

Review

# The Glymphatic and Meningeal Lymphatic Systems: Gatekeepers of Brain Health in Aging and Neurodegeneration

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**ABSTRACT:** The discovery of the glymphatic system and of meningeal lymphatic vessels has substantially revised our understanding of how the central nervous system clears waste and maintains neuroimmune homeostasis. Acting in series, these two pathways remove interstitial solutes, metabolic by-products, and neurotoxic proteins such as tau and amyloid- $\beta$  from the brain parenchyma and deliver them to the peripheral lymphatic system. Converging experimental and clinical evidence indicates that both pathways decline with age, and that impaired clearance contributes to the onset and progression of Alzheimer's disease, Parkinson's disease, and stroke, although the direction of causality in these associations is not yet fully resolved. In this review, we summarize current knowledge of the anatomy and physiology of the glymphatic and meningeal lymphatic systems; examine the molecular and cellular mechanisms by which their function deteriorates with age; appraise the imaging modalities and fluid biomarkers used to assess them; and evaluate the therapeutic strategies being developed to restore them. A clearer understanding of this clearance pathways may open new avenues for the treatment of age-related neurodegenerative disease.

**Keywords:** glymphatic system, meningeal lymphatic system, aging, neurodegeneration

## 1. Introduction

For decades, the central nervous system (CNS) was thought to lack a classical lymphatic drainage system, and its mechanisms of waste clearance remained obscure. This view changed with the description of the glymphatic system [1] and, subsequently, the identification of

functional meningeal lymphatic vessels (mLVs) [2]. The two pathways operate in series: the glymphatic system supports exchange between cerebrospinal fluid (CSF) and interstitial fluid (ISF) within the brain parenchyma, whereas mLVs provide the downstream route by which solutes and immune cells leave the CNS for the deep cervical lymph nodes. Together they clear neurotoxic

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debris and support neuroimmune surveillance. Their function declines with age, however, resulting in impaired clearance, neuroinflammation, and aggravated proteinopathy, which are hallmarks of neurodegenerative disease. In this review, we integrate recent experimental and clinical findings on the anatomy and physiology of these pathways, the mechanisms by which they fail in aging and disease, the imaging modalities and fluid biomarkers used to assess them, and the therapeutic strategies intended to restore them, with an emphasis on translational relevance and unresolved questions.

Because terminology in this field is applied inconsistently, we adopt the following conventions. “Glymphatic flow” denotes the bulk transport of CSF along periaxonal spaces, driven in part by arterial pulsatility, followed by efflux along perivenous pathways. “CSF-ISF exchange” denotes the movement of water and solutes between the CSF and interstitial compartments, which may proceed by convection, by diffusion, or by both. “Glymphatic activity” is used operationally in human neuroimaging studies to denote measures of

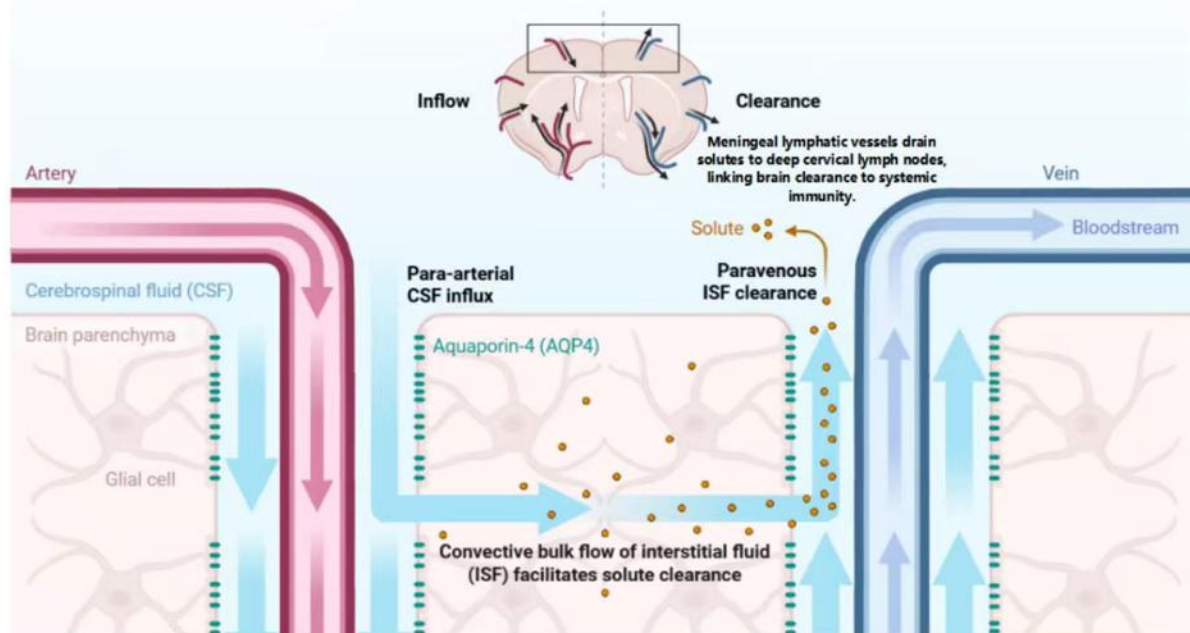
clearance efficiency; given the methodological limitations of these approaches, particularly in humans, such measures should be interpreted as indirect indicators of glymphatic function rather than as direct evidence of convective flow. The relative contributions of convection and diffusion to CSF-ISF exchange remain under active investigation.

## 2. Anatomy and Function of Brain Clearance Systems

### 2.1 The Glymphatic System

The glymphatic system was first described in rodent models and functions as a lymphatic-like pathway in which CSF enters the brain along periaxonal spaces and ISF drains along perivenous routes [1]. Astrocytic aquaporin-4 (AQP4) channels are important mediators of the convective fluid movement that supports this exchange [1] (Fig. 1). Glymphatic activity is modulated by the sleep-wake cycle [3], arterial pulsatility [4], respiration [5], and body posture [6].

### Interstitial Solute & Fluid Clearance in the Glymphatic System



**Figure 1. Schematic illustration of brain clearance pathways.** CSF enters periaxonal spaces, exchanges with ISF through astrocytic AQP4 water channels, and exits along perivenous routes. mLVs then drain solutes to the deep cervical lymph nodes, linking brain clearance to systemic immunity.

### 2.2 mLVs

mLVs are embedded in the dura mater, most prominently alongside the superior sagittal and transverse sinuses, and transport macromolecules and immune cells from the CSF

to the deep cervical lymph nodes. They express the canonical lymphatic endothelial markers LYVE-1, PROX1, and VEGFR-3, and interact with adjacent blood vessels and immune cells [2]. Through this dual role in

drainage and immune surveillance, they connect the CNS to peripheral lymphoid organs.

For clarity and comparison, we summarize the distinct contributions of the glymphatic and meningeal

lymphatic systems to cerebral waste clearance and neurodegenerative disease in Table 1.

