Non-invasive imaging of CSF-mediated brain clearance pathways via assessment of perivascular fluid movement with diffusion tensor MRI

IF Harrison[1], B Siow[1,2], AB Akilo[1], PG Evans[1], O Ismail[1], Y Ohene[1], P Nahavandi[1], DL Thomas[3,4], MF Lythgoe[1], JA Wells[1]

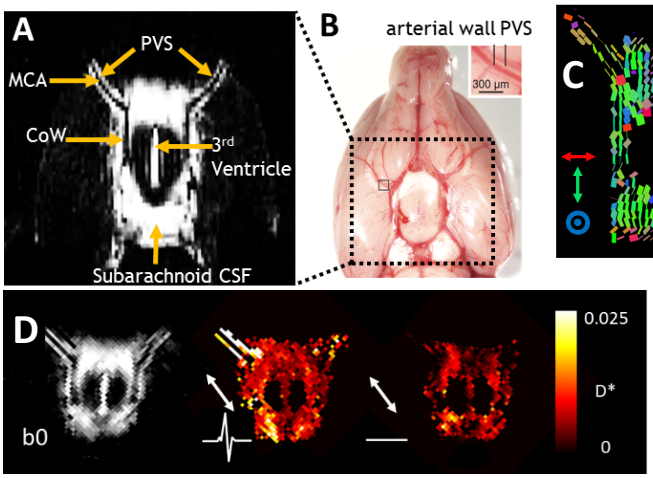
1.UCL Centre for Advanced Biomedical Imaging. 2. The Francis Crick Institute. 3. Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology. 4. Leonard Wolfson Experimental Neurology Centre, UCL Institute of Neurology

Introduction The exchange of CSF with the brain's interstitial fluid (ISF) is an established mechanism underlying the parenchymal clearance of amyloid beta (Aβ), a leading molecular candidate to initiate Alzheimer's disease (AD) [2-7] [1]. The development of non-invasive methods to image CSF-mediated brain clearance pathways, such as the glymphatic system, would enable practical measurement in the human brain which will help characterise the role of CSF-mediated clearance pathways in pathology. The perivascular space is a fluid filled compartment that surrounds selected blood vessels in the brain and forms a central component of the glymphatic pathway that is said to drive rapid CSF-ISF exchange [2]. Here, we present the first non-invasive technique for the assessment of glymphatic inflow by using an ultra-long echo time, low b-value diffusion weighted MRI sequence to assess perivascular fluid movement in the rat brain.

Methods 27 male Sprague Dawley rats were used in these experiments (isoflurane anaesthesia, 9.4T Agilent). An ultra long TE (142ms) was employed to attenuate the signal from the surrounding arterial blood and tissue relative to the MRI signal from CSF in the subarachnoid space and fluid in perivascular channels. An axial slice was positioned at the ventral aspect of the brain at the level of the Circle of Willis (CoW - see Figure 1 A). A FSE diffusion weighted sequence was then applied with the following parameters: TR = 5s, ETL = 16 FOV = 25 x 25 mm, matrix size = 128 x 128, ST= 1 mm, NA =12 with either 3 or 6 diffusion weighted directions (n=10 for multi-direction DWI, n=6 for DTI respectively). Additional experiments were performed gated to the r-wave (ECG) to investigate the effect of arterial pulsatility on the measured pseudo-diffusion coefficient (D*) of the PVS (n=5) and before and after adrenoceptor agonist dobutamine (n=6).

Results: Bright tracts appear either side of both MCA branches (Figure 1A) which, due to the ultra-long echo time, must derive from fluid filled compartments of similar composition to the CSF in the subarachnoid space. This observation, together with the characteristic morphology that runs alongside and parallel to the MCA, is consistent with the description of the perivascular space as a fluid filled compartment that surrounds major blood vessels feeding the brain. Indeed, the location of this compartment is highly consistent with direct assessment from a previous study (Figure 1B, adapted from [2]). The principle direction of the D* tensors was found to be parallel to the orientation of the PVS (Figure 1C), providing evidence that the technique is sensitive to PVS fluid movement. A striking and highly directional dependence of D* on cerebral vascular pulsation was observed in the PVS (Figure 1D). D* in the PVS was ~ 300% greater during arterial pulsation relative to diastole when motion probing gradients were applied parallel to the principle orientation ($p<0.01$). A 65% increase in D* along PV channels was recorded ($p<0.01$) following dobutamine.

Figure 1



A. *Example b0 MRI image. Bright signal can be observed from fluid filled compartments: CSF in the subarachnoid space around the Circle of Willis (CoW); fluid in the perivascular space that surrounds the MCA;the ventral aspect of the third ventricle.* ***B.*** *Photograph of the ventral aspect of the rat brain surface.* ***C.*** *Example map of pseudo-diffusion tensor ellipsoids with corresponding b0 image (insert).* ***D.*** *b0 image (first column) and D* maps during arterial pulsation (second column) and during diastole (third column) from a single animal [the white arrows represent the direction of the applied 'diffusion' gradients].*

Conclusion: In this study, we introduce a novel MRI method to measure a distinct feature of brain physiology that, to date, has only be assessed using invasive methods – the movement of fluid in the perivascular space. Efforts are ongoing to investigate the sensitivity of the method to detect dysfunction of PVS fluid associated with ageing and models of pathological conditions.

[1] Iliff *et al.*, Sci Trans Med, 2012; [2] Lochead *et al.*, JCBFM 2014.