SYMPOSIUM ON STATISTICS AND DATA SCIENCE
HONORING EDWARD WEGMAN
RESTON, VIRGINIA

Uncovering the Mechanisms of General Anesthesia: where Neuroscience Meets Statistics

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Outline

1. A Clinical Look at General Anesthesia

2. Loss of Consciousness Induced by Propofol and Other Anesthetics

3. Anesthesia and the Aging Brain

Epilogue: Control of Medical Coma and Reanimation

Main Points

The brain under general anesthesia is dynamic and not turned off.

Mechanism of Action: One of the primary ways through which anesthetics create altered arousal states is by inducing and sustaining oscillations.

Monitoring and Control Strategy: These oscillations are readily visible in the EEG, change systematically with anesthetic and age of the patient and may be used to design anesthetic state control strategies.

Reanimation: Actively "turning the brain on" after general anesthesia may be a way to speed recovery and reduce post-operative cognitive dysfunction.

Data Analysis and Statistical Modeling

Multitaper Spectral Methods

Global Coherence Analyses

Point Process Generalized Linear Models

State-Space Methods

Bayes and Empirical Bayes Methods

What is General Anesthesia?

A drug-induced, reversible state comprised of

Unconsciousness

Amnesia (loss of memory)

Analgesia (loss of pain perception)

Akinesia (loss of movement)

and

Stability and Control of the cardiovascular, respiratory thermoregulatory and autonomic nervous systems.

How Drugs Create General Anesthesia is Unknown.

Brown, Lydic, Schiff *NEJM* (2010)

Balanced General Anesthesia

-Unconsciousness (barbiturates, propofol, inhalational drugs)

-Analgesia (opioids, inhalational drugs)

-Amnesia (benzodiezapines, hypnotics, inhalational drugs)

-Immobility (anticholinergics, inhalational drugs)

- Hemodynamic Stability

EEG States of Propofol-Induced Unconsciousness

Awake

Paradoxical Excitation

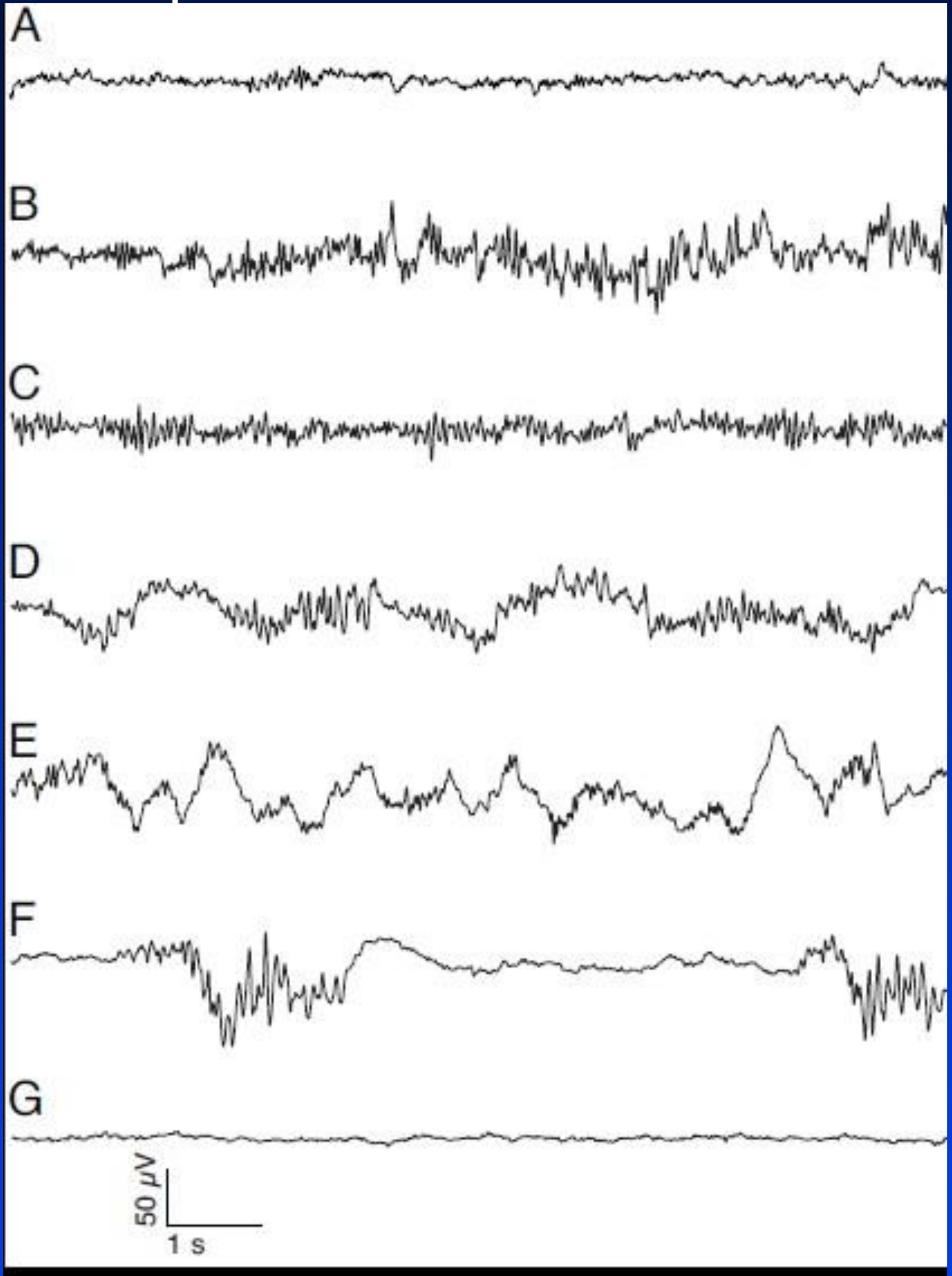
Sedation

Slow-Alpha Oscillations
(<1 Hz) (8-12 Hz)

