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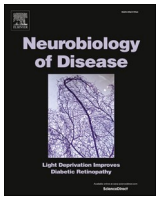

Review

Vascular and glymphatic dysfunction as drivers of cognitive impairment in Alzheimer's disease: Insights from computational approaches

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ABSTRACT

Alzheimer's disease (AD) is driven by complex interactions between vascular dysfunction, glymphatic system impairment, and neuroinflammation. Vascular aging, characterized by arterial stiffness and reduced cerebral blood flow (CBF), disrupts the pulsatile forces necessary for glymphatic clearance, exacerbating amyloid-beta (Aβ) accumulation and cognitive decline. This review synthesizes insights into the mechanistic crosstalk between these systems and explores their contributions to AD pathogenesis. Emerging machine learning (ML) tools, such as DeepLabCut and Motion sequencing (MoSeq), offer innovative solutions for analyzing multimodal data and enhancing diagnostic precision. Integrating ML with imaging and behavioral analyses bridges gaps in understanding vascular-glymphatic dysfunction. Future research must prioritize these interactions to develop early diagnostics and targeted interventions, advancing our understanding of neurovascular health in AD.

1. Introduction

Alzheimer's disease (AD) is broadly a neurodegenerative disorder that affects millions of individuals worldwide, mainly the elderly. Characterized by memory loss, cognitive decline, and behavioral changes, AD imposes a significant burden on patients, caregivers, and healthcare systems (Cummings, 2004; Blennow et al., 2006; Burns and Iliffe, 2009; Harper, 2020). Even after much research, the exact etiology and pathophysiological mechanisms underlying AD remain incompletely understood (Lane et al., 2018). Traditionally, the amyloid cascade hypothesis has dominated the field, which posits that the accumulation of amyloid-beta (Aβ) plaques initiates a cascade of neurodegenerative processes (Hardy and Selkoe, 2002). However, recent studies have suggested a more complicated interplay of multiple factors, including tau pathology, neuroinflammation, and vascular contributions (De Strooper and Karran, 2016; Ridler, 2018). Patients with AD and vascular disease have a mixed pattern of pathologies (Schneider et al., 2007; Attems and Jellinger, 2014; Agrawal and Schneider, 2022). AD and vascular dementia (VaD) are considered the most common forms of dementia in the elderly (Román, 2003).

One emerging area of interest in AD research is the role of the lymphatic and glymphatic systems in maintaining brain homeostasis and their potential association with the disease's progression (Louveau et al., 2017; Da Mesquita et al., 2018a). Traditionally, the lymphatic system, known for its critical role in immune surveillance and fluid balance, includes the recently discovered meningeal lymphatic vessels (mLVs) that drain interstitial and cerebrospinal fluids (CSF) from the brain (Iliff et al., 2012; Absinta et al., 2017). The glymphatic system, a brain-wide perivascular network, facilitates the clearance of metabolic waste products, including Aβ and tau, through the convective flow of CSF (Nedergaard, 2013).

The solute transport within the brain parenchyma is primarily driven by diffusion rather than convection and that this process operates independently of aquaporin-4 (AQP4) water channels (Smith et al., 2017). Some findings suggest that diffusion alone can account for the movement of solutes in the brain, challenging the necessity of convective bulk flow in glymphatic transport (Asgari et al., 2016). Some predominant model suggests that CSF flows into the brain via periarterial spaces and mixes with ISF, which is then cleared through perivenous routes, largely influenced by astrocytic AQP4 channels (Iliff et al.,

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2012). Another review examines evidence supporting the movement of ISF through specific pathways in the brain and its interaction with CSF. The bulk transport of ISF plays a crucial role in non-synaptic cell-to-cell communication, drug delivery and clearance, as well as the removal of β-amyloid deposits (Abbott, 2004).

Some results indicate that both convective bulk flow and diffusion contribute to the removal of interstitial waste solutes from the brain parenchyma (Kaur et al., 2024). However, neither the glymphatic hypothesis nor the classical model fully account for the mechanisms governing the movement of solutes and fluid into, within, and out of the brain (Hladky and Barrand, 2022). Both diffusion and convective flow play a role in the clearance of solutes from the central nervous system (CNS). However, determining their relative contributions is challenging, as slight variations in physiological conditions can significantly impact experimental outcomes (Mestre et al., 2020). The glymphatic system facilitates the movement of CSF into the brain through periarterial spaces, while ISF is cleared via perivenous pathways (Mestre et al., 2020). Understanding the specific mechanisms by which these systems influence AD pathology could reveal novel therapeutic targets and strategies for enhancing brain clearance functions (Hadaczek et al., 2006; Jessen et al., 2015; Tarasoff-Conway et al., 2015).

The use of machine learning (ML) in AD research has accelerated novel approaches to understanding and treating this disease over the past few years (Mathotaarachchi, Pascoal et al., 2017). ML techniques can be used to analyze lymphatic and glymphatic data, identify dysfunctional biomarkers, and model the influence of impaired clearance on disease progression (Martinac and Bilston, 2020; Avberšek and Repovš, 2022; Burgos, 2023).

This review focused on an extensive study of the latest research on the involvement of the lymphatic and glymphatic systems including CI in AD and the capability of analyzing behavioral changes and vascular patterns in brain imaging via integrating observation from ML applications.

2. Risk factors for the development of cerebrovascular dysfunction in AD

The development of cerebrovascular dysfunctions in AD is influenced by a complex interplay of risk factors. Among these, hypertension stands out as a major contributor, with approximately 7.5 million deaths globally attributed to high blood pressure annually (Mendis, 2014; Singh et al., 2017). Hypertension is strongly linked to both vascular cognitive impairment (VCI) and AD, often manifesting as a co-occurring risk factor in dementia-related conditions (Erem et al., 2009; Mishra and Kumar, 2011; Ahmed et al., 2014; Abebe et al., 2015; Arvanitakis et al., 2019; Ou et al., 2020; Canavan and O'Donnell, 2022). Mechanistically, chronic high blood pressure compromises the integrity of cerebral blood vessels, leading to endothelial dysfunction, reduced vascular density, BBB disruption, and an increased accumulation of Aβ (Applegate et al., 1994; Skoog et al., 1996; Alpérovitch et al., 2014; Gottesman et al., 2017a; Abell et al., 2018; Canavan and O'Donnell, 2022).

Diabetes Mellitus (DM) represents another significant risk factor for cerebrovascular dysfunction in AD (Rockwood et al., 1998; Athanasaki et al., 2022). This chronic metabolic disorder, increasingly prevalent with age, disrupts glucose metabolism and insulin signaling, resulting in oxidative stress and the accumulation of metabolic byproducts such as Aβ (Gottesman et al., 2017b; Athanasaki et al., 2022). DM-related vascular changes, including endothelial dysfunction and small vessel disease, exacerbate cerebrovascular pathology, increasing the risk of cognitive decline and dementia (Beul, 1994; Knopman et al., 2001; Peila et al., 2002). Epidemiological studies reveal that diabetic individuals are 1.5 times more likely to develop dementia than their non-diabetic counterparts (Li et al., 2016; Wu et al., 2023).

Traumatic brain injury (TBI) is a well-recognized risk factor for the premature onset of dementia, including Alzheimer's disease (Iliff et al., 2014). Brain swelling following TBI occurs due to disrupted fluid clearance via the glymphatic system and its connected lymphatic drainage (Iliff et al., 2014). Long-term dysfunction of the glymphatic pathway after TBI may play a crucial role in making the injured brain more susceptible to tau accumulation and the development of neurodegeneration (Hussain et al., 2023).

Aging significantly contributes to cerebrovascular dysfunctions, which are integral to the pathogenesis of AD (Neuropathology, 2001; White et al., 2002; Kalaria, 2010). As individuals age, several physiological changes predispose them to cerebrovascular impairments, AD, and cognitive development (Snowdon et al., 1997; Schneider et al., 2004; Gorelick et al., 2011). These changes include arterial stiffening, endothelial dysfunction, reduced cerebral blood flow (CBF), and the breakdown of the BBB (Moreau et al., 2005; Csiszar et al., 2008; Kaneko et al., 2011; Toth et al., 2015; Ungvari et al., 2018). These age-related vascular changes can exacerbate the pathological processes of AD, including Aβ deposition, tau pathology, and neuroinflammation (Jack Jr et al., 2018; Sweeney et al., 2019; Chen and Yu, 2023). Growing evidence associates AD with a range of sleep disorders, such as obstructive sleep apnea (OSA) (Semelka et al., 2016; Chang et al., 2020; Cui et al., 2022). Aging impacts mLVs, impairing glymphatic-lymphatic clearance of toxic substances, including Aβ, which in turn becomes a significant risk factor for developing neurodegenerative conditions like AD (Weller et al., 2008; Tarasoff-Conway et al., 2015; Kylkilahti et al., 2021; Voumvourakis et al., 2023).

