Journal of Experimental and Basic Medical Sciences 2025;6(2):53-59

Review

The Glymphatic System and Brain Health: A New Frontier in Neurodegeneration Prevention

Meyserel Ayverdi[1], Oytun Erbaş[1]

ABSTRACT

The glymphatic system is a recently discovered fluid clearance pathway in the brain that plays a central role in removing metabolic waste through the exchange of cerebrospinal fluid and interstitial fluid. It is especially active during sleep and influenced by circadian rhythms, vascular pulsatility, and astrocytic aquaporin-4 channels. Growing evidence links dysfunction of this system to neurodegenerative diseases such as Alzheimer's and Parkinson's. This review outlines the anatomical structure and physiological function of the glymphatic network, discusses its role in brain health and disease, and highlights both current diagnostic methods and emerging therapeutic strategies. Finally, it explores preventive approaches and future directions for clinical translation, emphasizing the system's potential in protecting brain function across the lifespan.

Keywords: Alzheimer's disease, aquaporin-4, brain clearance, CSF, glymphatic system, sleep.

The human brain accounts for approximately 20% of the body's energy consumption, yet it lacks a classical lymphatic system. This anatomical absence raised longstanding questions about metabolic waste clearance in the central nervous system. Researchers proposed a glia-dependent clearance pathway, now known as the glymphatic system, which facilitates cerebrospinal fluid (CSF) influx along periarterial spaces and its exchange with interstitial fluid (ISF).[1]

Facilitated by aquaporin-4 (AQP4) water channels on astrocytic endfeet, this exchange ensures efficient solute removal. Glymphatic activity has been shown to increase significantly during sleep, particularly during slow-wave phases. In rodent models, this was accompanied by a marked increase in interstitial volume, enabling enhanced CSF exchange and waste removal.[2] These findings suggest a close link between sleep physiology and brain homeostasis and may help explain the correlation between poor sleep and increased risk of neurodegenerative conditions. Dysfunctions in glymphatic clearance have been implicated in the pathogenesis of multiple neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and traumatic brain injury. Impaired flow can lead to the accumulation of neurotoxic proteins, worsening inflammation, and neuronal damage. Understanding the structure, regulation, and potential therapeutic modulation of this system may open new paths for prevention and treatment.[3,4]

This review aims to provide an updated synthesis of the glymphatic system, with a focus on its anatomical basis, functional mechanisms, clinical implications, and current research perspectives.

ANATOMICAL ARCHITECTURE

Cerebrospinal Fluid

The glymphatic system is a brain-wide perivascular network that facilitates fluid movement between the CSF and ISF compartments. Cerebrospinal fluid enters the brain parenchyma primarily through periarterial spaces, which are anatomical channels surrounding penetrating arteries.[5,6] These spaces serve as entry points, allowing CSF to move into deeper cortical and subcortical areas.

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Meyserel Ayverdi. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: ayverdi.meyserel@gmail.com

Cite this article as: Ayverdi M, Erbaş O. The Glymphatic System and Brain Health: A New Frontier in Neurodegeneration Prevention. JEB Med Sci 2025;6(2):53-59.

doi: 10.5606/jebms.2025.1111

Received : July 12, 2025
Accepted : July 22, 2025
Published online : November 29, 2025

Astrocytic Mediation and Aquaporin-4 Dynamics

Fluid movement within the parenchyma relies significantly on astrocytes, particularly on AQP4 water channels located on their endfeet. These endfeet are components of the glia limitans and wrap around the blood vessels, establishing a controlled interface between fluid compartments.[7]

The polarized expression of AQP4 at perivascular endfeet is essential for convective bulk flow and solute clearance. Experimental knockouts of AQP4 have demonstrated significantly reduced glymphatic activity, confirming its central role.[5]

Waste Clearance via Perivenous Drainage

After mixing with ISF, waste-laden fluid is directed toward perivenous spaces, following the opposite path of inflow. Clearance then occurs along the venous drainage system, including large surface veins and meningeal lymphatic vessels. The system creates a loop-like structure: CSF enters periarterially, exchanges with ISF, and exits perivenously. The glymphatic circuit is not uniform across all brain regions; regional variations in vascular density and astrocyte configuration influence local flow dynamics.[8,9]

