Viewpoints

Beyond Pathology: Perivascular Spaces as Dynamic Players in Neurodevelopment and Brain Health

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Perivascular spaces (PVS) have historically been viewed as radiological markers of aging and cerebrovascular pathology. However, this narrow perspective overlooks accumulating evidence that PVS likely undergo dynamic, prolonged maturation across the lifespan and may play an essential role in healthy brain development. This Viewpoint article challenges the prevailing paradigm by positioning PVS not as passive anatomical structures or mere disease indicators, but as active participants in postnatal neurodevelopment whose morphology and function evolve to meet the metabolic and waste clearance demands of the maturing brain. We integrate evidence from advanced neuroimaging, developmental neuroscience, and neurobiology studies to highlight that PVS structure and fluid dynamics may be coupled with several neurodevelopmental processes, impacted by early experiences, and mature through adolescence to facilitate healthy brain development and cognitive functioning. We advocate for longitudinal, lifespan approaches to PVS research, because understanding normative PVS development is paramount for interpreting pathological changes. This developmental reframing highlights new opportunities for early identification of at-risk individuals and preventive interventions targeting the brain's waste clearance system during sensitive developmental windows.

Key words: **brain clearance system; brain development; childhood; perivascular space**

Significance Statement

The brain has fluid-filled channels known as perivascular spaces (PVS) that are part of the larger brain waste clearance system. PVS have been studied most extensively as markers of aging and neurodegenerative diseases. There is a knowledge gap regarding when, where, and how PVS pathways develop. Studies thus far indicate that PVS develop gradually across gestation and postnatal life in animal models. In humans, MRI-based evidence from childhood and adolescence points to individual differences during maturation that may predict neurocognition and brain health. A new focus is essential in PVS research to gain a detailed understanding of normal developmental mechanisms. Such information will provide a foundation for informing early detection and prevention strategies during sensitive developmental windows.

Introduction

Perivascular spaces (PVS), largely surrounded and structurally supported by astrocytes, form brain-wide passageways around small blood vessels and play an essential role in cerebrospinal fluid (CSF) circulation and the larger waste clearance system (Plog and Nedergaard, 2018; Wardlaw et al., 2020; Shulyatnikova and Hayden, 2023). Over the past decade, animal studies and human magnetic resonance imaging (MRI) research have highlighted the importance of PVS changes and their potential role in neurological health and disease (Iliff et al., 2012; Jessen et al., 2015; Xu et al., 2015; Sepehrband et al., 2019c). Yet despite clinical recognition of nonpathological PVS enlargement (Jungreis et al., 1988; Groeschel et al., 2006), systematic research has focused predominantly on pathological markers in

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neurodegeneration and age-related cognitive decline, leaving a critical gap: when and how do these clearance pathways mature? PVS appear to play a fundamental role in maintaining brain homeostasis, and thus, the developmental processes that establish their structure and function, long before aging and pathology, may be linked to brain health across the lifespan. We posit that PVS are dynamic across the lifespan, with development representing a foundational process that may shape brain health trajectories from childhood onward. As with other brain histogenic processes, identifying factors that perturb PVS maturation may help to differentiate healthy variation from early pathological changes. New data may also help to identify critical windows for intervention. This developmental perspective is essential because it reframes PVS from indicators of disease to dynamic structures potentially involved in the processes that accompany healthy brain development and maturation.

Here, we briefly review PVS anatomy and physiology and then turn to neuroimaging evidence demonstrating that PVS are present and measurable in humans across the lifespan. Next, we synthesize developmental data from animal and human studies and discuss genetic and lifestyle moderators. We then propose a developmental framework for PVS maturation as well as future directions for the field. Overall, this perspective aims to advance a view of PVS as dynamic, developmentally regulated structures with potential relevance to lifelong brain health.

PVS: Anatomy, Physiology, and the Brain Waste Clearance System

Several excellent in-depth reviews cover PVS anatomy, physiology, and their role in brain fluid dynamics (Jessen et al., 2015; Wardlaw et al., 2020; Hablitz and Nedergaard, 2021; Rasmussen et al., 2022). Here, we provide a brief overview of this foundational biology as context for the developmental framework proposed in the sections that follow. Although "Virchow-Robin spaces" has historically been used as a synonym for PVS, contemporary usage has narrowed the term to describe only the larger, macroscopic or MRI-visible PVS surrounding major arteries and veins (Ineichen et al., 2022). We therefore use the broader term "perivascular spaces" (PVS) throughout.

Anatomical structure of PVS and physiological mechanisms of fluid movement

PVS exist as fluid-filled channels, or passageways, surrounding arterioles, capillaries, and venules throughout the brain. Their precise anatomical configuration varies by location and vessel type (Bedussi et al., 2016; Wardlaw et al., 2020; Rasmussen et al., 2022). Several physiological forces contribute to fluid movement through PVS (Rasmussen et al., 2022). The arterial pulsation with each heartbeat appears particularly important; unlike in the rest of the body, where these pulses dampen quickly, the skull's rigidity helps maintain pulsations throughout the brain's blood vessels, creating a pumping action that propels fluid movement (Mestre et al., 2018b; Wardlaw et al., 2020). Breathing also contributes by creating rhythmic pressure changes that drive CSF in and out of the skull (Dreha-Kulaczewski et al., 2015; Wardlaw et al., 2020; Rasmussen et al., 2022). Notably, brain clearance activity and CSF movement are ongoing processes that are substantially enhanced during sleep (Xie et al., 2013).

Beyond the physiological forces driving perivascular fluid movement, the vasculature itself is anatomically heterogeneous across brain regions, with direct implications for how MRI-visible PVS should be interpreted. Cortical arteries supply the cerebral cortex via a dense, highly branched network confined largely to cortical layers I–VI, whereas the underlying subcortical white matter is supplied by a comparatively sparse population of medullary arteries (Duvernoy et al., 1981). The majority of cortical vessels do not extend into white matter at all, and where they do cross the gray–white matter junction, they typically bend to run parallel to the cortical surface rather than penetrating deep into the white matter (Duvernoy et al., 1981; Ringstad, 2024; Stamenkovic et al., 2025). Correspondingly, at least four anatomically distinct perivascular compartments have been described: PVS of cortical arteries (PVS_CA); of juxta-cortical arteries, which briefly penetrate into superficial white matter before bending to run parallel with the cortex (PVS_JCA); of medullary arteries, which supply the outer two-thirds of the subcortical white matter and represent the primary source of MRI-visible white matter PVS (PVS_MA); and of basal ganglia arteries (PVS_BGA; Cengija et al., 2025). Critically, PVS_MA are not thought to be in direct continuity with PVS_CA or PVS_JCA, given the sparse and largely nonoverlapping vascular supply to the white matter relative to the cortex (Cengija et al., 2025). The distinctness of these compartments is further supported by intrathecal CSF tracer kinetics: PVS_BGA, which are in direct continuity with subarachnoid CSF, enhance early and in step with subarachnoid CSF enhancement, whereas PVS_MA enhance later, more slowly, and to a lesser degree, with tracer continuing to accumulate at a time point when subarachnoid CSF has already entered its clearance phase (Cengija et al., 2025). Together, these anatomical and kinetic differences indicate that the mechanisms governing fluid movement in superficial, periarterial PVS should not be assumed to generalize to the deep, MRI-visible PVS of subcortical white matter and basal ganglia, which represent distinct anatomical and functional compartments.

The brain clearance system and role of PVS

The brain clearance system comprises a pathway spanning the entire brain enabling the flow of CSF through the brain parenchyma (Hablitz and Nedergaard, 2021; Ding et al., 2023; Shulyatnikova and Hayden, 2023). The key components of the brain clearance system include PVS and the aquaporin-4 (AQP4)-dependent trans-astrocytic water pathway (Hablitz and Nedergaard, 2021; Liu et al., 2021). The term "glymphatic system" was coined to describe the proposed brain-wide pathway for waste clearance that depends on the coordinated function of PVS and astroglial water channels (Iliff et al., 2012; Plog and Nedergaard, 2018; Rasmussen et al., 2018, 2022). Within this framework, PVS serve as fluid-filled spaces that facilitate exchange between CSF and parenchymal interstitial fluid (ISF; Fig. 1), while AQP4 channels are proposed to facilitate the movement of water and solutes between the perivascular compartment and the brain interstitium (Iliff et al., 2012; Mestre et al., 2018b).

Within this brain waste clearance system, one prevailing hypothesis is that PVS accommodate the influx of CSF into the brain parenchyma through the periarterial space and the efflux of ISF to the lymphatic system through the perivenous space (Tarasoff-Conway et al., 2015; Rasmussen et al., 2022). Through this mechanism, metabolic waste can exit the brain, drain into cervical lymph nodes, and subsequently be degraded in the liver. This removal of metabolic by-products, neurotoxicants, and other substances is essential for maintaining brain health, as buildup is thought to contribute to neuroinflammation, oxidative stress, and/or poor neural functioning (Rasmussen et al., 2018). Despite significant advances, key questions about