Finally, genetic risk factors influence the efficiency of the glymphatic system to different extents (Hu et al., 2024). Genetic risk factors are linked to both familial AD (FAD) and sporadic AD (SAD) (Hu et al., 2024). APOE4 is the most significant genetic risk factor for AD (Mahley and Rall Jr, 2000; Hu et al., 2024). The Fig. 1 underscores the impact of risk factors such as hypertension, DM, and genetic predispositions (e.g., AQP4) variations on glymphatic function, highlighting their role in disease progression.

2.1. Mechanisms linking risk factors to vascular and glymphatic dysfunction in AD

Vascular risk factors are commonly associated with reduced CBF, and the resulting chronic cerebral hypoperfusion is believed to play a critical role in the development of AD (Dickstein et al., 2010; Scheffer et al., 2021), This hypoperfusion leads to impaired delivery of oxygen and nutrients to brain tissues, exacerbating neuronal dysfunction and promoting the accumulation of toxic proteins such as amyloid-beta and tau in neurodegenerative diseases (Hardy and Selkoe, 2002; Dickstein et al., 2010). Age-related changes in sleep patterns may influence the activation and functioning of the glymphatic system. Additionally, aging is linked to structural and functional alterations within the glymphatic system itself (Hablitz and Nedergaard, 2021). Research indicates that glymphatic clearance becomes less effective with age, potentially leading to the buildup of waste products in the brain (Benveniste et al., 2019; Hablitz and Nedergaard, 2021). The buildup of waste products can harm brain health, cause memory loss, and elevate the risk of neurodegenerative diseases like AD (Shokri-Kojori et al., 2018). Over time, these processes contribute to cognitive decline and the progressive neurodegeneration characteristic of AD (Shokri-Kojori et al., 2018; Yi et al., 2022).

3. Mechanistic crosstalk between vascular dysfunction and glymphatic impairment

3.1. Vascular dysfunction in AD

Increased vascular permeability is linked with reduced CBF, weakened hemodynamic responses, and compromised BBB integrity (Iadecola, 2004; Zlokovic, 2011; Zhao et al., 2015; Sweeney et al., 2016; Sweeney et al., 2018). PET imaging in AD patients reveals reduced CBF and glucose metabolism, suggesting increased vascular resistance in the

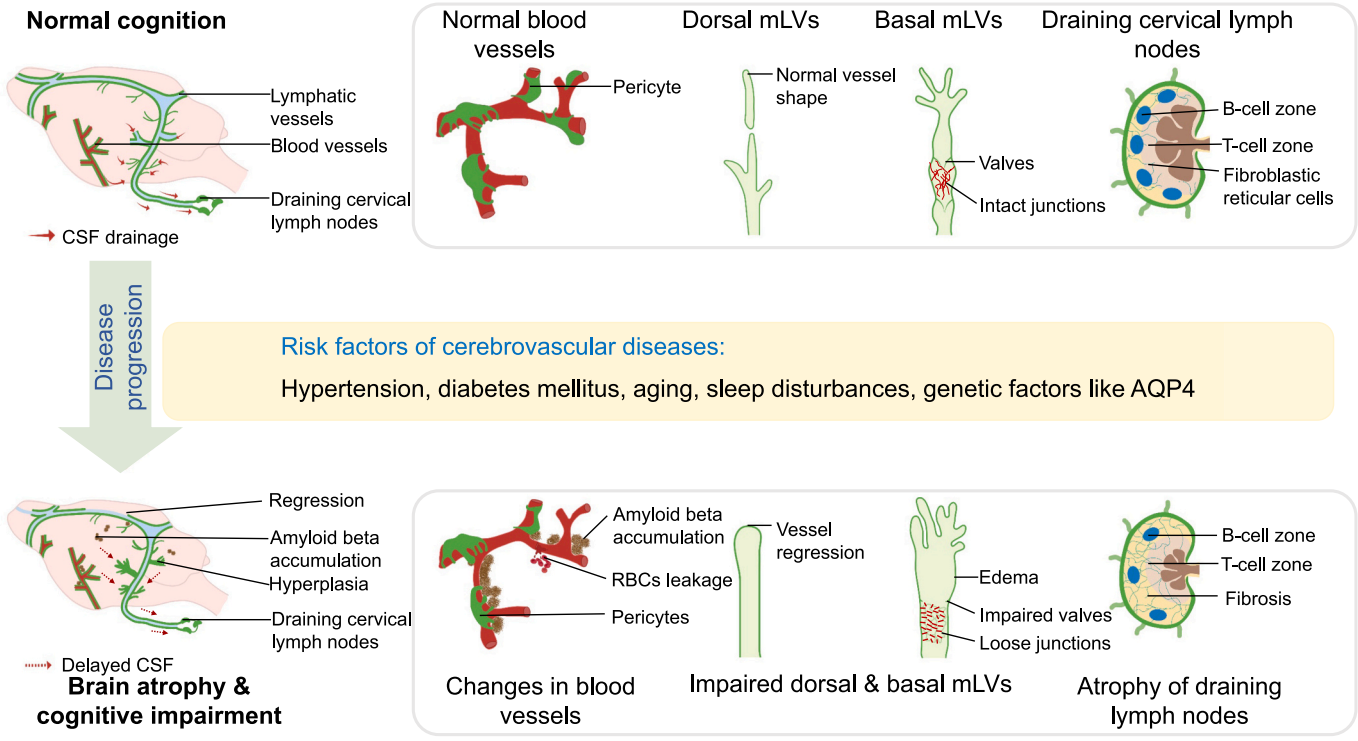


Fig. 1. Cerebrovascular disease progression: effects on brain morphology, function, and blood-lymphatic systems. This figure illustrates cerebrovascular disease progression from a healthy state, with intact mLVs and BBB function and draining cervical lymph nodes, to advanced pathology characterized by pericyte dysfunction, capillary constriction, Aβ accumulation, and reduced cerebral blood flow. Risk factors, including hypertension, diabetes, obesity, and genetic predispositions (AQP4), drive these changes. mLV alterations, such as basal lymphatic hyperplasia and dorsal lymphatic regression, disrupted CSF drainage, leading to edema. Impaired lymphatic valves and endothelial junctions exacerbate neuroinflammation, altered toxic fluid clearance, and changes in draining cervical lymph nodes; resulting in brain atrophy and cognitive decline. Abbreviations: mLVs, meningeal lymphatic vessels; BBB, blood-brain barrier; Aβ, amyloid-beta; AQP4, aquaporin-4; CSF, cerebrospinal fluid.

brain (Mattsson et al., 2014; Korte et al., 2020). Studies have shown focal constrictions in capillaries, plaque buildup, and reduced cerebrovascular reactivity and neurovascular coupling in AD mouse models, indicating that reduced blood flow may accompany blood vessel loss in human AD brains (Kimura et al., 1991; Girouard and Iadecola, 2006; Tong et al., 2012; Hansra et al., 2019). Evidence suggests that early changes in blood flow play a causal role in cognitive decline at the onset of AD, even preceding synaptic or neuronal loss. CBF has decreased in the early preclinical stages of AD, occurring more rapidly than axonal or tau deposition (Mattsson et al., 2014; Wierenga et al., 2014; Iturria-Medina et al., 2016; Korte et al., 2020), with metabolic rates declining early in the disease course (Kennedy et al., 1995; Minoshima et al., 1997).

Cerebral amyloid angiopathy (CAA) is often found sporadically in elderly individuals, commonly co-occurring with AD. In CAA, the blood vessel structure weakens, increasing the risk of intracerebral hemorrhage (ICH) (van Etten et al., 2016; Greenberg et al., 2020; Jäkel et al., 2022). Hemorrhagic lesions associated with CAA include significant symptomatic ICH, smaller asymptomatic cerebral microbleeds, and bleeds within cortical sulci (Greenberg and Charidimou, 2018). Aβ deposits in CAA and AD demonstrate the connection between neurodegenerative and cerebrovascular mechanisms, which contribute to CI. As summarized in Table 1, the interconnections among AD, CAA, and VaD reveal overlapping yet distinct features of these conditions, such as differences in onset age, causes, vascular changes, and biomarkers. Understanding these shared and unique pathways provides crucial insights into how cerebrovascular and neurodegenerative processes converge in CI.

White matter hyperintensities (WMHs) are bright areas of the white matter of diseased brain which are visible on MRI scans (Wardlaw et al., 2015; Tubi, Feingold et al., 2020), commonly associated with cerebral small vessel disease and chronic ischemia (Prins and Scheltens, 2015; Karvelas and Elahi, 2023). These lesions have been linked to cognitive decline, particularly in processing speed and executive function (Prins and Scheltens, 2015), as well as an increased risk of stroke, dementia (Wardlaw et al., 2015), and functional impairment (Prins and Scheltens, 2015). However, the connection between WMH volume and cognitive performance varies, possibly due to differences in its segmentation and the presence of AD-related pathology (Tubi, Feingold et al., 2020).