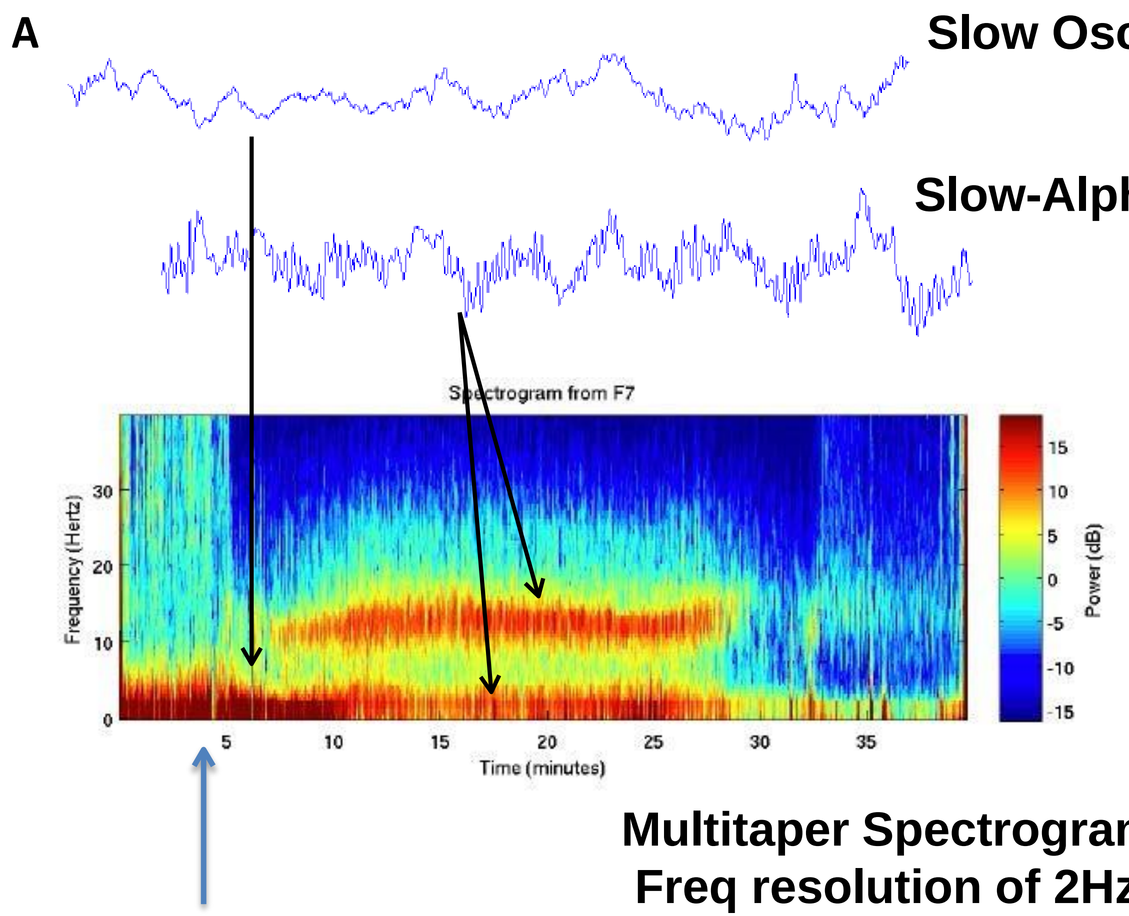
Induction
Slow Oscillations(<1 Hz)

Burst Suppression

Isoelectric

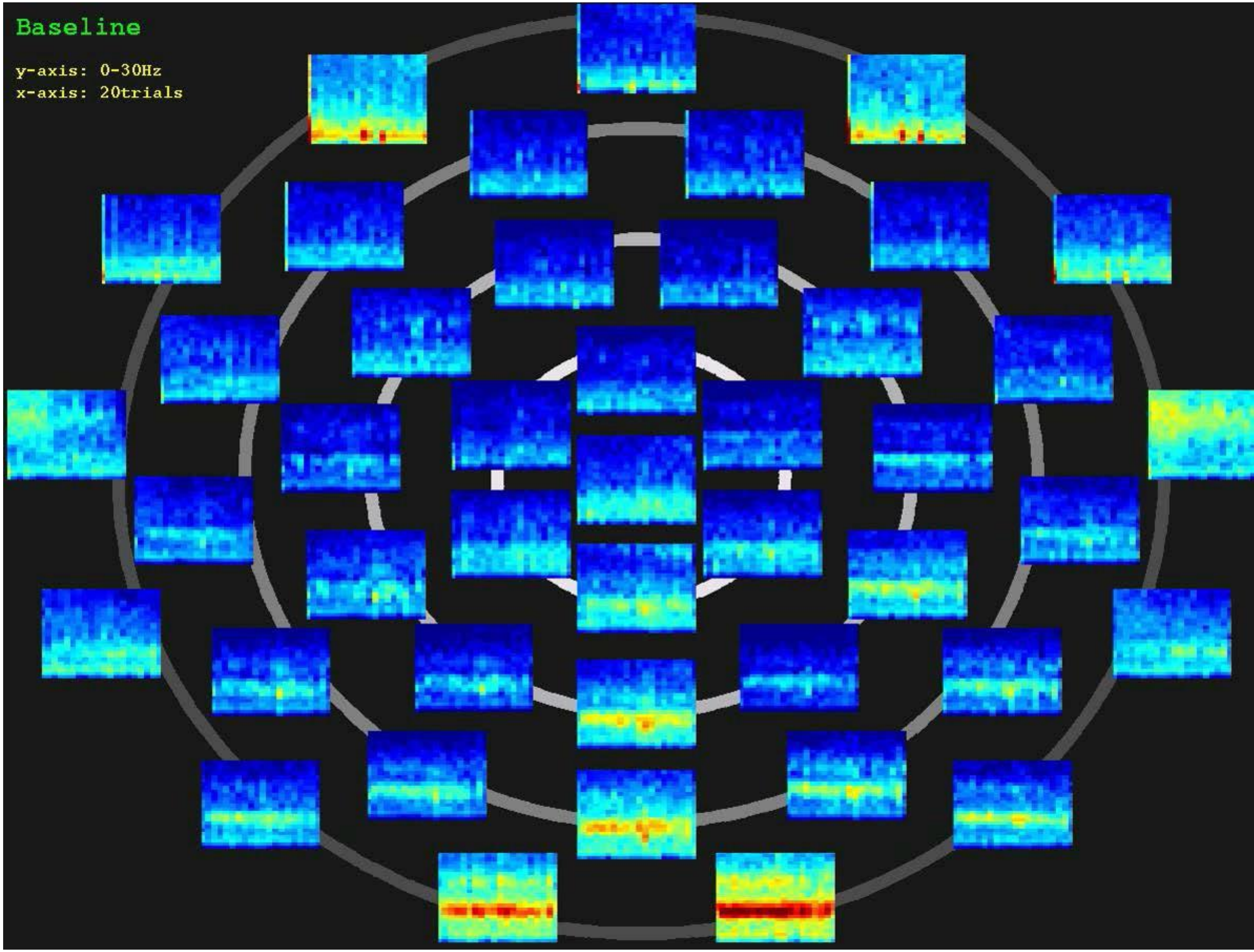


Clinical Electroencephalography of Propofol



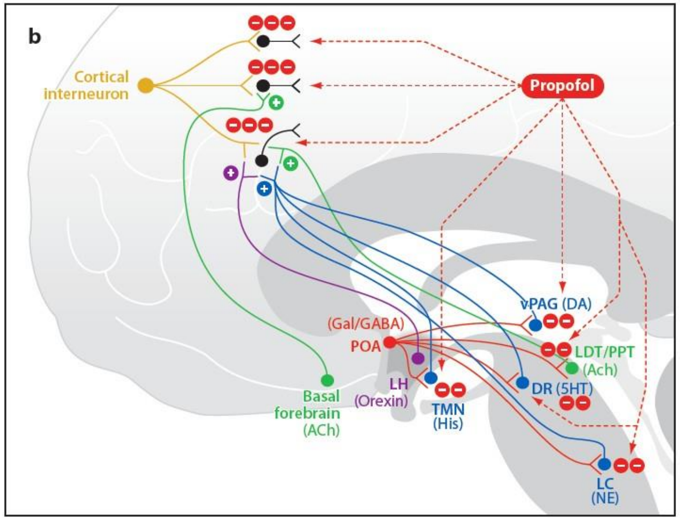
Multitaper Spectrogram
Freq resolution of 2Hz
Tapers: 5

