HETEROGENOUS OXYGEN EXTRACTION IN THE VISUAL CORTEX DURING ACTIVATION IN MILD HYPOXIC HYPOXIA REVEALED BY QUANTITATIVE FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Introduction: BOLD fMRI exploits mismatch between oxygen delivery and consumption for non-invasive mapping of brain activity [1, 2]. The quantitative relationships between oxygen delivery and consumption in the brain are characterized during rest and activation [3, 4], but physiologic mechanisms underlying the decline in oxygen extraction ratio (OER) due to brain activation are not known [5]. We have used quantitative fMRI to study the haemodynamic and metabolic responses in human visual cortex during varying blood oxygen saturation levels (Y_{sat}) and stimulation with contrast reversing checkerboards. Visual evoked responses (VEP) were recorded to directly assess the neuronal functions in the visual cortex at reduced levels of Y_{sat}.

Methods: The protocol was approved by the Manchester Local Research Ethical Committee. Ten healthy volunteers (26-49 years, 2 females) gave written informed consent. FIO_2 was either room air or 12% (in a non-rebreathing circuitry, Hans Rudolph Inc). Y_{sat} and pulse rate were monitored with a pulse oximeter. Visual stimulation was accomplished with a contrast-reversing (8 Hz) BW-checkerboard. VEPs were recorded from occipital scalp electrodes. A clinical Philips Intera 1.5 T MRI scanner with a standard body coil transmission and SENSE head coil (in quadrature mode) reception was used. In BOLD, transverse 3.5 mm were acquired with a single shot GRE-EPI (FOV 240 mm, 128x128, TR = 1 s, TE = 40 ms, flip angle 54º). Cerebral T_2* was quantified with four TEs of 11, 30, 64 and 82 ms, TR = 3 s. A pulsed ASL (PASL) was used to quantify perfusion changes ([6] with FOV = 240 mm, 10 mm slice covering the area with strongest BOLD activation, 64x64, TR = 6 s, TE = 10 ms, inversion delay = 1000 ms). OER was quantified using the method based on vascular space occupancy (VASO) fMRI [7], with parameters as follows: FOV = 240 mm, 5 mm slice, 80x80, TR = 3 s, double GRE (TE pairs of 11/64 and 30/82 ms), inversion time 767 ms. 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). In the analysis of VASO fMRI data, only the pixels with S/N ≥10 were used. For OER analysis, voxel series were collected from all echo series based on activation map obtained with the shortest TE images [8]. Physiologic variables required in OER calculations were from Lu et al. [8]

Results: The heart rate increased from 62±8 in normoxia to 74±13 in hypoxia. Parenchymal T_2* was 63.4±2.5 ms in normoxia and 61.5±1.0 ms in hypoxia (n.s.). The VEP amplitude remained constant over the Y_{sat} range from 1.0 to 0.82 (Fig. 1). CBF responses were not influenced by Y_{sat} either in terms of amplitude of the response or number of activated pixels (Fig. 2). In contrast, the volume of cortex showing BOLD decreased as a function of Y_{sat}, but the magnitude of BOLD response (1.51±0.34%) was unchanged (Fig. 2). OER during visual activation was 0.26±0.03 at Y_{sat} of 0.99±0.005. At lowered Y_{sat}, two OER patterns were observed. Firstly, OER of 0.14±0.03 was determined in the cortex showing BOLD response of 1.5% during activation in hypoxia (Fig. 3). Secondly, T_2*-weighted MRI revealed signal increases only by 0.74±0.46% upon checkerboard stimulation in hypoxia in other parts of the cortex showing BOLD in normoxia. Because these structures displayed similar CBF increases both in normoxia and hypoxia, attenuated T_2*-weighted signal increase upon visual activation in hypoxia is likely to be due to high OER during stimulation in these parts of the visual cortex, i.e. close to that encountered in resting brain (OER ~ 0.35).

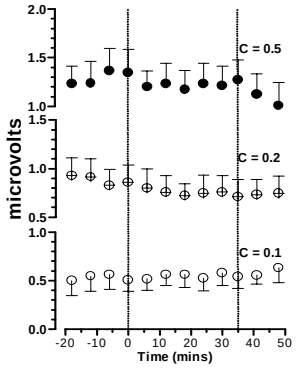

Figure 1 (left). VEP amplitudes (mean ±S.D.) from the group of subjects with three different contrast levels as a function of time. FIO2 was 12% between the dotted lines. No changes in VEP amplitudes are observed.

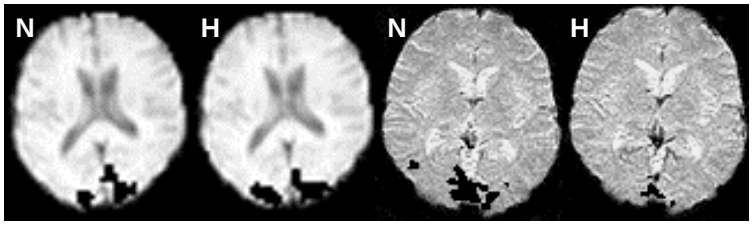

Figure 2. PASL- (left) and BOLD- (right) images in normoxia (N) and hypoxia (H, Y_{sat} = 0.83) overlaid with black activation areas. In PASL activated area remains intact, while BOLD fMRI shows a decline in the size of activation area.

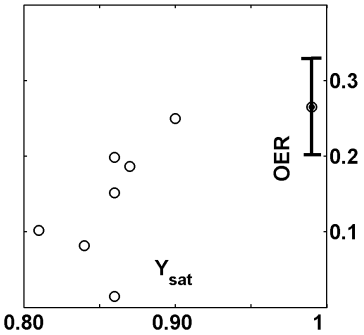

Figure 3. OER as a function of oxygen saturation (Y_{sat}).

Conclusions: The present results show that both integrated function and neuro-metabolic coupling is unchanged under the mild hypoxic conditions in the visual cortex, consistently with a previous study [9]. The present results indicate that close to a full arterial oxygenation (Y_{sat}>0.98) renders the mismatch between CBF and oxygen metabolism during brain activation. When oxygen availability decreases, spatial heterogeneity in OER ensues as follows: firstly, haemodynamic and metabolic responses approach a quantitative state present in the resting brain. In the cerebral tissue displaying this pattern oxygen availability may regulate blood flow and overall energetics, as previously suggested [10]. Secondly, visual cortex structures are also found, where OER proceeds at a very low level during visual processing. Importantly, these structures show strong BOLD response. It is very likely that in these structures metabolic requirement for oxygen is not needed to elicit the CBF response. Our findings suggest that within the activated cortical structures, as revealed by BOLD fMRI, oxygen requirement and its coupling to the haemodynamic response are non-uniform. The present data agree with a recent notion that oxygen metabolism and CBF changes in functioning visual system are spatially different [11].

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