The Effect of Anesthetics on the Developing Brain

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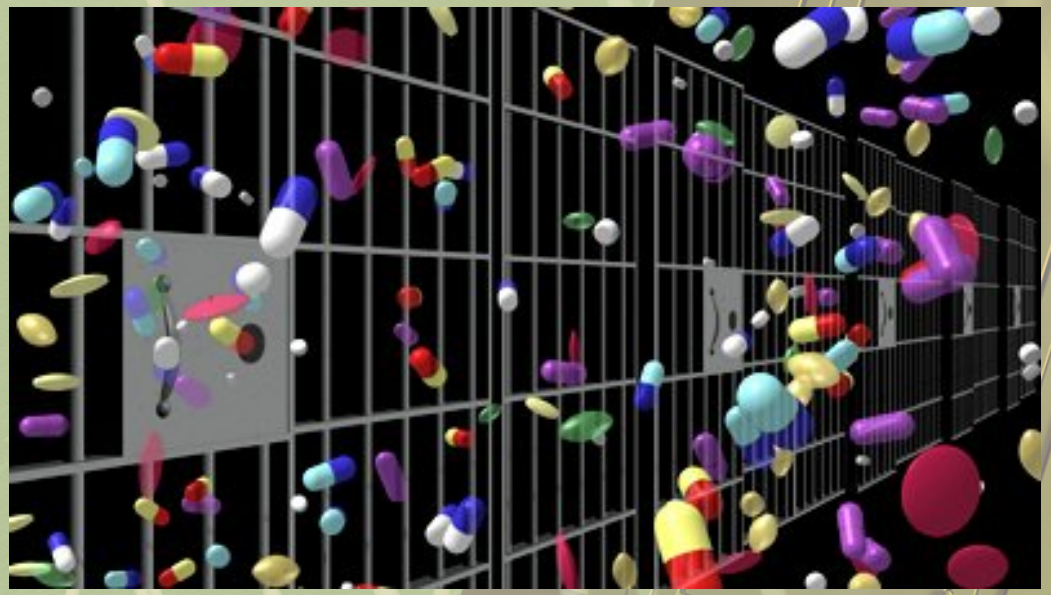
Outline

What is the issue?

- GABA, Glutamate-NMDA
- Apoptosis
- Hippocampus
- Deficits in learning and memory
- Abnormal social behavior (Autism spectrum)
- 4 years or younger

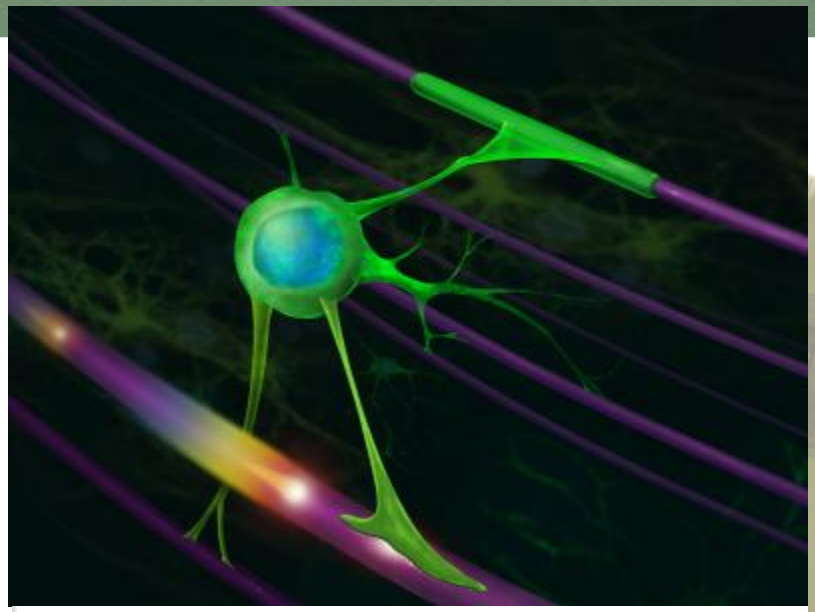
Implicated Drugs:

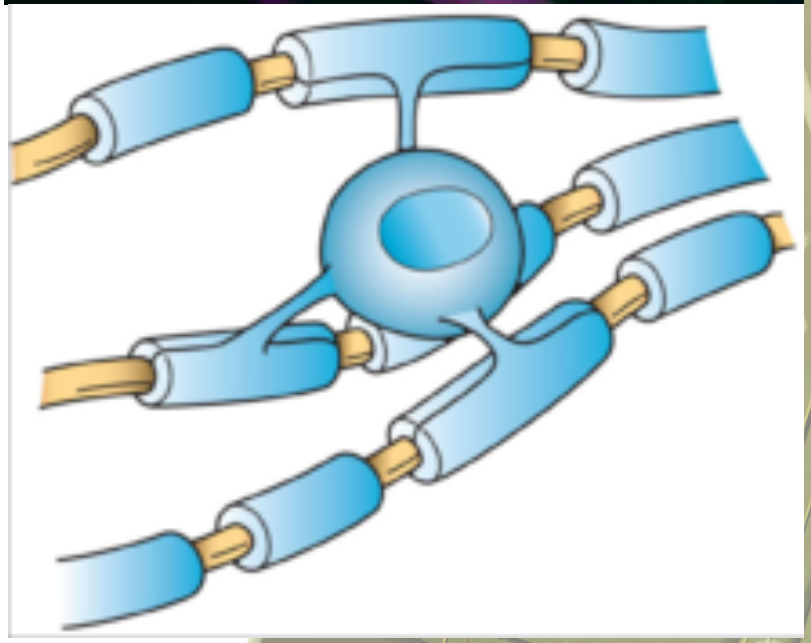
- Nitrous Oxide
- Inhaled anesthetics
- Propofol
- Midazolam
- Ketamine



Fundamentals of the developing brain

1. Increased brain volume
2. Increased white/grey matter
3. Typical pattern of development
4. Degree of myelination
5. Muscle tone and reflexes
6. Parasympathetically driven





