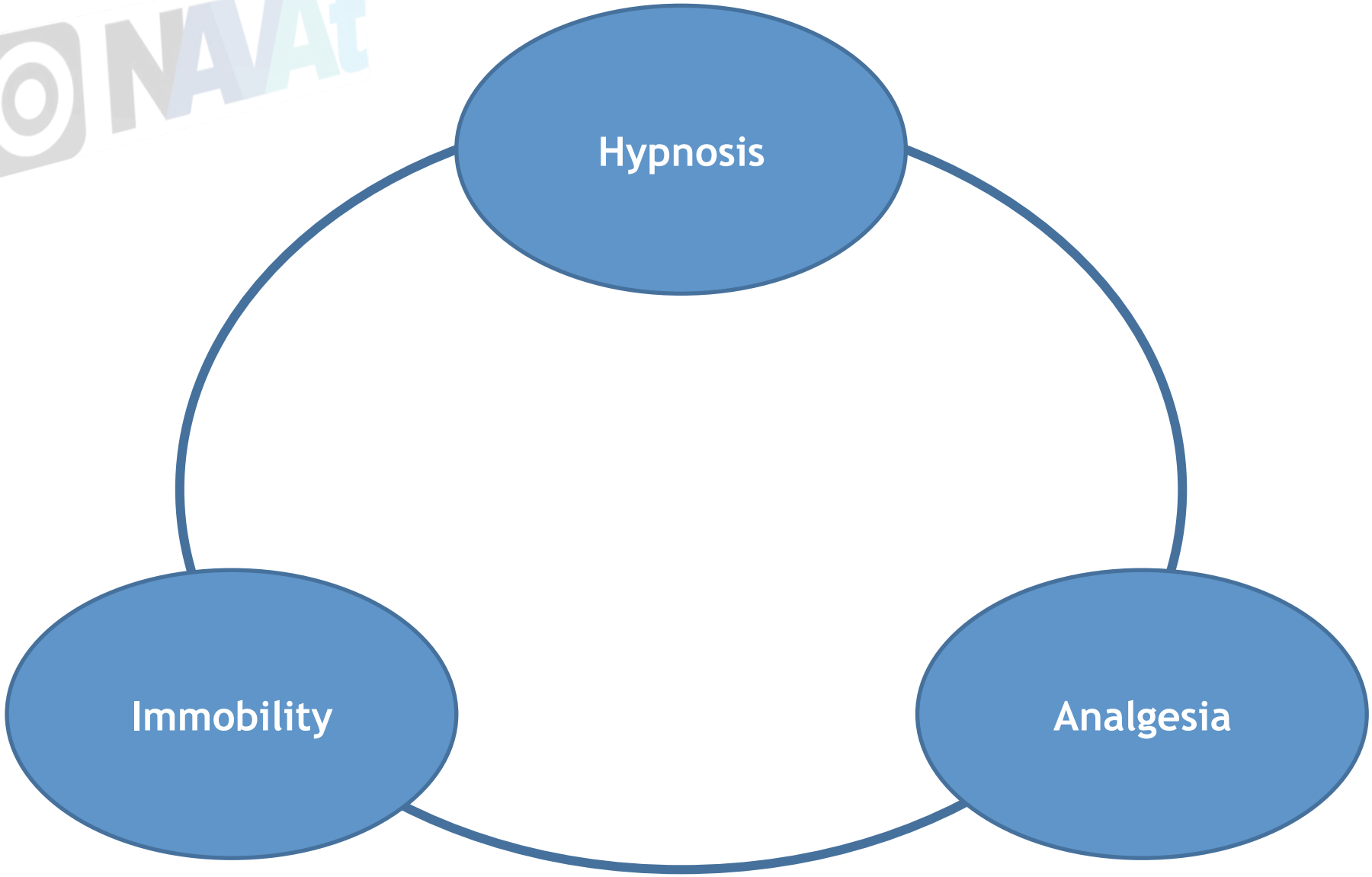
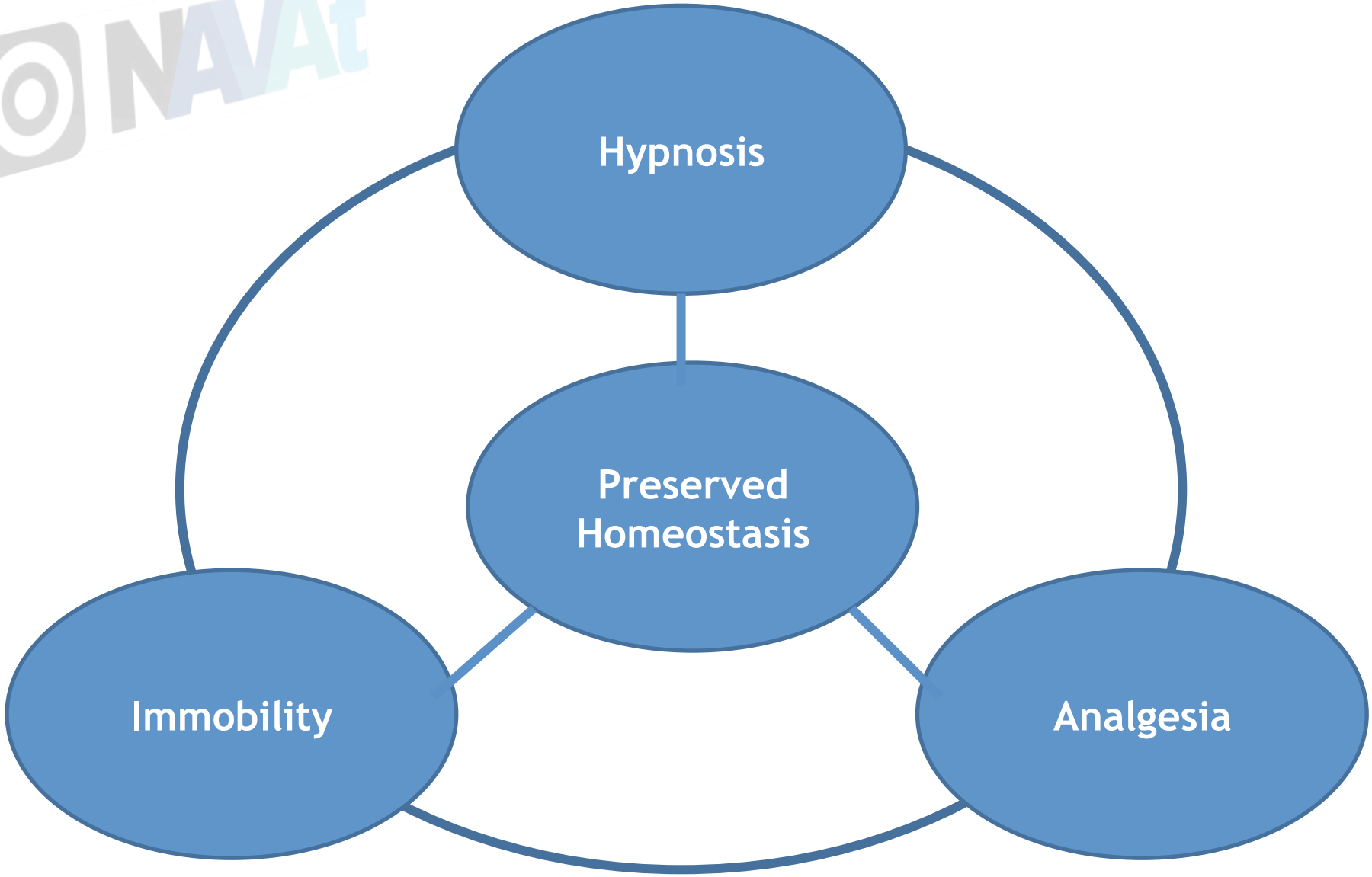
Anesthesia depth: EEG or non-EEG derived or both?

