A turn-key solution for the quantification of brain oxygen metabolism

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INTRODUCTION: Cerebral metabolic rate of oxygen ($CMRO_2$) is an important index of tissue viability and brain function, but traditionally the quantification of this parameter is a "niche market" of Positron Emission Tomography (PET). MRI measurements of $CMRO_2$ have been proposed based on ^{13}C NMR (1), ^{17}O NMR (2), and biophysical models of blood susceptibility (3-5). However, they are not yet widely available for clinical applications due to various technical and feasibility reasons. The present study proposes a non-invasive (no exogenous agent), fast (<5 min in scan time), and reliable (Coefficient of variation, CoV<3%) method to quantify global $CMRO_2$ on a standard 3T system. Although this method does not provide spatial information, the simplicity and reliability features of this technique are highly desirable for many researchers and may significantly enhance the clinical utility of this important parameter in understanding many brain diseases that are of diffused or neurodegenerative nature. This method may also find applications in situations when PET method is not justifiable or feasible such as studies in children. We tested intra-session, inter-session, inter-subject reproducibility of the $CMRO_2$ measure and compared the results to those of CBF and venous oxygenation.

METHODS: *Framework of the $CMRO_2$ measurement:* The theoretical basis of the method is the Fick Principle: $CMRO_2=CBF\cdot(Y_a-Y_v)\cdot C_a$, where CBF is the whole-brain blood flow, Y_a and Y_v are oxygen saturation fraction in arterial and venous blood, respectively; C_a is the amount of oxygen molecules that a unit volume of blood can carry and is well established in physiology literature (6). Therefore, once CBF, Y_a, and Y_v are experimentally measured, $CMRO_2$ can be determined from the above equation. We propose to measure Y_a with pulse oximetry and use TRUST MRI (7) and Phase-contrast (PC) MRI to determine Y_v and CBF, respectively. The MRI procedure for a complete $CMRO_2$ dataset is illustrated in Fig. 1. Compared to an earlier report (8), we have made two improvements. First, the TRUST protocol has incorporated recent improvements so that the scan duration is reduced by 70% while the precision is increased (9). Second, the PC MRI now employs separate acquisitions for each feeding artery (left and right internal carotid, left and right vertebral), allowing true perpendicular positioning of PC MRI with respect to individual artery. Importantly, the total duration of all scans is less than 5 minutes.

Reproducibility assessment: Seven young, healthy subjects (3 males, 26.4±4.0 years) were studied on a Philips 3T scanner. Each subject was scanned on 5 separate sessions within a 10 day period. During each session, the above-described $CMRO_2$ procedure was performed twice without repositioning the subject. The imaging parameters of TRUST MRI were: voxel size 3.44x3.44x5mm^3, TR=3000ms, TI=1200ms, four effective TEs: 0ms, 40ms, 80ms and 160ms, with a τ_{CPMG}=10ms. The PC MRI scan used the following parameters: voxel size 0.45x0.45x5 mm^3, maximum velocity 80cm/s, 4 averages. Data processing of TRUST and PC MRI followed methods used previously (7,8). Intra-session, inter-session, and inter-subject Coefficient of Variation (CoV=SD/mean) was computed for Y_v (using TRUST data), Y_a-Y_v (also called oxygen extraction fraction) (using pulse oximetry and TRUST data), CBF (using PC MRI data), and CMRO2 (using all data acquired).

