POCD: What is it and do the anesthetics play a role?

Deborah J. Culley, M.D.
Associate Professor
Harvard Medical School
Brigham & Women's Hospital

Conflicts of Interest

NIH/NIGMS/NIA
ABA: Director
ABMS: Chair 3C
ACGME: Ad Hoc RRC member
Anesthesiology: Executive Editor

Objectives

- Define POCD (and delirium)
- Discuss outcomes associated with POCD (and delirium)
- Discuss whether anesthetics contribute to POCD or delirium

Clinical Diagnosis of Delirium: APA DSM-V criteria

- ✓ *Inattention* (reduced ability to direct, focus, sustain, and shift attention) and *reduced awareness* (orientation to the environment)
- ✓ Represents an *acute change from baseline attention and awareness*, and *tends to fluctuate in severity during the course of a day*
- ✓ *Disturbance in cognition* (e.g.memory deficit, disorientation, language, visuospatial ability, or perception)
- ✓ Not explained by a *pre-existing, established or evolving neurocognitive disorder* or in the context of a severely reduced level of arousal (coma)
- ✓ A direct physiological consequence of *another medical condition, substance intoxication or withdrawal*

European Delirium Association, BMC Medicine 2014, 12:141

Diagnosing Delirium

Confusion Assessment Method (CAM)

1. Acute onset & fluctuating course
2. Inattention

} Both

3. Disorganized thinking
4. Altered level of consciousness

} 1 of 2

Inouye SK, et al. Ann Int Med 113: 941, 1990

Delirium

Predictor of Morbidity and Mortality

- Increases
  - Duration of mechanical ventilation
  - Length of stay
  - Discharge to long-term care facility
  - Mortality
  - Costs a LOT - *$38 - $152 B per year*

Kiely DK, et al., J Gerontology 62A: 174, 2007
Zakriya K, et al., Anesth Analg 98: 1798, 2004
Leslie DL et al. Arch Int Med 168: 27 - 32, 2008

Postoperative Cognitive Dysfunction (POCD)

Research Classification (Not a disease; No ICD-10)

✓ *Postop vs. preop performance on neuropsych tests*

No universally accepted test battery / standards

✓ *Criteria have major influence on prevalence of POCD*

Efforts must be made to reach a consensus in definition and diagnosis for future research

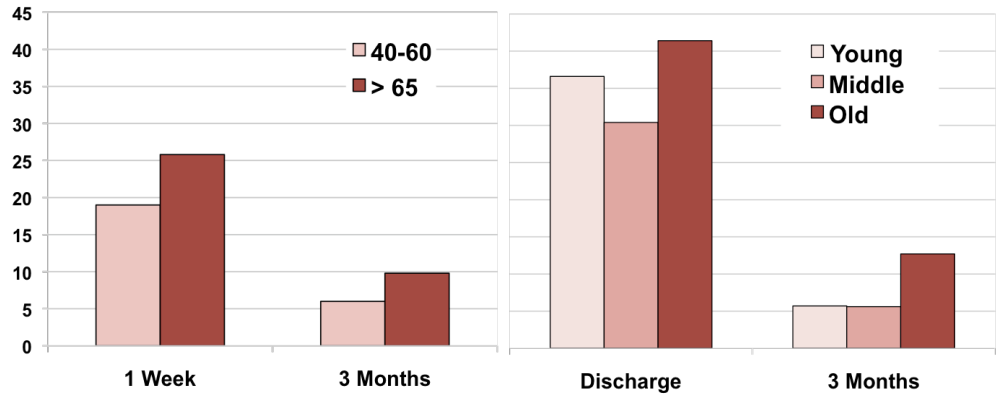
✓ *Acta Anaesthesiol Scand. 2016;60:1043-58*

Prevalence of POCD Varies Greatly With How Tests Are Scored

	Proportion at 2nd test (%)	Proportion at 3rd test (%)
Deterioration of 1 SD in 1 test	29.0	16.5
Deterioration of 1 SD in 2 tests	6.8	1.7
Deterioration of 1 SD in 3 tests	0	0
Deterioration of 20% in 2 tests	15.9	4.5
Deterioration of 25% in 1 test	40.3	25
Deterioration of 25% in 2 tests	9.1	4.0
Z-score above 2 in 2 tests	0.6	0.6
Composite Z-score above 2	2.8	4.5
Criterion 7 or 8	3.4	4.5
Criterion used in ISPOCD	3.4	2.8

Rasmussen LS, et al. Acta Anaesth Scand 45: 275, 2001

POCD – How Common Is It ?



