Acta Neuropathologica Communications https://doi.org/10.1186/s40478-025-02203-9

Article in Press

The glymphatic system in neurodegenerative diseases and brain tumors: mechanistic insights, biomarker advances, and therapeutic opportunities

Received: 24 October 2025

Accepted: 1 December 2025

Published online: 13 December 2025

Cite this article as: Jia L., Chen Y., Li H. *et al.* The glymphatic system in neurodegenerative diseases and brain tumors: mechanistic insights, biomarker advances, and therapeutic opportunities. *acta neuropathol commun* (2025). https://doi.org/10.1186/s40478-025-02203-9

Liyun Jia, Yue Chen, Hengzeng Li, Kai Zhao, Shuo Ge, Cong Wang, Jiayuan Zhao, Feifei Li, Leilei Zhang & Anhui Yao

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

ARTICLE IN PRESS

The Glymphatic System in Neurodegenerative Diseases and Brain Tumors: Mechanistic Insights, Biomarker Advances, and Therapeutic Opportunities

Authors: Liyun Jia [a,*], Yue Chen [a], Hengzeng Li [b], Kai Zhao [c], Shuo Ge [a], Cong Wang [d], Jiayuan Zhao [e], Feifei Li [a], Leilei Zhang [a], Anhui Yao [d,*]

Affiliations:

[a] Department of Medical Genetics & Cell Biology, School of Basic Medical Sciences, Zhengzhou University, Zhengzhou, Henan Province, 450001, PR China.

[b] The First Clinical School of Medicine, Zhengzhou University, Zhengzhou, Henan Province, 450000, PR China

[c] Beijing Institute for Brain Research, Beijing, 102206, PR China.

[d] Department of Neurosurgery, 988th Hospital of Joint Logistic Support Force of PLA, Zhengzhou, Henan Province, 450052, PR China

[e] The Third Clinical College, Henan Medical University, Xinxiang, Henan Province, 453003, PR China

[*] **Correspondence to:**

Dr Anhui Yao, Department of Neurosurgery, 988th Hospital of Joint Logistic Support Force of PLA, Zhengshang Road 602, Zhengzhou, Henan 450051, P.R. China, E-mail: yaoanhui@aliyun.com.

Dr Liyun Jia, Department of Medical Genetics and Cell Biology, School of Basic Medical Sciences, Zhengzhou University, Kexue Avenue 100, Zhengzhou, Henan 450001, P.R. China, E-mail: jialiyun0410@zzu.edu.cn

ARTICLE IN PRESS

ARTICLE IN PRESS

Abstract

Dysfunction of the glymphatic system (GS), a brain-wide waste clearance pathway dependent on polarized aquaporin-4 (AQP4) water channels on astrocytic endfeet, is increasingly recognized as a critical mechanism in both neurodegenerative diseases and brain tumors. In Alzheimer's (AD) and Parkinson's (PD) diseases, impaired glymphatic function leads to the accumulation of neurotoxic proteins, including amyloid-β (Aβ), tau, and α-synuclein (α-syn). Contributing factors include loss of AQP4 polarization, reduced arterial pulsatility, genetic risks (e.g., *APOE4*, *FAM171A2* mutations), and sleep disturbances. These functional impairments can be quantified using neuroimaging biomarkers such as the diffusion tensor imaging along the perivascular space (DTI-ALPS) index and choroid plexus volume (CPV), which correlate with pathological burden and clinical decline, though the direct physiological interpretation of these metrics requires further validation. Conversely, in glioblastoma and other brain tumors, mechanical compression and lactate-driven acidosis obstruct perivascular fluid transport, promoting an immunosuppressive tumor microenvironment that limits T-cell infiltration and confers therapeutic resistance. Here, too, glymphatic dysfunction is reflected by a reduced ALPS index, which correlates with tumor grade, peritumoral edema, and survival. Emerging therapeutic strategies aimed at restoring GS function include pharmacological interventions (e.g., circadian regulators, AQP4 modulators), non-invasive techniques (e.g., cervical lymphatic stimulation, gamma entrainment, exercise), and surgical approaches (e.g., lymphatic-venous anastomosis). Advances in multimodal MRI and artificial

ARTICLE IN PRESS

ARTICLE IN PRESS

intelligence (AI)-enhanced analytics further support novel diagnostic capabilities. This review highlights the dual role of the GS across neurological disorders and underscores its potential as a therapeutic target for enhancing waste clearance and immune modulation. However, significant challenges remain, including the validation of human biomarkers, elucidating bidirectional tumor–glymphatic crosstalk, and translating preclinical discoveries into clinical practice.

Keywords: glymphatic system; AQP4; proteinopathy; tumor microenvironment; neuroimmunology; DTI-ALPS index

ARTICLE IN PRESS

Introduction

The glymphatic system (GS) is a recently identified macroscopic waste clearance network in the central nervous system that facilitates the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF). This process is driven by cerebrospinal fluid influx along periarterial spaces, which then penetrates the brain parenchyma via astrocytic aquaporin-4 (AQP4) water channels polarized on their endfeet. Subsequently, fluid and solutes, including metabolic waste and proteins, are cleared along perivenous and perineural pathways, ultimately draining into the meningeal lymphatics and cervical lymphatic vessels (cLVs) as a major efflux route[1-3]. It is important to note that waste solutes and ISF are cleared via multiple parallel pathways; a significant portion also exits the cranium through alternative routes, including the traditionally described arachnoid villi into the dural venous sinuses, along perineural pathways (e.g., olfactory and optic nerves) to the nasal mucosa and cervical

ARTICLE IN PRESS

lymphatics, or directly into the venous blood circulation[4-6]. Structurally, the GS utilizes the perivascular spaces (PVS) formed by astrocyte endfeet ensheathing cerebral arteries, capillaries, and veins[7]. Seminal work by Iliff et al. (2012) established that CSF influx occurs primarily along para-arterial routes, while interstitial solutes such as amyloid-β (Aβ) are cleared via paravenous drainage, with AQP4-dependent astrocytic water transport driving this bulk flow[2]. These PVS communicate directly with the subarachnoid space, enabling low-resistance CSF flow into deep brain regions[8]. Neuroimaging studies using intrathecal contrast agents have demonstrated that CSF enters the brain along major ventral arteries—specifically, via the anterior cerebral artery to the mediobasal frontal lobe and cingulate cortex, via the middle cerebral artery to the insula, and via posterior circulation pathways to limbic structures. From these entry points, contrast agent distributes rostrally and dorsally to cortical areas and deeper structures, including the corpus callosum and basal ganglia[9,10]. Recent anatomical mapping in Prox1-GFP mice has further delineated the outflow pathway of CSF through meningeal lymphatics at the skull base, which connects to extracranial lymphatic vessels, including periorbital, olfactory, nasopharyngeal, and hard palate lymphatics, ultimately draining into superficial cervical lymph nodes (CLNs)[11] (Figure 1). At the dura mater level, mast cells have been identified as key regulators of CSF dynamics at arachnoid cuff exit (ACE) points, where they modulate CSF–dura exchange through histamine release, influencing perivascular space morphology and immune cell recruitment[12].

Beyond its role in waste clearance, the GS regulates neuroimmune interactions,

ARTICLE IN PRESS

thereby influencing the progression of neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's (PD), as well as cerebral malignancies[13]. Emerging evidence highlights its context-dependent duality: impaired glymphatic function contributes to the accumulation of neurotoxic proteins (e.g., Aβ and tau) in neurodegenerative conditions and aging, whereas in brain tumors, including gliomas and lymphomas, glymphatic activity may facilitate the formation of an immunosuppressive tumor microenvironment (TME), promoting therapeutic resistance[14]. This dichotomous role underscores the system's critical dependence on specific tissue microenvironments and pathological contexts.

Clinical and preclinical studies indicate that glymphatic function is vulnerable to age-related decline, surgical stress, and pharmacological modulation. Perioperative studies in aged mouse models demonstrate that anesthesia combined with laparotomy synergistically impairs glymphatic clearance, correlating with postoperative delirium and accelerated accumulation of Aβ and tau[15]. Disruptions in sleep architecture—particularly non-rapid eye movement (non-REM) sleep, which is critical for glymphatic regulation—suppress CSF-ISF exchange, exacerbating protein aggregation[16]. Age-related reduction in glymphatic efficiency is associated with decreased meningeal lymphatic density and impaired nitric oxide (NO) signaling. Notably, non-invasive mechanical stimulation of cervical lymphatics using force-regulated devices has been shown to restore lymphatic contractility, double CSF outflow in aged models, and reverse functional impairment[11]. Conversely, emerging neuromodulatory approaches such as 40 Hz sensory stimulation enhance glymphatic

flow via adenosine A2A receptor (A2AR) signaling, offering translational potential for mitigating neuroinflammation[17]. Despite these advances, critical knowledge gaps remain regarding bidirectional glymphatic–tumor interactions, the validation of neuroimaging biomarkers for early disease detection, and the mechanistic links between AQP4 polarization and immune cell trafficking[14].

This review synthesizes contemporary insights into glymphatic pathophysiology, emphasizing its integral role in neurodegeneration and brain tumors. We critically evaluate the molecular mechanisms driving glymphatic impairment, emerging diagnostic tools, and innovative therapeutic strategies, with the aim of catalyzing interdisciplinary research that bridges mechanistic discovery and clinical translation.

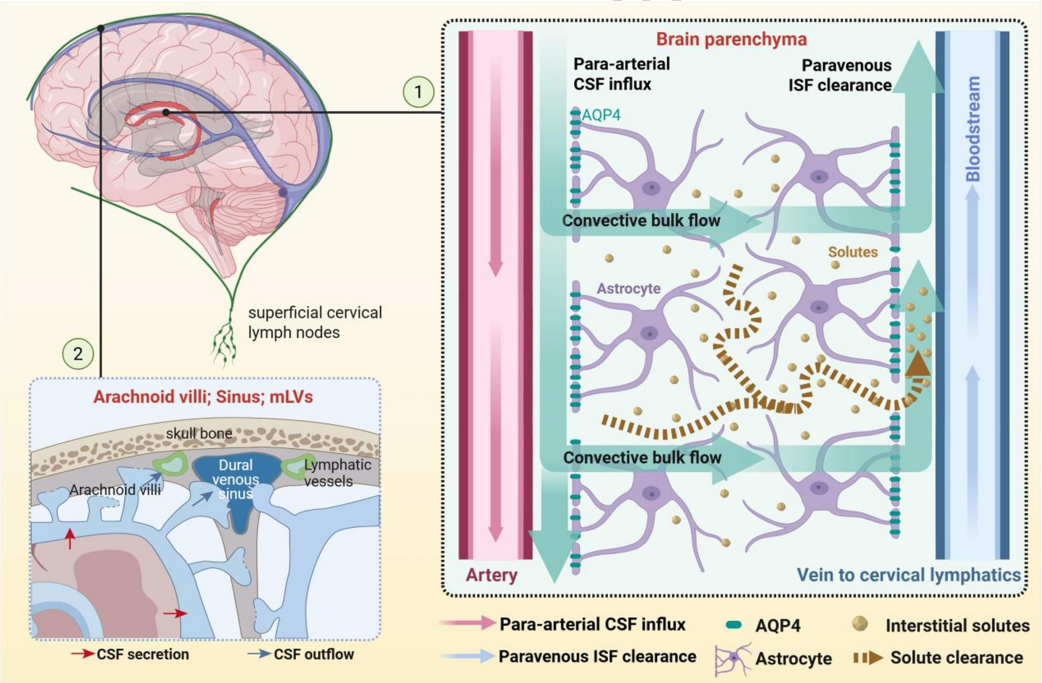

Fig. 1 Interstitial Solute and Fluid Clearance in the Glymphatic System. (1) Driven by arterial pulsations and the polarized distribution of aquaporin-4 (AQP4) channels on astrocytic endfeet, cerebrospinal fluid (CSF) undergoes convective bulk flow into the brain parenchyma. Within the

ARTICLE IN PRESS

interstitial space, CSF mixes with interstitial fluid (ISF), facilitating the clearance of solutes, including metabolic waste, misfolded proteins, and extracellular molecules, via bulk fluid transport. Solute-laden ISF is subsequently cleared along paravenous routes adjacent to veins, ultimately draining into the cervical lymphatic system and systemic circulation. (2) Concurrently, CSF exits the cranial compartment through arachnoid granulations into the dural venous sinuses and via meningeal lymphatic vessels (mLVs) within the dura mater.

1. Mechanisms of Glymphatic Dysfunction in Neurodegenerative Diseases

1.1 Glymphatic Dysfunction in AD and PD

1.1.1 Glymphatic Dysfunction in AD

The GS is a crucial regulator of brain homeostasis, and its dysfunction represents a pivotal mechanism in the pathogenesis of AD. Central to this system is AQP4, a water channel protein densely polarized at astrocytic endfeet that orchestrates CSF–ISF exchange. In AD, disrupted polarization of AQP4 significantly reduces the efficiency of CSF–ISF exchange by 40–60%, which strongly correlates with Aβ plaque deposition, tau hyperphosphorylation, and early cognitive decline[18,19]. This dysregulation initiates a self-reinforcing cycle of impaired protein clearance and neurotoxicity. Postmortem analyses confirm a marked reduction in perivascular AQP4 localization in AD patients[19]. Pharmacological inhibition of AQP4 (e.g., using TGN-020) accelerates tau propagation and compromises the clearance of pathogenic proteins, further exacerbating disease progression[20].

Sleep deprivation increases interstitial tau in mice and CSF tau in humans, and promotes tau pathology spread in seeding models, underscoring the critical influence

ARTICLE IN PRESS

of the sleep–wake cycle on tau dynamics[21]. Accumulating evidence implicates glymphatic dysfunction in AD pathogenesis, demonstrating strong associations with Aβ accumulation and related pathology[22]. Advanced neuroimaging provides robust diagnostic and prognostic biomarkers of this impairment. The diffusion tensor image analysis along the perivascular space (DTI-ALPS) index—a non-invasive metric of glymphatic function—is consistently reduced in AD patients. This reduction correlates with enlarged PVS in the basal ganglia (BG-PVS), diminished Aβ clearance, poorer cognitive performance, and cerebral atrophy[23-28]. Importantly, the ALPS index predicts Aβ deposition, clinical progression, and cognitive decline, with amyloid pathology and neurodegeneration mediating the relationship between lymphatic dysfunction and cognitive impairment[24]. Moreover, the cerebrospinal fluid fraction (CSFF) also shows promise as a biomarker, exhibiting a positive correlation with Aβ deposition at the individual level and spatial correspondence between regions of Aβ accumulation and impaired glymphatic clearance[29]. Alterations in putative MRI-based biomarkers of GS function and CSF AQP4 levels further underscore the interplay between glymphatic impairment and neurodegeneration in AD[30]. A recent study using intravoxel incoherent motion (IVIM) MRI reported that the pseudodiffusion coefficient is significantly reduced following sleep deprivation and tends to be lower in older adults compared to younger individuals, supporting the utility of non-contrast MRI in detecting sleep- and aging-related impairments in CSF dynamics[31].

Multiple factors contribute to glymphatic dysfunction in AD. Genetic susceptibility

ARTICLE IN PRESS

plays a key role: the apolipoprotein E ε4 (*APOE4*) allele significantly increases AD risk, with heterozygous and homozygous carriers facing 4-fold and 12-fold higher risks, respectively[32]. In vivo evidence suggests that APOE impedes Aβ clearance across the blood–brain barrier (BBB)[33]. Mutations in the Family With Sequence Similarity 171 Member A2 (*FAM171A2*) gene disrupt the stability of progranulin (PGRN) in CSF, thereby contributing to neurodegenerative pathogenesis[34,35]. Vascular aging synergizes with these mechanisms; arteriolosclerosis diminishes arterial pulsatility (reducing glymphatic efficiency), and hypertension exacerbates inadequate CSF propulsion, leading to greater tau accumulation in uncontrolled hypertension[36,37]. Romay et al. (2023) demonstrated that Neurogenic Locus Notch Homolog Protein 3 (*NOTCH3*) mutations cause glymphatic dysfunction and accelerate brain senescence in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[38]. Ischemic heart disease (IHD) independently increases AD risk by impairing glymphatic function[39]. Furthermore, impaired perivascular CSF pulsation conduction in AD compromises vascular pulsatile function, diminishing Aβ clearance[40]. The bidirectional relationship between sleep disturbances and AD is mediated through APOE4-dependent reductions in AQP4 polarization and sleep deprivation-induced microglial dysregulation[41,42].

The choroid plexus (CP), the primary producer of CSF, also plays a role: increased choroid plexus volume (CPV) and blood flow in AD correlate with tau levels, suggesting its involvement in disease progression[43]. Proteomic studies have

ARTICLE IN PRESS

identified seven key proteins (NSUN6, GRAAK, OLFML3, ACTN2, RUXF, SHPS1, and TIM-4) that link immune response alterations to GS failure in the elderly, potentially serving as biomarkers for predicting mild cognitive impairment (MCI) and AD[44]. Meningeal lymphatic vessels (mLVs) are severely compromised; AD mouse models exhibit approximately 70% reduction in mLV drainage volume compared to wild-type controls, with further decline as the disease progresses[45]. Novel imaging techniques such as dual-contrast functional photoacoustic microscopy, capable of depth imaging up to 3.75 mm, are elucidating mLV morphology and dynamics, confirming directional CSF flow toward lymph nodes and identifying a peak drainage window 20–40 minutes post-injection[45].

