The CBF response is a time invariant linear transform of the underlying neural activity: fMRI and electrophysiological study of the rat brain

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SYNOPSIS
CBF-neuronal activity coupling is important in neuroimaging because CBF is used as an indicator for neural activity. We investigated the assumption that the coupling is linear and time invariant by combining the modified fMRI method for high temporal CBF measurement with local measurements of evoked field potential in a rat forepaw stimulation model. Since the coupling was found to be linear and time invariant with neuronal activity, the CBF response may be used to derive the neural activity time course when stimulus duration is longer than 4 seconds in the rat forepaw stimulation model.

INTRODUCTION
To use changes in CBF as an indicator for alterations in neural activity in neuroimaging it has been assumed that the CBF response is a time invariant linear transform of the underlying neural activity. If a system is truly linear and time invariant, then the input and output can be linked by an impulse-response function via the convolution theorem. This assumption applied to the coupling between CBF and neural activity therefore provides a very simple framework for the neurophysiologist to use the CBF response to infer the neural response or vice versa [1]. In rat, CBF responses measured by the laser-Doppler flowmetry (LDF) were not linearly correlated with somatosensory evoked field potential (EFP) signals [2]. However, theoretical predictions based on relationship between stimulus paradigms and CBF responses in human indicate CBF responses are linear and time invariant with neuronal activity [1]. The conflicting results may be due to methodological difference (MRI vs LDF) or different temporal resolution (~500ms vs ~4s). Therefore in this study, we used a modified fMRI method to measure CBF at the hundred millisecond scale [3] in order to test the assumption that the CBF-neural activity coupling is linear and time invariant with local measurements of EFP from the activated focus in a rat forepaw model.

MATERIALS and METHODS
Animal preparation: Male Sprague-Dawley rats were tracheotomized and artificially ventilated. Intraperitoneal lines were inserted for administration of α-chloralose (80 mg/kg followed by 20 mg/kg/½hr) and D-tubocurarine chloride (0.5 mg/kg/½hr). An arterial line was used to monitor physiology throughout the experiment. A block design forepaw stimulation (2 mA; 3 Hz) protocol was performed with different stimulus durations (4, 8, 16, and 32 s). *MRI measurements (n = 10):* All fMRI data were obtained on a modified 7T Bruker horizontal-bore spectrometer with gradient-echo EPI (TR = 500 ms): slice thickness = 2 mm; TE = 20 ms. ΔCBF/CBF was measured by T_1-weighted BOLD signal method [3]. *Extracellular recordings (n = 10):* The skull above the forepaw region (4 mm lateral, 0.5 mm anterior to bregma) was opened and the microelectrode (Impedance: 2-4 MΩ) was inserted. The extracellular signals were filtered and amplified (×1000). The N_1-P_2 amplitudes of EFP were obtained from the extracellular data. *Data analysis*: We employed a convolution model where the CBF response, CBF(t), is related to the EFP time course, EFP(t), by an impulse function, IF(t), via convolution, CBF(t) = IF(t)*EFP(t), for each stimulus duration. If the system is truly linear, then the impulse function should be independent of the stimulus duration.

RESULTS and DISCUSSION
Fig. 1 shows time courses of normalized CBF response and evoked field potential during 32 second stimulation. The CBF response reached a peak at 5±1 second for all stimulus durations and then decreased with short stimulus durations (e.g., stimulus duration<8 s) or plateaued with longer stimulus durations (e.g., stimulus duration>16 s). The amplitude of EFPs decreased to a half at ~ 4 seconds and maintained a steady state activity at half of amplitude in case of increased stimulus duration (e.g., stimulus duration>8 s). The impulse function was determined by deconvoluting normalized EFPs to fit CBF responses measured by MRI for each stimulus duration. Small differences were obtained with application of impulse functions for all stimulus durations. Fig. 2 shows a comparison between the measured CBF responses with standard deviation (vertical dotted lines) and the predicted CBF responses generated by using the four different impulse functions. Good agreement between the measured and predicted values indicated that the CBF response due to sensory stimulation for this rat model is linear and time invariant with respect to the EFP. These results support the theoretical prediction for human [1], but not the rodent by laser-Doppler flow measurements [2].

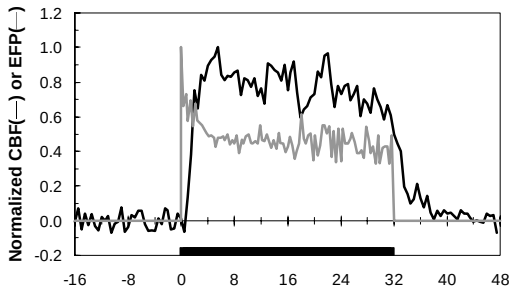

Figure 1

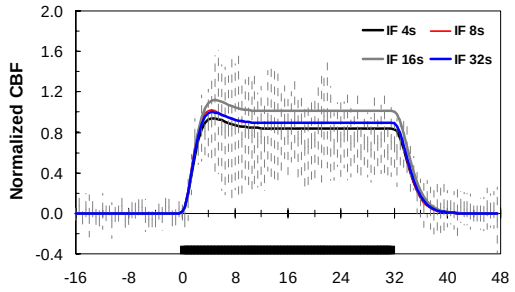

Figure 2

CONCLUSION
In the rat forepaw model, the CBF response is linear and time invariant with neuronal activity. Thus, the CBF response may be used to derive the neural activity time course when stimulus durations are longer than 4 seconds. Methodological differences between MRI and LDF and/or partial volume effects may lead to the conflicting results.

REFERENCES
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