Moller JT, et al. Lancet 351: 857, 1998

Johnson T, et al., Anesthesiology 96: 1351, 2002

Monk TG, et al., Anesthesiology 108: 18, 2008

POCD

Predictor of Morbidity and Mortality

Increases

- ✓ Impairment ADLs
- ✓ Premature loss from workforce
- ✓ Mortality

Moller JT, et al. Lancet 351: 857, 1998

Monk TG, et al., Anesthesiology 108: 18, 2008

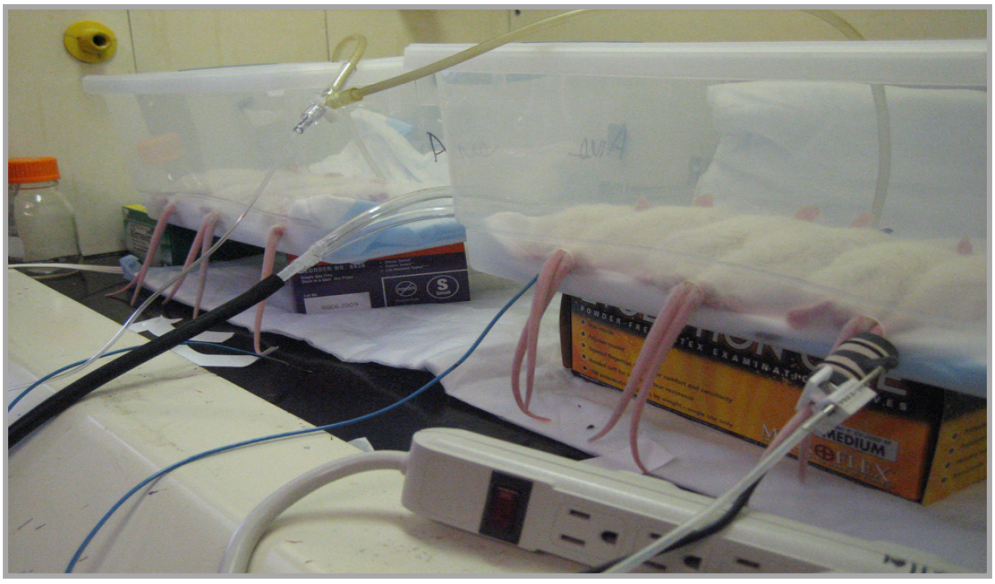
Steinmetz J, et al. Anesthesiology 110: 548, 2009

Does Anesthesia or Depth of Anesthesia Matter?

Rodents are not Human

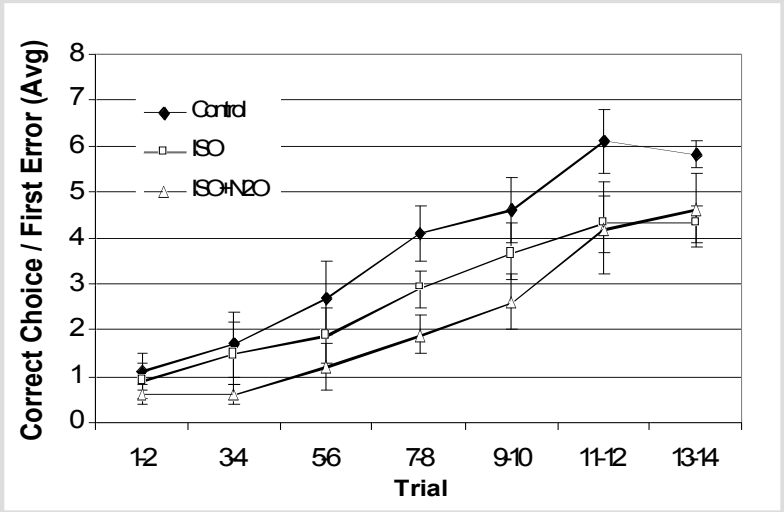
Some Humans may be Rodents

"Rat Tales"



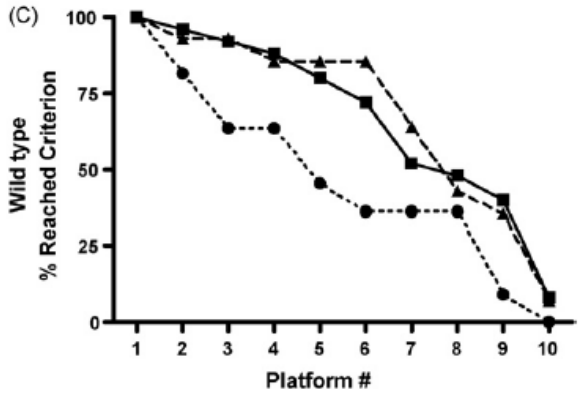
Could it be the anesthetic?