19 year-old female
200 mg propofol bolus
Maintenance w/ 100 mcg/kg/min propofol


Baseline
y-axis: 0-30Hz
x-axis: 20trials

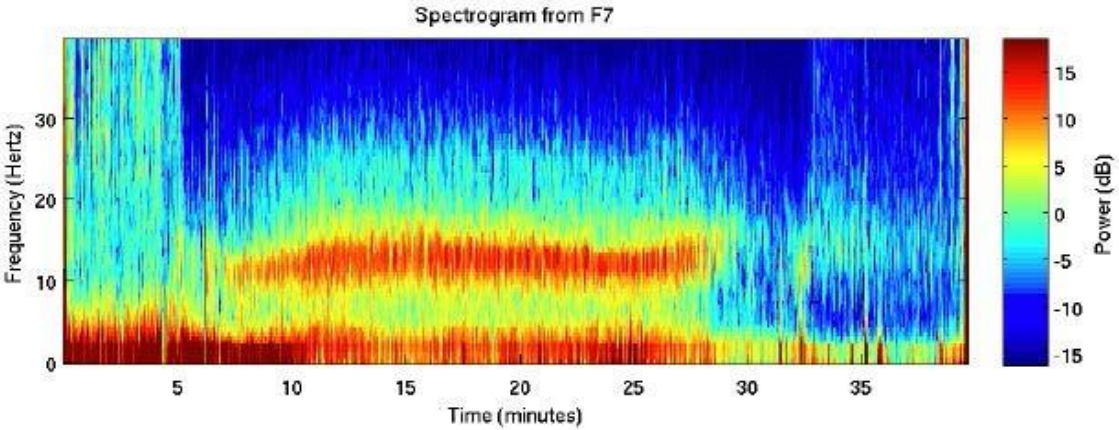
Alpha Oscillations Are Coherent Thalamocortical Rhythms

Enhanced GABAergic Inhibition



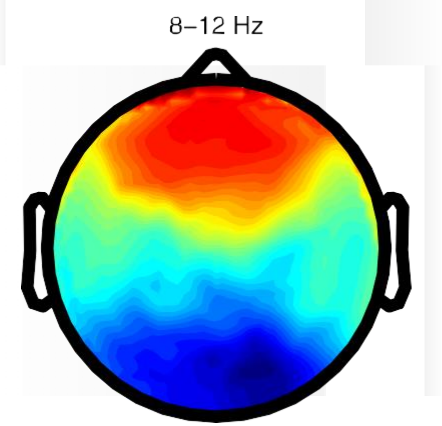
Brown, Purdon, Van Dort, ARN 2011

The View in the Operating Room



Purdon et al. Anesthesiology, 2015

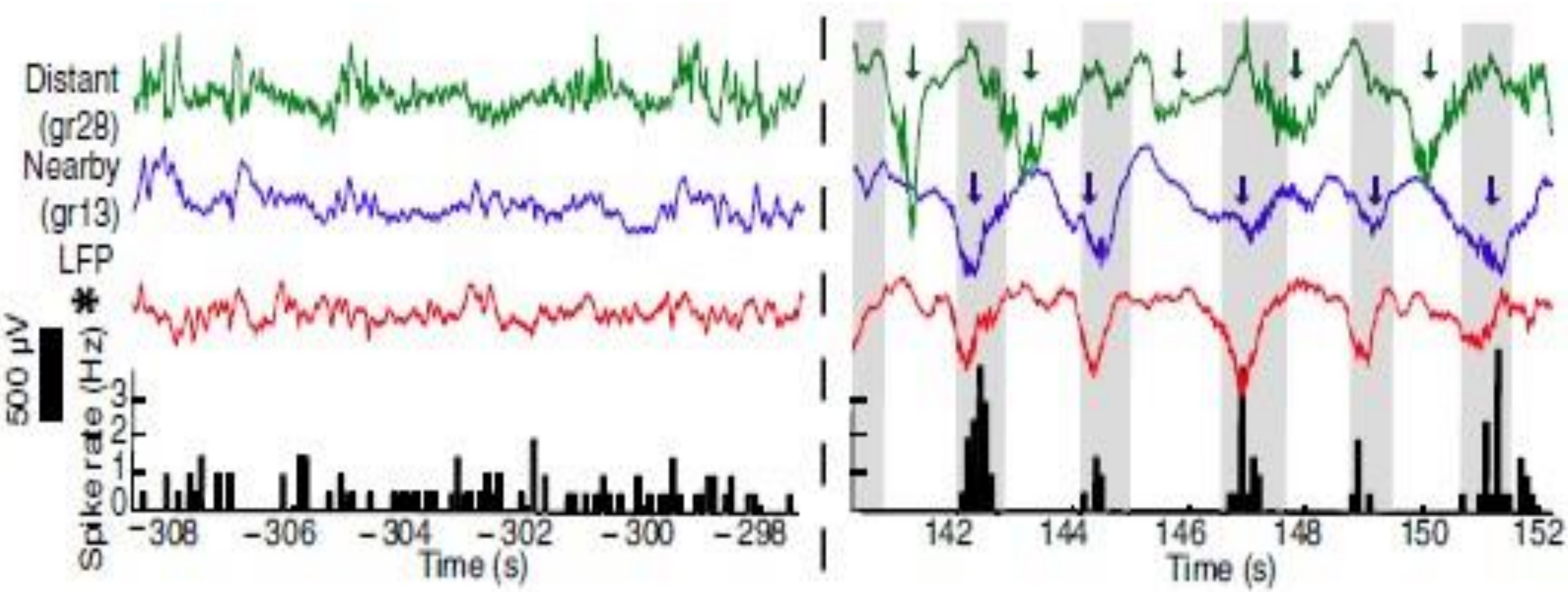
The alpha oscillations are frontally coherent



The alpha oscillations are thalamo-cortical dynamics

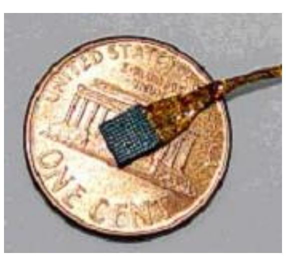
Ching et al. *PNAS*, 2010; Cimenser et al. *PNAS*, 2011; Purdon et al. PNAS 2013

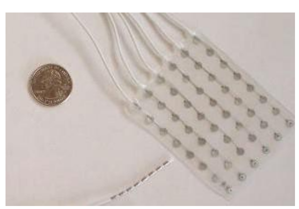
Slow Oscillations Gate Phase-Limited Spiking Activity

