Evidence for a vascular component in the diffusion FMRI signal: A hypercapnia study

K. L. Miller[1], D. P. Bulte[1], H. Devlin[1], M. D. Robson[2], R. G. Wise[3], M. W. Woolrich[1], P. Jezzard[1], and T. E. Behrens[1]

[1]FMRIB Centre, Oxford University, Oxford, United Kingdom, [2]OCMR, Oxford University, Oxford, United Kingdom, [3]CUBRIC, University of Cardiff, Cardiff, United Kingdom

INTRODUCTION. Diffusion-weighted MRI exhibits signal changes that correlate with brain activity [1-5]. Recent work has suggested that strong diffusion weighting (*b*>1000 s/mm^2) yields a signal that is directly related to neuronal activity [5], unlike BOLD FMRI measures that are mediated by the vasculature. Findings from [5] included: (a) a percent signal change that increases with *b*-value, and (b) signal changes at high *b*-value that precede the BOLD response. A pilot study in our centre replicating the protocol in [5] was able to reproduce the former result (Fig. 1b), but not the latter (Fig. 1a). To avoid the difficulty in detecting subtle timing differences, we conducted a similar experiment to [5] which uses a mild hypercapnia stimulus. Hypercapnia induces changes in blood flow with minimal change in neuronal activity. If diffusion FMRI detects neuronal activity directly, one would not expect to see signal modulation due to hypercapnia; conversely signal modulation with hypercapnia would indicate a vascular contribution to the diffusion FMRI signal.

EXPERIMENT. Seven healthy subjects were scanned during a mild hypercapnia stimulus (1 minute blocks of 4% inspired CO_2 in balance air, followed by 1 minute of normal air, cycled 3 times). Subjects were all experienced with hypercapnia and tolerated the challenge well. Other aspects of the experiment were closely matched to [5]. Imaging used a Siemens 3T scanner (12-channel receive coil, 40 mT/m gradients). The diffusion sequence used a dual spin-echo [6], single-shot EPI acquisition (T_E=100ms, T_R=1s, FOV=22cm, 64x64x7 matrix, 6/8 partial k-space, BW=1628 Hz/pix). Five diffusion-weighted runs were acquired at the same *b*-values used in [5] (b=0, 600, 1200, 1800, 2400 s/mm^2). Two additional runs were acquired to enable independent selection of voxels: one repeat of the highest *b*-value (2400 s/mm^2), and one (*b*=0) GRE run with identical EPI and T_E=30ms for standard BOLD contrast.

ANALYSIS. The stimulus model used end-tidal CO_2 waveforms, which were low-pass filtered (delay=5s, σ=15s) to match the haemodynamic response. Following standard FMRI analysis, all runs were aligned and several ROIs were generated by thresholding the statistical maps: (1) BOLD (z_{BOLD}≥10.0), (2) the additional "high-b" run (z_{DIFF}≥3.0), (3) intersection of BOLD and "high-b", and (4) mean-z over the 5 b-values (z_{MEAN}≥3.0). The first three ROIs use independent data to avoid bias in the final analysis, while the fourth provides equal weighting to all *b*-values to avoid bias for the extremes of *b*=0 or 2400 s/mm^2.

