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Coupling of hemodynamic and neuronal activity in rat somatosensory cortex

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Introduction

Neural activity changes in brain tissue are coupled to changes in blood flow, blood volume and blood oxygenation, called collectively the hemodynamic response. The hemodynamic response is important for understanding Blood Oxygen Level Dependent functional magnetic resonance imaging (BOLD fMRI). The present study addresses the question of neuro-vascular coupling employing simultaneous optical measurements of blood oxygenation and blood flow, and electrophysiological recordings in rat somatosensory cortex.

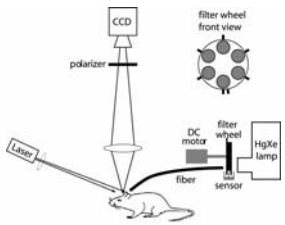
Methods

Rats were anesthetized with urethane, and an area of skull overlying the primary somatosensory cortex was thinned with a dental drill until transparent (~150 μm). A well of petroleum jelly was build around the border of the thinned skull and filled with mineral oil. A small hole was made in the thinned skull over the center of a barrel (as determined by optical imaging) for insertion of the recording electrode.

The light from a mercury xenon arc lamp was directed through a 6 position continuously rotating filter wheel and was coupled to a 12 mm fiber bundle that illuminated the cortex. The filters were 10 nm bandpass centered at wavelength of 560, 570, 580, 590, 600 and 610 nm. Images were acquired by a cooled 12-bit CCD camera at 18 Hz. Blood flow was measured using laser speckle contrast imaging (Dunn et al. 2001) using a pulsing diode laser (785 nm) that was synchronized with rotation of the filter wheel.

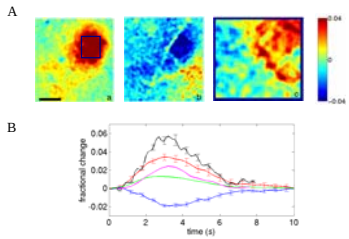
Electrophysiological recordings were performed using either single metal electrodes (2-4 MΩ) or laminar multi-electrodes (Ulbert et al. 2001). The signals were filtered at 0.1-500 Hz to record local field potential (LFP) and at 150-5000 Hz to record multiunit spike activity (MUA). The MUA signal was subsequently thresholded for spike counting.

A single whisker was deflected by a computer controlled piezoelectric stimulator using randomized event-related stimulus presentation (Dale 1999). For each type of stimulus used we summed MUA across trials, and subtracted an analogous measure for blank trials. MUA is expressed in spikes per second. LFP was averaged across trials for each type of stimulus, rectified on the time axis, and integrated over a poststimulus time window. For each type of the stimulus we subtracted an analogous measure for blank trials. LFP is expressed in units of standard deviation derived from the blank trials.



The instrument for simultaneous laser speckle contrast imaging of blood flow and spectral imaging of hemoglobin oxygenation.

Simultaneous imaging of blood flow and oxygenation

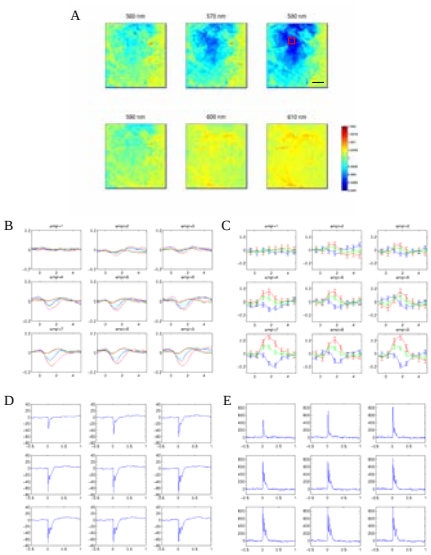


A. Ratio images of oxyhemoglobin (a,HbO), deoxyhemoglobin (b,Hb), and blood flow (c) following 2 sec of stimulation at 8 Hz (block design, 20 sec interstimulus interval (ISI)). Signals were averaged from the region of interest (ROI) marked on the HbO map (blue square). Scale bar = 0.5 mm.

