



modeling the macroscopic neurovascular coupling in the rat somatosensory cortex

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the objective of the study is to integrate scalp electroencephalography (EEG) and diffuse optical imaging (DOI) to investigate the neurovascular coupling in rats. We used parametric event-related electrical stimulation of the forepaw to activate the somatosensory cortex. By measuring simultaneously neural activity and vascular response we are able to evaluate the coupling between the electrical somatosensory evoked potentials (SEP) and hemodynamic (oxy- and deoxy-hemoglobin changes (HbO and HbR)) responses.

DOI system

- 18 laser diode sources (690 & 830 nm) frequency encoded
- 16 parallel APD detectors
- detector's output is digitized at ~40kHz on-line, individual source signals obtained off-line by infinite-impulse-response filters
- acquisition time per image (16x18 channels) can be as short as 10ms!!!
- 8 auxiliary channels record the stimulation trigger and physiological parameters such as blood pressure, pulse oximeter SpO_2 , heart rate, respiration and end tidal CO_2

measurement setup

EEG system

- 40 channel monopolar digital amplifier
- maximum sampling rate of 1000 Hz
- connects to laptop via USB
- reference and ground channels are part of the 40 channels; EEG, EMG and EOG can be recorded
- 8 bit stimulus and 4 bit response inputs
- event related potentials (SEP) can be averaged and processed in real-time
- acquired data are exported to Matlab for subsequent analysis



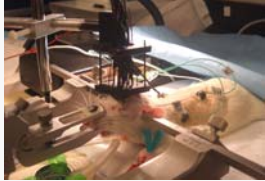
Techen Inc., Milford, MA, <http://www.nirsoptix.com>



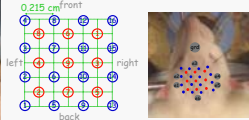
Neuroscan Labs, <http://www.neuro.com>

animal prep

- male Harlan Sprague-Dawley rats (weight 250-350g)
- anesthesia for surgery a gas mixture of ~80% air, ~20% oxygen, and 1-3% isoflurane administered via face mask
- tracheotomy and cannulation of the femoral artery and vein
- ventilation parameters are adjusted to maintain $PaCO_2$ between 35 and 45 mmHg, PaO_2 between 140 and 180 mmHg, and pH between 7.35 and 7.45
- after surgery isoflurane is discontinued; anesthesia is maintained with a continuous intravenous infusion of alpha-chloralose at 40 mg/kg/hr
- heating blanket circulating warm water maintains core temperature of 37-38°C
- stimulation experiments are delayed by at least 1 hr to allow the anesthetic transition



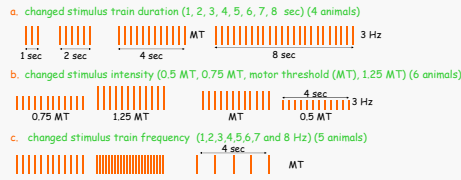
probe geometry



● sources ○ detectors * electrodes

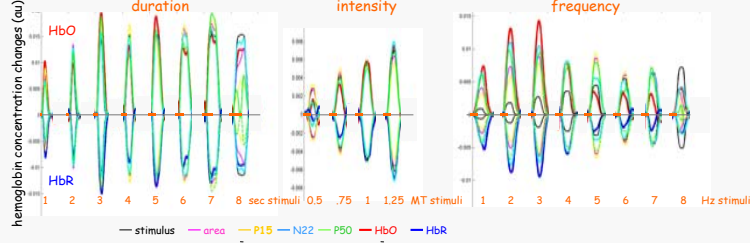
experimental protocols

- left and right electrical forepaw stimulation
- 200 ms, 0.2 mA electrical stimuli delivered in trains
- 12.6-min runs on each paw alternatively
- 4 conditions per run randomized in sequence
- delay between trains (average 15A 12s)
- 3 different paradigms in 3 groups of animals:



results

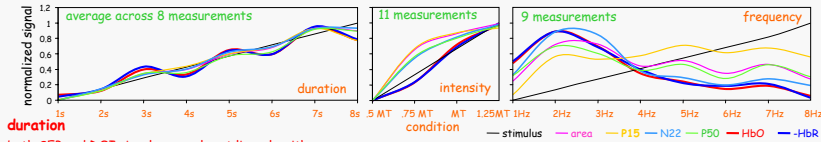
temporal traces of the averaged hemodynamic response on 3 individual animals compared with predicted responses assuming linear relation with either stimulus pulses or SEP signals



red and blue lines = DOI response for each stimulus condition
black line = predicted DOI response assuming linear relation with individual stimulus pulses (stimulation amplitude used for the stimulus pulses)
other colors lines = predicted DOI response assuming linear relation with SEP:
magenta=SEP area; yellow=P15; light blue=N22; green=P50

linearity/non-linearity of the hemodynamic response

normalized (between 0 and 1) DOI and SEP responses averaged across animals

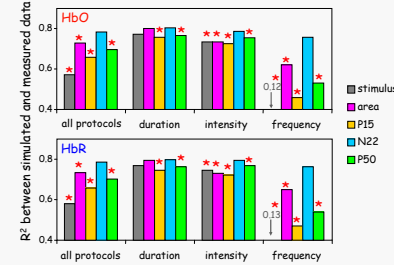


both SEP and DOI signals grow almost linearly with stimulus train duration ⇒ strong correlation between SEP and DOI
the oscillations on the curves are due to the fact that we apply the 1,3,5,7 sec and 2,4,6,8 sec stimuli in different runs, alternately.