3.2. *Glymphatic and lymphatic system changes in AD*

The glymphatic system's primary role is to clear metabolic waste and toxins from the brain, thereby supporting overall brain health and function. The perivascular space (PVS), a key component of the glymphatic system, measures approximately 40 μm in width and facilitates the rapid transport of small soluble molecules, while larger molecules including particles, oligomers, and fibers experience restricted movement (Hasegawa et al., 2022; Sun et al., 2025). Over the past decade, research has highlighted the glymphatic system's essential role in brain waste clearance and intracranial pressure regulation. Notably, growing interest in this system stems from its critical function in the removal of pathogenic proteins, such as Aβ and α-synuclein, which are implicated in the development of AD, Parkinson's disease (PD), and other neurodegenerative disorders (Iliff et al., 2012; Da Mesquita et al., 2018b; Gao et al., 2023). This system is primarily active during sleep. This heightened activity is thought to be due to an increase in the brain's interstitial space during sleep, which enhances the efficiency of waste clearance (Xie et al., 2013; Yamada and Iwatsubo, 2024).

As Aβ is cleared by the glymphatic system (Iliff et al., 2012), the system's role in AD pathogenesis has attracted considerable scientific interest. The exacerbated accumulation of Aβ and related

Table 1
The interrelationship of AD, CAA and VaD and their progression towards cognitive impairment.

Feature	Alzheimer's disease	Cerebral amyloid angiopathy	Vascular Dementia	References
Onset	Gradual onset, typically after age 65, with an insidious progression over years.	Typically occurs in mid- to later life with a gradual progression but may present acutely in cases of hemorrhage.	Often follows a stepwise progression related to vascular events, such as strokes or transient ischemic attacks.	AD: (Sirkis et al., 2022; Kumar et al., 2024) CAA: (Vargas-George and Dave, 2022, Banerjee et al., 2023a, 2023b) VaD: (del Ser et al., 2005, Iadecola et al., 2019)
Causes	Multifactorial, including genetic risk factors (e.g., APOE4 allele), Aβ accumulation, tau pathology, and chronic inflammation.	Aβ deposition in cerebral blood vessels leading to microvascular damage and cortical hemorrhages.	Primarily caused by cerebrovascular disease, such as ischemic strokes, chronic hypertension, and arteriosclerosis.	AD: (Silva et al., 2019; Yamazaki et al., 2019; Hu et al., 2024) CAA: (Miao et al., 2005; Gireud-Goss et al., 2021) VaD: (Song et al., 2014, Vijayan and Reddy, 2016)
Risk Factors	Advanced age, genetic predisposition (e.g., APOE4), cardiovascular disease, DM, hypertension, obesity, and lifestyle factors (e.g., smoking, sedentary behavior).	Advanced age, arterial hypertension, genetic factors (e.g., APP mutations), cardiovascular disease, and DM.	Hypertension, DM, smoking, high cholesterol, atrial fibrillation, and previous strokes.	AD: (Khan et al., 2023; Li et al., 2024a) CAA: (Vasilevko et al., 2010; Banerjee et al., 2023a, 2023b) VaD: (Breteler, 2000, Sahathevan et al., 2012)
Symptoms	- Memory Loss: Progressive decline in short- and long-term memory. - Cognitive Impairment: Difficulties with language, reasoning, and spatial awareness. - Behavioral Changes: Anxiety, depression, mood swings, or agitation. - Disorientation: Confusion about time, place, and familiar people. - Difficulty with Daily Activities: Impairment in managing tasks, finances, or self-care.	- Cognitive Decline: Gradual worsening of memory and executive functions. - Neurological Symptoms: Weakness, sensory disturbances, transient neurological episodes, and visual field deficits. - Seizures: Common due to cortical irritation. - Headaches: Associated with small hemorrhages or microbleeds. - TIAs: Episodes resembling strokes.	- Stepwise Cognitive Decline: Often follows vascular events like strokes. - Executive Dysfunction: Difficulty with planning, organizing, and problem-solving. - Gait Disturbances: Balance issues, falls. - Mood Changes: Depression, apathy, emotional instability. - Focal Neurological Deficits: Impairments related to affected brain regions, such as speech or vision problems.	AD: (Kumar et al., 2018; Kamatham et al., 2024) CAA: (Boyle et al., 2015; Wang et al., 2024) VaD: (Kalaria, 2016, Delgado et al., 2022)
Vascular changes	Disruption of BBB, chronic hypo perfusion, capillary degeneration, and microvascular dysfunction contributing to neurodegeneration and inflammation	Aβ infiltration in cerebral vessel walls, leading to microbleeds, microvascular fragility, and cortical hemorrhages, with potential for perivascular inflammation.	Vascular lesions, arteriosclerosis, chronic ischemia, infarcts (small and large), white matter lesions, and reduced CBF leading to neuronal death and cognitive impairment.	AD: (Govindpani et al., 2019; Chen et al., 2023) CAA: (Mandybur, 1986; Singh et al., 2022) VaD: (Kalaria, 2016, Wallin et al., 2018)
Biomarkers	Aβ and tau proteins (measured via CSF, PET imaging); neuroinflammatory markers; atrophy detected via MRI.	Presence of Aβ deposits in cortical blood vessels (detected by imaging or histopathology); microbleeds visible on MRI (e.g., gradient-echo sequences).	White matter hyperintensities, evidence of past strokes on neuroimaging (CT/MRI), reduced cerebral perfusion, and infarct-related biomarkers.	AD: (Bomasang-Layno and Bronsther, 2021; Maschio and Ni, 2022) CAA: (Greenberg and Charidimou, 2018; Perosa et al., 2023) VaD: (Alber et al., 2019, Bir et al., 2021)
Diagnosis	Clinical assessment, cognitive testing (e.g., MMSE, MoCA), MRI/PET imaging for Aβ and tau, and CSF analysis for biomarkers.	MRI for detecting microbleeds, cortical hemorrhages, and Aβ deposits; clinical evaluation for neurological deficits and symptoms.	Clinical history of cerebrovascular events, neuroimaging (MRI/CT) to identify infarcts, white matter lesions, and assessment of cognitive decline related to vascular causes.	AD: (Pinto et al., 2019; Dangi et al., 2021) CAA: (Ni et al., 2014; Sembill et al., 2023) VaD: (Kalaria, 2016, Cipollini et al., 2019)
Cognitive impairment	Neurological and depressive behaviors in early AD, while depressive and cognitive symptoms more pronounced in late AD.	Accumulation Aβ peptides resulting in vascular damage, reduced blood flow, and progressive cognitive decline.	In VaD ischemic or hemorrhagic brain tissue damage leading to clinically significant cognitive impairment.	AD: (Bature et al., 2017) CAA: (Cozza et al., 2023) VaD: (Bir et al., 2021)

neurofunctional impairments observed in AQP4-deficient APP transgenic mice indicate that the glymphatic system plays a vital role as a primary clearance pathway for Aβ (Xu et al., 2015; Abe et al., 2020). The detection of Aβ in human lymph nodes further supports the hypothesis that the glymphatic and lymphatic systems may play a role in Aβ clearance from the human brain (Nauen and Troncoso, 2022). Moreover, as Fig. 1 illustrates, disruptions in glymphatic-lymphatic clearance pathways can lead to impaired CSF drainage, basal lymphatic hyperplasia, and dorsal lymphatic regression. Alterations in the structural integrity of glymphatic vessel networks, modulation of specific molecules (Naganawa and Taoka, 2022), and age-related vascular changes, such as reduced CBF and increased BBB permeability (Banks et al., 2021), may contribute to the decline in glymphatic function observed in aging individuals.

3.3. Glymphatic system modulation as a potential therapy for neurodegenerative disorders

The concept of targeting the glymphatic system as a therapeutic strategy for neurodegenerative diseases is promising, as it offers a novel approach to enhancing waste clearance from the brain. Given the growing evidence linking glymphatic dysfunction to conditions such as AD, PD, and VaD, interventions aimed at optimizing this system could potentially mitigate protein accumulation, reduce neuroinflammation, and improve cognitive function. Modulating sleep architecture presents a promising therapeutic approach, not only for neurodegenerative diseases but also for conditions such as stroke, traumatic brain injury, and other neurological disorders (Gao et al., 2023). Additionally, AQP4 has emerged as a potential target for neurological diseases. Studies in animal models have demonstrated that both genetic modifications and pharmacological inhibition of AQP4 expression can effectively reduce brain edema and enhance recovery outcomes in ischemic stroke (Yao et al., 2015; Pirici et al., 2017).

