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Lymphatic Surgery to Improve Brain Function – Preclinical and Clinical Evidence and Potential Robotic Applications

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Background

The central nervous system (CNS) was historically considered to lack lymphatic drainage. However, the recent (re)-identification of meningeal lymphatic vessels (MLVs) and the glymphatic system has significantly advanced our understanding of cerebrospinal fluid (CSF) dynamics and neuroimmune regulation. Emerging clinical observations suggest that cervical lymphatic microsurgery may improve neurological function, particularly in neurodegenerative disorders. Nonetheless, robust preclinical and clinical evidence is lacking to support its efficacy.

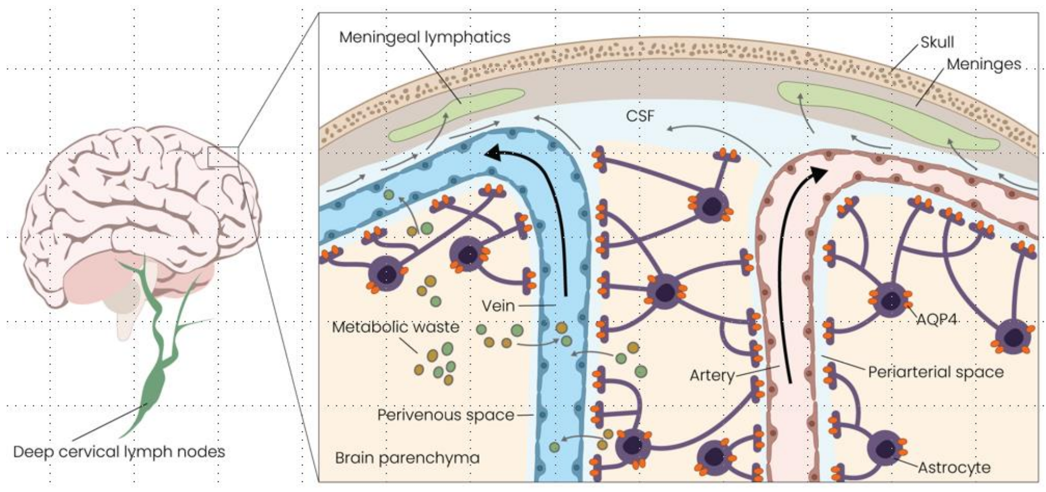

Fig. 1.The glymphatic and meningeal lymphatic pathways in central nervous system clearance. Facilitated by astrocytic aquaporin-4 (AQP4) water channels, CSF enters the brain parenchyma, mixing with interstitial fluid (ISF) and facilitating metabolic waste clearance.

Methods

A systematic review was conducted using PubMed, EMBASE, Web of Science, and Scopus to identify animal studies investigating interventions aimed at enhancing meningeal lymphatic drainage in models of neurological disease. Inclusion criteria were limited to peer-reviewed, English-language studies utilizing animal models to examine MLV function in brain disorders. Additionally, clinical outcomes from a previous cases involving lymphatic reconstruction in the deep cervical region and face were retrospectively analyzed for potential neurological effects.

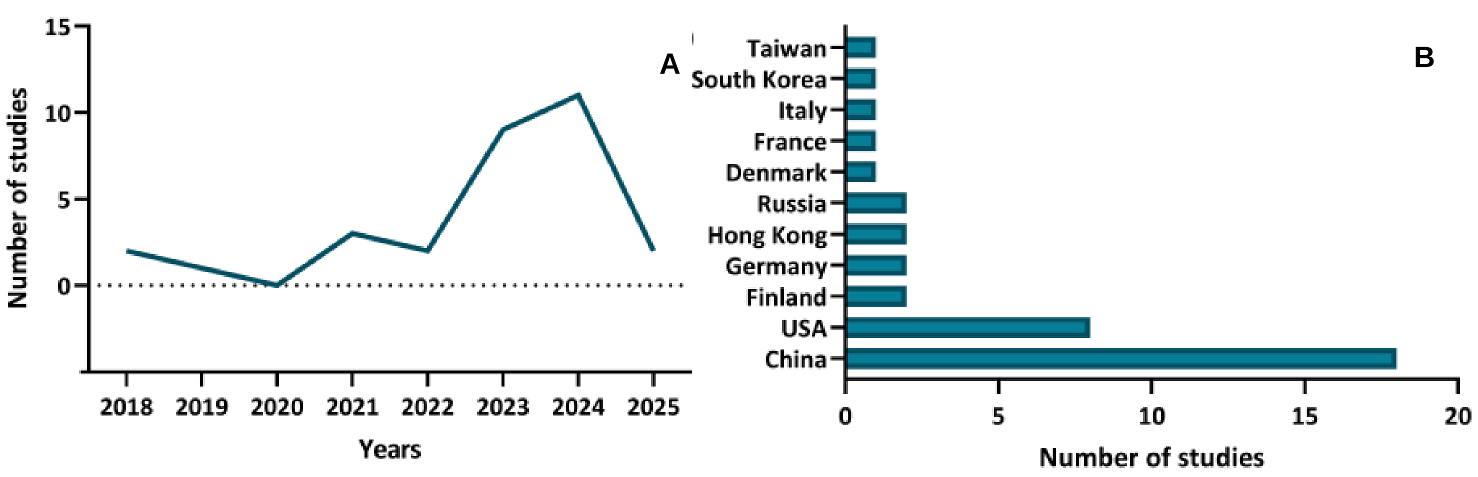

Fig. 2 (A) **Number of studies published per year**, showing trends over time. (B) **Number of studies conducted by country**, highlighting the geographic distribution of research activity.