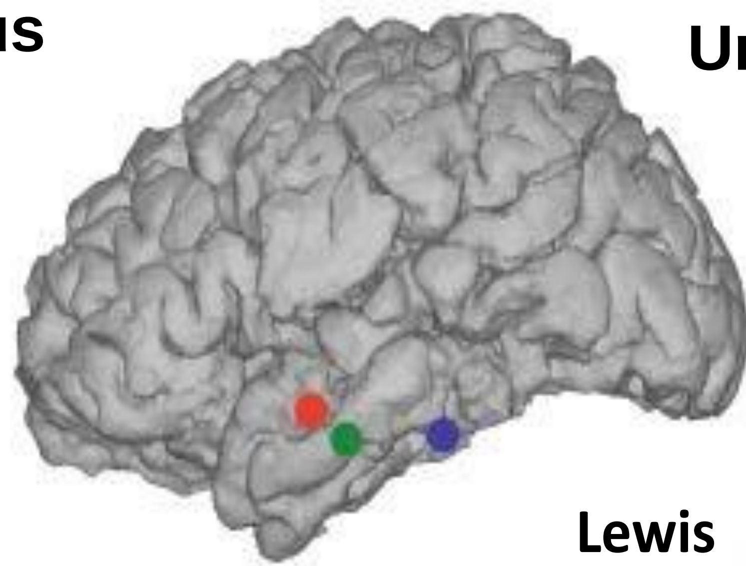


Conscious

Unconscious


Grid Electrodes

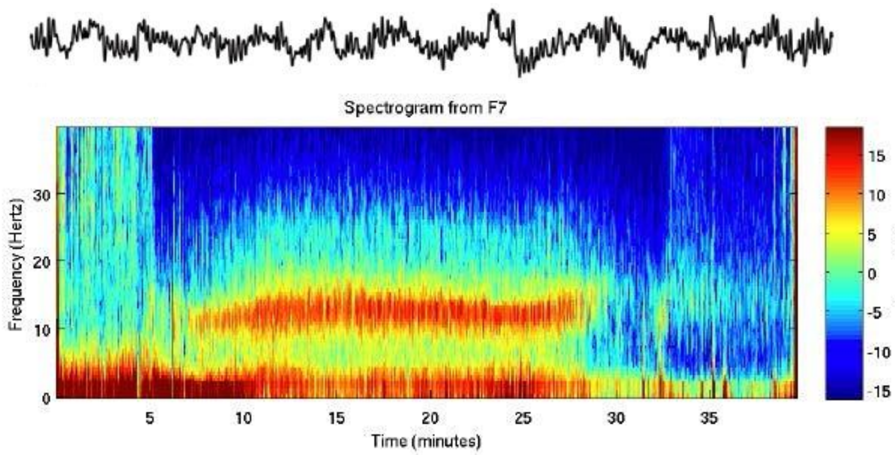

Microelectrodes



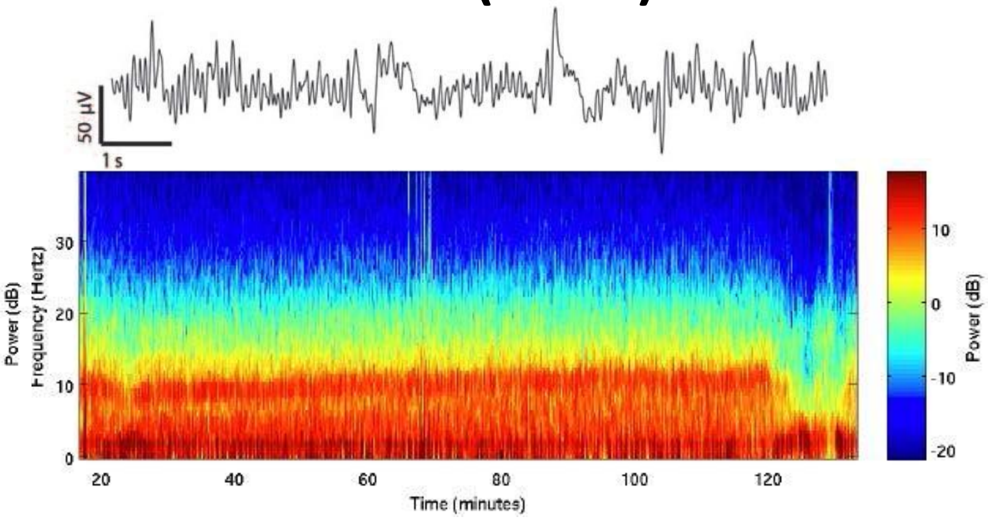
Lewis et al. PNAS, 2012

Different Anesthetics Have Different EEG Signatures

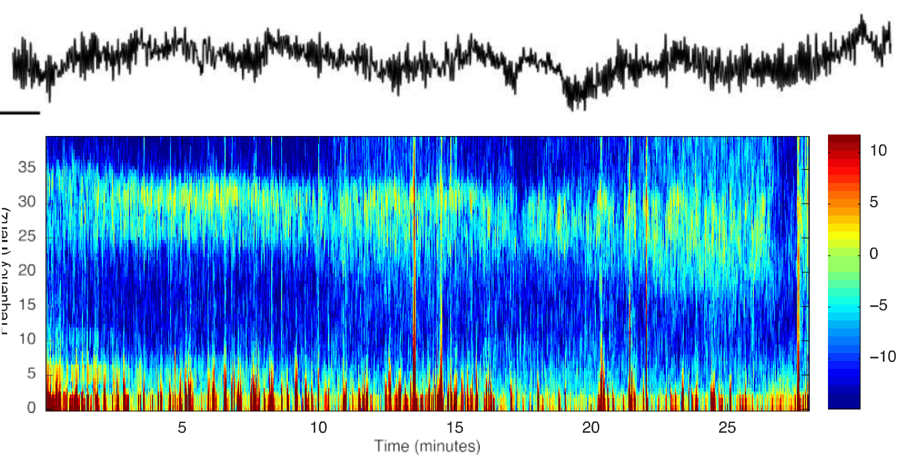
Propofol



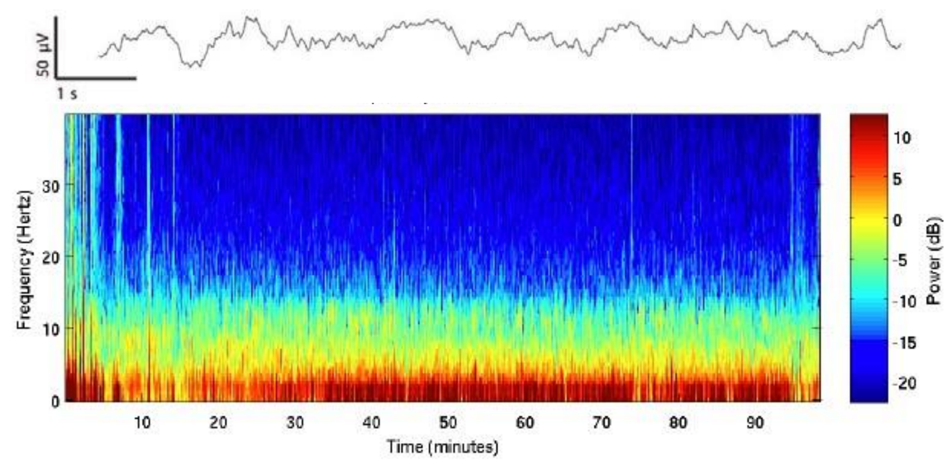
Sevoflurane (ether)



