pEEG – More than a number

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AAGBI Core Topics – Nottingham
December 2019

Association of Anaesthetists

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Declarations

Honoraria for educational work from Medtronic (BIS) & MSD (Bridion).

NarcoTrend on long term loan.

Objectives

-Appreciate the range of real time and processed parameters pEEG monitors display.

-Define, and appreciate the use of the pEEG in identifying burst suppression.

-Consider the association between “deep” anaesthesia and patient outcome.

-Recognise the effects of the extremes of age on the EEG and how these may impact the pEEG index.

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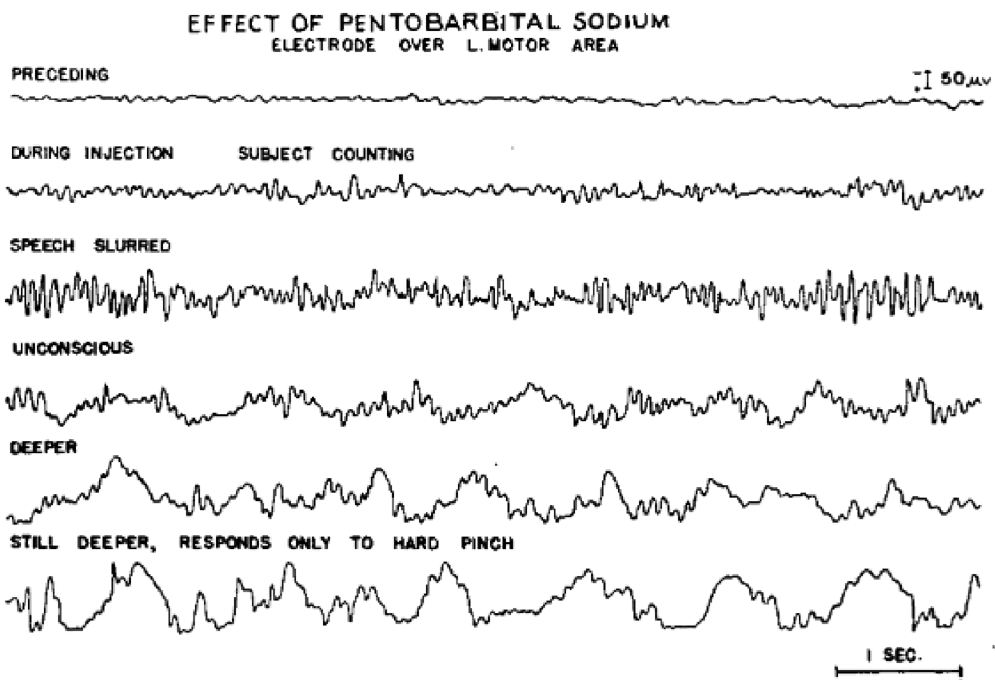
Historical perspectives

“The anesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of both heart and brain.”



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Gibbs, F., Gibbs, E., Lennox, W.(1937). **The Effect on the Electro-Encephalogram of Certain Drugs Which Influence Nervous Activity.**
https://dx.doi.org/10.1001/archinte.1937.00180010159012

Historical perspectives

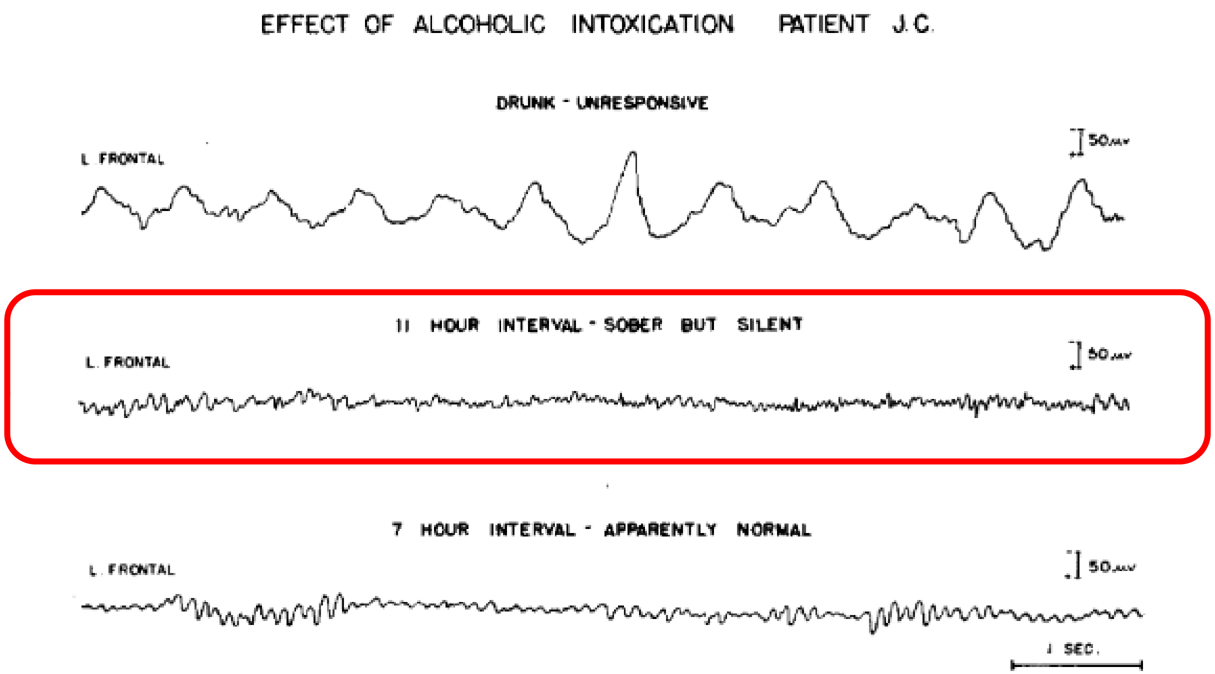

Fig. 6.—The effect of alcohol intoxication. In this instance the first strip was taken from a record made when the patient was drunk and unresponsive to any but painful stimuli. The middle strip is from a record taken eleven hours later, when he could be called sober but when he was unnaturally silent and morose. The bottom strip shows the change that had occurred seven hours later, when the patient was normal.

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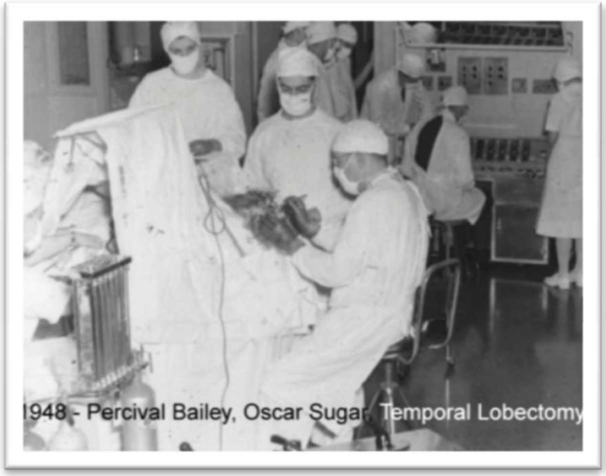
Historical perspectives



Very distracting
Complex equipment
Artifacts
Specialist knowledge

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Vannemreddy, P., Stone, J., Slavin, K.(2012). Frederic Gibbs and His Contributions to Epilepsy Surgery and Electroencephalography https://dx.doi.org/10.1227/neu.0b013e3182351699

1996

2000

2003

NeuroWAVE

qCon

BARM

PSI/SedLine
[PSI - 2002]

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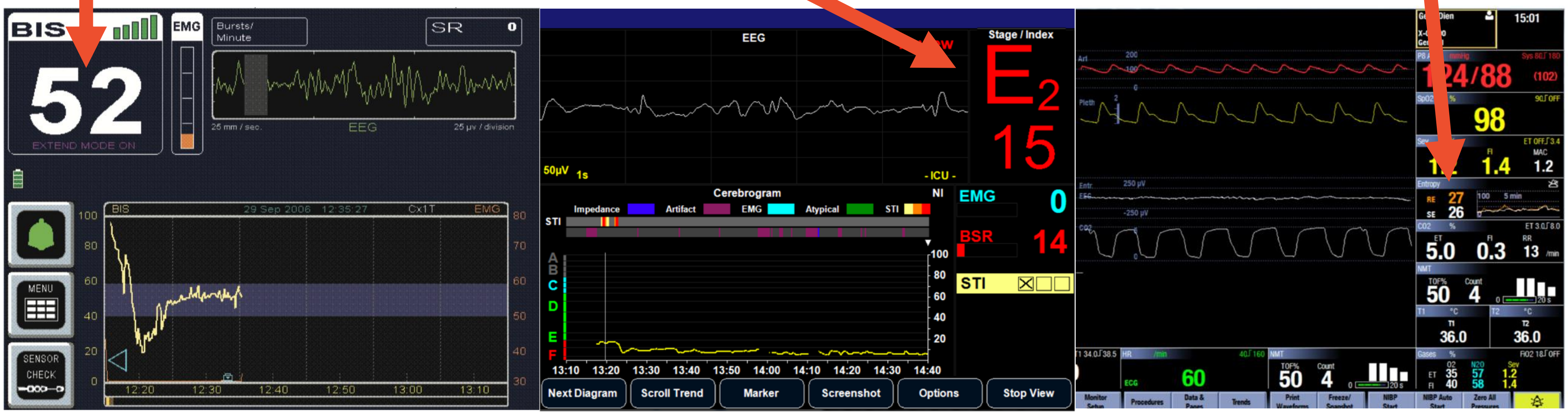
What number…?

