A comparison of BOLD fMRI, electrophysiology, and oxygen signals in the whisker barrel cortex of the awake rabbit

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Introduction. Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) relies upon the coupling between neuronal electrical activity and localized hemodynamic changes to map neuronal activation. A comprehensive understanding of this relationship is vital for the accurate interpretation of fMRI results and for the application of fMRI techniques to more sophisticated and detailed neurophysiological questions. For this purpose, the use of electrodes to record oxygen tension (PO_2) allows us to measure the oxygenation changes that underlie the BOLD signal more directly, as compared to derived measures such as $CMRO_2$. Previously we have studied how the relationship between the BOLD signal, local field potentials (LFP), and single-unit (SU) activity changes under anesthesia. Here we seek to investigate how changes in BOLD and electrophysiological signals are related to changes in oxygen by direct measurement of PO_2. We have performed fMRI, electrophysiological and PO2 recordings in whisker barrel cortex of the rabbit during whisker stimulation both in the awake state and under isoflurane anesthesia. These results will help us to build a more detailed picture of the relationship between neuronal activity, cerebral oxygen metabolism, and the BOLD signal.

Methods. Dutch-Belted rabbits were chronically implanted with manipulators containing one bundle of 4 microwire gold-silver electrodes aimed at the whisker barrel cortex. MR imaging experiments were performed on a 9.4T Bruker BioSpec imaging spectrometers. fMRI data were acquired from four consecutive 1mm-thick slices in the coronal plane using a single-shot, gradient-echo multi-slice EPI sequence with a repetition time (TR) of 2 s, an echo time (TE) of 11 ms, a 30mm×30mm field of view (FOV), and a matrix size of 80×80, corresponding to an in-plane resolution of 375 µm x 375 µm. The slices included the whisker cortex and whisker thalamus. Each experiment consisted of 10 trials. Trials were inspected for remaining head movement after registration, and any trials exhibiting movement were excluded from analysis. The remaining trials were averaged for each experimental condition. Activated voxels were detected in the averaged data by cross-correlation to a boxcar function at a statistical threshold corresponding to p<.001. Neuronal activity was recorded using Neuralynx system, the signals were amplified, band-pass filtered (300 Hz-3 kHz for SU and 1-150 Hz for local field potentials (LFP)), and digitized (32 kHz/channel). Data were analyzed after removal of blocks of gradient interference. To record PO_2 changes an oxygen sensitive electrode was polarized to −0.7 V with respect to a silver-chloride reference electrode, and the current was measured with a Keithley model 614 electrometer. BOLD activation and PO_2 data or BOLD activation and electrophysiological data were recorded simultaneously. Whisker vibration system used an oscillating coil to drive a fiber band that delivered a well-controlled vibration stimulus at amplitude of ±1.0 mm with a frequency of 50 Hz.

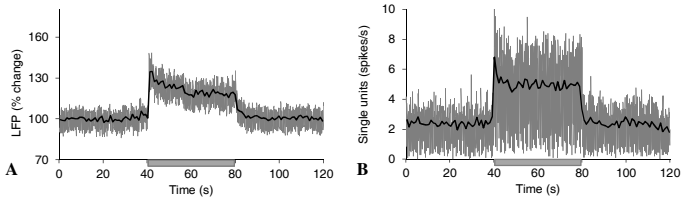

Fig. 1. LFP (A) and SU (B) responses in barrel cortex during whisker stimulation in awake animal. Responses are shown using both 100 ms (gray) and 1 s (black) bins. LFP activity was normalized to the baseline level before stimulus presentation. The gray bar indicates the stimulus presentation.

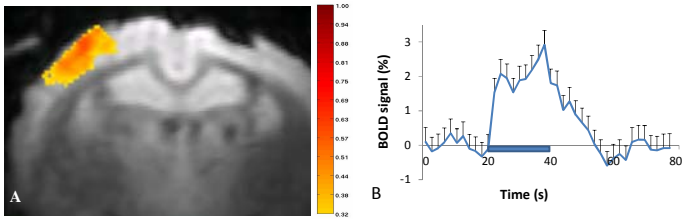

Fig. 3. Functional activation map of the stimulation of three whiskers (C1-C3) generated from cross-correlation analysis (A) and BOLD temporal profiles (B) in awake rabbits (N=2). The blue bars indicate the stimulus presentation. The in-plane resolution of the gradient-echo EPI images was 210x210 µm, with a 1mm slice thickness. The color bar indicates the magnitude of the correlation coefficient.

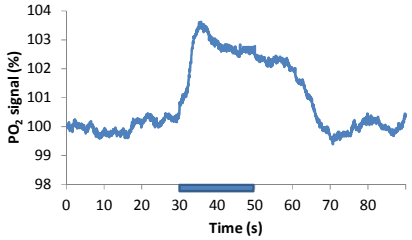

Fig. 2 The PO_2 response in the whisker barrel cortex to whisker stimulation. The blue bar indicates the stimulus presentation.

Results. As shown in Fig. 1, LFP and SU responses to whisker stimulation consisted of initial peak followed by a plateau indicative of neuronal signal adaptation. The PO_2 response (Fig. 2) was similar in shape but much longer in duration. In comparison, the BOLD response (Fig. 3) showed no corresponding level of adaptation.
The duration of the PO_2 response exceeded the duration of both the electrophysiological responses and the BOLD response, and often decreased below the initial baseline in the post-stimulus period. Similar behavior was observed in the BOLD but not the electrophysiological responses.

Discussion. Oxygen consumption increases in the brain as a response to elevated neuronal activity, and the fMRI BOLD signal is closely related to the cerebral blood flow that supplies oxygen to activated brain areas. Thus, a good correlation between oxygen, electrophysiological, and BOLD signals is expected. Our results demonstrate the striking differences in cortical BOLD, oxygen, and electrophysiological responses produced by whisker stimulation. The electrophysiological and oxygen signals showed adaptation of neuronal response during stimulation, whereas no corresponding adaptation was observed in the BOLD response. The shape of oxygen response appears more closely related to the shape of both electrophysiological responses than to the shape of BOLD signal, likely because the oxygen response more directly reflects the profile of localized activity generated by these responses. However extended duration of the PO_2 response more closely resembles the post-stimulus offset and subsequent undershoot that characterize the BOLD response, which likely reflect the sensitivity of this signal to longer-duration hemodynamic factors, specifically the tonic function of vessels.

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