SVOA Neurology

e-ISSN 2753-9180

ScienceVolks Open Access

Review Article

Dysfunction of the Blood-Brain Barrier and Glymphatic System in Alzheimer's Disease: An Integrative Review

Daniel Nuciatelli P. de Mello[1], Irineu Gregnanin Pedron[2*]

[1]DDS, Specialist in Oral Implantology, São Paulo, Brazil; Master's Student in Clinical Neuroscience, University of Roehampton, London, UK.

[2]Professor, Department of Periodontology and Integrated Clinic, School of Dentistry, Centro Universitário Braz Cubas, Mogi das Cruzes, Brazil.

***Corresponding Author:** Irineu Gregnanin Pedron, Professor, Department of Periodontology and Integrated Clinic, School of Dentistry, Universidade Braz Cubas, Mogi das Cruzes, Brazil.

DOI: https://doi.org/10.58624/SVOANE.2026.07.009

Received: March 05, 2026

Published: March 25, 2026

Citation: de Mello DNP, Pedron IG. Dysfunction of the Blood-Brain Barrier and Glymphatic System in Alzheimer's Disease: An Integrative Review. *SVOA Neurology* 2026, 7:2, 51-58. doi. 10.58624/SVOANE.2026.07.009

Abstract

Alzheimer's disease (AD) represents the most prevalent cause of dementia globally, characterised neuropathologically by amyloid-β plaques and tau neurofibrillary tangles. While these hallmarks remain central to diagnosis, the modest clinical efficacy of amyloid-targeting therapies necessitates exploration of complementary pathogenic mechanisms. This review synthesises contemporary evidence implicating the coupled dysfunction of the blood-brain barrier (BBB) and glymphatic system as critical, early contributors to Alzheimer's pathophysiology. The BBB, a selective vascular interface, and the glymphatic system, a brain-wide clearance network dependent on astrocytic aquaporin-4 (AQP4), are fundamental to cerebral homeostasis. Their impairment facilitates neuroinflammation, reduces clearance of neurotoxic proteins, and exacerbates neuronal injury. We integrate mechanistic insights from animal models with human neuroimaging studies, demonstrating that BBB permeability and glymphatic inefficiency often precede significant atrophy and predict cognitive decline. Key modulators including ageing, APOE4 genotype, chronic sleep disruption, and systemic inflammation are examined. Notably, emerging links between peripheral conditions like periodontitis and BBB integrity are explored. The review also critically evaluates nascent therapeutic strategies aimed at restoring vascular integrity and clearance function, alongside essential ethical and social considerations. We emphasise that biological sex differences and sociocultural constructs of race and ethnicity significantly influence disease risk, research participation, and healthcare access, demanding inclusive scientific practices. Ultimately, viewing Alzheimer's disease through the lens of brain homeostasis failure offers a transformative framework for developing early biomarkers, preventive interventions, and novel treatments that move beyond exclusively amyloid-centric models.

Keywords: *Alzheimer's Disease, Blood-Brain Barrier, Glymphatic System, Neuroinflammation, Sleep Quality, Aquaporin-4, Periodontitis, Neuroimaging.*

Introduction

Alzheimer's disease (AD) constitutes a profound global health crisis, with projections suggesting nearly 152 million affected individuals by 2050 [1]. Clinically defined by progressive amnestic cognitive impairment and neuropsychiatric symptoms, its pathological signature includes extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau [2]. Despite decades of research dominated by the amyloid cascade hypothesis, disease-modifying treatments remain limited. Recent antibody therapies like Lecanemab show modest slowing of decline but carry significant risks, underscoring that Aβ and tau pathology alone provide an incomplete explanation for disease onset and progression [3].

This therapeutic impasse has catalysed a paradigm shift towards investigating how the brain's microenvironment and homeostatic systems fail, creating a permissive milieu for neurodegeneration. This homeostasis perspective aligns with the concept of integrated brain clearance routes, encompassing vascular transport, paravascular/glymphatic exchange, and meningeal outflow pathways [4-5].

