

Anesthetic Neurotoxicity in the Developing Brain

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A fundamental premise of modern general anesthesia is that the brain is structurally left in the same condition that was prior to the administration of the anesthetic

Is it time to modify this premise?

SCIENCE NEWS

- Anesthesia increased in cell death
- Anesthesia led to poor performance on tests of learning and memory

“.. If surgery does not have to be performed early in life, it would be prudent to postpone it.”

J. W. Olney

Anesthetic Effects on the Developing Nervous System

If You Aren't Concerned, You Haven't Been Paying Attention

Introduction

- Review of anesthetic neurotoxicity
- Pathology
- Relevance to humans and to clinical practice

Drugs with Developmental Neurotoxicity

- Anti-epileptic agents

- ◆ Valproate, vigabatrin, phenytoin
- ◆ Phenobarbital, diazepam, clonazepam

GABA-A agonists

- Alcohol

**GABA-A agonist
NMDA antagonist**

- NMDA antagonists

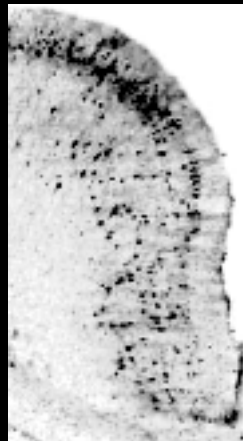
Do anesthetics injure the brain?

Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

- Isoflurane 0.75% to 1.5%
- Midazolam
- N₂O 80%



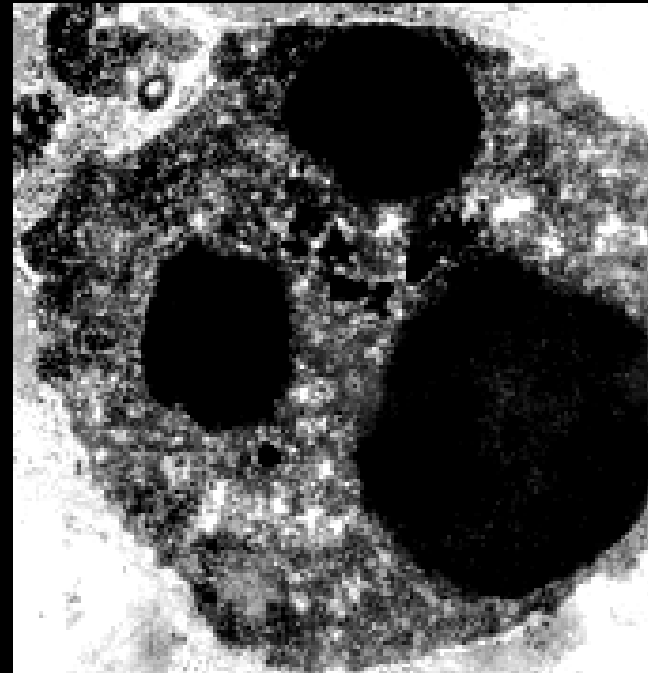
Control



Isoflurane



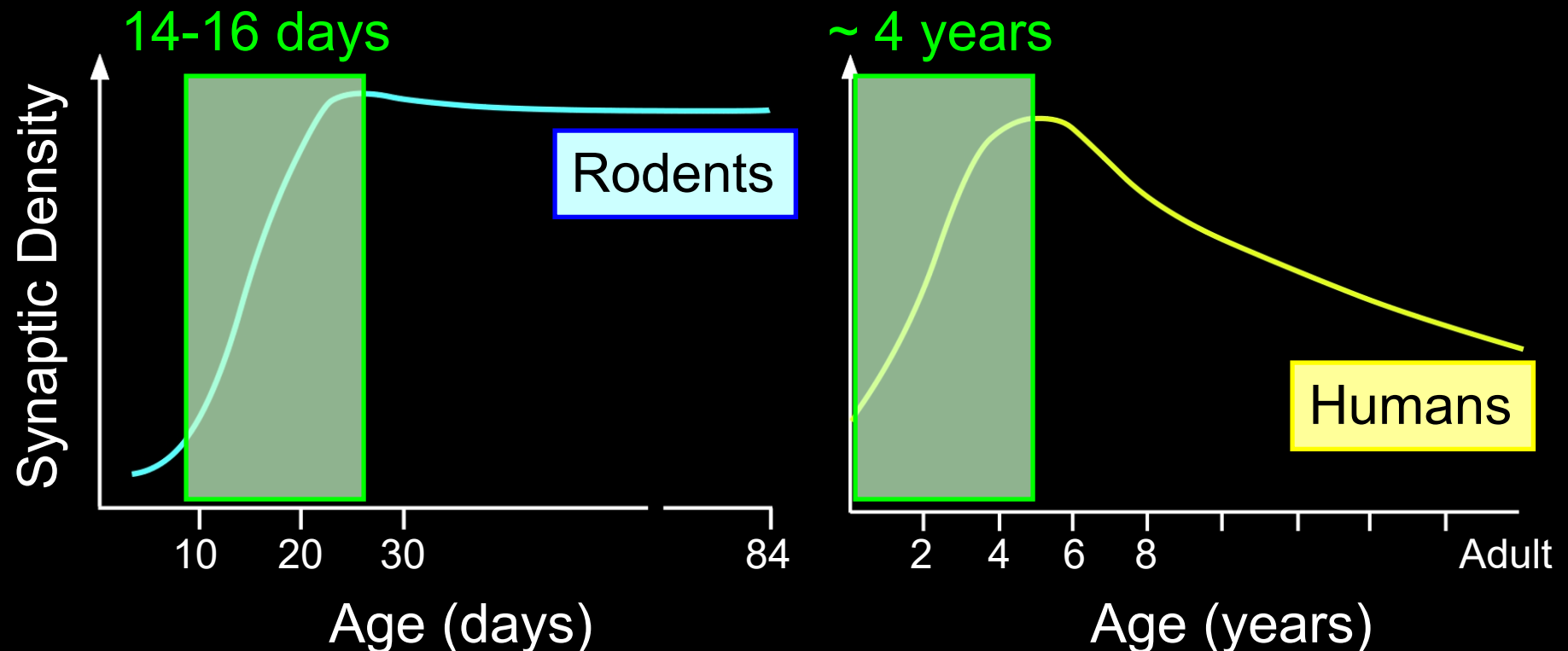
Combination



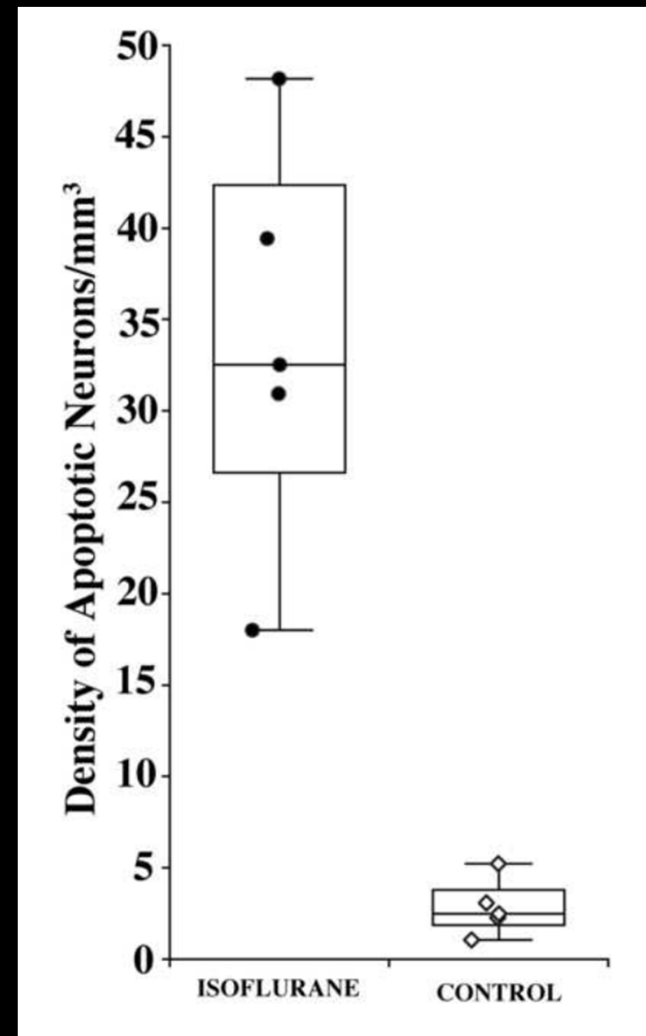
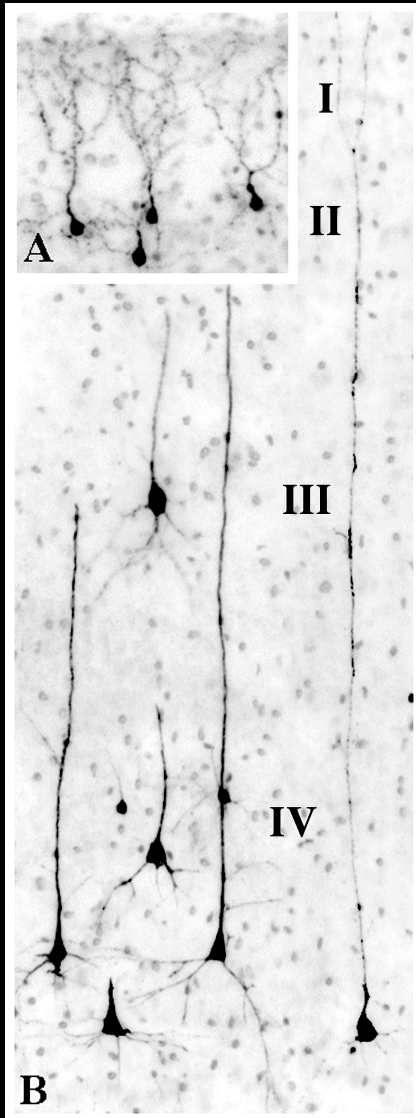
Anesthetics cause widespread apoptotic neurodegeneration

Vulnerability Greatest During Synaptogenesis

- About 6 hours of anesthesia required to demonstrate injury
- Exposure during synaptogenesis particularly deleterious

