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The Lymphatic System of the Brain (Glymphatic and Meningeal Lymphatics): Implications for Waste Clearance and Immunosurveillance

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Abstract

For decades, the brain was considered an immune-privileged organ lacking a traditional lymphatic system; however, the recent discoveries of the glymphatic pathway and meningeal lymphatic vessels have fundamentally reshaped our understanding of central nervous system (CNS) waste clearance and immune surveillance. This review aims to highlight the current state of knowledge on these systems, emphasizing their integrated role in neural health and disease. We first detail the anatomy and physiology of the glymphatic and meningeal lymphatic components, outlining their distinct and collaborative functions. We then explore the mechanisms of glymphatic solute transport and its regulation by factors such as sleep, respiration, and arterial pulsatility. The discussion extends to the structural organization and systemic connections of meningeal lymphatic vessels, highlighting their role in immune cell trafficking. A summary of advanced neuroimaging techniques, from magnetic resonance to optical methods, is provided to illustrate how these pathways can be visualized and assessed *in vivo*. Furthermore, we examine clinical evidence linking dysfunction in these clearance systems to neurodegenerative, cerebrovascular, and neuroinflammatory disorders. Finally, we survey emerging therapeutic strategies that target these pathways to enhance waste removal and modulate neuroimmunity. Future research should focus on elucidating the precise molecular crosstalk within this neuro-lymphatic interface and translating non-invasive modulation techniques into effective clinical interventions for a range of neurological conditions

Keywords: Aquaporin-4, Cerebrospinal fluid, Glymphatic system, Immunosurveillance, Meningeal lymphatic vessels, Neurodegeneration, Neuroimaging, Waste clearance

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Introduction

The lymphatic system of the brain, encompassing the glymphatic pathway and meningeal lymphatic vessels, has emerged as a critical component in maintaining cerebral homeostasis through waste clearance and immunosurveillance [1-10]. Recent advances, as summarized in multiple studies, have significantly expanded our understanding of these systems' anatomy, physiology, and their implications in neurological health and disease (Figure 1) [6].

The glymphatic system, a perivascular network facilitating the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF), plays a pivotal role in removing metabolic waste products from the brain parenchyma. Yankova et al. [3] highlights the recent characterization of the glymphatic pathway and its close relationship with meningeal lymphatic vessels, emphasizing their integrated function in CNS clearance. The system's reliance on astrocytic aquaporin-4 channels underscores its cellular basis, facilitating fluid movement along perivascular spaces [11]. This pathway enables the brain to efficiently clear neurotoxic substances such as amyloid-β, which is particularly relevant in neurodegenerative diseases like Alzheimer's disease. Complementing the glymphatic pathway, meningeal lymphatic vessels provide an anatomical route for waste drainage from the CNS to peripheral lymph nodes. The discovery of these vessels has refined the traditional view that the brain lacks a lymphatic system, revealing a specialized network that communicates with systemic immune responses [12]. Imaging techniques, including diffusion tensor imaging along the perivascular space (DTI-ALPS), have been instrumental in visualizing these pathways and assessing their function *in vivo* [13]. Zhang et al. [13] also discusses the potential of enlarged perivascular spaces as neuroimaging biomarkers, reflecting alterations in glymphatic and meningeal lymphatic function in various neurological conditions.

The functional dynamics of these systems are influenced by physiological factors such as arterial pulsatility, respiration, and neural activity. For instance, Ozturk et al. [14] demonstrated that positive airway pressure enhances CSF flow and glymphatic transport,

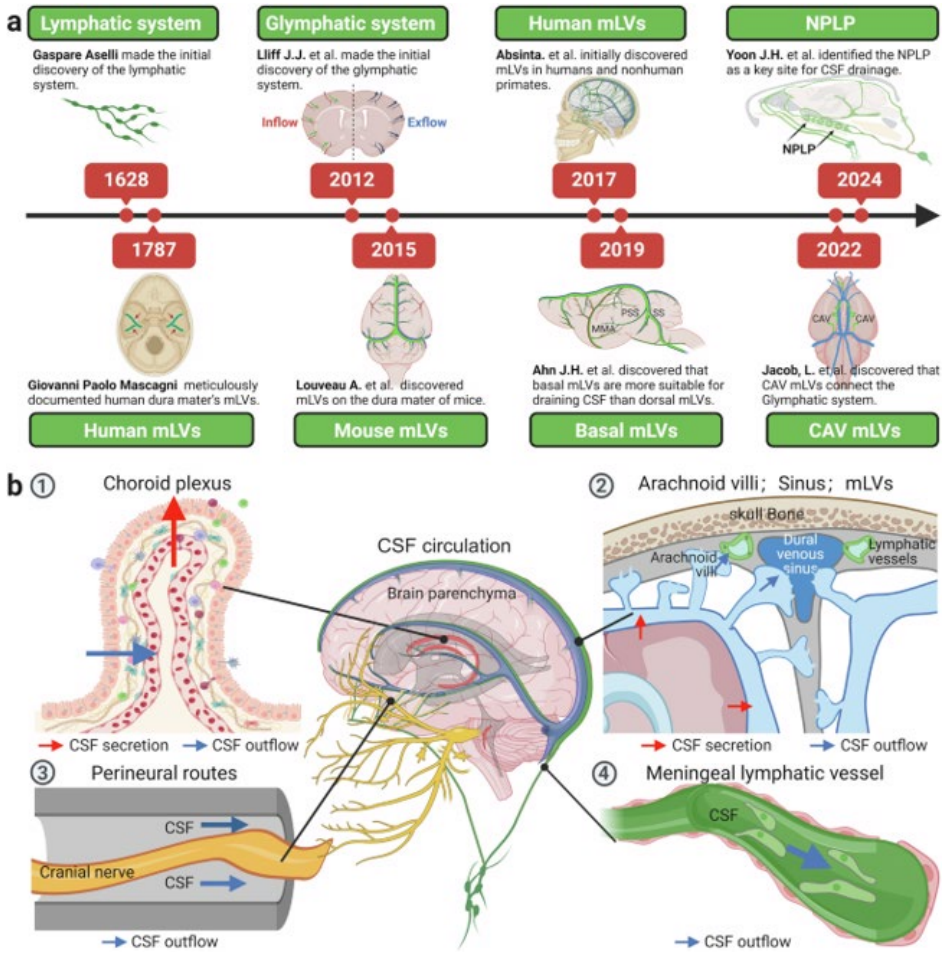

Figure 1: (a) A chronological overview of pivotal discoveries and significant milestones in the study of meningeal lymphatic vessels and their role in brain fluid drainage. **(b)** The flow and circulation of CSF [6].

indicating that respiratory support can modulate brain waste clearance. Similarly, physical exercise has been shown to promote meningeal lymphatic flow, suggesting lifestyle factors can influence these clearance pathways [15]. These findings underscore the importance of systemic physiological states in regulating CNS lymphatic function. Pathological conditions, including neuroinflammation, stroke, and neurodegenerative diseases, are associated with impaired glymphatic and meningeal lymphatic function. Hsu et al. [16] propose that neuroinflammation-driven lymphangiogenesis may be a double-edged sword, potentially offering therapeutic targets but also contributing to disease progression. In particular, the accumulation of waste products and immune cells due to dysfunctional clearance systems can exacerbate neurodegeneration. Bah et al. [17] emphasize that aging-related decline in these pathways correlates with increased susceptibility to dementia, including Alzheimer's disease, highlighting the systems' relevance in age-related neurovascular and neurodegenerative pathologies.