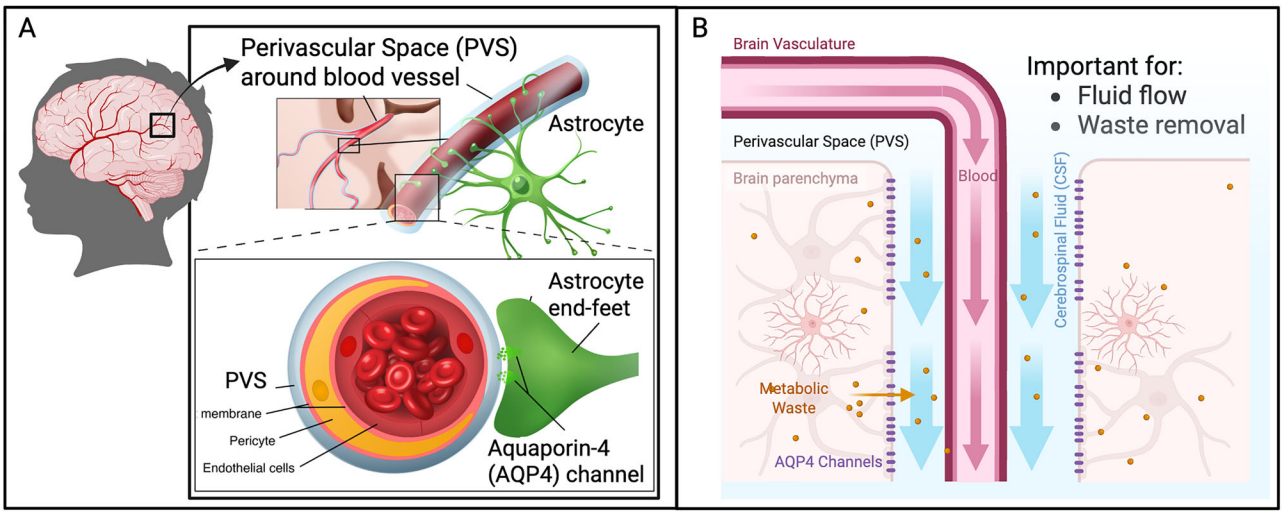


Figure 1. PVS. ***A***, Anatomical schematic representation of the location and components of the PVS unit. Arterioles entering through the base of the brain are wrapped in dual layers of leptomeninges, while those entering through the cortical surface and all venules have only a single membrane layer, potentially affecting how fluids move through these regions. Where blood vessels become very small capillaries, the membrane structure transitions to a basement membrane encased by specialized projections from astrocytes forming end feet. ***B***, The functional model of PVS, which supports fluid exchange between blood vessels and brain parenchyma through AQP4 channels on astrocyte end feet. Arrows indicate direction of fluid movement: pink, blood; blue, CSF inflow; orange, metabolic waste efflux. Figure created with BioRender.com.

brain fluid drainage remain (Wardlaw et al., 2020; Rasmussen et al., 2022). CSF entry along arterial spaces is well supported (Iliff et al., 2012; Mestre et al., 2018a), but exit routes are actively debated; candidate pathways include perivenous drainage (Tarasoff-Conway et al., 2015), arterial and capillary basement membranes (Weller et al., 2015; Albargothy et al., 2018), meningeal lymphatics (Aspelund et al., 2015; Louveau et al., 2015), and olfactory nerve-associated lymphatics (Kida et al., 1993), with their relative contributions in humans still unclear. The role of AQP4 in facilitating fluid movement is similarly unsettled, with conflicting findings that appear to depend heavily on experimental methodology (Smith et al., 2017; Mestre et al., 2018b; Rasmussen et al., 2022).

Early experimental studies by McComb and colleagues demonstrated that CSF drainage is pressure-responsive and occurs primarily via the lymphatic system, with most CSF, including macromolecules, leaving the CNS through cranial nerves, particularly the olfactory nerve, rather than the arachnoid granulations (McComb et al., 1983, 1984; Shen et al., 1985; Erlich et al., 1986, 1989; McComb and Hyman, 1990). Because perivascular and lymphatic pathways are structurally organized yet adaptable, they may be particularly sensitive to alterations in pressure gradients and tissue compliance during periods when vascular architecture, astrocytic end foot polarization, and extracellular matrix composition are still maturing, with early-life perturbations in CSF dynamics potentially influencing long-term PVS structural maturation and glymphatic function (Kahle et al., 2016; Munk et al., 2019; Garic et al., 2023).

Mechanistic debates aside, PVS have been repeatedly linked to brain structure and function. Animal studies have demonstrated direct connections between PVS function and brain tissue integrity. Research in aging mice has shown that perivascular clearance pathways become progressively altered with age, correlating with reduced waste removal efficiency (Kress et al., 2014). Experimental models of vascular dysfunction have revealed that disruption to cellular components surrounding blood vessels can lead to enlarged PVS and white matter damage. Specifically, mice deficient in pericytes [i.e., cells that help support the blood–brain barrier (BBB)] develop BBB breakdown and PVS enlargement in white matter regions, accompanied by white matter dysfunction (Wardlaw et al., 2020). Considering the high metabolic demand of neurodevelopment (Kuzawa et al., 2014), with processes such as myelination requiring efficient delivery of glucose and oxygen (Rinholm et al., 2011) and synaptic pruning generating cellular waste (Stevens et al., 2007; Paolicelli et al., 2011), efficient nutrient delivery and waste clearance through perivascular pathways may be particularly critical during development (Rasmussen et al., 2022). However, this remains an important gap in the literature, as the role of PVS function during development and the factors that impact glymphatic efficiency are largely unexplored (see Charting PVS Development Section below).

Advanced MRI Reveals PVS across the Lifespan with Links to Brain Function

For a comprehensive overview of the neuroimaging methods used to characterize PVS structure and function, we direct readers to several excellent reviews and meta-analyses (Hilal et al., 2018; Francis et al., 2019; Barisano et al., 2022; Pham et al., 2022; Okar et al., 2023).

Advanced MRI methodology

Historically, PVS dilation (i.e., enlargement) and increased count of MRI-visible PVS (i.e., burden) have been the primary methods of PVS quantification, with greater dilation and higher counts interpreted as markers of cerebrovascular disease, neurodegeneration, and other brain pathologies (Kisler et al., 2017; Wardlaw et al., 2020; Barisano et al., 2022). However, emerging evidence suggests that PVS dilation and increased visibility are not exclusively pathological (Groeschel et al., 2006), with age-related increases in MRI-visible PVS observed even in healthy aging populations (Maclullich et al., 2004; Ramirez et al., 2015; Banerjee et al., 2017; Laveskog et al., 2020; Lynch et al., 2023). As such, current efforts include mapping normative PVS structure, distribution, and fluid diffusion across the lifespan. This goal has only recently become possible with the

development of advanced MRI techniques that overcome prior limitations in imaging resolution that could not visualize most PVS, relied only on manual counting, and did not consider biophysical properties of the brain white matter (Barisano et al., 2022).

On structural MRI, PVS appear as small, linear or dot-like fluid-filled structures that follow the direction of perforating blood vessels (Fig. 2). They are hypointense on T1-weighted images and hyperintense on T2-weighted images, with signal intensity similar to CSF (Barisano et al., 2022). PVS visibility depends on magnetic field strength and spatial resolution, with recent advances in MRI providing superior detection compared with conventional field strengths (Barisano et al., 2021, 2022). The field has evolved over the past decade from simple visual rating scales, which manually score PVS burden in specific brain regions, to sophisticated automated segmentation algorithms using filter-based (Ballerini et al., 2018; Sepehrband et al., 2019c) or deep learning approaches (Boutinaud et al., 2021; Lan et al., 2023; Huang et al., 2024; Fig. 2). These computational methods can now quantify morphological features beyond counts, including PVS volume (cubic millimeters), caliber, tortuosity, and solidity, to provide multidimensional characterization of PVS (Zong et al., 2016; Boespflug et al., 2018; Barisano et al., 2022).

Furthermore, several MRI-based approaches offer functional insight into glymphatic-related fluid dynamics beyond static structural measures of PVS (Barisano et al., 2022). Gadolinium-based contrast-enhanced MRI represents the closest