B. Timecourse of HbO (red), Hb (blue), total hemoglobin (HbT, green), blood flow (black) and cerebral metabolic rate of oxygen consumption ($CMRO_2$, magenta) within the ROI. The stimulus was delivered at t = 0.

Blood oxygenation tracks neural activity when both LFP and MUA increase

a single deflection stimulus at 9 amplitudes



A. Ratio images of hemodynamic activation for each of 6 filters using one stimulus amplitude. The filter wavelength is indicated above each image. The ratio was calculated by dividing the response 1-3 sec following the stimulus by the prestimulus (baseline) level. Scale bar = 200 μm.

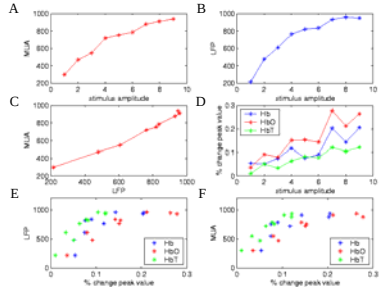
B. Signal timecourse obtained within the ROI (red square in A) for each of 6 filters (colored traces). Each panel represents one of the 9 stimulus amplitudes used. The stimulus was delivered at t = 0.

C. Timecourse of HbO (red), Hb (blue) and HbT (green) calculated from data in B.

D. Local field potential (LFP) for each of the stimulus amplitudes.

E. Multiple unit activity (MUA) for each of the stimulus amplitudes.

All conditions were randomized for stimulus amplitude, presented with a 1 sec interstimulus interval (ISI), and including 25% blank trials (0 amplitude). Each of the timecourses in B-C represents an average of 1080 trials.



A. MUA as a function of stimulus amplitude, expressed in spikes per second.

B. LFP as a function of stimulus amplitude, expressed in units of standard deviation.

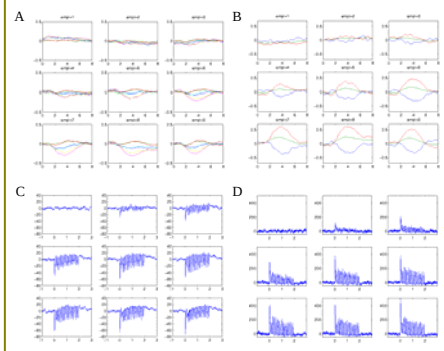
C. MUA as a function of LFP. Note the linear relationship.

D. Near linear relation between peak value of Hb, HbO and HbT and stimulus amplitude.

E. LFP, and F. MUA as a function of percent change in Hb, HbO and HbT.

Blood oxygenation and neural activity do not saturate at the same rate

2sec 8Hz stimulus at 9 amplitudes



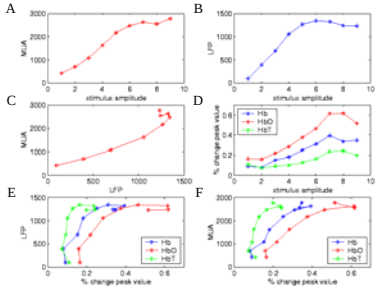
A. Signal timecourse for each of 6 filters (colored traces). Stimuli were delivered at t = 0. Notice the longer duration of the hemodynamic response compared to a single deflection.

B. Timecourse of HbO (red), Hb (blue) and HbT (green) calculated from data in A.

C. LFP for each of the 9 stimulus amplitudes.

D. MUA for each of the 9 stimulus amplitudes.

All conditions were randomized, presented with 3 sec ISI, and included 25% blank trials. Each timecourse in A-B is an average of 210 trials.



