Anesthetic Neurotoxicity – Harm or Hype?

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Disclosures

None
Objectives

1. To evaluate and appraise the preclinical literature surrounding anesthetic neurotoxicity in the young and old brain

2. To evaluate and appraise the clinical literature surrounding anesthetic neurotoxicity in the young and old brain
Outline

• Young brain
• Old Brain
• Research Challenges
• Summary

"Just wait until you're my age and you forget what it's like to be your age!"

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THE YOUNG BRAIN
Laboratory Evidence

Accumulating laboratory evidence suggests that commonly used anesthetics may cause harm to the developing brain.
Laboratory Evidence

Ikonomidou et al., 2000:

- **Intrauterine exposure to alcohol:** FAS
- **Similar findings in neonatal rats**
- **Postnatal ethanol exposure:** neuroapoptosis

Apoptosis occurred in brain regions affected by both NMDA antagonism and GABAergic agonism.

Laboratory Evidence

Jevtovic-Todorovic et al., 2003:

- Commonly used anesthetics act via GABA agonism and NMDA antagonism
- Similar neuroapoptotic risk with anesthetics?
- Midazolam, nitrous oxide, isoflurane, 7-d-old rats

Jevtovic-Todorovic et al; J Neurosci. 2003 Feb 1;23(3):876-82
Laboratory Evidence

Jevtovic-Todorovic et al., 2003:

- Midazolam, nitrous oxide, isoflurane exposure (6h):

Neuroapoptosis

Learning, memory impairment

Jevtovic-Todorovic et al; J Neurosci. 2003 Feb 1;23(3):876-82
Laboratory Evidence

**Jevtovic-Todorovic et al., 2003:**

- Midazolam, nitrous oxide, isoflurane exposure (6h):

  Neuroapoptosis

  Learning, memory impairment

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Jevtovic-Todorovic et al.; J Neurosci. 2003 Feb 1;23(3):876-82
Young et al., 2005:

- Neuroapoptosis redemonstrated with ketamine, midazolam
- Dose-dependent, likely additive mechanism
Isoflurane

- **Neuroapoptosis**
  - Young et al. 2008
  - Head et al. 2009
  - Brambrick et al. 2010
  - Wang et al. 2015

- **Synaptic impairment**
  - Head at el. 2009

- **Learning impairment**
  - Stratmann et al. 2009
  - Palanisamy et al. 2010
  - Murphy et al. 2013
Sevoflurane

- **Neuroapoptosis**
  - Zhang et al. 2008

- **Synaptic impairment**
  - Ji et al. 2012

- **Learning impairment**
  - Satomoto et al. 2009
  - Shih et al. 2012

*However, *reversed with environmental enrichment*
Desflurane

- **Neuroapoptosis**
  - Istaphanous et al. 2011
  - Kodama et al. 2015

Propofol

- **Neuroapoptosis**
  - Cattano et al. 2008
  - Kahraman et al. 2008 (in vitro cultures)
Anesthetics associated histopathologic toxicity, learning impairment in the developing brain pre-clinically...

...**CLINICAL CORRELATION**?
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

Retrospective, birth cohort study

Olmsted County, Minnesota (1976-1982)

GA group (n=593), non-exposed group (n=4,764)

GA group: one (or more) exposures to GA before age 4

Broad surgical exposure (general, urology, ENT…)

Wilder et al.; Anesthesiology. 2009 Apr;110(4):796-804
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

• Exposure to GA, correlation with learning disabilities (LD)
  - Single exposure: HR 1.00 (95% CI, 0.79-1.27)
  - Two exposures: HR 1.59 (95% CI, 1.06–2.37)
  - Three exposures: HR 2.60 (95% CI, 1.60–4.24)
  - LD increased longer cumulative duration of anesthesia exposure (P=0.016)

Wilder et al.; Anesthesiology. 2009 Apr;110(4):796-804
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort

Robert T. Wilder, M.D., Ph.D.,* Randall P. Flick, M.D., M.P.H.,† Juraj Sprung, M.D., Ph.D.,‡ Slavica K. Katusic, M.D.,§ William J. Barbaresi, M.D.,∥ Christopher Mickelson, M.D.,¶ Stephen J. Gleich, M.D.,,** Darrell R. Schroeder, M.S.,†† Amy L. Weaver, M.S.,‡‡ David O. Warner, M.D.†

