

Brain Damage in the OR: Anesthesia and Neurotoxicity

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Disclosures



TIME Study: Anesthesia in Infancy Linked to Later Disabilities

General anesthesia in infancy
linked to higher risk of ADHD 

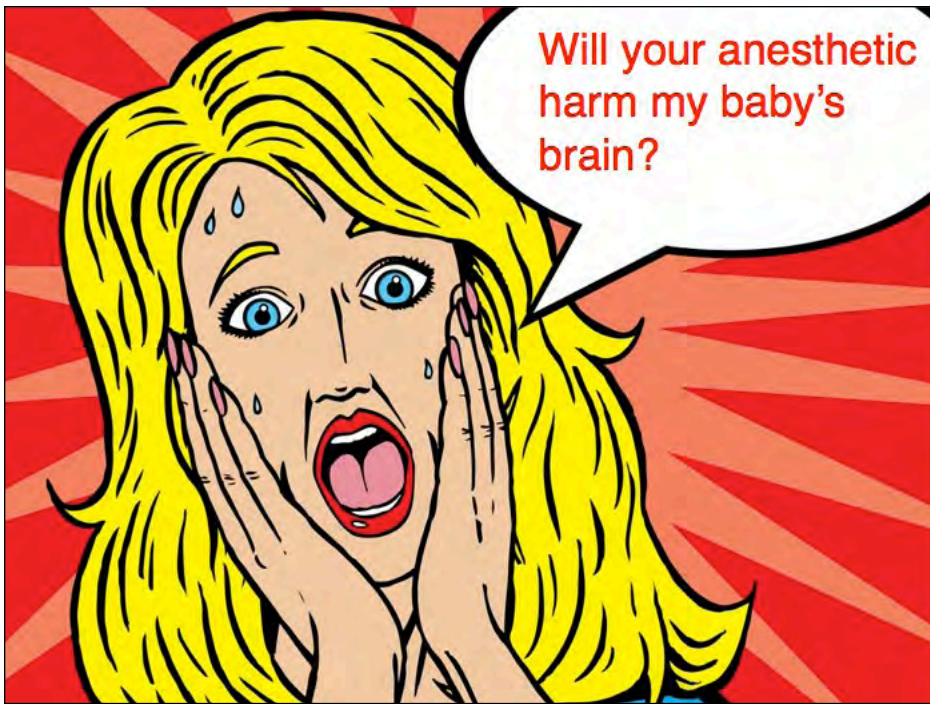
In Newsweek Magazine

Could Anesthesia Cause Developmental Disorders?

Should Babies Get Anesthesia? 

News Tonight Baby Brains Are Harmed
By Anesthesia





Neurotoxicity in Animal Models

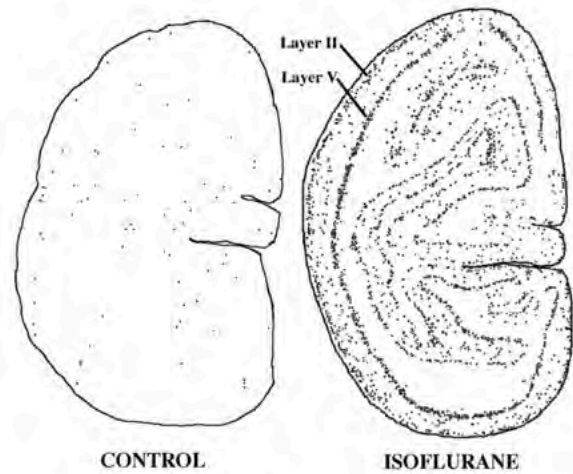
more than 300 articles, numerous abstracts

