Measuring absolute $CMRO_2$ using Asymmetric Spin Echo and hyperoxic calibrated BOLD

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Target Audience: Researchers and clinicians interested in a quantitative measure of absolute cerebral oxygen metabolism.

Purpose: Dual calibrated FMRI (dcFMRI) offers an MR technique capable of measuring absolute $CMRO_2$[1-3] regionally. It is an extension of the calibrated BOLD methodology[4,5]. CBF and BOLD time-series are acquired during a hypercapnic-hyperoxic (HC-HO) respiratory manipulation and estimates of absolute $CMRO_2$ are produced using a BOLD signal model. However hypercapnia (HC) is associated with air hunger, intolerability[6] and sensory stimulation[7] as well as some reports of it modulating $CMRO_2$ itself[8]. A key parameter in the models is M, the maximum BOLD signal change at [dHb]=0. The potential to relate M to R_2' is reported[9] and is given as $M = TE \cdot R_2'$. The measure of R_2' with asymmetric spin echo (ASE) has been demonstrated[10]. The ability of ASE to measure M presents an opportunity to replace the use of HC in dcFMRI, making dcFMRI more comfortable and convenient to implement.

Theory: An ASE pulse sequence with τ shift is shown in **Fig1a.** The shifted 180° pulse allows R_2' weighting of the signal described by **Eqn1**. Hyperoxia (HO) calibrated BOLD[5], measures BOLD signal change caused by increasing arterial oxygen content (C_aO_2) and is described by **Eqn2**. In standard hyperoxic calibrated BOLD, M is estimated with both measured ($\frac{\Delta S}{S_0}$, ΔC_aO_2) and assumed (φ, [Hb], S_vO_2, β) model parameters. However if M is known, then S_vO_2 can be given by **Eqn2**. Assuming arterial blood is fully saturated ($OEF = 1 - S_vO_2$) and CBF can be measured using ASL, absolute $CMRO_2$ is given by Fick's principle, **Eqn3**. This is analogous to the dcFMRI approach taken by *Bulte et al.*[1] where M is given by HC calibration.

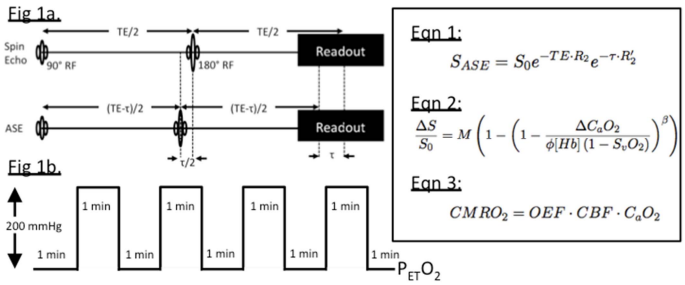

Figure1: Fig1a is a schematic demonstrating the τ shift in ASE. Fig1b shows the timing of the hyperoxic respiratory manipulation. Eqns. 1, 2 & 3 are used in the Theory section.

