# Functional $CMRO_2$ Study in Cat Visual Cortex: Findings and Implications

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**Introduction** How much increases of the cerebral metabolic rate of oxygen ($CMRO_2$) are needed, or can be provided by brain for elevated neuronal activity? This question has been debated for long time [1-3] due to the lack of reliable techniques for direct measurement of $CMRO_2$. Recent development in the high-field $^{17}O$ MRS [4-7] provides a promising tool for determining $CMRO_2$ and its change in the living brain. We have applied *in vivo* 3D $^{17}O$ MR spectroscopic imaging (MRSI) approach for studying the role of oxidative metabolism in brain function by directly and non-invasively imaging $CMRO_2$ in the cat primary visual cortex (V1) at rest and during visual stimulation. This functional $CMRO_2$ study in cat brain has revealed several important findings which could have profound implications for understanding the fundamental role of oxidative metabolism in bioenergetics associated with brain function and disease.

**Method** Artificial ventilation and gaseous anesthesia (0.9-1.2 % isoflurane in a mixture of 70% nitrous oxide and 30% oxygen) were applied to female adolescent cats for MR studies conducted on a 9.4T horizontal magnet (Magnex Scientific, UK) interfaced with a Varian INOVA console (Varian Inc., Palo Alto, CA). The cat eyes were refracted and focused on the visual stimulus consisting of a binocular high-contrast square-wave moving and rotating gratings (0.3 cyc/deg, 2 cyc/sec and 16°-rotation for every 4sec) to achieve optimal activity in the cat primary visual cortex. The cats were placed in a cradle with head position restrained by the mouth and ear bars. The animal physiological condition was continuously monitored and maintained. A multinuclear RF probe consisted of a $^{17}O$ surface coil covering the V1 area and a larger $^{1}H$ coil for anatomic and functional imaging was used. The spatial localization of $^{17}O$ MRS imaging was achieved by using the 3D Fourier series window approach [8]. The acquisition time for each 3D $^{17}O$-MRS image was 12.5 seconds (total scan number=1028; FOV=3×3×2.5 $cm^3$, 9×9×5 phase encodes, voxel size=0.12ml (nominal voxel size=43μl)). A 17×17×9 matrix of FIDs were generated from the original 9×9×5 phase encode data for each 3D $^{17}O$ image. Two 2-minute $^{17}O_2$ (up to 89% $^{17}O$ enrichment) inhalation studies were performed for each cat with and without visual stimulation, respectively. The linear fitting model for calculating the $CMRO_2$ value, which has be established in the rat study [5-7], was applied to quantify the absolute $CMRO_2$ values and their changes induced by visual stimulation in the cat brain. Six studies in five cats were performed and experimental results were presented as Mean±SD. All animal surgical procedures and experimental protocol were approved by the Institutional Animal Care and Use Committee of the University of Minnesota.

