A STUDY OF POST-STIMULUS UNDERSHOOT IN THE VISUAL CORTEX DURING MILD HYPOXIA USING BOLD AND VASCULAR SPACE OCCUPANCY fMRI

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Introduction: Positive BOLD response elicited by neuronal activation is often followed by a negative signal change in T_2*-weighted GRE images [1-3], commonly referred to as a post-stimulus undershoot. The underlying substrate physiology of the undershoot is not fully understood and is still widely debated. To date, two main hypotheses explaining the presence of the undershoot exist. The first is concerned with the haemodynamic control of the BOLD response, whilst the second is focused on the metabolic aspect of the response. The balloon model [4], explains this undershoot through a haemodynamic model, with regard to the increase of volume of deoxygenated blood in the dilated postcapillary venous bed. A previous study carried out in the primary and supplementary motor area [5] suggested a modified balloon model whereby BOLD contributing elements, i.e. CBF, $CMRO_2$ and CBV functioning on different time courses, resulted in the post stimulus undershoot. In contrast, the metabolic approach suggests physiological substrates of the post-stimulus undershoot may be involved in sustaining oxygen metabolism to restore ionic homeostasis without concomitant CBF increase, i.e. high oxygen extraction. In this regard, physiology of the post-stimulus undershoot may be similar to the so-called initial dip [3, 6], which is difficult to reveal by standard T_2*-weighted fMRI at low magnetic field strength [7]. We have used BOLD and vascular space occupancy dependent (VASO) fMRI [8] to study the characteristics of the post-stimulus undershoot in human visual cortex during varying blood oxygen saturation levels (Y_{sat}).

Methods: The protocol was approved by the Manchester Local Research Ethical Committee. Six healthy volunteers (age range 26-49 years, 2 females) gave written informed consent before participation. Inhaled O_2 content (FIO_2) was either room air or 12% (balanced with N_2 in a non-rebreathing circuitry, Hans Rudolph Inc, Kansas City, USA). Y_{sat} and pulse rate were monitored with a pulse oximeter. After an adaptation of about 5 minutes to FIO_2 of 12%, the MRI protocol was started and scans were run in a pseudo-randomised fashion for further 20 minutes. Visual stimulation was accomplished with a contrast-reversing (8 Hz) BW-checkerboard. A clinical Philips Intera 1.5 T MRI scanner with a standard head coil transmission and surface coil reception was used. A transverse 5 mm slice was placed through the primary visual cortex according to the localizer images and T_2*-weighted BOLD images were acquired with a single shot GRE-EPI (FOV 240 mm, matrix 64x64, TR = 0.5 s, TE = 40 ms, flip angle 50º). Microvascular CBV changes were assessed with the VASO fMRI [8], with scanning parameters as follow: FOV = 240 mm, 5 mm slice, matrix 64x64, TR = 2 s, TE = 11 ms, inversion time 665 ms to achieve effective blood nulling. Statistical analysis of the fMRI data was carried out using the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl/, $p<0.01$, corrected). After delineation of activated brain areas, in-house Matlab™ routines were used for estimation of BOLD and VASO response amplitudes and pixel count determinations. In the analysis of VASO fMRI data, only the pixels with signal to noise ratio ≥10 were used.

Results: No adverse effects were reported during exposure to FIO_2 of 12%, and an observed increase in heart rate by about 15%. A typical BOLD response trace is shown from normoxia (Fig. 1). Post-stimulus undershoot is present after a 10 s checkerboard stimulus lasting for 30±9 s in normoxia. The signal characteristics are shown in Table. Hypoxia, with an average Y_{sat} of 88±1.2 (translating to a decrease in P_aO_2 by ~50%), did not influence either positive or negative (i.e. post-stimulus undershoot) characteristics of the BOLD response (Table). Peak negative VASO responses were also observed to have a mean response of -1.4±0.6% at 13.3±1.6 s in normoxia, and in hypoxia a response of -2.5±0.9%, at 13±1.5 s. Corresponding VASO values indicating the microvascular CBV during the maximum BOLD response and during the post stimulus undershoot were obtained (Table). At P_{max}, corresponding VASO data were seen to be closer to the baseline in hypoxia, however overall, no significant changes in trends between normoxia and hypoxia VASO data were observed. In addition, during the BOLD post stimulus undershoot, the VASO response seems to be terminating, and no outstanding changes in the VASO response are observed at this point.