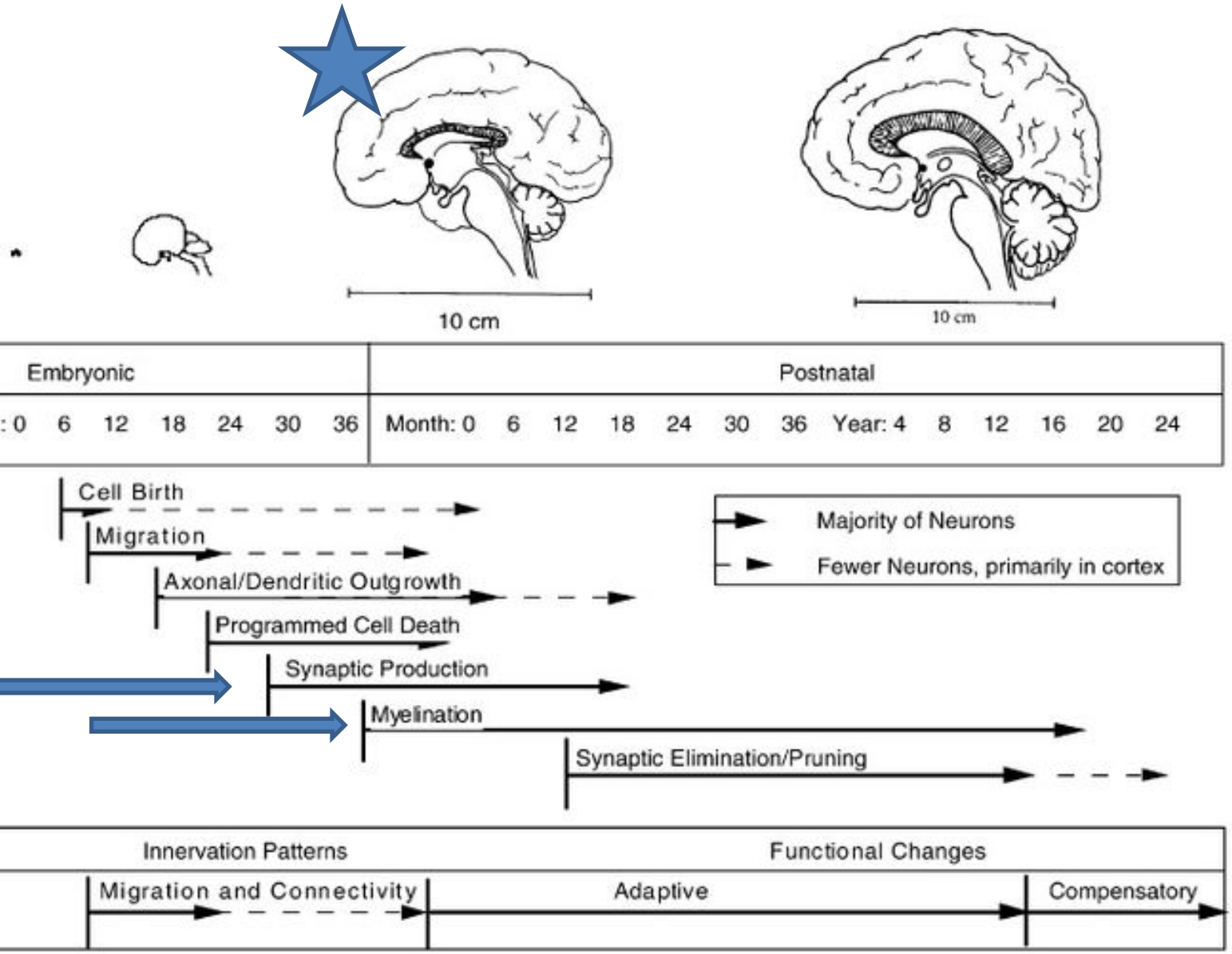


Fig. 1. The stages of brain development (top) and different windows of vulnerability (bottom). Developmental processes occur in phases, setting the stage for potential periods of vulnerability. Insults early in life (bottom) will be assimilated into innervation patterns, whereas a later pre-pubertal insult will cause functional changes that are more adaptive.

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

Vesna Jevtovic-Todorovic,[1] Richard E. Hartman,[2] Yukitoshi Izumi,[3] Nicholas D. Benshoff,[3] Krikor Dikranian,[3] Charles F. Zorumski,[3] John W. Olney,[3] and David F. Wozniak[3]

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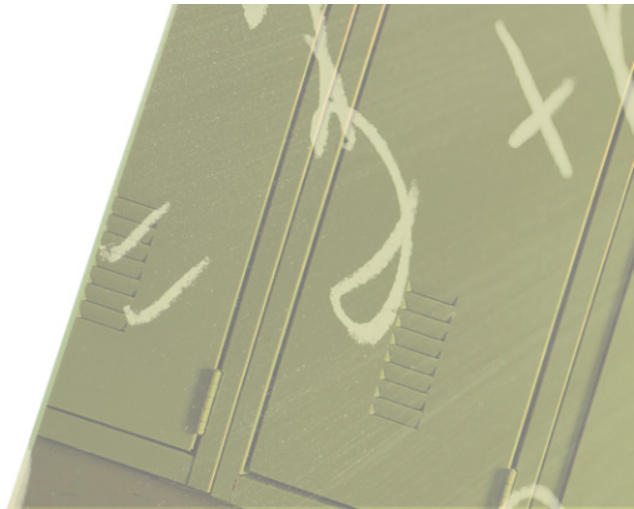