Proprietary indices (qEEG)

BIS Value

NarcoTrend Index

Response Entropy
State Entropy



EMG
Power
REAL TIME

EEG
REAL TIME

Suppression
Ratio
Delay

Core non-proprietary indices (pEEG)

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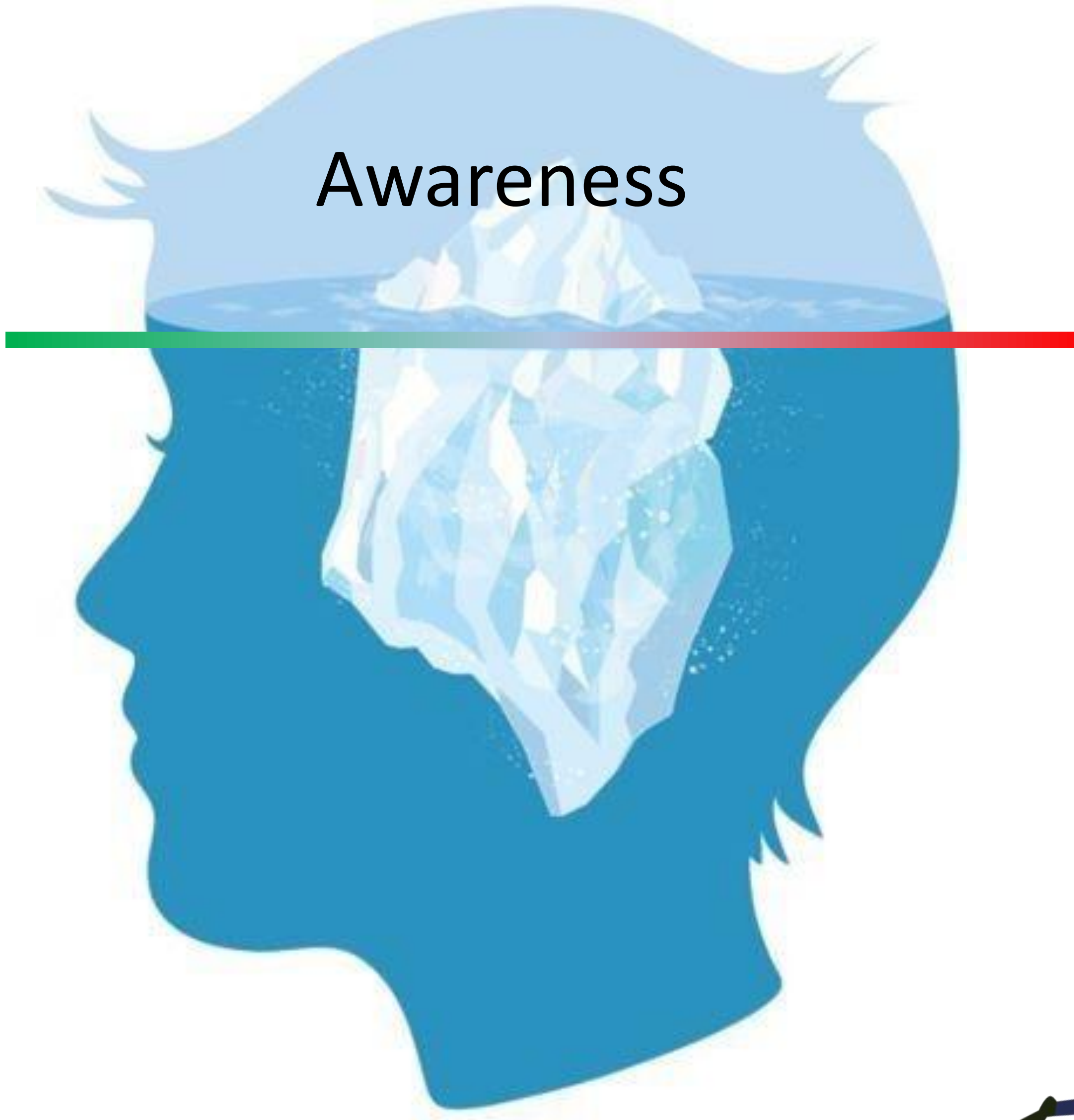

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"Awareness Trials"

"B-aware" 2004

- BIS vs "routine care".
- High risk patients.
- Paralysed.
- BIS kept **55-70** during closure(!).
- Brave MAC and [TCI].
- Some patients BIS>60.
- 13 cases definite awareness (Brice)
  - 2 BIS
  - 11 ETAG

"B-Unaware" 2008

- BIS vs ETAG >0.7 – 1.3 (alarm).
- Vapour only.
- 6 cases definite awareness (Brice)
  - 4 BIS
  - 2 ETAG
- 50% patients BIS >60.
- "Control" group 75% outside range

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Myles, P., Leslie, K., McNeil, J., et al. (2004). **Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial.** https://dx.doi.org/10.1016/s0140-6736(04)16300-9
Avidan, M., Zhang, L., Burnside, B., et al. (2008). **Anesthesia Awareness and the Bispectral Index** https://dx.doi.org/10.1056/nejmoa0707361

“Awareness Trials”

“BAG-Recall” 2011

- Same protocol as B-unaware.
- ETAC 0.7-1.3
- Larger cohort, multicenter, international.
- 6000 patients.
- 9 cases definite awareness (Brice)
  - 2 ETAG
  - **7 BIS**

“MACS” 2012

- Randomised **21,000**.
- Similar protocol, recruited **low** risk patients. ETAC > 0.5 MAC
- ETAC alarm AND PAGING ALERTS

Study abandoned due to futility.

BUT

Post hoc analysis

Against a Control group

BIS monitoring was associated with a 4.7-fold reduction in awareness

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Avidan, M., Jacobsohn, E., Glick, D., et al. (2011). **Prevention of intraoperative awareness in a high-risk surgical population.** https://dx.doi.org/10.1056/nejmoa1100403

Mashour, G., Shanks, A., Tremper, K., et al. (2012). **Prevention of Intraoperative Awareness with Explicit Recall in an Unselected Surgical Population.** https://dx.doi.org/10.1097/aln.0b013e31826904a6

“Awareness” and TIVA

Chinese multicentre study.

5228 Patients

1% incidence AAGA (vs. 0.1% US).

Propofol + Anaesthetists choice of analgesia.

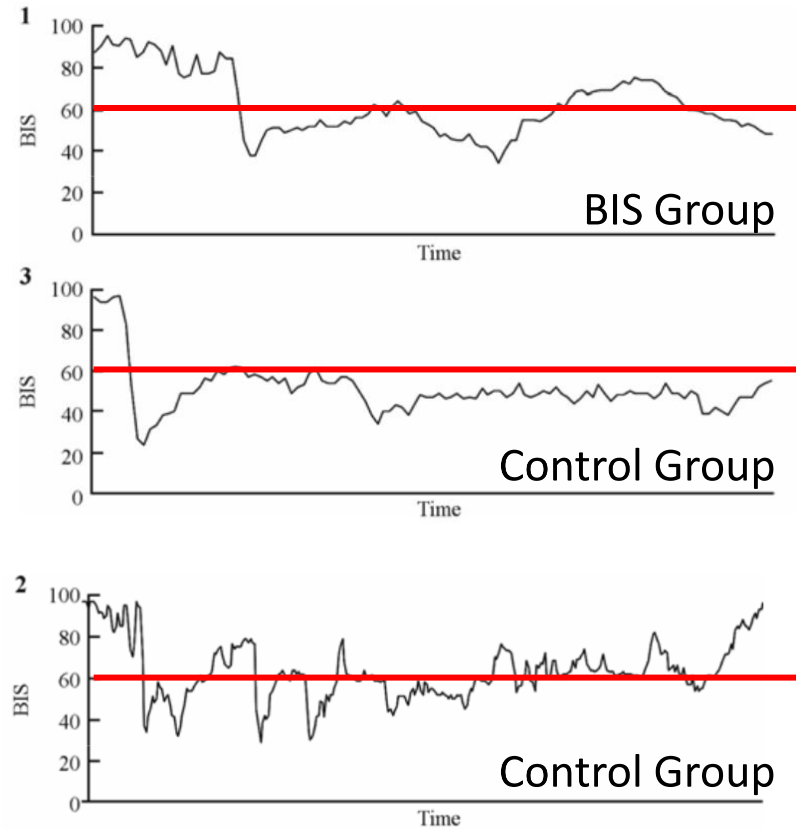
BIS vs “clinical signs”.

16 cases of AAGA:

4 BIS

12 Control

78% reduction in AAGA



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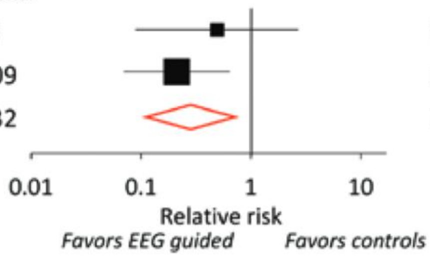
Zhang, C., Xu, L., Ma, Y., et al. (2011). **Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized, double-blinded, multi-center controlled trial.** https://www.ncbi.nlm.nih.gov/pubmed/22340221

"Awareness" – Pooled Data

Total intravenous anesthesia

Trials (year)	EEG-guided Events/Total	Control Events/Total	Relative risk (Random effect, 95%CI)
B-Aware, 2004	2 / 532	4 / 523	0.49 (0.09-2.67)
Zhang, *et al*, 2011	4 / 2,919	15 / 2,309	0.21 (0.07-0.64)
Overall effect	6 / 3,451	19 / 2,832	0.27 (0.11-0.68)

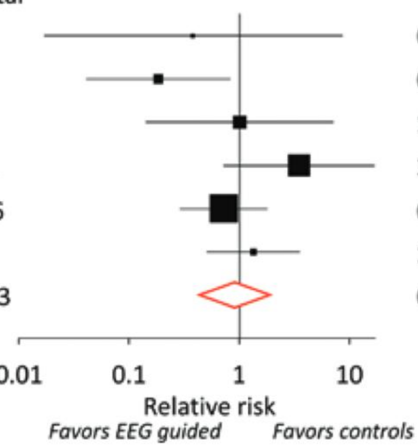
(*z* value=-2.772, *p*=0.006; *p*=0.413 for heterogeneity; I^2=0.00%)



Volatile-based anesthesia

Trials (year)	EEG-guided Events/Total	Control Events/Total	Relative risk (Random effect, 95%CI)
Puri, *et al*, 2003	0 / 14	1 / 16	0.38 (0.02-8.59)
B-Aware, 2004	0 / 693	7 / 715	0.07 (0.01-1.20)
B-Unaware, 2008	2 / 967	2 / 974	1.01 (0.14-7.14)
BAG-RECALL, 2011	7 / 2,861	2 / 2,852	3.49 (0.73-16.8)
MACS, 2012	8 / 9,640	11 / 9,376	0.72 (0.29-1.79)
Mozafari, 2014	9 / 163	7 / 170	1.34 (0.51-3.52)
Overall effect	26 / 14,158	30 / 14,103	0.98 (0.47-2.04)

(*p* = 0.051 for heterogeneity; I^2 =38.3%)