In summary, glymphatic and meningeal lymphatic dysfunction, characterized by impaired AQP4 polarization and failure of clearance pathways, constitutes a central mechanism in AD. This dysfunction is intimately linked to Aβ and tau pathology, vascular risk factors, genetic susceptibility, and sleep disruption. Advances in imaging (e.g., ALPS index, CSFF, photoacoustic microscopy) and biomarker research are deepening our understanding and providing new diagnostic tools. Emerging therapeutic strategies targeting fluid dynamics, AQP4, mLVs, and clearance pathways hold significant promise for mitigating AD progression by restoring brain homeostasis[46,47].

ARTICLE IN PRESS

1.1.2 Glymphatic Dysfunction in PD

PD pathophysiology is characterized by significant glymphatic impairment. Central to this dysfunction is the obstruction of PVS by α-syn aggregates, which reduces

ARTICLE IN PRESS

clearance efficiency by approximately 30% and accelerates dopaminergic neurodegeneration[14]. This impairment is mechanistically linked to matrix metalloproteinase-9 (MMP-9)-mediated cleavage of β-dystroglycan, disrupting the critical polarization of AQP4 water channels[48]. The resulting failure in AQP4-mediated fluid dynamics creates a self-perpetuating cycle of impaired protein clearance. Environmental factors further exacerbate this pathology; exposure to air pollution induces neuroinflammation and sleep abnormalities that collectively impair glymphatic function, representing a proposed etiological mechanism in neurodegenerative progression[49]. Aging synergistically promotes dysfunction through astrocytic senescence and extracellular matrix remodeling mediated by MMP-9 activation[48].

Clinical evidence highlights the CP as a key component of GS dysfunction in PD. CP enlargement is associated with baseline frontal/executive dysfunction and early dementia progression[50], while its volume (CPV)—readily quantifiable on routine brain MRI—shows potential as a biomarker for both baseline motor disability and its longitudinal progression[51]. Glymphatic dysfunction also mediates the impact of peripheral inflammation on motor symptoms in PD, with distinct inflammatory characteristics observed between tremor-dominant (TD) and postural instability/gait difficulty (PIGD) subtypes[52].

Advanced neuroimaging reveals consistent biomarkers of glymphatic impairment in PD. The DTI-ALPS index is reduced in PD patients, initially declining in the left hemisphere with subsequent involvement of the right[53]. This reduction correlates

ARTICLE IN PRESS

with increased PVS burden[54] and is closely associated with both aging and disease progression, particularly with enlarged PVS (EPVS) in the BG region[55,56]. The ALPS index shows promise not only for differentiating PD patients from healthy controls but also for predicting longitudinal motor decline[13]. PVS alterations are especially prominent in familial PD (FPD) and carriers of leucine-rich repeat kinase 2 (*LRRK2*) mutations[57]. Furthermore, glymphatic dysfunction correlates with cognitive decline in PD, where regional cortical degeneration may link impaired clearance to cognitive deficits[58], and is associated with motor symptom severity and subtype[59]. A novel functional indicator, decoupling between global blood-oxygen-level-dependent (gBOLD) signals and CSF inflow dynamics, correlates with longitudinal motor impairment and psychiatric symptoms in PD, potentially serving as a biomarker of glymphatic dysfunction and revealing new lymphatic mechanisms underlying PD pathophysiology[60,61].

Alpha-synucleinopathy represents a common pathological feature in both idiopathic REM sleep behavior disorder (iRBD) and PD, with AQP4-mediated glymphatic activity critically regulating parenchymal α-syn dynamics[14,62]. Consequently, restoring glymphatic function emerges as a promising therapeutic strategy to delay PD progression. Meningeal lymphatic dysfunction is specifically implicated in idiopathic PD (iPD), suggesting that enhancing meningeal lymphatic drainage offers a viable therapeutic target[63]. Interventions targeting the GS, such as CP regulation or AQP4 restoration, represent promising approaches for modifying disease progression[19,64]. Modulation of GS function may enable innovative therapeutic

ARTICLE IN PRESS

strategies through early biomarker identification, control of genetic and vascular risk factors, and multimodal interventions, though further research is needed to validate and standardize these approaches[65].

1.1.3 Conclusion

Glymphatic dysfunction represents a critical convergent mechanism in both AD and PD, fundamentally disrupting brain homeostasis and driving core pathological features. In AD, impaired polarization of AQP4 at astrocytic endfeet initiates a self-sustaining cycle of reduced CSF–ISF exchange, pathological accumulation of Aβ and tau, and cognitive decline. This process is exacerbated by genetic factors (e.g., *APOE4*), vascular abnormalities (e.g., diminished arterial pulsatility), and lifestyle contributors (e.g., sleep disruption), with mLV drainage severely compromised. In PD, obstruction of PVS by α-syn aggregates reduces clearance efficiency, accelerating dopaminergic degeneration. MMP-9-mediated disruption of AQP4 polarization and meningeal lymphatic impairment further propagate pathology, compounded by environmental triggers (e.g., air pollution) and aging.

Advanced neuroimaging biomarkers quantitatively capture this dysfunction: the DTI-ALPS index correlates with Aβ and tau burden as well as cognitive decline in AD, while in PD it tracks motor progression, hemispheric asymmetry, and cognitive impairment. CP enlargement serves as a structural indicator in both diseases. Crucially, the glymphatic–meningeal lymphatic axis influences disease-specific manifestations—Aβ/tau deposition and memory loss in AD, and α-syn spread accompanied by motor/cognitive decline in PD. Figure 2 provides a schematic

summary of these key mechanisms underlying glymphatic dysfunction in AD and PD.

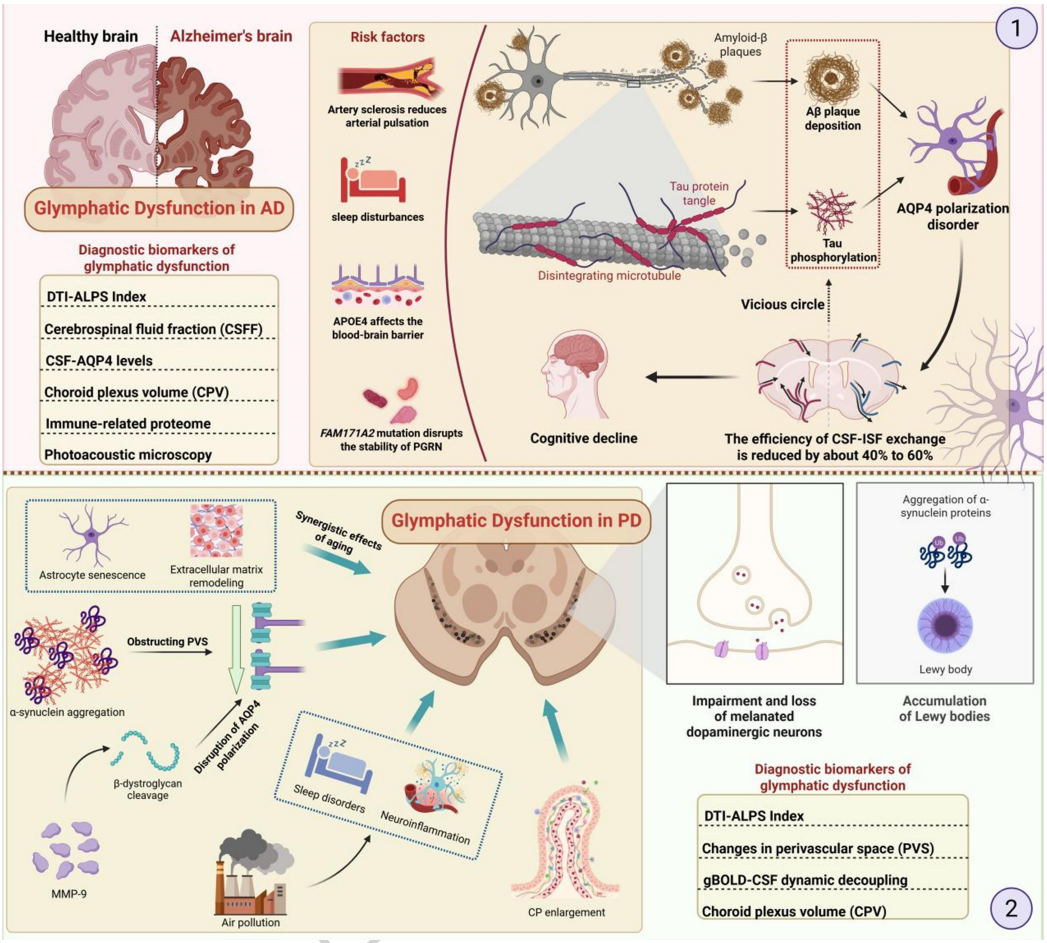

Fig. 2 Glymphatic dysfunction in Alzheimer's disease (AD) and Parkinson's disease (PD). The glymphatic system, driven by aquaporin-4 (AQP4)-mediated cerebrospinal fluid–interstitial fluid (CSF–ISF) exchange, is a critical regulator of protein clearance and brain homeostasis. (1) In AD: Loss of AQP4 polarization at astrocytic endfeet reduces CSF–ISF exchange efficiency by ~40–60%, leading to impaired clearance of amyloid-β (Aβ) and hyperphosphorylated tau. This clearance failure initiates a vicious cycle, where protein accumulation exacerbates glymphatic dysfunction and accelerates cognitive decline. Risk factors including small artery sclerosis, sleep disturbances, apolipoprotein E4 (*APOE4*) genotype, and genetic mutations (e.g., family with sequence similarity 171 member A2 (*FAM171A2*)) further impair glymphatic transport. Diagnostic

ARTICLE IN PRESS

biomarkers of glymphatic dysfunction in AD include diffusion tensor imaging along the perivascular space (DTI-ALPS) index, cerebrospinal fluid fraction (CSFF), CSF-AQP4 levels, choroid plexus volume (CPV), immune-related proteome, and photoacoustic microscopy. (2) In PD: α-synuclein aggregates obstruct perivascular spaces (PVS) and disrupt AQP4 polarization, reducing glymphatic clearance efficiency by ~30% and contributing to Lewy body formation, dopaminergic neurodegeneration, and motor/cognitive decline. Converging mechanisms include β-dystroglycan cleavage mediated by matrix metalloproteinase-9 (MMP-9), neuroinflammation, astrocytic senescence, extracellular matrix remodeling, and environmental exposures such as air pollution. Aging exerts synergistic effects, while choroid plexus (CP) enlargement reflects altered CSF dynamics and correlates with motor and cognitive decline. Diagnostic biomarkers include the DTI-ALPS index, perivascular space changes, global blood oxygen level-dependent cerebrospinal fluid (gBOLD-CSF) dynamic decoupling, and CPV.

1.2 Glymphatic Dysfunction in Amyotrophic Lateral Sclerosis (ALS)

Emerging evidence indicates that glymphatic impairment represents a common pathogenic mechanism across neurodegenerative disorders, including ALS. The GS, which facilitates metabolic waste clearance via CSF–ISF exchange, exhibits early dysfunction in ALS. This impairment correlates with clinical disability progression and sleep disturbances, largely independent of the rate of disease progression[66]. Similar glymphatic deficits are observed in multiple sclerosis (MS) and traumatic brain injury (TBI) models (see Section 1.3), where they exacerbate neuroinflammation and cognitive deficits, whereas restoring glymphatic function improves outcomes[67,68].

ARTICLE IN PRESS

Age-related decline in glymphatic efficiency is thought to contribute to the accumulation of pathological proteins, particularly TAR DNA-binding protein 43 (TDP-43) in ALS and ALS–frontotemporal dementia (ALS–FTD), as well as dysregulation of glutamate, which may drive early neuronal hyperexcitability[69,70]. Non-REM slow-wave sleep, a key regulator of glymphatic activity, represents a modifiable risk factor, with sleep disturbances potentially accelerating neurodegenerative processes[71].

Advanced neuroimaging markers, such as the ALPS index and CPV, offer insights into glymphatic function. One study found these markers to be significantly negatively correlated and functionally linked to glymphatic dysfunction, with both measures also associated with aging[72]. DTI-ALPS reveals reduced glymphatic indices in ALS patients compared to both healthy controls and individuals with primary lateral sclerosis, suggesting a disease-specific pathophysiology[66]. Longitudinal studies in TDP-43 mouse models demonstrate altered glymphatic flux occurring prior to motor symptom onset, alongside dysregulation of AQP4 and progressive neurodegeneration, highlighting its potential as a presymptomatic biomarker[69,73].

Although current human imaging modalities remain limited, emerging technologies such as three-photon microscopy show promise for providing deeper mechanistic insights[74], but this technique requires a cranial window and is invasive, making it unsuitable for human use. The temporal relationship between glymphatic decline and disease onset underscores the therapeutic potential of early intervention. Preclinical

evidence indicates that enhancing glymphatic function could mitigate protein aggregation and neurotoxicity, warranting further clinical investigation[75,76].

Critical knowledge gaps persist regarding fluid transport dynamics and blood–lymphatic interactions in neurodegeneration, necessitating multidisciplinary approaches to optimize CSF-directed interventions and biomarker development[70]. Systematic investigation of sleep modulation and glymphatic enhancement during presymptomatic and early stages of ALS may yield innovative strategies to slow disease progression (as summarized in Figure 3).

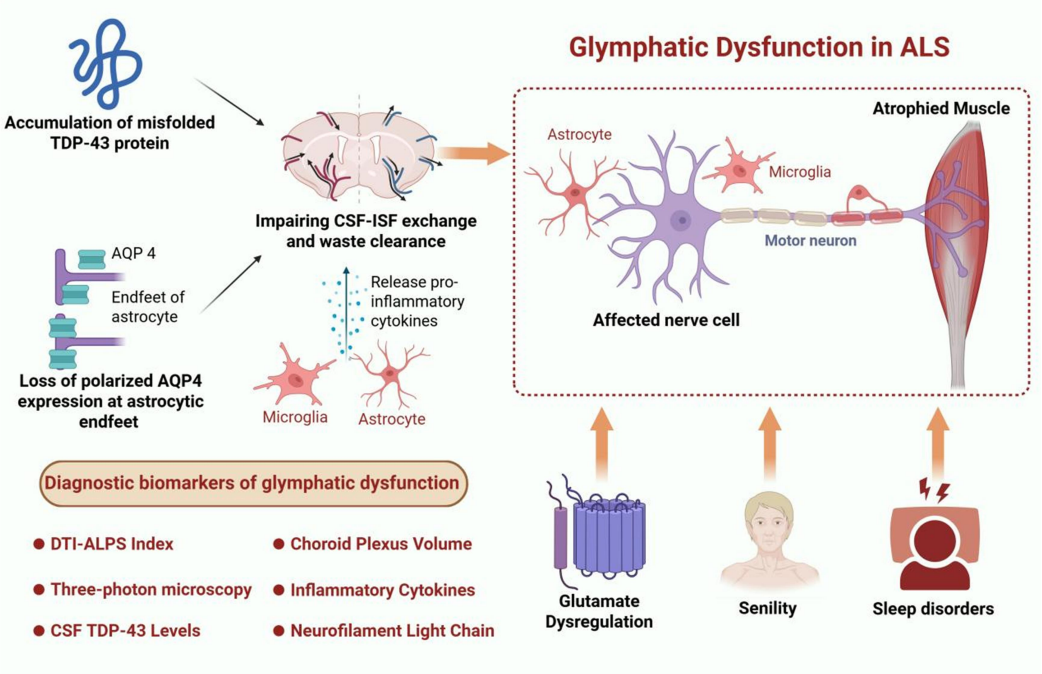

Fig. 3 Glymphatic dysfunction in amyotrophic lateral sclerosis (ALS). In ALS, glymphatic system impairment disrupts cerebrospinal fluid–interstitial fluid (CSF–ISF) exchange and waste clearance, contributing to the accumulation of misfolded TAR DNA-binding protein 43 (TDP-43) and promoting neurotoxicity. Loss of polarized aquaporin-4 (AQP4) expression at astrocytic endfeet, together with microglia- and astrocyte-mediated neuroinflammation, further impairs clearance

ARTICLE IN PRESS

pathways. These processes lead to motor neuron degeneration and muscle atrophy, with contributing factors including glutamate dysregulation, aging, and sleep disturbances. Glymphatic dysfunction precedes overt neurodegeneration, suggesting its role as an early pathogenic event. Diagnostic biomarkers include diffusion tensor imaging–along the perivascular space (DTI-ALPS) index, three-photon microscopy, cerebrospinal fluid TDP-43 levels, choroid plexus volume (CPV), inflammatory cytokines, and neurofilament light chain (NfL).

