ANESTHESIA AND THE DEVELOPING BRAIN

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MSA 2021

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LEARNING OBJECTIVE

- 1. Understand how anesthesia may affect the long-term development of children.
- 2. Understand perioperative changes in behavior and cognition in children.
- 3. Be able to inform children and families on the potential impact of anesthesia on the developing brain.
- Disclosures: none

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MANY CHILDREN REQUIRE ANESTHESIA AND SURGERY AS AN ESSENTIAL PART OF THEIR HEALTHCARE

- Each year, 3.8 million surgeries are performed on children.(Rabbitts 2020)
- 15% of children needed at least one episode of general anesthesia before the age of 3 years (Shi 2018), the rate goes up to 25% before the age of 5 (Shi 2021).
- In this country, the most common reasons children under the age of 5 needing anesthesia include ENT procedures (60%); imaging and diagnostic procedures (11%); urology (7%); and general surgery (6%).(Shi 2021)
- Therefore, anesthesia plays an important role in child health. Any effects of anesthesia on children have public health implications.

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FDA Drug Safety Communication: FDA approves label changes for use of general anesthetic and sedation drugs in young children

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This is an update to the **FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women** issued on December 14, 2016.

Safety Announcement

[4-27-2017] The U.S. Food and Drug Administration (FDA) is notifying the public that we have approved previously announced label changes regarding the use of general anesthetic and sedation medicines in children younger than 3 years. These changes include:

- A new Warning stating that exposure to these medicines for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years.
- Addition of information to the sections of the labels about pregnancy and pediatric use to describe studies in young animals and pregnant animals that showed exposure to general anesthetic and sedation drugs for more than 3 hours can cause widespread loss of nerve cells in the developing brain; and studies in young animals suggested these changes resulted in long-term negative effects on the animals' behavior or learning.

List of General Anesthetic and Sedation Drugs Affected by this Label Change*

Generic Name	Brand Name
desflurane	Suprane
etomidate	Amidate
halothane	Only generic is available
isoflurane	Forane
ketamine	Ketalar
lorazepam injection	Ativan
methohexital	Brevital
midazolam injection, syrup	Only generic is available
pentobarbital	Nembutal
propofol	Diprivan
sevoflurane	Ultane, Sojourn

*This list includes anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity. No specific medications have been shown to be safer than any other.

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ANIMAL EVIDENCE

- Young neurons and glia are vulnerable to anesthesia-induced morphologic and functional impairments.
- Not only that significant apoptotic damage could be detected, but importantly, of synaptic dysfunction, and attrition, as well as impaired connectivity and faulty formation of neuronal circuits.

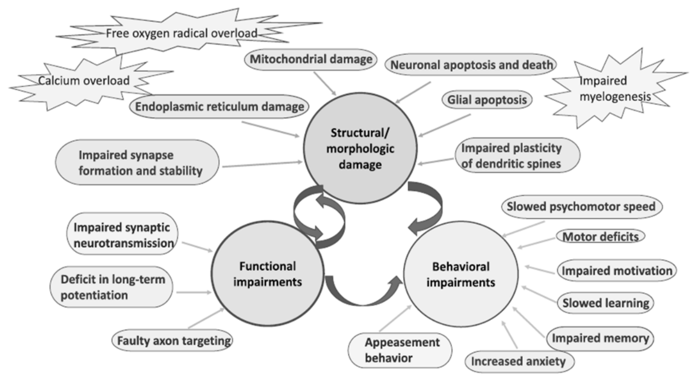

Fig. 1. The summary of proposed mechanisms and processes responsible for anesthesia-induced developmental neurotoxicity.

