High Resolution Mapping of Intravascular Water Molecule Lifetime in the Rhesus Macaque Brain

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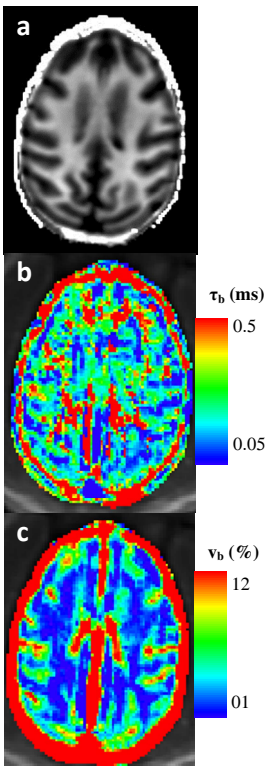
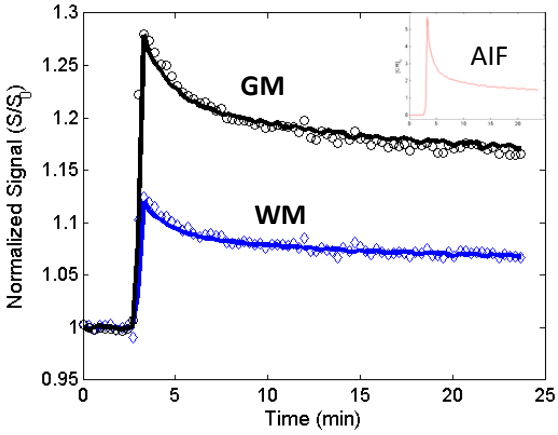
Introduction: Dynamic contrast-enhanced (DCE) MRI is useful in examining cerebral pathology. Pharmacokinetic modeling of DCE-MRI data provides access to physiologically relevant parameters that characterize vascular properties *in-vivo*. Parameters such as blood volume fraction (v_b) and mean intravascular water molecule lifetime (τ_b) are sensitive to vascular changes related to disease state (*submitted).* Quantitative T_1 mapping techniques have been shown to be sensitive to vascular water exchange, but these techniques are time intensive and often have limited tissue coverage. 3D Gradient Recalled Echo (GRE) sequences offer full brain coverage with a relatively short acquisition time, allowing for high spatial and temporal resolution DCE-MRI measurements. Here, we investigate the feasibility of measuring v_b and τ_b with 3D GRE DCE-MRI in Rhesus Macaque brain. Contrast Agent (CA) does not extravasate to any appreciable extent during CA first-pass in the normal brain; following this assumption, a 2-site-exchange [2SX] shutter-speed paradigm [SSP] DCE-MRI analysis can be employed to obtain v_b and τ_b.(1,2)

Methods: Four healthy adult males were selected from our free-range colony. All images were acquired on a Siemens 3T TIM Trio instrument with a 15 channel Tx/Rx coil (Quality Electrodynamics, Mayfield, OH). The DCE-MRI measurement was achieved with a 3D FLASH sequence (TR/TE/FA: 9 ms/2.46 ms/20°) with 32 2.0-mm transverse head slices. The nominal in-plane resolution was $[1.25\ mm]^2$. Animals were anesthetized and a 0.3 mmol(gadoteridol)/kg CR bolus was administered, in the left s.v. in 10 - 15 s, ten or twenty image frames after starting the DCE-MRI acquisition, which lasted 18 minutes. The inter-image interval was 18 s. The arterial input function (AIF) was obtained from the DCE-MRI time-course of a *sagittal sinus* region-of-interest (ROI). The AIF from one animal was selected for use in all analyses and amplitude adjusted based on quantitative 3D R_1 maps obtained before and after the DCE time series acquisition. All images were coregistered and segmented using FSL's FLIRT and FAST tools, respectively.(3,4) Whole-brain WM and GM intensity-average signals were fitted with the Fast-Exchange-Regime-allowed SSP (5) to extract v_b, and τ_b values. Parametric maps were similarly created by voxel-wise fittings. Parameter estimation precision was evaluated via 1000 Monte Carlo simulations on each ROI fitting.



Results: Whole-brain ROI population average parameter values are given in the **Table** with standard deviation of means for the four animals given in parentheses**.** Parameter precisions are high based on Monte Carlo simulations with mean τ_b, v_b variances of 9.5 ms, 0.07% and 10 ms, 0.14% for WM and GM, respectively. **Figure 1** shows a representative high resolution transverse quantitative R_1 ($\equiv 1/T_1$) map (**a**) and corresponding τ_b (**b**) and v_b (**c**) parametric maps; the color scale is given adjacent to each map. Increased τ_b and v_b values in the subarachnoid and ventricular cerebrospinal fluid are artificial due to model insufficiency. Representative whole-brain signal-averaged WM and GM tissue response curves (hollow data points) and their respective fitted curves (solid lines) are shown in **Figure 2**. The AIF used for all analyses is displayed in the inset.

Tissue	τ_b (msec)	v_b (%)
WM (SD)	178 (±36.3)	3.17 (±0.46)
GM (SD)	291 (±28.6)	7.59 (±0.77)



Discussion: WM τ_b values found here are smaller than have been previously reported (~300ms) in humans or Japanese Macaque.(6) GM τ_b values are also lower than reported in human brain (~260ms)(1); although human brain measurements were collected in the un-sedated state. Average WM v_b are in good agreement with that previously reported in Japanese Macaque.(6) Elevated GM v_b compared to WM is consistent with its highly vascularized nature. Importantly, the measurements in (6) were sparsely sampled over nearly an hour and required a K^{trans} correction, which had significant effects on parameter estimation. Reported human parameters are for conscious subjects; the effects of anesthesia on τ_b is unknown. Even though these data were not B_1 corrected, our initial experience is that the corrections are minor. Measurements across animals showed consistent results with low variance and high parameter precision, suggesting that our approach does indeed extract v_b, and τ_b values from 3D GRE DCE-MRI data. These parameters have potential as novel biomarkers of disease-related vascular changes *in-vivo*; the ability to collect whole-brain maps of these parameters in a clinically appropriate scan time has been demonstrated and may be of great importance in studying disease processes and in evaluation of therapy efficacy.

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References: **1.** Rooney, *et al*, *PISMRM* 11:2188 (2003). **2.** Rooney, *et al, PISMRM* 12:1390 (2004). **3.** Jenkinson, *et al*, *NeuroImage* 17(2):825-841 (2002). **4.** Zhang, *et al*, *IEEE Trans Med Imag* 20(1):45-57 (2001). **5.** Li, *et al, JMR* 218:77-85 (2012). **6.** Njus, *et al, PISMRM* 17:1480 (2009).