Age-related differences in CBF, CVR, M, OEF and CMRO2 using MRI QUO2 and dual-echo pCASL

Isabelle Lajoie[1], Kenneth S Dyson[2], Scott Nugent[2], Felipe D Tancredi[1,3], and Richard D Hoge[2]

[1]*Centre de recherche de l'IUGM, Université de Montréal, Montreal, Quebec, Canada,* [2]*McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada,* [3]*Albert Einstein Jewish Hospital, Brazil*

Target audience: Researchers interested in quantitative fMRI and its application in aging and neurodegenerative conditions.

Purpose: Our team has recently introduced a noninvasive MRI imaging technique, dubbed QUO2, that allows quantitative measurement of the cerebral metabolic rate of O_2consumption ($CMRO_2$). The approach comprises simultaneous measurement of BOLD and CBF changes during a respiratory manipulation that alternates periods of hypercapnia (HC) with hyperoxia (HO). The resulting measures of BOLD and CBF serve as inputs to a Generalized Calibration Model (GCM) [1] yielding a system of two equations with two unknowns: the BOLD calibration parameter *M* (i.e. the extrapolated maximum BOLD signal increase when venous saturation approaches 100%) and the brain Oxygen Extraction Fraction (OEF; the fraction of delivered oxygen that is consumed by the cerebral tissue). The product of baseline CBF by arterial O_2 content and OEF gives the absolute $CMRO_2$ in units of µmol/100g/min. To demonstrate the potential of this technique for characterizing inter-group differences in cerebral physiology, we present results comparing $CMRO_2$ in young control (YC) subjects with that measured in elderly control (EC) subjects.

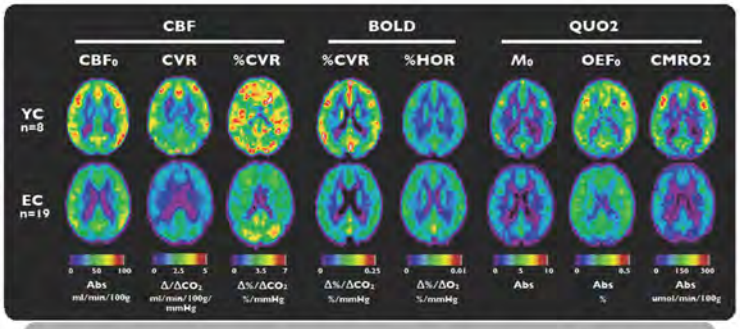

Figure 1. Group-average maps of young control (YC) and elderly control (EC) population.

Methods: Eight healthy young participants (4 females, mean age of 30 ± 6 years) and 24 elderly controls (17 females, mean of age of 74 ± 4 years) were enrolled in the study. Images were acquired on a 3T Siemens Tim Trio scanner using the vendor's 32-channel receive-only head coil. Each session included an anatomical, $1mm^3$ MPRAGE acquisition (TR/TE/flip angle = 2.3s/3ms/9°, 256x240 matrix) and a functional scan lasting 18 minutes. A dual-echo pCASL sequence was used to record simultaneous measures of BOLD and CBF in 21 slices with 4.5mm thickness, 0.5mm gap and at 4.5mm2 in plane resolution. Sequence parameters were: labeling duration = 2s, nominal post-labeling delay = 1.4s, BW = 3255 Hz/px, TR/TE1/TE2/alpha = 4.12s/8.4ms/30ms/90°, GRAPPA factor = 2, and partial sampling of k-space = 7/8. The 18 minute respiratory manipulation scan consisted of alternating two 2-minute blocks of HC with two 3-minute blocks of HO, separated by baseline periods of normocapnia/normoxia as described in [2]. Participants breathed gas mixtures through a circuit developed in our group in an effort to optimize safety, comfort, and control over inspired CO_2 and O_2 doses. To induce HC, a gas mixture of 5% CO_2 in medical air was administered; to induce HO, 50% (in EC) to 60% (in YC) O_2 mixture was inspired. Respiratory O_2 and CO_2 were continuously monitored using BIOPAC MP150. A linear model described in [3] was used to compute end-tidal (ET) levels during baseline periods and changes induced during HC and HO blocks. Four elderly participants were excluded from the analysis due to very low SNR in their ASL scans, believed due to significant motion and/or problems in labeling efficiency. MRI and respiratory data was analyzed using a combination of in-house software and FSL. Motion correction was applied to the series, then the BOLD and ASL series were separated using linear surround subtraction. A GLM fit was used to estimate the responses induced by HC and HO. ASL was converted into physiological units of CBF (mL/100g/min) as in [4]. Voxels considered to be non-parenchymal (wherein $\Delta CBF_{HO} < -50$ mL/100g/min or $\Delta\%BOLD_{HC} > 10\%$) or in regions affected by susceptibility artifacts arising from O2 inhalation ($BOLD_{HO} < -5\%$) were removed from the analysis. Spatial filtering was then performed (6mm FWHM 3D Gaussian kernel) with an adjustment for voxels excluded based on the criteria mentioned above. Grey-matter (GM) averaged values were computed using a probability mask (computed from the anatomical scan using FSL's routine) that was thresholded to 50%. Because of the low SNR inherent to ASL and the nearly unchanged CBF during HO induced by 50%-60% O_2, it was assumed that CBF did not change during HO. Finally, $ETO2_{0/HC/HO}$, $CBF_{0,}$ $CBF_{HO/HC}$and $BOLD_{HC/HO}$ were input to the GCM, resulting in resting OEF, *M* and $CMRO_2$.

