Concurrent *f*MRI and optical imaging spectroscopy at high field (7T): Investigation of the haemodynamic response underlying the BOLD signal

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Introduction:
Variations in functional magnetic resonance imaging (fMRI) Blood Oxygenation Level Dependent (BOLD) signals are based upon neurally elicited changes in blood flow (CBF), volume (CBV) and oxygenation (Y). Without prior understanding of the links between these haemodynamic variables the interpretation of BOLD data in terms of the underlying neuronal activity is problematic. Improvement of the haemodynamic response models underlying *f*MRI signals, an essential precondition for the correct interpretation of human BOLD data requires invasive multimodal animal imaging. Therefore the purpose of the present study was to adapt and develop concurrent *f*MRI and 2D optical imaging spectroscopy techniques originally developed at 3 Tesla (Kennerley et.al. 2005) for use in modern MRI scanners with high magnetic field strengths (7 Tesla +). OIS independently measures changes in total haemoglobin (Hbt) and oxygen saturation (Y). This concurrent technique therefore allows us to disambiguate BOLD, Hbt and Y and investigate the relationships between them. Using the rodent barrel cortex as an experimental model, we performed simultaneous measurements of *f*MRI and 2D Optical Imaging Spectroscopy (2D - OIS) following electrical stimulation of the whisker pad, forepaw or hypercapnic challenge. Thus far we have used this methodology to i) investigate the haemodynamics underlying the negative BOLD response, ii) investigate haemodynamic interactions between two adjacent somatosensory cortical regions and iii) test and refine biophysical models of the BOLD signal using the concurrent data sets.

Methods:
MRI measurements were made at 7 Tesla in a small animal magnet facility (Bruker BioSpec, 310mm bore). Urethane anaesthetized animals were artificially ventilated and cannulated for monitoring arterial blood pressure and intravenous infusion. A thinned skull cranial window allowed direct imaging of the cortex. Both MRI measurements of the BOLD and CBV signal changes were obtained concurrently with optical measurements of Hbt and Y changes using an MR compatible endoscope. The 'endoscope' assembly incorporated a 2.0cm diameter surface coil fixed to the head around the cranial window (Fig 1) to form a well. The well was filled with deuterium oxide to avoid air-tissue susceptibility artifacts around the thinned cranial window.

*f*MRI data were acquired in both the coronal and topographic reference frames (Fig 1) using a single shot GE-EPI sequence during electrical stimulation and hypercapnic challenges (64*64, samp int =5μs, FOV = 30mm, sl. thk =1mm, TR/TE=1000/12ms, α 70°). Following BOLD measurements, MRI was used to estimate baseline blood volume fraction and normalised change in CBV (40mg/Kg dose MION contrast agent) following neuronal activation. Combined measurements from *f*MRI, CBV-MRI and optical imaging spectroscopy were used to examine the degree of concordance between the two imaging methods.

2D OIS used a Lambda DG-4 switching Galvanometer (Sutter Instruments) using 4 λ (495, 586, 559 and 575nm). The frame rate of the CCD was 32Hz, giving an 8Hz effective frame rate for each λ. The spectral analysis was based upon the path length scaling algorithm (PLSA) described previously (Mayhew et.al. 1999) incorporating either a homogeneous or heterogeneous tissue model. The later was based on previous MRI data (Kennerley et.al. 2009). The spectral analysis produced 2D images over time, of oxy, deoxy (Fig 1) and total haemoglobin changes (HbO_2, Hbr and Hbt respectively).

