, while honoring the restorative power of sleep, we may be providing the most potent therapy yet for safeguarding the integrity of the aging brain.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Gerardo Villalobos-Valdez, Karyme M. Alemán-Villa, Alberto K. De la Herrán-Arita

Writing–original draft: Gerardo Villalobos-Valdez, Karyme M. Alemán-Villa, Alberto K. De la Herrán-Arita

Writing–review & editing: David A. Armienta-Rojas, Alberto K. De la Herrán-Arita

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. *Neurochem Res*. 2015;40(12):2583-2599.

   doi: 10.1007/s11064-015-1581-6

2. Iliff JJ, Wang M, Liao Y, *et al.* A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4(147):147ra111.

   doi: 10.1126/scitranslmed.3003748

3. Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. *Science*. 2020;370(6512):50-56.

   doi: 10.1126/science.abb8739

4. De la Herrán-Arita, A.K. When sleep fails, brain clearance suffers: the role of glymphatic impairment in clinical neurology. *Acta Neurol Belg.* 2025.

   doi: 10.1007/s13760-025-02959-w

5. Xie L, Kang H, Xu Q, *et al.* Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373-377.

   doi: 10.1126/science.1241224

6. Iliff JJ, Wang M, Zeppenfeld DM, *et al.* Cerebral arterial pulsations drive paravascular CSF–interstitial fluid exchange in the murine brain. *J Neurosci*. 2013;33(46):18190-18199.

   doi: 10.1523/ JNEUROSCI.1592-13.2013

7. Mestre H, Tithof J, Du T, *et al.* Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat Commun*. 2018;9(1):4878.

   doi: 10.1038/s41467-018-07318-3

8. Mortensen KN, Sanggaard S, Mestre H, *et al.* Impaired Glymphatic Transport in Spontaneously Hypertensive Rats. *J Neurosci*. 2019;39(32):6365-6377.

   doi: 10.1523/JNEUROSCI.1974-18.2019

9. Li M, Kitamura A, Beverley J, *et al.* Impaired glymphatic function and pulsation alterations in a mouse model of vascular cognitive impairment. *Front Aging Neurosci.* 2022;13:788519.

   doi: 10.3389/fnagi.2021.788519

10. Hofer S, Schnieder M, Polster L, Dechent P, Bähr M. Atrial fibrillation reduces CSF flow dynamics. A multimodal MRI study. *Neuroimage*. 2025;317:121337.

doi: 10.1016/j.neuroimage.2025.121337

11. Gardarsdottir M, Sigurdsson S, Aspelund T, *et al.* Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. *Europace*. 2018;20(8):1252-1258.

doi: 10.1093/europace/eux220

12. Jefferson AL. Cardiac output as a potential risk factor for abnormal brain aging. *J Alzheimers Dis*. 2010;20(3):815-825.

doi: 10.3233/JAD-2010-100081

13. Aspelund A, Antila S, Proulx ST, *et al.* A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. 2015;212(7):991-999.

doi: 10.1084/jem.20142290

14. Louveau A, Smirnov I, Keyes TJ, *et al.* Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015;523(7560):337-341.

doi: 10.1038/nature14432

15. Ahn JH, Cho H, Kim JH, *et al.* Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. *Nature*. 2019;572(7767):62-66.

doi: 10.1038/s41586-019-1419-5

16. Mathiisen TM, Lehre KP, Danbolt NC, Ottersen OP. The perivascular astroglial sheath provides a complete covering of the brain microvessels: an electron microscopic 3D reconstruction. *Glia*. 2010;58(9):1094-1103.

doi: 10.1002/glia.20990

17. Verkhratsky A, Nedergaard M. Physiology of astroglia. *Physiol Rev*. 2018;98(1):239-389.

doi: 10.1152/physrev.00042.2016

18. Mestre H, Hablitz LM, Xavier AL, *et al.* Aquaporin-4-dependent glymphatic solute transport in the rodent brain. *eLife*. 2018;7:e40070.

doi: 10.7554/eLife.40070

19. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. *Lancet Neurol*. 2018;17(11):1016-1024.