Jevtovic-Todorovic, 2018

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HUMAN STUDIES PRIOR TO FDA WARNING

Far less conclusive than animal studies

Most were retrospective

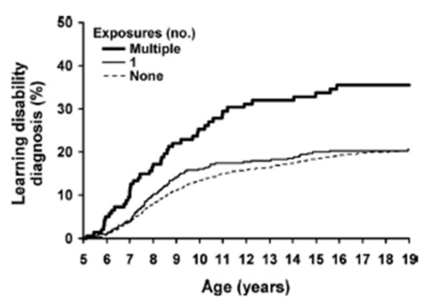

Fig. 1. Cumulative percentage of learning disabilities diagnosis by the age at exposure shown separately for those that have zero, one, or multiple anesthetic exposures before age 4 yr.

Anesthesiology 2009; 110:796–804

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

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INVESTIGATION TO ESTABLISH THE EVIDENCE IN CHILDREN

Neurodevelopment in children is very complex and involve many areas including cognition, behavior, and emotion, etc.

It is very challenging to choose the right study outcome in order to characterize the potential phenotype of anesthesia induced neurotoxicity in children.

Assessment tools:

- **Testing of children**
- **Questionnaires for parents**
- **Medical record: diagnoses**
- **School record and standard test results**
- **Imaging: MRI**

Developmental outcomes

- Cognition
- Behavior
- Emotion

- Intelligence (IQ)
- Problem solving
- Planning and organization
- Attention and memory
- Processing speed
- Language
- Academic skills
- Visual perception
- Control over hand movements
- Depression and anxiety
- Aggression and impulsive behavior
- Social skills

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3 MAJOR PROSPECTIVE STUDIES

Anesthesia exposure was not associated with lower FSIQ.

MASK: multiply exposed had lower processing speed and fine motor

- The GAS trial enrolled children scheduled for inguinal hernia repair (mean age ~70 days) and randomized them to receive either general anaesthesia with sevoflurane or regional anaesthesia with spinal or caudal blocks with neurodevelopmental evaluation at 5 yr of age. (McCann 2019)
- The two other studies relied on an 'ambi-directional' observational approach, with children old enough to undergo prospective neuropsychological testing retrospectively identified as having been exposed to surgery and anaesthesia at 3 yr of age.
- The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study included siblings discordant for exposure to hernia surgery with neurodevelopmental evaluation at 15 yr of age. (Sun 2016)
- The Mayo Anesthesia Safety in Kids (MASK) study included children undergoing a variety of surgical procedures with children singly or multiply exposed to general anaesthesia before age 3 yr propensity matched to unexposed children with neurodevelopmental evaluation at 12 or 15 yr. Multiple exposure was associated with lower processing speed and fine motor skills.(Warner 2018)

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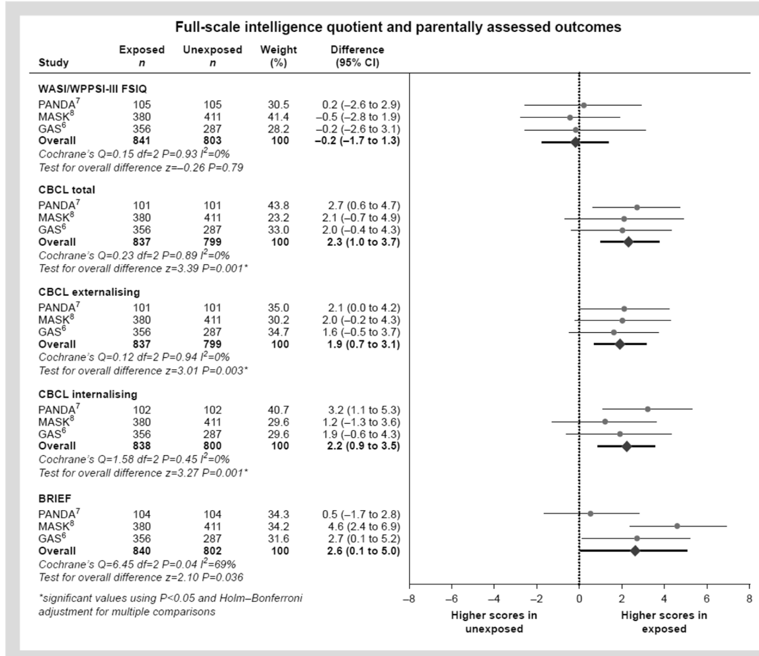
BEHAVIORAL OUTCOMES

A recent paper performed a meta-analysis on the results of the 3 studies: confirmed that no association between single anesthesia exposure and FSIQ.