The clinical implications of these systems extend to cerebrovascular diseases such as stroke and small vessel disease. Wang et al. [18] review how lymphatic drainage pathways influence brain injury outcomes post-ischemia, suggesting that enhancing lymphatic function could be a novel therapeutic strategy. Similarly, Tian et al. [19] provides a framework linking glymphatic and meningeal lymphatic dysfunction to the progression of cerebral small vessel disease, which is a major contributor to vascular cognitive impairment. These insights point toward the potential of targeting lymphatic pathways to mitigate disease progression and improve neurological outcomes. Emerging therapeutic approaches aim to modulate these clearance systems. Salehpour et al. [20] discuss photobiomodulation therapy as a promising method to augment glymphatic function, particularly in removing amyloid-β. Additionally, Murdock et al. [21] demonstrates that multisensory gamma stimulation can enhance glymphatic clearance, offering a non-invasive intervention to facilitate waste removal. Pharmacological and mechanical interventions, such as continuous positive airway pressure, have also been shown to improve CSF flow and glymphatic transport [14], further emphasizing the therapeutic potential of modulating these pathways.

The cellular components involved in these systems are integral to their function. Smyth et al. [22] detail the cellular contributions, including glial cells and immune cells, to waste clearance processes. The interaction between neural cells, such as microglia and astrocytes, and the lymphatic structures underscores a complex neuroimmune interface that regulates both waste removal and immune surveillance [23]. This interplay is crucial for understanding how dysfunctions in cellular mechanisms contribute to disease states.

In summary, the recent research underscores the significance of the brain's lymphatic system, comprising the glymphatic pathway and meningeal lymphatics, in maintaining neural health through efficient

waste clearance and immune regulation. These systems are dynamically regulated by physiological factors and are susceptible to impairment in various neurological diseases. Advances in imaging, physiological modulation, and cellular understanding are paving the way for novel therapeutic strategies aimed at restoring or enhancing these clearance pathways, with promising implications for neurodegenerative, cerebrovascular, and neuroinflammatory conditions. As research continues to elucidate the detailed mechanisms and systemic interactions, the lymphatic system of the brain stands out as a vital frontier in neuroscience and clinical neurology.

Anatomy and Physiology of the Brain's Lymphatic Systems

The anatomy and physiology of the brain's lymphatic systems are fundamental to understanding their roles in waste clearance and immunosurveillance, which are critical processes for maintaining neural health and preventing neurological diseases [24-30]. Recent literature provides comprehensive insights into the structural components, functional mechanisms, and physiological significance of these systems, emphasizing their interconnectedness and importance in brain homeostasis (Table 1).

The glymphatic system, a recently characterized pathway, is central to the brain's waste clearance mechanism. Zhang et al. [13] offers an in-depth review of the basic anatomy and physiology of the glymphatic system, highlighting its role in facilitating the movement of CSF through perivascular spaces to clear metabolic waste products from the brain parenchyma. This system relies on the unique architecture of perivascular spaces, which serve as conduits for fluid exchange, driven by arterial pulsatility and astroglial water channels, particularly aquaporin-4. The glymphatic pathway thus acts as a clearance highway, removing neurotoxic substances such as amyloid-β, which are implicated in neurodegenerative diseases. Complementing the glymphatic system, meningeal lymphatic vessels have been identified as crucial anatomical structures that facilitate the drainage of waste and immune cells from the CNS. Resolving the mysteries of brain clearance, recent studies emphasize that these lymphatic vessels are located within the meninges, particularly in the dura mater, and connect to deep cervical lymph nodes, providing a pathway for immune surveillance and waste removal (Figure 2) [8]. The anatomical connections of these meningeal lymphatics have been further elucidated, revealing their role in maintaining water and ion balance within the ISF, as well as in the reabsorption of macromolecular solutes [6].

The components of the lymphatic system, including lymphatic vessels, lymph nodes, and lymphoid organs, are integral to this clearance process. Null et al. [31] describes these components, emphasizing that lymphatic vessels form a network that collects lymph from tissues and directs it toward lymph nodes, where immune responses can be initiated or modulated. In the context of the brain, the meningeal lymphatic vessels serve as the primary drainage route, linking the CNS to peripheral lymphatic structures and facilitating immune cell trafficking. Physiologically, the lymphatic drainage system supports critical functions such as fluid homeostasis, immune surveillance, and waste clearance. The physiology of glymphatic solute transport and waste clearance has been extensively studied, revealing that the efficiency of these processes declines with aging, contributing to the accumulation of neurotoxic waste and increased vulnerability to neurodegenerative conditions. The lymphatic system's role in immune surveillance is underscored by its capacity to transport immune cells and antigens from the CNS to lymph nodes, enabling immune responses to be mounted against pathogens or abnormal proteins [32].

Recent advances have also highlighted the dynamic nature of these systems. The brain's drainage pathways are not static; they respond to physiological states and pathological conditions. For instance, the decline in meningeal lymphatic function has been associated with impaired waste clearance and increased risk of neurological disorders such as multiple sclerosis and Alzheimer's disease [32]. The three-dimensional modeling of the brain's drainage system further illustrates how CSF, ISF, and meningeal lymphatic flows form an integrated network that supports both waste removal and immune surveillance [23]. Moreover, the meningeal lymphatic vessels participate actively in CNS immunosurveillance, facilitating the trafficking of immune cells and antigens between the brain and peripheral lymphatic tissues.

Table 1: Summary of brain lymphatic system components and functions.

System	Anatomy	Physiology/Functional role	Key components
Glymphatic system	• Perivascular spaces surrounding arteries and veins • Dependent on astrocytic end feet lining vasculature • Linked to CSF-ISF exchange	• Facilitates convective flow of CSF through brain parenchyma • Removes metabolic waste (e.g., amyloid-β, tau) • Enhanced during sleep • Driven by arterial pulsatility and aquaporin-4 channels	• Aquaporin-4 channels on astrocytic end feet • Astrocytes, perivascular macrophages • Sleep/wake cycles modulate activity
Meningeal lymphatic vessels	• Located within the meninges (especially dura mater) • Connect to deep cervical lymph nodes • Associated with skull bone marrow channels	• Drains CSF and ISF waste products from CNS to peripheral lymph nodes • Facilitates immune cell trafficking and antigen presentation • Supports immunosurveillance	• Lymphatic endothelial cells • Vascular endothelial growth factor C (VEGF-C) signaling for lymphangiogenesis • Skull-meningeal connections for immune exchange
Integrated brain clearance network	• Glymphatic (influx) + meningeal lymphatics (efflux) • Connected via perivenous spaces, bridging veins, cranial nerves	• Coordinated waste clearance: glymphatic removes intraparenchymal waste; meningeal lymphatics export it systemically • Maintains fluid and ion homeostasis • Regulates neuroimmune interface	• Aquaporin-4-dependent fluid movement • Neuro-glia-vascular unit interactions • Immune cells (microglia, T cells, macrophages)
Regulatory factors	• Physiological: arterial pulsatility, respiration, neural activity • Lifestyle: sleep, exercise, diet • Pathological: aging, neuroinflammation, vascular disease	• Sleep promotes glymphatic flow • Exercise enhances meningeal lymphatic drainage • Aging and disease impair clearance efficiency	• Circadian rhythms • Autonomic and respiratory modulation • Inflammatory mediators (cytokines, chemokines)
Imaging biomarkers	• MRI-based: DTI-ALPS index, perivascular space volume fraction (PVSVF) • Positron emission tomography (PET) imaging for amyloid clearance • Optical/photoacoustic imaging in models	• Non-invasive assessment of glymphatic and meningeal lymphatic function • Correlates with cognitive decline, amyloid burden, disease progression	• Enlarged perivascular spaces • Free water fraction in white matter (FW-WM) • ALPS index as proxy for glymphatic activity

