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Review

Imaging of enlarged perivascular spaces in Alzheimer's disease with MRI techniques

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Abstract

The development of Alzheimer's disease (AD) is closely associated with the integrity and function of the perivascular space (PVS). The PVS has essential roles in transporting cerebrospinal fluid and exchanging intracellular substances necessary to clear metabolic waste from the brain. An enlarged PVS (ePVS) is now acknowledged as a major factor in AD development, thus indicating a complex interplay with other pathogenic factors. Herein, we present a detailed examination of the imaging features of PVS, as depicted by various MRI modalities, highlighting how these techniques have advanced understanding of AD pathogenesis. Furthermore, we critically assess the strengths and limitations of these imaging approaches and discuss prospective enhancements that may provide refined insights. Further understanding of the PVS may reveal new diagnostic biomarkers and inform targeted therapeutic approaches, thus improving clinical management for patients with AD.

Keywords: Alzheimer's disease, Perivascular spaces, MRI, Enlarged PVS

1. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the primary cause of dementia in older people [1]. As the global population continues to age, it is anticipated that the prevalence of AD will continue to rise, resulting in a considerable social and economic burden [2]. A leading hypothesis in AD pathogenesis is an imbalance in the production and clearance of β-amyloid (Aβ) and tau proteins [3, 4]. Perivascular spaces (PVSs) surround the blood vessels in the brain and are involved in clearing waste products from the brain [5]. Magnetic resonance imaging (MRI), distinguished by its high spatial resolution, ability to perform multicontrast imaging, and noninvasive nature, is an invaluable tool for the detailed and comprehensive evaluation of the perivascular interstitial PVS. Previous studies have demonstrated higher frequency and severity of PVS abnormalities in people with AD than in controls without dementia [6, 7]. Moreover, one study has shown that hypertension disrupts the perivascular pump and markedly slows the transport of cerebrospinal fluid (CSF) in the PVS, whereas arterial hypertension promotes the accumulation and aggregation of Aβ; therefore, hypertension-induced decreases in PVS fluid transport may directly contribute to the association between arterial hypertension and AD [8]. In addition, some studies have reported that an increased PVS volume is also positively associated with sleep disturbance. For example, in aging populations, sleep disturbance during non-rapid eye movement is associated with Aβ and tau protein aggregation, and sleep disturbance in normal older adults increases AD risk [9]. The intricate relationships between PVS burden and the levels of hypertension and sleeping disorder underscore the potential effects of PVS on AD pathogenesis and suggest potential directions for future research [8–10]. From a clinical medicine perspective, greater understanding of the clinical significance of PVS in AD is necessary, including how PVS enlarges, at what stage of AD the enlargement occurs, what the consequences are, and to what extent PVS visible on MRI suggests AD risk. Recognizing these factors will be critical to enable clinicians to intervene effectively and potentially mitigate the onset and advancement of AD.

This review emphasizes novel MRI techniques that offer quantitative and functional insights into the PVS in the context of AD. These methods allow for observation of PVS alterations throughout AD progression and offer a window into the pathogenic processes at play. Integrating these imaging strategies with clinical evaluations can enhance understanding of AD, and improve patient outcomes through early detection and targeted

therapeutic interventions. In conclusion, exploration of the PVS through advanced neuroimaging techniques is a promising frontier in AD research. A deeper understanding of PVS dynamics and clinical implications has the potential to drive the development of new therapeutic strategies to alleviate AD burden, and offers hope for improved outcomes for patients with this devastating condition.

2. RELEVANCE OF EPVS TO AD PATHOLOGY

The PV, a fluid-filled area surrounding cerebral blood vessels, including the periaortic, pericapillary, and perivenous spaces [5, 11], is a normal anatomical structure of the central nervous system. The PVS is formed by the endothelial basement membrane on the inner side of the blood vessels, and by the compacted astrocyte end-foot processes and overlying parenchymal basement membrane on the outer side [12, 13]. This structure plays crucial roles in regulating waste clearance and maintaining proper functioning of the brain.

Unlike the peripheral vascular system, the brain does not possess a conventional lymphatic drainage system. However, a recently discovered glymphatic system has been identified to use the PVS as a pathway for removal of toxic waste from the brain's interstitium. This glymphatic system has a crucial role in maintaining the brain's waste clearance process and overall homeostasis [14]. The glymphatic hypothesis proposes that CSF enters the brain through para-arterial spaces and then mixes with interstitial fluid (ISF) within the parenchyma, in a manner involving aquaporin-4 (AQP4) channels. The waste-containing fluid then exits the brain along para-venous spaces surrounding venules and veins. This glymphatic system provides a mechanism for waste clearance and the removal of toxic substances from the brain's interstitial space (**Figure 1**) [13–15]. AQP4 channels, situated on the astrocytic end-feet, are selective

