Biophysical Models of Neuronal Dynamics during General Anesthesia and Burst Suppression

Anesthesia and Sleep Disorders Workshop

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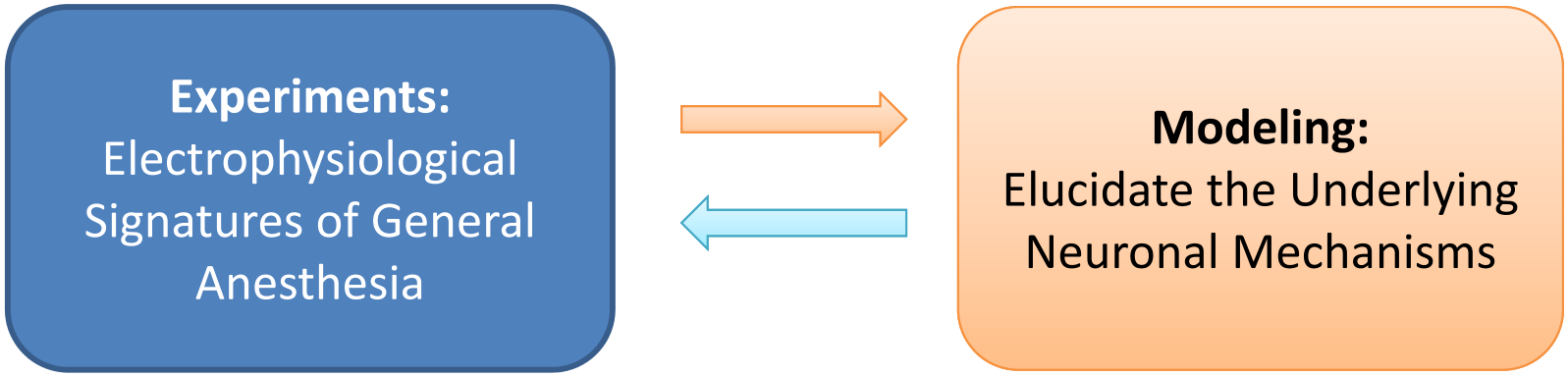
Introduction

- Understanding general anesthesia is interesting, important and of immediate medical relevance.

- The study of general anesthesia provides insights into the dynamics of the comatose brain.



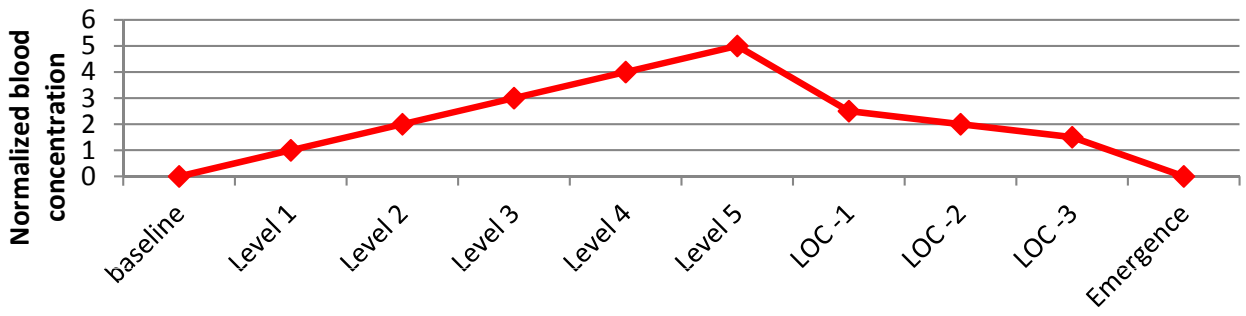
Outline

- **Part 1**: Frontal alpha rhythm associated with loss of consciousness under propofol-anesthesia

- **Part 2:** Neuronal and metabolic dynamics of burst suppression

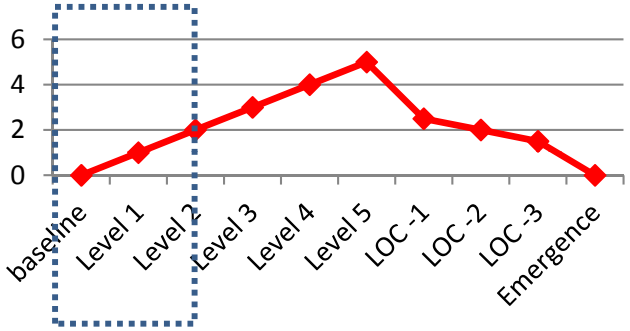
EEG Study of Propofol Anesthesia

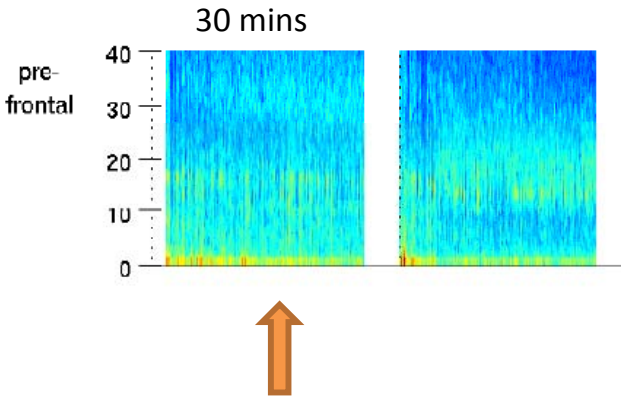
- **Recap from yesterday:** Spectral signatures associated with loss of consciousness during propofol general anesthesia



- EEG recorded during gradual propofol infusion
- Subjects are performing an auditory task

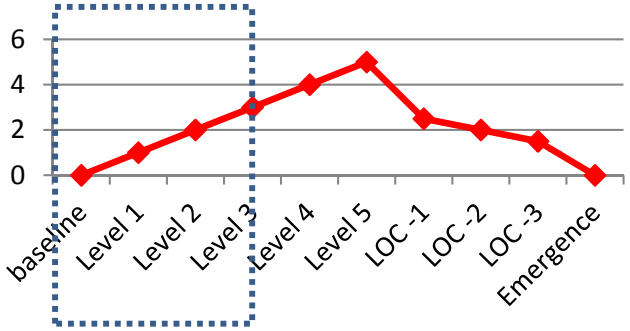
Dominant frequency bands associated with experiment: Baseline

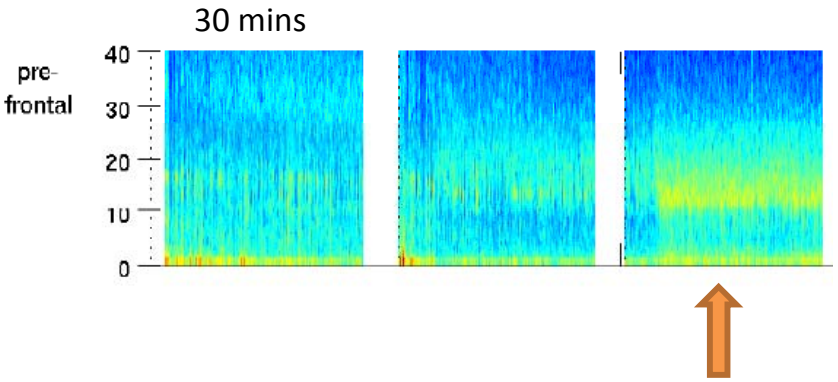




No dominant frequency bands

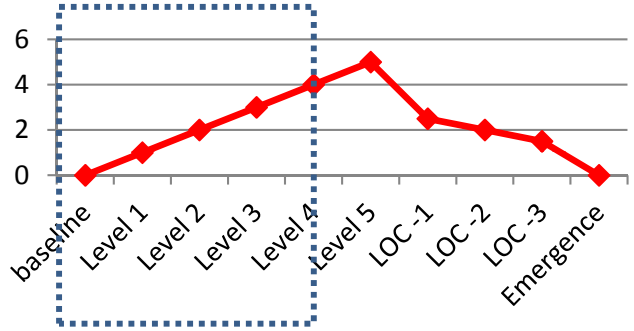
Dominant frequency bands associated with experiment: Early LOC

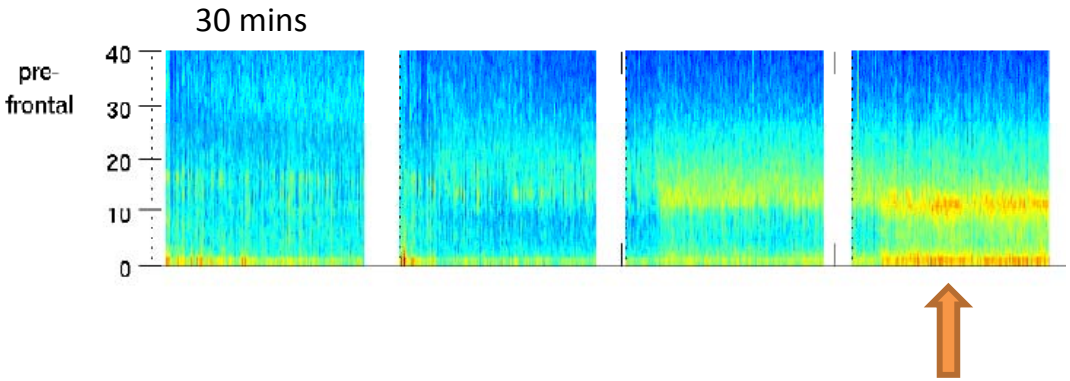




Diffuse activity from 15-20 Hz

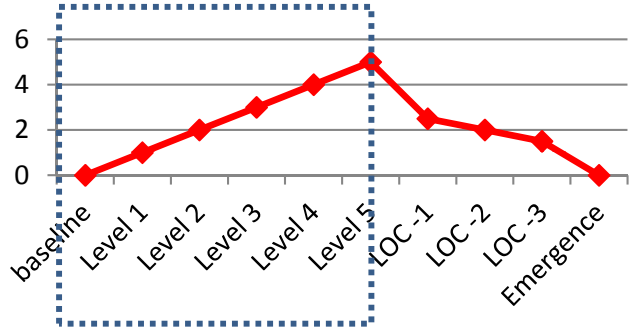
Dominant frequency bands associated with experiment: LOC