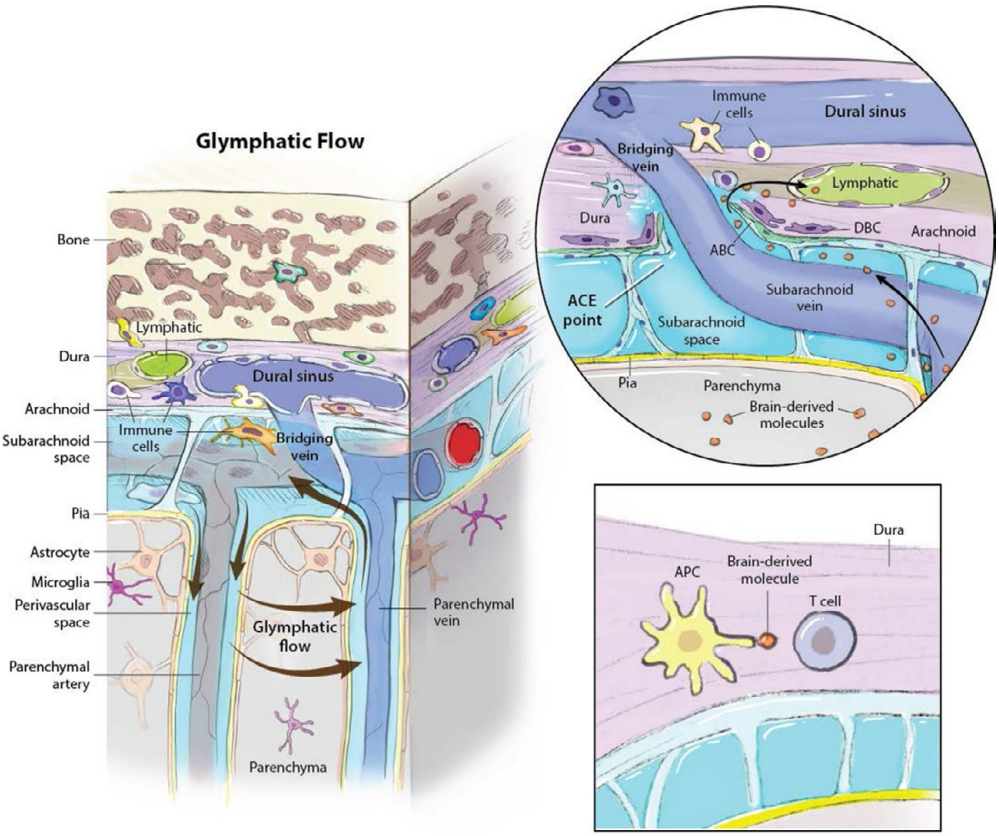

Figure 2: Immune surveillance at the brain's borders [8].

Leveraging these pathways has potential therapeutic implications, especially in neuroinflammatory and neurodegenerative diseases. Experimental studies demonstrate that enhancing meningeal lymphatic function can improve waste clearance and modulate immune responses, offering promising avenues for intervention [33].

In summary, the anatomy of the brain's lymphatic systems encompasses the glymphatic pathways within the brain parenchyma and the meningeal lymphatic vessels located in the meninges. Their physiology involves fluid movement driven by arterial pulsatility, astroglial water channels, and lymphatic vessel contractility, which collectively facilitate waste clearance and immune cell trafficking. The decline of these systems with age or disease underscores their importance in maintaining neural health and preventing pathology. Understanding these interconnected structures and functions provides a foundation for developing targeted therapies aimed at enhancing brain waste clearance and immunosurveillance, thereby addressing a range of neurological disorders

The Glymphatic Pathway: Mechanisms and Functional Role

The glymphatic pathway has emerged as a critical component in understanding the mechanisms of waste clearance and immunosurveillance within the CNS [34-41]. This system, primarily characterized by its reliance on glial cells and perivascular channels, facilitates the removal of metabolic waste products, including neurotoxic proteins such as amyloid-β, thereby maintaining neural homeostasis and potentially influencing neurodegenerative and neurovascular diseases.

Fundamentally, the glymphatic system operates through a network of perivascular spaces that enable the convective flow of CSF through the brain parenchyma. Wostyn et al. [42] highlighted that recent advances in molecular biology and neuroimaging have revealed that CSF physiology is more complex than previously understood, with the glymphatic pathway playing a pivotal role in this intricate system. The pathway's function involves the movement of CSF along periarterial spaces, which then exchanges with ISF, facilitating the clearance of solutes and metabolic waste. This process is believed to be driven by arterial pulsatility and is heavily dependent on the presence and polarization of aquaporin-4 channels on astrocytic end feet, which regulate water fluxes necessary for effective waste removal [43]. The functional role of the glymphatic system extends beyond waste clearance to encompass immunosurveillance. The clearance of potentially harmful proteins and cellular debris is essential for preventing neuroinflammation and maintaining immune homeostasis within the CNS. The anatomical and physiological features of the perivascular unit, which includes the glymphatic pathway, are crucial for understanding how immune cells and signaling molecules traverse the CNS environment. Troili et al. [44] emphasized that the perivascular unit serves as an anatomical crossroads where immune, vascular, and nervous systems interact, highlighting its importance in neuroinflammatory processes and neurodegenerative disorders.

Sleep has been identified as a significant modulator of glymphatic function. Christensen et al. [45] discussed the hypothesis that sleep facilitates the clearance of metabolic waste via the glymphatic pathway, with reduced glymphatic activity observed during wakefulness. Reduced advection and impaired solute transport during sleep

deprivation have been demonstrated through advanced imaging techniques, such as DTI-ALPS, which quantifies glymphatic activity *in vivo* [46]. Vinje et al. [47] further supported this by showing that sleep deprivation diminishes solute clearance, emphasizing the importance of sleep in maintaining glymphatic efficiency. The structural components underpinning the glymphatic system, particularly aquaporin-4 channels, are vital for its proper functioning. Liu et al. [43] demonstrated that impairment of aquaporin-4, especially following events like subarachnoid hemorrhage, leads to decreased ISF drainage and accumulation of neurotoxic substances. Similarly, the polarization of aquaporin-4 channels on astrocytic end feet is crucial; disruption of this polarization, as shown in studies involving dystrophin deficiency, results in glymphatic dysfunction and subsequent brain edema [48]. These findings underscore the importance of astrocytic water channels in facilitating effective waste clearance.

Pathological conditions such as neurodegenerative diseases, stroke, and metabolic syndromes have been linked to glymphatic impairment. For instance, in Alzheimer's disease, the accumulation of amyloid-β is associated with reduced glymphatic clearance, which can be quantified using magnetic resonance imaging (MRI)-based biomarkers like DTI-ALPS [46]. Moreover, the response of the glymphatic system to systemic metabolic disturbances, such as obesity and diabetes, involves astrocytic changes and enlarged perivascular spaces, which may further hinder waste removal [49, 50]. Boyd et al. [50] demonstrated that in a rat model of type 2 diabetes, glymphatic impairment exhibits region-dependent sensitivity, suggesting that metabolic disorders can exacerbate CNS waste accumulation. Recent research has expanded the understanding of the glymphatic pathway's anatomical and functional complexity. Liao et al. [11] provided a comprehensive review of the structural components, including the perivascular spaces, aquaporin-4 channels, and the meningeal lymphatic system, emphasizing their coordinated roles in waste clearance. Natale et al. [25] proposed that peripheral pathological conditions could influence CNS health via the glymphatic pathway, highlighting its role as a gateway connecting neurodegeneration from the periphery to the CNS (Figure 3).