Regional and Structural Variability

Structurally, the glymphatic system overlaps with traditional neurovascular units but introduces a functional layer of solute transport and fluid homeostasis. It is distinct from the recently discovered meningeal lymphatics, which drain into the cervical lymph nodes, but both systems may interact at critical outflow points.[9]

PHYSIOLOGICAL ROLE

Glymphatic Transport and Solute Clearance

The glymphatic system plays a vital role in maintaining brain homeostasis by facilitating the clearance of metabolic waste from the central nervous system. Through a perivascular influx of CSF and its subsequent exchange with ISF, it enables the convective transport of solutes such as amyloid-beta, lactate, and tau protein.[2,4,10]

Sleep-Dependent Glymphatic Activation

A central physiological feature of the glymphatic system is the system's sleep-dependent activation. Researchers demonstrated that during natural sleep, particularly slow-wave sleep, the interstitial space expands by up to 60%, significantly enhancing glymphatic flow.[2] This alteration in interstitial volume dynamics allows more efficient removal of neurotoxic substances and may explain the observed association between poor sleep quality and cognitive decline.

Circadian Modulation of Glymphatic Flow

The system's function is also modulated by circadian rhythms. Evidence suggests that glymphatic clearance is more active during the night and reduced during wakefulness, pointing to a circadian modulation of clearance efficiency.[11] This appears linked to vascular tone and circadian influences.

Role in Nutrient Distribution and Osmotic Homeostasis

In addition to waste clearance, the glymphatic system contributes to nutrient distribution and volume regulation in the brain. It serves as a homeostatic mechanism, maintaining osmotic balance and ensuring that excess fluid does not accumulate in the parenchyma.[10,12]

Comparison with Peripheral Lymphatic Function

While the peripheral lymphatic system relies on lymph nodes for immune surveillance and drainage, the glymphatic pathway lacks such structures. Instead, it integrates with meningeal lymphatics and perivenous routes to channel waste toward cervical lymph nodes.[12] This highlights the brain's distinct adaptation for managing solute removal in the absence of peripheral lymph nodes.

GLYMPHATIC DYSFUNCTION IN NEUROLOGICAL DISEASE

General Mechanisms of Dysfunction

Dysfunction of the glymphatic system has been increasingly recognized as a potential contributor to the pathogenesis of several neurodegenerative diseases. Given the system's role in clearing neurotoxic proteins and maintaining ISF balance, its impairment may exacerbate the accumulation of misfolded proteins and contribute to progressive neuronal damage.[7,10,13]

Alzheimer's Disease: Amyloid and Tau Accumulation

In AD, glymphatic dysfunction is linked to impaired clearance of amyloid-beta and tau proteins- key pathological hallmarks of the disorder. Animal models have demonstrated reduced perivascular CSF influx and solute efflux in aging and AD-like conditions, leading to amyloid accumulation in cortical and hippocampal regions.[7,9] Loss of AQP4 polarization on astrocytic endfeet has been observed in AD brains, compromising fluid transport and solute clearance efficiency.[7,14]

Parkinson's Disease and Protein Clearance Impairment

Similar mechanisms may underlie PD, where alpha-synuclein aggregates accumulate in the substantia nigra. Studies suggest that impaired glymphatic flow, coupled with astroglial dysfunction, may hinder the removal of alpha-synuclein, thereby facilitating neurotoxicity and motor symptoms.[10] In multiple system atrophy, another proteinopathy, glymphatic alterations have also been observed, although human data remain limited.[13]

Age-Related Glymphatic Decline

Aging itself represents a major risk factor for glymphatic inefficiency. Reduced vascular pulsatility, AQP4 depolarization, and astrocytic senescence collectively diminish convective CSF-ISF exchange in the aging brain.[9] These changes may reduce clearance capacity and facilitate protein accumulation.

