Multi-site evaluations of a TRUST MRI technique to measure brain oxygenation

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INTRODUCTION: Cerebral metabolic rate of oxygen ($CMRO_2$) is a key marker for tissue viability and brain function (1). However, quantification of absolute $CMRO_2$ is not trivial. Up until recently, it was considered a "niche market" of PET, which requires an onsite cyclotron, three types of radiotracers, and an arterial line for dynamic blood sampling. Therefore, there is a growing interest in the MR field to quantify $CMRO_2$ with non-invasive methods. It is well established that $CMRO_2$ can be calculated from three parameters, specifically CBF, arterial and venous oxygenation, of which venous oxygenation (Y_v) measurement has presented most technical challenges. Recently, a T_2-Relaxation-Under-Spin-Tagging (TRUST) MRI technique was developed which is capable of measuring global Y_v in the superior sagittal sinus (2-3). Although lacking spatial information, TRUST has several attractive features including the absence of any exogenous agent, short scan duration of 1.2 min, and feasibility on a standard 3T. Moreover, previous single-site study has shown that test-retest variations of TRUST measurement were <2% (4), which was lower than most other functional brain markers available to date. The goal of the present work is to evaluate the applicability and reliability of the TRUST technique in a multi-site setting. We compared Y_v values (i.e. accuracy) as well as standard errors of Y_v estimation (i.e. precision) across six imaging centers.

TRUST sequence: TRUST MRI is based on the principle that T_2 relaxation time of the blood has an established relationship with Y_v, thus one can measure pure blood T_2 and then convert T_2 to Y_v using a calibration plot (5). It applies the spin labeling principle on the venous side (Fig. 1a) and acquires control and labeled images, the subtraction of which yields pure venous blood signal (Fig. 1b). The label and control scans are performed with various numbers of flow-insensitive T_2-preparation pulses to modulate the signal with different T2 weightings (Fig. 1b). The monoexponential fitting of the blood signal to the T_2-preparation duration (termed effective TE [eTE]) then gives the T_2 value of the venous blood (Fig. 1c). Due to relatively large flow velocities, TRUST measurement in large venous vessels, e.g. sagittal sinus, was found to be particularly robust (4) and is the focus of this study.

METHODS: *Sites and subjects:* The six participating sites, 4 in the Unites States and 2 in Canada, are all equipped with a 3T Achieva Philips MRI system. Each site scanned a minimum of 5 healthy volunteers, with a total of 135 healthy subjects (68 females and 67 males with an age range of 18-82 yrs). Site "a" is the site of the lead authors and data with a relatively large sample size and age range were included, so that they can serve as a reference for comparison with other sites. The detailed site information is listed in Table 1. The TRUST data from the other five sites were acquired by adding the sequence to existing research studies, thus the sample sizes and age ranges were not matched across sites. *TRUST sequence:* Identical pulse sequence and imaging parameters were used in all sites by transferring of customized sequence code to each site. The imaging parameters were: voxel size 3.44x3.44x5mm^3, TR=3000ms, TI=1022ms, four eTEs: 0, 40, 80 and 160ms, labeling thickness 100mm, gap 22.5mm, scan duration 1.2min. To ensure consistent slice positioning across sites, a written instruction including several examples was transmitted to each site and the operator was instructed to position the TRUST imaging slice to be parallel to anterior-commissure posterior-commissure line with a distance of 20mm from the sinus confluence (Fig. 1a). *Data analysis:* The TRUST data were processed using a custom-written processing tool, based on a procedure described previously (2). Briefly, after pairwise subtraction between control and label images, a preliminary region of interest (ROI) was manually drawn to include the superior sagittal sinus. Then the 4 peak voxels in the ROI were chosen as the final mask for spatial averaging. The averaged venous blood signals were used to fit a monoexponential model to obtain T_2, which was in turn converted to Y_v via a calibration plot (5). From each dataset, the algorithm also gives a confidence interval of the estimated T_2, which was used to compute the standard error of the estimated Y_v. *Statistical analysis:* Using the results obtained from all sites, a multivariate regression analysis was conducted with age and gender as continuous variables and site as a categorical variable. If a significant site-effect was detected, each site was compared to the reference site, Site "a", to identify which site(s) is different and whether the TRUST performance at that site is better or worse than the Site "a". This analysis was conducted for both Y_v and standard error of Y_v.