Imaging techniques have been instrumental in elucidating glymphatic function *in vivo*. MRI-based methods, such as gadolinium contrast-enhanced imaging, allow visualization of CSF-ISF exchange

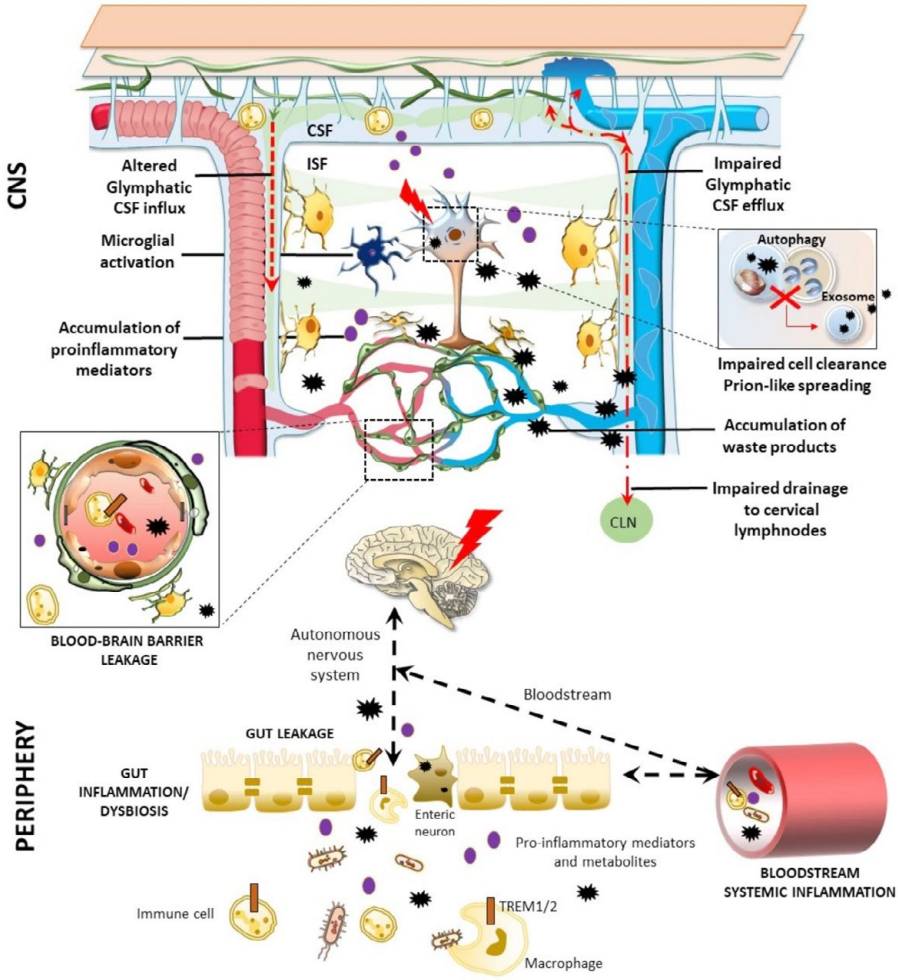

Figure 3: Under pathological conditions, the glymphatic system may become dysfunctional, contributing to the buildup of extracellular waste products—including abnormal proteins—in the brain. This dysfunction can involve changes in meningeal lymphatic vessel structure and drainage, disruptions in CSF inflow and outflow, and the release of pro-inflammatory cytokines and immune cells. Importantly, a bidirectional gut–brain axis allows gastrointestinal disturbances to influence the CNS and vice versa. Harmful substances, such as misfolded proteins, can travel from the brain to the gut via the autonomic nervous system, triggering inflammation (brain-first pathway). Conversely, gut dysbiosis, inflammation, or increased permeability can allow harmful molecules—including misfolded proteins like α-synuclein, microbes, cytokines, and activated immune cells—to spread upward to the brain via vagal or circulatory routes (body-first pathway), potentially bypassing and impairing the glymphatic system and blood–brain barrier. Additionally, when intracellular clearance mechanisms such as autophagy are compromised, neurons may release undigested harmful material via exosomes, further worsening extracellular waste accumulation and glymphatic dysfunction [25].

and solute clearance dynamics [51]. Lee et al. [51] summarized current imaging modalities and discussed how factors like sleep, age, and disease states influence glymphatic activity. These techniques have also been used to assess the impact of interventions aimed at restoring or enhancing glymphatic function, such as pharmacological agents or lifestyle modifications. The clinical relevance of glymphatic dysfunction extends to various neurological and systemic diseases. For example, in the context of glaucoma, Wostyn et al. [52] hypothesized that impaired glymphatic flow at the lamina cribrosa could contribute to disease pathogenesis, linking CSF dynamics to ocular health. Similarly, in neuro-oncology, radiation therapy has been shown to impair glymphatic function, potentially affecting tumor treatment outcomes [53]. The recognition of glymphatic impairment as a common feature in neurodegenerative and neurovascular disorders underscores its importance as a therapeutic target.

In summary, the glymphatic pathway represents a vital mechanism for waste clearance and immunosurveillance in the CNS. Its reliance on astrocytic water channels, perivascular spaces, and the dynamic exchange of CSF and ISF positions it as a central player in maintaining neural health. Disruptions to this system, whether due to structural alterations, sleep disturbances, or systemic diseases, can lead to the accumulation of neurotoxic substances and contribute to disease progression. Advances in neuroimaging and molecular biology continue to shed light on the intricate mechanisms governing glymphatic function, opening avenues for targeted therapies aimed at restoring or enhancing this essential clearance pathway.

Meningeal Lymphatic Vessels: Structure and Systemic Connections

The meningeal lymphatic vessels have emerged as a critical component in maintaining CNS homeostasis through their roles in waste clearance and immunosurveillance [54-60]. Recent research underscores their complex structure and systemic connections, which facilitate the removal of metabolic waste and enable immune interactions within the brain and its surrounding tissues.

Structurally, meningeal lymphatic vessels are specialized lymphatic channels located within the meninges, the protective membranes enveloping the brain and spinal cord. These vessels are distinct from the classical lymphatic system but serve analogous functions in draining ISF, CSF, and CNS-derived molecules. According to recent insights, these vessels form a network that connects to cervical lymph nodes, providing a pathway for waste removal and immune cell trafficking [61]. The anatomical pathways mediating meningeal lymphatic access to the systemic circulation have been elucidated, revealing a brain-wide pathway for waste clearance that is captured by the meningeal lymphatic system [62]. The connection between meningeal lymphatic vessels and the glymphatic system, a brain-wide perivascular pathway responsible for clearing interstitial waste, has been a focal point of recent studies. The glymphatic system facilitates the influx of CSF into the brain parenchyma and the subsequent clearance of metabolic waste products, such as amyloid-β, through perivascular spaces. The meningeal lymphatic vessels serve as an efflux route, draining these waste products from the glymphatic system into the systemic lymphatic circulation [63]. This functional relationship underscores a coordinated system where the glymphatic pathway handles intra-parenchymal waste removal, and the meningeal lymphatic vessels provide the exit route, linking brain waste clearance to systemic immune surveillance [23].

The systemic connections of meningeal lymphatic vessels extend beyond mere waste disposal. They are integral to immune surveillance, allowing immune cells to traffic between the CNS and peripheral lymphoid tissues. The vessels connect to cervical lymph nodes through channels in the meninges, facilitating immune cell migration and the presentation of CNS antigens to the immune system [61]. This connection is vital for immune responses to CNS pathogens and for maintaining immune tolerance, which has implications for neuroinflammatory and neurodegenerative diseases [6]. Recent studies have also highlighted the role of meningeal lymphatic vessels in clearing CNS-derived molecules, including proteins and solutes, from the brain interstitium and CSF. This clearance is essential for preventing the accumulation of neurotoxic substances and maintaining neural health. Evidence suggests that impairment of meningeal lymphatic function correlates with increased accumulation of waste products and neuroinflammation, contributing to conditions such as cerebral small vessel disease (Figure 4) [64]. The structural integrity and functional capacity of these vessels are thus crucial for effective waste clearance and immune regulation within the CNS.

Furthermore, the connection between the skull bone marrow, skull meninges channels, and meningeal lymphatic vessels has been identified as a novel pathway for immune cell and solute exchange. These channels facilitate communication between the skull bone marrow and the meninges, supporting immune surveillance and waste clearance processes [61]. This anatomical feature adds a new dimension to our understanding of CNS immune interactions, emphasizing the systemic integration of meningeal lymphatic vessels with other cranial structures.

