Perspective

Neuroscience

Combined Dysfunction of Glymphatic System and Mitochondria

A Noval Causal Contributor to Alzheimer's Disease?

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DOI: https://doi.org/10.15354/si.25.pe245
Funding: No funding source declared.
COI: The author declares no competing interest.
AI Declaration: The author affirms that artificial intelligence did not contribute to the process of preparing the work.

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder, is traditionally attributed to amyloid-beta (Aβ) accumulation and tau pathology. However, emerging evidence suggests that broader systemic dysfunctions may underlie or contribute to these hallmark features. Two biological systems—the glymphatic clearance pathway and mitochondrial energy metabolism—have independently gained attention for their roles in neurodegeneration. The glymphatic system facilitates cerebrospinal fluid (CSF) flow and waste clearance, including Aβ, while mitochondria regulate neuronal bioenergetics and redox homeostasis. By interlinking impaired clearance of neurotoxins and disrupted cellular energy metabolism, a vicious cycle may emerge that accelerates cognitive decline. We argue that integrated dysfunction could serve as an upstream event contributing to disease onset and progression. Understanding this combined pathology may not only redefine causality in AD but also offer novel therapeutic strategies targeting the neurovascular-energetic interface.

Keywords: Alzheimer's Disease; Glymphatic System; Mitochondria; Combination Dysfunction; Homeostasis

Science Insights, July 31, 2025; Vol. 47, No. 1, pp.1883-1887.

ALZHEIMER'S DISEASE (AD) continues to impose a formidable burden on healthcare systems worldwide, not only due to its prevalence but also due to its complex, multifactorial etiology (Han, 2025). For decades, the amyloid cascade hypothesis has dominated research and therapeutic design, positing that amyloid-beta (Aβ) accumulation initiates a pathogenic cascade leading to tau hyperphosphorylation, synaptic failure, and neuronal death (Fedele, 2023). Yet, despite robust efforts to target Aβ therapeutically, clinical trials have largely been disappointing, prompting a search for alternative or complementary mechanisms. In this context, two systems—the glymphatic clearance network and mitochondrial bioenerget-

ics—have emerged as critical but underappreciated contributors to the neuropathological landscape of AD(Gao et al., 2023). While each has been explored in isolation, it is the combined dysfunction of these two systems may serve as a more fundamental and perhaps causal contributor to disease pathogenesis.

The glymphatic system, a brain-wide perivascular pathway driven by cerebrospinal fluid (CSF) flux, was only recently characterized, revolutionizing our understanding of how the brain clears metabolic waste (Corbali & Levey, 2025). This system relies heavily on the proper functioning of astroglial aquaporin-4 (AQP4) water channels and the regular pulsing of cerebral arteries (Ding et al., 2023). In healthy brains, the glymphatic pathway is particularly active during sleep, enabling the clearance of solutes such as Aβ and tau. In aging and neurodegenerative conditions, however, glymphatic flow is significantly impaired. Reduced AQP4 polarization, vascular stiffening, and sleep disturbances—all common in elderly populations—can compromise glymphatic efficiency, resulting in the accumulation of neurotoxic proteins.

Simultaneously, the mitochondria—crucial for ATP production, calcium homeostasis, and reactive oxygen species (ROS) buffering—also undergo progressive dysfunction with aging (Silva et al., 2023). Mitochondrial deficits in AD are well-documented, encompassing impaired oxidative phosphorylation, increased mitochondrial DNA (mtDNA) mutations, and aberrant dynamics of fission and fusion. This energetic shortfall not only compromises synaptic function but also enhances neuronal susceptibility to oxidative stress. Moreover, dysfunctional mitochondria can release damage-associated molecular patterns (DAMPs) that activate neuroinflammation, creating a milieu conducive to neurodegeneration (Dhariwal et al., 2025).

Though the dysfunction of these systems has typically been studied in isolation, a growing body of evidence suggests their interdependence. The glymphatic system relies on adequate cerebrovascular health, which is intrinsically tied to mitochondrial energy production (Kylkilahti et al., 2021). Conversely, mitochondria are sensitive to the accumulation of toxic metabolites, such as Aβ and tau, which glymphatic pathways are responsible for clearing. This bidirectional relationship may be the fulcrum upon which cognitive decline pivots. If either system is disrupted, the burden on the other increases; when both are impaired, the result may be a pathogenic synergy, wherein waste clearance and cellular energy metabolism collapse simultaneously (Jiang-Xie et al., 2024).