Methods: 8 normal healthy participants (aged 24 - 39) were scanned on a 3T GE HDx MRI using a protocol lasting ~15mins. All participants had high-res structural scans available. CBF and BOLD data were acquired with a dual GRE, spiral readout, PICORE QUIPSSII acquisition ($TR/TE_1/TE_2$=2.2s/3ms/29ms, FOV 22cm, matrix 64x64, 12 slices of 7mm thick (1mm gap), TI_1/TI_2=700/1600ms, 20cm tag thickness) during a HO respiratory challenge lasting 9 mins **Fig1b**. The same anatomical area was scanned using an ASE spiral acquisition with τ = 0, 20, 25 & 30ms. τ was chosen in the monoexponential regime of the signal model[11]. A GRE readout with spiral k-space acquisition was used (TE=44ms, TR=3s, flip angle 90°). In-plane resolution was the same as for the earlier dual echo scan but 32 slices with 2mm thickness (1mm gap) were acquired. Smaller slice thickness reduced the effects B_0 inhomogeneities[12]. 20 volumes (1min) were acquired at each τ. Two GRE's were collected at TE = 7 & 9 ms to correct for through slice dephasing. Each ASE(τ) was averaged over 20 volumes to give $S_{ASE(\tau)}$ maps and corrected for signal attenuation due to through-slice dephasing using a sinc function[11]. Mean grey matter (GM) signal, $S_{ASE(\tau)}$, was extracted using GM segmented ROI's from the high resolution images. These ROI measures were then used to produce estimates of M from the different τ acquisitions giving $M_{\tau 20}$, $M_{\tau 25}$ and $M_{\tau 30}$ using **Eqn1** and $M_{\tau fit}$, was determined by fitting **Eqn1** to all τ's. GM BOLD and CBF ROI time-series were produced alongside $P_{ET}O_2$, time-series, periods of normoxia were averaged as were periods of HO to estimate changes from baseline. During HO no change in CBF was assumed. C_aO_2, was calculated from $P_{ET}O_2$. M_τ's were then used in **Eqn2** to measure S_vO_2. Baseline CBF was taken from periods of normoxia and used with S_vO_2 to calculate absolute $CMRO_2$ **Eqn3**.

HO-M_τ	M	S_vO_2	$CMRO_2$
τ=Fit	0.11 ± 0.01	0.05 ± 0.14	189 ± 37
τ=30ms	0.10 ± 0.01	0.48 ± 0.14	197 ± 37
τ=25ms	0.10 ± 0.01	0.53 ± 0.14	178 ± 38
τ=20ms	0.08 ± 0.02	0.63 ± 0.14	140 ± 35

CBF_{base}= 50 ± 10 ml/100g/min

Table 1: Group mean M, S_vO_2 and $CMRO_2$ (μmol/100g/min) values in GM measured using combined ASE- $M_{R_2'}$ & HO calibrated BOLD.

Results & Discussion: Tab1. shows group mean M, S_vO_2 and $CMRO_2$ values in GM (N=8). Values of M measured using ASE vary with τ. This has previously been observed as changes in R_2' with τ and has been attributed to the multi-compartment structure of brain tissue[13]. As a result values of S_vO_2 and $CMRO_2$ vary with τ but are in the range of accepted values from PET[14] and MR[3]. Further work is required to optimise the τ used which could be chosen to localise the ASE signal to the relevant vasculature to measure S_vO_2 (venules and veins).

Conclusion: Using ASE to measure R_2' and infer M alongside a hyperoxic calibrated BOLD technique has the potential to provide regional measures of S_vO_2 and absolute $CMRO_2$. This is an extension of the dcFMRI protocol which circumvents issues associated with hypercapnia and may have the potential to provide whole brain maps in a short scan time. However, more work is required to optimise the measure of M with ASE.

References: 1. Bulte et al. NeuroImage. 2012,60: 582; **2. Gauthier et al.** NeuroImage. 2012,60:1212; **3. Wise et al.** NeuroImage. 2013,83:135; **4. Davis et al.** PNAS. 1998,95:1834; **5. Chiarelli et al.** NeuroImage. 2007,37:808; **6. Mohtasib et al.** NeuroImage. 2012,59:1143; **7. Kannurpatti et al.** NeuroImage. 2008,40:1567; **8. Zappe et al.** Cerebral Cortex. 2008,18:2666; **9. Blockley et al.** NeuroImage 2012,60:279-289; **10. Wismer et al.** J Comput Assist Tomogr. 1988, 12:259 **11. Blockley et al.** NMRBiomed. 2012,26:987; **12. Franconi et al.** NMRBiomed. 2006,19:527; **13. Fujita et al.** NeuroImage. 2003,20:2071; **14. Ibaraki et al.** JCBFM. 2010,30:1296.