**Table 1.** Differential roles of the glymphatic and meningeal lymphatic systems in brain waste clearance and neurodegenerative pathology [1, 2, 4, 7–21]

| Feature                                                           | Glymphatic system                                                                                                                     | Meningeal lymphatic system                                                                                                                                                          |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anatomical location</b>                                        | Perivascular spaces inside cerebral parenchyma                                                                                        | Dural lymphatic vessels distributed along intracranial venous sinuses                                                                                                               |
| <b>Driving forces</b>                                             | Arterial pulsation and AQP4 mediated CSF-ISF bidirectional exchange                                                                   | Rhythmic contraction of lymphatic smooth muscle, interstitial fluid pressure gradient and unidirectional lymphatic valves; deep cervical lymph nodes act as final drainage terminus |
| <b>Core physiological function</b>                                | Mediate CSF-ISF substance exchange within brain parenchyma; mobilize waste solutes out of parenchymal tissue                          | Transport CSF-derived solutes and immune cells out of cranial cavity for peripheral clearance and immune surveillance                                                               |
| <b>Inflammatory role</b>                                          | Indirect inflammatory effect: secondary inflammation induced by insufficient waste clearance                                          | Direct inflammatory regulation: mediates immune cell trafficking and central nervous system immune surveillance                                                                     |
| <b>Age-related susceptibility</b>                                 | AQP4 polarization loss and weakened arterial pulsation with aging                                                                     | Lymphatic vessel regression, reduced vessel coverage and declined drainage capacity in aged brains                                                                                  |
| <b>Amyloid-<math>\beta</math> (A<math>\beta</math>) clearance</b> | Impairment is associated with reduced A $\beta$ clearance and increased parenchymal accumulation                                      | Impairment blocks A $\beta$ drainage from CSF compartments, causing A $\beta$ deposition in meningeal perilymphatic spaces                                                          |
| <b>Tau clearance</b>                                              | Impairment accelerates intracellular tau hyperphosphorylation and aggregation in neurons                                              | Impairment prolongs extracellular tau retention and hinders tau outflow, exacerbating tau spread across brain regions                                                               |
| <b>Role in Parkinson's disease</b>                                | Impairment promotes intraneuronal $\alpha$ -synuclein aggregation and increases vulnerability of dopaminergic neurons                 | Impairment triggers persistent meningeal inflammation and facilitates interregional $\alpha$ -synuclein spreading                                                                   |
| <b>Role in stroke</b>                                             | Impairment blocks perivascular clearance of cellular debris and inflammatory mediators; aggravates cerebral edema and neuronal injury | Impairment delays post-stroke functional recovery, sustained neuroinflammation due to impaired cranial waste efflux                                                                 |
| <b>Animal model evidence</b>                                      | Tracer and in vivo imaging confirm obvious suppression of parenchymal solute clearance after glymphatic impairment                    | Artificial surgical disruption aggravates lymphatic drainage failure, immune imbalance and tau-associated pathological lesions                                                      |
| <b>Human clinical evidence</b>                                    | Abnormal MRI glymphatic transport metrics correlate with cerebral amyloid burden and progressive cognitive decline                    | Aging impairs meningeal lymphatic drainage                                                                                                                                          |

### 3. Mechanisms Underlying Dysfunction of the Brain Clearance System in Aging and Disease

#### 3.1 Aging and Structural Degeneration

Aging is associated with depolarization of AQP4 away from astrocytic endfeet [18, 22], diminished arterial pulsatility secondary to vascular stiffening [23], and astroglial senescence [24]. Together, these changes reduce CSF-ISF exchange [25]. In parallel, aging is accompanied by structural and functional deterioration of mLVs, including reduced lymphangiogenesis, decreased vessel caliber, and altered permeability, which may compromise downstream CSF drainage and waste egress

[7, 26, 27]. Figure 2 summarizes these age-related changes in the brain clearance system.

#### 3.2 Neuroinflammation and Immune Dysregulation

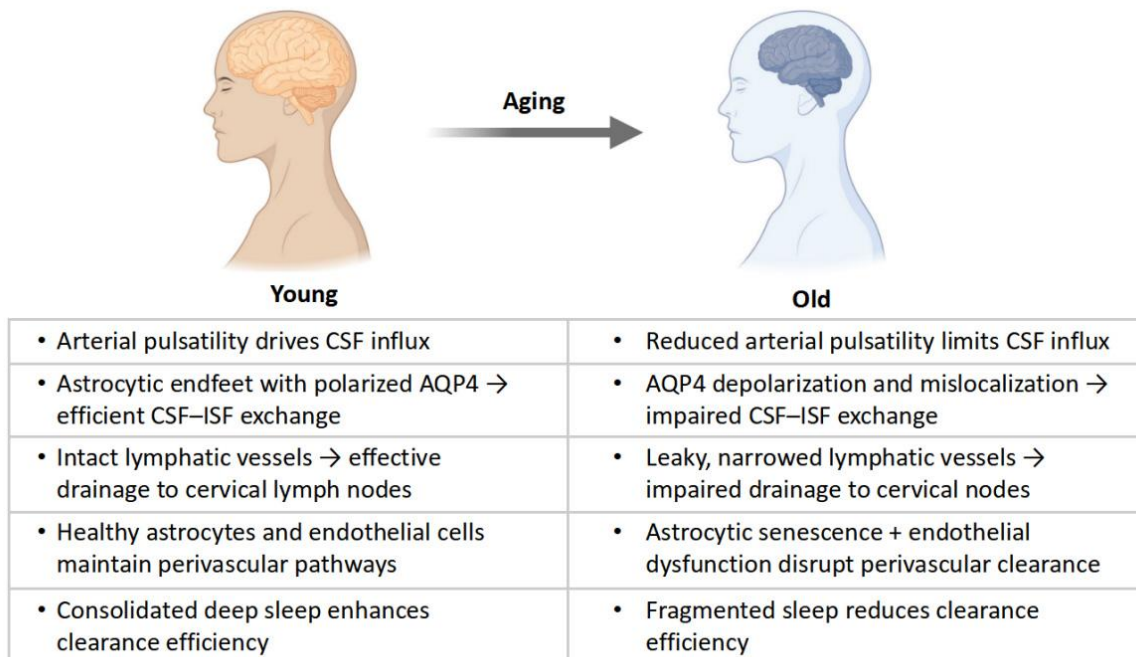
Neuroinflammation and immune dysregulation contribute to age-related failure of clearance across both the glymphatic and the meningeal lymphatic pathways [28–30].

Glymphatic dysfunction can be considered at three interrelated levels: perivascular remodeling, astroglial AQP4 disruption, and barrier impairment. At the perivascular level, TGF- $\beta$ -related signaling may promote basement membrane fibrosis and microvascular remodeling [31, 32], thereby reducing perivascular CSF

distribution in the aged, injured brain [31]. At the astroglial level, loss or redistribution of AQP4 polarization at astrocytic endfeet may impair extracellular solute clearance [33], and neuroinflammation-related astrogliosis may further disrupt AQP4 distribution, CSF-ISF exchange, and CSF flow [34, 35]. At the barrier level, sustained inflammatory signaling may reduce tight-junction integrity and increase blood–brain barrier (BBB) permeability [36, 37], while age-related dysfunction of the

BBB and neurovascular unit (NVU) may exacerbate edema, neuroinflammation, and the retention of neurotoxic compounds [38]. Downstream lymphatic CSF outflow may be further compromised by age-related changes in meningeal immunity [30]. Taken together, these changes may hinder the removal of neurotoxic proteins and metabolic waste, rendering the aging brain more vulnerable to further injury [39].

#### Age-Related Changes in Brain Clearance Pathways



**Figure 2. Age-related changes in brain clearance pathways: comparison of clearance capacity and mechanisms in the young and the aged brain.** In the young brain, strong arterial pulsatility, polarized AQP4, intact astrocytes, and functional mLVs support efficient CSF-ISF exchange and sleep-driven clearance. With aging, arterial stiffening, AQP4 depolarization, astrocytic senescence, lymphatic vessel rarefaction, and disturbed sleep together impair clearance and promote metabolite accumulation.