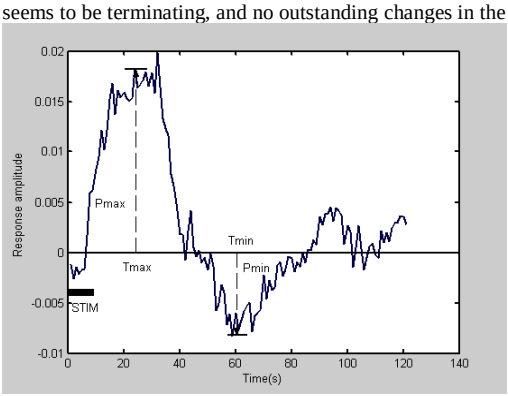

Figure 1: A typical BOLD response. Parameters of interest were: maximum positive response (P_{max}), corresponding time (T_{max}), minimum undershoot peak (P_{min}) and its corresponding time (T_{min}).

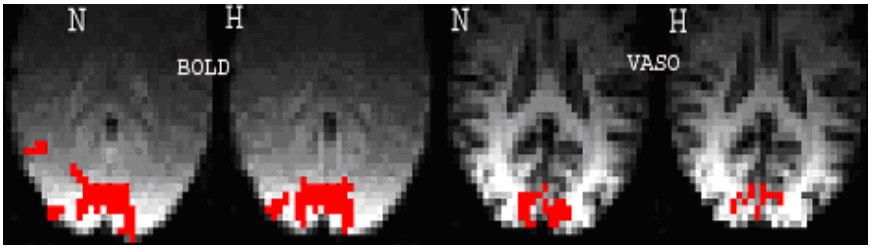

Figure 2: Images showing typical BOLD (from the left) and VASO responses in both normoxia (N) and hypoxia (H).

Table: Data summary of BOLD responses and correlating VASO responses in both normoxia and hypoxia. $P_{max\ corr\ VASO}$ relates to the VASO response that occurs at T_{max}. $P_{min\ corr\ VASO}$ relates to the VASO response that occurs at T_{min}.

	Normoxia	*Hypoxia*
P_{max} *(%)*	3.2±1.8	2.9±1.7
$P_{max\ corrVASO}$ *(%)*	-1.4±0.6	-1.3±1.5
T_{max} *(s)*	12.2±1.4	11.5±2.5
P_{min} *(%)*	-1.1±0.7	-1.9±0.5
$P_{min\ corrVASO}$ *(%)*	0.2±0.5	0.0±0.5
T_{min} *(s)*	30±9	27±6

Conclusions: BOLD signal upon visual stimulation shows consistent post-stimulus undershoot with a T_2*-weighted signal change of ~ -1.1%. This negative signal is not influenced by mild hypoxia, during which oxygen delivery to the visual cortex was curtailed by ~15%. We observed that the VASO signal was at the control in the presence of undershoot in BOLD, arguing against involvement of altered CBV. Because CBF response upon visual stimulation under the oxygenation conditions used is the same [9], oxygen delivery to the visual cortex must have been in excess to satisfy the needs of oxidative metabolism in both oxygenation states. This indicates that oxygen supply to the brain under 'stressed' conditions is 'luxurious' suggesting that demand of this substrate may not be the primary signal for the CBF response [3, 9].

Acknowledgements: Supported by grants from Marie-Curie Programme by EU and MRC, UK, the University of Kuopio Foundation and the Ella and Georg Ehrnrooth Foundation. Expert technical help in scanning by Ms. Lisa Leahy and Mr. Barry Whitnall are greatly acknowledged.

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