Central to this revised framework are two interconnected systems: the blood-brain barrier (BBB) and the glymphatic system. The BBB is a highly specialised multicellular structure, primarily formed by capillary endothelial cells sealed with tight junctions, supported by pericytes, astrocytes, and a basement membrane. It meticulously regulates the exchange of molecules, nutrients, and cells between the bloodstream and the central nervous system (CNS), while shielding the neural parenchyma from toxins and peripheral immune activation [6]. The glymphatic system, a more recently characterised macroscopic waste clearance pathway, facilitates the bulk flow of cerebrospinal fluid (CSF) into the brain along periarterial spaces, where it mixes with interstitial fluid to clear solutes, including Aβ and tau, via perivenous drainage routes [7]. This process is critically governed by the polarised expression of aquaporin-4 (AQP4) water channels on astrocytic endfeet ensheathing cerebral vasculature.

Accumulating evidence positions dysfunction within these homeostatic systems not as a late-stage epiphenomenon of neuronal death, but as an early and active driver of Alzheimer's pathogenesis [8]. Breakdown of the BBB's selective permeability allows unregulated entry of neuroactive plasma proteins, immune cells, and inflammatory mediators. Concurrently, glymphatic impairment, often linked to disrupted sleep or loss of AQP4 polarity, leads to the stagnation of metabolic waste within the interstitial space. This dual failure fosters a neuroinflammatory cascade and accelerates protein aggregation. This narrative literature review aims to critically evaluate the experimental, clinical, and neuroimaging evidence for this integrated BBB-glymphatic axis in AD. Furthermore, it will address the ethical imperative and scientific necessity of considering biological variables (sex) and social determinants (race, ethnicity, socioeconomic status) that shape both disease risk and the translational applicability of research findings.

Methods

This narrative review employed a comprehensive literature search across PubMed, Scopus, and Web of Science databases for articles published between 2012 and 2024. Search terms included: "Blood-brain barrier AND Alzheimer's disease", "glymphatic system AND Alzheimer's", "aquaporin-4 AND neurodegeneration", "meningeal lymphatics", "sleep AND amyloid clearance", and "periodontitis AND blood-brain barrier". Inclusion criteria prioritised: (1) original research articles in peer-reviewed journals; (2) review articles from high-impact journals; (3) human neuroimaging studies; (4) mechanistic animal studies. Exclusion criteria included: non-English publications, conference abstracts without full-text availability, and studies not directly relevant to BBB or glymphatic function in AD. The synthesis approach was thematic, organising findings around key mechanistic pathways, clinical correlates, and therapeutic implications.

The Glymphatic System: Mechanisms, Regulation, and Disruption in Alzheimer's Disease

The glymphatic system operates as the brain's functional analogue to the peripheral lymphatic system, responsible for the clearance of bulk interstitial waste, and its failure has been proposed as a final common pathway to dementia [9]. The proposed model involves CSF influx from the subarachnoid space into the brain parenchyma via periarterial Virchow-Robin spaces. Driven by arterial pulsatility and facilitated by AQP4 channels on astrocytic endfeet, CSF mixes with interstitial fluid, collecting soluble metabolites and protein aggregates like Aβ. This convective flow then directs waste toward perivenous spaces, ultimately draining into the CSF or the recently rediscovered network of meningeal lymphatic vessels, which ferry solutes and immune cells to the cervical lymph nodes for systemic disposal, with additional CSF egress routes through arachnoid granulations that may interface with dural/bone marrow immune niches [7,10-11]. The polarised localisation of AQP4 to astrocytic endfeet is paramount; it creates an osmotic gradient that drives fluid movement. Loss of this polarity, a common feature of ageing and neuroinflammation, severely compromises glymphatic influx and waste clearance efficiency [12].

Experimental evidence robustly links glymphatic dysfunction to Alzheimer's pathology. In mouse models, genetic deletion or mislocalisation of AQP4 results in a ~70% reduction in interstitial Aβ clearance and exacerbates amyloid plaque deposition [7]. Similarly, glymphatic suppression accelerates tau aggregation and spread in tauopathy models. Ageing is a primary risk factor for glymphatic decline, associated with astrogliosis, reduced arterial pulsatility, and the aforementioned loss of AQP4 polarity [13].

Neuroinflammation further disrupts this delicate system; activated microglia and reactive astrocytes release cytokines and alter extracellular matrix composition, effectively "clogging" the perivascular highways necessary for fluid transport [14-15].