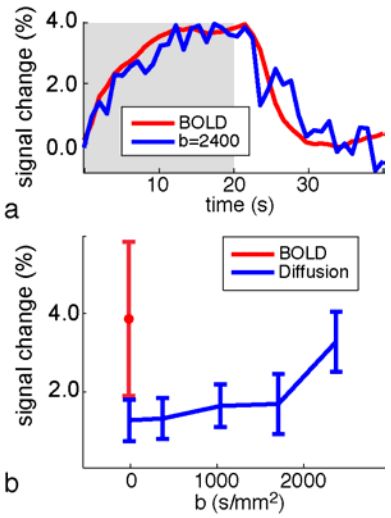
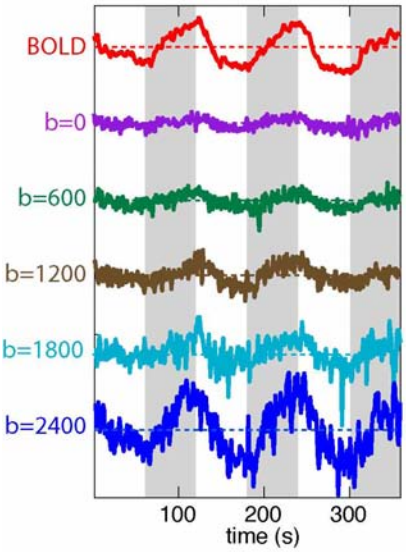
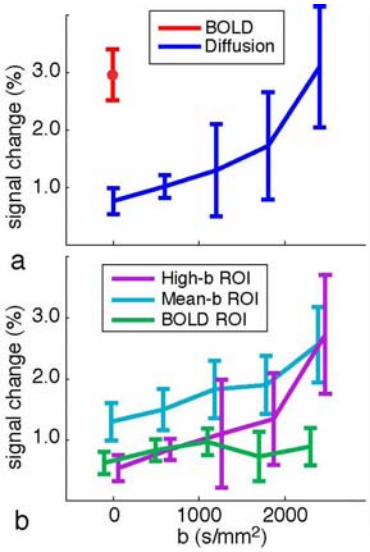


Figure 1. (a) The diffusion response did not precede BOLD (unlike [5]). (b) % signal changes increased with b (like [5]).

RESULTS. The inter-subject mean time-courses from the intersection ROI are shown in Fig. 2. All subjects exhibited statistically significant signal changes under all conditions, with a significant increase in percent change with increased b-value (paired t-test, p<0.01). This increase is clearly demonstrated in Fig. 3 (inter-subject mean) in the various ROIs. In all but the BOLD ROI, the signal change exhibits a statistically significant increase with b-value, and similar magnitude change in the b=2400 s/mm^2 and BOLD runs (2.5-3%, shown for the intersection ROI in 3a). The similarity of Fig. 3a to Fig. 1b (and to Fig. 2a in [5]) is striking. Fig. 4 shows fixed-effects group maps for BOLD (z>10.0, blue) and combined b≥1800 s/mm^2 runs (z>3.0, red). Both maps are largely confined to gray matter, although frontal and occipital areas have limited diffusion activation.





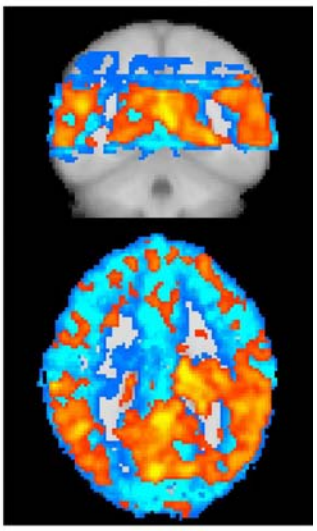


Figure 2 (left). Signal change for different conditions. Plots are inter-subject means scaled as percent change. Gray swathes indicate CO_2 blocks. Time-courses for individuals were highly similar.

Figure 3 (middle). (a) Inter-subject mean contrast (±stderr.) in the intersect ROI. Contrast increases with b-value. (b) Similar results are found for alternate ROIs

Figure 4 (right). Group fixed effects maps of high-b diffusion *b*≥1800 s/mm^2 (red) and BOLD (blue). Activation is primarily in gray matter.

SUMMARY. Hypercapnia induces signal changes in diffusion-weighted FMRI that increase with b-value, similarly to a previous visual study [5]. These results indicate a significant vascular component of this signal even at very high *b*-value.

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[1] LeBihan & Turner, MRM 1991. [2] Song et al, MRM 1996. [3] Darque et al, PNAS 2001. [4] Gangstead & Song, MRM 2002. [5] LeBihan et al, PNAS 2006. [6] Reese et al, MRM 2003.