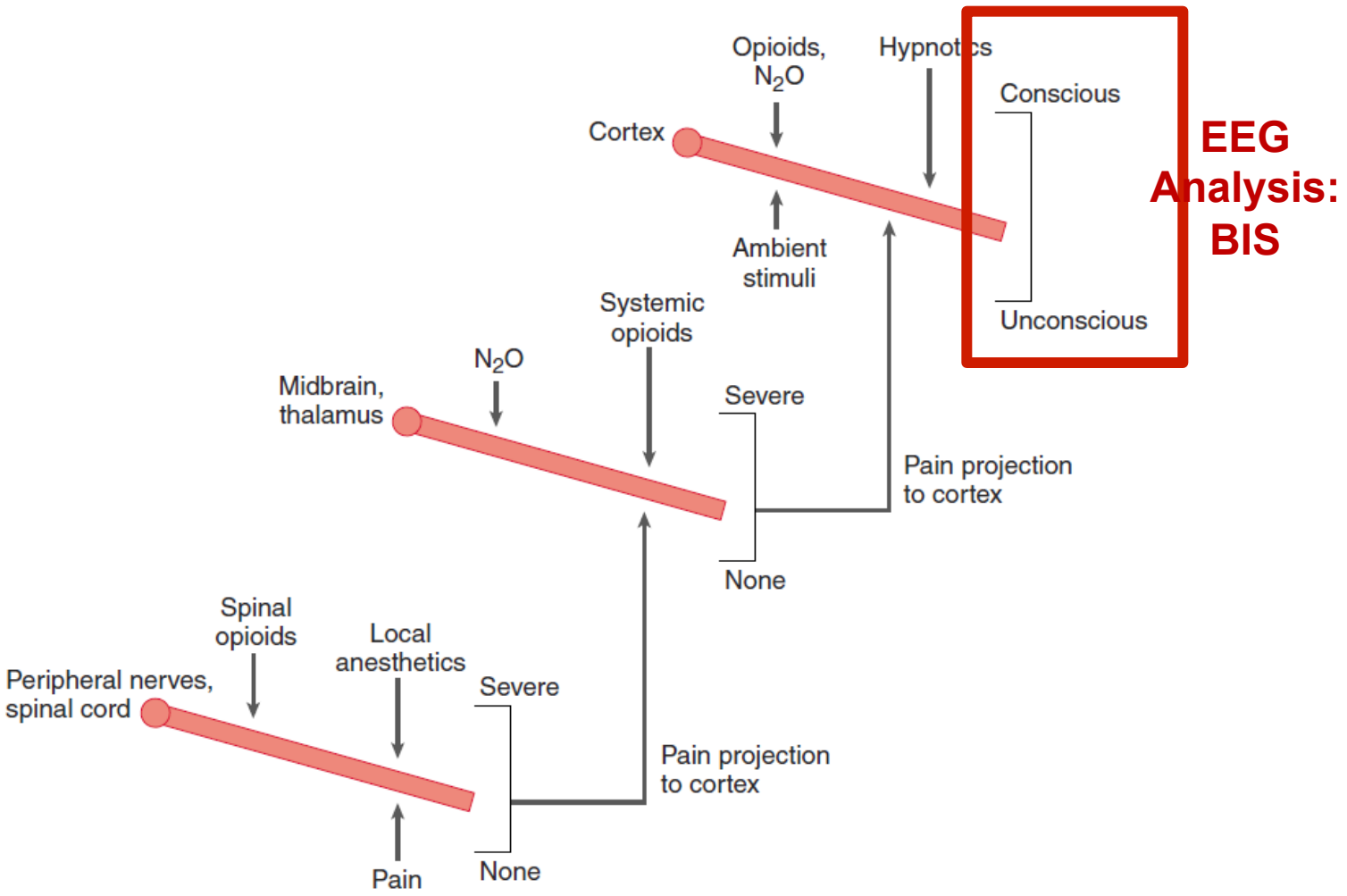
P. L. Gambús
Servei de Anestesia; Hospital CLINIC de Barcelona

Adjunct Associate Professor
Department of Anesthesia and Perioperative Care
University of California San Francisco (UCSF)


Hypnosis
Immobility
Analgesia


Hypnosis
Preserved Homeostasis
Immobility
Analgesia

"Hierarchical" Model of the Anesthetic State



Stanski DR Shafer SL; Miller's Anesthesia, 2007

Quantifying Anesthetic State

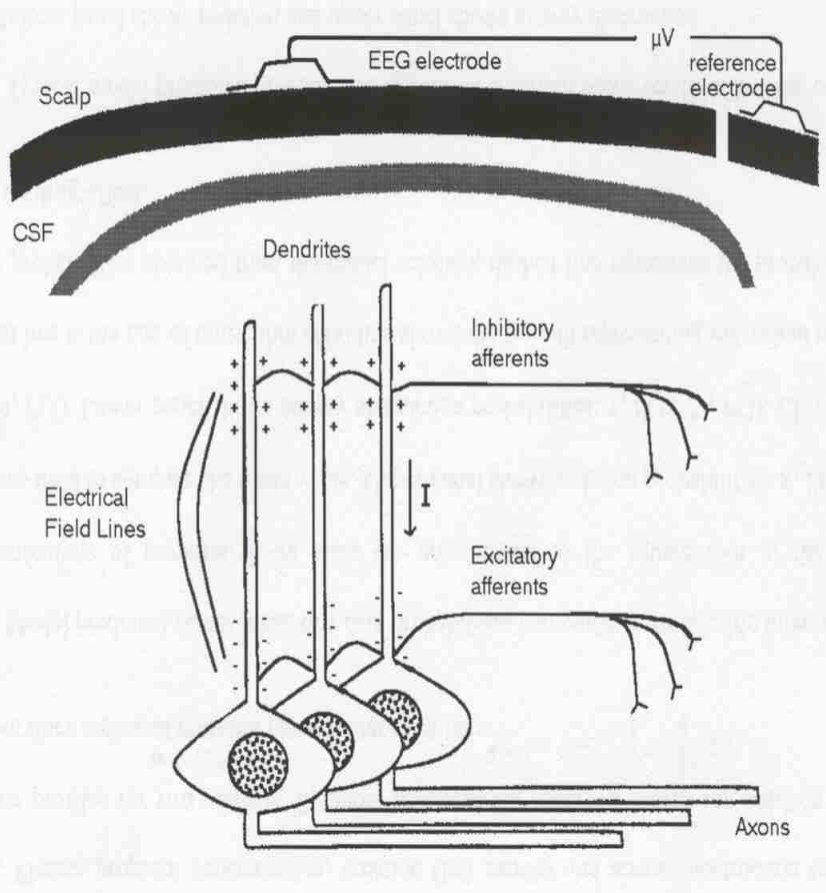
- **Hypnosis**
  - **EEG signal Analysis**
  - Diverse mathematical approaches
    - Spectral, bispectral
    - Fuzzy Logic
    - Entropy
    - …
  - **Synthesize in one value all the information relevant only to hypnosis**
    - Visualize brainwaves
  - Predictors based in drug concentrations: NSRI
- **Analgesia**
  - Signs: movement, pupil, sweat, tear, …
  - Hemodynamics
  - ANS reactivity:
    - Variability HR
    - Respiratory Sinus Arrythmia
    - Plethysmogram
  - Predictors based in drug concentrations: NSRI
  - **EEG**

How each component potentiates the other

Hypnotic Component

What is the EEG?

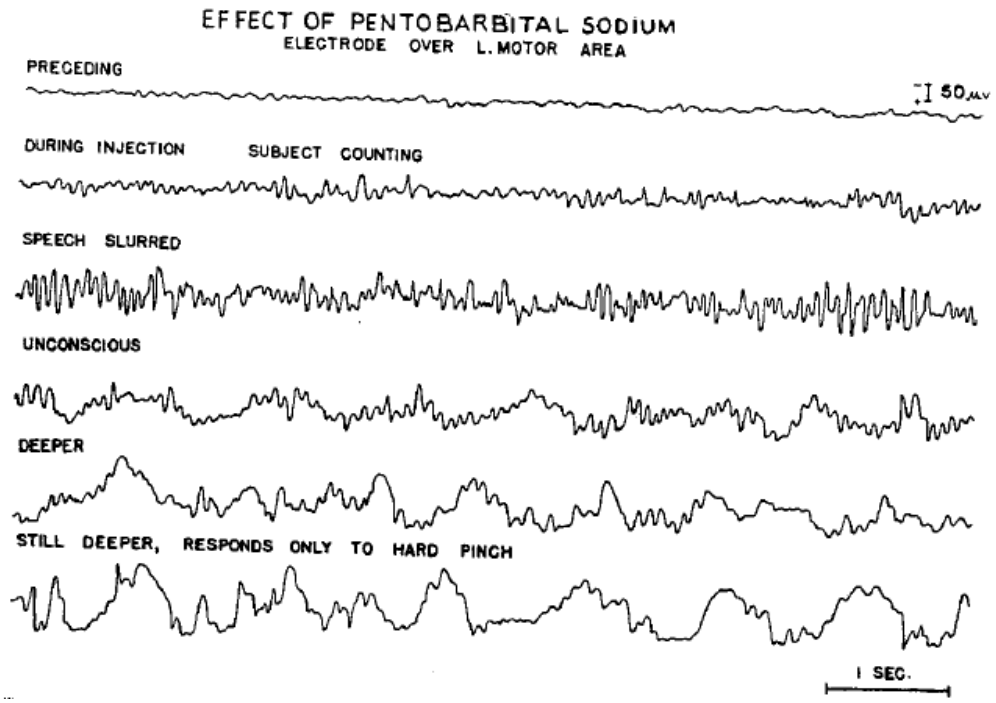
- Window to Central Nervous System
- **“Surrogate” measure**
- Incruent
- Continuous
- Consistent
- Sensitive to anesthetic drug effects
- **Reflects individual response**
- Non intuitive
- **Small wave amplitude**
  - **Noise**
- **Topography Dependent**
- Complex, multidimensional