Neuroinflammation and Astrocytic Dysregulation

Inflammatory states- both acute and chronic- also modulate glymphatic function. Astrocyte activation, a hallmark of neuroinflammation, alters AQP4 expression and distribution, disrupting the perivascular interface essential for CSF flow.[10] Microglial cytokine release and blood-brain barrier permeability shifts may further compromise interstitial clearance mechanisms.[12]

Glymphatic Impairment After Traumatic Brain Injury

Traumatic brain injury represents another context in which glymphatic impairment may contribute to secondary brain damage. Post-traumatic edema, astrocyte swelling, and altered vascular dynamics interfere with glymphatic flow, resulting in delayed clearance of excitotoxins and cellular debris.[14]

Clinical Relevance and Research Outlook

Collectively, these findings support the notion that glymphatic dysfunction is not merely a consequence but may be a driving factor in the initiation and progression of several neurological disorders. Whether as a therapeutic target or a diagnostic biomarker, the glymphatic system may serve as a critical entry point for understanding and potentially intervening in chronic brain pathology.[12-15]

DIAGNOSTIC AND RESEARCH METHODS

Preclinical Imaging and Experimental Approaches

Investigating the glymphatic system requires advanced imaging and experimental techniques, given its dynamic and perivascular nature. Most foundational insights into glymphatic flow have been derived from rodent models using intracisternal injections of fluorescent or radiolabeled tracers, followed by real-time imaging.[13] Two-photon microscopy has played a crucial role in visualizing CSF influx and ISF efflux at micrometer resolution, particularly within superficial cortical layers.[13,15]

Clinical Neuroimaging Modalities

In translational research, magnetic resonance imaging (MRI) has become a key non-invasive modality for assessing glymphatic function in clinical studies. Contrast-enhanced MRI using intrathecal gadolinium-based tracers allows for the visualization of CSF flow and solute clearance patterns over time. This technique, referred to as dynamic contrast-enhanced MRI, has been applied to detect altered glymphatic function in patients with idiopathic normal pressure hydrocephalus, AD, and traumatic brain injury.[7]

Diffusion Tensor Imaging and ALPS index

Diffusion tensor imaging (DTI), particularly the analysis of the DTI-along the perivascular space (ALPS) index, has gained attention as a potential biomarker for glymphatic activity. This method utilizes the directional anisotropy of water movement along perivascular routes to infer clearance efficacy. Although it shows promise, DTI is still an indirect measure and can be affected by confounding factors from other changes in white matter.[15]

Limitations of Animal Models and Translation to Humans

Animal studies provide critical mechanistic insights but also present limitations in their translatability. Rodent brains are significantly different from human brains in terms of size, vascular structure, and sleep patterns. Nonetheless, animal models enable the accurate alteration of factors like AQP4 expression, vascular pulsatility, and anesthetic state - all of which affect glymphatic flow.[3,16]

Challenges in Standardization and Reproducibility

A growing challenge in the field is the standardization of protocols and the reproducibility of results. Discrepancies in imaging timing, anesthetic protocols, and tracer types can lead to significant variability between studies. Ethical and technical considerations limit the application of intrathecal contrast agents in healthy human populations, restricting some of the most revealing methods to clinical or postmortem contexts.[16]

Future Innovations and Multimodal Tools

Despite these limitations, diagnostic tools continue to evolve. Integration of multimodal imaging, machine learning-based flow mapping, and the use of novel biomarkers may enhance our ability to monitor glymphatic function in both health and disease.[15-17]

THERAPEUTIC PERSPECTIVES

Modulating the glymphatic system for therapeutic benefit is an emerging concept in neuroscience and translational medicine. Given its role in maintaining neurochemical homeostasis and clearing toxic metabolites, interventions aimed at enhancing glymphatic function offer potential for delaying or even preventing neurodegenerative progression.[14]

Sleep Optimization as a Foundational Pillar

Sleep represents the most potent physiological enhancer of glymphatic activity. During slow-wave sleep, the interstitial spaces expand substantially during deep sleep, which supports fluid exchange and metabolic clearance. This expansion is mediated by reductions in noradrenergic tone, leading to reduced vascular resistance and increased paravascular flow.[1,2]