nematodes, chicks, mice, rats, guinea pigs, pigs, and rhesus monkeys





Isoflurane-Induced Apoptosis in Newborn Monkeys



Brambrink et al., Anesthesiology 2010

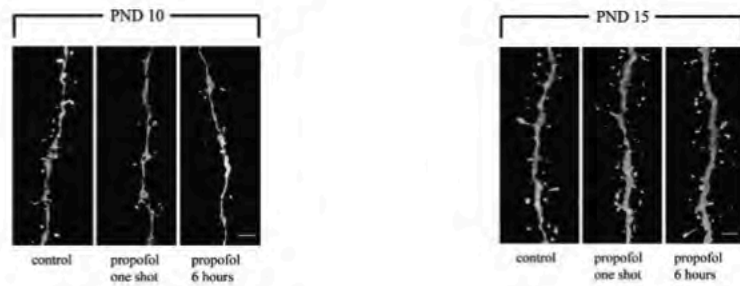
Apoptosis

Programmed Cell Death



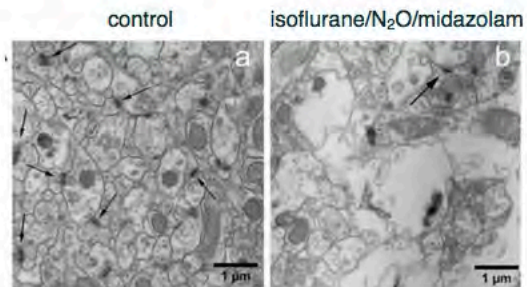


Anesthesia Changes Dendritic Density



Briner et al., Anesthesiology 2011

Anesthesia Reduces Number of Synapses



Lunardi et al., Neurotox Res 2010

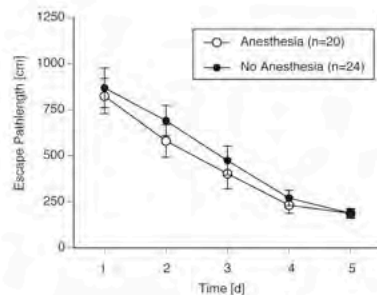
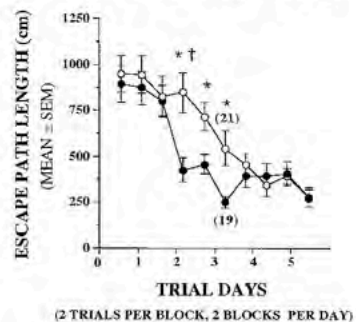


**Anesthesia is Associated with
Learning Impairment**



Long-term Neurocognitive Performance

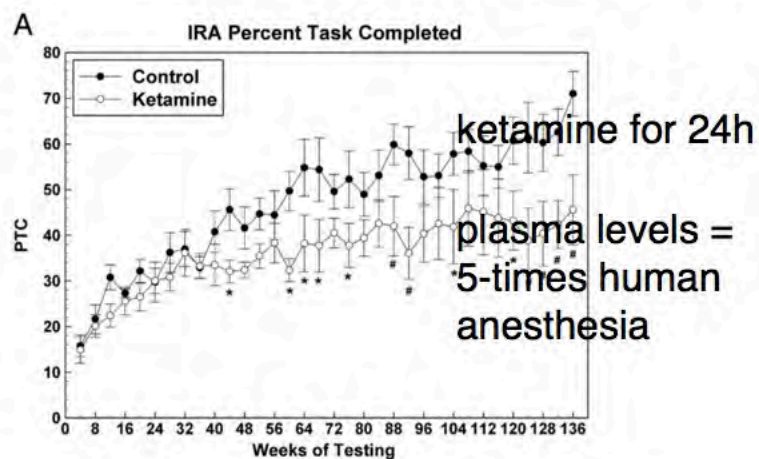
a. PLACE TRIALS (Age P32)