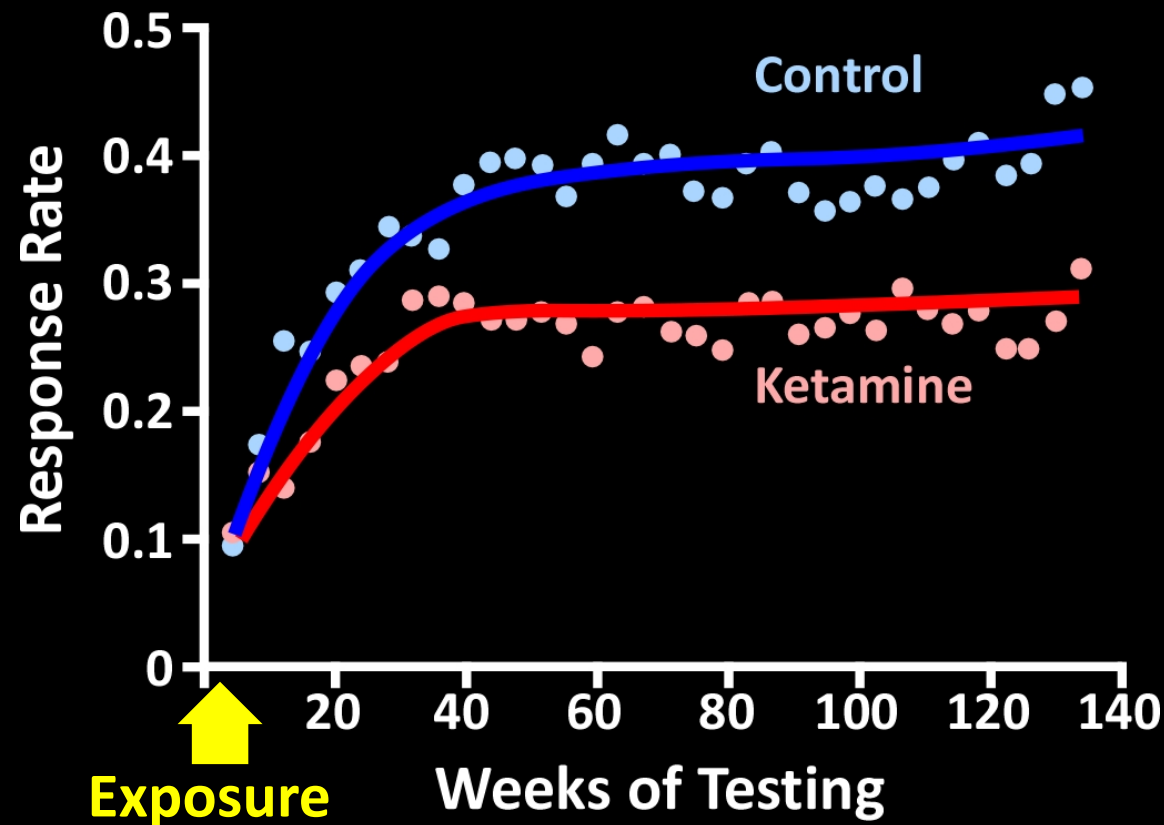


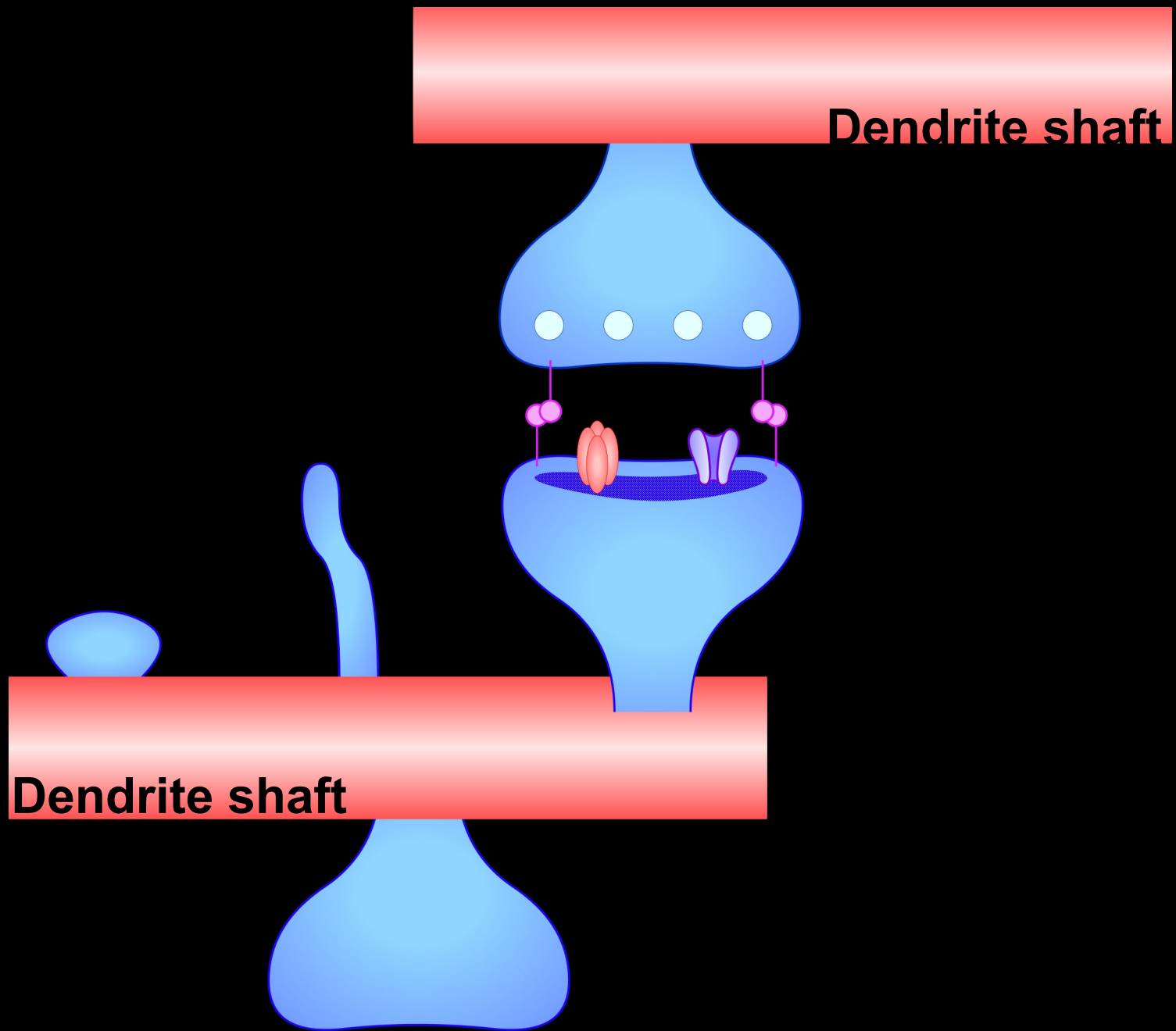
Isoflurane Neurotoxicity in Primates



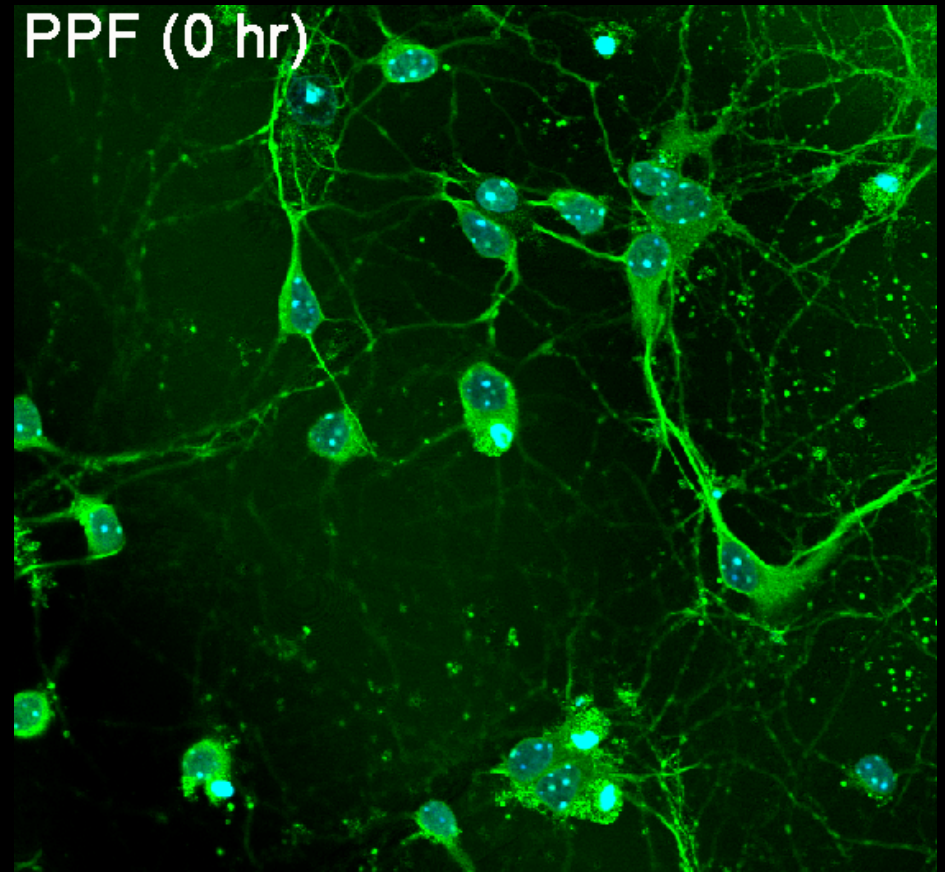
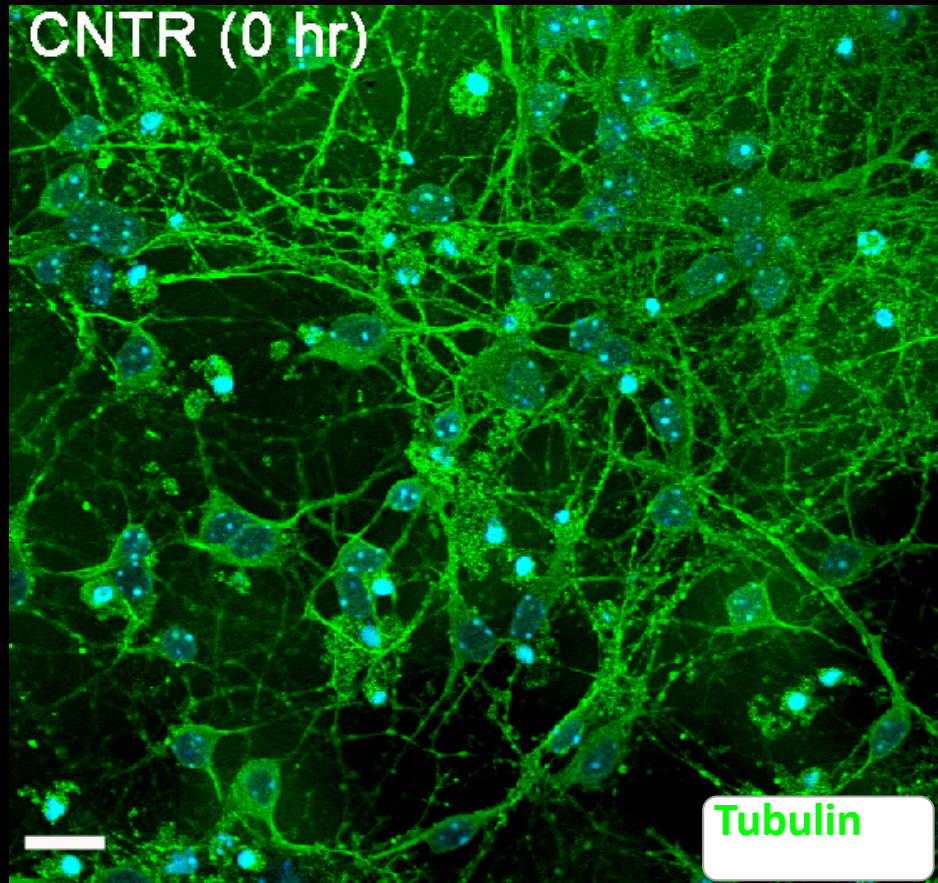
Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys

M.G. Paule^{a,*}, M. Li^a, R.R. Allen^b, F. Liu^a, X. Zou^a, C. Hotchkiss^c, J.P. Hanig^d, T.A. Patterson^a, W. Slikker, Jr^a, C. Wang^a

