Assessment of T1rho Sensitivity to pH and Glucose for Human Brain Imaging at 3T

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PURPOSE: Abnormal brain pH and glucose metabolism have been linked to a variety of psychiatric and neurological diseases. These biochemical abnormalities may precede irreversible neural damage and thus provide early indicators of disease and treatment efficacy. Furthermore, functional changes in pH and glucose with neural-evoked brain activity may precede a hemodynamic response and thus provide a unique measure of metabolic brain activity. New tools are needed to noninvasively image these metabolic factors with high spatial and temporal resolution. One promising technique is quantitative mapping of T1 relaxation in the rotating frame (T1ρ), which has been shown to be sensitive to pH and glucose concentration via proton chemical exchange with amide and hydroxyl groups [1-3]. A recent study has found baseline T1ρ abnormalities in bipolar disorder possibly due to abnormal metabolism [4]. In addition, functional T1ρ mapping has been used to assess brain activity independent of the hemodynamic response in animals at 9.4T [5] and humans at 3T [6,7]. The majority of work to characterize the sensitivity of T1ρ to pH and glucose has been done at ultra-high field (>3T); more investigation is needed at clinical field strengths (≤3T). Additionally, even if T1ρ is sensitive to pH and/or glucose, specificity remains a major challenge due to the sensitivity of T1ρ to a variety of non-metabolic factors including cellular density, water content, and cerebral blood volume [8,9]. One potential solution is to acquire multiple maps of relaxation parameters with different sensitivities (e.g., T1ρ, T2, and T1) to better separate metabolic and non-metabolic factors. The purpose of this study was to assess the sensitivity of T1ρ to pH and glucose compared to T1 and T2 in protein phantoms at 3T. This is a first step toward development of spin-lock imaging methods sensitive and specific to pH and metabolites at clinical field strength.

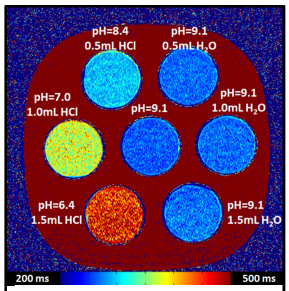

Fig. 1: pH-sensitive T1ρ map.

METHODS: Experiments were conducted on a 3T Siemens TIM Trio MRI system with a 12-channel receiver head coil and transmit body coil.

▪ *Experiment 1: T1ρ sensitivity to pH*. Seven 50 mL vials were filled with liquid egg white and HCl was added to adjust pH. Four vials had 0, 0.5, 1.0, and 1.5 mL 1.0M HCl solution added, yielding pH=9.1, 8.4, 7.0, and 6.4, respectively (pH measured using an Accumet AB15 pH meter). The other three vials had 0.5, 1.0, and 1.5 mL deionized H_2O added as a control for water content. For imaging, the vials were placed vertically in a water-filled container. A 2D coronal slice (FOV=12.8×12.8 cm^2; slice thickness=5.0 mm) of the phantom was imaged with the following quantitative mapping methods: (i) T1ρ; (ii) T2; (iii) T1; (iv) B_1; and (v) B_0. T1ρ and T2 were acquired using the same turbo spin echo sequence but with different prep pulses. Shared parameters were: matrix=512×256; resolution=0.3×0.5 mm^2; TR/TE=5000/14 ms; BW=130 Hz/px; and turbo factor=4. Prep pulse parameters were: (i) T1ρ: self-compensating spin-lock with frequency=400 Hz and TSLs=0 and 100 ms; and (ii) T2: MLEV-4 with TEs=0 and 100 ms. Spin-lock frequency was limited to a reasonable level for human imaging given RF heating constraints. T1 was acquired using an inversion-recovery SE sequence with parameters: matrix=256×64; resolution=0.5×2.0 mm^2; TR/TE=10,000/12 ms; BW=130 Hz/px; and TIs=50, 300, 500, 900, 1500, and 2300 ms. Relaxation time maps were calculated using mono-exponential signal models, and median relaxation times were computed for each vial. B_1 and B_0 maps were also acquired to check for influence of field inhomogeneities.