One of the most significant and modifiable regulators of glymphatic function is sleep. During non-rapid eye movement (NREM) slow-wave sleep, neuronal activity becomes synchronised, and the interstitial space volume expands by over 60%, dramatically increasing convective fluid exchange and solute clearance [16]. This has led to the compelling hypothesis that sleep represents a state of "brain cleansing." Consequently, chronic sleep disruption or fragmentation, highly prevalent in ageing and AD populations, impairs glymphatic clearance, leading to increased interstitial Aβ levels as demonstrated in both animal and human studies [17]. This establishes a vicious cycle where sleep disturbance promotes pathology, and progressing neurodegeneration further erodes sleep architecture, highlighting sleep hygiene as a critical, non-pharmacological intervention point. Recent syntheses emphasise glymphatic-mediated mechanisms as a plausible link between sleep disorders and AD pathophysiology [18].

Blood-Brain Barrier Dysfunction: An Early Gateway to Neurodegeneration

The BBB is a dynamic and complex neurovascular unit essential for maintaining the precise chemical environment required for neuronal signalling. Its integrity relies on continuous communication between endothelial cells (with their tight junctions, adherens junctions, and efflux transporters), contractile pericytes embedded in the basement membrane, and the endfeet of astrocytes [19]. Beyond being a passive barrier, it actively transports nutrients (e.g., glucose via GLUT1), regulates ion balance, and mediates immune surveillance.

In Alzheimer's disease, compelling data from post-mortem tissue and advanced neuroimaging indicate that BBB breakdown is an early pathological event, including in the ageing human hippocampus [20]. Histological studies show decreased expression of tight junction proteins (claudin-5, occludin) and markers of pericyte degeneration in the hippocampi and cortices of AD patients, even at mild cognitive impairment (MCI) stages. In vivo, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) allows quantification of BBB leakage via the transfer constant (Ktrans). Using this technique, Montagne et al. (2015, 2020) demonstrated regionally specific increases in BBB permeability in the hippocampus and medial temporal lobe of cognitively normal older adults and individuals with MCI, which strongly predicted future cognitive decline independent of amyloid and tau burden measured by PET. This positions BBB dysfunction as a proximate driver of pathology rather than a secondary consequence.

Genetic susceptibility plays a key role. The APOE ε4 allele, the strongest genetic risk factor for sporadic AD, is intimately linked to BBB vulnerability. APOE4 is associated with pericyte dysfunction, accelerated breakdown of the BBB, and impaired clearance of Aβ across the barrier. Carriers exhibit increased CSF levels of pericyte injury biomarkers and higher Ktrans values on MRI [8]. Once compromised, the leaky BBB allows infiltration of multiple harmful blood-derived constituents: fibrinogen deposits activate microglia and promote oxidative stress; pro-inflammatory cytokines amplify neuroinflammation; and albumin extravasation can cause excitotoxic oedema. Furthermore, BBB disruption is closely tied to cerebral hypoperfusion, creating a damaging synergy of reduced nutrient delivery and impaired waste removal [21].

An increasingly recognised source of systemic inflammation that can compromise the BBB originates from outside the CNS, particularly the oral cavity. Periodontitis, a chronic inflammatory disease driven by dysbiotic microbial communities, is associated with a ~1.7-fold increased risk for dementia. Porphyromonas gingivalis, a keystone periodontal pathogen, and its proteolytic enzymes (gingipains) have been identified in the brains of AD patients. In mouse models, oral infection with P. gingivalis or systemic administration of its lipopolysaccharide leads to increased BBB permeability, microglial activation, elevated brain Aβ levels, and tau phosphorylation [22-23]. This pathway may involve both direct bacterial invasion and indirect effects via systemic inflammatory mediators (e.g., IL-1β, TNF-α) that weaken endothelial tight junctions. This connection underscores the importance of an interdisciplinary, whole-body approach to brain health, positioning oral healthcare as a potential modifiable risk factor in AD prevention. This relationship has also been comprehensively synthesised in recent Dental Neuroscience literature exploring periodontal–Alzheimer mechanisms [24].