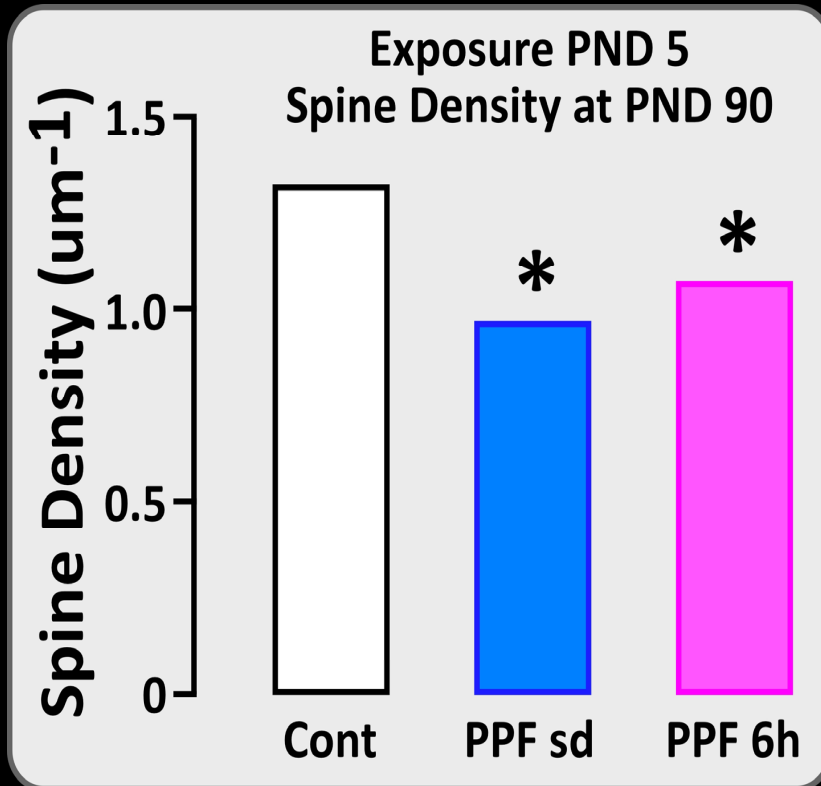
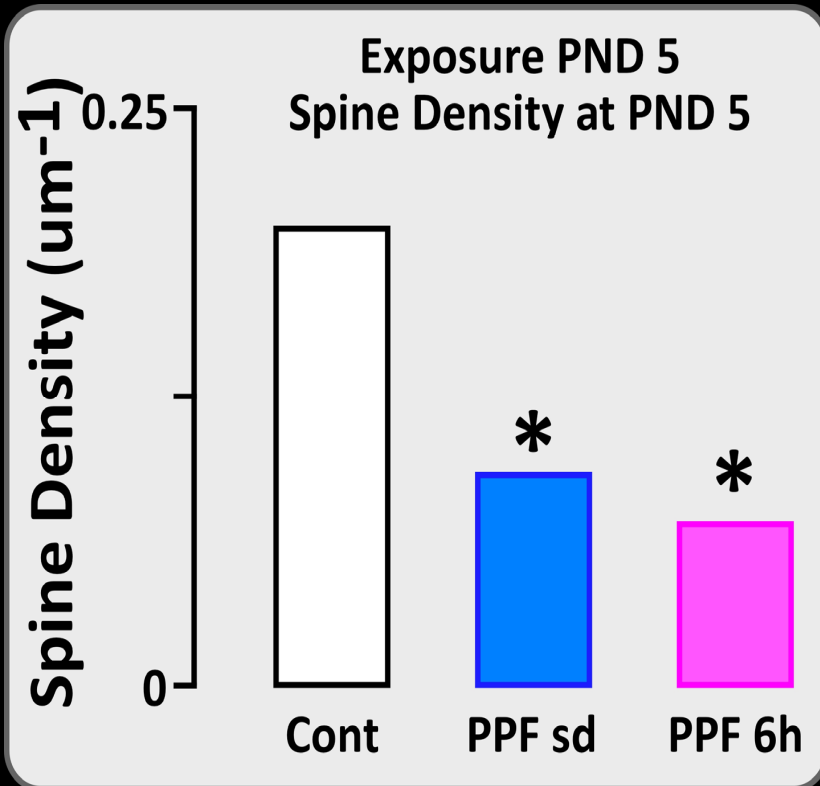