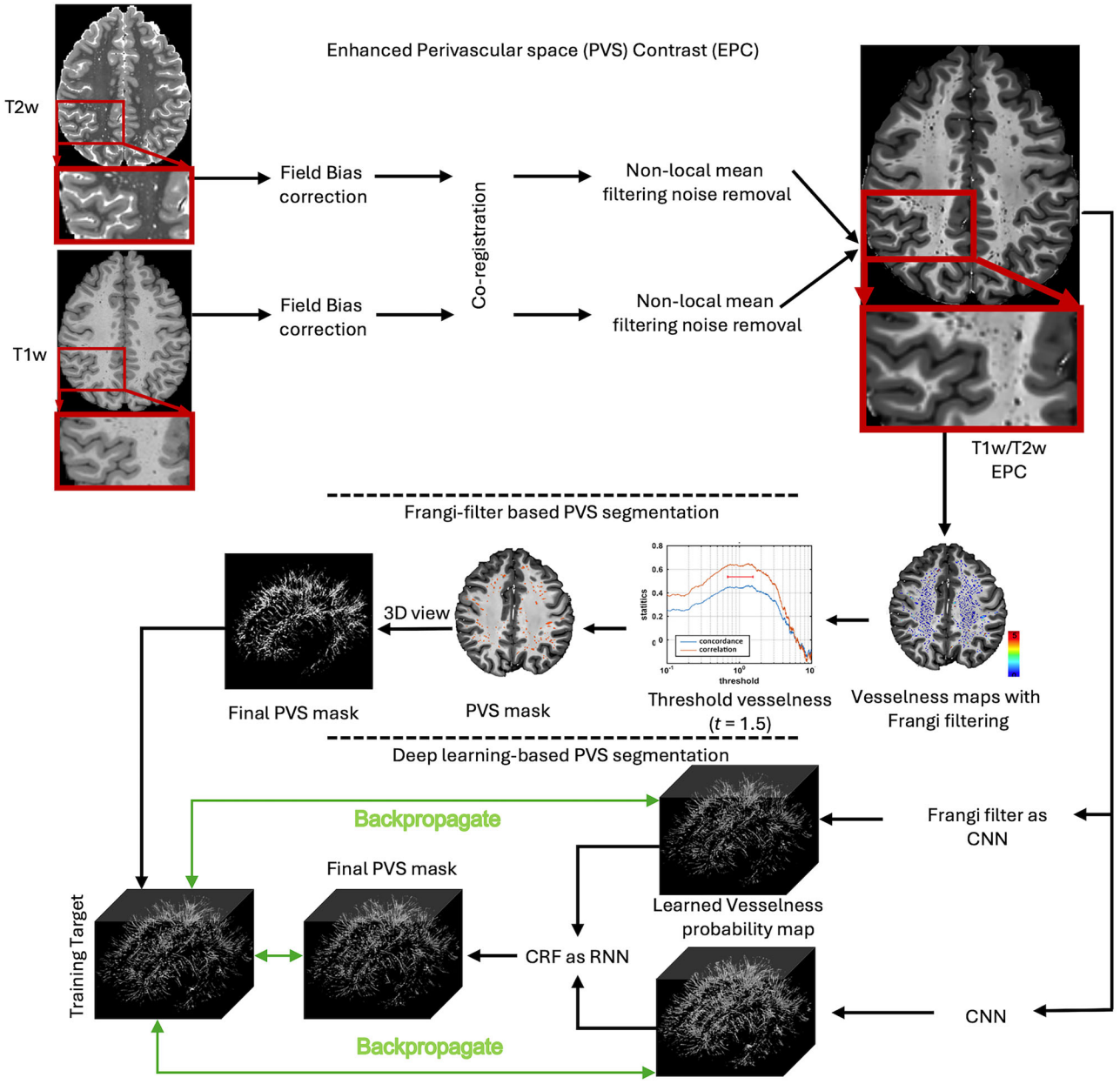


Figure 2. Workflow for PVS segmentation. Top, Enhanced PVS contrast (EPC) is generated by combining T1-weighted (T1w) and T2-weighted (T2w) images following preprocessing. The voxel-wise T1w/T2w ratio enhances the visibility of small tubular PVS structures (Sepehrband et al., 2019c). Middle, Frangi vesselness filtering is applied to EPC images to produce vesselness probability maps, and an optimal threshold is determined based on concordance with expert readings to generate PVS masks (Sepehrband et al., 2019c). Bottom, An example deep learning–based PVS segmentation where EPC images and Frangi-based PVS masks are used to train a convolutional neural network for improved PVS detection.

approach to a direct, gold-standard measure of glymphatic CSF–ISF exchange and solute clearance, tracking contrast agent distribution through CSF and brain tissue over several hours (Barisano et al., 2022). However, this approach requires lumbar puncture and off-label intrathecal contrast administration, and its use has so far been limited to specific patient populations, such as patients with idiopathic normal pressure hydrocephalus, restricting its broader applicability as a routine research tool in healthy and developing populations. As a result, several noninvasive alternatives have been developed using more widely applicable diffusion MRI sequences.

Diffusion tensor image analysis along the PVS (DTI-ALPS) compares water diffusivity along PVS to diffusivity along adjacent white matter fiber tracts, with lower ratios commonly interpreted as reflecting impaired glymphatic clearance (Taoka et al., 2017). However, DTI-ALPS cannot fully disentangle the diffusion contribution of the PVS from that of the surrounding white matter tracts running parallel to it, and because it relies on a mono-exponential model, it reflects the diffusion properties of both tissue and fluid together, limiting its specificity as a glymphatic marker (Barisano et al., 2022; Taoka et al., 2024; Mossige et al., 2026). Multicompartment diffusion modeling, including tissue tensor imaging (TTI), addresses this limitation by acquiring data across multiple b values to separate the fast, CSF-like diffusion signal of PVS fluid from the slower, hindered diffusion of surrounding tissue, yielding PVS-specific fractional anisotropy (fFA) and mean diffusivity (fMD) estimates (Sepehrband et al., 2019a; Barisano et al., 2022). A recently proposed technique using ultrahigh-field 7T MRI measures CSF mobility within the PVS surrounding penetrating vessels, an approach inspired by the long echo-time diffusion tensor imaging (DTI) method (Hirschler et al., 2025). In this technique, the CSF signal is isolated by suppressing signal from blood and brain tissue. Specifically, by adding motion-sensitizing gradients, the method measures CSF mobility in six directions and uses these measurements to calculate fractional anisotropy (FA) and the principal direction of CSF movement (Hirschler et al., 2025). However, this technique has not yet been tested in children or adolescents.

These advanced, noninvasive structural and diffusion MRI techniques have been successfully applied to cross-sectional samples to characterize PVS across childhood, adolescence, and young adulthood (Lynch et al., 2023, 2025; Yamamoto et al., 2025), normal aging (Barisano et al., 2021; Shih et al., 2023), and neurodegenerative diseases (Sepehrband et al., 2019b). Importantly, these semiautomated methods have identified substantially more PVS (over 100 per brain region) than prior visual rating studies, which identified fewer than five in the same regions (Hilal et al., 2018), providing unprecedented granularity for understanding PVS morphology and distribution (Zong et al., 2020; Barisano et al., 2021; Lynch et al., 2023). Substantial intersubject variability is observed even in healthy populations, with some 8-year-olds exhibiting MRI-visible PVS counts and volumes comparable to those of 90-year-olds (Lynch et al., 2023). These emergent lifespan findings highlight that PVS variations have been insufficiently characterized outside of aging and pathological contexts, underscoring the need for establishing a systematic developmental framework.

PVS and brain function

The number and visibility of PVS have been associated with dysfunction of brain clearance activity (Ringstad et al., 2018; Wardlaw et al., 2020; Barisano et al., 2022). As such, the theoretical framework in aging/neurological diseases is that enlarged PVS reflect impaired waste removal, neuroinflammation, and accumulation of waste aggregates, ultimately contributing to impaired neural functioning (Berezuk et al., 2015; Ramirez et al., 2015; Banerjee et al., 2017). This hypothesis is supported by some studies reporting an association of enlarged PVS with lower cognitive performance in otherwise healthy aged individuals, as well as cognitive decline, mental health problems, and neurodegenerative disorders (Ferguson et al., 2003; Maclullich et al., 2004; Chen et al., 2011, 2024; Ramirez et al., 2015; Ding et al., 2017; Francis et al., 2019; Passiak et al., 2019; Vilor-Tejedor et al., 2021; Barisano et al., 2022; Li et al., 2022; Wang et al., 2022; Garic et al., 2023), albeit with mixed evidence (Hilal et al., 2018; Libecap et al., 2022). These studies are primarily cross-sectional, limiting the ability to account for substantial intersubject variability in PVS volume across ages (Lynch et al., 2023).

Conditions such as hydrocephalus illustrate the consequences of disrupted CSF, ISF, and intracellular fluid exchange, underscoring the importance of perivascular pathways in maintaining homeostatic brain fluid dynamics (Oreskovic et al., 2017; Rasmussen et al., 2018). Alterations in PVS may reflect changes in CSF circulation, intracranial pressure gradients, arterial pulsatility, and glymphatic transport (Tullberg et al., 2002; Oreskovic et al., 2017; Ringstad et al., 2018; Eide and Ringstad, 2019). Although PVS enlargement is commonly observed across pathological states, the underlying mechanisms likely vary and may include mechanical distortion from ventricular expansion, impaired pulsatility-driven periarterial inflow, obstruction of perivenous outflow due to blood or inflammation, altered CSF absorption, or parenchymal atrophy (Tullberg et al., 2002; Del Bigio, 2010; Iliff et al., 2013; Oreskovic et al., 2017; Ringstad et al., 2018). Together, these processes illustrate how disturbances in global CSF dynamics may translate into regionally specific PVS remodeling (Rasmussen et al., 2018).

Charting PVS Development

Childhood and adolescence represent a critical period of brain development characterized by dendritic arborization, synaptic pruning, and myelination (Goldman-Rakic, 1987; Benes, 1989; Huttenlocher, 1990; LaMantia and Rakic, 1990; Huttenlocher and Dabholkar, 1997). The developing brain is highly metabolically active (Kuzawa et al., 2014), particularly during periods of rapid synapse formation, reorganization, and myelination (Huttenlocher and Dabholkar, 1997; Chugani, 1998), generating substantial metabolic by-products that must be efficiently cleared to maintain optimal neural function. Building on prior reviews of glymphatic and brain fluid system development (Fame and Lehtinen, 2020; Rasmussen et al., 2022; Li et al., 2023), here we synthesize animal, molecular, and human neuroimaging evidence into a unified developmental timeline (Fig. 3). As we describe below, the temporally staged development of PVS suggests that the capacity for efficient waste clearance emerges gradually and regionally across prenatal and postnatal periods. We hypothesize that PVS continue to develop alongside energy-intensive cellular, molecular, and system-level maturational processes during childhood and adolescence. In this section, we use "PVS maturation" to refer to this coordinated set of changes in morphology, fluid dynamics, and cellular support mechanisms (e.g., AQP4 expression, astrocyte end feet) that together determine brain waste clearance capacity. This is a working definition rather than an established consensus, as detailed below in the Synthesis and Future Directions Section.