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Chan, M., Hedrick, T., Egan, T., et al (2019). American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes https://dx.doi.org/10.1213/ane.0000000000004502

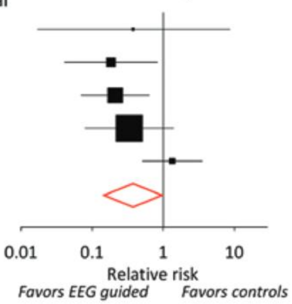
“Awareness” – Pooled Data

Set ETAG alarms to 0.7 aaMAC

EEG-guided vs Routine care anesthesia

Trials (year)	EEG-guided Events/Total	Control Events/Total	Relative risk (Random effect, 95%CI)
Puri, *et al*, 2003	0 / 14	1 / 16	0.38 (0.02-8.59)
B-Aware, 2004	2 / 1,225	11 / 1,238	0.18 (0.04-0.83)
Zhang, *et al*, 2011	4 / 2,919	15 / 2,309	0.21 (0.07-0.64)
MACS, 2012	3 / 6,076	5 / 3,384	0.33 (0.08-1.40)
Mozafari, 2014	9 / 163	7 / 170	1.34 (0.51-3.52)
Overall effect	18 / 10,397	39 / 7,117	0.39 (0.16-0.97)

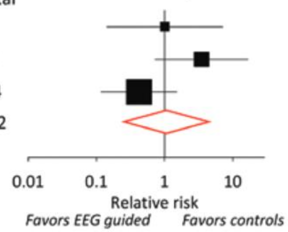
(*z* value=-2.018, *p*=0.044; *p*=0.082 for heterogeneity; I^2=51.72%)



EEG-guided vs ETAG-guided anesthesia

Trials (year)	EEG-guided Events/Total	Control Events/Total	Relative risk (Random effect, 95%CI)
B-Unaware, 2004	2 / 967	2 / 974	1.01 (0.14-7.14)
BAG-RECALL, 2011	7 / 2,861	2 / 2,852	3.49 (0.73-16.8)
MACS, 2012	3 / 6,076	11 / 3,384	0.42 (0.12-1.51)
Overall effect	12 / 9,904	15 / 13,202	1.08 (0.29-4.03)

(*z* value=0.111, *p*=0.911; *p*=0.123 for heterogeneity; I^2=52.37%)



“Routine care”
(no ETAG Alarms)

With ETAG Alarms

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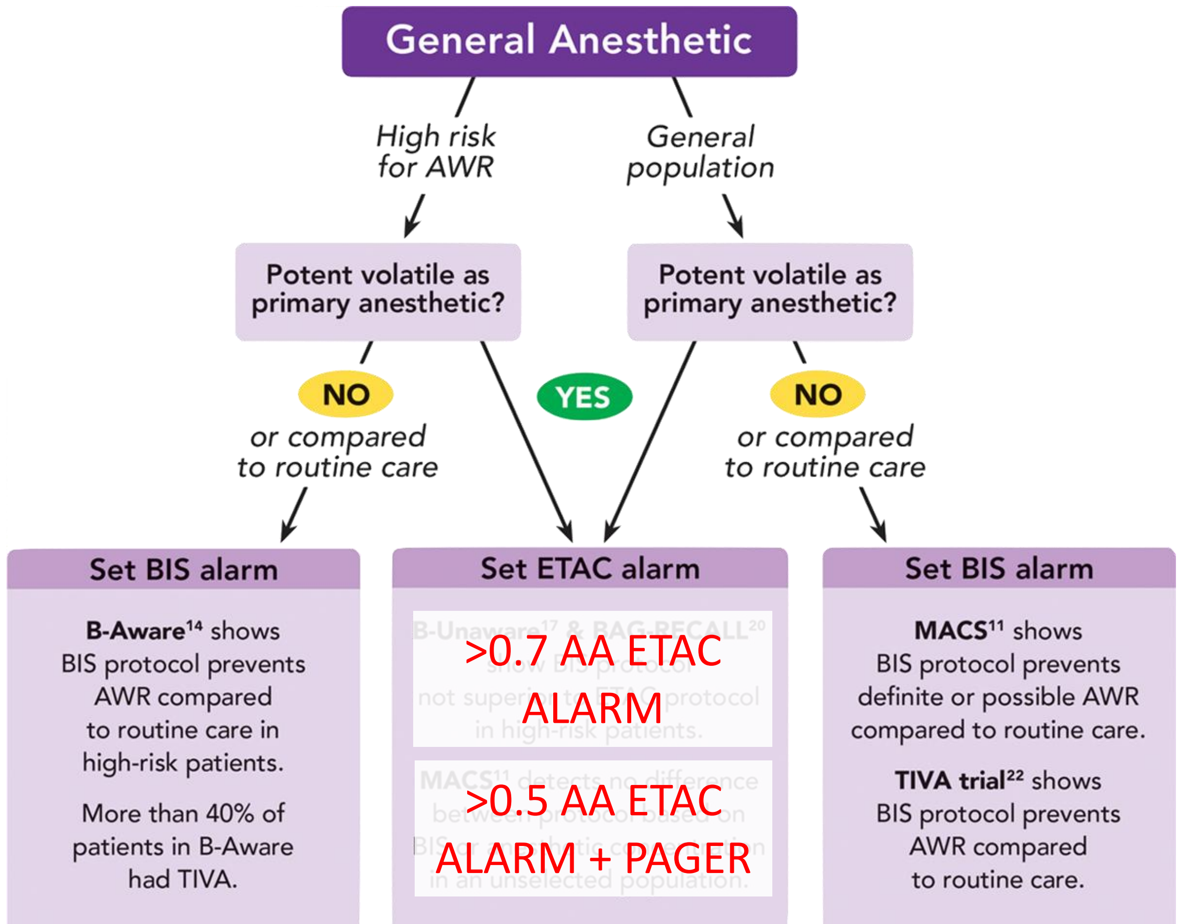
Chan, M., Hedrick, T., Egan, T., et al (2019). American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes https://dx.doi.org/10.1213/ane.0000000000004502

Pragmatic approach to AAGA



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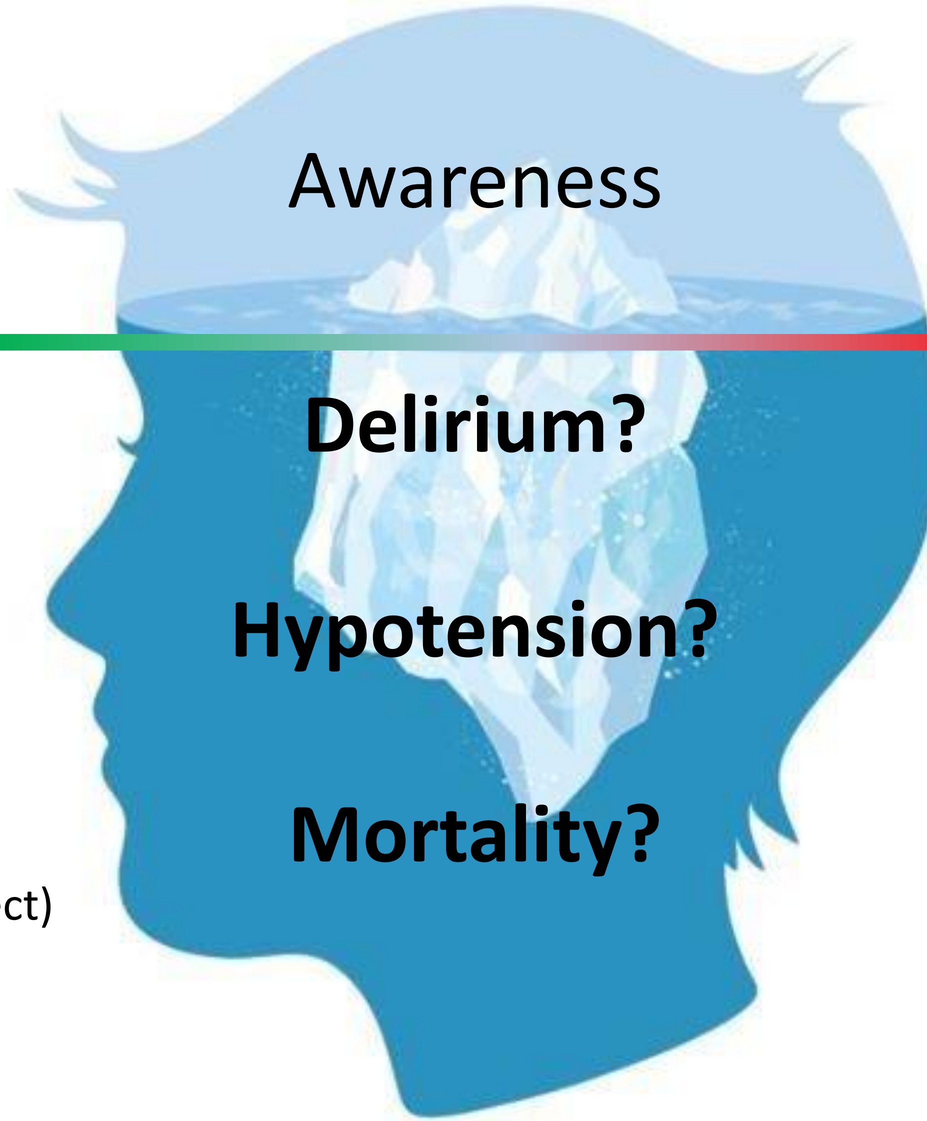
Avidan, M., Mashour, G. (2013). **Prevention of Intraoperative Awareness with Explicit Recall Making Sense of the Evidence** https://dx.doi.org/10.1097/aln.0b013e31827ddd2c

ALARMS
>0.7 MAC
ETAC



No TIVA
equivalent

pEEG is modality for
measuring PKPD (effect)

