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EDITORIAL

Glymphatic imaging: a critical look at the DTI-ALPS index

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Derived from rodent studies, the glymphatic system was described in 2012 as a pathway facilitating perivascular clearance of solutes from the brain interstitial fluid (ISF) [1]. The term "glymphatic" is an abbreviation for glia-lymphatic, reflecting the presence of glial cells (astrocytic end feet) that ensheath all brain blood vessels, creating a pseudo-lymphatic system. The glymphatic clearance process is facilitated by an influx of cerebrospinal fluid (CSF) from the brain's surface along penetrating arteries, leading to an exchange with ISF (CSF-ISF exchange), followed by subsequent clearance of solutes from the brain along veins. Glymphatic activity is associated with sleep, also in humans [2], and its clearance function concerns primarily endogenous waste products such as amyloid-β and hyperphosphorylated tau, which accumulate in various neurodegenerative disorders [3].

In this edition of *Neuroradiology*, Yin and colleagues report on disrupted glymphatic function in children with periventricular leukomalacia (PVL), assessed with the diffusion tensor imaging along the perivascular space (DTI-ALPS) index [4]. First proposed by Taoka et al. in 2017, the index was developed to serve as a non-invasive marker of glymphatic function [5]. Applied in cerebral white matter, and typically on the left side, the region of interest is positioned at level with the upper part of the lateral ventricles, where deep medullary veins run transversally and mainly in parallel to the image slice orientation (Fig. 1a). Here, the method's aim is to isolate and measure water diffusivity within perivascular spaces running in parallel to these veins. The current study by Yin et al. adds to a rapidly growing body of research employing DTI-ALPS, where a change in index has led authors to conclude about impaired glymphatic function in various conditions, from neurodegenerative diseases like Alzheimer's disease [6] and Parkinson's disease [7] to gliomas [8], stroke [9], and even fibromyalgia [10]. Typically, studies of the DTI-ALPS index have compared patients with healthy controls. Studies reporting negative results with this methodology are exceptions [11].

Non-invasive approaches to MRI of human brain clearance have typically focused on cerebral white matter. Similar to the DTI-ALPS index, assessment of enlarged perivascular spaces in white matter has also been proposed to serve as a surrogate marker of glymphatic function [12, 13]. However, the initial description of the glymphatic system in vivo stemmed from the cortex, using two-photon microscopy of rodents, offering a field of view up to ~ 0.2 mm beneath the cortical surface [1]. Furthermore, whole-brain images revealed entry from the surface into the cortex of a fluorescent tracer, but with very limited penetration into the deep cerebral white matter [1]. Human studies using intrathecal injection of CSF tracer (gadobutrol) later confirmed this observation, showing sparse or undetectable tracer enhancement (i.e., CSF-ISF exchange) in areas of deep white matter, which includes the DTI-ALPS region of interest (Fig. 1b) [14, 15]. Hence, CSF-ISF exchange, and thus glymphatic clearance, seems to play a minor role in brain clearance in deep white matter, where other established clearance pathways, such as transport over the blood–brain-barrier and local proteolytic degradation [16], likely dominate. One study did compare DTI-ALPS with intrathecal enhanced MRI, which can be considered the gold standard for assessment of CSF-ISF exchange, however, only investigating intrathecal contrast enhancement in regions distant to the DTI-ALPS measurement, including subcortical and CSF locations [17]. In fact, to which extent glymphatic clearance contributes to total brain clearance capacity in general remains uncertain, since spatial and temporal variations in CSF-ISF exchange throughout the human brain have been demonstrated [2, 14]. A limited DTI measurement in white matter can hardly account for this.

