

# Calibrated fMRI reveals altered neurovascular coupling with age during a cognitive stroop task

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**Introduction:** Calibrated fMRI is a technique that allows quantitative estimates of the relative changes in cerebral metabolic rate of oxygen ( $\Delta\text{CMRO}_2$ ) and cerebral blood flow ( $\Delta\text{CBF}$ ) that accompany neural activation, thus providing a way to investigate the coupling between neural and vascular activity in the human brain. In this study we consider differences in neurovascular coupling between a young and a healthy old group during a cognitive Stroop task. Previous work using the Stroop task has shown increased Blood-Oxygenation-Level-Dependent (BOLD) response with increasing age in the frontal cortex<sup>1-3</sup>, attributed to increased neural processing in this region due to impaired inhibition. However, it is not clear whether it is the neuronal response or vascular confounders that drive these differences, which the present study aims to address.

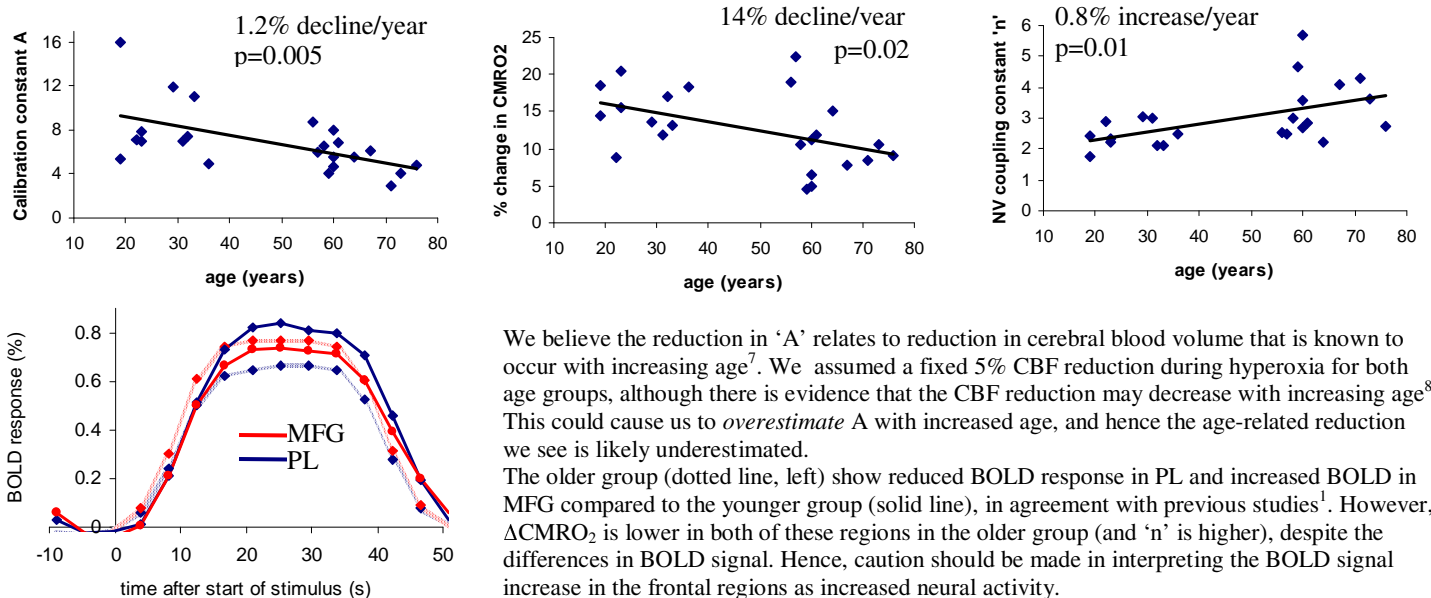
**Methods:** 10 young (age range 19-36, 4 male) and 13 older (age range 55-76, 2 male) volunteers took part in the experiment which was approved by the University research ethics committee. Participants were carefully screened to avoid any neurological or vascular disease.

**Task:** A color-word Stroop task was used. Subjects had to decide if the meaning of a word presented in white print at the bottom of the screen matched the print color of the top word and responded with a choice of two buttons with the right hand. Stimuli were self-paced with a minimum time of 1.5 s (young) or 2 s (old) between stimuli. 8 active blocks of 30 s were interspersed with 30 s fixation cross, giving a run time of 8 mins. For the BOLD calibration scan, oxygen was delivered via an open mask (2 sessions of 3 mins) interspersed with breathing normal air. The gas composition inside the subject's nose was continuously sampled at intervals of 1ms via a nasal cannula connected to an oxygen analyser.