1.3 Glymphatic Dysfunction in TBI

TBI profoundly disrupts both the GS and meningeal lymphatic drainage, contributing significantly to acute and chronic neurological impairments. This dysfunction arises through multiple interconnected mechanisms. An early critical event is the post-TBI "noradrenergic storm," characterized by hyperactivation of noradrenergic pathways that suppress glymphatic influx and impair cervical lymphatic contractility[77,78]. This leads to "glymphatic-stagnated edema," marked by fluid retention and compromised waste clearance. Elevated intracranial pressure (ICP) further impedes lymphatic flow, with the severity of glymphatic-lymphatic fluid transport system (GLFTS) impairment correlating directly with ICP levels[68,79]. Pre-existing lymphatic dysfunction exacerbates neuroinflammation and cognitive deficits[68].

A central pathophysiological feature is the mislocalization or depolarization of AQP4 at astrocytic endfeet, which is essential for efficient fluid clearance[80,81]. Blast-induced TBI models reveal delayed glymphatic dysfunction specifically associated with AQP4 mislocalization[81]. This disruption aggravates edema

ARTICLE IN PRESS

formation and impairs the clearance of neurotoxic waste, including phosphorylated tau and Aβ[77,80,82]. The resulting failure of clearance mechanisms perpetuates a vicious cycle: impaired removal of neurotoxic debris and danger-associated molecular patterns (DAMPs) sustains neuroinflammation, while edema and elevated ICP further disrupt fluid homeostasis, compounded by microglial dysfunction and immune dysregulation[83].

Clinically, chronic glymphatic impairment is evidenced by an increased burden of MRI-visible PVS in blast-exposed veterans and individuals with repetitive head injuries, which correlates with post-concussive symptoms, neurodegeneration risk, and poorer verbal memory performance[81,84-86]. A single moderate-to-severe TBI is also associated with greater EPVS burden, indicating persistent GS dysfunction[86]. Advanced neuroimaging techniques confirm these deficits: dynamic contrast-enhanced MRI (DCE-MRI) and the DTI-ALPS index provide quantitative evidence of glymphatic impairment, linking it to cytotoxic edema and proteinopathies[87]. Biomarkers such as reduced serum/CSF neurofilament light (NF-L) ratios following subarachnoid hemorrhage (SAH) indicate disrupted glymphatic efflux and predict clinical outcomes[88]. Preliminary studies using 3D arterial spin labeling (ASL) MRI also show potential for identifying delayed glymphatic clearance after TBI[89].

In summary, glymphatic and meningeal lymphatic dysfunction represents a convergent pathophysiological mechanism in TBI, bridging acute injury to chronic neurodegeneration risk through impaired clearance of proteins (e.g., tau, Aβ, and

α-syn)[90], neuroimmune dysregulation, and disrupted fluid homeostasis. The integration of biomarkers, such as PVS burden, NF-L ratios, DCE-MRI, and the DTI-ALPS index, strengthens the association between glymphatic impairment and clinical outcomes[87,88](as summarized in Figure 4). Future therapeutic strategies should prioritize targeting this system—via adrenergic signaling, AQP4 dynamics, lymphatic remodeling, sleep regulation, or novel technologies—to disrupt this pathological cycle and improve outcomes. Non-invasive biomarkers like the ALPS index and interventions that enhance drainage hold transformative potential for TBI and related conditions[70,91].

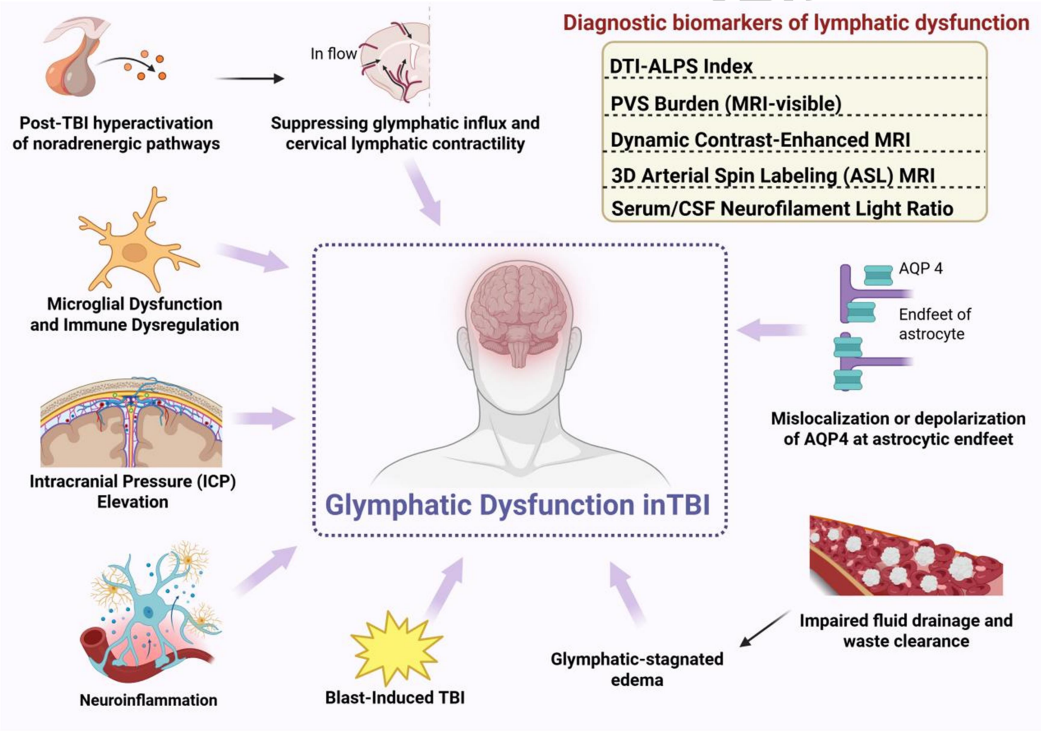

Fig. 2 Glymphatic dysfunction in traumatic brain injury (TBI). TBI disrupts both glymphatic and meningeal lymphatic clearance pathways, contributing to acute and chronic neurological deficits. Post-TBI hyperactivation of noradrenergic pathways ("noradrenergic storm") suppresses glymphatic influx and cervical lymphatic contractility, promoting fluid stagnation and impaired

ARTICLE IN PRESS

waste removal. Elevated intracranial pressure (ICP), blast-induced injury, and aquaporin-4 (AQP4) mislocalization at astrocytic endfeet further exacerbate glymphatic-stagnated edema and reduce clearance of toxic solutes such as phosphorylated tau and amyloid-beta (Aβ). Neuroinflammation and microglial dysfunction perpetuate a vicious cycle of impaired clearance, immune dysregulation, and edema. Clinically, this dysfunction manifests as increased perivascular space (PVS) burden and cognitive decline, with advanced imaging biomarkers—including diffusion tensor imaging along the perivascular space (DTI-ALPS) index, dynamic contrast-enhanced magnetic resonance imaging (MRI), arterial spin labeling (ASL) MRI, and serum/cerebrospinal fluid (CSF) neurofilament light ratios—providing quantitative evidence of impaired glymphatic function.

2.Glymphatic Dysfunction in Brain Tumors

2.1 Tumor Microenvironment (TME) and Metabolic Dysregulation

The GS, a crucial pathway for brain waste clearance, is profoundly disrupted in glioblastoma (GBM) and other intracranial malignancies. GBM exerts mechanical stress exceeding 5 kPa, compressing PVS and reducing the rate of CSF–ISF exchange[92]. This compression-driven dysfunction is compounded by significant metabolic alterations. Hypoxia-inducible factor 1α (HIF-1α) signaling mediates lactate accumulation, acidifying the TME and impairing the polarization of AQP4[93]. Notably, accumulated lactate activates the G-protein coupled receptor GPR81 on tumor-associated immune cells, triggering cAMP–PKA signaling that suppresses natural killer (NK) cell cytotoxicity and restricts infiltratio of cytotoxic T lymphocytes[93,94]. Concurrently, lactate promotes histone lactylation in immune

ARTICLE IN PRESS

cells—an epigenetic modification that drives the expression of immunosuppressive genes such as *VEGF* and *ARG1*[93]. These pathological changes collectively disrupt fluid dynamics, trapping lactate and pro-inflammatory mediators within the TME and fostering an immunosuppressive niche that accelerates tumor progression and confers therapeutic resistance[93-96].

Experimental evidence confirms that the solid pressure generated by growing tumors directly impedes lymphatic fluid transport, independent of cancer cell biochemistry[92]. Studies in rats with spontaneous pituitary tumors further demonstrate compromised glymphatic transport, which increases the risk of neurodegeneration and may underlie cognitive impairment in patients with pituitary tumors[97]. This reduction in glymphatic clearance leads to the accumulation of toxic waste solutes and pro-inflammatory signaling molecules, potentially exacerbating GBM progression[96].

ARTICLE IN PRESS

2.2 Clinical Evidence and Neuroimaging Biomarkers

Clinical studies corroborate these mechanistic insights. In a cohort of 84 brain tumor patients and 59 controls, patients exhibited significantly reduced glymphatic function alongside elevated CSF volume. Tumor volume was inversely correlated with the DTI-ALPS index. AQP4 expression positively correlated with peritumoral edema volume and inversely with proton density in edematous regions[98]. Further stratification revealed that patients with GBM had lower ALPS-index values than those with lower-grade gliomas. *IDH1*-wildtype tumors exhibited more severe glymphatic dysfunction than *IDH1*-mutant tumors. Notably, *IDH1*-wildtype gliomas

ARTICLE IN PRESS

and those with larger peritumoral brain edema (PTBE) volumes were associated with a lower ALPS index, reflecting impaired glymphatic function. Worse contralateral glymphatic function correlated with shorter survival, underscoring its prognostic relevance[99-101]. A recent large-scale retrospective study of 437 glioma patients further demonstrated that a lower ALPS index was significantly associated with more aggressive tumor phenotypes—including higher grade, IDH-wildtype status, and intact 1p19q—and served as an independent predictor of shorter overall survival. The ALPS index correlated with radiomic features reflecting edema geometry and intratumoral heterogeneity. Its integration with radiomic data improved the accuracy of survival prediction, highlighting its potential as a noninvasive prognostic biomarker in glioma[102].

In meningiomas, PTBE volume negatively correlates with the ALPS index, suggesting that PTBE formation may be linked to GS dysfunction[103]. In pediatric medulloblastoma (MB) patients, radiotherapy may transiently increase PVS volume, while chemotherapy or radiotherapy can reduce PVS over time. Anesthesia and diversion surgery also significantly influence PVS measurements[104].

2.3 Glymphatic Dysfunction in Cerebral Metastases

Although most evidence regarding glymphatic dysfunction in brain tumors derives from primary malignancies such as glioma and meningioma, its role in cerebral metastases, the most common intracranial tumors, is increasingly recognized. Similar to primary tumors, brain metastases exert mass effects and disrupt local fluid dynamics. A key clinical manifestation is PTBE, which has traditionally been

ARTICLE IN PRESS

attributed solely to BBB breakdown and increased vascular permeability due to angiogenic factors. However, emerging data indicate that impaired glymphatic clearance is a significant and underappreciated contributing factor.

Neuroimaging studies in patients with brain metastases reveal that a lower DTI-ALPS index, indicative of worse glymphatic function, independently correlates with larger PTBE volume. This association persists after controlling for tumor volume and intratumoral hemorrhage, suggesting that edema accumulation results not only from barrier leakage but also from inadequate fluid drainage via perivenous glymphatic pathways. Concurrently, higher tumor apparent diffusion coefficient (ADC) values may reflect increased water influx into the interstitial space, further supporting the model of disrupted inflow-clearance homeostasis[105].

These findings posit glymphatic dysfunction as a key parallel mechanism in the pathogenesis of PTBE in metastatic disease, complementing classical vascular theories. This expanded understanding could inform novel therapeutic strategies aimed at modulating fluid clearance to alleviate edema and potentially improve drug delivery in patients with brain metastases. Comparative characteristics of glymphatic dysfunction in primary brain tumors and cerebral metastases are summarized in Table 1.

ARTICLE IN PRESS

ARTICLE IN PRESS

Table 1: Comparative Characteristics of Glymphatic Dysfunction in Primary Tumors and Cerebral Metastases

Tumor Type	DTI-ALPS Index Changes	Prognostic/Clinical Correlations	Key Pathogenic Features	Potential Therapeutic Implications	References
Glioma	Significantly reduced vs. controls	(1) Inversely correlates with tumor volume; (2) Lower in GBM vs. lower-grade gliomas; (3) Lower in IDH1-wildtype vs. IDH1-mutant tumors; (4) Contralateral reduction correlates with shorter survival	(1) Strong inverse correlation with PTBE volume; (2) Impaired AQP4 polarization due to mechanical compression (>5 kPa) and lactate-driven acidosis	Targeting glymphatic restoration may alleviate PTBE, enhance drug delivery, and improve immunotherapy response.	[98-101]
Meningioma	Reduced (inversely correlates with PTBE volume)	(1) PTBE volume negatively correlates with ALPS index, Suggesting glymphatic impairment contributes to edema formation	(1) Peritumoral edema pathogenesis linked to GS dysfunction;	Reducing tumor mass effect and enhancing perivenous drainage	[103]

ARTICLE IN PRESS

Tumor Type	DTI-ALPS Index Changes	Prognostic/Clinical Correlations	Key Pathogenic Features	Potential Therapeutic Implications	References
			(2) Compression of perivascular spaces by tumor mass	could mitigate edema and improve outcomes.	
Medulloblastoma	Limited direct ALPS index data reported	(1) PVS dynamics altered by therapy: a. Transient PVS increase post-radiotherapy; b. PVS reduction post-chemotherapy/radiotherapy (2) Anesthesia and diversion surgery affect PVS measurements	(1) CSF outflow obstruction suspected (similar to glioma models) (2) Therapeutic interventions significantly alter glymphatic/ PVS morphology	Monitoring and preserving PVS integrity during treatment may reduce long-term cognitive sequelae.	[104]
Cerebral	Reduced (lowe	(1) Independent	(1)	Modulating	[105]

ARTICLE IN PRESS

Tumor Type	DTI-ALPS Index Changes	Prognostic/Clinical Correlations	Key Pathogenic Features	Potential Therapeutic Implications	References
Metastases	r ALPS index correlates with larger PTBE)	association with PTBE volume after controlling for tumor volume and hemorrhage; (2) Higher ADC values suggest interstitial fluid influx	Glymphatic dysfunction contributes to PTBE along side BBB breakdown; (2) Tumor mass effect and local fluid dynamic disruption	glymphatic clearance (e.g., via cervical lymphatic stimulation) may represent a novel strategy to alleviate edema and enhance drug penetration.	

2.4 Insights from Preclinical Models

Preclinical models offer valuable mechanistic insights into glymphatic dysfunction in brain tumors. In glioma-bearing mice, CSF outflow is significantly reduced. Tracer studies reveal that CSF is rerouted into the spinal space due to cranial outflow obstruction, with compensatory lymphatic drainage through the sacral spine observed in some cases, demonstrating the adaptability of fluid clearance pathways under

ARTICLE IN PRESS

pathological stress[106]. Anatomical studies in rats have delineated brain lymph fluid (BLF) pathways, identifying deep CLNs as critical drainage hubs. Nuclear magnetic resonance spectroscopy shows that BLF exhibits a richer metabolic profile than CSF, suggesting its potential as a biomarker for central nervous system (CNS) disorders[107].

2.5 Emerging Therapeutic Strategies and Future Directions

Emerging therapeutic strategies aim to address these challenges by enhancing drug delivery and mitigating glymphatic impairment. Convection-enhanced delivery (CED) employs computational modeling to account for tissue anisotropy and optimize infusate distribution, while advances in catheter design and placement protocols seek to improve intratumoral drug delivery[108]. Together, these findings underscore the interplay between tumor-induced mechanical compression, glymphatic dysfunction, and altered fluid dynamics, supporting the integration of DTI-ALPS and multiparametric MRI in neuro-oncological assessment and treatment planning.

ARTICLE IN PRESS

Future research should prioritize therapeutic strategies focused on restoring glymphatic function. The DTI-ALPS index shows promise as a prognostic marker for high-grade glioma[109]. The modified ALPS-index (mALPS-index), derived from DTI, demonstrates 92% concordance with gadolinium clearance rates, providing a quantitative measure of perivascular deformation in gliomas[64]. Techniques such as $H_2{}^{17}O$ MRI enable real-time visualization of CSF dynamics, though the bidirectional diffusion of ^{17}O-labeled water between blood and brain parenchyma makes it difficult to distinguish glymphatic from vascular contributions. CSF proteomics has identified

potential biomarkers including PGRN and MMP-9[110,111]. Importantly, delayed gadolinium clearance has been shown to predict GBM progression[92], underscoring the clinical relevance of glymphatic assessment. These developments are summarized in Figure 5).

