Why is it so difficult to demonstrate anesthesia-related neurotoxicity in humans?

10 years after…



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Pediatric Anesthesia Unit; Department of Anesthesiology, Pharmacology and Intensive Care, University Hospital of Geneva
Department of Neuroscience, University of Geneva Medical School

Why is it so difficult to demonstrate anesthesia related neurotoxicity in humans?

☞ Because neurotoxicity **does not** exist

"we would advise people to relax because if it really was that harmful to be anesthetized early life, we would most likely have suspected this phenomenon for ages ago"

(Hansen & Lonnqvist 2016)

☞ Neurotoxicity **does** exist - but we have numerous technical difficulties to prove

"concerns grow around anesthesia effects on babies - more funding and research is absolutely needed"

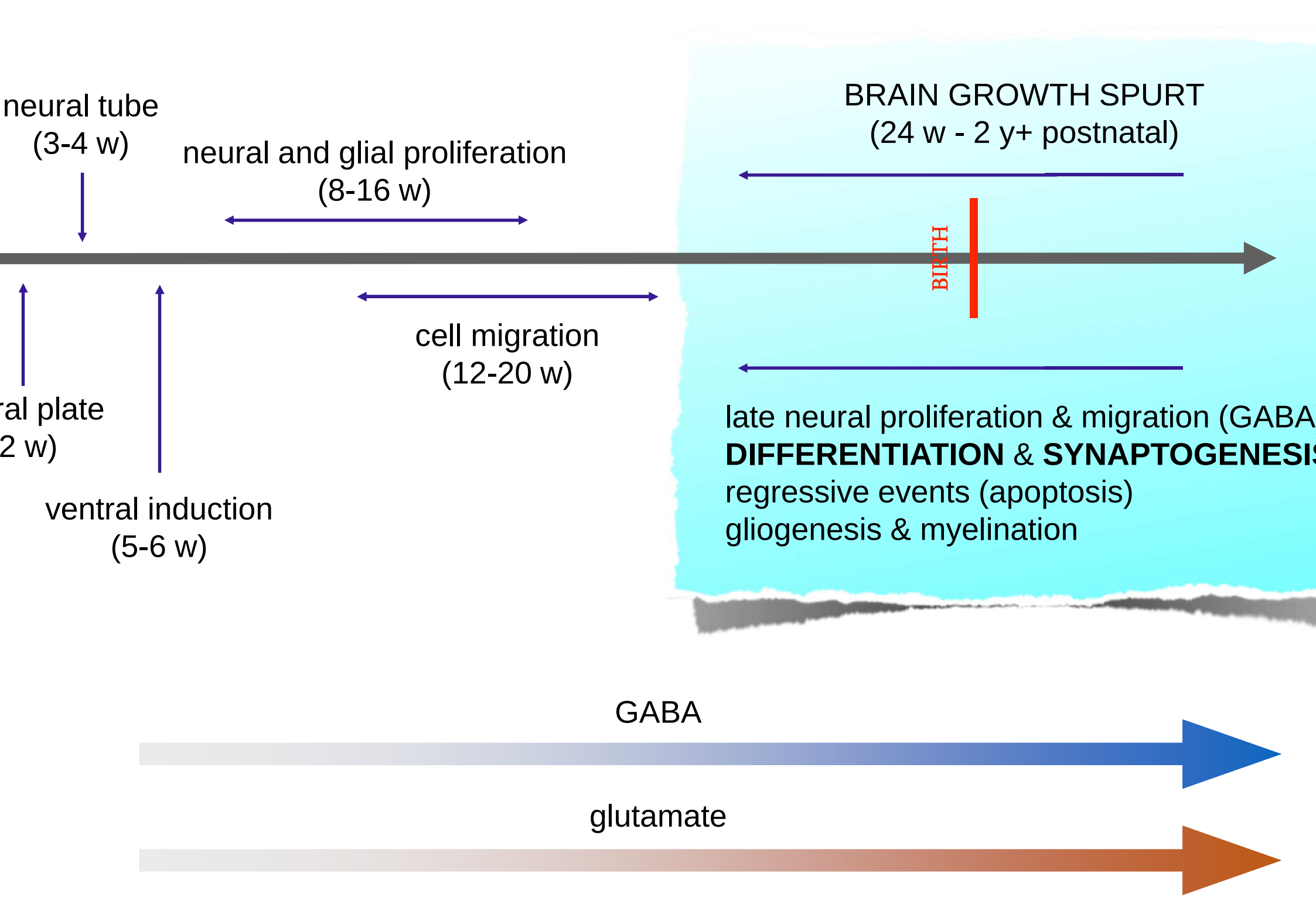
(smarttots.org)

Can we (at least) consider the possibility of developmental anesthesia neurotoxicity?