In summary, meningeal lymphatic vessels are vital for maintaining CNS health through their dual roles in waste clearance and immune surveillance. Their structural organization within the meninges, connection to the glymphatic system, and systemic links to cervical lymph nodes and skull marrow highlight their importance in brain homeostasis. The recent elucidation of these pathways offers promising avenues for understanding and potentially treating neurodegenerative and neuroinflammatory diseases, where waste accumulation and immune dysregulation are prominent features

Imaging Techniques for Visualizing Brain Lymphatic Pathways

The visualization of brain lymphatic pathways involved in waste clearance and immunosurveillance has become a focal point in neuroimaging research, driven by the recognition that these pathways play crucial roles in maintaining neural homeostasis and their dysfunction is implicated in neurodegenerative and cerebrovascular diseases [65-70]. A variety of imaging techniques, ranging from MRI-based modalities to optical and positron emission tomography imaging, have been employed to elucidate the anatomy, physiology, and pathological alterations of these pathways (Table 2).

One of the pioneering approaches in this field was introduced by Iliff et al. [71], who utilized contrast-enhanced MRI to map a brain-wide pathway responsible for waste clearance. Their study demonstrated that soluble amyloid-β clearance depends on the glymphatic pathway, suggesting that failure of this system may contribute to amyloid plaque accumulation characteristic of Alzheimer's disease. This work laid the foundation for subsequent MRI-based investigations into glymphatic function, emphasizing the potential of MRI as a non-invasive tool for assessing brain waste clearance *in vivo*. Building on this, Taoka and

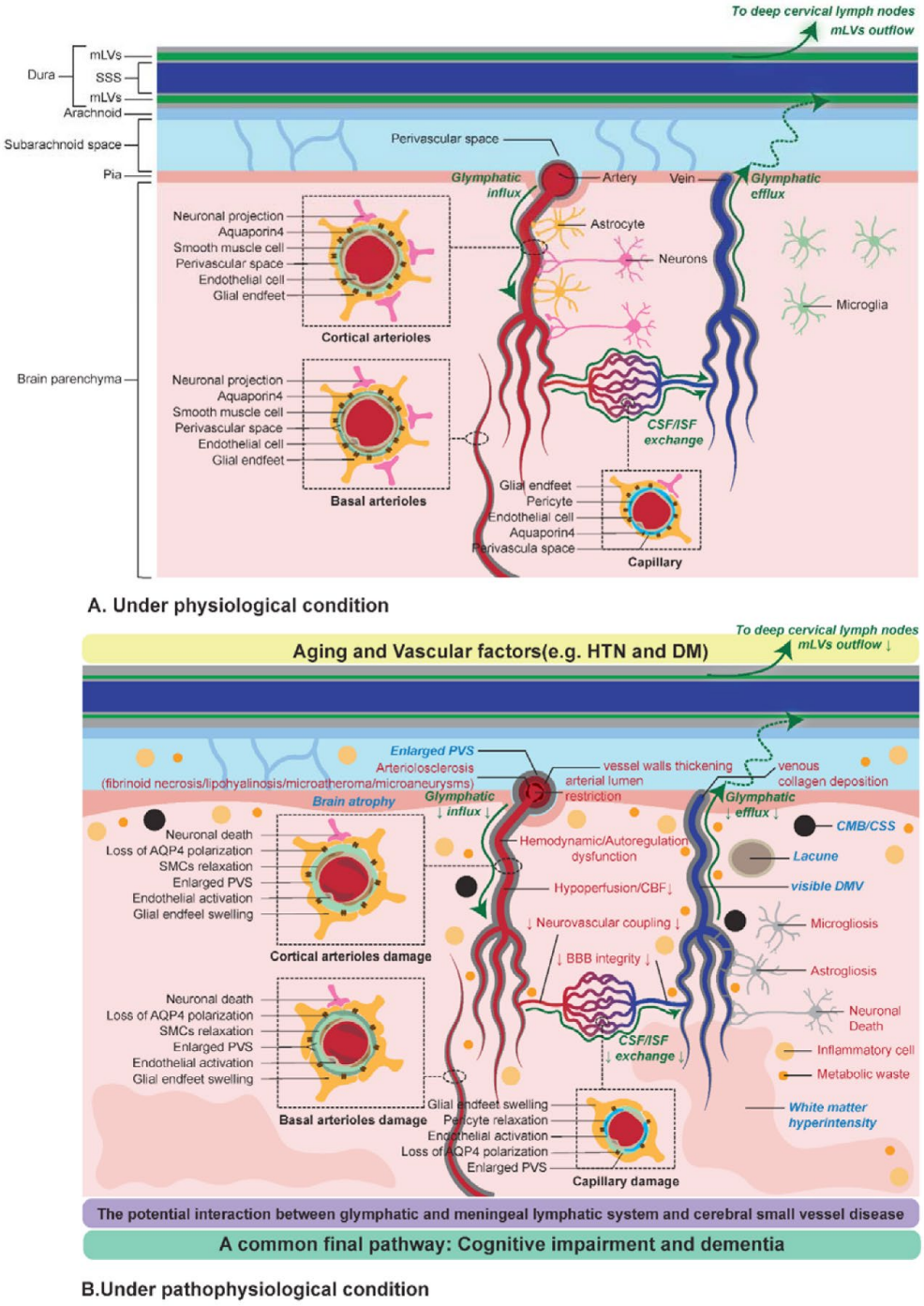

Figure 4: One possible hypothesis is the potential interaction between cerebral small vessel disease and the glymphatic and meningeal lymphatic systems [64].

Naganawa [72] employed MRI to specifically image the glymphatic system using tracer techniques in mice, marking the first *in vivo* visualization of this pathway. Their study utilized fluorescent tracers injected into the cisterna magna, visualized via 2-photon microscopy, which provided detailed insights into the dynamics of glymphatic flow. This approach underscored the importance of advanced MRI techniques in capturing physiological processes underlying waste clearance and highlighted the potential for translating such methods into human studies.

In human subjects, Ringstad and Eide [73] advanced the field by combining MRI with CSF tracers to visualize clearance pathways to dural lymphatics. Their findings demonstrated that trans-arachnoid molecular passage occurs in humans, with the parasagittal dura serving as a critical bridge between the brain and dural lymphatic vessels. This study exemplifies the application of MRI to directly observe the anatomical routes of brain waste clearance, supporting the concept that meningeal lymphatic vessels are integral to neuroimmunological processes. Further elucidating the relationship between aging, neurodegeneration, and lymphatic pathways, Zhou et al. [74] conducted an observational cohort study using MRI to

Table 2: Overview of imaging modalities used to visualize and assess the glymphatic and meningeal lymphatic systems *in vivo*.