Rampil IJ, 1992

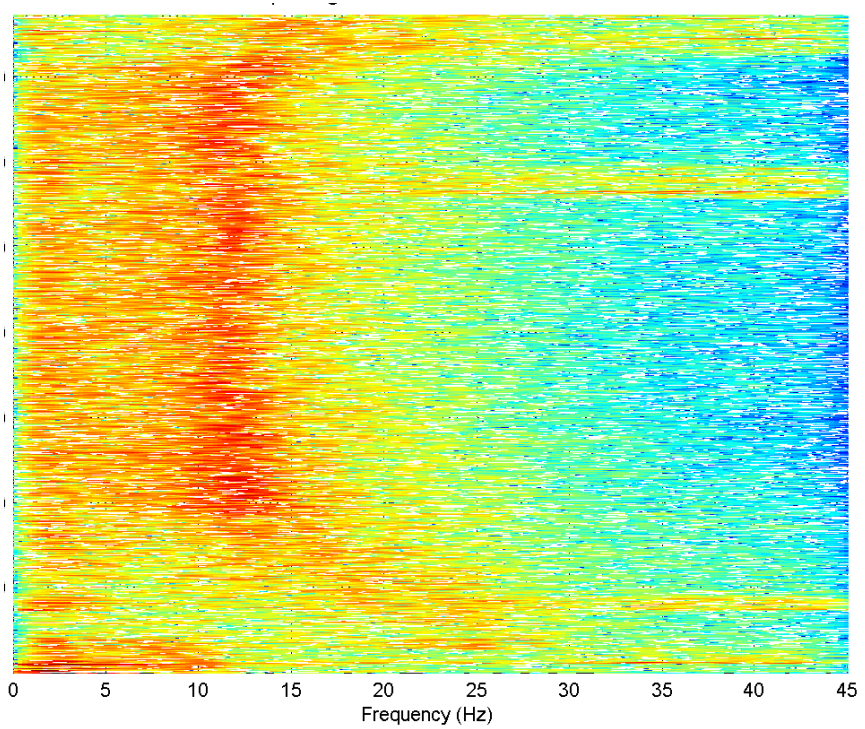
EEG: measure of drug effect

Raw EEG



Gibbs, Archives Internal Med, 1937

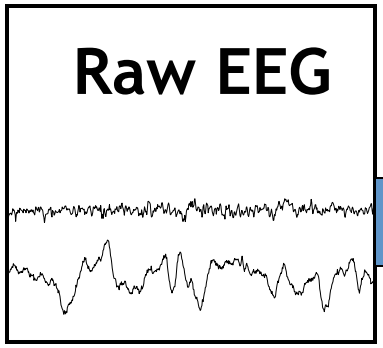
Processed EEG: Spectral

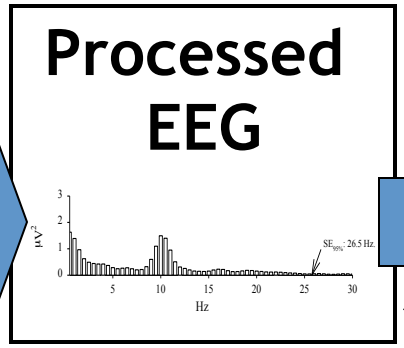


EEG: measure of drug effect

Extract from the complexity of the EEG the information relevant to anesthetic drug effect only

EEG: measure of drug effect analysis and parameters





- Frequency:
  - $SE_{95\%}$
  - $SE_{50\%}$
- Power:
  - total
  - bands
- Amplitude:
  - Supression Ratio
- Canonical Analysis:
  - Opioids
  - Propofol
  - Inhalatory
  - Midazolam
- Entropy:
  - Shannon
  - Aproximate
  - Espectral
- ANFIS
  - Q-CON
- Bispectral Index
- Discriminant Analysis: PSI

Clinical Validation

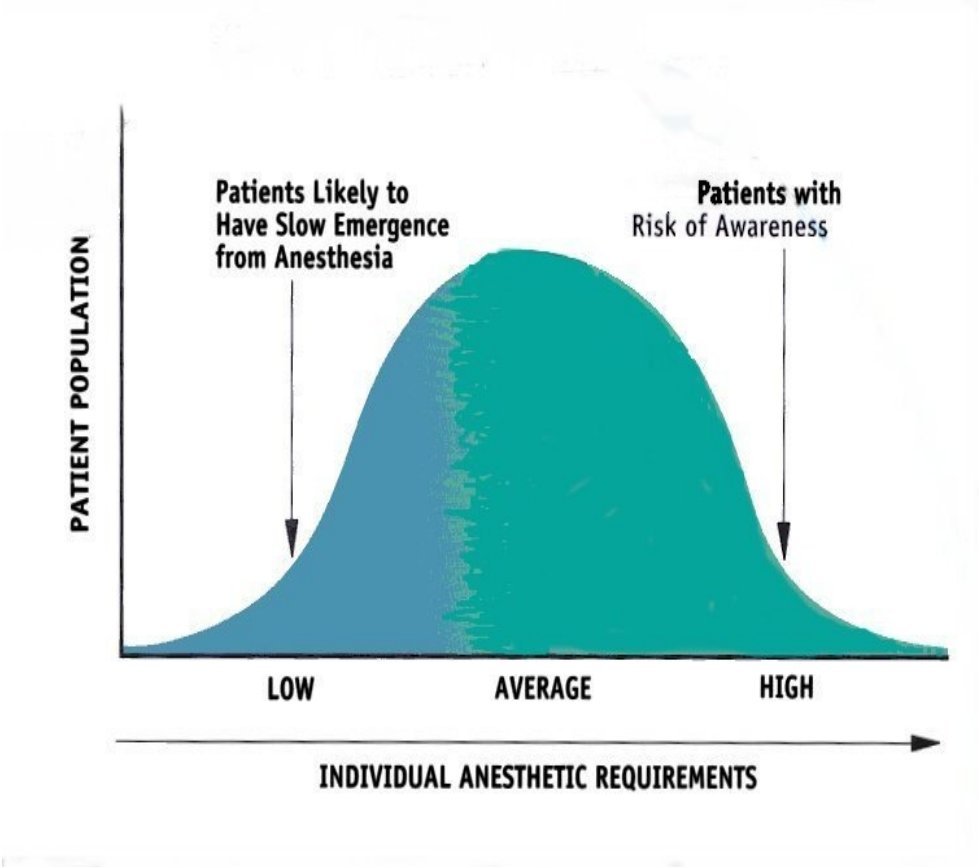
Analysis Methods

- Aperiodic
- Spectral:
  - Fourier (FFT)
  - Frequency
- Bispectral
- Complexity
- ANFIS, Discriminant

Parameters

EEG: advantages of measuring drug effect

- A new perspective in **Anesthesia Quantification**
- **Measure**
  - Direct hypnotic effect
  - Indirect NOX response
- Decrease **Variability**
- **"Personalize"** anesthetic drugs input to:
  - Patient
  - Procedure
- Learned to look beyond the Operating Room:
  - **Outcomes**
  - **Neuroscience**