### 3.3 Neurodegenerative Diseases

Neurodegenerative disorders are characterized by progressive neuronal dysfunction and death, which impairs cognitive and motor functions. Failure of brain waste clearance is increasingly recognized as one contributor to this process: when clearance is impaired, neurotoxic proteins accumulate in the parenchyma and injure neurons. This pattern is evident, to differing degrees, in Alzheimer's disease, Parkinson's disease, and stroke, which we consider in turn below.

**Alzheimer's disease (AD):** Impaired clearance contributes substantially to AD pathophysiology. Deficient glymphatic and meningeal lymphatic clearance promotes the abnormal accumulation of A $\beta$  and hyperphosphorylated tau, which culminates in extracellular senile plaque deposition and intracellular

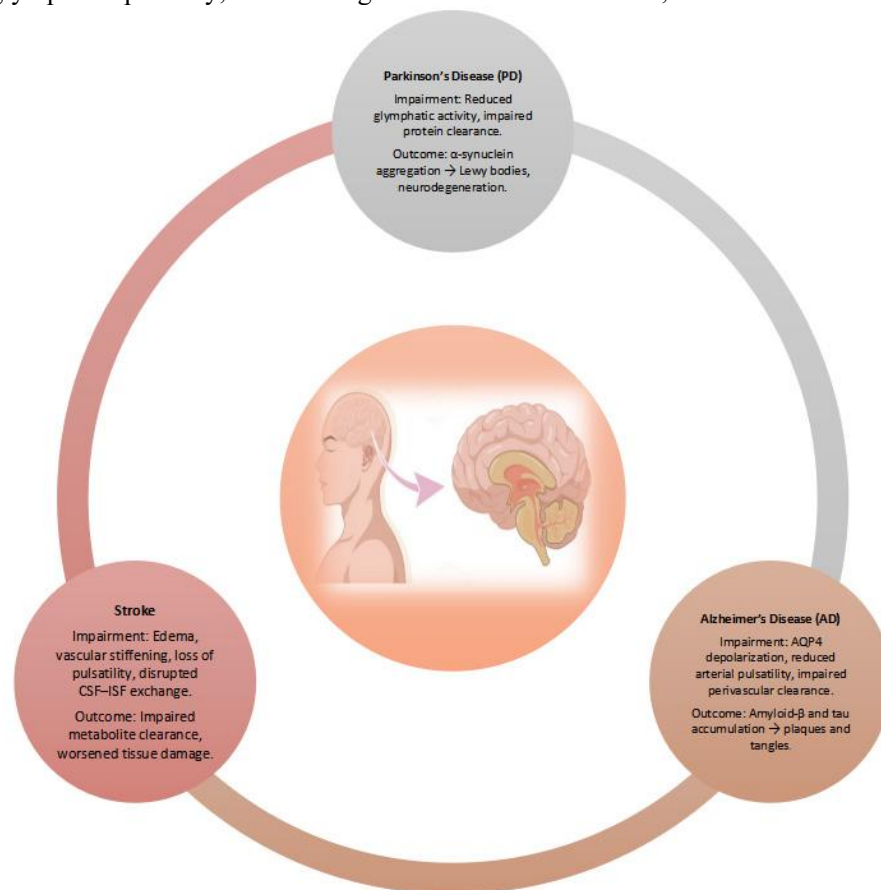
neurofibrillary tangle formation [40]. In murine AD models, long-term high-fat diet (HFD) reduces cerebral A $\beta$  clearance and accelerates A $\beta$  aggregation [41]. Loss of AQP4 polarization, which is required for efficient glymphatic clearance of A $\beta$ , appears to be a central mechanism of HFD-induced glymphatic dysfunction, suggesting that chronic HFD may impair A $\beta$  clearance by disrupting glymphatic transport [41]. Meningeal lymphatic dysfunction is likewise present in aged animal models of AD, where it further compromises CNS lymphatic drainage and increases cerebral A $\beta$  deposition [7, 9]. In patients with AD, clinical studies show impaired CSF clearance that correlates strongly with brain amyloid load [42]. On current evidence, glymphatic dysfunction appears to play a more proximal role than meningeal lymphatic dysfunction in AD, although the two are difficult to separate experimentally.

**Parkinson's disease (PD):** Impaired brain waste clearance may contribute to  $\alpha$ -synuclein aggregation in PD. Animal studies have shown that glymphatic impairment limits the clearance of misfolded  $\alpha$ -synuclein and promotes its propagation to other brain regions [10]. In parallel, PD-associated meningeal lymphatic dysfunction impedes CSF drainage and the removal of  $\alpha$ -synuclein and inflammatory mediators, thereby aggravating neuroinflammation [9, 43]. Recent imaging studies report reduced perivascular transport in patients with PD, which correlates with disease progression and with non-motor features such as sleep disturbance [44]. Thus, while meningeal lymphatic dysfunction contributes to impaired clearance of inflammatory mediators, glymphatic dysfunction may be more directly implicated in  $\alpha$ -synuclein spread in PD.

**Stroke and cerebrovascular injury:** In stroke and cerebrovascular injury, impaired brain clearance appears to arise predominantly from altered CSF flow [45] and from disrupted glymphatic transport and drainage [46, 47]. Acute ischemic stroke triggers a rapid increase in CSF influx into the glymphatic pathway, contributing to

tissue swelling and edema formation [45]. Subsequent AQP4 depolarization may further impair glymphatic clearance and aggravate brain edema [46]. Consistent with these findings, contrast-enhanced MRI tracer studies show that glymphatic transport kinetics are suppressed after ischemic edema, in association with AQP4 depolarization, indicating reduced clearance capacity in the post-ischemic brain [47]. Meningeal lymphatic dysfunction additionally impairs downstream CSF clearance, delaying the removal of lesion-derived waste products and inflammatory mediators and thereby increasing neuroinflammation after cerebrovascular insult [9, 48]. Stroke-related clearance failure therefore has a predominantly transport-centric phenotype, driven mainly by altered perivascular CSF influx [45] and defective glymphatic clearance [46, 47].

Figure 3 summarizes the pathological significance of brain clearance failure across these disorders, illustrating how disrupted CSF-ISF exchange contributes to protein aggregation, impaired metabolite clearance, and progressive neurodegeneration in Alzheimer's disease, Parkinson's disease, and stroke.



**Figure 3. Disease-specific impairments in brain clearance.** Alzheimer's disease (AD): impaired glymphatic clearance promotes A $\beta$  and tau accumulation. Parkinson's disease: defective drainage promotes  $\alpha$ -synuclein aggregation. Stroke: ischemic injury disrupts vascular pulsatility and glymphatic flow, aggravating edema and waste accumulation.

### 3.4 Sex-Dependent Regulation of Brain Clearance in Aging and Neurodegeneration

Epidemiological data show clear sex differences in susceptibility to neurodegenerative disease. AD is more prevalent in women, particularly after menopause [49]. This sexual dimorphism extends to core AD pathological features, including glial reactivity, A $\beta$  deposition, and CSF biomarker profiles. The biological basis of the higher AD susceptibility in women remains poorly defined, particularly with respect to how sex hormones regulate the AQP4-dependent glymphatic system, a principal route for clearing neurotoxic solutes such as A $\beta$  [49].