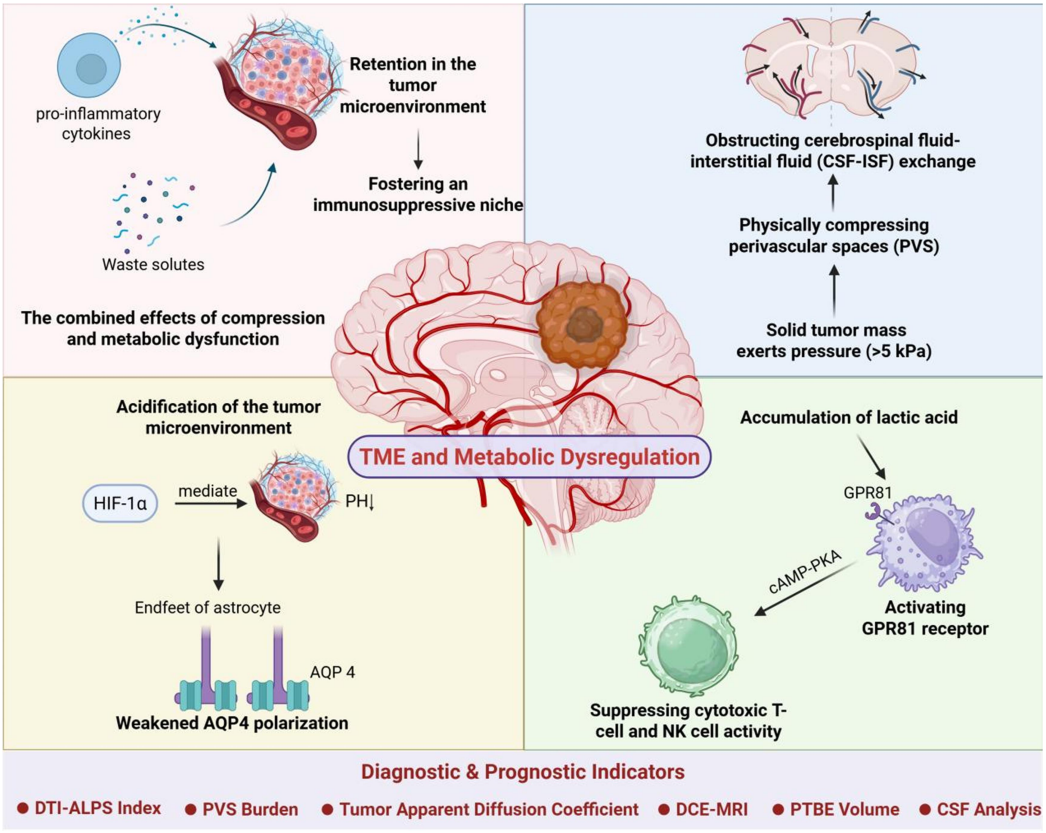

Fig. 3 Tumor microenvironment (TME) and metabolic dysregulation impair glymphatic function in glioblastoma (GBM). GBM disrupts glymphatic clearance through both mechanical and metabolic mechanisms. The solid tumor mass exerts pressures exceeding 5 kPa, physically compressing perivascular spaces (PVS) and obstructing cerebrospinal fluid–interstitial fluid (CSF–ISF) exchange. Concurrently, hypoxia-inducible factor 1α (HIF-1α) signaling drives lactate accumulation, leading to acidification of the TME and weakening aquaporin-4 (AQP4) polarization at astrocytic endfeet. Excess lactate activates the G protein-coupled receptor 81

ARTICLE IN PRESS

(GPR81) on immune cells, initiating cyclic AMP–protein kinase A (cAMP-PKA) signaling that suppresses cytotoxic T-cell and natural killer (NK) cell activity while fostering an immunosuppressive niche. This immunometabolic reprogramming is reinforced by histone lactylation, promoting expression of immunosuppressive genes such as vascular endothelial growth factor (VEGF) and arginase 1 (ARG1). Together, impaired waste clearance, metabolic acidification, and cytokine retention perpetuate an immunosuppressive and pro-inflammatory microenvironment that accelerates tumor progression and resistance to therapy. Diagnostic and prognostic indicators include Diffusion Tensor Imaging–Along the Perivascular Space (DTI-ALPS) index, PVS burden, tumor apparent diffusion coefficient, Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI), peritumoral brain edema (PTBE) volume, and CSF analysis.

3.Therapeutic Strategies Targeting the GS

3.1 Pharmacological modulation

3.1.1 Pharmacological modulation in AD

Recent advances have highlighted the GS as a pivotal therapeutic target in neurodegenerative diseases. Pharmacological modulation of circadian rhythms using melatonin and dual orexin receptor antagonists (DORAs) has been shown to enhance glymphatic clearance efficiency by 30–50%. Concurrent administration of adrenergic agonists can optimize AQP4 polarization at astrocytic endfeet, thereby improving interstitial fluid dynamics[112-115]. Additionally, borneol-based micelles (BO-Ms) promote Aβ clearance through the mLVs, effectively ameliorating amyloid pathology[116]. Oxytocin administration represents another multimodal therapeutic strategy, demonstrating efficacy in reversing glymphatic and meningeal lymphatic

ARTICLE IN PRESS

dysfunction in aged AD models. This effect is mediated through transcriptional regulation of cerebral hemodynamics and lymphangiogenesis, which enhances Aβ drainage to CLNs and improves cognitive outcomes[117].

3.1.2 Pharmacological modulation in TBI

Emerging therapeutic strategies for TBI focus on counteracting glymphatic dysfunction through targeted pharmacological interventions. Inhibition of pan-adrenergic receptors using a combination of prazosin (an α1-adrenergic receptor antagonist), atipamezole (an α2-adrenergic antagonist), and propranolol (a β-adrenergic antagonist) has been shown to mitigate several deleterious effects—reducing cerebral edema, phosphorylated tau accumulation, and neuroinflammation, while promoting functional recovery[77,78].

Modulation of AQP4 dynamics represents another promising approach, particularly through influencing channel trafficking rather than direct inhibition. Strategies such as calmodulin inhibition via trifluoperazine or Transient Receptor Potential Vanilloid 4 (TRPV4) channel antagonism have demonstrated potential in reducing edema and improving neurological outcomes[80].

Notably, elevated levels of Macrophage colony-stimulating factor, interleukin-6, and Transforming growth factor-β (collectively termed M6T) in CSF and plasma correlate with improved recovery after TBI. M6T therapy accelerates the infiltration and polarization of blood-derived macrophages toward a tissue-repair phenotype, mirroring the neuroprotective functions of microglia in angiogenesis and cell migration. This treatment improved neurological function in TBI models, whereas

ARTICLE IN PRESS

blocking M6T exacerbated injury[118].

Additional pharmacological agents show complementary benefits: Fingolimod alleviates whole-brain inflammation and glymphatic impairment following diffuse brain injury[119]. Cannabidiol (CBD) improves motor, memory, and cognitive functions in TBI models, reduces phosphorylated tau and Aβ burden, and enhances tracer clearance alongside AQP4 repolarization[82]. Activation of the brain's glucagon-like peptide-1 receptor (GLP-1 R) with Exendin-4 (Ex-4), a structurally modified GLP-1 analog, restores lymphatic transport, alleviates BBB damage and neuronal apoptosis, and improves cognitive function[120].

Other agents, such as transferrin receptor-targeted liposomes (TPL-Flv), interleukin-33 (IL-33), ketoprofen, and vascular endothelial growth factor C (VEGF-C), also exhibit neuroprotective potential, though further mechanistic validation is required[121-123]. Innovatively, co-encapsulation of VEGF-C with microenvironmental regulators in nanostructures (e.g., "Nano-plumber") enhances glymphatic-lymphatic drainage, suppresses chronic neuroinflammation, and improves long-term outcomes by facilitating the clearance of DAMPs[124].

ARTICLE IN PRESS

3.1.3 Pharmacological modulation in brain tumors

For brain edema, standard treatment involves hyperosmotic agents (e.g., mannitol or saline) and corticosteroids. In life-threatening cases, decompressive craniotomy may be necessary[125]. Dexamethasone has demonstrated efficacy in reducing peritumoral edema[126]. However, the molecular pathogenesis of tumor-associated edema fundamentally differs from edema resulting from trauma or stroke, primarily

ARTICLE IN PRESS

driven by tumor neoangiogenesis characterized by deficient tight junction protein expression[127].

A recent study proposed that AQP4 isoforms present in glioma-derived extracellular vesicles (EVs) modulate tumor behavior: EVs derived from cells expressing AQP4 tetramers promote cell migration, whereas those expressing AQP4 organized in orthogonal arrays of particles (OAPs) induce apoptosis[128]. Nevertheless, the relationship between AQP4-mediated EV signaling, the pathogenesis of tumor-associated edema, and AQP4 mislocalization remains unexplored and warrants further investigation.

3.2 Non-pharmacological interventions

Non-pharmacological interventions represent promising approaches to restore glymphatic function and facilitate waste clearance. For instance, high-intensity interval training (HIIT) has been shown to restore astrocytic AQP4 polarization and promote dual brain-kidney clearance of Aβ and phosphorylated tau, highlighting systemic synergies in waste removal[129].

3.2.1 Non-pharmacological interventions in AD

Multiple non-invasive modalities demonstrate efficacy in ameliorating glymphatic dysfunction in AD. Physical exercise, particularly HIIT, improves AD-like pathology by regulating astrocyte phenotype and restoring AQP4 polarization, thereby facilitating clearance of Aβ and tau[129]. Sensory-based interventions such as multisensory gamma stimulation enhance CSF influx and ISF efflux, mediated by increased AQP4 polarization and mLVdilation[130]. Phototherapeutic approaches,

ARTICLE IN PRESS

including low-intensity 40 Hz blue light irradiation, have been shown to prevent memory and motor deficits, restore AQP4 polarity, improve drainage efficiency, and reduce hippocampal lipid accumulation[131].

Neuromodulation techniques also confer benefits: repetitive transcranial magnetic stimulation (rTMS) enhances brain clearance system function, reduces Aβ deposition and neuroinflammation, and improves memory and neuronal activity[132]. Focused ultrasound (FUS) safely opens the BBB and may activate perivenous drainage pathways, though its mechanistic details require further elucidation[133]. Visual circuit activation alleviates clinical symptoms such as memory impairment and apathy[131].

Mechanical stimulation of superficial CLNs using force-regulated devices—which compress lymphatics without disrupting spontaneous contractions—has been shown to double CSF outflow in aged models. This approach restores cLVs contraction frequency via prostaglandin F2α-mediated smooth muscle activation, reverses aging-related lymphatic impairment by 35%, and enhances brain waste clearance nearly threefold[11]. These findings support its potential as an adjunct strategy for improving glymphatic function in AD.

At the molecular level, genetic manipulation represents another promising avenue. Overexpression of the Down syndrome critical region 1 gene (*DSCR1*/*RCAN1*) specifically increases dorsal mLV branching and volume, enhances lymphatic clearance, ameliorates Aβ pathology, and restores cognitive function in AD models[134].

ARTICLE IN PRESS

3.2.2 Non-pharmacological interventions in TBI

Non-invasive neuromodulation techniques show promise for enhancing glymphatic function following TBI. Very low-intensity ultrasound (VLIUS) promotes glymphatic influx and supports Aβ clearance via TRPV4–AQP4 pathways without inducing tissue damage[135]. Additionally, rTMS significantly improves the drainage efficiency of brain clearance pathways, including mLVs[132]. These approaches represent safe and innovative strategies for mitigating post-TBI glymphatic impairment and supporting neurological recovery

3.2.3 Non-pharmacological interventions in brain tumor

Mechanotherapy approaches such as MRI-guided FUS have emerged as promising strategies for modulating the tumor microenvironment. This technique reduces tumor-induced mechanical stress and enhances drug delivery efficiency by approximately 20%[136], offering a potential adjunct to conventional treatments for improving therapeutic outcomes in brain tumor patients.

ARTICLE IN PRESS

3.3 Surgical intervention

3.3.1 Lymphatic-Venous Anastomosis (LVA)

Cervical deep LVA is an emerging microsurgical technique, primarily developed in China, that aims to enhance CSF-ISF clearance by reconstructing drainage pathways between meningeal lymphatics and the venous system[137]. In a clinical study of fifty AD patients, Xie et al. reported that LVA led to measurable improvements in cognitive function, memory, and behavior, as evaluated by standardized mental status examinations and the Montreal Cognitive Assessment[138]. Exploratory multi-center

studies across China (including Shanghai, Nanjing, and Zhengzhou) have reported enhanced cognitive performance, favorable shifts in imaging biomarkers, and improved metabolic clearance efficiency post-LVA[137]. Technical refinements, such as transitioning from conventional lymphatic-venous to lymphatic-valve-vein anastomosis, correlate with increased procedural safety and sustained cognitive benefits in AD cohorts[139]. Furthermore, integrated perioperative care appears to optimize clinical outcomes[140]. The surgical intervention of LVA is depicted in Figure 6.

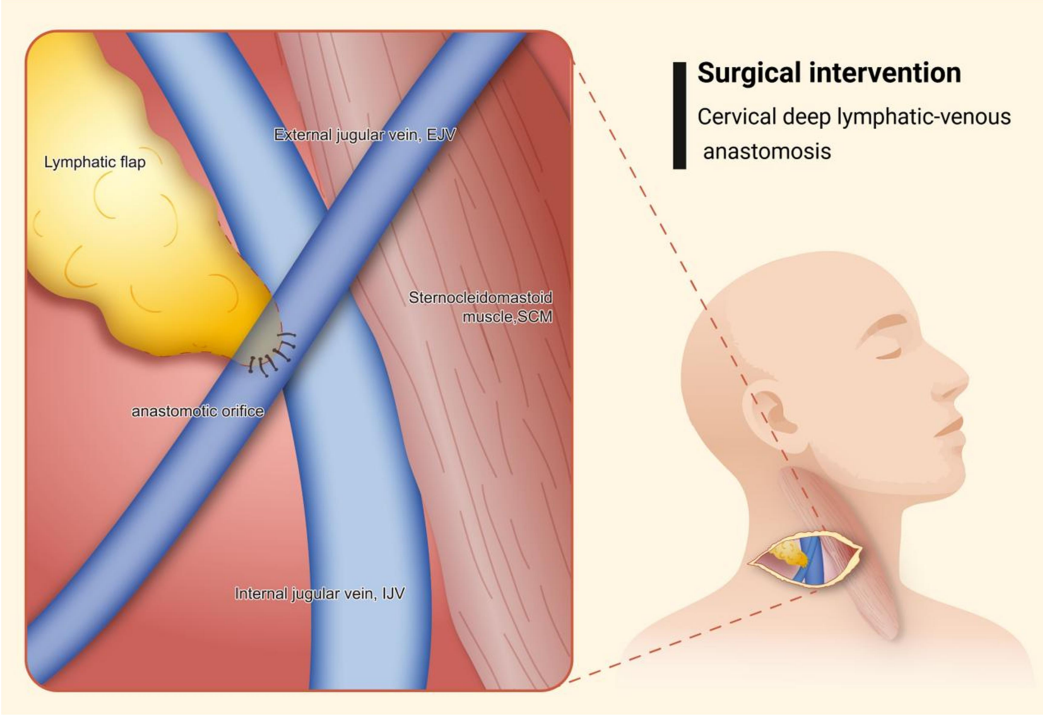

Fig. 6 Cervical deep lymphatic-venous anastomosis. This illustration depicts a surgical procedure in which a deep cervical lymphatic vessel (lymphatic flap) is anastomosed to the external jugular vein (EJV) to facilitate lymphatic drainage into the venous system. The anastomotic orifice is microsurgically created and sutured to enable direct lymph-to-vein flow. The internal jugular vein (IJV) and sternocleidomastoid muscle (SCM) are shown for anatomical reference.

ARTICLE IN PRESS

3.3.2 Controversies and Regulatory Status

Despite some promising early reports, cervical deep LVA is a subject of substantial controversy and regulatory challenges. The field is hampered by a number of methodological limitations, such as small sample sizes, brief follow-up durations, non-randomized study designs employing inconsistent metrics, an incomplete grasp of the underlying mechanism, and persistent safety and ethical questions. These issues collectively result in evidence of low quality and insufficient reliability[137,138]. In July 2025, China's National Health Commission banned the use of cervical deep LVA for treating AD. The commission stated that the treatment's efficacy was unsubstantiated and its safety profile was unclear. This decision underscores that large-scale, rigorous clinical trials are necessary before the therapy can be reconsidered for clinical use.

Consequently, cervical deep LVA remains strictly investigational. Its translational potential is currently hampered by the lack of mechanistic validation, unresolved ethical issues, safety risks, and the absence of high-quality clinical evidence. Although LVA is presently contentious, non-invasive alternatives such as mechanical cervical lymphatic stimulation have demonstrated comparable efficacy in animal models[11].