Ketamine



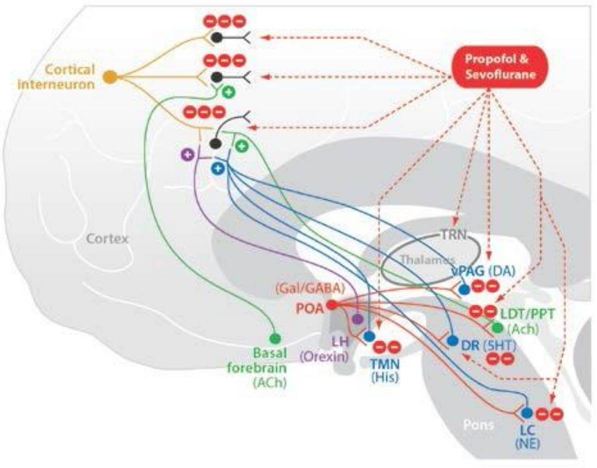
Dexmedetomidine



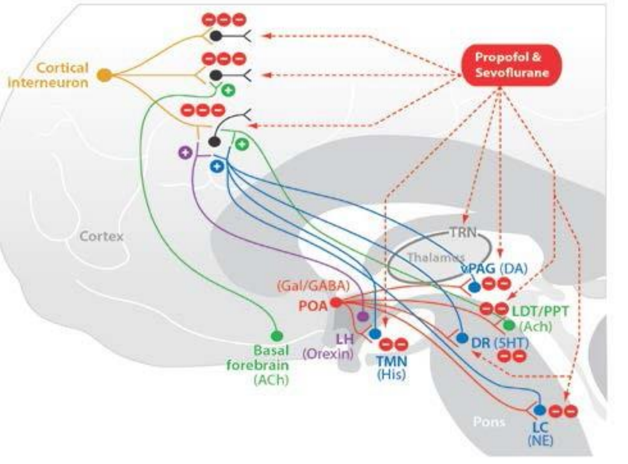
eegforanesthesia.iars.org

Purdon et al. *Anesthesiology* 2015

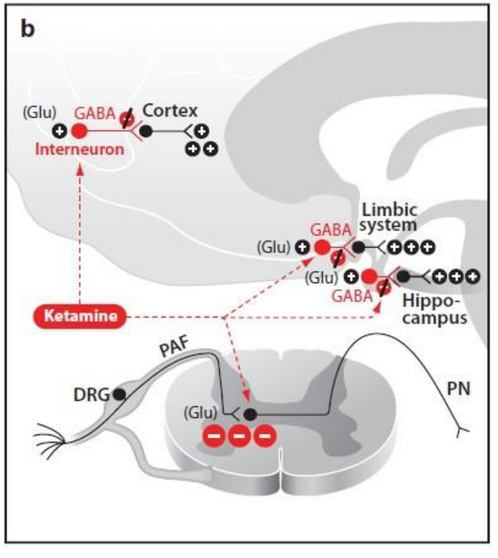
Different EEG Signatures Are Associated with Different Mechanisms

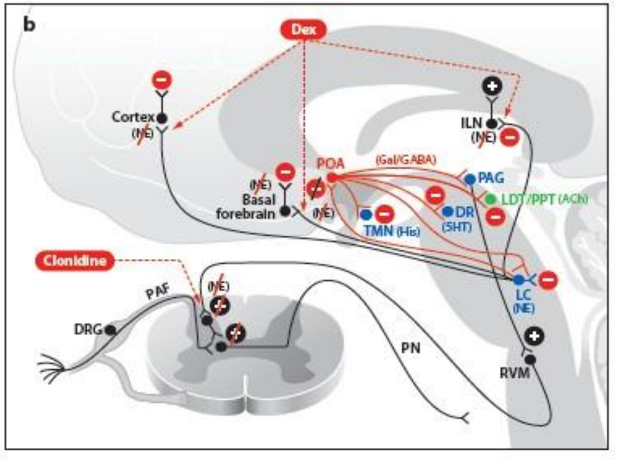


Propofol (+GABA)



Sevoflurane (+GABA)



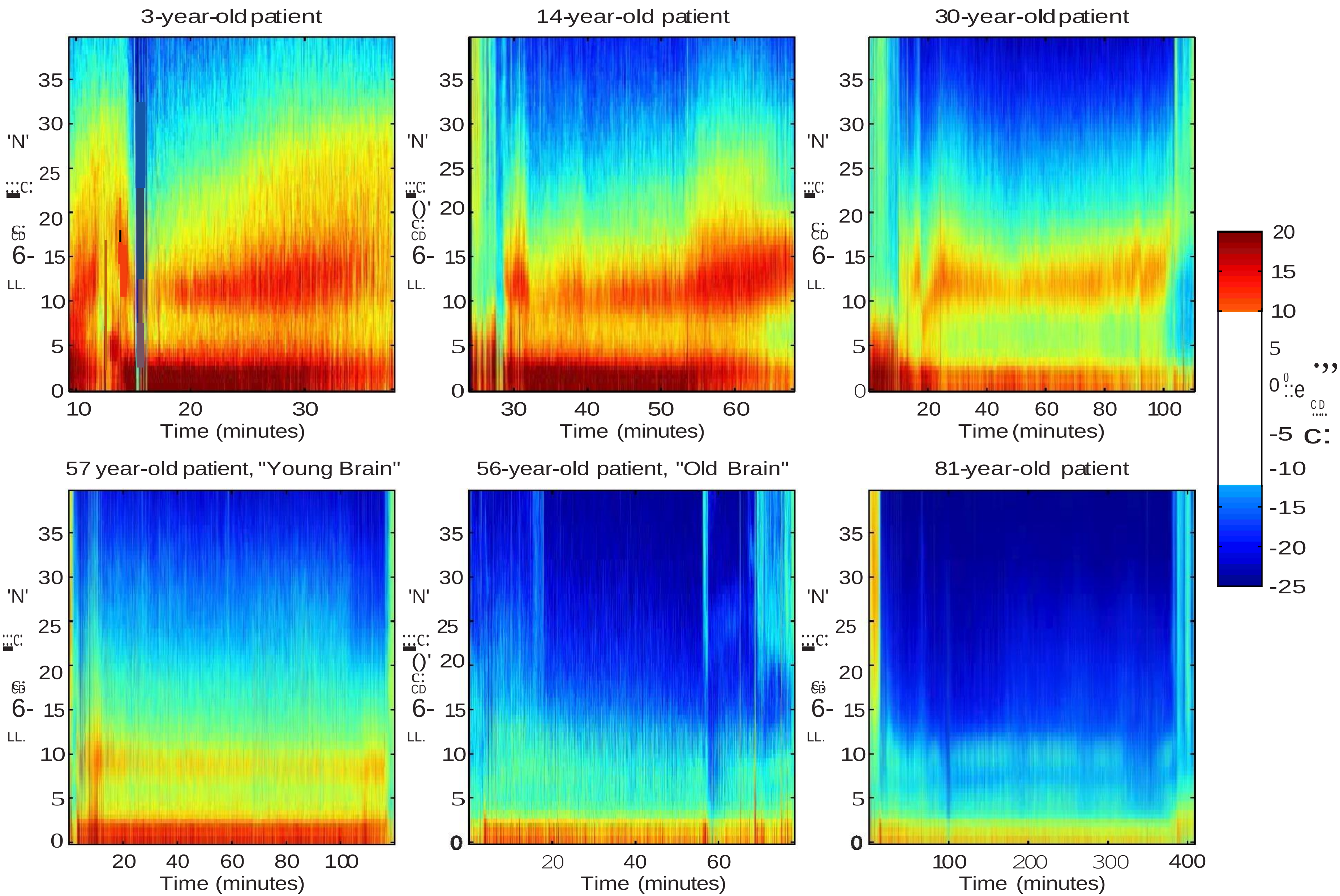


Ketamine (-NMDA)

Dexmedetomidine (+Alpha2 Adrenergic)