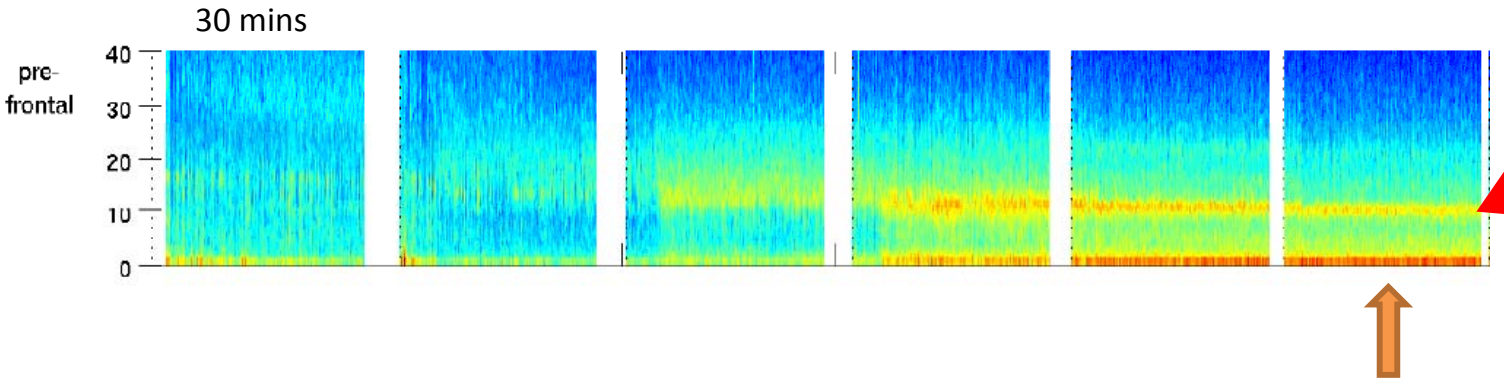




Consolidation of power into “alpha”