doi: 10.1016/S1474-4422(18)30318-1

20. Bedussi B, van der Eerden A, de Vos J, *et al.* Paravascular channels, cisterns, and the subarachnoid space in the rat brain. *J Cereb Blood Flow Metab*. 2017;37(4):1374-1385.

doi: 10.1177/0271678X16655550

21. Dreha-Kulaczewski S, Joseph AA, Merboldt KD, Ludwig HC, Gärtner J, Frahm J. Inspiration is the major regulator of human CSF flow. *J Neurosci*. 2015;35(6):2485-2491.

doi: 10.1523/JNEUROSCI.3246-14.2015

22. Yamada S, Miyazaki M, Yamashita Y, *et al.* Influence of respiration on cerebrospinal fluid movement using magnetic resonance spin labeling. *Fluids Barriers CNS*. 2013;10(1):36.

doi: 10.1186/2045-8118-10-36

23. Vinje V, Eide PK, Løkken KK, *et al.* Respiratory influence on cerebrospinal fluid flow—a computational study based on long-term intracranial pressure measurements. *Sci Rep*. 2019;9(1):9732.

doi: 10.1038/s41598-019-46055-5

24. Helakari H, Korhonen V, Holst SC, *et al.* Human NREM sleep promotes brain-wide vasomotor and respiratory pulsations. *J Neurosci*. 2022;42(12):2511-2523.

doi: 10.1523/JNEUROSCI.0934-21.2022

25. van Veluw SJ, Hou SS, Bako M, *et al.* Vasomotion as a driving force for paravascular clearance in the awake mouse brain. *Neuron*. 2020;105(3):549-561. doi 10.1016/j.neuron.2019.10.033

26. Lee H, Xie L, Yu M, *et al.* The effect of body posture on brain glymphatic transport. *J Neurosci*. 2015;35(31):11034-11044.

doi: 10.1523/JNEUROSCI.1625-15.2015

27. Hablitz LM, Plá V, Giannetto M, *et al.* Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun*. 2020;11(1):4411.

doi: 10.1038/s41467-020-18115-2

28. Lewis LD. The interconnected causes and consequences of sleep in the brain. *Science*. 2021;374(6567):564-568.

doi: 10.1126/science.abi8375

29. Eide PK, Vinje V, Pripp AH. Sleep deprivation impairs molecular clearance from the human brain. *Brain*. 2021;144(3):863-874.

doi: 10.1093/brain/awaa443

30. Reddy OC, van der Werf YD. The sleeping brain: harnessing the power of the glymphatic system through lifestyle choices. *Brain Sci*. 2020;10(11):868.

doi: 10.3390/brainsci10110868

31. Camberos-Barraza J, Alemán-Villa KM, De la Herrán-Arita AK. The mind awake at night: Glymphatic dysfunction as a mechanistic bridge linking multifactorial sleep disturbances to neurodegeneration. *J Clin Basic Psychosom*. 025390076.

doi: 10.36922/JCBP025390076

32. Abbott NJ, Pizzo ME, Preston JE. The role of brain barriers in fluid movement in the CNS: is there a 'glymphatic' system? *Acta Neuropathol*. 2018;135(3):387-407.

doi: 10.1007/s00401-018-1812-4

33. O'Donnell J, Ding F, Nedergaard M. Distinct Functional States of Astrocytes During Sleep and Wakefulness: Is Norepinephrine the Master Regulator? *Curr Sleep Med Rep*. 2015;1(1):1-8.

doi: 10.1007/s40675-014-0004-6

34. Hablitz LM, Vinitsky HS, Sun Q, *et al.* Increased glymphatic

influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Sci Adv*. 2019;5(2):eaav5447.

doi: 10.1126/sciadv.aav5447

35. Fultz NE, Bonmassar G, Setsompop K, *et al.* Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science*. 2019;366(6465):628-631.

doi: 10.1126/science.aax5440

36. Scuteri A, Nilsson PM, Tzourio C, Redon J, Laurent S. Microvascular brain damage with aging and hypertension. *J Hypertens*. 2011;29(8):1469-1477.