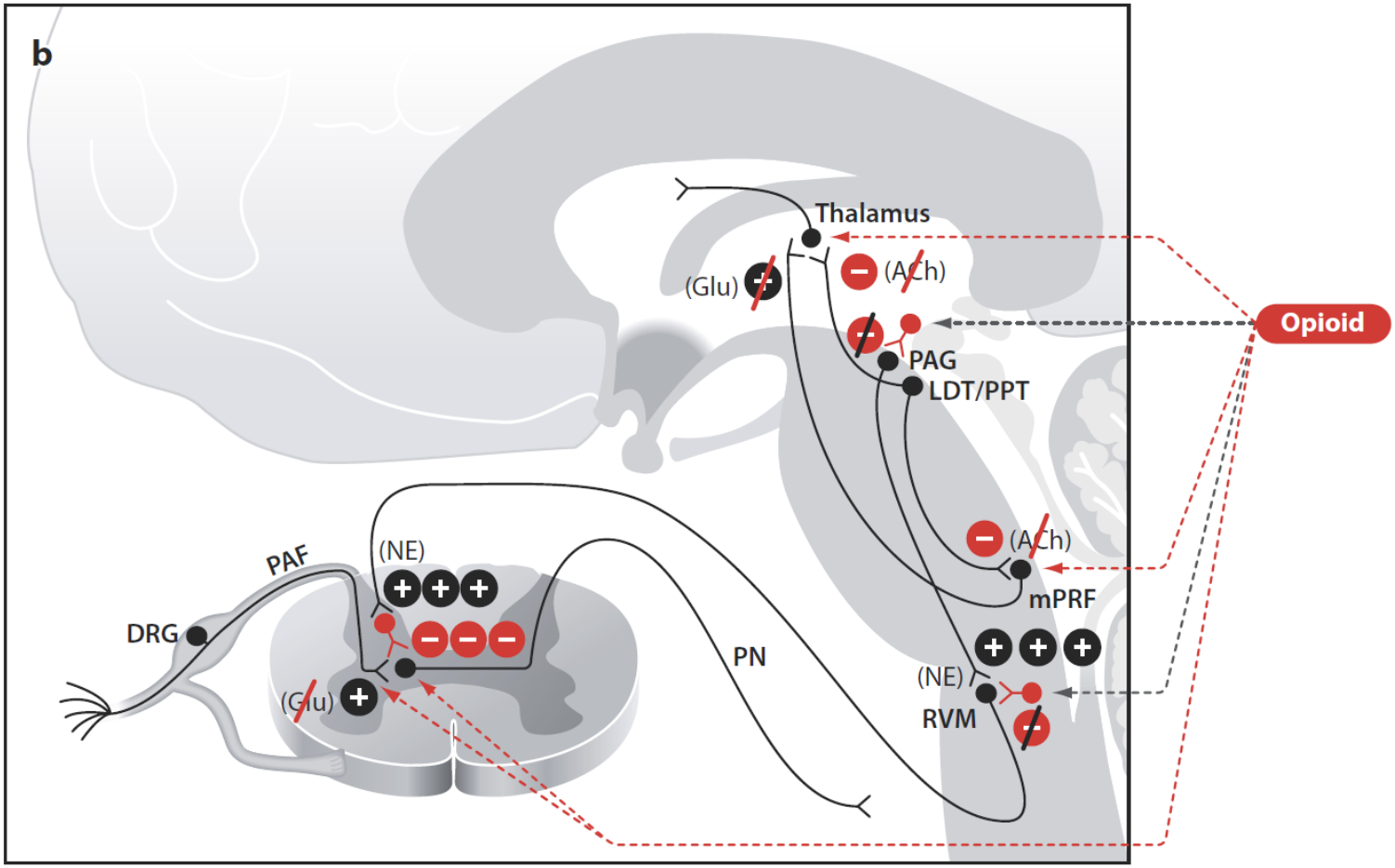
Analgesic Component

Analgesic Component

Effect of analgesic drugs

Effect of noxious stimulation

Opioids and the brain: opioid effect

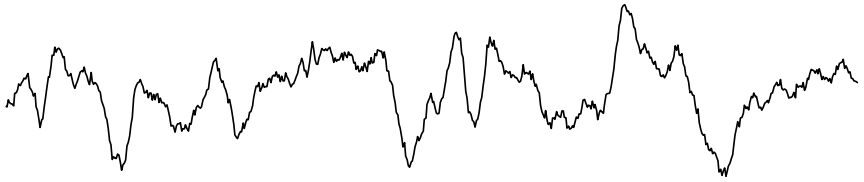


Brown,EN. Ann Rev Neurosci. 2011

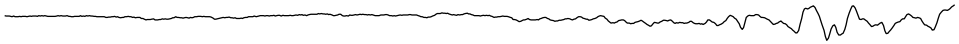
Opioids and EEG

Basal

Opioid



Propofol



Opioids and EEG

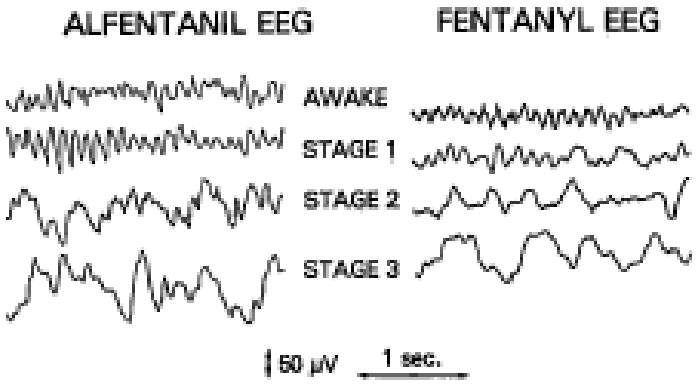


FIG. 1. EEG Stages for fentanyl and alfentanil. Awake—mixed alpha (8–13 Hz) and beta (>13 Hz) activity. Stage 1—slowing with alpha spindles. Stage 2—more slowing, theta activity present (4–7 Hz). Stage 3—maximal slowing, delta waves present (<4 Hz) with high amplitude.