The regulation of pulsations and cardiac cycles is a new perspective for the treatment of neurological diseases. Adrenergic drugs are another way to improve glymphatic flow (Gao et al., 2023). Astrocyte exocytosis may play a role in facilitating material transport within the PVS, suggesting that ultrasound-based techniques could enhance the clearance of neurotoxic substances from the brain parenchyma (Sun et al., 2025). Additionally, research has shown that focused ultrasound with microbubbles (FUS-MB) can induce pulsation-like effects in arterioles, venules, and capillaries, thereby strengthening the driving force for glymphatic fluid movement and accelerating substance exchange (Ye et al., 2023). Furthermore, deep brain stimulation remains a widely used and effective therapeutic approach for treating various neurological disorders (Ashkan et al., 2017).

Valnes et al. (Valnes et al., 2018) investigated whether diffusion alone could explain brain-wide distribution of a CSF tracer providing a different perspective on fluid movement mechanisms in the brain. Some articles highlight ongoing debates about the existence and functionality of the glymphatic system, emphasizing areas where experimental data are lacking and what is still debated (Mestre et al., 2020).

3.4. Impact of vascular aging on glymphatic dysfunction and amyloid clearance

Vascular aging significantly impacts glymphatic function, compromising the clearance of Aβ and other metabolic waste products, which accelerates AD progression. Age-related arterial stiffness, caused by the loss of vascular elasticity and increased collagen deposition, disrupts the pulsatile forces generated by arterial pulsations that drive CSF through PVS (Iliff et al., 2013; Da Mesquita et al., 2018b). These pulsatile forces are critical for maintaining glymphatic flow, and their reduction leads to impaired CSF and ISF exchange, resulting in the accumulation of neurotoxic proteins like Aβ (Iliff et al., 2012; Xu et al., 2015; Louveau et al., 2017). Hypertension, a common consequence of vascular aging, further exacerbates glymphatic dysfunction by increasing endothelial damage and altering CBF, which disrupts the perivascular transport necessary for glymphatic clearance (Iliff et al., 2013; Banks et al., 2021). Additionally, the breakdown of the BBB associated with vascular aging introduces inflammatory mediators and impairs the PVS where glymphatic flow occurs, compounding the inefficiency of waste clearance (Banks et al., 2021; Yamada and Iwatsubo, 2024). Recent studies using imaging modalities such as two-photon microscopy and diffusion magnetic resonance imaging (MRI) have confirmed that glymphatic flow is markedly reduced in aged animal models, correlating with increased Aβ deposition and cognitive deficits (Iliff et al., 2012; Iliff et al., 2013; Nauen and Troncoso, 2022). These findings underscore the bidirectional relationship between vascular aging and glymphatic dysfunction, where reduced vascular function directly hampers waste clearance, while glymphatic inefficiency feeds back to worsen vascular health, creating a self-reinforcing cycle that exacerbates neurodegeneration (Breslin et al., 2018; Rasmussen et al., 2018). Understanding this interplay offers a critical avenue for therapeutic interventions aimed at preserving vascular elasticity and optimizing glymphatic flow to mitigate AD progression (Xie et al., 2013; Lee et al., 2020).

4. Overview of machine learning methods for assessment of vascular dysfunction and CI

ML has significantly advanced the study of vascular dysfunction and CI in AD, enabling precise imaging and behavioral data analysis. By leveraging ML models across different imaging modalities and behavioral tests, researchers can detect subtle changes linked to early AD progression.

4.1. ML techniques in vascular imaging

ML techniques are essential for extracting detailed information from vascular imaging data, including immunofluorescent imaging such as confocal and light-sheet fluorescence microscopy (LSFM), MRI, PET (Zhao et al., 2023) and CT scans, to identify early markers of vascular dysfunction associated with AD. As illustrated in Fig. 2, ML methods rely on precise input data to classify and analyze vascular networks and patterns. These parameters are central to models designed to detect subtle changes in imaging data. For example, blood vessels (Fig. 2A) (Bumgarner and Nelson, 2022) and pulmonary tree structures (Fig. 2B and C) (Xie et al., 2025) are segmented into components such as airway, artery, and vein, which could be similar to the segmentation of blood or lymphatic vessel branches in vascular imaging. Convolutional Neural Networks (CNNs), a subset of deep learning neural network models, have demonstrated high sensitivity to structural changes in the brain, such as BBB leakage and reductions in CBF, which are linked to early AD. Support Vector Machines (SVMs) are a ML model that is frequently used for early AD diagnosis, particularly in classifying structural and functional MRI (fMRI) data to differentiate AD from mild cognitive impairment (MCI) and normal aging (Pan et al., 2020). Hybrid models that combine CNNs with SVMs or other ML methods have improved performance, distinguishing AD from other dementias, such as VaD (Pan et al., 2020).

Deep Belief Networks (DBNs), paired with ensemble learning (EL) methods, effectively integrate multimodal data, such as MRI and fMRI, to improve diagnostic outcomes. These methods allow the model to learn from multiple sources, reducing error and enhancing the robustness of pattern recognition across imaging modalities (Pan et al., 2020). Techniques like autoencoders and sparse regression reduce the dimensionality of MRI data, making it easier to detect subtle vascular changes without overwhelming computational resources (Alarjani and Almarri, 2024).

Graph-based ML methods like Node2vec from fMRI data have been used to classify CI stages and vascular dysfunctions (Alarjani and Almarri, 2024). Zoom-in neural networks (ZNNs) have shown promise

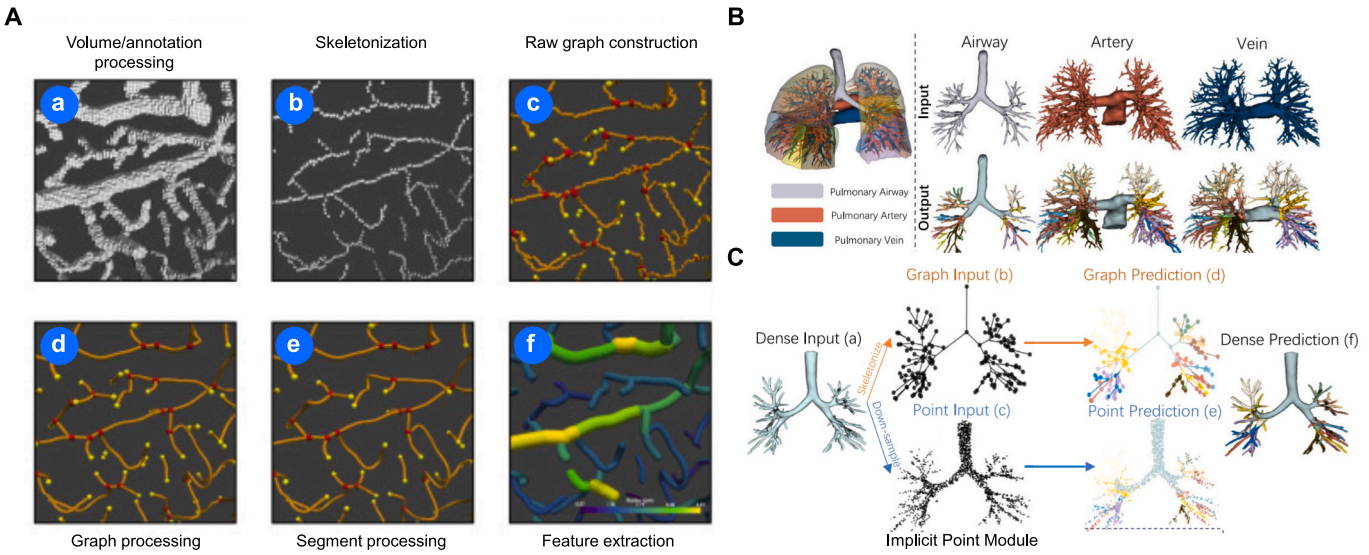


Fig. 2. Graph-based segmentation and analysis of vascular networks: applications and methodologies. This figure illustrates advanced vascular network segmentation and analysis methodologies, emphasizing their potential applications in cerebrovascular disease studies. (A) Overview of the VesselVio pipeline for processing vascular networks, which involves extracting centerlines from datasets to create undirected graphs. The process includes centerline smoothing, removal of spurious branch points, and feature extraction, enabling precise segmentation and characterization of complex vascular structures. (3–8). Figures obtained and modified from (Bumgarner and Nelson, 2022). (B) (B) Pulmonary tree labeling, where binary volumes representing tree structures are segmented into three key anatomical components (airway, artery, and vein) and further classified into 19 categories (18 pulmonary segments plus background). This method enables voxel-level labeling of branching regions for accurate structural delineation. (C) The IPGN framework for pulmonary tree labeling, which converts dense volumes into graph and point cloud data. The Point-Graph Fusion layers enhance feature representation through contextual learning, while the implicit point module provides efficient dense segmentation based on deep sparse data representation. This approach demonstrates potential adaptability for analyzing cerebrovascular alterations relevant to AD progression, including microvascular changes and network disruptions. Figures obtained and modified from (Xie et al., 2025). Abbreviation: IPGN, implicit point-graph network.

in identifying AD-affected regions and stages with high accuracy (Alarjani and Almarri, 2024). Additionally, evolutionary algorithms combined with artificial neural networks (ANNs) enhance feature selection from MRI data, improving AD detection (Alarjani and Almarri, 2024).

