Regional and state-dependent properties of M 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, using deoxyhemoglobin as an endogenous paramagnetic contrast agent, exposes regions of interest in fMRI. Interest in quantitative fMRI has renewed awareness in oxidative neuroenergetics[1]. Relationships between BOLD signal and underlying neurophysiological parameters allow determination of changes in oxygen consumption (CMR_{O2}) by "calibrated fMRI," requiring multi-modal measurements of BOLD signal (with gradient echo or spin echo MRI) along with cerebral blood flow (CBF) and volume (CBV). Another component of calibrated fMRI is the BOLD signal weighting for pure deoxyhemoglobin (paramagnetic) or oxyhemoglobin (diamagnetic). The dynamic range of the BOLD signal, ranging from 0% to 100%, is reflected by a constant parameter M, which depends on physics and physiology because it accounts for the echo time (TE) used in the fMRI experiment, magnetic field strength, and rest values of CBV, CBF, and CMR_{O2} (i.e., deoxyhemoglobin vs. oxyhemoglobin ratio)[2]. Since magnetic properties of changing blood oxygenation (Y) affect the tissue water MRI signal due to intravoxel spin dephasing, the change in Y can be captured with the transverse relaxation rates measured by gradient echo ($R_2^* = R_2'(Y) + R_2(Y) + \ldots$) and spin echo ($R_2 = R_2(Y) + \ldots$) where $R_2'(Y)$ and $R_2(Y)$ represent the reversible and nonreversible relaxation components[3]. Phenomenologically M is simply R_2' multiplied by TE[4]. In human studies M is derived by data fitting from BOLD and CBF/CBV measurements during gas (CO_2 or O_2 or mixtures of the two) challenges[2]. However this method requires additional experimental setups (i.e., gas lines and blood gas or exhaled air measurements), technical assumptions (i.e., CMR_{O2} changes are negligible during gas challenges), and data fitting for M with BOLD and CBF/CBV data. Since it remains uncertain if the wide range of M values reported in human calibrated fMRI studies[5] are due to regional and/or state differences, this study was designed to test if M can be directly estimated from an R_2' measurement (i.e., $R_2' \approx R_2^* - R_2$) under well-shimmed conditions. Furthermore this R_2' mapping approach was used to examine regional and brain-state dependencies of M in rat brain.

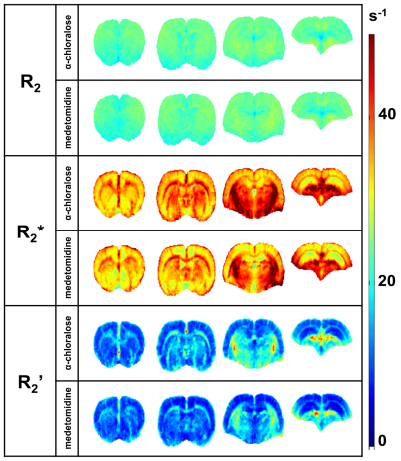

Figure 1. Mean R_2, R_2^*, and R_2' maps for representative slices (of 64 slices in total) with rats under α-chloralose (top, n = 8) and medetomidine (bottom, n = 6).

METHODS: Sprague-Dawley rats were artificially ventilated (70% N_2O, 30% O_2) to maintain normal physiology and anesthetized with α-chloralose (i.p. 80 mg initial dose, then 40mg/kg/hr, n = 8) and medetomidine (i.v. 0.1mg/kg/h, n = 6). A femoral arterial line was used for monitoring blood pressure (~90±10 mmHg), pH (~7.4±0.2), and blood gases (pO_2 = 100±15 mmHg, pCO_2 = 37±3 mmHg). fMRI data were obtained at 9.4T using a ^{1}H quadrature surface coil and shimming minimized static field inhomogeneities. Multi-slice R_2^* and R_2 images were acquired with gradient echo (TE = 5-40 ms) and spin echo (TE = 10-80 ms) sequences, respectively. Data were processed in MATLAB and BioImage Suite. R_2 and R_2^* images were registered to a reference rat brain atlas and edge artifacts due to misregistration were removed. R_2' images were calculated as the R_2^* and R_2 difference. A template containing 22 regions of interest (ROIs) was used to calculate mean values across regions. The 22 ROIs covered white matter and multiple gray matter regions in the cortex and subcortex, avoiding regions affected by residual static field inhomogeneities.

RESULTS: Figure 1 shows representative R_2^* and R_2 maps for α-chloralose (low baseline activity) and medetomidine (high baseline activity), and from which the R_2' maps were calculated. While the gray and white matter differences were exaggerated in the R_2^* maps, the R_2 maps showed largely uniform values throughout the brain regardless of the state with mean values of ~20 s^{-1}. The R_2' maps showed regional differences that were state-dependent (i.e., slightly higher and lower global values for α-chloralose and medetomidine, respectively). Since the R_2' maps were calculated from the absolute difference between R_2^* and R_2 maps, the R_2^* and R_2' maps were highly correlated ($R^2 = 0.93$). A two-way ANOVA on the whole brain indicated that in general the brain state was strongly correlated to R_2^* and R_2' ($p < 0.01$), but not to R_2 ($p = 0.75$). Figure 2 shows that M, calculated from R_2' with TE of 35 ms, was largely uniform among the cortical gray matter regions. Student's t-tests (unequal variances) with one (see * in Figure 2, $p < 0.1$) and two (see + in Figure 2, $p < 0.05$) tails showed several cortical and subcortical regions were dependent on the state and a two-way ANOVA of the ROIs indicated that the state was strongly correlated to M ($p < 0.01$).

DISCUSSION: Given a TE of 35 ms, M values in cortical regions were between 40% and 50% for α-chloralose and between 30% and 40% for medetomidine. The lower M values for higher brain activity are consistent with prior observations[4]. The M values in rat brain at 9.4T are significantly higher than M reported from human brain at 1.5-4T[5], which were mainly below 10%.

CONCLUSION: Since quite homogenous M values were observed in the rat cerebral cortex regardless of the brain state, the direct R_2' mapping method may provide more accurate M values for calibrated fMRI studies in both animals and humans.

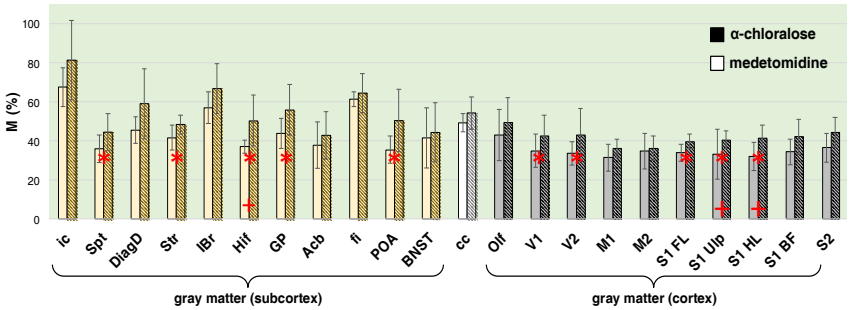

Figure 2. Variations of M across regions for α-chloralose (dark shade) and medetomidine (light shade). Student's t-tests (unequal variances) with one (*, $p < 0.1$) and two (+, $p < 0.05$) tails showed several cortical and subcortical regions were dependent on the state. A two-way ANOVA of these 22 ROIs indicate that the state was strongly correlated to M ($p < 0.01$).

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