The impact of echo time on the calibration parameter M

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Introduction Calibrated functional MRI[1] (fMRI) uses gas challenges such as hypercapnia[2] (increased CO_2) or hyperoxia[3] (increased O_2) to estimate the calibration parameter M, which represents the maximum possible BOLD signal that could theoretically be evoked. Once M is known, it is possible to calculate relative or absolute changes in cerebral metabolic rate of oxygen consumption ($CMRO_2$).[4]

M is a mixed system/physiological parameter which will vary depending on the type of tissue, field strength and scanner hardware used. Its value also depends on scanning parameters such as the echo time (TE), as this affects the size of the measured BOLD signal. It is commonly assumed that M is directly proportional to TE,[5] allowing for experimental values to be linearly scaled for comparisons between studies.[6] However, this has never been experimentally verified, and it is not known if other factors contributing to M may have some additional, non-linear dependence on TE.

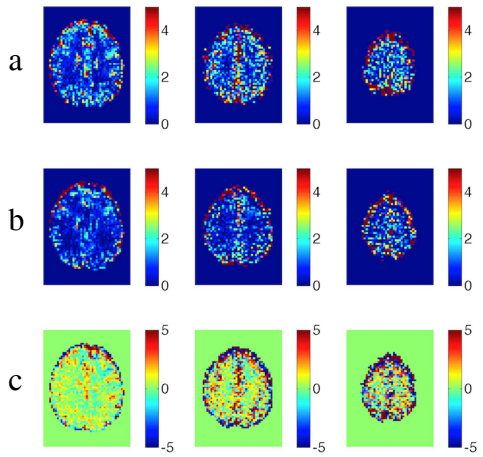

Figure 1. *Percentage change in BOLD signal in response to hypercapnia with (a) crushers off and (b) crushers on. (c) Subtraction of a-b.*

Methods A pseudo-continuous arterial spin labelling (PCASL) sequence was implemented on a Siemens 3T scanner, with 5 echoes acquired at 20/35/49/64/78ms (resolution 3.4×3.4×7.5mm; GRAPPA 3; PLD 1.8s; TR 4s). The option of playing out bipolar flow crushing gradients immediately before the first echo was added; where used, these were set to have a cutoff velocity of 1.9cm/s.

8 healthy volunteers (5 female, age 24 ± 2 years) were scanned after giving informed consent. Two CO_2 blocks of 3 minutes were delivered through a nasal cannula and mixed with room air, resulting in a CO_2 stimulus of approximately 4%. Hypercapnic stimuli were interleaved with 2-minute periods of baseline, breathing medical air. This protocol was repeated twice, with and without flow crushing gradients respectively. Post-processing was performed using FSL (http://www.fmrib.ox.ac.uk/fsl) and MATLAB (The MathWorks Inc., Natick, Massachusetts, USA). A grey matter region of interest (ROI) was created for each subject from resting perfusion and statistically significant BOLD responses for at least 3 of the 5 TEs. Excessively noisy voxels were excluded from analysis, and M values were calculated within the remaining ROI from ASL (first echo only) and BOLD responses (for each TE individually).

Results and Discussion As expected, BOLD signal response to hypercapnia was reduced in the presence of intravascular crushers (see figure 1 for images from one representative subject, TE=35ms). The magnitude of M is also reduced with crushers present. The relationship between M and TE was found to be linear, as shown in figure 2 (average across all subjects). However the intercept is not zero as has previously been assumed, but decreases when crusher gradients are added. The same trends are observed for BOLD signal response to hypercapnia (data not shown). This suggests that the non-zero intercept is likely an artifact of intravascular BOLD signal contributions. It is possible that a non-zero BOLD signal change would be seen at a theoretical TE of 0ms, as a result of changes in blood susceptibility due to increased blood flow and concurrent reductions in deoxyhemoglobin concentration. However, it cannot be conclusively determined from this data whether the linear relationship between M (or BOLD signal) and TE continues all the way to TE=0.

Figure 3 shows M values that have been linearly scaled to an "optimal" TE of 35ms (assuming zero intercept), and gives an idea of the errors introduced by this common scaling method. When crushers were turned on, these errors all but disappeared. M values are generally scaled and quoted between studies for a coarse comparison only, and the additional error or variability introduced by assuming a linear scaling with zero intercept is likely to be small compared to other considerations (e.g. differences in hardware and sequence design between imaging centres).

Conclusion M was shown to be a linear function of TE, but with a non-zero intercept. Use of crusher gradients significantly reduces the value of this intercept, suggesting that the deviation from theory arises from the false assumption of negligible intravascular BOLD signal contribution. Where two echoes are acquired (e.g. by using a dual echo pulse sequence), it would be possible to estimate the intercept on a study- or subject-specific basis, which could significantly improve the accuracy of scaling M to an "optimal" echo time.

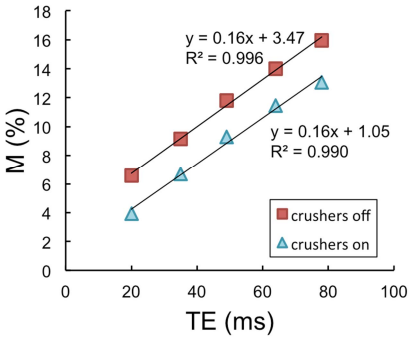

Figure 2. *M as a function of echo time.*

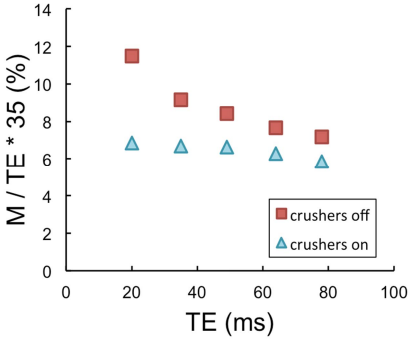

Figure 3. *M scaled to optimal echo time (35ms), assuming an intercept of zero.*

References 1. Hoge RD. *Neuroimage* 2012; 62: 930-7. 2. Davis TL et al. *PNAS* 1998; 95: 1834-9. 3. Chiarelli PA et al. *Neuroimage* 2007; 37: 808-20. 4. Bulte DP et al. *Neuroimage* 2012; 60: 582-591. 5. Hoge RD et al. *MRM* 1999; 42: 849-863. 6. Gauthier CJ et al. *Neuroimage* 2011; 54: 1001-11.