General Anesthesia: A Case Study in Combining Neuroscience, Statistics and Modeling

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Outline

1. A Clinical Look at General Anesthesia

2. Loss of Consciousness Induced by Propofol and Other Anesthetics

3. Defining the Anesthetic State as a Function of Age

4. Closed Loop Control of Medical Coma

5. Anesthesia and Age Revisited

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

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

Neuroscience, statistics and modeling have been crucial for studying these oscillations.
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 Cause General Anesthesia is Unknown?

Brown, Lydic, Schiff *NEJM* (2010)
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
### General Anesthesia and Sleep

#### Awake

<table>
<thead>
<tr>
<th>Awake with eyes open (minimally conscious state)</th>
<th>Awake with eyes closed (minimally conscious state)</th>
</tr>
</thead>
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#### General Anesthesia

<table>
<thead>
<tr>
<th>Phase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradoxical excitation (minimally conscious state)</td>
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<tr>
<td>Phase 2 (vegetative state, coma)</td>
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<tr>
<td>Phase 3: Burst suppression (coma)</td>
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<td>Phase 4: Isoelectric (coma, brain death)</td>
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#### Sleep

<table>
<thead>
<tr>
<th>REM</th>
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<tbody>
<tr>
<td>Non-REM stage 1</td>
</tr>
<tr>
<td>Non-REM stage 2 (vegetative state)</td>
</tr>
<tr>
<td>Non-REM stage 3, or slow-wave (vegetative state, coma)</td>
</tr>
</tbody>
</table>

Brown, Lydic and Schiff, New England Journal of Medicine 2010
Clinical Electroencephalography of Propofol

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

Slow-Alpha Oscillation

Burst Suppression

52 year-old female
Propofol boluses of 100, 50, and 50 mcg

Zipper Opening
Baseline
y-axis: 0-30Hz
x-axis: 20trials
Mechanisms for Alpha and Slow Oscillations

GABA Inhibition at Inhibitory Interneurons

Brown, Purdon, Van Dort, ARN 2011

Alpha: Pathological Oscillation

8–12 Hz

Grid Electrodes

Microelectrodes

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

Lewis et al. PNAS, 2012
Thalamocortical Coherence Measured in Rodents

Coherence around LORR

- Delta (1-5 Hz)
- Alpha (9-15 Hz)
- Beta (20-30 Hz)

Flores, Unpublished
Mathematical Modeling

Awake with eyes open (minimally conscious state)

<table>
<thead>
<tr>
<th>B</th>
<th>General Anesthesia</th>
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Paradoxical excitation (minimally conscious state)

Phase 1

Phase 2 (vegetative state, coma)

Phase 3: Burst suppression (coma)

Phase 4: Isoelectric (coma, brain death)

Mc Carthy et al. *J. Neurosci* 2008

Ching et al. *PNAS*, 2010

Brown et al. *NEJM* 2010

Ching et al. *PNAS*, 2012
Anteriorization

Electroencephalogram

Tinker and Michenfelder (1977)

Mathematical Modeling

Ching et al. *PNAS*, 2010

Vijayan et al. *J. Neurosci*, 2013
Summary

Why Does Propofol Make You Unconscious?

Cortex and Thalamus

**alpha (8-12 Hz) rhythms** strongly couple the thalamus and cortex restricting communication

**slow-wave (< 1 Hz) rhythms** create local islands preventing communication within the cortex

**anteriorization** as a mechanism for frontal-parietal disconnection

Brain Stem

**blocking the brain stem arousal pathways** prevents communication of the lower parts of the brain with the cortex
Different Anesthetics Have Different EEG Signatures

Propofol (+GABA)

Dexmedetomidine (+Alpha2 Adrenergic)

Ketamine (-NMDA)

Brown et al. 2011; Brown et al, 2014
Different Anesthetics Have Different EEG Signatures

Sevoflurane (+GABA)

Brown et al 2011; Brown et al 2014
Purdon et al 2015

EEG Education Program

www.eeganaesthesia.com or www.anesthesseeg.com
Defining the Anesthetic State As a Function of Age

Laura Cornelissen

Seun Akeju

Seong-Eun Kim

Charles Berde

Patrick Purdon
Spectrograms of the Ages

3-year-old patient

14-year-old patient

30-year-old patient

57-year-old patient, "Young Brain"

56-year-old patient, "Old Brain"