Jevtovic-Todorovic et al., J Neurosci 2003

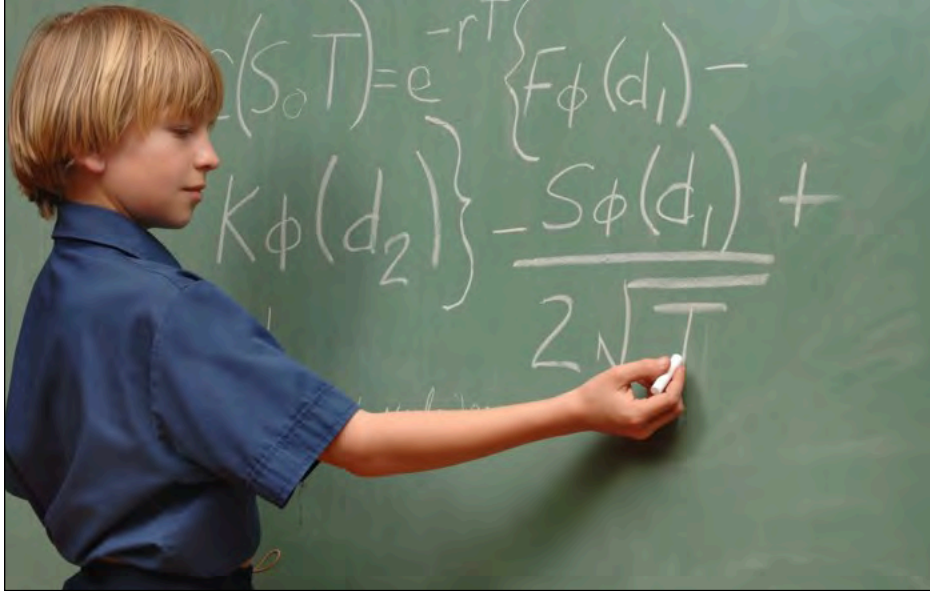
Loepke et al., Anes Analg 2009

Long-term Learning Impairment in Monkeys



Paule et al., Neurotoxicol Teratol 2011

Diminished Academic Performance



Epidemiological Studies

Anesthetic	Surgery	Abnormalities	Assessment	Reference
Halothane, N ₂ O, 10% ketamine	any	(+) 2 exposures >2 h	school records	Wilder 2009
not specified	inguinal hernia repair	+	Medicaid database	DiMaggio 2009
not specified	any	(+) 2 exposures	Medicaid database	DiMaggio 2011
not specified	any	+	language, cognitive, vocabulary tests	Ing, in press
Halothane, N ₂ O, 10% ketamine	any	(+) 2 exposures	school records	Flick 2011
not specified	c-section	-	school records	Sprung 2010
not specified	inguinal hernia repair	(-) non-attainment	school records	Hansen 2011
sedatives not specified	any, NICU	-	Kaufmann battery	Rozé 2009
Opioids, anesthetics, benzodiazepines	cardiac surgery	-	Bayley scales	Guerra 2011
not specified	any	-	CITO test	Bartels 2009

Correlation \neq Causation

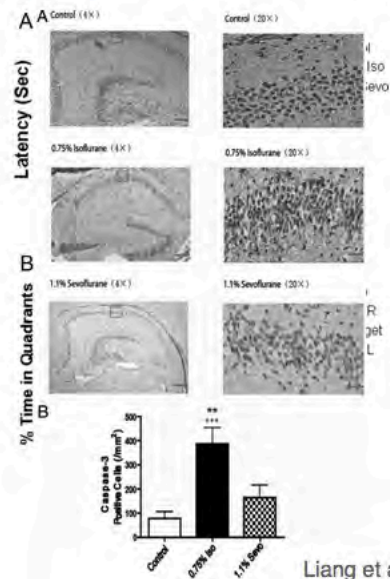


Uncertainties

Is toxicity similar among all anesthetics?

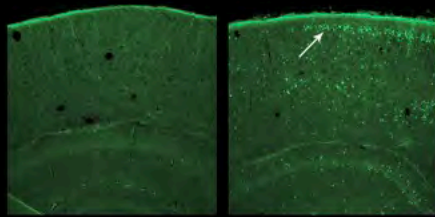


Isoflurane vs. Sevoflurane

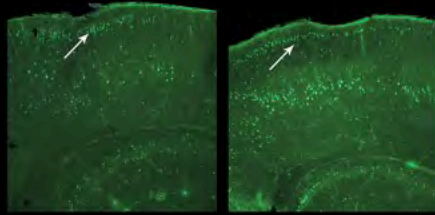


Liang et al., Anesthesiology 2010

Comparative Toxicity



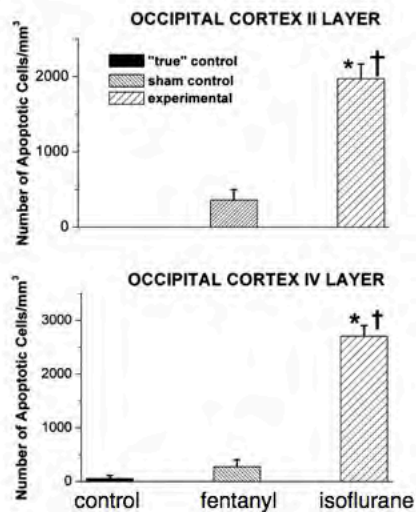
No Anesthesia Desflurane



Isoflurane Sevoflurane

Istaphanous et al., Anesthesiology 2011

Isoflurane/N₂O/midazolam vs. fentanyl



Rizzi et al., Ann N Y Acad Sci 2010

Ameliorating Strategies for Anesthesia-Induced Cell Death

Estradiol
Melatonin
Pilocarpin
Lithium
Hypothermia
Xenon
Dexmedetomidine
Isoflurane