A. MUA as a function of stimulus amplitude.

B. LFP as a function of stimulus amplitude. Note response saturation.

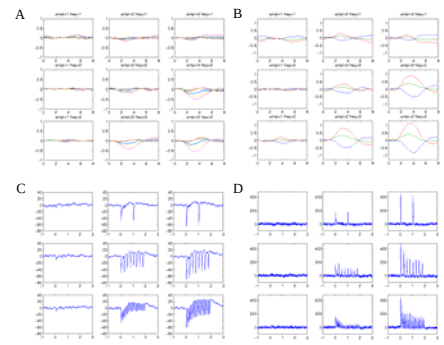
C. MUA as a function of LFP.

D. Peak value of Hb, HbO and HbT as a function of stimulus amplitude. At amplitudes where LFP has already reached a plateau, the hemodynamic response continues to grow.

E. LFP, and F. MUA as a function of percent change in Hb, HbO and HbT. Note the highly non-linear relationship.

When LFP and MUA change in different directions, blood oxygenation follows MUA

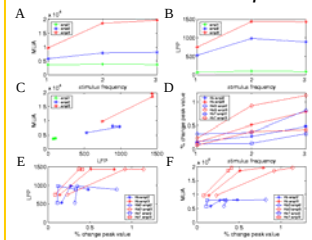
2sec stimulus at 3 amplitudes and 3 frequencies



A-D. Signal timecourses, hemodynamic responses, LFP and MUA using 3 stimulus amplitudes and 3 stimulus frequencies .

All conditions were randomized, presented with 3 sec ISI, and included 25% blank trials. Each timecourse in A-B is an average of 210 trials.

as a function of frequency



A. MUA **increases** with stimulus frequency.

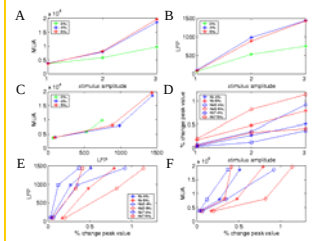
B. LFP **decreases** from 4 Hz to 8 Hz.

C. MUA as a function of LFP.

D. Peak value of Hb, HbO and HbT **increases** with stimulus frequency.

E. LFP, F. MUA as a function of percent change in Hb, HbO and HbT. Note that LFP decreases as hemodynamic response increases.

as a function of amplitude



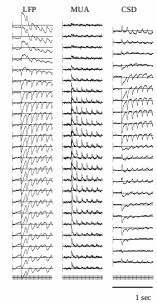
A-B. Both MUA and LFP increase as a function of stimulus amplitude.

C. MUA increases in parallel with LFP.

D. Peak values of Hb, HbO and HbT increase as a function of stimulus amplitude.

E. LFP, F. MUA increase as a function of the percent change in Hb, HbO and HbT.

Laminar recordings



An example of laminar recording of LFP and MUA. Each trace shows a recording from one of 23 contacts along the electrode shaft covering the full thickness of rat cortex (2.3 mm). Profiles change with laminar depth. The column marked CSD is the calculated current source density. Stimulus: 2 sec 8 Hz block design.

Conclusions

1. Blood oxygenation increases monotonically with increasing neural activity under conditions when both LFP and MUA increase without saturation (see panel: single deflection, 9 amplitudes).

2. It is valid to model hemodynamic response as a linear function of neural activity only under specific stimulus conditions.

3. The relation of blood oxygenation to neural activity is sigmoidal (see panel: 8 Hz, 9 amplitudes). Some stimuli produce reliable neuronal activity but are subthreshold for hemodynamic changes.

4. Blood oxygenation and neuronal activity do not saturate at the same rate. Each reaches a plateau at a different level of stimulation (see panel: 8 Hz, 9 amplitudes).

5. Within the stimulus range where LFP decreases as MUA increases, blood oxygenation continues to increase. This suggests that LFP does not reliably correlate with hemodynamic response under all conditions.

References

A. Dunn, H. Bolay, M. Moskowitz, and D. Boas, Journal of Cerebral Blood Flow and Metabolism 21, 195 (2001).

A.M. Dale, Human Brain Mapping 8, 109 (1999).

I. Ulbert, E. Halgren, G. Heit, G. Karmos, Journal of Neuroscience Methods 106, 69 (2001).