Introduction

Given the aerobic nature of cerebral metabolism, the rate of cerebral metabolic oxygen consumption (CMRO2) offers a measure of the brain’s energy consumption. Relative changes in CMRO2 can be measured using carbon dioxide or oxygen challenges to calibrate the BOLD signal [1-3]. However, interpretation of task-induced or short-term relative changes in CMRO2 is difficult when the baseline CMRO2 may be altered through long-term changes in neural activity, disease or drug action. PET is the gold standard for measurement of absolute CMRO2 [4] but requires radioactive tracers limiting its use in healthy volunteers and in longitudinal studies.

We present an FMRI-based method which employs respiratory manipulations, both hypercapnia and hyperoxia, to measure oxygen extraction fraction (OEF) and absolute CMRO2 on a regional basis in the brains of healthy volunteers. We demonstrate this method in volunteers at rest and presented with continuous visual stimulation. The proposed method has the potential to study changes in absolute levels of CMRO2 and therefore to offer a valuable marker of neurological and psychiatric disease.

Methods

Our proposed measurement uses a hypercapnic challenge (raised arterial PCO2) to first establish Mnc, the BOLD calibration parameter according to the model for the hypercapnia-induced fractional BOLD signal change, \( \Delta S_{nc}/S_0 = M_{nc} \left( 1 - f_{nc} \right) \) (eq.1), [1,2], in which \( f_{nc} \) represents the fractional change in CBF, hypercapnia is assumed not to alter cerebral metabolism, \( \alpha \) is the Grubb exponent (assumed to be 0.38) [5] and \( \beta = 1.5 \) is assumed.

We then estimate the resting concentration of venous deoxyhaemoglobin [dHb]0 using an analogous formulation of the BOLD signal model [3] for mild hyperoxia in which unaltered CBF is assumed. The hyperoxia-induced relative BOLD signal change is \( \Delta S_{ho}/S_0 = M \left( 1 - \left( [dHb]_{ho} / [dHb]_0 \right)^\beta \right) \) (eq.2), where [dHb]0 is the venous deoxyhaemoglobin concentration in hyperoxia. If we assume that hyperoxia does not change CMRO2 and results in negligible change in dissolved venous oxygen, then the change in venous deoxyhaemoglobin concentration in hyperoxia is given by \( \Delta [dHb]_0 = [dHb]_{ho} - [dHb]_0 = (CaO_{2ho} - CaO_{2no})/\phi \), where \( \phi = 1.34 \) ml O2/g Hb (oxygen carrying capacity of Hb) and CaO2 and CaO2no are the arterial oxygen content in normoxia and hyperoxia. CaO2 and CaO2no can be calculated from the measured end-tidal O2 values using the O2 dissociation curve and the known solubility of O2 in plasma. Using Mnc estimated from hypercapnia and rearranging eq.2 gives us \( [dHb]_0 = \Delta [dHb]_0 / \left\{ (1 - \Delta S_{ho}/S_0 \phi M_{nc})^{1/\beta} - 1 \right\} \) (eq.3) and therefore venous oxygenation (SvO2), OEF and CMRO2 = CBF·OEF·CaO2 (eq.4).

8 healthy volunteers underwent 2 scans using a PICORE QUIPS II dual-echo ASL sequence (64x64 matrix, spiral gradient echo, TE=1.5ms, TR=2200ms, FOV=22cm, 10 slices with thickness/gap=7/mm, TI1=700ms, T2=1600ms, reps=532, scan duration 19.5mins). One scan was performed with a visual fixation task during normo- and hypercapnia, the latter having lower CMRO2 and therefore shows no suggestion of altered CBF, OEF or CMRO2. Our proposed method may offer a future basis for non-invasive measures of regional absolute CMRO2 in health and disease.

Results

Mean (±SD) end-tidal PCO2 during normo- and hypercapnia was 35.5±2.3 and 43.7±2.1 mmHg respectively. End-tidal PO2 during normo- and hyperoxia was 120.4±5.8 and 332.7±6.6 mmHg respectively. In 3 of the 8 subjects poor CBF responses to hypercapnia were observed and data from these subjects does not contribute to the results presented. A significant increase in CBF was seen in visual cortex (one-tailed, paired t-test, p<0.01) in response to visual stimulation.

Discussion

Our values of absolute CMRO2 are consistent although slightly higher for grey matter regions than observed using PET (typically 2.2-3.6 ml/100g/min [4]). This may result from larger estimates of regional CBF, as our OEF estimates are similar to previously reported values [4]. The CMRO2 estimates are consistent with whole-brain MR-based measures of Xu et al [7] (approx. 3.2 ml/100g/min) given that Xu’s measurement includes both grey and white matter, the latter having lower CMRO2. Our proposed method has the advantage, however, of regional specificity. We observed a significant increase in CBF in visual cortex with stimulation and trends for increased absolute CMRO2 and decreased OEF. The lack of statistical significance in these parameters is probably explained by the small cohort. The stimulation-related changes are expected in visual cortex and contrast with the thalamus which is not expected to be strongly affected by the stimulus and therefore shows no suggestion of altered CBF, OEF or CMRO2. With further optimisation the proposed approach may offer a future basis for non-invasive measures of regional absolute CMRO2 in health and disease.

References