Wilder et al.; Anesthesiology. 2009 Apr;110(4):796-804

• Strengths:
  • Detailed medical, educational data available (designed cohort)
  • Cohort from the same community: same school systems, same healthcare systems; similar socioeconomic, demographic variables
  • Detailed anesthetic exposure, duration of exposure
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

• Caveats:
  • Impossible to separate anesthetic-specific contributions to LD (i.e. surgery, hospitalization, underlying illness, etc. all confounders)
  • Inherently higher illness burden (higher ASA scores) in patients requiring multiple operations), though univariate analysis did not reveal LD correlation with higher ASA scores (confirmed with subsequent adjustment – Flick et al., Pediatrics. 2011 Nov;128(5):e1053-61
  • Halothane was the primary maintenance agent
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort

Charles DiMaggio, PhD,*† Lena S. Sun, MD,† and Guohua Li, MD, DrPH*†

DiMaggio et al.; Anesth Analg. 2011 Nov;113(5):1143-51

• New York State Medicaid program (1990-2005)

• Retrospective analysis, children < 3 years old
  • Sibling births (minimized demographic, genetic variance)
  • Exposed to GA (n=304)
  • Unexposed to GA (n=10,146)
  • Noncardiac, non-neurologic, non-ENT surgery

• Incidence of developmental and behavioral disorders assessed
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort
Charles DiMaggio, PhD,*† Lena S. Sun, MD,‡ and Guohua Li, MD, DrPH*†

DiMaggio et al.; Anesth Analg. 2011 Nov;113(5):1143-51

- Exposure to GA, correlation with behavioral and developmental disorders – entire group cohort:
  - Single exposure: HR 1.1 (95% CI, 0.8–1.4)
  - Two exposures: HR 2.9 (95% CI, 2.5–3.1)
  - Three+ exposures: HR 4.0 (95% CI, 3.5–4.5)
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort

Charles DiMaggio, PhD,*† Lena S. Sun, MD,‡ and Guohua Li, MD, DrPH*†

DiMaggio et al.; Anesth Analg. 2011 Nov;113(5):1143-51

• Exposure to GA, correlation with behavioral and developmental disorders – sibling-matched analysis:

• Matched relative risk (138 sibling pairs): 0.9 (95% CI, 0.6–1.4)
Retrospective Associations
Surgery, Anesthesia, and Neurodevelopment

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort

Charles DiMaggio, PhD,*† Lena S. Sun, MD,‡ and Guohua Li, MD, DrPH*†

DiMaggio et al.; Anesth Analg. 2011 Nov;113(5):1143-51

• **Strengths:**
  - Minimized demographic, genetic variables
  - Large cohort, relatively contemporary dataset

• **Caveats:**
  - Sample restricted to Medicaid population
  - No details regarding zygosity of sibling pairs
  - No detailed anesthetic information available
Retrospective Associations

Surgery, Anesthesia, and Neurodevelopment

• Possible link between surgery, anesthesia, and neurodevelopment

• Stronger association with increased exposure

• *Very* hard to isolate anesthetic-specific contributions to developmental impairment

• *…Prospective, controlled, analysis required…*
Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Doris, Graham Bell, Robyn Sturgatt, David C Belfinger, Tibor Schuster, Sarah J Armup, Polyanne Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium*
Pediatric Anesthesia and NeuroDevelopment Assessment

- Large, multi-center study
- Sibling-matched cohort study (8 – 15 yo)
  - Sibling *retrospectively exposed* to GA (<36 months)
    - ASA I-II, inguinal hernia repair, single exposure
  - Sibling *not retrospectively exposed to GA*
- Prospective cognitive testing battery (~2 hours)
  - Global *and* domain-specific testing
**Pediatric Anesthesia and NeuroDevelopment Assessment**

- **Pilot results** (96.7% success obtaining necessary retrospective data, 28 sibling pairs):

<table>
<thead>
<tr>
<th>Group</th>
<th>Verbal IQ (SD)</th>
<th>Performance IQ (SD)</th>
<th>Full IQ (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA Exposure</td>
<td>106.1 (±16.3)</td>
<td>109.1 (±16.0)</td>
<td>108.2 (±14.0)</td>
</tr>
<tr>
<td>No Exposure</td>
<td>109.2 (±17.9)</td>
<td>113.9 (±15.9)</td>
<td>112.8 (±16.8)</td>
</tr>
</tbody>
</table>

No statistically significant differences in cognitive testing between exposed and unexposed groups from pilot data.

Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Sturgatt, David C Bellingar, Tibor Schuster, Sarah J Arnup, Polyanne Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium*
General Anaesthesia compared to Spinal Trial

- Large, multi-center, international study
  - Infants < 60 weeks; randomly assigned GA vs. spinal (1:1)
  - Hernia repair, single-exposure (sevoflurane)
- Cognitive testing:
  - Primary outcome: cognitive testing, 5 yo
  - Secondary outcome: cognitive testing, 2 yo
- Power for equivalence, 5 year outcome
**Interim analysis...**

Interpretation: For this secondary outcome, we found no evidence that just less than 1 h of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia.

<table>
<thead>
<tr>
<th>Group</th>
<th>Composite Cognitive Score (SD)</th>
<th>Statistical Inference (mean difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>98.2 (±14.7)</td>
<td>0.458 [-2.02-2.94] 95% CI</td>
</tr>
<tr>
<td>Awake-regional</td>
<td>98.6 (±14.2)</td>
<td></td>
</tr>
</tbody>
</table>

Equivalence *a priori*: mean scores lie within **5 points**, 95% CI
THE OLD BRAIN
Surgery, Anesthesia, and Neurodegeneration

EARLY AND MIDLIFE EXPOSURE TO ANESTHESIA AND AGE OF ONSET OF ALZHEIMER’S DISEASE

Alzheimer’s Disease and Cumulative Exposure to Anesthesia: A Case-Control Study
Nicolaas I.L.J. Bohnen, MD, PhD,† Mark A. Warner, MD,* Emre Kokmen, MD,† C. Mary Beard, RN, MPH, and Leonard T. Kurland, MD, DrPH

Parkinsonian Symptoms during Emergence from General Anesthesia
Stanley Muravchick, M.D., Ph.D.,* David S. Smith, M.D., Ph.D.†
Postoperative Cognitive Dysfunction (POCD)

Cognitive testing battery, POCD: >2 SDs worse than mean (Z-score)

13 hospitals, Europe and the United States

POCD in 25.8% of patient at 1 week, 9.9% of patients at 3 months

Duration of anesthesia, OR 1.1 (1.0-1.3, 95% CI), p=0.01

...anesthetic contribution to cognitive dysfunction after surgery?
2004...

**Halothane**-induced Aβ oligomerization; from Eckenhoff et al., Anesthesiology. 2004 Sep;101(3):703-9

*In vitro cell cultures*
Alzheimer’s Disease (AD) Pathophysiologic Hallmarks:

Beta-Amyloid Plaque

Tangles inside dying nerve cell

Tangles are forming

Healthy area

National Institute on Aging

Alzheimer’s Association
Isoflurane-associated caspase activation, Aβ production *in vitro*

*Xie et al., 2006 Anesthesiology. 2006 May;104(5):988-94*
2008...

**Desflurane**: no increased in caspase activation or Aβ production *in vitro* unless accompanied by hypoxia

*Zhang et al.* J Biol Chem. 2008 May 2;283(18):11866-75
2009...

Sevoflurane: increased caspase activation, increased Aβ levels

Propofol: tau phosphorylation in hippocampal cells, both normothermic and hypothermic conditions.

2012 – Present

Mechanisms:

• Isoflurane:
  • Endoplasmic reticulum (ER) stress
  • Ryanodine receptor (RyR) activation
  • Inhibited with dantrolene

2012 – Present

Mechanisms

• **Isoflurane**
  • Mitochondrial permeability
  • ROS production

• **Desflurane** not associated with above findings

Zhang et al., Ann Neurol. 2012 May; 71(5): 687–698
Based on *in vitro* models…

**2012 – Present**

Isoflurane Desflurane

ER stress, Mitochondrial dysfunction, ROS, etc.

Dantrolene

Vitamin C

Celastrol

(Anti-inflammatory)

Caspase activation

?Neurotoxicity

⇒?Aβ, apoptosis, etc.

