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Glymphatic System Analysis via Diffusion MRI

Whitepaper

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The glymphatic system is the glial-dependent waste-clearance pathway of the CNS, analogous to the lymphatic system of peripheral tissues. Operating at the paravascular level, it mediates the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF), but is also thought to be important for the distribution of electrolytes, lipids and other macromolecules throughout the brain. It has been demonstrated that glymphatic activity is enhanced during sleep and suppressed during wakefulness. It also reduces sharply during aging. This decline has been linked to the hallmark protein aggregation of neurodegenerative diseases, and indeed, evidence supports the role of glymphatic system dysfunction in the age-related accumulation of beta-amyloid. For this reason, interest in the system has been growing ever since the term was first coined in a study of rodents back in 2012.

The initial definition of the glymphatic system was based upon in-vivo 2-photon and ex-vivo fluorescence imaging in rodent brain slices. This was both inherently limited in its ability to capture dynamic 3D data of the whole brain as well as in its scalability to clinically-relevant human research. Thus, the following year the same group developed a method based on contrast-enhanced MRI to visualize CSF-ISF exchange. This included the definition of some simple kinetic parameters to describe the flux of the gadolinium-based contrast agents throughout the brain volume. The technique has since been successfully deployed in humans, although to a limited extent given the requirement for intrathecally administered tracers with serial imaging to measure fluid movement over time.

The suitability of a non-invasive MR imaging technique, namely diffusion tensor imaging (DTI), for investigating the glymphatic system was first demonstrated in 2017. DTI seeks to characterize the properties and orientation of the diffusion of water molecules, and so its use in measuring diffusivity along the perivascular space is a logical application.

At the level of the lateral ventricle body, the medullary veins - and by extension the perivascular space - run perpendicular to the ventricular wall. In the axial plane this constitutes the x-direction. Perpendicularly in the same region, association fibers are organized anteriorly to posteriorly (y-direction) and projection fibers from head to foot (z-direction). As no major white matter tracts run parallel to the x-direction, by examining microstructural changes in the fibers of the y and z-directions, one can near-independently examine the diffusivity and (by assumption) the integrity of the perivascular space, or glymphatic system. See an illustration of this concept taken from the original proof-of-concept study below.

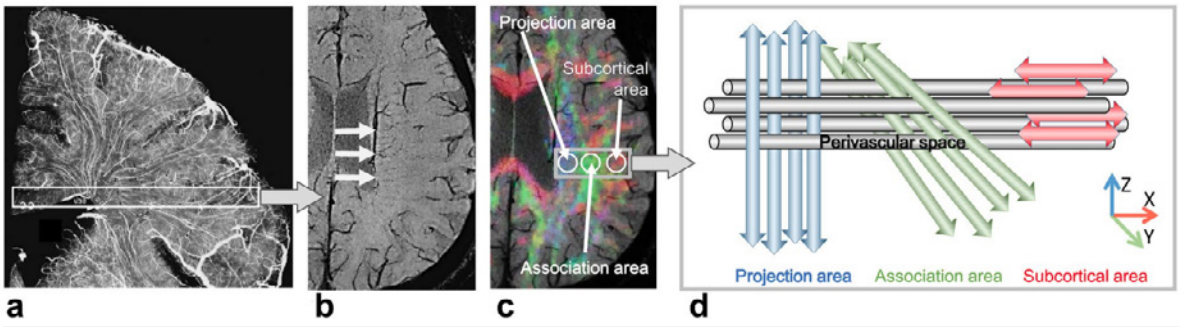

Figure: Concept for the diffusion tensor image analysis along the perivascular space (DTI-ALPS) method. **a** Roentgenogram of an injected coronal brain slice showing parenchymal vessels that run horizontally on the slice (white box) at the level of the lateral ventricle body. **b** Axial SWI on the slice at the level of the lateral ventricle body indicates that parenchymal vessels run laterally (x-axis). **c** Superimposed color display of DTI on SWI indicating the distribution of projection fibers (z-axis: blue), association fibers (y-axis: green), and the subcortical fibers (x-axis: red). Three ROIs are placed in the area with projection fibers (projection area), association fibers (association area) and subcortical fibers (subcortical area) to measure diffusivities of the three directions (x, y, z). **d** Schematic indicating the relationship between the direction of the perivascular space (gray cylinders) and the directions of the fibers. [Taoka et al. 2017]

The technique can be performed using standard diffusion MRI acquisitions alongside conventional structural images. Image processing is similarly simple and may follow common DTI processing pipelines, up to and including the point of diffusivity and FA maps generation. Thereafter, a color-coded FA map in the axial plane of the lateral ventricle is used to guide the placement of three spherical ROIs: in the area of projection fibers, association fibers and subcortical fibers. Diffusivity in the x, y and z-directions are calculated in each ROI. Finally, the activity of the glymphatic system is evaluated via calculation of the so-called ALPS ('along the perivascular space') index:

$$\textbf{ALPS index} = \textbf{mean}(D_{xproj}, D_{xassoc}) / \textbf{mean}(D_{yproj}, D_{zassoc})$$

This ratio essentially renders differences between x-axis diffusivity in projection/association areas and diffusivity perpendicular to this as attributable to the existence of the perivascular space. A value close to 1 suggests minimal water diffusion along the perivascular space, and larger values greater diffusivity and therefore glymphatic activity. It is owing to this index that the technique is referred to in the literature as DTI-ALPS.

The utility of DTI-ALPS as a biomarker of neurodegenerative disease is already showing great promise. The index positively correlates with the MMSE clinical score of cognitive impairment. Significant differences have been observed between cognitively normal and AD/MCI groups, as well as in PD patients, where a lower ALPS index is associated with longer disease duration.

References and further reading:

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@QMENTA_Inc

qmenta_inc

qmenta.com

info@qmenta.com

US Headquarters
75 State Street, Suite 100, Boston, MA 02109
+1 339 368 8040

EU Offices
C/ Roger de Llúria 46, Pral. 1ª, 08009 Barcelona, Spain
+34 933 282 007