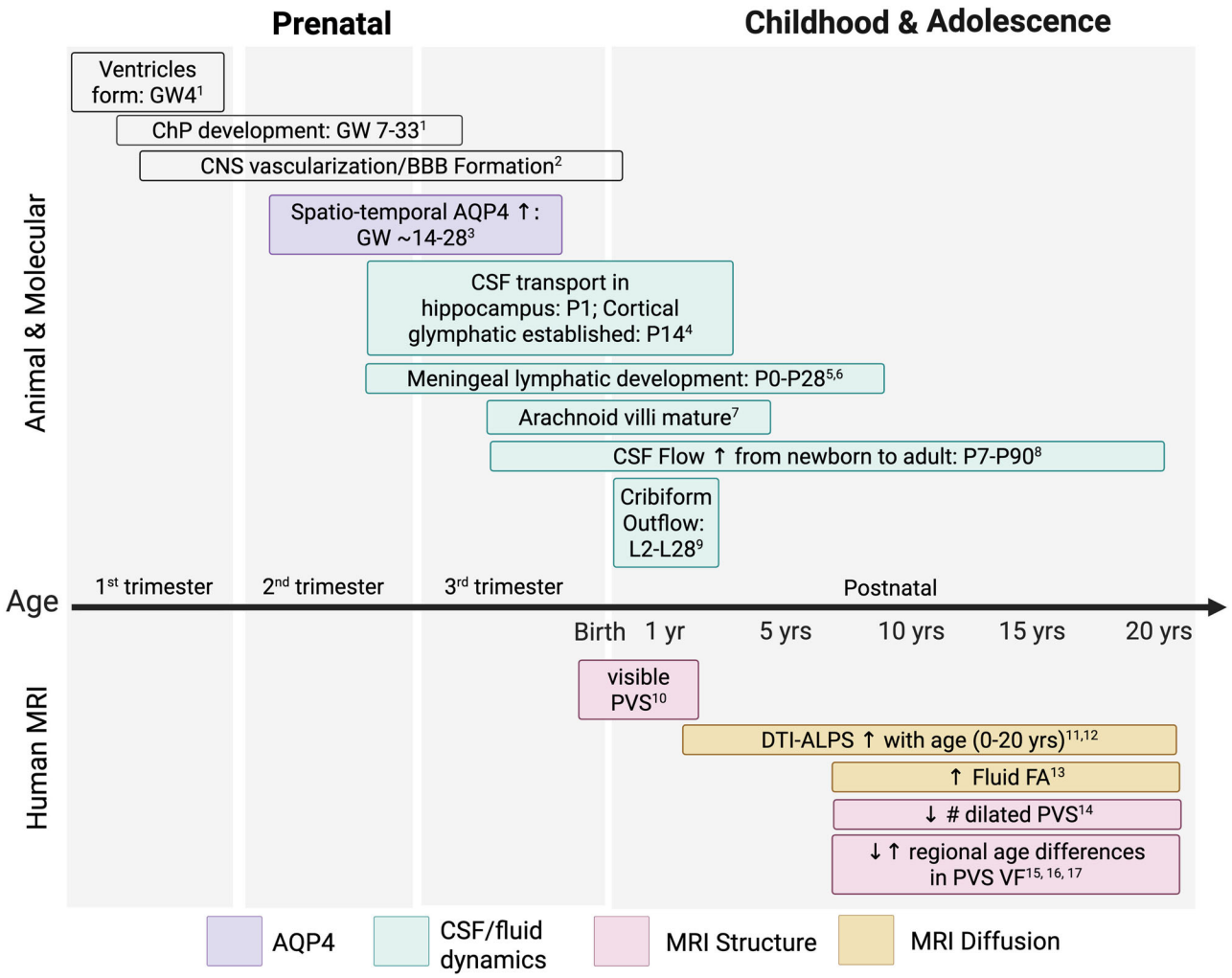


Figure 3. Developmental timeline of glymphatic system maturation. Visual schematic of a developmental timeline that integrates animal and molecular findings (above age axis) with human MRI findings (below age axis). The upper milestones are based on human gestational weeks (GW), early rodent postnatal days (P), or neonatal ages in lambs (L). The lower *x*-axis reflects age in years for human MRI studies. Color coding: purple, AQP4 expression and molecular development; teal, CSF and fluid dynamics; pink, human MRI-based PVS morphology; orange, human diffusion MRI. ↑, increase; ↓, decrease; AQP4, aquaporin-4 channel; BBB, blood–brain barrier; ChP, choroid plexus; CNS, central nervous system; CSF, cerebrospinal fluid; DTI-ALPS, diffusion tensor image analysis along the perivascular space; FA, fractional anisotropy; PVS, perivascular space; VF, volume fraction. Citations: [1] Fame and Lehtinen, 2020; [2] Boutom et al., 2024; [3] Castaneyra-Ruiz et al., 2022; [4] Munk et al., 2019; [5] Antila et al., 2017; [6] Tavares et al., 2026; [7] Gomez et al., 1982; [8] Di Palma et al., 2018; [9] Papaiconomou et al., 2002 & Papaiconomou et al., 2004; [10] Kim et al., 2023b; [11] Wong et al., 2025; [12] Huang et al., 2025; [13] Lynch et al., 2025; [14] Kim et al., 2023a; [15] Piantino et al., 2020; [16] Lynch et al., 2023; [17] Yamamoto et al., 2025. Figure created with BioRender.com.

Anatomical and functional development of the glymphatic pathway

The anatomical components of the waste clearance and brain fluid systems mature according to a specific developmental timeline (Fig. 3); readers are referred to Fame and Lehtinen (2020) and Rasmussen et al. (2022) for comprehensive reviews of this sequence. Brain ventricles form at ~4 gestational weeks (Fame and Lehtinen, 2020), while choroid plexus development begins at the seventh gestational week and continues for ~33 weeks (Lun et al., 2015). Around the eighth gestational week, the perineural vascular plexus covering the surface of the neural tube sends out branches that penetrate the brain parenchyma and start to form an intrinsic vascular plexus (Zhao et al., 2015). These vessels grow into the nervous tissue within a funnel defined by basement membrane and external glial end feet, which will form future PVS (Rasmussen et al., 2022; Boutom et al., 2024). During this same angiogenic process, pericytes are recruited to this developing vascular plexus via platelet-derived growth factor B (PDGF-B) signaling from endothelial cells, positioning them along the vessel wall from an early stage to later mediate the end feet's polarized AQP4 expression (Rasmussen et al., 2022).

Systematic mapping of AQP4 expression in the human fetal brain reveals a corresponding spatiotemporal gradient during the second and third trimesters. Expression is first detected in the ventricular zone of the future archicortex, with dorsal hippocampal expression emerging at ~13 postconceptional weeks (~14–15 gestational weeks) and progressing in a medial-to-lateral and archicortex-to-neocortex direction thereafter (Gomori et al., 2006; Castaneyra-Ruiz et al., 2022). Critically, the polarized perivascular configuration at astrocyte end feet that underlies functional glymphatic activity is not established until ~25 postconceptional weeks (~27–28 gestational weeks; Castaneyra-Ruiz et al., 2022). This expression pattern has been hypothesized to reflect a broader developmental program for cortical functional maturation, with the archicortex (the more primitive cortex) acquiring functional capacity earliest in gestation, while the frontal and occipital poles, among the last regions to mature structurally and functionally, acquire it latest (Castaneyra-Ruiz et al., 2022). Complementary preclinical evidence further illustrates a relatively protracted developmental trajectory with structural scaffolding preceding its functional maturation. In mice, AQP4 expression

has been detected in radial glial cell processes early in gestation, progressing from ventral to lateral and dorsal areas of the forebrain, and with AQP4 restricted to astroglial end feet by the early postnatal period (Fallier-Becker et al., 2014).

The earliest sign of PVS CSF transport occurs by embryonic day 17.5 in mice (~24–28 gestational weeks in humans) at the circle of Willis, followed by regional differences in the emergence of CSF transport postnatally (Munk et al., 2019). Specifically, CSF transport first emerges in the hippocampus in newborn mice, developing in a ventral-to-dorsal direction, and reaching functional cortical maturation by postnatal day 14 (approximately infancy in humans; Munk et al., 2019). Using a genetic knockout model for PDGF-B, this same study also established that glymphatic function depends on the formation of both astrocytic end feet coverage of blood vessels and proper polarization of AQP4 expression, with PDGF-B loss eliminating AQP4 polarization likely via reduced pericyte recruitment rather than a direct effect on end feet formation (Munk et al., 2019). Rodent MRI using DOTA-gadolinium tracer imaging has also found that CSF tracer penetration increases in the forebrain following the first postnatal week, throughout adolescence and into adulthood (Di Palma et al., 2018).

Developmental data on perivenous drainage of ISF from the parenchyma remain comparatively sparse. Of the candidate routes for CSF efflux from the subarachnoid space, arachnoid villi mature structurally between ~35 and 39 gestational weeks in humans, increasing in number and complexity with development (Gomez et al., 1982). Similarly, lateral lacunae paralleling the superior sagittal sinus are structurally detectable in the human fetus (Rasmussen et al., 2022). Yet the functional capacity of both structures to support CSF egress during development remains unconfirmed. Olfactory nerve-associated lymphatic outflow, in contrast, has been documented in neonatal lambs. Surgically sealing the cribriform plate significantly impaired CSF absorption, demonstrating the essential role of olfactory nerve-associated lymphatic transport at a stage when arachnoid projections remain poorly formed (Papaiconomou et al., 2002, 2004). Meningeal lymphatic vessels, also thought to be an important route for CSF efflux, sprout just before birth and continue maturing through the first postnatal month in mice (Antila et al., 2017), with refinement of the meningeal lymphatic network continuing through adolescence (Tavares et al., 2026).

Therefore, disruption to this early system development is likely consequential. For example, glymphatic drainage is impaired by the second postnatal week in a rat genetic model of hydrocephalus caused by ciliary dysfunction (Emmert et al., 2019). Early-life stress in rodents has also been found to produce abnormal glymphatic organization and disrupted AQP4 polarization that persist into adulthood, correlated with significantly reduced expression of genes regulating AQP4 polarization (Song et al., 2024). Moreover, a recent study demonstrated a marked defect in meningeal lymphatic development in the BTBR mouse model of autism spectrum disorder, in which impaired refinement of perisinusal lymphatic sprouts left an excess, immature meningeal lymphatic network into adolescence (Tavares et al., 2026).

Developmental patterns of MRI-PVS morphology and fluid diffusion

Emergent findings by our team and others suggest that PVS maturation extends into late adolescence and early adulthood (Piantino et al., 2020; Kim et al., 2023a,b; Lynch et al., 2023; Yamamoto et al., 2025; Fig. 3). While PVS are visible on MRI in neonates and infants (Garic et al., 2023; Kim et al., 2023b), both PVS morphology and fluid diffusion properties continue to mature into young adulthood, with substantial individual variability throughout this trajectory (Lynch et al., 2023, 2025; Huang et al., 2025; Wong et al., 2025; Yamamoto et al., 2025; Morrel et al., 2026). Analysis of the Human Connectome Project-Development (HCP-D) sample (ages 8–21) identified regionally dependent patterns of PVS count and volume fraction (VF) across development (Lynch et al., 2023). For instance, regions with large PVS VF at age 8 (such as basal ganglia) showed minimal age-related differences, while regions with lower baseline PVS VF (frontal, temporal, and lateral occipital cortex) demonstrated significant increases with age, suggesting region-specific trajectories that may reflect local metabolic demands and myelination patterns (Lynch et al., 2023). A subsequent longitudinal study in 12–21-year-olds revealed increasing white matter PVS volume but decreasing basal ganglia PVS volume into young adulthood (Yamamoto et al., 2025).