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Burst Suppression

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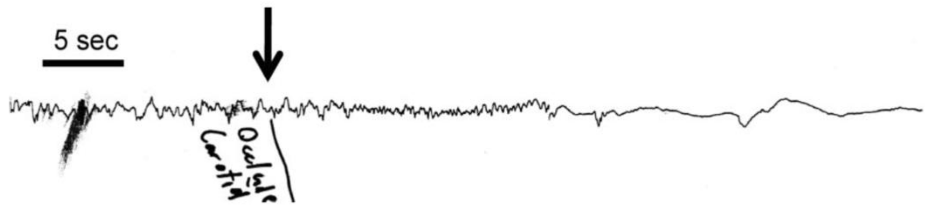
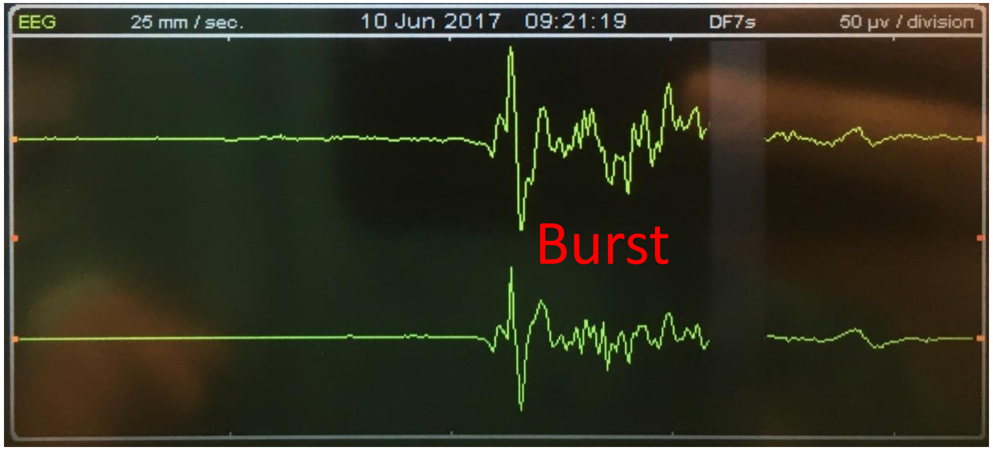
Burst Suppression





Morphology same as

Burst suppression Ratio : % 63 second epoch with voltage < ±5µV

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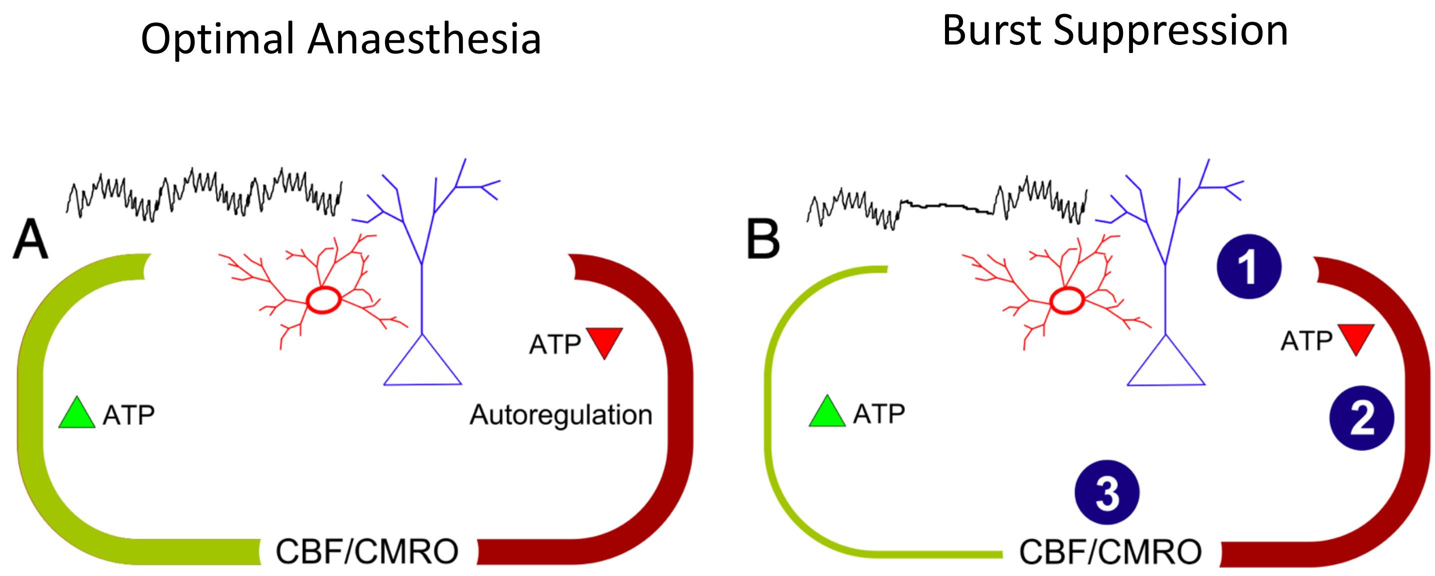
Cause? Metabolic theory



Aetiologies:
1: Anaesthetics reduce neuronal activity
2: Autoregulatory mechanisms
3: Reduction in CBF/CMRO

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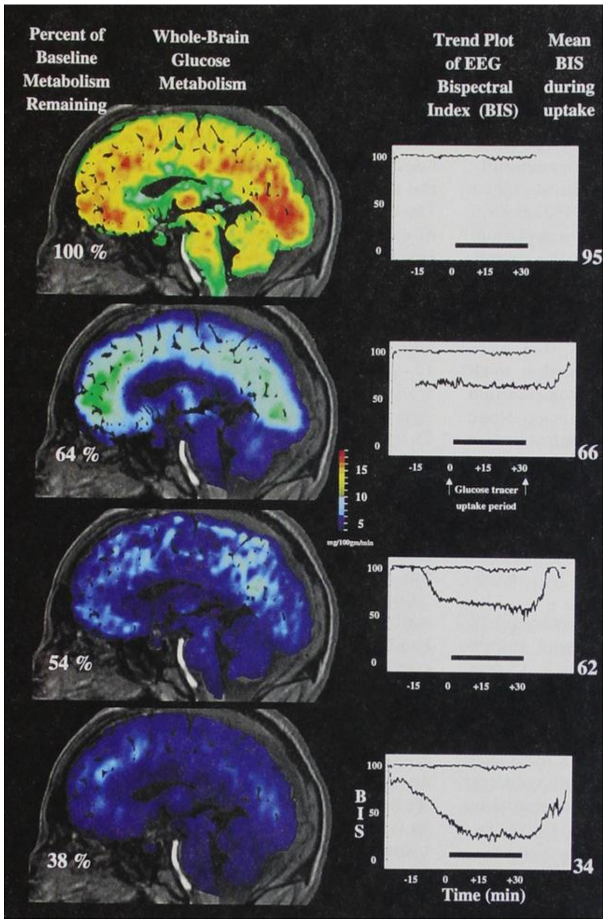
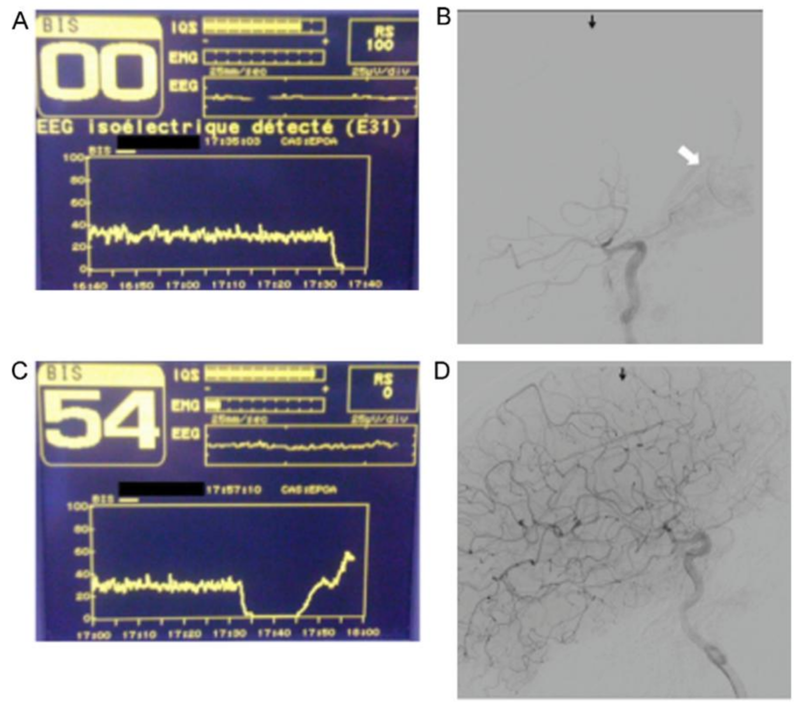
Ching, S., Purdon, P., Vijayan, S., Kopell, N., & *Brown, E.* (2012). **A neurophysiological–metabolic model for burst suppression.** https://doi.org/10.1073/pnas.1121461109

pEEG = cerebral metabolism





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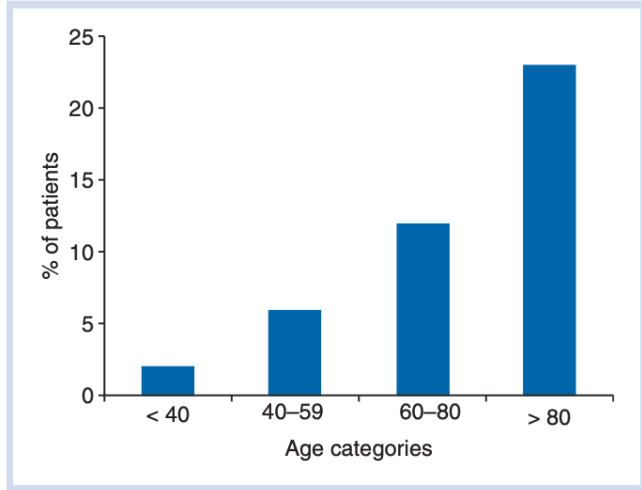
Alkire, M. T. (1998). Quantitative EEG correlations with brain glucose metabolic rate during anesthesia in volunteers. *Anesthesiology*, *89*(2), 323–333.
Uhrig, L., Devys, J., Piotin, M., Taylor, G.(2014). Bispectral index transiently decreased to “0” during per-embolization rupture of an intracranial aneurysm Annales Françaises d'Anesthésie et de Réanimation 33(1), e15-e17.

Incidence & risk

Older males with coronary artery disease.