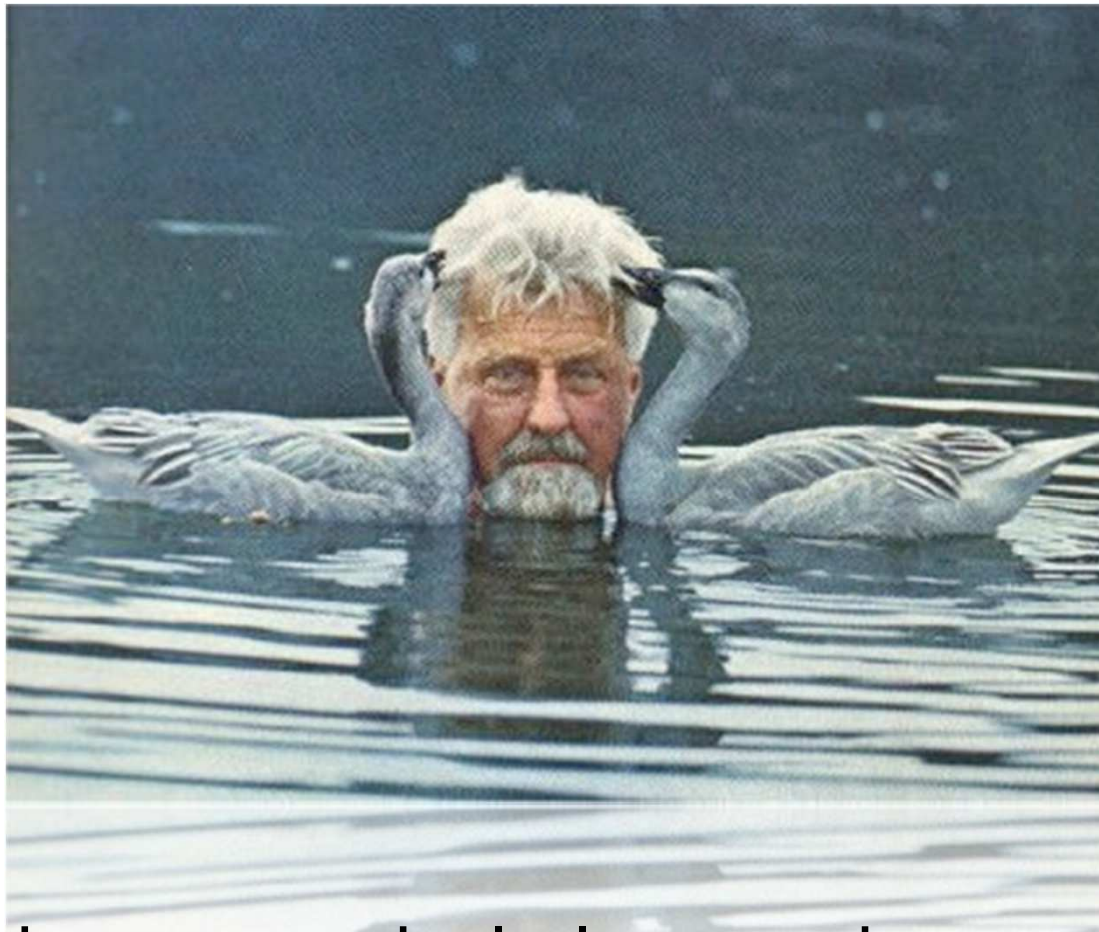
Is there a biological rational for suspecting long-term effects of early life anesthesia exposure on the nervous system?

	Nicotinic receptor superfamily				Ionotropic glutamate receptors		
	$GABA_A$	Glycine	nACh	$5\text{-}HT_3$	AMPA	kainate	NMDA
Etomidate	++	+	-	0	ND	ND	ND
Propofol	++	+	-	-	-	0	-
Barbiturates	++	+	--	--	--	--	-
Ketamine	+	0	--	--	0	0	--
Isoflurane	++	++	--	--	--	++	-
Sevoflurane	++	++	--	--	ND	ND	ND
Nitrous oxide	+	+	--	--	-	--	--

; significant potentiation; +: weak potentiation; ; significant inhibition; ; weak inhibiti

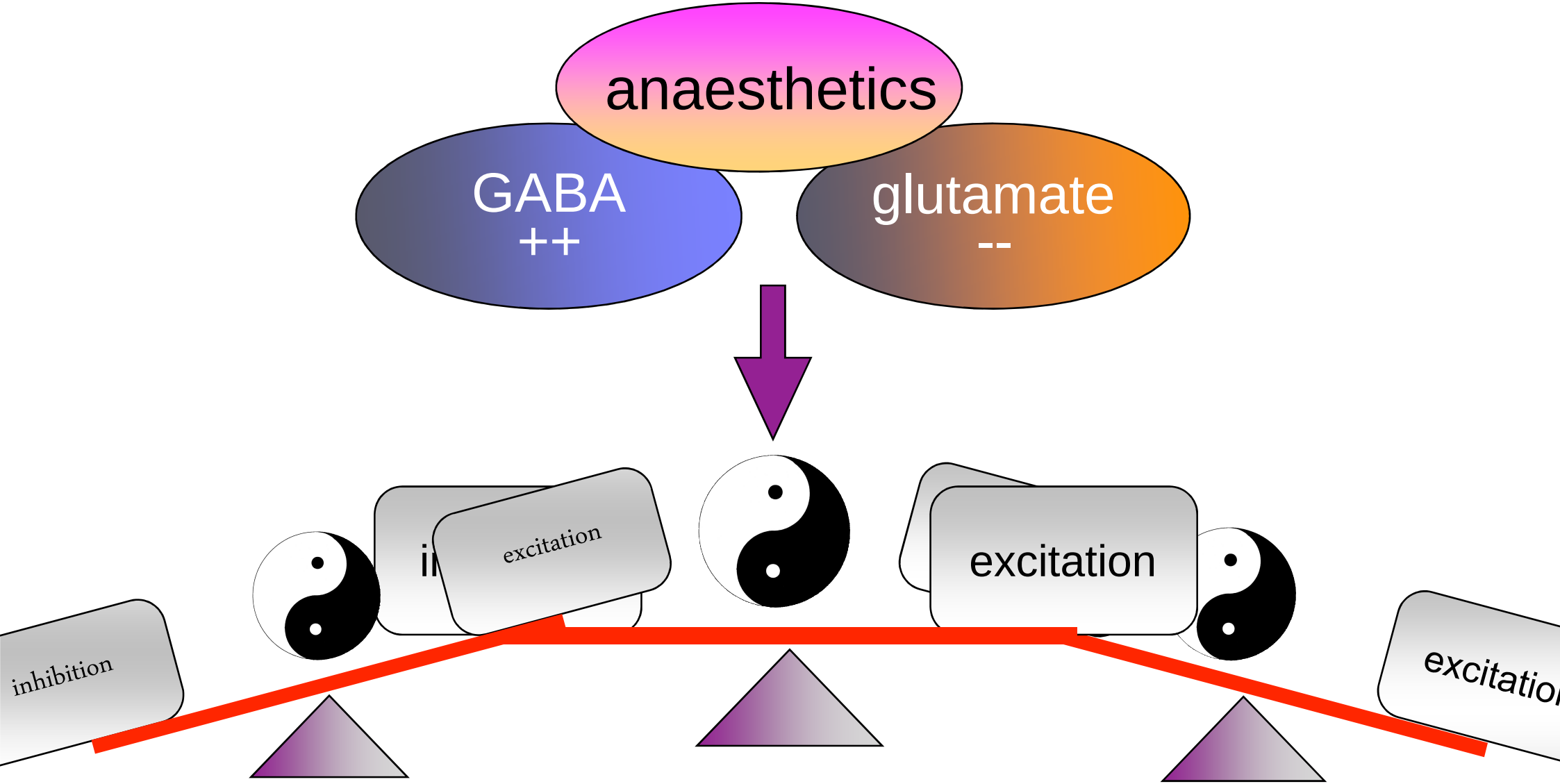

neural tube
(3-4 w)
neural and glial proliferation
(8-16 w)
BRAIN GROWTH SPURT
(24 w - 2 y+ postnatal)
BIRTH
cell migration
(12-20 w)
ral plate
2 w)
ventral induction
(5-6 w)
late neural proliferation & migration (GABA
DIFFERENTIATION & SYNAPTOGENESI
regressive events (apoptosis)
gliogenesis & myelination
GABA
glutamate





def: time windows when brain circuitry are particularly receptive to acquiring certain kinds of information or even need that instructive s for their continued development

role for neuronal activity: GABA & glutamate
(timing and duration)

