

Time invariant BOLD impulse response functions for brief- and long-lasting stimuli

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INTRODUCTION

Quantitative mapping of changes in cerebral oxygen consumption (CMR_{O_2}) with BOLD calibration has become a popular modality for studying functional brain activity [1] because it is proportional to changes in energy consumption associated with alterations in neuronal activity induced by the stimulation [2]. This approach, termed calibrated fMRI, is based on a model which describes tissue oxygen extraction at steady-state [3-4], and this model is not proved to use for calculation of dynamic CMR_{O_2} . It is unclear whether calculation of CMR_{O_2} will differ between short and long stimuli. If it is possible to experimentally demonstrate linearity between neural and BOLD-related responses to short and long-lasting stimulations in wide range of stimulation conditions, then that is an empirical proof of the feasibility of the steady-state BOLD model to dynamic events and it may be possible to use calibrated fMRI in a dynamic manner. Using fMRI and electrophysiology in α -chloralose anesthetized rats during forepaw stimulation, we show that the transfer functions generated by convolution analysis with neural activity are time invariant, for events in the millisecond to minute range and for stimulation frequencies.

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. Femoral arterial line was used for monitoring blood pressure, acid-base balance and blood gases throughout the experiment. **Stimulation:** Copper needles were inserted below the skin of the forepaw. Each stimulus train used 2 mA in amplitude and 0.3 ms in duration. All stimulus presentation was controlled by a μ -1401 analog-to-digital converter unit (CED, Cambridge, UK) running custom-written script. The inter-pulse intervals ranged from 167, 333, and 667 ms which corresponded to stimulus frequencies of 1.5, 3, and 6 Hz, respectively. The stimulus number was varied from 1 to 4 for brief stimuli. 90 pulses with 3 Hz frequency was used for long stimulation. **BOLD** ($n=12$): All fMRI data were obtained on a modified 11.74T Bruker horizontal-bore spectrometer (Billerica, MA) using a 1H 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** ($n=14$): In a 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 M Ω) were inserted with stereotaxic manipulator. Electrical signals were digitized with CED μ -1401 using Spike 2 software (Cambridge Electronic Design, Cambridge, UK) at 20 kHz. Local field potentials (LFP) were obtained applying low pass filter (<150Hz) to the raw time series then integrated into 0.02s bins. **Convolution analysis:** 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. The input signal covered not only one stimulus response, but consecutively all of the short stimulus conditions (4 different durations x 3 frequencies). The individual events were normalized to the largest evoked potential. The convolution of the input signal on the transfer function provided the modeled response signal. The difference between the model and the measurement is the residual signal (Figure 1).

RESULTS and DISCUSSION

Single transfer function was calculated, which could be used to describe the various responses of the BOLD signal. The same transfer function was used not only for modeling event-related responses, but for long lasting stimulation events too. The precision of the simulated signal was checked by the comparison of the residual signal (i.e. difference between the modeled and measured signal) (Figure 1) and the standard deviation of the measured signal. We considered the precision of the model adequate when the RMS (root mean square) of the residual signal was smaller than the mean Standard Deviation (SD) of the measured signal (Table 1 for 1.5 and 6 Hz stimulation data, and Figure 1 for 3 Hz stimulation data). Since we got similar results from other modalities (CBV and CBF) (data not shown), the steady-state BOLD model [3] may be used for dynamic CMR_{O_2} calculation.

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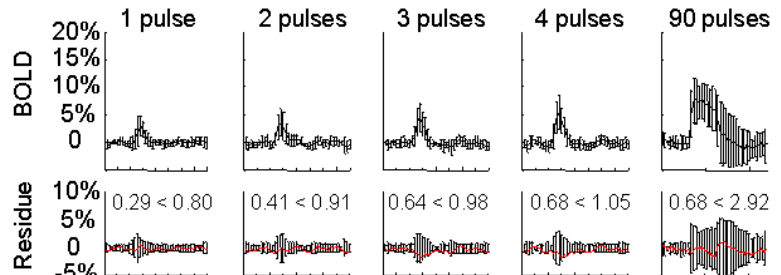


Fig. 1. Measured BOLD (top) and calculated residual signals (bottom). By convolution each of the BOLD responses with a single universal transfer function, modeled BOLD signals were generated which when differenced with the measured BOLD signals showed residual signals which were smaller than the measurement uncertainty. The root mean square (RMS) of the residual signal (left number) was compared with the averaged standard deviation (SD) of the measured data (right number). In every case, the RMS of the residual was lower than the measured SD.

BOLD	1.5 Hz	6 Hz
2 pulses	0.48 < 1.17	0.40 < 1.08
3 pulses	0.46 < 1.37	0.33 < 1.01
4 pulses	0.54 < 1.55	0.48 < 0.95

Table 1. Precision of linear convolution analysis. Root mean squares (RMS) of the residual signal (left number) were compared with the averaged standard deviation (SD) of the measured data (right number). In every case, the RMS residual signal was lower than the measured SD of the signal.