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REVIEW

Imaging of brain barrier inflammation and brain fluid drainage in human neurological diseases

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Abstract

The intricate relationship between the central nervous system (CNS) and the immune system plays a crucial role in the pathogenesis of various neurological diseases. Understanding the interactions among the immunopathological processes at the brain borders is essential for advancing our knowledge of disease mechanisms and developing novel diagnostic and therapeutic approaches. In this review, we explore the emerging role of neuroimaging in providing valuable insights into brain barrier inflammation and brain fluid drainage in human neurological diseases. Neuroimaging techniques have enabled us not only to visualize and assess brain structures, but also to study the dynamics of the CNS in health and disease in vivo. By analyzing imaging findings, we can gain a deeper understanding of the immunopathology observed at the brain–immune interface barriers, which serve as critical gatekeepers that regulate immune cell trafficking, cytokine release, and clearance of waste products from the brain. This review explores the integration of neuroimaging data with immunopathological findings, providing valuable insights into brain barrier integrity and immune responses in neurological diseases. Such integration may lead to the development of novel diagnostic markers and targeted therapeutic approaches that can benefit patients with neurological disorders.

Keywords Imaging · Leptomeninges · Dural lymphatics · Choroid plexus · Perivascular spaces · Glymphatic system

Abbreviations

BBB	Blood–brain barrier
CE	Contrast enhanced
CNS	Central nervous system
CSF	Cerebrospinal fluid
CVOs	Circumventricular organs
DCE-MRI	Dynamic contrast-enhanced MRI
DTI-ALPS	Diffusion tensor imaging along perivascular space
EAE	Experimental autoimmune encephalomyelitis
EDSS	Expanded Disability Status Scale
GBCA	Gadolinium-based contrast agent
GM	Gray matter
IT	Intrathecal
IV	Intravenous
LME	Leptomeningeal (contrast) enhancement
MRI	Magnetic resonance imaging
MVPVS	MRI-visible perivascular spaces
MS	Multiple sclerosis
NMOSD	Neuromyelitis optica spectrum disorder
PSD	Parasagittal dura
PVS	Perivascular spaces
Real-IR	3D real-inversion recovery
T_1w-BB	T1-weighted black-blood
T_2w-FLAIR	T2-weighted fluid-attenuated inversion recovery
WM	White matter

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Introduction

Research in the last 2 decades has begun to uncover how the brain's functioning and malfunctioning are influenced by its interaction with the periphery (e.g., brain–immune axis, brain–gut microbiota axis) as well as by central nervous system (CNS) mechanisms of self-cleansing. At the same time, human imaging in vivo, including magnetic resonance imaging (MRI), has become an essential tool in today's clinical practice, allowing the investigation of some aspects of neurophysiology and neuropathology in vivo. Complementary to animal models, human imaging data can provide novel information about the longitudinal evolution of physiological and pathological processes within the CNS in large and representative cohorts of human subjects. Considering these two approaches, in this review, we will explore how in vivo imaging findings can mirror the inflammatory immunopathology seen at the brain–immune interface barriers, providing a complementary approach to their study.

In the next five sections, we detail immunopathological evidence and current imaging observations of the brain borders (i.e., meninges, choroid plexus, perivascular spaces) as well as recent advances in understanding the physiopathology of brain fluid drainage, especially focusing on multiple sclerosis (MS), a paradigmatic neuroinflammatory disease. To give a more complete overview of the translational approach provided by the in vivo imaging studies, we briefly discuss when these correlative imaging findings (e.g., leptomeningeal enhancement) have been explored in other inflammatory and non-inflammatory diseases of the CNS as well as in healthy aging.

Overall, these data collectively demonstrate the importance of the brain borders as active immunological sites shaping brain functioning, providing insight into their relative contributions in immune cell trafficking and surveillance in CNS physiology and neuropathology. A summary of the cytoarchitecture of the brain borders with representative in vivo human imaging correlates is shown in Fig. 1.

Leptomeningeal inflammation in autoimmunity

Immunopathology

The leptomeninges consists of two continuous layers, termed "pia mater" (directly covering the cortical surface) and "arachnoid mater" (enclosing the subarachnoid space, which is filled with the cerebrospinal fluid; CSF). In virtually all diseases of the CNS (i.e., autoimmune, inflammatory, infectious, neoplastic), leptomeningeal inflammation plays a role in initiation or progression of the pathological process. Growing evidence highlights the blood–meningeal barrier (Fig. 1) as an immune-active critical border of the CNS. Serving as a typical example, hereafter we summarize recently acquired knowledge about the role of the inflamed leptomeninges in MS.

The immunological processes leading to MS are generally thought to start outside the CNS (the "periphery") but over time become compartmentalized within the CNS. The leptomeninges are among the key locations for the propagation of CNS antigen-specific responses and for interactions among CNS-infiltrating autoreactive $CD4^+$ T cells, proinflammatory B cells, and antigen-presenting myeloid cells. Intrathecal expansion of clonal plasmablasts toward CNS antigens occurs in the earliest stages of the disease, as demonstrated by the presence of CSF-restricted oligoclonal bands—a cardinal diagnostic feature of MS. By histopathology, sparse leptomeningeal infiltrates comprising brain-homing T cells (both $CD4^+$ and $CD8^+$), memory B cells, plasmablasts, and myeloid cells are common across disease stages but may be most prominent in progressive MS cases, where they may develop into ectopic lymphoid follicles [1, 2].

Immune cell infiltrates in the leptomeninges have been reported to be critical sources of pro-inflammatory cytokines and cytotoxic soluble molecules that can propagate inflammatory neurodegenerative processes within the underlying CNS parenchyma directly or by activation of glial parenchymal cells [3, 4]. This concept is supported by the pathological and radiological demonstration of a "surface-in" gradient pattern of tissue damage in the subpial cortex, periventricular white matter (WM), subependymal thalamus, and spinal cord [5–9]. Specific CSF protein profiles have been associated to the "surface-in" gradient tissue damage in MS, and they include cytokines and chemokines governing lymphoid neogenesis (CXCL13, CCL19, CXCL10), B-cell proliferation (BAFF, APRIL, LIGHT, TWEAK), and adaptive and innate immune activity, as well as inflammatory mediators such as fibrinogen, lymphotoxin α, IFNγ, IL2, and sTNFR1 [10, 11]. Sustained elevation of CSF proinflammatory cytokines by lentiviral vectors (IFNγ, TNF) [12] or stereotaxic meningeal injections (lymphotoxin α) [13] partially recapitulate cortical inflammatory demyelination in animals. The extent of lymphocyte infiltration within the leptomeninges correlates also with the presence of chronic active lesions in the WM [14], a subtype of chronically demyelinated lesion showing unresolved smoldering inflammatory demyelination at the lesion edge [15, 16]. This observation supports the notion that compartmentalization of the inflammation occurs similarly in both WM and gray matter (GM) [17, 18]. Our view of the formation and development of demyelinated lesions in the WM and human imaging correlates have been extensively reviewed elsewhere [17–19].

