

## Supplementary Online Content

Banerjee P, Rossi MG, Angheliescu DL, et al. Association between anesthesia exposure and neurocognitive and neuroimaging outcomes in long-term survivors of childhood acute lymphoblastic leukemia. *JAMA Oncol*. Published online June 20, 2019. doi:10.1001/jamaoncol.2019.1094

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eMethods 1: Modified Poisson approach

A modified Poisson approach was conducted to generate quasi-likelihood estimators for the relative risk and confidence intervals by using robust error variances (GENMOD procedure, with Poisson distribution and Log link), with adjustment for age at diagnosis, sex, total intrathecal count, and cumulative high-dose intravenous methotrexate. The specific model fitted was:

$$\log(\text{prob}(\text{global neurocognitive impairment})) = \text{intercept} + \beta_1 * (\text{age at diagnosis with 1-year increase}) + \beta_2 * \text{female} + \beta_3 * (\text{total intrathecal chemotherapy per count}) + \beta_4 * (\text{cumulative high-dose intravenous methotrexate dose per g/m}^2 \text{ increase}) + \beta_5 * (\text{propofol cumulative dose per 100 mg/kg increase}^a) + \text{error}$$

<sup>a</sup> Each of the anesthetic agents and anesthesia duration, as shown in eTable 1, were used in place of propofol in separate models.

## eMethods 2: Multivariable general linear model approach

Multivariable general linear models (GLM procedure) were applied to examine the association of cumulative dose of each anesthetic agent with test-specific neurocognitive performance and neuroimaging outcomes, where the least squares approach provides maximum likelihood estimates of linear parameters.

The specific model fitted for each neurocognitive outcome was:

$$Y = \text{intercept} + \beta_1 * (\text{age at diagnosis with 1-year increase}) + \beta_2 * \text{female} + \beta_3 * (\text{total intrathecal chemotherapy per count}) + \beta_4 * (\text{cumulative high-dose intravenous methotrexate dose per g/m}^2 \text{ increase}) + \beta_5 * (\text{propofol cumulative dose per 100 mg/kg increase}^a) + \text{error}$$

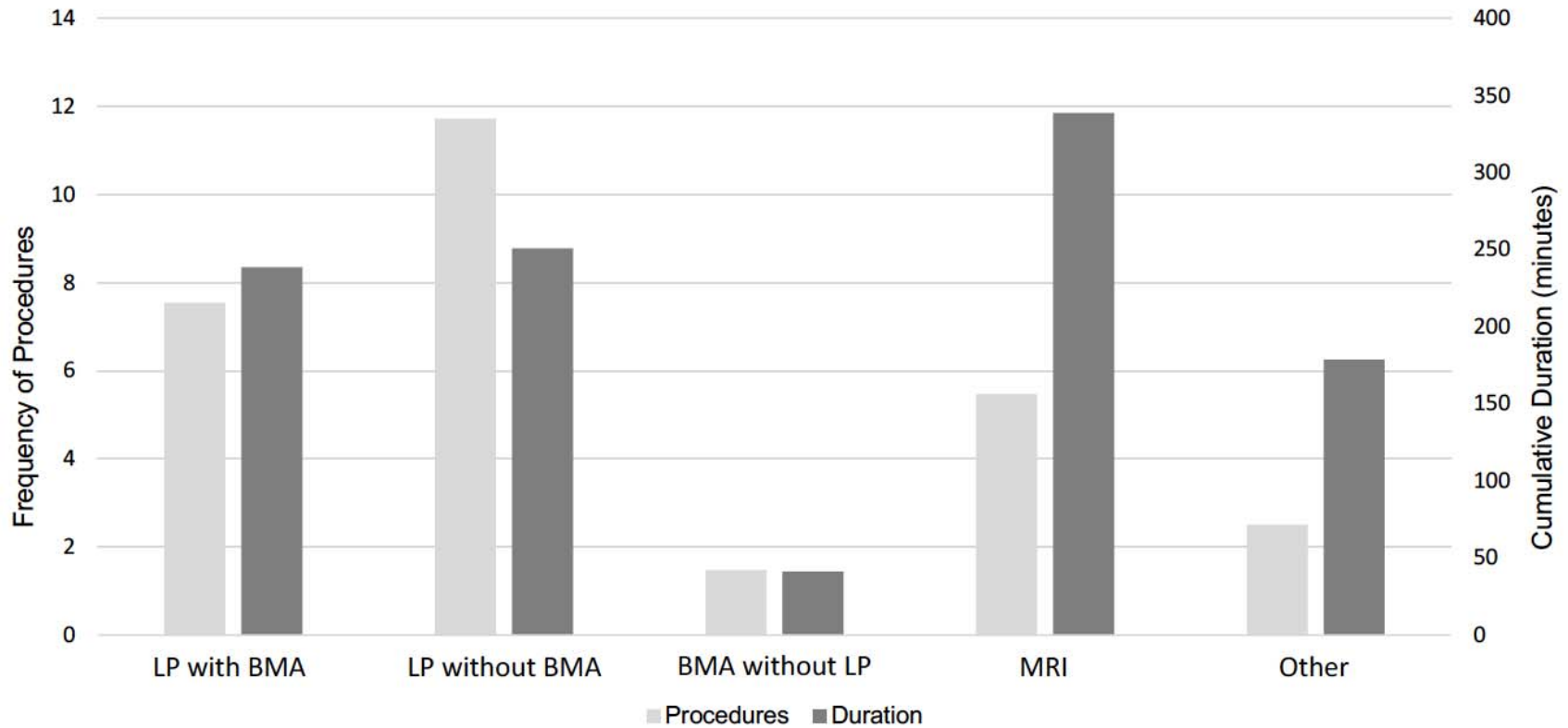
The specific model fitted for each neuroimaging outcome was:

$$Y = \text{intercept} + \beta_1 * (\text{age at diagnosis with 1-year increase}) + \beta_2 * (\text{age at MRI with 1-year increase}) + \beta_3 * \text{female} + \beta_4 * (\text{total intrathecal chemotherapy per count}) + \beta_5 * (\text{cumulative high-dose intravenous methotrexate dose per g/m}^2 \text{ increase}) + \beta_6 * (\text{propofol cumulative dose per 100 mg/kg increase}^a) + \text{error}$$

<sup>a</sup> Fluranes (per exposure) and duration (per hour) were used in place of propofol in separate models.



**eFigure 1. Mean Frequency and Mean Cumulative Duration of Procedures Requiring Anesthesia per Participant**



Frequency of procedures reflects the mean number of procedures in each category that a participant underwent. Duration of procedures reflects the mean cumulative time that a participant spent under anesthesia for each category of procedure. Other category includes placement and removal of central venous lines and subcutaneous ports, debridement and wound care, dental procedures, echocardiograms, and surgeries. Abbreviations: LP = Lumbar Puncture; BMA = Bone Marrow Aspiration; MRI = Magnetic Resonance Imaging

**eTable 1. Univariate models predicting global neurocognitive impairment**

Parameters	Global Neurocognitive Impairment		
	RR	95% CI	<i>P</i>
Propofol (per 100 mg/kg)	1.34	1.12 - 1.59	0.001
Fentanyl (per 10 mcg/kg)	1.11	0.93 - 1.33	0.25
Midazolam (per 1 mg/kg)	0.93	0.37 - 2.39	0.89
Meperidine (per 1 mg/kg)	1.00	0.95 - 1.06	0.88
Morphine (per 1 mg/kg)	0.58	0.24 - 1.36	0.21
Pentobarbital (per 10 mg/kg)	1.07	0.96 - 1.18	0.22
Glycopyrrolate (per 1 mcg/kg)	1.01	1.00 - 1.01	0.03
Fluranes (per exposure <sup>a</sup> )	1.08	0.98 - 1.18	0.11
Duration (per hour)	1.03	1.00 - 1.05	0.06

Global neurocognitive impairment is defined as 3 or more tests falling more than 2 standard deviations below the age-adjusted population normative means. <sup>a</sup> Number of exposures was identified for fluranes because cumulative dose cannot be accurately captured for inhaled anesthetic agents. Abbreviations: RR = relative risk; CI = confidence interval; mg = milligram; mcg = microgram; kg = kilogram.