Convergent Pathways: The Interdependence of BBB and Glymphatic Systems

The BBB and glymphatic system are not independent entities but components of an integrated network maintaining brain homeostasis, with astrocytes serving as the central orchestrators. Astrocytic endfeet form a continuous layer covering over 99% of the cerebrovascular surface, directly contributing to both BBB induction/maintenance and glymphatic fluid transport. This anatomical and functional coupling means that pathology in one system invariably impacts the other, creating a vicious, self-reinforcing cycle of dysfunction. [10,12]

BBB breakdown directly impairs glymphatic function. The influx of protein-rich plasma components like fibrinogen into the perivascular space increases interstitial viscosity and alters osmotic gradients, potentially stifling the convective currents essential for glymphatic flow [12]. Furthermore, vascular damage and pericyte loss may reduce arterial pulsatility, a key driver of CSF movement along periarterial spaces. Conversely, glymphatic failure has deleterious effects on the BBB. Accumulation of neurotoxic proteins (Aβ, tau) and inflammatory cytokines in the interstitial fluid can directly damage endothelial cells and pericytes. Aβ itself has been shown to have angiotoxic effects, promoting oxidative stress and disrupting tight junctions. This bidirectional relationship suggests that therapeutic strategies may need to target both systems simultaneously for optimal effect.

The meningeal lymphatic vessels, located in the dura mater, act as a crucial downstream conduit for this integrated clearance system. They collect CSF and interstitial solutes that have drained from the brain parenchyma and glymphatic pathways, shuttling them to deep cervical lymph nodes for immune surveillance and ultimate disposal. Impairment of meningeal lymphatic function, whether through ageing, genetic manipulation, or physical obstruction, has been shown in mice to reduce clearance of Aβ and tau, exacerbate neuroinflammation, and worsen cognitive performance [25]. Enhancing this drainage, for example via viral delivery of vascular endothelial growth factor C (VEGF-C) to promote lymphangiogenesis, can improve protein clearance and mitigate pathology in AD models, highlighting its therapeutic potential [26]. This completes the picture: the BBB regulates what comes in, the glymphatic system handles internal waste processing, and the meningeal lymphatics manage final export. Recent comprehensive reviews further consolidate the role of meningeal lymphatics across CNS diseases and highlight translational considerations for AD [27].

Discussion

Clinical and Neuroimaging Correlates in Human Populations

Advances in neuroimaging have facilitated the translation of preclinical findings to human Alzheimer's disease. Dynamic contrast-enhanced MRI (DCE-MRI) is the gold standard for assessing blood–brain barrier integrity, with studies consistently demonstrating elevated Ktrans, particularly in the hippocampus, in individuals with mild cognitive impairment and Alzheimer's disease compared with cognitively normal controls. Notably, BBB leakage is detectable in pre-symptomatic APOE4 carriers and correlates with cerebrospinal fluid markers of neuronal injury, supporting its role as an early pathological event [8].

Assessing glymphatic function in vivo remains challenging due to its dependence on fluid dynamics. The most promising indirect measure is the diffusion tensor image analysis along the perivascular space (DTI-ALPS) index, which quantifies water diffusion along perivascular pathways as a surrogate of glymphatic activity. Reduced ALPS values, indicating impaired perivascular flow, have been reported in Alzheimer's disease, mild cognitive impairment, and sleep disorders, and correlate with cognitive performance and amyloid-β burden on PET imaging [28]. Recent human studies report reduced ALPS indices in AD and related phenotypes and link these measures to cognition and amyloid burden [29-30], while complementary MRI markers of perivascular space burden and multimodal clearance metrics further support glymphatic impairment in AD [31-32]. Although further validation is required, DTI-ALPS represents an important step toward non-invasive glymphatic assessment. More direct approaches, such as intrathecal contrast-enhanced MRI, track cerebrospinal fluid movement through glymphatic pathways but are inherently invasive.

Epidemiological evidence reinforces these imaging findings. Vascular risk factors including hypertension, diabetes, and obesity conditions known to compromise BBB integrity are strongly associated with dementia risk. Likewise, sleep disorders such as obstructive sleep apnoea, characterised by intermittent hypoxia and sleep fragmentation, are linked to an increased incidence of mild cognitive impairment and Alzheimer's disease, likely through combined disruption of BBB function and glymphatic clearance. Together, these associations provide real-world support for the mechanistic pathways described and identify modifiable targets for dementia prevention. [8,21]

Therapeutic and Preventative Implications

The reconceptualisation of AD as a disorder of brain homeostasis opens a diverse array of novel therapeutic and preventive avenues that extend beyond targeting protein aggregates themselves. These strategies can be categorised into lifestyle interventions, pharmacological approaches, and biomarker-guided treatment.