3.3.3 Conclusion

Structural remodeling of fluid drainage pathways represents an emerging therapeutic frontier for addressing glymphatic-lymphatic dysfunction. While cervical deep LVA has shown preliminary cognitive benefits in reported AD case series[137,139], its clinical application remains restricted due to significant

ARTICLE IN PRESS

controversy and regulatory prohibition. Complementary approaches, such as Idiopathic Normal Pressure Hydrocephalus (iNPH) shunting[141] and VEGF-C/VEGFR3-targeted therapies in preclinical models[142], highlight the broader potential of surgically enhancing clearance pathways. Future innovations should prioritize non-invasive strategies, such as mechanical cervical lymphatic stimulation, combined neuromodulation, and circadian rhythm optimization, to counteract age-related glymphatic impairment. Together with pharmacological and physical interventions, these approaches position the GS as a multifaceted and promising therapeutic target in neurodegenerative diseases.

3.4 Emerging Paradigms and Mechanistic Insights

The limitations of conventional amyloid-targeting monoclonal antibodies, including safety concerns such as amyloid-related imaging abnormalities and encephalitis[143], have spurred growing interest in glymphotherapeutics, defined here as therapeutic strategies aimed at restoring AQP4-mediated perivascular clearance of Aβ and tau. This approach is supported by evidence showing that modulating the subcellular localization of AQP4 (rather than direct channel inhibition) mitigates CNS edema and enhances recovery in preclinical models[80]. Ocular pathology studies further implicate AQP4 in Aβ transport along the PVS of the optic nerve, linking retinal changes to central glymphatic dysfunction in AD. Meanwhile, studies of border-associated macrophages (BAMs) highlight their role in preserving glymphatic efficiency. Notably, chronic infections can worsen neurodegeneration by impairing BAM function[144]. After SAH, external CSF drainage has been shown to restore

ARTICLE IN PRESS

glymphatic and meningeal lymphatic function in preclinical models, suggesting a potential procedural adjunct to improve recovery[145].

Obstruction of CSF circulation may result from extensive astrocyte proliferation, redirecting glymphatic flow of amyloid species toward caudal regions. Targeting cerebral fluid circulation thus represents a promising therapeutic strategy for AD[146]. For instance, mixed electro-optical stimulation has been shown to restore glymphatic function by regulating AQP4 polarization and reducing pro-inflammatory cytokine accumulation (e.g., IL-1β), thereby improving neurological, motor, and cognitive outcomes, particularly following ischemic brain injury[147].

Advanced in vivo two-photon optical imaging with particle tracking has quantitatively demonstrated that aging reduces contraction frequency of cLVs by 43% in mice, primarily due impaired lymphatic pump function. Local application of prostaglandin F2α to stimulate smooth muscle contraction restored lymphatic pump activity in aged mice, increasing CSF clearance efficiency by 35% compared to young controls and enhancing waste clearance nearly threefold[148]. Long-term voluntary wheel running (VWR) in AD model mice significantly improved sleep architecture—increasing REM sleep and restoring circadian gene expression—while reducing phosphorylated tau levels, ameliorating cognitive deficits and neuroinflammation[149]. Exercise conferred protection against AD by enhancing mLVs plasticity and drainage via downregulation of the ELL-associated factor 2 (EAF2)–p53–thrombospondin-1 (TSP-1) pathway in reactive astrocytes[150]. Moreover, neuronal rhythmic activity critically regulates parenchymal CSF influx and

ARTICLE IN PRESS

waste clearance[151].

Functional mLVs also play a key role in viral clearance, serving as a conduit for viral transit from the CNS to CLNs. Strategies targeting mLVs may alleviate infection-related neural damage[152]. Near-infrared light therapy enhances the waste-clearance capacity of meningeal lymphatic endothelial cells (mLECs), reducing Aβ deposition, neuroinflammation, and neuronal damage, ultimately improving cognitive function[153].

Genetic interventions, such as CRISPR-Cas9-mediated *APOE4* correction, have reduced tau pathology by 58%, offering a precision approach to mitigating proteinopathy[154]. Similarly, neural stem cell transplantation reduced α-syn burden by 40% in PD models[155,156], though immunogenicity related to the CRISPR system remains a consideration in gene-editing applications[157].

Additionally, brain aging in conditions such as CADASIL is linked to lymphatic dysfunction, with reduced AQP4 expression identified as a central factor. Targeted enhancement of AQP4 may thus represent a viable therapeutic strategy[158]. Non-invasive mechanical stimulation of superficial cervical lymphatic vessels (scLV-1/scLV-2) significantly improved CSF drainage efficiency in aged mice and reversed aging-related lymphatic impairment, offering a novel non-pharmacological approach for AD and stroke[11].

Nanoparticle-mediated glymphatic targeting represents a transformative strategy for enhancing CNS drug delivery. Recent advances in intrathecally administered nanoparticles (NPs) demonstrate their ability to bypass the blood–cerebrospinal fluid

ARTICLE IN PRESS

barrier (BCSFB) and leverage glymphatic pathways for broad CNS distribution. Engineered NPs (e.g., lipid-based, polymeric, or biomimetic vesicles) exhibit prolonged retention within the leptomeningeal and perivascular spaces, facilitating sustained drug release and deeper parenchymal penetration. Approximately 80% of CSF-administered NPs are cleared via perivascular glymphatic routes, with microglial activity further aiding paravascular clearance. Optimal NP properties for glymphatic trafficking include a size range of 37–39 nm and a positive surface charge, which enhance BCSFB permeability and minimize rapid clearance. This approach not only improves drug bioavailability but also synergizes with immunomodulatory and protein-clearance therapies, offering a promising platform for combinatorial treatment in neurodegeneration and oncology[159].

4. Limitations and Future Directions

While this review synthesizes critical advancements in understanding glymphatic dysfunction across neurodegenerative diseases and brain tumors, several limitations warrant consideration, alongside opportunities for future research.

4.1 Current Limitations

First, the variability in preclinical models, such as transgenic rodents, injury paradigms, and tumor xenografts, makes it difficult to apply these findings to human physiology. Key differences in areas like AQP4 polarization or meningeal lymphatic structure can limit their translational relevance.

Second, mechanistic insights into bidirectional glymphatic–tumor interactions remain limited. Although mechanical compression and metabolic dysregulation are

ARTICLE IN PRESS

implicated, the spatiotemporal interplay between tumor-derived factors (e.g., lactate, cytokines) and glymphatic remodeling is not yet fully elucidated, particularly in human cohorts.

Third, although neuroimaging biomarkers such as the ALPS index and DTI-ALPS show diagnostic potential, they require further clinical validation. A major limitation of DTI-ALPS is its susceptibility to confounding variables, including age and cerebrovascular disease, which independently modify PVS morphology and diffusion parameters, thereby reducing its diagnostic specificity for neurodegenerative conditions[160]. Moreover, technical variations in MRI acquisition protocols (e.g., b-values, spatial resolution) across institutions also hinder cross-center comparability and large-scale validation efforts[161]. Multicenter studies are essential to standardize imaging protocols, define normative values, and assess sensitivity in early disease stages. Similarly, the prognostic value of glymphatic metrics in predicting treatment resistance or survival warrants longitudinal assessment. Furthermore, fundamental questions remain regarding the physiological interpretation of the DTI-ALPS index itself. It is crucial to note that a higher ALPS-index ‘only’ indicates predominant Brownian motion of water molecules in the radial direction at the lateral ventricular body level and does not reflect the entirety of the complex GS. DTI-ALPS does not directly measure the convective bulk flow that is characteristic of glymphatic function, but most likely captures localized diffusion within a small area of the brain at the level of the lateral ventricles. Moreover, this technique primarily assesses diffusion in deep white matter regions, where vasculature and PVS are sparse (constituting only

ARTICLE IN PRESS

about 1% of the tissue). Consequently, the diffusion signal measured by DTI-ALPS in these areas most likely represents axonal diffusion rather than diffusion specifically within the PVS, potentially confounding its association with true glymphatic activity[162,163].

Fourth, the clinical standardization of the DTI-ALPS index remains challenging. Its diagnostic utility is constrained by the lack of robust correction methods for physiological confounders, such as age-related PVS enlargement and comorbid vascular pathologies, which may obscure disease-specific glymphatic impairment[160]. The development of AI-driven harmonization tools, for instance, deep learning algorithms trained on multi-scanner datasets to mitigate protocol-related variances, along with confounder-adjusted predictive models, could improve reproducibility and diagnostic accuracy[164-166].

Lastly, while the review highlights genetic and environmental modifiers of glymphatic function (e.g., *APOE4*, air pollution), it overlooks their potential synergistic effects. Epigenetic regulation, microbiota interactions, and sex-specific vulnerabilities remain underexplored, representing fertile ground for systems-level investigations.

ARTICLE IN PRESS

4.2 Future Directions

Addressing these limitations demands interdisciplinary collaboration, leveraging computational modeling and multi-omics integration to unravel the role of the GS in health and disease. Critical unresolved questions include bidirectional tumor–glymphatic interactions, nanoparticle delivery optimization in compressed PVS, and

ARTICLE IN PRESS

validation of glymphatic biomarkers in oncological contexts[98,167]. Furthermore, the identification of impaired capillary–venous drainage as a contributor to white matter hypoperfusion opens new therapeutic avenues for preserving deep tissue perfusion during aging, which may complement glymphatic-targeted interventions[168]. Systems biology approaches are needed to identify conserved regulators of AQP4 dynamics, while AI-driven hybrid PET–MRI analytics and ultra-fast Magnetic resonance encephalography (MREG) promise to resolve spatiotemporal glymphatic flux with unprecedented precision[169]. Although encouraging results have been achieved in improving brain function through surgical LVA, unresolved issues persist regarding long-term efficacy, potential side effects, and scalability in larger patient populations[170]. Additionally, leveraging the direct connection between CSF, meningeal dura mater, and skull bone marrow may enable targeted therapies and drug delivery strategies to recruit reparative immune cells or suppress inflammation in various diseases without affecting peripheral immunity[171]. Combinatorial strategies integrating glymphatic restoration with immunotherapies or vascular remodeling may bridge mechanistic insights into actionable clinical paradigms. Prioritizing human studies will be pivotal in translating preclinical findings into therapeutic breakthroughs.

To translate glymphatic research into clinical impact, we must first develop human imaging methods that can directly measure CSF influx, solute clearance, and meningeal lymphatic function. Promising techniques like intrathecal contrast-enhanced MRI and novel PET ligands are now making this possible. A

ARTICLE IN PRESS

critical next step is to validate these direct measurements against established radiographic proxies (e.g., the ALPS index) in patient populations. By fusing invasive data from animal models with multi-modal human imaging, we can achieve a unified understanding of glymphatic dysfunction.

AQP4, expressed on astrocytic endfeet, requires precise polarization to maintain glymphatic function. Impaired AQP4 polarization reduces CSF–ISF exchange and metabolic waste clearance efficiency, exacerbating disease progression[162]. Neuroinflammation, a hallmark of CNS disorders including AD, PD, and ALS, further disrupts AQP4 polarization, compounding glymphatic dysfunction[172]. The GS sustains CNS homeostasis by facilitating CSF–ISF exchange and clearing metabolic waste and inflammatory mediators[173,174], positioning it as a central regulatory hub across pathologies. Notably, the GS exhibits context-dependent roles: in the TME, it may promote immunosuppression by modulating immune cell infiltration and activity, potentially facilitating tumor growth and metastasis[175]; in neurodegenerative diseases, it mitigates neuroinflammation and delays progression by clearing inflammatory factors and waste products[173]. This functional duality suggests that glymphatic activity is modulated by multiple factors, including inflammatory status, immune cell dynamics, and AQP4 polarization. Future research must delineate disease-specific glymphatic mechanisms to enable targeted therapeutic strategies.

ARTICLE IN PRESS

4.3 Translational Challenges

The field must also confront challenges in harmonizing experimental models with clinical realities. For instance, while preclinical studies highlight the therapeutic

ARTICLE IN PRESS

potential of circadian modulation or AQP4-targeted therapies, translating these into safe, effective human interventions requires rigorous validation. Similarly, the development of non-invasive biomarkers (e.g., the ALPS index) necessitates standardized protocols and multicenter validation to ensure diagnostic reliability. Emerging techniques like non-invasive cervical lymphatic stimulation, which bypasses surgical risks while enhancing glymphatic function, exemplify strategies poised to overcome these translational barriers[11]. Furthermore, recent evidence highlights the role of dural mast cells in modulating CSF flow and meningeal immunity at ACE points. Targeting mast cell degranulation or histamine signaling may represent a novel therapeutic strategy to enhance CSF clearance and neuroimmune defense, particularly in infections like bacterial meningitis[12]. Finally, the integration of glymphatic biology with emerging disciplines, such as neuroimmunology, bioengineering, and AI-driven diagnostics, will be essential to unlock transformative therapeutic strategies for neurodegeneration and cancer.

By addressing these limitations and embracing interdisciplinary innovation, future research can refine our understanding of the GS as both a mediator and a therapeutic target in neurological disorders.

Conclusions

The GS emerges as a central pathway in the pathophysiology of both neurodegenerative diseases and brain tumors, linking molecular dysfunction to clinical manifestations. Core to its function is AQP4-mediated CSF–ISF exchange, which governs metabolic waste clearance and neuroimmune homeostasis. In

ARTICLE IN PRESS

neurodegenerative disorders such as AD and PD, glymphatic impairment drives the accumulation of pathogenic proteins (e.g., Aβ, α-syn) through disrupted AQP4 polarization, vascular aging, and circadian dysregulation. These processes are exacerbated by genetic factors (e.g., *APOE4*, *FAM171A2* mutations) and environmental insults (e.g., air pollution), collectively reducing clearance efficiency and accelerating neuroinflammation. Similarly, in ALS and TBI, glymphatic dysfunction precedes symptomatic onset, correlating with TDP-43 accumulation and post-injury edema, respectively.

In brain tumors, mechanical compression and lactate-driven acidosis disrupt perivascular fluid dynamics, fostering an immunosuppressive microenvironment that impedes cytotoxic T-cell infiltration and diminishes therapeutic efficacy. In cerebral metastases, impaired glymphatic clearance independently contributes to peritumoral edema, highlighting its role as a parallel pathological mechanism beyond traditional vascular theories. Neuroimaging biomarkers, such as the ALPS index and CPV, provide non-invasive insights into glymphatic integrity, demonstrating prognostic value in glioma stratification, metastatic edema assessment, and prediction of cognitive decline. However, ongoing efforts to refine these tools and establish their direct link to underlying glymphatic physiology are crucial for their ultimate clinical utility. Recent advances in non-contrast MRI techniques, including IVIM and multi-echo ASL, have further elucidated the effects of sleep and aging on glymphatic function, offering new avenues for early detection and intervention[31].

Therapeutic innovations span a broad spectrum, including circadian modulation,

ARTICLE IN PRESS

CRISPR-based *APOE4* correction, mechanotherapies (e.g., FUS), non-invasive cervical lymphatic stimulation, and surgical approaches (e.g., LVA), each targeting distinct aspects of glymphatic dysfunction. Emerging insights into dural mast cell function reveal their critical role in regulating CSF dynamics and meningeal immunity, suggesting that mast cell-targeted interventions could enhance CNS clearance and defense in neuroinflammatory and infectious contexts[12]. Nonetheless, clinical translation remains challenged by species-specific model limitations, incomplete validation of imaging biomarkers, and unresolved bidirectional tumor–glymphatic interactions.

Future research should prioritize human-centric studies that integrate AI-driven analytics, ultrafast neuroimaging, and multi-omics approaches to unravel spatiotemporal glymphatic dynamics. Combinatorial strategies synergizing glymphatic restoration with immunotherapy or vascular remodeling hold transformative potential. By transcending traditional disciplinary boundaries, this evolving paradigm promises to redefine therapeutic interventions for neurodegeneration and cancer, positioning the GS not as a passive bystander but as a dynamic and actionable therapeutic frontier.

The DTI-ALPS index, as an imaging biomarker for evaluating GS function, faces core challenges in clinical standardization, including insufficient cross-center comparability due to variations in scanning protocols and a lack of correction models for confounders such as age and cerebrovascular disease, which limit its independent diagnostic value. To improve early recognition of neurodegenerative diseases (e.g.,

ARTICLE IN PRESS

AD), a multimodal diagnostic framework is recommended: combining dynamic CSFF monitoring, quantitative PET-Aβ deposition, and the DTI-ALPS index to cross-validate spatiotemporal correlations between GS dysfunction and pathological protein accumulation, thereby establishing a more sensitive disease warning model. Additionally, research suggests that GS functional decline may precede clinical symptoms, particularly in the prodromal stages of diseases such as ALS[73,75]. By enhancing glymphatic clearance through improved sleep rhythms and targeted AQP4 modulation, timely intervention could clear toxic proteins before they aggregate, preventing neuronal damage and disease onset.

