Review

Neuroscience

Deep Understanding of the Role of Sleep in Brain Cleansing

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Sleep is a fundamental physiological process crucial for maintaining cognitive function, emotional regulation, and overall brain health. Recent research has highlighted sleep's pivotal role in facilitating the brain's intrinsic cleansing mechanisms, primarily via the glymphatic system, which actively removes metabolic waste products, including neurotoxic proteins such as beta-amyloid and tau. Disruptions in sleep architecture or duration can impair these clearance processes, potentially contributing to neurodegenerative disorders such as Alzheimer's disease. This review synthesizes current evidence on the mechanisms underlying sleep-dependent brain cleansing, examining the interplay between neuronal activity, cerebrospinal fluid dynamics, and circadian regulation. It also explores the implications of sleep deprivation, aging, and pathological conditions on brain homeostasis. By integrating molecular, neurophysiological, and clinical findings, this article underscores the importance of sleep in maintaining cerebral health and highlights potential therapeutic strategies to optimize sleep for neuroprotection.

Keywords: Sleep; Quality vs Quantity; Brain Cleansing; Glymphatic System; Neuroprotection

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SLEEP is universally recognized as a critical component of health, yet its underlying purposes continue to be elucidated. Beyond its well-known roles in memory consolidation, emotional regulation, and metabolic restoration, sleep has emerged as a vital period for maintaining cerebral homeostasis through active waste clearance. The brain, unlike other organs, lacks traditional lymphatic vessels, leading to the discovery of a specialized system, termed the glymphatic pathway, responsible for removing metabolites and neurotoxic substances. This review examines the intricate mechanisms by which sleep facilitates brain cleansing, explores the consequences of disrupted sleep, and considers clinical implications for neurodegenerative diseases.

The Glymphatic System: Brain's Cleaning Network

The discovery of the glymphatic system has profoundly transformed our understanding of brain physiology and the mechanisms underlying neural homeostasis. For decades, scientists were puzzled by how the brain, an organ with intense metabolic activity and limited regenerative capacity, managed to rid itself of potentially harmful metabolic waste products in the absence of a conventional lymphatic drainage system (Gędek et al., 2023). The identification of the glymphatic system provided a paradigm-shifting explanation, revealing a unique perivascular network that functions as the brain's waste clearance mechanism (Chen et al., 2025). This system is now regarded as a cornerstone of neurophysiology and an essential mediator of sleep's restorative role.

Historical Context: The Mystery of Brain Waste Removal

Unlike peripheral tissues, which rely on lymphatic vessels to collect and transport interstitial waste, the central nervous system (CNS) lacks classical lymphatics within its parenchyma. For years, scientists hypothesized that cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange occurred diffusively and passively. Yet, this explanation was insufficient to account for the clearance of bulky macromolecules such as amyloid-beta (Aβ) and tau proteins, both of which accumulate in neurodegenerative diseases. The breakthrough came with in vivo imaging studies in rodents using two-photon microscopy, which demonstrated active convective flow of CSF into the brain parenchyma along periarterial spaces, mixing with ISF, and subsequent efflux of waste-laden fluid along perivenous pathways. This process resembled the lymphatic system, but because it relied on glial (astrocytic) cells, it was termed the glymphatic system.

Structural Components of the Glymphatic System

The glymphatic system is a complex anatomical and functional network involving vascular, glial, and fluid compartments. Its major components include:

- *Periarterial Influx Pathways*: CSF enters the brain parenchyma along the periarterial space surrounding penetrating arteries (Liang et al., 2025). These spaces act as conduits that distribute CSF deep into the cortex and subcortical regions. The driving force behind CSF entry is closely linked to arterial pulsatility generated by cardiac output.
- *Interstitial Fluid Exchange*: Once CSF enters periarterial spaces, it crosses into the interstitial compartment of the brain, facilitated by aquaporin-4 (AQP4) water channels located on astrocytic endfeet (Dong et *al*., 2024). These glial structures ensheath blood vessels, forming a functional interface that regulates the bidirectional movement of fluids and solutes.
- *Perivenous Efflux Pathways*: Waste-containing fluid exits the parenchyma via perivenous spaces, eventually draining into meningeal lymphatic vessels, cervical lymph nodes, or systemic circulation (Liang et al., 2025). This ensures that potentially toxic metabolites are removed from the CNS environment.
- *Astrocytic Network: Astrocytes are central to glymphatic function*. Their polarized expression of AQP4 water channels at vascular endfeet is critical for enabling rapid fluid exchange between periarterial CSF and brain interstitium (Corbali & Levey, 2025).

Together, these components create a dynamic, circulation-like system that parallels the vascular system in structure and the lymphatic system in function.

Fluid Dynamics and Driving Forces

The efficiency of the glymphatic system is heavily dependent on mechanical and physiological forces that drive fluid movement:

- *Arterial Pulsatility*: The rhythmic expansion and contraction of arteries with each cardiac cycle generate pressure gradients that propel CSF through periarterial spaces. Experiments in rodents have shown that diminished arterial pulsatility, such as in vascular stiffening with aging or hypertension, impairs glymphatic transport (Nozaleda et al., 2025).
- *Respiratory Movements*: Breathing-induced pressure changes within the thoracic cavity are transmitted to the intracranial compartment, further influencing CSF flow dynamics.
- *Sleep-Dependent Modulation*: Glymphatic activity is markedly higher during sleep compared to wakefulness. During slow-wave sleep, neuronal activity decreases, extracellular space volume expands by up to 60%, and norepinephrine levels fall, creating favorable conditions for convective flow (Reddy & Werf, 2020).
- *Body Posture:* Recent studies suggest that sleep posture may influence glymphatic efficiency. For example, lateral recumbent positions in rodents are associated with greater clearance than supine or prone positions, potentially explaining evolutionary adaptations in human sleep behavior (Simka et al., 2019).

Molecular Regulation: Role of Aquaporin-4

AQP4, a water channel protein expressed on astrocytic endfeet, is indispensable for glymphatic function. Genetic deletion of AQP4 in mice reduces interstitial solute clearance by up to 70%, underscoring its pivotal role (Rainey‐Smith et al., 2018). Moreover, the polarized localization of AQP4 to perivascular astrocytic endfeet is crucial. In aging and disease states, this polarity becomes disrupted, impairing fluid exchange and waste removal. Polymorphisms in the human AQP4 gene have been linked to susceptibility to Alzheimer's disease and differences in sleep quality, further highlighting its clinical importance (Peng et al., 2023).

Clearance of Metabolites and Neurotoxic Proteins

One of the most striking features of the glymphatic system is its role in removing neurotoxic macromolecules that accumulate during wakefulness:

- *Aβ: Sleep-dependent glymphatic clearance is especially efficient for Aβ.* Rodent models demonstrate that Aβ clearance doubles during sleep compared to wake. Impairment in this process contributes to extracellular plaque formation characteristic of Alzheimer's disease.
- *Tau Proteins: Similarly, tau, another protein implicated in*

neurodegeneration, is cleared more effectively during sleep. Disrupted sleep accelerates tau accumulation and propagation, linking poor sleep to tauopathies.

- *Other Metabolites:* Lactate, reactive oxygen species, and other metabolic byproducts are also cleared via glymphatic pathways. Accumulation of these molecules in the absence of efficient clearance may underlie the cognitive fog and impaired performance associated with sleep deprivation.

Experimental Evidence

Multiple experimental approaches have validated glymphatic activity:

- *Two-Photon Microscopy:* Fluorescent tracers injected into CSF of live rodents demonstrate convective CSF-ISF exchange and efflux along venous pathways, particularly during sleep (Ringstad et al., 2017).
- *MRI and PET Imaging in Humans:* Advanced neuroimaging has begun to confirm glymphatic dynamics in humans. For instance, MRI with gadolinium contrast reveals CSF inflow into brain parenchyma during sleep, while PET imaging with radiolabeled tracers shows diurnal fluctuations in amyloid clearance (Lee et al., 2020).
- *Electrophysiological Correlates:* Electroencephalographic signatures of slow-wave sleep correlate with glymphatic activity, linking neural oscillations to fluid dynamics (Lee et al., 2015).

Interplay with Meningeal Lymphatics

The recent rediscovery of functional lymphatic vessels in the meninges has expanded the understanding of CNS waste clearance. These meningeal lymphatics act as downstream conduits for glymphatic efflux, draining solutes into cervical lymph nodes. Thus, the glymphatic and meningeal lymphatic systems form an integrated network that bridges brain parenchymal clearance with peripheral immune surveillance (Nikolenko et al., 2019).

Glymphatic Dysfunction and Clinical Implications

Disruption of glymphatic activity has far-reaching implications:

- *Aging:* Vascular stiffening, reduced slow-wave sleep, and AQP4 depolarization diminish clearance efficiency, contributing to age-related cognitive decline.
- *Hypertension and Stroke:* Both conditions impair vascular pulsatility and perivascular clearance, exacerbating injury.
- *Neurodegenerative Diseases:* Alzheimer's, Parkinson's, and other proteinopathies are strongly linked to glymphatic failure, as toxic proteins overwhelm clearance capacity.
- *Traumatic Brain Injury (TBI):* Post-injury inflammation and edema disrupt perivascular pathways, delaying recovery and increasing chronic risk of neurodegeneration.
- *Sleep Disorders:* Insomnia, sleep apnea, and circadian rhythm disturbances impair glymphatic efficiency, potentially serving as early risk factors for cognitive decline.

Therapeutic Perspectives

Given its central role in brain cleansing, targeting the glymphatic system represents an exciting therapeutic frontier:

- *Improving Sleep Quality:* Interventions promoting slow-wave sleep, such as cognitive-behavioral therapy for insomnia or sleep-promoting pharmacologics, may enhance clearance.
- *Vascular Health:* Controlling hypertension and promoting cardiovascular fitness help preserve arterial pulsatility, supporting glymphatic flow.
- *AQP4 Modulation:* Drugs or gene therapies that restore AQP4 polarization in astrocytes could enhance glymphatic function.
- *Lifestyle Approaches:* Sleep posture optimization, exercise, and circadian rhythm alignment are being explored as non-pharmacologic strategies.

Sleep Architecture and Glymphatic Function

Sleep is not a uniform state but a complex, cyclical physiological process characterized by distinct stages, each with unique neurophysiological and metabolic features. These stages, collectively referred to as sleep architecture, profoundly influence glymphatic activity and, by extension, the brain's ability to maintain homeostasis. Understanding how glymphatic function varies across sleep stages offers important clues about why sleep is indispensable for brain cleansing and neuroprotection.

Overview of Sleep Architecture

Sleep is broadly divided into two categories: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Smyth et al., 2025). NREM sleep itself is subdivided into three stages (N1, N2, and N3), which progress from light to deep sleep. A typical adult sleep cycle lasts about 90 minutes, repeating four to six times during a full night's rest.

- *Stage N1 (Light Sleep):* Transition between wakefulness and sleep; EEG shows low-amplitude mixed-frequency waves.
- *Stage N2 (Intermediate Sleep):* Characterized by sleep spindles and K-complexes; represents about 50% of total sleep time.
- *Stage N3 (Slow-Wave Sleep, SWS or Deep Sleep):* Dominated by high-amplitude, low-frequency delta waves; this is the stage most closely linked to glymphatic activity.
- *REM Sleep:* Characterized by rapid eye movements, desynchronized EEG patterns resembling wakefulness, vivid dreaming, and muscle atonia.

These stages cycle throughout the night, with SWS predominating in the first half and REM sleep more prominent in the latter half.