Lifestyle and Non-Pharmacological Interventions: Given the potent influence of sleep on glymphatic clearance, sleep optimisation emerges as a frontline strategy. This includes treating sleep disorders (e.g, CPAP for sleep apnoea), promoting good sleep hygiene, and exploring chronotherapeutic interventions. Regular aerobic exercise has also been shown to improve cerebrovascular health, increase slow-wave sleep, and may enhance glymphatic function, offering a multi-modal benefit. Dietary approaches like the Mediterranean or MIND diets, rich in anti-inflammatory compounds and antioxidants, may help mitigate systemic inflammation and support BBB integrity. As discussed, comprehensive oral healthcare to manage periodontitis could be a novel public health strategy to reduce a source of chronic systemic inflammation. [16,18]

Pharmacological and Biological Strategies: Direct therapeutic modulation is in preclinical or early clinical stages. Targeting AQP4 to restore its polarised localisation is a logical goal, though challenging due to the channel's ubiquitous role in water homeostasis. Small molecules or biologics that stabilise tight junction complexes (e.g, by activating the Wnt/β-catenin pathway) could fortify the BBB. Promoting meningeal lymphangiogenesis via VEGF-C analogues is a promising approach from animal studies but requires precise delivery to avoid oedema or aberrant growth. Another innovative approach involves using focused ultrasound in combination with microbubbles to temporarily and reversibly open the BBB, which could enhance the delivery of therapeutic agents or potentially flush out accumulated toxins by increasing bulk flow. [6,12]

Biomarkers and Personalised Medicine: The development of reliable, accessible biomarkers for BBB permeability (e.g., via simplified MRI protocols or blood-based markers like soluble platelet-derived growth factor receptor β) and glymphatic function will be crucial. These could enable early detection of homeostatic failure before irreversible neurodegeneration occurs, identifying individuals who would benefit most from preventive interventions. They could also serve as dynamic biomarkers in clinical trials to monitor treatment response, moving beyond static measures of amyloid or atrophy. [21,28]

Critical Challenges and Translational Hurdles: Significant obstacles remain. The complexity and interdependence of the BBB-glymphatic axis mean that modulating one component may have unintended consequences on another. For instance, aggressively sealing a leaky BBB might also impede the efflux of waste products. The heterogeneity of AD pathology also suggests that not all patients will have significant homeostatic dysfunction, necessitating precision medicine approaches. Furthermore, many promising interventions (like VEGF-C delivery) require sophisticated methods like intrathecal administration or gene therapy, posing practical and safety challenges for widespread use in an elderly population. [27]

Biological Sex, Race, Ethnicity, and Ethical Imperatives in Research and Care

A comprehensive understanding of Alzheimer's disease and the development of equitable therapies demand serious engagement with biological and sociodemographic variables.

Biological Sex: Women have a higher age-adjusted incidence of AD, partly due to longer lifespan but also influenced by sex-specific biological factors. The decline in neuroprotective oestrogens after menopause may affect BBB integrity and neuroinflammation. Emerging neuromodulatory and network-activity–based mechanisms influencing glymphatic clearance and homeostatic brain function have also been described in experimental models, highlighting the importance of neurophysiological regulation of clearance pathways [33]. Historically, preclinical research has over-relied on male animals, potentially obscuring these vital differences. Future mechanistic studies and clinical trials must be designed to actively investigate and account for sex as a biological variable.

Race, Ethnicity, and Social Determinants of Health: It is essential to distinguish between genetic ancestry, a biological factor, and race/ethnicity, which are social constructs with profound real-world consequences. Individuals from marginalised racial and ethnic groups (e.g., Black and Hispanic populations in the US and UK) often experience a higher burden of AD and related dementias. This disparity is not driven by biology but by structural inequities: higher prevalence of vascular risk factors (hypertension, diabetes) due to unequal access to healthcare and nutritious food, increased exposure to psychosocial stress and environmental toxins, lower educational attainment, and systemic biases in diagnosis and care [34].

