Transcortical BOLD impulse response functions: Implications for layer-specific CMR_{O2} calculation

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INTRODUCTION:

The extraction of oxygen consumption (CMR_{O2}) signal from BOLD signal using multi-modal measurements of blood flow (CBF) and volume (CBV) has become an accepted fMRI technique [1-2]. This calibrated fMRI technique can be used for the description of the oxidative energetics of neurons, and for the indirect and non-invasive measurement of neural activities. This approach is based on a model which describes tissue oxygen extraction at steady-state [3-4]. It is not clear how the cortical localization of the measurements can modify the calibration procedure. It is well known that the neuronal and vascular microstructure is not homogenous across the cortex, because they form histological and anatomical defined layers. How are the neural signals connected to the functional BOLD responses in different layers of the cortex? Using convolution analysis we described the impulse response functions in the upper, middle and lower cortical layers. We used two groups of rats with the same experimental model (electrical forepaw stimulation) to measure the fMRI-BOLD signals and the conjunctive neural responses. The high definition local field potentials (LFP) served as input functions of the convolution analysis, while the output function of the model were compared to the measured BOLD signals (Figure 1).

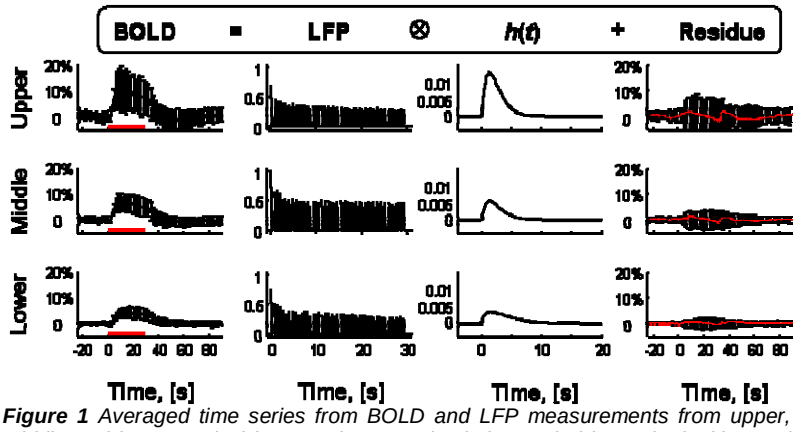

Figure 1 *Averaged time series from BOLD and LFP measurements from upper, middle and lower cortical layers. The 30s stimulation period is marked with a red bar. The measured BOLD signal is the sum of the modeled response (the convolution of the input signal and the h, transfer function) and the residual signal (red line). The residue signals in every case are within the variability of the BOLD measurement, which indicates a good fit of the convolution model.*

MATERIALS and METHODS:

Sprague-Dawley rats were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). The anesthesia was switched to i.p. α-chloralose (80mg initial dose, then 40 mg/kg/hr) from Halothane or Isoflurane (1-2%) after the surgery. A femoral arterial line was used for monitoring blood pressure, acid-base balance and blood gases throughout the experiment. ***Forepaw stimulation:*** Copper needles were inserted below the skin of the forepaw. Each stimulus train lasted 30s with 3Hz frequency, 2 mA in amplitude and 0.3 ms in duration. ***BOLD*** *(n=7):* All fMRI data were obtained on a modified 11.74T Bruker horizontal-bore spectrometer (Billerica, MA) using a ^{1}H resonator/surface coil RF probe. All images were acquired with gradient echo EPI (TR/TE=1000/12.53 ms). All fMRI data were subjected to a translational movement criterion [5]. ***Electrophysiology*** *(n=31)* In separate group of animals after surgery the rat was placed in a stereotaxic holder (Kopf Instruments, Tujunga, CA) on a vibration-free table inside a Faraday cage. Tiny burr holes above the somatosensory region [4.4 mm lateral and 1.0 mm anterior to bregma] were drilled and high impedance microelectrodes (2-4 MΩ) were inserted step-by-step into three different depths of the cortex (upper, lower and middle part; 0.3 mm, 1mm and 1.5mm, respectively) with stereotaxic manipulator. Electrical signals were digitized with CED μ-1401 using Spike 2 software (Cambridge Electronic Design, Cambridge, UK) at 20 kHz. Data were collected in 120 s windows: 30 s before and 60 s after the 30 s forepaw stimulation. Local field potentials (LFP) were obtained applying low pass filter (<150Hz) to the raw time series then integrated into 0.02s bins (Figure 1). ***Transfer function***: The transfer function, *h*(*t*), can be achieved by deconvolution between the LFP and the BOLD signal. A modified form [6] of the gamma variate function (GVF) was used for transfer function model [7]. The parameters of the transfer function were calculated with iterative steps within Matlab (Natick, MA). The input function was defined as the average of the LFP series, where the individual events were normalized to the largest evoked potential (first EP in the middle layer).