Clinical data suggest that sleep deprivation affects not only memory consolidation but also reduces glymphatic clearance of amyloid-beta and tau proteins, accelerating neurodegenerative pathology. Consequently, interventions aimed at improving sleep quantity and quality- such as cognitive behavioral therapy for insomnia, circadian rhythm entrainment, and melatonin supplementation- may exert neuroprotective effects via the glymphatic pathway. [10,13]

Pharmacological Modulation of Astroglial and Vascular Targets

Aquaporin-4 channels, predominantly localized on the astrocytic endfeet, are critical for glymphatic fluid transport. Experimental modulation of AQP4 expression or polarization has been shown to directly alter glymphatic efficacy. Pharmacological agents such as TGN-020 (an AQP4 inhibitor) have demonstrated modulatory effects on CSF-ISF flow in preclinical models.[10]

Vascular pulsatility plays a key role in propelling fluid along the perivascular spaces. Pharmacological enhancement of cerebral arterial compliance- or reduction of microvascular resistance- may augment perivascular CSF inflow. Agents that reduce central sympathetic tone (e.g., α2-agonists) could potentially enhance glymphatic clearance, although clinical validation is pending. [3]

Anti-inflammatory agents that modulate astrocyte and microglial activation states may also restore glymphatic function in chronically inflamed or aged brains. Minocycline and low-dose corticosteroids have been shown to normalize AQP4 expression patterns in animal models of neuroinflammation. [10]

Lifestyle Interventions: Physical Activity, Diet, and Hydration

Beyond pharmacology, lifestyle-based interventions offer an accessible, widely applicable intervention for enhancing glymphatic activity. Aerobic exercise has been associated with improved CSF circulation and vascular pulsatility, as well as enhanced expression of glymphatic-associated proteins.[8] Regular physical activity reduces risk factors such as hypertension and diabetes, both of which impair perivascular clearance.

Adequate hydration is essential for maintaining CSF production and volume. Dehydration can lead to increased CSF viscosity and reduced flow dynamics, potentially impairing glymphatic function. Dietary factors, including high-sodium intake and chronically elevated glucose levels, may also alter osmotic gradients that regulate fluid transport within the brain. Preliminary investigations have examined dietary interventions- such as ketogenic regimens or intermittent fasting- as modulators of neuroinflammation and glymphatic efficiency.[13]

Non-Invasive Techniques and Neuromodulation

In addition to pharmacological and lifestyle approaches, some non-invasive techniques have shown potential for supporting glymphatic activity. For example, transcranial low-frequency stimulation and focused ultrasound are being explored in experimental models for their effects on fluid transport and vascular tone.[13-17] While still early-stage, these approaches may offer future alternatives to directly influence glymphatic flow without drugs.

Chronotherapy and Circadian Targeting

The circadian modulation of glymphatic activity has prompted growing interest in time-aligned interventions. Since glymphatic clearance is most active during deep sleep, researchers are investigating whether aligning treatments with sleep cycles- so-called chronotherapy- could enhance their effectiveness.[1,13-19]

Personalized Monitoring and Technological Integration

Finally, new technologies such as wearable EEG devices and imaging tools may help monitor individual sleep and clearance patterns, making more personalized strategies possible in the future. [13]

PREVENTIVE PERSPECTIVES

Glymphatic Maintenance Through Lifestyle and Vascular Modulation

Recent research suggests that daily behaviors strongly influence glymphatic function. Sleep patterns, aerobic activity, and cardiovascular health have been associated with more effective CSF-ISF exchange. In contrast, chronic sleep deprivation or systemic inflammation can impair clearance- partly by disrupting AQP4 polarization on astrocytic endfeet.[6,20-22]

Vascular compliance appears particularly relevant: age-related arterial stiffening may diminish the pulsatility driving perivascular flow. Interventions such as moderate endurance training or antihypertensive control may support fluid movement indirectly.[5,17]

In addition, chrononutrition- synchronizing food intake with circadian rhythms- might help stabilize osmotic and metabolic gradients relevant to glymphatic activity, though clinical validation is pending.[22-24]