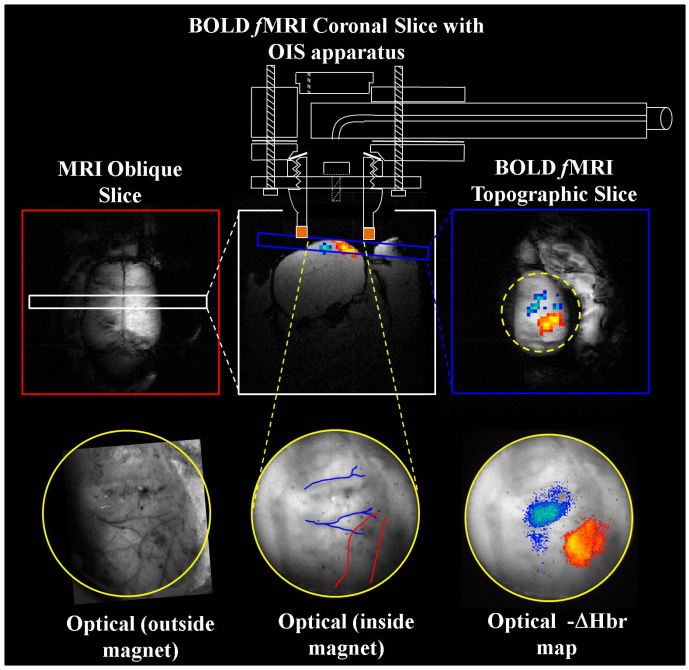

Fig 1. Concurrent 7T BOLD *f*MRI and optical measures of volume and saturation were conducted. *f*MRI activation maps in both the coronal and topographic (in-plane with OIS measurements) were taken. fMRI activation maps were related to optical measures of changes in Hbr and regions of activity identified by the overlying vasculature.

Summary of Results:
Using these concurrent techniques we:

- found a prolonged negative BOLD response (Shumel et.al. 2006) in cortical areas adjacent to the well characterised positive BOLD signal in the barrel cortex. Coronal scans show that the negative BOLD effect originates in deeper cortical layers. A corresponding increase in Hbr and decrease in Hbt was measured in regions surrounding the whisker barrel cortex area. Interestingly upon cessation of stimulation these negative regions often showed a sharp increase in Hbt. We show similar results with CBV-MRI, indicating that haematocrit levels are constant.
- show direct haemodynamic interaction between the whisker and forepaw somatosensory cortex. We investigated this phenomenon at high fMRI resolution (raw data matrix = 128*128, TR=2000ms) and show that spatial maps of BOLD and -ΔHbr are similar (Fig 1).
- input data into a dynamic model of oxygen transport to tissue (Zheng et.al. 2002), which was used to separate the changes in blood volume and oxygenation in the arteriolar, venous and capillary compartments. These parameters were then input into a Monte Carlo simulation of MR signal attenuation to relate these changes to the observed BOLD signal changes (Martindale et.al. 2008). We show that using OIS data analyzed with a heterogeneous tissue (instead of a homogeneous) model is a better predictor of positive BOLD signal. Neither tissue model yields accurate predictions for regions exhibiting a negative BOLD. We are currently investigating this result further and we will report our findings at the conference.

Conclusions & Discussion:
This study establishes concurrent 2D-OIS and high field fMRI for the investigation of the haemodynamics underlying the BOLD signal changes in rat somatosensory cortex. The increased polarisation and thus SNR of high field fMRI allowed us to use the methodology to explore the haemodynamics underlying the negative BOLD phenomenon and cortical region interaction. Data were used to test and refine a biophysical model of the BOLD signal. We are currently adapting the technique to investigate neurovascular coupling mechanisms in Epilepsy and Stroke models. This multimodal imaging data will greatly increase our understanding of neurovascular coupling in both active and surrounding brain regions in health and disease.

References: (1) Kennerley, A.J. et.al. (2005) *Magn Reson Med 54:354-365*; (2) Kennerley, A.J. et.al (2009) *NeuroImage 47:1608-1619*; (3) Martindale, J. et.al. (2008) *Magn Reson Med 59:607-618*; (4) Mayhew, J.E. et.al. (1999) *NeuroImage 10(3 Pt 1): 304-326*; (5) Shumel, A. et.al. (2006) *Nature Neuroscience 9(4) 569-577*; (6) Zheng Y, et.al. (2002) *Neuroimage;16:617-637*.