4.2. ML applications for characterizing structural and anatomical transformations in the vascular and lymphatic networks

The integrated workflow, which combines CNN and transformer models, delivers exceptional performance and functionality, offering physicians an effective tool for visualizing vascular structures (Zhou et al., 2024b). A preliminary approach for utilizing deep CNN to segment the vascular system in time-of-flight magnetic resonance angiography (TOF MRA) images of the brain was created (Phellan et al., 2017). Later, multiple researchers refined the U-Net architecture to improve cerebrovascular segmentation (Guo et al., 2021; Mu et al., 2023).

Four machine learning algorithms; extreme gradient boosting (XGB), random forest (RF), SVM, and the generalized linear model (GLM) were utilized to identify five key model genes associated with lymphatic vessels: MET, HHIP, SPRY1, CSF1, and TOX (Lin et al., 2024). A comprehensive review of lymphatic histopathology image analysis methods based on machine vision (MV), covering datasets, evaluation techniques, image preprocessing, segmentation, feature extraction, classification, and detection with various algorithms, including CNN, EfficientNet, ResNet121, Transformer models, SVM, SVM-RFE, LDA, and a region-growing approach combined with MRF, are analyzed and summarized (Chen et al., 2024b).

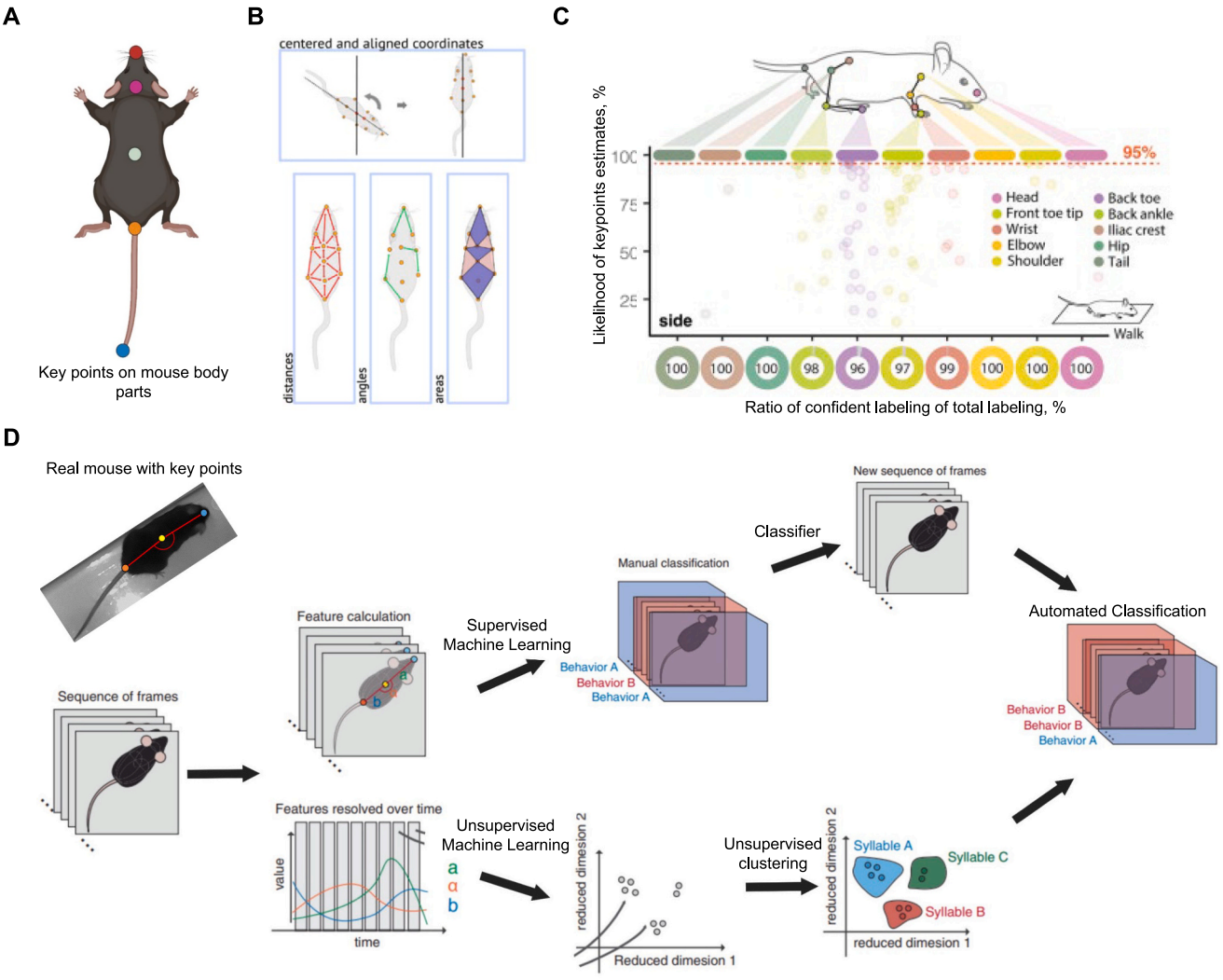
4.3. Advanced vascular imaging modalities enhanced by ML

Vascular imaging modalities such as arterial spin labeling (ASL) (Borogovac and Asllani, 2012), fMRI (Lajoie et al., 2017), and CT (Zhang et al., 2017b) perfusion imaging have become instrumental in identifying vascular changes in AD. ASL is a non-invasive MRI technique that quantifies CBF, which is crucial for assessing cerebrovascular health in AD (Borogovac and Asllani, 2012). ASL provides a non-invasive method for measuring CBF by using magnetically labeled water molecules in the blood, offering a quantitative approach to study brain perfusion (Wang et al., 2011). ASL is increasingly used in clinical research to assess brain hemodynamics in conditions such as AD, where reduced blood flow is often observed in specific brain regions (Wierenga et al., 2014). In ASL, water molecules in the arterial blood are magnetically tagged near the region of interest. Blood flow is subsequently measured using a standard MRI sequence, with the labeled image being compared to a control image without labeling. ASL techniques are categorized into continuous ASL (CASL), pulsed ASL (PASL), and pseudo-continuous ASL (pCASL), depending on the method of labeling the arterial water (Alsop et al., 2015, Zhang et al., 2017a).

By applying ML models to ASL data, researchers can accurately quantify blood flow reductions associated with early AD, even when changes are visually imperceptible. ML algorithms applied to fMRI data capture subtle brain activity patterns, revealing early impairments in neural networks affected by AD (Lajoie et al., 2017). CNN (LSFM) enables high-resolution, whole-brain imaging, revealing detailed vascular structures in animal models (Perens et al., 2021; Zhang et al., 2021; Chen et al., 2024a). Enhanced by tissue-clearing techniques like CLARITY (Chung and Deisseroth, 2013) and iDISCO (Renier et al., 2014), LSFM enables three-dimensional visualization of cerebrovascular changes, such as Aβ plaque distribution and BBB disruptions.