…if you are an old rat



Culley DJ, et al., Anesth Analg 99: 1393 – 7, 2004

…or an old mouse



Bianchi SL , et al. Neurobiology of Aging 29 (2008) 1002–1010

A number of potential mechanisms

- ✓ Neurodegenerative Diseases
- ✓ Neuroinflammation
- ✓ Blood Brain Barrier Disruption
- ✓ Synapse Loss
- ✓ OMICs: Proteomics, Genomics

And a number of potential therapeutics

The Clinical Data Suggest Something Different

General versus spinal anaesthesia and postoperative delirium (Meta-analysis)

	REGIONAL (497)	GA (929)
Delirium	15.7%	19.5%

Scott JE, et al., **Gen Hosp Psychiatry. 2015 May-Jun;37(3):223-9.**

General versus spinal anaesthesia and postoperative delirium

	REGIONAL (151)	GA (167)
Delirium	54%	50%

Ilango S et al., Australas J Ageing. 2016 Mar;35(1):42-7.

Does anaesthesia cause postoperative cognitive dysfunction?

	REGIONAL (176)	GA (188)
1 Wk Postop	12.5% 95% CI (14.3%-26.1%)	19.7% 95% CI (14.3%-6.1%)
3 Mo Postop	13.9% 95% CI (9.0%-20.2%)	14.3% 95% CI (9.5%-20.4%

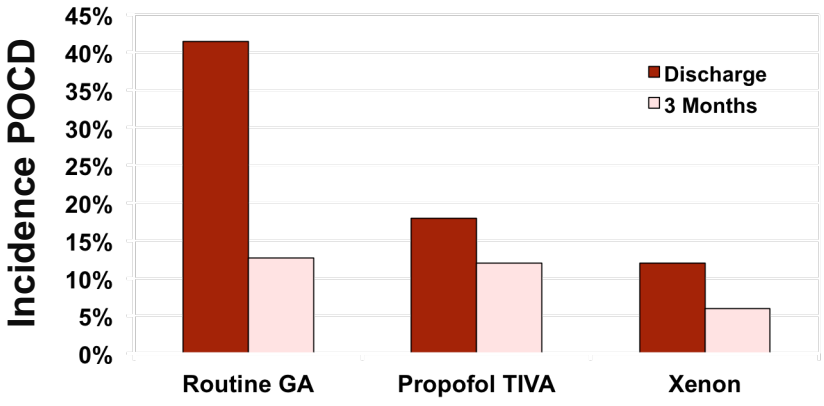
Rasmussen LS, et al. Acta Anaesthesiol Scand 47: 260 - 266, 2003

Incidence of postoperative cognitive dysfunction after general or spinal anesthesia

	REGIONAL (48)	GA (50)
1 Wk Postop *P = 0.16*	11.9% 95% CI (4.0%-33.9%)	4.1% 95% CI (0.5%-14%)
3 Mo Postop *P = 0.07*	19.6% 95% CI (9.4%-33.9%)	6.8%, 95% CI (1.4%-18%)

Silbert BS, et al. BJA 113: 784 - 91, 2014

Specifics of General Anesthesia



Monk TG, et al. Anesthesiology 108: 18 – 30, 2008

Hocker J, et al. Anesthesiology 110: 1068 – 76, 2009

Type of GA and POCD

Table 4
Incidence of POCD[a] ($n = 50$ patients in each group).

	N (%)	Isoflurane	Propofol	Sevoflurane	*P* value		
					Isoflurane vs. propofol	Isoflurane vs. sevoflurane	Propofol vs. sevoflurane
D1	POCD +	25 (50%)	5 (10%)	15 (30%)	<0.001	0.041	0.012
	POCD −	25 (50%)	45 (95%)	35 (70%)			
D3	POCD +	15 (30%)	2 (4%)	10 (20%)	<0.001	0.248	0.013
	POCD −	35 (70%)	48 (96%)	40 (80%)			

The data were presented with number (%).
POCD, postoperative cognitive dysfunction; D1, postoperative day 1; D3, postoperative day 3.
[a] POCD was defined as a >20% decrease in performance in at least two tests compared to baseline.