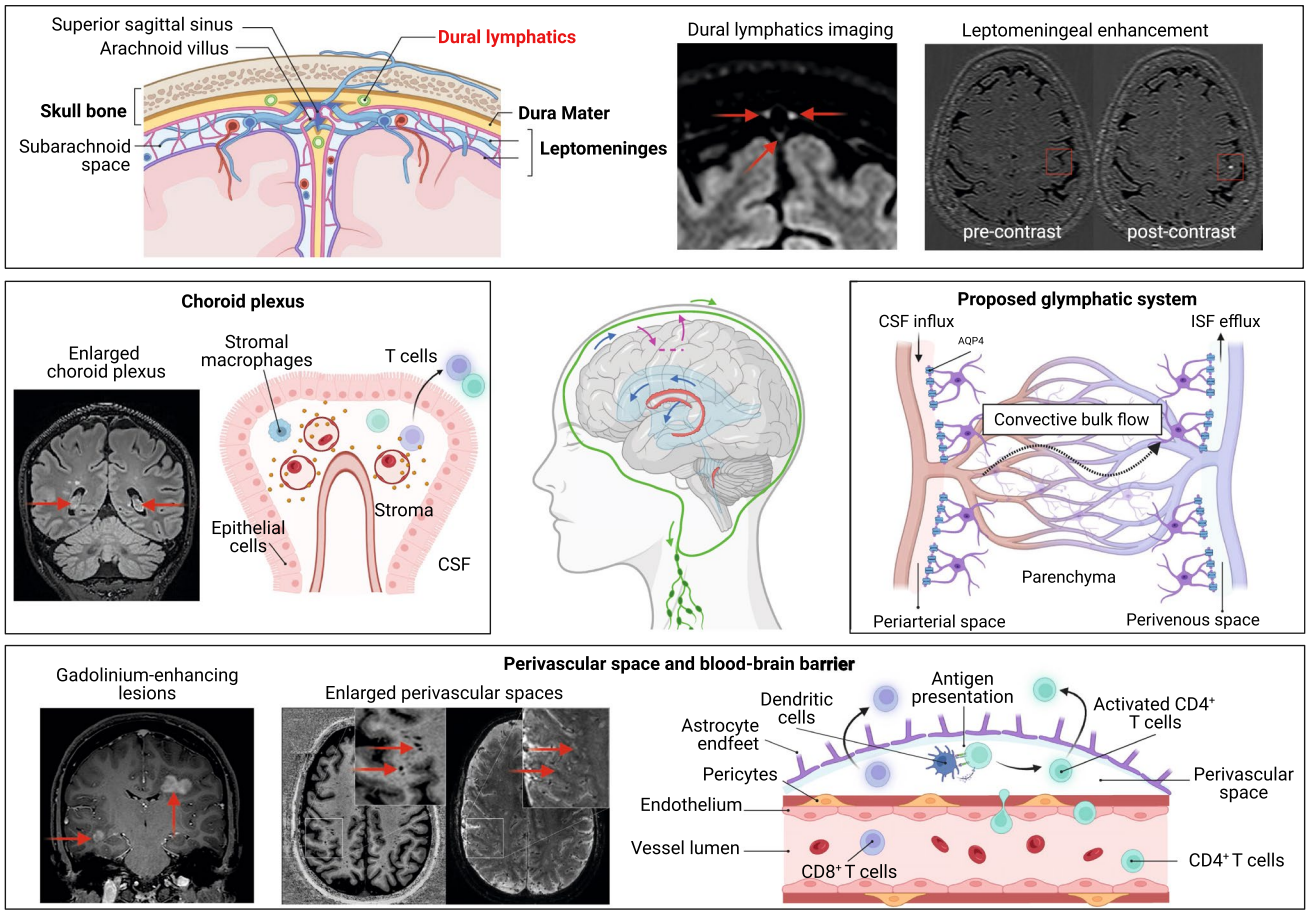

Fig. 1 In vivo human imaging correlates of the brain–barrier interface in health and neuroinflammation. Neuro-immune crosstalk at distinct brain borders, including meninges, choroid plexus, perivascular spaces, blood–brain barrier, and the glymphatic system, plays a key role in promoting and sustaining neuroinflammatory processes. In the center of the figure, a composite schematic model of CSF circulation and waste drainage, for each component of which some experimental support exists, is shown: choroid plexus → ventricular system (blue arrows in center of brain) → subarachnoid space (blue arrow above brain) → periarterial space (inward purple arrow) → parenchyma (dotted purple line) → perivenous space (outward purple arrow) → dural lymphatic vessels (green line and arrow) → deep cervical lymph nodes. *Choroid plexus* Within the ventricles of the brain, the choroid plexus is not only responsible for CSF production but acts as an on-alert gate for the recruitment of immune cells by integrating signals from the CNS parenchyma and circulating immune cells. Representative examples of MRI correlates: in neuroinflammatory diseases, bilateral prominence of choroid plexus (arrows) can be visualized on T_2w-FLAIR images (53-year-old man with MS). *Proposed glymphatic system* This is reported to be a glial-dependent waste clearance pathway in the brain that regulates waste clearance and brain immunity. To date, although different variants of neuroimaging have been proposed, no definitive imaging correlate has been identified. *Perivascular space and blood–brain barrier* Integrity of the blood–brain barrier is critical for the brain's well-being. Perivascular spaces of the blood–brain barrier provide critical cues directing immigrant lymphocytes into the CNS parenchyma upon presentation of autoantigens by perivascular macrophages. Representative examples of MRI correlates: (a) the abrupt opening of the blood–brain barrier is associated with the formation of new MS lesions and can be visualized by the parenchymal leakage of contrast agent on 3 T T_1-weighted images (20-year-old woman with MS and multiple new enhancing lesions, arrows); (2) MRI-visible enlarged perivascular spaces (arrows) exhibit CSF signal properties on 7 T T_1-weighted MP2RAGE (hypointense) and T_2*-weighted images (hyperintense) with a vascular trajectory distribution (52-year-old man with MS). *Meninges* The three-layered membranous structure of the meninges (especially the leptomeninges) forms a key location for the propagation of CNS antigen-specific responses. The dura mater also encloses lymphatic vessels that have been shown to be relevant for CNS antigen and waste drainage toward the deep cervical lymph nodes. Representative examples of MRI correlates: (a) lymphatic vessels (arrows) within the parasagittal dura are visible on 3 T delayed post-contrast T_2w-FLAIR image (coronal view; 46-year-old man with MS); (b) a nodular leptomeningeal enhancement (box) is seen on 3 T delayed post-contrast T_2w-FLAIR image only (64-year-old woman with MS). Created with BioRender.com

Under physiological conditions, the blood–leptomeningeal barrier prevents the leakage into the CNS of circulating fluids and small molecules but allows regulated lymphocyte patrolling of the CNS. In the blood–leptomeningeal barrier, the endothelium of the venules crossing the trabeculae of the leptomeninges is composed of a layer of non-fenestrated

cells bonded by tight junctions but lacking pericytes and astrocyte end-feet as are found at the blood–brain barrier (BBB) [20]. In inflammatory conditions, the leptomeningeal specialized vasculature permits immune cell trafficking and surveillance through the upregulation of VCAM1 and ICAM engaged by VLA4 or LFA1, respectively, and production of CCL5 and CXCL9-11 by leptomeningeal macrophages [21]. It is assumed that the immunological events described above can also lead to smoldering increased permeability of the blood–meningeal barrier, potentially localized where higher immune cell infiltrates are seen. Abnormal permeability of the blood–meningeal barrier is supported also by the detection of serum proteins within the CSF such as fibrinogen, haptoglobin, and free hemoglobin, all of which might further exacerbate downstream toxic processes [22]. Integrin α4β1 (VLA4), LFA1, and constitutive expression of P-selectin are implicated in the more efficient infiltration of leukocytes across the blood–meningeal barrier than the BBB [21]. Concomitant blood–meningeal barrier breakdown, meningeal follicle-like structures, and adjacent cortical pathology have been recently recapitulated using a SJL/J mice with experimental autoimmune encephalomyelitis (EAE) by immunization with proteolipid protein peptide ($PLP_{139–151}$) [23].