The rationale behind assessing perivascular space diffusivity in white matter as a marker of glymphatic function

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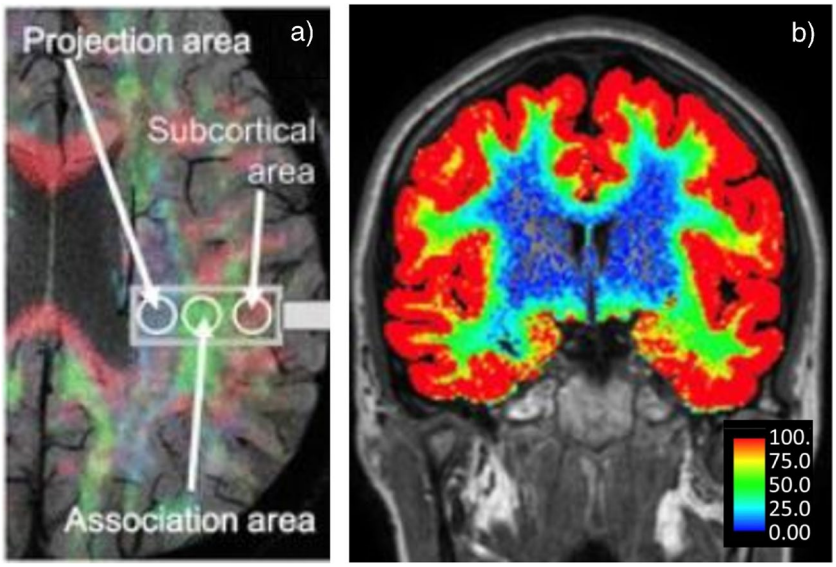

Fig. 1 The DTI-ALPS index is calculated from DTI at level with the lateral ventricles, where deep medullary veins run mainly in parallel with the image slice orientation (overlay of DTI color map and susceptibility-weighted image, (SWI)) (**a**). The aim is to isolate water diffusivity in the direction of perivascular spaces in the image plane and is interpreted as a surrogate marker of glymphatic function, i.e., CSF-ISF exchange (from Taoka et al. in the *Japanese Journal of Radiology*, 2017 [5] by permission from SpringerLink through a CCC license). However, intrathecal enhanced MRI demonstrates that CSF-ISF exchange in white matter occurs to a minor degree, particularly in deep white matter (**b**). Other clearance pathways than the glymphatic system therefore seem to dominate in this region. The color scale bar indicates a percentage increase of normalized signal units at T1 due to penetration into the brain from the surface (after intrathecal contrast administration) (from Agarwal et al. in *Journal of Magnetic Resonance Imaging*, 2023 [15], reprinted under the terms of the Creative Commons CC BY license)

seems further based on the anticipation that perivascular spaces are continuous between white matter and cortex. If so, white matter perivascular spaces deep into the cortex could be affected indirectly by impaired perivascular clearance within the cortex. However, blood vessels are much richer in the cortex than in subcortical white matter, and the majority of cortical vessels do not connect directly with vessels in the underlying white matter [18]. The minor proportion of vessels crossing the grey-white matter junction typically turns to run in parallel with the cortex subcortically (Fig. 2). Considering medullary veins, which can be visualized at susceptibility-weighted