**MRI methods:** All scanning was performed on a 3 T Siemens Trio system. Images were acquired using a QUIPSSII Arterial Spin Labeling sequence<sup>4</sup>. Acquisition parameters were: TR 2.13 s, TI<sub>1</sub> 0.7 s, TI<sub>2</sub> 1.4 s, TE 25 ms and crusher gradients with  $b=5 \text{ mm}^2$ . 12 slices of 3.5 mm thickness covered frontal, motor and parietal cortices. A 1mm isotropic structural MPRAGE image was also collected.

**Analysis:** Label and control images were added (BOLD) or subtracted (CBF) to produce BOLD and CBF time courses which were co-registered to the T<sub>1</sub>-weighted image and transformed into Talairach space using BrainVoyager. Regions of interest (ROI) were found on an individual basis where the Stroop activity accounted for significant variance in both the BOLD and CBF time-courses at a threshold of  $p<0.05$  (corrected for FDR). Data were recorded from 8 ROIs: M1 and SMA, left and right parietal lobe (PL), medial frontal gyrus (MFG) and frontal cortex (FC). In each ROI individual signal time courses were recorded for BOLD and CBF for both the Stroop and hyperoxia stimuli. The calibration constant A was calculated using the Chiarelli and Bulte hyperoxia model<sup>5</sup> with  $\alpha = 0.38$ ,  $\beta = 1.5$ , baseline oxygen extraction fraction (OEF) of 0.4 and an assumed reduction in CBF of 5% during hyperoxia. The parameters  $\Delta\text{BOLD}$ ,  $\Delta\text{CBF}$  and  $\Delta\text{CMRO}_2$  were calculated using the model described by Buxton<sup>6</sup>. Regional and global differences between the groups were tested.

**Results and Discussion:** Both groups performed the task well: mean accuracy 96% for both groups, mean response times 1061 ms (old) and 1045 ms (young). The BOLD response to hyperoxia was reduced in the older group compared to the younger group, leading to a reduction in calibration constant A as shown on the left figure. Each point shows the average value for an individual over all regions. In addition we find a reduction in  $\Delta\text{CMRO}_2$  with increasing age as shown in the middle figure. Globally  $\Delta\text{CBF}$  did not change with age, and hence the neurovascular coupling parameter  $n=\Delta\text{CBF}/\Delta\text{CMRO}_2$  increased with age (right figure).



We believe the reduction in 'A' relates to reduction in cerebral blood volume that is known to occur with increasing age<sup>7</sup>. We assumed a fixed 5% CBF reduction during hyperoxia for both age groups, although there is evidence that the CBF reduction may decrease with increasing age<sup>8</sup>. This could cause us to *overestimate* A with increased age, and hence the age-related reduction we see is likely underestimated. The older group (dotted line, left) show reduced BOLD response in PL and increased BOLD in MFG compared to the younger group (solid line), in agreement with previous studies<sup>1</sup>. However,  $\Delta\text{CMRO}_2$  is lower in both of these regions in the older group (and 'n' is higher), despite the differences in BOLD signal. Hence, caution should be made in interpreting the BOLD signal increase in the frontal regions as increased neural activity.

This work is important as it demonstrates the care needed in interpretation of differences in the BOLD response between groups where the neurovascular coupling and resting blood volume may be altered, such as in two groups of different ages or in comparisons of a clinical and control group. Calibrated fMRI allows the possibility to quantify underlying physiological changes.

**References:** 1. Milham et al, Brain and Cognition 49:277-196, 2002. 2. Langenecker et al, Neuroimage 21:192-200, 2004. 3. Zysset et al, Neurobiology of aging 28, 937-947, 2007. 4. Wong et al, MRM 39 (5): 702-708, 1998. 5. Chiarelli and Bulte, Neuroimage 37:808-820 2007. 6. Buxton et al, Neuroimage 23:S220-S233, 2004. 7. Wenz et al 14(2): 157-162, 1996. 8. Watson et al, Eur J of Anaesthesiol. 17 :152-159, 2000.