Quantitative β mapping for high-field calibrated fMRI in rat brain

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TARGET AUDIENCE: Neurophysiologists interested in the metabolic basis of calibrated fMRI, clinicians interested in using calibrated fMRI.

PURPOSE: The BOLD signal is derived from the relaxation rate of tissue water (R_2') that is heavily dependent on deoxyhemoglobin-based susceptibility[1]. This R_2' term is measureable from the transverse relaxation rates of gradient echo ($R_2^{GE} \approx R_2' + R_2$) and spin echo ($R_2^{SE} \approx R_2$), where R_2' and R_2 represent the reversible and nonreversible components[2]. This relaxation rate term is related to the susceptibility of deoxyhemoglobin by a power-law relationship containing the scaling exponent β[1,3], where $R_2' \propto$ (susceptibility of deoxyhemoglobin) $^{\beta}$. Since the level of deoxyhemoglobin-based susceptibility depends on the interaction between cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMR_{O2}), β is the basis of calibrated fMRI[2,3]. Since the physiological basis of β is not yet determined in vivo, it is common to use a value of 1.5 determined by simulations from behavior of water molecules within blood vessels at 2T[1,4]. Subsequently, the same value has been applied in the large majority of studies in all brain regions. Because R_2' is dependent on the subject's physiological conditions and the field strength of the magnet being used, there is a need for measuring β in vivo for calibrated fMRI in clinical settings. This study proposes an experimental approach to measure β in vivo. We enhanced susceptibility through injecting multiple doses of a superparamagnetic contrast agent and assumed that susceptibility of blood is proportional to the amount of contrast agent. With sequential increasing dose, we measured R_2' (i.e., $R_2' = R_2^{GE} - R_2^{SE}$) as a function of the contrast agent concentration, and then β was determined from linearizing the power-law relationship between R_2' and concentration of contrast agent. Since we used Feraheme (i.e., an FDA-approved contrast agent), this method can be easily translated to humans[5].

METHOD: Sprague-Dawley rats were anesthetized with α-chloralose (80 mg initial dose, then 40mg/kg/hr). A femoral arterial line was used for monitoring blood pressure. fMRI data were obtained on a 9.4T spectrometer with optimal shimming. Feraheme was injected intravenously three times, each at a dose of 3.5 mg/kg. Following each injection, multi-slice R_2^{GE} and R_2^{SE} images were acquired with gradient echo (TE = 5-40 ms) and spin echo (TE = 10-80 ms) sequences, respectively. R_2^{GE} and R_2^{SE} images were registered to a reference rat brain atlas and edge artifacts due to misregistration were removed. R_2' images were calculated from the R_2^{GE} and R_2^{SE} difference. β was fitted according to the linearized equation: $\beta = \text{Ln}(R_2'/R_2'_0) / \text{Ln}(C/C_0)$, where 0 represents the initial conditions. A template containing 22 regions of interest (ROIs) was used to calculate mean across regions, avoiding regions with field inhomogeneities.

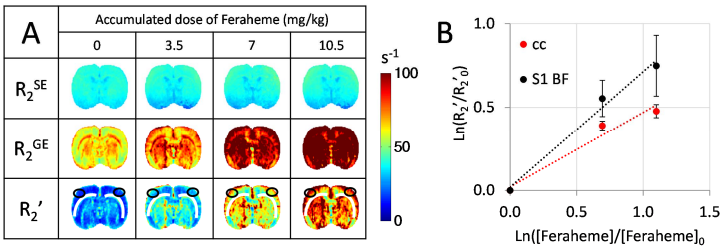

Figure 1. (A) R_2^{SE}, R_2^{GE}, R_2' in rat brain at different Feraheme concentrations. Images reflect mean value of three subjects. (B) Example of linear fitting according to R_2' measurements in corpus callosum (cc) and somatosensory barrel field (S1BF), indicated by the white and black lines on the R_2' maps in A. Data points are mean value with standard deviation from each region.

RESULTS: In Figure 1(A), as the amount of contrast agent is doubled and tripled in the blood, R_2^{GE} and R_2' increase significantly while R_2^{SE} changes were small. In Figure 1(B), two examples of linear fits give a higher slope of fitting for cortical ROI compared to white matter ROI. β for various cortical and subcortical regions are shown in Figure 2. From the anterior to posterior sections of the brain, β are consistently uniform in the cortical regions. White matter and most subcortical regions have lower β. Mean values of β for each ROI are computed and shown in Figure 3. Consistent with the images in Figure 2, β in the cortical regions are generally uniform, with mean values around 0.8 and standard deviations on the order of 24% of mean. In the corpus callosum β is about 0.6. In other regions β values are between 0.4 and 0.7.

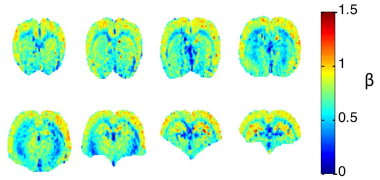

Figure 2. β was calculated from R_2' data in Figure 1. Representative slices (total 64 slices) of the rat brain are shown. The images reflect mean values.

DISCUSSION: The β values measured here are lower than simulation results[1,4] and therefore reduces the BOLD signal's dependencies on CBF and CMR_{O2}[2,3]. Due to β's heterogeneities across regions, calibrated fMRI studies should consider measuring β directly given that it varies across ROIs. Because data fitting is based on the ratios of concentration, dose of Feraheme can be within FDA regulation for human studies (510 mg per injection per week for adult, bodyweight non-specified), making this method translational for human subjects.

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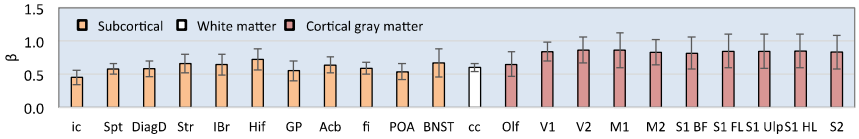

Figure 3. Regional β values shown as mean with standard deviation, in 22 ROIs in rat brain.