---


Cognitive Function – Aged Animals

• Aged rats: spatial memory impairment (maze testing) 2 weeks after isoflurane-nitrous oxide anesthesia
  
  *Culley et al., Anesth Analg. 2004 Nov; 99(5): 1393–7*

• Aged rats: cognitive impairment up to 1 month after isoflurane anesthesia
  
  *Bianchi et al., Neurobiol Aging. 2008 Jul; 29(7): 1002–10*

• Aged rats: no differences in spatial memory impairment or fear conditioning 4 months after isoflurane anesthesia
  
  *Stratmann et al., Anesthesiology. 2010 Feb; 112(2): 305–15*
Aged Rodents – Cognitive Impairment (*Isoflurane* vs. control)

- **Spatial memory impairment**
  - Culley et al. 2004

- **Spatial, reference memory impairment**
  - Bianchi et al. 2008

- None
  - Stratmann et al. 2010

Timeline:
- Anesthetic Exposure
- 2 weeks
- <1 month
- 4 months
Anesthetics associated with AD precursors and cognitive impairment in laboratory models…

...CLINICAL CORRELATION?
Comparisons Among Agents

The Effects of Isoflurane and Desflurane on Cognitive Function in Humans

Bin Zhang, MD, MS,* Ming Tian, MD, PhD,* Yu Zhen, MD, PhD,* Yun Yue, MD, MS,# Janet Sherman, PhD,† Hui Zheng, PhD,‡ Shuren Li, MD,* Rudolph E. Tanzi, PhD,§
Edward R. Marcantonio, MD, MS,|| and Zhongcong Xie, MD, PhD¶

Pilot study: n = 45; spinal group (15), spinal + desflurane group (15), spinal + isoflurane group (15)

Cognitive function battery assessed in each group post-op
### Table 2

Postoperative Cognitive Decline Incidence and the Number of Subjects Who Declined by 1 SD or More on Each Cognitive Test at 1 Week Relative to Preoperation

<table>
<thead>
<tr>
<th>Name of the cognitive tests</th>
<th>S (n = 15)</th>
<th>SD (n = 15)</th>
<th>SI (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hopkins Verbal Learning Test-Revised (HVLT-R)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test-Revised (BVMT-R)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Benton Judgment of Line Orientation Test</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Digit Span Test</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Symbol Digital Modalities Test</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HVLT-R Delayed Recall Test</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HVLT-R Recognition Discrimination Index</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>BVMT-R Delayed Recall Test</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>BVMT-R Recognition Discrimination Index</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Trail making test</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Verbal fluency test</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean number of cognitive function decline\(^\text{†}\)  

\[1.13 \pm 0.99 \quad 1.07 \pm 1.16 \quad 1.40 \pm 1.76\]  

\[P = 0.770, \text{NS}\]

The POCD incidence (defined by decline in four or more cognitive tests)\(^\text{‡}\)  

\[(0\%) \quad (0\%) \quad (27\%)\]  

\[P = 0.028^*\]
• Limited sample size (n=45)
• Limited follow-up duration (1 week)
• Evolving definition of POCD
## Comparisons Among Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
</table>
| Rortgen et al. 2010* | **Sevoflurane** vs. **Desflurane** | • No overall difference in POCD at 3 days  
• Some battery tests favored desflurane  
• Faster emergence profiles with desflurane |
| Zhang et al. 2012*   | **Isoflurane** vs. **Desflurane** | • POCD at 1 week in isoflurane group  
• Cognitive testing battery favors desflurane group |
| Meineke et al. 2014  | **Sevoflurane** vs. **Desflurane** | • MMSE scores lower at 1 hour in Sevoflurane group  
• Normalized by 6 hours |
| Lindqvist et al. 2014| **Propofol** vs. **Desflurane** | • No difference using self-reported cognitive measures |