However, when looking at behavioral outcomes reported by parents, history of anesthesia exposure was related to more behavioral problems as measured by CBCL and BRIEF. (Ing 2020)



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MORE QUESTIONS

If statistically significant results are meaningful clinically or in real life.

It is reassuring that no major deficits were found in children who had a single exposure. But are there any children who are more vulnerable to the effect of anesthesia?

Are there potential moderators existing in the relationship between development and anesthetic exposure?

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MULTIPLE EXPOSURES

(>=2 EPISODES)

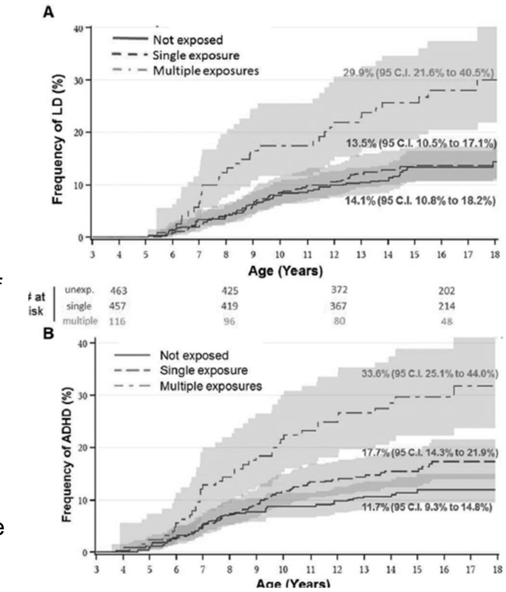
Newer study with Olmsted population (Hu 2017) Figure→

National cohort study: Compared with unexposed children, a single exposure to anesthesia was associated with a HR of 1.39, (95% confidence interval [CI], 1.32,1.47) for ADHD. Multiple exposures were associated with a HR of 1.75 (95% CI, 1.62,1.87). (Shi 2021)

Children with cancer:

In survivors of childhood medulloblastoma, a neurodevelopmentally vulnerable population, greater exposure to anesthesia significantly and independently predicts deficits in neurocognitive and academic functioning.(Jacola 2020)

In childhood ALL survivors, cumulative anesthesia exposure associated with neurocognitive impairments and neuroimaging abnormalities. (Banerjee 2019)



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AGE AT EXPOSURE

Most studies included children had exposure before age 3.

Similar association between anesthesia and ADHD has been found in older children as well.(Ing 2017)(Shi 2021)

No increased risk was found among infants.

Table 3 Risk of attention-deficit/hyperactivity disorder based on age of exposure in the single-exposure group and frequency of exposure in the multiple-exposure group. *Event rate: weighted event rate, per 100 person-years. CI, confidence interval; HR, hazard ratio.

	No. of patients	Event rate*	HR (95% CI)
Age at anaesthesia			
(only among singly exposed group)			
<1 yr	7160	0.78	Reference
1–3 yr	13 500	0.78	1.00 (0.89–1.13)
3–5 yr	9606	0.80	1.04 (0.92–1.18)
Number of anaesthesia exposures			
(only among multiply exposed group)			
Two anaesthesia exposures	9981	0.92	Reference
Three anaesthesia exposures	3221	1.16	1.27 (1.08–1.48)
Four or more anaesthesia exposures	3143	1.18	1.28 (1.07–1.53)

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OTHER POTENTIAL MODERATORS

Few studies looked at moderators (most of studies limited by sample size)

Shi 2021: Sex, prematurity, household income, index of comorbidity: no interaction with anesthesia;

Exposure increased the incidence of ADHD to a greater extent in non-White compared with White children.