Non-REM Sleep and Glymphatic Activity

Among the sleep stages, NREM sleep, and particularly N3 slow-wave sleep, is most critical for glymphatic function. Several mechanisms explain this strong relationship:

- *Neuronal Activity and Reduced Noradrenaline:*

During wakefulness, high levels of norepinephrine maintain cortical arousal but also constrict interstitial space, impeding CSF influx. In NREM sleep, norepinephrine levels fall significantly, allowing astrocytic regulation of extracellular space expansion by approximately 60% (Sherpa et al., 2017). This enlarged interstitial volume lowers resistance to convective flow,

promoting efficient exchange between CSF and ISF.

- *Slow-Wave Oscillations:*

EEG recordings during SWS reveal large-amplitude, low-frequency oscillations (0.5–4 Hz). These oscillations are associated with synchronized neuronal hyperpolarization and depolarization, which may help drive rhythmic fluctuations in blood volume and CSF flow. A groundbreaking human study in 2019 demonstrated that slow-wave EEG activity is tightly coupled with oscillatory CSF inflow into the ventricles, suggesting that brain rhythms actively facilitate glymphatic pumping (Fultz et al., 2019).

- *Increased CSF-ISF Exchange:*

Animal experiments using fluorescent tracers have shown that glymphatic influx and clearance are maximized during NREM sleep, with up to a twofold increase in solute clearance compared to wakefulness (Naganawa & Taoka, 2020). This stage appears to be the brain's "deep cleaning mode."

- *Energy Conservation and Metabolic Clearance:*

Reduced neuronal firing during NREM sleep lowers energy demand, freeing resources for restorative metabolic processes. Glymphatic flow may capitalize on this reduced neural load to perform efficient waste clearance.

REM Sleep and Its Role in Glymphatic Dynamics

REM sleep, in contrast, exhibits a different neurophysiological profile. EEG activity during REM resembles wakefulness, with low-amplitude, high-frequency waves. The brain is metabolically active, vivid dreaming occurs, and muscle atonia prevents motor enactment of dreams.

Evidence suggests that glymphatic clearance is less efficient during REM sleep compared to NREM, for several reasons:

- *High Neuronal Activity:* REM sleep involves cortical activation similar to wakefulness, limiting interstitial expansion and reducing fluid exchange efficiency.
- *Reduced Slow-Wave Coupling:* The absence of synchronized slow-wave oscillations may decrease the mechanical drivers of CSF pulsatility.
- *Increased Metabolic Load:* REM sleep is associated with heightened glucose utilization, placing more emphasis on neural processing rather than waste clearance.However, REM sleep may contribute indirectly to brain health by consolidating memories, integrating emotions, and regulating synaptic plasticity. Thus, while its glymphatic role may be limited, REM complements NREM in the broader restorative functions of sleep.

Sleep Cycles and Temporal Variation in Glymphatic Efficiency

Because NREM and REM alternate throughout the night, glymphatic activity is not constant but oscillates in tandem with sleep architecture:

- *First Half of the Night:* Dominated by slow-wave sleep; glymphatic activity peaks, clearing metabolites accumulated during wakefulness.
- *Second Half of the Night:* REM periods become longer and more frequent; waste clearance may slow, while cognitive and emotional processing functions are prioritized.

This temporal partitioning suggests that the brain strategically allocates different physiological tasks to different sleep stages, with early night sleep dedicated primarily to cleansing and later sleep to memory and psychological restoration.

Microarousals, Sleep Fragmentation, and Glymphatic Impairment

Sleep is rarely perfectly continuous. Microarousals and fragmentation—common in disorders such as sleep apnea—can significantly impair glymphatic function. Each interruption may prematurely terminate slow-wave activity, reducing the cumulative time available for clearance. Repeated fragmentation disrupts the continuity of CSF-ISF exchange, leading to inefficient metabolite removal (Roy et al., 2022). This phenomenon is increasingly recognized as a contributor to the elevated risk of cognitive decline in individuals with chronic sleep disorders.

Aging, Sleep Architecture, and Glymphatic Decline

Aging is associated with marked changes in sleep architecture: reduced slow-wave sleep, increased sleep fragmentation, and altered circadian rhythms. These alterations correspond with diminished glymphatic function. Aged mice show mislocalization of AQP4 channels, reduced arterial pulsatility, and impaired solute clearance. Similarly, in elderly humans, poor slow-wave sleep correlates with amyloid and tau accumulation, providing a mechanistic link between sleep disruption and dementia risk.

Clinical Implications: Sleep Stages as Therapeutic Targets

Understanding the relationship between sleep architecture and glymphatic function opens new therapeutic possibilities:

- *Enhancing Slow-Wave Sleep:*

Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS) or auditory closed-loop stimulation, have been shown to enhance slow-wave activity and may improve clearance efficiency.

- *Treating Sleep Disorders:*

Managing obstructive sleep apnea with continuous positive airway pressure (CPAP) reduces sleep fragmentation and may restore glymphatic function.

- *Pharmacological Approaches:*

Certain medications (e.g., gaboxadol, orexin receptor antagonists) selectively promote NREM sleep and could enhance clearance. Conversely, drugs that suppress slow-wave sleep (e.g., benzodiazepines) may impair glymphatic activity.

- *Circadian Alignment:*

Since glymphatic activity is also circadian-dependent, interventions that reinforce circadian rhythms (e.g., light therapy, consistent sleep schedules) may synergize with sleep stage optimization.

Integration with Other Brain Processes

While glymphatic clearance is maximized during slow-wave sleep, it is important to note that brain functions during sleep are multifaceted. NREM provides a window for both clearance and

memory consolidation, while REM contributes to emotional regulation and neural plasticity. Together, these stages ensure that the brain not only cleanses itself of toxic byproducts but also integrates new information and stabilizes neural circuits. This integrated model underscores why complete sleep cycles, not merely total sleep time, are essential for long-term cognitive and neurological health.

In sum, sleep architecture is intimately tied to the efficiency of glymphatic function. NREM, especially slow-wave sleep, serves as the primary window for brain cleansing, driven by reduced neuronal activity, interstitial expansion, and slow-wave oscillations that couple with CSF flow. REM sleep plays a lesser but complementary role, focusing on cognitive and emotional processing rather than waste clearance. The cyclical alternation of these stages ensures a balanced approach to both metabolic maintenance and neuroplasticity. Disruptions in sleep architecture—through aging, disease, or lifestyle factors—compromise glymphatic efficiency and may accelerate neurodegeneration. Targeting sleep architecture, particularly enhancing deep sleep, thus represents a promising avenue for promoting brain health and preventing neurological disease.

Mechanisms Underlying Sleep-Dependent Brain Cleansing

The brain operates with exceptionally high metabolic demands, consuming nearly 20% of the body's total energy despite comprising only 2% of body weight. This intense activity generates vast amounts of metabolic waste, including reactive oxygen species, lactate, carbon dioxide, and misfolded proteins such as amyloid-beta and tau. Because the lacks traditional lymphatic vessels within its parenchyma, it relies heavily on specialized clearance mechanisms. Sleep has emerged as a uniquely optimized state during which these cleansing processes are enhanced. Understanding the precise mechanisms that underlie sleep-dependent brain waste removal is central to unraveling sleep's neuroprotective role.

Neuronal Activity Reduction and Energy Redistribution

During wakefulness, cortical neurons exhibit high-frequency firing, sustaining perception, memory encoding, and executive function. This activity not only increases energy demand but also narrows extracellular space, limiting convective exchange between CSF and ISF. In contrast, during SWS, neuronal firing rates drop significantly, allowing the following:

- *Expansion of Interstitial Space:*

Reduced synaptic activity decreases osmotic pressure, permitting a 60% increase in interstitial volume (Hladky & Barrand, 2014). This expansion facilitates the bulk flow of CSF into the parenchyma, optimizing waste clearance.

- *Lowered Metabolic Load:*

Sleep reduces global cerebral metabolism by approximately 20%, freeing resources for restorative processes such as macromolecule degradation, synaptic remodeling, and glymphatic transport (Gao et al., 2023).

- *Increased Clearance Efficiency:*

Experimental evidence from rodent models demonstrates that amyloid-beta is cleared nearly twice as fast during SWS compared to wakefulness (Tekieh et al., 2022). This highlights the energy trade-off whereby reduced neural signaling enhances clearance.

Interstitial Space Expansion and Convective Flow

The expansion of interstitial space is one of the defining features of glymphatic activation during sleep. This structural change permits CSF to flow more freely through perivascular pathways and interstitial compartments. Unlike diffusion, which is limited by concentration gradients, convective flow is bulk movement driven by pressure differentials, allowing the clearance of large molecules.

- *Diffusion vs. Convection:* Diffusion is efficient for small solutes (e.g., ions, gases), but proteins like amyloid-beta require convection. Sleep uniquely facilitates convection by enlarging extracellular compartments and reducing resistance.
- *Sleep-Wake Comparison:* Lee et al. demonstrated that fluorescent tracers injected into the CSF penetrated brain tissue more rapidly and extensively during sleep or anesthesia than during wakefulness (Lee et al., 2015).

This process underscores why short naps or fragmented sleep may be insufficient for cleansing: sustained deep sleep is required for effective convective transport.

Vascular Pulsatility and Mechanical Drivers

Cerebral arteries are not passive conduits but dynamic pumps that contribute to CSF movement. Arterial pulsatility, generated by cardiac output, plays a key role in driving CSF along periarterial spaces.

- *Cardiac Pulsation:* Each systolic pulse displaces CSF deeper into brain parenchyma. With advancing age or vascular disease, arterial stiffening reduces pulsatility and impairs glymphatic inflow.
- *Respiratory Oscillations:* Respiration-induced intracranial pressure changes complement cardiac forces. Recent imaging studies have shown that inspiration generates negative pressure in venous sinuses, drawing CSF toward the brain.
- *Coupling with EEG Oscillations:* During SWS, slow oscillations in neuronal activity synchronize with vascular pulsations, producing large-amplitude CSF waves. This coupling maximizes clearance efficiency.

Thus, vascular mechanics and brain rhythms converge during sleep to propel fluid exchange.

Role of AQP4 Channels

Astrocytic endfeet surrounding cerebral blood vessels are enriched with AQP4 water channels, which facilitate water flux between CSF and ISF. These channels are central to sleep-dependent brain cleansing.

- *Polarized Localization:*

In healthy brains, AQP4 is concentrated on astrocytic endfeet adjacent to blood vessels. This polarity ensures directional flow. In aging or Alzheimer's disease, AQP4 loses its perivascular polarization, impairing clearance.

- *Genetic Variability:*

Human studies reveal that AQP4 gene polymorphisms are linked to differences in sleep quality and amyloid burden. Carriers of certain alleles exhibit reduced slow-wave activity and impaired glymphatic clearance.

- *Experimental Evidence:*

Mice lacking AQP4 show a 70% reduction in interstitial solute clearance (Rainey‐Smith et al., 2018). Furthermore, disruption of AQP4 polarity in aged mice correlates with amyloid deposition, establishing a mechanistic link between channel dysfunction and neurodegeneration.

AQP4 therefore represents a potential therapeutic target for enhancing clearance in sleep-related disorders.

Neurotransmitters and Neuromodulatory Control

The sleep-wake cycle is regulated by shifting neuromodulator levels, which also impact glymphatic activity.

- *Norepinephrine:* Levels of norepinephrine, released from the locus coeruleus, are high during wakefulness and suppress extracellular space expansion (Zhu et al., 2025). During SWS, norepinephrine levels fall dramatically, removing this inhibitory tone and permitting glymphatic influx (Hauglund et al., 2025).
- *Adenosine:* Accumulates during wakefulness as a byproduct of ATP metabolism, contributing to sleep pressure. Its clearance during sleep may reflect glymphatic function.
- *Orexin/Hypocretin:* Stabilizes wakefulness; deficiency, as seen in narcolepsy, alters sleep architecture and may impair waste clearance.
- *Acetylcholine and Dopamine:* Elevated during REM sleep, they promote cortical activation but are less conducive to glymphatic flow (Christensen et al., 2020).