Geng YJ J Clin Anesth. 2017 May;38:165-171

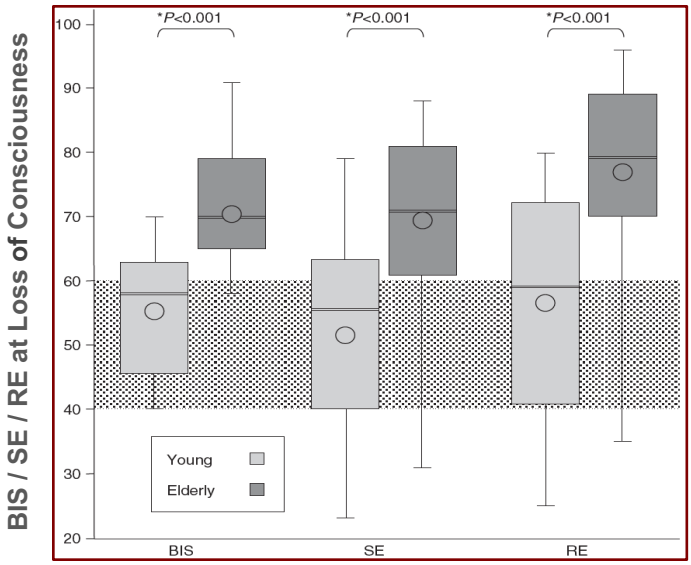
Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicentre trial

Mark D Neuman,[1,2,3,4] Susan S Ellenberg,[5] Frederick E Sieber,[6] Jay S Magaziner,[7] Rui Feng,[5] Jeffrey L Carson,[8] and the REGAIN Investigators

BMJ Open. 2016;6:e013473

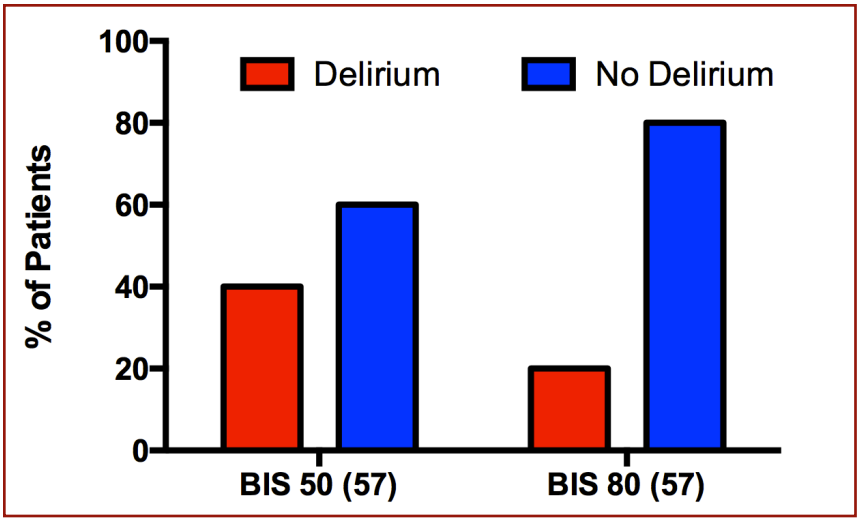
What about depth of anesthesia?

Propofol Sedation in Elders - Less Is More



Lysakowski C, et al. Br J Anaesth 103: 387 – 93, 2009

Depth of "Sedation"



