Robustly accounting for vascular reactivity differences across subjects using breath-hold

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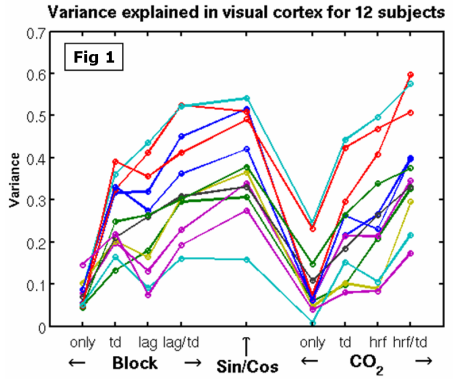
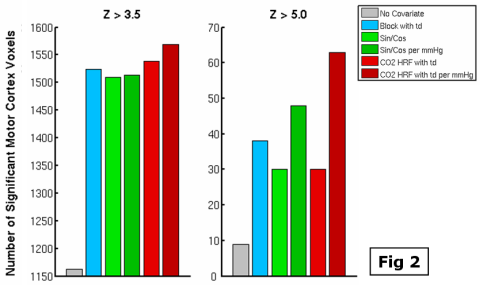
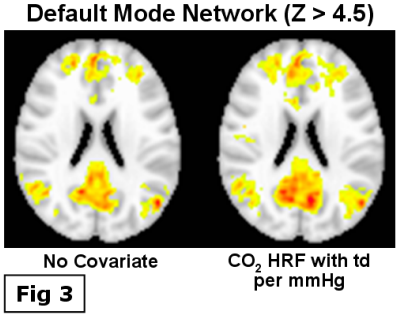
Introduction Changes in the BOLD signal associated with neuronal activity reflect increased metabolic demand, cerebral blood flow (CBF) and cerebral blood volume (CBV). Inter-subject differences in local CBF and CBV contribute to differences in BOLD signal reactivity and, therefore, unmodelled variance in group level fMRI analyses. Characterisation of vascular (BOLD signal) responsiveness is often achieved using hypercapnic challenges that purport to increase CBF and CBV without a concomitant increase in the metabolic oxygen consumption rate [1,2]. A simple but effective way of elevating blood CO_2 concentrations to measure vascular reactivity is breath-holding which has been successfully employed to reduce variability between groups [3]. However, two aspects of this vascular reactivity measure are often neglected: 1) breath-holds are usually modelled as blocks even though CO_2 accumulates over time, resulting in a more complicated BOLD response; and, 2) increases in CO_2 differ between subjects, which must be considered when using vascular reactivity as a group calibration tool. This study first determines the appropriate technique to model the BOLD response during breath-holds and also demonstrates that individual differences in the CO_2 response are reflected in vascular reactivity measures.

Methods *Imaging:* FMRI was performed on a 3T GE MRI scanner equipped with an 8-element head coil. Single shot, GE-EPI was used for functional scans on 12 subjects. *Scanning Parameters*: TR=3s, TE=35ms, matrix=64x64, FOV/slice=20.5cm/3.2mm, flip=90º, 53 slices. CO_2 traces were recorded using a nasal cannula connected to a capnograph. *Tasks:* The breath-hold task consisted of 30s paced breathing followed by a 20s breath-hold after expiration followed by a further exhalation prior to restarting paced breathing. In a separate scan, an event-related visual/auditory/motor task was presented. A further 10min resting state scan was also acquired. *Analyses:* Nine GLM analyses were performed to determine the regressors that best fit the BOLD breath-hold response: (1) simple block task-timing convolved with the standard HRF; (2) the block regressor along with its temporal derivative (td); (3) the block regressor delayed by 9s; (4) the 9s-delayed regressor with its td; (5) a sine and cosine wave at the task frequency; (6) the unprocessed end-tidal CO_2 trace; (7) the CO_2 trace with its td; (8) the CO_2 trace convolved with the standard HRF; and, (9) the HRF-convolved CO_2 trace with its td. Fits to the breath-holding data were determined and the absolute range of the fitted model was used as the measure of the vascular response. To correct for vascular reactivity differences across subjects, voxel-dependent group level covariates were included in group level analyses of the sensory tasks. The importance of accounting for subject differences in end-tidal CO_2 increases during breath-hold was investigated. The influence of vascular reactivity differences on resting state connectivity measures was also determined with seed region analyses using ROIs in the left motor cortex and the PCC. Group level analyses with and without breath-hold covariates determined the vascular reactivity influence on connectivity results.



Results Baseline end-tidal CO_2 levels varied substantially across subjects (mean 39.7 mmHg; range 35.8 – 44.4 mmHg). The absolute range of end-tidal CO_2 increases during breath-hold was 13.4±2.2 mmHg (range: 9.5 – 17.3 mmHg). Modelling the breath-hold response with a simple block does not fit the data well (Fig 1); often resulting in a negative fit due to the temporal lag of the BOLD response. An explicitly defined lag of 9s along with the temporal derivative forms the best block-based approach. The sin/cos modelling fits the BOLD breath-hold response better than any block model and is only improved in 7 subjects by modelling the HRF-convolved CO_2 trace and its temporal derivative.
After building group level voxel-wise covariates from BOLD increases during breath-hold, correspondence with the end-tidal CO_2 increases is observed across grey matter indicating that the covariates are contaminated by subject differences in CO_2 response to breath-hold. Covariates in which the BOLD signal change was expressed per mmHg increase in CO_2 were created to reflect the more general measure of vascular reactivity rather than the vascular response to the specific breath-hold. Figure 2 demonstrates that after including the covariates in a group level analysis, the greatest increase in spatial extent of significant task-related activity occurs when the covariate is expressed in these terms. Similar spatial extent increases are observed when resting state connectivity measures are corrected for vascular reactivity differences across subjects. At strict thresholds, the number of activated voxels in the contralateral motor cortex increases two-fold. Similar improvements are evident in the default mode network (Fig 3).





Conclusions Correcting for variations in vascular reactivity using BOLD signal increases to breath-hold in group level analyses increases statistical significance. Variance in breath-hold data is explained best by fitting the end-tidal CO_2 trace convolved with a HRF and its temporal derivative. The absolute increase in end-tidal CO_2 during breath-hold should be considered to provide a measure of vascular reactivity to CO_2 – converting covariates to BOLD increases per mmHg rise in CO_2 results in more statistically active voxels in both task-related and resting state analyses.

Acknowledgements Funded by Pfizer Ltd., NSERC.
References [1] Davis (1998), PNAS:95,1834; [2] Hoge (1999), MRM:42,849; [3] Handwerker (2007), HBM:28,846