▪ *Experiment 2: T1ρ sensitivity to glucose*. Four 50 mL vials were filled with 0, 20, 50, and 100 mM D-glucose dissolved in a 6% egg white protein, 0.1 mM $MnCl_2$, pH=7 PBS solution. Vials were imaged and analyzed as in Experiment 1 except, for T1, TR=5000 ms and TIs=50, 150, 250, 450, 750, and 1150 ms.

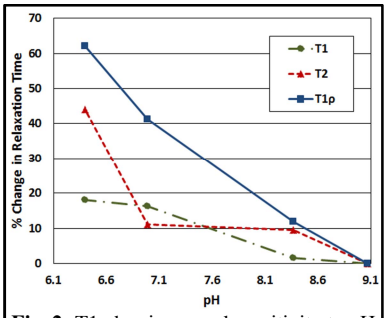

Fig. 2: T1ρ has increased sensitivity to pH at 3T compared to T2 and T1. T1ρ also best represents the linear change in pH.

RESULTS: All quantitative maps were of good quality with no evidence of degrading artifact within the vials due to B_1 or B_0 inhomogeneities. A representative map is shown in Fig. 1.

▪ *Experiment 1*. T1ρ, T2, and T1 were all sensitive to pH, but T1ρ was the most sensitive (Fig. 2). The sensitivity to added H_2O in the control vials was minimal. T1ρ increased linearly over the pH range with a slope of approximately 2.5% change per 0.1 pH unit. T2 and T1 also increased with pH, but with reduced sensitivity. This suggests that T1ρ is a sensitive pH measure and can potentially be combined with T2 to improve specificity to a pH change versus other factors that may more similarly alter T1ρ and T2.

▪ *Experiment 2*. T1ρ, T2, and T1 had similar sensitivity to glucose concentration, linearly decreasing as glucose concentration increased (Fig. 3). T1ρ and T2 changed by approximately 0.05% per 1.0 mM glucose change. This suggests that T1ρ is not a sensitive measure of proton-hydroxyl chemical exchange that may be altered by glucose concentrations at 3T.

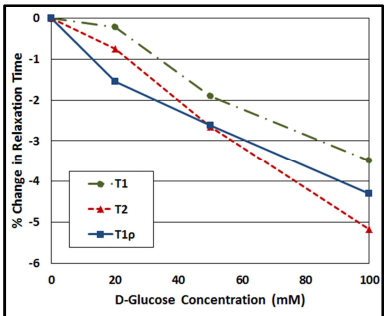

Fig. 3: T1ρ and T2 have the same sensitivity to glucose concentration at 3T.

DISCUSSION: The results demonstrate that T1ρ imaging at clinical field strength is more pH sensitive than other relaxation parameters (i.e., T1 and T2). The increased pH sensitivity of T1ρ is likely due to proton chemical exchange with protein amides, which occurs with relaxation rates in the range of the spin-lock frequency (400 Hz) [1]. The shape of the T2 pH curve suggests that hydrogen exchange in the water is its dominant factor [10]. Glucose sensitivity for all three relaxation times is likely driven by viscosity, which also varies linearly with glucose concentration [11]. This study lays the groundwork for investigation of spin-lock pulse variants (e.g., T1ρ dispersion and adiabatic methods) to better leverage the T1ρ pH sensitivity for imaging of the functional and dysfunctional human brain at 3T.

References: **[1]** Jin T, et al. MRM 2011. **[2]** Jin T, et al. J Cereb Blood Flow Metab 2014. **[3]** Zu Z, et al. MRI 2014. **[4]** Johnson CP, et al. Biol Psychiatry (in press). **[5]** Jin T, et al. NeuroImage 2013. **[6]** Magnotta VA, et al. PNAS USA 2012. **[7]** Magnotta VA, et al. Biol Psychiatry 2014. **[8]** Michaeli S, et al. J Neurosci Methods 2009. **[9]** Kettunen MI, et al. MRM 2002. **[10]** Mathew JB, et al. J Biol Chem 1983. **[11]** Khanuja P, et al. J Chem Pharm Res 2012.