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Diffusion-weighted 2D cortical slice mapping to spatially resolve distinct neurofluid flow regimes

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Synopsis

Keywords: Neurofluids, Velocity & Flow, Glymphatic-lymphatic

Motivation: While glymphatic-lymphatic function has been observed using two-photon imaging and contrast-enhanced MRI, noninvasively quantifying CSF neurofluid flow regimes poses significant challenges.

Goal(s): This study aims to establish methods to noninvasively map CSF flow regimes, namely within the perivascular space and parenchyma.

Approach: Using diffusion-weighted 2D cortical slice mapping, we resolve vessels tangent to the surface of the rat cortex under varying anesthesia conditions of isoflurane and dexmedetomidine. We segmented individual vessels and their corresponding perivascular and parenchymal spaces then classified apparent arterioles and venules.

Results: Diffusion coefficients within these regions of interest show significant differences between the isoflurane and dexmedetomidine anesthesia conditions.

Impact: The measurement of spatially resolved flow regimes using the novel technique of 2D cortical slice diffusion-weighted MRI has the potential to improve clinical assessments of CSF neurofluid dynamics in the glymphatic-lymphatic system.

Introduction

The glymphatic-lymphatic system, a recently identified brain-wide circulation system of cerebrospinal fluid (CSF) critical for the elimination of waste, has been shown to play a critical role in many neurologic conditions including Alzheimer's disease, Parkinson's disease, aging, and brain injury, among others[1,2]. It is characterized by the motion of CSF through three different flow regimes: first, CSF enters the brain through periarterial spaces, then sweeps across the parenchyma, and finally exits the brain through the perivenous spaces (Figure 1a). While this system has previously been observed with two-photon imaging[1] and contrast-enhanced MRI[3], there remains an urgent need for improved non-invasive CSF transport imaging strategies to enable quantifiable assessments of glymphatic-lymphatic function within different neurofluid flow regimes, namely the perivascular spaces and the parenchyma. In this study, we establish methods to spatially resolve and measure CSF transport in perivascular and parenchymal regimes by time-of-flight (TOF) and T2* mapping of arterioles and venules in 2D cortical slices and diffusion-weighted MRI (DW-MRI) in the same space. This strategy has been successfully applied to study the functional MRI signal[4], but it has not yet been implemented for DW-MRI. Our objective is to map the cortex with high resolution to visualize single vessels tangential to the surface and quantify the neurofluid dynamics in separate flow regimes associated with glymphatic-lymphatic waste clearance (Figure 1b&c). To accomplish this, we imaged rats under isoflurane (ISO) anesthesia, mimicking low CSF flow rates, and dexmedetomidine (DEX) anesthesia, inducing high CSF flow rates[5]. We measured changes in directional diffusion coefficients within perivascular and parenchymal ROIs to probe CSF fluid dynamics.

Methods

Rats were each imaged using different anesthesia paradigms in a single scan session (Figure 2a) on a Bruker 7T Biospec 70/20 pre-clinical MRI scanner with ParaVision 360 3.5 software, 86 mm quadrature birdcage transmit coil, and 4 channel rat brain surface array RF receive coil. Single slices with high in-plane resolution were placed tangential to the cortical surface to collect TOF, multi-gradient echo (MGE), and DWI data (Figure 2b). DWIs were acquired with 2D echo planar imaging and the same diffusion desensitization applied along three orthogonal directions. An overview of processing methods is described in Figure 3. In Matlab, MGE and DWI were resized to match the resolution of the TOF images, then landmark registration was manually performed using vascular landmarks to move all images into the same space as the initial TOF scan. A mask of the cortex was drawn and divided into 16 sub-regions. Thresholding was performed on each sub-region of the TOF image to identify blood vessels with intensities greater than 98.5% of the sub-region. Individual vessels, perivascular space, and parenchyma masks were segmented. Perivascular space masks were defined as one pixel around the vessel mask. Parenchymal masks were defined as all remaining regions, excluding any identified vessels and perivascular spaces. Apparent arterioles and venules were identified by a respective increase or decrease in MGE from the ISO to the DEX anesthesia condition. Finally, the apparent diffusion coefficients (ADCs) in the z-direction were calculated from the DWI images.