ARTICLE IN PRESS

List of Abbreviations

Aβ: Amyloid-β

ADC: Apparent diffusion coefficient

AD: Alzheimer's disease

AI: Artificial intelligence

ALPS: Along perivascular spaces

ALS: Amyotrophic lateral sclerosis

ALS-FTD: Amyotrophic lateral sclerosis - Frontotemporal dementia

APOE4: Apolipoprotein E ε4 allele

AQP4: Aquaporin-4

ASL: Arterial spin labeling

BAMs: Border-associated macrophages

ARTICLE IN PRESS

BBB: Blood-brain barrier

BCSFB: Blood-cerebrospinal fluid barrier

BG: Basal ganglia

BG-PVS: Basal ganglia-perivascular space

BLF: Brain lymph fluid

BO-Ms: Borneol micelle

CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

CED: Convection-enhanced delivery

CLNs: Cervical lymph nodes

CP: Choroid plexus

CPV: Choroid plexus volume

CSF: Cerebrospinal fluid

CSFF: Cerebrospinal fluid fraction

ARTICLE IN PRESS

DAMP: Damage-associated molecular pattern

DCE-MRI: Dynamic contrast-enhanced MRI

DORAs: Dual orexin receptor antagonists

DSCR1/RCAN1: Down syndrome critical region 1 / Regulator of calcineurin 1

DTI: Diffusion tensor imaging

DTI-ALPS: Diffusion tensor image analysis along the perivascular space

EAF2: ELL-associated factor 2

EPVS: Enlarged PVS

ARTICLE IN PRESS

FPD: Familial Parkinson's disease

FUS: Focused ultrasound

GBM: Glioblastoma

gBOLD: Global blood-oxygen-level-dependent

GPR81: G-protein coupled receptor 81

GS: Glymphatic system

HIF-1α: Hypoxia-inducible factor 1-alpha

HIIT: High-intensity interval training

IHD: Ischemic heart disease

ICP: Intracranial pressure

IDH1: Isocitrate dehydrogenase 1

iNPH: Idiopathic normal pressure hydrocephalus

iPD: Idiopathic PD

iRBD: idiopathic REM sleep behavior disorder

ISF: Interstitial fluid

LRRK2: Leucine-Rich Repeat Kinase 2

LVA: Lymphatic vein anastomosis / Lymphatic-venous anastomosis

mALPS-index: Modified ALPS index

MB: Medulloblastoma

MCI: Mild cognitive impairment

mLECs: Meningeal lymphatic endothelial cells

mLVs: Meningeal lymphatic vessels

ARTICLE IN PRESS

ARTICLE IN PRESS

MMP-9: Metalloproteinase-9 / Matrix metalloproteinase-9

MREG: Magnetic resonance encephalography

NF-L: Neurofilament light

NK: Natural killer (cells)

NOTCH3: Neurogenic locus notch homolog protein 3

NPs: Nanoparticles

PD: Parkinson's disease

PET-MRI: Positron Emission Tomography–Magnetic Resonance Imaging

PGRN: Progranulin

PIGD: Postural instability/gait difficulty (subtype of PD)

PTBE: Peritumoral brain edema

PVS: Perivascular space

rTMS: Repetitive transcranial magnetic stimulation

SAH: Subarachnoid hemorrhage

TBI: Traumatic brain injury

TDP-43: TAR DNA-binding protein 43

TD: Tremor-dominant (subtype of PD)

TSP-1: Thrombospondin-1

VEGF-C: Vascular endothelial growth factor C

VEGFR3: Vascular endothelial growth factor receptor 3

VLIUS: Very low-intensity ultrasound

VWR: Voluntary wheel running

ARTICLE IN PRESS

ARTICLE IN PRESS

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

ARTICLE IN PRESS

Funding

The present study was supported by The Plan for Key Scientific Research Projects of Higher Education Institutions in Henan Province for 2026 (grant no. 26A310011), the research project of 988th Hospital of Joint Logistic Support Force of PLA (grant no. YNZX2024005), the joint construction project of Henan Province (grant no. LHGJ20230703), and the opening project of State Key Laboratory of Explosion Science and Technology (Beijing Institute of Technology) (grant no. KFJJ23-09M). The funding organizations played no role in the scientific conduct of this research, including but not limited to: study conceptualization, data acquisition/processing/interpretation, manuscript composition, or publication decision-making.

Authors' contributions

ARTICLE IN PRESS

Y.C., and H.L. contributed to the conceptualization, literature review, and initial drafting of the manuscript. H.L., K.Z., S.G., C.W., J.Z., F.L., and L.Z. assisted with figure preparation and manuscript editing. A.Y. and L.J. provided critical revisions and contributed to refining the intellectual content. A.Y. and L.J. supervised the project, provided overall guidance throughout the writing process, and were responsible for funding acquisition. All authors contributed to the conception of the work and approved the final manuscript.

Acknowledgements

Figures were created through BioRender.com.

ARTICLE IN PRESS

References

1 Rasmussen, M. K., Mestre, H. & Nedergaard, M. The glymphatic pathway in neurological disorders. *Lancet Neurol* (2018). **17**, 1016-1024.

2 Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A. *et al.* A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med* (2012). **4**, 147ra111.

3 Iliff, J. J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M. *et al.* Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest* (2013). **123**, 1299-1309.

4 Shen, Y., Zhang, L., Ding, G., Boyd, E., Kaur, J., Li, Q. *et al.* Vascular Contribution to Cerebral Waste Clearance Affected by Aging or Diabetes. *Diagnostics (Basel)* (2025). **15**.

5 Hu, J., Shen, Y., Fahmy, L. M., Krishnamurthy, S., Li, J., Zhang, L. *et al.* The role of the

ARTICLE IN PRESS

parenchymal vascular system in cerebrospinal fluid tracer clearance. *Eur Radiol* (2023). **33**, 656-665.

6 Kaur, J., Fahmy, L. M., Davoodi-Bojd, E., Zhang, L., Ding, G., Hu, J. *et al.* Waste Clearance in the Brain. *Front Neuroanat* (2021). **15**, 665803.

7 Wardlaw, J. M., Benveniste, H., Nedergaard, M., Zlokovic, B. V., Mestre, H., Lee, H. *et al.* Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat Rev Neurol* (2020). **16**, 137-153.

8 Tithof, J., Kelley, D. H., Mestre, H., Nedergaard, M. & Thomas, J. H. Hydraulic resistance of periarterial spaces in the brain. *Fluids Barriers CNS* (2019). **16**, 19.

9 Ringstad, G., Vatnehol, S. A. S. & Eide, P. K. Glymphatic MRI in idiopathic normal pressure hydrocephalus. *Brain* (2017). **140**, 2691-2705.

10 Ringstad, G., Valnes, L. M., Dale, A. M., Pripp, A. H., Vatnehol, S. S., Emblem, K. E. *et al.* Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. *JCI Insight* (2018). **3**.

11 Jin, H., Yoon, J. H., Hong, S. P., Hwang, Y. S., Yang, M. J., Choi, J. *et al.* Increased CSF drainage by non-invasive manipulation of cervical lymphatics. *Nature* (2025). **643**, 755-767.

12 Mamuladze, T., Zaninelli, T. H., Smyth, L. C. D., Wu, Y., Abramishvili, D., Silva, R. *et al.* Mast cells regulate the brain-dura interface and CSF dynamics. *Cell* (2025).

13 Ren, J., Xie, D., Wang, L., Wu, Z., Lin, S., Jin, Q. *et al.* Glymphatic system dysfunction as a biomarker of disease progression in Parkinson's disease: neuroimaging evidence from

ARTICLE IN PRESS

ARTICLE IN PRESS

longitudinal cohort studies. *J Neurol* (2025). **272**, 196.

14 Si, X., Guo, T., Wang, Z., Fang, Y., Gu, L., Cao, L. *et al.* Neuroimaging evidence of glymphatic system dysfunction in possible REM sleep behavior disorder and Parkinson's disease. *NPJ Parkinsons Dis* (2022). **8**, 54.

15 Chen, K., Du, X., Chao, M. A., Xie, Z. & Yang, G. Surgery impairs glymphatic activity and cognitive function in aged mice. *Mol Brain* (2025). **18**, 7.

16 Hauglund, N. L., Andersen, M., Tokarska, K., Radovanovic, T., Kjaerby, C., Sørensen, F. L. *et al.* Norepinephrine-mediated slow vasomotion drives glymphatic clearance during sleep. *Cell* (2025). **188**, 606-622.e617.

17 Sun, X., Dias, L., Peng, C., Zhang, Z., Ge, H., Wang, Z. *et al.* 40 Hz light flickering facilitates the glymphatic flow via adenosine signaling in mice. *Cell Discov* (2024). **10**, 81.

18 Harrison, I. F., Ismail, O., Machhada, A., Colgan, N., Ohene, Y., Nahavandi, P. *et al.* Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain* (2020). **143**, 2576-2593.

19 Simon, M., Wang, M. X., Ismail, O., Braun, M., Schindler, A. G., Reemmer, J. *et al.* Loss of perivascular aquaporin-4 localization impairs glymphatic exchange and promotes amyloid β plaque formation in mice. *Alzheimers Res Ther* (2022). **14**, 59.

20 Pirici, I., Balsanu, T. A., Bogdan, C., Margaritescu, C., Divan, T., Vitalie, V. *et al.* Inhibition of Aquaporin-4 Improves the Outcome of Ischaemic Stroke and Modulates Brain Paravascular Drainage Pathways. *Int J Mol Sci* (2017). **19**.

ARTICLE IN PRESS

ARTICLE IN PRESS

21 Holth, J. K., Fritschi, S. K., Wang, C., Pedersen, N. P., Cirrito, J. R., Mahan, T. E. *et al.* The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* (2019). **363**, 880-884.

22 Li, Y., Rusinek, H., Butler, T., Glodzik, L., Pirraglia, E., Babich, J. *et al.* Decreased CSF clearance and increased brain amyloid in Alzheimer's disease. *Fluids Barriers CNS* (2022). **19**, 21.

23 Li, Y., Wang, L., Zhong, J., Xu, H., Han, Y., Zuo, C. *et al.* Impaired glymphatic function as a biomarker for subjective cognitive decline: An exploratory dual cohort study. *Alzheimers Dement* (2024). **20**, 6542-6555.

24 Huang, S. Y., Zhang, Y. R., Guo, Y., Du, J., Ren, P., Wu, B. S. *et al.* Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. *Alzheimers Dement* (2024). **20**, 3251-3269.

25 Hsu, J. L., Wei, Y. C., Toh, C. H., Hsiao, I. T., Lin, K. J., Yen, T. C. *et al.* Magnetic Resonance Images Implicate That Glymphatic Alterations Mediate Cognitive Dysfunction in Alzheimer Disease. *Ann Neurol* (2023). **93**, 164-174.

26 Kamagata, K., Andica, C., Takabayashi, K., Saito, Y., Taoka, T., Nozaki, H. *et al.* Association of MRI Indices of Glymphatic System With Amyloid Deposition and Cognition in Mild Cognitive Impairment and Alzheimer Disease. *Neurology* (2022). **99**, e2648-e2660.

27 Zhang, X., Wang, Y., Jiao, B., Wang, Z., Shi, J., Zhang, Y. *et al.* Glymphatic system impairment in Alzheimer's disease: associations with perivascular space volume and cognitive function. *Eur Radiol* (2024). **34**, 1314-1323.

ARTICLE IN PRESS

ARTICLE IN PRESS

28 Schirge, P. M., Perneczky, R., Taoka, T., Ruiz-Rizzo, A. L., Ersoezlue, E., Forbrig, R. *et al.* Perivascular space and white matter hyperintensities in Alzheimer's disease: associations with disease progression and cognitive function. *Alzheimers Res Ther* (2025). **17**, 62.

29 Zhou, L., Nguyen, T. D., Chiang, G. C., Wang, X. H., Xi, K., Hu, T. W. *et al.* Parenchymal CSF fraction is a measure of brain glymphatic clearance and positively associated with amyloid beta deposition on PET. *Alzheimers Dement* (2024). **20**, 2047-2057.

30 Sacchi, L., D'Agata, F., Campisi, C., Arcaro, M., Carandini, T., Örzsik, B. *et al.* A "glympse" into neurodegeneration: Diffusion MRI and cerebrospinal fluid aquaporin-4 for the assessment of glymphatic system in Alzheimer's disease and other dementias. *Hum Brain Mapp* (2024). **45**, e26805.

31 Rane Levendovszky, S., Flores, J., Peskind, E. R., Václavů, L., van Osch, M. J. & Iliff, J. Preliminary investigations into human neurofluid transport using multiple novel non-contrast MRI methods. *J Cereb Blood Flow Metab* (2024). **44**, 1580-1592.

32 Holtzman, D. M., Herz, J. & Bu, G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. *Cold Spring Harb Perspect Med* (2012). **2**, a006312.

33 Zlokovic, B. V. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron* (2008). **57**, 178-201.

34 Suárez-Calvet, M., Capell, A., Araque Caballero, M., Morenas-Rodríguez, E., Fellerer, K., Franzmeier, N. *et al.* CSF progranulin increases in the course of Alzheimer's disease and is associated with sTREM2, neurodegeneration and cognitive decline. *EMBO Mol Med* (2018). **10**.

ARTICLE IN PRESS

ARTICLE IN PRESS

35 Xu, W., Han, S. D., Zhang, C., Li, J. Q., Wang, Y. J., Tan, C. C. *et al.* The FAM171A2 gene is a key regulator of progranulin expression and modifies the risk of multiple neurodegenerative diseases. *Sci Adv* (2020). **6**.

36 Ma, Y. & Han, Y. Targeting the brain's glymphatic pathway: A novel therapeutic approach for cerebral small vessel disease. *Neural Regen Res* (2026). **21**, 433-442.

37 Biskaduros, A., Glodzik, L., Saint Louis, L. A., Rusinek, H., Pirraglia, E., Osorio, R. *et al.* Longitudinal trajectories of Alzheimer's disease CSF biomarkers and blood pressure in cognitively healthy subjects. *Alzheimers Dement* (2024). **20**, 4389-4400.

38 Romay, M. C., Knutsen, R. H., Ma, F., Mompeón, A., Hernandez, G. E., Salvador, J. *et al.* Age-related loss of Notch3 underlies brain vascular contractility deficiencies, glymphatic dysfunction, and neurodegeneration in mice. *J Clin Invest* (2024). **134**.

39 Wang, M. L., Yu, M. M., Sun, Z., Zhang, J. J., Zhang, J. K., Wu, X. *et al.* Associations of ischemic heart disease with brain glymphatic MRI indices and risk of Alzheimer's disease. *J Prev Alzheimers Dis* (2025). **12**, 100045.

40 Rajna, Z., Mattila, H., Huotari, N., Tuovinen, T., Krüger, J., Holst, S. C. *et al.* Cardiovascular brain impulses in Alzheimer's disease. *Brain* (2021). **144**, 2214-2226.

41 Sadleir, K. R. & Vassar, R. Connections between ApoE, sleep, and Aβ and tau pathologies in Alzheimer's disease. *J Clin Invest* (2023). **133**.

42 Lacerda, R. A. V., Desio, J. A. F., Kammers, C. M., Henkes, S., Freitas de Sá, M., de Souza, E. F. *et al.* Sleep disorders and risk of alzheimer's disease: A two-way road. *Ageing Res Rev*

ARTICLE IN PRESS

ARTICLE IN PRESS

(2024). **101**, 102514.

43 Li, J., Hu, Y., Xu, Y., Feng, X., Meyer, C. H., Dai, W. *et al.* Associations between the choroid plexus and tau in Alzheimer's disease using an active learning segmentation pipeline. *Fluids Barriers CNS* (2024). **21**, 56.

44 Cullell, N., Caruana, G., Elias-Mas, A., Delgado-Sanchez, A., Artero, C., Buongiorno, M. T. *et al.* Glymphatic system clearance and Alzheimer's disease risk: a CSF proteome-wide study. *Alzheimers Res Ther* (2025). **17**, 31.

45 Yang, F., Wang, Z., Shi, W., Wang, M., Ma, R., Zhang, W. *et al.* Advancing insights into in vivo meningeal lymphatic vessels with stereoscopic wide-field photoacoustic microscopy. *Light Sci Appl* (2024). **13**, 96.

46 Hong, H., Hong, L., Luo, X., Zeng, Q., Li, K., Wang, S. *et al.* The relationship between amyloid pathology, cerebral small vessel disease, glymphatic dysfunction, and cognition: a study based on Alzheimer's disease continuum participants. *Alzheimers Res Ther* (2024). **16**, 43.

47 Lopes, D. M., Wells, J. A., Ma, D., Wallis, L., Park, D., Llewellyn, S. K. *et al.* Glymphatic inhibition exacerbates tau propagation in an Alzheimer's disease model. *Alzheimers Res Ther* (2024). **16**, 71.

48 Si, X., Dai, S., Fang, Y., Tang, J., Wang, Z., Li, Y. *et al.* Matrix metalloproteinase-9 inhibition prevents aquaporin-4 depolarization-mediated glymphatic dysfunction in Parkinson's disease. *J Adv Res* (2024). **56**, 125-136.

