INTRAVASCULAR VS. EXTRAVASCULAR CONTRIBUTIONS TO FMRI SIGNAL CHANGE FOR VISUAL STIMULI AND HYPERCAPNIA

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Introduction Hypercapnic fMRI calibration, where the functional BOLD response is interpreted in relation to the BOLD response to CO_2 [1], has the potential to further the ultimate goal of quantitative fMRI. However, the technique makes the assumption that the spatial origins of the signal are equivalent for metabolic and hypercapnia-induced activation. We tested this assumption using a diffusion-weighted fMRI paradigm to investigate the relative intravascular (IV) and extravascular (EV) contributions to the BOLD signal for a visual stimulus and for hypercapnia.

Simulation A theoretical model, based on that described in [2], was used to predict the BOLD signal at 3T with and without IV contributions. The model differed from [2] in that parameters were modified for 3T and the effect of EV field gradients on IV spins was ignored. For typical 60-80% flow changes seen in primary sensory functional activation (Fig 1) the model predicts an attenuation in the BOLD response of ~40% when all IV components of the signal are suppressed. Also predicted is a greater potential contribution to the signal from venules than capillaries. The velocity threshold of ~0.01mm· s^{-1} for our maximum b-value (b=437 s·mm^{-2}) is significantly less than the average velocity of capillary blood (~1mm· s^{-1} [3]), so in theory substantial IV suppression should be achieved, leaving just EV signal.

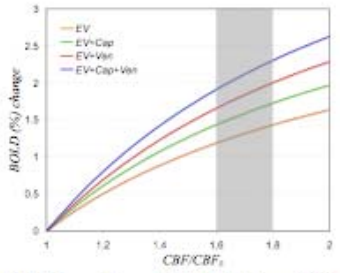

Figure 1. Simulated GRE (T_E=30ms) fMRI signal at 3T with and without IV contribution. Shaded area indicates typical flow change of 60-80% [2]

Experimental All scans were carried out on a 3T Siemens scanner. Diffusion-weighted BOLD data were acquired in 10 subjects during visual activation and hypercapnia. During the visual run subjects viewed a flashing checkerboard stimulus with on/off blocks lasting 42/56s, repeated six times. For the hypercapnia run, subjects breathed a 4% CO_2-in-air mix during two periods of four minutes, alternated with normal air during four-minute 'off' periods. An asymmetric spin-echo (ASE) acquisition was used, with T_R/T_E=2s/72ms and a gradient echo that formed 30ms after the spin echo to yield the equivalent contrast as a GRE sequence with T_E=30ms. The sequence cycled through 7 levels of diffusion weighting [b = 0, 73, 146, 219, 292, 364, 437 s·mm^{-2}], such that the effective T_R for a single b-value was 14s. Diffusion weighting was applied isotropically according to an optimised scheme described in [4], modified to insert a refocusing pulse at $T_E/2$. Finally, a standard GRE BOLD visual run was acquired for region-of-interest (ROI) selection. One subject was scanned a second time on a separate day with the same gas challenge but with graded visual stimulus (four luminance levels, the highest being the same as the stimulus used in expt. 1), previously shown to produce graded levels of CBF change [5].
Diffusion-weighted fMRI data were split into separate time-series for different b-values. BOLD (%) change was estimated within an ROI, which was defined by thresholding the GRE BOLD visual data at z=5. Analyses were carried out using the FSL software package [6].

Results Averaged over the group, magnitudes of BOLD change for ASE data (b=0) were well matched for visual (BOLD=2.6±0.5%) and CO_2 (2.8±0.5%) stimuli. At the maximum b-value the BOLD response to visual stimulus (Fig 2a) was reduced to 0.604 of the signal change observed without diffusion weighting, consistent with our model predictions. For the CO_2 data (Fig 2a), the signal change at b_{max} was 0.753 of that for b=0. Although differences in attenuation of BOLD (%) across the whole range of b-values were not significant in a paired t-test comparison between visual and CO_2 data, the difference in attenuation from b=0 to the first level of diffusion weighting (b=73 s·mm^{-2}) was significant ($p<0.05$). The single subject data (Fig 2b) showed similar attenuation curves across the four different intensities of visual stimulus but less attenuation for the CO_2 response.

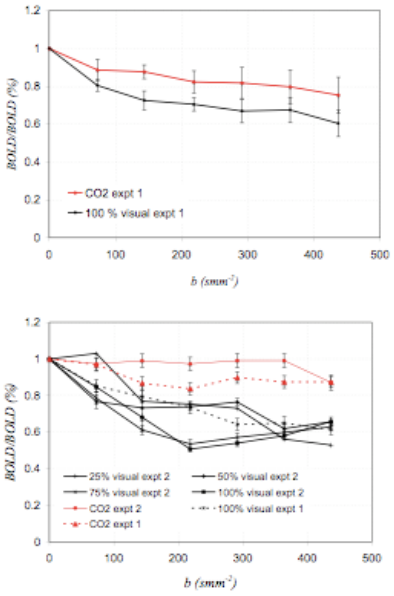

Figure 2. Percent signal change as a function of b-value (normalised to BOLD at b=0) for visual and hypercapnia data **(a)** averaged over 10 subjects **(b)** for a single subject with graded visual data

Discussion and Conclusions Our results imply that the relative intravascular and extravascular contributions may not be comparable for functional and hypercapnic stimuli. The single subject data suggest that this is not merely due to the average flow change being higher for the visual stimulus, as similar attenuation curves were seen for different intensities of visual stimulus (Fig. 2b). Results of simulations (not shown) suggest a number of possible explanations for the different attenuations seen: 1) There is a smaller IV BOLD contribution for hypercapnia; 2) Functional stimuli elicit a large flow change that is localised to a subset of vessels, compared to smaller but more global flow increases for hypercapnia; 3) The flow-volume relationship (characterised by the Grubb coefficient) is different for functional and hypercapnic activation. A further possibility is that the IV contribution in hypercapnia is more strongly weighted toward the venules, which are not entirely suppressed due to partial flow rephasing [7].
Further investigation, including reproduction of figure 2b with n>1, is required to pinpoint which of these possible explanations is most likely. Nevertheless, these findings suggest that it may not be fully appropriate to calibrate functional BOLD data with hypercapnia.

[1] Davis, TL *et al*. (1998) *PNAS* **95**: 1834-9 [2] Boxerman, JL *et al*. (1995) *MRM* **34**: 4-10 [3] Hutchinson, B *et al.* (2006) Neuroimage **32**:520-30 [4] Wong, EC *et al*. (1995) *MRM* **34**:139-143 [5] Chiarelli, PA *et al*. (2007) MRM **57**:538-47 [6] Smith, SM *et al*. (2004) *Neuroimage* **23**:208-9 [7] Jochimsen, TH et al. (2004) *MRM* **52**:724-732