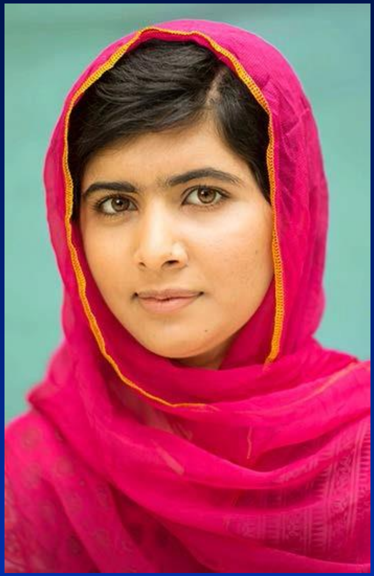
Brown et al. NEJM 2010 Brown et al. Ann Rev Neuro 2011; Purdon et al. Anesthesiology, 2015

The Brain Response to Anesthesia Changes with Age



Akeju et al. *British Journal of Anaesthesia* 2015 Purdon et al. *British Journal of Anaesthesia* 2015

Medical Coma is a Life-Saving Therapy

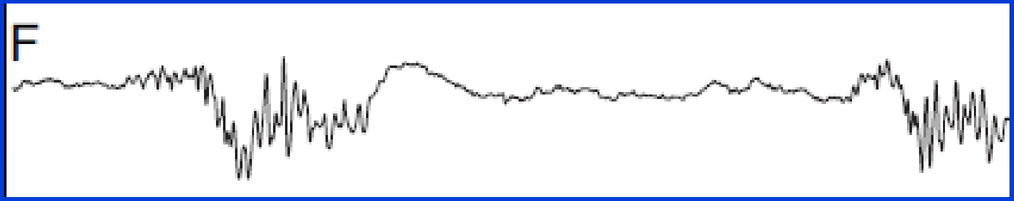


Malala Yousafzai

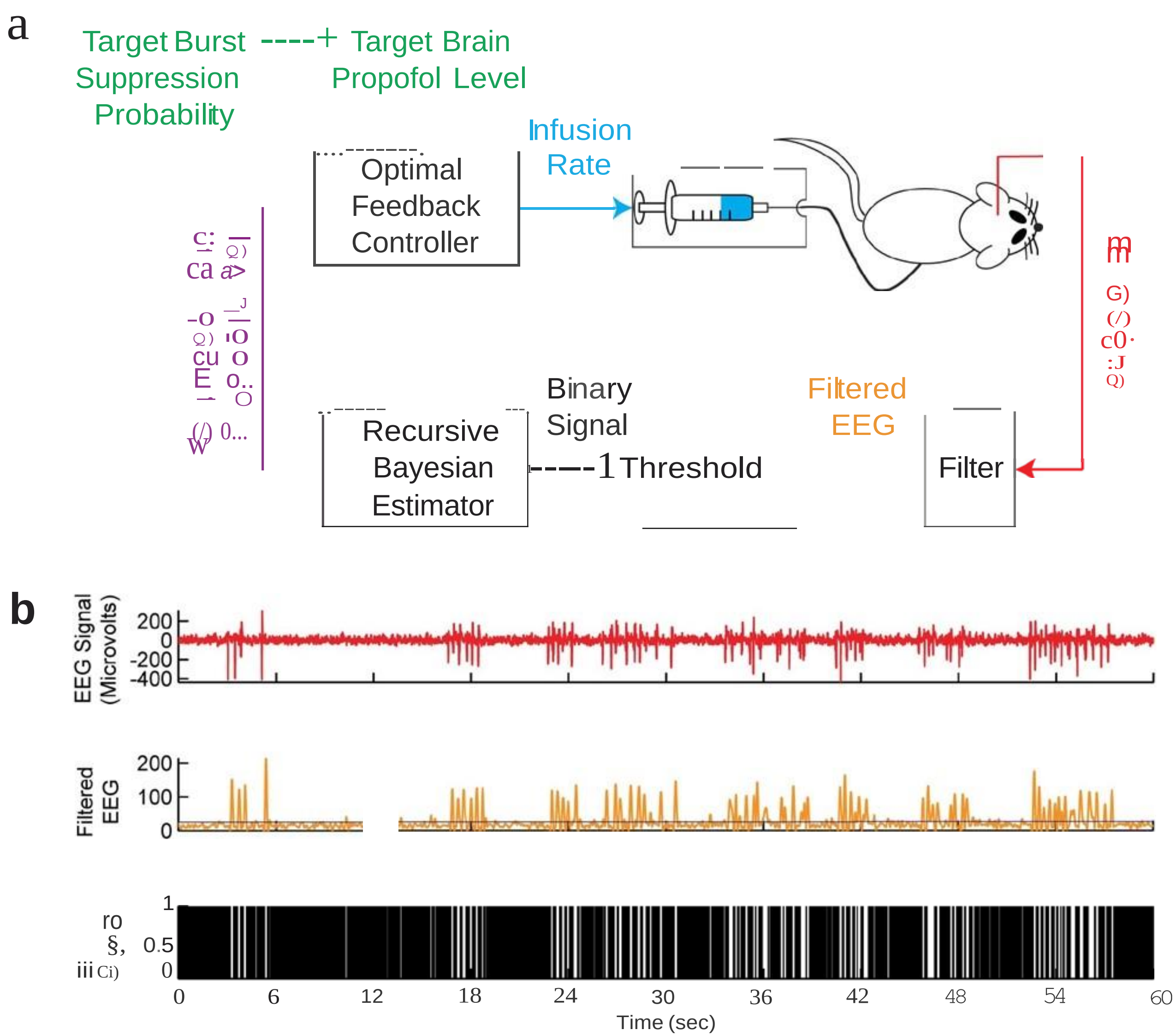
Gabrielle Giffords

Michael Schumacher

Medical coma is a state of profound brain inactivation achieved by continuously administering anesthetic (propofol) to keep the brain in the state of burst suppression often for many days to allow it to rest after an injury or to stop intractable seizures.



Closed-Loop Control of Medical Coma



Shanechi et al. PLoS Comp Bio 2013

Ching et al. Anesthesiology 2013

Westover et al. J Neuro Eng 2015

A Brain-Machine Interface

for Control of Medically-Induced Coma

M. Shanechi, J. Chemali, M. Liberman, K. Solt, E. Brown
PLoS Computational Biology
Oct. 2013

Closed Loop Control of Medical Coma is Feasible.

