Regional Variability of the BOLD Response to CO_2 Revealed by Spontaneous Fluctuations in End-Tidal CO_2

R. G. Wise[1,2], M. J. Poulin[3], I. Tracey[1,2]

[1]Department of Human Anatomy and Genetics, Oxford University, Oxford, United Kingdom, [2]FMRIB Centre, Department of Clinical Neurology, Oxford University, Oxford, United Kingdom, [3]Department of Physiology & Biophysics, University of Calgary, Calgary, Alberta, Canada

Introduction

We have previously demonstrated that spontaneous fluctuations in the partial pressure of end-tidal carbon dioxide (PET_{CO_2}) in volunteers at rest, are associated with significant low frequency (0 – 0.05 Hz) BOLD signal fluctuations at 3 Tesla [1]. Trans-cranial Doppler (TCD) ultrasound measurements of blood velocity in the middle cerebral artery (MCA) suggest that such BOLD signal fluctuations are mediated by CBF changes induced by fluctuations in arterial carbon dioxide (Pa_{CO_2}), CO_2 being a potent modulator of cerebral blood flow. These BOLD signal fluctuations can be regarded as a source of physiological noise in FMRI. However, here we demonstrate that they are useful for investigating the regional BOLD signal sensitivity to CO_2 and the delay of the BOLD response to CO_2. Previously this has only been investigated using administered hypocapnic (hyperventilation) or hypercapnic (breath-hold or breathing CO_2) challenges.

Methods

Nine volunteers (4 male) aged 30±7 years (mean ±SD) underwent gradient-echo echo-planar imaging at 3T (Varian Unity Inova) for 12.5 min (TR=3s TE=30s, in-plane resolution 3x4 mm, 24x6 mm axial slices covering the whole brain, flip angle 90°). T1 weighted structural scans were also acquired. At rest, changes in PET_{CO_2} reflect changes in Pa_{CO_2}. Volunteers' PET_{CO_2} was recorded (MR Equipment Corp. Multigas 9500) via a nasal cannula. Volunteers were asked to close their eyes and no functional paradigm was presented. The transit delay of gas through the nasal cannula was subtracted before analysis.

FMRI data were slice-timing corrected, motion corrected, spatially filtered (FWHM=5mm) and high-pass temporally filtered (Guassian weighted straight line fitting with FWHM~45 s) to remove very low frequencies (FEAT, FMRI Expert Analysis Tool [2]). The PET_{CO_2} signal was also temporally filtered and was convolved with a gamma-variate haemodynamic response function to provide a physiologically reasonable dispersion. Following co-registration of the FMRI volumes and the T1 weighted individual structural scan (FMRIB Linear Image Registration Tool [2]), regions of grey and white matter were automatically identified from the T1 weighted scans (FMRIB Automated Segmentation Tool [2]). FMRI volumes were further registered to the standard brain of the Montreal Neurological Institute (MNI). Nine different regions of grey matter were defined, as listed below, using the standard brain of the MNI. For each subject, the mean FMRI time course of each region was cross-correlated with the PET_{CO_2} signal. For each region, the peak of the group mean cross-correlation function (CCF) indicated the lag of the BOLD signal after PET_{CO_2} signal changes (Fig. 1). The group-mean lag was applied to the regional FMRI time-series for each subject and this was regressed against the PET_{CO_2} signal to identify the regional sensitivity of BOLD signal to changes in PET_{CO_2} (regression coefficient, $\%\Delta S_{BOLD}$/mmHg).

Results and Discussion

Abbreviations for brain regions (grey matter unless otherwise stated): st – striatum, th – thalamus, cb – cerebellum, fr – frontal cortex, in – insular cortex, pp – posterior parietal cortex, te – temporal cortex, sn – sensory cortex (primary and secondary combined), oc – occipital cortex, gm – grey matter and wm – white matter. For each region, left and right sides of the brain were pooled.

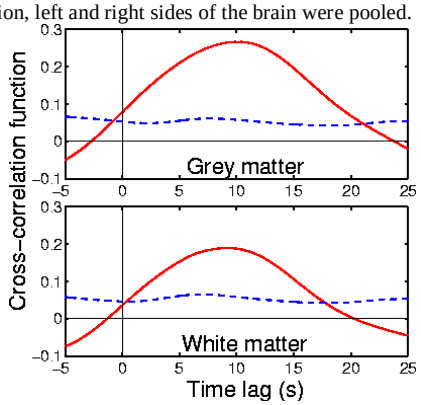

Fig. 1. **Group mean (n=9) cross-correlation function** (continuous line) and standard errors (broken line), between PET_{CO_2} and regional mean BOLD signal at rest. Positive times indicate that BOLD lags PET_{CO_2}.