**Just postpone surgeries?
Is anesthesia safe after age 4?**

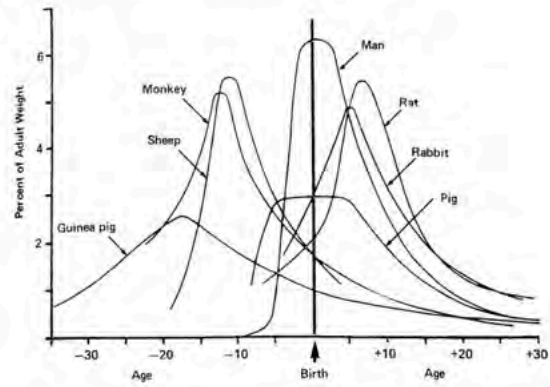




Monkey = Infant = Rodent?

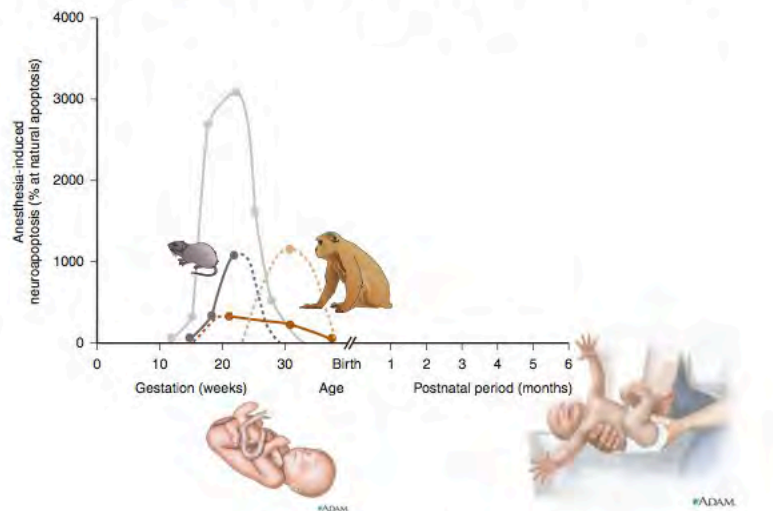


Based on Old Data



Dobbing and Sands, Arch Dis Child 1973

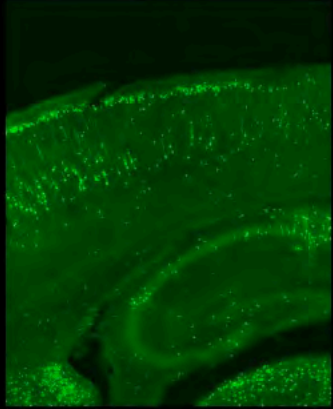
Developmental Equivalency



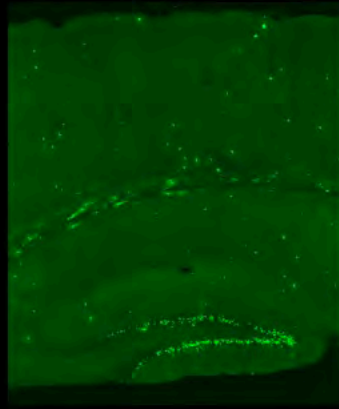
modified from Loepke AW & Davidson AJ:
Chapter 23: Surgery, Anesthesia, and the Immature Brain.
in Coté et al., A Practice of Anesthesia for Infants and Children, in press