Preclinical studies have begun to define how gonadal hormones regulate AQP4 function under neuroinflammatory conditions. Depletion of gonadal hormones (estrogen, progesterone, and testosterone) triggers a cascade of pathological events across multiple disease models, including ischemic stroke and traumatic brain injury; these events include the release of pro-inflammatory cytokines (IL-6, IFN- $\gamma$ ), microgliosis, and activation of NF- $\kappa$ B signaling [50]. Loss of astrocytic endfoot AQP4 polarization impairs glymphatic transport efficiency and compromises BBB integrity, providing a mechanistic link between neuroinflammation and defective brain clearance [51]. Sex-specific hormonal regulation of AQP4 and glymphatic flow may therefore help explain the higher AD risk and earlier onset observed in postmenopausal women. Testing this hypothesis will require combining *in vivo* glymphatic imaging with targeted hormonal or anti-inflammatory interventions to determine whether restoring hormonal signaling or AQP4 polarity reduces proteinopathy and modifies AD progression [50].

Human neuroimaging and postmortem studies support sex-dependent differences in brain clearance. MRI- and PET-based perivascular CSF mapping reveals significant sex differences in parenchymal CSF distribution among patients with AD, even after adjustment for age and diagnostic status, consistent with sexually divergent fluid dynamics in neurodegeneration [52, 53]. Postmortem analyses have identified age-related abnormalities in perivascular AQP4 localization that correlate with cerebral amyloid pathology, linking glymphatic dysfunction to toxic protein accumulation [54]. Consistent with sex-specific responses governing protein clearance and glial activation, women show a stronger correlation between amyloid burden and CSF neurodegenerative biomarkers [52].

Sex-dependent vulnerability to neurodegeneration and clearance dysfunction is not restricted to AD. In PD, pronounced sex differences in brain morphology have been documented [55]: men with suspected REM sleep behavior disorder show more severe gray matter atrophy

and greater disruption of frontotemporal network connectivity than women, and these morphological differences correlate with cognitive performance, supporting sex as an important modulator of neurodegenerative susceptibility and clearance function [55]. Beyond classic neurodegenerative disease, sex-specific meningeal lymphatic dysfunction also affects neuropsychiatric disorders. In a mouse model of sub-chronic fluctuating stress, meningeal lymphatic integrity is selectively impaired in females but not in males [56]; manipulating meningeal lymphatic function alters activity in emotion-regulating brain regions and mediates sex differences in stress-induced depressive-like behavior, suggesting that meningeal lymphatic dysfunction increases female susceptibility to stress-related psychiatric disorders [56].

Aging appears to drive glymphatic deterioration in a sex-specific manner, with women showing an accelerated decline in clearance after middle age. This pattern suggests that hormonal change and menopause impair cerebral waste clearance and thereby raise the risk of neurodegeneration in aging women [57].

Collectively, biological sex is an important modifier of age-related decline in brain clearance and of the progression of diverse neurodegenerative disorders. Stratification by sex as a biological variable is therefore essential both for elucidating glymphatic and meningeal lymphatic dysfunction and for developing targeted therapeutic strategies.

## 4. Imaging Modalities and Biomarkers

Accurate assessment of glymphatic and meningeal lymphatic function is essential for defining their contributions to physiological aging and to neurological disease. These systems are inherently complex, mediating interactions among the CSF, the cerebral vasculature, and the immune system, and their evaluation therefore requires both dedicated imaging techniques and molecular biomarkers. Advances in neuroimaging, from diffusion MRI sequences to novel contrast agents, now allow non-invasive visualization of CSF-ISF exchange and lymphatic drainage *in vivo*. Complementary fluid and molecular biomarkers, including CSF proteins, AQP4 isoforms, and lymphatic endothelial markers, provide further insight into the function of these clearance pathways.

### 4.1 Neuroimaging

#### 4.1.1 Diffusion Tensor Imaging Analysis Along the Perivascular Space (DTI-ALPS)

DTI-ALPS is a non-invasive MRI technique that assesses water diffusivity within perivascular spaces and thereby

provides an indirect index of glymphatic function. The method quantifies the anisotropy of water diffusion along white matter tracts that run adjacent to perivascular pathways, allowing glymphatic function to be estimated in living subjects [58]. DTI-ALPS has been applied across a range of neurological disorders: in AD and mild cognitive impairment (MCI), lower ALPS values are associated with higher amyloid load and poorer cognition [59–61]; in PD, lower ALPS values correlate with disease severity and with non-motor symptoms including sleep disturbance [44, 62]; and in idiopathic normal pressure hydrocephalus (iNPH), ALPS values have been used to evaluate clearance and disease severity [63]. In rodent models of vascular disease, reduced ALPS parameters correlate with impaired glymphatic function, providing further validation of the technique [64]. Together, these observations support DTI-ALPS as a candidate biomarker of glymphatic failure.

In a prospective clinical cohort with acute subcortical infarction, DTI-ALPS derived from 3T MRI predicted cognitive impairment with favorable diagnostic accuracy and high sensitivity [65], suggesting that the index may help detect cognitive impairment associated with glymphatic failure [65]. A separate study reported inverse correlations between the ALPS index and A $\beta$  PET and tau PET in patients with AD and MCI [66], indicating a quantitative association between molecular pathology and DTI-ALPS-derived measures of glymphatic dysfunction [66].

#### 4.1.2 Gadolinium-enhanced MRI

Gadolinium-enhanced MRI is primarily a clinical approach in which gadolinium-based contrast agents are administered intrathecally or intravenously and then tracked by serial MRI as they distribute through the CSF and interstitial compartments. Unlike diffusion-based methods, it provides direct visualization of CSF influx, perivascular transport, and clearance into mLVs.

Intrathecally delivered gadolinium-based tracers have been used in preclinical studies to quantify glymphatic influx along periaxonal spaces, efflux through perivenous pathways, and CSF distribution. In humans, gadolinium-enhanced MRI has been applied to AD [67], iNPH [68], and age-related change [69, 70]. Ringstad et al. reported delayed clearance of intrathecal gadolinium tracer in patients with iNPH compared with healthy controls [71]. MRI after intrathecal gadolinium injection shows a progressive signal increase in both the CSF and the cervical lymph nodes [72, 73]. Time-series analysis indicates that CSF enhancement precedes parenchymal glymphatic enhancement and peaks at 4–6 h after injection, whereas cervical lymph node enhancement follows the glymphatic peak and reaches its maximum at

24 h [72, 73]. This temporal pattern provides direct *in vivo* evidence of CSF outflow to the cervical lymph nodes in humans.

Several challenges remain. Intrathecal administration is invasive, and repeated dosing carries a non-negligible risk of gadolinium retention in the brain. Nevertheless, data from a cohort of 100 patients indicate that intrathecal gadobutrol for glymphatic MRI is clinically feasible; all observed adverse reactions were mild and transient, supporting the safety of this modality for evaluating glymphatic clearance [74]. Intravenous delivery is less invasive but has low sensitivity for glymphatic-specific transport [75]. Current work focuses on optimizing contrast agents, refining imaging protocols, and validating quantitative biomarkers to support broader clinical translation.

#### 4.1.3 Near-Infrared Fluorescence Imaging (NIRF)

Near-infrared fluorescence (NIRF) imaging uses contrast agents that emit within the 650–900 nm near-infrared window [76]. This spectral range affords greater tissue penetration and lower background autofluorescence, enabling sensitive, high-resolution visualization of tracer distribution within superficial CNS-associated lymphatic vasculature, particularly the mLVs [77, 78]. Outside the CNS, NIRF has been used to investigate lymphatic pathology in patients with cancer [79, 80]. In rodents, NIRF permits direct visualization of lymphatic drainage and CSF efflux [81], and indocyanine green (ICG)-assisted NIRF allows dynamic quantification of lymphatic drainage efficiency *in vivo* [82, 83]. Subsequent preclinical work has shown that aging [84] and chronic disease [85] slow lymphatic flow, and NIRF has also been used to assess the effects of lymphangiogenic agents such as VEGF-C [86].

