Effect of anesthesia on neurovascular coupling

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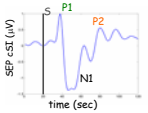
Background



In response to somatosensory stimulation, thalamic afferent activity in layer IV generates the first SEP component P1. This is followed by secondary activity in superficial layers (N1), and later by cortico-cortical interactions (P2 and N2).

The hemodynamic response following stimulation has been historically attributed to the initial neuronal activity in layer IV (P1). In our recent work (Franceschini et al., *Neuroimage*, 2008) we found N1 and P2 as better predictors of hemodynamic response than P1. Using Alpha-Chloralose as the anesthetic and a variety of parametric stimuli, we were not able to detect differences between N1 and P2. In the present work, modulating the electrical and hemodynamic responses with different anesthetics we are able to uncouple N1 and P2 and determine which SEP components are responsible for the hemodynamic response.

Experimental setup

We integrated scalp Electroencephalography (EEG) and Diffuse Optical Imaging (DOI) to investigate the neurovascular coupling in rats. We use Diffuse Correlation Spectroscopy (DCS) to monitor baseline CBF.

DOI system (HbO, HbR)

- ✓ 18 laser diode sources (690 & 830 nm) frequency encoded
- ✓ 16 parallel APD detectors
- ✓ image acquisition rate 10Hz
- ✓ off-line Matlab data analysis
- ✓ auxiliary channels record the stimulation trigger and physiological parameters

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

EEG system (SEP)

- ✓ 40-channel monopolar digital amplifier
- ✓ sampling rate 1000 Hz
- ✓ 8-bit stimulus input
- ✓ off-line Matlab data analysis

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

DCS system (CBF)

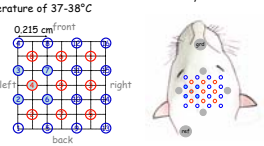
- ✓ 1 solid-state long coherence length laser @785 nm
- ✓ 4 photon-counting avalanche photodiodes
- ✓ intensity autocorrelation function computed by a digital correlator
- ✓ data fitted off-line to a correlation diffusion model to obtain blood velocity

Instrument replica of: T. Durduran, & A. G. Yodh, Opt Lett, 2004

Animal prep

- ✓ Male Harlan Sprague-Dawley rats (weight 309 ±16g)
- ✓ Anesthesia for surgery: gas mixture of 80% air & 20% O_2, and 1-3% isoflurane administered via face mask
- ✓ Tracheotomy for mechanical ventilation and cannulation of the femoral artery and vein
- ✓ Heating blanket maintains core temperature of 37-38°C

probe geometry



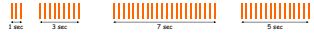
Measurement protocol

⇨ After surgery Isoflurane is discontinued, and anesthesia maintained with either:

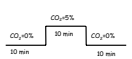
- Alpha-Chloralose
- Pentobarbital
- Ketamine-Xylazine
- Isoflurane
- Propofol

⇨ After anesthetic transition, electrical forepaw stimulation experiments are performed:

- 5 runs on left and right paw performed alternatively
- 200 ms, >0.2 mA (motor threshold, MT) electrical stimuli delivered in trains @ 3 Hz
- Changed train duration: 1, 3, 5, 7, 9, 11, 13 sec (7 conditions)
- Event-related presentation with average ISI of 12s



⇨ At the end of the functional study, we performed a hypercapnia cycle to measure vascular reactivity