Dominant frequency bands associated with experiment: Deepest LOC

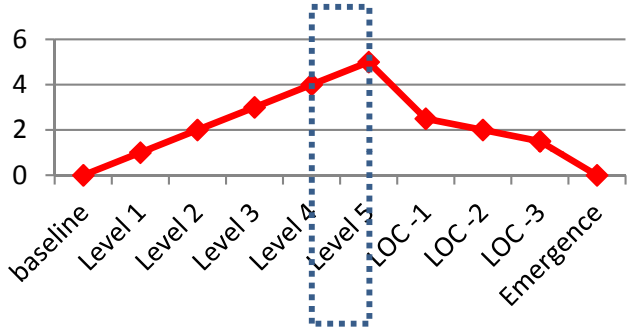


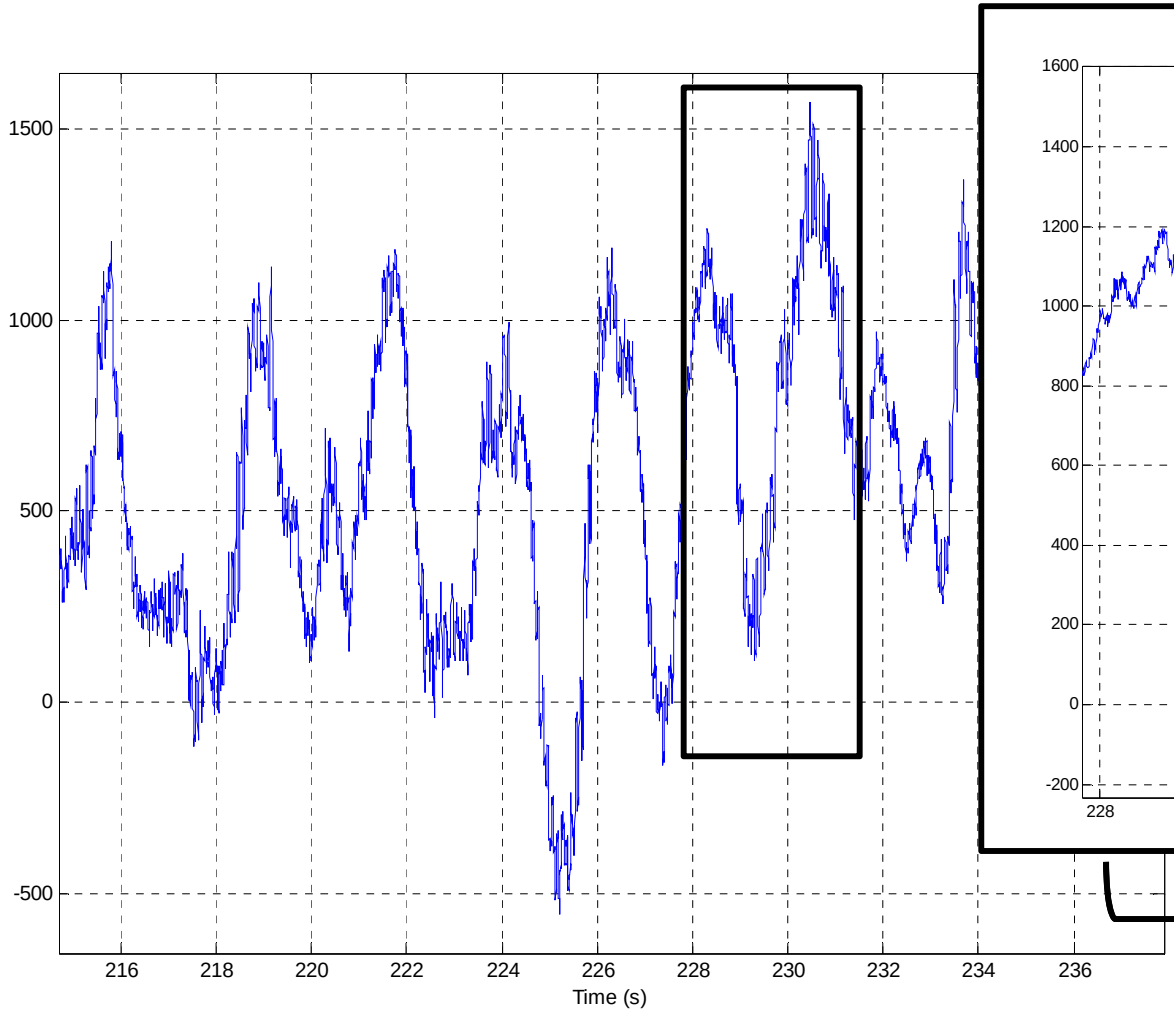


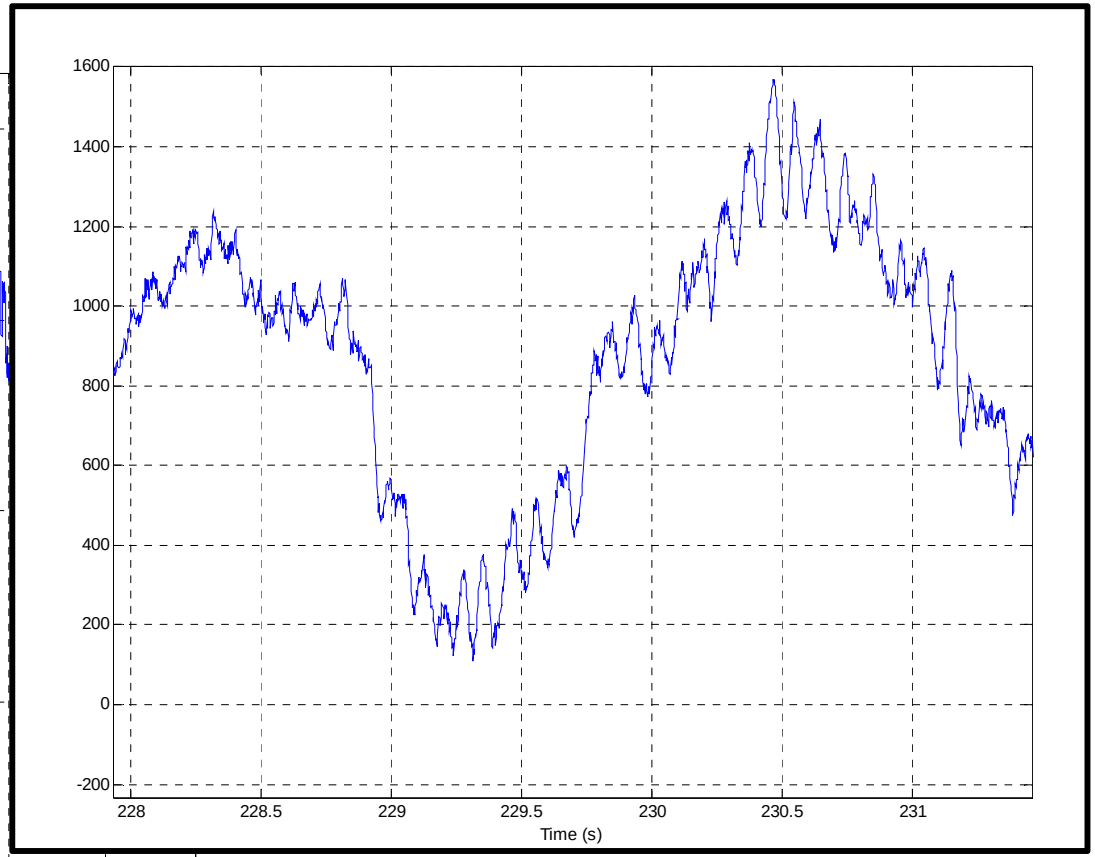
~11 Hz

Well-defined “alpha” oscillation with simultaneous <1Hz activity

Waveform morphology

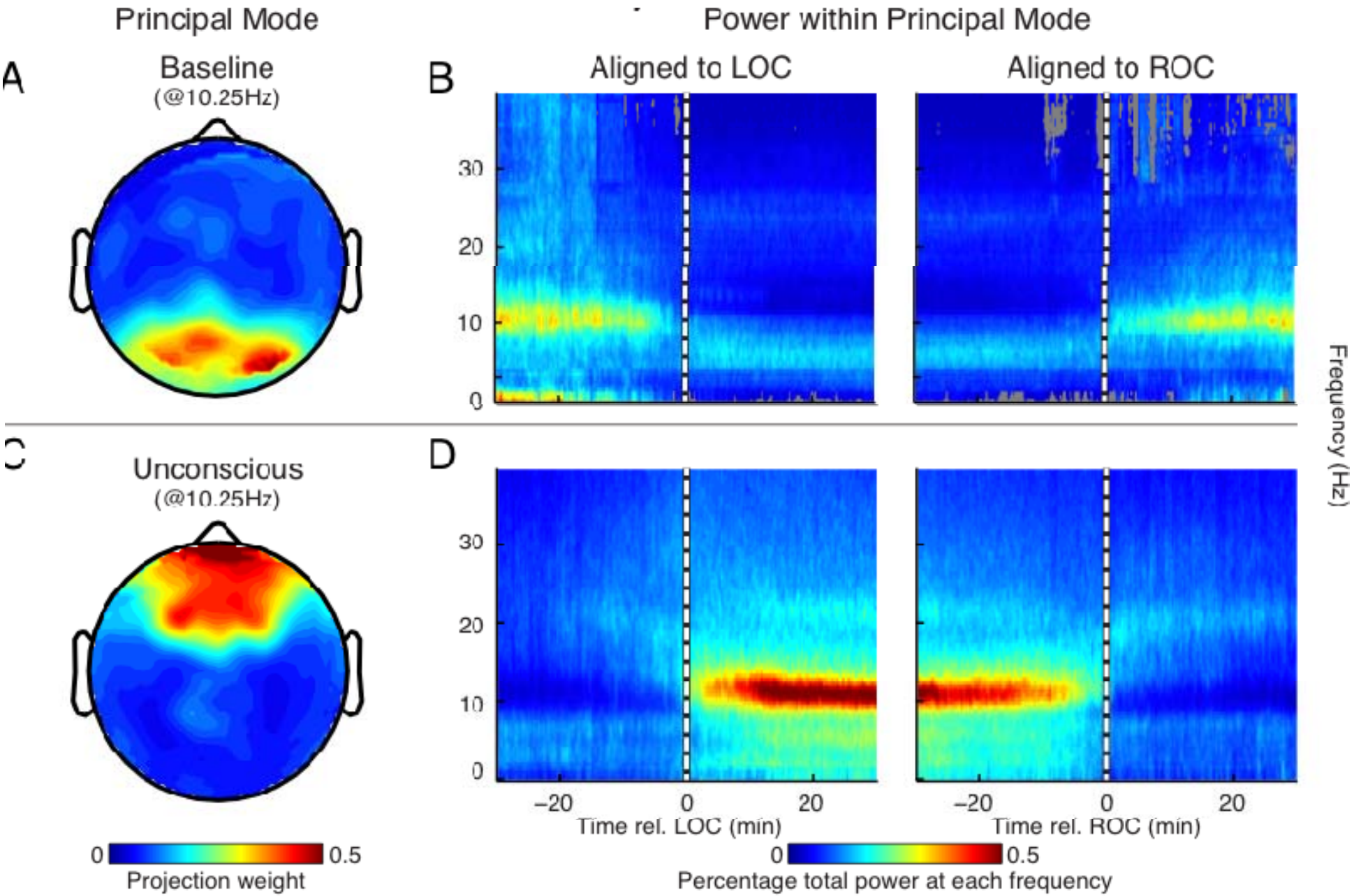






3 sec

Coherent Alpha Rhythms



Biophysical modeling: Network mechanisms

Previous modeling studies:

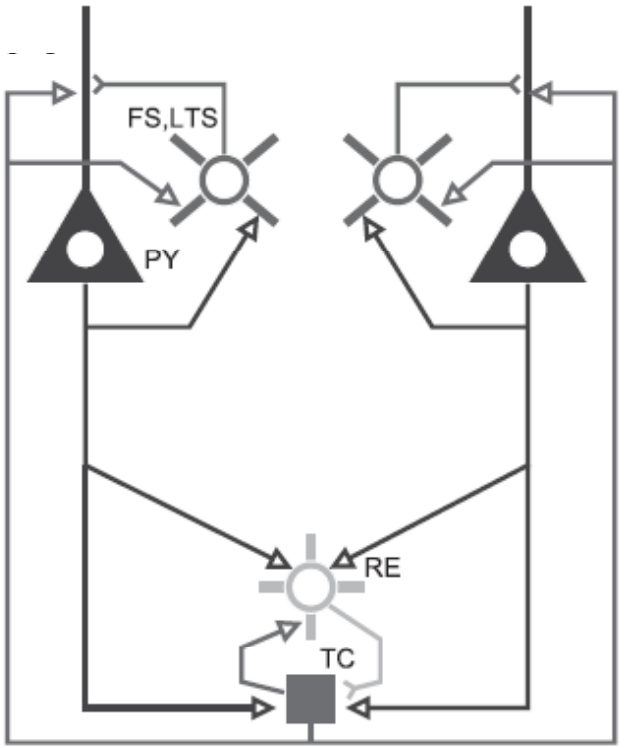
- Propofol and cortex
  - Low dose paradoxical excitation *(McCarthy, Kopell & Brown, 2009)*
- Thalamus & Alpha rhythms
  - Spindles: (*Destexhe & Sejnowski, 2001 ,Timofeev & Bazhenov , 2005)*

Investigate effects of propofol on thalamocortical networks:

- Perturb dynamics in a manner consistent with propofol; Investigate cortical coherence via thalamus

Network schematic and features

- Network structure schematic



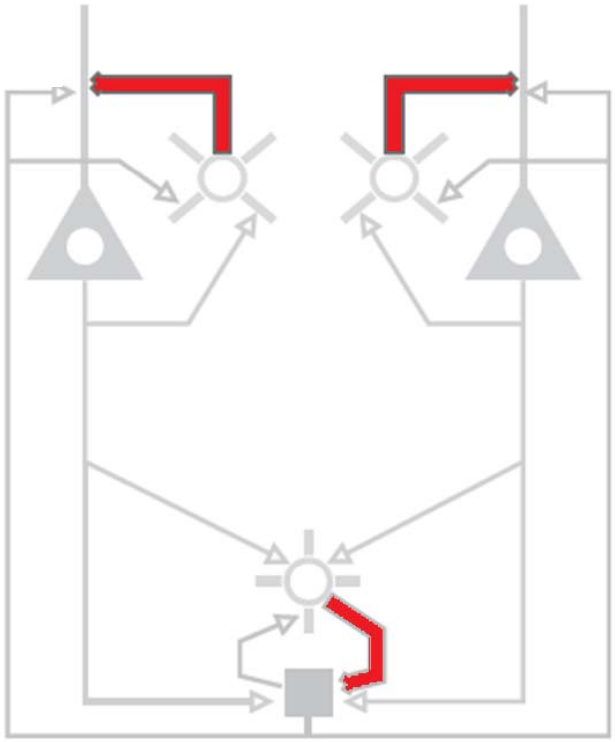
- Disparate cortical populations (Pyramidal cells, FS/LTS interneurons)
- Thalamic population (Thalamocortical relay cells, Reticular cells)

$$c_m \frac{dV}{dt} = -\sum I_{\text{memb}} - \sum I_{\text{syn}} + I_{\text{app}}$$

- *Perturb dynamics in a manner consistent with propofol*

Modeling the effects of propofol

- Propofol acts primarily through potentiation of the $GABA_A$ synaptic current



$$c_m \frac{dV}{dt} = -\sum I_{\text{memb}} - \sum I_{\text{syn}} + I_{\text{app}}$$

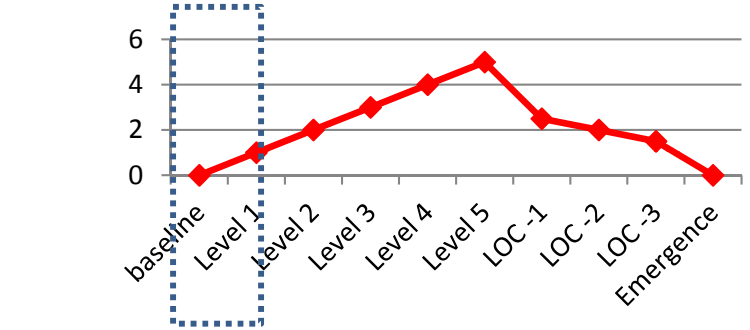
- Increase maximal conductance and decay-time