Although the sensitivity and specificity of NIRF remain insufficiently validated in human cohorts, second-window near-infrared (NIR-II) imaging offers the spatiotemporal resolution needed to capture changes in glymphatic influx, including adaptive changes under hypothermia [87]. NIR-II nanoprobes operating above 1200 nm achieve high-definition structural mapping of perivascular spaces and real-time tracking of tracer transport [88, 89]. NIR-II fluorescence imaging thus enables deep-tissue visualization of vasculature and lymphatic vessels, making it a useful tool for studying diseases associated with lymphatic dysfunction and CNS injury [90–92].

A distinctive advantage of NIRF is real-time dynamic recording of tracer movement, which permits quantitative measurement of glymphatic clearance rates across physiological and pathological states [93]. Its principal limitation is restricted tissue penetration, which confines

it largely to preclinical work or intraoperative navigation rather than routine clinical examination [94–96]. To address this, hybrid multimodal strategies that combine NIRF with MRI or CT are under development, aiming to pair the sensitivity of NIRF with the depth penetration of cross-sectional tomography, while advances in long-wavelength NIR-II nanoprobe continue to improve spatial resolution.

#### 4.1.4 Two-Photon Microscopy

Two-photon laser scanning microscopy (2PLSM) uses femtosecond near-infrared pulsed lasers (700–1100 nm) to generate high-resolution cellular images *in vivo* [97, 98]. Unlike conventional confocal microscopy, it relies on the near-simultaneous absorption of two low-energy photons, which confines excitation to the focal plane and reduces off-target phototoxicity [97]. This excitation pattern enables deep-tissue imaging to depths of approximately 700  $\mu\text{m}$  within the cerebral cortex and supports repeated longitudinal imaging in live animals [99]. However, the invasive cranial window surgery required for intracranial imaging currently restricts 2PLSM to animal models.

2PLSM has become an indispensable tool for investigating brain clearance pathways, allowing direct visualization of CSF influx into periarterial spaces, AQP4-facilitated ISF exchange, and waste efflux along perivenous routes [1, 100]. It also permits dynamic monitoring of perivascular solute transport under different physiological conditions; for example, two-photon imaging has shown that glymphatic clearance is markedly more efficient during sleep than during wakefulness [3]. Evidence from 2PLSM further indicates that pathological insults including ischemic stroke, traumatic brain injury, and aging disrupt perivascular fluid circulation and astrocytic signaling [101–104].

A particular strength of 2PLSM is its capacity to record tracer movement and cellular activity simultaneously [105]. This capability has been used to characterize interactions among astrocytic endfeet, perivascular macrophages, and microglia, and to show how neuroinflammation remodels glymphatic transport [106]. Despite its power in preclinical neuroscience, the translational value of 2PLSM remains limited: in humans it has been tested only for superficial cutaneous imaging and skin cancer diagnosis, with insufficient safety evidence to support routine clinical use [107].

2PLSM therefore delivers microstructural resolution superior to that of most other modalities, but its clinical translation faces two obstacles: the inherent invasiveness of intracranial imaging, and the absence of established sensitivity and specificity thresholds for diagnostic use.

#### 4.1.5 BBB imaging based on Arterial Spin Labeling (ASL) techniques

ASL uses endogenous arterial blood-borne water molecules as intrinsic tracers to quantify interstitium-vascular water exchange for estimating the BBB water-exchange rate ( $K_{\text{w}}$ ) and may sensitively detect functional changes of the BBB. In addition to non-contrast ASL techniques such as diffusion-prepared pseudo-continuous ASL (DP-pCASL) and multi-echo ASL (ME-ASL) [108, 109], the experimental niche variant contrast-enhanced ASL (CE-ASL) amplifies signals originating from BBB leakage and enables cross-validation of these non-contrast approaches [110]. Combining multiple ASL protocols enable comprehensive profiling of regional BBB water exchange, cerebral blood flow (CBF), and neurofluid transport [110–112].

These modalities allow quantitative analysis of age- and disease-related crosstalk between the BBB and the glymphatic system. Reduced  $k_{\text{w}}$  and glymphatic system impairment have been consistently observed in aging and in AD [113], and preclinical work indicates a 31% increase in exchange time in AQP4-deficient mice compared to their wild-type counterparts, providing a mechanistic basis for these  $k_{\text{w}}$  changes [114].

Derived ASL metrics such as the  $k_{\text{w}}$ /CBF ratio further characterize BBB homeostasis, including developmental trajectories and regional brain iron balance [115]. Reduced  $k_{\text{w}}$  correlates with elevated cerebral iron burden and  $\beta$ -amyloid deposition in a dose-dependent manner, and this signature is more pronounced in APOE  $\epsilon 4$  carriers [116], suggesting that BBB clearance is already impaired at the prodromal stage of AD. Longitudinal trials of anti-amyloid therapeutics report that abnormal  $k_{\text{w}}$  elevation precedes detectable amyloid lesions on imaging and correlates with cognitive performance [117]. These ASL-based quantitative pipelines are now being validated and deployed in clinical cohorts for translational research [118].

#### 4.1.6 Photoacoustic Imaging

Photoacoustic imaging has substantially advanced *in vivo* visualization of the structural and functional characteristics of the glymphatic system and the mLVs. Co-localized photoacoustic microscopy allows real-time mapping of glymphatic drainage at micrometer-level resolution, enabling dynamic tracking of perivascular CSF movement in the brain [119]. Beyond microscopy, photoacoustic tomography has emerged as a promising quantitative technique for evaluating glymphatic clearance. Choi et al. showed that photoacoustic computed tomography can monitor CSF dynamics in real

