Negative BOLD and CBF responses are predicted by natural variations in evoked EEG response to a median nerve stimulus in humans.

K. J. Mullinger[1], S. D. Mayhew[2], A. P. Bagshaw[2], R. W. Bowtell[1], and S. T. Francis[1]
[1]Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom,
[2]Birmingham University Imaging Centre, School of Psychology, University of Birmingham, Birmingham, United Kingdom

Introduction: Stimulus induced decreases in BOLD-fMRI signal, also known as negative BOLD responses (NBR) have been reported in visual [1] and somatosensory cortices [2]. Although its cause remains unclear, calibrated fMRI studies suggest that at least 60% of the NBR is neuronal [3] as opposed to being a haemodynamic (or steal) artefact. In addition, the magnitude of the NBR has been shown to increase with the intensity of visual and median nerve stimulation (MNS) in a similar manner to positive BOLD [1,4]; and NBR is closely associated with decreases in neural activity (local-field potentials and spiking activity) in monkeys [3]. Here, we use simultaneous EEG-BOLD-ASL recordings during MNS in humans to show a significant correlation between the magnitude of both the negative BOLD/CBF and the evoked EEG response, providing new evidence for a neural component underlying the negative BOLD response.

Methods: fMRI and EEG data were acquired simultaneously using a Philips Achieva 3T MR scanner and a 64-channel EEG system (Brain Products). A GE-EPI BOLD localiser scan was used to position 10 contiguous axial slices encompassing the primary somatosensory cortex (S1). A FAIR Double Acquisition Background Suppression (DABS) [5] sequence was used for simultaneous acquisition of background suppressed ASL and BOLD data (TR=2.6s, TE=13/33ms (ASL/BOLD), label delay=1400ms, 3x3x5mm^3 voxels, 212mm FOV, SENSE factor 2; background suppression at TI1/TI2=340ms/560ms). Cardiac pulse and respiration were monitored using the scanner's physiological logging. The scanner and EEG clocks were synchronised [6]. Electrode positions on the scalp were digitized using a Polhemus (Isotrack) system. Data were acquired on nine, right-handed subjects. MNS was applied to the median nerve of the right wrist (0.5ms duration pulses, Digitimer DS7A) at 2Hz and an amplitude just above the motor threshold so as to cause thumb distension. Data were recorded over 40 blocks (10s on and 20s off, 20 MNS pulses per block).

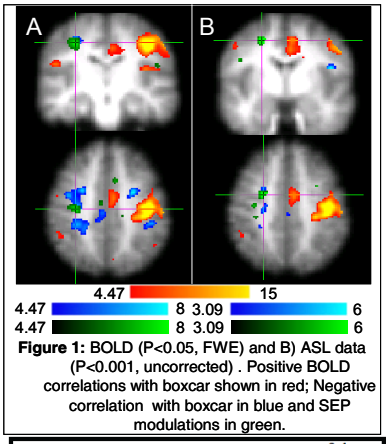

Figure 1: BOLD (P<0.05, FWE) and B) ASL data (P<0.001, uncorrected) . Positive BOLD correlations with boxcar shown in red; Negative correlation with boxcar in blue and SEP modulations in green.

Analysis: *EEG:* Gradient and pulse artefact correction was implemented in Brain Vision Analyzer2 [7-8]. Four subjects were excluded from further analysis due to insufficient data quality caused by gross (>3mm) or stimulus-locked movement. In the remaining five subjects, noisy channels and/or blocks were rejected, data were down-sampled to 600Hz, re-referenced to an average of all non-noisy channels and filtered 2-40Hz. Virtual electrode (VE) time courses of electrical activity were extracted from the location of the peak pseudo t-stat (Ŧ) value in contralateral sensory-motor (S1/M1) cortex using a regularised, scalar beamformer [9] (active/passive window: 0.01s-0.16/0.3-0.45s). Somatosensory evoked potentials (SEP) were averaged across the 20 stimuli in each block, and the peak-to-peak P100-N150 amplitude of each block SEP was measured using an automated linear regression method [10].

fMRI: fMRI data were motion corrected using FLIRT (FSL), and BOLD data physiologically corrected using RETROICOR. ASL data were interpolated to an effective TR of 2.6s, and tag-control pairs then subtracted to create perfusion-weighted images. BOLD and ASL data sets were normalised to the standard MNI template, smoothed with a 5mm kernel, and then analysed in SPM by modelling the data with two regressors, each convolved with the canonical HRF: i) a boxcar model of constant block amplitude; ii) a boxcar parametrically modulated by the variation in the SEP block amplitudes. A second level, fixed-effects analysis was then performed. Areas of significant positive/negative correlation (P<0.05, FWE corrected) between BOLD and the simple boxcar model were found in contralateral/ipsilateral sensorimotor cortex (S1/M1). These group clusters were used to define regions of interest (ROIs) and the mean BOLD response in each ROI was extracted. Similarly, areas showing significant positive/negative correlations between CBF and the boxcar model (P<0.001, uncorrected) were identified from the ASL data. These data were masked by the BOLD boxcar model (P<0.001, uncorrected) data, and mean timecourses extracted from these CBF ROIs. Areas showing significant modulation with SEP amplitude in BOLD (P<0.05, FWE) and ASL (P<0.001, uncorrected) data were also identified, masked by BOLD boxcar model data (P<0.001, uncorrected), and timecourses extracted. Individual's average fMRI timecourses were converted to % change relative to the final 3s of their timecourse, and averaged over subjects.

