Assessment of the BOLD effect and vascular reactivity during visual stimulation in the presence of hypoxic hypoxia

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INTRODUCTION:

Hypoxic hypoxia has been used to modulate oxygen availability to study cerebral oxygen metabolism and hemodynamic signal changes. In particular, hypoxia has been applied to study the BOLD signal. BOLD is widely used in fMRI owing to its high contrast-to-noise ratio, yet is relatively difficult to interpret in terms of physiological substrates. Recent studies exploiting hypoxia addressing BOLD physiology have provided inconsistent results: Relative BOLD signal changes have been found to decrease [1,2], stay the same [3] or increase [4] during hypoxic stimulations. To clarify the issue, the present study addressed both the BOLD and the vascular space occupancy (VASO) signals [5] during brain activation in normoxia and moderate hypoxia. The approach aimed to assess vascular responsiveness to the BOLD signal [7] using the CBV-weighted [6] VASO technique, which provides both high spatial and temporal resolutions comparable to that of BOLD fMRI.

METHODS: Eight healthy subjects (5 males, 3 females; aged from 24 to 51 years) gave informed consent prior to enrolling in the study. B/W checkerboard was used for visual stimulation with 100% contrast at 8Hz frequency. Each run consisted of 5 blocks (3 baselines, 2 stimulations) of 15 volumes (45s) per block. Dual-echo single shot gradient echo EPI either without or with an inversion recovery pulse for nulling blood (VASO) in both normoxic and hypoxic conditions were acquired using a Philips Achieva 3.0T imager. BOLD EPI: TR=3s, TEs=5/40msec, 1 slice along the calcarine sulcus, slice thickness=5mm, flip angle=90°, matrix=128x128, FOV=224x224mm. Dual-echo VASO IR: Similar to BOLD EPI parameters, except for TI=889msec, TEs=10.3/56msec. Hypoxic hypoxia was induced by reducing inhaled O_2 to 12% in a non-rebreathing circuitry. Blood oxygen saturation (Y_{sat}) and heart rate were monitored using a pulse oximeter. T-tests were used to detect task-related signal changes in fMRI time series. R_2* was calculated as $R_2^*=(\ln S_1/S_2)/(TE_2-TE_1)$. To compare BOLD and VASO responses, only voxels that were activated in both the normoxia and hypoxia conditions for each particular scan were considered. R_2* and VASO signals determined in hypoxia were normalized to the respective normoxia baselines.

RESULTS:

R_2* and VASO task-related activations were seen in both normoxia and hypoxia (Y_{sat} ranging from 0.92-0.79, pulse rate increased by 15-30%). Thresholded BOLD and VASO activated areas were around 50% and 60% smaller, respectively in hypoxia than in normoxia. Fig 1a shows that: (i) R_2* amplitude changes due to activation (both during and post stimulus 'undershoot') were dampened in hypoxia; and (ii) a pronounced 'overshoot' in the early part of activation seen in normoxia flattened out in hypoxia. For VASO, relative task-related responses (negative signal change) were larger in hypoxia than normoxia (Fig. 1b). Given that the baseline signal intensities were lowered in hypoxia, it is more pertinent to consider responses normalized to the normoxic baseline. Table 1 shows a significantly reduced normalized BOLD response in hypoxia (paired-t=-3.07, p=0.02), while the VASO responses are similar in normoxia and hypoxia (paired-t=0.82, p=0.45). The hypoxic effect is also evident in the reactivity graphs (Fig 2), where R_2* shows decreased response regardless of baseline correction (***relative***: r=-0.74; ***normalized***: r=-0.64), whereas the VASO response appears to increase with lowered Y_{sat}(r=0.35), but remains constant once the hypoxic baseline is corrected (r=-0.01).

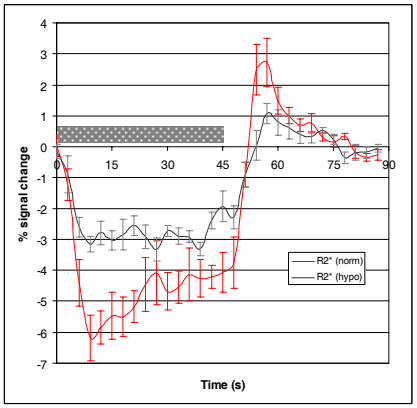

Fig 1a: R_2* averaged timecourses in normoxia and hypoxia. The gray bar denotes stimulation duration. Note the flat hypoxic response as opposed to the early, sharp normoxic 'overshoot'.

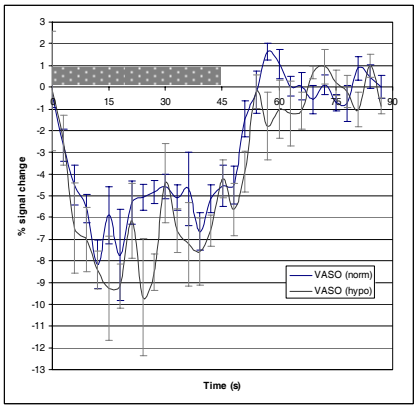

Fig 1b: VASO averaged time courses in normoxia and hypoxia.

DISCUSSION:

Our results show reduced task-related BOLD response during hypoxia, both in relative terms and normalized to the normoxic baseline. The magnitude of the R_2* changes due to the BOLD response is proportional to the [Hb/HbO$_2$] ratio [8]. Evoked responses in visual cortex are not affected by hypoxia of this depth [3] suggesting that the neural responses are sustained. Indeed, $CMRO_2$ does not appear to change with moderate hypoxia [9]. We observed that the normalized task-related VASO response is similar in size under all oxygenation conditions. These results are consistent with similar, quantitative CBF increases in the visual cortex to stimulation over a Y_{sat} range from 0.8 to 1 [3]. The absence of sharp BOLD overshoot in hypoxia may be due to altered $CMRO_2$/CBF ratio under these conditions, leading to more efficient oxygen extraction in hypoxia. To conclude, this study shows that while the task-related vasoreactivity is less dependent on Y_{sat}, the task-related BOLD response is significantly modulated by Y_{sat}.

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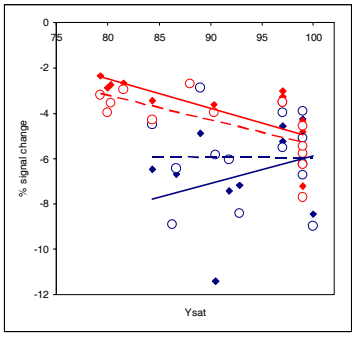

Fig 2: Reactivity with decreasing levels of Y_{sat}: ***Relative*** R_2* (solid red) and VASO (solid blue); and ***normalized*** R_2* (broken red) and VASO (broken blue). After normalization, VASO changes did not appear to be modulated by Y_{sat} levels.

Table 1: Absolute & normalized values for R_2* and VASO.

R_2*	Absolute signal		Normalised	
	Normoxia	Hypoxia	Normoxia	Hypoxia
Base (mean)	22.4	25.4	1.00	1.14
Act (mean)	21.2	24.6	0.947	1.10
	Normalised (Act-Base) =		-0.0525	-0.0353

VASO	Absolute signal		Normalised	
	Normoxia	Hypoxia	Normoxia	Hypoxia
Base (mean)	134	109	1.00	0.813
Act (mean)	127	102	0.947	0.758
	Normalised (Act-Base) =		-0.0531	-0.0545

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