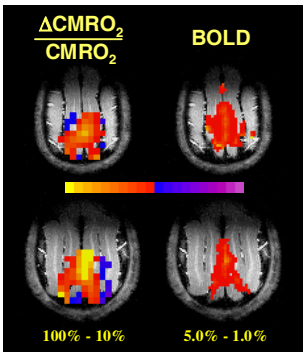


**Fig. 1** Functional BOLD and $CMRO_2$ images during visual stimulation in a representative cat brain.

**Results** We were able to obtain 3D $CMRO_2$ images of cat brain at resting state and during visual stimulation via two consecutive 2-min $^{17}O_2$ inhalations. Based on these absolute $CMRO_2$ images, we generated $\Delta CMRO_2/CMRO_2$ activation maps induced by the visual stimulation for each cat brain. An example of functional $CMRO_2$ and corresponding BOLD images from two representative image slices is shown in Fig. 1. Significant $CMRO_2$ increases were observed in the activated V1 areas. The averaged $CMRO_2$ value in the cat primary visual cortex was 0.97 ± 0.04 μmol/g/min at resting state, and was 1.26 ± 0.09 μmol/g/min during visual stimulation indicating a 32.3 ± 10.8 % increase (n=6) in the activated brain regions. As shown in Fig. 1, we also consistently observed $CMRO_2$ decrease in the areas surrounding the activated brain regions. If both positive and negative $CMRO_2$ changes were counted in the calculation, the averaged net $CMRO_2$ increase due to visual stimulation became 9.7±1.9 % (n=6). In addition, when comparing the paired values of relative $CMRO_2$ change versus the baseline $CMRO_2$ at resting state measured in different cat brains, a close correlation between the task-evoked $CMRO_2$ changes and their baseline $CMRO_2$ levels was evident (see Fig. 2)

**Discussion and Conclusions** Our results have not only demonstrated the capability of the *in vivo* $^{17}O$ MRS imaging approach as a promising tool for studying the oxidative metabolism in living brain via direct mapping absolute $CMRO_2$ at ultrahigh fields, they also presented crucial evidence supporting the central role of cerebral oxidative metabolism in brain function during brain activation. The spatial distribution of the $CMRO_2$ changes across different brain regions varied significantly and displayed both positive and negative values. This result suggests a possible brain energy compensation mechanism for supporting the increasing energy demand in activated brain region through suppression of metabolic activity in the surrounding deactivated brain regions. The observed close correlation between elevated $CMRO_2$ changes during visual stimulation and their baseline $CMRO_2$ levels has provided direct evidence indicating the strong influence of baseline metabolic activity on the relative $CMRO_2$ change in response to brain stimulation [9]. Following the trend as shown in Fig. 2C, we could further speculate that the task-evoked $CMRO_2$ change in the awaked brain (e.g., humans) would be less pronounced as compared to the anesthetized brain owing to higher level of baseline $CMRO_2$. Clearly, this prediction deserves further investigation.

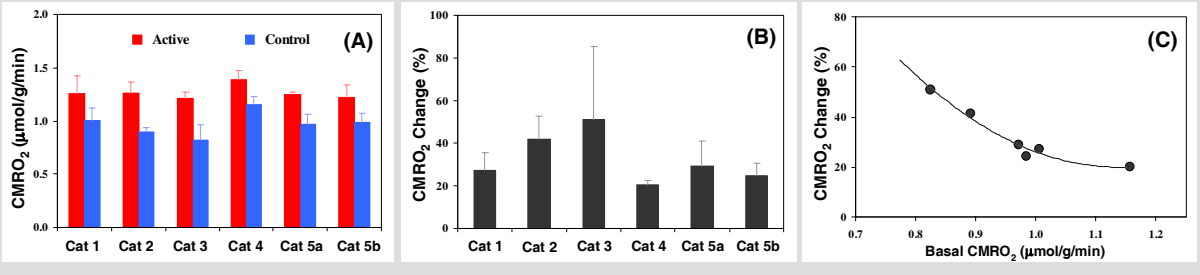


**Fig. 2** Absolute $CMRO_2$ values for each cat brain at rest and during visual stimulation (A); the relative $CMRO_2$ increases evoked by visual stimulation (B); and the correlation between the relative $CMRO_2$ changes and baseline $CMRO_2$ values (C).

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**References** [1] Hoge RD et al. *PNAS* 1999;96: p9403. [2] Hyder F et al. *JCBFM* 2000;20: p485. [3] Fox PT et al. *Science* 1988;241: p462. [4] Zhu XH, et al. *PNAS* 2002; 99: p13194. [5] Zhang NY et al. *JCBFM* 2004;24: p840. [6] Zhu XH, et al. *NMR Biomed.* 2005;18: p83. [7] Zhu XH, et al. *JCBFM* 2006 (in press). [8] Hendrich K, et al. *JMR* 1994;105: p225. [9] Hyder F et al. *PNAS* 2002;99: p10771.