The underrepresentation of these populations in neuroscience research from basic science using diverse cell lines to large clinical cohorts like the UK Biobank means that findings on BBB or glymphatic function may not generalise, perpetuating health inequities. Actively building trust, fostering community partnerships, and designing inclusive recruitment strategies are ethical and scientific imperatives.

Ethical Considerations in Diagnosis and Prevention

The emergence of sensitive biomarkers for early homeostatic dysfunction raises ethical concerns comparable to those associated with pre-symptomatic amyloid testing. Early detection may cause psychological distress, stigma, and discrimination in employment or insurance, particularly in the absence of effective preventive therapies. Equitable access to novel diagnostic tools and subsequent interventions is essential to prevent the widening of existing health disparities. Consequently, the neuroscience community should collaborate with bioethicists, patient advocacy groups, and the public to establish frameworks that safeguard autonomy, promote justice, and ensure that scientific advances benefit all sectors of society.

Final Considerations

Dysfunction of the blood–brain barrier and glymphatic system represents an early and fundamental disruption of cerebral homeostasis that significantly contributes to the pathogenesis of Alzheimer's disease [9]. Evidence from molecular studies, animal models, and human neuroimaging converges on a pathogenic cycle in which BBB permeability enables neurotoxic influx and inflammation, while impaired glymphatic clearance allows waste accumulation, further compromising vascular integrity. This axis is influenced by ageing, genetic risk, sleep, and systemic health, including emerging factors such as oral infection.

This integrative framework provides a more holistic and actionable understanding of Alzheimer's disease. It reconciles vascular and neurodegenerative models, offers mechanistic insight into established risk factors such as sleep apnoea and hypertension, and identifies a broad range of therapeutic targets, from sleep optimisation to lymphatic modulation. Future research priorities should include: (1) the development and standardisation of non-invasive biomarkers of BBB and glymphatic function; (2) longitudinal studies clarifying the temporal relationship between homeostatic failure and amyloid and tau pathology; (3) clinical trials evaluating lifestyle and pharmacological interventions aimed at stabilising this axis; and (4) a sustained commitment to inclusive research that accounts for sex, ancestry, and social determinants of health. Ultimately, preserving the brain's internal environment may be as critical as targeting pathological protein accumulation. By prioritising the systems that maintain cerebral homeostasis, more effective strategies may emerge to prevent, delay, or treat Alzheimer's disease, shifting care from a reactive to a proactive and preventive model. [4,9]

Declaration of Competing Interests

The authors declare no competing interests.

References

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. Alzheimers Dement. 2023 Apr;19(4):1598-1695.

2. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. Lancet. 2021 Apr;397(10284):1577-1590.

3. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell. 2019 Oct;179(2):312-339.

4. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, et al. Clearance systems in the brain-implications for Alzheimer disease. Nat Rev Neurol. 2015 Aug;11(8):457-470.

5. Gouveia-Freitas K, Bastos-Leite AJ. Perivascular spaces and brain waste clearance systems: relevance for neurodegenerative and cerebrovascular pathology. Neuroradiology. 2021 Oct;63(10):1581-1597.

6. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. Physiol Rev. 2019 Jan;99(1):21-78.

7. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. 2012 Aug;4(147):147ra111.

8. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature. 2020 May;581(7806):71-76.

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

10. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol. 2022 Apr;21(4):355-365.

11. Shah T, Leurgans SE, Mehta RI, Yang J, Galloway CA, de Mesy Bentley KL, et al. Arachnoid granulations are lymphatic conduits that communicate with bone marrow and dura-arachnoid stroma. J Exp Med. 2023 Feb 6;220(2):e20220618.

12. Mestre H, Hablitz LM, Xavier AL, Feng W, Zou W, Pu T, et al. Aquaporin-4-dependent glymphatic solute transport in the rodent brain. eLife. 2018;7:e40070.

13. Hablitz LM, Vinitsky HS, Sun Q, Stæger FF, Sigurdsson B, Mortensen KN, et al. Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. Sci Adv. 2020 Apr;6(17):eaav5447.