Moving beyond morphology, novel multicompartment diffusion biophysical modeling sensitized to bulk fluid flow demonstrated that free water fluid fractional anisotropy (fFA) surrounding brain parenchyma was positively associated with age from 8 to 21 years (Lynch et al., 2025). While perivascular free water measures were strongly correlated with PVS diameter, age remained a significant predictor of these fluid metrics even after accounting for diameter, suggesting that age-related change in PVS fluid dynamics is not fully explained by morphological enlargement alone (Lynch et al., 2025). Complementary evidence from DTI-ALPS assessment in 72 typically developing children (ages 0–19.8 years) demonstrated significant positive correlations between age and bilateral ALPS indices (Wong et al., 2025). Notably, longitudinal data demonstrate that the ALPS index follows divergent trajectories across the lifespan: increasing over ~2 years in children (ABCD Study; mean baseline age ~10 years) but declining over a similar follow-up period in middle-aged and older adults (UK Biobank; mean baseline age ~62 years), reinforcing the concept of progressive maturation during development before a reversal in later life (Huang et al., 2025). As previously noted, however, DTI-ALPS reflects diffusion anisotropy in perivascular regions rather than direct measurement of fluid flow, and its validity as a specific index of glymphatic function remains debated (Ringstad, 2024; Taoka et al., 2024; Mossige et al., 2026). Findings should therefore be interpreted as suggestive of age-related changes in white matter tissue properties, including PVS, rather than confirmed glymphatic activity.

These developmental patterns can be situated within broader lifespan trajectories. Across three complementary studies using HCP lifespan data (ages 8–100 years), dilated PVS ratings and volume showed a biphasic trajectory, declining through the mid-30s before rising again in aging (Kim et al., 2023a), while PVS VF and free water FA increased during development but diverged in aging (Lynch et al., 2023, 2025). These studies illustrate that the same MRI measures likely capture fundamentally different biological meaning across the lifespan (Fig. 4), underscoring the need for age-specific reference ranges rather than a single normative benchmark applied uniformly from childhood through late life. Importantly, Figure 4 draws on three HCP lifespan cohorts beginning at age 8. Although PVS are already MRI-visible in neonates and infants (Garic et al., 2023; Kim et al., 2023b), and human postmortem, rodent postnatal, and other MRI evidence suggest that PVS-related maturation may begin as early as the prenatal period (see sections above; Fig. 3), continuous lifespan MRI data linking this early evidence to the developmental trajectories plotted in Figure 4 remain

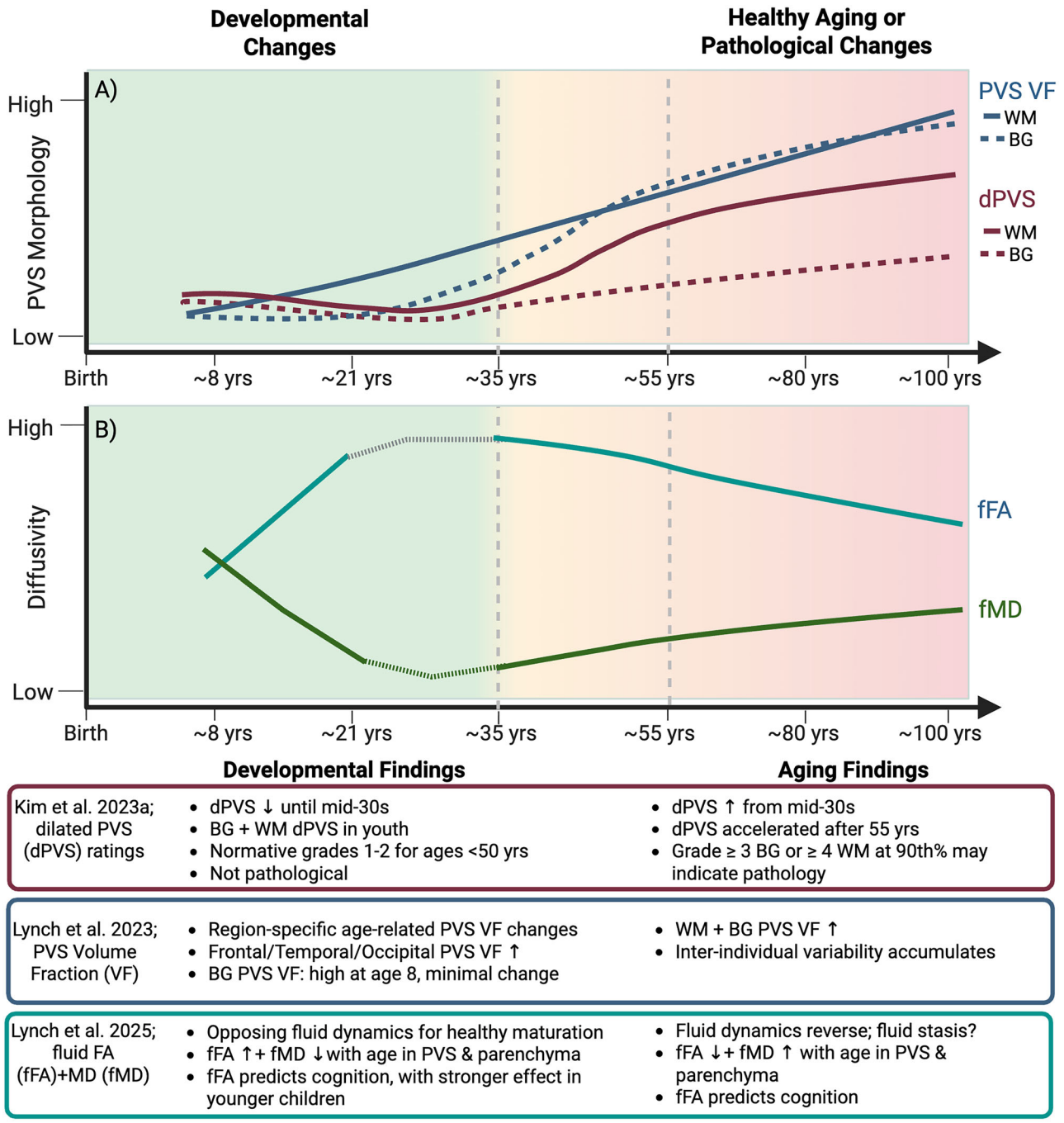


Figure 4. Age-related differences in PVS metrics across the lifespan derived from three studies using Human Connectome Project (HCP) datasets. The top panel depicts a schematic of PVS metrics for (***A***) morphology [i.e., diameter, counts, or volume fraction (VF)] and (***B***) diffusivity as a function of age, spanning ages 8 to ~100 years. The green zone indicates a period of adaptive developmental change; the transitional zone (~35–55 years) is shaded in yellow; and the red zone indicates a period where PVS changes may reflect healthy aging or emerging pathology. Dashed vertical lines denote inflection points at ~35 and ~55 years based on Kim et al. (2023a). The bottom panel summarizes empirical findings from each study, organized by developmental (left) and aging (right) interpretations. Kim et al. (2023a; red) and Lynch et al. (2023; blue) both drew on all three HCP lifespan cohorts—Development (HCP-D; ages 8–21 years), Young Adult (HCP-YA; ages 22–35 years), and Aging (HCP-A; ages 36–100 years)—providing continuous lifespan coverage. Kim et al. (2023a) quantified dilated PVS (dPVS) volume using visual grading and volumetry across BG and WM regions, while Lynch et al. (2023) characterized PVS VF across WM, cortical, and BG regions. Lynch et al. (2025; green) applied multicompartment diffusion models (i.e., TTI) to quantify fFA and fMD within automatically segmented PVS and surrounding parenchyma, using HCP-D ($n = 468$; ages 8–21 years) and HCP-A ($n = 507$; ages 35–90 years). dPVS, dilated PVS; fFA, fluid fractional anisotropy; fMD, fluid mean diffusivity; BG, basal ganglia; PVS, perivascular space; WM, white matter; VF, volume fraction. Figure created with BioRender.com.

incomplete prior to age 8 (see Synthesis and Future Directions Section below).

PVS development and brain function

The relationship between PVS and brain function likely differs fundamentally between development and aging or disease. While enlarged PVS in older adults are typically interpreted as reflecting impaired clearance and pathology, developmental changes in PVS may instead represent enhanced clearance capacity necessary to support the substantial metabolic demands of synaptic reorganization, myelination, and neural circuit refinement (Huttenlocher and Dabholkar, 1997; Stevens et al., 2007; Paolicelli et al., 2011; Rinholm et al., 2011; Kuzawa et al., 2014; Di Palma et al., 2018; Munk et al., 2019). However, whether

PVS enlargement itself is a reliable marker of this adaptive capacity or whether specific metrics of PVS structure and fluid dynamics diverge in what they capture remains unresolved (see Synthesis and Future Directions Section below). This distinction is essential for interpreting pediatric neuroimaging findings, and the magnitude and direction of associations between PVS characteristics and brain functioning likely vary by age, metric, and overall brain health. In aging, PVS enlargement has been attributed to reduced perivascular pulsatility (Kress et al., 2014; Mestre et al., 2018a), BBB breakdown, neuroinflammation, and/or accumulation of perivascular deposits that impede fluid drainage (Tarasoff-Conway et al., 2015; Weller et al., 2015; Wardlaw et al., 2020). In development, in contrast, enlargement may reflect active remodeling of the perivascular compartment to accommodate increasing metabolic demands (Huttenlocher and Dabholkar, 1997; Kuzawa et al., 2014) and expanding CSF production relative to drainage capacity during maturation (Lun et al., 2015; Fame and Lehtinen, 2020). We speculate that the relationship between PVS enlargement and brain health may follow an inverted *U*-shape across the lifespan. That is, a degree of enlargement may be necessary and adaptive to accommodate developmental metabolic demand and increased parenchymal growth, while enlargement beyond this adaptive range, whether reached prematurely in development or persistently in aging, may instead signal impaired clearance, like the potential pathological enlargement observed later in life. These distinct candidate mechanisms and the possibility of a shared nonlinear relationship between magnitude of enlargement and function across ages remain to be tested directly (see Synthesis and Future Directions Section below).

