Interplay between oxygenation use and delivery in graded stimulation

Y-C. L. Ho[1,2], I. Zimine[1], E. T. Petersen[1,2], X. Golay[1,3]

[1]Neuroradiology, National Neuroscience Institute, Singapore, Singapore, Singapore, [2]Bioengineering, Nanyang Technological University, Singapore, Singapore, Singapore, [3]Electrical & Electronic Engineering, Nanyang Technological University, Singapore, Singapore, Singapore

Introduction:

The BOLD signal, which depends on CBF, CBV and $CMRO_2$ responses, is an indirect measure of neuronal activity. To correctly interpret the BOLD signal, we have to understand the relationships among the various haemodynamic parameters. The relationship between CBF and $CMRO_2$ is unclear, with CBF appearing to increase disproportionately to $CMRO_2$ during neuronal activation despite good temporal correlation [1-3]. Additionally, $CMRO_2$ and thus BOLD are functions of CBV changes, which have traditionally been studied in animals with potent contrast reagents [4-6], hence necessitating the need for characterizing the CBV response in humans. Furthermore, these haemodynamic relationships could vary with different types and levels of stimulation [7]. Here we utilize a recently developed method (Vascular Space Occupancy or VASO) of measuring CBV changes without contrasts agents or CO_2 administration [8]. The aim was to investigate the linearity of the relationship between BOLD, CBV, CBF and $CMRO_2$ over graded visual stimuli.

Methods: ***Experiments.*** All sequences were implemented on a clinical 3.0T imager (Philips Medical Systems) with parallel imaging capabilities (SENSE). Six healthy subjects (5 males, 1 female; mean age 29.7±1.6) were presented with graded visual stimuli and scanned using both VASO [8] and BOLD sequences.

MR parameters. For both functional sequences: TR 3 s, slice thickness 5 mm and FOV 224x224 mm. Specific to VASO sequence: TI 90 ms, TE 12 ms and flip angle 90º. For the BOLD sequence: TE 35 ms, flip angle 90º. High-resolution T1-weighted spin echo images were also acquired. For all sequences, a single slice (5mm) per subject was acquired in a plane along the calcarine sulcus to image the primary visual area. The functional paradigm was a black-white visual checkerboard pattern with a white arrowhead in the centre (frequency 8Hz) that alternated with a baseline condition (white arrowhead on a iso-luminance gray (50%) background). To keep subjects focused over the entire length of each functional run, each subject had to respond to the direction of the arrowhead by pressing one of four response keys. There were three visual checkerboard conditions with three levels of grey scale contrast – 100%, 50%, and 25%. These three contrast conditions were presented in pseudo-randomized order in each functional run. Each checkerboard condition was 30 s (10 volumes) and the baseline condition was 45 s (15 volumes). The VASO run was 12 mins long, with 9 blocks of visual stimuli regularly alternated with 10 blocks of the baseline condition. The BOLD runs were 8 min 15 s each with 6 blocks of visual stimuli with 7 blocks of the baseline condition. The BOLD runs were shorter because of their higher signal-to-noise ratio.

Data Analysis. All processing was done on Windows PCs using IDL and AIR software on a subject-by-subject basis. The functional images were realigned within and between functional scans. Detrending was done to remove baseline drifts. Voxels with less than a signal-to-noise ratio of 10 were excluded from the analysis in the VASO scans. A cluster threshold of 3 voxels was applied. Dynamics 15 s from the start of each baseline condition and 3 s from the start of each visual checkerboard condition were excluded from the statistical analyses. T-tests ($p<0.001$, uncorrected) were performed on a voxel-by-voxel basis to determine the areas of significant activation in both functional datasets. Only commonly activated voxels were selected for further analysis. CBF was estimated from the CBV data using Grubb's equation [4] ($CBV = \beta CBF^{\alpha}$ with $\alpha=0.5$, $\beta=0.5$ [9]. $CMRO_2$ was calculated from: $(1+\Delta OEF/OEF)+(1+\Delta CBF/CBF) = 1+\Delta CMRO_2/CMRO_2$