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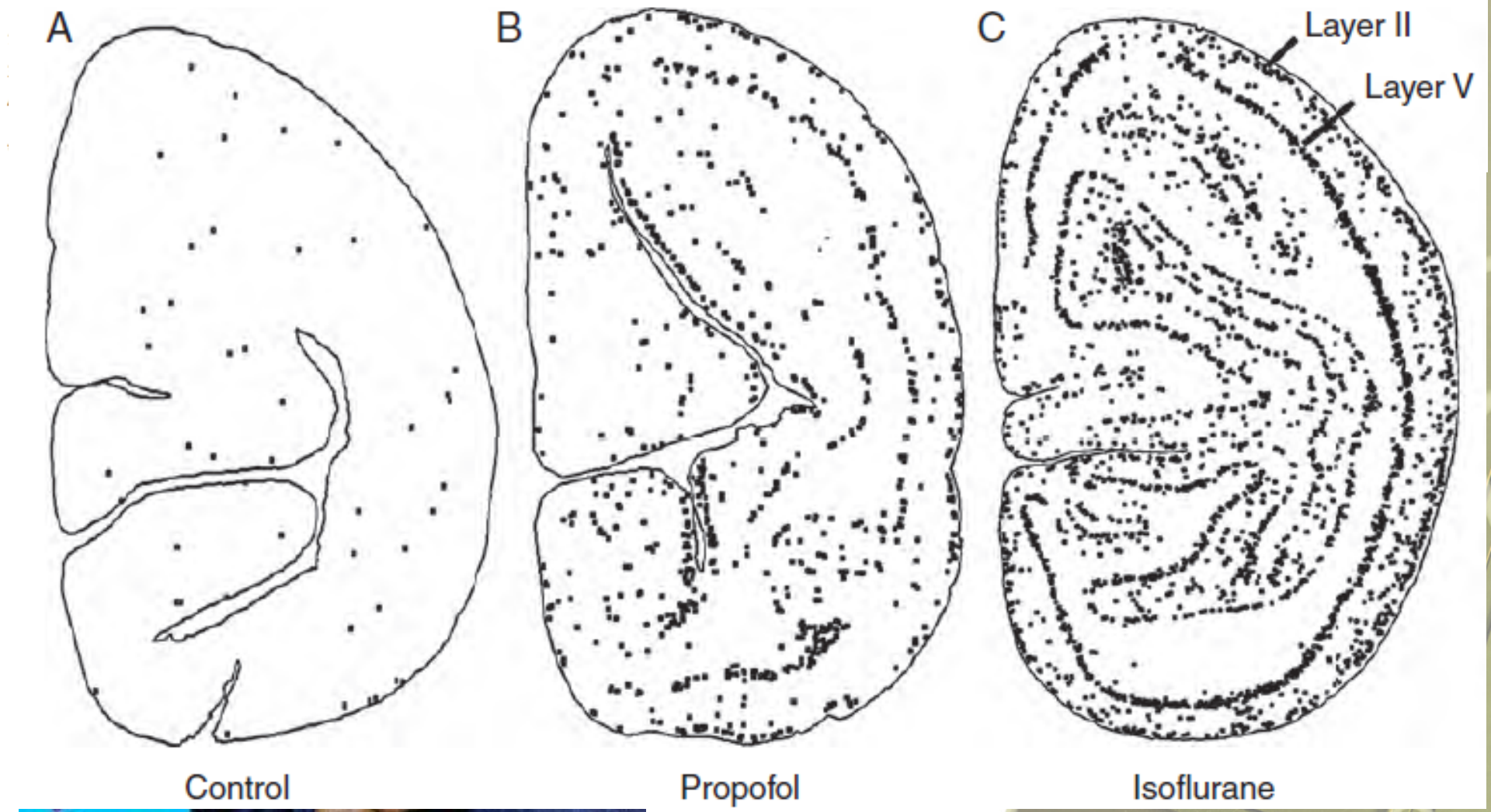
doi:10.1093/bja/aet173