Table 2 Association between anaesthesia exposure and attention-deficit/hyperactivity disorder in the birth cohort. *Event rate: weighted event rate, per 100 person-years. CI, confidence interval; HR, hazard ratio.

Subgroup	Unexposed		Singly exposed			Multiply exposed			P for interaction
	No. of patients	Event rate* (95% CI)	No. of patients	Event rate (95% CI)	HR (95% CI)	No. of patients	Event rate (95% CI)	HR (95% CI)	
All patients	138 391	0.57 (0.55 −0.59)	30 266	0.78 (0.75 −0.82)	1.39 (1.32 −1.47)	16 345	0.99 (0.93 −1.05)	1.75 (1.62 −1.87)	
Sex									0.653
Female	71 809	0.34 (0.32 −0.35)	12 651	0.50 (0.45 −0.54)	1.48 (1.33 −1.63)	6280	0.64 (0.56 −0.73)	1.91 (1.66 −2.19)	
Male	6658	0.80 (0.77 −0.82)	17 615	1.06 (1.01 −1.12)	1.35 (1.27 −1.44)	10 065	1.32 (1.24 −1.42)	1.67 (1.54 −1.80)	
Race									0.006
White	98 638	0.62 (0.61 −0.64)	23 627	0.83 (0.79 −0.87)	1.35 (1.27 −1.43)	13 154	1.01 (0.94 −1.08)	1.62 (1.51 −1.75)	
Non-White	39 753	0.43 (0.40 −0.45)	6639	0.65 (0.59 −0.72)	1.54 (1.37 −1.74)	3191	0.94 (0.81 −1.10)	2.23 (1.89 −2.63)	
Birth maturity									1.000
Normal	129 339	0.56 (0.55 −0.58)	27 670	0.77 (073 −0.81)	1.38 (1.31 −1.46)	14 085	0.99 (0.92 −1.05)	1.77 (1.64 −1.91)	
Premature	9052	0.70 (0.64 −0.77)	2596	0.99 (0.87 −1.14)	1.44 (1.22 −1.71)	2260	1.04 (0.89 −1.22)	1.52 (1.26 −1.84)	
Annual household income (US$)									0.566
More than 40 000	131 264	0.57 (0.55 −0.58)	28 750	0.77 (0.74 −0.81)	1.38 (1.31 −1.46)	15 485	0.97 (0.91 −1.03)	1.72 (1.60 −1.85)	
Less than 40 000	7127	0.67 (0.60 −0.75)	1516	1.03 (0.86 −1.23)	1.58 (1.28 −1.97)	860	1.43 (1.13 −1.82)	2.25 (1.71 −2.96)	
Elixhauser index									1.000
0–1 comorbidities	125 804	0.53 (0.52 −0.55)	25 579	0.74 (0.70 −0.78)	1.41 (1.33 −1.49)	11 190	0.94 (0.87 −1.01)	1.77 (1.63 −1.92)	
2+ comorbidities	12 587	0.87 (0.81 −0.93)	4687	1.11 (1.01 −1.23)	1.29 (1.14 −1.47)	5155	1.38 (1.25 −1.52)	1.65 (1.45 −1.87)	

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SHORT TERM EFFECT FROM ANESTHESIA AND SURGERY

Postoperative behavioral changes

Please compare your child's **current** behavior to his or her behavior **before the surgery**

		much less than before	less than before	same as before	more than before	much more than before
1	Does your child make a fuss about going to bed at night?	1	2	3	4	5
2	Does your child make a fuss about eating?	1	2	3	4	5
3	Does your child spend time just sitting or lying and doing nothing?	1	2	3	4	5
4	Does your child need a pacifier?	1	2	3	4	5
5	Does your child seem to be afraid of leaving the house with you?	1	2	3	4	5
6	Does your child seem uninterested in what goes on around him/her?	1	2	3	4	5
7	Does your child wet the bed at night?	1	2	3	4	5
8	Does your child bit his/her fingernails?	1	2	3	4	5