The relationship between MRI-visible PVS and cognitive functioning during human development remains an important open question. Preliminary findings from the HCP-D dataset showed no main effect of free water FA (fFA) in either the parenchyma or PVS on overall cognitive performance on the NIH Toolbox (Lynch et al., 2025). Instead, age moderated this relationship, with fFA showing a stronger positive association with total cognition in younger children than in older adolescents (Lynch et al., 2025). In the Adolescent Brain Cognitive Development (ABCD) Study, higher PVS count was similarly associated with poorer cognitive performance across several cognitive domains, with associations varying by brain region at ages 9–10 years (Morrel et al., 2026). These findings may indicate that PVS structure and fluid dynamics relate meaningfully to cognition during this late childhood and early adolescent developmental window. The regional specificity of the ABCD count–cognition associations further suggests these relationships may not be uniform across the brain, echoing the region-dependent developmental trajectories described above for PVS morphology (Lynch et al., 2023).

When development is perturbed, however, PVS alterations may take on a different character. Alterations in PVS and brain clearance are noted across several neurodevelopmental disorders (Bruna et al., 2009), including developmental delay (Rollins et al., 1993), autism spectrum disorder (ASD; Taber et al., 2004; Li et al., 2022; Garic et al., 2023), and attention-deficit/hyperactivity disorder (Vilor-Tejedor et al., 2019; Chen et al., 2024). A recent study implementing advanced PVS mapping across 72 brain regions in children with ASD (ages 1–9 years) revealed that enlarged PVS in the bilateral rostral middle frontal white matter—key components of the dorsolateral prefrontal cortex—were associated with overall clinical severity as well as specific symptoms including verbal dysfunction, stereotypies, and hypersensoriality, suggesting this prefrontal region as a critical convergence point for glymphatic dysfunction in ASD (Sotgiu et al., 2025). Moreover, different ASD symptoms demonstrated distinct spatial patterns of PVS localization, with severe language impairment associated with left pallidum enlarged PVS, motor stereotypies with left insular enlarged PVS, and sensory overload with right basal ganglia enlarged PVS, indicating that symptom-specific neural circuit dysfunction may be reflected in regionally specific glymphatic alterations (Sotgiu et al., 2025). Emerging evidence also reveals an association between glymphatic alterations and potential adolescent-onset mental health problems, including depression, schizophrenia, and substance use. Animal models of depressive-like behavior, including chronic unpredictable mild stress paradigms, show decreased glymphatic influx alongside altered astrocytic AQP4 expression and polarization (Xia et al., 2017; Lyu et al., 2025). In humans, structural PVS alterations have also been associated with adult major depressive disorder (MDD), with total PVS volume correlating with psychological trauma exposure in patients with major depression (Ranti et al., 2022) and, in a separate young adult sample, with the severity of depression and anxiety symptoms (Li et al., 2025). A recent meta-analysis also found reduced DTI-ALPS in adult patients with major depression relative to controls, correlating with symptom severity (Zhang et al., 2026). Findings in adolescents, however, are inconsistent: one study found an elevated DTI-ALPS index in adolescents with MDD with suicidality (Jiang et al., 2026), while another found no difference (Zhang et al., 2025), underscoring how little is currently understood about glymphatic–psychiatric relations during this developmental period. Adults with schizophrenia have also been found to show reduced DTI-ALPS relative to healthy controls, and this reduction is associated with poorer cognitive performance (Wu et al., 2025a). Glymphatic fluid changes have similarly been observed following both acute and chronic alcohol consumption in mouse models (Lundgaard et al., 2018; Liu et al., 2020), and altered DTI-ALPS indices have been reported in adult alcohol use disorder, associated with cognitive impairment (Dai et al., 2024). Notably, unlike MDD, no structural PVS evidence currently exists for schizophrenia or alcohol use disorder, and much of the human data across all three conditions relies on DTI-ALPS, which has limitations as a glymphatic marker, as noted previously (see Advanced MRI methodology Section above). Whether and how aberrant PVS maturation itself contributes to the emergence of these conditions during adolescence remains largely unexplored (see Synthesis and Future Directions Section below).

Biological Characteristics, Genetic Architecture, and Modifiable Lifestyle Factors

The influence of biological characteristics, genetic variants, and lifestyle factors on PVS likely varies across the lifespan, as gene–environment interactions may operate differently during periods of active brain development versus periods of maintenance and decline. During childhood and adolescence, when PVS networks are forming and glymphatic pathways are being established, these factors may interact to shape the developing clearance system, whereas in aging they may primarily modulate the rate of functional decline. Understanding these developmental differences is critical: genetic risk variants may confer vulnerability specifically during sensitive periods when environmental exposures, such as poor sleep, low physical activity, or metabolic dysregulation, could have particularly consequential effects on establishing healthy glymphatic function.

Biological sex and body composition

Among the most consistent modulators of PVS during childhood and adolescence are biological sex and body mass index (BMI). Robust sex differences, with males showing greater PVS count, volume, or VF than females, have been repeatedly observed across multiple independent pediatric and lifespan studies (Piantino et al., 2020; Kim et al., 2023a; Lynch et al., 2023; Yamamoto et al., 2025). The mechanisms underlying these sex differences (e.g., metabolic, vascular, hormonal) remain unknown and warrant dedicated investigation. Beyond sex, BMI shows consistent associations with PVS characteristics across multiple pediatric samples (Piantino et al., 2020; Kim et al., 2023a; Lynch et al., 2023; Yamamoto et al., 2025), suggesting metabolic and systemic physiological factors likely influence brain waste clearance pathways even in youth. The mechanisms underlying BMI–PVS associations remain unclear but may involve inflammatory processes, altered cerebrovascular function, or changes in CSF dynamics related to body composition—pathways that appear to operate across the lifespan, given parallel BMI–PVS associations in adult populations (Barisano et al., 2021; Shih et al., 2023; Sun et al., 2024). Understanding these sources of variability will be essential for distinguishing pathological PVS structure and dysfunction from normal developmental variation in pediatric populations.

Genetics

The number of MRI-visible PVS is heritable (Duperron et al., 2018; Choi et al., 2020; Barisano et al., 2021), and recent work suggests that genetic variation in genes expressed in astrocytic end feet—which support the outer wall of PVS—may be particularly important (Wardlaw et al., 2020). At the molecular level, the *AQP4* gene, which encodes the astrocytic water channel essential for perivascular CSF flow into the interstitial space, is a key regulator of glymphatic function (Nagelhus and Ottersen, 2013; Mestre et al., 2018a,b). Single-nucleotide polymorphisms (SNPs) in AQP4 have been associated with up to a 20% reduction in expression (Woo et al., 2018) and associations with altered brain–CSF homeostasis (Sorani et al., 2008). Beyond CSF transport, AQP4 is also implicated in neural excitation, synaptic plasticity, neuroinflammation, and BBB permeability (Jazaeri et al., 2023), and AQP4 polarization and genetic variants have been linked to cognitive performance and brain plasticity in humans (Burfeind et al., 2017; Zeppenfeld et al., 2017; Woo et al., 2018; Chandra et al., 2021).

Building on this molecular foundation, the functional aspects of brain clearance also demonstrate substantial heritability at the population level. A broader network of genes is associated with both PVS morphology and glymphatic function. Three recent genome-wide association studies (GWAS) of the ALPS index in the UK Biobank have converged on a consistent genetic architecture, identifying 6–25 significant loci despite methodological differences (Huang et al., 2025; Ran et al., 2025; Wu et al., 2025b). SNP-based heritability estimates ranged from 28.4 to 32.5% in the largest study [$N > 31{,}000$ (Huang et al., 2025)], and Mendelian randomization analyses suggested that genetically determined lower ALPS is a causal risk factor for Alzheimer's disease and multiple sclerosis (Wu et al., 2025b). A cross-ancestry GWAS of PVS burden ($N = 40{,}095$) identified 22 SNPs, several of which were validated in an independent sample of healthy young adults ($N = 1{,}748$, mean age ~22 years; Duperron et al., 2023). Notably, some identified genetic variants map to genes expressed in fetal brain endothelial cells (e.g., PNPT1) or lie near genes encoding proteins highly expressed in human astrocytes, such as the Na^+/dicarboxylate cotransporter-3 (SLC13A3) and glial fibrillary acidic protein (GFAP) (Duperron et al., 2023), suggesting functional implications for BBB transport and astrocyte structural integrity and pointing to developmental origins of PVS differences (Seifert et al., 2006; Vasile et al., 2017). Complementing this, cell-type enrichment analysis of the ALPS index GWAS identified 17 genome-wide significant loci and 161 candidate genes—disproportionately expressed in oligodendrocyte progenitor cells, oligodendrocytes, and astrocytes—associated with glial cell development, neurogenesis, and anatomical structure development (Huang et al., 2025). Critically, examining these variants across younger cohorts (ABCD Study, $N = 4{,}307$, mean age 9.9 years; IMAGEN, $N = 1{,}589$, mean age 14.0 years; HCP, $N = 219$, mean age 28.9 years) revealed that some loci show age-independent effects consistent from childhood through older adulthood, while others show age-dependent effects concentrated in aging and neurodegeneration (Huang et al., 2025). This distinction suggests that different genetic factors may underlie glymphatic system development in early life versus its decline with aging—with implications for understanding both neurodegenerative and neurodevelopmental disorders.