Human imaging

As discussed above, leptomeningeal inflammation is recognized as a key driver of cortical pathology in MS, and its visualization in vivo would hold particular clinical significance [1, 4]. The currently predominant imaging approach employed for detecting leptomeningeal inflammation relies on gadolinium-enhanced MRI, leveraging the signal provided by gadolinium-based contrast agents (GBCA) in regions exhibiting disruption of the blood–meningeal barrier [24]. The assessment of leptomeningeal contrast enhancement (LME) on delayed contrast-enhanced (CE), T_2-weighted (w) fluid-attenuated inversion recovery (T_2w-FLAIR) imaging has been shown to have higher sensitivity to detect GBCA enhancement in the subarachnoid space compared to the T_1w imaging that is commonly used for brain parenchymal GBCA enhancement [25–27] (Fig. 2). Studies employing CE-T_2w-FLAIR imaging have used a variety of magnetic field strength (typically ranging from

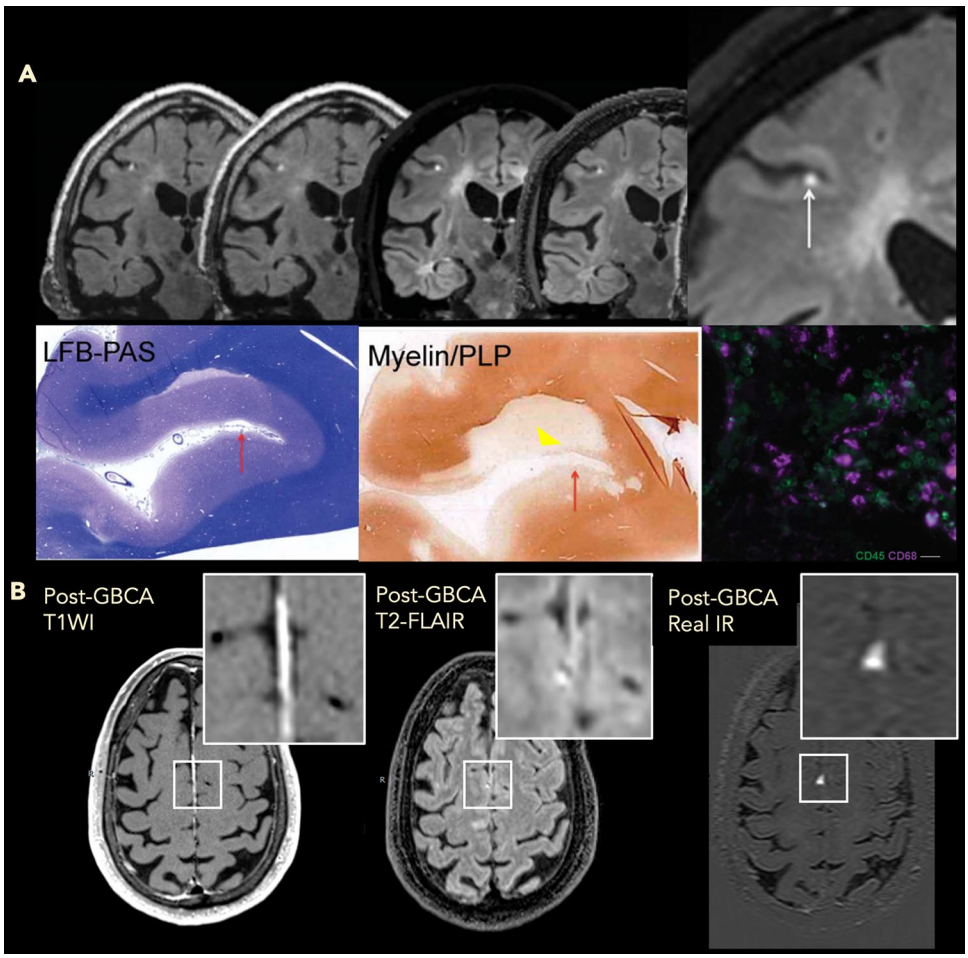

Fig. 2 **A** Leptomeningeal enhancement (LME) observed on post-GBCA T_2w-FLAIR images abuts an area of subpial demyelination, as evidenced by LFB-PAS and myelin/PLP staining. In addition, the autopsy tissue shows signs of meningeal inflammation, characterized by the presence of leukocytes (CD45 +), including macrophages (CD68 +) (adapted from Absinta M et al. Neurology 2015) [29]. **B** Images from a 52-year-old woman with RRMS following the administration of a gadolinium-based contrast agent (GBCA). The appearance of LME depends on the imaging sequence acquired after GBCA administration. T_1w images may not provide sufficient clarity for visualizing nodular LME. By contrast, both T_2w-FLAIR and Real-IR techniques show LME, with Real-IR demonstrating superior contrast compared to T_2w-FLAIR, making it an effective choice for LME visualization (Okar et al. Investigative Radiology 2023)

1.5 T to 7 T), sample size, and image post-processing techniques including image subtraction algorithms [28].

In general, LME is defined as an area exhibiting signal augmentation on the pial surface of the cortex that appears more hyperintense compared to the cortex itself on post-GBCA T_2w-FLAIR images [29, 30]. The literature has generally described two main configurations of LME with variable nomenclature: nodular and spread-fill (linear, laminar, and plate-like) patterns. These two phenotypes have been commonly employed in studies to characterize and classify LME in MS [31]. In the literature, a similar imaging phenomenon seen on delayed CE-T_2w-FLAIR in older individuals, including those with mild cognitive impairment and Alzheimer's disease, was also referred as "pericortical enhancement" [32].

The available data concerning the biological underpinnings of LME in MS are currently restricted to two autopsy cases [29] (Fig. 2). These provided evidence that areas exhibiting LME, as detected through 3 T CE-T_2w-FLAIR MRI, may indicate areas of leptomeningeal inflammation and potentially adjacent subpial cortical demyelination. A possible mechanism underlying focal GBCA accumulation in the leptomeninges is abnormal vascular permeability and local fibrosis due to ongoing or prior inflammation [33]. The focal nature of this enhancement, more pronounced on T_2w-FLAIR imaging, suggests that it arises from localized trapping of contrast material. Collagen deposition and the activation of reactive fibroblasts, influenced by inflammatory chemokines and cytokines, might contribute to compartmentalization of inflammatory cells and formation of tertiary lymphoid-like structures [34]. Concordantly, a recent post-mortem study revealed the presence of focal leptomeningeal fibrosis in MS, typically accompanied by signs of inflammation [35]. A parallel or complementary explanation for focal GBCA accumulation involves phagocytosis by leptomeningeal macrophages. Indeed, Weng et al. employed mass spectrometry to demonstrate that macrophages can take up various formulations of GBCA, even at low concentrations, following a 24-h incubation [36]. In two autopsy MS cases, Absinta et al. observed high density of CD68-positive macrophages in the inflamed leptomeninges corresponding to the in vivo LME foci [29] (Fig. 2). However, the rapid GBCA uptake observed in leptomeningeal enhancement, which may occur even in less than 10 min, challenges this theory [37].

