An assessment of the post-stimulus undershoot using hyperoxic BOLD contrast and ASL

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Introduction: The origin of the post-stimulus undershoot (PSU) is under debate [1,2,3], with proposed mechanisms being (1) uncoupling of CBF and vCBV whilst CBF remains tightly coupled to $CMRO_2$ [2], or (2) uncoupling of CBF and $CMRO_2$ with $CMRO_2$ remaining elevated relative to CBF [1,3]. Here, we measure the response to a motor task during a hyperoxic challenge using a combined BOLD/ASL acquisition at 7T to simultaneously measure BOLD, cerebral blood flow (CBF) and venous cerebral blood volume (vCBV) changes in response to activation.

Methods: The study was approved by the local ethics committee and all subjects gave written consent. Three subjects (1 male and 2 female, aged 25±1 yrs) were scanned on a Philips Achieva 7T system (head volume transmit and 32 channel receive coil). *Paradigm:* End-tidal O_2 ($P_{ET}O_2$) and CO_2 ($P_{ET}CO_2$) were controlled using a sequential gas delivery breathing circuit and a prospective, feed-forward gas delivery system (Respiract™, Thornhill Research Inc., Toronto, Canada). Subjects were visually cued to perform a bilateral finger tapping task, consisting of 57s OFF followed by four trials of 18s ON, 57s OFF, and a subsequent 57s OFF period. This was repeated for normoxia (targeted at the subject's resting value, $P_{ET}O_2$ ~110 mmHg) and hyperoxia (targeted at 500 mmHg $P_{ET}O_2$) to measure vCBV changes; the order of the gas challenge was reversed across subjects. Isocapnia was maintained throughout ($P_{ET}CO_2$ ~40 mmHg).

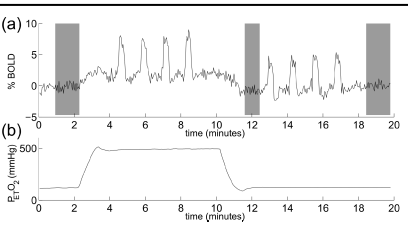

Figure 1: (a) %BOLD timecourse for a single subject, normalised to normoxia baseline (grey boxes). (b) Corresponding $P_{ET}O_2$ timecourse.

	Positive BOLD:	PSU:
BOLD	3.56 ± 0.26	-1.18 ± 0.19
vCBV	47.2 ± 11	4.6 ± 4.0
CBF	42.0 ± 1.0	-9.0 ± 1.8

Table 1: % change in parameters for the positive peak and PSU (mean ± sterr) across subjects.

Acquisition: A GE-EPI BOLD localiser scan was used to position 5 contiguous axial slices encompassing the primary motor cortex (M1). Data were acquired using a QUIPSS FAIR Double Acquisition Background Suppression (DABS) sequence [4] for concurrent acquisition of ASL and BOLD data (background suppression TI1/TI2=402/639 ms; label delay=1550ms; TR=3 s, TE_{ASL}/TE_{BOLD} =14/25 ms, 2x2x3mm^3 voxels, 224 mm FOV, SENSE factor 3, 5 contiguous axial slices). *Analysis:* BOLD data was realigned (MCFLIRT, FSL) and motion parameters applied to the ASL data. Interpolation and subtraction were performed on the ASL data and high-pass temporal filtering (cut-off 150s). Linear detrending was performed on BOLD datasets. Data were spatially smoothed (3mm). Active regions of interest (ROIs) were determined (FEAT, FSL) for BOLD and ASL (Z>5, $P_{cluster}$=0.05) and a common ROI of both was formed. BOLD data were normalized to the normoxic baseline, and vCBV was calculated from the equation:

$$vCBV = \frac{(\%BOLD_{act,HO} - \%BOLD_{act,NO}) - (\%BOLD_{rest,HO} - \%BOLD_{rest,NO})}{(\%BOLD_{rest,HO} - \%BOLD_{rest,NO})}$$

where %BOLD changes are relative to the normoxic baseline ($\%BOLD_{rest,NO}$ = 0) [4]. To examine the spatial location of the positive BOLD and PSU, BOLD percentage change maps were obtained for both time periods.