Scott, Anesthesiology 1985

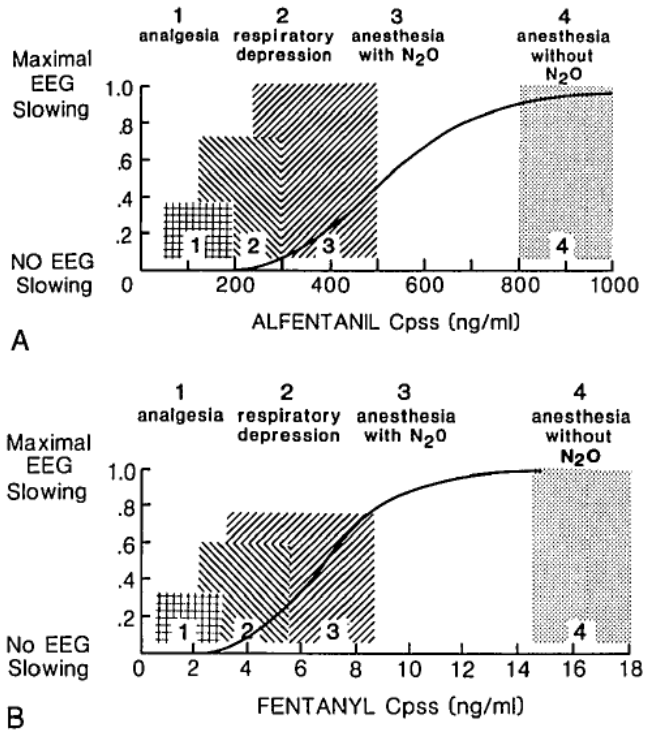
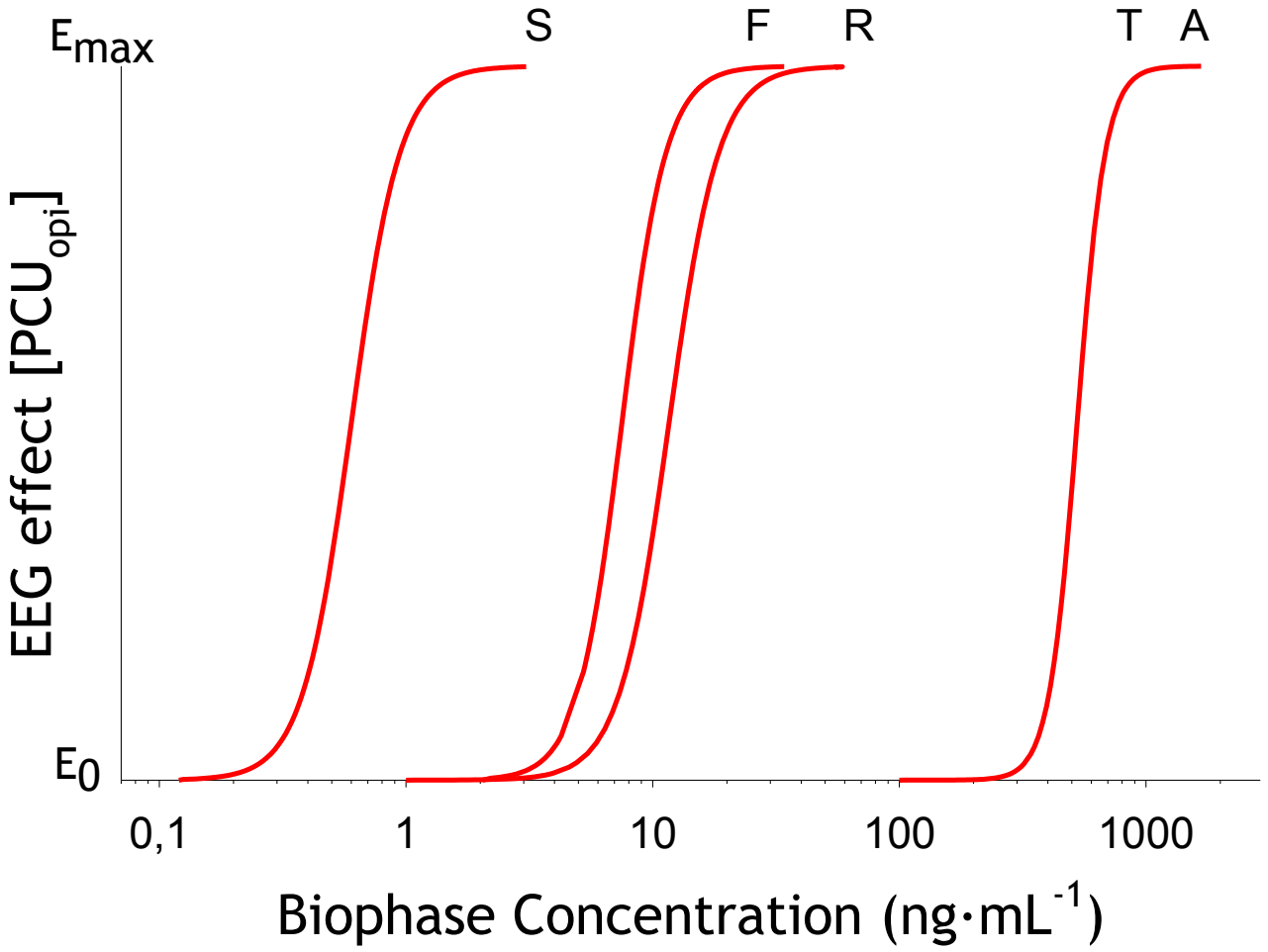


FIG. 1. The overlap between alfentanil (*A*) and fentanyl (*B*) steady-state plasma concentrations required to produce EEG slowing and concentrations required to produce clinical stages of anesthesia. Anesthesia without nitrous oxide refers to "cardiac" anesthesia when the opioid is supplemented with a benzodiazepine or scopolamine to produce amnesia. Data have been adapted from references 1–4.