RESULTS and DISCUSSION: Fig. 2 shows an example of TRUST and PC MRI data for the measurement of venous oxygenation and CBF, respectively. Table 1 summarizes the intra-session, inter-session, and inter-subject CoV. It can be seen that the intra-session CoV, which reflects the measurement noise, is less than 3% for all parameters, suggesting high reliability of the techniques used. Fig. 3 shows a scatter plot between two $CMRO_2$ measures in the same session, demonstrating a strong correlation (p<0.0001). Inter-session CoV, which contains measurement noise, reposition inconsistency, and day-to-day physiologic fluctuations, was higher than intra-session CoV, but was less than 8% for all parameters. For inter-subject CoV, which contains measurement noise and person-to-person differences, was greater (Table 1). Interestingly, although the two multiplying factors in the equation, CBF and Y_a-Y_v, both have relatively large CoV, their product, $CMRO_2$, was actually less variable across subjects. This was because CBF and Y_a-Y_v were highly correlated (p=0.002) across subjects and across sessions (Fig. 4). An individual with higher CBF tends to have a lower oxygen extraction fraction and vice versa. That is, although vascular parameters (blood flow and blood oxygenation) show large inter-subject variations due to numerous physiologic reasons (e.g. breathing pattern, blood pressure, consumption of caffeine), the brain's metabolic rate does not show much variability across days or across individuals of similar age, making this parameter an excellent biomarker for studies of diseased conditions.

In the present study, we proposed a turn-key solution for quantitative assessment of global $CMRO_2$. While the lack of spatial resolution is the main limitation of the proposed method, it is non-invasive, fast, and reliable and can be performed on a standard clinical scanner. These features afford this technique great potentials for immediate clinical applications.

REFERENCES : 1) de Graaf et al, NMR Biomed 16:339, 2003; 2) Zhu et al, PNAS 99, 2002; 3) Kim et al, MRM 41:1152, 1999; 4) An et al, NMR Biomed 14:441, 2001; 5) He et al, MRM 60:882, 2008; 6) Guyton and Hall, Textbook of medical physiology, 2005; 7) Lu and Ge, MRM 60:357, 2008 ; 8) Xu et al. MRM 62 :141, 2009; 9) Xu et al., MRM in press, 2011.

Fig. 1 The proposed MRI procedure for a complete $CMRO_2$ dataset.

Sequence	Duration (min)	Purpose
Angiogram	0.8	PC positioning
TRUST MRI	1.2	Y_v measurement
PC on left ICA	0.5	CBF Measurement
PC on right ICA	0.5	CBF Measurement
PC on left VA	0.5	CBF Measurement
PC on right VA	0.5	CBF Measurement

Fig. 3 Scatter plot of two $CMRO_2$ measures in the same session.

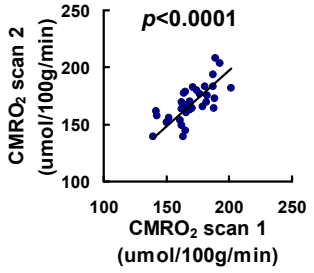

Table 1 The intra-session, inter-session, and inter-subject CoV from the seven subjects (Mean±SD).

	Y_v	Y_a-Y_v	CBF	$CMRO_2$
Mean	61.73±4.62%	37.06±4.88%	60.57±9.70 ml/100g/min	169.39±11.13 μmol/100g/min
Intra-session variability				
CoV	2.15±1.03%	1.31±0.79%	1.85±0.75%	2.77±1.29%
Inter-session variability				
CoV	4.75±3.22%	7.64±4.64%	6.95±3.35%	5.92±1.60%
Inter-subject variability				
CoV	7.49%	13.17%	16.02%	6.57%

Fig. 2 An example of TRUST (a) and PC MRI (b, left ICA in red circle) data.

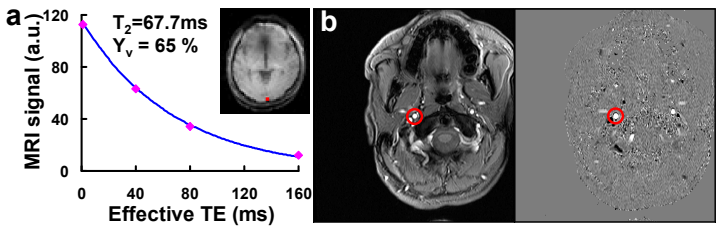

Fig. 4 Scatter plot of CBF and Y_v measures across subjects and across sessions. Each color represents one subject, each dot represents a session. p=0.002 from Mixed Effect Model analysis.