Sieber FE, et al. Mayo Clin Proc 85: 18 – 26, 2010

Depth of Anesthesia and Delirium

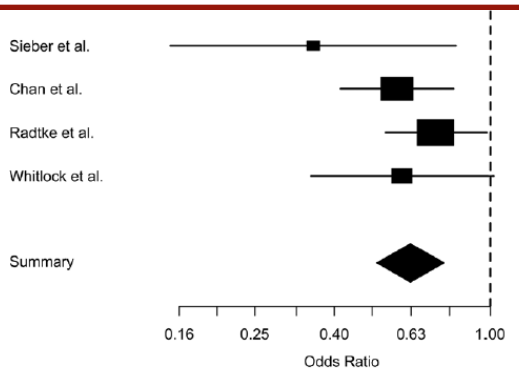


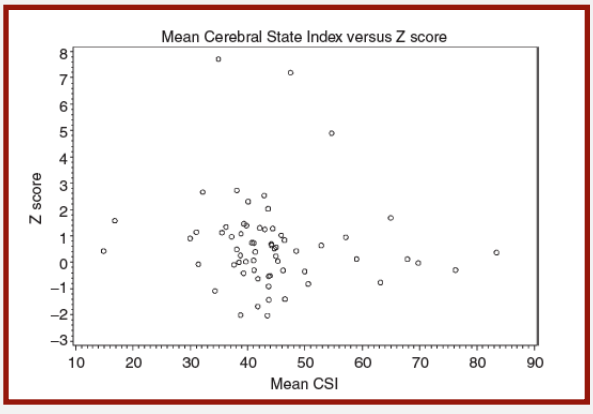
Figure 2. Meta-analysis of randomized controlled trials assessing postoperative delirium with intraoperative Bispectral Index (BIS) guidance of anesthesia compared with an alternative approach (i.e., usual care or an alternative protocol). Odds ratios <1 favor BIS guidance.

Whitlock EL, Anesth Analg. 2014;118:809-17

Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study: a pragmatic, randomised clinical trial

T S Wildes,[1] A C Winter,[2] H R Maybrier,[1] A M Mickle,[1] E J Lenze,[3] S Stark,[4,5] N Lin,[6] S K Inouye,[7,8] E M Schmitt,[8] S L McKinnon,[1] M R Muench,[1] M R Murphy,[1] R T Upadhyayula,[1] B A Fritz,[1] K E Escallier,[1] G P Apakama,[1] D A Emmert,[1] T J Graetz,[1] T W Stevens,[1] B J Palanca,[1] R L Hueneke,[1] S Melby,[9] B Torres,[1] J Leung,[10] E Jacobsohn,[11] M S Avidan[1]

Depth of Anesthesia and POCD



Steinmetz J, et al., Acta Anaesthesiol Scand 54:162, 2010

British Journal of Anaesthesia **110** (S1): i98–i105 (2013)
Advance Access publication 28 March 2013 · doi:10.1093/bja/aet055

Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction

F. M. Radtke[1†], M. Franck[1†], J. Lendner[1], S. Krüger[1], K. D. Wernecke[2] and C. D. Spies[1*]

[1] Department of Anaesthesiology and Surgical Intensive Care Medicine, Campus Charité Mitte and Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Charitéplatz 1, Berlin 10117, Germany
[2] Charité-Universitätsmedizin Berlin and SoStAna GmbH, Wildensteiner Straße 27, Berlin 10318, Germany
* Corresponding author. E-mail: claudia.spies@charite.de

BIS-guided Anesthesia Decreases Postoperative Cognitive Decline

	BIS Guided	Blinded BIS	P = 0.025
POCD	10.2%	14.7	OR 0.67 95% CI (0.32-0.98)

Chan MTV, et al., J Neurosurg Anesthesiol 2013;25:33–42

Rationale and Design of the Balanced Anesthesia Study: A Prospective Randomized Clinical Trial of Two Levels of Anesthetic Depth on Patient Outcome After Major Surgery

Timothy G. Short, MBChB, MD, FANZCA,* Kate Leslie, MBBS, MD, MEpi, FANZCA,†‡§
Matthew T. V. Chan, MBBS, FANZCA,‖ Douglas Campbell, BM, FRCA, FANZCA,*
Christopher Frampton, BSc (Hons), PhD (Cant),¶ and
Paul Myles, MBBS, MPH, MD, FCARCSI, FANZCA, FRCA#**

Take Home Messages

- POCD and Delirium are real and associated with significant morbidity and mortality
- Inconclusive evidence that regional is any better than general anesthesia
- BIS guided anesthesia may lead to decreases in delirium but the data are inconclusive with regards to POCD

Laboratory for Aging Neuroscience

aka Crosby –Culley Lab

Delirium

Mark Baxter Ph.D (MSSM)
Javedan Houman, M.D. (BWH)
Sharon Inouye MD (BI)
Ed Marcantonio MD (BI)
James Rudolph, MD (VA)
Frederick Sieber MD (Hopkins)

POCD

Mark Baxter Ph.D (MSSM)
Dick Deth Ph.D (NU)
Brian Head PhD (UCSD)
Piyush Patel MD (UCSD)
Rudi Tanzi Ph.D (MGH)
Zhongcong Xie MD, Ph.D (MGH)

Cognitive Testing

Angela Bader, MD, MPH (BWH)
Deborah Blacker, MD (MGH)
Chantal Dufreny, MS4
Devon Flaherty, MD, MPH (BWH)
Javedan Houman, MD (BWH)
Brad Hyman, MD, PhD (MGH)
James Rudolph, MD (VA)
Srini Reddy, MS2

gcrosby@bwh.harvard.edu
dculley@bwh.harvard.edu