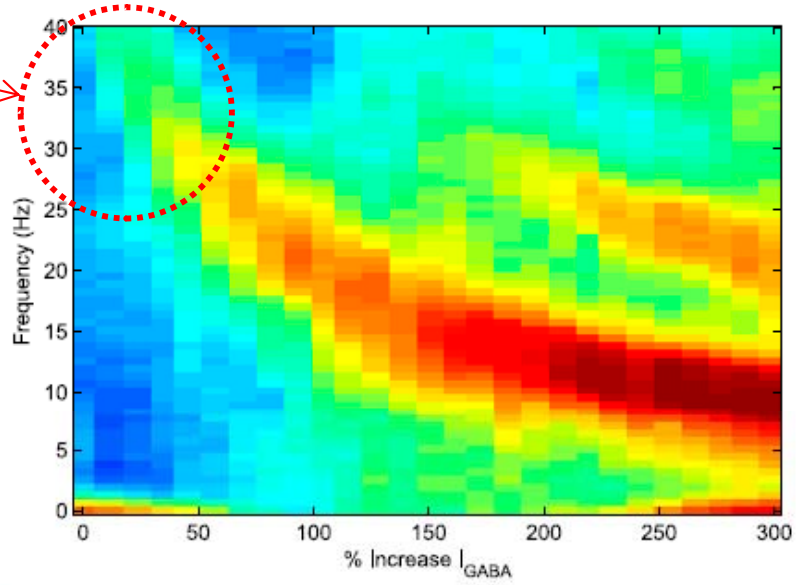
$$I_{\text{GABA}} = g_{\text{GABA}}\, x(V - E_{\text{GABA}})$$

$$\dot{x} = 2(1 + \tanh(V/4))(1 - x) - x/\tau_{GABA}$$

Simulation results

- Model produces weak gamma baseline

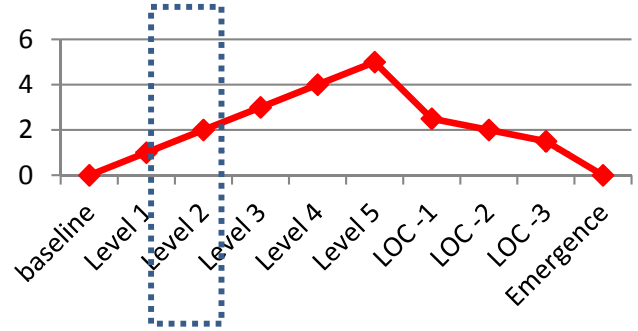


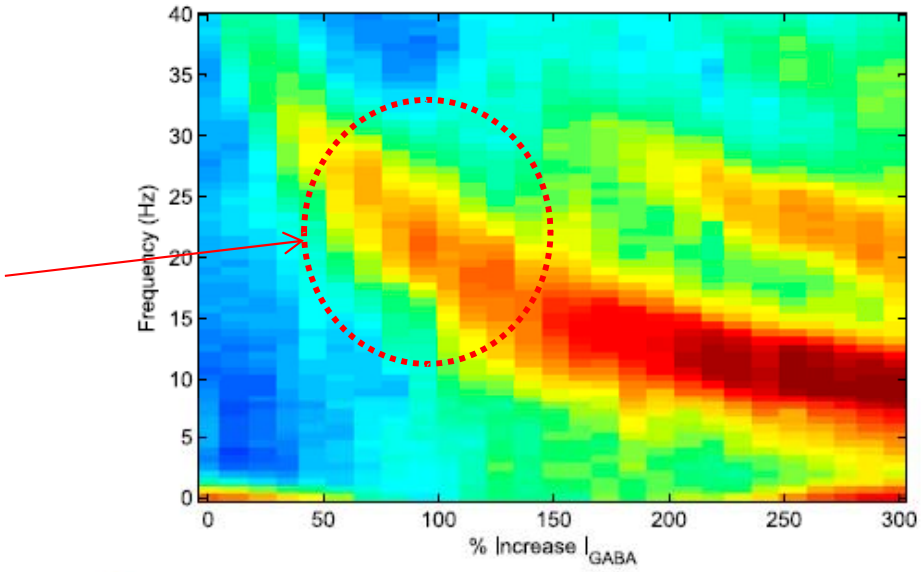


Drug effect

Simulation results

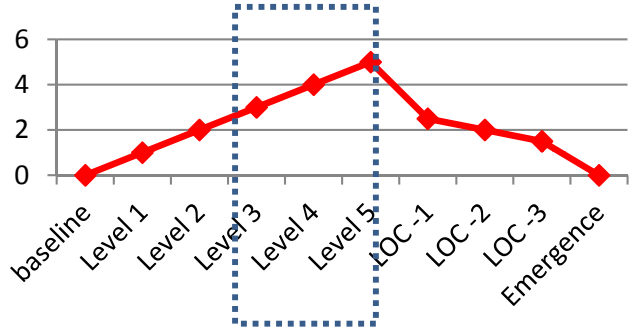
- Slowing of cortical rhythms as GABAa increases