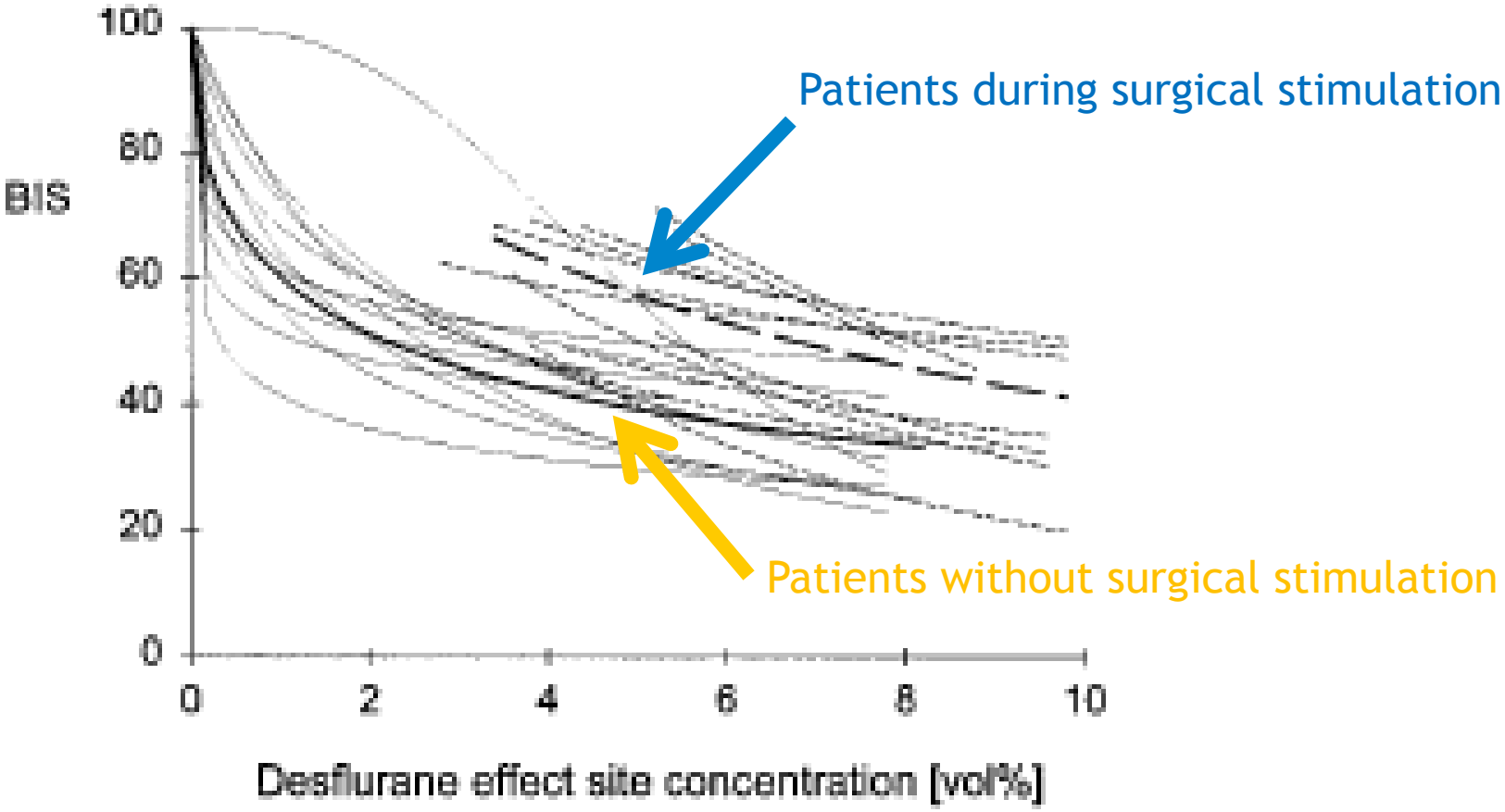
Ebling WF, Anesthesiology 1990

EEG effects of opioids



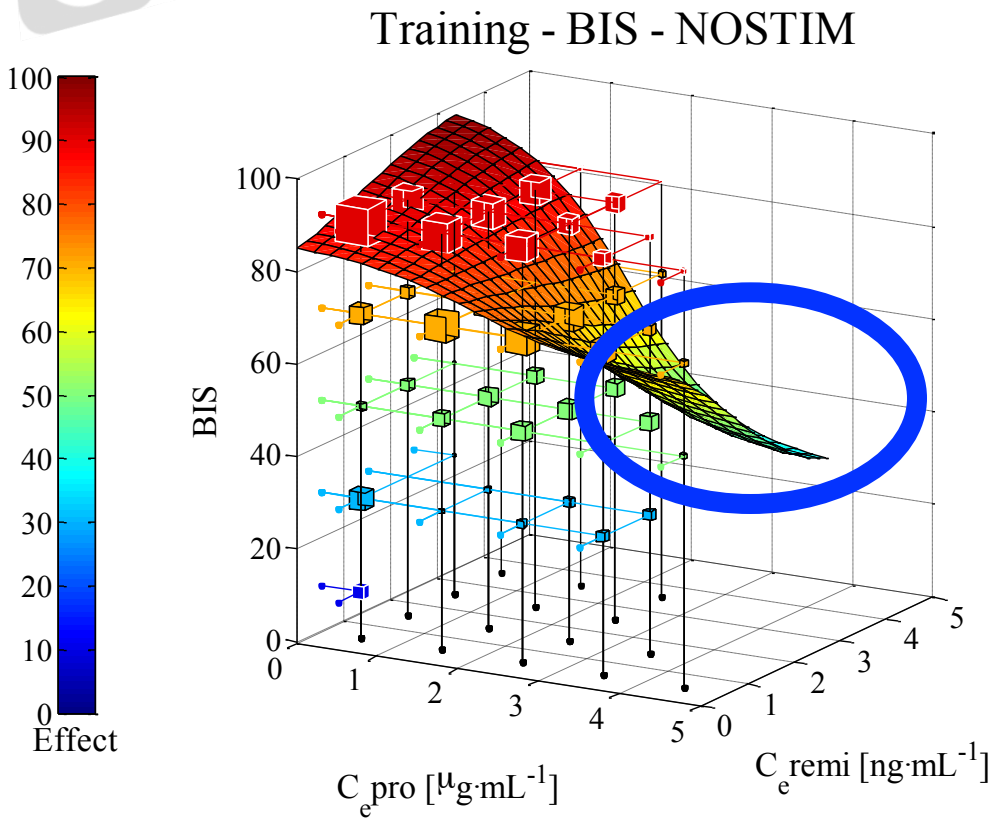
Gambus, Anesthesiology 1995

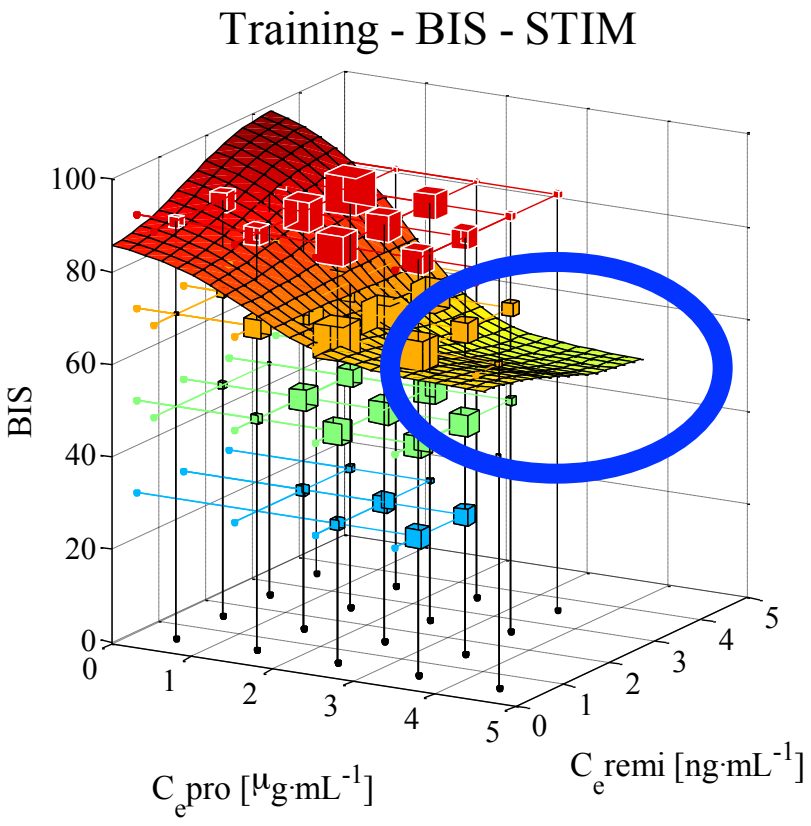
EEG and Nociceptive Stimulation



Röpcke H, Anesthesiology, 2001

BIS vs propofol and remifentanil: presence/absence of STIM



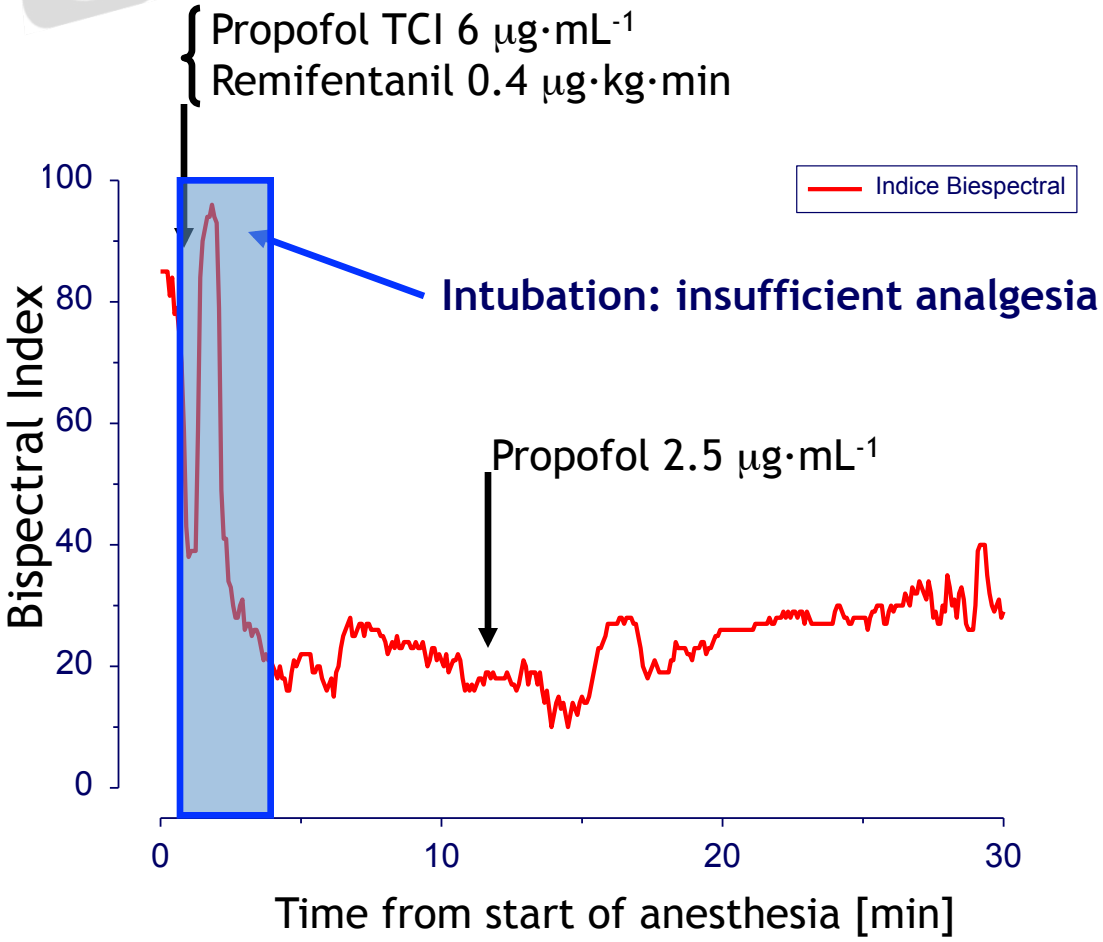


Size of squares proportional to number of data points

Color proportional to intensity of effect on the BIS

Gambús P.; Anesthesia & Analgesia 2011

Analgesic Effects under Hypnosis



- Low dose
- Timing:
  - No remifentanil bolus
  - Intubation before remifentanil concentration reaches therapeutic levels

EEG: hypnotics-opioids

- Opioids act on the brain
  - Delta waves
- **Effect of opioids is apparent and quantifyable in EEG**
  - PKPD models currently used
- **Noxious stimulation affects EEG**
  - Inhalation agents
  - Propofol
  - Opioids
- **EEG changes at a range of concentrations**
  - Clinically relevant for propofol
  - Too high clinically for opioids
- **Changes on "processed EEG" from opioids are overshadowed by changes induced by hypnotics**

Composite Variability Index (CVI)

- EMG voltage average, standard deviation of BIS and EMG, as well as its combination, are indicators of nociceptive stimulation.