81-year-old patient
Total EEG Power (1 to 50 Hz) Illustrative Examples

Brain Developmental Milestones

Development of Thalamocortical Connections

Critical Period

Rakhade and Jensen, Nat Rev Neurol, 2009

CopperKettle, 2006
Closed-Loop Control of Medical Coma

ShiNung Ching

Maryam Shanechi

Ken Solt

Jessica Chemali

Patrick Purdon
Brain States Associated with Burst Suppression

General Anesthesia

Hypothermia

Early-Infantile Epileptic Encephalopathy (Ohtahara’s Syndrome)

Newborn with Refractory Seizures

Coma

Ching et al. PNAS, 2012

Fig 1. Neonatal EEG showing burst suppression pattern in a newborn with multiple seizures type, refractory to antiepileptic drugs. Arrows indicate myoclonic seizures. 1s/scale.
Burst Suppression: EEG, Model Prediction & Experimental Verification

Model Prediction

\[ I_{KATP} = g_{KATP} z (v - E_K) \]
\[ z = \frac{1}{(1 + 10 [ATP])} \]
\[ [Na] = F_{Na} - 3K_m [Na]^3 [ATP] \]
\[ [ATP] = J_{ATP} ([ATP]_{max} - [ATP]) - K_m [Na]^3 [ATP] \]

- 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)

Ching et. al. PNAS 2012

ATP

% Increase in Conductance ATP

Deoxyhemoglobin

Oxyhemoglobin
A Brain-Machine Interface

for Control of Medically-Induced Coma

PLoS Computational Biology
Oct. 2013
Medical Coma BMI Error Analysis

Reliable Control:
20 of 20 levels: abs error < 0.15

Highly Reliable Control:
17 of 20 levels: abs error < 0.10
Spectra of Anesthetized Children as a Function of Age

11 0 to 3 Months of Age

(A) Individual infants

1 month

2 month

3 month

(B) Group

0-3 months

19 4 to 6 Months of Age

(C) 4 month

5 month

6 month

(D) 4-6 months
Spectra and 95% Confidence Intervals for Spectral Differences

A

Power (dB)

Frequency (Hz)

0-3 months
4-6 months

Cornelissson et al. eLife 2015
Comparing the Spectra of Two Time Series: Bootstrap

Estimate $\hat{f}_x(\omega)$ and $\hat{f}_y(\omega)$ by multitaper methods.

$$x' = Fx \approx N(0, D(\hat{f}_x(\omega))) \quad y' = Fy \approx N(0, D(\hat{f}_y(\omega)))$$

where $F$ is the Fourier transform.

If we assume that $x$ and $y$ stationary.
Compute the 95% Confidence Interval for

\[ \Delta = f_x(\omega) - f_y(\omega) \]

using the bootstrap.

1. Draw

\[ x^* = (x_1^*, x_2^*, \ldots, x_n^*) \]
\[ N(0, D(\hat{f}_x(\omega))) \]

\[ y^* = (y_1^*, y_2^*, \ldots, y_n^*) \]
\[ N(0, D(\hat{f}_y(\omega))) \]

2. Compute

\[ \hat{\Delta}^*(\omega) = \hat{f}_x(\omega)^* - \hat{f}_y(\omega)^* \]

3. Repeat steps 1 and 2 1,000 times.

4. Order

\[ \hat{\Delta}^*_{(1)}(\omega), \hat{\Delta}^*_{(2)}(\omega), \ldots, \hat{\Delta}^*_{(1,000)}(\omega) \]

\[ \hat{\Delta}^*_{(25)}(\omega) \text{ Lower Confidence Bound} \]
\[ \hat{\Delta}^*_{(975)}(\omega) \text{ Upper Confidence Bound} \]

Hurvich and Zeger, 1987; Ramos 1988
Spectra and 95% Confidence Intervals for Spectral Differences

A

![Graph showing spectra and confidence intervals for 0-3 months and 4-6 months.](image)

B

C

D

E

![Graph showing power difference for different frequencies.](image)

Cornelissen et al. *eLife* 2015
Sevoflurane Spectrograms

A 0-3 months

B 4-6 months

Cornelisson et al. eLife 2015
Spectra and 95% Confidence Intervals for Frontal-Occipital Spectral Differences

0 to 3 Months of Age

4 to 6 Months of Age

Cornelissen et al. eLife 2015
Conclusion

The integration of neuroscience, statistics and mathematical modeling has been critical for helping to decipher how anesthetics act in the brain to create the altered states of arousal which constitute general anesthesia.
Brain Stem Effects of Propofol
A. Apnea
B. Atonia
C. Unconsciousness

Brown, Purdon, Van Dort, Annual Review of Neuroscience (2011)
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