Sleep and physical activity

Sleep (Fame and Lehtinen, 2020; Chong et al., 2022) and physical activity (Olegario et al., 2024) are emerging as important modulators of PVS integrity through their effects on CSF flow, cerebrovasculature, and neuroinflammation (Ding et al., 2023). Sleep is essential to BBB integrity as well as to replenishment and waste removal from the brain via the brain clearance system (Pan and Kastin, 2016; Cuddapah et al., 2019). Sleep efficiency and other sleep behaviors have also been shown to relate to PVS burden in adult MRI studies (Berezuk et al., 2015), and sleep has been postulated as an important factor regarding PVS variability in adolescents (Piantino et al., 2020). Physical activity may also influence PVS morphology and function by enhancing BBB integrity (Malkiewicz et al., 2019) and improving fluid exchange and clearance—effects supported by animal studies demonstrating that voluntary exercise promotes CSF inflow, accelerates protein clearance, and upregulates AQP4 expression (He et al., 2017; von Holstein-Rathlou et al., 2018). An active lifestyle has also been linked to intrinsic CSF outflow, which has been hypothesized to occur through the PVS pathway (Miyazaki et al., 2023). Given potential links between physical activity and overall health, perhaps unsurprisingly, other cardiovascular risk factors have also shown association with PVS features (Gutierrez et al., 2013; Laveskog et al., 2020; Shi et al., 2023), although these studies were unable to account for sleep or physical activity. Taken together, these findings suggest that part of the individual differences in normative patterns of PVS are likely to be influenced by both sleep and physical activity.

Synthesis and Future Directions: A Roadmap for Developmental PVS Research

Building on the evidence covered in this Viewpoint, Figure 5 synthesizes the proposed relations between modulators of PVS maturation, brain waste clearance capacity, neurodevelopmental processes, and brain functioning (e.g., cognition, mental health) into a unified developmental framework. This synthesis is meant to encourage greater focus on gaining a mechanistic understanding of PVS development and their role in healthy and disrupted brain development through adolescence.

Biological characteristics (e.g., sex, body mass), genetic factors, and lifestyle factors (e.g., sleep, physical activity) are

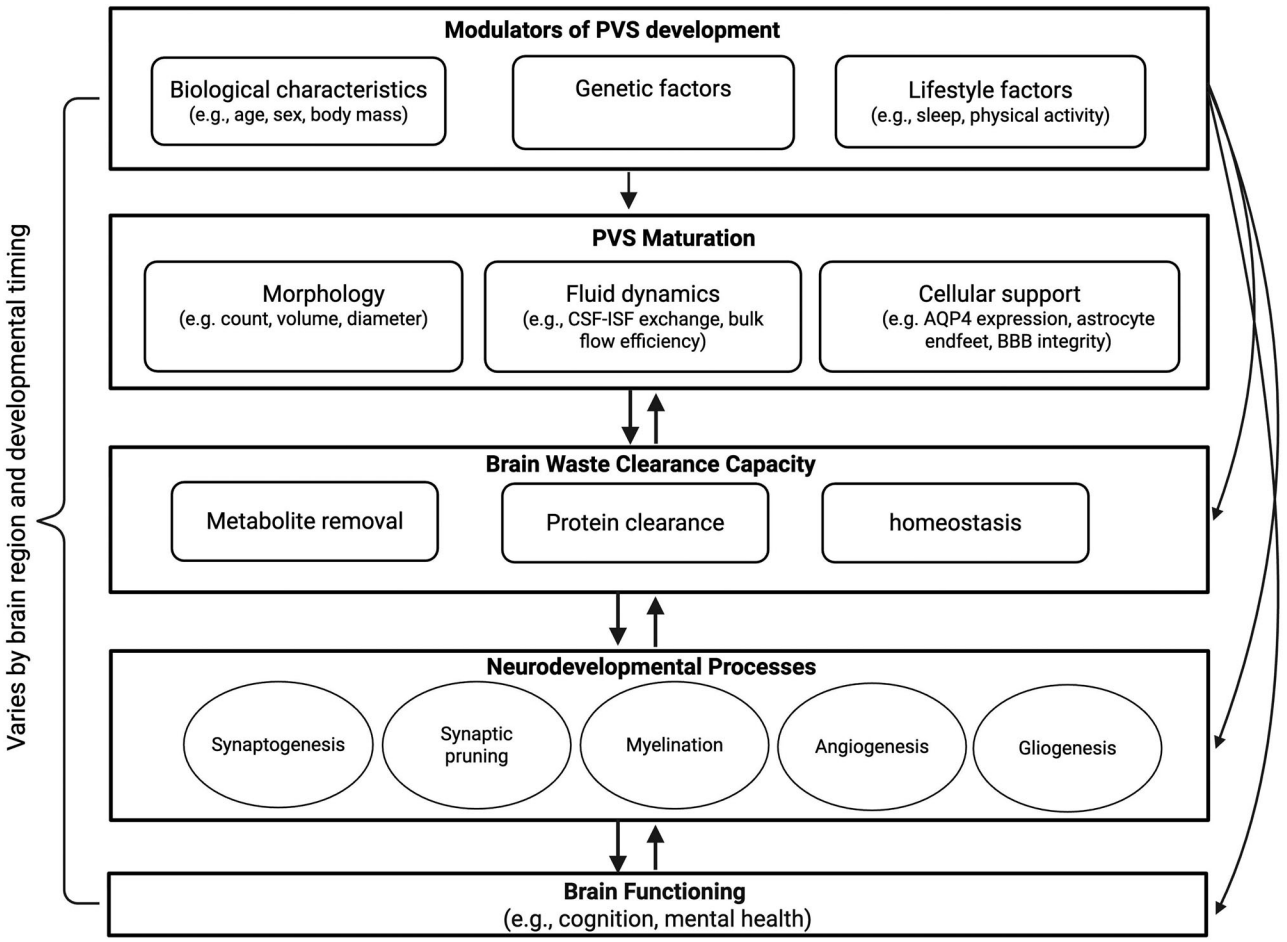


Figure 5. An integrated developmental framework for PVS maturation and brain health. Boxes represent hierarchically organized levels from modulators of PVS development (top) through PVS maturation and brain waste clearance capacity to neurodevelopmental processes and brain functioning (e.g., cognition, mental health; bottom). Solid arrows indicate hypothesized directional or reciprocal relationships between levels. The bidirectional arrow between PVS maturation and brain waste clearance capacity reflects the hypothesis that these processes are reciprocally coupled: PVS maturation supports clearance capacity, while the metabolic demands and parenchymal growth of ongoing neurodevelopment may, in turn, drive continued PVS maturation via increased clearance demand, at least postnatally. Processes at each level vary by brain region and developmental timing, such that biological, genetic, and lifestyle modulators may differentially shape PVS morphology, fluid dynamics, and neurodevelopmental processes across regions and maturational windows. AQP4, aquaporin-4; BBB, blood–brain barrier; CSF, cerebrospinal fluid; ISF, interstitial fluid; PVS, perivascular space. Figure created with BioRender.com.

hypothesized to shape postnatal PVS maturation—encompassing morphology (e.g., count, diameter, regional variation), fluid dynamics (e.g., CSF–ISF exchange, bulk flow efficiency), and cellular support mechanisms (e.g., AQP4 expression, astrocyte end feet, BBB integrity)—which in turn supports brain waste clearance capacity, including metabolite removal, protein clearance, and homeostasis. We propose that the substantial metabolic demands of neurodevelopment, driven by synaptogenesis, synaptic pruning, myelination, and related processes, render efficient waste clearance essential during brain maturation, at least postnatally. Ongoing clearance demand requires coordinated PVS maturation. Under this framework, PVS maturation is not merely a prerequisite for clearance capacity but is reciprocally shaped by the clearance demands that neurodevelopment imposes, such that disruption to this coupling at any point—whether in PVS maturation itself, clearance capacity, or the metabolic demands of development—may compromise healthy brain function. Extending this logic, because clearance capacity supports ongoing neurodevelopmental processes, disruptions anywhere in this cascade may have downstream consequences for cognitive and emotional functioning. Critically, these relationships are not static or uniform across the brain: processes that occur over a developmental timeline at each level likely vary by brain region (e.g., cortical white matter, basal ganglia; early sensorimotor vs later prefrontal and association cortices), such that the same modulator or maturational process may exert different effects depending on the region and age examined. Some modulators may also influence neurodevelopmental processes through pathways that do not act primarily through PVS-mediated waste clearance, reflecting the likelihood that PVS maturation is one of several converging mechanisms linking these factors to postnatal brain development.

It is clear that causal relationships among PVS development, glymphatic function, and neurodevelopmental outcomes remain to be established. The associations reviewed here are largely drawn from cross-sectional, correlational, and animal model data. Additional longitudinal human studies and mechanistic animal research are needed to confirm the directionality of these influences. The field is nascent but has grown in recent years with the use of noninvasive imaging techniques, with much foundational work remaining to be done. The outline below reflects what we view as the most pressing priorities for advancing the field, including foundational anatomical and mechanistic questions, the methodological and normative infrastructure needed

to study PVS in children and youth, and the potential to leverage PVS clinically even while these deeper questions remain open.

Resolving anatomical and mechanistic questions

A fundamental anatomical question that warrants prioritization is whether superficial and deep PVS compartments are continuously connected and whether the pulsatility-driven fluid dynamics characterized in superficial periarterial PVS extend to the deeper MRI-visible spaces that are the primary focus of human neuroimaging research. This question is complicated by evidence that basal ganglia and cortical PVS may differ structurally, as basal arterioles are surrounded by two leptomeningeal membranes that connect directly to the subarachnoid space, whereas cortical arterioles have only one membrane and are thought to communicate with the subpial space, a distinction that could underlie functional differences between regions (Wardlaw et al., 2020). Resolving this question is essential for grounding functional interpretations of MRI-visible PVS and will likely require combining high-resolution animal models with advances in human in vivo imaging. In addition, determining whether the mechanisms underlying PVS structural and functional changes are shared across development and aging or are fundamentally distinct is a critical priority. Here, we hypothesize that these are distinct, reflecting adaptation during development versus deterioration in aging, but dedicated mechanistic work is needed to confirm this.