Support for this integrated hypothesis comes from several domains. First, animal models with glymphatic impairment exhibit not only elevated Aβ levels but also signs of mitochondrial dysfunction, including increased oxidative stress and ATP depletion (Lin et al., 2022). Mice lacking functional AQP4 channels show accelerated Aβ accumulation and exacerbated neuroinflammation, which in turn hampers mitochondrial respiration (Kopeć et al., 2023). Sleep-deprived mice—another model of glymphatic dysfunction—show increased Aβ burden and mitochondrial swelling, underscoring the link between clearance deficits and cellular energy crises (Voumvourakis et al., 2023).

Second, mitochondrial dysfunction has been shown to impair perivascular pumping mechanisms necessary for glymphatic flow. Cerebral arterial pulsatility, partially maintained by mitochondrial-derived ATP in vascular smooth muscle cells, is essential for driving CSF through the perivascular space (Mestre et al., 2018). In mitochondrially impaired vessels, reduced pulsatility leads to stagnant glymphatic flow, thereby compromising waste clearance (Jukkola et al., 2024). Additionally, oxidative stress, which is a sign of problems with mitochondria, can cause issues in pericytes and astrocytes, making the glymphatic system work even worse (Kopeć et al., 2023).

Third, both systems appear to converge on the neuroinflammatory axis. Dysfunctional mitochondria release pro-inflammatory DAMPs such as mtDNA and cardiolipin, while impaired glymphatic clearance leads to the accumulation of extracellular inflammatory mediators (Cai et al., 2024). These processes synergize to activate microglia and astrocytes, creating a chronic inflammatory environment that amplifies neuronal injury. Moreover, inflammatory cytokines such as IL-1β and TNF-α have been shown to downregulate AQP4 expression and inhibit mitochondrial respiration, forming a feedback loop of mutual deterioration (Xu et al., 2015).

Clinically, this convergence could explain why AD manifests with such diverse neuropathological features—amyloid plaques, tau tangles, neuroinflammation, vascular compromise, and synaptic loss—all within a single disease continuum. Traditional linear models of causality may fail to account for this complexity, but a systems-based approach recognizing the dual failure of clearance and bioenergetics might (Bredesen et al., 2023). This integrated model also resonates with epidemiological observations: sleep deprivation, chronic vascular disease, and metabolic syndrome are all risk factors for AD, and each can independently impair both glymphatic and mitochondrial function.

From a diagnostic standpoint, this hypothesis encourages a broader set of biomarkers. For instance, MRI-based imaging of glymphatic flow (e.g., DTI-ALPS) and PET imaging of mitochondrial metabolism could together provide a more nuanced assessment of early AD risk (Johnson et al., 2023). Moreover, CSF analysis for mitochondrial DAMPs or impaired lactate clearance may offer additional clues. Importantly, these biomarkers would reflect upstream dysfunction rather than downstream consequence, potentially allowing for earlier intervention.

Therapeutically, this perspective opens novel avenues. Most current AD therapies target amyloid deposition or neurotransmission, often too late in the disease course. Interventions aimed at enhancing glymphatic function—such as improving sleep quality, optimizing AQP4 function, or using low-frequency ultrasound to stimulate perivascular flow—may augment clearance before pathological buildup (Kylkilahti et al., 2021). Simultaneously, therapies that bolster mitochondrial health—like NAD+ precursors, mitochondrial antioxidants, or metabolic modulators—could restore neuronal resilience (Shinn & Lagalwar, 2021). Combination therapies targeting both systems might synergistically halt or reverse early-stage disease.

Moreover, lifestyle interventions gain a mechanistic rationale under this hypothesis. Regular exercise, intermittent fasting, and cognitive enrichment have all been shown to support both glymphatic function and mitochondrial health. Exercise increases cerebral blood flow and AQP4 polarization, while

also stimulating mitochondrial biogenesis and mitophagy (Yoo et al., 2025). Sleep hygiene improves glymphatic clearance and reduces oxidative stress (Reddy & Werf, 2020). These findings suggest that non-pharmacological approaches, long known to mitigate cognitive decline, may be particularly effective because they simultaneously target both dysfunctional systems.