14. Ben-Nejma IRH, Keliris AJ, Vanreusel V, Ponsaerts P, Van der Linden A, Keliris GA. Altered dynamics of glymphatic flow in a mature-onset Tet-off APP mouse model of amyloidosis. Alzheimers Res Ther. 2023 Jan 28;15(1):23.

15. Szlufik S, Kopeć K, Szleszkowski S, Koziorowski D. Glymphatic system pathology and neuroinflammation as two risk factors of neurodegeneration. Cells. 2024 Feb 5;13(3):286.

16. 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;342(6156):373-377.

17. Eide PK, Vinje V, Pripp AH, Mardal KA, Ringstad G. Sleep deprivation impairs molecular clearance from the human brain. Brain. 2021 Mar;144(3):863-874.

18. Astara K, Tsimpolis A, Kalafatakis K, Vavougios GD, Xiromerisiou G, Dardiotis E, et al. Sleep disorders and Alzheimer's disease pathophysiology: the role of the glymphatic system. A scoping review. Mech Ageing Dev. 2024 Feb;217:111899.

19. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015 Jan;7(1):a020412.

20. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015 Jan;85(2):296-302.

21. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med. 2019 Feb;25(2):270-276.

22. Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, et al. Porphyromonas gingivalis in Alzheimer's disease brains: evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv. 2019 Jan;5(1):eaau3333.

23. Lei Y, Yang Y, Li X, Liu Y. The role of oral microbiome in the pathogenesis of Alzheimer's disease. Int J Oral Sci. 2023 Jan;15(1):3.

24. de Mello DNP, Leviski GL, de Souza Pacheco CB, Sánchez BO, Pedron IG. The Importance of Dental Neuroscience Highlighting the Connection Between Periodontal Disease and Alzheimer’s Disease. SVOA Dentistry. 2025;6(6):195-200.

25. Da Mesquita S, Fu Z, Kipnis J. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature. 2018 Aug;560(7717):185-191. doi:10.1038/s41586-018-0368-8.

26. Da Mesquita S, Papadopoulos Z, Dykstra T, Brase L, Farias FG, Wall M, et al. Meningeal lymphatics affect microglia responses and anti-Aβ immunotherapy. Nature. 2021 May;593(7858):255-260.

27. Salvador AFM, Abduljawad N, Kipnis J. Meningeal lymphatics in central nervous system diseases. Annu Rev Neurosci. 2024 Aug;47(1):323-344.

28. Taoka T, Naganawa S. Glymphatic imaging using MRI. J Magn Reson Imaging. 2022 Feb;55(2):325-345.

29. Hsu JL, Wei YC, Toh CH, Hsiao IT, Lin KJ, Yen TC, et al. Magnetic resonance images implicate that glymphatic alterations mediate cognitive dysfunction in Alzheimer disease. Ann Neurol. 2023 Jan;93(1):164-174.

30. Li Y, Wang L, Zhong J, Xu H, Han Y, Zuo C, et al. Impaired glymphatic function as a biomarker for subjective cognitive decline: an exploratory dual cohort study. Alzheimers Dement. 2024 Sep;20(9):6542-6555.

31. Zhang X, Wang Y, Jiao B, Wang Z, Shi J, Zhang Y, et al. Glymphatic system impairment in Alzheimer's disease: associations with perivascular space volume and cognitive function. Eur Radiol. 2024 Feb;34(2):1314-1323.

32. Zhou L, Butler TA, Wang XH, Xi K, Tanzi EB, Glodzik L, et al. Multimodal assessment of brain fluid clearance is associated with amyloid-beta deposition in humans. J Neuroradiol. 2024 Jun;51(4):101164.

33. Murdock MH, Yang CY, Sun N, Pao PC, Blanco-Duque C, Kahn MC, et al. Multisensory gamma stimulation promotes glymphatic clearance of amyloid. Nature. 2024 Mar;627(8002):149-156.

34. Manly JJ, Mayeux R. Ethnic differences in dementia and Alzheimer's disease. In: Anderson NB, Bulatao RA, Cohen B, editors. Critical perspectives on racial and ethnic differences in health in late life. Washington (DC): National Academies Press; 2004. p.95-141.