Voxel-wise Estimation of M and $CMRO_2$ at 7T

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Introduction: The Davis model [1] is widely used for calibrated BOLD to estimate the change in $CMRO_2$ to a neuronal stimulus:

$$\frac{\Delta BOLD}{BOLD} = M\left[1-\left(\frac{CMRO_2}{CMRO_{2,0}}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right] \text{ where } M = \frac{BOLD_{HC}/BOLD_o}{1-(CBF_{HC}/CBF_0)^{\alpha-\beta}} \quad \textit{Eqn. [1]}$$

($_o$ indicates baseline, $_{HC}$ indicates hypercapnia). This requires the measurement of the CBF and BOLD response to a stimulus and to hypercapnia. Calibration is usually performed by averaging over an ROI but this will cause errors due to the inclusion of draining veins and the non-linear relationship between *M* and CBF. The increased sensitivity to CBF and BOLD at 7T should allow voxelwise assessment of *M* and $CMRO_2$, and multiphase ASL methods can measure CBF corrected for transit time changes that occur on hypercapnia or activation [4-7]. **Aim:** To estimate *M* and $CMRO_2$ for a motor task, on a voxel-by-voxel basis compared to standard ROI analysis, using Look Locker (LL)-ASL for transit time independent estimation of CBF.

Methods: 5 healthy subjects were recruited with approval of the local ethics committee. Data were acquired using a Philips Achieva 7.0 T system with head volume transmit and 16-channel SENSE receive coil. Data acquisition: LL-FAIR ASL data for CBF: TI/ΔTI/TR=350/300/3000ms, 8 GE_EPI readouts per TR, FA=35°, vascular crushing using bipolar gradients ($v_{cut\text{-}off}$=50mms^{-1}), 5 slices, 2x2x3mm^3, FOV=192x192mm^2, SENSE factor 2, partial k–space factor 0.8, TE=23ms. The last readout of the control data was used for BOLD measurement. Hypercapnia protocol: To target $P_{ET}CO_2$ and $P_{ET}O_2$ independently, a feed-forward, low gas flow system (RespirAct™, Thornhill Research Inc., Toronto, Canada) and a sequential gas delivery breathing circuit were used [8]. The hypercapnic challenge started with 2 min of baseline $P_{ET}CO_2$ followed by 4 cycles of 90 s of $P_{ET}CO_2$ targeted at (baseline+10 mmHg) alternating with 90 s of baseline. $P_{ET}O_2$ was targeted to remain constant throughout. Motor task: 5 cycles of 30s bilateral finger tap /30s rest at normocapnia. An EPI image was acquired with long TR, and an inversion recovery EPI with 11 TI's (0.1-4s) acquired for T_1 mapping. Data Analysis LL-FAIR data was divided into hypercapnic and normocapnic periods by discarding the first 30s of each cycle and then averaging over the remainder. BOLD data was temporally filtered and linearly regression was used to remove signal drift. Data were spatially smoothed with a Gaussian kernel (σ=1.3mm). Two ROIs were formed in the motor cortex: a CBF_ROI from correlating the CBF timecourse with a boxcar convolved with an HRF (cc>0.2) and a BOLD_ROI for task related changes >2%. The LL-FAIR signals were fitted for CBF, arrival time (Δ_a) and exchange time (τ_{exc}) (from which arrival time at the tissue can be estimated (Δ_{tissue}= Δ_a+τ_{exc}), and label duration [9] on a voxel-by-voxel basis (1 sub. excluded due to low SNR) and also from the average signal from each ROI. BOLD and CBF data were then used to calculate *M* and $CMRO_2$ using Equation 1 assuming α=0.38 and β=1 (for 7T) [10-12]. Data was fitted voxelwise for each of the ROI before averaging, and also from the mean ROI CBF and BOLD data. For the voxelwise data, if *M*<0 or $CMRO_2$<0 (likely to correspond to white matter or large vein respectively) then the data were excluded from all voxelwise metrics.

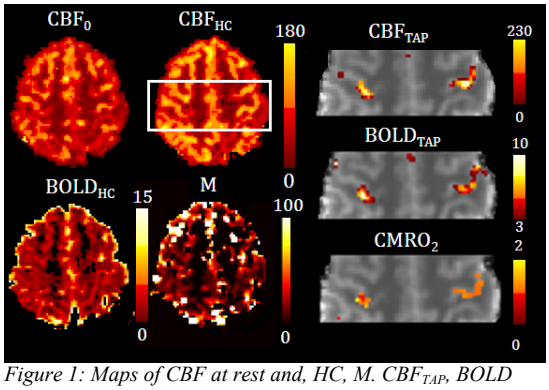

Figure 1: Maps of CBF at rest and, HC, M. CBF_{TAP}, BOLD and $CMRO_2$ overlaid onto T_1 map (subject 1) for area indicated by box. $CMRO_2$ ROI defined from CBF.

