Direct Imaging of $CMRO_2$ in Cat Visual Cortex at Rest and Visual Stimulation

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Introduction The blood oxygenation level dependent (BOLD) based functional MRI (fMRI) technique has been used prevalently to map brain function. However, the question of whether there is a tight coupling between changes in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) associate with the changes in neuronal activity is still the subject of debate [1-3], and it becomes the obstacle for fully understanding the BOLD mechanism and for quantitatively interpreting the fMRI results. One of the major hurdles for resolving the controversy is due to the lack of reliable techniques for direct measurement of $CMRO_2$. Recent development in the high-field ^{17}O MRS [4-6] provides a promising tool for measuring $CMRO_2$ and its change in the living brain. We have applied *in vivo* 3D ^{17}O MR spectroscopic imaging (MRSI) approach for imaging $CMRO_2$ in the cat primary visual cortex (V1) and its change induced by visual stimulation. Our primary result indicates a substantial $CMRO_2$ increase in the cat visual cortex which can be readily mapped during few minutes inhalation of $^{17}O_2$ gas.

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 an ^{17}O surface coil covering the V1 area and a larger half-volume ^{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 [7]. 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, 0.12 ml voxel size). 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 been established in the rat study [5-6], was applied to quantify the absolute $CMRO_2$ values and their changes induced by visual stimulation in the cat brain. All animal surgical procedures and experimental protocol were conducted under the guidelines of the National Institutes of Health and the Institutional Animal Care and Use Committee of the University of Minnesota.

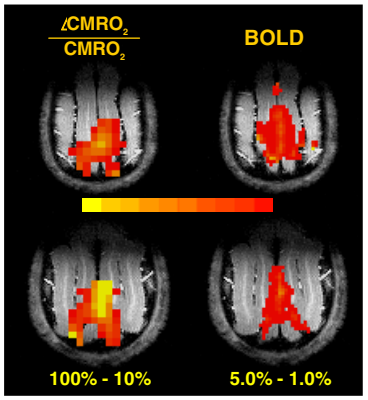

Fig.1 Maps of BOLD and $CMRO_2$ changes during visual stimulation in a representative cat brain.

Results Figure 1 shows BOLD and $\Delta CMRO_2/CMRO_2$ activation maps due to the visual stimulation in two image slices from a representative cat brain. Significant $CMRO_2$ increases were observed in the activated visual cortex regions. The size and location of the activated region shown in the $CMRO_2$ maps approximately coincide with that mapped by BOLD-based fMRI. Figure 2 summarizes the averaged $CMRO_2$ results from five studies in 4 cats. The absolute $CMRO_2$ values from four adjacent brain slices (i.e., A, B, C and D arranging from posterior to anterior) at resting (blue bar) and during visual stimulation (red bar) are shown in Fig. 2a, and the relative $CMRO_2$ changes associated with the visual stimulation are shown in Fig. 2b. The averaged $CMRO_2$ value in the cat primary visual cortex at resting state was 0.96 ± 0.15 μmol/g/min, and was 1.27 ±0.17 μmol/g/min during visual stimulation in the activated regions indicating a 33.3 ±11.4 % increase. Another interesting finding from this study was the consistent observation of $CMRO_2$ decrease in the areas surrounding the activated brain regions.

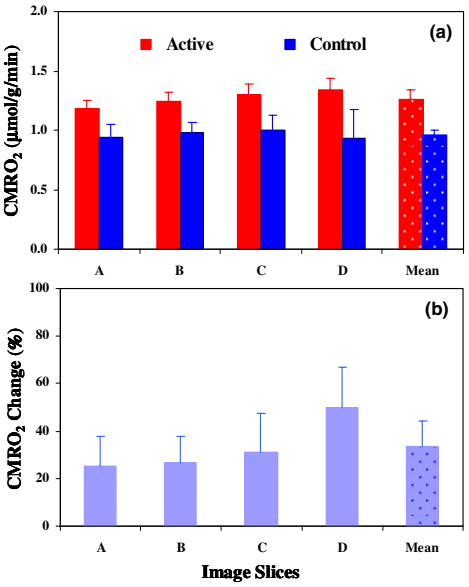

Fig.2 Summary of absolute CMRO2 values with and without visual stimulation (a) and their changes (b) in cat brain (n=5) under isoflurane anesthesia.

Discussion and Conclusions Our results demonstrate again that the developed *in vivo* ^{17}O MRS imaging approach is promising for 3D mapping of $CMRO_2$ in cat brain with 2-min inhalation of $^{17}O_2$ gas at ultra-high fields. The $CMRO_2$ value obtained with the linear fitting model is in general agreement with the literature report [8]. Furthermore, the ^{17}O MRS approach allows us to perform multiple $CMRO_2$ measurements on the same cat under different condition. Voxel-by-voxel based comparison for the $CMRO_2$ values obtained at different conditions will provide the map of $CMRO_2$ change caused by physiological perturbation. In this study, we were able to obtain not only the absolute $CMRO_2$ maps of the cat brain but also the map of $CMRO_2$ percentage change in response to the visual stimulation. Substantial $CMRO_2$ increases during visual stimulation were observed in all cats studied. These results reveal the important role of oxidative metabolism in cerebral bioenergetics and brain function. Finally, by combining with the BOLD, CBF and/or CBV results reported for the same cat model, one should be able to address the question of coupling between CBF and $CMRO_2$, which should have a significant impact on understanding BOLD mechanism and fMRI application in the neuroscience researches.

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