Additional studies using CE-T_2w-FLAIR on 3 T or 7 T scanners aimed to characterize LME in MS and to understand its associations with demographic, clinical, and radiological markers of the disease in vivo. These studies showed that LME is common in MS, with reported prevalence ranging from 25% [29] to 50% [38] at 3 T and 66% [39] to 90% at 7 T [30]. One study compared the prevalence of LME on 3 T CE-T_2w-FLAIR in MS vs non-MS and healthy individuals and reported that LME is ~ fourfold more frequent in neuroinflammatory conditions than non-inflammatory neurological disease and healthy individuals [40]. Age and/or disease duration [27, 29, 41], Expanded Disability Status Scale (EDSS) [27–29], WM lesion volume [28, 38, 39], cortical volume [27, 28, 30, 39, 42, 43], and cortical lesions [39] have all been found to be associated with LME. However, it is important to note that there are also conflicting findings. Some studies have reported contradictory evidence regarding the association of LME with age [28], EDSS [41], WM lesion volume [30, 41], and cortical lesions [43]. Furthermore, in studies assessing the association between LME and cortical volume, adjustments for age, which is a confounding factor for cortical volume, were made in only two studies. One study reported no clear association between the two findings [30], whereas the other found a significant association [27] after adjustment for age. Addressing the controversies on the associations of LME in MS and other neuroinflammatory diseases, a recent meta-analysis suggested that the presence of LME is associated with worse clinical outcomes (higher EDSS) and imaging outcomes (lower cortical volume, higher WM lesion volume) in MS [31].

A recent study comparing CE 3D real inversion recovery (Real-IR), a newer 3 T CE MRI technique that is sensitive to low concentration of GBCA in the CSF [44], with CE-T_2w-FLAIR showed that Real-IR can detect ~ fourfold more LME foci, including all foci detected with CE-T_2-FLAIR, with ~ 2.5-fold higher contrast-to-noise ratio and an overall prevalence (73%) comparable to 7 T T_2w-FLAIR studies in MS and other inflammatory neurological diseases [37]. This study also showed an association between LME and paramagnetic rim lesions, which describe the MRI appearance of a subset of WM lesions with chronic active inflammation. This result aligns with tissue-based studies showing an association between meningeal inflammation and mixed active/inactive WM lesions [14].

LME in MS is typically a persistent imaging characteristic [45]. Currently, longitudinal data on the response of LME to disease-modifying therapies in humans are limited and conflicting [46–49]. Of note, LME is not exclusive to MS but can be observed in various neurological diseases, including neurosarcoidosis [50–53], neuromyelitis optica spectrum disorder (NMOSD) [54–56], MOG-associated antibody disease [57, 58], primary angiitis of central nervous system [59, 60], Susac syndrome [61–64], HIV [40], COVID [65–67], meningitis (bacterial, viral, or aseptic) [68–70], HTLV-1-associated myelopathy/tropical spastic paraparesis [37, 40], and autoimmune encephalitis [71]. In addition, LME can be seen in certain non-inflammatory conditions, including leptomeningeal carcinomatosis [72–74], stroke [75–77], and neurodegenerative diseases [32].

The neuroimmune interface of the meningeal lymphatic system

Immunopathology

Differently from the leptomeninges, which play a clear role in the establishment of the autoimmunity in MS, recent evidence has also investigated the potential contribution of the dura mater and dural lymphatics to CNS autoimmunity. The dura mater has fenestrated capillaries and, unlike the other layers, contains an evolutionarily conserved lymphatic network draining CNS waste via CSF, restricted along the dural venous sinuses [78]. In particular, lymphatics are located in close proximity to regions where CSF accesses the dura mater, potentially facilitating CNS-derived waste drainage [79]. Noteworthy, CNS-derived antigens in CSF have been demonstrated to accumulate around the dural venous sinuses, which thereby act as regional hubs for immune surveillance in which antigens captured by local antigen-presenting cells are presented to patrolling T cells [79]. At this site, recognition of CSF-derived antigens by T cells induces effector and likely regulatory functions within the dura.

A recent study using a mouse EAE model and autopsy MS lesions demonstrated that constitutive differences in the meningeal vasculature and autoantigen availability are responsible for differential involvement of the meningeal layers in neuroinflammation and CNS autoimmunity [80]. Reactivation of T cells in the dura, as well as the levels of proinflammatory cytokines and chemokines, were significantly lower compared to the leptomeninges and the CNS parenchyma, suggesting limited participation of the dura in initiation of the autoimmune process. In particular, the reduced T-cell reactivation in the dura was reported to relate to insufficient quantities of CNS autoantigens reaching it [80]. Consistently, data on human samples reported only sparse immune cells (e.g., $CD8^+$ T lymphocytes) in the dura, compared to the high cell density in the leptomeninges [80]. These results suggest that, although the dura permits immune surveillance, upon pathological interactions, inflammation proceeds to and predominates within the leptomeninges and the brain parenchyma. The actual site(s) of initiation of these immune interactions in human disease remain unknown and the role of dural lymphatic vessels in CNS immune surveillance remains controversial. A recent study highlighted that, in mice, inhibition of the VEGF-C/VEGFR3 signaling pathway, which is essential for development and maintenance of dural lymphatic vessels, impaired those vessels but did not affect the development of CNS autoimmunity [81].

Recently, the bone marrow in the skull and vertebrae, which contains hematopoietic stem cells and supportive stromal niches, enabling the formation of lymphoid and myeloid immune cell lineages, has been demonstrated to directly connect to the underlying dura via ossified vascular channels [82–84]. Such channels have been described as a trafficking route, distinct from the blood route, allowing not only the migration of myeloid and lymphoid cells from the skull bone marrow to the dura, but also direct access of bone marrow to CSF [85]. Accordingly, after CNS injury or infection, the skull bone marrow has been shown to sense dysfunction in the underlying tissues via soluble cues in the CSF, thereby responding to CNS perturbations with a tailored immune response by promoting skull bone myelopoiesis and trafficking of mature myeloid cells to the brain borders [85, 86].

Human imaging

The identification of lymphatic channels within the parasagittal dura (PSD) in mice [87, 88] has sparked efforts to noninvasively visualize these structures in humans (Fig. 1). Absinta, Ha et al. demonstrated the presence of lymphatic vessels running within the PSD in humans and marmoset monkeys through the utilization of CE MRI techniques complemented by histopathological examination and validation [89]. In this study, T_2w-FLAIR and T_1-weighted black-blood (T_1w-BB) imaging techniques on a 3 T scanner were employed to compare the enhancement patterns following the intravenous administration of two GBCA with distinct properties. As mentioned above, the dura mater has a fenestrated endothelium. Based on this notion, dural lymphatic vessels enhanced after injection of gadobutrol, a standard GBCA that can diffuse across the permeable capillary endothelia of the dura mater, but not after gadofosveset, a GBCA with high affinity to blood albumin that predominantly remains within the blood compartment. Jacob et al. employed imaging techniques in both mice, using ovalbumin tracer injection into the CSF, and humans, with T_1w-BB imaging following intravenous gadobutrol injection. Their work revealed a consistent three-dimensional meningeal lymphatic vessel network that closely aligns with the dural venous sinuses, with a particular focus on the area around the cavernous sinus [90]. Interestingly, this network was not tied to CSF outflow through the cribriform plate but instead had exit routes through the foramina of emissary veins. Several human imaging studies employed various approaches to investigate the structural and functional properties of dural lymphatic vessels in vivo. These approaches can be categorized into two main groups: intravenous (IV) or intrathecal (IT) GBCA enhanced and non-GBCA MRI techniques. Supplementary Table 1 provides a comprehensive summary of the existing literature on the imaging of dural lymphatic vessels. Figure 3A shows GBCA enhancement within the PSD shown with T_1w-BB imaging.