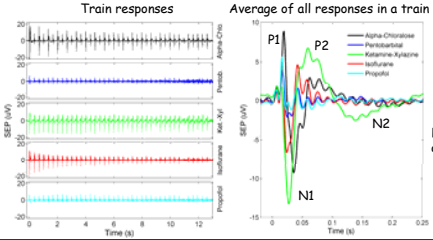
Anesthesia, Physiology & CBF

	Alpha-Chloralose	Pentobarbital	Ketamine-Xylazine	Isoflurane	Propofol
# of rats discarded	0	1	2	0	2
# of rats included	6	6	5	5	6
# of sides excluded	1	3	1	0	2
Anesthesia type	i.v.	i.p.	i.v.	gas %	i.v.
Loading dose	50 mg/Kg	50 mg/Kg	100 mg/Kg	1.24±0.02%	10 mg/Kg
Maintaining dose	40 mg/Kg/h	25 mg/Kg	400 mg/Kg/h	1.24±0.02%	50 mg/Kg/h
Weight (g)	309±51	289±35	320±18	290±20	317±27
pH	7.32±0.05	7.36±0.04	7.37±0.07	7.43±0.04	7.36±0.04
PCO_2 (mmHg)	43±1	35±6	37±8	34±5	40±7
PO_2 (mmHg)	184±16	181±31	163±20	191±17	173±20
Resp. Rate (br./min)	43.2±1.4	41.0±0.4	39.9±0.4	42.5±2.7	40.3±0.5
Heart Rate (Hz)	5.8±0.3	6.4±0.4	4.6±0.1	6.2±0.3	5.7±0.1
MBP (mmHg)	98±7	120±7	110±7	99±7	125±5
BF index (au)	1.9±0.3	1.1±0.1	0.7±0.1	2.4±.2	1.9±04
ΔBF index 5% CO_2 (%)	14.5	25.1	8.4	33.2	9.8
ΔBF/ΔPCO$_2$ (%/mmHg)	1.0	2.7	0.7	6.2	0.8

Animals mechanically ventilated 20% O_2 80% air, SaO_2 maintained between 98-100%

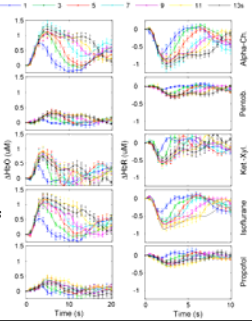
Methods

SEP responses under different anesthetics



Hemoglobin response for different stimulus durations

For each anesthetic, averages across all animals and all runs

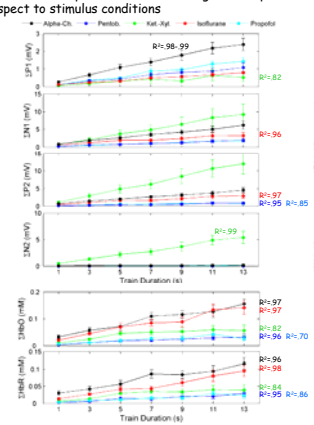


SEP and Hb responses are not normalized

Results

Linearity / non-linearity of the responses with stimulus conditions

We used the integrated responses to assess the linearity of the SEP components and the hemoglobin response with respect to stimulus conditions



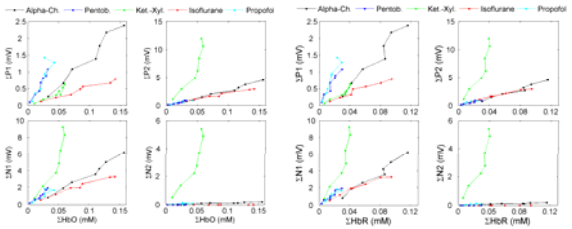
Error bars = standard errors
Missing R^2 are 0.98-0.99

- In most cases SEP responses are linear (R^2 0.95-0.99) with stimulus duration. Some nonlinearity found with ketamine-Xylazine and Propofol.
- Hemoglobin responses are also linear (R^2 0.95-0.98) with stimulus durations except with Ketamine-Xylazine and Propofol

ΣP1, ΣN1, ΣP2, and ΣN2 = integrated SEP responses = for each component we calculated the sums of the areas within a train

ΣHbO & ΣHbR = integrated hemoglobin responses = we calculated the area under the hemoglobin curves

Scatter plots of integrated HbO and HbR vs. integrated SEP responses



- The hemodynamic responses
  - correlate well with P2 across all anesthetics, except Ketamine-Xylazine.
  - do not correlate with P1
- Ketamine-Xylazine is the only anesthetic with pronounced N2
- Interestingly Ketamine-Xylazine is the only anesthetic we used which is not GABAergic but act on NMDA receptors.