RESULTS and DISCUSSION:

The neural and BOLD functional responses show layer specific change in the amplitude as measured through cortical layers (Figure 1). The BOLD signal has the largest response in the upper layer and decreases toward the deeper cortical layers. The LFP signal is the most explicit in the middle layer and the smallest in the lower layer. The amplitude of transfer function, h(t), follows the amplitude of the functional BOLD response: it decreases toward the deep regions. The normalized signals however show very good correlation between the layers (Figure 2). BOLD signals show the best correlation between the upper and middle layers, while the slightly different shape of the lower layer signal brings a small hysteresis into the correlation, but it still has a high correlation coefficient. The very good correlation between the electrical signals is expected because of the high number data point and similar pattern of the signals: increases and decreases of intensities follow each other in the same rhythm. However the correlation of the normalized transfer functions clearly reveals the differences between the functional responses of the lower layer and the upper two layers. The transfer functions of the upper and middle layers are similar. Therefore, despite the differences in amplitudes, the normalized responses are interchangeable for CMR_{O2} calculation. On the other hand, the lower layer of the cortex is needed for calibration separately.

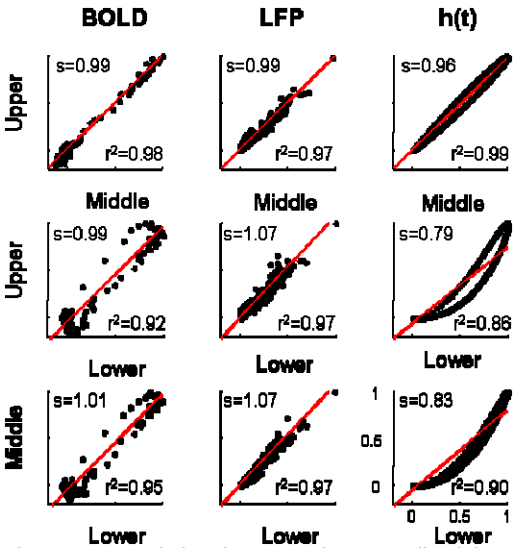

Figure 2 *Correlation between the normalized layer-specific (upper-middle, upper-lower and middle-lower) BOLD, LFP signals, and transfer functions, h(t), respectively. The slope (s) and the correlation coefficient (r^2) of the linear regression fit (red line) are shown in every panel.*

REFERENCES [1] Hyder et al (2001) *NMR Biomed* 14, 413-431. [2] Kida et al (2000) *J Cereb Blood Flow Metab* 20, 847-860. [3] Ogawa et al (1993) *Magn Reson Med* 29:205-210 [4] Kennan et al. (1994) *Magn Reson Med* 31, 9-21. [5] Chahboune et al (2007) *NMR Biomed* 20: 375-382 [6] Madsen (1992) *Phys Med Biol* 37, 1597-1600. [7] Boynton et al (1996) *J Neurosci* 16, 4207-4221.

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