Intravenous GBCA-enhanced MRI techniques Studies have used T_2w-FLAIR and T_1w-BB imaging to observe dural lymphatic vessels after GBCA administration in

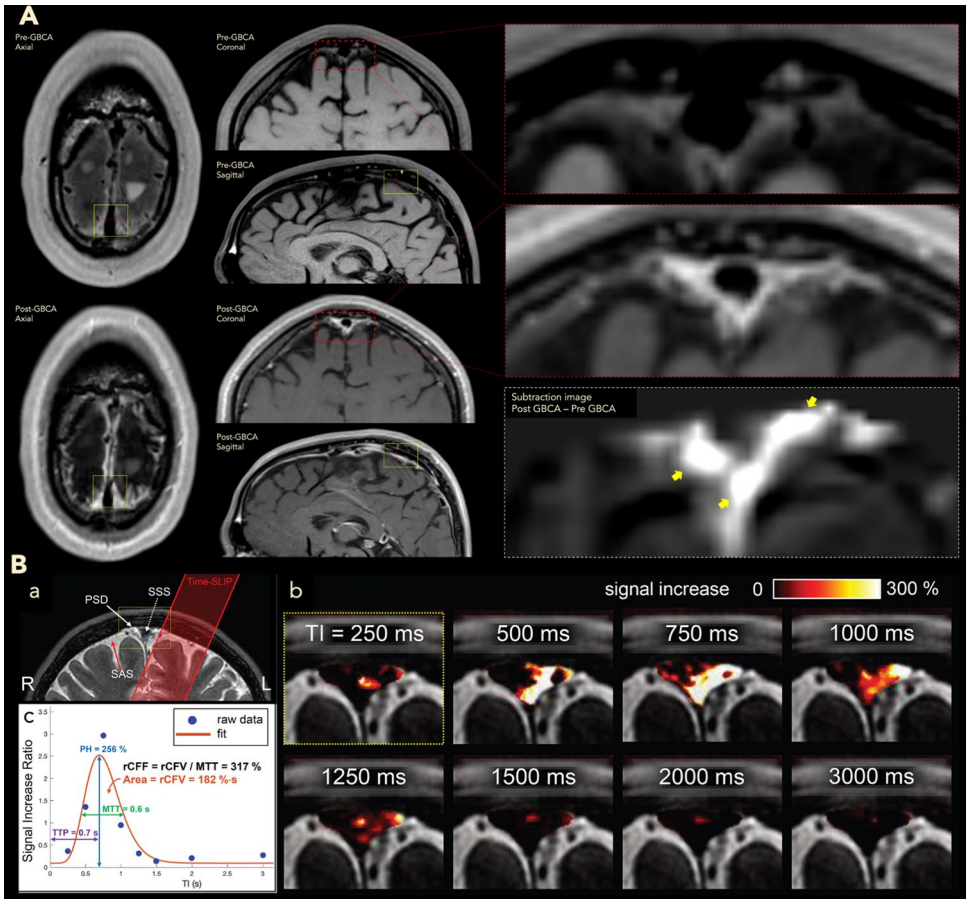

Fig. 3 **A** T_1w images (DANTE sequence) from a 24-year-old man with multiple sclerosis display contrast enhancement surrounding the parasagittal dura (PSD) with a focus on the posterior portion (yellow rectangles). A cross-sectional area is reviewed on coronal reformat (red dashed line and rectangle). Both raw post-GBCA images and subtraction images (see magnified views) illustrate areas of contrast enhancement, putatively corresponding to meningeal lymphatic channels. **B** Spin-labeling MRI without GBCA for PSD transition dynamics. **a** A coronal 3D centric ky–kz single-shot fast spin echo (cSSFSE) image with a spin labeling tag pulse (red box), positioned about 10 mm from the SSS. **b** Coronal fusion images at various inversion times (TI) displaying tagged MRI signals moving from the tag pulse to the dura mater and PSD into the superior sagittal sinus (SSS). **c** CSF outflow dynamics at the PSD. Measurements include peak height (PH), mean transition time (MTT), time to peak (TTP), relative CSF volume (rCFV) (area under the curve), and relative CSF flow (rCFF). (Panel B is adapted from Malis V. et al. Magnetic Resonance in Medical Sciences 2022; this corresponds to panel B of Figure 3 only, not the whole figure) [112]

healthy individuals [90–92], aging [93], reversible cerebral vasoconstriction syndrome [94], and small vessel disease [95]. Two studies quantified dynamic GBCA enhancement in lymphatic-enriched dural areas, revealing peak enhancement at 7-min post-GBCA injection in healthy individuals, with a subsequent 13-min wash-out.[91, 96].

Using 3 T Real-IR, Naganawa found GBCA spreading from cortical bridging veins to the PSD, more pronounced with age [44, 97]. In a subsequent study of 42 individuals with endolymphatic hydrops, putative dural lymphatic vessels in the sigmoid sinus wall was observed, with peak enhancement occurring at 4 h in 54% of participants, and it was associated with a slower CSF wash-out [98].

Three studies have utilized dynamic contrast-enhanced (DCE) MRI following intravenous GBCA administration to assess the transition dynamics of GBCA in the dural lymphatic vessel regions. Joo et al. demonstrated that DCE-MRI can effectively assess dynamic changes in putative dural lymphatic vessels within the PSD. Their findings reveal distinct enhancement patterns in the PSD compared to venous structures, with older individuals showing a more pronounced delay in lymphatic drainage, suggesting a potential impact of aging [99]. Ding et al. employed DCE-MRI to explore dural lymphatic flow in individuals with idiopathic Parkinson's disease and atypical parkinsonian disorders. They noted reduced flow through dural lymphatic vessels and delayed deep cervical lymph node perfusion in idiopathic Parkinson's disease compared to atypical parkinsonism, raising questions about the potential role of dural lymphatic dysfunction [100]. In a cohort with 68 participants

with NMOSD, DCE-MRI suggested the presence of slower flow through the PSD during acute attacks. This reduction in flow was found to be associated with disease severity, underscoring the potential significance of dural lymphatic vessel dysfunction in NMOSD relapses [101].

Intrathecal GBCA-enhanced MRI techniques The safety of lumbar IT injection of low-dose gadobutrol has been suggested in two cohorts, initially comprising 100 [102] and subsequently extended to 149 patients [103] with diverse neurological diseases. These studies demonstrated that this approach was well-tolerated without significant adverse effects [102, 103]. Ringstad et al. conducted serial T_1w-BB and T_2w-FLAIR scans before and at multiple time points (3, 6, 12, and 48 h) following lumbar IT injection of low-dose GBCA (gadobutrol 0.5 ml). The study involved 18 patients with possible CSF disorders of various etiologies. The findings demonstrated tracer enrichment in the PSD over 24 h, followed by subsequent wash-out over 48 h, suggesting that the PSD may serve as a connecting link for CSF drainage and molecular exchange [104]. In subsequent studies, Eide et al. utilized IT gadobutrol injection as a tracer for CSF flow from the PSD. They reported simultaneous enrichment of CSF and increased blood concentration of GBCA along this pathway [105]. These investigations suggested that the functionality of this pathway might be altered in various conditions, including idiopathic normal pressure hydrocephalus [105, 106], idiopathic intracranial hypertension [107], spontaneous intracranial hypotension [108], and sleep disturbances [108, 109].

MRI techniques without GBCA administration Arterial spin-labeling is a noninvasive MRI technique that utilizes the natural flow of arterial blood water as an internal tracer, allowing for the measurement and quantification of tissue perfusion and/or flow without the need for external contrast agents [110, 111]. Malis and Miyazaki et al. reported the feasibility of using spin-labeling to quantify CSF outflow to the PSD in healthy adults [112]. Their findings included a decline in CSF outflow associated with aging and sedentary lifestyle [112, 113] (Fig. 3B). Alternative approaches for assessing dural lymphatic vessels without the need for external contrast agents involve structural assessments based on the signal properties of T_1 and/or T_2-w imaging [114, 115]. One study introduced an inter-slice blood perfusion MRI technique with alternate ascending/descending directional navigation (ALADDIN) and reported comparable results to CE T_1w-BB imaging [116].

