Calibrated fMRI during a cognitive Stroop task in the aging brain

R. S. Mohtasib[1,2], V. Sluming[1,2], and L. Parkes[1,3]

[1]Magnetic Resonance and Image Analysis Research Centre (MARIARC), The University of Liverpool, Liverpool, United Kingdom, [2]Medical Imaging Department, The University of Liverpool, United Kingdom, [3]Imaging Science and Biomedical Engineering, School of Cancer and Imaging Sciences, The University of Manchester, United Kingdom

Introduction: Functional MRI has been used recently to study the neural substrates of age-related cognitive decline. FMRI studies typically measure changes in the blood oxygenation level dependent (BOLD) signal in response to a functional task and use this signal as an indirect measure of neural activity. However, there is evidence to suggest that the BOLD signal may also reflect changes in the cerebrovascular system due to factors such as age, disease, and medication[1,] Calibrated fMRI is a new technique that allows quantitative estimates of the relative changes in cerebral metabolic rate of oxygen ($\Delta CMRO_2$) and cerebral blood flow (ΔCBF) that accompany neural activation, consequently providing a way to investigate the coupling between neural and vascular activity in the human brain. Here we extend our previous work[2] (increasing the sample and using an identical paradigm for all volunteers) to study changes in neurovascular coupling over an age range during a cognitive Stroop task. Other studies using the Stroop task reported an increased BOLD response with increasing age in the frontal cortex[3-5]. The amplitude and shape of BOLD responses in fMRI studies varies across brain regions, subjects, and populations. This variability may be secondary to neural activity. In this study we aim to investigate to what extent neuronal and vascular effects contribute to this variability.

Methods: 37 volunteers (age range 20-70) took part in this study which was approved by the University research ethics committee. Participants were carefully screened to avoid any neurological or vascular disease and contra-indications to MRI.

Task: A color-word stroop task was used. Subjects had to decide if the meaning of a word presented in white ink at the bottom of the screen matched the ink 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 2s 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 1 ms via a nasal cannula connected to an oxygen analyser.

MRI methods: A 3 T Siemens Trio system was used to acquire images using a QUIPSSII Arterial Spin Labeling sequence[6]. Acquisition parameters were: TR 2.13 s, TI_1 0.7 s, TI_2 1.4 s, TE 25 ms. Bipolar gradients were added to remove intravascular signal. 12 slices of 3.5 mm thickness covered frontal, motor and parietal cortices. A 1mm isotropic structural MPRAGE image was also collected.

Analysis: We used BrainVoyager software to analyse all scans. Label and control images were added (BOLD) or subtracted (CBF) to produce BOLD and CBF time courses which were co-registered to the T_1-weighted image and transformed into Talairach space. Regions of interest 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 false detection rate). Data were recorded from all active regions including motor cortex, supplementary motor area, left and right parietal lobes, frontal lobes and insular. In each region 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[7] 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. By using the model described by Buxton[8] we calculated the parameters $\Delta BOLD$, ΔCBF and $\Delta CMRO_2$. We tested the regional and global dependence of the calculated parameters with age using regression analysis.

Results and Discussion

The age-related effects appeared to be similar across all regions, hence we report the global results only (found by averaging over all active regions). The BOLD response to the Stroop task was found to increase with increasing age, particulary in frontal regions, as shown in previous studies. As shown in figure1, the calibration constant A was found to reduce with age, due to a reduced BOLD response to hyperoxia with age. Additionally we found a trend to reduced $\Delta CMRO_2$ with increasing age (figure2). Globally ΔCBF did not change with age, and therefore the neurovascular coupling parameter n=ΔCBF/$\Delta CMRO_2$ increased with age (figure3). These results are in agreement with our previous findings[2]. The reduction in 'A' could relate to a reduction in cerebral blood volume that is known to occur with increasing age[9] Increased 'n', due to reduced $\Delta CMRO_2$, may be related to a reduction in neuronal density with increasing age. These results are important as they show the care needed in analysis of differences in the BOLD response between groups where the neurovascular coupling and resting blood volume may be altered, for example in two groups of different ages or in comparisons of a clinical and control group. This work also shows that calibrated fMRI allows the possibility to quantify underlying physiological changes.
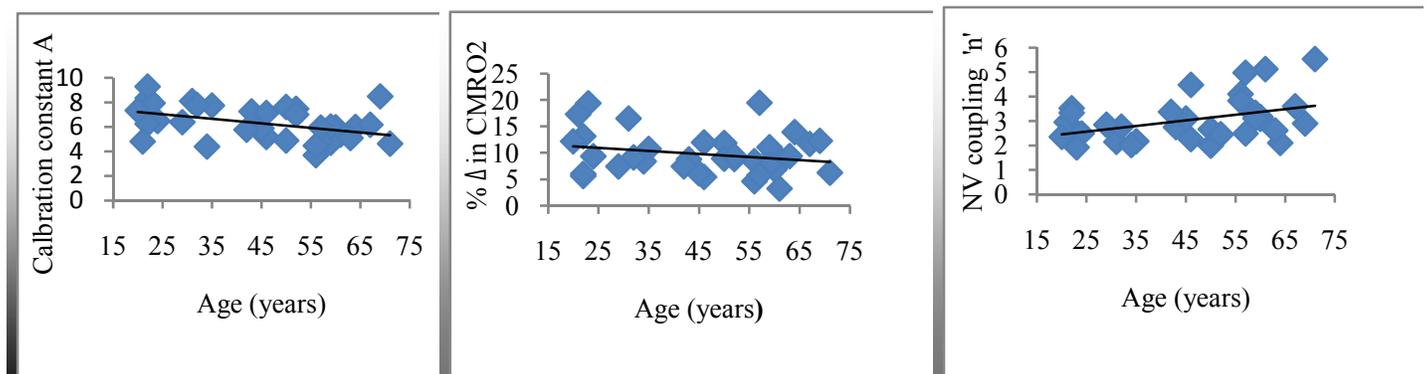
Figure 1
1.2% decline/year
p=0.007

Figure 2
0.7% decline/year
p=0.163

Figure 3
1% increase/year
p=0.012

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