ARTICLE IN PRESS

ARTICLE IN PRESS

49 Hussain, R., Graham, U., Elder, A. & Nedergaard, M. Air pollution, glymphatic impairment, and Alzheimer's disease. *Trends Neurosci* (2023). **46**, 901-911.

50 Jeong, S. H., Jeong, H. J., Sunwoo, M. K., Ahn, S. S., Lee, S. K., Lee, P. H. *et al.* Association between choroid plexus volume and cognition in Parkinson disease. *Eur J Neurol* (2023). **30**, 3114-3123.

51 Jeong, S. H., Park, C. J., Jeong, H. J., Sunwoo, M. K., Ahn, S. S., Lee, S. K. *et al.* Association of choroid plexus volume with motor symptoms and dopaminergic degeneration in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2023). **94**, 1047-1055.

52 Lin, R., Cai, G., Chen, Y., Zheng, J., Wang, S., Xiao, H. *et al.* Association of glymphatic system function with peripheral inflammation and motor symptoms in Parkinson's disease. *NPJ Parkinsons Dis* (2025). **11**, 62.

53 Cai, X., Chen, Z., He, C., Zhang, P., Nie, K., Qiu, Y. *et al.* Diffusion along perivascular spaces provides evidence interlinking compromised glymphatic function with aging in Parkinson's disease. *CNS Neurosci Ther* (2023). **29**, 111-121.

54 Shen, T., Yue, Y., Ba, F., He, T., Tang, X., Hu, X. *et al.* Diffusion along perivascular spaces as marker for impairment of glymphatic system in Parkinson's disease. *NPJ Parkinsons Dis* (2022). **8**, 174.

55 Meng, J. C., Shen, M. Q., Lu, Y. L., Feng, H. X., Chen, X. Y., Xu, D. Q. *et al.* Correlation of glymphatic system abnormalities with Parkinson's disease progression: a clinical study based on non-invasive fMRI. *J Neurol* (2024). **271**, 457-471.

ARTICLE IN PRESS

ARTICLE IN PRESS

56 Wood, K. H., Nenert, R., Miften, A. M., Kent, G. W., Sleyster, M., Memon, R. A. *et al.* Diffusion Tensor Imaging-Along the Perivascular-Space Index Is Associated with Disease Progression in Parkinson's Disease. *Mov Disord* (2024). **39**, 1504-1513.

57 Donahue, E. K., Murdos, A., Jakowec, M. W., Sheikh-Bahaei, N., Toga, A. W., Petzinger, G. M. *et al.* Global and Regional Changes in Perivascular Space in Idiopathic and Familial Parkinson's Disease. *Mov Disord* (2021). **36**, 1126-1136.

58 Zhao, Y., Xu, C., Chen, Y., Gong, T., Zhuo, M., Zhao, C. *et al.* Glymphatic dysfunction exacerbates cognitive decline by triggering cortical degeneration in Parkinson's disease: evidence from diffusion-tensor MRI. *Brain Commun* (2025). **7**, fcaf029.

59 Qin, Y., He, R., Chen, J., Zhou, X., Zhou, X., Liu, Z. *et al.* Neuroimaging uncovers distinct relationships of glymphatic dysfunction and motor symptoms in Parkinson's disease. *J Neurol* (2023). **270**, 2649-2658.

60 Wang, Z., Song, Z., Zhou, C., Fang, Y., Gu, L., Yang, W. *et al.* Reduced coupling of global brain function and cerebrospinal fluid dynamics in Parkinson's disease. *J Cereb Blood Flow Metab* (2023). **43**, 1328-1339.

61 Hua, L., Zeng, X., Zhang, K., Zhao, Z. & Yuan, Z. Reduced glymphatic clearance in early psychosis. *Mol Psychiatry* (2025).

62 Zhang, Y., Zhang, C., He, X. Z., Li, Z. H., Meng, J. C., Mao, R. T. *et al.* Interaction Between the Glymphatic System and α-Synuclein in Parkinson's Disease. *Mol Neurobiol* (2023). **60**, 2209-2222.

ARTICLE IN PRESS

ARTICLE IN PRESS

63 Ding, X. B., Wang, X. X., Xia, D. H., Liu, H., Tian, H. Y., Fu, Y. *et al.* Impaired meningeal lymphatic drainage in patients with idiopathic Parkinson's disease. *Nat Med* (2021). **27**, 411-418.

64 Zhou, C., Jiang, X., Guan, X., Guo, T., Wu, J., Wu, H. *et al.* Glymphatic system dysfunction and risk of clinical milestones in patients with Parkinson disease. *Eur J Neurol* (2024). **31**, e16521.

65 Li, Y., Zhang, T., Wang, C., Geng, L., Liu, T., Lu, T. *et al.* The Impact of Sleep Disorders on Glymphatic Function in Parkinson's Disease Using Diffusion Tensor MRI. *Acad Radiol* (2025). **32**, 2209-2219.

66 Sharkey, R. J., Cortese, F., Goodyear, B. G., Korngut, L. W., Jacob, S. M., Sharkey, K. A. *et al.* Longitudinal analysis of glymphatic function in amyotrophic lateral sclerosis and primary lateral sclerosis. *Brain* (2024). **147**, 4026-4032.

67 Carotenuto, A., Cacciaguerra, L., Pagani, E., Preziosa, P., Filippi, M. & Rocca, M. A. Glymphatic system impairment in multiple sclerosis: relation with brain damage and disability. *Brain* (2022). **145**, 2785-2795.

68 Bolte, A. C., Dutta, A. B., Hurt, M. E., Smirnov, I., Kovacs, M. A., McKee, C. A. *et al.* Meningeal lymphatic dysfunction exacerbates traumatic brain injury pathogenesis. *Nat Commun* (2020). **11**, 4524.

69 Zamani, A., Walker, A. K., Rollo, B., Ayers, K. L., Farah, R., O'Brien, T. J. *et al.* Impaired glymphatic function in the early stages of disease in a TDP-43 mouse model of amyotrophic lateral sclerosis. *Transl Neurodegener* (2022). **11**, 17.

ARTICLE IN PRESS

ARTICLE IN PRESS

70 Nguyen, B., Bix, G. & Yao, Y. Basal lamina changes in neurodegenerative disorders. *Mol Neurodegener* (2021). **16**, 81.

71 Wafford, K. A. Aberrant waste disposal in neurodegeneration: why improved sleep could be the solution. *Cereb Circ Cogn Behav* (2021). **2**, 100025.

72 Choi, Y., Jung, H. J., Jung, H. K., Jeong, E., Kim, S., Kim, J. Y. *et al.* In vivo imaging markers of glymphatic dysfunction in amyotrophic lateral sclerosis: Analysis of ALPS index and choroid plexus volume. *J Neurol Sci* (2025). **469**, 123393.

73 Zamani, A., Walker, A. K. & Wright, D. K. Glymphatic dysfunction and neurodegeneration in ALS: Longitudinal insights from rNLS8 TDP-43 mice. *Neurobiol Dis* (2025). **206**, 106832.

74 Abdelfattah, A. S., Ahuja, S., Akkin, T., Allu, S. R., Brake, J., Boas, D. A. *et al.* Neurophotonic tools for microscopic measurements and manipulation: status report. *Neurophotonics* (2022). **9**, 013001.

75 Liu, S., Sun, X., Ren, Q., Chen, Y., Dai, T., Yang, Y. *et al.* Glymphatic dysfunction in patients with early-stage amyotrophic lateral sclerosis. *Brain* (2024). **147**, 100-108.

76 Ng Kee Kwong, K. C., Mehta, A. R., Nedergaard, M. & Chandran, S. Defining novel functions for cerebrospinal fluid in ALS pathophysiology. *Acta Neuropathol Commun* (2020). **8**, 140.

77 Hussain, R., Tithof, J., Wang, W., Cheetham-West, A., Song, W., Peng, W. *et al.* Potentiating glymphatic drainage minimizes post-traumatic cerebral oedema. *Nature* (2023). **623**, 992-1000.

ARTICLE IN PRESS

ARTICLE IN PRESS

78 Eide, P. K. & Ringstad, G. Glymphatic-stagnated edema induced by traumatic brain injury. *Trends Pharmacol Sci* (2024). **45**, 388-390.

79 Xiang, T., Feng, D., Zhang, X., Chen, Y., Wang, H., Liu, X. *et al.* Effects of increased intracranial pressure on cerebrospinal fluid influx, cerebral vascular hemodynamic indexes, and cerebrospinal fluid lymphatic efflux. *J Cereb Blood Flow Metab* (2022). **42**, 2287-2302.

80 Salman, M. M., Kitchen, P., Halsey, A., Wang, M. X., Törnroth-Horsefield, S., Conner, A. C. *et al.* Emerging roles for dynamic aquaporin-4 subcellular relocalization in CNS water homeostasis. *Brain* (2022). **145**, 64-75.

81 Braun, M., Sevao, M., Keil, S. A., Gino, E., Wang, M. X., Lee, J. *et al.* Macroscopic changes in aquaporin-4 underlie blast traumatic brain injury-related impairment in glymphatic function. *Brain* (2024). **147**, 2214-2229.

82 Dong, S., Zhao, H., Nie, M., Sha, Z., Feng, J., Liu, M. *et al.* Cannabidiol Alleviates Neurological Deficits After Traumatic Brain Injury by Improving Intracranial Lymphatic Drainage. *J Neurotrauma* (2024). **41**, e2009-e2025.

83 Bolte, A. C. & Lukens, J. R. Neuroimmune cleanup crews in brain injury. *Trends Immunol* (2021). **42**, 480-494.

84 Jung, L. B., Wiegand, T. L. T., Tuz-Zahra, F., Tripodis, Y., Iliff, J. J., Piantino, J. *et al.* Repetitive Head Impacts and Perivascular Space Volume in Former American Football Players. *JAMA Netw Open* (2024). **7**, e2428687.

85 Garcia, K. J., Brolly, G., Ng, D., Bederson, M., Martinez, P., Jr. & Whiting, M. D. Lifetime

ARTICLE IN PRESS

ARTICLE IN PRESS

history of head injury is associated with reduced perivascular space number in acute mild traumatic brain injury. *Brain Commun* (2024). **6**, fcae314.

86 Hicks, A. J., Sinclair, B., Shultz, S. R., Pham, W., Silbert, L. C., Schwartz, D. L. *et al.* Associations of Enlarged Perivascular Spaces With Brain Lesions, Brain Age, and Clinical Outcomes in Chronic Traumatic Brain Injury. *Neurology* (2023). **101**, e63-e73.

87 Klostranec, J. M., Vucevic, D., Bhatia, K. D., Kortman, H. G. J., Krings, T., Murphy, K. P. *et al.* Current Concepts in Intracranial Interstitial Fluid Transport and the Glymphatic System: Part II-Imaging Techniques and Clinical Applications. *Radiology* (2021). **301**, 516-532.

88 Garland, P., Morton, M., Zolnourian, A., Durnford, A., Gaastra, B., Toombs, J. *et al.* Neurofilament light predicts neurological outcome after subarachnoid haemorrhage. *Brain* (2021). **144**, 761-768.

89 Joseph, C. R., Lim, J. K., Grohol, B. N., Zivcevska, M., Lencke, J., Rich, E. D. *et al.* Identifying delay in glymphatic clearance of labeled protons post-acute head trauma utilizing 3D ASL MRI (arterial spin labeling): a pilot study. *Sci Rep* (2024). **14**, 6188.

90 Lopes, D. M., Llewellyn, S. K. & Harrison, I. F. Propagation of tau and α-synuclein in the brain: therapeutic potential of the glymphatic system. *Transl Neurodegener* (2022). **11**, 19.

91 Formolo, D. A., Yu, J., Lin, K., Tsang, H. W. H., Ou, H., Kranz, G. S. *et al.* Leveraging the glymphatic and meningeal lymphatic systems as therapeutic strategies in Alzheimer's disease: an updated overview of nonpharmacological therapies. *Mol Neurodegener* (2023). **18**, 26.

92 Siri, S., Burchett, A. & Datta, M. Simulating the impact of tumor mechanical forces on

ARTICLE IN PRESS

ARTICLE IN PRESS

glymphatic networks in the brain parenchyma. *Biomech Model Mechanobiol* (2024). **23**, 2229-2241.

93 Zhang, Y., Peng, Q., Zheng, J., Yang, Y., Zhang, X., Ma, A. *et al.* The function and mechanism of lactate and lactylation in tumor metabolism and microenvironment. *Genes Dis* (2023). **10**, 2029-2037.

94 Meng, X., Wu, W., Tang, Y., Peng, M., Yang, J., Yuan, S. *et al.* Lactate/Hydroxycarboxylic Acid Receptor 1 in Alzheimer's Disease: Mechanisms and Therapeutic Implications-Exercise Perspective. *Mol Neurobiol* (2024). **61**, 7717-7731.

95 Mestre, H., Hablitz, L. M., Xavier, A. L., Feng, W., Zou, W., Pu, T. *et al.* Aquaporin-4-dependent glymphatic solute transport in the rodent brain. *Elife* (2018). **7**.

96 Kaur, J., Ding, G., Zhang, L., Lu, Y., Luo, H., Li, L. *et al.* Imaging glymphatic response to glioblastoma. *Cancer Imaging* (2023). **23**, 107.

97 Li, L., Ding, G., Zhang, L., Luo, H., Davoodi-Bojd, E., Li, Q. *et al.* Glymphatic transport is reduced in rats with spontaneous pituitary tumor. *Front Med (Lausanne)* (2023). **10**, 1189614.

98 Gao, M., Liu, Z., Zang, H., Wu, X., Yan, Y., Lin, H. *et al.* A Histopathologic Correlation Study Evaluating Glymphatic Function in Brain Tumors by Multiparametric MRI. *Clin Cancer Res* (2024). **30**, 4876-4886.

99 Toh, C. H. & Siow, T. Y. Factors Associated With Dysfunction of Glymphatic System in Patients With Glioma. *Front Oncol* (2021). **11**, 744318.

100 Zhu, H., Xie, Y., Li, L., Liu, Y., Li, S., Shen, N. *et al.* Diffusion along the perivascular space as

ARTICLE IN PRESS

ARTICLE IN PRESS

a potential biomarker for glioma grading and isocitrate dehydrogenase 1 mutation status prediction. *Quant Imaging Med Surg* (2023). **13**, 8259-8273.

101 Zeng, S., Huang, Z., Zhou, W., Ma, H., Wu, J., Zhao, C. *et al.* Noninvasive evaluation of the glymphatic system in diffuse gliomas using diffusion tensor image analysis along the perivascular space. *J Neurosurg* (2025). **142**, 187-196.

102 Li, Q., Tao, X., Li, X., Zhang, X., Wang, H., Qin, J. *et al.* Noninvasive assessment of glymphatic system alterations as potential biomarkers for predicting overall survival in glioma. *J Neurosurg* (2025). 1-13.

103 Toh, C. H., Siow, T. Y. & Castillo, M. Peritumoral Brain Edema in Meningiomas May Be Related to Glymphatic Dysfunction. *Front Neurosci* (2021). **15**, 674898.

104 Song, R., Glass, J. O., Wu, S., Li, Y., Robinson, G. W., Gajjar, A. *et al.* Perivascular space imaging during therapy for medulloblastoma. *PLoS One* (2025). **20**, e0318278.

105 Toh, C. H., Siow, T. Y. & Castillo, M. Peritumoral Brain Edema in Metastases May Be Related to Glymphatic Dysfunction. *Front Oncol* (2021). **11**, 725354.

106 Ma, Q., Schlegel, F., Bachmann, S. B., Schneider, H., Decker, Y., Rudin, M. *et al.* Lymphatic outflow of cerebrospinal fluid is reduced in glioma. *Sci Rep* (2019). **9**, 14815.

107 He, W., You, J., Wan, Q., Xiao, K., Chen, K., Lu, Y. *et al.* The anatomy and metabolome of the lymphatic system in the brain in health and disease. *Brain Pathol* (2020). **30**, 392-404.

108 Mehta, A. I., Linninger, A., Lesniak, M. S. & Engelhard, H. H. Current status of intratumoral therapy for glioblastoma. *J Neurooncol* (2015). **125**, 1-7.

ARTICLE IN PRESS

ARTICLE IN PRESS

109 Wang, L., Liu, L., Zhang, H. & Yue, Q. Diffusion tensor imaging changes along the perivascular spaces may serve as a prognostic factor for high-grade glioma. *Eur J Radiol* (2025). **184**, 111993.

110 Ran, L., Fang, Y., Cheng, C., He, Y., Shao, Z., Kong, Y. *et al.* Genome-wide and phenome-wide studies provided insights into brain glymphatic system function and its clinical associations. *Sci Adv* (2025). **11**, eadr4606.

111 Alshuhri, M. S., Gallagher, L., Work, L. M. & Holmes, W. M. Direct imaging of glymphatic transport using H217O MRI. *JCI Insight* (2021). **6**.

112 Lohela, T. J., Lilius, T. O. & Nedergaard, M. The glymphatic system: implications for drugs for central nervous system diseases. *Nat Rev Drug Discov* (2022). **21**, 763-779.