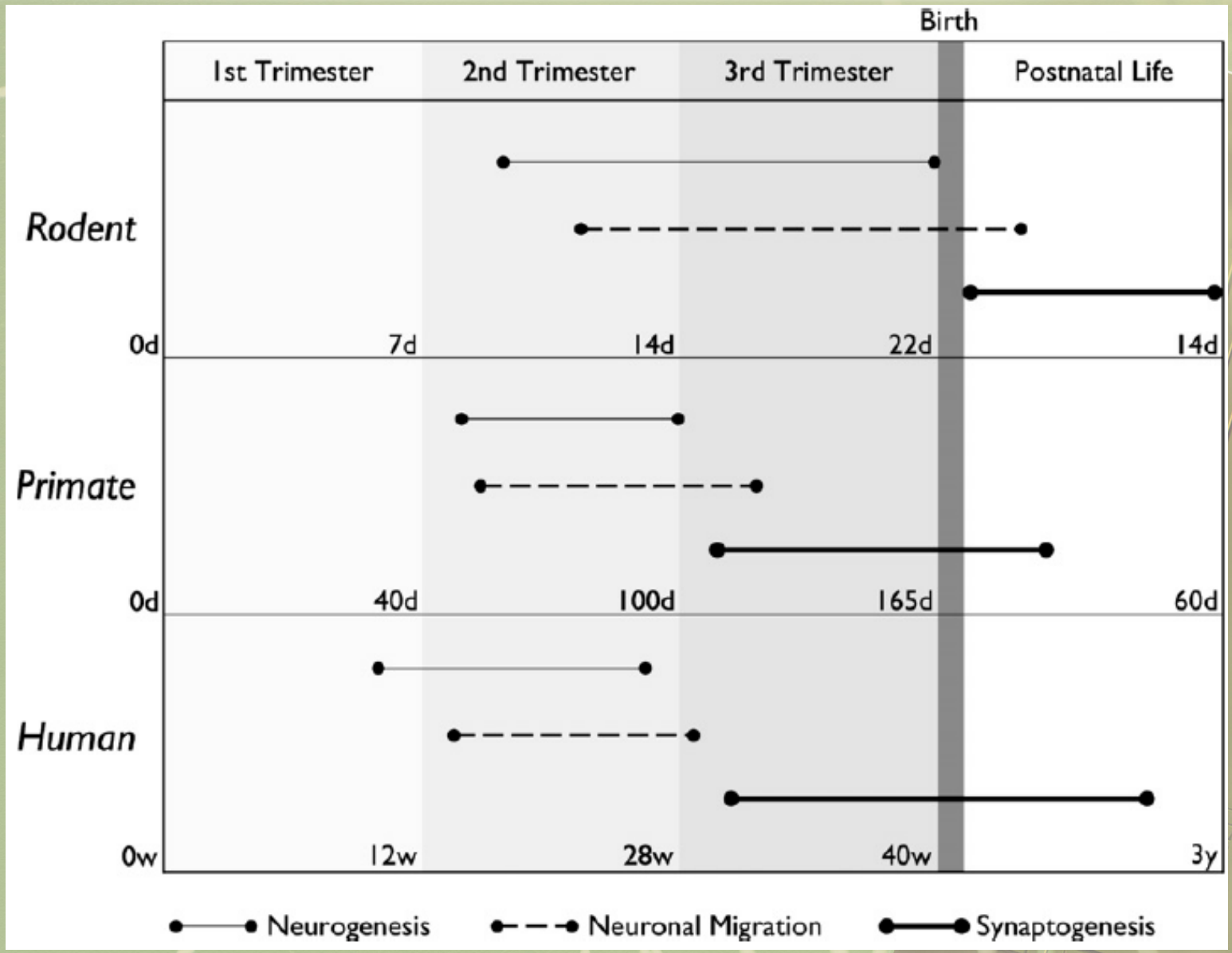
BJA

Propofol-induced apoptosis of neurones and oligodendrocytes in fetal and neonatal rhesus macaque brain

C. Creeley[1], K. Dikranian[2], G. Dissen[3], L. Martin[3], J. Olney[1] and A. Brambrink[3,4]*



Can we generalize animal studies to humans?



Actual human studies!!!

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

BUT WAIT…

TABLE 4 Differences Between the Mean Scores of Unexposed and Exposed Children at Age 10

Neuropsychological Domain	Neurodevelopmental Test Score	Unexposed Test Scores, Mean (SD)	Exposed Test Scores, Mean (SD)	Score Difference between Unexposed and Exposed	*P*
Language	CELF Total Score	96.2 (15.1)	92.6 (17.1)	3.7	.003[a]
	CELF Receptive Score	101.9 (15.8)	98.2 (18.1)	3.7	.006[a]
	CELF Expressive Score	91.9 (14.9)	88.3 (16.8)	3.6	.004[a]
	PPVT Standard Score	104.2 (12.1)	103.1 (12.5)	1.2	.2
Cognition	CPM Total Score	31.2 (3.6)	30.2 (4.3)	1.0	.002[a]
	Written SDMT Score	34.6 (7.5)	33.7 (7.8)	0.9	.1
	Oral SDMT Score	43.9 (10.3)	43.2 (10.7)	0.7	.4
Behavior	CBCL Total Score	47.4 (11.5)	48.7 (10.6)	1.4	.06
	CBCL Internalizing Score	49.3 (10.6)	50.2 (10.4)	1.0	.2
	CBCL Externalizing Score	47.3 (10.8)	47.8 (10.4)	0.5	.5
Motor function	MAND NDI Score	94.3 (13.8)	92.6 (14.7)	1.7	.1

NDI, Neuromuscular Development Index Score.

[a] Significant values using $P < .05$ and Holm-Bonferroni adjustment for multiple comparisons.

MAYO CLINIC

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

TABLE 3. Exposure to Procedures Requiring Anesthesia Before Age 2 Years and Risk for ADHD

	Unadjusted		Covariate adjusted[a]		Propensity stratified[b]	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Procedure/anesthesia exposure						
None (n=5007)	1.0[c]		1.0[c]		1.0[c]	
1 (n=286)	1.52 (1.02-2.25)	.039	1.35 (0.90-2.02)	.148	1.18 (0.79-1.77)	.414
≥2 (n=64)	2.59 (1.38-4.85)	.003	2.49 (1.32-4.71)	.005	1.95 (1.03-3.71)	.042
Total duration of anesthesia (min)						
Continuous (per 30 min)	1.03 (1.00-1.05)	.020	1.03 (1.01-1.06)	.015	1.02 (0.99-1.04)	.160
Categorical (min)						
0 (n=5007)	1.0[c]		1.0[c]		1.0[c]	
1-30 (n=65)	1.00 (0.37-2.68)	.999	1.00 (0.37-2.68)	.999	0.83 (0.31-2.24)	.715
31-60 (n=68)	1.64 (0.78-3.47)	.195	1.59 (0.75-3.36)	.229	1.34 (0.63-2.84)	.448
61-90 (n=90)	1.40 (0.69-2.83)	.347	1.06 (0.50-2.25)	.879	1.05 (0.52-2.14)	.884
91-120 (n=46)	2.50 (1.18-5.30)	.016	2.09 (0.98-4.43)	.055	1.83 (0.86-3.91)	.118
≥121 (n=81)	2.24 (1.23-4.08)	.009	2.23 (1.21-4.10)	.010	1.70 (0.92-3.15)	.089