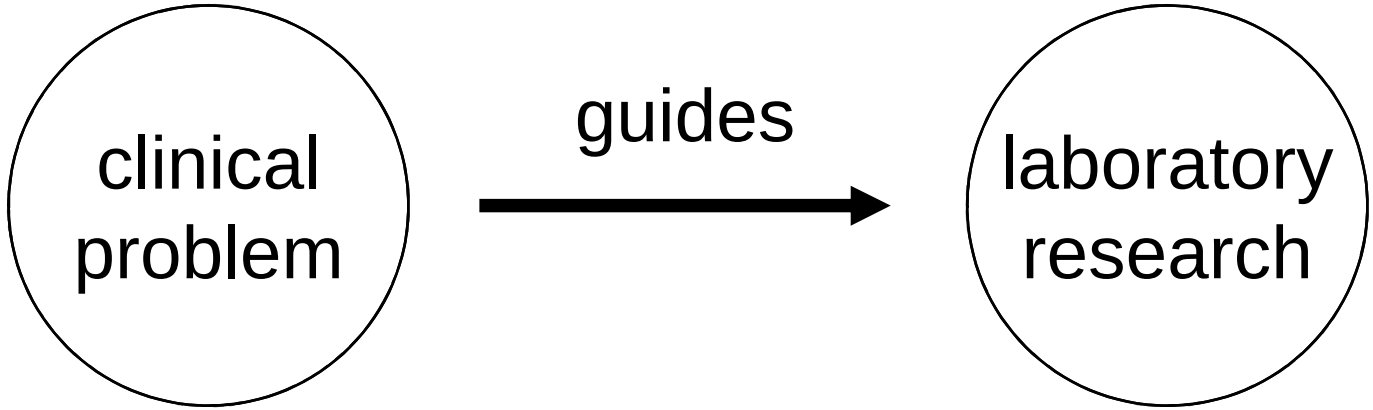


activity-dependent shaping of

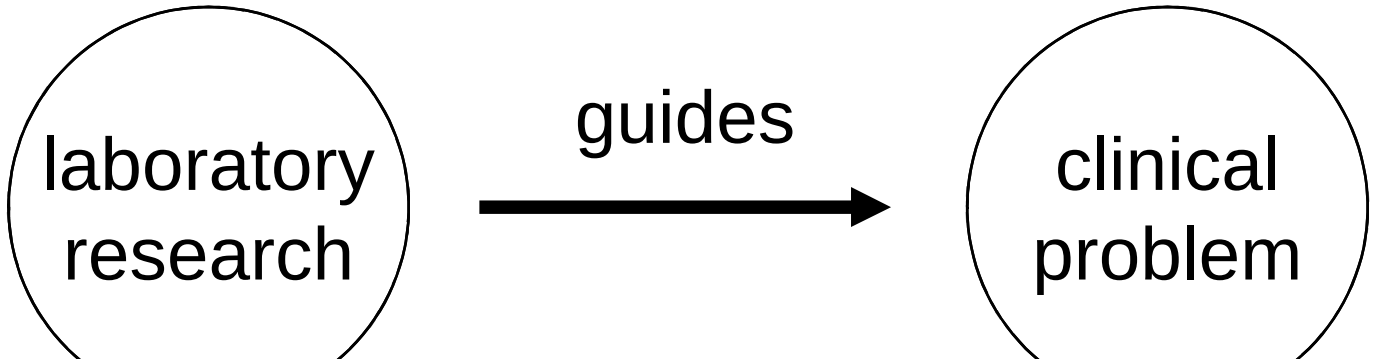
there is a theoretical possibility…..

but do we really have a problem?

☞ the usual flow of translational research:



☞ the flow of developmental anesthesia neurotoxicity research:



The commencement: the story behind the scenes

- research on fetal alcohol syndrome



When you drink alcohol,
your unborn child drinks it, too



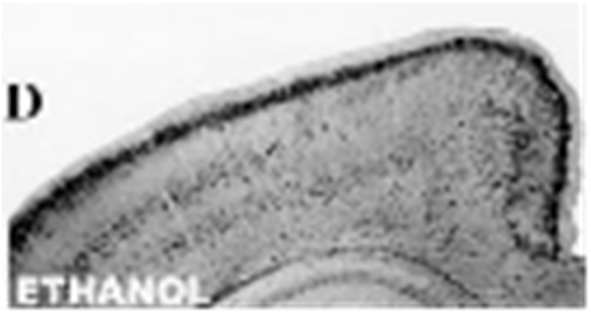


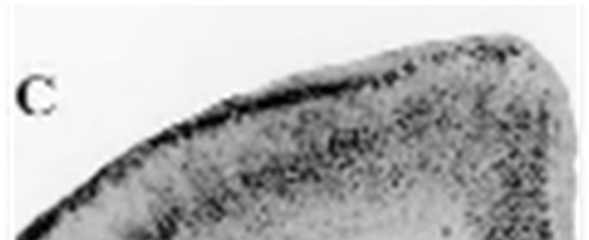
John Olney (1932-2015)

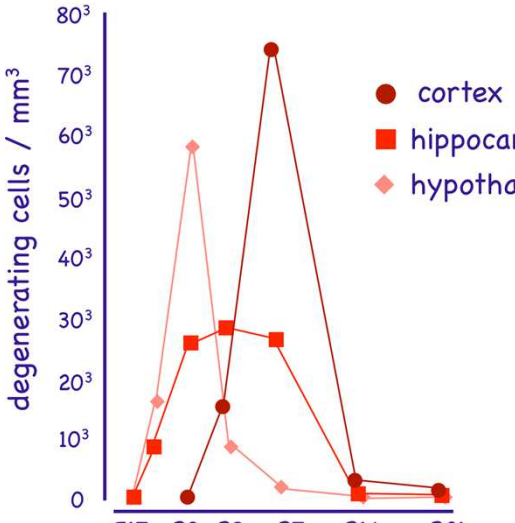
Science **287**, 1056 (2000)