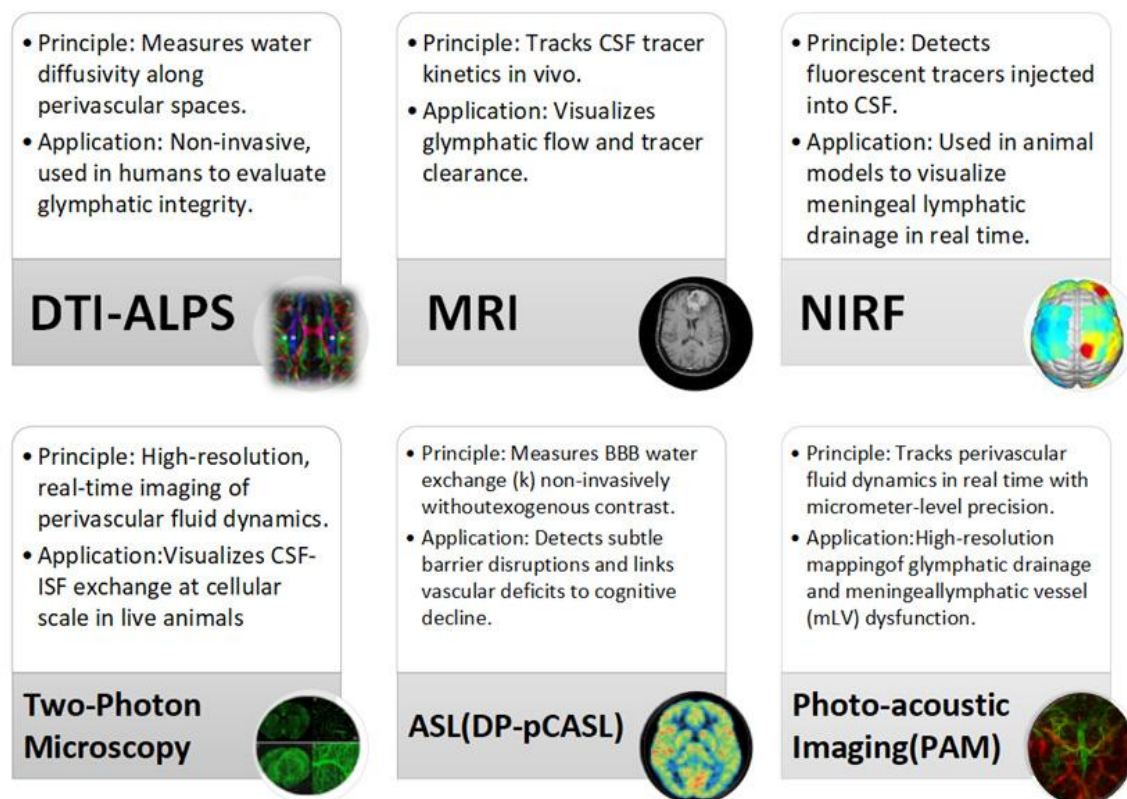
time and detect impaired glymphatic clearance in animal models of AD, providing direct in vivo evidence of glymphatic dysfunction under pathological conditions [120].

In mice, dual-contrast functional photoacoustic microscopy (DCF-PAM) has achieved wide-field imaging of cerebral lymphatic structures, covering both the mLVs and the glymphatic system [121]. This modality supports simultaneous observation of vascular, lymphatic, and glymphatic interactions in the brain and, being label-free, facilitates the investigation of neuroinflammation, neurodegenerative pathogenesis, and CSF flow dynamics [120, 122].

Photoacoustic imaging also enables high-resolution, depth-resolved visualization of mLVs structure and

drainage function, with an effective imaging depth of 3.75 mm in brain tissue. Functional imaging with this technique has shown that meningeal lymphatic drainage efficiency is reduced by approximately 70% in AD animal models [121]. These findings illustrate the value of photoacoustic imaging for in situ functional measurement of cerebral lymphatic systems and for exploring how mLVs and glymphatic function change in neurological disease.

As shown in Figure 4, the principal techniques for functional imaging of brain clearance pathways and for assessing cerebrospinal fluid clearance are summarized and compared.



**Figure 4. Imaging modalities for assessing brain clearance pathways.** Diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) [123] measures water diffusivity. Gadolinium-enhanced MRI [124] tracks CSF tracer kinetics. Near-infrared fluorescence (NIRF) [125] visualizes lymphatic drainage in animals. Two-photon microscopy enables high-resolution observation of perivascular fluid dynamics in vivo [126]. ASL (DP-pCASL) [109] measures BBB water exchange without contrast. Photoacoustic imaging (PAM) [127] offers high-resolution dynamic mapping of fluid clearance.

#### 4.2 Comparing the Translational Scalability of Imaging Modalities

The imaging modalities developed to characterize glymphatic and meningeal lymphatic activity differ greatly in their translational potential. High-resolution optical techniques, including NIR-II imaging and two-

photon microscopy, are powerful tools for elucidating the mechanistic basis of lymphatic drainage and perivascular solute transport [100, 128]. However, their invasiveness, shallow tissue penetration, and incompatibility with long-term human study restrict them to preclinical animal models [129]. Photoacoustic imaging, in the forms of photoacoustic microscopy and photoacoustic computed

tomography, is likewise used mainly in animal experiments [121].

By contrast, MRI-derived methods have clear clinical applicability. DTI-ALPS is a dedicated MRI approach for the specific assessment of glymphatic function [130, 131]. ASL is likewise clinically translatable and can quantify cerebral perfusion in aging and neurodegenerative disease, although it cannot directly measure meningeal lymphatic or glymphatic function [132]. The invasiveness, limited in vivo durability, and restricted spatial coverage of current preclinical techniques therefore remain the principal barriers to their clinical application, particularly in elderly and cognitively impaired populations.

### 4.3 Fluid and Molecular Biomarkers

#### 4.3.1 CSF Biomarkers

Altered CSF profiles are among the best-established indicators of impaired brain clearance. Reduced A $\beta$ <sub>42</sub> and elevated phosphorylated tau reflect inefficient removal of neurotoxic proteins through glymphatic and lymphatic pathways and correlate with AD progression [133–135]. Elevated neurofilament light chain (NfL) in both CSF and plasma indicates axonal injury and has been proposed as a downstream marker of chronic glymphatic dysfunction [136, 137]. Studies further show that reduced CSF turnover, measured by dilution or tracer clearance rate, predicts faster cognitive decline, supporting the use of CSF biomarkers as functional readouts of clearance efficiency [138–140].

#### 4.3.2 AQP4 Isoforms and mLEC Markers

AQP4 is the principal astrocytic water channel driving CSF-ISF exchange. Age-related loss of AQP4 polarization and shifts in AQP4 isoform expression, notably the M1/M23 ratio, have been proposed as contributors to reduced glymphatic transport and increased amyloid accumulation [141, 142]. On the lymphatic side, markers used to identify mLECs, such as LYVE-1, PROX1, podoplanin, and VEGFR-3, have been well characterized in peripheral and pulmonary lymphatic vessels [21, 143–146], and their utility for assessing meningeal lymphatic density and function is increasingly recognized in experimental animal models [147]. Systematic quantification of these markers in human CNS tissue nonetheless remains limited.

#### 4.3.3 Circulating Exosomal miRNAs and Inflammatory Cytokines

Peripheral biomarkers are emerging as promising non-invasive surrogates for brain clearance function and

immune-lymphatic interaction [148]. Elevated systemic cytokines such as IL-6, TNF- $\alpha$ , and TGF- $\beta$  have been associated with reduced lymphatic drainage and BBB breakdown in aging and neurodegeneration [37, 149, 150]. Circulating exosomal microRNAs (miRNAs) derived from astrocytes or endothelial cells constitute a second class of peripheral biomarkers. Preliminary evidence suggests that these exosomal miRNAs track changes in glymphatic and vascular regeneration [151, 152], although it remains unclear whether they passively reflect such changes or actively contribute to them. Downregulation of miR-124 and miR-146a, for example, has been linked to enhanced neuroinflammation and impaired perivascular drainage [153, 154]; the association of neuroinflammation with perivascular drainage may be mediated indirectly through neuroinflammation-driven glymphatic disruption. Although work on both biomarker classes remains exploratory, these circulating molecular profiles hold promise for the non-invasive assessment of neuro-immune-glymphatic communication in humans [136].

### 5. Therapeutic Strategies Targeting Brain Clearance

Restoring or enhancing the efficiency of the brain's glymphatic and meningeal lymphatic systems has become a promising therapeutic objective for mitigating age-related neurodegeneration. Pharmacological strategies target the molecular and cellular components that regulate CSF dynamics, astroglial function, and lymphatic vessel integrity. By modulating factors such as AQP4 channel localization, vascular pulsatility, neuroinflammation, and lymphangiogenesis, these approaches seek to re-establish effective waste clearance and neuroimmune homeostasis [155, 156].