Neuroinflammation, Senescence, and Early Screening

Emerging data indicate that psychological stress may impair glymphatic clearance through glial reactivity and subtle disruptions in blood-brain barrier permeability.[19] Anti-inflammatory approaches, including stress-reducing practices or specific dietary patterns, are under investigation as modulators of glymphatic efficiency. [25]

Aging compounds these risks. Declines in vascular pulsatility and astrocytic function reduce convective transport, potentially accelerating neurodegeneration. Early detection- via imaging or biomarkers- may enable preventive action before irreversible changes occur.[4,20,23]

CLINICAL TRANSLATION AND FUTURE DIRECTIONS

From Research Tools to Diagnostic Applications

Glymphatic imaging is entering early clinical use. Techniques like DTI-ALPS and contrast-enhanced MRI are being applied to detect impaired clearance in disorders such as idiopathic normal pressure hydrocephalus and mild cognitive impairment.[15,20] While still under evaluation, these tools offer promise as non-invasive monitors of brain fluid dynamics.

Beyond diagnostics, non-pharmacological interventions- such as low-frequency stimulation and focused ultrasound- are being studied for their potential to improve CSF movement without altering neural activity. Early findings show favorable modulation of fluid transport through external methods.[11,16,20]

Personalization, Precision, and Interdisciplinary Collaboration

Individualized strategies may soon become a central component of neuropreventive care. Wearable EEG devices, vascular risk profiling, and circadian-based therapeutics (chronotherapy) could allow interventions tailored to each patient's clearance profile. [3,12,16]

Ongoing advances will require collaboration across neuroscience, sleep medicine, and imaging science. Integrating these fields may help glymphatic insights become useful tools, especially for managing neurodegenerative risk in older adults.[14,19,26,27]