Ethanol-Induced Apoptotic Neurodegeneration and Fetal Alcohol Syndrome

Chrysanthy Ikonomidou,[1] Petra Bittigau,[1] Masahiko J. Ishimaru,[2] David F. Wozniak,[3] Christian Koch,[1] Kerstin Genz,[1] Madelon T. Price,[3] Vanya Stefovska,[1] Friederike Hörster,[1] Tanya Tenkova,[3] Krikor Dikranian,[3] John W. Olney[3]*



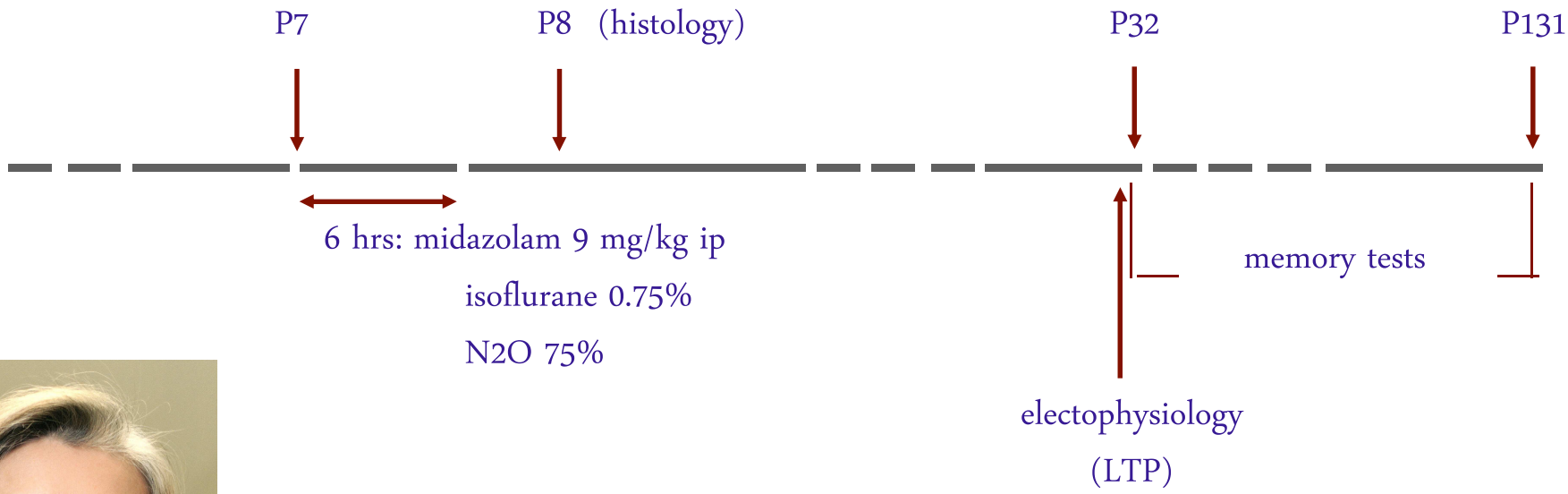




The commencement: the story behind the stories

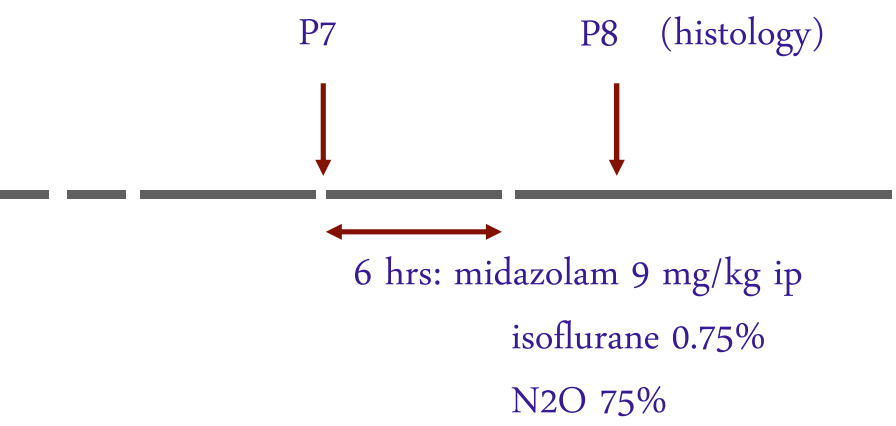
Do anesthetics also induce developmental neuroapoptosis?

If yes, what is the functional relevance?