doi: 10.1097/hjh.0b013e328347cc17

37. Pase MP, Himali JJ, Mitchell GF, *et al.* Association of aortic stiffness with cognition and brain aging in young and middle-aged adults: the Framingham Third Generation Cohort Study. *Hypertension*. 2016;67(3):513-519.

doi: 10.1161/HYPERTENSIONAHA.115.06610

38. Alemán-Villa KM, Armienta-Rojas DA, Camberos-Barraza J, *et al.* Neuroinflammation across the spectrum of neurodegenerative diseases: mechanisms and therapeutic frontiers. *Neuroimmunomodulation*. 2025;32(1):278–305.

doi: 10.1159/000548021

39. Min J, Rouanet J, Martini AC, *et al.* Modulating heart rate oscillation affects plasma amyloid beta and tau levels in younger and older adults. *Sci Rep*. 2023;13(1):3967.

doi: 10.1038/s41598-023-30167-0

40. Wurm R, Prausmüller S, Ponleitner M, *et al.* Serum Markers of Neurodegeneration Are Strongly Linked to Heart Failure Severity and Outcome. *JACC Heart Fail*. 2024;12(6):1073-1085.

doi: 10.1016/j.jchf.2024.03.005

41. Oberlin LE, Manuck SB, Gianaros PJ, *et al.* Blood pressure interacts with APOE ε4 to predict memory performance in a midlife sample. *Neuropsychology*. 2015;29(5):693-702.

doi: 10.1037/neu0000177.

42. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696.

doi: 10.1016/S1474-4422(19)30079-1

43. Zhang W, Zhou Y, Wang J, *et al.* Glymphatic clearance function in patients with cerebral small vessel disease. *Neuroimage*. 2021;238:118257.

doi: 10.1016/j.neuroimage.2021.118257

44. Lu W, Zhu S, Chen R, *et al.* Glymphatic system dysfunction mediates the relationship between deep medullary vein alterations and cognitive impairment in cerebral small vessel disease. *BMC Neurol*. 2025;26(1):40.

doi: 10.1186/s12883-025-04535-4

45. Ding J, Zhao C, Hao X, Jiao H. Glymphatic and meningeal lymphatic dysfunction in Alzheimer's disease: Mechanisms and therapeutic perspectives. *Alzheimers Dement*. 2025;21(10):e70709.

doi: 10.1002/alz.70709

46. Pase MP, Pinheiro A, Rowsthorn E, *et al.* MRI Visible Perivascular Spaces and the Risk of Incident Mild Cognitive Impairment in a Community Sample. *J Alzheimer's Dis*. 2023;96(1):103-112.

doi: 10.3233/JAD-230445

47. Rainey-Smith SR, Mazzucchelli GN, Villemagne VL. Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-amyloid burden. *Transl Psychiatry*. 2018;8(1):47.

doi: 10.1038/s41398-018-0094-x

48. Holth JK, Fritschi SK, Wang C. The sleep-wake cycle regulates brain interstitial fluid tau in mice and humans. *Science*. 2019;363(6429):880-884.

doi: 10.1126/science.aav2546

49. Ju YS, Ooms SJ, Sutphen C. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain*. 2017;140(8):2104-2113.

doi: 10.1093/brain/awx148

50. Castellano JM, Kim J, Stewart FR, *et al.* Human apoE isoforms differentially regulate brain amyloid-β peptide clearance. *Sci Transl Med*. 2011;3(89):89ra57.

doi: 10.1126/scitranslmed.3002156

51. Da Mesquita S, Louveau A, Vaccari A, *et al.* Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature*. 2018;560(7717):185-191.

doi: 10.1038/s41586-018-0368-8

52. Chen A, Kuang Z, Khong PL, *et al.* Glymphatic Function in Prodromal Parkinson's Disease: Associations With Symptoms, Gray Matter Volume, and Phenoconversion Risk. *Eur J Neurol*. 2025;32(10):e70389.

