CBF modulation of task-positive and task-negative BOLD responses to a cognitive task: differential effects in the default mode network

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Purpose: Examine the effects of baseline cerebral blood flow (CBF) on BOLD activation and deactivation in a cognitive task.

Introduction: It has been shown that the positive BOLD response to a visual stimulus[1] or finger tapping[2] is reduced with increasing baseline CBF. This is consistent with the model of Davis *et al*[3] that also predicts a reduction in the amplitude of the negative BOLD signal change with increased CBF. These predictions (Fig 1) follow from an assumption of the task-related increase or decrease in the rate of oxygen consumption ($CMRO_2$) is unaltered by the increased CBF. Here we examine the effect of baseline CBF on BOLD activation (task-positive BOLD signal change) and deactivation (task-negative BOLD signal change) resulting from a cognitive task (a working memory, WM task) to identify if the modulation of BOLD contrast by CBF is consistent with these model predictions.

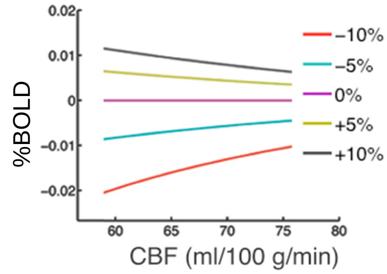

Fig 1. Model predicted %BOLD response with varying baseline CBF for tasks inducing 5 levels of relative $CMRO_2$.

Methods: Sixteen subjects were imaged twice at 3 T (GE HDx). Participants wore a tight-fitting facemask and two conditions were compared: normocapnia and hypercapnia (end-tidal PCO_2 increased by ~8mmHg above baseline). During both conditions, BOLD data were acquired (TR/TE = 3s/35ms, 64x64 matrix, FOV=22.5 cm^2) while subjects performed a WM task consisting of sequential 30s blocks of rest, a 3-back task and a 0-back task. For all analyses, the task will refer to the comparison of 3-back vs. 0-back. Data were analysed using FSLtools (www.fmrib.ox.ac.uk/fsl). A voxel-wise, whole brain analysis was performed to identify task-related activation and deactivation changes with hypercapnia. Such modulation was also investigated by a region of interest (ROI) analysis. Task positive and task negative regions were defined from the pooled normocapnic and hypercapnic data, as the intersection of a 15mm radius sphere centred on the peak *Z*-statistic and the atlas-defined (Harvard-Oxford atlas) anatomical region.

Results: Fig 2 (column 1) shows the hypercapnic modulation of the WM task-related BOLD signal (unthresholded *Z*-statistics); green indicates more negative (less positive) signal in hypercapnia and yellow indicates less negative (more positive) signal in hypercapnia. Column 2 shows the WM task-positive and task-negative signal changes (pooled hypercapnia and normocapnia data) used for the ROI analysis. The voxel-wise whole brain analysis showed statistically significant reductions in the amplitude of the BOLD signal with hypercapnia (column 3). ROIs with WM task-positive BOLD signal show a decrease in activation with hypercapnia. ROIs with WM task-negative BOLD signal, that are generally considered to be a part of the default mode network (e.g., posterior cingulate, precuneus, paracingulate), show increased negativity with hypercapnia while other WM task-negative ROIs (e.g., post-central gyrus, Heschl's gyrus) appear to have decreased negativity with hypercapnia (Table).

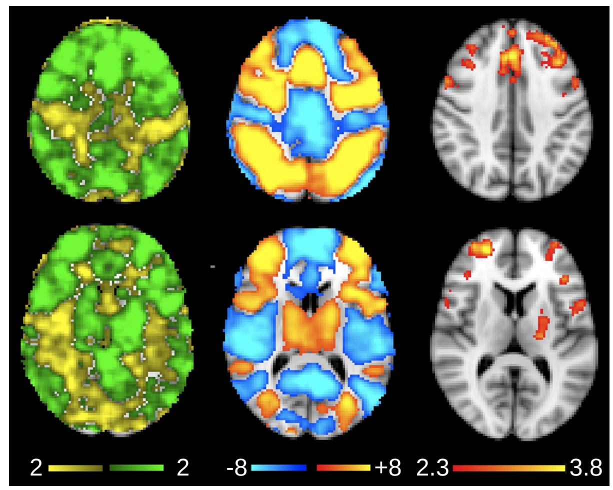

Fig 2. Column 1: CO_2 response where green is decreasing BOLD signal and yellow is increasing BOLD signal with hypercapnia. Column 2: task related activation (red-yellow) and deactivation (blue-cyan). Column 3: voxel-wise analysis showing regions with significantly decreased activation during hypercapnia.

*Table. %BOLD changes during the WM task at normocapnia and hypercapnia in selected regions (mean ± standard deviation) * significant difference (paired t-test)*

	Normocapnia	Hypercapnia
Task positive regions		
Angular Gyrus - right	0.73±0.46	0.70±0.43
Angular Gyrus - left	0.77±0.56	0.67±0.47
Anterior Cingulate*	0.64±0.42	0.51±0.31
Frontal Pole – left*	0.60±0.49	0.47±0.50
Frontal Pole – right*	0.81±0.41	0.63±0.44
Middle Frontal Gyrus – right*	0.82±0.38	0.63±0.36
Middle Frontal Gyrus – left*	0.63±0.40	0.47±0.39
Cuneus	0.45±0.74	0.38±0.55
Task negative regions		
Posterior Cingulate	-0.54±0.27	-0.57±0.20
Frontal Pole – left	-0.68±0.27	-0.75±0.37
Frontal Pole – right*	-0.52±0.35	-0.67±0.39
Paracingulate	-0.42±0.25	-0.50±0.32
Precuneus	-0.53±0.29	-0.59±0.30
Insula - left	-0.34±0.26	-0.26±0.21
Insula - right	-0.37±0.26	-0.23±0.15

Discussion: In general, there was a stronger modulatory effect of elevated baseline CBF on WM task-positive compared to task-negative signal. A hypercapnia-induced increase in baseline CBF tends to decrease task-positive BOLD signal changes, consistent with the predictions of the Davis model[3] (Fig 1). The model's predictions are also consistent with certain WM task-negative ROIs in showing a decreased negativity, albeit not always significantly. However, ROIs commonly referred to as default mode network show increased task-negativity (often non-significant at elevated CBF. This could be explained by (i) regional differences in the vascular response to CO_2 or (ii) greater task-induced decreases in $CMRO_2$ during hypercapnia. Such alterations in the task-induced $CMRO_2$ may arise from greater reductions in neural activity, perhaps related to the cognitive interference produced by the subjective effects of hypercapnia or regionally specific suppressive effects of hypercapnia on neuronal excitability.[4]

Conclusion: Baseline CBF effects on BOLD deactivation appears to differ between default mode network and other cognitive task-negative regions.

References: 1. Cohen *et al*. 2002. *JCBFM* 22: 1042.
2. Brown *et a*l. 2003. *JCBFM* 23: 829. 3. Davis *et al.* 1998. PNAS 95: 1834
4. Zappe *et al*. 2008. CC 18: 26666.