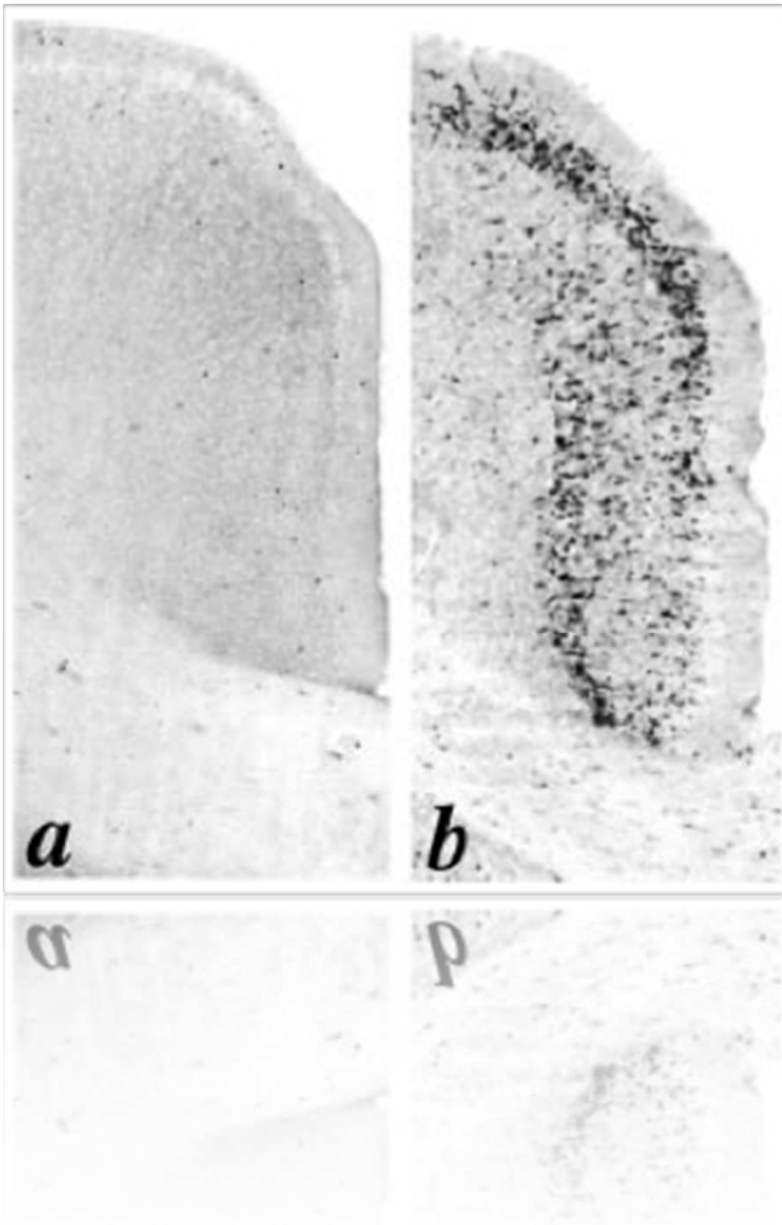
in the developing brain



1. Arterial blood gas analysis

al blood gas	Controls ($n = 8$)	Treated ($n = 8$)
	7.52 ± 0.05	7.49 ± 0.02
₂ (mmHg)	30 ± 8	29 ± 2.7
(mmHg)	117 ± 13	93 ± 11
⁻ (mmol/l)	23 ± 3	22 ± 1.5
(%)	99 ± 0.3	96 ± 1.1