Risk factors	Odds ratio (95% CI)	*P*-value
Age		
<40 yr	1.00	
40–59 yr	2.16 (0.81–5.75)	0.068
60–80 yr	4.80 (1.85–12.43)	0.027
>80 yr	10.59 (3.76–29.81)	<0.0001
$T_{BIS\ 40-60}$	0.97 (0.96–0.98)	<0.0001
Coronary artery disease		
No	1.00	
Yes	2.53 (1.47–4.37)	0.001
Gender		
Female	1.00	
Male	1.57 (1.03–2.40)	0.03



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Besch, G., Liu, N., Samain, E., Pericard, C., Boichut, N., Mercier, M., Chazot, T., Pili-Floury, S. (2011). Occurrence of and risk factors for electroencephalogram burst suppression during propofol–remifentanil anaesthesia https://dx.doi.org/10.1093/bja/aer235

Sensitive but non-specific

Major clinical events cause burst suppression

Hypothermia
Hypoxia
Hypotension
Hypoglycaemia
Vascular brain injury
Brain death

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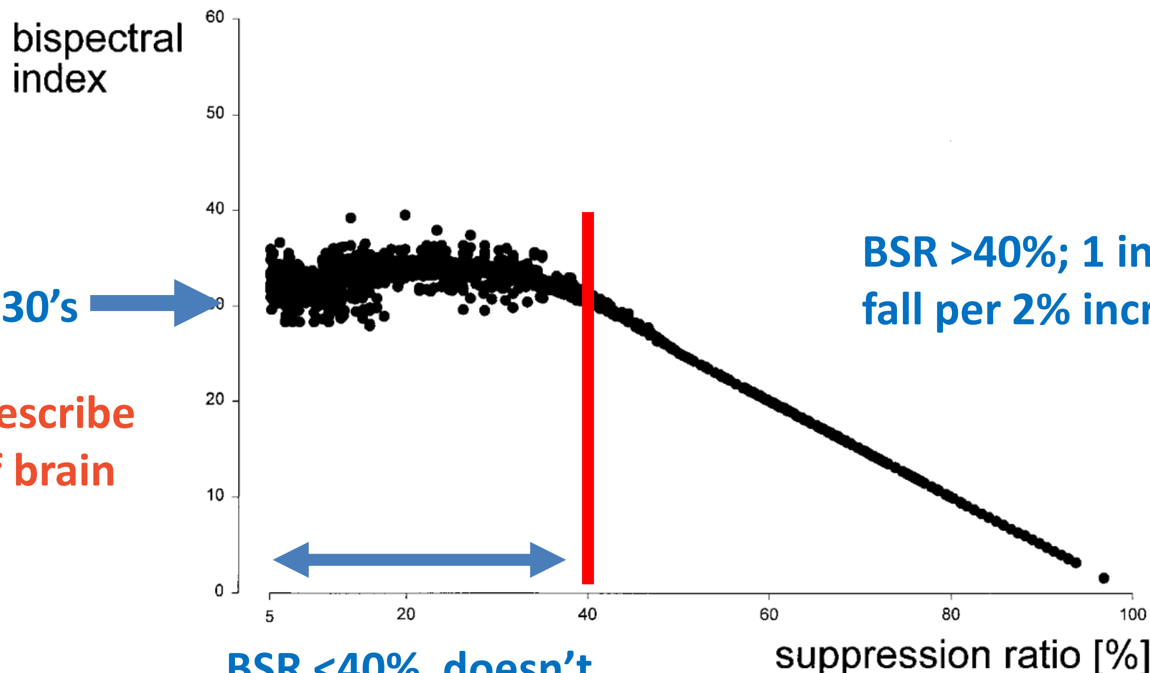
BIS and the BSR Algorithm

Suppression ≠ low BIS value



Plateau in 30's

Values in 30's describe quite a range of brain states

BSR >40%; 1 index value fall per 2% increase BSR

BSR <40% doesn't influence BIS Index

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Bruhn, J., Bouillon, T., Shafer, S.(2000). Bispectral Index (BIS) and burst suppression: revealing part of the BIS algorithm. Journal of Clinical Monitoring and Computing 16(8), 593 596.

Koitabashi, T. (2004). **Integration of suppression ratio in the bispectral index** Journal of Anesthesia 18(2), 141-143. https://dx.doi.org/10.1007/s00540-003-0217-1

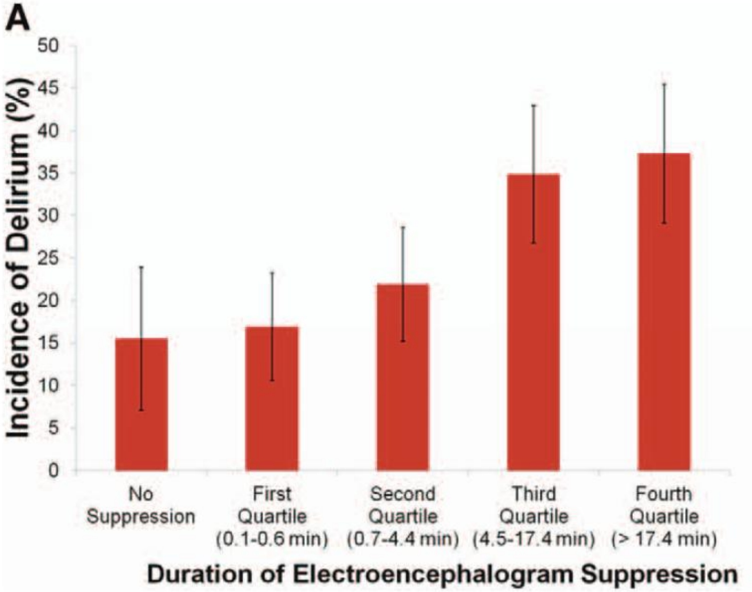
Delerium

Delirium affects >20% of post surgical adults.

Associated with “deep” or burst suppressed EEG:

Unmasks subclinical underlying disease?
Susceptibility to anaesthesia?
“Overdose” of anaesthesia?

Cochrane Meta-analysis – 32% **reduction** in delirium with pEEG montoring.



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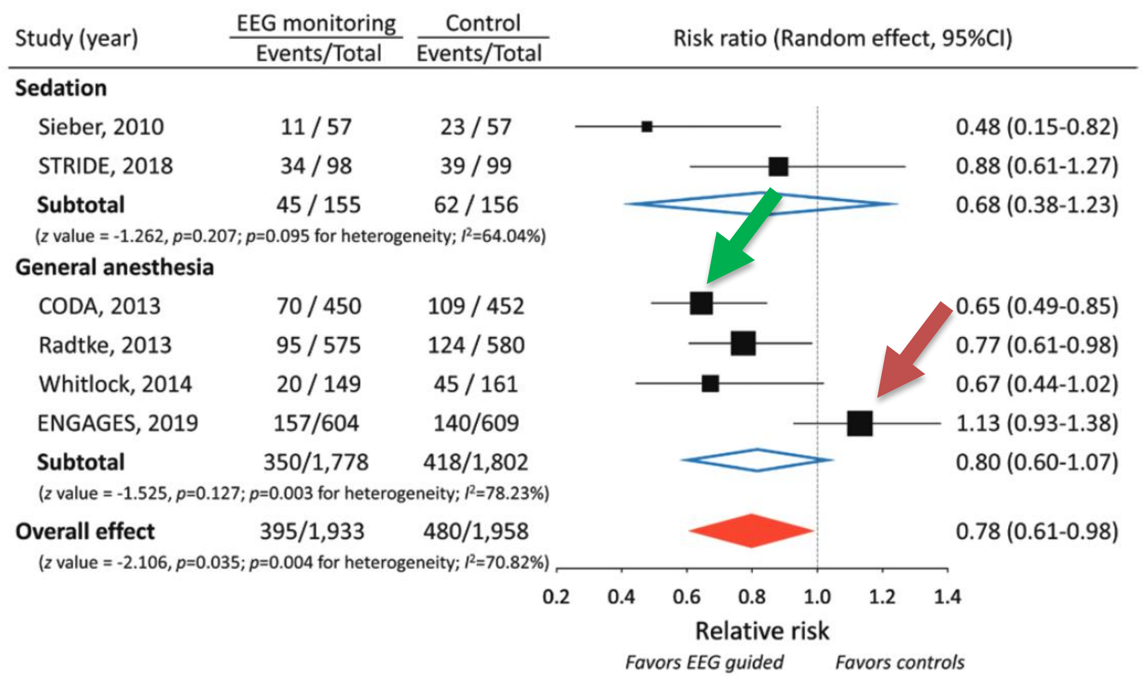
Punjasawadwong, Y., Chau-in, W., Laopaiboon, M., Punjasawadwong, S., Pin-on, P.(2018). **Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults.** Cochrane Database of Systematic Reviews 5(5), CD011283.

Delerium

pEEG monitoring reduces delirium risk



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Delerium - Engages

- 1232 Adults >60, major surgery.
- “Expert assisted” BIS vs aaETAC.
- NO difference in delirium rate (26 vs. 23%)

- BUT BIS Group:
  - Mean **7 mins** of burst suppression.
  - Mean 32 mins with BIS <40.
  - Lower MORTALITY
  - Lower ETAC (0.69 vs 0.8)
  - Less hypotension

	BIS guided	Usual care	
End-tidal volatile agent concentration, MAC[d]	0.69 (0.62 to 0.77)	0.80 (0.71 to 0.86)	−0.11 (−0.13 to −0.10)
Duration of BIS <40, min[e]	32 (9 to 81)	60 (19 to 132)	−28 (−38.0 to −18.0)
Time with SR >1%, min[f]	7 (1 to 23)	13 (2 to 58)	−6 (−9.9 to −2.1)
MAP, mean (SD), mm Hg	81.2 (8.26)	79.6 (7.68)	1.5 (0.63 to 2.42)
Duration of MAP <60 mm Hg, min	7 (2 to 19)	7 (1 to 19)	0 (−1.7 to 1.7)

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Fritz, B., Kalarickal, P., Maybrier, H., Muench, M., Dearth, D., Chen, Y., Escallier, K., Abdallah, A., Lin, N., Avidan, M.(2016). **Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium** https://dx.doi.org/10.1213/ane.0000000000000989

Wildes, T., Mickle, A., Avidan, M. (2019). **Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery ENGAGES** https://dx.doi.org/10.1001/jama.2018.22005

Delerium - Engages

Figure S5. Difference in time (min) with BIS < 40 (normalized by surgical duration) in the CODA[53] and the ENGAGES trials[45].