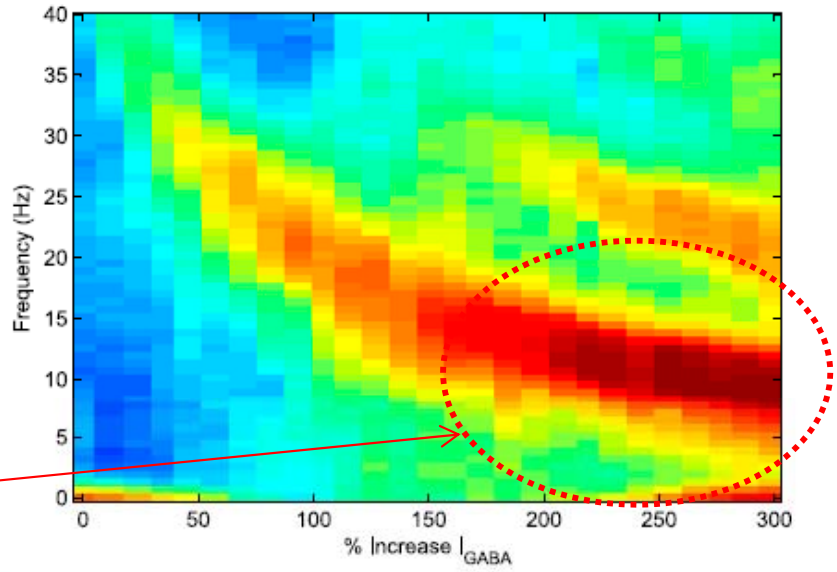




Drug effect

Simulation results

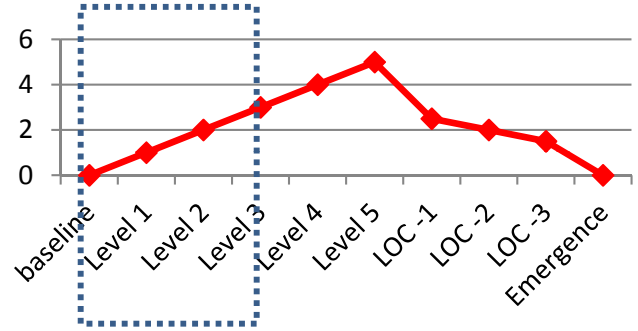


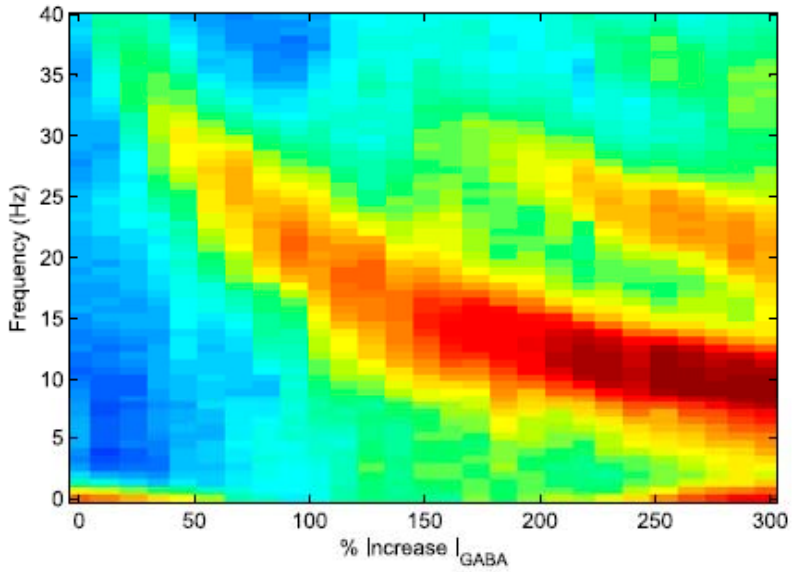


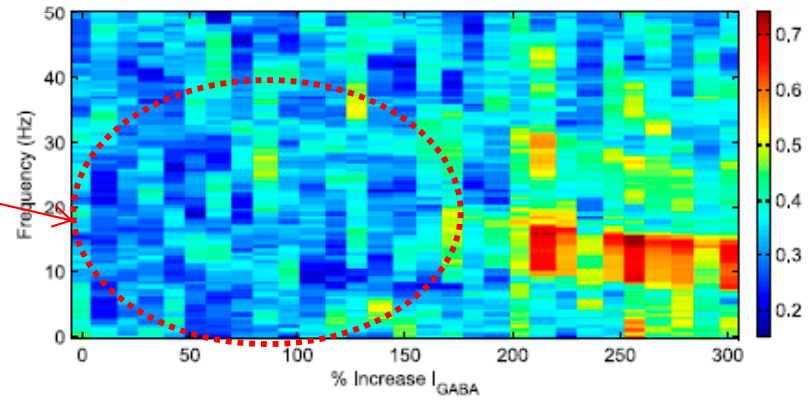
Drug effect

- Converges to alpha rhythm

Simulation results



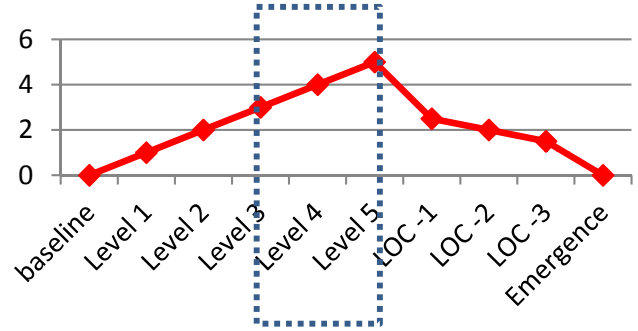


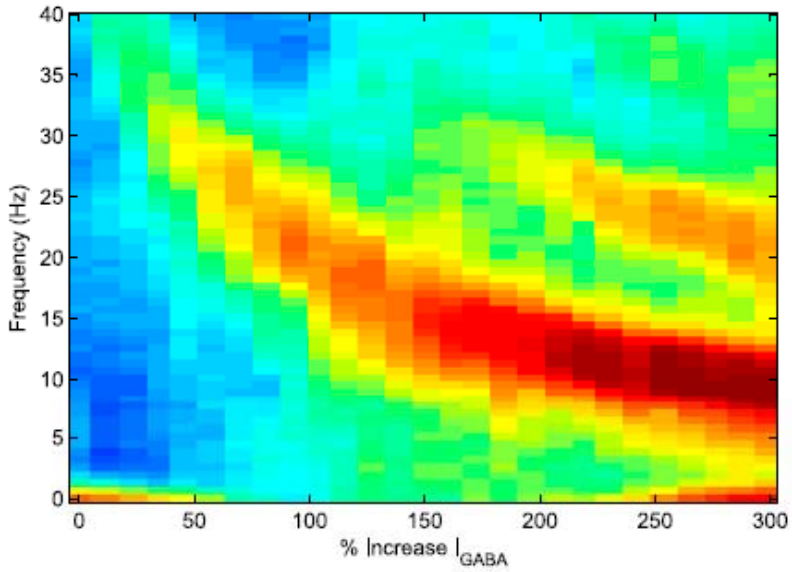


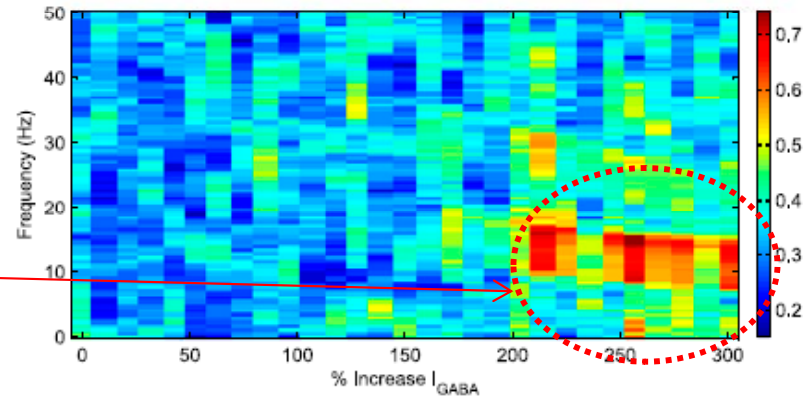
- No coherence at baseline and small dose levels

Drug effect

Simulation results



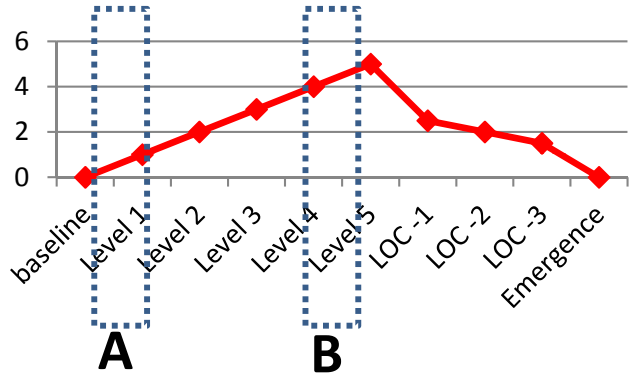


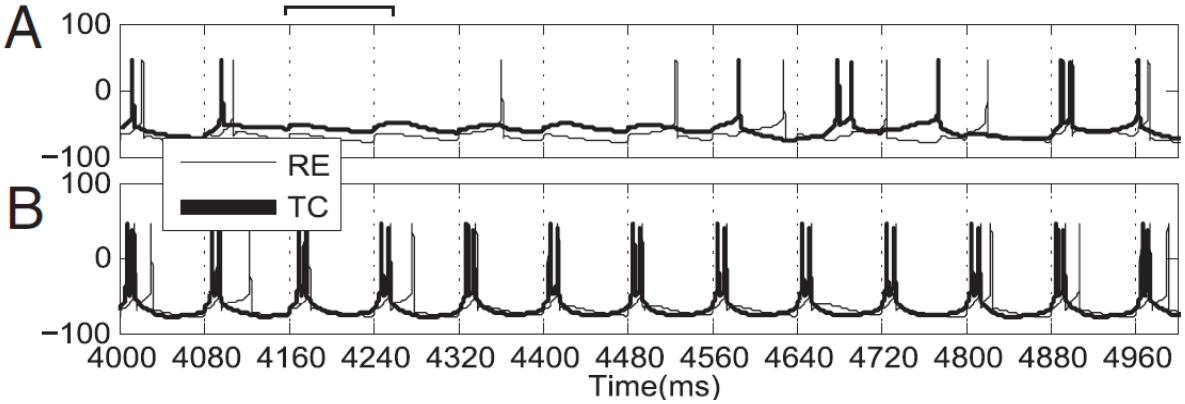


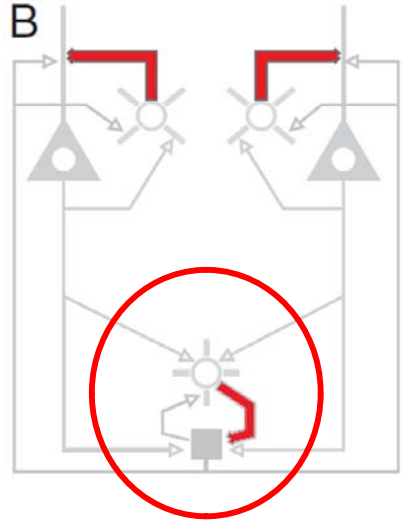
- At 3x baseline, coherence is exhibited between the cortical populations

Drug effect

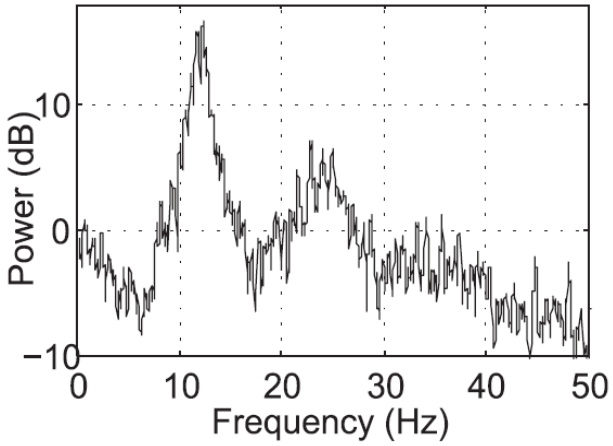
Network mechanisms for enhanced ‘alpha’ oscillation: Thalamic entrainment







Response to white excitation

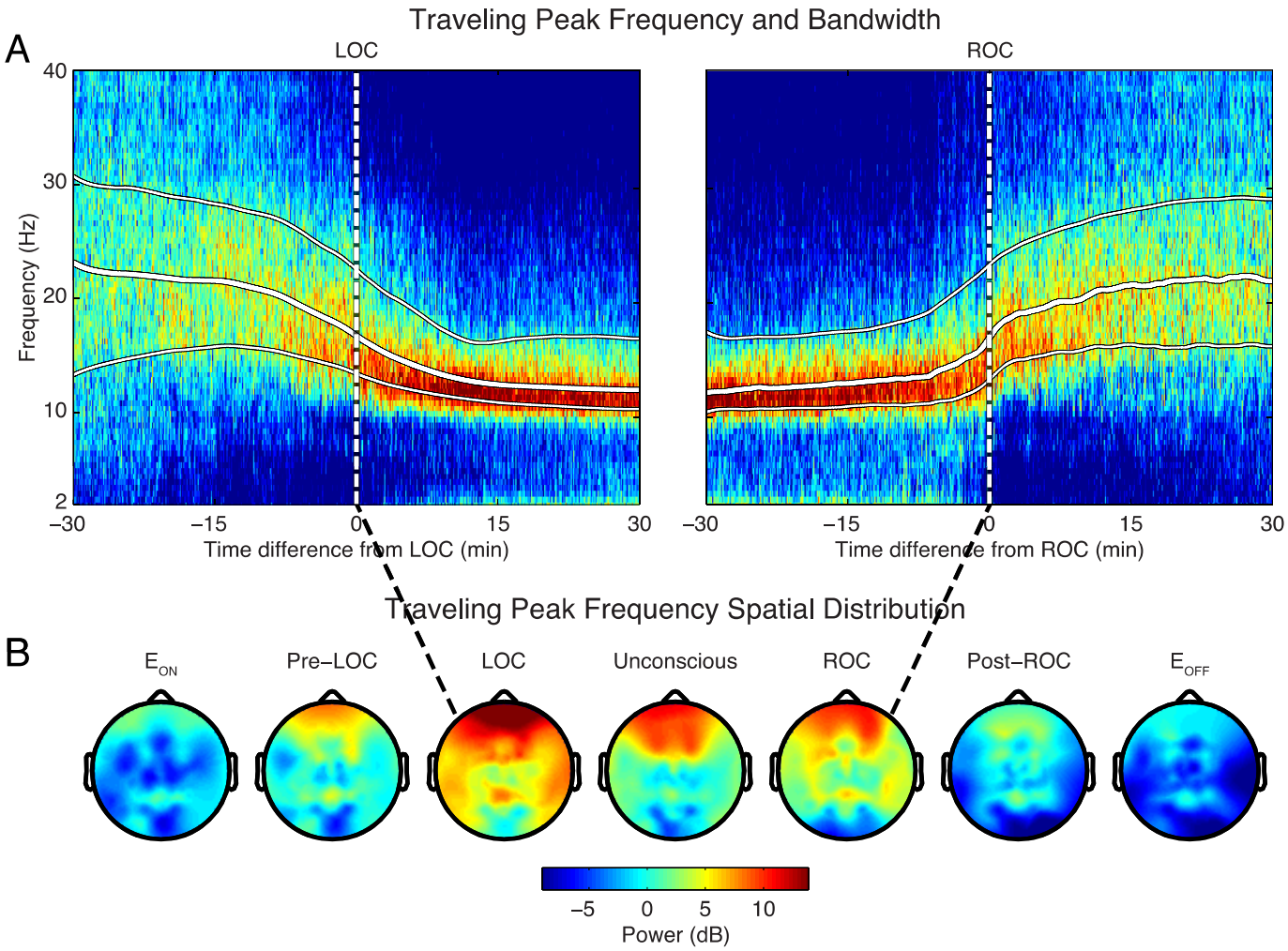


- TC cells on a more hyperpolarized background → propensity for alpha rebound spiking