**eTable 2. Multivariable models predicting test-specific neurocognitive performance**

Outcomes	Propofol (per 100 mg/kg)			Fluranes (per exposure <sup>a</sup> )			Duration (per hour)		
	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P
<b>Intelligence</b>									
Block Design	-0.14	0.12	0.24	-0.06	0.04	0.15	-0.02	0.01	0.09
<b>Attention</b>									
CPT Omissions	-0.46	0.20	0.02	-0.09	0.07	0.20	-0.03	0.02	0.20
Digits Forward	-0.07	0.13	0.58	-0.06	0.05	0.22	-0.02	0.01	0.09
Spatial Forward	-0.24	0.12	0.04	-0.01	0.04	0.79	-0.01	0.01	0.36
<b>Processing Speed</b>									
Color Naming	-0.17	0.11	0.13	-0.09	0.04	0.03	-0.02	0.01	0.07
Digit Symbol	-0.17	0.11	0.15	-0.08	0.04	0.04	-0.03	0.01	0.03
Verbal Fluency	-0.12	0.13	0.34	-0.04	0.05	0.41	-0.03	0.01	0.04
Number Sequencing	-0.18	0.14	0.19	0.00	0.05	0.92	-0.02	0.01	0.13
Letter Sequencing	-0.30	0.15	0.04	-0.14	0.05	0.01	-0.04	0.01	0.003
Dominant Hand Speed	-0.11	0.20	0.58	-0.01	0.07	0.86	0.00	0.02	0.82
Non-Dominant Hand Speed	-0.33	0.20	0.11	-0.07	0.07	0.36	-0.03	0.02	0.12
<b>Executive Function</b>									
Rey Complex Figure Copy	-0.50	0.31	0.11	-0.25	0.11	0.03	-0.03	0.03	0.27
20 Questions	-0.19	0.13	0.17	-0.07	0.05	0.13	-0.01	0.01	0.45
Digits Backward	-0.18	0.13	0.18	-0.06	0.05	0.18	-0.02	0.01	0.23
Color-Word Inhibition	-0.23	0.13	0.09	-0.05	0.05	0.26	-0.01	0.01	0.33
CPT Commissions	-0.11	0.15	0.48	-0.09	0.05	0.09	-0.01	0.02	0.41
CPT Perseverations	-0.42	0.24	0.09	-0.09	0.09	0.31	-0.02	0.02	0.38
Color-Word Inhibition-Switching	-0.10	0.13	0.46	-0.03	0.05	0.54	-0.02	0.01	0.15
Number-Letter Sequencing	-0.28	0.15	0.06	-0.08	0.05	0.16	-0.03	0.02	0.05

Models are adjusted for age at diagnosis, sex, total intrathecal chemotherapy count, and cumulative dose of high-dose intravenous methotrexate. Estimates are reflected in z-scores, with a mean of 0 and standard deviation of 1. <sup>a</sup> Number of exposures was identified for fluranes because cumulative dose cannot be accurately captured for inhaled anesthetic agents. Abbreviations: SE = standard error; CPT = Conners' Continuous Performance Test - 2<sup>nd</sup> Edition; mg = milligram; kg = kilogram.