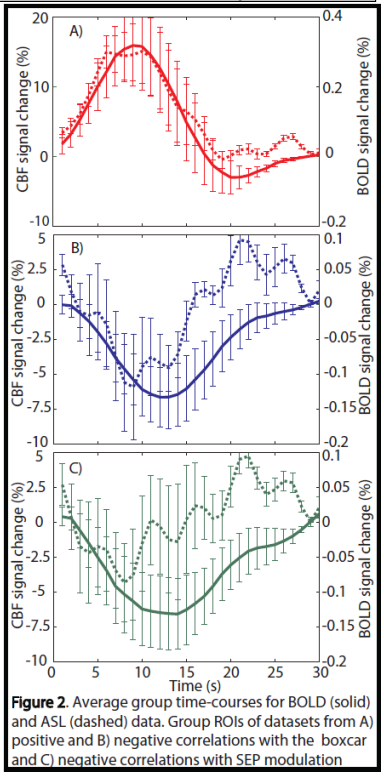

Figure 2. Average group time-courses for BOLD (solid) and ASL (dashed) data. Group ROIs of datasets from A) positive and B) negative correlations with the boxcar and C) negative correlations with SEP modulation

Results: The positive CBF response to the boxcar model showed high spatial correlation with the positive BOLD response in contralateral S1/M1 (Fig. 1). No positive correlations of the fMRI data with the SEP modulations were found in this region. Negative BOLD and CBF responses to the boxcar model were found in ipsilateral S1/M1, with part of this region showing significant modulation with SEP amplitude. Figure 1A illustrates that although the extent of the NBR is larger for the boxcar than SEP model, the SEP model is spatially more consistent with the site of the positive BOLD correlation in response to the boxcar model in the opposite hemisphere (MNI co-ordinates of peak voxel (x,y,z): (-42,-18,48)/(34,-14,56) for BOLD positive/negative correlation with the boxcar model, and (36,-18, 52) for BOLD negative correlation to SEP model, all three sets of co-ordinates falling within S1/M1 cortex. Figure 1B shows a negative CBF response in ipsilateral S1/M1 identified using both boxcar and SEP models. Interestingly, the CBF signal correlated better with the SEP model than the boxcar model (higher T-stat and greater spatial extent). Figure 2 shows the group averaged block timecourses for the group ROIs of the BOLD (solid line) and ASL (dashed line) data. Figure 2A shows the positive response in contralateral S1/M1 to the boxcar model (percentage changes are relatively low due to the use of a group ROI to allow comparisons of positive and negative timecourses. ROIs from voxels showing significant positive correlations for individuals gave greater signal changes of 0.83% BOLD and 37% CBF). The timecourse of negative responses in ipsilateral S1/M1 from ROI's identified using the boxcar and SEP modulation models are shown in Figs. 2B&C. All four timecourses show a clear decrease from baseline during stimulation. The magnitude of both BOLD and CBF negative responses are ~60% smaller than the positive response, in agreement with previous data [1]. Despite the lower SNR, there is a clear reduction in CBF during stimulation with a possible rebound effect on cessation.

Discussion: Here we show for the first time that the magnitude of NBR in ipsilateral S1 is correlated with the amplitude of concurrent EEG responses localised in contralateral S1/M1. The region showing a NBR correlated with SEP amplitude is comparable to that identified by Klinger et al [4] in a study correlating NBR and MNS intensity. In contrast to Klinger, we did not observe any positive correlation of fMRI data and SEP in S1; we believe this is a result of our supra-threshold stimulus evoking a robust positive BOLD response (well explained by the boxcar model) compared with Klinger's sub-threshold stimuli that induce variable BOLD responses. Previous hypotheses of blood-steal by brain areas of positive BOLD response [11] cannot explain our observed robust NBR in ipsilateral S1, as the two hemispheres are fed from different vascular territories. We suggest that this NBR-SEP relationship arises because the NBR results from inhibition of task irrelevant processing in ipsilateral S1, which also increases the excitability of contralateral S1 as indexed by increasing SEP amplitude. In future work we plan to use the concurrent CBF and BOLD measures in this data set to investigate $CMRO_2$ consumption in areas of negative (ipsilateral S1) and positive (contralateral S1) signal changes.

References [1] Shmuel *et al* Neuron **36**(6);2002. **[2]** Kastrup *et al* Neuroimage **41**(4);2008. **[3]** Shmuel *et al* Nat Neurosci. **9**(4);2006.**[4]** Klinger *et al* Neuroimage **53**(1);2010 **[5]** Wesolowski *et al*. Proc. ISMRM, 6132;2009. **[6]** Mandelkow *et al*. NeuroImage, **32**(3);2006 **[7]** Allen *et al* NeuroImage **8**(3);1998 **[8]** Allen *et al* NeuroImage **12**(2);2000 **[9]**Brookes *et al* NeuroImage **40**(3);2008 **[10]** Mayhew *et al* Clin. Neurophysiol. **117**(6);2006 **[11]** Wade *et al* Neuron **36**(6);2002.