Imaging technique	Method/Principle	Applications	Key insights/Advantages
MRI – Contrast-enhanced	Intravenous or intrathecal contrast agents (e.g., gadolinium) to trace CSF/ISF flow	• Mapping glymphatic clearance routes • Assessing meningeal lymphatic drainage in humans	• Non-invasive visualization of brain-wide waste clearance • First *in vivo* evidence of glymphatic pathway in humans
Diffusion tensor imaging – ALPS index	Measures diffusivity along perivascular spaces to estimate glymphatic activity	• Biomarker for glymphatic dysfunction in Alzheimer's disease, mild cognitive impairment • Correlating with amyloid burden and cognitive decline	• Quantitative, non-invasive metric • Strong correlation with CSF amyloid-beta 42, fluorodeoxyglucose-PET (FDG-PET), and cognitive scores
MRI – intravoxel incoherent motion	Separates diffusion and perfusion components to assess microvascular flow and interstitial movement	• Evaluating perivascular fluid dynamics • Studying small vessel disease and glymphatic impairment	• Provides insight into both diffusion and convective flow • Useful in clinical research on neurodegeneration
Chemical exchange saturation transfer	Detects exchange between solute protons and water protons; sensitive to protein accumulation	• Imaging amyloid-β and tau aggregates • Assessing neuroinflammatory markers in perivascular spaces	• Molecular specificity without radiotracers • Potential for early detection of proteinopathies
2-photon microscopy and confocal imaging	High-resolution fluorescent imaging in live animals using tracers injected into CSF (e.g., cisterna magna)	• Real-time visualization of glymphatic flow in rodents • Studying perivascular macrophage activity	• Cellular-level detail • Dynamic assessment of tracer distribution and clearance
Stereoscopic wide-field photoacoustic microscopy	Combines optical excitation and acoustic detection for deep-tissue, high-resolution imaging	• Intravital imaging of meningeal lymphatic vessels and glymphatic pathways in mice	• High spatial resolution *in vivo* • Capable of imaging deep meningeal structures without craniotomy
PET	Radiotracers (e.g., amyloid-specific ligands) combined with artificial intelligence enhanced reconstruction for three-dimensional imaging	• Visualizing amyloid-β clearance pathways • Assessing meningeal lymphatic function in neurodegeneration	• Molecular and metabolic specificity • Can be integrated with MRI for multimodal assessment
ALADDIN (inter-slice blood perfusion MRI)	Non-contrast MRI technique using interslice blood perfusion contrasts to visualize meningeal lymphatic vessels	• Clinical imaging of meningeal lymphatics without contrast agents • Monitoring lymphatic function in tumor patients	• Safe for repeated use • Demonstrates altered meningeal lymphatic vessel wash-in/wash-out in intracranial tumors
Nanoparticle-based imaging	Use of upconverting nanoparticles or other tracers for long-term lymphatic tracking	• Long-term monitoring of meningeal lymphatic clearance in animal models	• Enables longitudinal studies • Can be combined with fluorescence or MRI readouts
Diffusion MRI for CSF dynamics	Advanced diffusion-weighted sequences to quantify CSF movement and solute transport	• Measuring net CSF flow (e.g., in Huntington's disease) • Assessing aqueductal and ventricular CSF dynamics	• Detects hyperdynamic CSF flow in disease states • Correlates with ventricular volume and disease severity

measure glymphatic clearance in humans. They quantified signal ratios at multiple locations along the glymphatic pathway and meningeal lymphatic vessels, revealing that aging impairs these clearance routes. Their work highlights the utility of MRI in detecting age-related changes in lymphatic function, which may serve as biomarkers for neurodegenerative disease susceptibility.

Complementing these studies, Kaur et al. [75] reviewed various MRI techniques, including intravoxel incoherent motion, diffusion tensor imaging, and chemical exchange saturation transfer, for imaging the glymphatic system and dural lymphatic channels [76]. They emphasized that ongoing advancements in MRI methodologies are expanding our capacity to non-invasively assess brain waste clearance pathways, with potential clinical applications in diagnosing and monitoring neurodegenerative conditions. Beyond MRI, optical imaging techniques have also contributed significantly. Bedussi et al. [77] employed confocal fluorescence imaging in mice to trace interstitial and CSF distribution, revealing the anatomical structures involved in fluid convection towards the ventricular system. Similarly, Yang et al. [78] utilized stereoscopic wide-field photoacoustic microscopy to achieve intravital imaging of meningeal lymphatic vessels and glymphatic pathways, providing high-resolution visualization of these structures *in vivo*. These optical modalities offer detailed spatial and functional insights, especially in small animal models, and are instrumental in understanding the microanatomy of lymphatic pathways.

Nanoparticle-based imaging has also been explored for tracking waste clearance. Park et al. [79] used upconverting nanoparticles to non-invasively monitor lymphatic clearance in mice over a month, demonstrating the potential for long-term tracking of lymphatic flow. Such techniques could be adapted for human studies to evaluate lymphatic function dynamically. In the realm of human neuroimaging, diffusion MRI techniques are gaining prominence. Wright et al. [80] reviewed current and emerging diffusion MRI methods for measuring CSF dynamics, which are critical for understanding glymphatic function. These techniques aim to quantify fluid movement and solute transport, providing indirect assessments of lymphatic pathway integrity. Similarly, Zhang et al. [13] discussed the use of DTI-ALPS as a biomarker for neurodegenerative diseases, emphasizing the importance of diffusivity measures in evaluating perivascular space enlargement and glymphatic dysfunction.

The recent development of non-invasive imaging of meningeal lymphatic vessels has been exemplified by Kim et al. [81], who proposed an inter-slice blood perfusion MRI technique called ALADDIN for visualizing meningeal lymphatic vessels without contrast agents. This method addresses the challenge of imaging these small vessels in humans and opens avenues for routine clinical assessment of lymphatic pathways. In addition to structural visualization, functional imaging approaches are being developed. Vinje et al. [47] highlighted the role of sleep in modulating glymphatic clearance, with MRI-informed biophysical models quantifying solute transport during sleep and sleep deprivation. These studies underscore the dynamic nature of lymphatic pathways and their susceptibility to physiological states, which can be monitored through advanced MRI techniques. Finally, the integration of multimodal imaging approaches is evident in recent studies. Shim et al. [82] introduced three-dimensional positron emission tomography

imaging with artificial intelligence enhanced reconstruction to visualize amyloid-β clearance pathways, suggesting that positron emission tomography can complement MRI by providing molecular specificity and higher spatial resolution. Such hybrid techniques are poised to offer comprehensive insights into the anatomy and function of brain lymphatic pathways, especially in the context of neurodegenerative diseases.

In summary, the landscape of imaging techniques for visualizing brain lymphatic pathways is diverse and rapidly evolving. MRI-based methods, including contrast-enhanced imaging, diffusion techniques, and novel non-invasive approaches like ALADDIN, have been instrumental in mapping the anatomy and assessing the function of glymphatic and meningeal lymphatic systems. Optical imaging and nanoparticle tracking further enhance our understanding at microvascular levels, primarily in animal models. The integration of these modalities, along with emerging positron emission tomography techniques, holds promise for advancing our understanding of brain waste clearance and immunosurveillance, ultimately contributing to improved diagnosis and therapeutic strategies for neurological disorders.

Regulation by Physiological and Lifestyle Factors

The regulation of waste clearance and immunosurveillance is influenced by a variety of physiological and lifestyle factors. These factors play a crucial role in maintaining the body's homeostasis and preventing diseases, including neurodegenerative disorders and cancer. The interplay between lifestyle choices, physiological processes, and immune function is complex, involving multiple systems such as the glymphatic system in the brain and the immune system's natural killer cells. Understanding these interactions can provide insights into optimizing health and preventing disease.

- Natural killer cells activity: Lifestyle factors such as smoking, alcohol consumption, stress, and obesity are linked to reduced natural killer cell function, which is crucial for immunosurveillance against cancer and viral infections. Conversely, healthy lifestyle choices like adequate sleep, moderate exercise, and stress reduction can enhance natural killer cell activity and overall immune function [83].

- Physical activity: Regular exercise promotes the exchange of immune cells between tissues and bloodstream, enhancing immune surveillance and reducing systemic inflammation. This includes improved natural killer cell function and modulation of other immune cells, which can influence cancer outcomes and support antitumor immunity [84].

- Brain waste clearance: The glymphatic system, a glial-dependent pathway, facilitates the clearance of metabolic waste from the brain. This system is crucial for removing amyloid-β and other by-products, potentially lowering the risk of neurodegenerative diseases like Alzheimer's [22].

- Influence of sleep and diet: Sleep and diet significantly impact glymphatic activity. Proper sleep enhances the efficiency of waste clearance, while a healthy diet supports vascular health, which is essential for optimal glymphatic function [85].

- Circadian influence: Circadian rhythms regulate immune-vascular interactions, affecting leukocyte behavior and immune surveillance. Disruptions in circadian rhythms can exacerbate conditions like atherosclerosis by altering immune responses [86].