#### 5.1 Pharmacological Approaches

##### 5.1.1 AQP4 Modulators

Aquaporin-4 (AQP4) modulators act on two core properties of the channel: its transmembrane water transport activity and its polarized subcellular distribution at astrocytic endfeet. These properties determine the efficiency of perivascular CSF-ISF exchange and of glymphatic and meningeal lymphatic clearance. According to their binding mode and direction of effect, AQP4 modulators can be grouped into direct AQP4-targeted agents and indirect pathway regulators.

Researchers have identified multiple direct AQP4-targeted compounds to modulate the water permeability of AQP4. In an in vitro functional assay, carbonic anhydrase inhibitors acetazolamide, 6-ethoxybenzothiazole-2-sulfonamide and 4-acetamido-

benzulfonamide suppressed human AQP4-M23-dependent water transport with respective inhibitory efficiencies of 80%, 68% and 23% [157]. TGN-020, a selective AQP4 inhibitor, could mitigate brain injury in ischemic mouse models through glymphatic pathway [158].

Beyond direct AQP4 binders, a range of indirect pharmacological interventions improve glymphatic and meningeal lymphatic drainage by restoring physiological AQP4 polarity. Such compounds modulate AQP4 anchoring at astrocytic endfeet by tuning signaling cascades linked to the dystrophin–syntrophin complex, thereby altering brain waste clearance. In MPTP-induced Parkinson's disease mice, agomelatine restores AQP4 polarity and accelerates brain lymphatic transport [159]. In epilepsy, pan-adrenergic receptor antagonism preserves AQP4 polarization, increases lymphatic flow during status epilepticus [160]. In rodent models of TBI, vasopressin V1a antagonists could reverse pathological AQP4 dysregulation, suggesting that vasopressin inhibition indirectly remodels glymphatic function [161]. Melatonin mitigates sleep restriction-induced glymphatic dysfunction in mice by regulating AQP4 polarization, and also relieves neuroinflammation and reduces cerebral A $\beta$  and tau accumulation [162]. In APP/PS1 mice, intranasal oxytocin strengthens AQP4 polarization and promotes cerebral lymphangiogenesis, which together enhance glymphatic and meningeal lymphatic drainage, lower parenchymal A $\beta$  burden, and accelerate toxic protein clearance [163].

### 5.1.2 Vascular Endothelial Growth Factor C (VEGF-C) Administration

VEGF-C is a leading preclinical candidate for therapeutic lymphangiogenesis. In preclinical mouse models, VEGF-C delivery restores impaired meningeal lymphatic architecture and improves cognitive function after stroke-, TBI-, or aging-induced clearance dysfunction [164–166]; by contrast, clinical evidence for its effects on human glymphatic clearance remains limited [167]. In a separate animal study, adeno-associated virus (AAV)-mediated VEGF-C delivery increased tracer uptake and increased CSF drainage to the deep cervical lymph nodes by enhancing lymphatic growth [48].

### 5.1.3 Anti-inflammatory and Anesthetic Agents

Neuroinflammation impairs cerebral clearance through several converging mechanisms, including microglial activation, cytokine-mediated vascular injury, BBB disruption, astroglial dysfunction, AQP4 depolarization, and reduced CSF-ISF exchange [155, 156]. These cascades collectively compromise perivascular

glymphatic transport and meningeal lymphatic drainage, providing the rationale for anti-inflammatory and neuroprotective therapies directed at the glymphatic-lymphatic system [155, 156]. Consistent with this principle, several pharmacological interventions have been shown in preclinical studies to modulate brain clearance by acting on neuroinflammation.

Ketoprofen, a typical non-steroidal anti-inflammatory drug, exerts direct modulatory effects on meningeal lymphatic function. In a rat model of TBI, ketoprofen preserves the integrity of mLVs, improves lymphatic vessel function, and facilitates extracranial CSF drainage and the resolution of cerebral edema [147]. Mechanistically, it attenuates neuroinflammation and reactive oxygen species production while upregulating the expression of lymphatic endothelial markers (VEGFR3, PROX1, LYVE1, and FOXC2), thereby maintaining lymphatic homeostasis [147].

Anesthetic agents can also modulate glymphatic function through neuroinflammation-related, AQP4-dependent signaling. Dexmedetomidine rescues sevoflurane-induced glymphatic perfusion deficits by activating the PI3K/AKT/ $\Delta$ FosB/AQP4 signaling axis, thereby restoring brain clearance and ameliorating deficits in learning and working memory [168].

## 5.2 Non-Pharmacological Interventions

### 5.2.1 Sleep Hygiene and Chronotherapy

Sleep hygiene interventions and chronotherapy, including regular sleep–wake scheduling, controlled light exposure, and behavioral sleep modification, are effective non-invasive approaches to optimizing sleep architecture. These strategies prolong and consolidate slow-wave sleep (SWS), the stage associated with the highest glymphatic clearance efficiency. Consistent with this, preclinical studies have shown that the clearance of neurotoxic metabolites such as A $\beta$  is markedly accelerated during SWS-rich sleep, which is characterized by robust slow-wave neuronal activity, relative to wakefulness [3].

### 5.2.2 Physical Activity

Aerobic exercise improves cerebrovascular physiology by enhancing vascular compliance and amplifying arterial pulsatility, two mechanical drivers of intracranial glymphatic fluid flux [169–171]. Consistent with these vascular benefits, preclinical studies have shown that voluntary wheel running increases CSF-ISF exchange efficiency and reduces the cerebral accumulation of misfolded proteins through activation of the glymphatic system [104].

### 5.2.3 Non-invasive Neuromodulation

A range of non-invasive neuromodulatory strategies can regulate glymphatic function, either through signal-based modulation or through mechanical force. Signal-based approaches, including photobiomodulation (PBM), transcranial magnetic stimulation (TMS), and electroacupuncture, enhance glymphatic tracer clearance, restore AQP4 polarization, ameliorate perioperative neurocognitive disorder, and thereby mitigate A $\beta$  pathology in AD [172–174]. Distinct from sleep-dependent glymphatic regulation, 40 Hz gamma multisensory light stimulation augments glymphatic influx independently of sleep state by activating astrocytic A2A receptors and preserving AQP4 polarity, as shown in preliminary human and animal studies [175]. Mechanical approaches, including low-frequency transcranial pulsation and transcranial focused ultrasound (FUS), modulate CSF circulation and vascular tone through skull-transmitted mechanical energy [176–180]. Low-frequency transcranial pulsation improves perivascular transport efficiency [181, 182], whereas low-intensity FUS facilitates CSF-ISF exchange and elevates glymphatic tracer influx in rodent models [183]. FUS combined with microbubbles (FUSMB) further enhances CSF tracer clearance [100]. Clinically, repeated MRI-guided low-intensity FUS induces reversible BBB opening, remodels intracranial fluid and solute dynamics, and reduces amyloid plaque burden in patients with AD [184]. A phase 1 trial in mild-to-moderate AD further showed that FUS-mediated BBB opening alters serum A $\beta$ 42, tau, and phosphorylated tau levels, accompanied by delayed local amyloid deposition on PET imaging [185]. Collectively, these signal-based and mechanical neuromodulation approaches show promise for treating cerebral clearance dysfunction caused by aging and neurodegenerative disease.