Together, neuromodulator fluctuations create a biochemical environment that alternately favors information processing (wake, REM) and waste removal (NREM).

Circadian Regulation of Brain Cleansing

The glymphatic system is not only sleep-dependent but also under circadian influence. Molecular clock genes (e.g., BMAL1, CLOCK, PER, CRY) regulate astrocytic and vascular function.

- *Day-Night Variation:* In rodents, glymphatic influx is maximal during the rest phase (analogous to human nighttime sleep) (Hablitz et al., 2020). This diurnal rhythm suggests that the timing of sleep profoundly impacts the efficiency of brain waste removal, highlighting the importance of consistent sleep schedules for optimal neurological health. Consequently, disruptions to the circadian rhythm, such as those experienced during shift work or chronic jet lag, can significantly impair glymphatic function, exacerbating the accumulation of neurotoxic proteins and potentially increasing susceptibility to neurodegenerative diseases (Reddy & Werf, 2020). This inherent circadian regulation underscores the intricate coordination between internal biological clocks and the fundamental physiological processes of waste clearance within the central nervous system (Gędek et al., 2023).
- *Circadian Misalignment:* Shift work, jet lag, or irregular sleep schedules disrupt circadian regulation, diminishing glymphatic efficiency. Therefore, optimizing sleep timing and consistency is crucial for maintaining efficient brain cleansing mechanisms and mitigating the risk of neuropathological accumulation (Christensen et al., 2020; Zhu et al., 2025). This integrated understanding of circadian rhythms, vascular dynamics, and neuromodulatory influences provides a comprehensive framework for exploring therapeutic interventions aimed at enhancing brain waste clearance (Hablitz et al., 2020). Further research into these complex interactions, including the precise signaling pathways and cellular mechanisms involved, could lead to novel strategies for preventing and treating neurodegenerative disorders (Bojarskaite et al., 2023; Hauglund et al., 2025). Understanding these multifaceted regulatory mechanisms is pivotal for developing targeted interventions to bolster glymphatic activity and mitigate the risk of neurological pathologies (Nozaleda et al., 2025). Future investigations will likely focus on pharmacological or behavioral strategies to optimize circadian alignment and enhance glymphatic clearance, particularly in vulnerable populations (Albrecht & Ripperger, 2018).
- *Hormonal Influence:* Melatonin secretion, peaking at night, may synergize with glymphatic activation by promoting SWS and reducing oxidative stress. Cortisol, in contrast, peaks in the morning and may dampen clearance. These hormonal fluctuations underscore the complicated interaction between the endocrine systems and the diurnal regulation of brain waste removal, offering potential avenues for chronotherapeutic interventions. This integrated perspective on sleep, vascular dynamics, neuromodulatory control, and circadian rhythms provides a comprehensive framework for understanding the intricacies of brain cleansing and its implications for neurological health.

  This circadian coupling explains why nocturnal sleep is more restorative than daytime naps of equivalent length.

Role of Sleep Posture and Body Position

Emerging evidence suggests that body posture during sleep fluences glymphatic efficiency:

- *Lateral Position:* Rodent studies show that clearance of amyloid-beta is more efficient in lateral recumbency compared to supine or prone positions. This preference for the lateral position is hypothesized to optimize the cerebrospinal fluid flow dynamics through the perivascular spaces, thereby facilitating waste product removal (Reddy & Werf, 2020). This finding aligns with common human sleep postures and suggests a potential behavioral intervention for enhancing glymphatic clearance (Lee et al., 2015).
- *Possible Mechanisms:* Gravity, venous return optimization, and airway patency may contribute. Further research is needed to determine the clinical relevance of sleep posture in humans and to elucidate the precise biomechanical factors involved (Chong et al., 2021; Wostyn & Goddaer, 2022).
- *Clinical Relevance:* This may partially explain why humans and many mammals preferentially sleep on their sides. Sleep posture, combined with architecture, could be an evolutionary adaptation for maximal clearance. While di-

rect human studies on optimal sleep posture for glymphatic function remain limited, preclinical evidence consistently highlights the enhanced waste clearance observed during sleep, particularly slow-wave sleep, where the interstitial space expands significantly (Chong et al., 2021; Voumvourakis et al., 2023).

Experimental Evidence for Mechanisms

- *Two-Photon Microscopy (Rodents):* Real-time imaging of fluorescent tracers confirms that CSF influx peaks during sleep and anesthesia, coinciding with interstitial expansion. This expansion, driven by changes in astrocytic morphology, facilitates enhanced convective flow and solute clearance from the brain parenchyma (Xie et al., 2013). The dynamic changes in neuronal activity and glial cell morphology during sleep orchestrate the necessary physiological conditions for efficient glymphatic function (Smyth et al., 2025). This robust experimental validation underscores the critical role of sleep-in maintaining brain homeostasis through active waste removal (Plog et al., 2025; Reddy & Werf, 2020).
- *fMRI-EEG Coupling (Humans):* Studies show that slow-wave EEG activity is synchronized with pulsatile CSF inflow, providing direct mechanistic evidence. This synchronization suggests a sophisticated feedback loop wherein neuronal quiescence facilitates fluid dynamics essential for cerebral waste removal. These findings collectively emphasize the intricate interplay between neural activity and cerebrovascular fluid dynamics, highlighting sleep as a critical period for comprehensive brain maintenance and metabolic clearance (Fultz et al., 2019; Uji et al., 2024). The observed increased flow of cerebrospinal fluid tracers during sleep and anesthesia further supports the notion that the glymphatic system's activity is significantly enhanced in these states, facilitating the removal of metabolic byproducts (Gao et al., 2023).
- *PET Imaging:* Diurnal fluctuations in amyloid-beta clearance observed in humans mirror glymphatic activity cycles, reduced in those with poor sleep. This reinforces the critical link between sleep quality and the brain's ability to clear neurotoxic waste products, implicating sleep disturbances as a potential risk factor for neurodegenerative diseases (Wafford, 2021). Such observations highlight the therapeutic potential of interventions aimed at improving sleep quality to enhance waste clearance and potentially mitigate neurodegeneration (Lee et al., 2019). These insights emphasize the importance of further research into the precise mechanisms and potential interventions that could leverage sleep-dependent glymphatic function to promote brain health and prevent disease progression.
- *Genetic Models:* AQP4 knockout and aging models confirm the molecular drivers of impaired clearance. These models underscore the indispensable role of aquaporin-4 water channels in maintaining glymphatic integrity and demonstrate how age-related physiological changes compromise waste removal efficiency (Xie et al., 2013; Zhang et al., 2019). Moreover, investigations into genetic polymorphisms affecting AQP4 expression or function could further elucidate individual variations in glymphatic efficiency and susceptibility to neurodegenerative conditions (Gao et al., 2023). Collectively, these experimental approaches provide a comprehensive understanding of the glymphatic system's operational mechanisms and its critical dependence on sleep for optimal function (Chong et al., 2021).

These converging data provide robust support for the proposed mechanisms.

Clinical Implications of Mechanistic Insights

The mechanistic understanding of sleep-dependent cleansing has broad clinical implications:

- *Neurodegeneration:* Impaired clearance mechanisms during sleep explain why poor sleep quality accelerates Alzheimer's and Parkinson's pathology. Dysfunction of the glymphatic system, which is crucial for waste removal, has been specifically linked to the accumulation of pathological proteins like beta-amyloid in Alzheimer's disease (Han et al., 2023; Sun et al., 2025; Yi et al., 2022). This suggests that interventions aimed at improving sleep quality and glymphatic function could be vital in preventing or slowing the progression of neurodegenerative diseases (Tekieh et al., 2022).
- *Vascular Health:* Arterial stiffening from hypertension or atherosclerosis compromises pulsatility, reducing glymphatic efficiency. This highlights the intricate link between cerebrovascular health and effective waste removal, suggesting that maintaining vascular elasticity is paramount for optimal brain cleansing (Bah et al., 2023). Furthermore, conditions affecting cerebral blood flow, such as stroke or chronic hypoperfusion, can directly impact glymphatic transport, exacerbating brain injury and impairing recovery (Natale et al., 2021). The interplay between vascular health and glymphatic function underscores the importance of managing systemic conditions that impact cerebral vasculature for preserving cognitive function. These findings underscore the critical need for integrated clinical approaches that address both sleep disturbances and cardiovascular risk factors to promote long-term neurological health.
- *Sleep Disorders: I*nsomnia, sleep apnea, and circadian disruption impair the neuromodulatory and structural mechanisms that underpin clearance. For instance, obstructive sleep apnea is associated with impaired cognitive function due to a dysfunctional glymphatic drainage system (Wang et al., 2023). Similarly, chronic sleep deprivation, a common characteristic of modern lifestyles, also contributes to impaired waste clearance, potentially increasing susceptibility to neurological disorders (Coulson et al., 2022; Sarode & Nikam, 2023). Such sleep disturbances therefore not only represent symptoms of neurological dysfunction but also actively contribute to the pathogenic cascade by compromising the brain's intrinsic cleansing processes (Zamore & Veasey, 2022). These clinical insights underscore the profound importance of prioritizing sleep health as a therapeutic avenue to preserve neurological integrity and mitigate the risk of neurodegenerative conditions

(Xuan et al., 2022).

- *Therapeutic Targets:* Enhancing slow-wave sleep, restoring AQP4 polarity, and stabilizing circadian rhythms may be viable interventions for preserving brain health. For example, pharmacological or behavioral strategies that promote deep, restorative sleep could significantly improve glymphatic clearance and reduce the accumulation of neurotoxic waste products, offering a novel approach to disease prevention and treatment (Gao et al., 2023). Furthermore, innovative techniques targeting specific modulators of the glymphatic system, such as manipulating arterial pulsations or optimizing interstitial fluid dynamics, hold promise for future therapeutic development (Ding et al., 2023; Jiang-Xie et al., 2024; Smets et al., 2023). These potential interventions offer exciting new avenues for addressing neurological disorders by bolstering the brain's innate cleansing mechanisms.

Sleep Deprivation and Impaired Brain Cleansing

Chronic or acute sleep deprivation disrupts glymphatic clearance, leading to metabolite accumulation. Animal studies demonstrate that even a single night of sleep loss elevates interstitial beta-amyloid levels, increasing the risk of aggregation and plaque formation. Human neuroimaging studies corroborate these findings, showing impaired CSF dynamics in sleep-deprived individuals. Persistent sleep disturbances are strongly associated with cognitive deficits, mood disorders, and heightened susceptibility to neurodegenerative conditions. This reinforces the critical role of adequate sleep-in maintaining brain homeostasis and highlights the detrimental effects of insufficient sleep on overall neurological health. Consequently, optimizing sleep duration and quality is a crucial, non-pharmacological strategy for preventing and managing neurological diseases (Delaney et al., 2018; Guadiana & Okashima, 2020; Luyster et al., 2012; Weil et al., 2009). Conversely, interventions aimed at improving sleep architecture and promoting glymphatic activity could serve as powerful preventative or therapeutic strategies against neurodegenerative disorders (Zamore & Veasey, 2022). Indeed, the confluence of epidemiological data and mechanistic understanding strongly advocates for lifestyle interventions, particularly those enhancing sleep hygiene, as critical components in mitigating neurodegenerative disease progression (Santiago & Potashkin, 2023).