Several further mechanistic questions remain open about the developing glymphatic pathway and broader waste clearance system (Fame and Lehtinen, 2020; Rasmussen et al., 2022). Beyond pericyte-dependent AQP4 polarization, the additional molecular cues and cell types governing PVS structural remodeling during development are largely unidentified. A related, unaddressed question is whether the glymphatic pathway itself contributes functionally to postnatal neurodevelopment, for example, by supporting synapse formation, maturation, and pruning or myelination: processes that, if disrupted, could directly link early PVS and/or glymphatic dysfunction to the neurodevelopmental outcomes this Viewpoint proposes (Tavares et al., 2026). Finally, although meningeal lymphatic maturation is known to overlap with PVS development, whether or how the timing of this maturation is coordinated to support the functions of the larger brain waste clearance system remains unclear. This question is consistent with recent calls to understand the glymphatic system and meningeal lymphatics as a coupled "glymphatic–lymphatic axis" rather than as independent systems (Sun et al., 2026).

A related open question concerns the striking regional heterogeneity observed in both animal and human studies and whether these patterns are mechanistically connected. In rodents, CSF transport does not emerge uniformly across the brain. Rather, it appears first in the hippocampus and then spreads in a ventral-to-dorsal direction before reaching cortical maturity (Munk et al., 2019). A parallel regional pattern has been observed in the human fetal brain, where AQP4 expression progresses from the archicortex to the neocortex, hypothesized to reflect a broader developmental program of regional cortical functional maturation (Castaneyra-Ruiz et al., 2022). Human neuroimaging studies likewise report pronounced regional differences in PVS across the lifespan (Lynch et al., 2023), and longitudinal work finds divergent trajectories between white matter and basal ganglia PVS into young adulthood (Yamamoto et al., 2025). Whether these regionally distinct human trajectories reflect the same ventral-to-dorsal developmental sequence identified in rodents or arise from entirely separate region-specific mechanisms remains unknown. Recent evidence reinforces the idea that clearance pathways are unlikely to be spatially uniform; rather, the drainage route taken by neuronal proteins is determined by their anatomical site of origin (Chayama et al., 2026). Resolving this question will require more than cataloging regional differences. Dedicated work is needed to determine how these regional trajectories develop over time, what cellular or vascular mechanisms drive them, and whether regions that mature earliest or latest have windows of heightened vulnerability to disruption during maturation. Answering the questions above will largely depend on animal models and mechanistic work. A separate set of priorities applies to human neuroimaging research on PVS, for which methodological and normative gaps currently limit what can be concluded from existing studies.

MRI-PVS development: methodological harmonization and longitudinal normative studies

Progress in developmental MRI-PVS research depends on three interdependent pieces of infrastructure: harmonized imaging contrasts and analysis methods, longitudinal data, and normative criteria. Methodological harmonization across scanners, acquisition protocols, and analysis pipelines is foundational, since variability in upstream MRI decisions can rival true biological effects and will undermine cross-study comparisons unless systematically addressed through international consortia and consensus guidelines (Barisano et al., 2022, 2025; Lan et al., 2025). However, harmonized methods alone cannot answer developmental questions without the longitudinal data to which they are applied. To date, only two studies have examined PVS longitudinally in youth—one assessing PVS volume between the ages of 12 and 21 years (Yamamoto et al., 2025) and one examining DTI-ALPS from ages 9 to 12 years (Huang et al., 2025). Neither captured fine-grained regional patterns of change or intra- or interindividual differences in morphology and diffusion properties across the full developmental window, leaving the field without normative PVS trajectories during the very period when PVS may be actively maturing.

Filling this gap demands large-scale, longitudinal studies that can establish when and where PVS development unfolds, identify the biological and lifestyle factors that drive individual variability, and determine whether differences in PVS maturation carry consequences for cognitive and mental health. This information is required for meaningful interpretation of pediatric neuroimaging findings and for the identification of individuals at risk for aberrant PVS development. Establishing normative PVS trajectories will require imaging data spanning the full developmental window, from the prenatal period through adolescence, yet at present, normative data are absent for the earliest of these stages. Although ventricular volumes have been quantified via fetal MRI, we were unable to identify any studies quantifying PVS in utero, and the earliest available human PVS imaging evidence instead comes from postnatal scanning, including preterm infants imaged near term-equivalent age. Evidence from the perinatal period offers a partial bridge across this gap. Preterm-born neonates show reduced DTI-ALPS indices relative to term-born peers, a finding reported in two independent cohorts (Lin et al., 2024; Peng et al., 2025), though DTI-ALPS carries the same interpretive limitations noted above, and it remains unclear whether this reflects impaired perinatal maturation of PVS-related structures specifically or broader white matter differences associated with prematurity. Resolving this will require normative, continuous data spanning the neonatal period through childhood using the same volumetric and diffusion metrics applied later in development. Establishing normative trajectories across the entire

prenatal and postnatal developmental windows is also a prerequisite for developing standardized criteria to distinguish physiological PVS changes from pathological ones—a gap that persists even in the adult PVS literature (Wardlaw et al., 2020). This carries particular weight in pediatric populations, where normal developmental changes in PVS may be inadvertently misclassified as markers of disease.

A related and equally urgent priority concerns imaging markers of PVS maturation, which are not yet clearly defined. It remains unclear which imaging metrics (e.g., volume, count, diffusion properties) or biological correlates most reliably index PVS maturation. Establishing this is a prerequisite for tracking individual developmental trajectories and identifying deviations from normative patterns. This is compounded by the fact that existing studies have relied on disparate metrics, often in different cohorts and age ranges, with no study to date directly comparing how these features change over time within the same developmental sample. Head-to-head comparisons are essential to clarify whether these metrics index a common underlying maturational process or capture distinct, potentially dissociable aspects of PVS development. Evidence from the same HCP-D cohort illustrates this ambiguity, as PVS VF and count increase with age across childhood and adolescence (Lynch et al., 2023), and fFA is itself strongly correlated with PVS diameter, yet age continues to predict fFA even after accounting for diameter (Lynch et al., 2025). This pattern is consistent with morphological and fluid-dynamic measures capturing partially overlapping but nonidentical maturational information; however, resolving this will require studies explicitly designed to compare these metrics directly within the same participants over time. Here again the broader neuroimaging field offers instructive precedent: the development of normative brain charts for cortical thickness, white matter microstructure, and other structural measures has transformed the interpretation of individual differences in pediatric populations, and analogous normative PVS charts could offer a similarly transformative advance.

PVS biomarker utility and clinical translation

Importantly, the utility of MRI-visible PVS as markers of brain health does not depend entirely on resolving their precise mechanistic role in waste clearance. Group-level associations between PVS and outcomes can advance independently of mechanism, but translating PVS into an individually interpretable, clinically actionable measure still depends on the harmonized acquisition protocols and normative reference data described above. The accumulating associations between MRI-PVS and cognitive outcomes, aging trajectories, and neurodevelopmental conditions support their value as neuroimaging markers independent of the mechanistic questions that remain open. Future work should therefore pursue parallel tracks, including investigating the mechanistic basis of PVS function while simultaneously leveraging their value as accessible markers of brain health across different brain regions and across the lifespan. While several human studies have begun to link PVS to developmental disorders in childhood (e.g., ASD, ADHD), and animal models and human studies suggest glymphatic involvement in conditions with adolescent onset such as depression, alcohol use disorder, and schizophrenia (see PVS development and brain function Section above), understanding how aberrant PVS maturation specifically relates to the emergence of these conditions during adolescence remains one particularly important and largely unexplored avenue for translational work.

Establishing directionality between PVS structure and downstream outcomes will require moving beyond cross-sectional structural imaging alone. Combining PVS neuroimaging with metabolomics, CSF biomarkers, and functional imaging will provide new opportunities to link structural changes to biological function. Complementary, non-PVS-specific MRI measures may be particularly well suited to this integrative approach. For example, phase-contrast MRI (PC-MRI)-derived CSF and blood flow dynamics, as well as vascular pulsatility, correlate with the physiological forces believed to drive perivascular clearance (Sakhare et al., 2019), while diffusion-prepared pseudo-continuous arterial spin labeling (DP-pCASL) quantifies the water exchange rate across the BBB (Shao et al., 2019) and has recently been applied in a pediatric sample to characterize brain iron and BBB function across childhood (Uchida et al., 2023). Lastly, intervention studies targeting modifiable factors such as sleep and physical activity, both of which modulate glymphatic function in adults and animal models, offer a more direct route to establishing a causal influence on PVS development in youth. These same factors carry immediate translational relevance given that short sleep durations are the norm among adolescents despite higher sleep needs (Andrade et al., 1993; Hagenauer et al., 2009; Crowley et al., 2018), and physical activity levels notably decrease across childhood and adolescence (Chaput et al., 2020; Sampasa-Kanyinga et al., 2020; Cruz et al., 2024).

Conclusion

The developmental focus that this Viewpoint article has taken invites a fundamental reframing of PVS—from structures studied predominantly in the context of aging and neurological disease to developmentally dynamic structures whose maturation may be intertwined with building healthy brain architecture across at least postnatal development, from early childhood through adolescence and beyond. This has potentially major clinical implications. Childhood and adolescence may represent a sensitive window for PVS maturation, and understanding what is normative during this period is essential before pathological changes can be meaningfully interpreted. This developmental reframing creates new opportunities to expand efforts toward early identification of at-risk individuals and preventive interventions targeting the brain's waste clearance system during distinct developmental windows.

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