Still, many questions remain. It is unclear whether glymphatic or mitochondrial dysfunction typically occurs first, or whether their deterioration is truly synchronous. Genetic factors, such as APOE4, may differentially influence each system. For instance, APOE4 has been associated with impaired AQP4 distribution and mitochondrial respiratory chain deficits (Moreira et al., 2009). Does APOE4 confer risk precisely because it destabilizes the glymphatic-mitochondrial axis? Longitudinal human studies integrating genetic, imaging, and molecular data are needed to resolve these dynamics.

Another important consideration is the heterogeneity of AD. Not all patients present with the same constellation of symptoms or pathology, and it is possible that glymphatic-mitochondrial dysfunction defines a particular subtype of the disease. For instance, individuals with prominent vascular comorbidities may exhibit more severe glymphatic impairment, while those with metabolic syndrome may show greater mitochondrial compromise (San-Millán, 2023). Personalized medicine approaches could benefit from stratifying patients according to their dominant pathophysiological profile.

Finally, the concept of combined system failure also has implications for other neurodegenerative disorders. Parkinson's disease, Huntington's disease, and even normal aging may involve analogous glymphatic-mitochondrial disruptions (Gao et al., 2023). The notion of a neurovascular-metabolic interface as a common denominator in neurodegeneration invites a rethinking of disease classification and cross-condition therapeutic strategies.

In conclusion, while Alzheimer's disease remains a daunting clinical challenge, reframing its pathogenesis through the lens of combined glymphatic and mitochondrial dysfunction offers a more integrated and potentially causal model. Rather than viewing protein aggregation as the primary trigger, we propose that impaired waste clearance and cellular energetics form a vicious cycle that initiates and sustains neurodegeneration. This dual-system perspective harmonizes disparate findings across neuropathology, neuroimaging, and systemic physiology. It encourages a paradigm shift toward systems neuroscience, wherein interconnected biological networks—not isolated pathways—dictate health and disease. If validated, this model could pave the way for earlier diagnosis, multi-targeted therapeutics, and personalized prevention strategies that strike at the core of the disease process.■

Received: March 28, 2025 | Revised: May 20, 2025 | Accepted: June 02, 2025

References

Bredesen, D. E., Toups, K., Hathaway, A., Gordon, D., Chung, H., Raji, C., Boyd, A., Hill, B. D., Hausman-Cohen, S., Attarha, M., Chwa, W. J., Kurakin, A., & Jarrett, M. (2023). Precision Medicine Approach to Alzheimer's disease: rationale and implications. Journal of Alzheimer S Disease, 96(2), 429–437. DOI: https://doi.org/10.3233/jad-230467

Cai, Y., Zhang, Y., Leng, S., Ma, Y., Jiang, Q., Wen, Q., Ju, S., & Hu, J. (2024). The relationship between inflammation, impaired glymphatic system, and neurodegenerative disorders: A vicious cycle. Neurobiology of Disease, 192, 106426. DOI: https://doi.org/10.1016/j.nbd.2024.106426

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

Dhariwal, R., Jain, M., Mir, Y. R., Singh, A., Jain, B., Kumar, P., Tariq, M., Verma, D., Deshmukh, K., Yadav, V. K., & Malik, T. (2025). Targeted drug delivery in neurodegenerative diseases: the role of nanotechnology. Frontiers in Medicine, 12. DOI: https://doi.org/10.3389/fmed.2025.1522223

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

Fedele, E. (2023). Anti-Amyloid therapies for Alzheimer's Disease and the Amyloid cascade hypothesis. International Journal of Molecular Sciences, 24(19), 14499. DOI: https://doi.org/10.3390/ijms241914499

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

Han, L. (2025). AD-Diff: enhancing Alzheimer's disease prediction accuracy through multimodal fusion. Frontiers in Computational Neuroscience, 19. DOI: https://doi.org/10.3389/fncom.2025.1484540