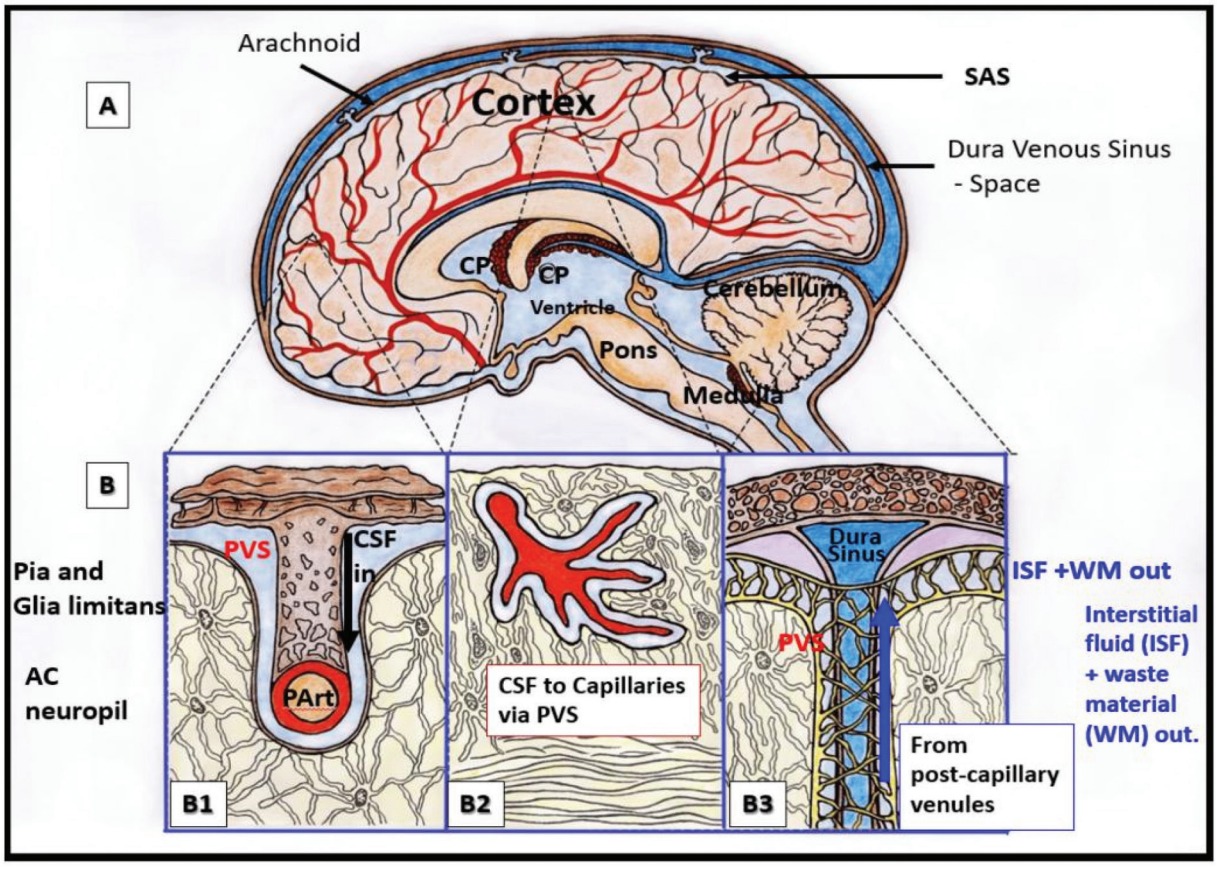

Figure 1 | Relationship of perivascular spaces (PVS) to the whole brain.
(a) Structurally labeled whole brain with demarcations of specific regions (dashed lines). (b) Pia artery within the subarachnoid space (SAS) that penetrates the deeper brain structures in a perpendicular manner, with adjacent PVS with blue coloration (B1) and horizontally–diagonally (B2), wherein the PVS allow for the influx (black arrow) of cerebrospinal fluid (CSF) to the parenchymal interstitial fluid space (ISF) via the arteriolar PVS. Panel (B3) depicts the efflux (blue arrow) of the interstitial fluid metabolic waste material (WM) of the pial venular PVS to the pial vein PVS, by entering the subarachnoid space and eventually draining into the dural venous sinus space. Reproduced under the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/) [13].

for water and facilitate the transfer of ISF within the PVS to the neuronal ISF, thus enabling the integration of CSF with ISF [16, 17]. Tracer studies and two-photon microscopy imaging have revealed that mice lacking AQP4 channels, in contrast to mice with functional AQP4 channels, demonstrate a significant 70% decrease in the clearance of ISF through paravascular drainage pathways [18]. This finding underscores the critical role of AQP4 channels in facilitating the glymphatic system's clearance of metabolic waste from the brain.

The PVS is considered an important node of the glymphatic system, by acting as a channel for transporting various signaling molecules and functioning as a neurotoxic waste disposal system that contributes to regulating the balance of fluid circulation within the brain [19]. Dilation of the PVS can indicate hindered outward flow of fluids along the arterioles that the PVS surrounds, thus disrupting the normal circulation of fluids within the brain. This disturbance can affect the brain's ability to clear waste, and potentially overall brain health and function [20]. Consequently, inefficient removal of metabolic waste from the brain leads to the accumulation of proteins and other waste that can damage brain tissue [14, 21].