Results & Discussion: All subjects showed significant activations ($p<0.001$, uncorr.) in the primary visual cortex. Fig. 1 shows an example of the voxels activated in BOLD and VASO, together with their area of intersection. As expected, the VASO data showed a smaller extent of activation, as it is sensitive only to extravascular changes [8]. Figs. 2a and 2b show the CBV and BOLD time curves, averaged across time and subjects, for each visual contrast level. Clear differences can be seen between the 100% and 25% contrast levels, while the values for 50% contrasts tend towards those of the 100% contrasts. It is possible that saturation of the neuronal response to visual contrast could have happened before or around the 50% contrast level, as suggested by visual evoked potential (VEP) studies. It is interesting that the CBV time curves appear to overshoot upon activation, dissimilar to that which is predicted by current haemodynamic models [10]. VASO appears to be a very focal measure of extravascular signal changes, including only signal occurring from vessel diameters from less than 200µm [11], so it is possible that conventional models are not as applicable here. On the other hand, the possibility cannot be excluded that the VASO signal is not a pure measure of CBV. The BOLD time curves show the canonical overshoot and prolonged undershoot. Table 1 shows the means and S.E.M.s of the activation and baseline conditions for each contrast level by BOLD, CBV, CBF and $CMRO_2$. The calculated CBF values are in agreement with the literature for high-resolution measurements [12]. Figure 3 shows a positive, linear trend between CBV and $CMRO_2$ changes with no clear differences between the visual contrasts, as also expected from both VASO and BOLD signal amplitudes. However it has to be kept in mind that correlation between parameters do not necessarily mean that their relationships are causal. Nonetheless we report differences in the amplitude of HRF responses to 100% and 25% visual contrasts with corresponding $CMRO_2$ modulations. Future extensions of this preliminary study would include comparable CBF measurements and visual evoked potentials to determine a range of visual contrasts before neuronal saturation.

References: [1] Fox P.T. et al (1986) *PNAS* **83**:1140-1144. [2] Oja J.M. et al (1999) *JCBFM* **19**:1289-1295. [3] Lu H. et al. (2004). *JCBFM*. **24:**764–770. [4] Grubb R.L. et al. (1974). *Stroke*. **5:**630-639. [5] Mandeville J.B. et al (1998) *MRM* **39**:615-624. [6] van Bruggen et al (1998) *JCBFM* **18**:1178-1183. [7] Hoge R.D. et al. (1999). *Magn Reson Med*; **42**:849-863. [8] Lu H. et al. (2003). *MRM*. **50:**263–274. [9] van Zijl P.C.M. et al. (1998). *Nat Med*. **4(2)**:159-167. [10] Buxton R.B. et al (2004). *NeuroImage*; **23**:S220-233. [11] Harrison RV, et al (2002) *Cereb Cortex* **12**:225–233. [12] Pfeuffer et al (2002) *MRM* **47**:903-911.

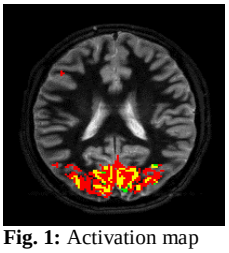

Fig. 1: Activation map overlaid onto an inversed T1-weighted image. Commonly activated voxels (yellow), BOLD alone (red) and VASO alone (green).

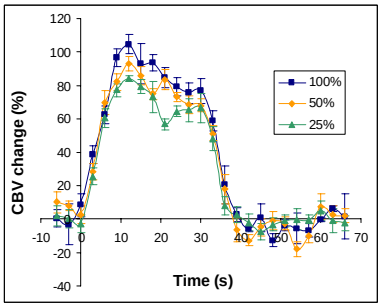

Fig. 2a: Averaged CBV % changes for the three contrasts levels (100%, 50%, 25%).

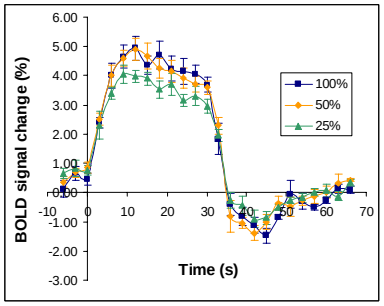

Fig. 2b: Averaged BOLD signal changes for the three contrast levels (100%, 50%, 25%).

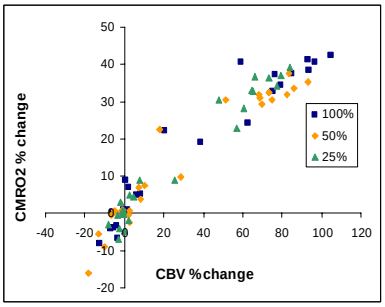

Fig. 3: $CMRO_2$ plotted across CBV changes by contrasts levels (100%, 50%, 25%).

	BOLD			CBV			CBF			$CMRO_2$		
Contrasts	100%	50%	25%	100%	50%	25%	100%	50%	25%	100%	50%	25%
Activation (%)	4.2±0.3	4.1±0.3	3.5±0.2	81±8	73±8	65±7	231±29	203±24	175±22	35±3	30±3	30±4
Baseline (%)	-0.4±0.3	-0.2±0.3	-0.1±0.2	-2.3±2.1	-2.1±3.6	-0.7±1.3	9.9±4.0	18.0±7.0	6.3±2.6	5.3±2.2	6.6±2.7	3.1±1.3

Table 1: BOLD, CBV, CBF, $CMRO_2$ mean and S.E.M. change (%) for the three graded visual contrasts (100%, 50%, 25%) over the activation and baseline conditions.