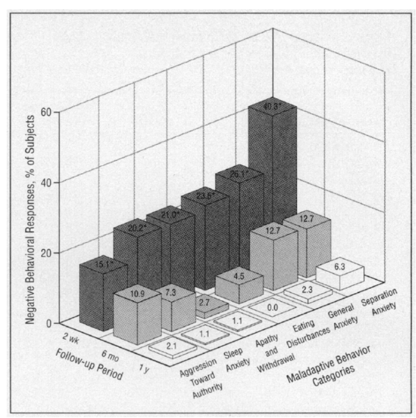

Figure 2. *Changes over time in the prevalence of negative behavioral responses based on the 6 maladaptive behavior categories of the Post Hospitalization Behavior Questionnaire. Separation anxiety was the most common maladaptive behavior reported by parents at both 2-week (40.3%) and 6-month (12.7%) follow-ups. The prevalence of behaviors in all 6 categories decreased significantly from 2-week to 6-month and 1-year follow-ups. Asterisk indicates* P<.05.

Kain 1996

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SHORT TERM COGNITIVE CHANGES

Previous studies with older children found transient declines in cognition that recovered withing days.

We recently conducted a study looking at short term trajectory of cognition in younger children undergoing anesthesia for elective surgery. (Shi, in press)

Surgery and anesthesia in children aged 2.5 to 6 years was not associated with declines in processing speed, working memory, and fine motor skills in the first three months postoperatively.

Statistically significant improvements are consistent with a known practice effect from repetition of tasks (improved familiarity with the test), rather than true improvements in function.

Limitations: underpowered to detect the effect of history of previous anesthetic exposure; study population may not be representative.

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CHILDREN'S DEVELOPMENT IS FAR MORE COMPLEX THAN THAT OF LAB ANIMALS

- Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats (Shih 2012)

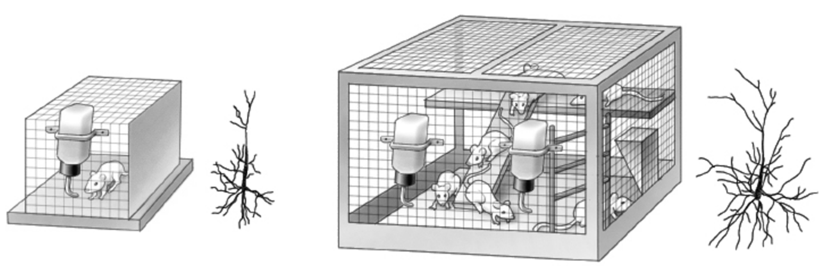

Figure 3.8
Myers/DeWall, *Psychology in Everyday Life*, 4e, © 2017 Worth Publishers

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NEUROPLASTICITY IN CHILDREN

- Developmentally, younger brains are more plastic and receptive to environmental influences during a period when multiple abilities develop interdependently as a result of gene-environment interactions.
- Interventions to improve cognition and behavior:
- Physical exercise
- Cognitive training
- Parental skills training

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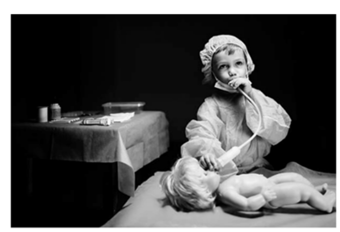
SUMMARY

- Single exposure to anesthesia in young children was associated with modest changes in behavioral outcome in the long term.
- Multiple exposures were related to slightly lower processing speed and fine motor skills; also increased the risk of ADHD.
- Short term behavioral changes are likely due to stress response to surgery and anesthesia. No obvious decline in cognition could be measured up to 3 months after anesthesia.
- Future studies: vulnerable population and trajectory of changes.
- Families should be reassured that anesthesia does not cause major developmental deficits. Many ways to raise happy and smart children.



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