*Cognitive testing battery used*
## Comparisons Among Techniques

### Table 1.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Size (Patients)</th>
<th>Methodology</th>
<th>Surgery Type</th>
<th>Anesthetics</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al.</td>
<td>2006</td>
<td>92</td>
<td>Prospective</td>
<td>Abdominal surgery</td>
<td>GA vs. GA/EA combination</td>
<td>No significant difference in POCD</td>
</tr>
<tr>
<td>Anwer et al.</td>
<td>2006</td>
<td>60 (elderly)</td>
<td>Prospective</td>
<td>Urologic, orthopedic</td>
<td>GA vs. RA</td>
<td>More POCD up to 3 days post-op for GA patients</td>
</tr>
<tr>
<td>Rasmussen, et al.</td>
<td>2003</td>
<td>438</td>
<td>Prospective</td>
<td>Major non-cardiac</td>
<td>GA vs. RA</td>
<td>POCD higher in GA group (p=0.04) up to 7 days with per protocol approach</td>
</tr>
<tr>
<td>Williams-Russo, et al.</td>
<td>1995</td>
<td>262</td>
<td>Prospective</td>
<td>Orthopedic</td>
<td>GA vs. EA</td>
<td>No significant difference in POCD</td>
</tr>
<tr>
<td>Chung et al.</td>
<td>1989</td>
<td>44</td>
<td>Prospective</td>
<td>Urologic</td>
<td>GA vs. SA</td>
<td>No significant difference in POCD</td>
</tr>
<tr>
<td>Ghoneim et al.</td>
<td>1988</td>
<td>105</td>
<td>Prospective</td>
<td>Urologic, orthopedic</td>
<td>GA vs. SA/EA</td>
<td>No significant difference in POCD</td>
</tr>
</tbody>
</table>

Anesthesia and POCD/POD

- Journal of Alzheimer’s Disease, 2010
- Meta-analysis, GA vs. non-GA techniques
- 21 trials included


OR 0.88, (0.51-1.51) 95% CI
Anesthesia and POCD/POD

- Journal of Alzheimer’s Disease, 2010
- Meta-analysis, GA vs. non-GA techniques
- 21 trials included

Differential Effects of Various Anesthetic Agents on Cognitive Function in Patients With Alzheimer's Disease

Markers of Alzheimer's Disease After Propofol or Isoflurane Anesthesia (MAD-PIA)

Inhalational Anesthesia and Precipitation of Dementia: Is There a Link?
Anesthesia and POCD/POD

Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins


- Danish national registry, 8,503 twins – data obtained from longitudinal cohort studies

- Exposed twin, one of four groups:
  - Major surgery (cardiothoracic, vascular, major GI, major orthopedic)
  - TKA/THA
  - Minor procedures
  - Other

- Unexposed twin
Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins


- Five cognitive function tests evaluated (available in cohort studies sampled)

<table>
<thead>
<tr>
<th>Surgical Procedure Groups</th>
<th>n</th>
<th>Differences in Cognitive Scores (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major†</td>
<td>1,546</td>
<td>-0.27 (-0.48 to -0.06)</td>
</tr>
<tr>
<td>Minor</td>
<td>1,729</td>
<td>-0.06 (-0.27 to 0.14)</td>
</tr>
<tr>
<td>Knee and Hip replacement</td>
<td>171</td>
<td>0.35 (-0.18 to 0.87)</td>
</tr>
<tr>
<td>Other</td>
<td>2,092</td>
<td>-0.08 (-0.27 to 0.10)</td>
</tr>
<tr>
<td>Without surgery</td>
<td>2,965</td>
<td>Reference</td>
</tr>
</tbody>
</table>

0.1 SD, clinically insignificant (<1 word named on fluency test)
Anesthesia and POCD/POD

Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins


- Five cognitive function tests evaluated (available in cohort studies sampled)
- Exposure to 3 or more past major surgeries:
  - -0.5 (-0.84-0.15) 0.2 SD
- No differences in timing of surgery
  - (3 months → 24 years) and outcomes
- Intra-pair twin analyses (n=211 pairs): no difference
Anesthesia and POCD/POD
Clinical Trial Design - Challenges

Anesthetics Nested Within...

-- Comorbidities
-- Demographics/education
-- Home medications
-- Pain
-- Analgesic/sedative burden
-- Inflammation
-- Sleep Deprivation
-- Etc.

Internal vs. External Validity
SUMMARY

• **The young brain**: large, multi-center trials ongoing. Encouraging preliminary data thus far.

• **The old brain**: laboratory, preliminary clinical evidence suggests certain anesthetics (i.e. desflurane) *may* be less (transiently?) neurotoxic, though clinical confirmation pending.

• *Neurological effects may be transient*

• *Very challenging to design, implement these clinical trials.*
Questions?