Anticorrelated fMRI signal changes of hemodynamic origin in large cerebral vessels

Molly Gallogly Bright[1,2], Marta Bianciardi[2,3], Jacco A. de Zwart[2], and Jeff H. Duyn[2]

[1]*CUBRIC, School of Psychology, Cardiff University, Cardiff, United Kingdom,* [2]*Advanced MRI Section, LFMI, NINDS, National Institutes of Health, Bethesda, MD, United States,* [3]*A.A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, United States*

Introduction: Negative signal changes in BOLD-weighted fMRI have been interpreted as neuronal deactivation [1], a vascular steal phenomenon [2], or the result of data processing and analysis techniques [3]. Knowledge of the true source could have implications for how we collect and understand fMRI data. Recently, negative fMRI signal changes in large vessels surrounding the ventricles and in the cortical sulci, fluctuating in sync with low-frequency resting state fluctuations, were shown [4]. Data indicated that these negative signals did not originate from local increases in [dHb] but rather local increases in cerebral blood volume (CBV) in voxels with large CSF content. These effects were interpreted to originate from large vessels supplying (or draining) the activated region. If disproportionally large, such signals can locally overwhelm any positive BOLD effect. To further investigate this, we applied a Cued Deep Breathing (CDB) challenge [5] that uses two cycles of short, deep breaths to create transient hypocapnia and a resultant global fMRI signal decrease caused by constriction of cerebral arterioles. We hypothesize that a global stimulus will amplify the CBV effect in large vessels and that using a global *negative* stimulus will test whether these voxels exhibit *negative* or simply *anticorrelated* responses. Furthermore, we hypothesized that analysis of the relative timing of the positive and negative fMRI signal changes may give better insight into the underlying mechanisms.

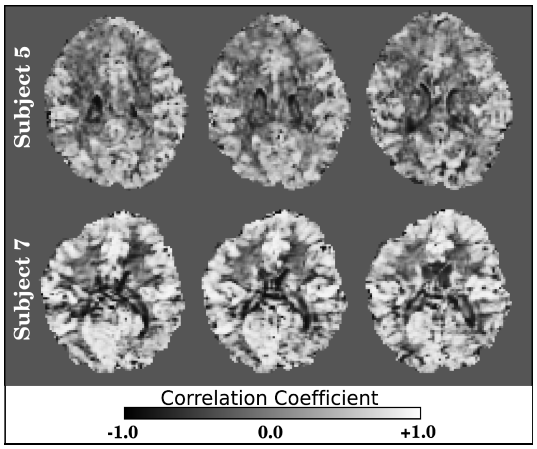

Figure 1. Voxelwise correlation with the global timeseries for two subjects

Methods: ***Data acquisition:*** Ten subjects were scanned using a 7 Tesla GE whole-body scanner (Milwaukee, WI, USA) with a 32-channel receive head coil. Subjects were cued to execute six CDB challenges interleaved with 75 s of normal breathing using spoken auditory commands. Data were acquired using BOLD-weighted gradient-echo EPI (TR/TE=2000/30 ms, FOV=260 mm, slice thickness=2 mm, 255 repetitions) for a total scan duration of 8.5 min and 2.0 x 2.0 x 2.0 mm^3 resolution. Twenty oblique slices were acquired to cover both motor and visual cortices. The EPI read-out occurred during the first 1500 ms of each TR, creating 500 ms breaks in the scanner noise for delivery of auditory commands ("Ready", "In", "Out", "In", "Out", "Normal", shortened from [5] for clarity) via the scanner intercom system. Subjects were fitted with respiratory bellows to monitor depth and rate of breathing, used to monitor compliance with the breathing task and to reduce respiration-driven scanning artefacts using real-time shimming [7]. Three subjects were excluded due to errors in collecting physiological data or poor task performance. In 6 of the 7 remaining subjects, the functional scan was repeated a second time. ***Data analysis:*** Data were preprocessed as follows: the first 9 volumes were removed, motion correction (MCFLIRT), brain extraction (BET), and slice timing correction (FSL) were applied, and 4-degree polynomial detrending was carried out. Temporal ICA (MELODIC) was then performed, and components identified to contain motion-related artefacts were removed. The whole-brain average timecourse was extracted to reflect the fMRI response to the six breathing challenges, and significantly correlated or anticorrelated voxels ($p<0.05$, Bonferroni corrected) were identified. The start of each breathing challenge was determined using respiratory bellows data. For every voxel, the fMRI data for each of the six challenges were combined and fitted with a double gamma-variate function as described previously [6, Fig 2b] at a temporal resolution of 0.25 s. The time-to-peak (TTP) of the absolute signal change was extracted. Using an n-way ANOVA (MATLAB) to account for inter-subject differences, the presence of scan repeats, and different numbers of voxels in the two populations, the TTPs of the significantly correlated and anticorrelated voxels were compared.