	Movement responses			
	LMA		Skin incision	
NFRT	0.77 (0.07)	p = 0.0001	0.72 (0.08)	p = 0.004
BIS	0.41 (0.08)	p = 0.29	0.56 (0.09)	p = 0.50
CVI	0.46 (0.13)	p = 0.76	0.48 (0.15)	p = 0.88
NSRI	0.49 (0.09)	p = 0.92	0.76 (0.07)	p = 0.0001
Propofol Ce	0.35 (0.07)	p = 0.04	0.66 (0.07)	p = 0.03
Remifentanil Ce	0.68 (0.07)	p = 0.01	0.72 (0.07)	P = 0.003

Von Dincklage, 2012

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Table 3. Prediction Probability Values

	$Parameter_{baseline}$ vs Ce_{remi}	$Parameter_{max}$ vs Ce_{remi}	$Parameter_{baseline}$ vs movement	$Parameter_{max}$ vs movement	Δ value vs movement
CVI	0.61 (0.04)	0.63 (0.04)	0.65 (0.06)	0.72 (0.06)	0.75 (0.06)
BIS	0.64 (0.04)	0.64 (0.04)	0.67 (0.06)	0.69 (0.06)	0.62 (0.07)
sBIS	0.52 (0.04)	0.55 (0.04)	0.60 (0.06)	0.61 (0.07)	0.61 (0.07)
sEMG	0.53 (0.04)	0.59 (0.04)	0.60 (0.06)	0.78 (0.05)	0.76 (0.06)*
Heart rate	0.70 (0.03)	0.70 (0.04)	0.79 (0.05)	0.81 (0.04)	0.53 (0.07)†
BP_{sys}	0.58 (0.04)	0.60 (0.04)	0.71 (0.05)	0.74 (0.05)	0.60 (0.06)

Ellerkman R, Anesth&Analg, 2013

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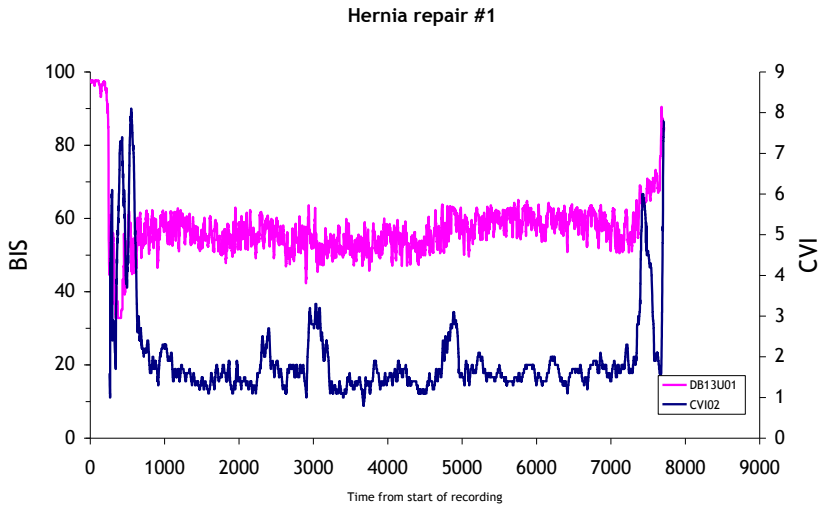
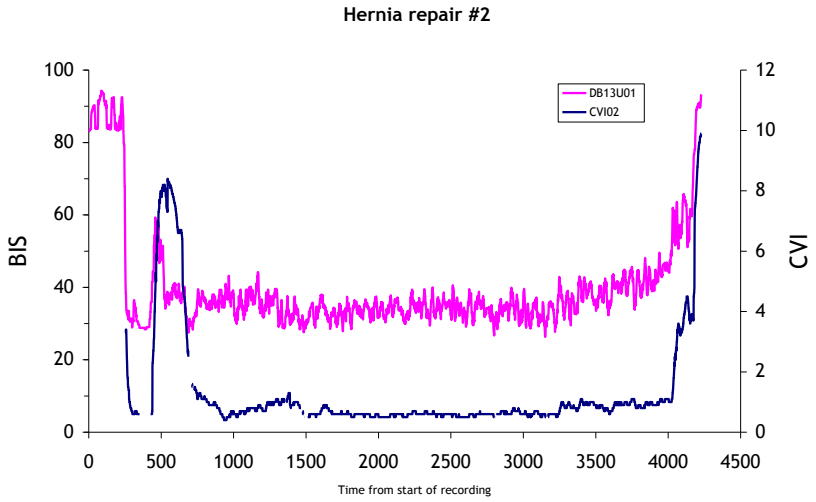
sEMG	0.53 (0.04)	0.59 (0.04)	0.60 (0.06)	0.78 (0.05)	0.76 (0.06)*

RESULTS: CVI and BIS more accurately correlate with somatic response to an Observer Assessment of Alertness and Sedation-noxious stimulation than HR, MAP, CeREMI, and propofol effect-site concentration (Tukey post hoc tests $P < 0.01$). Change in CVI is more adequate to monitor response to stimulation than changes in BIS, HR, or MAP (as described by the Mathews Correlation Coefficient with significance level set at $P < 0.001$). In contrast, none of the candidate analgesic state indices was uniquely related to a specific opioid concentration and is extensively influenced by the hypnotic state as measured by BIS.

Sahinovic M, Anesth&Analg, 2014

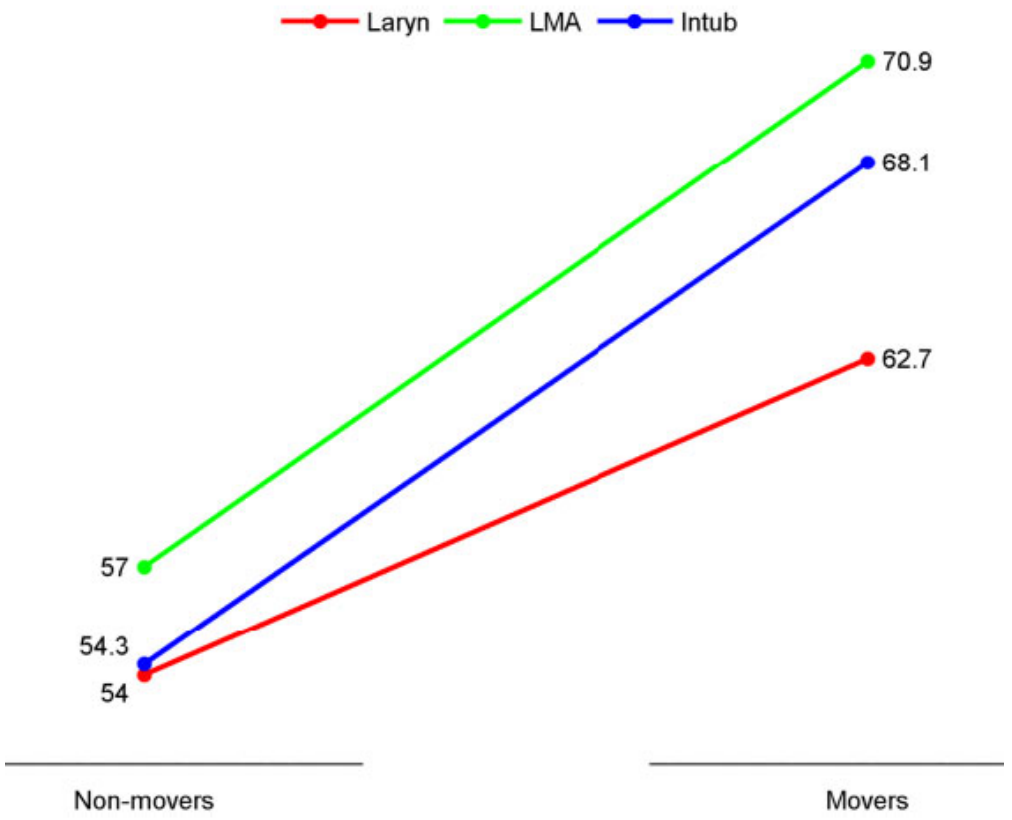
Composite Variability Index (CVI)