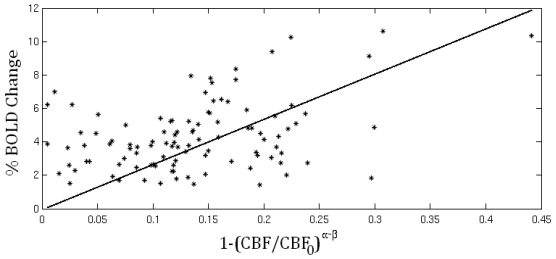

Figure 2: Voxelwise plot of BOLD % signal change versus 1-$CBF/CBF_0)^{\alpha-\beta}$ under hypercapnia for CBF ROI (Sub.1)

Table 1: Results for voxelwise (n=4) and ROI (n=5) analysis.	Voxel wise Analysis		ROI Analysis	
	BOLD ROI	CBF ROI	BOLD ROI	CBF ROI
BOLD CVR [%/mmHg]	0.6±0.1	0.53±0.02	0.7±0.2	0.59±0.06
$BOLD_{TAP}$ [%]	3.6±0.4	4.7±0.8	3.5±0.2	4.9±0.7
CBF CVR [%/mmHg]	6±1	5.2±0.8	1.8±0.9	5±1
CBF_{TAP} [%]	83±40	90±34	29±3	86±27
M [%]	34±5	23.3±0.7	92±29	27±4
$CMRO_2$ [Fraction]	1.2±0.1	1.16±0.06	1.11±0.01	1.16±0.08

Results: The average $P_{ET}CO_2$ change was 6.6±0.5 mmHg**.** Figure 1 shows voxelwise maps for Subject 1. Tissue arrival time (Δ_{tissue}) reduced by 27±4 % (average ± sterr across subjects) on hypercapnia and 32±6 % to the finger tap task (CBF_ROI). Table 1 compares the mean of the voxelwise fits with fitting the ROI signals. Figure 2 shows voxelwise BOLD change due to hypercapnia plotted against $1-(CBF/CBF_0)^{\alpha-\beta}$ for Sub.1 for a CBF ROI; linear fitting with a zero intercept gave *M*=27 agreeing well with *M*=25 from the voxelwise analysis for this CBF_ROI .

Conclusions: Voxelwise mapping of $CMRO_2$ has been achieved at 7T. This has many potential advantages, including allowing outlying voxels, for instance due to draining veins, to be excluded from the analysis. The CBF_ROI, which tends to exclude draining veins, gave similar values of M and $CMRO_2$ for voxelwise and ROI analysis. The voxelwise analysis of the BOLD_ROI analysis gave similar values to the CBF_ROI, where as the ROI analysis gave larger values of *M* and smaller changes in CBF, likely due to the inclusion of veins/white matter. Figure 2 is not linearly distributed as predicted by the Davis theory, suggesting that even the CBF_ROI contains some venous contribution; future work will consider further methods of selecting outlying voxels. The change in tissue arrival time on hypercapnia and task highlights the need for a CBF measurement independent of transit time. CBF reactivity measures agree well with literature values of 3-6.5 %/mmHg [6,14]. At 3T *M* in the motor cortex has been reported to vary from 4 [2] to 25% [3], but depends on field strength, a value of 28% has been measured for 7T using hyperoxia calibration [13].

References: [1] Davis et al. PNAS 95:1834-1839 (1998) [2] Chiarelli et al. MRM 57:538-547 (2007) [3] Uludag et al.NeuroImage 23:48-155 (2004) [4] Tancredi et al. 18th ISMRM (2010) 1761 [5] Buxton *et al.*MRM 40:383-396 (1998). [6] Winter *et al.* 18th ISMRM 1759 (2010). [7] Tannir *et al.* 15th ISMRM (2007) 312. [8] Slessarev *et al.* J. Physiology 581: 1207-19 (2007) [9] Francis *et al.* MRM 59:316-325 (2008).[10] Grubb et al. Stroke 5:630-639(1974) [11] Boxerman et al. MRM 34:555-566 (1995) [12] Driver et al. NeuroImage 51:274-279 (2009) [13] Driver et al. 19th ISMRM 3597 (2011) [14] Mark *et al.*MRM 64(3):749-756 (2010). *This work and ELH's studentship were funded by the MRC.*