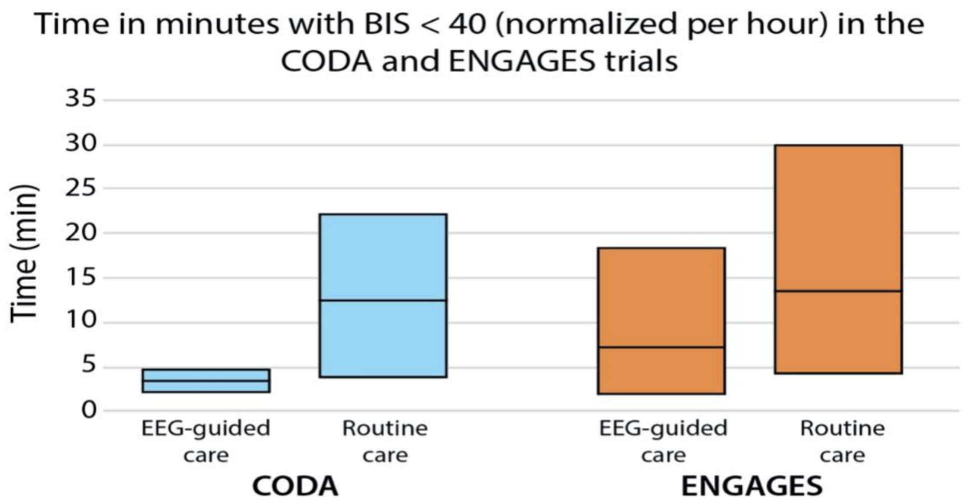
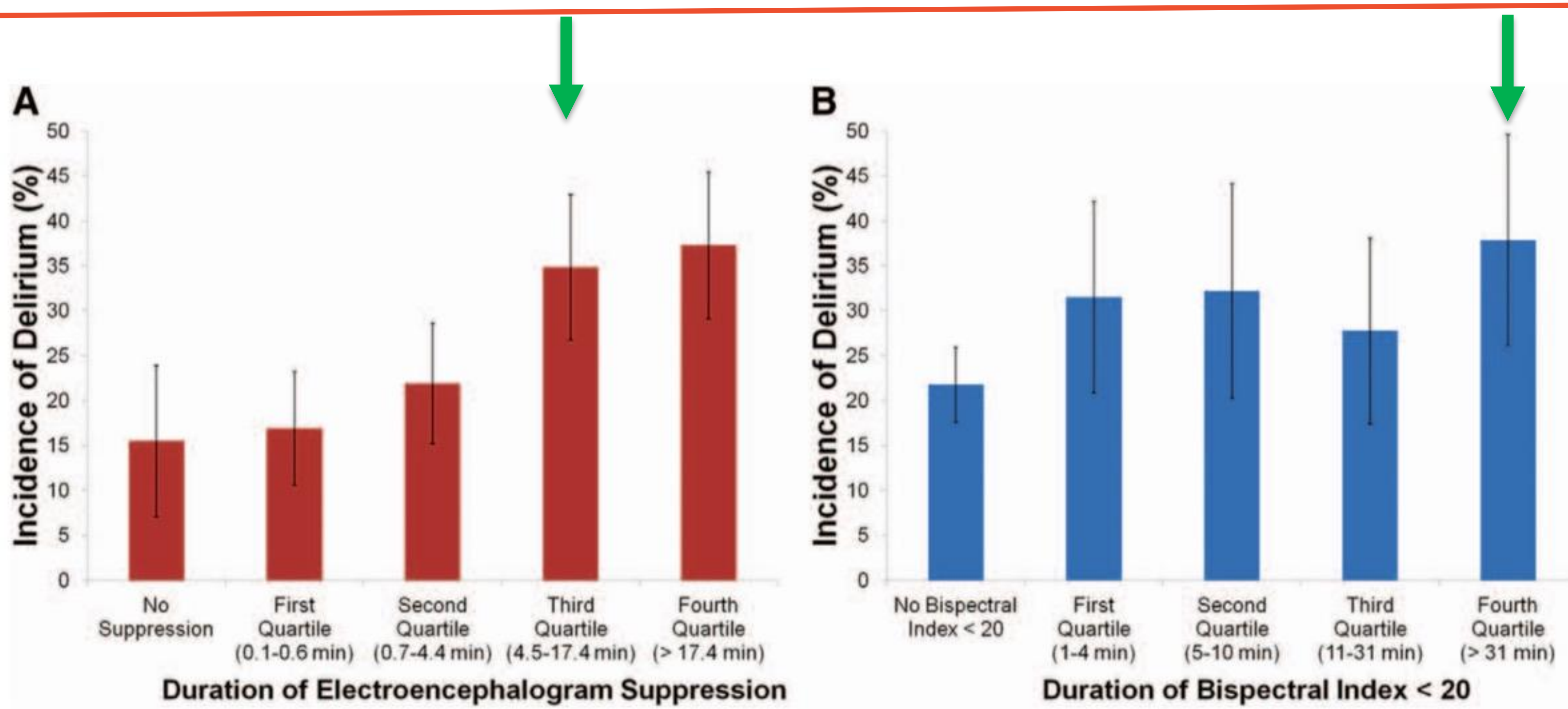


Figure 7. A comparison of time in minutes with BIS < 40 (normalized by mean surgery time) in the CODA and ENGAGES trials. Plots depict median and inter-quartile range for each study and group.

The box plots indicate median and interquartile range.

Delerium - Engages



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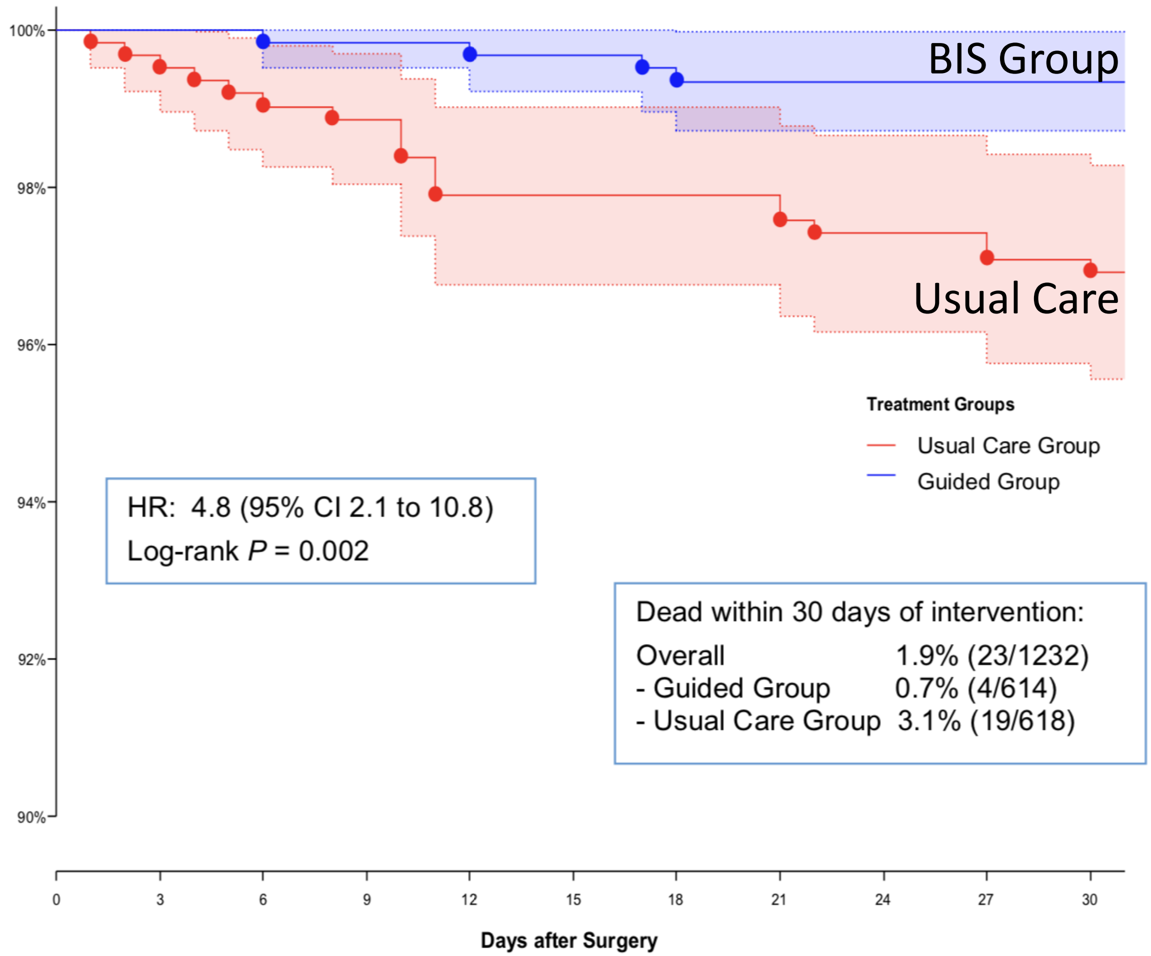
Fritz, B., Kalarickal, P., Maybrier, H., Muench, M., Dearth, D., Chen, Y., Escallier, K., Abdallah, A., Lin, N., Avidan, M.(2016). Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium https://dx.doi.org/10.1213/ane.0000000000000989

eFigure4: Kaplan-Meier Curve: 30 Day Survival

Kaplan-Meier curves of 30-day survival with 95% confidence intervals (CI), by treatment groups.



Wildes, T., Mickle, A., Avidan, M. (2019). **Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery ENGAGES** https://dx.doi.org/10.1001/jama.2018.22005

Balanced - outcome

International RCT – BIS 35 vs 50 (+/-5)
Higher risk patients (>60, >2hr surgery)
6449 patients

Difficulty tracking the study BIS ranges.
2489 *excluded for protocol violations!*

39% of patients <0.7 MAC = 1 case AAGA.

No mortality difference at 1 yr.

Broadens the range of "safe" anaesthesia.

Burst suppressed subgroup outcomes awaited!