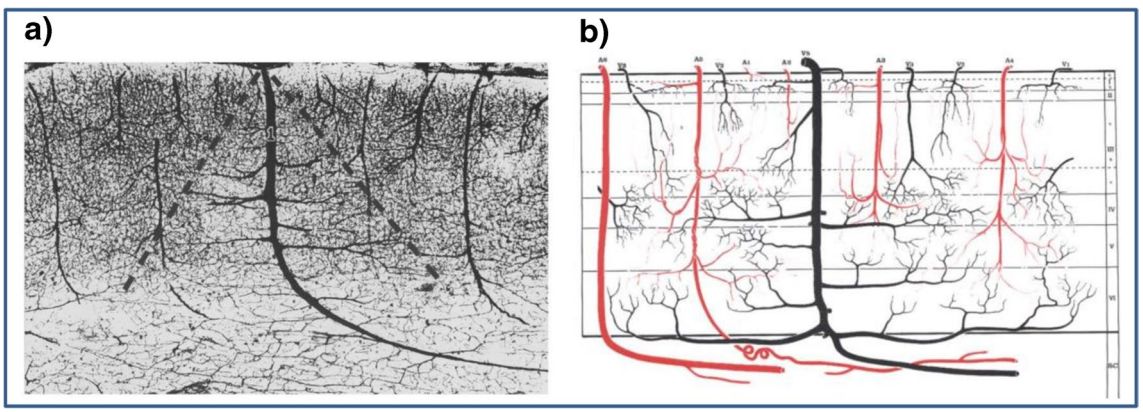

Fig. 2 As shown in **a**, the vascular network is much denser in the cortex than the underlying subcortical white matter (photograph with × 28 magnification after injection of India ink and gelatin, from the middle temporal gyrus). Dotted lines indicate the conically shaped vascular territory of the principal vein (marked "1"), which in the subjacent white matter has an almost parallel orientation to the cortex. The schematic drawing in **b** demonstrates that most vessels within cortical layers I–VI do not penetrate into subcortical white matter (SC). Images reprinted from Duvernoy et al. Cortical blood vessels of the human brain (Brain Research Bulletin, 1981) [18], permission provided by Elsevier through Copyright Clearance Center

imaging, only superficial medullary veins drain towards the surface. Deep medullary veins, which are also encompassed by the DTI-ALPS region of interest, drain into deep subependymal veins along the lateral ventricles [19]. Penetrating arteries from the surface that vascularize the white matter (medullary arteries) are relatively few [18].

Finally, perivascular spaces in white matter account for about 1% of the tissue [20]. It is therefore unlikely that the DTI-ALPS index can even distinguish perivascular water diffusivity from other sources of directional water motion, such as diffusion along fiber tracts, which are included in the region of interest. In addition, comes potential confounding factors, such as patient motion, blood flow, and the process of manually placing the region of interest.

One may speculate why imaging-based assessments of perivascular spaces in white matter have gained interest in attempts to assess glymphatic function. At MRI, most perivascular spaces are not visible; perivascular spaces are typically encountered when being enlarged within the basal ganglia or white matter. Perivascular spaces in the cortex are rarely enlarged, and thus not visualized at all, and except for intrathecal enhanced MRI, there are few remaining alternatives to image CSF-ISF exchange directly. Nevertheless, the overriding hypothesis that movement of water (the solvent) along white matter perivascular spaces can be a surrogate marker for brain-wide cortical clearance of much larger solutes (amyloid-β, tau) lacks foundation in existing knowledge. Hence, the validity of DTI-ALPS as a marker of glymphatic brain clearance is highly questionable. Even though many studies have shown an association between this index and neurological diseases, the association is not synonymous with causality, as confounding factors may be prevalent, including in children with PVL. Still, a causal relationship between DTI-ALPS and glymphatic function has generally been assumed, even if the disease`s impact on a DTI-based parameter appears almost inevitable, such as in multiple sclerosis [21]. More likely, the DTI-ALPS index expresses features of white matter only, suggested by the correlations with other DTI-based parameters, such as fractional anisotropy, mean, axial, and radial diffusivity and also age [22].

To this end, understanding the true extent and contribution of the glymphatic system to overall brain clearance capacity is crucial for advancing our knowledge of neurological diseases, particularly neurodegenerative diseases that are characterized by protein deposition in the cortex [23]. Attempts to develop new imaging tools for human brain clearance research should be applauded. However, before embracing these methods, we need to pay great attention to existing controversies within the basic sciences [24] and appreciate the complexity and diversity of mechanisms underlying the clearance of large-molecular endogenous solutes from the cortex. In this context, a clearance marker based on the mobility of water in the white matter seems, unfortunately, insufficient.

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Declarations

Ethics approval Not applicable.

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