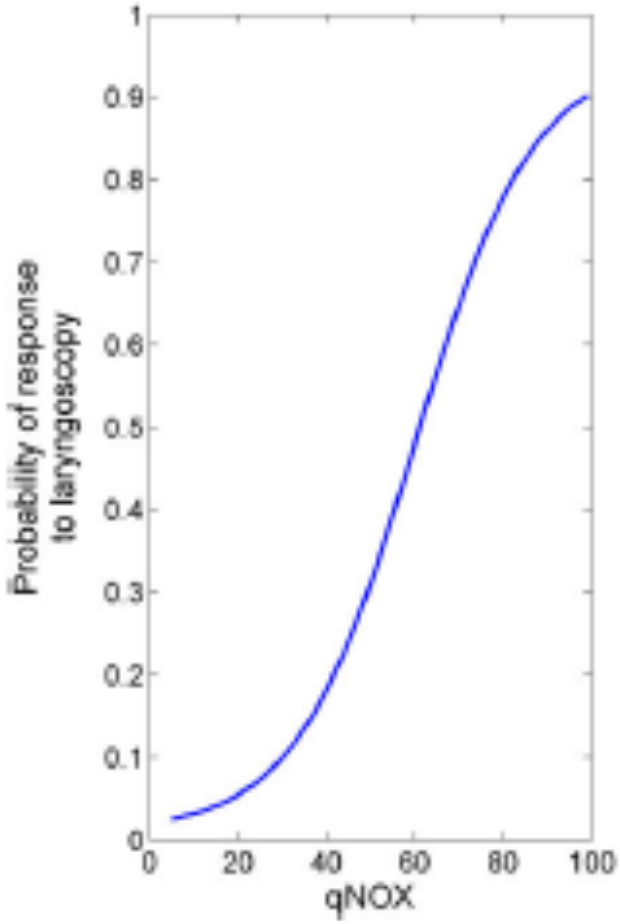
Q-NOX

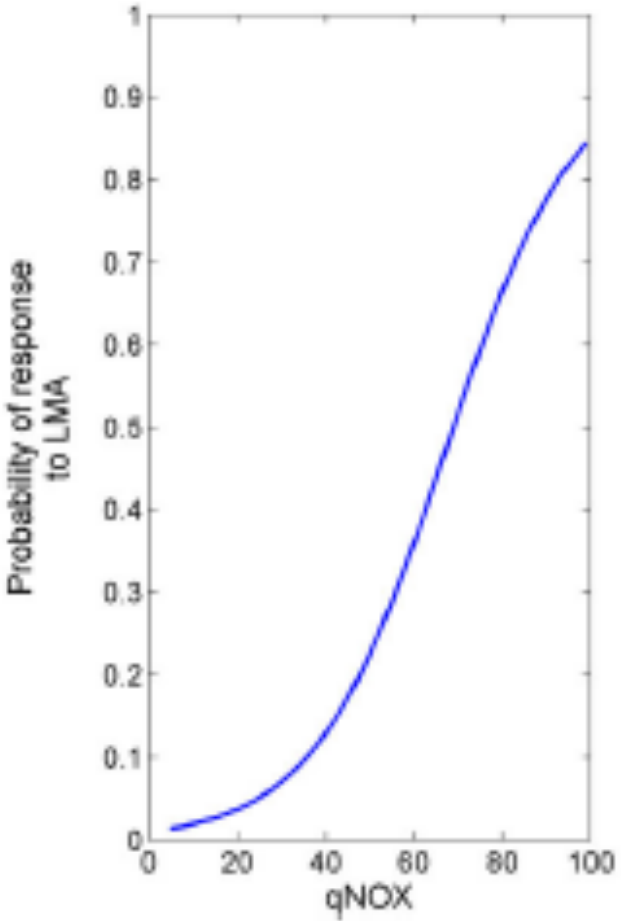
- Information from EEG freq bands 0.5-45Hz
  - ANFIS (fuzzy logic) approach
  - Predict movement response
- Correlates to opioid predicted concentrations
- Relation to probability of response to mov
  - Sedation-analgesia
  - TIVA

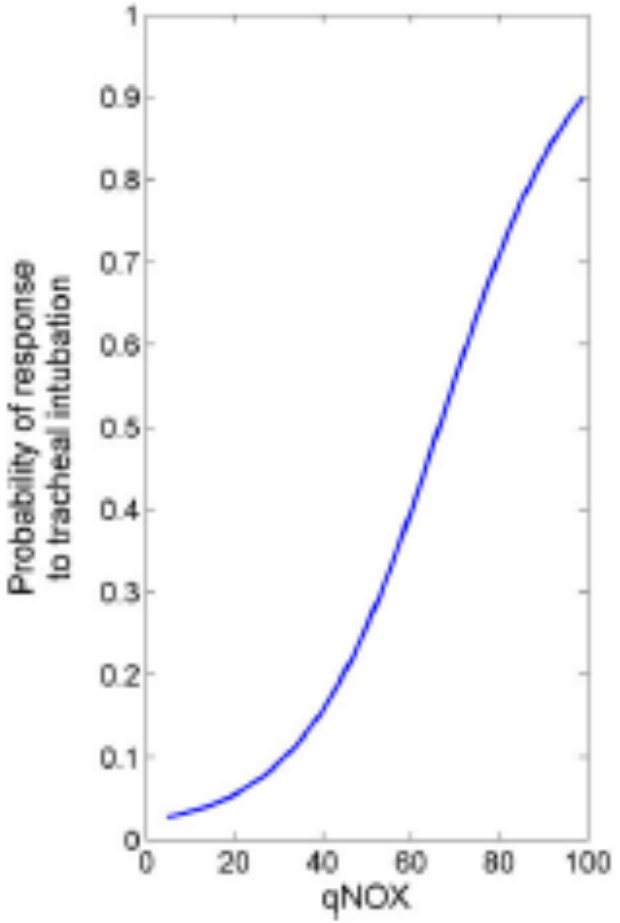


Jensen EW et al; Acta Anaesth Scand. 2014

Q-NOX







Jensen EW et al; Acta Anaesth Scand. 2014

Other approaches

Autonomous Nervous System

- Sympathetic tone
  - Pupil size
    - Opioid effect
  - Skin conductance
  - Plethysmographic signal analysis
- Parasympathetic tone
  - Respiratory Synus Arrythmia: ANI
- Multiparameter:
  - Response Entropy of the EEG:
    - Initial development
  - Surgical Stress Index (SSI) w/o EEG

    $100-(0.7*PPGA_{norm}+0.33*HBI)$
  - Surgical Pleth Index (SPI): based on two components of the plethysmographic signal

Anesthesia Nociception Index (ANI)

- Nociception reduces parasympathetic tone and this affects heart rate variability, from which the analgesia/ nociception index (ANI) can be derived
- Calculates the fraction of spectral power related to vagal activity
- Validation still in progress
- Requires a regular respiratory pattern: mechanical ventilation

- Predicts hemodynamic responses in different clinical scenarios
- Decrease postoperative pain
- Better titration of opioid administration during surgery

Conclusions

- Processed EEG indices are best indicators of **hypnotic effect**
- EEG as an indicator of **response to nociception**
  - Correlates with analgesic concentration
  - Differentiates noxious stimulation
  - Hypnotic effect sweeps all others
  - Clinically
    - Prediction ability suboptimal
    - Promising combinations have not succeed
- Non EEG derived as indicators of nociception
    - Limitations: induction, cardiac problems, specific drugs, …
    - Predict hemodynamic responses

Future

- **Indicators combining information?**
  - In one index?
  - Several at the same time?
  - Incorporating Predicted (measured) Drug Concentrations?
    - NSRI
    - Navigator Systems
- **Neurophysiologic measures with higher resolution than EEG?**
    - Direct vs surrogate
- **Imaging techniques in anesthesia?**

Reasons to believe in EEG as a measure of nociceptive response

- Slowing of raw EEG with increasing concentrations of opioids
- Able to predict movement to NOX
- Able to predict cortical effects of opioids
- Contribution to levels of anesthesia