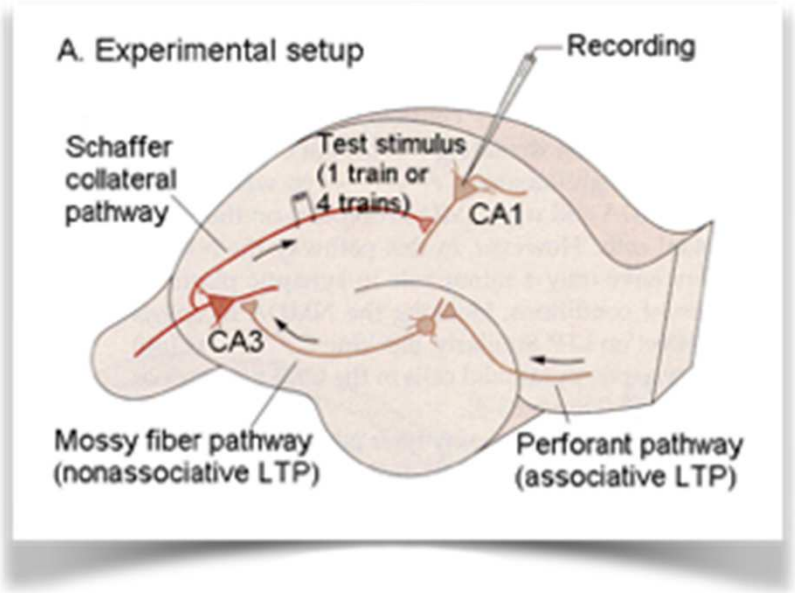
control anesthesia

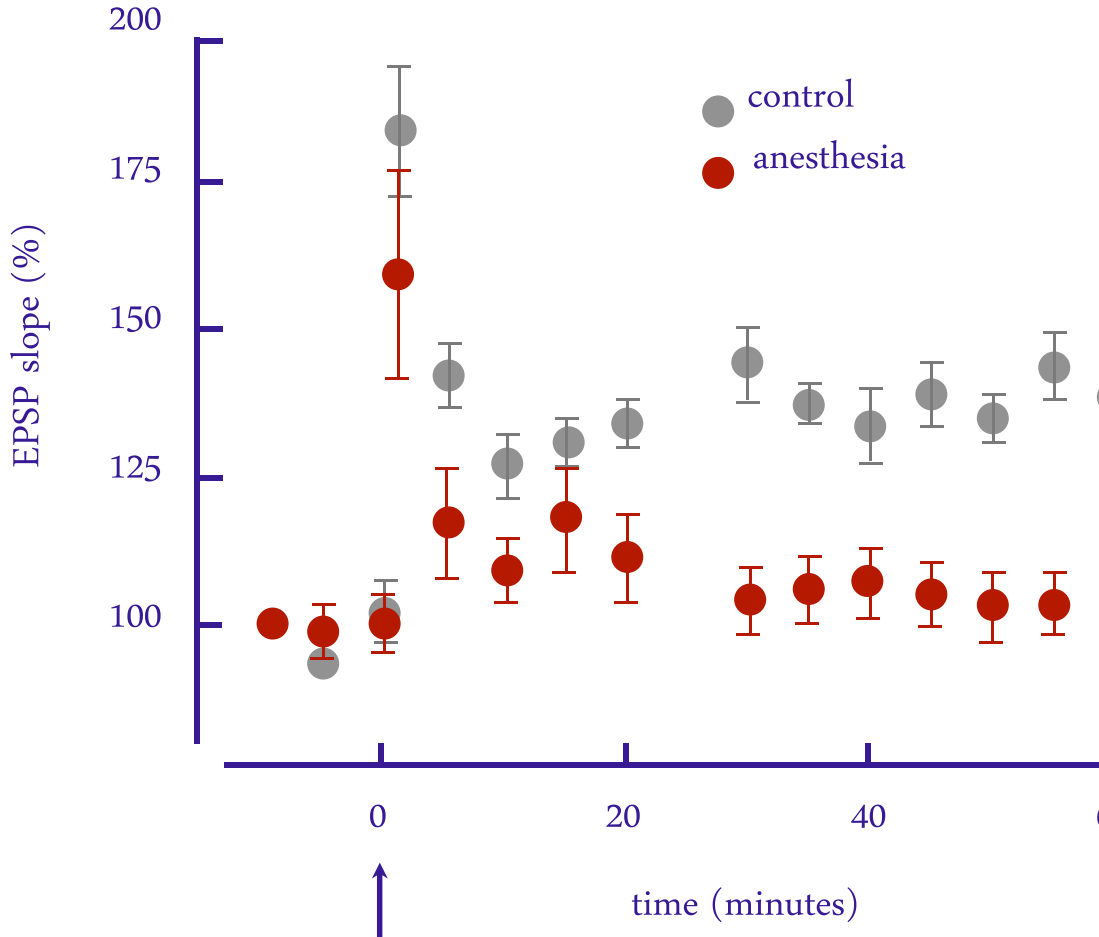


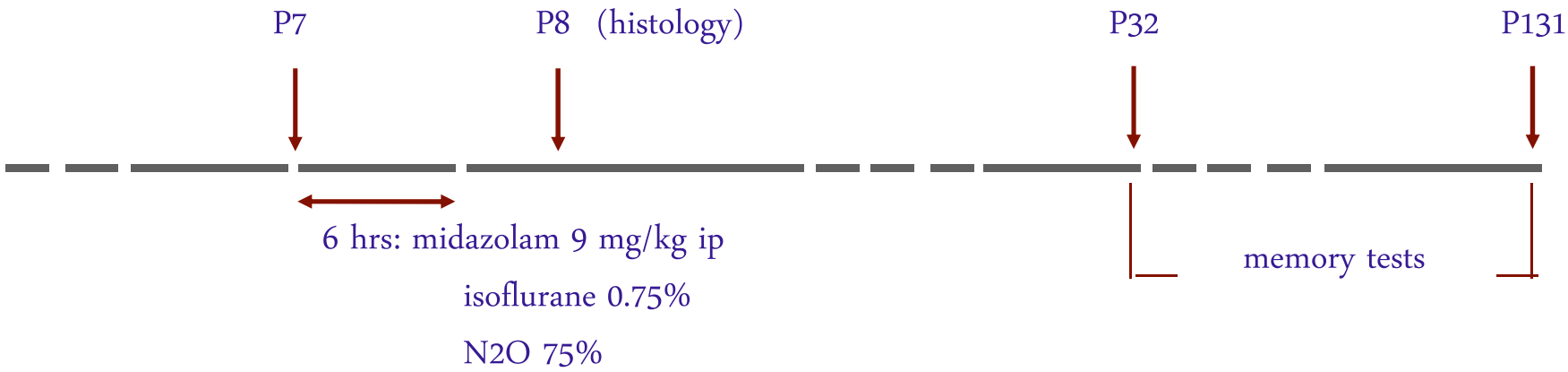
neural networks

P7 P8 (histology) P29-32: electrophysiology (LTP)

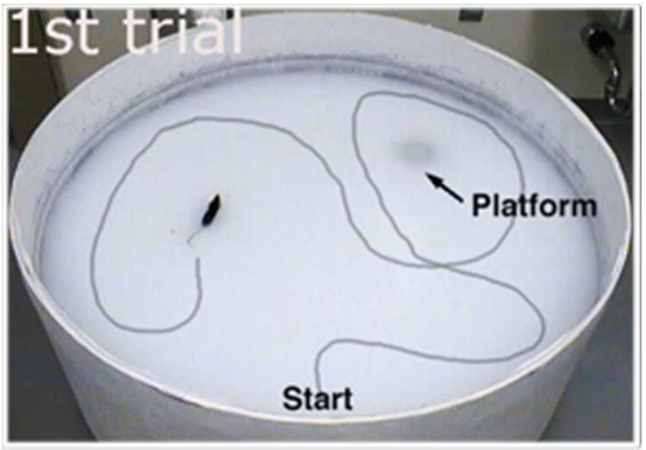
6 hrs: midazolam 9 mg/kg ip
isoflurane 0.75%
N2O 75%