Results: Correlation maps of individual voxel timecourses with the whole-brain average are presented in Fig. 1 for 3 slices of 2 subjects. Voxels near the edges of the ventricles exhibited fMRI signal changes that were significantly anticorrelated with the whole-brain response to the CDB challenges. Voxels near the edges of the cortex and in central areas of white matter superior to the ventricles, associated with larger vessels, also exhibited significant anticorrelation. Average timecourses of correlated and anticorrelated voxels of 1 subject are presented in Fig. 2a. TTP histograms for the significantly correlated and anticorrelated voxel populations are shown in Fig. 2c. Across the study, the TTP in anticorrelated voxels was found to be 1.75 s earlier than in positively correlated voxels ($p<0.001$, n-way ANOVA corrected for multiple comparisons, 95% confidence interval: 1.67-1.82 s).

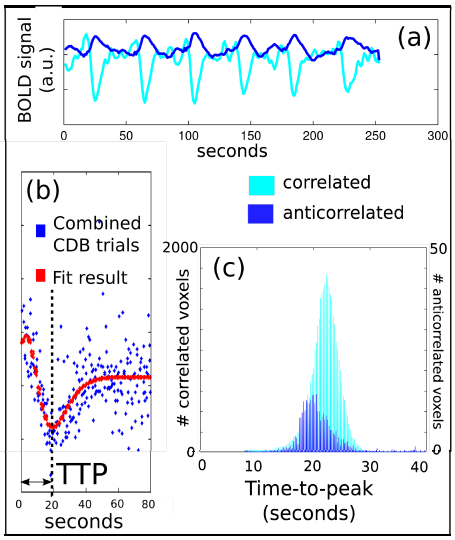

Fig 2. (a) The average fMRI signal timecourses of significantly correlated and anticorrelated voxel populations for 1 subject. (b) Example of double γ-variate fitting of the 6 combined CDB trials for a single gray matter voxel. (c) Histograms of the TTP of the significantly correlated and anticorrelated voxels for 1 subject.

Discussion: This study supports the findings of [4] and adds insight into the mechanism of the anticorrelated signal fluctuations. Using a global stimulus (hypocapnia challenge), rather than resting state flucutations, we have improved the contrast of the relevant fMRI signal changes and increased the number of voxels in both the correlated and anticorrelated populations. Secondly, the hypocapnia breathing challenge results in vasoconstriction and an fMRI signal *decrease* in most of gray matter, whereas the corresponding anticorrelated voxel timecourses exhibit an fMRI signal *increase*. We can therefore conclude that the periventricular fMRI signal changes are *anticorrelated* rather than *negative* in nature. Thirdly, the use of an isometabolic breathing challenge stimulus rather than resting state signal fluctuations (hypothesized to be metabolic in nature) supports the hypothesis that these anticorrelated signal changes are non-neuronal and purely hemodynamic in nature.

The use of the CDB challenge enables the voxelwise measurement of the dynamics of both the correlated and anticorrelated fMRI response. The positive, anticorrelated fMRI signal change in large periventricular and pial vessels occurs significantly earlier than the negative fMRI signal change occurring throughout gray matter. This suggests that the anticorrelated fMRI signal is *not* a downstream effect of the global gray matter response, and it is therefore unlikely to reflect changes in deoxyhemoglobin content. Instead, our results support the hypothesis that the anticorrelated signal changes reflect relative changes in the size of CSF and CBV compartments, as was hypothesized and modelled in [4]. The hypocapnia CDB challenge causes a global decrease in blood volume and blood flow, which may be matched by an expansion of the CSF compartment. This scenario would manifest as an fMRI signal increase in large vessels near ventricles or near the subarachnoid space and could explain the anticorrelated responses observed in this study.

Conclusions: We observe voxels adjacent to CSF that exhibit an anticorrelated fMRI response to a global physiological stimulus. This response reaches its maximum prior to the correlated response of most of gray matter, suggesting that it is caused by early changes in blood and CSF volume rather than downstream [dHb] effects. By incorporating a global gas challenge in scanning, it may be possible to distinguish hemodynamic "negative" (or "anticorrelated") fMRI signal changes from negative BOLD signals that are neuronal in origin.

References:

[1] Shmuel et al. 2006 Nat Neurosci 9:569-77
[2] Harel et al. 2002 JCBFM 22:908-17
[3] Murphy et al 2009 Neuroimage44:893-905
[4] Bianciardi et al 2011 JCBFM :401-12
[5] Bright et al. 2009 Neuroimage 48:166-75
[6] Bright et al. ISMRM 2011 Abstract #96
[7] van Gelderen et al. 2007 MRM 57:362-8