The PVS exhibits a unique histological signature arising from the intricate nature of adjacent tissue structures. However, it is only at a size that can be resolved by MRI technology that these structures become discernible on imaging, thus allowing for their differentiation [5, 22]. There is a clear correlation between the in vivo burden of MRI-visible PVS and the severity of histopathologically observed enlarged PVS (ePVS) in corresponding anatomical locations [20, 23]. The presence of ePVS has recently emerged as a proxy for glymphatic dysfunction and a contributing factor to AD [24].

The precise pathophysiological mechanisms underlying the enlargement of PVS and its role in the AD disease process have not been fully elucidated. Genetic, pathologic, and biomarker findings have shown that Aβ deposition is the crucial early impetus for AD [25, 26]. Aβ deposition characteristically occurs within the walls of cortical and leptomeningeal blood vessels, thus compromising the role of the PVS in clearing brain waste. Impaired perivascular clearance may delay the transport of brain wastes, including Aβ and tau, and further facilitate their attachment to and deposition in the corresponding basement membranes, thereby destroying perivascular clearance dysfunction in a vicious cycle, and leading to more severe brain damage and more pronounced cognitive dysfunction [3, 27–29]. Charidimou et al. have investigated the relationship between overall PVS burden and cortical retention of 11C-Pittsburgh compound B (PiB) positron emission tomography (PET, a radioligand that binds parenchymal and vascular fibrillar Aβ deposits), and have found that ePVS severity partly reflects the level of Aβ accumulation in the cerebral vasculature. This association may suggest that drainage impairment by progressive vascular Aβ deposition causes retrograde perivascular space dilation in the white matter [30]. That is, accumulation of vascular Aβ in cortical vessels leads to impaired clearance along these vessels, and consequently to fluid stagnation and PVS enlargement along associated perivascular compartments in the white matter of the same vessels [20]. In contrast, Aβ accumulation in the vascular basement membrane can lead to breakdown of the blood-brain barrier (BBB) [31], owing to the degeneration of endothelial cells and pericytes, as well as the loss of tight junctions [32, 33]. BBB leakage results in increased vascular permeability and allows influx of neurotoxic blood-derived substances into the brain, thereby promoting excess fluid accumulation in the PVS [13, 34, 35]. These findings suggest that early BBB malfunction may be indicated by ePVS, along with abnormal interstitial fluid dynamics.

Individuals with AD frequently show mixed pathologies [36]. Other etiological factors occurring before Aβ deposition causes irreversible damage have also received substantial attention. Vascular dysfunction is integral to AD etiology and pathophysiology [37]. In autopsies of individuals with dementia, AD pathology and cerebrovascular lesions are frequently found to coexist [38]. Several studies using diverse biomarkers (e.g., BBB integrity, cerebrovascular reactivity, resting cerebrovascular flow, and increased cerebrovascular resistance) have indicated that cerebrovascular deterioration occurs in early stages of AD progression [39]. Cerebral small vessel disease (CSVD) causes catastrophic damage involving small blood vessels throughout the brain [40], as well as cognitive impairment, and frequently co-exists with AD in older people. Both conditions are associated with several common vascular risk factors, including hypertension, hyperlipidemia, and diabetes [41, 42]. Moreover, the vascular alterations associated with CSVD can decrease cerebral blood flow, hypoxia, and inflammation, thereby exacerbating the neurodegenerative processes characteristic of AD [41]. ePVS is a key pathological feature of CSVD, as shown on MRI from patients with sporadic CSVD, and is associated with other CSVD features, including white matter hyperintensities, lacunes, and microbleeds [40]. Arteriole or venule stiffening associated with decreased vascular pulsatility leads to diminished fluid flow within the PVS, thus contributing to enlargement. In essence, ePVS may serve as a visible sign of the vascular and clearance dysfunction contributing to both CSVD and AD [43]. ePVS, CSVD, and AD are linked through their effects on cerebral blood flow, CSF clearance, and neuroinflammation. Further research is required to elucidate the effects of cSVD amelioration on the onset and progression of AD. Vascular changes can be prevented and regulated through lifestyle modifications and the use of medication [41].

Other common features of AD include synaptic dysfunction, such as synaptic damage, loss, and structural changes in the synapse, as well as demyelination, the loss of the protective myelin sheath surrounding nerve fibers in the brain. Dilatation of the PVS is a secondary

consequence of tissue loss surrounding the perivascular compartment [44]. The presence of ePVS, owing to loss of cortical integration and structural disconnection of white matter cortical tracts, can disrupt the integrity of the white matter brain network and normal cognitive function. Moreover, immunocytochemical research has verified that the PVS contains dispersed cells expressing CD45, which are crucial for initiating neuroinflammation and immune monitoring [45–47]. The discovery of specific genes associated with innate immune responses that elevate AD risk, along with elevated inflammatory markers in individuals with AD, indicates a substantial role of neuroinflammation in AD progression [48]. Whether ePVS is a driver or a consequence of neuroinflammation remains unclear. One study has suggested that PVS dilation might represent an initial congregation of immune cells that potentially precedes the formation of neuroinflammatory lesions [49].