Effect of Propofol on Neurites

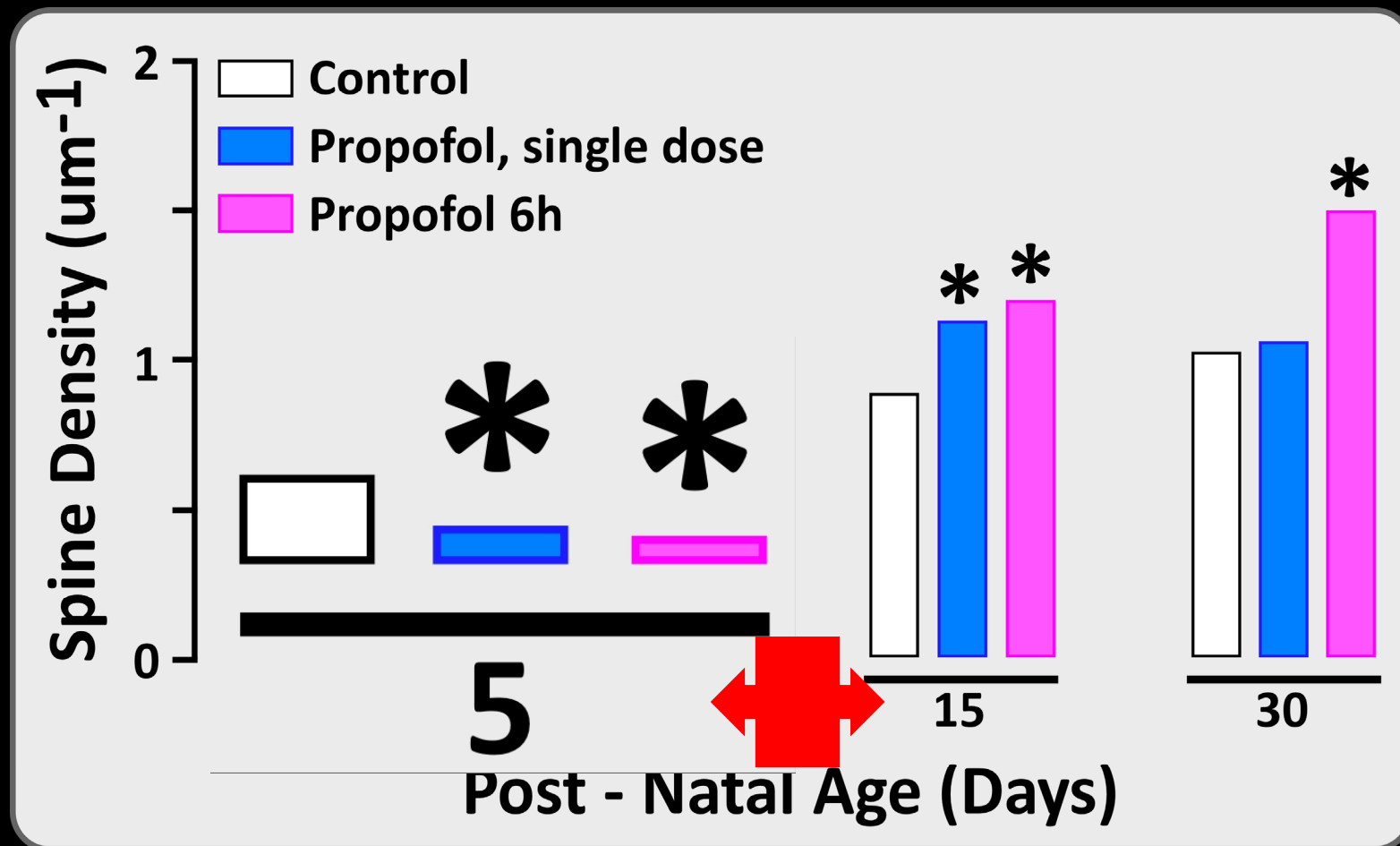


Effect of Propofol on Synaptic Density

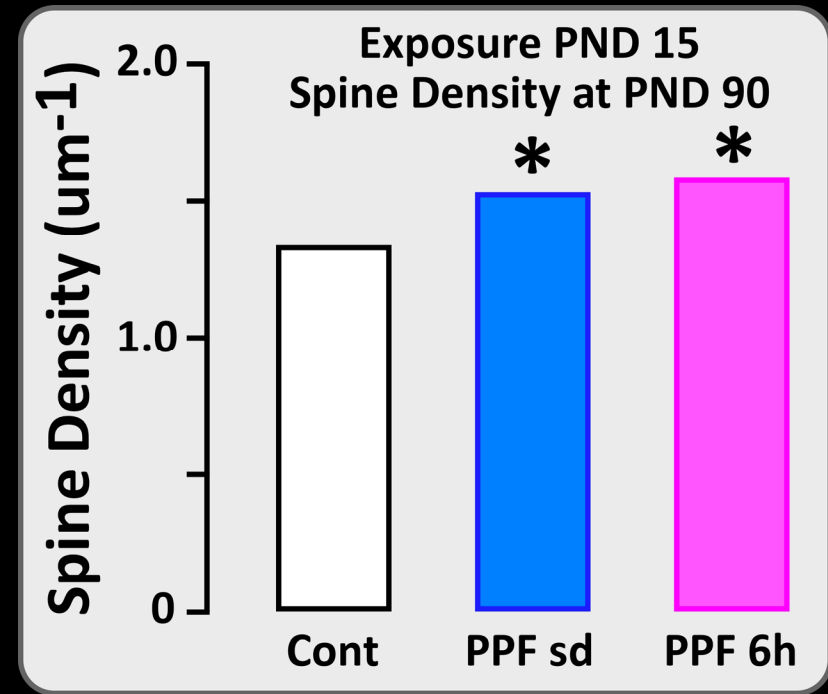
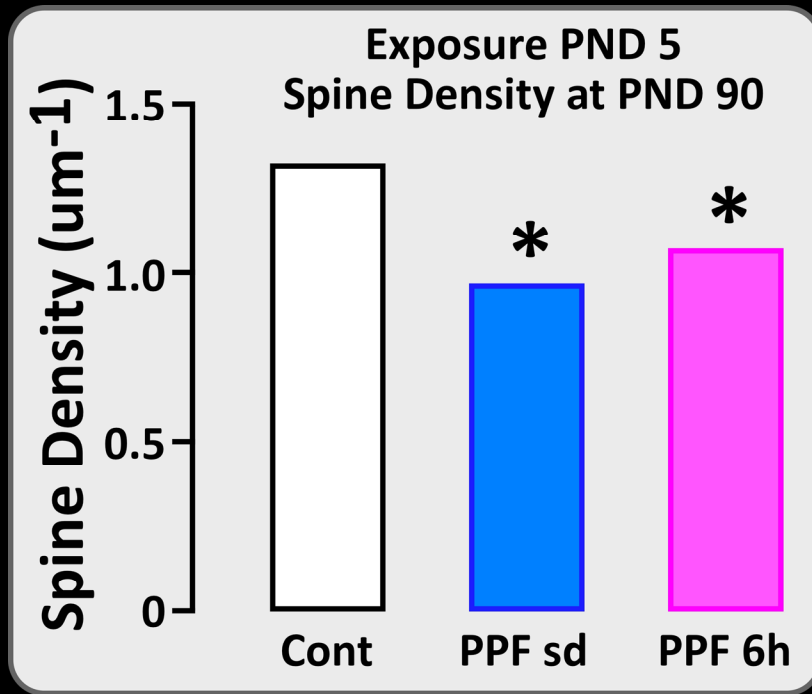