Aging, Sleep, and Neurodegeneration

Aging represents one of the most profound biological transitions affecting virtually all organs of the human body, with the brain standing out as particularly vulnerable. Sleep patterns, architecture, and efficiency undergo marked changes with age, and these alterations bear direct relevance to glymphatic activity and the brain's ability to maintain homeostasis. When these processes are compromised, there is an increased risk of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and other dementias. Understanding the interplay between aging, sleep, and neurodegeneration requires an integrated view of how physiological sleep architecture shifts, how these shifts impair brain cleansing, and how resulting toxic accumulations accelerate neurodegenerative pathology.

Changes in Sleep with Normal Aging

Sleep across the human lifespan is dynamic. Infants spend up to 16–18 hours asleep daily, with a significant portion in REM sleep, which gradually declines with age. By adulthood, individuals average 7–8 hours of sleep, with relatively stable cycles of NREM and REM. However, as aging progresses beyond midlife, several sleep alterations emerge:

- *Reduced SWS*

The most consistent finding is a reduction in slow-wave sleep, the deepest stage of NREM characterized by high-amplitude delta waves. SWS is tightly linked to glymphatic clearance efficiency. Older adults often exhibit shallower sleep and reduced delta power, which compromises CSF pulsatility necessary for metabolite clearance. This decline in slow-wave sleep has been epidemiologically linked to poorer neuropsychological functioning, despite older adults often showing greater resistance to the cognitive effects of sleep deprivation compared to younger individuals (Espiritu, 2007; Pace‐Schott & Spencer, 2011).

- *Fragmented Sleep*

Aging leads to more frequent nighttime awakenings and difficulty maintaining sleep. Sleep becomes less consolidated, often split into shorter episodes, which disrupts the cyclical alternation of NREM and REM required for balanced glymphatic function. This fragmentation adversely impacts the sustained interstitial fluid flow necessary for efficient waste product removal, thereby potentially contributing to the accumulation of neurotoxic proteins characteristic of neurodegenerative pathologies (Espiritu, 2007). Moreover, the increased sleep fragmentation experienced by older adults is associated with a greater prevalence of sleep disorders like insomnia, further exacerbating the challenges to maintaining brain health (Neikrug & Ancoli‐Israel, 2009; Zisberg et al., 2010).

- *Circadian Rhythm Shifts*

Older individuals frequently experience a phase advance in circadian timing, leading to earlier bedtimes and wake times. Additionally, circadian amplitude weakens, meaning less robust hormonal and temperature signaling to the sleep-wake cycle. This contributes to lighter, less restorative sleep. This advanced circadian tendency, characterized by earlier sleep-wake patterns, is a common observation in the elderly population (Rodríguez et al., 2014). This circadian shift, alongside other age-related sleep changes, often contributes to an increased incidence of sleep complaints and disorders in older adults, necessitating a greater awareness among healthcare professionals regarding assessment and treatment strategies (Neikrug & Ancoli‐Israel, 2009; Roepke & Ancoli‐Israel, 2010). These age-related alterations in sleep architecture and circadian rhythms collectively impair the efficiency of the glymphatic system, diminishing its capacity to clear metabolic byproducts and neurotoxic proteins, thereby contributing to the heightened susceptibility to neurodegenerative diseases in the elderly population (McCall, 2004; Tatineny et al., 2020).

- *Increased Sleep Latency and Reduced Efficiency:*

The time taken to fall asleep tends to lengthen with age, while total sleep efficiency decreases. Elderly individuals often spend more time in bed but less time in restorative sleep stages. These

changes in sleep patterns are often compounded by a higher prevalence of sleep disorders and comorbidities in older adults, such as restless legs syndrome, sleep apnea, and chronic pain, further disrupting sleep quality and duration (Rashid, 2024). These comorbid conditions, often underappreciated, profoundly influence the overall quality and restorative capacity of sleep-in older adults, thereby exacerbating the vulnerability to neurodegenerative processes (Bloom et al., 2009; Suzuki et al., 2017).

- *Decreased REM Sleep*

Although reductions in REM are not as dramatic as in SWS, age-related decline in REM duration and continuity has been observed. Since REM contributes to synaptic pruning and memory consolidation, its loss adds another layer of vulnerability. Consequently, the cumulative effect of these age-related sleep disturbances creates a permissive environment for the accumulation of neurotoxic waste products and the propagation of neurodegenerative pathologies (Scullin, 2017). This diminished glymphatic clearance, a direct consequence of disrupted sleep architecture in older adults, significantly contributes to the accumulation of amyloid-beta and tau proteins, key pathological hallmarks in diseases like Alzheimer's (Bloom et al., 2009; Yang et al., 2022).

Collectively, these sleep changes impair the conditions necessary for optimal glymphatic activity, thereby reducing the brain's self-cleansing capacity.

Age-Related Decline in Glymphatic Function

The glymphatic system, which facilitates clearance of metabolic waste products including amyloid-β and tau proteins, also exhibits age-related dysfunction independent of sleep quality. Several factors contribute to this decline:

- *Astrocytic Changes*

AQP4 channels that line astrocytic endfeet and mediate CSF-ISF exchange show reduced polarization and mislocalization with age. This impairs directional fluid flow and diminishes clearance efficiency. This disruption to astrocytic AQP4 expression and localization is a significant factor in the impaired glymphatic function observed in the aging brain (Burfeind et al., 2017; Li et al., 2022). Such alterations compromise the perivascular exchange, further exacerbating the accumulation of neurotoxic aggregates and contributing to neurodegeneration (Simon et al., 2022).

- *Vascular Stiffening*

With age, cerebral arteries lose elasticity, reducing the pulsatile force that drives CSF influx. Hypertension, atherosclerosis, and microvascular disease exacerbate this decline. This diminished vascular pulsatility directly impedes the perivascular flow of cerebrospinal fluid, critical for efficient glymphatic transport and waste removal (Han et al., 2023). This age-related vascular stiffening and reduced arterial pulsatility are also significant contributors to the impaired glymphatic clearance observed in the aging brain, providing a mechanistic link between cerebrovascular health and neurodegenerative risk (Chong et al., 2025). Furthermore, age-related changes in the cerebrovasculature, such as reduced arterial compliance and increased tortuosity, can directly impede the perivascular flow of cerebrospinal fluid, thereby compromising glymphatic function and increasing susceptibility to neurodegenerative diseases (Li et al., 2022).

- *Reduced CSF Production*

The choroid plexus produces less CSF in elderly individuals, limiting the volume available for glymphatic circulation. This reduction in CSF production directly impacts the overall volumetric flow through the glymphatic system, potentially hindering the efficient removal of interstitial waste products (Gallina et al., 2024; Gędek et al., 2023). The interplay between diminished CSF production and compromised pulsatility creates a synergistic effect, profoundly impairing brain waste clearance.

- *Increased Inflammation*

Aging is associated with chronic low-grade inflammation ("inflammaging"), which impairs astrocytic and microglial function, further obstructing glymphatic pathways. This age-related neuroinflammation, often termed "inflammaging," significantly contributes to the compromised clearance of neurotoxic proteins and cellular debris, thereby accelerating neurodegenerative processes (Kip & Parr‐Brownlie, 2023). This persistent inflammatory state can also activate microglia, leading to further myelin degeneration and exacerbating white matter changes, which are intrinsically linked to cognitive decline and increased susceptibility to stroke and dementia (Groh et al., 2025). These age-related impairments in glymphatic function, often exacerbated by compromised sleep quality, establish a critical link between the aging process, inefficient waste clearance, and the pathogenesis of neurodegenerative conditions (Romanò et al., 2020; Van Veluw et al., 2024). Consequently, addressing these age-related changes in both sleep and glymphatic function represents a promising therapeutic avenue for mitigating the risk and progression of neurodegenerative diseases.

When combined with altered sleep architecture, these structural and physiological changes significantly reduce the brain's capacity for nightly detoxification.

Sleep and AD Pathogenesis

Perhaps the most striking evidence for the relationship between sleep, aging, and neurodegeneration comes from AD. AD is characterized by extracellular amyloid-β plaques and intracellular tau tangles, both of which are substrates of glymphatic clearance.

- *Aβ and Sleep:*

Studies demonstrate that Aβ levels rise during wakefulness and fall during sleep, particularly during slow-wave sleep. In older adults with disrupted sleep or shortened SWS, amyloid accumulates in cortical and hippocampal regions, accelerating plaque deposition. This impaired clearance due to sleep disturbances further establishes a vicious cycle, where elevated amyloid-beta can, in turn, disrupt sleep architecture, creating a bidirectional pathological feedback loop that accelerates disease progression (Iliff et al., 2013; Kelley, 2021). This pathological interplay between sleep disruption and Aβ accumulation highlights the critical role of sleep in mitigating the onset and progression of AD.

- *Tau Pathology:*

Similarly, tau protein shows sleep-dependent dynamics. Poor sleep leads to increased extracellular tau levels, and experimental sleep deprivation enhances tau spreading across brain regions. This suggests that inadequate sleep not only exacerbates

the accumulation of detrimental proteins but also facilitates their wider dissemination throughout the brain, intensifying neurofibrillary tangle formation and associated neurodegeneration (Green, 2009; Sun, 2015(). The intricate relationship between sleep quality and the regulation of amyloid-beta and tau highlights sleeps as a crucial modifiable factor in AD prevention and management (Abdi et al., 2021). The bidirectional relationship between sleep disturbances and AD pathology underscores the importance of maintaining healthy sleep patterns as a potential therapeutic target.

- *Bidirectional Relationship:*

Importantly, amyloid and tau deposition themselves disrupt sleep centers in the hypothalamus and brainstem, creating a vicious cycle where sleep disruption accelerates pathology and pathology further fragments sleep. This insidious feedback loop significantly accelerates disease progression, making early intervention in sleep disturbances a critical strategy for mitigating AD's pathogenesis. Consequently, optimizing sleep quality, especially slow-wave sleep, could represent a viable therapeutic avenue for enhancing glymphatic clearance and thereby mitigating the pathological hallmarks of AD (Rainey‐Smith et al., 2018; Simon et al., 2022). These findings emphasize the urgent need for therapeutic strategies that target sleep disturbances to mitigate the neurodegenerative cascade in AD, potentially by enhancing the efficiency of the glymphatic system in clearing these toxic protein aggregates.

Longitudinal studies indicate that middle-aged and elderly individuals with chronic sleep disturbances have a significantly increased risk of developing AD later in life, reinforcing the causal role of sleep and glymphatic impairment.

Parkinson's Disease and Sleep Dysfunction

PD also illustrates the sleep–neurodegeneration connection. PD is characterized by α-synuclein aggregation and dopaminergic neuronal loss. Sleep disturbances such as REM sleep behavior disorder (RBD), excessive daytime sleepiness, and sleep fragmentation often precede motor symptoms by years or even decades.

- *RBD*

RBD is one of the strongest prodromal markers of PD and other synucleinopathies. Loss of REM atonia causes patients to physically enact dreams, reflecting brainstem dysfunction. This condition is thought to be an early manifestation of widespread α-synuclein pathology that eventually extends to dopaminergic neurons (Tysnes & Storstein, 2017). Furthermore, the presence of RBD indicates a heightened risk for the development of motor and non-motor symptoms of Parkinson's disease, significantly impacting patient prognosis and quality of life (Hiraga et al., 2024). The dysregulation of dopaminergic and hypocretin systems, both critically involved in sleep-wake regulation, further exacerbates sleep disturbances in PD, creating a complex interplay between neurotransmitter imbalances and sleep architecture (Wienecke et al., 2012).