RESULTS and DISCUSSION: The transfer of the TRUST technique to the participating sites went smoothly. The investigators and MR technologists of each site were able to install the sequence and properly position the slice by following the written instructions. There was no instance of a need for an onsite training. Results of Y_v from all subjects of all sites are plotted as a function of age in Fig. 2a. Multivariate regression analysis revealed that there was a significant effect of age (p=0.005), specifically that Y_v decreases with age at a rate of 1.0% per decade. This observation is consistent with a recent single-site report from a cognitive aging study (6). It was found that the performing site has no significant effect on the measured Y_v (p=0.15), indicating that there was no site dependence in Y_v estimation using TRUST. There was no gender difference in Y_v either (p=0.72).

Fig. 2b plots the standard error of Y_v, ε_{Yv}, as a function of age. Regression analysis revealed no age (p=0.23) or gender (p=0.68) effects, suggesting that the measurement precision was comparable between young and older subjects and between females and males. A site effect was observed for ε_{Yv} (p<0.001). Post-hoc comparison between the reference site and each of the participating site suggested that this was attributed exclusively to a higher ε_{Yv} in Site "d" (orange symbols in Fig. 2b, p<0.001), as the other sites showed no differences (p>0.20). Since this site currently only has 5 datasets, we will need more data to elucidate the source of this difference.

We also examined the potential correlation between ε_{Yv} and Y_v, with the notion that a noisy dataset may result in a systematic bias (higher or lower values). We did not observe a significant correlation (p=0.16, N=135), indicating that noise affects the precision but not accuracy of the estimation.

To our knowledge, this work represents the first effort to conduct a multi-site evaluation of an MR-based oxygenation technique, which is a critical step toward broader availability and potential clinical utilizations of these novel physiologic measures. We showed that the TRUST sequence can be implemented and performed on a standard 3T scanner at remote sites. The preliminary results from six imaging centers revealed that the estimated Y_v values are compatible across sites, although the precision of the estimation showed some difference in one participating site.

REFERENCES: 1) Kety and Schmidt, J Clin Invest 27:484, 1948; 2) Lu and Ge, MRM 60:357, 2008; 3) Xu et al, MRM 68:198, 2012; 4) Liu et al, MRM in press, 2012; 5) Lu et al, MRM 67:42, 2012; 6) Lu et al, Cereb Cortex, 21:1426, 2011.

Table 1. Subject information of all six sites.

Site	Subject number	Gender (F/M)	Age range (yrs)
a	63	25/38	18~80
b	18	18/0	51~59
c	18	8/10	34~82
d	5	1/4	22~24
e	24	11/13	18~24
f	7	5/2	22~35

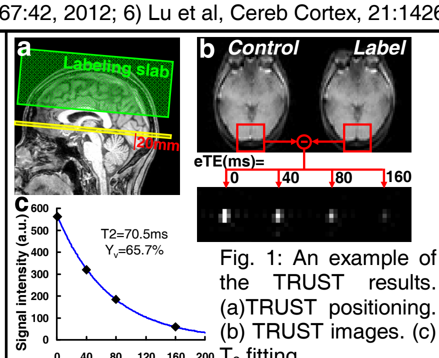

Fig. 1: An example of the TRUST results. (a)TRUST positioning. (b) TRUST images. (c) T_2 fitting.

Fig. 2: Results of the multisite data. (a) Scatter plot of the measured Y_v versus age from all sites. (b) Scatter plot of ε_{Yv} versus age from all site. N=135 in total.