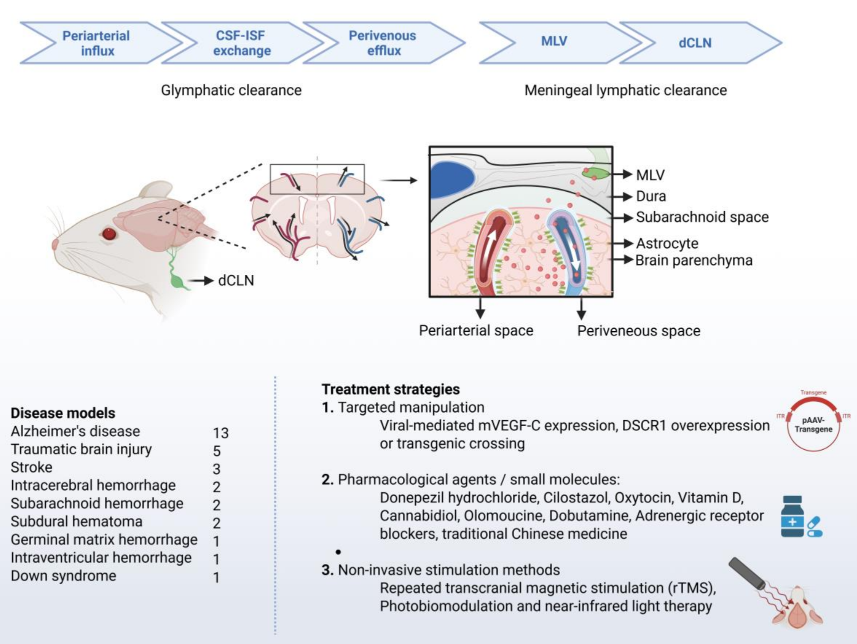

Fig. 3. Graphical overview of the preclinical studies, illustrating the treatments and interventions tested across different animal models. Various treatment methods were used to enhance meningeal lymphatic drainage, including VEGF-C administration, light-based therapies, pharmacological agents, genetic interventions, biomaterial-based delivery systems, and noninvasive stimulation methods. The outcome measures were mainly focused on histopathological changes, behavioral and cognitive performance, imaging-based assessment of lymphatic drainage, and analysis of neuroinflammatory markers.

Results

The review identified multiple experimental strategies to enhance MLV function, including VEGF-C administration, photobiomodulation, pharmacological agents, and genetic modulation. These interventions consistently improved MLV structure and function, promoted clearance of neurotoxic proteins such as amyloid-β, reduced neuroinflammation, and enhanced cognitive and motor performance in animal models of neurodegeneration. No preclinical studies evaluating the direct impact of cervical lymphatic surgery on brain function were identified. In our patient collective a lymphovenous anastomosis performed in the deep neck in May 2023 resulted in sustained neurological and cognitive improvement over a two-year follow-up in a patient with 13q deletion syndrome. Robotic-assisted LVA of 0.2 mm facial lymphatics to treat severe eyelid edema showed beneficial effects on memory and visual function 1 month postoperatively.