Target and Control

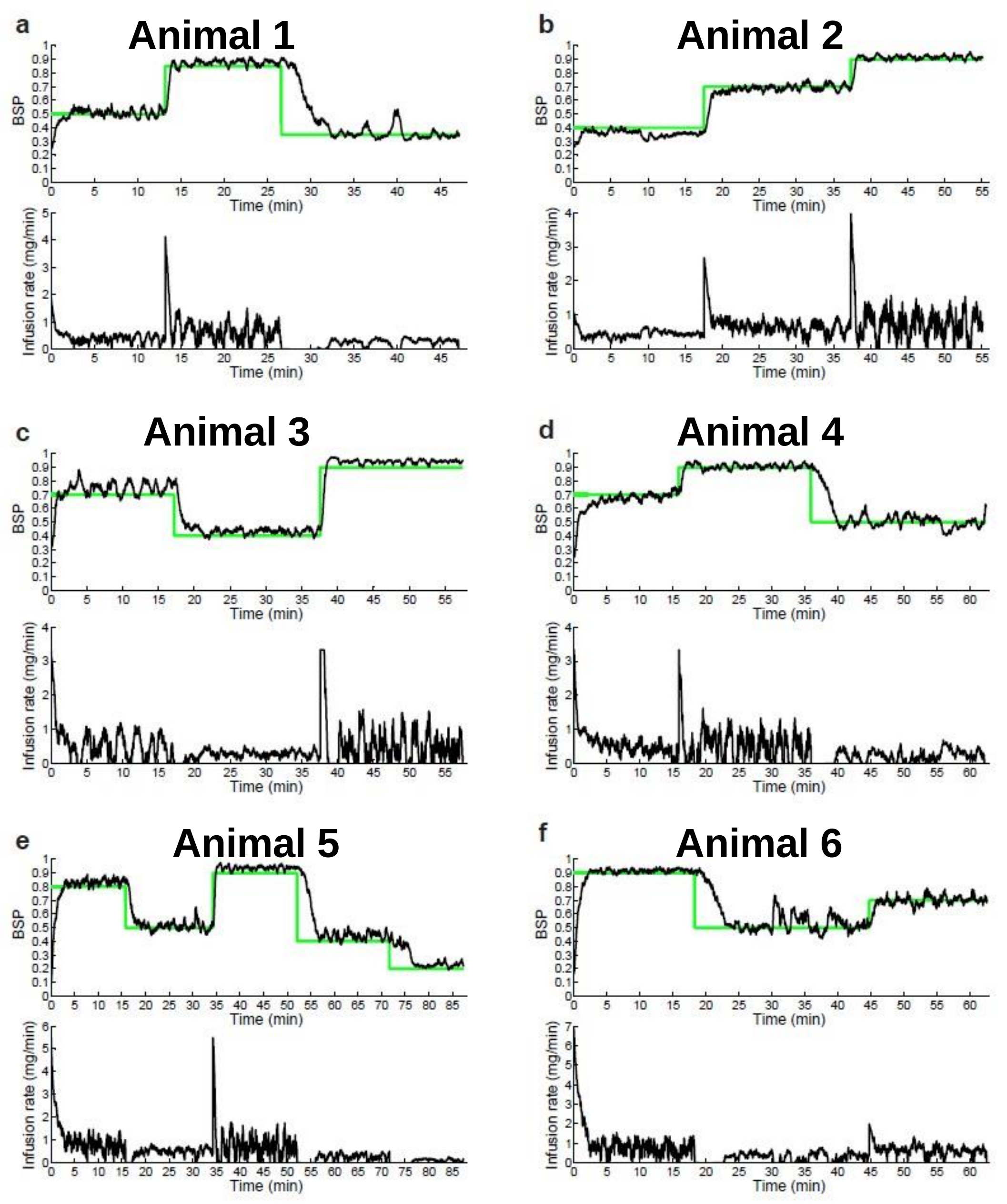
Infusion Rate

Target and Control

Infusion Rate

Target and Control

Infusion Rate

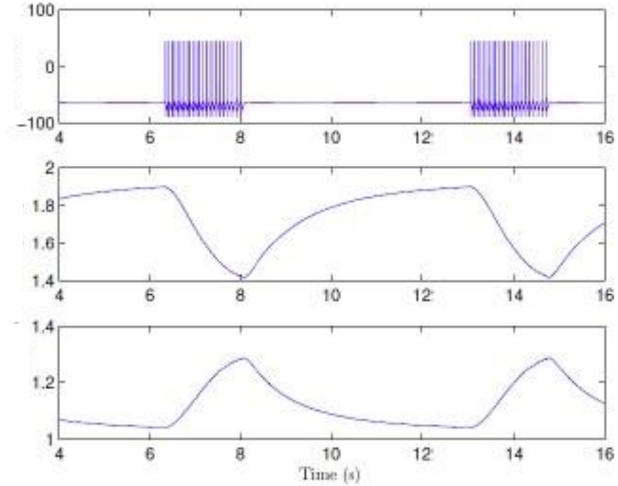


Shanechi et al. PLoS Comp Bio 2013

Burst Suppression: EEG, Model Prediction & Experimental Verification

Burst Suppression

Model Prediction



Burst Suppression

ATP

% Increase in Conductance ATP

Ching et. al. PNAS 2012

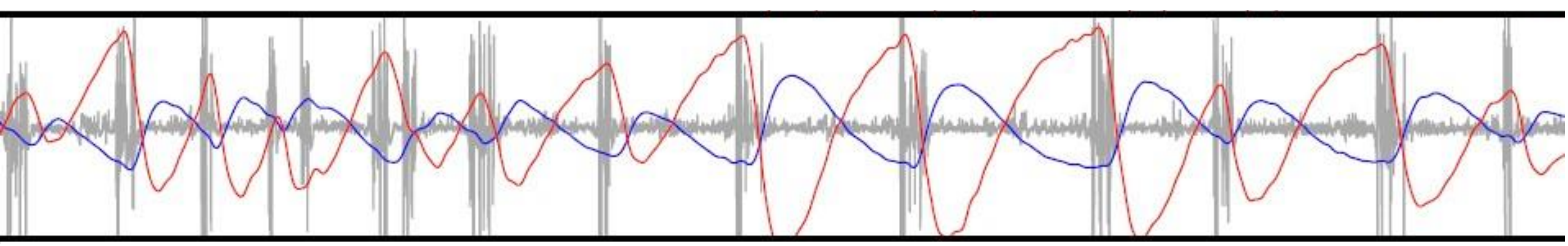
$$I_{K_{ATP}} = g_{K_{ATP}} z (v - E_K).$$

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

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

- The rate of ATP production (acting as a surrogate for cerebral metabolic rate of oxygen) dictates the ratio of quiescence to activity

Experimental Verification (courtesy of David Boas)



Deoxyhemoglobin

Oxyhemoglobin

Awakenings: Reanimation from General Anesthesia

To the Editor:

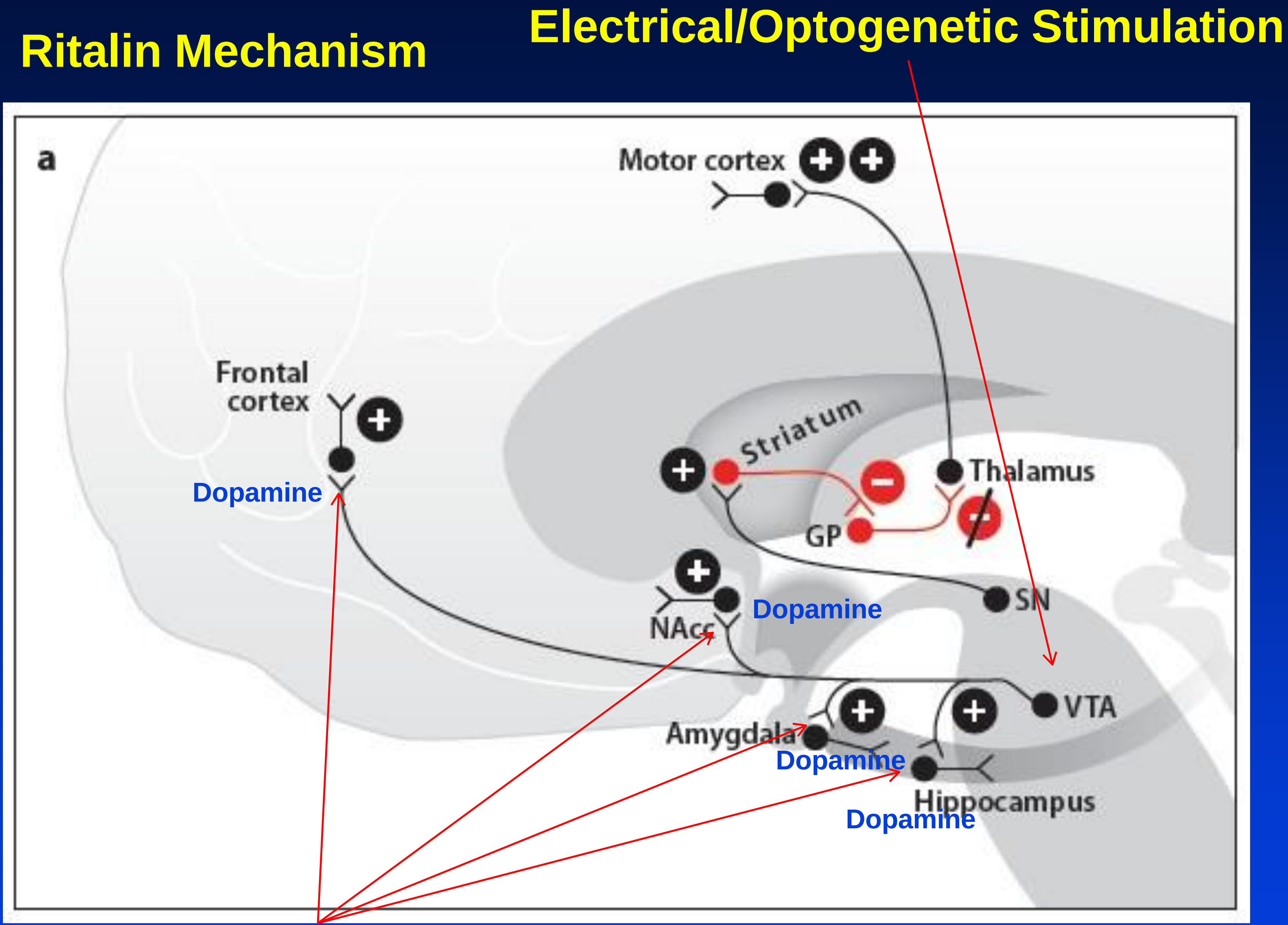
I had my first corrective surgery due to "infantile paralysis" in 1949. The bill from the anesthesiologist was $400. My mother was horrified, but my father calmed her when he said, "It was probably $50 for the procedure, but I gladly pay the other $350 because he knew how to wake her up."

Ina Pinkney
Chicago

New York Times, March 7, 2011

Reanimation after General Anesthesia

Ritalin Mechanism



Ritalin blocks dopamine reuptake in the brain

Solt et al. Anesthesiology, 2011, 2014

Taylor et al. PNAS, 2016

Summary

The brain under general anesthesia is dynamic and not turned off.

Mechanism of Action: One of the primary ways through which anesthetics create altered arousal states is by inducing and sustaining oscillations.

Monitoring and Control Strategy: These oscillations are readily visible in the EEG, change systematically with anesthetic and age of the patient and may be used to design anesthetic state control strategies.

Reanimation: Actively “turning the brain on” after general anesthesia may be a way to speed recovery and reduce post-operative cognitive dysfunction.

Does Sevoflurane Produce a Theta Oscillation at High Dose?

Sevoflurane

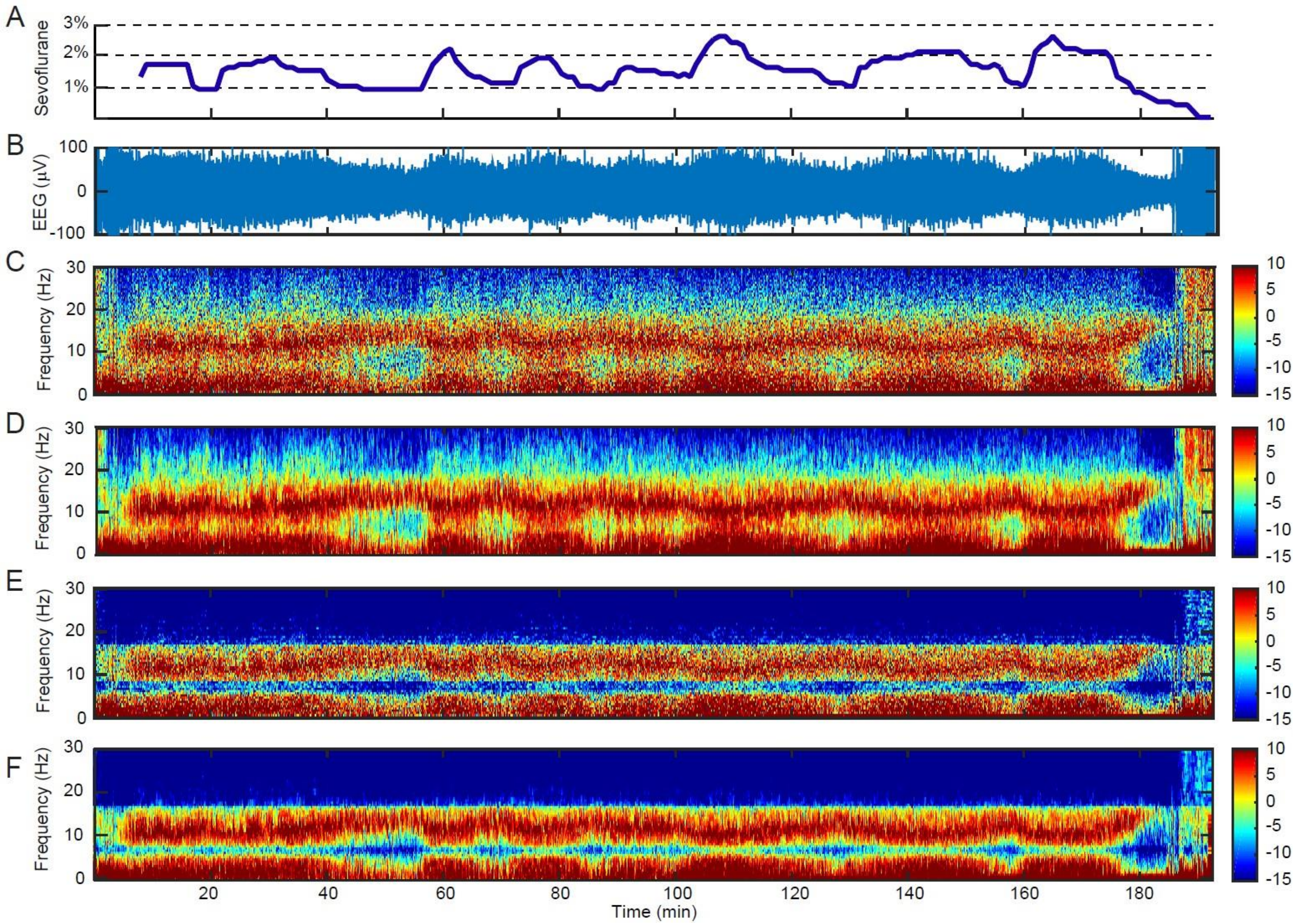
EEG

Periodogram

Multitaper

State-Space Periodogram

State-Space Multitaper



Maybe Not!

Kim et al. PNAS 2018

Personalized Anesthesia Care-Clinical Neuroscience