**eTable 3. Univariate Regression Models Predicting Test-Specific Neurocognitive Performance**

Outcomes	Propofol (per 100 mg/kg)			Fluranes (per exposure <sup>a</sup> )			Duration (per hour)		
	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P
<b>Intelligence</b>									
Block Design	-0.31	0.09	0.001	-0.03	0.04	0.58	-0.02	0.01	0.09
<b>Attention</b>									
CPT Omissions	-0.57	0.15	<0.001	-0.06	0.07	0.39	-0.04	0.02	0.05
Digits Forward	-0.18	0.10	0.07	-0.03	0.04	0.53	-0.02	0.01	0.06
Spatial Forward	-0.21	0.09	0.03	0.00	0.04	0.91	-0.01	0.01	0.32
<b>Processing Speed</b>									
Color Naming	-0.22	0.09	0.01	-0.08	0.04	0.04	-0.03	0.01	0.005
Digit Symbol	-0.35	0.09	<0.001	-0.05	0.04	0.25	-0.04	0.01	0.001
Verbal Fluency	-0.02	0.10	0.86	-0.05	0.04	0.29	-0.02	0.01	0.04
Number Sequencing	-0.19	0.10	0.07	0.02	0.05	0.73	-0.02	0.01	0.13
Letter Sequencing	-0.32	0.11	0.004	-0.11	0.05	0.04	-0.04	0.01	0.002
Dominant Hand Speed	-0.37	0.15	0.01	0.04	0.07	0.60	-0.01	0.02	0.43
Non-Dominant Hand Speed	-0.56	0.16	<0.001	0.01	0.07	0.93	-0.03	0.02	0.12
<b>Executive Function</b>									
Rey Complex Figure Copy	-0.31	0.24	0.18	-0.24	0.11	0.02	-0.04	0.03	0.16
20 Questions	-0.18	0.10	0.08	-0.06	0.05	0.17	-0.01	0.01	0.41
Digits Backward	-0.15	0.10	0.13	-0.05	0.04	0.25	-0.01	0.01	0.24
Color-Word Inhibition	-0.22	0.10	0.03	-0.05	0.05	0.27	-0.02	0.01	0.08
CPT Commissions	-0.21	0.12	0.08	-0.07	0.05	0.18	-0.01	0.01	0.32
CPT Perseverations	-0.36	0.18	0.04	-0.07	0.08	0.40	-0.02	0.02	0.38
Color-Word Inhibition-Switching	-0.14	0.10	0.18	-0.03	0.05	0.52	-0.03	0.01	0.04
Number-Letter Sequencing	-0.35	0.12	0.003	-0.05	0.05	0.36	-0.04	0.01	0.01

Estimates are reflected in z-scores, with a mean of 0 and standard deviation of 1. <sup>a</sup> Number of exposures was identified for fluranes because cumulative dose cannot be accurately captured for inhaled anesthetic agents. Abbreviations: SE = standard error; CPT = Conners' Continuous Performance Test - 2<sup>nd</sup> Edition; mg = milligram; kg = kilogram.

**eTable 4. Multivariable Regression Models Predicting Neuroimaging Variables**

Outcomes	Propofol (per 100 mg/kg)		Fluranes (per exposure <sup>a</sup> )		Duration (per hour)	
	Standardized Estimate	<i>P</i>	Standardized Estimate	<i>P</i>	Standardized Estimate	<i>P</i>
<b>Diffusion Tensor Imaging: Whole Brain</b>						
Fractional Anisotropy	-0.59	0.56	-0.15	0.88	-1.67	0.10
Mean Diffusivity	0.44	0.66	-0.09	0.93	1.32	0.19
<b>Diffusion Tensor Imaging: Corpus Callosum</b>						
Fractional Anisotropy						
Genu	0.19	0.85	1.13	0.26	-0.88	0.38
Body	-0.99	0.32	-0.45	0.66	-1.38	0.17
Splenum	-0.35	0.72	0.17	0.86	0.01	0.99
Mean Diffusivity						
Genu	-0.35	0.73	-0.87	0.38	0.23	0.82
Body	2.55	0.01	0.03	0.98	1.83	0.07
Splenum	1.76	0.08	1.32	0.19	2.40	0.02
<b>Diffusion Tensor Imaging: Frontal Lobes</b>						
Fractional Anisotropy	-0.84	0.40	-0.21	0.83	-1.58	0.12
Mean Diffusivity	0.15	0.88	-0.01	0.99	0.96	0.34
<b>Diffusion Tensor Imaging: Parietal Lobes</b>						
Fractional Anisotropy	0.26	0.80	0.06	0.95	-1.14	0.26
Mean Diffusivity	1.00	0.32	-0.17	0.87	1.90	0.06

Models are adjusted for age at diagnosis, age at imaging, sex, total intrathecal chemotherapy count, and cumulative dose of high-dose intravenous methotrexate. <sup>a</sup> Number of exposures was identified for fluranes because cumulative dose cannot be accurately captured for inhaled anesthetic agents. Abbreviations: mg = milligram; kg = kilogram.