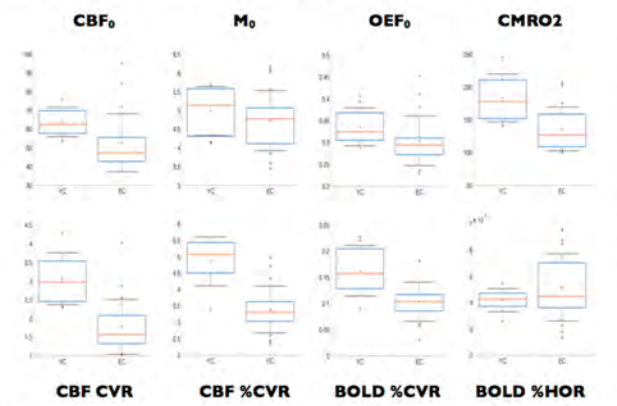

Figure 2. Box-and-whisker plots of grey matter (GM) values both young control (YC) and elderly control (EC). Boxes span the first and third quartile whereas whisker's ends exhibits above and below standard deviation.

Results: Group-average maps and group-average GM values are shown in Figure 1 and Figure 2 respectively. Parameters shown include: resting CBF (CBF_0), blood flow response to inhalation of CO_2 normalized by increase of $ETCO_2$ (CBF CVR), cerebrovascular reactivity expressed as a percent of resting CBF (CBF %CVR), BOLD responses to HC and HO, normalized by the increase in $ETCO_2$ and ETO_2 respectively (BOLD %CVR and BOLD %HOR), BOLD calibration parameter *M*, oxygen extraction fraction (OEF) and absolute $CMRO_2$. We observed an age-related diminution in both BOLD and CBF CVR. In addition, resting CBF and OEF appeared to decrease with age, consistent with a reduction in oxidative metabolism. Moreover, maps and whisker plots of M_0 exhibited a tendency toward a reduction associated with age which suggests a lower sensitivity of BOLD fMRI for detection of neuronal responses. On the other hand, the elderly group exhibited a slightly higher BOLD response to HO than young controls. Age-related reduction in CBF0, CVR and *M* are in agreement with observations made in [5]. Finally, a trend for decrease in $CMRO_2$ with age was also previously observed using PET [6].

Conclusion: We have demonstrated differences in cerebrovascular reactivity, vascular and metabolic function associated with age. Future work will be dedicated in the evaluation of the same measurements, using the QUO2 technique, in individuals diagnosed with Alzheimer's Disease and age-matched controls. Funding support from the FQRNT and CQDM, under the FOCUS program, is gratefully acknowledged.

References: 1) Gauthier, C.J., Hoge, R.D. Human Brain Mapping In Press, 2011a. 2) Bulte, D.P., et al. Neuroimage. 2011; 60, 582-591. 3) Tancredi FB, Hoge RD. JCBFM. 2013; 33:1066-1074. 4) Wang J, et al. Magn Reson Med2003; 50: 599–607. 5) Gauthier, C.J., et al. Neurobiology of Aging, 2013; 34: 1469-85. 6) Burns, A., et al. Age and Aging. 1992; 21:316-20