The cognitive and motor decline in AD correlates with various factors influencing PVS dynamics [50, 51]. The emergence of ePVS is clearly multifactorial; however, without longitudinal studies, the temporal progression of these factors cannot be defined. To untangle these complex interactions and advance understanding of AD pathology, novel neuroimaging techniques that can accurately visualize PVS are critical. Such methods are expected to shed light on the mechanisms of brain waste clearance and metabolite accumulation, thereby paving the way to targeted therapeutic strategies in AD management.

3. MRI METHODS TO VISUALIZE THE PVS

3.1 PVS structure

The PVS, visible within the brain's parenchyma on MRI, aligns with penetrating cerebral arterioles, which extend orthogonally from the brain's surface [52]. On imaging, PVS is isointense with the CSF, appearing linear alongside the trajectory of perforating vessels and round when captured perpendicularly to vessels [53, 54]. These spaces are observed predominantly in the centrum semiovale (CSO), basal ganglia (BG), midbrain, and hippocampus [5, 55]. Currently, controversy persists regarding the diagnostic criteria for EPVS, and no consensus has been reached. Wardlaw and colleagues, adhering to the STandards for ReportIng Vascular changes on Neuroimaging (STRIVE) criteria, have classified lesions 3 mm in diameter or smaller as PVS, and have prioritized lesion prevalence and distribution rather than size [54].

3.1.1 Visual rating scales. Visual rating scales are widely used in research and clinical practice for evaluating ePVS severity on MRI [56–58]. These scales, such as that developed by Wardlaw, provide a systematic approach to quantifying the burden of PVS within specific brain regions such as the CSO, BG, and midbrain [59]. Use of Wardlaw's scale is straightforward: a rater examines an MRI image, selects a typical axial slice for each brain region of interest, and applies the grading criteria. The ePVSs are then counted and assigned a score based on predefined categories: a score of 0 indicates no visible PVSs; 1 indicates 1–10 visible PVSs; 2 indicates 11–20 visible PVS; 3 indicates 21–40 visible PVS; and 4 indicates more than 40 PVSs **(Figure 2)**. This scale facilitates comparison across studies and participants by providing a consistent metric for quantifying and reporting the presence of PVSs. The strength of this grading scale is its reproducibility, allowing different graders to achieve similar results independently. This aspect is particularly important in large-scale studies or multi-site collaborations in which consistency in data interpretation is key. By assigning numerical values to the observed PVS, these scales also allow for statistical analysis of the relationship between PVS severity and various clinical outcomes or other neuroimaging findings.

Patients diagnosed with AD exhibit a greater degree of PVS than control individuals, particularly in the CSO and hippocampus [7, 61, 62]. Moreover, a longitudinal study has shown that higher severity of MRI-visible perivascular spaces, particularly those within the CSO, when assessed via a visual rating scale, correlates with elevated risk of cognitive deterioration and the development of dementia in community-living older adults [63]. CSO-PVS is associated with AD pathological biomarkers and with genetic predisposition to AD [20, 62, 64, 65]. These studies underscore the value of ePVS evaluation as a diagnostic and prognostic tool in AD.

The relationship between genetic factors and PVS is an area of substantial interest, because it could provide valuable information for understanding the pathology of various neurological conditions, including AD. The apolipoprotein E (APOE) ε4 allele is recognized as the primary genetic factor influencing AD risk [66]. In a notable postmortem study, individuals carrying two copies of the APOE-ε4 allele exhibited a greater PVS extent than those with either one or no copies of the allele [6]. Another study reported in 2022, in 3,564 individuals including 836 APOE-ε4 carriers, has corroborated the link between the APOE-ε4 allele and elevated incidence of ePVS, particularly within the CSO and the combined CSO and BG regions in MRI scans, thus challenging the conclusions drawn from earlier studies with smaller cohorts [67].

Indeed, the visual assessment of PVS has several limitations that can affect the accuracy and utility of the data obtained. For example, visual rating scales typically provide semi-quantitative data, such as counts or categorical ratings, which can be less informative than volumetric measurements. Without information on PVS volume, the true extent of perivascular pathology and its potential effects on brain function are difficult to gauge. In addition, the instruction for raters to use the hemisphere with the higher PVS count when a significant discrepancy exists could lead to critical information regarding the distribution and asymmetry of PVS being