Single exposure to propofol produces persistent changes in spine density

Effect of Propofol on Synaptic Density



Propofol Induces Persistent Changes in Synaptic Density

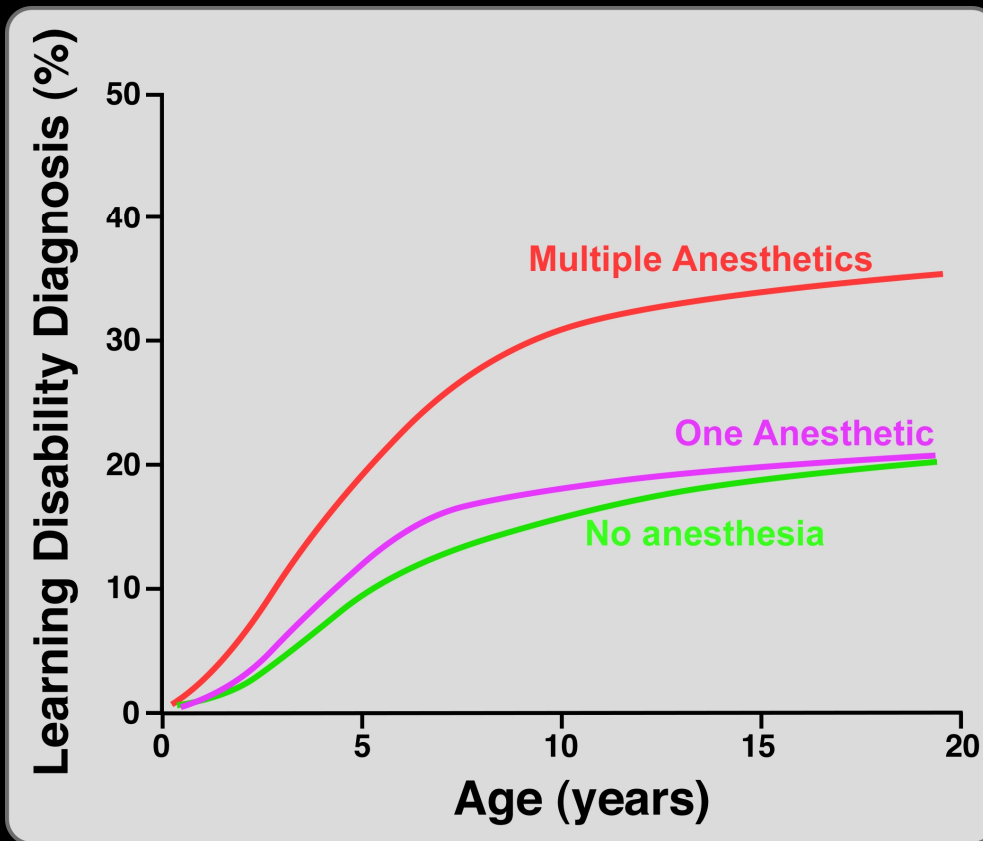


Single exposure to propofol produces persistent changes in spine density

**Is any of this relevant to
anesthesia in humans?**

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

- Population based retrospective cohort study
- Children anesthetized prior to 4 yr age
- Reading, written language, math learning disabilities



Anesthesia?

Surgery?

Need for surgery?

Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia

Juraj Sprung, MD, PhD; Randall P. Flick, MD, MPH; Slavica K. Katusic, MD; Robert C. Colligan, PhD; William J. Barbaresi, MD; Katarina Bojanić, MD; Tasha L. Welch, MD; Michael D. Olson, PA-C; Andrew C. Hanson, BS; Darrell R. Schroeder, MS; Robert T. Wilder, MD, PhD; and David O. Warner, MD

- **GA before 2 years of age (n = 5357)**
- **ADHD diagnosis by 19 years of age (n = 341)**

***Multiple procedures under GA
associated with increased risk of ADHD***

Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

Meike Bartels,^{1*} Robert R. Althoff,^{2*} and Dorret I. Boomsma¹

- **Monozygotic concordant – discordant twin design**
- **Anesthesia before age of 3 yr**
- **Anesthesia before age of 12 yr**
- **Results**
 - ◆ **Cognitive performance poor with anesthetic exposure**
 - ◆ **No difference between exposed and unexposed twin**

No evidence for causal relationship between anesthesia exposure and learning difficulty

Academic Performance in Adolescence after Inguinal Hernia Repair in Infancy

A Nationwide Cohort Study

Tom G. Hansen, M.D., Ph.D.,* Jacob K. Pedersen, M.Sc.,† Steen W. Henneberg, M.D., Ph.D.,‡
Dorthe A. Pedersen, M.Sc.,† Jeffrey C. Murray, M.D.,§ Neil S. Morton, M.D.,||
Kaare Christensen, M.D., Ph.D., D.M.Sc.#

- Inguinal hernia repair before 1 yr age under GA
- Age matched control group
- Test scores 9th grade

***No difference in scores after adjusting
for confounding variables***

Anesthetic Neurotoxicity: A Difficult Dragon to Slay

Joss Thomas, MPH,* Gregory Crosby, MD,† John C. Drummond, MD, FRCPC,‡§ and Michael Todd, MD*

- **Best studies have failed to demonstrate an adverse effect of anesthetics in infants**
- **Single, brief anesthetic is unlikely to harm infants**
- **Children who require more surgery are more likely to have problems**
- **No data to suggest change in medical, surgical and anesthesia practice**

Anesthetic neurotoxicity in children has become a modern day dragon in medicine. Dragons are very good at hiding from view, and they are hard to kill