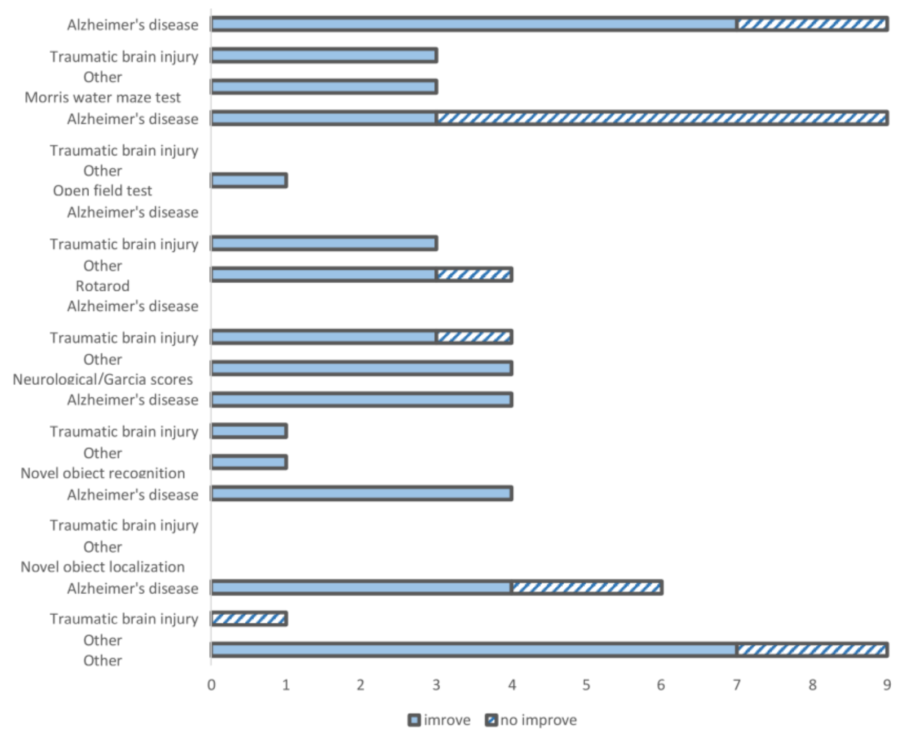

Fig. 4 Summary of behavioral improvements reported across disease models and behavioral tests. Alzheimer's disease (AD; n = 13 studies), traumatic brain injury (TBI; n = 5 studies), and a combined "other" category (n = 1–3 studies each, including stroke, hemorrhages, subdural hematoma, and Down syndrome). Behavioral tests that were applied in only 1–2 studies were grouped together under "Other" and include the hanging wire test, mesh hanging test, negative geotaxis, righting reflex, foot fault test, laterality index, Y maze, beam walk score, round stick balance score, and string suspension grip score.

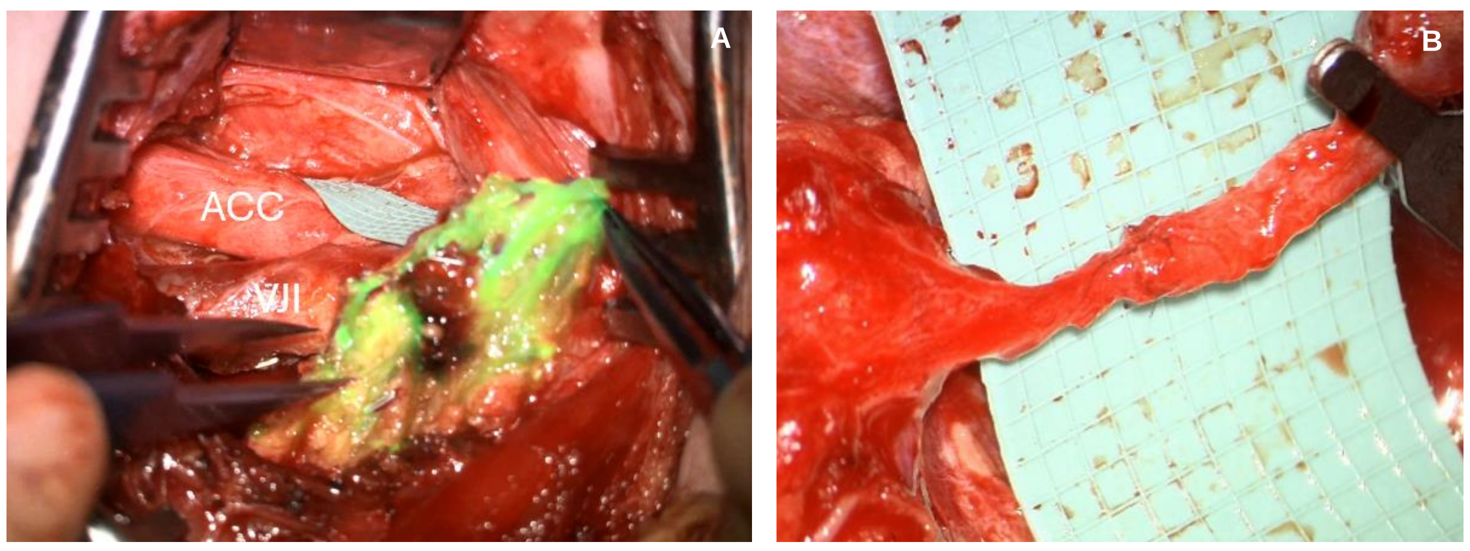

Fig. 5 (A) **Intraoperative image** after intranodal ICG application showing deep cervical lymphatic tissue in level II, III and V of the left neck dorsal and caudal to the common carotid artery (ACC) and internal jugular vein (VJI). (B) Three large lymphatic collectors were anastomosed to branches of the external jugular vein (dcLVAs).

Conclusion

These findings highlight the critical role of meningeal lymphatic drainage in neurological health and support further investigation into its therapeutic modulation. While current animal models provide compelling evidence for enhancing MLV function, clinical application remains underresearched. Deep cervical lymphatic reconstruction, potentially facilitated by robotic-assisted micro- and supermicrosurgery, may offer a novel therapeutic approach for neurodegenerative and neurodevelopmental disorders. Further mechanistic and translational studies are warranted.

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Von Reibnitz et al., Plast Reconstr Surg Glob Open 2025;13(8):e7030. Kollarik, Humer et al. Cell Mol Neurobiol. 2025 (in press), Watson et al., Plast Reconstr Surg Glob Open 2025 (in press).
Conflict of interest: NL acts as consultant and scientific advisor for Medical Microinstruments (MMI).