Comparative oxidative demands in cortex and subcortex revealed by high field calibrated fMRI

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INTRODUCTION:

The energetic basis of neural activity provides a solid foundation for non-invasive neuroimaging with calibrated functional magnetic resonance imaging (fMRI). Our earlier studies with calibrated fMRI have shown that changes in cortical electrical activity correlate well with changes in CMR_{O2} [1-5]. To convert cortical and subcortical BOLD signals into ΔCMR_{O2} by calibrated fMRI, we need reliable measurements of multi modal imaging signals (BOLD, CBV, CBF) and extracellular neural (LFP, MUA) recordings from both cortical and subcortical regions. Neural activity patterns and microvasculature are known to be different in cortical and subcortical regions [6]. Here we hypothesize that (i) Neurovascular coupling differs in subcortex compared to cortex. (ii) During unisensory stimuli subcortical energy demand is proportional to electrical activity, similar to that seen in the cortex. Because oxidative demands in cortex and subcortex are largely unknown, we evaluated regional energetics with high field calibrated fMRI in rat brain.

MATERIALS and METHODS:

Animal preparation: Sprague-Dawley male rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation 2% isoflurane was used for induction. Intraperitoneal line was inserted for administration of α-chloralose (46±4 mg/kg/hr) and D-tubocurarine chloride (1 mg/kg/hr). An arterial line was used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment. ***Forepaw stimuli*** (2mA, 0.3 ms, 3Hz): Stimulation was achieved by insertion of thin needle copper electrodes under the skin of the forepaw. ***fMRI (n=10):*** All fMRI data were obtained on a modified 11.7T Varian horizontal-bore spectrometer using a ^{1}H surface coil (Ø = 1.4 cm). The images were acquired with gradient echo EPI sequence (TR/TE = 1000/15). CBV measurements were performed in presence of contrast agent ferumoxtran (12mg/kg). ***Neural and CBF measurements (n=10):*** The rat was placed in a stereotaxic holder on a vibration-free table inside a Faraday cage. Tiny burr holes above the contralateral somatosensory regions [4.4 mm lateral and 1.0 mm anterior to bregma] and bilateral ventral posterior lateral (VPL) thalamic nuclei [3.0 mm lateral and 3.0 mm posterior to bregma] were drilled and tungsten microelectrodes (FHC Inc, Bowdoinham, ME) with fine laser Doppler flow probes (400 μm diameter) were inserted up to layer 4 for $S1_{FL}$ and 5 mm ventral for the thalamic nuclei (VPL) with stereotaxic manipulators (Kopf). Neural data from cortical and subcortical regions were acquired with high and low impedance electrodes, respectively, and the signals from the regions were normalized to the initial peak response during forepaw stimulation. All signals were then digitized (>20 kHz) with a μ-1401 interface using Spike2 software (CED, Cambridge, UK). Multi unit activity was processed using a RMS (root mean square) approach. CBF was measured as laser Doppler flux (LDF) by Oxyflo device (Oxford Optronics, UK) at 200Hz sampling rate and later downsampled to the BOLD temporal resolution. The LDF data were adjusted to the arterial spin labeling measurements to get the CBF data and CMR_{O2} was calculated using the measured hemodynamic signals as described by earlier [3-5].

RESULTS and DISCUSSION:

Unilateral forepaw (2mA, 3Hz, 0.3 ms) stimulation evoked a strong contralateral cortical $S1_{FL}$ and subcortical (thalamic nuclei) responses. We measured BOLD, CBV, and CBF to calculate ΔCMR_{O2} in cortex and subcortex and compared these with neural recordings **(Fig.1)**. Cortical BOLD, CBV and CBF responses were significantly larger as compared to the thalamic responses **(Fig.1A-C)**. However, we found no significant differences in the CMR_{O2} and neural (MUA) response in the cortex and thalamus during forepaw stimulation **(Fig.1D-E)**. We find that while BOLD-CBV and BOLD-CBF relationships differ significantly between cortex and subcortex, ΔCMR_{O2} values are quite similar in these regions. These regional energetic estimates from calibrated fMRI are in agreement with neural recordings. The neurovascular coupling in the thalamus is tighter; the oxygen utilization is higher during activation than in the cortex. The neocortex represents the final processing area of tactile (somatosensory) stimulation, which are connected to the evolutionary older subcortex (thalamus) by thalmocortical and corticothalamic pathways, where the information processing starts. The difference in the neurovascular coupling probably originates in the different neural and vascular structure of these two areas [6]. Thus these results suggest that neurometabolic couplings are similar in cortex and subcortex, but neurovascular couplings are quite different. Therefore understanding the role of subcortical regions in influencing cortical activation is vital for fMRI data interpretation.

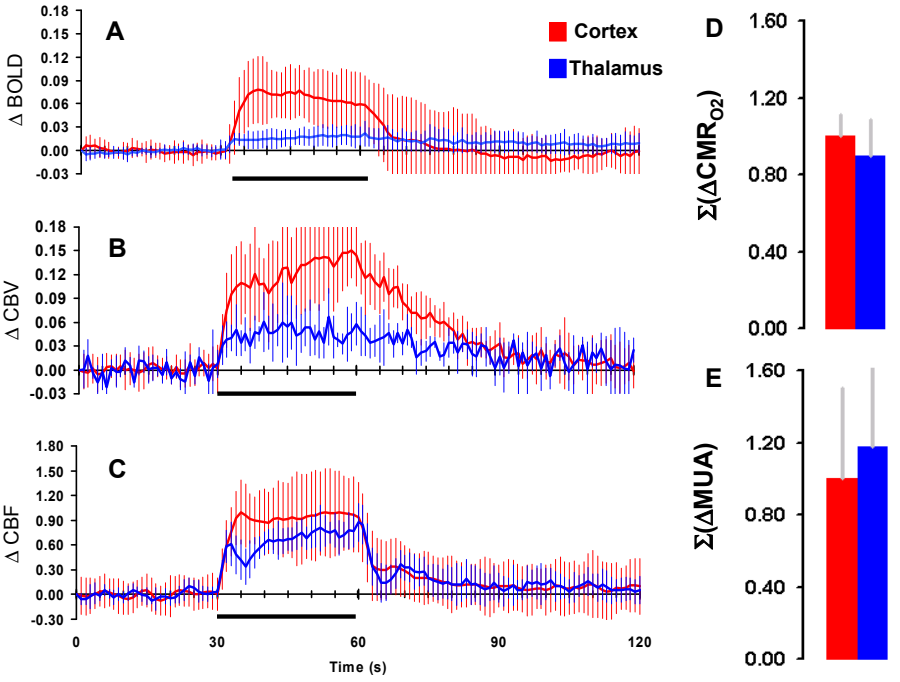

Fig.1. Multi modal measurements of BOLD (A), CBV (B), CBF (C) and multi unit activity (MUA) (E) responses at somatosensory cortex ($S1_{FL}$) and thalamus (VPL) of the rat brain during unilateral forepaw stimulation (2mA, 0.3ms, 30s). The stimulus presentation is indicated by horizontal black bar. Cerebral metabolic rate of oxygen consumption (CMR_{O2}) (D) were calculated by using the measured hemodynamic signals from both cortex and thalamus.

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ACKNOWLEDGEMENTS: This work was supported by grants from **NIH** (R01 MH-067528, P30 NS-52519).