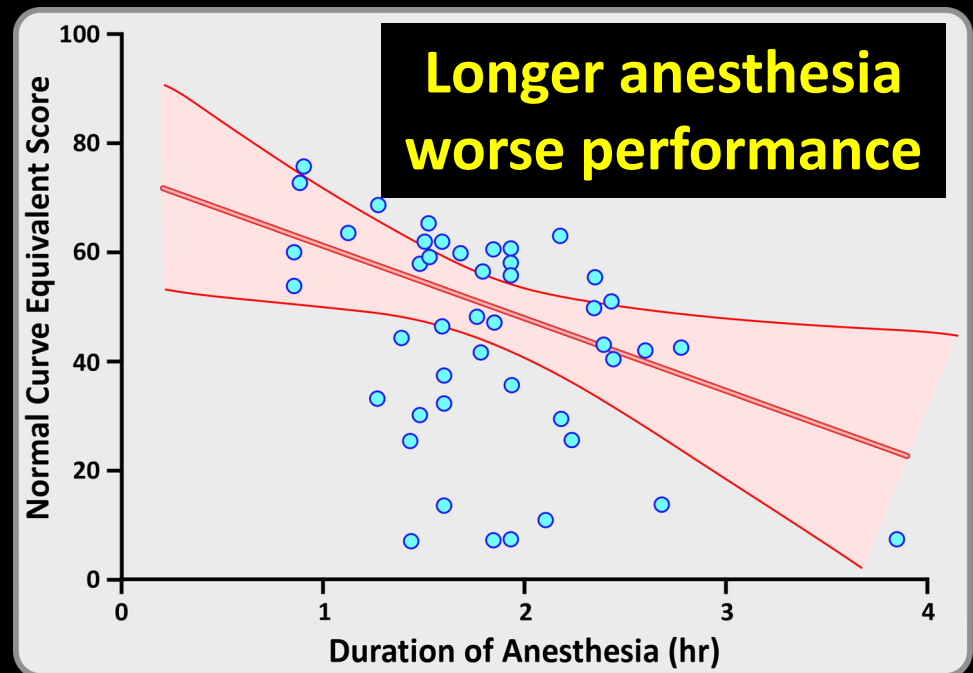
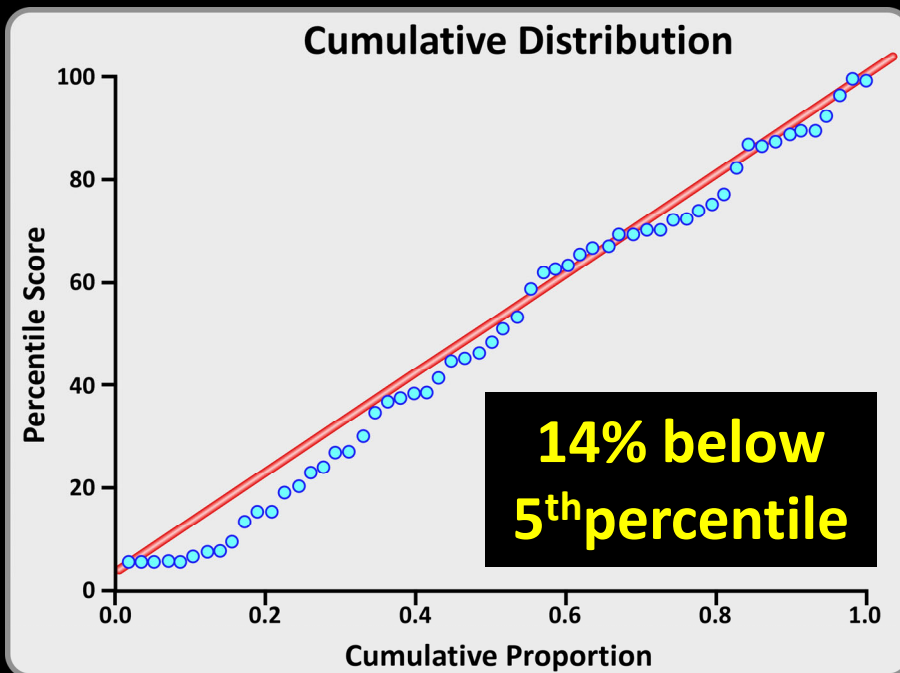
Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia

- **2608 children Western Australia**
 - ◆ 321 exposed ; 2287 unexposed
- **Language, cognition, behavior, motor function**
 - ◆ Testing: 1, 2, 3, 5, 8, 10, 13, 16 yr
- **Single exposure led to difficulty with:**
 - ◆ Receptive language
 - ◆ Expression language
 - ◆ Abstract reasoning
- **No motor or behavioral problems**
- **Multiple exposures did not exacerbate deficits**

Are Anesthesia and Surgery during Infancy Associated with Altered Academic Performance during Childhood?

Robert I. Block, Ph.D.,* Joss J. Thomas, M.D.,† Emine O. Bayman, Ph.D.,‡ James Y. Choi, M.D.,†
Karolie K. Kimble, R.N., B.A.,§ Michael M. Todd, M.D.||

- Pyloromyotomy, inguinal herniorrhaphy, circumcision under GA
- Iowa tests of basic skills, educational development (7-10 yr age)



Current Trials

FDA Funded Projects

- **Childrens' Hospital, Harvard University, Boston**
 - ◆ **General vs regional anesthesia**
- **Columbia University, New York**
 - ◆ **Cognitive, emotional and behavioral outcome after GA**
- **Mayo Clinic, Rochester**
 - ◆ **Long term cognitive development after GA**

Anesthetic Effects on Developing Brain

Multiple
anesthetics
Long duration

Single
anesthetic
Brief Duration

Toxicity

Awake

Multiple agents

GABA-A agonism, NMDA antagonism

Single agent, single anesthetic

isoflurane, sevoflurane, **desflurane**

propofol, midazolam, ketamine

Dexmedetomidine

Opiates

Summary

- Dose dependent widespread neurodegeneration
 - ◆ Rodents
 - ◆ Subhuman primates
- Agents demonstrated to have toxicity:
 - ◆ Volatile anesthetics
 - ◆ Barbiturates
 - ◆ Benzodiazepines
 - ◆ Propofol
 - ◆ Ketamine
- Agents with no demonstrated toxicity
 - ◆ Dexmedetomidine
 - ◆ Opiates
- Vulnerability during synaptogenesis
- Requires prolonged exposure
- Damage associated with electrophysiologic abnormality
- Long term reduction in cognitive function

Summary

Anesthesia produces structural changes in brain

Clearly, more basic and clinical research is needed

There are, however, no data to indicate that anesthesia care providers should alter their practice

