Redefining MRI:
From Image to Insight

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Fluids and Clearance in the Brain: What Can MRI Tell Us through DTI-ALPS and Neurofluid Imaging?

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Brain fluid dynamics have attracted increasing attention in neuroimaging, particularly in relation to the glymphatic system, interstitial fluid transport, and metabolic waste clearance. Diffusion tensor image analysis along the perivascular space (DTI-ALPS) was originally developed as a noninvasive MRI method for evaluating diffusivity related to the perivascular space. It has since been widely applied to studies of various diseases and status. However, the biological interpretation of the ALPS index has become increasingly complex.

This lecture will revisit what DTI-ALPS can and cannot tell us about fluids and clearance in the brain. The ALPS index should not be regarded as a direct measure of whole-brain glymphatic flow, CSF-ISF exchange, or macroscopic waste clearance. Diffusion MRI primarily reflects probabilistic displacement of water molecules rather than unidirectional bulk flow. Because the ALPS index is a ratio-based measure derived from directional diffusivity components in periventricular white matter, similar reductions may arise from different mechanisms, including reduced diffusivity along the presumed perivascular direction, increased denominator diffusivity related to white matter damage, or both.

Accumulating evidence indicates that the ALPS index is influenced by white matter microstructure, fiber orientation, crossing fibers, extracellular geometry, vascular configuration, aging, and acquisition or analysis conditions. These influences should not be viewed only as confounders. White matter architecture and extracellular geometry may themselves shape interstitial fluid transport, and brain fluid movement may occur preferentially along structurally defined pathways. Thus, the structure dependence of DTI-ALPS may reflect meaningful interactions between white matter organization and neurofluid dynamics.

The proposed framework is to understand DTI-ALPS as a structure-dependent, spatially fixed-point diffusion biomarker. It evaluates localized directional diffusivity within a standardized anatomical region and may serve as a composite marker of the brain tissue environment, integrating white matter microstructure, perivascular-related diffusion, extracellular space, vascular factors, and neurofluid-related physiology. This makes DTI-ALPS useful for longitudinal studies and multimodal neurofluid imaging, provided that acquisition, ROI placement, tensor orientation, and laterality are standardized.

The key message is that MRI can provide valuable information about brain fluids and clearance, but no single MRI biomarker can represent the entire glymphatic system. DTI-ALPS should be interpreted as one component of a broader multimodal framework.

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