Linear regression analysis (model testing) →

Conclusion

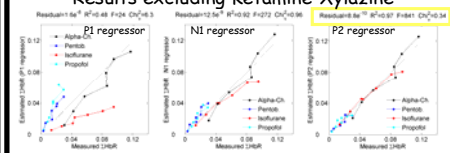
- ✓ With this experiment, we were able to disentangle the role of N1 and P2 on the hemodynamic response
- ✓ We demonstrated that the hemodynamic response is driven by the late cortico-cortical transmissions (P2-N2)
- ✓ The negative SEP components relate to vasoconstriction
- ✓ The above results imply that the hemodynamic response is not driven by MUA or initial LFP
- ✓ Baseline cerebral blood flow affects minimally neurovascular coupling
- ✓ Neurovascular coupling seems to be the same for these different anesthetics

SEP prediction of hemodynamic responses

Only results for HbR are shown results for HbO are similar.

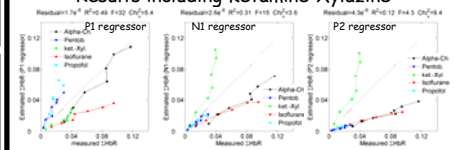
HbR predictions using 1 SEP component

Results excluding Ketamine-Xylazine



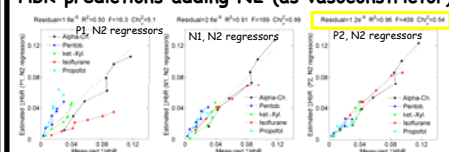
P2 prediction have significantly larger R^2 and F-score than P1 and N1

Results including Ketamine-Xylazine



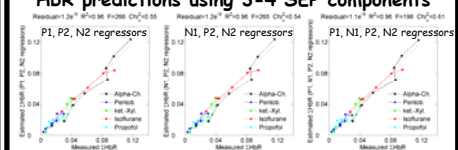
All predictions are significantly worse than without Ketamine-Xylazine

HbR predictions adding N2 (as vasoconstrictor)



P2-N2 prediction have significantly larger R^2 and F-score than P1-N2 and N1-N2

HbR predictions using 3-4 SEP components



Adding components does not increase R^2 and reduces F-scores

F-scores and R^2 for HbO and HbR predictions

	F-scores HbO		F-scores HbR		R^2 HbO		R^2 HbR	
	No Ket.-Xyl.	All	No Ket.-Xyl.	All	No Ket.-Xyl.	All	No Ket.-Xyl.	All
P1	16	21	24	32	0.38	0.39	0.48	0.49
N1	150	14	272	15	0.85	0.30	0.91	0.31
P2	**465**	5	**841**	4	**0.95**	0.12	**0.97**	0.12
P1-N1	234	17	314	24	0.95	0.52	0.96	0.60
P1-P2	332	15	421	21	0.96	0.48	0.97	0.57
P1-N2	8	11	12	16	0.39	0.40	0.48	0.50
N1-P2	315	34	416	52	0.96	0.68	0.97	0.77
N1-N2	117	99	161	170	0.90	0.86	0.93	0.91
P2-N2	424	**347**	433	**409**	**0.97**	**0.96**	0.97	**0.96**
P1-N1-P2	212	41	270	56	0.96	0.80	0.97	0.84
P1-N1-N2	153	155	203	189	0.95	0.94	0.96	0.95
P1-P2-N2	276	250	276	267	0.97	0.96	0.97	0.96
N1-P2-N2	292	263	276	265	0.97	0.96	0.97	0.96
P1-N1-P2-N2	221	191	198	196	0.97	0.96	0.97	0.96

Yellow cells: Best predictor of Hemodynamic response using least number of SEP components

Acknowledgments

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