- Lifestylopathy: This concept frames immune health as a balance of energy dynamics and lifestyle coherence. Chronic stress and poor lifestyle choices can disrupt this balance, leading to immune dysfunction. Conversely, lifestyle interventions can restore thermodynamic harmony and enhance immune resilience [87].

In summary, the primary focus is on enhancing waste clearance and immunosurveillance through lifestyle and physiological regulation, it is important to consider the broader implications of these systems. For instance, the immune system's role extends beyond defense to maintaining homeostasis and responding to non-pathogenic stimuli, which can influence conditions like autoimmune diseases. Additionally, the glymphatic system's role in brain health highlights the interconnectedness of lifestyle factors and physiological processes in disease prevention and health maintenance.

Clinical Studies

A study by Kaur et al. [75] investigated the mechanisms of brain waste clearance, focusing on the glymphatic system and the role of perivascular macrophages. The research demonstrated that both convective bulk flow and diffusion play significant roles in clearing interstitial waste solutes from the brain parenchyma. This finding addresses an ongoing debate regarding the presence of convective bulk flow within the brain's interstitial spaces. The study suggested that perivascular macrophages, which are immune cells located within perivascular spaces, may have an important function in glymphatic system-mediated interstitial waste clearance. This area had not been thoroughly explored previously. The investigation included examining tracer uptake by perivascular macrophages in the perivascular spaces surrounding both arteries/arterioles and veins/venules to understand their potential role in assisting the glymphatic system. The findings imply that both the glymphatic system and perivascular macrophages could be targeted to improve interstitial waste clearance in individuals suffering from waste-associated neurological conditions and those experiencing aging-related issues.

A study by Kamagata et al. [88] investigated the association of MRI indices of the glymphatic system with amyloid deposition and cognitive function in individuals with mild cognitive impairment and Alzheimer's disease. Patients with Alzheimer's disease exhibited significantly higher total, WM, and basal ganglia (BG) PVSVF (Cohen's d = 1.15 to 1.48; $p < 0.001$) compared to healthy controls. They also showed significantly higher fractional volume of FW-WM (Cohen's d = 0.73; $p < 0.05$) and a lower ALPS index (Cohen's d = 0.63; $p < 0.05$) than healthy controls. After adjusting for age, sex, years of education, scanning site, and apolipoprotein E (Epsilon 4) gene carrier status, the mean ALPS index ($p = 0.026$), diffusivity along the z-axis in the association-fibre region ($p = 0.006$), diffusivity along the y-axis in the projection-fibre region ($p = 0.003$), PVSVF-WM ($p < 0.001$), and PVSVF-BG ($p < 0.001$) were significantly different in Alzheimer's disease patients compared to controls. PVSVF-all regions (ALL) ($p <0.001$), PVSVF-WM ($p < 0.001$), and cerebral FW-WM ($p = 0.025$) were significantly higher in Alzheimer's disease patients than controls. Significant differences in PVSVF-ALL ($p < 0.001$) and PVSVF-WM ($p < 0.001$) were also observed between Alzheimer's disease patients and mild cognitive impairment patients. In model 4 (including gray matter volume fraction as a covariate), PVSVF-WM ($p < 0.001$), PVSVF-ALL ($p < 0.001$), and PVSVF-BG ($p = 0.020$) remained significantly higher in Alzheimer's disease patients than controls. The mild cognitive impairment group showed significantly higher total (Cohen's d = 0.99; $p < 0.05$) and WM (Cohen's d = 0.91; $p < 0.05$) PVSVF compared to healthy controls. PVSVF-ALL ($p = 0.006$) and PVSVF-WM ($p = 0.018$)

were significantly higher in mild cognitive impairment patients than controls. In model 4, PVSVF-ALL ($p = 0.003$) and PVSVF-WM ($p = 0.004$) remained significantly higher in mild cognitive impairment patients than controls. A low ALPS index was associated with lower CSF amyloid-beta 42 (Spearman's rank correlation coefficient (rs) = 0.41, false discovery rate–adjusted p-value (pfdr) = 0.026), higher FDG-PET uptake ($rs = 0.54$, $pfdr < 0.001$), and worse multiple cognitive domain deficits. Specifically, lower mean ALPS index correlated with lower CSF amyloid-beta 42 ($rs = 0.41$, $pfdr = 0.026$), higher FDG-PET standardized uptake value ratio ($rs = 0.54$, $pfdr < 0.001$), worse mini-mental state examination ($rs = −0.41$, $pfdr = 0.026$), worse functional activities questionnaire ($rs = −0.38$, $pfdr = 0.016$), worse clinical dementia rating – sum of boxes ($rs = −0.47$, $pfdr = 0.003$), worse Alzheimer's disease assessment scale-item11 ($rs = −0.40$, $pfdr = 0.013$), and worse Alzheimer's disease assessment scale-item13 scores ($rs = −0.33$, $pfdr = 0.041$). High FW-WM was associated with lower CSF amyloid-beta 42 ($rs = −0.47$, $pfdr = 0.021$) and worse cognitive performances. Higher FW-WM also correlated with worse mini-mental state examination ($rs = −0.41$, $pfdr = 0.021$) and worse functional activities questionnaire score ($rs = 0.36$, $pfdr = 0.044$). Higher PVSVF-BG was associated with worse functional activities questionnaire score ($rs = 0.42$, $pfdr = 0.026$). Correlations of PVSVF-ALL, PVSVF-WM, and PVSVF-hippocampus with neuropsychological scores, CSF biomarker values, PET standardized uptake value ratios, and hippocampus volume were not significant. In conclusion, the statistical findings demonstrate distinct alterations in glymphatic system MRI indices in mild cognitive impairment and Alzheimer's disease, with Alzheimer's disease showing more pronounced changes. These MRI measures, particularly ALPS index and FW-WM, are significantly correlated with key biomarkers of Alzheimer's disease pathology and cognitive decline, suggesting their potential as noninvasive indicators of glymphatic dysfunction and disease progression.

A study by Hett et al. [89] investigated CSF flow dynamics in Huntington's disease patients compared to healthy controls, revealing significant alterations linked to disease progression. Participants with Huntington's disease, including both premanifest and manifest cohorts, showed a significant decrease in net CSF flow through the cerebral aqueduct compared to non-Huntington's disease controls. The lowest net CSF flow was observed in the manifest Huntington's disease cohort (mean = 0.04 ± 0.25 mL/min), which was significantly lower than both non-Huntington's disease controls (mean = 0.32 ± 0.20 mL/min) and premanifest Huntington's disease cohorts (mean = 0.21 ± 0.27 mL/min). Huntington's disease participants exhibited a significant increase in peak CSF velocity. This increase was more pronounced in manifest Huntington's disease patients compared to both non-Huntington's disease controls and premanifest Huntington's disease cohorts. The reduction in net CSF flow was attributed to hyperdynamic CSF movement, characterized by higher caudal systolic CSF flow velocity and higher diastolic cranial CSF flow velocity across the cardiac cycle in Huntington's disease patients. Specifically, caudal flow was 0.17 ± 0.07 mL/s and cranial flow was 0.14 ± 0.08 mL/s in Huntington's disease, compared to 0.13 ± 0.06 mL/s and 0.11 ± 0.04 mL/s in controls, respectively. A significant increase was observed in both maximum caudal and maximum cranial CSF flow in Huntington's disease participants, with greater increases seen in motor manifest cohorts. A positive correlation was found between cranial diastolic flow and disease severity, as measured by the coronary artery calcium-age-product score ($p = 0.02$). Huntington's disease patients showed reduced striatal gray matter structures (caudate, putamen, globus pallidus) and larger lateral and third ventricles, as well as subarachnoid space volumes compared to non-Huntington's disease controls. The cross-sectional surface of the cerebral aqueduct was also larger among Huntington's disease participants. A positive correlation was observed between peak CSF flow velocity and the volumes of the third and fourth ventricles. Similarly, maximum caudal and cranial CSF flow also showed significant correlations with third ventricle volume. These volumetric changes explained a substantial portion of the variability in peak velocity (40%), maximum caudal flow (20%), and maximum cranial flow (22%). In summary, the study found that Huntington's disease is associated with reduced CSF flow and increased hyperdynamic CSF movement, particularly in more advanced stages. These changes correlate with disease severity and ventricular enlargement, highlighting the impact of Huntington's disease on CSF dynamics.