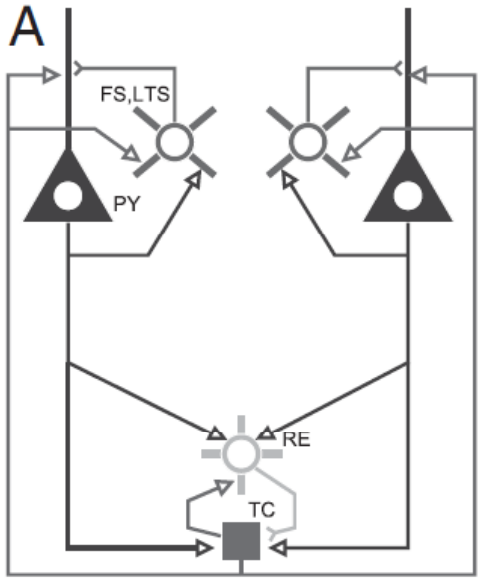
Traveling Peak

Continuous transformation in a *Traveling Peak*

Common frontal distribution



Summary and Interpretations



- A propofol-alpha rhythm…

1. Increased cortical inhibition causes a slowing of higher frequency rhythms

2. Increased thalamic inhibition causes persistent alpha-band oscillations

- Thalamic gate vs. thalamocortical dynamics
- Related to pathological states such as alpha coma

Outline

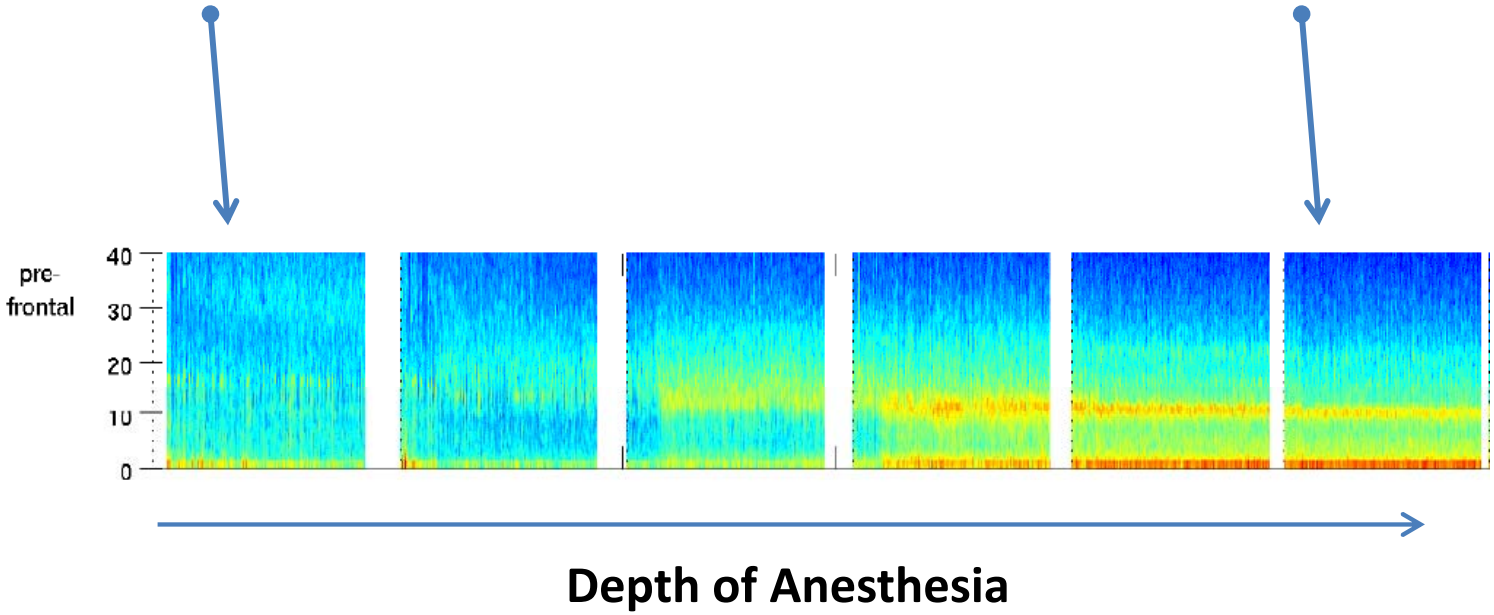
- **Part 1**: Frontal alpha rhythm associated with loss of consciousness under propofol-anesthesia

- **Part 2:** Neuronal and metabolic dynamics of burst suppression

What is burst suppression? : The anesthesia story (so far…)

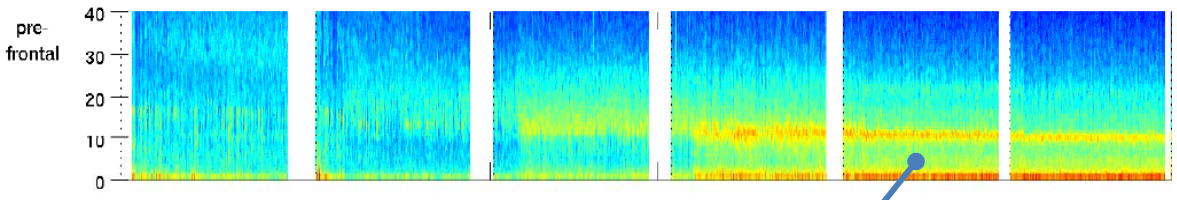
- Awake brain activity
  (No drug)

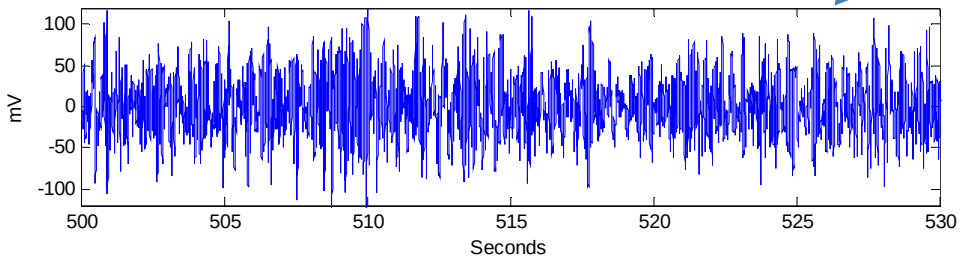
`Inactivated' alpha
(Surgical anesthesia)



What happens if we go deeper??

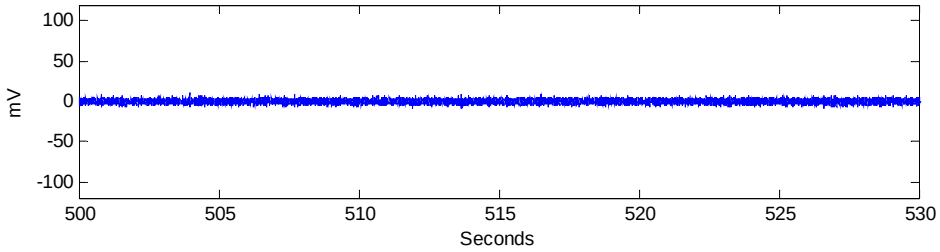
What is burst suppression? : The anesthesia story (so far…)



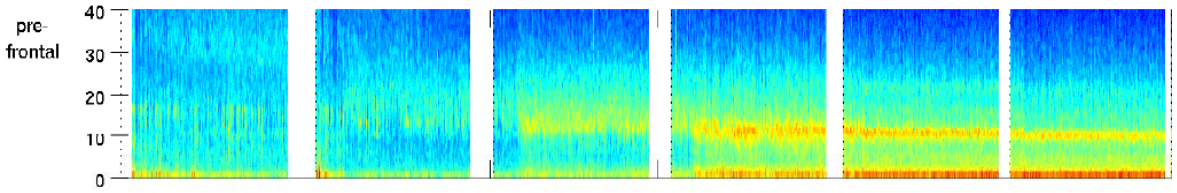


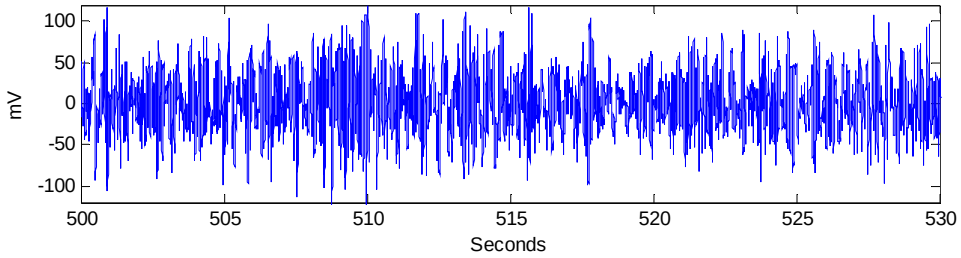
Deeper anesthesia

Isoelectric



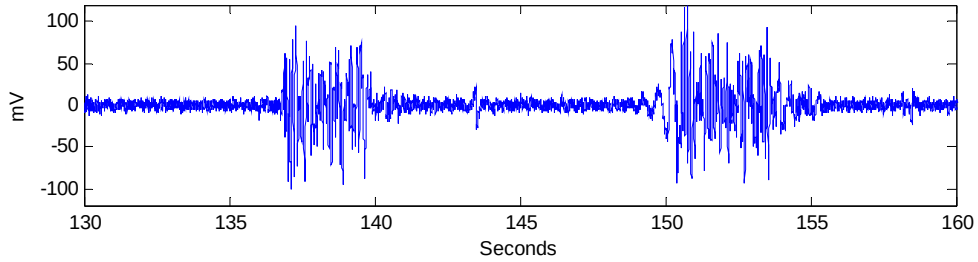
What is burst suppression? : The anesthesia story (deeper levels…)