Choroid plexus

Immunopathology

The choroid plexus consists of secretory cuboidal epithelial cells connected by tight junctions surrounding a network of permeable capillaries, along with a connective stroma and containing different innate and adaptive immune populations, such as macrophages and CNS-specific $CD4^+$ T cells, all of which play a key role in CNS immunosurveillance (Fig. 1) [117–119]. As a neuro-immune interface, the choroid plexus integrates signals from the CNS parenchyma and circulating immune cells, acting as an on-alert gate for the recruitment of immune cells. Trafficking through choroid plexus epithelium into the CSF has been shown to occur during inflammatory conditions [120], in line with evidence from three-dimensional imaging showing mobility and motility of choroid plexus immune cells upon immune challenge and focal injury [121]. Accordingly, T cells have been reported to extravasate across the endothelium, interact with epithelial cells, and enter the CSF [122, 123], a route used in the context of EAE initiation and progression [124]. This route has been found to rely on the expression of trafficking molecules at the choroid plexus, such as the integrin VCAM-1 [122]. In EAE, encephalitogenic $CD4^+$ Th1 T cells expressing the chemokine receptor CCR6 have been reported to engage CCL20 on choroid plexus epithelial cells to initiate EAE, specifically by crossing the blood–CSF barrier in the choroid plexus and traveling to the leptomeningeal (subarachnoid) spaces, where they accumulate and trigger neuroinflammation [123]. Beyond lymphocytes, evidence from the literature also reported monocyte invasion to the choroid plexus after head trauma [125] and trafficking of inflammation-resolving monocytes en route to the lesioned parenchyma [120]. In line with evidence implicating the choroid plexus as a critical gateway for immune cells and inflammatory molecules, changes in its permeability have also been reported following intestinal inflammation [126]. This latter has been shown to induce temporary changes in its vascular barrier as a protective program leading to choroid plexus closure [126].

Human imaging

In vivo imaging of the choroid plexus in humans has recently garnered significant interest in MS research. In a study conducted by Kim et al., the choroid plexus was studied using CE T_1w imaging, and the results showed increased thickness and enhancement of the choroid plexus in both MS and NMOSD patients compared to healthy controls [127]. A subsequent study with a larger sample size, conducted across four international centers, examined choroid plexus volume in individuals with MS and NMOSD and control groups, including healthy individuals and migraineurs. The study reported that choroid plexus volume was larger in individuals with MS compared to those with NMOSD and the control group. In addition, the increased choroid plexus volume was associated with WM lesion volume, highlighting a potential link between choroid plexus alterations and

MS-related pathology [128]. In a combined MRI and positron emission tomography study utilizing fluorine 18–DPA-714, a radiotracer that binds to the translocator protein expressed by activated microglia and other brain cells at sites of inflammation, researchers observed an enlarged and inflamed choroid plexus in individuals with MS compared to non-neurological controls. This finding was particularly prominent in the relapsing–remitting clinical phenotype of MS [129].

The relationship between chronic inflammation and choroid plexus enlargement was further examined in a study demonstrating that larger choroid plexus at baseline predicted WM lesion expansion over 2 years [130]. A longitudinal study in MS confirmed the presence of larger choroid plexus volume compared to non-neurological controls [131]. This study further investigated choroid plexus T_2 relaxation times using a pseudo-T_2 (pT_2) mapping method, which purports to reflect the inflammatory state of the choroid plexus based on the principle that increased water content leads to T_2 prolongation. The study findings demonstrated that, on average, individuals with higher baseline choroid plexus pT_2 values had clinical disability progression during a 5-year follow-up period.

As discussed above, the choroid plexus is considered an immune hub and a gateway for immune cells into the CSF (See "Immunopathology"). Choroid plexus enlargement in a neuroinflammatory milieu can indicate a bidirectional relationship, implying that increased permeability contributes to enhanced immune cell entry, whereas heightened cellularity leads to greater permeability of stromal capillaries and the blood–CSF barrier. This, in turn, can also potentially intensify the extravasation of contrast agents into the stroma, further enhancing choroid plexus contrast enhancement. Figure 4 presents a comprehensive visualization of the human choroid plexus using various MRI sequences.

Aside from MS, in recent years, there has been substantial interest in functional evaluation of the choroid plexus using MRI, reflecting the growing recognition of its importance in various neurological conditions and its potential role in brain health. Using a DCE-MRI approach to compare the dynamics of choroid plexus water efflux rate between individuals with mild cognitive dysfunction vs age-matched controls, Anderson et al. found an age-related decrease in choroid plexus-to-CSF efflux rate, suggesting potential alterations in choroid plexus function associated with cognitive dysfunction [132]. A different study reported an increase in choroid plexus volume with age, along with additional alterations such as increased T_1 and T_2 relaxation times, increased mean diffusivity, decreased fractional anisotropy, and decreased cerebral blood flow [133]. These findings collectively suggest microstructural changes and enlargement in choroid plexus associated with aging. Choroid plexus volume has also been found to be a potential MRI marker for Alzheimer's and Parkinson's diseases, correlating with the degree of cognitive impairment [134] as well as CSF amyloid-β, tau, and α-synuclein changes [135].

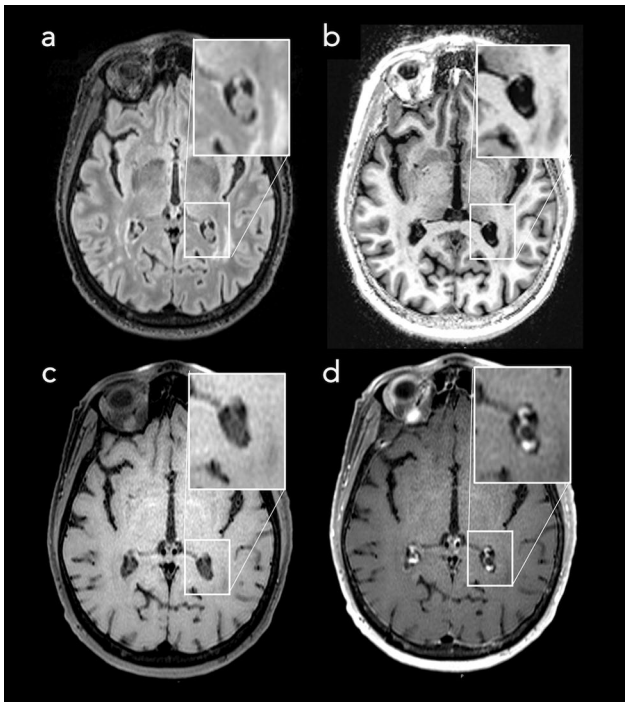

Fig. 4 Images from a 67-year-old woman with multiple sclerosis show varying signal characteristics of the choroid plexus on T_2w-FLAIR (**a**), T1-MP2RAGE (**b**), T_1w images without GBCA (**c**), and T_1w images after GBCA administration (**d**). Although the choroid plexus is prominent, contrast enhancement is primarily limited to its peripheral region

Perivascular spaces

Immunopathology

Mounting evidence indicates that the perivascular space plays an important role in immune surveillance and neuroinflammatory processes. The perivascular space is the anatomical compartment surrounding blood vessels (arteries, arterioles, venules, and veins) within the brain parenchyma and is situated between the parenchymal basement membrane of the glia limitans (the outer boundary, formed by compacted astrocyte foot processes and an overlying parenchymal basement membrane) and the endothelial basement membrane of the blood vessel (inner boundary) (Fig. 1). Of note, penetration of immune cells through the endothelial layer and their parenchymal invasion across the glia limitans have been reported to be two distinct and independently controlled processes [136].