In conclusion, the glymphatic system has gained increasing attention as a central component of brain homeostasis. Through coordinated exchange between cerebrospinal and ISF, it supports the clearance of metabolic waste and plays a role in protecting the brain against neurodegeneration. Current evidence suggests that impaired glymphatic flow may contribute to the pathophysiology of several neurological disorders, including AD and PD. While many of the mechanisms have been described in animal models, growing human data support their clinical relevance. Imaging techniques and experimental tools have helped clarify how the system works and how it may be influenced by sleep, vascular function, and astrocyte behavior. These insights open potential pathways for future interventions- ranging from lifestyle modifications to pharmacological approaches and non-invasive stimulation methods. Supporting glymphatic health may become an important strategy for maintaining brain function- especially as populations age and neurodegenerative diseases continue to rise.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015 Dec;40:2583-99.
2. Naganawa S, Taoka T, Ito R, Kawamura M. The Glymphatic System in Humans: Investigations With Magnetic Resonance Imaging. Invest Radiol. 2024 Jan 1;59:1-12.
3. Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Jpn J Radiol. 2017 Apr;35:172-8.
4. Lopes DM, Wells JA, Ma D, Wallis L, Park D, Llewellyn SK, et al. Glymphatic inhibition exacerbates tau propagation in an Alzheimer's disease model. Alzheimers Res Ther. 2024 Apr 5;16:71. Erratum in: Alzheimers Res Ther. 2024 Nov 28;16:258.
5. Gao Y, Liu K, Zhu J. Glymphatic system: an emerging therapeutic approach for neurological disorders. Front Mol Neurosci. 2023 Jul 6;16:1138769.
6. Thipani Madhu M, Balaji O, Kandi V, Ca J, Harikrishna GV, Metta N, et al. Role of the Glymphatic System in Alzheimer's Disease and Treatment Approaches: A Narrative Review. Cureus. 2024 Jun 29;16:e63448.
7. Nagelhus EA, Ottersen OP. Physiological roles of aquaporin-4 in brain. Physiol Rev. 2013 Oct;93:1543-62.
8. Prasuhn J, Xu J, Hua J, van Zijl P, Knutsson L. Exploring neurodegenerative disorders using advanced magnetic resonance imaging of the glymphatic system. Front Psychiatry. 2024 Apr 8;15:1368489.
9. Szlufik S, Kopeć K, Szleszkowski S, Koziorowski D. Glymphatic System Pathology and Neuroinflammation as Two Risk Factors of Neurodegeneration. Cells. 2024 Feb 5;13:286.
10. Das N, Dhamija R, Sarkar S. The role of astrocytes in the glymphatic network: a narrative review. Metab Brain Dis. 2024 Mar;39:453-65.
11. Ding Z, Fan X, Zhang Y, Yao M, Wang G, Dong Y, et al. The glymphatic system: a new perspective on brain diseases. Front Aging Neurosci. 2023 Jun 15;15:1179988.
12. Arı M, Erdogan MA, Erbaş O. Investigation of the protective effects of dichloroacetic acid in a rat model of diabetic neuropathy. BMC Pharmacol Toxicol. 2025 Jan 22;26:15.
13. Silva I, Silva J, Ferreira R, Trigo D. Glymphatic system, AQP4, and their implications in Alzheimer's disease. Neurol Res Pract. 2021 Jan 19;3:5.
14. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013 Oct 18;342:373-7.
15. Hablitz LM, Nedergaard M. The Glymphatic System: A Novel Component of Fundamental Neurobiology. J Neurosci. 2021 Sep 15;41:7698-711.
16. Mader S, Brimberg L. Aquaporin-4 Water Channel in the Brain and Its Implication for Health and Disease. Cells. 2019 Jan 27;8:90.
17. Solmaz V, Erdoğan MA, Alnak A, Meral A, Erbaş O. Erythropoietin shows gender dependent positive effects on social deficits, learning/memory impairments, neuronal loss and neuroinflammation in the lipopolysaccharide induced rat model of autism. Neuropeptides. 2020 Oct;83:102073.
18. Astara K, Pournara C, de Natale ER, Wilson H, Vavougios GD, Lappas AS, et al. A novel conceptual framework for the functionality of the glymphatic system. J Neurophysiol. 2023 May 1;129:1228-36.
19. Lee H, Xie L, Yu M, Kang H, Feng T, Deane R, et al. The Effect of Body Posture on Brain Glymphatic Transport. J Neurosci. 2015 Aug 5;35:11034-44.
20. Verghese JP, Terry A, de Natale ER, Politis M. Research Evidence of the Role of the Glymphatic System and Its Potential Pharmacological Modulation in Neurodegenerative Diseases. J Clin Med. 2022 Nov 25;11:6964.
21. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol. 2018 Nov;17:1016-24.
22. Nikolenko VN, Oganesyan MV, Vovkogon AD, Nikitina AT, Sozonova EA, Kudryashova VA, et al. Current Understanding of Central Nervous System Drainage Systems: Implications in the Context of Neurodegenerative Diseases. Curr Neuropharmacol. 2020;18:1054-63.
23. Bohr T, Hjorth PG, Holst SC, Hrabětová S, Kiviniemi V, Lilius, T et al. The glymphatic system: Current understanding and modeling. iScience. 2022 Aug 20;25:104987.
24. Chong PLH, Garic D, Shen MD, Lundgaard I, Schwichtenberg AJ. Sleep, cerebrospinal fluid, and the glymphatic system: A systematic review. Sleep Med Rev. 2022 Feb;61:101572.
25. Buccellato FR, D'Anca M, Serpente M, Arighi A, Galimberti D. The Role of Glymphatic System in Alzheimer's and Parkinson's Disease Pathogenesis. Biomedicines. 2022 Sep 13;10:2261.

26. Tanyeri G, Celik O, Erbas O, Oltulu F, Yilmaz Dilsiz O. The effectiveness of different neuroprotective agents in facial nerve injury: An experimental study. Laryngoscope. 2015 Nov;125:E356-64.
27. Altıok U, Erbaş O. Exploring Neuroplasticity: The Role of LSD, Methamphetamine, Cannabis, and Ketamine in Psychiatric Disorders. JEB Med Sci 2024;5:234-40.