

Hyperoxia calibrated fMRI of cerebral small vessel disease during a cognitive Stroop task

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Introduction

Calibrated functional magnetic resonance imaging (fMRI) is a technique that allows quantitative assessment of changes in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂) in response to neural activation. This may be particularly informative in clinical populations where functional metabolic activity in the brain is compromised, and the standard fMRI blood oxygen level dependent signal (BOLD) is difficult to interpret. Traditionally, calibrated fMRI studies have utilised a hypercapnia calibration model¹⁻³ and have been largely confined to studies of primary sensory areas in healthy populations. Recent advances to this technique include application in studies exploring age related neurovascular changes and cognitive decline^{4,5}, as well the introduction of a *hyperoxia* calibration model⁶, which has been shown to be less variable and potentially more tolerable in certain clinical populations. In this work we show preliminary results for an ongoing study exploring the use of hyperoxia calibrated fMRI, as a novel imaging technique for establishing sensitive markers of cerebral small vessel disease (cSVD), which is recognized as a key determinant in vascular cognitive decline and dementia.

Method

6 patients with symptomatic cSVD (defined by history of lacunar stroke and exclusion of alternative stroke aetiology) (mean age 62, 4_{male} / 2_{female}) and 15 healthy aged matched control subjects (mean age 62, 4_{male} / 11_{female}) were scanned (Siemens 3T), using an 8-channel RF coil. A Q2TIPS Arterial Spin Labeling sequence⁷ was used to collect simultaneous BOLD and CBF signal: TR 2.13s, TI₂ 1.4s, TE 20ms, 12 slices of 3.5mm covering frontal and motor cortices, during a Stroop task⁸, as well as a calibration scan. During the Stroop task, subjects had to decide if the meaning of a word presented at the bottom of the screen matched the ink color of the top word and respond with a choice of two buttons with the right hand. Stimuli were self-paced with a minimum time of 2 s between stimuli. 8 active blocks of 30 s were interspersed with 30 s fixation cross, giving a run time of 8 mins. For the calibration scan, oxygen was delivered via an open mask for two periods of 3 minutes interspersed with 3 minutes breathing normal air. End-tidal oxygen was continuously sampled via nasal cannula. We also collected standard diagnostic scans including FLAIR, T2-weighted, SWI, and angiography of the carotids and circle of Willis.

Analysis

ASL data analysis and ROI selection was performed on a group basis in Talairach space using BrainVoyager. BOLD and CBF time-courses were extracted for the Stroop task and hyperoxia scans in 8 regions of interest (ROIs): (Medial Frontal Gyrus (L&R), Motor-Cortex, Parietal-Lobe (L&R), MFG (L&R) and SMA), 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). Δ BOLD, Δ CBF, calibration constant 'A', Δ CMRO₂ and coupling parameter 'n' ($= \Delta$ CBF/ Δ CMRO₂) were calculated for each ROI using the hyperoxia model⁶ 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.

Results & discussion

cSVD patients were less accurate ($80 \pm 16\%$) and had a slower response time (2.0 ± 0.8 sec.) to the stroop task in comparison to the controls (accuracy: $97 \pm 2.9\%$, response time 1.1 ± 0.2 sec.), in agreement with previous work⁹.

The BOLD response to the Stroop task was higher in the frontal cortices for the cSVD group (top right), which corresponded with reduced values of Δ CMRO₂ in those regions. This agrees with previous work showing reduced glucose metabolism in frontal regions¹⁰. We also observed reduced BOLD activity in the patient group in primary motor cortex, compared to the control group, in agreement with previous work¹¹.

We found higher average values for the calibration parameter A in *all* ROIs for the cSVD patients compared to the controls (middle right). It was expected that A would be lower in the patient group due to expected reduction in baseline blood volume, mirroring baseline reductions in CBF which have been observed in cSVD¹². However this may be in part attributable to the use of an assumed 5% CBF reduction in the hyperoxia calibration model. Previous studies have suggested that this value is age dependent, and that hyperoxic induced changes in CBF become reduced with age¹³. This effect may be exaggerated in cSVD cases, where arteriopathy may impede vessel wall elasticity, resulting in smaller CBF reductions during hyperoxia, and therefore an overestimation of the value for A in our model. It should also be noted that A varies proportionally with baseline OEF, which may potentially be higher in this particular patient group¹⁴.

We found evidence for regional variation in the neurovascular coupling parameter n (bottom right), with average values across all regions of 2.95 ± 0.88 for stroke patients, and 3.13 ± 0.74 for the control group.

Summary

In this work we have presented preliminary data for an ongoing study investigating cognitive performance in patients with symptomatic cSVD using hyperoxia calibrated fMRI. We aim to recruit a sufficient number of subjects to fully evaluate the use of this methodology as a novel imaging technique for establishing sensitive markers of cSVD.

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