For leukocytes, the perivascular space contains the critical components needed to carry out CNS immune surveillance but also initiate neuroinflammation. To this end, within perivascular spaces, lymphocytes can encounter competent antigen-presenting cells, fundamental for T-cell activation and progress across the glia limitans in autoimmune disease, including EAE. Immunocytochemical analysis of both EAE and human tissues demonstrated the presence of $CD45^+$ myeloid cells with macrophage-like properties or dendritic cells in the perivascular space [137, 138], suggesting that foreign antigens may be taken up and processed by these resident antigen-presenting cells [139–141] and/or that antigen-loaded macrophages and dendritic cells might interact with lymphocytes from adjacent blood vessels or CSF [142]. Although the largest number of macrophages have been found in the subarachnoid spaces [143], Greter et al. showed that perivascular spaces around post-capillary venules also harbor a discrete population of vessel-associated $CD11c^+$ dendritic cells that are by themselves sufficient to present antigen to primed myelin-reactive T cells to promote CNS inflammation and clinical disease [142]. In line with these findings, the presence of $CD209\ (DC\text{-}SIGN)^+$ cells in close proximity to invading T cells was observed in acute and chronic active human MS lesions [142].

Studies in rodent and marmoset EAE models reported that inflammatory cells can be present within perivascular cuffs (leukocyte conglomerates within the perivascular spaces around postcapillary venules) for up to several weeks before parenchymal demyelination [144, 145]. By tracking pathogenic myelin basic protein-specific $CD4^+$ effector T cells in rodent EAE lesions, Kawakami et al. showed that $CD4^+$ T cells are stationary within perivascular spaces until they recognize their cognate antigen on perivascular antigen-presenting cells [146]. In line with this evidence, a follow-up study in rat EAE demonstrated that in the context of phagocyte-mediated T-cell activation, autoantigen availability was required for the locomotor behavior and pathological capacity of CNS autoimmune T cells [147]. By 2-photon imaging, real-time tracing of $CD4^+$ T-cell activation documented the cytoplasmic-nuclear translocation of a T-cell fluorescent activation indicator in the perivascular space, a process that did not occur within the vascular lumen, after contact with local antigen-presenting phagocytes [147]. A similar mechanism has also been proposed for MOG-associated antibody disease, in which perivascular MOG-laden macrophages were reported as characteristic features in the acute phase [148]. Taken together, there is convergent evidence to indicate that the presentation of autoantigens by perivascular macrophages, in part governed by intraparenchymal factors, provides immigrant T cells with the critical cues that direct them into the CNS parenchyma.

Human imaging

MRI studies have augmented the growing body of literature on the histology and ultrastructure of perivascular spaces. Although the spatial resolution of MRI is lower compared to tissue-based approaches for detecting perivascular spaces, the noninvasiveness and repeatability of MRI are crucial factors, considering the potential alterations in the configuration of perivascular spaces that may occur over time and upon death [149].

Depending on the resolution of the MRI technique used, perivascular spaces (PVS) that exceed a certain diameter become visible on MRI. These are often referred to as enlarged or dilated perivascular spaces, or sometimes Virchow-Robin spaces (Fig. 1) [150]. We prefer to utilize the term MRI-visible perivascular spaces (MVPVS) to acknowledge the currently limited understanding of the temporal dynamics of perivascular spaces [150]. PVS are indeed a physiological feature of the neuroaxis [150], whereas MVPVS are potentially associated with various factors, such as endothelial damage, disturbances in brain fluid exchange, and accumulation of immune cells during inflammation [149].

Identification of MVPVS is based on the signal properties of CSF, which is hypointense on T_1w imaging and hyperintense on T_2w imaging (Fig. 1). MVPVS have a linear appearance and abut parenchymal penetrating blood vessels, though the vessels themselves may not be visible on all imaging sequences [151]. Typically, MVPVS are observed in the basal ganglia, centrum semiovale, and pontomesencephalic junction [152]. However, less frequent locations have also been described, including hippocampus [153], insula [154], and cerebellum [155]. Despite recent advances in high-field MRI technology, which have enhanced the sensitivity and visualization of MVPVS [156], it is important to note that cortical perivascular spaces remain challenging to study. These challenges are likely attributable to factors such as the compaction of the glia limitans, pia mater, and vessel walls, as evident in both human and rodent cortices [149, 157, 158]. Enhancing the visualization of cortical perivascular spaces will advance our comprehension of their roles and contributions to neurological diseases, particularly within the context of the putative glymphatic system, wherein CSF from the subarachnoid space penetrates the brain parenchyma through the pial vasculature [159].

In most MRI studies, the emphasis lies on investigating the structural aspects of MVPVS and exploring the associations between MVPVS and various clinical and demographic parameters, particularly in the context of aging and neurological diseases. It has been observed that aging [160–163], systemic diseases that impact cerebrovascular health [164], small vessel ischemic disease [165–167], MS [156, 168–171], and other neuroinflammatory diseases

[172, 173] are commonly associated with a higher number of MVPVS. Interestingly, despite the primary pathology of perivenular inflammation in MS, a study of a postmortem cohort of six MS cases has surprisingly identified MVPVS as a characteristic feature of arterial pathology (Fig. 5A). The study compared pathological features of MS, such as perivascular cuffs, macrophage/microglia activation, axon damage, and fibrin deposition, between MVPVS and non-dilated PVS, revealing no association between MVPVS and these pathological features [174]. Therefore, their relevance for MS progression remains uncertain.

Glymphatic system

Immunopathology

The lymphatic vasculature of the dura mater does not directly contact the brain parenchyma under physiological conditions [175]. In the brain, a "glymphatic system" has been proposed as a CNS-specific drainage circuit consisting of the periarterial influx of fluid followed by aquaporin-4 facilitated, convective, trans-parenchymal fluid drainage and, finally, perivenous efflux [159, 176–178]. As such, it has been suggested to play a central role in regulating directional interstitial fluid movement, waste clearance, and, potentially, brain immunity [179, 180]. However, the nature and direction of the parenchymal fluid exchange pathways proposed by the glymphatic hypothesis remains controversial (the proposed model is shown in Fig. 1). Glymphatic system dynamics have been reported to be significantly impaired in adult mice following photodynamic ablation of dural lymphatic vessels, surgical ligation of lymphatic vessels afferent to deep cervical lymph nodes, or Prox1 haplodeficiency [181], suggesting that the glymphatic system and the dural lymphatic vessels are functionally connected [175, 181]. On a neuropathological level, the specific anatomical routes through which brain-derived molecules and waste products are cleared through CSF to reach the PSD and dural lymphatic vessels have not been fully elucidated.

Human imaging

Perivascular spaces around arterioles and venules are proposed to be the influx and efflux points of interstitial fluid to the extracellular matrix in the glymphatic model (Fig. 1), and accordingly several studies have focused on the potential glymphatic function of MVPVS. These studies can be categorized into two main groups: intravenous GBCA enhanced and non-GBCA MRI techniques.