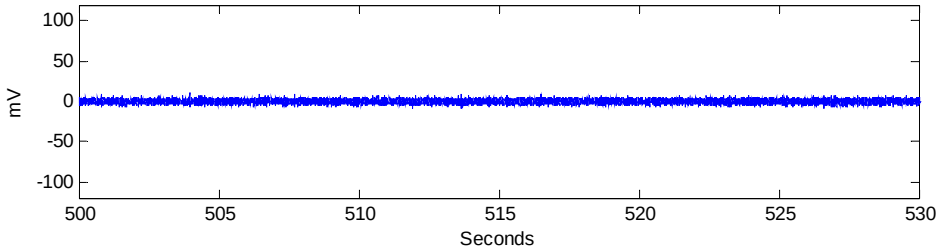


Burst suppression

Isoelectric



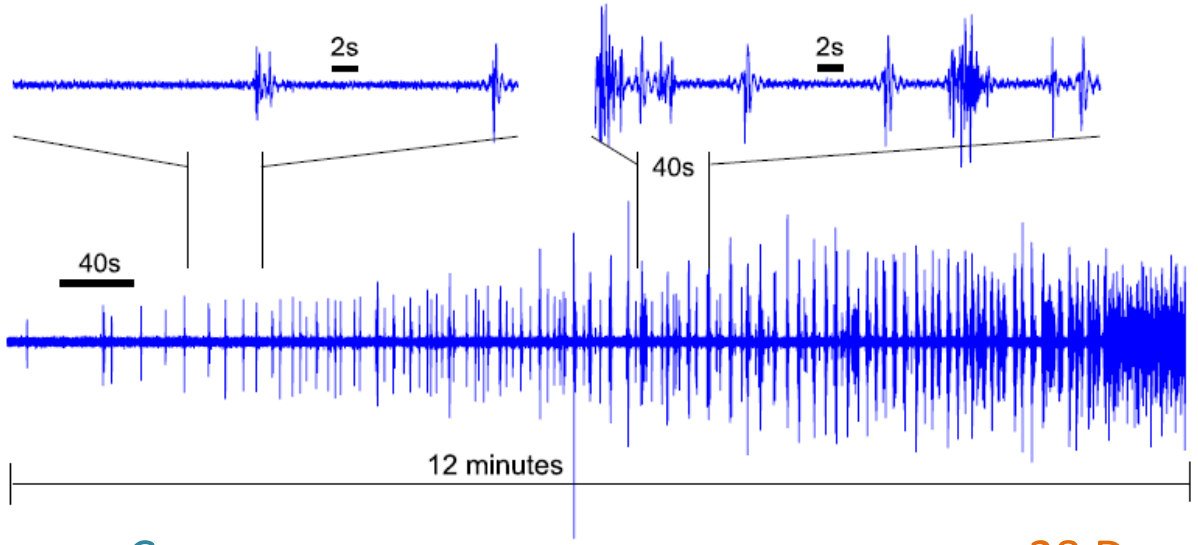
Alternating periods of activity (bursts) and quiescence (suppression)



Henry and Scoville, 1952
Steriade et. al. 1993

What is burst suppression? : More properties…

- Burst suppression is not strictly periodic and varies in propensity

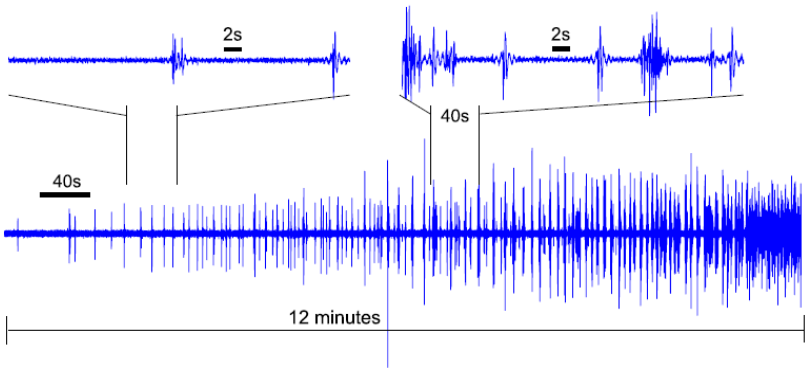


19 Degrees C

>28 Degrees C

- Burst suppression is not exclusive to general anesthesia.

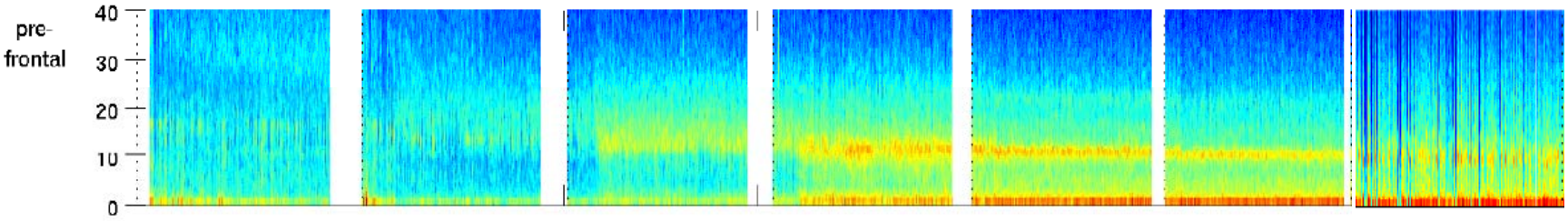
Conditions associated with burst suppression



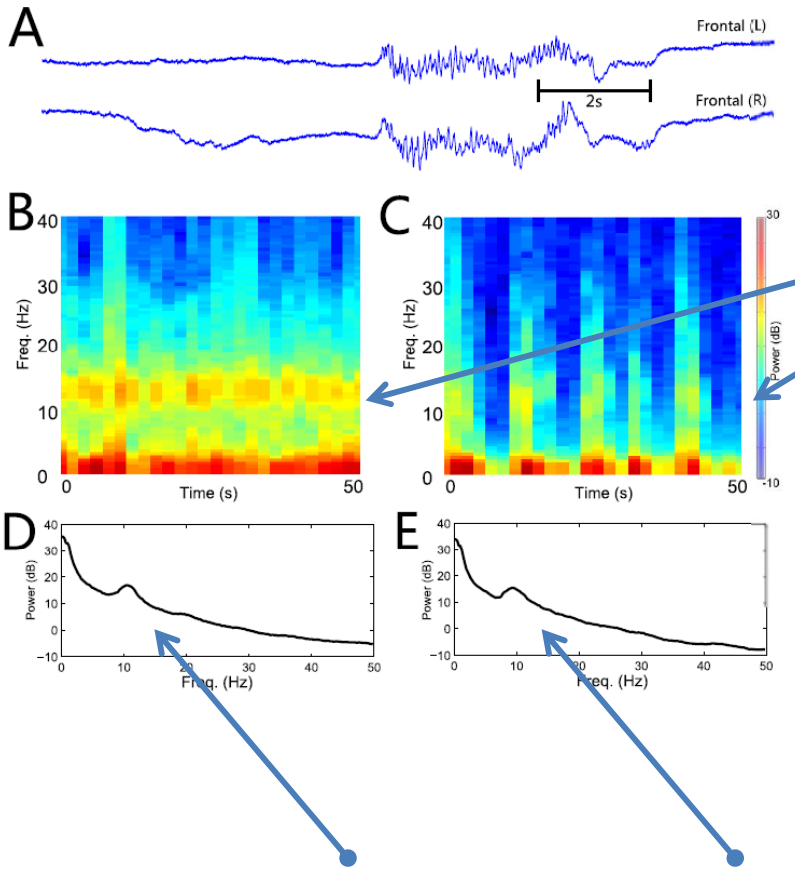
- Deep general anesthesia
- Hypothermia
- Hypoxic-ischemic events, Post-anoxic coma
- Infant encephalopathy

Multiple etiologies for a common phenomenon. Suggests a fundamental dynamic change.