doi: 10.1111/ene.70389

53. Huang M, Zhang P, Chen Z, *et al.* Impairment of the intracranial lymphatic system in Parkinson's disease: a combined study of the meningeal lymphatics vessels and glymphatic system based on noninvasive neuroimaging. *Eur J Med Res*. 2025;30(1):801.

doi: 10.1186/s40001-025-03048-7

54. Bae YJ, Choi BS, Kim JM, Choi JH, Cho SJ, Kim JH. Altered glymphatic system in idiopathic normal pressure hydrocephalus. *Parkinsonism Relat Disord*. 2021;82:56-60.

doi: 10.1016/j.parkreldis.2020.11.009

55. Romanò F, Suresh V, Galie PA, Grotberg JB. Peristaltic flow in the glymphatic system. *Sci Rep*. 2020;10(1):21065.

doi: 10.1038/s41598-020-77787-4

56. Taoka T, Masutani Y, Kawai H, *et al.* Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. *Jpn J Radiol*. 2017;35(4):172-178.

    doi: 10.1007/s11604-017-0617-z

57. Lee HJ, Lee DA, Shin KJ, Park KM. Glymphatic system dysfunction in obstructive sleep apnea evidenced by DTI-ALPS. *Sleep Med*. 2022;89:176-181.

    doi: 10.1016/j.sleep.2021.12.013

58. Barisano G, Lynch KM, Sibilia F, *et al.* Imaging perivascular space structure and function using brain MRI. *Neuroimage*. 2022;257:119329.

    doi: 10.1016/j.neuroimage.2022.119329

59. Ringstad G, Valnes LM, Dale AM, *et al.* Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. *JCI Insight*. 2018;3(13):e121537.

    doi: 10.1172/jci.insight.121537

60. Wu D, Song C, Chen R, *et al.* Glymphatic function as a prognostic biomarker in prolonged disorders of consciousness. *CNS Neurosci Ther.* 2025;31(7):e70526.

    doi: 10.1111/cns.70526

61. Li K, Bian Y, Xing Y, Jia X. Altered glymphatic function and cerebrovascular reactivity in white matter hyperintensities: Insights into cognitive impairment. *Brain Res Bull.* 2025;231:111552.

    doi: 10.1016/j.brainresbull.2025.111552

62. Lee MH, Lee WJ, Lee SK, *et al.* Impact of Sleep Apnea on Perivascular Diffusivity and Cognition: A 4-Year Prospective Cohort Study. *Am J Respir Crit Care Med*. 2025;211(12):2382-2392.

    doi: 10.1164/rccm.202411-2221OC

63. Osuna-Ramos JF, Camberos-Barraza J, Torres-Mondragón LE, *et al.* Interplay between the glymphatic system and the endocannabinoid system: implications for brain health and disease. *Int J Mol Sci*. 2023;24(24):17458.

    doi: 10.3390/ijms242417458

64. Rábago-Monzón ÁR, Osuna-Ramos JF, Armienta-Rojas DA, *et al.* Stress-Induced Sleep Dysregulation: The Roles of Astrocytes and Microglia in Neurodegenerative and Psychiatric Disorders. *Biomedicines*. 2025;13(5):1121.

    doi: 10.3390/biomedicines13051121

65. Ren H, Luo C, Feng Y, *et al.* Omega-3 polyunsaturated fatty acids promote amyloid-β clearance from the brain through mediating the function of the glymphatic system. *J Cereb Blood Flow Metab*. 2017;37(8):2844-2857.

    doi: 10.1096/fj.201600896

66. He XF, Liu DX, Zhang Q, *et al.* Voluntary exercise promotes glymphatic clearance of amyloid beta and reduces the activation of astrocytes and microglia in aged mice. *Front Mol Neurosci*. 2017;10:144.

    doi: 10.3389/fnmol.2017.00144

67. Cheng KP, Brodnick SK, Blanz SL, *et al.* Clinically-derived vagus nerve stimulation enhances cerebrospinal fluid penetrance. *Brain Stimul*. 2020;13(4):1024-1030.

    doi: 10.1016/j.brs.2020.03.012.

68. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*. 2017;96(1):17-42.

    doi: 10.1016/j.neuron.2017.07.030