Results: Fig. 1 shows a full BOLD time course normalised to the normoxia baseline, and the corresponding $P_{ET}O_2$ trace. Fig. 2 shows (a) the cycle averaged %BOLD for the hyperoxia and normoxia periods, (b) these timecourses normalised to their respective baseline periods (c) the resulting vCBV timecourse (d) the CBF average timecourse (averaged across subjects). Table 1 shows the BOLD, vCBV and CBF change for the positive peak and PSU (shaded in Fig.2b). Fig. 3 compares the spatial location of the positive BOLD, BOLD PSU and CBF activation. Fig 4 compares the amplitude of the positive peak and PSU on a voxelwise basis for the focal common ROI and the larger BOLD ROI which includes draining veins.

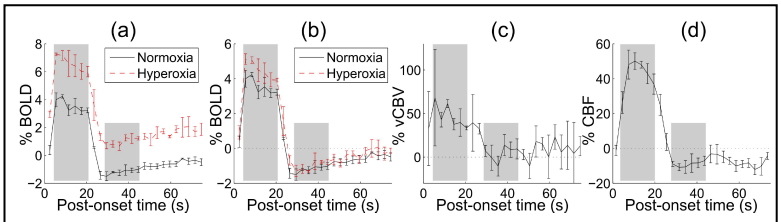

Figure 2: (a) Cycle averaged %BOLD normalised to normoxia baseline and (b) with hyperoxia trials normalised to a hyperoxia baseline. (c) %vCBV average trial. (d) %CBF average trial, formed from all trials. Error bars show sterr over subjects.

Discussion: A significant BOLD and CBF PSU was found, but with no significant change in vCBV from baseline, in contrast to a previous study using VERVE [5] which observed a 10-15s delay in vCBV return to baseline. The techniques are very different and susceptible to different systematic errors. In this method, BOLD, CBF and vCBV data are acquired simultaneously and requires no scans to measure blood oxygenation. The CBF undershoot suggests a neuronal origin for the PSU, but we also observe an uncoupling between CBF and vCBV, which could also indicate that the CBF PSU is related to vascular compliance. Fig. 3&4 show that at this spatial resolution the PSU is not more localised to the underlying neuronal response, as reported in animal models [6,7].

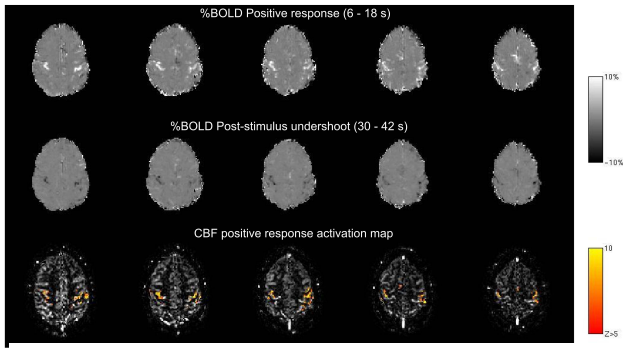

Figure 3: Maps showing the positive BOLD response (top), undershoot (middle) and, for comparison, CBF activation maps (bottom).

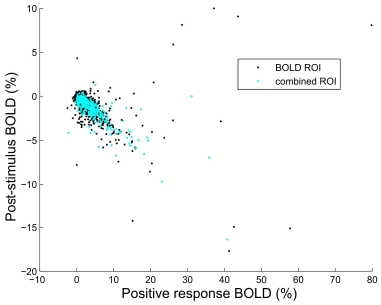

Figure 4: Voxelwise plot of post-stimulus undershoot against positive peak BOLD.

References: (1) Frahm et al., MRM 35, 143 (1996); (2) Mandeville et al., MRM 39, 615 (1998); (3) Sadaghiani *et al,* MRI **27**:1030 (2009); (4) Blockley *et al.* Proc. ISMRM 18, 3476 (2010); (5) Chen & Pike, Neuroimage 46: 559 (2009); (6) Yacoub *et al.*, JCBFM 26, 634 (2006); (7) Zhao *et al.*, Neuroimage 34, 1084 (2007). **Acknowledgements:** Funding was provided by the UK Medical Research Council.