Quantitative MRI of cerebral blood flow in the non-human primate

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Introduction: Macaque monkeys are routinely used as a model for studying human neurophysiology, and they have historically formed the basis of much of our current understanding about primate visual pathways. To advance the use of macaques to specifically address neurovascular coupling, we need to define cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral oxygen metabolism ($CMRO_2$) changes in response to neuronal activation. With knowledge of how CBF and CBV are changing, the BOLD effect can be used to measure the change in $CMRO_2$. In this study we optimized arterial spin labeling for macaque hemodynamics to measure CBF, and used this to quantify spatial variations in resting CBF in macaque cortex, and the CBF change to a global vasogenic (5% $FiCO_2$) stimulus. We also optimized VASO in macaque cortex to measure CBV changes.

Methods: MRI data was acquired in 2 male macaque monkeys under light (8mg/kg/hr) Saffan anesthesia on a GE EXCITE 3T MR scanner. Quantitative CBF data was acquired using PICORE-QUIPSS II ASL [1]. In order to set appropriate QUIPPSS II parameters for macaque brain, a non-quantitative PICORE sequence was used in five 6mm slices, T_E1 = 2.8 ms, T_E2 = 32 ms, T_R = 2000 ms, Flip angle = 90 degrees, 10 cm tag width, 1 cm gap between the tag and the proximal imaging slice without QUIPPSS pulses. A small diffusion gradient (b=2) was included to remove signal from large vessels. Inversion time was varied to measure CBF signal at fixed delay times. These were used to calculate τ and Δt for QUIPPSS pulse optimization. We compared transit times for 6 regions of macaque cortex (left and right anterior, middle, posterior cerebral artery territories). We quantified resting CBF in macaque cerebral cortex with QUIPPSS II ASL using our optimized parameters. CSF was used as a signal intensity reference [2]. Change in CBF with a CO_2 stimulus was measured for the same 6 cortical regions (inspired gas alternated between 100% O_2 (0% CO_2) and CO_2 enriched gas (5% CO_2, 95% O_2). We also measured CO2-induced CBV change in macaque cortex using a modified VASO sequence [3] with multislice capabilities and spiral readouts, T_R = 2000 ms, T_E = 2.8 ms, Flip angle = 90º, TI = 685 ms. In plane resolution 2.8mm, slice thickness 3mm.

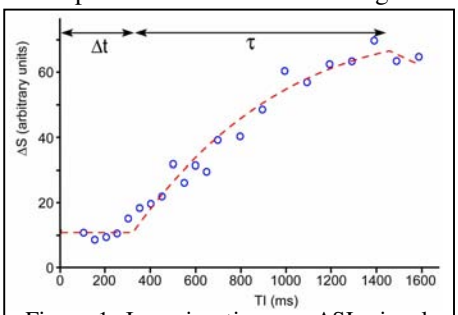

Figure 1: Inversion time vs. ASL signal to optimize transit delay timing.

Results: Figure 1 shows CBF vs. TI transit curve used to determine variables Δt (mean=514ms) and τ (mean=1020ms). These are used to optimize QUIPPSS II parameters TI_1 and TI_2 for quantitative CBF measurements in macaque cortex. Comparing 6 cerebral regions, there were no significant differences for Δt or τ (p=0.49, F=0.91, 2 way ANOVA). For CBF quantitation, the timing between inversion pusles, TI_2-TI_1, is chosen to be sufficiently large that all the tagged blood has reached the voxel by the time of the measurement (i.e., TI_2-TI_1>Δt). TI_1 is chosen such that TI_1< τ. TI1 = 700 ms, and TI2 = 1500 ms were determined to be optimum for macaque cortex from these curves. Figure 2 shows CBF images in macaque cortex using optimized QUIPPSS parameters. Mean resting CBF was 44 ml/100mg/min across the whole cortex,. This varied significantly (p< 0.05) for anterior, middle and posterior cerebral artery territories, measuring 48, 54 and 39 ml/100mg/min, respectively. Combining CBF, BOLD and CBV, Figure 3 demonstrates activation-induced changes following a CO_2 stimulus. Globally across gray matter, BOLD increased 3% & CBF increased 38% with a 5% CO_2 stimulus, while VASO signal decreased by 2%. Regionally, CO_2-induced CBF increases were 42% in anterior, 35% in middle and 38% in posterior cerebral artery territories.

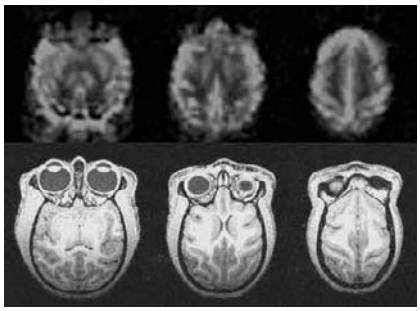
Figure 2: CBF maps of macaque cortex (upper). Anatomical location (lower).

Discussion: Macaque resting CBF is similar to resting CBF in human studies [4]. To examine CBF change with activation, we used the same stimulus & animal model originally described by Grubb et al [5] but we have expanded this to examine the spatial dependence of the CO_2/CBF relationship. Globally, we demonstrated a 38% increase with CO_2 stimulation, which is similar to humans studies (18% - 40%) [4, 6] underscoring the use of non-human primates as a model of human cerebral physiology. Using CBF parameters optimized for non-human primates, these data show the first quantitative measurements of resting and activation-induced CBF in macaque cortex, and provide a basis for further studies of the neurovasuclar relationship in primates.

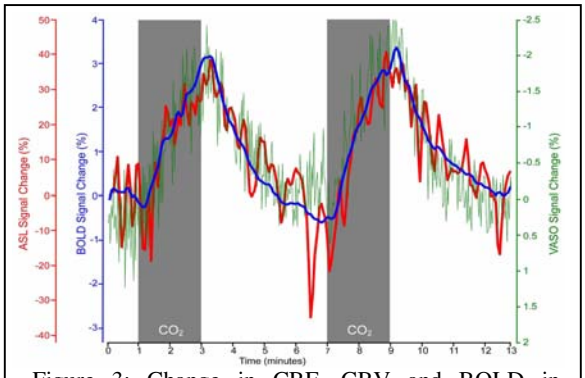

Figure 3: Change in CBF, CBV and BOLD in macaque cortex for CO_2 stimulus

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