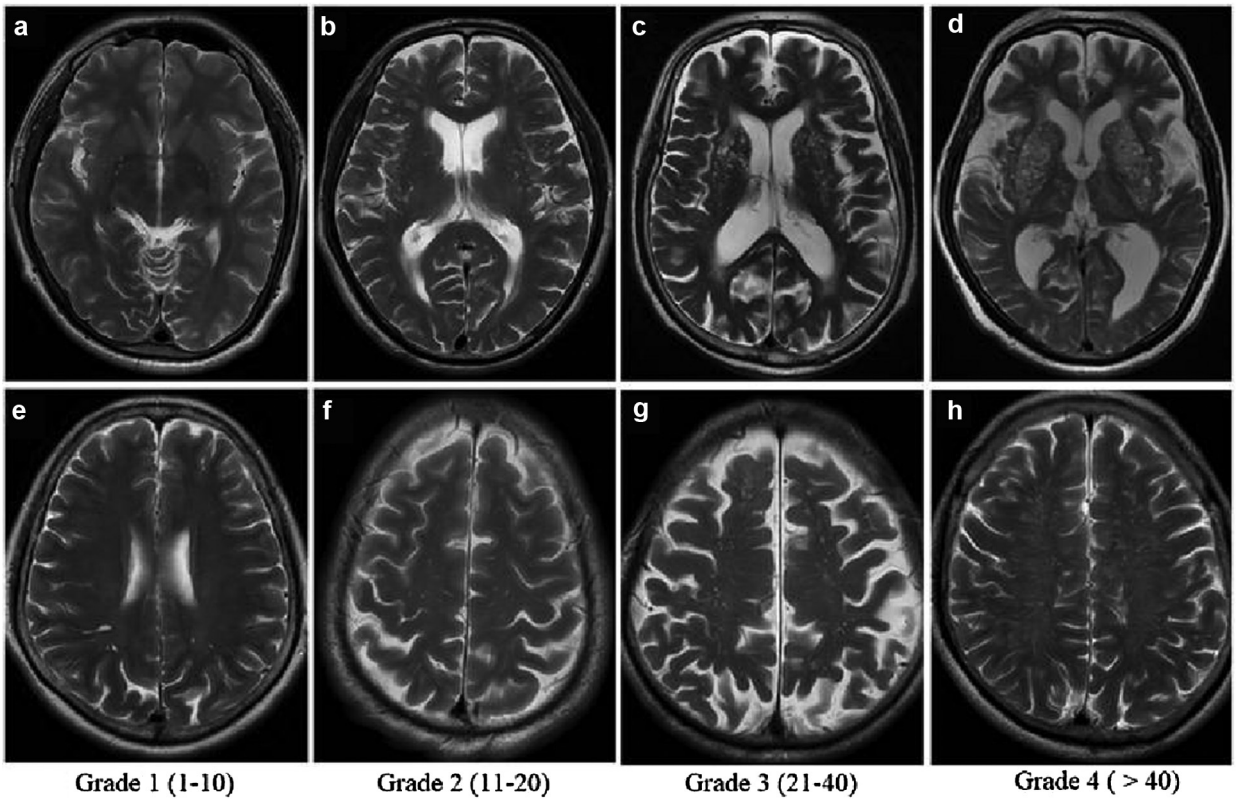

Figure 2 | Visual rating scores for ePVS on T2-weighted MRI.
The T2-weighted MRI scans showing different degrees of visibility of the perivascular space in the basal ganglia (top row, a–d) and the centrum semiovale (bottom row, e–h), with the corresponding scores [1–4] shown at the bottom. Each hemisphere is scored separately for PVS, and the higher of the two scores is used. Reproduced under the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/) [60].

overlooked. This aspect might be particularly relevant if the glymphatic system dysfunction has regional characteristics or is associated with specific morphological changes [68]. Moreover, longitudinal studies, which track changes over time, are hampered by potential detection bias arising from variability in how different investigators, or the same investigator at different times, might perceive and count PVSs. Investigators' skill and experience level can significantly influence the consistency and reliability of PVS detection across multiple time points [69]. These limitations highlight the need for more objective and quantifiable methods for evaluating PVS.

3.1.2 Automated segmentation of PVS. Automatic segmentation algorithms significantly enhance the analysis of PVS by providing a detailed, objective, and reproducible approach to measuring and characterizing these structures in MRI studies. They eliminate the subjective bias and variability associated with manual labeling, and facilitate nuanced investigation of PVS characteristics [70]. By automatically quantifying the severity, volume, and morphological attributes including length, width, sphericity, and orientation, these algorithms enable a sophisticated and detailed evaluation of PVS. Two main classifications of these algorithms exist: classical image processing techniques that use predefined rules to identify PVS, and machine learning algorithms that learn to recognize PVS patterns from large datasets, often with enhanced accuracy [71].

In classical approaches, PVSs were segmented with intensity-based thresholding approaches or vesselness filter approaches [72]. The number of PVSs and their morphological characteristics, such as PVS volume and mean cross-sectional diameter, were quantified. These measures provided by automatic segmentation algorithms have been proposed and demonstrated to correlate well with visual rating scales, thereby offering a more precise and reliable assessment of PVS on MRI studies [72–74]. For example, Kamagata et al. have used an automated tool to calculate the volume fraction of PVS known as PVSVF [61]. Their findings suggest that a higher PVSVF is associated with patients with MCI and AD than healthy controls, particularly within white matter regions of the brain. This elevated volume fraction may indicate PVS dilatation, which might in turn reflect underlying impairment in the glymphatic system—a brain waste clearance pathway.

Conventional methods typically have a limitation of requiring additional parameter tuning when applied to diverse datasets [71]. In contrast, machine learning algorithms can be trained for a specific task by using example data, and can automatically discern the defining characteristics of a target object, including its intensity, shape, and location [75]. Specifically for PVS segmentation, these algorithms undergo learning across numerous iterations or epochs, by using manually annotated images to identify features characteristic of PVS. After the completion of this training phase, the algorithm is equipped to autonomously recognize and label PVS structures in novel, previously unanalyzed data [76, 77]. For instance, the convolutional neural network (CNN) is a commonly used neural network method for image processing tasks. Lian et al. have designed a multi-scale, multi-channel CNN architecture incorporating both small and large contextual details for PVS segmentation, thus increasing PVS segmentation accuracy [78]. However, most machine learning approaches have been trained or tested using data from high-field MRI scanners, which are not commonly used in clinical settings.