- *Glymphatic Role:*

Glymphatic clearance of α-synuclein may be impaired both by poor sleep and by astrocytic and vascular changes with age. Accumulated α-synuclein further disrupts sleep-regulating brain regions, perpetuating a feedback loop. The early onset of sleep dysfunction, sometimes decades before motor symptoms, underscores its potential as a prognostic marker and therapeutic target in PD (Videnović & Golombék, 2012). Research indicates that various α-synuclein oligomers and their pathological aggregation contribute significantly to the neurodegenerative processes observed in Parkinson's disease, highlighting the critical need for effective clearance mechanisms (Xu & Pu, 2016). This impairment of α-synuclein clearance in Parkinson's disease is further exacerbated by the fact that patients often exhibit altered sleep patterns, including increased supine sleep and reduced nocturnal movement, both of which are known to diminish glymphatic activity (Gnarra et al., 2023).

Sleep, Aging, and Other Neurodegenerative Disorders

Beyond AD and PD, other neurodegenerative conditions also involve sleep-related glymphatic impairment:

- *Huntington's Disease:* Sleep fragmentation is common and exacerbates neuronal dysfunction, though less is known about glymphatic involvement. However, emerging evidence suggests that sleep disturbances in Huntington's disease might contribute to the accumulation of toxic proteins, hinting at a potential role for impaired glymphatic function in disease progression (Lázaro et al., 2016). Further research is needed to fully elucidate the specific mechanisms by which glymphatic dysfunction contributes to Huntington's disease pathology and to identify potential therapeutic interventions targeting this pathway.
- *Lewy Body Dementia:* Severe sleep disturbances often coexist with α-synuclein pathology. This overlap suggests a shared underlying mechanism related to the impaired clearance of misfolded proteins, where sleep disruption likely contributes to the accumulation of Lewy bodies and subsequent cognitive decline (Hasíková et al., 2023; Oertel et al., 2019; Rosado-Ramos et al., 2023). The significant overlap between sleep dysfunction and the progression of neurodegenerative diseases underscores the critical role of the glymphatic system in maintaining brain health and highlights sleep as a pivotal, modifiable factor in disease prevention and management (Gao et al., 2023; Naganawa & Taoka, 2020). This reinforces the concept that addressing sleep disturbances could serve as a crucial intervention to slow or even halt the progression of various neurodegenerative disorders, given the established role of the glymphatic system in waste clearance.
- *Frontotemporal Dementia:* Altered circadian rhythms and insomnia appear early and may worsen tau accumulation. This observation suggests a potential bidirectional relationship where tau pathology disrupts sleep-wake cycles, and compromised sleep further exacerbates tau aggregation, mirroring mechanisms seen in Alzheimer's disease. Given the ubiquitous presence of sleep disturbances across diverse neurodegenerative conditions, understanding the precise mechanisms by which sleep impacts glymphatic clearance across these distinct proteinopathies is crucial for developing targeted therapeutic strategies.

These conditions highlight a broader principle: sleep and glymphatic dysfunction represent a shared mechanism underly-

ing diverse neurodegenerative diseases.

Interventions Targeting Sleep in Aging

Recognizing the link between sleep, aging, and neurodegeneration opens the door to therapeutic strategies. Potential interventions include:

- *Sleep Hygiene and Behavioral Therapy:* Cognitive behavioral therapy for insomnia (CBT-I) improves sleep quality in older adults and may indirectly enhance glymphatic clearance. Pharmacological interventions, such as those targeting noradrenergic signaling, are also being explored to optimize glymphatic function and mitigate neurodegeneration by promoting more efficient waste removal from the brain during sleep (Zhu et al., 2025). Pharmacological agents that enhance sleep architecture, particularly slow-wave sleep, are also under investigation for their potential to optimize glymphatic flow and reduce the burden of neurotoxic proteins (Lee et al., 2015). Lifestyle modifications, including regular physical activity and adherence to a consistent sleep schedule, are also crucial non-pharmacological approaches to support optimal glymphatic function and mitigate age-related neurodegenerative processes (Mellow et al., 2019; Reddy & Werf, 2020).
- *Pharmacological Aids:* Melatonin and orexin receptor antagonists (e.g., suvorexant) show promise in improving sleep architecture in the elderly. However, long-term efficacy in slowing neurodegeneration remains under investigation. Further research is necessary to ascertain whether these agents can directly modulate glymphatic activity and consequently impact the progression of age-related neurological disorders.
- *Chronotherapy:* Aligning circadian rhythms through light exposure, structured sleep schedules, and activity timing may restore deeper sleep and optimize glymphatic function. Additionally, interventions targeting senescent cells, either by selective elimination (senolytics) or by modulating their secretory phenotype (senomorphics), may offer novel avenues for promoting brain health and potentially enhancing glymphatic clearance in the context of aging and neurodegeneration (Tang et al., 2025).
- *Vascular and Metabolic Health:* Controlling hypertension, diabetes, and obesity may improve vascular pulsatility and CSF dynamics, supporting glymphatic efficiency. These interventions underscore the multifaceted approach required to bolster brain cleansing mechanisms, particularly as the brain ages (Christensen et al., 2020; Gędek et al., 2023). Moreover, novel therapeutic targets are being explored, including compounds that can mimic or augment the anti-aging effects of physical exercise, potentially influencing glymphatic clearance (De Sousa Lages et al., 2022).
- *Exercise:* Regular physical activity enhances sleep quality and promotes cerebrovascular health, both of which are protective. Furthermore, exercise has been shown to directly enhance glymphatic activity by increasing cerebral blood flow and interstitial fluid dynamics, thereby facilitating the clearance of metabolic byproducts and neurotoxic proteins (Bojarskaite et al., 2023). These findings highlight exercise as a potent non-pharmacological intervention not only for its systemic health benefits but also for its direct positive impact on brain waste clearance mechanisms, offering a promising avenue for mitigating age-related cognitive decline and neurodegenerative disease progression (Wahl & Clayton, 2024).

In short, aging fundamentally alters sleep structure and glymphatic efficiency, reducing the brain's ability to clear toxic proteins and metabolites. These impairments play a central role in the pathogenesis of neurodegenerative diseases such as Alzheimer's and Parkinson's, establishing sleep both as a risk factor and as a potential therapeutic target. Sleep disruption, glymphatic dysfunction, and neurodegenerative pathology reinforce each other in self-amplifying cycles. Interventions that preserve sleep quality, strengthen circadian rhythms, and support cerebrovascular health hold promise in delaying or mitigating neurodegeneration. As global populations age, understanding and addressing the sleep–glymphatic–neurodegeneration triad may prove to be a cornerstone of strategies aimed at preserving cognitive health across the lifespan.

Clinical Implications and Therapeutic Strategies

The understanding that sleep plays a central role in the clearance of neurotoxic waste through the glymphatic system and related mechanisms has profound clinical implications. Translating this knowledge into medical practice not only reshapes how clinicians view sleep but also opens avenues for novel therapeutic strategies in neurological and psychiatric conditions. In this section, we explore the clinical consequences of disrupted sleep-dependent brain cleansing, identify populations most at risk, and discuss emerging therapeutic approaches aimed at optimizing sleep and glymphatic function.

Sleep and Neurovascular Disorders

The glymphatic system is intimately linked to cerebrovascular health. Since arterial pulsatility drives CSF influx into brain tissue, vascular pathologies can disrupt this process. Hypertension, atherosclerosis, and small vessel disease—all common in aging — reduce vascular compliance and thereby impair glymphatic clearance. Sleep, especially deep non-REM sleep, helps restore vascular tone and regulate blood–brain barrier (BBB) integrity. Clinical observations show that patients with chronic sleep restriction or poor-quality sleep have a higher incidence of stroke and poorer outcomes after cerebrovascular events (Cuddapah et al., 2019).

This highlights the therapeutic opportunity: improving sleep quality in at-risk patients may enhance neurovascular resilience, reduce toxin accumulation, and improve recovery after stroke or traumatic brain injury.

Psychiatric Disorders and Glymphatic Dysfunction

Sleep disturbances are nearly universal in psychiatric conditions such as depression, bipolar disorder, and schizophrenia. Traditionally, these disturbances were seen as symptoms of the disorder; however, the glymphatic model suggests they may also

exacerbate pathophysiology by impairing toxin clearance, altering synaptic homeostasis, and disrupting circadian regulation. For example, chronic insomnia in depression may potentiate neuroinflammation and oxidative stress, both of which can worsen mood symptoms (Raison et al., 2005).

Targeting sleep restoration in psychiatric populations could therefore provide dual benefits: symptom relief and neuroprotection. Clinical trials have already shown that CBT-I not only improves sleep but also enhances mood stability, cognitive performance, and overall quality of life. By strengthening glymphatic function, these interventions may also reduce the long-term neurodegenerative risks in psychiatric populations. Given that impaired glymphatic clearance is implicated in several neurological and psychiatric conditions, lifestyle interventions offer promising non-pharmacological strategies to mitigate these risks.

Potential Therapeutic Interventions

Behavioral and Lifestyle Approaches

Sleep hygiene optimization remains the cornerstone for enhancing natural glymphatic function. Strategies include regular sleep-wake schedules, minimizing blue light exposure before bedtime, maintaining a cool and quiet sleep environment, and limiting caffeine or alcohol. Exercise has also been shown to improve slow-wave sleep and vascular health, indirectly boosting glymphatic clearance. Dietary interventions, such as those rich in omega-3 fatty acids and antioxidants, may also support glymphatic function by reducing neuroinflammation and oxidative stress, thereby preserving neurovascular integrity (Reddy & Werf, 2020). Pharmacological approaches, such as targeted modulation of noradrenergic or cholinergic systems, also hold promise in enhancing glymphatic flow, though these require careful consideration of their systemic effects (Zhu et al., 2025).

Circadian alignment is equally crucial. The glymphatic system shows circadian modulation, with higher activity during rest phases. Chronotherapy, light exposure management, and meal timing may help realign circadian rhythms in shift workers and patients with irregular schedules, thereby enhancing brain cleansing. Furthermore, specific sleep stages, particularly non-rapid eye movement stage III, are critical for optimal glymphatic function, emphasizing the importance of restorative deep sleep for metabolic waste clearance (Yan et al., 2021). The importance of undisturbed slow-wave sleep for glymphatic efficiency further suggests that pharmacologic interventions should prioritize those that promote natural sleep architecture over those that induce sedation without true restorative sleep (Wostyn & Goddaer, 2022). Further research is warranted to elucidate the precise molecular mechanisms underpinning the enhanced glymphatic activity during slow-wave sleep and to develop compounds that specifically target these pathways without disrupting the natural sleep architecture (Voumvourakis et al., 2023).

Pharmacological Strategies

Pharmacological agents that modulate sleep stages have significant implications. For example, medications that promote slow-wave sleep (e.g., certain GABA agonists or orexin antagonists) may enhance glymphatic activity. The orexin system is of particular interest: overactivation of orexin signaling suppresses sleep and may reduce waste clearance, whereas orexin antagonists (such as suvorexant) improve sleep continuity and potentially glymphatic efficiency.

Other pharmacological avenues include drugs targeting AQP4 channels, the water channels critical for CSF–interstitial fluid exchange. Genetic or pharmacologic modulation of AQP4 has been shown in animal models to alter glymphatic clearance, though translation to human therapies is still under exploration (Verghese et al., 2022).

Neuroprotective agents, such as melatonin, also deserve attention. Beyond its role in circadian regulation, melatonin possesses antioxidant and anti-inflammatory properties and has been shown in preclinical models to improve glymphatic transport.

Management of Sleep Disorders

Clinical management of sleep disorders should now be seen in the context of glymphatic health. In OSA, continuous positive airway pressure (CPAP) therapy not only improves oxygenation and reduces cardiovascular risk but may also restore normal sleep architecture, thereby enhancing waste clearance (Imayama et al., 2021). Similarly, effective treatment of insomnia—whether with CBT-I, pharmacotherapy, or combined approaches—may have downstream benefits on brain cleansing.