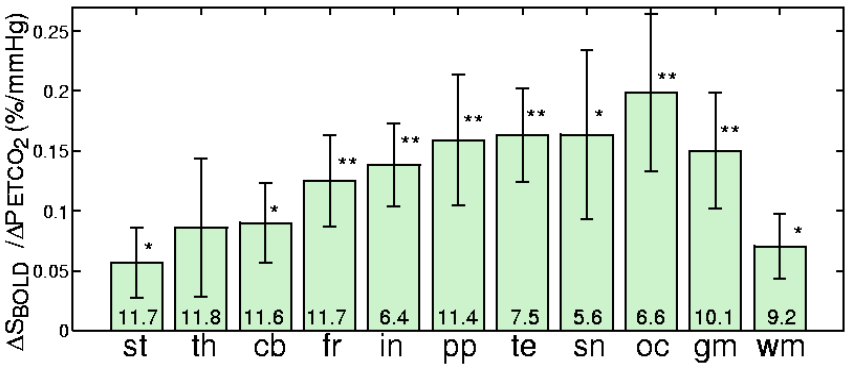

Fig. 2. **Group mean regional sensitivity of BOLD signal to resting fluctuations in PET_{CO_2}.** Error bars indicate the standard error. Mean greater than zero with $*P<0.05$ and $**P<0.01$ (one-tailed *t*-test, uncorrected). Numbers at the base of each bar give the time lag (s) of the BOLD signal changes after PET_{CO_2} changes, estimated from the group mean cross-correlation function.

The CO_2-related BOLD signal fluctuations were significant in most grey matter regions (Fig. 2), and in grey matter and white matter as a whole. The mean within-session standard deviation of PET_{CO_2} over time was 1.06 mmHg, producing BOLD signal fluctuations of up to 0.2% on average in occipital grey matter. A repeated measures (within subject) analysis of variance on the nine mean regional grey matter regression coefficients ($\%\Delta S_{BOLD}$/mmHg) showed a significant main effect of region (P=0.01). Post-hoc uncorrected paired one-tailed *t*-tests indicated a greater signal response to CO_2 in the posterior parietal, insular, frontal and temporal regions than the striatum (significance $P\leq0.01$) and greater responsiveness in the posterior parietal region than the thalamus (significance $P\leq0.01$). Similarly, insular, frontal, occipital, temporal and posterior parietal grey matter regions, and grey matter as a whole, showed greater responsiveness than white matter (significance $P\leq0.01$). This is consistent with previous studies of hypocapnia [3] and hypercapnia [4] reporting comparatively small BOLD-CO_2 responsiveness in white matter. Such studies also report a comparatively high response in occipital cortex [5] in agreement with our data. Differences in vascular density and blood flow response are likely to contribute to regional differences in the BOLD sensitivity to CO_2. Grey matter has a larger cerebral blood volume than white matter and occipital cortex contains a high concentration of venules [6]. Regional differences in baseline T_2* can also contribute to variability of BOLD sensitivity across the brain at a single echo-time. Cross-correlation indicated a similar temporal delay of the BOLD signal change for grey and white matter although it suggested differences between grey matter regions. Further investigation is needed to find out if theses are indicative of regional differences in the timing of the haemodynamic response function. Our observed time lag is in broad agreement with TCD measurements of spontaneous CO_2-induced MCA velocity fluctuations [7,8] and BOLD measurements during hypocapnia [3].

We have demonstrated regional differences in BOLD sensitivity to CO_2 using resting fluctuations, without the need for a potentially confounding and disruptive external hypo/hypercapnic stimulus. Such a test could be incorporated into FMRI scan sessions to asses inter-region and inter-subject BOLD signal sensitivity to PET_{CO_2} changes as well as using the PET_{CO_2} recordings to regress out this source of low frequency BOLD fluctuation from the FMRI time-series.

References [1] Wise *et al. Proc. Intl. Soc. Mag. Reson. Med.* **11**, 216, 2003. [2] http://www.fmrib.ox.ac.uk/fsl. [3] Posse, S. *et al. Am. J. Neuroradiol.* **18**, 1763-70, 1997. [4] Rostrup, E. *et al. NeuroImage.* **11**, 87-97, 2000. [5] Kastrup, A. *et al. NeuroImage*. **10**, 675-81, 1999. [6] Davis, T.L. *et al. Proc. Natl. Acad. Sci.* **95**: 1834-9, 1998. [7] Mitsis, G.D. *et al. Proc. Second Joint EMBS/BMES Conference (Houston Texas, USA)* **2**, 1341-1342, 2002. [8] Panerai, R.B. *et al. IEEE Trans. Biomed. Eng.* **47**, 419-23, 2000.