113 Ullah, A. & Dral, P. O. Predicting the future of excitation energy transfer in light-harvesting complex with artificial intelligence-based quantum dynamics. *Nat Commun* (2022). **13**, 1930.

114 Zhang, Z., Xue, P., Bendlin, B. B., Zetterberg, H., De Felice, F., Tan, X. *et al.* Melatonin: A potential nighttime guardian against Alzheimer's. *Mol Psychiatry* (2025). **30**, 237-250.

115 Li, Y., Zhang, J., Wan, J., Liu, A. & Sun, J. Melatonin regulates Aβ production/clearance balance and Aβ neurotoxicity: A potential therapeutic molecule for Alzheimer's disease. *Biomed Pharmacother* (2020). **132**, 110887.

116 Wu, Y., Zhang, T., Li, X., Wei, Y., Li, X., Wang, S. *et al.* Borneol-driven meningeal lymphatic drainage clears amyloid-β peptide to attenuate Alzheimer-like phenotype in mice. *Theranostics* (2023). **13**, 106-124.

ARTICLE IN PRESS

ARTICLE IN PRESS

117 Ye, C., Wang, S., Niu, L., Yang, F., Wang, G., Wang, S. *et al.* Unlocking potential of oxytocin: improving intracranial lymphatic drainage for Alzheimer's disease treatment. *Theranostics* (2024). **14**, 4331-4351.

118 Li, Z., Xiao, J., Xu, X., Li, W., Zhong, R., Qi, L. *et al.* M-CSF, IL-6, and TGF-β promote generation of a new subset of tissue repair macrophage for traumatic brain injury recovery. *Sci Adv* (2021). **7**.

119 Boortz-Marx, R. Factors affecting intracranial pressure: a descriptive study. *J Neurosurg Nurs* (1985). **17**, 89-94.

120 Lv, C., Han, S., Sha, Z., Liu, M., Dong, S., Zhang, C. *et al.* Cerebral glucagon-like peptide-1 receptor activation alleviates traumatic brain injury by glymphatic system regulation in mice. *CNS Neurosci Ther* (2023). **29**, 3876-3888.

121 Mi, L., Yuan, J., Jiang, Y., Hu, Y., Lv, C., Xu, Y. *et al.* Constructed transferrin receptor-targeted liposome for the delivery of fluvoxamine to improve prognosis in a traumatic brain injury mouse model. *Drug Deliv* (2025). **32**, 2486840.

122 Liu, M., Huang, J., Liu, T., Yuan, J., Lv, C., Sha, Z. *et al.* Exogenous interleukin 33 enhances the brain's lymphatic drainage and toxic protein clearance in acute traumatic brain injury mice. *Acta Neuropathol Commun* (2023). **11**, 61.

123 Liao, J., Zhang, M., Shi, Z., Lu, H., Wang, L., Fan, W. *et al.* Improving the Function of Meningeal Lymphatic Vessels to Promote Brain Edema Absorption after Traumatic Brain Injury. *J Neurotrauma* (2023). **40**, 383-394.

ARTICLE IN PRESS

ARTICLE IN PRESS

124 Tong, S., Xie, L., Xie, X., Xu, J., You, Y., Sun, Y. *et al.* Nano-Plumber Reshapes Glymphatic-Lymphatic System to Sustain Microenvironment Homeostasis and Improve Long-Term Prognosis after Traumatic Brain Injury. *Adv Sci (Weinh)* (2023). **10**, e2304284.

125 Jha, R. M., Kochanek, P. M. & Simard, J. M. Pathophysiology and treatment of cerebral edema in traumatic brain injury. *Neuropharmacology* (2019). **145**, 230-246.

126 Vecht, C. J., Hovestadt, A., Verbiest, H. B., van Vliet, J. J. & van Putten, W. L. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. *Neurology* (1994). **44**, 675-680.

127 Papadopoulos, M. C., Saadoun, S., Binder, D. K., Manley, G. T., Krishna, S. & Verkman, A. S. Molecular mechanisms of brain tumor edema. *Neuroscience* (2004). **129**, 1011-1020.

128 Simone, L., Pisani, F., Binda, E., Frigeri, A., Vescovi, A. L., Svelto, M. *et al.* AQP4-dependent glioma cell features affect the phenotype of surrounding cells via extracellular vesicles. *Cell Biosci* (2022). **12**, 150.

129 Feng, S., Wu, C., Zou, P., Deng, Q., Chen, Z., Li, M. *et al.* High-intensity interval training ameliorates Alzheimer's disease-like pathology by regulating astrocyte phenotype-associated AQP4 polarization. *Theranostics* (2023). **13**, 3434-3450.

130 Murdock, M. H., Yang, C. Y., Sun, N., Pao, P. C., Blanco-Duque, C., Kahn, M. C. *et al.* Multisensory gamma stimulation promotes glymphatic clearance of amyloid. *Nature* (2024). **627**, 149-156.

131 Wu, W., Zhao, Y., Cheng, X., Xie, X., Zeng, Y., Tao, Q. *et al.* Modulation of glymphatic

ARTICLE IN PRESS

ARTICLE IN PRESS

system by visual circuit activation alleviates memory impairment and apathy in a mouse model of Alzheimer's disease. *Nat Commun* (2025). **16**, 63.

132 Lin, Y., Jin, J., Lv, R., Luo, Y., Dai, W., Li, W. *et al.* Repetitive transcranial magnetic stimulation increases the brain's drainage efficiency in a mouse model of Alzheimer's disease. *Acta Neuropathol Commun* (2021). **9**, 102.

133 Mehta, R. I., Carpenter, J. S., Mehta, R. I., Haut, M. W., Wang, P., Ranjan, M. *et al.* Ultrasound-mediated blood-brain barrier opening uncovers an intracerebral perivenous fluid network in persons with Alzheimer's disease. *Fluids Barriers CNS* (2023). **20**, 46.

134 Choi, C., Park, J., Kim, H., Chang, K. T., Park, J. & Min, K. T. DSCR1 upregulation enhances dural meningeal lymphatic drainage to attenuate amyloid pathology of Alzheimer's disease. *J Pathol* (2021). **255**, 296-310.

135 Wu, C. H., Liao, W. H., Chu, Y. C., Hsiao, M. Y., Kung, Y., Wang, J. L. *et al.* Very Low-Intensity Ultrasound Facilitates Glymphatic Influx and Clearance via Modulation of the TRPV4-AQP4 Pathway. *Adv Sci (Weinh)* (2024). **11**, e2401039.

136 Martinez, P., Nault, G., Steiner, J., Wempe, M. F., Pierce, A., Brunt, B. *et al.* MRI-guided focused ultrasound blood-brain barrier opening increases drug delivery and efficacy in a diffuse midline glioma mouse model. *Neurooncol Adv* (2023). **5**, vdad111.

137 Ma, Y. N., Wang, Z. & Tang, W. Deep cervical lymphaticovenous anastomosis in Alzheimer's disease: A promising frontier or premature enthusiasm? *Biosci Trends* (2025). **19**, 144-149.

138 Xie, Q., Louveau, A., Pandey, S., Zeng, W. & Chen, W. F. Rewiring the Brain: The Next

ARTICLE IN PRESS

ARTICLE IN PRESS

Frontier in Supermicrosurgery. *Plast Reconstr Surg* (2024). **153**, 494e-495e.

139 Chen, J. Y., Zhao, D. W., Yin, Y., Gui, L., Chen, X., Wang, X. M. *et al.* Deep cervical lymphovenous anastomosis (LVA) for Alzheimer's disease microsurgical procedure in a prospective cohort study. *Int J Surg* (2025).

140 Chen, L., Peng, L., Guo, X., Liu, W., Shi, Q., Zhao, M. *et al.* Perioperative care and recovery outcome of deep jugular venous lymphatic anastomosis in Alzheimer's disease: A case report. *Journal of Alzheimer's Disease Reports* (2025). **9**.

141 Yang, Y., Yan, M., Liu, X., Li, S. & Lin, G. Alterations of Glymphatic System Before and After Shunt Surgery in Patients With Idiopathic Normal Pressure Hydrocephalus: A Longitudinal Study. *Eur J Neurol* (2025). **32**, e70200.

142 Lu, X., Bai, S., Feng, L., Yan, X., Lin, Y., Huang, J. *et al.* Cranial bone maneuver ameliorates Alzheimer's disease pathology via enhancing meningeal lymphatic drainage function. *Alzheimers Dement* (2025). **21**, e14518.

143 MohanaSundaram, A., Mofatteh, M., Ashraf, G. M. & Praticò, D. Glymphotherapeutics for Alzheimer's disease: Time to move the needle. *Ageing Res Rev* (2024). **101**, 102478.

144 Da Mesquita, S. & Rua, R. Brain border-associated macrophages: common denominators in infection, aging, and Alzheimer's disease? *Trends Immunol* (2024). **45**, 346-357.

145 Wang, J., Lv, T., Jia, F., Li, Y., Ma, W., Xiao, Z. P. *et al.* Subarachnoid hemorrhage distinctively disrupts the glymphatic and meningeal lymphatic systems in beagles. *Theranostics* (2024). **14**, 6053-6070.

ARTICLE IN PRESS

ARTICLE IN PRESS

146 Ben-Nejma, I. R. H., Keliris, A. J., Vanreusel, V., Ponsaerts, P., Van der Linden, A. & Keliris, G. A. Altered dynamics of glymphatic flow in a mature-onset Tet-off APP mouse model of amyloidosis. *Alzheimers Res Ther* (2023). **15**, 23.

147 Kim, M. J., Youn, J., Lee, H. J., Lee, S. Y., Kim, T. G., Jung, Y. J. *et al.* Hybrid Electro-optical Stimulation Improves Ischemic Brain Damage by Augmenting the Glymphatic System. *Adv Sci (Weinh)* (2025). **12**, e2417449.

148 Du, T., Raghunandan, A., Mestre, H., Plá, V., Liu, G., Ladrón-de-Guevara, A. *et al.* Restoration of cervical lymphatic vessel function in aging rescues cerebrospinal fluid drainage. *Nat Aging* (2024). **4**, 1418-1431.

149 Hu, Y., Niu, L., Chen, Y., Yang, H., Qiu, X., Jiang, F. *et al.* Voluntary wheel running exercise improves sleep disorder, circadian rhythm disturbance, and neuropathology in an animal model of Alzheimer's disease. *Alzheimers Dement* (2025). **21**, e70314.

150 Chen, Y., Cai, J., She, Y., He, X., Feng, H., Li, X. *et al.* Long-term exercise enhances meningeal lymphatic vessel plasticity and drainage in a mouse model of Alzheimer's disease. *Transl Neurodegener* (2025). **14**, 37.

151 Jiang-Xie, L. F., Drieu, A., Bhasiin, K., Quintero, D., Smirnov, I. & Kipnis, J. Neuronal dynamics direct cerebrospinal fluid perfusion and brain clearance. *Nature* (2024). **627**, 157-164.

152 Li, X., Qi, L., Yang, D., Hao, S., Zhang, F., Zhu, X. *et al.* Meningeal lymphatic vessels mediate neurotropic viral drainage from the central nervous system. *Nat Neurosci* (2022). **25**, 577-587.

ARTICLE IN PRESS

ARTICLE IN PRESS

153 Wang, M., Yan, C., Li, X., Yang, T., Wu, S., Liu, Q. *et al.* Non-invasive modulation of meningeal lymphatics ameliorates ageing and Alzheimer's disease-associated pathology and cognition in mice. *Nat Commun* (2024). **15**, 1453.

154 Wang, C., Xiong, M., Gratuze, M., Bao, X., Shi, Y., Andhey, P. S. *et al.* Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia. *Neuron* (2021). **109**, 1657-1674.e1657.

155 Stoker, T. B. in *Parkinson's Disease: Pathogenesis and Clinical Aspects* (eds T. B. Stoker & J. C. Greenland) (Codon Publications

Copyright: The Authors., 2018).

156 Oz, T., Kaushik, A. & Kujawska, M. Neural stem cells for Parkinson's disease management: Challenges, nanobased support, and prospects. *World J Stem Cells* (2023). **15**, 687-700.

157 Rahimi, A., Sameei, P., Mousavi, S., Ghaderi, K., Hassani, A., Hassani, S. *et al.* Application of CRISPR/Cas9 System in the Treatment of Alzheimer's Disease and Neurodegenerative Diseases. *Mol Neurobiol* (2024). **61**, 9416-9431.

158 Li, C., Li, H., Men, X., Wang, Y., Kang, X., Hu, M. *et al.* NOTCH3 Mutation Causes Glymphatic Impairment and Promotes Brain Senescence in CADASIL. *CNS Neurosci Ther* (2025). **31**, e70140.

159 Madadi, A. K. & Sohn, M. J. Advances in Intrathecal Nanoparticle Delivery: Targeting the Blood-Cerebrospinal Fluid Barrier for Enhanced CNS Drug Delivery. *Pharmaceuticals (Basel)* (2024). **17**.

ARTICLE IN PRESS

ARTICLE IN PRESS

160 Taoka, T. & Naganawa, S. Neurofluid Dynamics and the Glymphatic System: A Neuroimaging Perspective. *Korean J Radiol* (2020). **21**, 1199-1209.

161 Maier-Hein, K. H., Neher, P. F., Houde, J. C., Côté, M. A., Garyfallidis, E., Zhong, J. *et al.* The challenge of mapping the human connectome based on diffusion tractography. *Nat Commun* (2017). **8**, 1349.

162 Ringstad, G. Glymphatic imaging: a critical look at the DTI-ALPS index. *Neuroradiology* (2024). **66**, 157-160.

163 Taoka, T., Ito, R., Nakamichi, R., Nakane, T., Kawai, H. & Naganawa, S. Diffusion Tensor Image Analysis ALong the Perivascular Space (DTI-ALPS): Revisiting the Meaning and Significance of the Method. *Magn Reson Med Sci* (2024). **23**, 268-290.

164 Fortin, J. P., Parker, D., Tunç, B., Watanabe, T., Elliott, M. A., Ruparel, K. *et al.* Harmonization of multi-site diffusion tensor imaging data. *Neuroimage* (2017). **161**, 149-170.

165 Dinsdale, N. K., Jenkinson, M. & Namburete, A. I. L. Deep learning-based unlearning of dataset bias for MRI harmonisation and confound removal. *Neuroimage* (2021). **228**, 117689.

166 Pomponio, R., Erus, G., Habes, M., Doshi, J., Srinivasan, D., Mamourian, E. *et al.* Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan. *Neuroimage* (2020). **208**, 116450.

167 Okazawa, H., Nogami, M., Ishida, S., Makino, A., Mori, T., Kiyono, Y. *et al.* PET/MRI multimodality imaging to evaluate changes in glymphatic system function and biomarkers of Alzheimer's disease. *Sci Rep* (2024). **14**, 12310.

ARTICLE IN PRESS

ARTICLE IN PRESS

168 Stamenkovic, S., Schmid, F., Gurler, G., Abolmaali, F., Weitermann, N. A., Takasaki, K. T. *et al.* Impaired capillary-venous drainage contributes to gliosis and demyelination in mouse white matter during aging. *Nat Neurosci* (2025). **28**, 1868-1882.

169 Zaharchuk, G. Next generation research applications for hybrid PET/MR and PET/CT imaging using deep learning. *Eur J Nucl Med Mol Imaging* (2019). **46**, 2700-2707.

170 Zhang, Q., Niu, Y., Li, Y., Xia, C., Chen, Z., Chen, Y. *et al.* Meningeal lymphatic drainage: novel insights into central nervous system disease. *Signal Transduct Target Ther* (2025). **10**, 142.

171 Pinho-Correia, L. M., McCullough, S. J. C., Ghanizada, H., Nedergaard, M., Rustenhoven, J. & Da Mesquita, S. CSF transport at the brain-meningeal border: effects on neurological health and disease. *Lancet Neurol* (2025). **24**, 535-547.

172 Soden, P. A., Henderson, A. R. & Lee, E. A Microfluidic Model of AQP4 Polarization Dynamics and Fluid Transport in the Healthy and Inflamed Human Brain: The First Step Towards Glymphatics-on-a-Chip. *Adv Biol (Weinh)* (2022). **6**, e2200027.

173 Huang, H., Lin, L., Wu, T., Wu, C., Zhou, L., Li, G. *et al.* Phosphorylation of AQP4 by LRRK2 R1441G impairs glymphatic clearance of IFNγ and aggravates dopaminergic neurodegeneration. *NPJ Parkinsons Dis* (2024). **10**, 31.

174 Karran, E., Mercken, M. & De Strooper, B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* (2011). **10**, 698-712.

ARTICLE IN PRESS

ARTICLE IN PRESS

175 Li, C. Y., Park, H. J., Shin, J., Baik, J. E., Mehrara, B. J. & Kataru, R. P. Tumor-Associated Lymphatics Upregulate MHC-II to Suppress Tumor-Infiltrating Lymphocytes. *Int J Mol Sci* (2022). **23**.

ARTICLE IN PRESS