4.4. ML in behavioral and cognitive assessments

ML methods are increasingly used to automate behavioral and cognitive assessments in AD research, providing objective, quantifiable insights into cognitive decline and motor impairments. Fig. 3 demonstrates the application of supervised and unsupervised ML techniques for tracking and analyzing animal behaviors and traditional Cognitive



E

Aspect	Supervised Learning	Unsupervised Learning
Input Data	Labeled data required	No labels needed
Training Process	Manual labeling essential	Automatically identifies clusters
Type of Learning	Learns from labeled examples	Detects patterns from unlabeled data
Advantages	Accurate with enough labeled data	Discovers unknown patterns
Limitation	Time-consuming labeling; bias possible	Clusters may be unclear or meaningless
Use Cases	Works with well-known behaviors	Useful for exploring new behaviors
Novel Data	Struggles with unseen behaviors	Can identify novel behaviors
Flexibility	Less flexible, predefined labels needed	More flexible, adapts to new data
Automation	Needs accurate manual setup	Fully automated, but needs interpretation

(caption on next page)

Fig. 3. 2D open field tests for ML-based analysis of rodent's movement and anxiety behavior. (A) Schematic of a mouse with tracking markers on key body parts used during 2D open field tests, enabling precise movement analysis via DeepLabCut. (B) Tracked coordinates generate features such as inter-joint distances and spatial trajectories, quantifying locomotion and anxiety-related behaviors. Figure obtained and modified from (Bordes et al., 2023). (C) The likelihood of confident labeling (≥95 %) for individual anatomical landmarks during various tasks is shown from side and top views, with dots representing labeled landmarks and the red dotted line marking the 95 % confidence threshold. Figure obtained and modified from (Weber et al., 2022). (D) Original mouse photo with key points (shown alongside schematic) demonstrates the real-world application of the tracking system. A classifier, trained with manually annotated behaviors (e.g., 'Behavior A', 'Behavior B'), is used to categorize the mouse behavior in new sequences automatically. The classifier labels each time frame with the corresponding behavior class. A sequence of frames is fed into the system to compute time-resolved features. The system is trained to predict behaviors using supervised ML by correlating the extracted features with manually labeled behaviors from previous experiments. Unsupervised learning techniques reduce the high-dimensional feature space into a lower-dimensional representation. This allows for the clustering of behaviors based on movement patterns without the need for pre-defined labels. This classifier schematic is obtained and modified from (von Ziegler et al., 2021). (E) The table showing a comparison of supervised and unsupervised approaches demonstrates their effectiveness in detecting and categorizing behavioral changes in different mice models. Abbreviation: 2D, 2 dimensional; ML, machine learning. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Assessments Enhanced by ML. ML models applied to cognitive tests like the Mini-Mental State Examination (MMSE) (Kurlowicz and Wallace, 1999) and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) can predict cognitive decline more accurately by analyzing patterns in test responses. By identifying specific deficits, ML models help predict the likelihood of progression from MCI to AD (Qiu et al., 2018; Jeon et al., 2022; Luo et al., 2022), aiding in early intervention and treatment planning. The integration of ML techniques, as shown in Fig. 3, offers a more precise and scalable approach to analyzing animal behaviors in preclinical models.

The application of DeepLabCut, a marking based pose estimation tool, has been designed in tracking the movement of rodents during open field tests. Fig. 3A illustrates a schematic representation of tracking markers placed on key anatomical landmarks of the mouse, enabling detailed analysis of locomotor and anxiety-related behaviors. This method circumvents the need for physical markers, reducing stress on animals and improving the natural assessment of their movements. DeepLabCut has capabilities extend beyond simple tracking to the generation of complex behavioral metrics. As depicted in Fig. 3B, the software extracts feature such as inter-joint distances, velocities, and spatial trajectories. These quantitative metrics provide a deeper understanding of locomotion patterns, exploratory behaviors, and anxiety levels, which are critical for evaluating AD progression in rodent models. A significant advantage of ML approaches depends on their ability to ensure high reliability in data collection and analysis (Bordes et al., 2023). Fig. 3C demonstrates the confidence scores (≥95 %) of anatomical landmark labeling, emphasizing the robustness of DeepLabCut for consistent and accurate tracking. High-confidence labeling is particularly important for detecting subtle behavioral changes that may correlate with early stages of cognitive decline or motor impairments in AD models (Weber et al., 2022). Moreover, ML techniques enhance behavioral categorization through supervised and unsupervised learning approaches. Supervised methods rely on pre-labeled behaviors (e.g., rearing, grooming, or freezing) to train classifiers, which can then predict similar behaviors in new datasets. Fig. 3D illustrates how these classifiers label sequences of frames to identify specific behaviors automatically. In contrast, unsupervised techniques reduce the dimensionality of extracted features to cluster behaviors without predefined labels, uncovering novel patterns that may not be apparent through traditional approaches. This dual application enables researchers to detect both known and previously uncharacterized behavioral changes, broadening the scope of analysis (von Ziegler et al., 2021). The comparison between supervised and unsupervised approaches is summarized in Fig. 3E. Supervised techniques are ideal for tasks requiring high accuracy in predefined behavior detection, while unsupervised methods excel in exploring high-dimensional datasets to reveal hidden behavioral patterns. These complementary approaches collectively advance the precision and scope of behavioral assessments in AD research.

In preclinical AD models, ML tools such as DeepLabCut (Mathis et al., 2018) and MoSeq (Fig. 4A–C) (Wiltschko et al., 2020) provide precise, automated tracking of behaviors such as limb movement, posture, and complex 3D behaviors. For example, DeepLabCut tracks motor impairments in mice, which correlate with early AD symptoms (Liu et al., 2022). MoSeq further identifies complex sequences in behavior, revealing subtle cognitive and motor deficits indicative of AD progression (Fig. 4D) (Wiltschko et al., 2020). Fig. 4D highlights MoSeq's capability to uncover distinct behavioral patterns in preclinical AD models. Specifically, the pie charts demonstrate unsupervised clustering to differentiate between multiple behaviors syllables, such as walking, climbing attempts, or head movements, providing a quantitative assessment of motor and cognitive changes linked to AD progression. This detailed analysis underscores the utility of MoSeq in tracking subtle deficits that may not be apparent through traditional behavioral assessments. Fig. 4E and F (Datta, 2019), demonstrate MoSeq's capability to analyze changes in behavioral state maps. While not directly linked to AD, these panels illustrate the ability of MoSeq to detect transitions between behavioral syllables (nodes) and shifts in behavioral trajectories (edges) in response to stimuli, such as exposure to TMT, a fox odorant. This probabilistic modeling of behavioral sequences is a powerful example of how MoSeq could be applied to AD research to identify novel behavioral changes or motor deficits over time. Using DeepLabCut to analyze behavior in prenatal nicotine exposure models (Mathis et al., 2018) revealed deficits in working memory and social interactions, highlighting how ML can reveal intricate behavioral patterns relevant to AD and other neurological conditions (Zhou et al., 2024a).

However, limited data availability poses a challenge for maximizing ML's potential in AD research. Integrating imaging with behavioral data within ML frameworks provides a robust diagnostic tool, yet both fields struggle with data scarcity. Bridging this gap is essential to leverage ML's full diagnostic and predictive power. The Table 2 carefully delineates the distinctions between 2D and 3D analyses in machine learning-assisted behavioral and cognitive assessments. Drawing from our focused perspective, we have highlighted key differences in tools, applications, and challenges to emphasize the complementary strengths of each approach. By integrating insights from 2D and 3D methods, researchers can gain a comprehensive understanding of motor and cognitive patterns, providing a robust framework for advancing Alzheimer's disease research. This table encapsulates our careful examination of these modalities to ensure clarity and relevance for the field.

4.5. *ML approaches for mapping vascular structural changes to behavioral impairments*

Advancements in computer vision and ML techniques for pose estimation (such as DeepLabCut, SLEAP, and LightningPose) and behavioral segmentation (including MoSeq and VAME) now enable the breakdown of spontaneous mouse behavior into short postural units (motifs or syllables), while also uncovering their sequence and hierarchical organization. These cutting-edge approaches enhance the precision, scope, and sensitivity of behavioral analysis, potentially offering valuable insights into disease mechanisms (Miller et al., 2024). A study combines qEEG with sMRI to build a SVM classification model, which not only highlights the advantages in early identification of patients with VCI,