The lack of standardized benchmarks for automated 3D PVS segmentation has led to inconsistent methods and findings among researchers [68]. The use of varying imaging protocols and analysis techniques has further increased this inconsistency. The detectability of PVS is also affected by technical factors including magnetic field strength and imaging resolution, which can affect image quality and clarity [71]. Moreover, distinguishing PVSs from other brain abnormalities or artifacts, such as white matter hyperintensities, lacunes or microbleeds, can be difficult, thus complicating their accurate identification on MRI scans **(Figure 3)** [54].

In summary, the identification and assessment of PVSs on MRI have substantial potential for advancing understanding of AD pathology and progression. However, to unlock the full diagnostic and prognostic potential of PVSs, a pressing need exists for both improvements in imaging technologies and agreement on standardized protocols.

3.2 Fluid dynamics of PVS

As discussed earlier, widening of the PVS may indicate an obstruction caused by protein and cellular debris, thus resulting in turbulent fluid drainage [5, 46]. Insights into PVS fluid dynamics could shed light on the microstructure and functioning of these spaces, including how brain tissue and fluids move within and around them. This knowledge could also enhance understanding of the brain's ISF circulation efficiency. PVS enlargement is associated with a multitude of pathologies and is not unique to any single disease, thus limiting its diagnostic specificity [52]. Future research should focus on specific PVS fluid dynamics and their changes in conditions such as AD. Experimental techniques including two-photon microscopy and particle tracking velocimetry, particularly in animal models, hold promise for studying PVS fluid flow in living organisms [79, 80]. However, these methods are not practical for human studies. Current research is examining MRI-based technologies with the potential to analyze the hemodynamics surrounding human blood vessels.

3.2.1 contrast-enhanced MRI. The use of dynamic contrast-enhanced MRI with gadolinium-based contrast agents (GBCAs) facilitates the study of CSF and ISF exchange, as well as the functionality of the intracerebral glymphatic system, which is crucial for waste clearance in the brain [14]. This technique involves tracking the rate of contrast agent clearance by observing changes in signal intensity within the paravascular and ventricular compartments during imaging. In research, specifically in mouse models of AD, this method has effectively demonstrated a lower clearance rate in AD-affected mice than their normal counterparts, thus

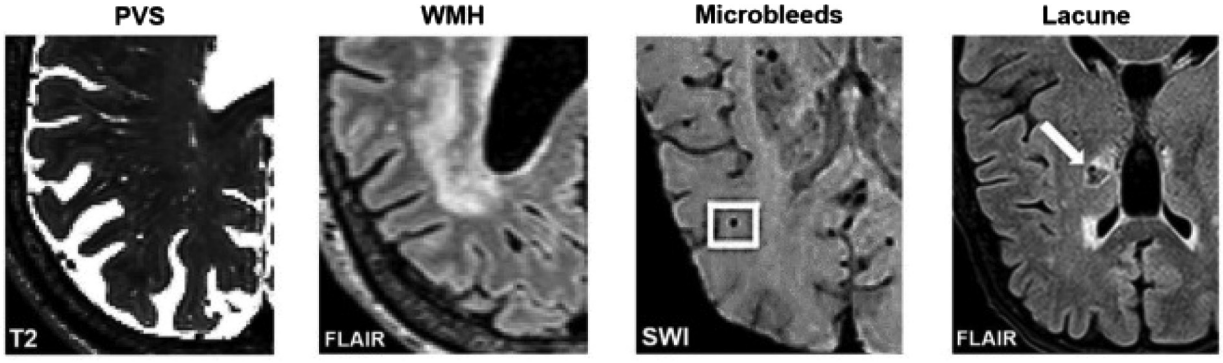

Figure 3 | Axial slices of MRI-visible brain lesions, including PVS, white matter hyperintensities, microbleeds, and lacunes. PVS appear as hyperintense and tubular shapes in T2-weighted MRI scans (left). White matter hyperintensities are prominent in FLAIR images (middle-left). Other lesions that can be confused with PVS include microbleeds (middle-right) and lacunes (right). In FLAIR scans, lacunes are surrounded by a hyperintense rim, whereas PVS are not. Imaging artifacts, such as Gibbs ringing, and motion artifacts can also hinder the automated detection of PVS. FLAIR, Fluid attenuated inversion recovery; SWI, susceptibility-weighted imaging. Reproduced under the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/) [71].

offering insights into the pathophysiological changes associated with the disease.

Indeed, using GBCAs via intrathecal injection for dynamic contrast-enhanced MRI poses substantial challenges and risks in humans. The process can be painful and time-consuming for patients; more concerningly, gadolinium may potentially be deposited within the brain tissue itself. Large-scale studies are difficult because of these associated risks, as well as the logistical complexities of performing such invasive and time-intensive procedures on many patients. Furthermore, intravenous administration of GBCAs, although less invasive, is not without risk. The need for high doses to obtain sufficient imaging detail has prompted concerns regarding the potential for harmful adverse effects, including nephrogenic systemic fibrosis in patients with pre-existing renal impairment, and the potential for gadolinium retention in the body after repeated use [81–83].