Spectrum during burst suppression



Burst suppression: Alpha within bursts



The mechanisms of the alpha rhythm survive the onset of burst suppression

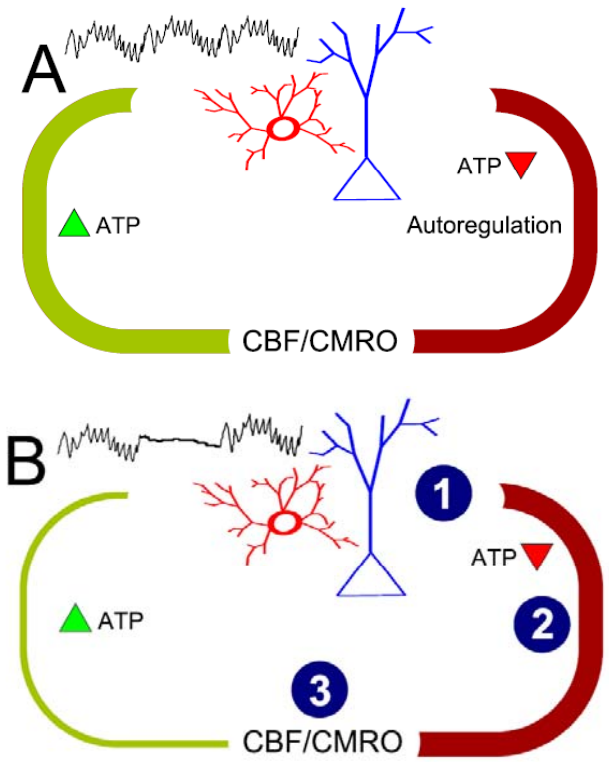
A link between burst-suppression etiologies

Deep general anesthesia 1 2

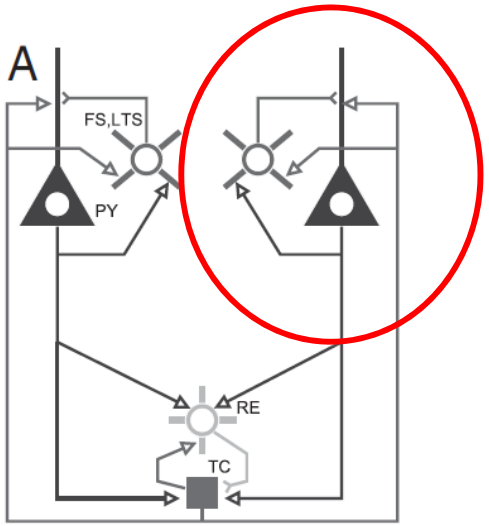
Hypothermia 3

Hypoxic-ischemic events, Post-anoxic coma 3

Infant encephalopathy 2 3



Model structure



- We consider the cortical component of our alpha model.
- Add the ATP-gated potassium current:

$$I_{K_{ATP}} = g_{K_{ATP}} z\,(v - E_K)\,.$$

$$z = \frac{1}{(1 + 10\,[ATP])}$$

$$[\dot{Na}] = F \cdot I_{Na} - 3K_m[Na]^3\,[ATP]$$
$$[\dot{ATP}] = J_{ATP}\,([ATP]_{\max} - [ATP]) - K_m[Na]^3\,[ATP]$$

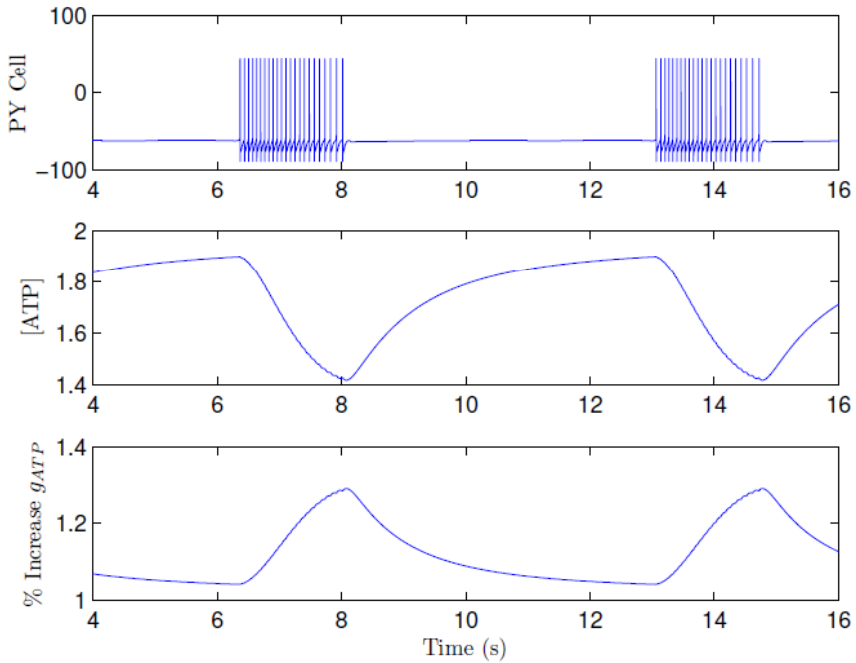
ATP dynamics in small network

- Sodium-ATP dynamics cause alternating periods of activity and quiescence

$$I_{K_{ATP}} = g_{K_{ATP}} z\,(v - E_K)\,.$$

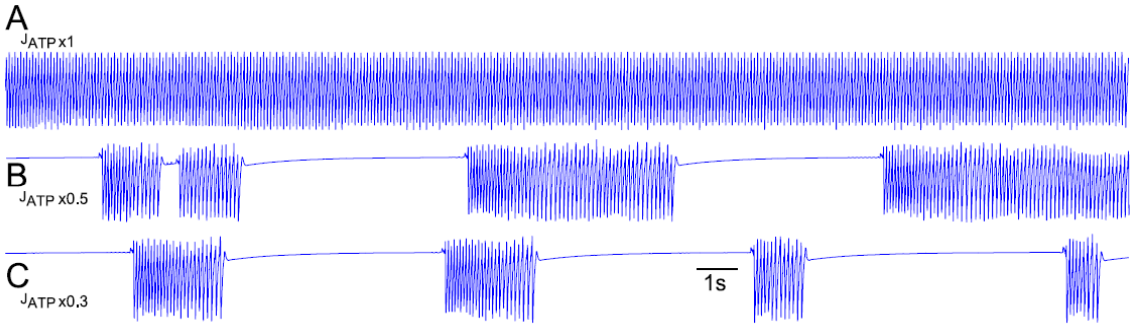
$$z = \frac{1}{(1 + 10\,[ATP])}$$

$$[\dot{Na}] = F \cdot I_{Na} - 3K_m[Na]^3\,[ATP]$$
$$[\dot{ATP}] = J_{ATP}\,([ATP]_{\max} - [ATP]) - K_m[Na]^3\,[ATP]$$



- The rate of ATP production dictates the ratio of quiescence to activity

- Alpha oscillatory dynamics survive



Consistency with previous studies

Kroeger & Amzica, J. Neurosci. 2007

Behavioral/Systems/Cognitive

Hypersensitivity of the Anesthesia-Induced Comatose Brain

Daniel Kroeger and Florin Amzica
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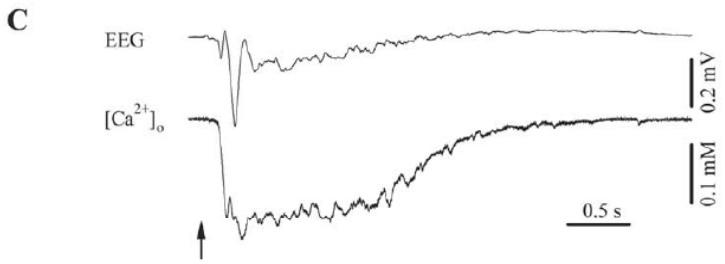


- Decreased sensitivity to external stimulation after the occurrence of a burst
- Bursts are correlated with fluctuations in calcium

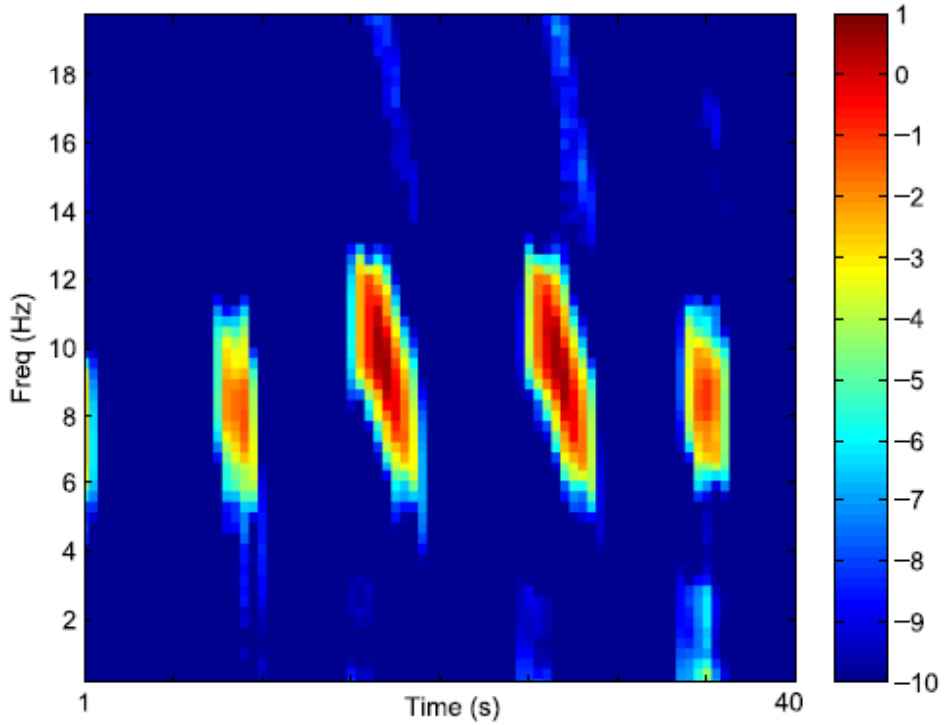
- Cardiac dynamics: ATP and oxidative stress leads to arrhythmias

- Our model is compatible and provides a unified link to each of the etiologies
- Yields predictions that can guide and focus more detailed experimental studies…

Model predictions

1. Regional variations in burst suppression. Neural and metabolic inhomogeneity.

2. Dynamic changes *within* each burst. e.g. Drift in frequency.



- Alpha frequency drifts within bursts

- Starts high and ‘fades’ out

- Due to gradual increase in K-ATP conductance through the course of the burst

Verifying predictions

Examining burst suppression in intracranial data:
Regional timing differences across ECoG grid

unpublished

Verifying predictions

Examining burst suppression in intracranial data:
Drift in alpha peak

unpublished

Summary

- A neurophysiological-metabolic model has been developed to suggest mechanisms of burst suppression

- The model provides a unified link between etiologies of brain inactivation

- Lots of opportunities for future investigation

    - NIRS and EEG
    - Coma and other pathologies
    - Neonatal development

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