intensity
SEP response saturates near MT
DOI response is very small for low stimulus intensities, increases rapidly around MT and starts to saturate for higher intensities
predicting HbR and HbO responses from SEP using a linear model leads to overestimation at low stimulus intensities and underestimation at high stimulus intensities
DOI measurements at low stimulus intensity may be insensitive because of low SNR, DOI measurements at high stimulus intensity may be corrupted by systemic hemoglobin responses
SEP and DOI uncoupling may also be due to a regulatory inhibition signal that subtracts in the EEG and adds in the hemodynamic response

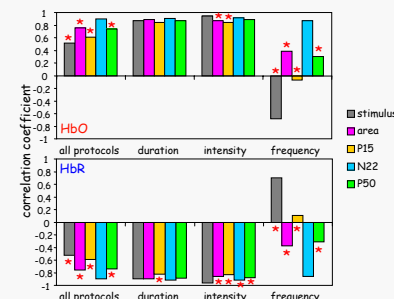
frequency
both DOI and SEP peak between 2 and 3 Hz and decrease afterward (apart for P15)
stimulation pulse does a poor job of predicting hemodynamic in this case also here the oscillations are due to the fact we apply the 1,3,5,7 sec and 2,4,6,8 Hz stimuli in different runs, alternately
strong correlation between SEP and DOI

R^2 between simulated and measured hemoglobin response across animals for the three protocols



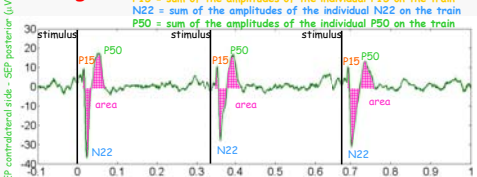
N22 produces the best estimate for both oxy- and deoxy-hemoglobin with the largest R^2 value between measured and simulated data in all protocols apart from the duration protocol, the R^2 for the N22 prediction is always statistically significant better than the R^2 using either stimulus pulses or other SEP parameters (* = statistically significant smaller R^2 than for N22 prediction, $P < 0.05$, paired t-test)

correlation coefficient between DOI and stimulus pulses or SEP signals across animals for the three protocols



N22 correlates best with oxy- and deoxy-hemoglobin in most cases no significant differences between parameters for the train duration protocol (HbO and HbR area = linear with train duration, HbO and HbR amplitude instead is not linear with train duration) for stimulus intensity protocol the stimulation pulses correlate better with the hemodynamic responses than the N22 SEP signal (* = statistically significant smaller correlation coefficient than the largest, $P < 0.05$, paired t-test)

SEP signals

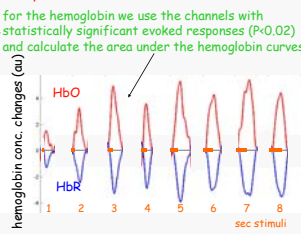


SEP on rats have been studied extensively
the first positive peak P12-14 originates on subcortical SI and thalamo cortical areas; it is known to be less sensitive to changes in stimulation frequency and intensity
N20-25 has localized cortical SI origin, while the late P35-P50 peak comes from a broader cortical area; both of these peaks decrease in amplitude with stimulation frequency and show habituation for high stimuli intensity and multiple run repetitions

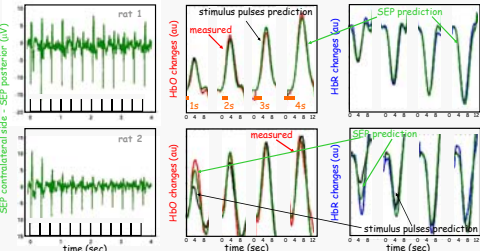
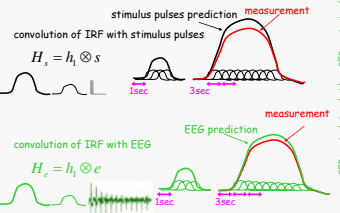
data analysis

DOI signals

- we want to test:
- whether the hemodynamic response is better predicted by a fixed input (stimulus pulses) or by the SEP neuronal input when using a linear model
 - to which SEP feature the DOI signal better correlates
 - linearity and non-linearity of the hemodynamic and SEP responses



predicting hemodynamic with SEP



in rat 1 the SEP response is constant during the train, the amplitude of the hemoglobin response (both HbO and HbR) increase linearly with stimulus duration ⇒ the stimulus pulses prediction works well; the same is true for the SEP prediction

in rat 2 the SEP response decreases in the train, the amplitude of the hemoglobin response doesn't increase with stimulus duration ⇒ the stimulus pulses prediction doesn't work well; prediction based on the EEG signal works better

summary

- the hemodynamic prediction using the N22 SEP signal results in a significantly higher R^2 value than using other SEP features or the stimulus pulses
- hemodynamic evoked response is not linear with respect to stimulation intensity and frequency, and correlates better with N22 SEP than with the other SEP features or with the stimulus pulses
- the stronger coupling of the hemoglobin response with N22 rather than P12 or P50 is expected, since N22 originates in SI cortical area
- neuronal habituation explains variability in the optical response
- these non-invasive measurements in rats will be translated directly to human measurements for testing neurovascular hypotheses in humans

acknowledgments

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