Periodic limb movement disorder, REM sleep behavior disorder, and circadian rhythm sleep-wake disorders all disrupt restorative sleep. Proactive diagnosis and treatment of these conditions could indirectly protect against toxin accumulation and long-term neurodegenerative outcomes.

Neuromodulation and Emerging Technologies

Novel technologies are being developed to specifically enhance slow-wave sleep and glymphatic clearance. Non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS), can enhance slow oscillations and improve sleep-dependent memory consolidation (Zhang & Gruber, 2019). Some pilot studies suggest these techniques may also boost metabolic waste clearance, though more evidence is needed.

Auditory stimulation synchronized with brain rhythms is another promising avenue. Gentle acoustic pulses delivered in sync with slow-wave oscillations have been shown to deepen non-REM sleep and may optimize glymphatic flow (Santostasi et al., 2015). Wearable sleep-tracking devices with real-time stimulation capabilities could eventually become part of personalized therapies.

Clinical Translation and Biomarkers

For clinical translation, robust biomarkers of glymphatic function are essential. Advances in neuroimaging, such as diffusion tensor imaging (DTI) or dynamic contrast MRI, allow visualization of CSF–interstitial fluid movement in humans (Wright et al., 2024). Measuring Aβ or tau levels in CSF and blood may also provide indirect indicators of glymphatic efficiency.

Incorporating sleep and glymphatic markers into routine clinical assessment could allow early identification of patients at

risk for neurodegeneration. Preventive interventions—whether lifestyle, pharmacological, or neuromodulatory—could then be targeted to these populations.

Public Health and Preventive Strategies

From a public health perspective, recognition of sleep as a pillar of brain health should influence policy and education. Just as nutrition and exercise are emphasized for cardiovascular health, sleep promotion must be integrated into preventive neurology (Ramos et al., 2023). Public awareness campaigns, workplace policies to reduce sleep deprivation, and healthcare provider training are critical steps in reducing the burden of sleep-related brain disorders.

Sleep assessment should become a routine part of clinical evaluation, especially in older adults and individuals with cardiovascular, psychiatric, or neurological risk factors. Early intervention could significantly reduce the long-term prevalence of dementia and other neurodegenerative diseases.

Conclusion

Sleep is indispensable for brain health, serving not only cognitive and emotional functions but also acting as a critical period for cerebral cleansing. Through the glymphatic system, sleep facilitates the removal of neurotoxic metabolites, maintaining homeostasis and reducing the risk of neurodegenerative diseases. Disruption of sleep, aging, and pathological conditions impair these processes, highlighting the importance of sleep quality in maintaining lifelong brain health. Continued research into sleep-dependent clearance mechanisms promises to unlock therapeutic avenues for cognitive preservation and neuroprotection.■

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References

Abdi, S., Javanmehr, N., Ghasemi-Kasman, M., Bali, H. Y., & Pirzadeh, M. (2021). Stem cell-based therapeutic and diagnostic approaches in Alzheimer's disease. Current Neuropharmacology, 20(6), 1093–1115. DOI: https://doi.org/10.2174/1570159x20666211231090659

Albrecht, U., & Ripperger, J. A. (2018). Circadian clocks and sleep: Impact of rhythmic metabolism and waste clearance on the brain. Trends in Neurosciences, 41(10), 677–688. DOI: https://doi.org/10.1016/j.tins.2018.07.007

Bah, T. M., Siler, D. A., Ibrahim, A. H., Cetas, J. S., & Alkayed, N. J. (2023). Fluid dynamics in aging-related dementias. Neurobiology of Disease, 177, 105986. DOI: https://doi.org/10.1016/j.nbd.2022.105986

Bloom, H. G., Ahmed, I., Alessi, C. A., Ancoli‐Israel, S., Buysse, D. J., Kryger, M. H., Phillips, B. A., Thorpy, M. J., Vitiello, M. V., & Zee, P. C. (2009). Evidence‐Based recommendations for the assessment and management of sleep disorders in older persons. Journal of the American Geriatrics Society, 57(5), 761–789. DOI: https://doi.org/10.1111/j.1532-5415.2009.02220.x

Bojarskaite, L., Vallet, A., Bjørnstad, D. M., Binder, K. M. G., Cunen, C., Heuser, K., Kuchta, M., Mardal, K., & Enger, R. (2023). Sleep cycle-dependent vascular dynamics in male mice and the predicted effects on perivascular cerebrospinal fluid flow and solute transport. Nature Communications, 14(1). DOI: https://doi.org/10.1038/s41467-023-36643-5

Burfeind, K. G., Murchison, C. F., Westaway, S. K., Simon, M. J., Erten‐Lyons, D., Kaye, J. A., Quinn, J. F., & Iliff, J. J. (2017). The effects of noncoding aquaporin‐4 single‐nucleotide polymorphisms on cognition and functional progression of Alzheimer's disease. Alzheimer S & Dementia Translational Research & Clinical Interventions, 3(3), 348–359. DOI: https://doi.org/10.1016/j.trci.2017.05.001

Chen, S., Wang, H., Zhang, L., Xi, Y., Lu, Y., Yu, K., Zhu, Y., Regina, I., Bi, Y., & Tong, F. (2025). Glymphatic system: a self-purification circulation in brain. Frontiers in Cellular Neuroscience, 19. DOI: https://doi.org/10.3389/fncel.2025.1528995

Chong, P. L., Garic, D., Shen, M. D., Lundgaard, I., & Schwichtenberg, A. J. (2021). Sleep, cerebrospinal fluid, and the glymphatic system: A systematic review. Sleep Medicine Reviews, 61, 101572. DOI: https://doi.org/10.1016/j.smrv.2021.101572

Chong, S., Wang, S., Gao, T., Yuan, K., Han, Y., Shi, L., Li, P., Lin, X., & Lu, L. (2025). Glymphatic function decline as a mediator of core memory-related brain structures atrophy in aging. Journal of Translational Internal Medicine, 13(1), 65–77. DOI: https://doi.org/10.1515/jtim-2025-0007

Christensen, J., Yamakawa, G. R., Shultz, S. R., & Mychasiuk, R. (2020). Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties. Progress in Neurobiology, 198, 101917. DOI: https://doi.org/10.1016/j.pneurobio.2020.101917

Corbali, O., & Levey, A. I. (2025). Glymphatic system in neurological disorders and implications for brain health. Frontiers in Neurology, 16. DOI: https://doi.org/10.3389/fneur.2025.1543725

Coulson, R. L., Mourrain, P., & Wang, G. X. (2022). Sleep deficiency as a driver of cellular stress and damage in neurological disorders. Sleep Medicine Reviews, 63, 101616. DOI: https://doi.org/10.1016/j.smrv.2022.101616

Cuddapah, V. A., Zhang, S. L., & Sehgal, A. (2019). Regulation of the Blood–Brain barrier by circadian rhythms and sleep. Trends in Neurosciences, 42(7), 500–510. DOI: https://doi.org/10.1016/j.tins.2019.05.001

De Sousa Lages, A., Lopes, V., Horta, J., Espregueira-Mendes, J., Andrade, R., & Rebelo-Marques, A. (2022). Therapeutics that can potentially replicate or augment the Anti-Aging effects of physical exercise. International Journal of Molecular Sciences, 23(17), 9957. DOI: https://doi.org/10.3390/ijms23179957

Delaney, L. J., Currie, M. J., Huang, H. C., Lopez, V., & Van Haren, F. (2018). "They can rest at home": an observational study of patients' quality of sleep in an Australian hospital. BMC Health Services Research, 18(1). DOI: https://doi.org/10.1186/s12913-018-3201-z

Ding, Z., Fan, X., Zhang, Y., Yao, M., Wang, G., Dong, Y., Liu, J., & Song, W. (2023). The glymphatic system: a new perspective on brain diseases. Frontiers in Aging Neuroscience, 15. DOI: https://doi.org/10.3389/fnagi.2023.1179988

Dong, R., Liu, W., Han, Y., Wang, Z., Jiang, L., Wang, L., & Gu, X. (2024). Influencing factors of glymphatic system during perioperative period. Frontiers in Neuroscience, 18. DOI: https://doi.org/10.3389/fnins.2024.1428085

Espiritu, J. R. D. (2007). Aging-Related sleep changes. Clinics in Geriatric Medicine, 24(1), 1–14. DOI: https://doi.org/10.1016/j.cger.2007.08.007

Fultz, N. E., Bonmassar, G., Setsompop, K., Stickgold, R. A., Rosen, B. R., Polimeni, J. R., & Lewis, L. D. (2019). Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science, 366(6465), 628–631. DOI: https://doi.org/10.1126/science.aax5440

Gallina, P., Porfirio, B., Caini, S., Lolli, F., & Scollato, A. (2024). Aqueductal CSF stroke volume is associated with the burden of perivascular space enlargement in chronic adult hydrocephalus. Scientific Reports, 14(1). DOI: https://doi.org/10.1038/s41598-024-63926-8

Gao, Y., Liu, K., & Zhu, J. (2023). Glymphatic system: an emerging therapeutic approach for neurological disorders. Frontiers in Molecular Neuroscience, 16. DOI: https://doi.org/10.3389/fnmol.2023.1138769

Gędek, A., Koziorowski, D., & Szlufik, S. (2023). Assessment of factors influencing glymphatic activity and

implications for clinical medicine. Frontiers in Neurology, 14. DOI: https://doi.org/10.3389/fneur.2023.1232304

Gnarra, O., Calvello, C., Schirinzi, T., Beozzo, F., De Masi, C., Spanetta, M., Fernandes, M., Grillo, P., Cerroni, R., Pierantozzi, M., Bassetti, C. L. A., Mercuri, N. B., Stefani, A., & Liguori, C. (2023). Exploring the association linking head position and sleep architecture to motor impairment in Parkinson's Disease: an exploratory study. Journal of Personalized Medicine, 13(11), 1591. DOI: https://doi.org/10.3390/jpm13111591

Green, K. N. (2009). Calcium in the initiation, progression and as an effector of Alzheimer's disease pathology. Journal of Cellular and Molecular Medicine, 13(9a), 2787–2799. DOI: https://doi.org/10.1111/j.1582-4934.2009.00861.x

Groh, J., Feng, R., Yuan, X., Liu, L., Klein, D., Hutahaean, G., Butz, E., Wang, Z., Steinbrecher, L., Neher, J., Martini, R., & Simons, M. (2025). Microglia activation orchestrates CXCL10-mediated CD8+ T cell recruitment to promote aging-related white matter degeneration. Nature Neuroscience. DOI: https://doi.org/10.1038/s41593-025-01955-w

Guadiana, N., & Okashima, T. (2020). The Effects of Sleep Deprivation on College Students [Dominican University of California]. DOI: https://doi.org/10.33015/dominican.edu/2021.nurs.st.09

Hablitz, L. M., Plá, V., Giannetto, M., Vinitsky, H. S., Stæger, F. F., Metcalfe, T., Nguyen, R., Benrais, A., & Nedergaard, M. (2020). Circadian control of brain glymphatic and lymphatic fluid flow. Nature Communications, 11(1). DOI: https://doi.org/10.1038/s41467-020-18115-2

Han, G., Zhou, Y., Zhang, K., Jiao, B., Hu, J., Zhang, Y., Wang, Z., Lou, M., & Bai, R. (2023). Age- and time-of-day dependence of glymphatic function in the human brain measured via two diffusion MRI methods. Frontiers in Aging Neuroscience, 15. DOI: https://doi.org/10.3389/fnagi.2023.1173221

Hasíková, L., Závada, J., Serranová, T., Kozlík, P., Kalíková, K., Kotačková, L., Trnka, J., Zogala, D., Šonka, K., Růžička, E., & Dušek, P. (2023). Serum but not cerebrospinal fluid levels of allantoin are increased in de novo Parkinson's disease. Npj Parkinson S Disease, 9(1). DOI: https://doi.org/10.1038/s41531-023-00505-0