A study by Wang et al. [90] investigated the relationship between meningeal lymphatic vessel function and intracranial malignant tumors, revealing significant differences in wash-in and wash-out functions in patients with tumors compared to control groups. These findings suggest a disturbed mLV function associated with malignancy and its progression. Patients with intracranial tumors exhibited a higher wash-in rate of meningeal lymphatic vessels compared to the control group. Specifically, the wash-in rate was 3.72 in the tumor group versus 2.87 in the control group ($p < 0.001$). The area under the curve for meningeal lymphatic vessels was also significantly higher in the intracranial tumor group (2,749) compared to the control group (2,110) ($p < 0.001$). The wash-out ratio of meningeal lymphatic vessels was lower in patients with intracranial tumors (0.65) compared to the control group (0.73) ($p < 0.001$). A decreased wash-out function of meningeal lymphatic vessels was found to be associated with tumor progression ($\beta = −0.118$; $p < 0.001$). Long-term decreased meningeal lymphatic vessel wash-out function was identified as a risk factor for tumor progression. High-grade glioma was associated with a lower meningeal lymphatic vessel wash-out function ($\beta = −0.057$, $p = 0.044$). The isocitrate dehydrogenase wild type was also linked to a lower meningeal lymphatic vessel wash-out function ($\beta = −0.069$, $p = 0.047$). In summary, the study concluded that intracranial malignant tumors are associated with elevated meningeal lymphatic vessel wash-in function and decreased meningeal lymphatic vessel wash-out function. Furthermore, specific tumor characteristics like high-grade glioma and isocitrate dehydrogenase wild type are linked to reduced meningeal lymphatic vessel wash-out, which in turn serves as a risk factor for tumor progression.

Therapeutic Approaches Targeting Brain Lymphatic Clearance

The emerging understanding of brain waste clearance and immunosurveillance has significantly advanced with the recognition of specialized lymphatic and glymphatic systems. These systems are increasingly viewed as promising therapeutic targets for various neurological disorders, including brain tumors, stroke, neuroinflammation, and neurodegenerative diseases. The literature underscores the potential of manipulating these pathways to enhance waste removal and immune responses, thereby offering novel avenues for intervention.

A foundational aspect of this field is the structural and functional elucidation of the meningeal lymphatic system. Historically, the brain was considered devoid of lymphatic vessels, but recent studies have identified meningeal lymphatics as critical conduits for CSF and ISF drainage [11]. These vessels, located within the meninges, facilitate

the removal of metabolic waste and immune cell trafficking. Song et al. [91] demonstrated that VEGF-C-driven lymphatic drainage enhances immune surveillance in the brain, particularly in the context of glioblastoma. Their work showed that manipulating meningeal lymphatics could potentiate antigen-specific immune responses, suggesting a therapeutic strategy to bolster anti-tumor immunity. Complementing these findings, the glymphatic system has been characterized as a brain-wide network that mediates waste clearance through CSF-ISF exchange, primarily driven by aquaporin-4 channels on astrocytic end feet [11, 92]. The glymphatic pathway's efficiency is influenced by sleep architecture, vascular pulsatility, and respiratory function. Ozturk et al. [14] provided evidence that supporting respiratory function via continuous positive airway pressure enhances glymphatic transport, indicating that physiological modulation can improve waste clearance. Similarly, Gao et al. [92] highlighted the therapeutic potential of targeting the glymphatic system in neurological disorders, emphasizing the importance of aquaporin-4 and sleep regulation in maintaining pathway integrity.

Dysfunction of these clearance pathways has been implicated in the pathogenesis of several CNS diseases. For instance, glymphatic impairment exacerbates tau propagation in Alzheimer's disease models, as shown by Lopes et al. [93], who demonstrated that pharmacological inhibition of aquaporin-4 worsens tau spread, underscoring the importance of glymphatic integrity in neurodegeneration. Likewise, Ding et al. [94] reviewed how glymphatic and meningeal lymphatic dysfunction contribute to Alzheimer's disease progression by promoting amyloid-β and tau accumulation, neuroinflammation, and vascular impairment. In cerebrovascular diseases, such as ischemic stroke and intracerebral hemorrhage, the role of lymphatic and glymphatic pathways has garnered attention. Wang et al. [18] summarized the significance of lymphatic drainage in post-stroke brain injury, proposing that enhancing these pathways could mitigate injury severity. Tsai et al. [95] further investigated the meningeal lymphatic system in intracerebral hemorrhage, revealing that pharmacological enhancement of lymphatic function promotes hematoma resolution and brain recovery, thus presenting a promising therapeutic approach.

Therapeutic strategies targeting these systems are diverse. One promising approach involves VEGF-C administration to promote lymphangiogenesis and improve drainage, as demonstrated by Song et al. [91], who showed that VEGF-C enhances immune responses against brain tumors. Similarly, Kim et al. [96] explored hybrid electro-optical stimulation to augment glymphatic function, finding that such neuromodulation can ameliorate ischemic brain damage, indicating that targeted stimulation of the glymphatic pathway could be neuroprotective. Surgical and interventional techniques are also under investigation. Lahmar et al. [97] reviewed lymphatic surgical procedures, such as lymphatico-venous anastomoses, aimed at enhancing CNS waste clearance, especially in neurodegenerative conditions like Alzheimer's and Parkinson's diseases. These approaches aim to bypass or augment natural drainage pathways, offering a novel therapeutic frontier. The role of neuroinflammation in modulating lymphatic and glymphatic pathways is another critical aspect. Hsu et al. [16] discussed how neuroinflammatory processes can induce lymphangiogenesis, which may be harnessed therapeutically to treat CNS infections, stroke, and autoimmunity.

Overall, the literature converges on the concept that enhancing brain lymphatic and glymphatic function holds significant therapeutic promise. Strategies include pharmacological agents like VEGF-C, neuromodulation techniques such as hybrid electro-optical stimulation, and surgical interventions to improve drainage pathways. Additionally, understanding the physiological factors that influence these systems, such as sleep and respiratory function, offers non-invasive avenues to optimize waste clearance. As research progresses, integrating these approaches could lead to comprehensive therapies for a range of neurological diseases characterized by impaired waste removal and immune dysregulation.

In summary, targeting brain lymphatic and glymphatic pathways represents a burgeoning frontier in neurotherapeutics. The evidence underscores their vital roles in maintaining CNS homeostasis, mediating immune responses, and preventing neurodegeneration. Future research aimed at refining these strategies and elucidating their mechanisms will be crucial in translating these insights into clinical practice, ultimately improving outcomes for patients with neurological disorders.

Conclusion

In conclusion, the brain's lymphatic architecture—comprising the glymphatic pathway and meningeal lymphatics—constitutes a sophisticated and indispensable system for maintaining cerebral homeostasis. By facilitating the clearance of metabolic waste and enabling vigilant immune surveillance, these pathways play a central role in preserving neural integrity. Their function is dynamically influenced by physiological rhythms, lifestyle factors, and systemic health, yet vulnerable to disruption in aging and a spectrum of neurological disorders. Advances in neuroimaging and deepening cellular understanding have not only illuminated their complex operations but also unveiled promising therapeutic avenues aimed at restoring or augmenting their clearance capacity. As research continues to unravel the nuanced interactions within this neuro-lymphatic network, targeting these systems offers a transformative frontier for mitigating the progression of neurodegenerative, cerebrovascular, and neuroinflammatory diseases, heralding a new era in brain health and therapeutic innovation.

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Conflict of Interest

None.

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