GBCA-enhanced MRI techniques MVPVS typically do not exhibit GBCA enhancement [182]. However, recent studies have demonstrated GBCA enhancement within MVPVS areas on delayed heavily T_2w-FLAIR images acquired approximately 4 h after GBCA administration [183]. This phenomenon was observed even in neurologically healthy individuals. Further exploration revealed

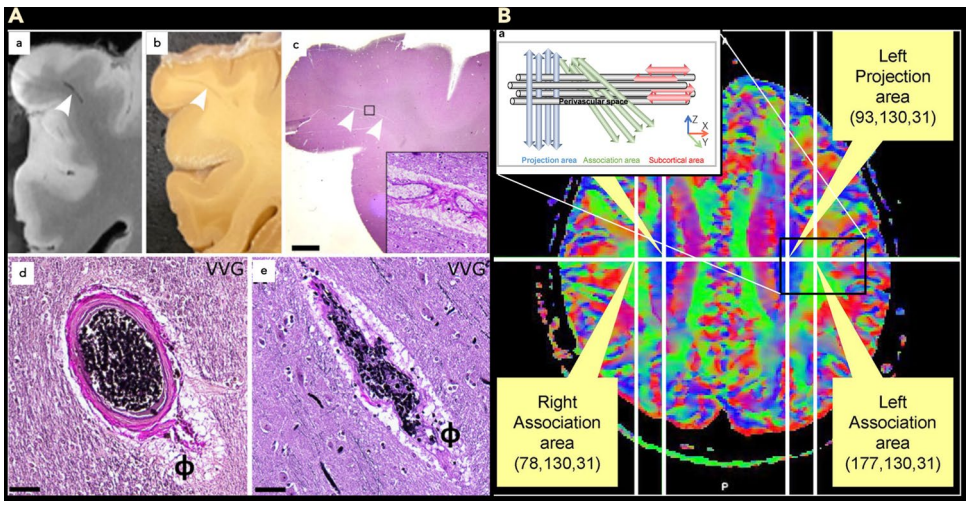

Fig. 5 **A** Virchow-Robin spaces (VRS) as seen in postmortem T_1w MRI scans from an individual with MS (**a**) were corresponded with brain tissue blocks and paraffin tissue slices (**b, c** inlet with 200× magnification). VRS were primarily associated with arteries (**d**) and much more rarely with veins (**e**). (Adapted from Ineichen BV et al., EBioMedicine. 2023) [174]. **B** The DTI-ALPS (diffusion tensor image analysis along the perivascular spaces) method is depicted, illustrating the ALPS index determined by the mean ratio of diffusion tensor values along projection and association fibers. (**a**) The ALPS index reflects the relationship between the perivascular space direction and the orientations of fibers in a hemisphere. Regions of interest used to calculate the ALPS index are strategically placed at the centers of regions with projection and association fibers (projection area and association area) to measure diffusivity in the x, y, and z directions (**b**). (Adapted from Taoka et al. 2022, Japanese Journal of Radiology; this corresponds to panel B of Figure 5 only, not the whole figure) [190]

distinct enhancement of MVPVS in the basal ganglia, along with concurrent enhancement of CSF within the basal cisterns and Sylvian fissures, but no enhancement of white matter MVPVS. These findings suggest the possibility of a drainage function-related MVPVS, an interesting possibility that warrants further investigation [184]. One technique that might prove useful in this context is DCE-MRI, which can assess BBB function and detect subtle changes in aging and disease [185–188], but this technique has not yet been applied to measure BBB integrity specifically around MVPVS.

Studies utilizing lumbar IT GBCA injection have provided some evidence supporting the role of the perivascular spaces as a component of the proposed glymphatic system in solute transport from CSF to the brain parenchyma. These studies have observed T1w signal changes within the cerebral parenchyma over a 48-h period following IT GBCA administration. In addition, they have noted differences in the reversal rates of GBCA-related changes, particularly delayed GBCA clearance in various conditions, including idiopathic intracranial hypertension [107] and chronic sleep disturbances [109]. Based on these findings, researchers have proposed the possibility that the glymphatic system serves as the uptake mechanism for GBCA tracers directly injected into the CSF, facilitating their transport to the brain parenchyma. In addition, they speculate that glymphatic dysfunction might contribute to delayed GBCA clearance [107, 109].

MRI techniques without GBCA administration The diffusion tensor imaging along perivascular space (DTI-ALPS) index is reported to enable quantification of water diffusivity along some perivascular spaces by exploiting the approximately perpendicular relationship between veins and axon fibers adjacent to the lateral ventricles [189, 190] (Fig. 5B). Pathological alterations in the CNS that occur in the same direction as the perivascular space (i.e., predominately the mediolateral direction) equally impact both projection and association fibers at the level of the lateral ventricular bodies. By dividing the diffusivity along the perivascular axis by the diffusivity along axes perpendicular to the dominant fiber axes, the DTI-ALPS index is taken to reflect pathological changes involving the perivascular space, purportedly serving as an indicator of glymphatic system function [189–191]. The DTI-ALPS index has been shown to be abnormal in various conditions, including aging [192–195], hypertension [192], small vessel ischemic disease [196], MS [197], cognitive impairment [195, 198–200], Parkinson's disease [193, 201–203], rapid eye movement sleep behavior disorder [203, 204], traumatic brain injury [205], and corticobasal syndrome [206].

A possible alternate route for solutes to access the glymphatic system via the CSF is through the circumventricular organs (CVO). Animal studies using intravenous GBCA administration have revealed heightened signal within the CSF spaces, while T_2w-FLAIR imaging has illustrated the distribution of GBCA in the CSF, implying that the CSF may offer a pathway for GBCA to enter the brain [207, 208]. In a DCE-MRI study with 20 healthy individuals, researchers investigated the permeability of CVO, which lack a blood–brain barrier [209]. The authors found that both secretory and sensory CVO exhibited significantly higher blood-to-brain transfer compared to normal brain tissue, supporting the concept of highly permeable CVO, with secretory CVO demonstrating the most robust transfer [210]. Consequently, this route suggests that ISF and solutes may follow the same path into the CSF, subsequently infiltrating the brain through the glymphatic system.

Conclusion and future perspective

The role of neuroimaging in bridging the gap between immunopathological processes and neuro-immune interfaces in various neurological diseases is crucial. By utilizing advanced neuroimaging techniques, valuable insights into brain barriers, inflammation, and fluid drainage dynamics can be gleaned, helping to fill knowledge gaps regarding the intricate interplay between the immune system and the CNS. Translational studies coupling neuroimaging and tissue histopathology may enable a more comprehensive understanding of aspects of neuroimmune interfaces in health and disease, providing new avenues for diagnostic and therapeutic advances.

Disclosures

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Availability of data and materials The authors declare that all data and materials referenced in this review are available in the sources cited within the manuscript. Any additional data or materials that were generated during the review process are available upon reasonable request to the corresponding authors.

Declarations

Ethics approval and consent to participate This review focuses on the synthesis and analysis of existing published literature and does not involve primary data collection from human participants, with the exception of the representative images in Figure 2B, 3A, and 4. The data depicted in these figures were obtained following approval from the Institutional Review Board and after securing written informed consent from the participants. This process was conducted as part of the National Institute of Neurological Disorders and Stroke's 'Evaluation of Progression in Multiple Sclerosis by Magnetic Resonance Imaging' protocol (NCT00001248).

Consent for publication The authors affirm that Figs. 2A, 3B, and 5 have been adapted and reused in this work after obtaining permissions and complying with copyright agreements. The original sources are appropriately acknowledged in the reference list. The original sources of all materials used in this review are appropriately acknowledged in the reference list.

Competing interests The authors have no competing interests related to the content presented in this review.

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