## 5.3 Surgical and Experimental Approaches

### 5.3.1 CSF Diversion

Surgical interventions such as ventriculoperitoneal shunting redirect CSF to alternative body compartments, lowering intracranial pressure and restoring physiological CSF dynamics. The resulting normalization of pressure gradients within the CSF system permits greater glymphatic influx and efflux, accelerating the clearance of solutes that have accumulated in the interstitial space. Optimized CSF circulation also facilitates CSF outflow into mLVs, indirectly enhancing cerebral immune surveillance and metabolic waste clearance. Such interventions have therapeutic implications for patients with hydrocephalus and for certain dementias [186, 187].

### 5.3.2 Lymphatic Vessel Transplantation and Tissue Engineering

Regenerative bioengineering approaches to reconstructing damaged meningeal lymphatic circuits fall into two categories: lymphatic vessel transplantation and lymphangiogenic tissue engineering. Lymphatic vessel transplantation involves implanting lymphatic tissue or biomaterial scaffolds seeded with lymphatic endothelial cells (LECs). Preclinical experiments in lymphedema animal models have shown that transplanted lymphatic constructs can integrate with the host lymphatic network, promote lymphangiogenesis, and re-establish directional lymphatic drainage [188]. In lymphangiogenic tissue engineering, biomimetic tunable hydrogel scaffolds are designed to recapitulate the structural and molecular microenvironment required for LECs proliferation and vessel maturation. Supported by biochemical cues such as VEGF-C, these engineered matrices promote LECs aggregation and de novo lumen formation, providing a foundation for translating such strategies to the central nervous system [189, 190].

Although these regenerative techniques remain at an early preclinical stage, they hold therapeutic promise for disorders driven by meningeal lymphatic rarefaction or dysfunction, including age-related insufficiency of cerebral waste clearance, traumatic brain injury [190], and AD [191–193]. Future work may combine bioengineered lymphatic grafts with pro-lymphangiogenic interventions (for example, VEGF-C supplementation or PROX1 upregulation), offering long-term strategies to restore meningeal lymphatic drainage and sustain cerebral neuroimmune homeostasis.

## 6. Interplay with Vascular and Immune Systems

Brain clearance is intrinsically coupled to the cerebral vasculature and the immune network, and they together form an integrated neurovascular–glymphatic–immune axis. Age-related vascular stiffening and endothelial dysfunction reduce arterial pulsatility [23], a primary mechanical driver of glymphatic fluid circulation. Hypertension and atherosclerotic lesions further compromise arterial compliance, restricting cerebrospinal fluid perfusion within perivascular spaces and thereby disrupting glymphatic transport [4, 194, 195]. From an immunological perspective, aging triggers microglial priming and low-grade chronic neuroinflammation, alongside diminished immune cell trafficking through mLVs [196, 197]. This cascade elevates cerebral levels of pro-inflammatory cytokines, which damage the vascular endothelial barrier and further impair brain waste clearance. Cumulatively, these vascular and immune

aberrations create a self-amplifying loop that progressively degrades glymphatic and meningeal lymphatic function, underscoring the need for multi-target therapeutic interventions [198, 199].

## 7. Future Directions and Challenges

Although preclinical investigations have established the importance of glymphatic and meningeal lymphatic drainage for brain homeostasis, several barriers must be overcome before these insights can be applied clinically.

### 7.1 Challenges

**Limited human-specific imaging tools:** As discussed above, most established methods for quantifying glymphatic function, such as two-photon microscopy and intrathecal contrast-enhanced MRI, are either invasive or restricted to preclinical animal models. Emerging non-invasive sequences, including DTI-ALPS, dynamic contrast-enhanced MRI, and high-resolution phase-contrast MRI, show promising translational value for human research, but substantial work remains to validate their diagnostic reliability, standardize acquisition protocols, and conduct large-scale multicenter trials across heterogeneous cohorts. Tools that enable direct functional assessment of mLVs in human subjects are scarcer still.

**Lack of standardized biomarkers:** No biomarker of brain clearance dysfunction is universally accepted for early identification or longitudinal assessment. Candidate markers such as AQP4-related markers in CSF, mLEC-associated markers, and circulating exosomal miRNAs remain at the experimental and preclinical stage. Standardizing assays and detection methods, validating them in large clinical cohorts, and establishing clinically relevant threshold values are essential steps toward their adoption in routine clinical practice.

**Translational gaps in therapeutics:** Many therapeutic interventions designed to restore or enhance glymphatic and meningeal lymphatic clearance, including VEGF-C delivery, AQP4-targeted modulators, and focused ultrasound, yield encouraging outcomes in preclinical animal models. Their translation into clinical practice is nonetheless hampered by obstacles relating to regulatory approval, biosafety, and demonstrated efficacy. In addition, marked interspecies differences between rodents and humans, encompassing neuroanatomical structure, CSF kinetics, astrocytic organization, baseline physiology, and disease course, further restrict the direct translation of preclinical results to human trials.

### 7.2 Future Directions for Translating Glymphatic and Meningeal Lymphatic Research

Addressing these translational gaps will require future studies to integrate advanced imaging, molecular, and computational technologies.

**Advances in multimodal neuroimaging:** A core research priority is to develop integrated multimodal protocols that combine anatomical MRI, molecular imaging, and quantitative measurement of cerebrospinal fluid hemodynamics in order to visualize cerebral clearance processes in real time. Such combined strategies would enable systematic characterization of glymphatic transport, perivascular fluid circulation, and meningeal lymphatic drainage under both physiological and pathological conditions.

**Single-cell and spatial transcriptomics:** Single-cell RNA sequencing and spatial transcriptomics can resolve molecular alterations in the cell populations that constitute the cerebral clearance system, including perivascular astrocytes, vascular endothelial cells, pericytes, and meningeal lymphatic endothelial cells (mLECs). These profiling approaches allow comprehensive identification of age- and disease-associated changes in AQP4 polarity, NVU integrity, inflammatory signaling cascades, and meningeal lymphatic remodeling.

**Artificial intelligence (AI)-guided data integration:** Machine learning and AI can be deployed to integrate large-scale multimodal datasets spanning neuroimaging measurements, circulating biomarkers, CSF profiling, and clinical outcomes. AI-based predictive modeling serves two core translational purposes: the early identification of mild cerebral clearance dysfunction, and the stratification of patients according to likely therapeutic response, thereby advancing precision medicine for neurological disorders.

**Computational fluid dynamics (CFD) models:** Patient-specific CFD simulations can quantify how vascular compliance, CSF circulation, arterial pulsatility, intracranial pressure, and surgical intervention modulate glymphatic and meningeal lymphatic function. These computational frameworks deepen mechanistic insight into how chronic factors including vascular stiffening, sleep–wake cycles, hypertension, and neuroinflammation reshape long-term glymphatic–lymphatic transport dynamics. Integrating technological innovation, molecular profiling, and in silico modeling should drive a shift toward precise, individualized diagnostic and therapeutic regimens. Such integrated methodologies will be pivotal in translating encouraging preclinical discoveries about cerebral clearance into clinically viable platforms for the prevention and treatment of age-associated neurodegenerative disorders.

## 8. Conclusion

Progressive dysfunction of the glymphatic system and the meningeal lymphatic vasculature is an underrecognized but potentially pivotal contributor to age-related neurological disease. As mechanistic understanding of these cerebral clearance circuits continues to expand, targeting endogenous brain waste clearance pathways is emerging as a plausible therapeutic strategy for aging populations. To translate these promising preclinical insights into tangible clinical gains, future research must prioritize the validation, standardization, and optimization of therapeutic strategies that modulate glymphatic and meningeal lymphatic function.

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## Competing Interests

The authors declare no competing interests.

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