[a] Analysis was performed using proportional hazards regression with covariates included for sex, birth weight, and gestational age. We excluded 336 individuals from the covariate-adjusted analysis because of missing covariate information. CI = confidence interval.

[b] Analysis was performed using stratified proportional hazards regression with 5 strata defined based on propensity score. We excluded 364 individuals from the propensity-stratified analysis because of missing data for variables included in the propensity score or because the propensity score was outside the range of overlapping scores for those exposed vs unexposed to anesthesia before age 2 years (see Methods).

[c] Reference value.

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

Behavior and development in children and age at the time of first Anesthetic exposure

Kalkman, et al.

UMC
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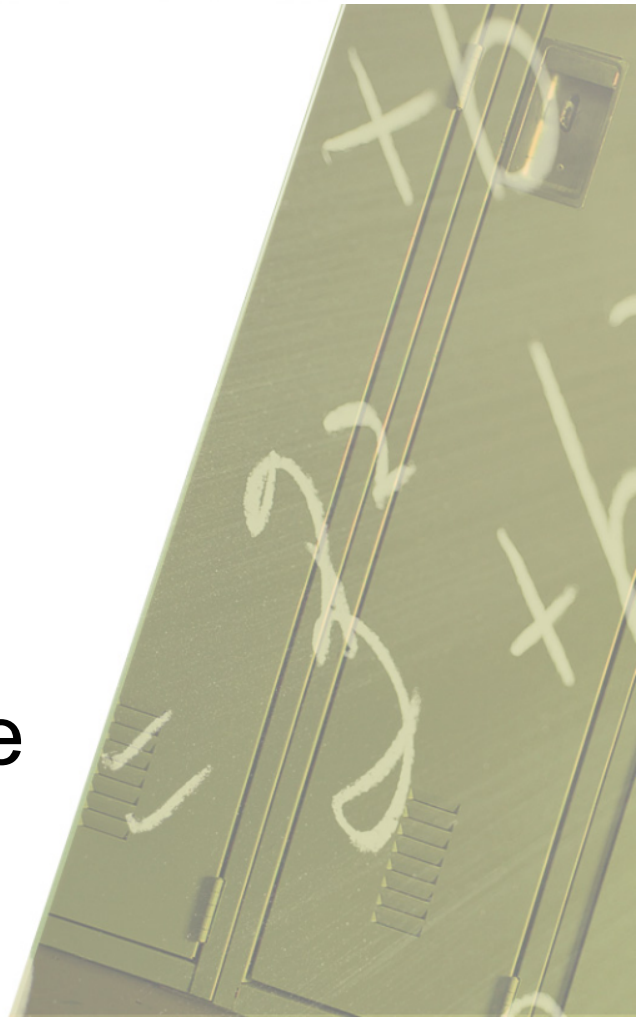
Possible protective strategies

- Spinal anesthesia
- Lithium
- Xenon
- Hypothermia
- Melatonin
- Dexmedetomidine
- Erythropoietin
- Bumetanide

Future Research

Human studies:

1. GAS study
2. PANDA study
3. MASK study



Primate study:

1. Long-Term Outcome of Single vs. Triple Anesthesia Exposure of Infant Monkeys

What do I say to parents??

Smart Tots website – consensus statement

- ✓ Previous research in young animals and children has raised concerns that exposure to commonly used anesthetics may produce adverse neurobehavioral effects.
- ✓ These studies had limitations that prevent experts from drawing conclusions on whether the harmful effects were due to the anesthesia or to other factors, including surgery, hospitalization, or pre-existing conditions.
- ✓ In the absence of conclusive evidence, it would be unethical to withhold sedation and anesthesia when necessary.
- ✓ Smart Tots 2013 FDA Statement

THANK YOU!

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