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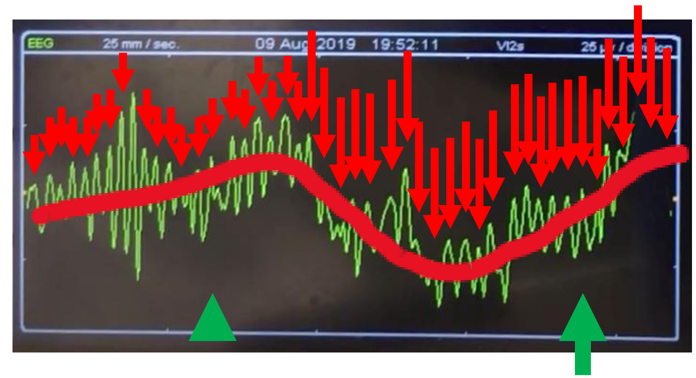
Short, T., Campbell, D., et al (2019). **Anaesthetic depth and complications after major surgery: an international, randomised controlled trial**. The Lancet, https://doi.org/10.1016/S0140-6736(19)32315-3

EEG - Anaesthesia



Slow Waves: 0.5 Hz [Delta / SW]
Faster Waves: 10.5 Hz [Alpha]

Maybe we don't need numbers?

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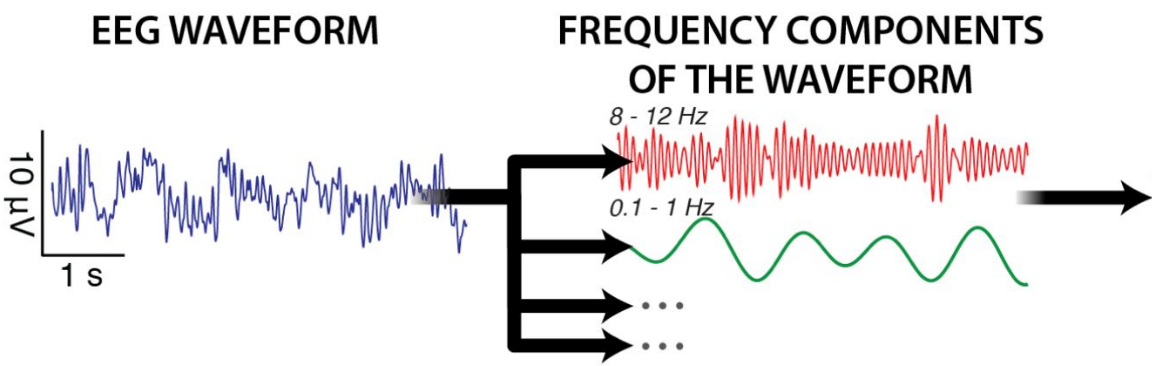
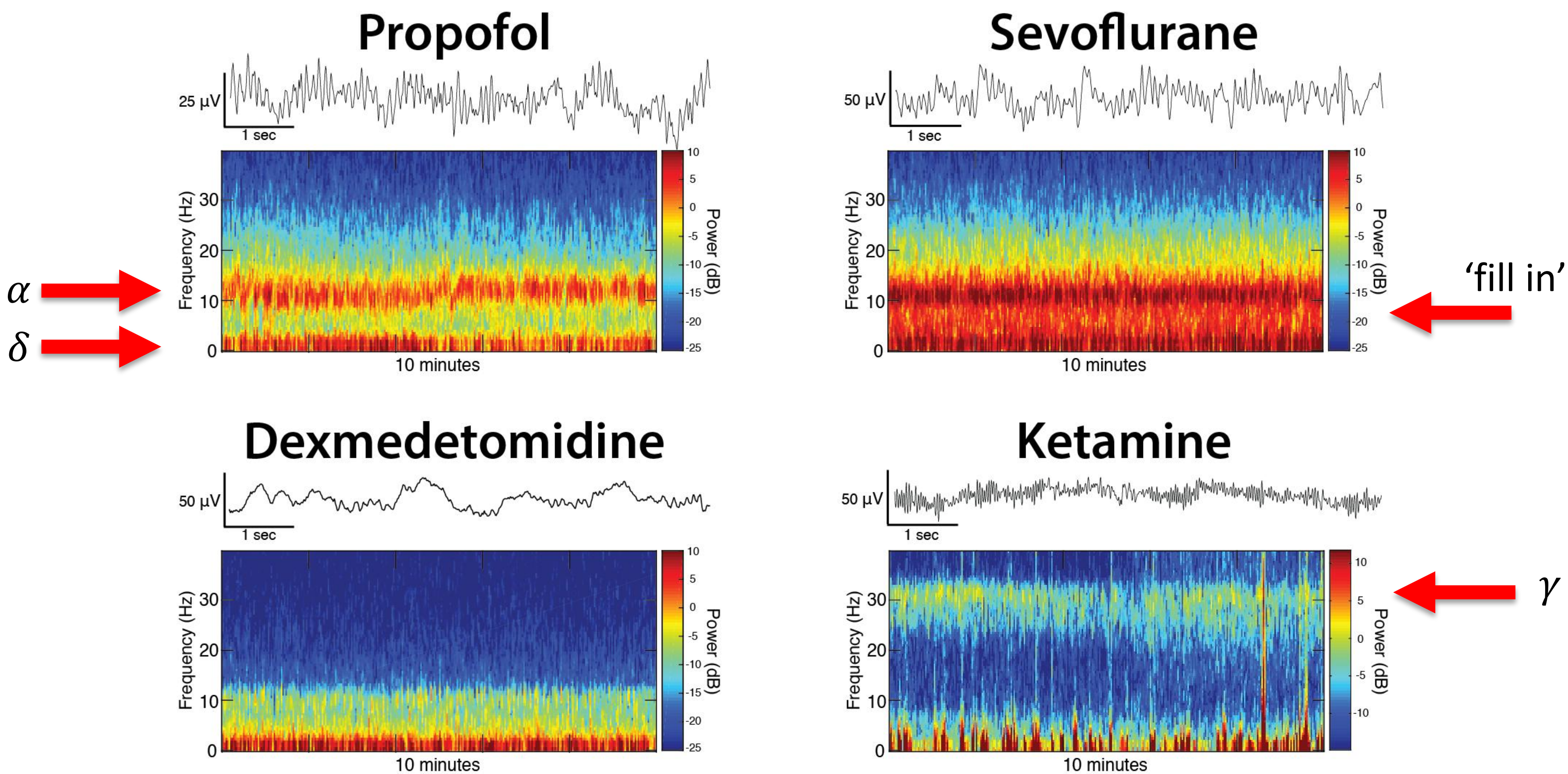
Spectrogram



Purdon, P., Sampson, A., Pavone, K., Brown, E. (2015). **Clinical Electroencephalography for Anesthesiologists Part 1: Background and Basic Signatures** https://dx.doi.org/10.1097/aln.0000000000000841

Electroencephalo-pharmacology



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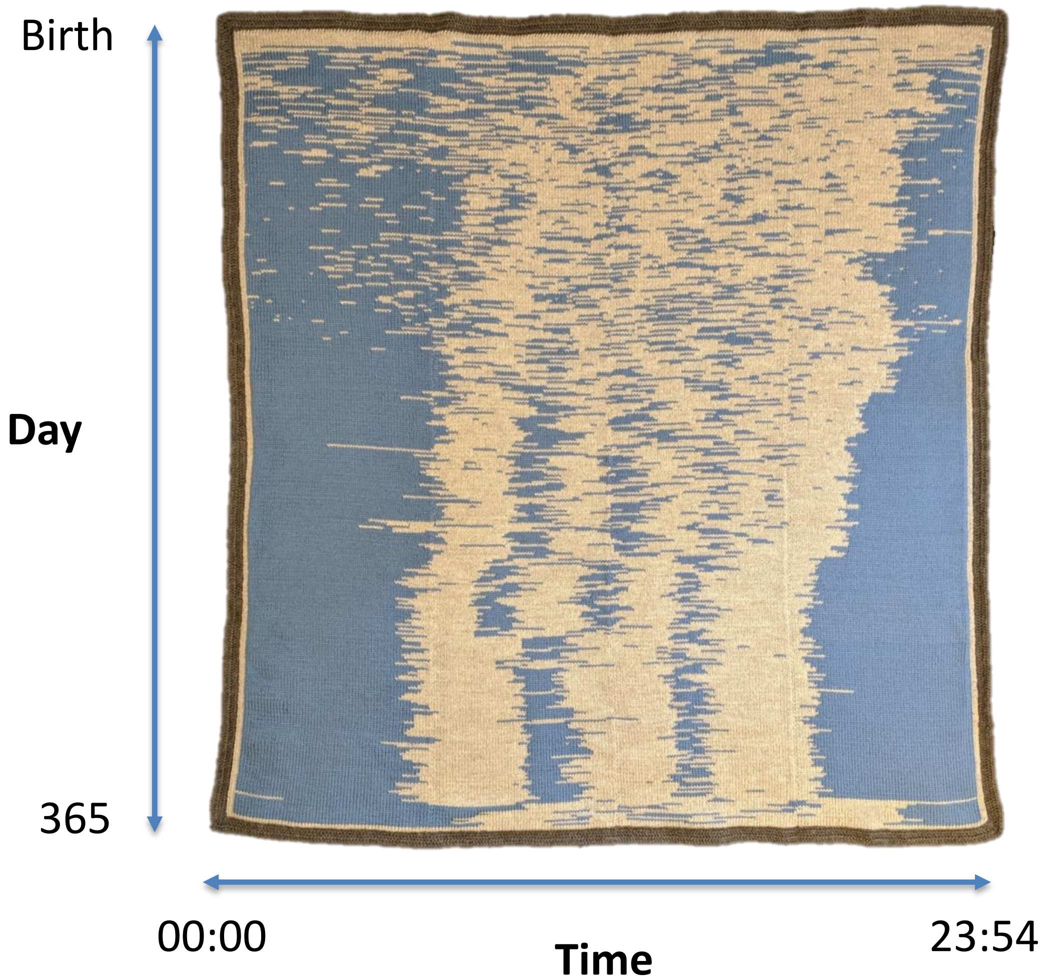
The sleep blanket