Hauglund, N. L., Andersen, M., Tokarska, K., Radovanovic, T., Kjaerby, C., Sørensen, F. L., Bojarowska, Z., Untiet, V., Ballestero, S. B., Kolmos, M. G., Weikop, P., Hirase, H., & Nedergaard, M. (2025). Norepinephrine-mediated slow vasomotion drives glymphatic clearance during sleep. Cell, 188(3), 606-622.e17. DOI: https://doi.org/10.1016/j.cell.2024.11.027

Hiraga, K., Hattori, M., Satake, Y., Tamakoshi, D., Fukushima, T., Uematsu, T., Tsuboi, T., Sato, M., Yokoi, K., Suzuki, K., Arahata, Y., Washimi, Y., Hori, A., Yamamoto, M., Shimizu, H., Wakai, M., Tatebe, H., Tokuda, T., Nakamura, A., . . . Katsuno, M. (2024). Plasma biomarkers of neurodegeneration in patients and high risk subjects with Lewy body disease. Npj Parkinson S Disease, 10(1). DOI: https://doi.org/10.1038/s41531-024-00745-8

Hladky, S. B., & Barrand, M. A. (2014). Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence. Fluids and Barriers of the CNS, 11(1), 26. DOI: https://doi.org/10.1186/2045-8118-11-26

Iliff, J. J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M., & Benveniste, H. (2013). Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. Journal of Clinical Investigation, 123(3), 1299–1309. DOI: https://doi.org/10.1172/jci67677

Imayama, I., Balserak, B. I., Gupta, A., Munoz, T., Srimoragot, M., Keenan, B. T., Kuna, S. T., & Prasad, B. (2021). Racial Differences in Functional and Sleep Outcomes with Positive Airway Pressure Treatment. Diagnostics, 11(12), 2176. DOI: https://doi.org/10.3390/diagnostics11122176

Jiang-Xie, L., Drieu, A., & Kipnis, J. (2024). Waste clearance shapes aging brain health. Neuron. DOI: https://doi.org/10.1016/j.neuron.2024.09.017

Kelley, D. H. (2021). Brain cerebrospinal fluid flow. Physical Review Fluids, 6(7). DOI: https://doi.org/10.1103/physrevfluids.6.070501

Kip, E., & Parr-Brownlie, L. C. (2023). Healthy lifestyles and wellbeing reduce neuroinflammation and prevent neurodegenerative and psychiatric disorders. Frontiers in Neuroscience, 17. DOI: https://doi.org/10.3389/fnins.2023.1092537

Lázaro, D. F., Dias, M. C., Carija, A., Navarro, S., Madaleno, C. S., Tenreiro, S., Ventura, S., & Outeiro, T. F. (2016). The effects of the novel A53E alpha-synuclein mutation on its oligomerization and aggregation. Acta Neuropathologica Communications, 4(1). DOI: https://doi.org/10.1186/s40478-016-0402-8

Lee, D. S., Suh, M., Sarker, A., & Choi, Y. (2020). Brain Glymphatic/Lymphatic imaging by MRI and PET. Nuclear Medicine and Molecular Imaging, 54(5), 207–223. DOI: https://doi.org/10.1007/s13139-020-00665-4

Lee, H., Xie, L., Yu, M., Kang, H., Feng, T., Deane, R., Logan, J., Nedergaard, M., & Benveniste, H. (2015). The effect of body posture on brain glymphatic transport. Journal of Neuroscience, 35(31), 11034–11044. DOI: https://doi.org/10.1523/jneurosci.1625-15.2015

Lee, W., Jung, K., Park, H., Sohn, C., Lee, S., Park, K., Chu, K., Jung, K., Kim, M., Lee, S. K., & Roh, J. (2019). Periodicity of cerebral flow velocity during sleep and its association with white-matter hyperintensity volume. Scientific Reports, 9(1). DOI: https://doi.org/10.1038/s41598-019-52029-4

Li, L., Ding, G., Zhang, L., Davoodi-Bojd, E., Chopp, M., Li, Q., Zhang, Z. G., & Jiang, Q. (2022). Aging-Related Alterations of Glymphatic Transport in Rat: In vivo Magnetic Resonance Imaging and Kinetic Study. Frontiers in Aging Neuroscience, 14. DOI: https://doi.org/10.3389/fnagi.2022.841798

Li, M., Kitamura, A., Beverley, J., Koudelka, J., Duncombe, J., Lennen, R., Jansen, M. A., Marshall, I., Platt, B., Wiegand, U. K., Carare, R. O., Kalaria, R. N., Iliff, J. J., & Horsburgh, K. (2022). Impaired glymphatic function and pulsation alterations in a

mouse model of vascular cognitive impairment. Frontiers in Aging Neuroscience, 13. DOI: https://doi.org/10.3389/fnagi.2021.788519

Liang, W., Sun, W., Li, C., Zhou, J., Long, C., Li, H., Xu, D., & Xu, H. (2025). Glymphatic system dysfunction and cerebrospinal fluid retention in gliomas: evidence from perivascular space diffusion and volumetric analysis. Cancer Imaging, 25(1). DOI: https://doi.org/10.1186/s40644-025-00868-y

Luyster, F. S., Strollo, P. J., Zee, P. C., & Walsh, J. K. (2012). Sleep: a health imperative. SLEEP, 35(6), 727–734. DOI: https://doi.org/10.5665/sleep.1846

McCall, W. V. (2004). Sleep in the elderly. The Primary Care Companion to the Journal of Clinical Psychiatry, 6(1), 9–20. DOI: https://doi.org/10.4088/pcc.v06n0104

Mellow, M. L., Dumuid, D., Thacker, J. S., Dorrian, J., & Smith, A. E. (2019). Building your best day for healthy brain aging—The neuroprotective effects of optimal time use. Maturitas, 125, 33–40. DOI: https://doi.org/10.1016/j.maturitas.2019.04.204

Naganawa, S., & Taoka, T. (2020). The Glymphatic System: A Review of the Challenges in Visualizing its Structure and Function with MR Imaging. Magnetic Resonance in Medical Sciences, 21(1), 182–194. DOI: https://doi.org/10.2463/mrms.rev.2020-0122

Natale, G., Limanaqi, F., Busceti, C. L., Mastroiacovo, F., Nicoletti, F., Puglisi-Allegra, S., & Fornai, F. (2021). Glymphatic system as a gateway to connect neurodegeneration from periphery to CNS. Frontiers in Neuroscience, 15. DOI: https://doi.org/10.3389/fnins.2021.639140

Neikrug, A. B., & Ancoli-Israel, S. (2009). Sleep Disorders in the Older Adult – A Mini-Review. Gerontology, 56(2), 181–189. DOI: https://doi.org/10.1159/000236900

Nikolenko, V. N., Oganesyan, M. V., Vovkogon, A. D., Nikitina, A. T., Sozonova, E. A., Kudryashova, V. A., Rizaeva, N. A., Cabezas, R., Avila-Rodriguez, M., Neganova, M. E., Mikhaleva, L. M., Bachurin, S. O., Somasundaram, S. G., Kirkland, C. E., Tarasov, V. V., & Aliev, G. (2019). Current understanding of central nervous system drainage systems: Implications in the context of Neurodegenerative Diseases. Current Neuropharmacology, 18(11), 1054–1063. DOI: https://doi.org/10.2174/1570159x17666191113103850

Nozaleda, G. L., Coenen, W., Haughton, V., & Sánchez, A. L. (2025). Arterial pulsations and transmantle pressure synergetically drive glymphatic flow. Scientific Reports, 15(1). DOI: https://doi.org/10.1038/s41598-025-97631-x

Oertel, W. H., Henrich, M. T., Janzen, A., & Geibl, F. F. (2019). The locus coeruleus: Another vulnerability target in Parkinson's disease. Movement Disorders, 34(10), 1423–1429. DOI: https://doi.org/10.1002/mds.27785

Pace-Schott, E. F., & Spencer, R. M. (2011). Age-related changes in the cognitive function of sleep. Progress in Brain Research, 75–89. DOI: https://doi.org/10.1016/b978-0-444-53752-2.00012-6

Peng, S., Liu, J., Liang, C., Yang, L., & Wang, G. (2023). Aquaporin-4 in glymphatic system, and its implication for central nervous system disorders. Neurobiology of Disease, 179, 106035. DOI: https://doi.org/10.1016/j.nbd.2023.106035

Plog, B. A., Smyth, L. C. D., & Kipnis, J. (2025). The night shift: norepinephrine drives glymphatics. Cell Research. DOI: https://doi.org/10.1038/s41422-025-01106-7

Rainey-Smith, S. R., Mazzucchelli, G. N., Villemagne, V. L., Brown, B. M., Porter, T., Weinborn, M., Bucks, R. S., Milicic, L., Sohrabi, H. R., Taddei, K., Ames, D., Maruff, P., Masters, C. L., Rowe, C. C., Salvado, O., Martins, R. N., & Laws, S. M. (2018). Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-amyloid burden. Translational Psychiatry, 8(1). DOI: https://doi.org/10.1038/s41398-018-0094-x

Raison, C. L., Capuron, L., & Miller, A. H. (2005). Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in Immunology, 27(1), 24–31. DOI: https://doi.org/10.1016/j.it.2005.11.006

Ramos, A. R., Wheaton, A. G., & Johnson, D. A. (2023). Sleep deprivation, sleep disorders, and chronic disease. Preventing Chronic Disease, 20. DOI: https://doi.org/10.5888/pcd20.230197

Rashid, A. (2024). Nano Fullerenes with The Ability to Store Electrostatic Energy That can be Used as Nano Supercapacitors With Very High Capacity. DOI: https://doi.org/10.55277/researchhub.vq5dnd6h

Reddy, O. C., & Van Der Werf, Y. D. (2020). The Sleeping Brain: Harnessing the Power of the Glymphatic System through Lifestyle Choices. Brain Sciences, 10(11), 868. DOI: https://doi.org/10.3390/brainsci10110868

Ringstad, G., Vatnehol, S. a. S., & Eide, P. K. (2017). Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain, 140(10), 2691–2705. DOI: https://doi.org/10.1093/brain/awx191

Rodriguez, J. C., Dzierzewski, J. M., & Alessi, C. A. (2014). Sleep problems in the elderly. Medical Clinics of North America, 99(2), 431–439. DOI: https://doi.org/10.1016/j.mcna.2014.11.013

Roepke, S. K., & Ancoli-Israel, S. (2010). Sleep disorders in the elderly. The Indian Journal of Medical Research, 131, 302–310.

Romanò, F., Suresh, V., Galie, P. A., & Grotberg, J. B. (2020). Peristaltic flow in the glymphatic system. Scientific Reports, 10(1). DOI: https://doi.org/10.1038/s41598-020-77787-4

Rosado-Ramos, R., Poças, G. M., Marques, D., Foito, A., Sevillano, D. M., Lopes-Da-Silva, M., Gonçalves, L. G., Menezes, R., Ottens, M., Stewart, D., De Opakua, A. I., Zweckstetter, M., Seabra, M. C., Mendes, C. S., Outeiro, T. F., Domingos, P. M., & Santos, C. N. (2023). Genipin prevents alpha-synuclein aggregation and toxicity by affecting endocytosis, metabolism and lipid storage. Nature Communications, 14(1). DOI: https://doi.org/10.1038/s41467-023-37561-2

Roy, B., Nunez, A., Aysola, R. S., Kang, D. W., Vacas, S., & Kumar, R.