Anesthesia Eliminates Different Neurons Dependent on Age at Exposure

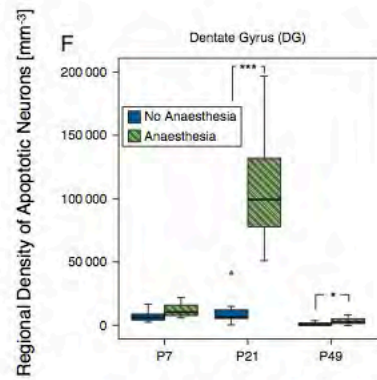
P7



P21

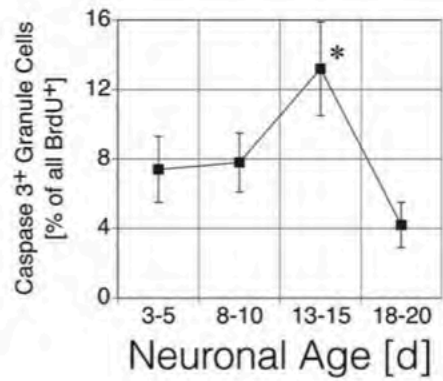


Dentate Granule Cell Vulnerability is Delayed



Deng et al. Br J Anaes 2014

Vulnerability Related to Neuronal Age



Hofacer et al. Ann Neurol 2013

Cell death does not predict disability

Anesthetic	Species	Apoptosis	Impairment	Reference
Isoflurane, N ₂ O, midazolam	rats	+	+	Jevtovic-Todorovic 2003
Isoflurane	rats	+	+	Stratmann 2009
Isoflurane on 4 consecutive days	rats & mice	+	+	Blomgren 2010
Isoflurane	mice	+	-	Loepke 2009
Midazolam	mice	?	-	Xu 2009
Isoflurane or sevoflurane	mice	+	-	Wei 2010
CO ₂ 15-30%	rats	+	-	Stratmann 2009

Untreated pain is deleterious to the developing nervous system

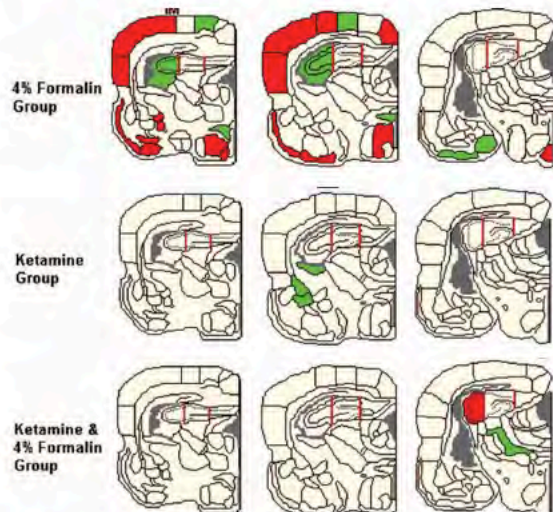
Widespread neurodegeneration, behavioral abnormalities, learning impairment

Altered subsequent pain responses, impairment in cognitive and motor development

Anand et al. *Physiol Behav* 1999, *Pediatr Res* 2007
Boasen et al. *Neonatology* 2009
Taddio et al. *Lancet* 1997, Grunau et al. *Pain* 2009



Anesthesia Reduces Cell Death



Anand et al. *Pediatr Res* 2007

Genetic predisposition for neurological impairment following anesthetic exposure



Bartels 2009

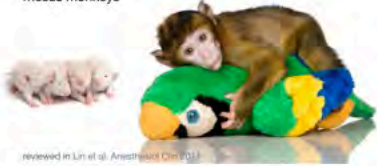
Summary



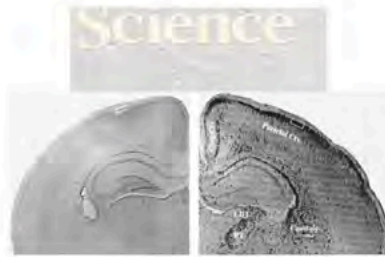
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nematodes, chicks, mice, rats, guinea pigs, pigs, and rhesus monkeys



reviewed in Liu et al. Anesthesiology Oct 2011



Bonomidou et al. Science 1999

Physiological
apoptosis
eliminates neurons



Anesthesia is Associated with Learning Impairment



Diminished Academic Performance



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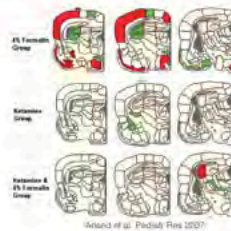


Widespread neurodegeneration, behavioral abnormalities, learning impairment

Altered subsequent pain responses, impairment in cognitive and motor development

Arundt et al. *Physiol Behav* 1998; Pachatz *Res* 2017;
 Bostain et al. *Neonatology* 2008;
 Tachibai et al. *Lancet* 1997; Grunser et al. *Proc* 2009

Anesthesia Reduces Cell Death



Arundt et al. *Pediatr Res* 2007

Pediatric Anesthesia?