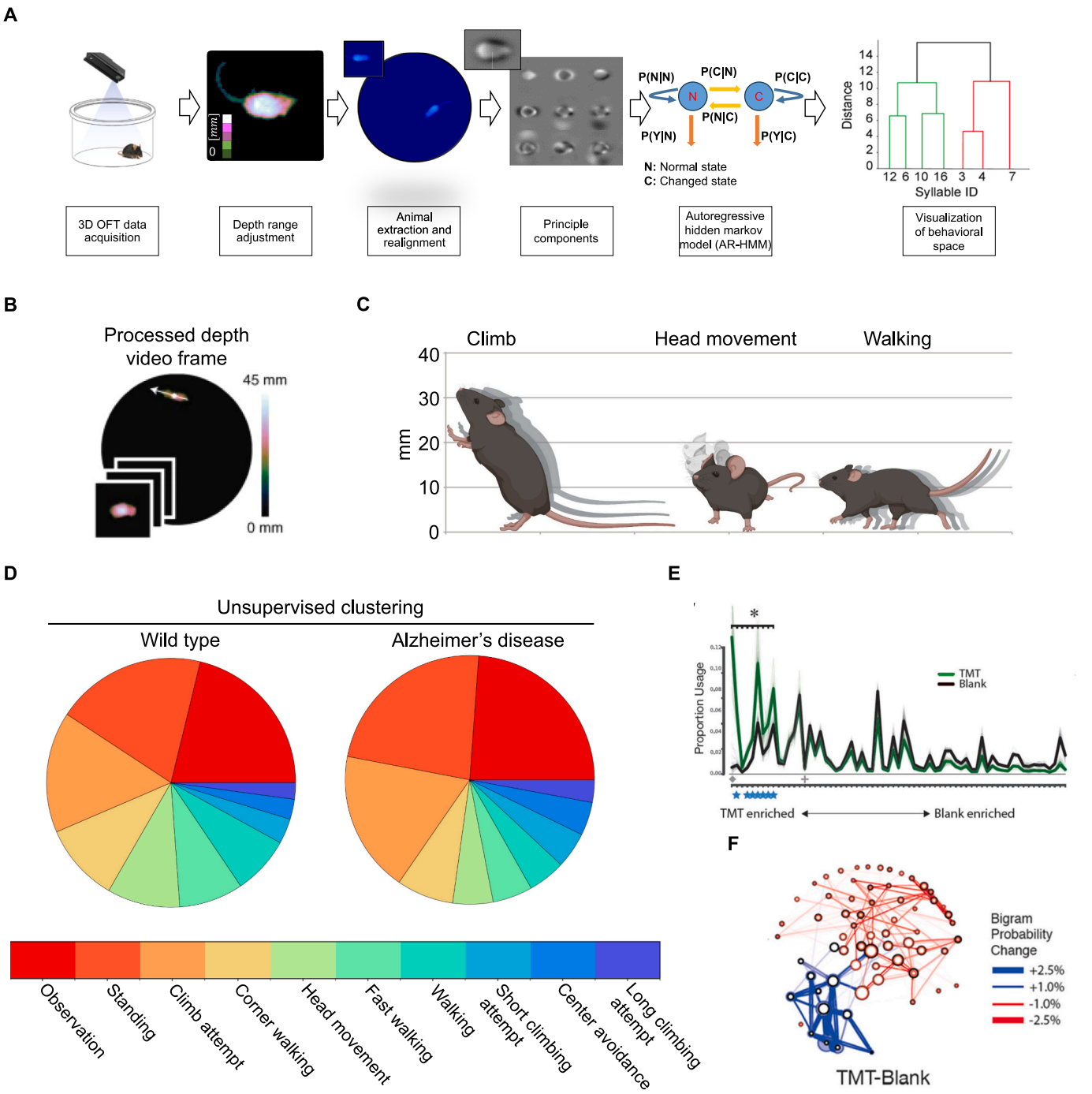


Fig. 4. 3D depth video and motion sequencing for high-resolution behavioral profiling in different rodent models. (A) Schematic of 3D depth video setup capturing rodent movements in a behavioral arena to track spatial positioning and motion. Depth data was processed for arena detection, PCA-based dimensionality reduction, and AR-HMM modeling to segment behavioral syllables, compute syllable-specific statistics, and visualize transition probabilities for detailed behavioral analysis. (B) Extracted motion data, including position and velocity vectors, enables detailed locomotor and spatial analysis (Wiltschko et al., 2020). (C) Schematic showing behavioral segmentation breaks movements into discrete 'behavioral syllables' using algorithms like MoSeq. (D) ML models are employed for behavioral classification, with supervised learning using labeled data and unsupervised clustering revealing novel movement patterns, figure represents authors' original data (unpublished). (E–F) Adapted from open-access source (Datta, 2019), these panels illustrate analyses of behavioral motifs and transitions. The usage proportion graph shows how often specific behavioral syllables are used in different experimental conditions (e.g., Fox odorant TMT vs. blank), while the network graph visualizes transitions between different behavioral syllables, indicating changes in behavior probabilities between conditions. Abbreviation: 3D, 3 dimensional; PCA, principal component analysis; AR-HMM, auto-regressive hidden markov model; MoSeq, motion sequencing; ML, machine learning; TMT, trimethylthiazoline.

but also helps to explore biomarkers with significant differences between patients with VCI and normal subjects (Li et al., 2024b). AI and digital tools promise to facilitate the early detection of neurodegenerative diseases, potentially leading to earlier interventions that could slow disease progression (Chudzik et al., 2024).

AI-based vascular imaging tools will also provide support for diagnostic, prognostic, and intraoperative settings. AI can also aid with integrating care data points, thereby promoting the holistic, interdisciplinary care that is critical to optimizing management and outcomes (Flores et al., 2021). To gain a deeper understanding of the intricate fluid

Table 2
Comparison of 2D and 3D analyses in ML-assisted behavioral and cognitive assessments.

Aspect	2D analysis	3D analysis
Definition	Tracks behaviors using keypoint detection and computation of metrics such as distances, angles, and areas (Mathis et al., 2018).	Captures behaviors in three-dimensional space, analyzing complex motion sequences and spatial relationships (Wiltschko et al., 2020).
Tools Used	DeepLabCut for 2D keypoint detection and tracking of movements (e.g., limb movement, posture) (Mathis et al., 2018).	MoSeq for tracking complex 3D behaviors, analyzing sequences of actions, and behavioral trajectories (Wiltschko et al., 2020).
Focus	Focuses on simple motor behaviors like limb movements and postural adjustments (Nath et al., 2019).	Identifies complex behavioral sequences and transitions between states, including shifts in behavioral trajectories (Datta et al., 2019).
Applications in AD Research	Detects early motor impairments in animal models, correlating them with AD symptoms (Dombeck and Reiser, 2012).	Reveals subtle cognitive and motor deficits by analyzing behavioral state maps and transitions over time (Wiltschko et al., 2020).
Advantages	Easier to implement; requires less computational power and simpler data input (Mathis et al., 2018).	Provides a richer, more detailed understanding of behavior; useful for studying intricate cognitive impairments (Datta et al., 2019).
Example Output	Tracks anatomical landmarks with high accuracy using confidence thresholds for precise motor and cognitive analysis (Mathis et al., 2018).	Models probabilistic transitions between behavioral syllables, mapping responses to stimuli like fox odorant (TMT) (Wiltschko et al., 2015, Datta, 2019).
Challenges	Limited to simpler spatial representations; may miss depth-related behavior patterns (Nath et al., 2019).	Higher computational demands and data requirements; limited by availability of high-resolution 3D datasets (Datta et al., 2019).

dynamics within the glymphatic system, a four-compartment poroelasticity model that accurately represents the cerebral environment was developed (Chou and Chen, 2024). Recently, to evaluate glymphatic function and white matter integrity in children with autism spectrum disorder (ASD), multi-parametric MRI combined with machine learning to assess its effectiveness in ASD detection were utilized (Wang et al., 2025).

4.6. Comparative analysis of AI tools in AD research

Table 3 includes a comprehensive comparison of various artificial intelligence (AI) techniques utilized in AD research. These methods span from deep learning (DL) and traditional ML algorithms to radiomics and natural language processing (NLP), each contributing unique strengths to AD diagnosis and analysis. DL models demonstrate high accuracy in detecting and segmenting vascular defects, whereas ML offers robust performance on smaller datasets, particularly for classification and regression tasks. The table also highlights specific methodologies such as MoSeq and DeepLabCut, emphasizing their roles in behavioral data analysis and physiological assessments, underscoring their versatility in preclinical models.

4.7. ML for automated detection of perivascular changes, DTI-ALPS metrics, and White matter hyperintensities in glymphatic dysfunction

Several studies have employed ML approaches to analyze PVSs, extract diffusion tensor imaging along the perivascular space (DTI-ALPS) indices, and measure WMH, all of which are associated with glymphatic dysfunction. Rashid et al. (Rashid et al., 2023) introduced a deep learning framework using a lightweight U-Net model to detect enlarged PVS on brain MRI. Sinclair et al. (Sinclair et al., 2024) developed PINGU (Perivascular space Identification Nnunet for Generalised Usage), a nnUNet-based model trained on a heterogeneous dataset from six different sources. Jeong and Choi (JEONG and CHOI) investigated the relationship between the glymphatic system (assessed via the DTI-ALPS index), PVS, and WMH across different age groups. They utilized deep learning. Guerrero et al. (Guerrero et al., 2018) developed a convolutional neural network capable of segmenting WMH and

Table 3
Comparison of commonly used AI methods.