These concerns have prompted a search for safer alternatives and non-invasive imaging techniques that could provide similar insights without the risks associated with GBCA-based methods. Phase-contrast MRI, a promising non-invasive method for measuring the plane velocity of flowing fluids in individual slices, allows for the measurement of fluid flow dynamics and vascular pulsatility in the CSF and blood, and is currently used to measure the aqueducts at the level of the occipital foramen magnum. Future studies may be able to apply a similar method to directly measure the flow of fluids in the PVS [53, 84, 85].

3.2.2 Non-contrast-enhanced MRI. Diffusion MRI (dMRI), the primary technique used to image PVS fluid movement, enables the study of PVS fluid properties and microstructural changes with significant implications in pathophysiology. In the context of the ISF, dMRI can detect water molecule displacement patterns along the PVS, which have a microscopic tubular structure [43].

Diffusion tensor imaging (DTI) is a dMRI technique used to evaluate water diffusion within brain tissue, represented by ellipsoids in a tensor model. This modality provides measures including fractional anisotropy (FA) and mean diffusivity (MD) for inferring tissue microstructure. One DTI-based method is DTI analysis along the perivascular space (DTI-ALPS) [86]. The DTI-ALPS method distinguishes the diffusion characteristics of vascular structures from those of the surrounding white matter tracts by analyzing the anisotropy of water diffusion along the axes that are parallel and orthogonal to the PVS. The ALPS index, a derivative of this method, quantifies changes in diffusion parallel to the PVS, which are believed indicate the efficiency of glymphatic clearance [86, 87]. Previous DTI-ALPS studies have indicated that patients with AD have lower ALPS indices than controls [86]. The ALPS index is negatively correlated with the deposition of amyloid and tau on PET images [88, 89]. However, the ALPS index is limited to assessing glymphatic function at a specific brain area, the lateral ventricular body, because of its reliance on the arranged relationship between fibers and blood vessels in that area. This method cannot offer a comprehensive view of the glymphatic system throughout the entire brain [86]. Moreover, the index does not reflect only perivenous space diffusivity but also is modulated by the nearby white matter's microstructure [90, 91]. Consequently, the ALPS index should be interpreted with caution, and additional research is needed to fully understand its significance and utility.

DTI captures the diffusion properties of both tissue and fluid, thus hindering isolation of the diffusion effects of PVS from those caused by water molecule movement within white matter tracts adjacent to the PVS. This conflation masks the precise effects of the PVS on overall diffusion measurements [92, 93]. Previous studies have indicated that increased PVS fluid volume results in increased MD and decreased FA, potentially because of the greater diffusivity of fluid within the PVS than the white matter [94]. Therefore, using a multi-shell acquisition approach enables the diffusion signals attributable to PVS to be distinguished from those of the surrounding parenchyma, thus providing deeper insights into diffusion signal variations. Multi-shell diffusion MRI analyzes the behavior of the water diffusion signal across a range of b-values or gradient strengths, by using multi-compartment diffusion models to identify distinct diffusion profiles of individual tissue compartments [53]. Specifically, diffusion-weighted images obtained at low b-values enhance the detection of CSF dynamics and the rapid dispersion characteristic of PVS, thereby enabling multi-compartment models to precisely quantify PVS diffusion profiles [95]. For example, the difference in DTI metrics between patients with MCI and unaffected controls becomes less significant after accounting for the effect of PVS signaling scores, thus suggesting that diffusion alterations associated with cognitive decline might be more attributable to PVS changes rather than compromised integrity of cerebral white matter [96]. Furthermore, intravoxel incoherent motion imaging, which leverages data from low b-value acquisitions to model intracapillary blood and intra-parenchymal water diffusivities, includes multi-compartmental modeling. This approach enables the differentiation of diffusive signals between water and blood, and quantification of the dynamics of trace and complex CSF movements. Recently, the approach has advanced through the application of non-negative least squares for modeling intermediate diffusion volume fractions, which are believed to represent PVS expansion [97]. Additional research is required to establish the reliability of these multi-compartment models in measuring the diffusion characteristics associated with the PVS.

The multi-compartment model facilitates the evaluation of CSF-ISF exchange within the PVS in the brain parenchyma. Specifically, the neurite orientation dispersion and density imaging approach, a sophisticated

Table 1 | MRI Methods to Measure Fluid Dynamics Within the PVS.

MRI methods	PVS-related measures	Corresponds to	Indications	References
Diffusion tensor image analysis along the perivascular space (DTI-ALPS)	ALPS index	Diffusivity in the assumed direction of the PVS along the medullary veins	A significant positive correlation is observed between diffusivity along perivascular spaces, as indicated by the ALPS index and MMSE score	[86]
Multi-shell diffusion MRI	PVS signal fraction	Anisotropic diffusion within the ePVS	The PVS signal fraction is the primary feature distinguishing healthy controls from individuals with MCI	[94]
Multi-component T2-relaxometry	Cerebrospinal fluid fraction (CSFF)	Freely mobile water residing in the PVS	CSFF is positively associated with Aβ accumulation in individuals	[103]

multi-compartmental diffusion model, discriminates between diffusion signals originating from interstitial and intra-axonal water [98]. This model enables investigation of variations in water content across compartments, examination of how ePVS influences the surrounding tissue water content, and delineation of a spatial pattern of water content in relation to ePVS [99]. The specific efficacy of these dMRI metrics in the quantification of PVS is expected to be further evaluated in the future.