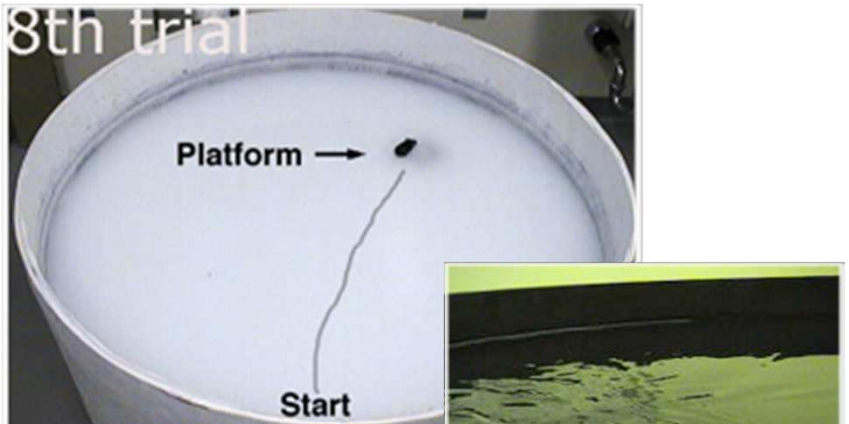


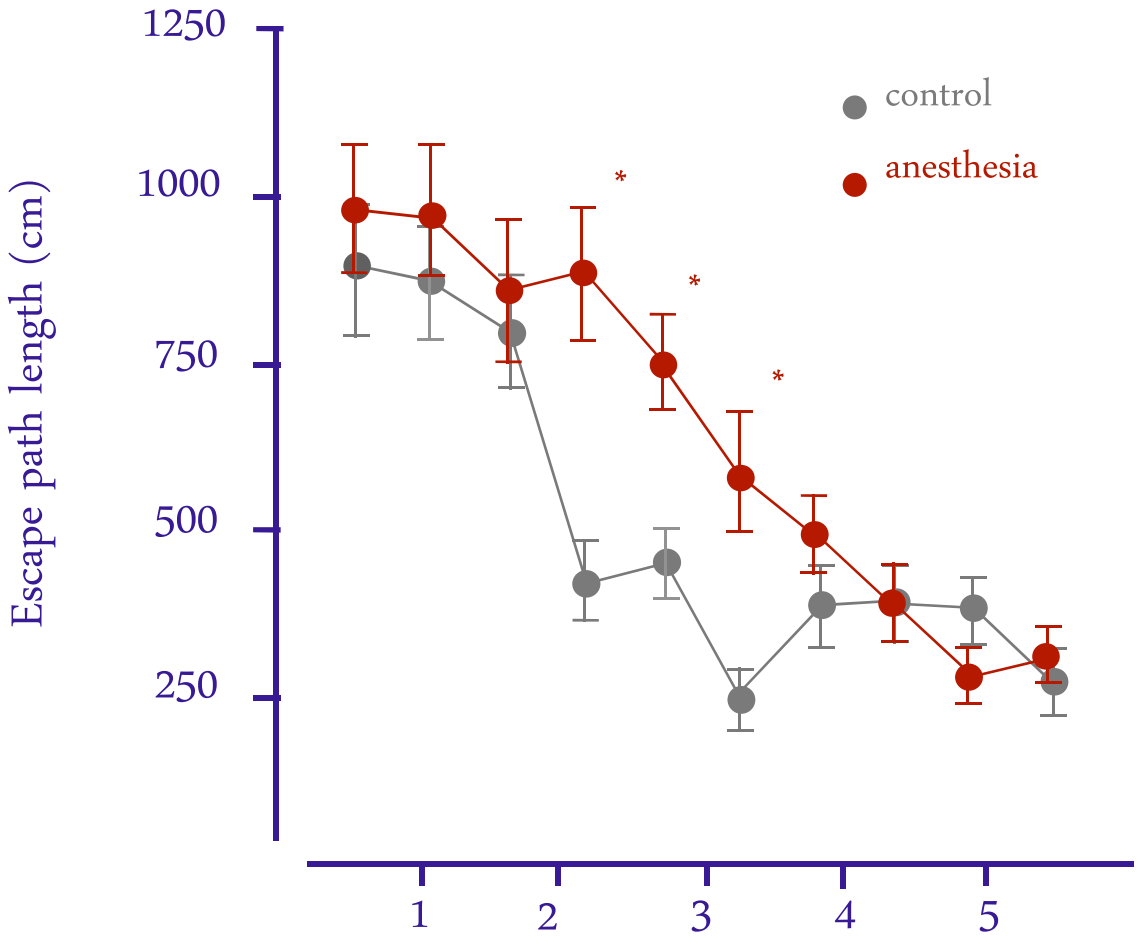




Morris Water Maze







What do we know? - animal data

- Most general anesthetics have a variety of effects on the developing brain (from rodents to monkeys)

  cell death, impaired neuro- and synaptogenesis, behavioural / cognitive dysfunction

- These effects depend on age, dose, length of exposure, gender

- The strongest evidence for morphological/behavioral change is for agents acting on $GABA_A$ and/or NMDA receptors

What do we know? - animal data

- There is weak evidence that opioids and alpha 2 agonists have no effect, or even a protective effect
- There is good evidence that local or regional anesthesia does not produce changes
- Some interventions might mitigate the changes in the animal model

hat we don´t know? - animal data

- We do not know the actual mechanisms, or how the observed possible mechanisms are linked, if they are indeed linked.
- We cannot guarantee that opioids and alpha 2 agonists have no effect.
- We have incomplete data on the effect of surgery *per se*.
- We don’t know how surgery interacts with observed effects.

What do we know? - translation

- There is now reason to suggest that changes observed in animals would not occur when the developing human brain exposed to sufficient doses of general anesthetics
- There are many modifying factors when translating animal to humans
- There are precedents for animal models being irrelevant to humans (e.g. neuroprotection)

What we don´t know? - translation

- If these morphologic effects are seen in humans, we don't know at what age, or at what dose they are likely to be see
- If there are morphological changes, we have incomplete da on which neurological domains in humans are likely to be affected, if any
- If neurological domains are affected, then how does age of exposure and dose change this

What do we know? - human studies

A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN

RELATIONSHIP OF ANESTHESIA TO POSTOPERATIVE PERSONALITY CHANGES IN CHILDREN

JAMES E. ECKENHOFF, M.D.

PHILADELPHIA

1953.

prospective observational (questionnaire) study

1008 children (all children admitted to ORL procedures durign an 18-month-long period)

612 response received

Qs: bedwetting, nightmares, temper tantrums etc)

17% with behavioral changes

< 3yrs: 57%; 4yrs: 38%; 6yrs: 32%; 8yrs: 14%

☞ Identification of appropriate endpoints:

☛ global IQ

☛ targeted areas of neurocognitive function:

- executive function
- attention
- memory
- behavior
- motor function

complex neurpsychological testing rather than "diagnosis"

☛ need to perform long-term follow-up

☛ comparison group: age-matched siblings without history of anesthesia exposure

☞ Choice of epidemiological approach:

☞ Direct prospective neuropsychological evaluation

☞ ambidirectional:

retrospective "recent" birth cohorts - prospective neuropsychological evaluation

☞ retrospective "historical" birth cohorts -

non-prospective neuropsychological evaluation

(Mayo Clinic / Olmsted Medical Center)

☛ 1976 - 1982: 8548 birth

☛ 5357 children with detailed follow-up (medical + academic) up to 19 years of age