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

Johnson, E. C. B., Bian, S., Haque, R. U., Carter, E. K., Watson, C. M., Gordon, B. A., Ping, L., Duong, D. M., Epstein, M. P., McDade, E., Barthélemy, N. R., Karch, C. M., Xiong, C., Cruchaga, C., Perrin, R. J., Wingo, A. P., Wingo, T. S., Chhatwal, J. P., Day, G. S., . . . Ringman, J. (2023). Cerebrospinal fluid proteomics define the natural history of autosomal dominant Alzheimer's disease. Nature Medicine, 29(8), 1979–1988. DOI: https://doi.org/10.1038/s41591-023-02476-4

Jukkola, J., Kaakinen, M., Singh, A., Moradi, S., Ferdinando, H., Myllylä, T., Kiviniemi, V., & Eklund, L. (2024). Blood pressure lowering enhances cerebrospinal fluid efflux to the systemic circulation primarily via the lymphatic vasculature. Fluids and Barriers of the CNS, 21(1). DOI: https://doi.org/10.1186/s12987-024-00509-9

Kopeć, K., Szleszkowski, S., Koziorowski, D., & Szlufik, S. (2023). Glymphatic system and mitochondrial dysfunction as two crucial players in pathophysiology of neurodegenerative disorders. International Journal of Molecular Sciences, 24(12), 10366. DOI: https://doi.org/10.3390/ijms241210366

Kylkilahti, T. M., Berends, E., Ramos, M., Shanbhag, N. C., Töger, J., Bloch, K. M., & Lundgaard, I. (2021). Achieving brain clearance and preventing neurodegenerative diseases—A glymphatic perspective. Journal of Cerebral Blood Flow & Metabolism, 41(9), 2137–2149. DOI: https://doi.org/10.1177/0271678x20982388

Lin, X., Fan, Y., Zhang, F., & Lin, Y. (2022). Cerebral microinfarct is emergency consequence of Alzheimer's disease: a new insight into development of neurodegenerative diseases. International Journal of Biological Sciences, 18(4), 1569–1579. DOI: https://doi.org/10.7150/ijbs.55419

Mestre, H., Tithof, J., Du, T., Song, W., Peng, W., Sweeney, A. M., Olveda, G., Thomas, J. H., Nedergaard, M., & Kelley, D. H. (2018). Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nature Communications, 9(1). DOI: https://doi.org/10.1038/s41467-018-07318-3

Moreira, P. I., Zhu, X., Wang, X., Lee, H., Nunomura, A., Petersen, R. B., Perry, G., & Smith, M. A. (2009). Mitochondria: A therapeutic target in neurodegeneration. Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease, 1802(1), 212–220. DOI: https://doi.org/10.1016/j.bbadis.2009.10.007

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

San-Millán, I. (2023). The key role of mitochondrial function in health and disease. Antioxidants, 12(4), 782. DOI: https://doi.org/10.3390/antiox12040782

Shinn, L. J., & Lagalwar, S. (2021). Treating Neurodegenerative Disease with Antioxidants: Efficacy of the Bioactive Phenol Resveratrol and Mitochondrial-Targeted MitoQ and SkQ. Antioxidants, 10(4), 573. DOI: https://doi.org/10.3390/antiox10040573

Silva, J., Alves, C., Soledade, F., Martins, A., Pinteus, S., Gaspar, H., Alfonso, A., & Pedrosa, R. (2023). Marine-Derived Components: Can they be a potential therapeutic approach to Parkinson's disease? Marine Drugs, 21(8), 451. DOI: https://doi.org/10.3390/md21080451

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

Xu, Z., Xiao, N., Chen, Y., Huang, H., Marshall, C., Gao, J., Cai, Z., Wu, T.,

Hu, G., & Xiao, M. (2015). Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain Aβ accumulation and memory deficits. Molecular Neurodegeneration, 10(1). DOI: https://doi.org/10.1186/s13024-015-0056-1

Yoo, R., Kim, J., Moon, H. Y., Park, J. Y., Cheon, S., Shin, H., Han, D., Kim, Y., Park, S., & Choi, S. H. (2025). Long-term physical exercise facilitates putative glymphatic and meningeal lymphatic vessel flow in humans. Nature Communications, 16(1). DOI: https://doi.org/10.1038/s41467-025-58726-1