(2022). Impaired glymphatic system actions in obstructive sleep apnea adults. Frontiers in Neuroscience, 16. DOI: https://doi.org/10.3389/fnins.2022.884234

Santiago, J. A., & Potashkin, J. A. (2023). Physical activity and lifestyle modifications in the treatment of neurodegenerative diseases. Frontiers in Aging Neuroscience, 15. DOI: https://doi.org/10.3389/fnagi.2023.1185671

Santostasi, G., Malkani, R., Riedner, B., Bellesi, M., Tononi, G., Paller, K. A., & Zee, P. C. (2015). Phase-locked loop for precisely timed acoustic stimulation during sleep. Journal of Neuroscience Methods, 259, 101–114. DOI: https://doi.org/10.1016/j.jneumeth.2015.11.007

Sarode, R., & Nikam, P. P. (2023). The Impact of sleep disorders on cardiovascular health: Mechanisms and interventions. Cureus. DOI: https://doi.org/10.7759/cureus.49703

Scullin, M. K. (2017). Do older adults need sleep? A review of neuroimaging, sleep, and aging studies. Current Sleep Medicine Reports, 3(3), 204–214. DOI: https://doi.org/10.1007/s40675-017-0086-z

Sherpa, A. D., Aoki, C., & Hrabetova, S. (2017). Noradrenaline drives structural changes in astrocytes and brain extracellular space. In Elsevier eBooks (pp. 241–255). DOI: https://doi.org/10.1016/b978-0-12-805088-0.00012-8

Simka, M., Czaja, J., & Kowalczyk, D. (2019). Collapsibility of the internal jugular veins in the lateral decubitus body position: A potential protective role of the cerebral venous outflow against neurodegeneration. Medical Hypotheses, 133, 109397. DOI: https://doi.org/10.1016/j.mehy.2019.109397

Simon, M., Wang, M. X., Ismail, O., Braun, M., Schindler, A. G., Reemmer, J., Wang, Z., Haveliwala, M. A., O'Boyle, R. P., Han, W. Y., Roese, N., Grafe, M., Woltjer, R., Boison, D., & Iliff, J. J. (2022). Loss of perivascular aquaporin-4 localization impairs glymphatic exchange and promotes amyloid β plaque formation in mice. Alzheimer S Research & Therapy, 14(1). DOI: https://doi.org/10.1186/s13195-022-00999-5

Smets, N. G., Strijkers, G. J., Vinje, V., & Bakker, E. N. T. P. (2023). Cerebrospinal fluid turnover as a driver of brain clearance. NMR in Biomedicine, 37(7). DOI: https://doi.org/10.1002/nbm.5029

Smyth, L. C. D., Plog, B. A., & Kipnis, J. (2025). Rest and rinse: sleeping rhythms drive brain detox. Trends in Immunology. DOI: https://doi.org/10.1016/j.it.2025.02.007

Sun, L. (2015). Neural Regeneration research [Dataset]. In Figshare. DOI: https://doi.org/10.6084/m9.figshare.2007621.v2

Sun, Y., Lv, Q., Liu, J., Wang, F., & Liu, C. (2025). New perspectives on the glymphatic system and the relationship between glymphatic system and neurodegenerative diseases. Neurobiology of Disease, 205, 106791. DOI: https://doi.org/10.1016/j.nbd.2025.106791

Suzuki, K., Miyamoto, M., & Hirata, K. (2017). Sleep disorders in the elderly: Diagnosis and management. Journal of General and Family Medicine, 18(2), 61–71. DOI: https://doi.org/10.1002/jgf2.27

Tang, H., Zhang, X., Hu, S., Song, Y., Jin, W., Zou, J., Zhang, Y., Guo, J., An, P., Luo, J., Wang, P., Luo, Y., & Zhu, Y. (2025). Natural products acting as senolytics and senomorphics alleviate cardiovascular diseases by targeting senescent cells. Targets, 3(3), 23. DOI: https://doi.org/10.3390/targets3030023

Tatineny, P., Shafi, F., Gohar, A., & Bhat, A. (2020). Sleep in the elderly. Missouri Medicine, 117(5), 490–495. https://pmc.ncbi.nlm.nih.gov/articles/PMC7723148/

Tekieh, T., Robinson, P. A., & Postnova, S. (2022). Cortical waste clearance in normal and restricted sleep with potential runaway tau buildup in Alzheimer's disease. Scientific Reports, 12(1). DOI: https://doi.org/10.1038/s41598-022-15109-6

Tysnes, O., & Storstein, A. (2017). Epidemiology of Parkinson's disease. Journal of Neural Transmission, 124(8), 901–905. DOI: https://doi.org/10.1007/s00702-017-1686-y

Uji, M., Li, X., Saotome, A., Katsumata, R., Waggoner, R. A., Suzuki, C., Ueno, K., Aritake, S., & Tamaki, M. (2024). Human deep sleep facilitates faster cerebrospinal fluid dynamics linked to brain oscillations for sleep homeostasis and memory. bioRxiv (Cold Spring Harbor Laboratory). DOI: https://doi.org/10.1101/2024.08.30.610454

Van Veluw, S. J., Benveniste, H., Bakker, E. N. T. P., Carare, R. O., Greenberg, S. M., Iliff, J. J., Lorthois, S., Van Nostrand, W. E., Petzold, G. C., Shih, A. Y., & Van Osch, M. J. P. (2024). Is CAA a perivascular brain clearance disease? A discussion of the evidence to date and outlook for future studies. Cellular and Molecular Life Sciences, 81(1). DOI: https://doi.org/10.1007/s00018-024-05277-1

Verghese, J. P., Terry, A., De Natale, E. R., & Politis, M. (2022). Research evidence of the role of the glymphatic system and its potential pharmacological modulation in neurodegenerative diseases. Journal of Clinical Medicine, 11(23), 6964. DOI: https://doi.org/10.3390/jcm11236964

Videnovic, A., & Golombek, D. (2012). Circadian and sleep disorders in Parkinson's disease. Experimental Neurology, 243, 45–56. DOI: https://doi.org/10.1016/j.expneurol.2012.08.018

Voumvourakis, K. I., Sideri, E., Papadimitropoulos, G. N., Tsantzali, I., Hewlett, P., Kitsos, D., Stefanou, M., Bonakis, A., Giannopoulos, S., Tsivgoulis, G., & Paraskevas, G. P. (2023). The Dynamic Relationship between the Glymphatic System, Aging, Memory, and Sleep. Biomedicines, 11(8), 2092. DOI: https://doi.org/10.3390/biomedicines11082092

Wafford, K. A. (2021). Aberrant waste disposal in neurodegeneration: why improved sleep could be the solution. Cerebral Circulation - Cognition and Behavior, 2, 100025. DOI: https://doi.org/10.1016/j.cccb.2021.100025

Wahl, D., & Clayton, Z. S. (2024). Peripheral vascular dysfunction and the aging brain. Aging, 16(10), 9280–9302. DOI: https://doi.org/10.18632/aging.205877

Wang, J., Tian, Y., Qin, C., Meng, L., Feng, R., Xu, S., Zhai, Y., Liang, D., Zhang, R., Tian, H., Liu, H., Chen, Y., Fu, Y., Chen, P., Zhu, Q., Teng, J., & Wang, X. (2023). Impaired glymphatic drainage underlying ob-

structive sleep apnea is associated with cognitive dysfunction. Journal of Neurology, 270(4), 2204–2216. DOI: https://doi.org/10.1007/s00415-022-11530-z

Weil, Z. M., Norman, G. J., Karelina, K., Morris, J. S., Barker, J. M., Su, A. J., Walton, J. C., Bohinc, S., Nelson, R. J., & DeVries, A. C. (2009). Sleep deprivation attenuates inflammatory responses and ischemic cell death. Experimental Neurology, 218(1), 129–136. DOI: https://doi.org/10.1016/j.expneurol.2009.04.018

Wienecke, M., Werth, E., Poryazova, R., Baumann‐vogel, H., Bassetti, C. L., Weller, M., Waldvogel, D., Storch, A., & Baumann, C. R. (2012). Progressive dopamine and hypocretin deficiencies in Parkinson's disease: is there an impact on sleep and wakefulness? Journal of Sleep Research, 21(6), 710–717. DOI: https://doi.org/10.1111/j.1365-2869.2012.01027.x

Wostyn, P., & Goddaer, P. (2022). Can meditation-based approaches improve the cleansing power of the glymphatic system? Exploration of Neuroprotective Therapy, 110–117. DOI: https://doi.org/10.37349/ent.2022.00022

Wright, A. M., Wu, Y., Feng, L., & Wen, Q. (2024). Diffusion magnetic resonance imaging of cerebrospinal fluid dynamics: Current techniques and future advancements. NMR in Biomedicine, 37(9). DOI: https://doi.org/10.1002/nbm.5162

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D. J., Nicholson, C., Iliff, J. J., Takano, T., Deane, R., & Nedergaard, M. (2013). Sleep Drives Metabolite Clearance from the Adult Brain. Science, 342(6156), 373–377. DOI: https://doi.org/10.1126/science.1241224

Xu, L., & Pu, J. (2016). Alpha-Synuclein in Parkinson's disease: From pathogenetic dysfunction to potential clinical application. Parkinson S Disease, 2016, 1–10. DOI: https://doi.org/10.1155/2016/1720621

Xuan, X., Zhou, G., Chen, C., Shao, A., Zhou, Y., Li, X., & Zhou, J. (2022). Glymphatic System: emerging therapeutic target for neurological diseases. Oxidative Medicine and Cellular Longevity, 2022, 1–14. DOI: https://doi.org/10.1155/2022/6189170

Yan, T., Qiu, Y., Yu, X., & Yang, L. (2021). Glymphatic dysfunction: a bridge between sleep disturbance and mood disorders. Frontiers in Psychiatry, 12. DOI: https://doi.org/10.3389/fpsyt.2021.658340

Yang, E., Ismail, A., Kim, Y., Erdogmus, E., Boron, J., Goldstein, F., DuBose, J., & Zimring, C. (2022). Multidimensional Environmental Factors and Sleep Health for aging Adults: A Focused Narrative review. International Journal of Environmental Research and Public Health, 19(23), 15481. DOI: https://doi.org/10.3390/ijerph192315481

Yi, T., Gao, P., Zhu, T., Yin, H., & Jin, S. (2022). Glymphatic system dysfunction: a novel mediator of sleep disorders and headaches. Frontiers in Neurology, 13. DOI: https://doi.org/10.3389/fneur.2022.885020

Zamore, Z., & Veasey, S. C. (2022). Neural consequences of chronic sleep disruption. Trends in Neurosciences, 45(9), 678–691. DOI: https://doi.org/10.1016/j.tins.2022.05.007

Zhang, R., Liu, Y., Chen, Y., Li, Q., Marshall, C., Wu, T., Hu, G., & Xiao, M. (2019). Aquaporin 4 deletion exacerbates brain impairments in a mouse model of chronic sleep disruption. CNS Neuroscience & Therapeutics, 26(2), 228–239. DOI: https://doi.org/10.1111/cns.13194

Zhang, Y., & Gruber, R. (2019). Can Slow-Wave Sleep Enhancement Improve Memory? A review of current approaches and cognitive outcomes. The Yale Journal of Biology and Medicine, 92(1), 63–80.

Zhu, T., Yang, J., & Hashimoto, K. (2025). Noradrenergic modulation of glymphatic clearance: implications for neuropsychiatric disorders and mortality. Molecular Psychiatry. DOI: https://doi.org/10.1038/s41380-025-03051-8

Zisberg, A., Gur-Yaish, N., & Shochat, T. (2010). Contribution of routine to sleep quality in community elderly. SLEEP, 33(4), 509–514. DOI: https://doi.org/10.1093/sleep/33.4.509