Notably, although more advanced diffusion MRI models have greatly enhanced the sensitivity and specificity for detecting microstructural changes within the brain, intrinsic confounding factors can affect the accuracy of diffusion measurements. For instance, diffusion signals captured at low b-values are particularly susceptible to interference from vascular pulsation and perfusion-related effects. A study using low b-value diffusion acquisitions, alongside ultra-long echo times, has revealed that diffusivity in PVS during arterial systole is as much as threefold higher than that during diastole [8]. This finding suggests that vascular pulsation affects the diffusion signal within the PVS. Multiple factors affecting the diffusion coefficient of the PVS must be considered in future dMRI studies, including blood flow, vascular pulsation, and white matter axonal arrangement in the PVS. Furthermore, previous studies were based on the assumption that the PVS fluid chamber is isotropic and the diffusivity is fixed; future studies must consider that fluid diffusion within the PVS is anisotropic and that fluid diffusivity may not be constant [94].

Multi-component T2 relaxometry is an advanced MRI technique providing quantitative assessment of the microstructural attributes of various tissue compartments [100]. By analyzing multi-echo T2-weighted MRI data, this modality can accurately measure the transverse relaxation times (T2 times) and water volume fractions of distinct cellular compartments, including parenchymal CSF, intra- and extracellular water, and myelin water. The fluid in PVS is CSF-like water, which is freely mobile and shows long MR T2 times [101, 102]. The water in the extracellular space is constrained by the extracellular matrix, and myelin water is confined in the myelin sheath, thus decreasing the MR T2 time of the water molecule. The parenchymal CSF fraction (CSFF), the component of the total T2 signal with a long T2 time that theoretically corresponds to the freely mobile water residing in the PVS, might serve as a quantitative biomarker of PVS dilation on the microscopic scale [102]. A significant association has been observed between MR T2 relaxometry-based CSFF and Aβ deposition assessed by PiB PET; therefore, CSFF may serve as a biomarker of parenchymal perivascular space [103].

Each non-contrast-enhanced MRI measurement may reflect different properties of the PVS (**Table 1**). Therefore, these MRI measurements of the fluid dynamics of the PVS must be integrated to comprehensively elucidate the mechanisms of its action in AD.

4. CONCLUSION AND PROSPECTS

Recent studies indicating that Aβ antibody immunotherapy trials promote Aβ protein clearance and slow cognitive decline during the mildly symptomatic phase of AD have provided clinical support for the pathogenic primacy of Aβ misfolding and aggregation in AD [26]. Despite these promising developments, the modest clinical efficacy observed in trials underscores the need to refine understanding of AD mechanisms and to prioritize preventive strategies [5, 26].

The role of the PVS in the pathophysiology of AD has gained increasing attention in the scientific community. Damage to the PVS can lead to accumulation of metabolic waste products, formation of Aβ plaques, aggregation of proteins, and ultimately cellular damage [5, 13, 14]. The presence of ePVS in the brain may indicate an imbalance in the brain's internal stability occurring before cognitive impairment in AD [19]. Restoring or enhancing PVS dynamics and glymphatic function might be a promising avenue to delay the onset or slow the progression of AD, but further extensive research will be necessary to advance the field from concepts to practical therapy [17, 104].

To elucidate the contribution of PVS to AD pathology, further research, including longitudinal neuroimaging studies, will be essential. Several challenges

persist, owing to the complexity and microscopic scale of the PVS. PVS visualization on MRI is contingent on the presence of fluid, because PVSs are typically identified according to their fluid-filled nature, which contrasts with the surrounding brain parenchyma. Histological examinations in patients with cerebral amyloid angiopathy have revealed that ePVS may also encompass other substances, such as fibrin/fibrinogen, extracellular matrix components, and hemosiderin deposits, thus posing additional visualization challenges [20, 105]. Furthermore, MRI studies often depict peri-arterial rather than peri-venous gaps, possibly because of the smaller size or different fluid content of the perivenous PVS. Visualizing the enlarged perivenous PVS thus remains a difficult task [106, 107]. Moreover, PVS assessments are subject to various influencing factors, including circadian rhythms, vascular pulsations, and pharmacological interventions [8, 108, 109]. The introduction of ultra-high-resolution MRI has the potential to revolutionize PVS studies by offering near-microscopic detail of their anatomy and internal fluid dynamics [22]. Such technological advancements may usher in a new era in PVS research.

Overall, a pressing need exists for more extensive research to harness the information offered by the PVS. Many prevalent assumptions require additional empirical validation. Careful investigation of each AD-related process and validation of hypotheses will enhance understanding of the disease and aid in identifying novel AD therapeutic targets.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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