AI method	Description	Advantages	Disadvantages	References
DL Models for Imaging	Uses artificial neural network to learn complex patterns from medical images	High accuracy in detecting and segmenting vascular defects. Can handle large datasets. Can identify subtle features that may be missed by human experts	Requires a large amount of labeled data for training. Black box nature can make it difficult to understand how the model works	(Zhou et al., 2021)
ML for Medical Imaging	Uses various algorithms (unsuppressed and supervised) to learn from data and make prediction	Easier to interpret than DL models. Can be used with smaller datasets. Can be used for a variety of tasks, such as classification, regression, and clustering	May not be as accurate as DL models for complex tasks	(Varoquaux and Cheplygina, 2022)
Radiomics	Uses quantitative features extracted from medical images to predict the presence or severity of vascular defects	Can be used to identify subtle changes in the appearance of blood vessels that may be missed by human experts.	May not be as accurate as other AI methods for image-based analysis of vascular defects	(Kumar et al., 2012, Angelica et al., 2021)
Computer Vision for Imaging	Uses algorithms to analyze and interpret visual information	Can be used to analyze a variety of medical images including X-rays, CT scans, and MRIs. Can be used to automate tasks such as segmentation and detection of vascular defects	May not be as accurate as DL models for complex tasks	(Wismüller et al., 2002)
NLP for cognition	Uses algorithms to analyze and understand human language or animal behavior sequencing	Can be used to analyze text data, such as medical reports and clinical notes, to identify patients with vascular defects. Can be used to extract information from medical records to help with diagnosis and treatment	May not be as accurate as other AI methods for image-based analysis of vascular defects	(Reznikova, 2007, Hauk and Weiss, 2020)
Moseq	Combines multiple DL and ML model to improve accuracy and robustness in behavior data	Can leverage the strengths of different models. Can be more robust to noise and variations in data	Requires careful design and training. May be more computationally expensive than single models	(Wiltschko et al., 2020, Weinreb et al., 2023)
DeepLabCut	Open-source software for marker less pose estimation in animal videos	Enables automatic tracking of animal movement without the need for markers. Can be used to study vascular function and other physiological processes	Requires high quality video data. May not be accurate for complex movements or occlusions	(Mathis et al., 2018)

differentiating them from stroke lesions. Ghafoorian et al. (Ghafoorian et al., 2017) introduced location-sensitive deep convolutional neural networks for WMH segmentation.

5. Proposed ML algorithms for vascular and behavior analysis

We propose an integrated automated pipeline to facilitate the detection and analysis of vascular changes in AD through advanced ML and DL approaches. This pipeline incorporates traditional ML techniques and more complex DL architectures, offering a comprehensive tool for identifying and characterizing vascular dysfunction markers.

5.1. Proposal I- automated pipeline for AD vascular detection with ML and DL

Following sample preparation, light-field imaging captures high-resolution, three-dimensional images of the stained tissue slices. This imaging modality provides a detailed view of biomarkers' structural and spatial arrangement, capturing depth information and intricate vascular networks. The raw images are then preprocessed through DL-based techniques, such as noise reduction, normalization, and correction of imaging artifacts, to ensure consistent and high-quality input data across all samples. Next, an advanced image stitching algorithm, powered by CNNs such as U-Net and its derivatives, is applied to align and seamlessly integrate individual light-field images. The stitched image captures critical features such as vessel density, branching patterns, tortuosity, and microvascular architecture, which are critical for understanding disease pathology and vascular integrity. The stitched structural representation is further analyzed using DL models designed for feature extraction, segmentation, and classification of vascular markers. Specifically, CNNs are trained and optimized using large datasets to accurately identify structural patterns and classify different states of vascular health.

Multimodal fusion strategies need to be utilized to enrich the analysis further. These strategies integrate the structural imaging data with additional histological and biochemical markers, providing a comprehensive view of the vascular and glymphatic alterations in the tissue. Advanced DL architectures, such as attention mechanisms and transformer-based models, are leveraged to capture intricate relationships between different biomarkers, offering insights into complex interactions and potential disease pathways. The end-to-end pipeline thus integrates light-field imaging, DL-driven preprocessing, stitching, and advanced analytical modeling to offer a robust and scalable solution for analyzing vascular biomarkers in whole stained mouse tissue slices. This approach can potentially revolutionize the study of neurovascular and glymphatic dysfunction in disease models, offering unprecedented precision and automation in biomarker detection and characterization.

5.2. Proposal II- DeepLabCut for behavior analysis and MoSeq for sequencing: a unified methodology

We propose a streamlined, integrated platform for automated behavior analysis using DeepLabCut, MoSeq, and YOLOv8, designed to enhance precision and scalability in high-throughput studies of animal models. This platform utilizes cutting-edge DL techniques to automate behavior tracking and analysis, providing unprecedented resolution and quantification of subtle behavioral changes.

The first component of the platform employs DeepLabCut, an open-source DL framework for precise, marker-less tracking of key body points in mice across various experimental conditions (Fig. 3A). This tool captures movement dynamics, such as time spent in specific regions of interest (ROIs) and locomotion patterns, focusing on detecting behavioral anomalies like increased peripheral movement and wall-jumping tendencies indicative of anxiety and cognitive deficits in AD knock-in mouse models. The second component, MoSeq, utilizes motion sequencing to classify and sequence complex behaviors through unsupervised learning. This approach identifies behavioral asymmetries and cognitive irregularities, particularly in different genotypes, particularly AD knock-in mice models. The third experimental component integrates YOLOv8, a state-of-the-art real-time object detection framework, to analyze and quantify nesting behavior in mice. YOLOv8 detects and segments nesting areas, providing accurate, reproducible measures of nest-building capabilities. Combining data from DeepLabCut, MoSeq, and YOLOv8, this platform offers an end-to-end solution for capturing both spatial and temporal dimensions of behavioral patterns. This comprehensive approach enhances our ability to characterize disease phenotypes, providing robust tools for preclinical studies and therapeutic development in AD and related neuropathies.

6. Conclusion and future perspectives

The intertwined roles of vascular dysfunction and glymphatic system impairment in AD pathogenesis highlight a complex yet critical area of research. Vascular aging disrupts pulsatile forces and endothelial integrity essential for glymphatic flow, leading to impaired clearance of Aβ and other neurotoxic metabolites, which accelerates neuroinflammation and neurodegeneration (Dickstein et al., 2010, Iliff et al., 20121, Banks et al., 2021, Yamada and Iwatsubo, 2024). The breakdown of the BBB exacerbates these processes, introducing inflammatory mediators that further impair glymphatic flow and waste clearance (Iliff et al., 2013; Da Mesquita et al., 2018b). Imaging and computational advancements have significantly enhanced our understanding of these interactions, with ML techniques offer unprecedented opportunities to integrate multimodal datasets, elucidating the complex vascular-glymphatic interplay in AD (Borogovac and Asllani, 2012; Lajoie et al., 2017).

This study underscores the power of computational approaches in elucidating the glymphatic system's role in AD. By leveraging ML techniques for imaging, vascular analysis, and behavioral tracking, we establish a direct link between vascular dysfunction and impaired glymphatic clearance. Specifically, ML-based image processing techniques applied to ASL and LSFM enable high-resolution mapping of cerebrovascular networks and glymphatic transport dynamics. These approaches allow for the precise quantification of CSF and ISF exchange, revealing how vascular stiffness and endothelial dysfunction compromise glymphatic clearance. High-resolution vascular imaging, enhanced by ML-driven segmentation, reveals structural and functional changes in cerebrovascular networks that correlate with impaired glymphatic clearance. Furthermore, behavioral analysis using MoSeq and DeepLabCut uncovers subtle neurocognitive impairments linked to glymphatic dysfunction, providing novel biomarkers for early-stage AD diagnosis. These methodologies offer an unprecedented ability to track fluid dynamics, identify early biomarkers, and establish causal links between vascular pathology and neurodegeneration.

Future research should focus on elucidating the precise mechanisms by which vascular aging influences glymphatic transport dynamics, particularly the effects of arterial stiffness, disrupted pulsatile flow, and BBB permeability (Iliff et al., 2013; Da Mesquita et al., 2018b; Korte et al., 2020). Longitudinal studies combining advanced imaging techniques, such as ASL and LSFM, are essential for tracking vascular and glymphatic changes across disease stages (Borogovac and Asllani, 2012; Zhang et al., 2021; Chen et al., 2024a). Moreover, ML can be leveraged to integrate behavioral, imaging, and genetic data, enabling the identification of composite biomarkers for early diagnosis and disease progression prediction (Iturria-Medina et al., 2016; Lajoie et al., 2017). Therapeutic interventions targeting both vascular and glymphatic dysfunction are promising. However, significant knowledge gaps persist. Translational studies in human populations will be crucial to validate findings from preclinical models and ensure their applicability in clinical settings. By addressing these priorities, future research can pave the way for innovative diagnostic and therapeutic solutions, mitigating the combined effects of vascular and glymphatic dysfunction on AD

progression.

CRediT authorship contribution statement

Gehan Fatima: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization. **Akm Ashiquzzaman:** Writing – original draft, Visualization, Software. **Sang Seong Kim:** Writing – review & editing. **Young Ro Kim:** Writing – review & editing, Funding acquisition. **Hyuk-Sang Kwon:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Conceptualization. **Euiheon Chung:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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