In-vivo measurement of cerebral metabolic rate of oxygen consumption in an animal model of multiple sclerosis using combined MRI and near-infrared spectroscopy

Thomas W. Johnson[1,2], Linhui Yu[3], Kartikeya Murari[3], and Jeff F. Dunn[1,2]

[1]*Radiology, University of Calgary, Calgary, Alberta, Canada,* [2]*Hotchkiss Brain Institute, Calgary, Alberta, Canada,* [3]*Electrical Engineering, University of Calgary, Calgary, Alberta, Canada*

Target audience: Scientists and clinicians interested in metabolic change in gray matter in multiple sclerosis (MS) as well as those using animal models to study metabolic and physiological changes in MS and those interested in measuring metabolic rate with MRI.

Purpose: To determine if there are changes in oxygenation, perfusion and oxygen uptake in the cortex of the experimental autoimmune encephalopathy (EAE) model of MS using a multimodal near-infrared spectroscopy (NIRS)/magnetic resonance imaging (MRI) system.

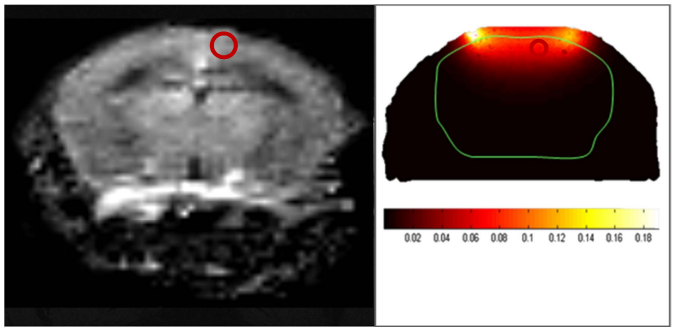

Figure 1: Photon transport modelling through mouse head. *(**Left**): Axial Perfusion-weighted MR image with ROI shown with red circle. (**Right**): Results of photon transport simulation with optodes spaced 6mm apart. The green outline indicates boundaries of brain tissue. Whiter colours indicate a greater contribution to the signal from that region. The classic "banana" shape of the photon path is clearly visible.*

Methods: Control (n=8) and long term EAE (day 35; n=3) C57BL/6 mice were spontaneously ventilated with 2% isofluorane, 30% O_2, and 68% N_2. Breathing, heart rate and temperature were monitored. $CMRO_2$ was calculated using the Fick principle, given by $CMRO_2 = 54.85(\mu mol \cdot g^{-1}) \times CBF \times (S_a - S_v) \times [tHb]$. Cerebral blood flow ($CBF$) was obtained with ASL-MRI; S_a is arterial blood saturation and is obtained through pulse oximetry; S_v is venous blood saturation and is obtained with NIRS by assuming the following relation: $S_a - S_c = \frac{3}{4}(S_a - S_v)$, where S_c is the capillary saturation as measured with NIRS; and $[tHb]$ is total hemoglobin concentration, also obtained with NIRS. Arterial spin labelling data was collected with a 9.4T Bruker system with a CASL-HASTE sequence (matrix 128 x 128, FOV=3cm, TE=2.66ms, TR=3000ms). Broadband NIRS data were obtained using transmit/receive fibers tipped with collimators and prisms to direct the light 90^O downward when placed on the head. Data were digitized with a CCD spectrometer and processed using in-house MATLAB software based on a second-differential spectrum least-squares fitting algorithm and a hypoxia calibration[1,2], giving [Hb] and [tHb]. Transport of NIR light in skin, skull and brain tissue was modelled using a finite element mesh derived from an MR image of a mouse in the NIRFAST software package[3] and MRI ROIs were placed in the centre of the light path.

Results: The results of NIR photon transport modelling, showing the sensitive region in the GM are shown in Fig. 1. $CMRO_2$ for the control group (n=8) was found to be 2.69 ± 0.84 µmol O_2/g/min; $CMRO_2$ for the EAE mice was found to be significantly increased ($p<0.001$) at 6.09 ± 1.14 µmol O_2/g/min. Control values agree with previously reported values for mice[4].

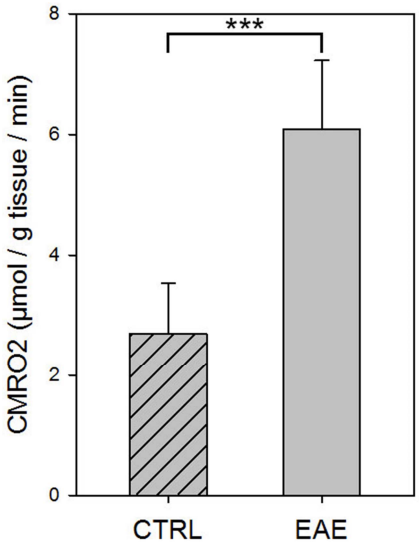

Figure 2: $CMRO_2$ differences between control mice and long term EAE mice. *$CMRO_2$ for the control group (n=8) was found to be 2.69 ± 0.84 µmol O_2/g/min; $CMRO_2$ for the EAE mice (n=3) was found to be 6.09 ± 1.14 µmol O_2/g/min, ($p < 0.001$, mean ± S.D).*

Discussion: There is strong evidence that MS has significant GM involvement and so oxidative metabolism should be abnormal. Metabolism could increase if mitochondria were uncoupled[5] or decrease if axonal loss reduced metabolic rate. The EAE model has been shown to have histological degeneration in long term mice[6] and if metabolism is also abnormal, this provides evidence that inflammation induced metabolic impairment could occur in MS.

Conclusion: We developed a new combined NIRS/MRI system to quantify $CMRO_2$ in GM of mouse models of neurological disease. We are the first to use this method, and we applied it to show that, in the long term EAE model of MS, there is increased $CMRO_2$ in GM. This supports GM involvement in the progression of MS.

References:

1. Matcher, S. J. & Cooper, C. E. *Phys. Med. Biol.* 39, 1295 (1999). **2.** Zhang, Q. *et al. J. Neurosci. Methods* 188, 181–186 (2010). **3.** Dehghani, H. *et al. Commun Numer Methods Eng* 25, 711–732 (2008). **4.** Cui, W. *et al. J. Cereb. Blood Flow Metab.* 33, 1846–1849 (2013). **5.** Trapp, B. D. & Stys, P. K. *Lancet Neurol.* 8, 280–291 (2009). **6.** MacKenzie-Graham, A. *et al. NeuroImage* 60, 95–104 (2012).