Results & Discussion

We evaluated diffusion coefficients in ROIs relevant to glymphatic-lymphatic flow across ISO and DEX anesthesia conditions that provide slow and fast CSF flow respectively (Figures 4 & 5). Using a paired t-test, we observed that statistically significant differences in ADC values exist between the ISO and DEX conditions in the vessel (p=1.27e-14), perivascular (p=4.9e-21), and parenchymal (p=3.01e-45) ROIs. Surprisingly, a decrease in ADC was observed in the fast flow DEX condition, especially in the parenchymal ROI. This could be due to increased phase contributions in the high flow condition or influences from cortical microstructure, which are areas of future research.

Conclusion

By delineating spatially resolved flow regimes within vascular, perivascular, and parenchymal spaces with 2D cortical slice DW-MRI, a novel diffusion technique, we may identify unique features of diffusion in each flow regime to fill a fundamental knowledge gap regarding CSF flow dynamics in the glymphatic-lymphatic system. The development of tools to characterize CSF flow supports a wide range of neurologic disorder studies in which CSF transport and waste clearance are implicated. Future directions of this work include improving vessel segmentation through adaptive thresholding, improving arteriole-venule identification, and validation with tandem in vivo optical imaging. Furthermore, we plan to expand ROI-based analysis by investigating phase contrast MRI to determine what velocities contribute to the signal in vivo[6].

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Figures

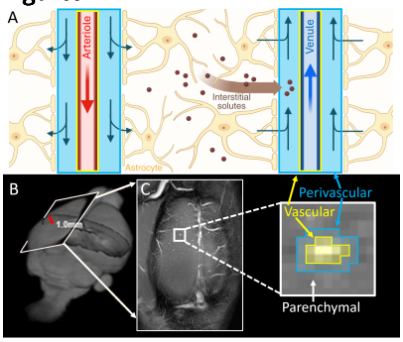

Figure 1: Overview of glymphatic theory and cortical slice mapping. (A) Proposed movement of glymphatic flow in the surface of the cortex (created with BioRender). (B) Location of the 2D cortical slice adapted from Yu et al[4]. (C) 2D cortical slice TOF image with labeled ROIs.

A

Group	Anesthesia 1	Anesthesia 2	n
1	ISO	ISO	4
2	DEX	DEX	4
3	ISO	DEX	6

B

Specifications	TOF	MGE	DWI
Echo time (ms)	3.35	2.8	46
Repetition time (ms)	80	50	3000
Flip angle (degrees)	60	50	-
Averages	20	40	1
Acquisition matrix (voxels)	296 x 400	254 x 304 x 6	128 x 152 x 123
Resolution (mm)	0.075 x 0.075 x 0.8	0.09 x 0.1 x 0.8	0.175 x 0.200 x 0.8
B-values (s/mm^2)	-	-	0, 400, 600, 800
Segments	-	-	4
Scan time	7 min 53 sec	12 min 23 sec	8 min 15 sec

Figure 2: (A) Experimental design across three groups in which the anesthesia conditions are varied. (B) MRI acquisition specifications.

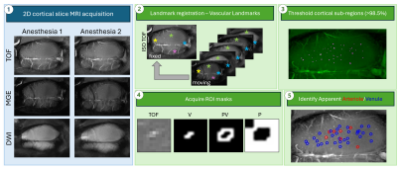

Figure 3: Data processing methods. After 2D cortical slices were acquired under the ISO and DEX anesthesia conditions, images were processed in Matlab. Landmark registration was manually performed using vascular landmarks, then images were thresholded to identify blood vessels. Vessel (V), perivascular (PV) and parenchymal (P) masks were generated. Arterioles and venules were identified by MGE increase or decrease from the ISO to DEX condition.

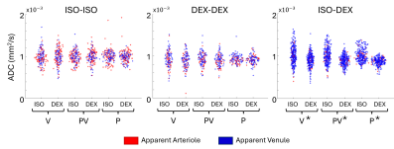

Figure 4: ADC change across ISO and DEX anesthesia conditions in the ROIs. Asterisks indicates p-value < 0.0001 with the x-axis labels corresponding to vessel (V), perivascular (PV) and parenchymal (P) regions.

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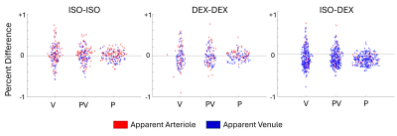

Figure 5: Percent difference of ADC change across ISO and DEX anesthesia conditions in the ROIs.