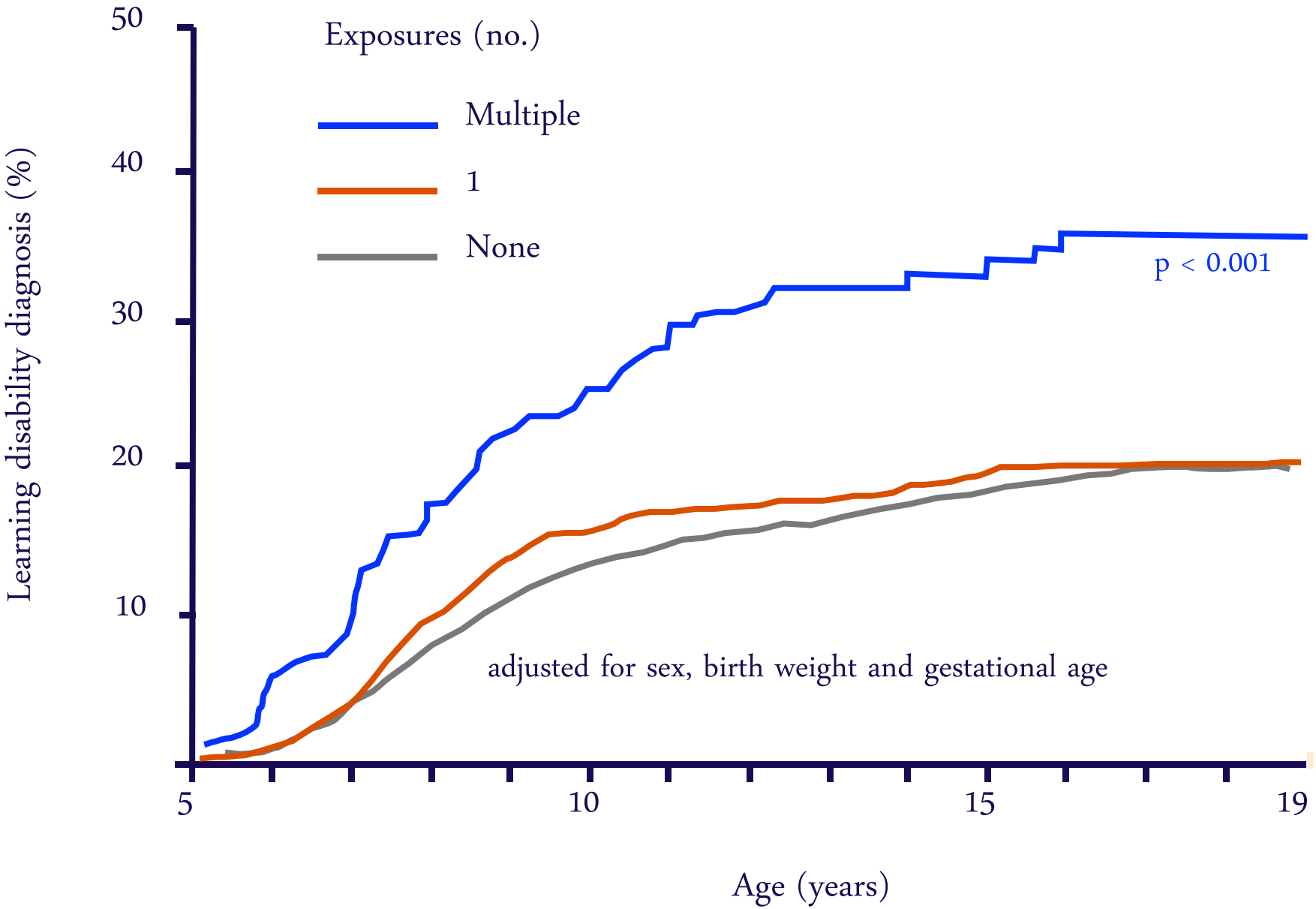
☛ 593 underwent procedures requiring general anesthesia before 4 years of age

☛ 144 children received multiple anesthesia

Q: incidence of learning deficits?

(i) no anesthesia (ii) 1 anesthesia < 4 (iii) multiple anesthesia < 4

adjusted for sex, birth weight and gestational age


Exposures (no.)
Multiple
1
None
p < 0.001
adjusted for sex, birth weight and gestational age
Learning disability diagnosis (%)
50
40
30
20
10
5
10
15
19
Age (years)

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

Anesthesiology

ademic Performance in Adolescence after Inguinal rnia Repair in Infancy

Anesthesiology 2011; 114:1076–85

lationwide Cohort Study

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

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

www.anesthesia-analgesia.org

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

Cognitive and Behavioral Outcomes After
Exposure to Anesthesia and Surgery

PEDI

Correlative epidemiological evidence suggests association between anesthesia /(surgery) exposure in early childhood and altered neurobehavioral outcome

etrospective Cohort Study of the Association of
hesia and Hernia Repair Surgery With Behavioral
d Developmental Disorders in Young Children

les DiMaggio, PhD, MPH, PA-C, Lena S. Sun, MD,† Athina Kakavouli, MD,‡*
Mary W. Byrne, PhD, MPH (*J Neurosurg Anesthesiol* 2009;21:286–291)

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

Anesthesiology 2009; 110:796–804

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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.,§*

Anesthesiology 2009; 111:302–10

Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams &

Anesthesia for Cesarean Delivery and Learning Disabili in a Population-based Birth Cohort

Juraj Sprung, M.D., Ph.D., Randall P. Flick, M.D., M.P.H.,† Robert T. Wilder, M.D., Ph.D.,‡ Slavica K. Katusic, M.D*
*Tasha L. Pike, M.S.,‖ Mariella Dingli, M.D.,# Stephen J. Gleich, M.D.,** Darrell R. Schroeder, M.S.,††*
*William J. Barbaresi, M.D.,‡‡ Andrew C. Hanson, B.S.,§§ David O. Warner, M.D.**

Conclusion

- No differences in neurobehavioral scores at the age of 2 following neonatal hernia surgery under general vs regional anesthesia (less than 1 hour of duration)

- So far, most data comes from retrospective cohort studies (without detailed clinical records) are available
- The interim (2 yr) analysis of the only available RCT shows no difference in neurocognitve outcome between general and regional anesthesia groups
- In humans, there is a weak and mixed evidence for an association between surgery (and anesthesia) in early childhood and increased risk of poor neurodevelopmental outcome
- In humans, there is a weak and mixed evidence that exposure to multiple anesthetics is associated with greater risk of poor neurobehavioral outcome

What we don´t know? - human studies

- We have incomplete knowledge of which children are at greatest risk of poor developmental outcome: dose, age o exposure
- We have incomplete knowledge of which domains are involved
- We do not know what other factors might contribute to poo outcome: inflammation, hypotension, hypocarbia, etc…
- We do not know how these factors interact (anesthetics could even be protective!)
- We do not know which interventions would reduce the risk

Other related issues

- Socio-economic status as a confounding factor
- The relativity of “intelligence”
- Neonatal anesthesia is relatively high risk for multiple reasons
- Infants need good analgesia
- The hemodynamic and neuro-edocrine stress response ar likely bad and anesthesia should aim to reduce this
- Limited data on how to do this best
- Unclear if infants need to be “unconscious” or indeed how much to give to make them unconscious

- There are known knowns; there are things we know that we know
- There are known unknowns; there are things we know that we don’t know
- But there are also unknown unknowns; there are things we don’t know that we don’t know



December 2012

SmartTots
Funding anesthesia research to ensure pediatric

arly, additional research is urgently needed to identify any possible risks to young dren. In the absence of conclusive evidence, it would be unethical to withhold sedatio d anesthesia when necessary. Instead, healthcare providers should do the following:

- Discuss with parents and other caretakers the risks and benefits of procedures requiring anesthetics or sedatives, as well as the known health risks of *not treating* certain conditions
- Stay informed of new developments in this area
- Recognize that current anesthetics and sedatives are necessary for infants and children who require surgery or other painful and stressful procedures

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European