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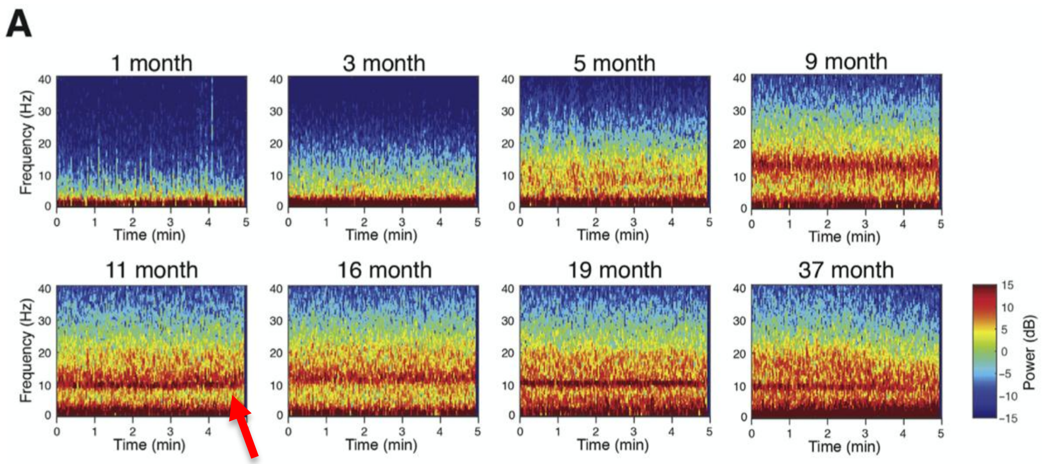
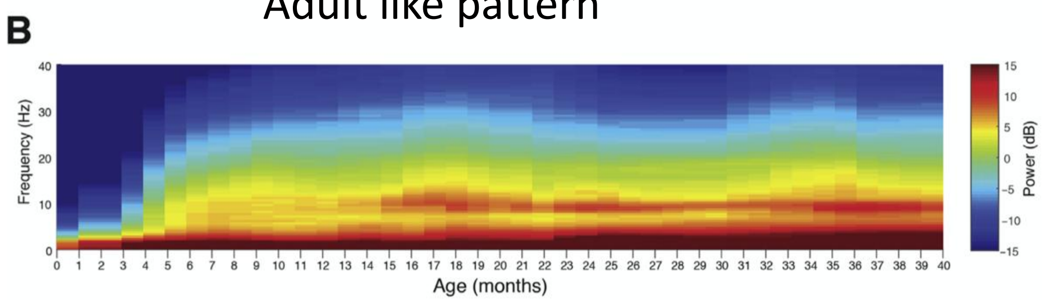
Permission obtained. Seung Lee @lagomorpho 12/7/19

Paediatric Brain

Brain development continues during early years of life…

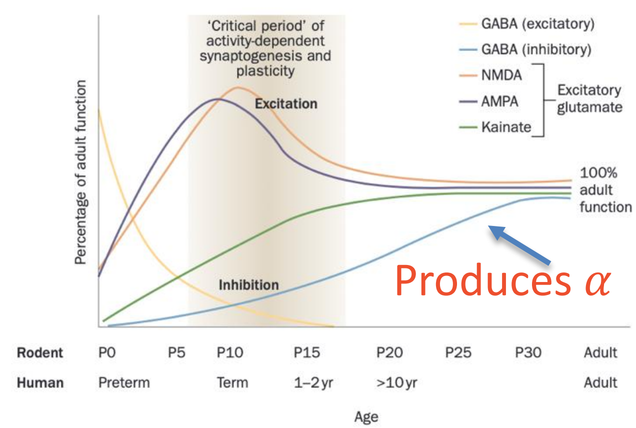


Adult like pattern



Delta / slow waves from birth
Theta / alpha from 4/12

Frontal alpha from 7-9/12
Frontal coherence from 10/12



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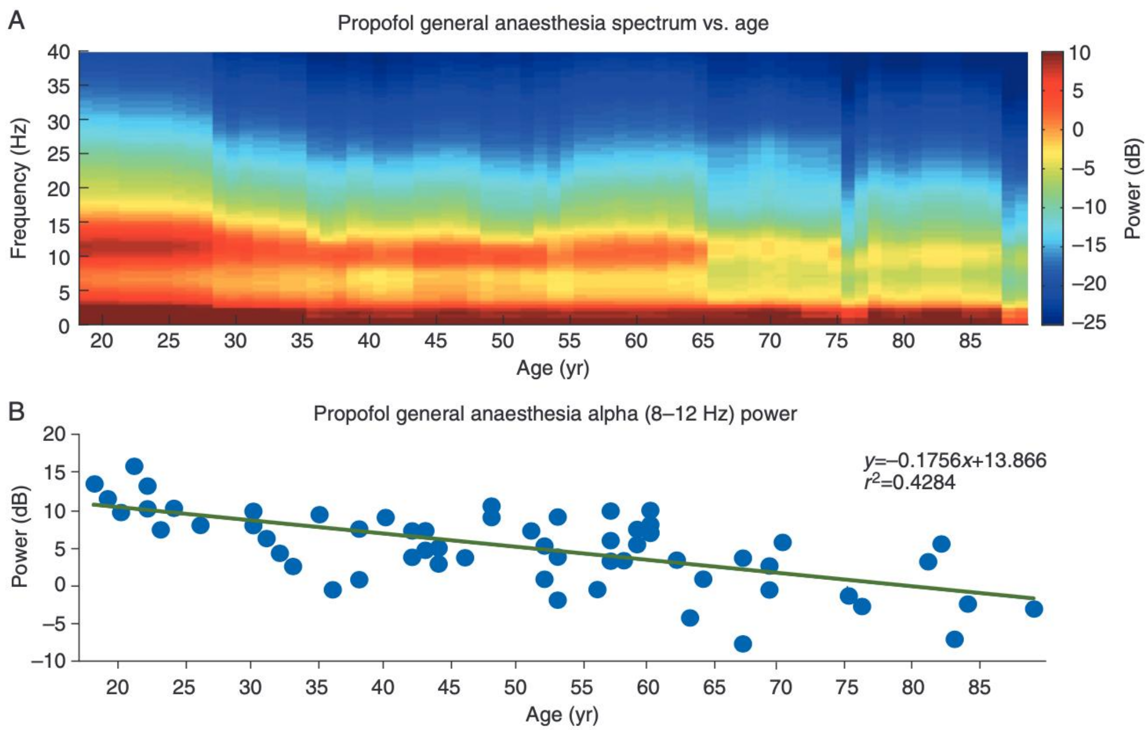
Cornelissen, L., Kim, S., Lee, J., et al (2018). **Electroencephalographic markers of brain development during sevoflurane anaesthesia in children up to 3 years old.** https://doi.org/10.1016/j.bja.2018.01.037
Rakhade, S., & Jensen, F. (2009). **Epileptogenesis in the immature brain: emerging mechanisms.** https://doi.org/10.1038/nrneurol.2009.80

Aging brain

Alpha oscillations diminish with age



Mechanisms

- Reduction in brain volume
- Cortical thinning
- Decrease neurone size and number
- Decrease mitochondrial function
- Susceptible to oxidative stress
- Loss of white matter
- Reduced neurotransmitter release

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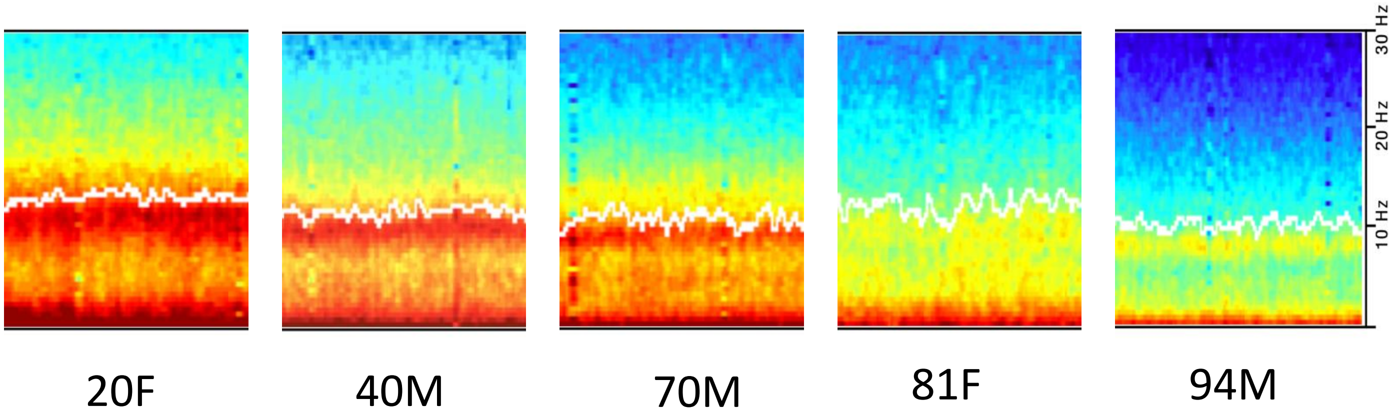
Purdon, P., Pavone, K., Akeju, O., et al. (2015). **The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia**
https://dx.doi.org/10.1093/bja/aev213
Brown, E., Purdon, P. (2013). **The aging brain and anesthesia**
https://dx.doi.org/10.1097/aco.0b013e328362d183

A tale of five brains



Note reduction in power of the alpha oscillations with age.

Lower power alpha band correlates with POCD / delerium risk

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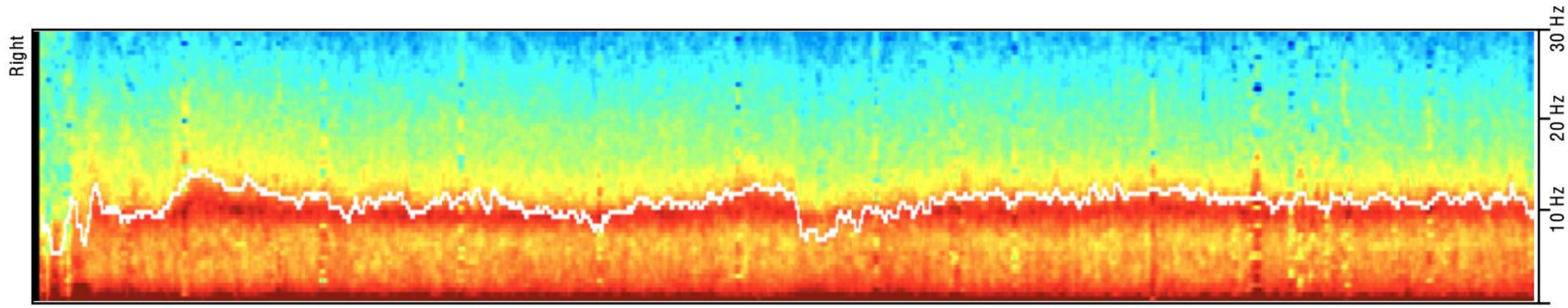
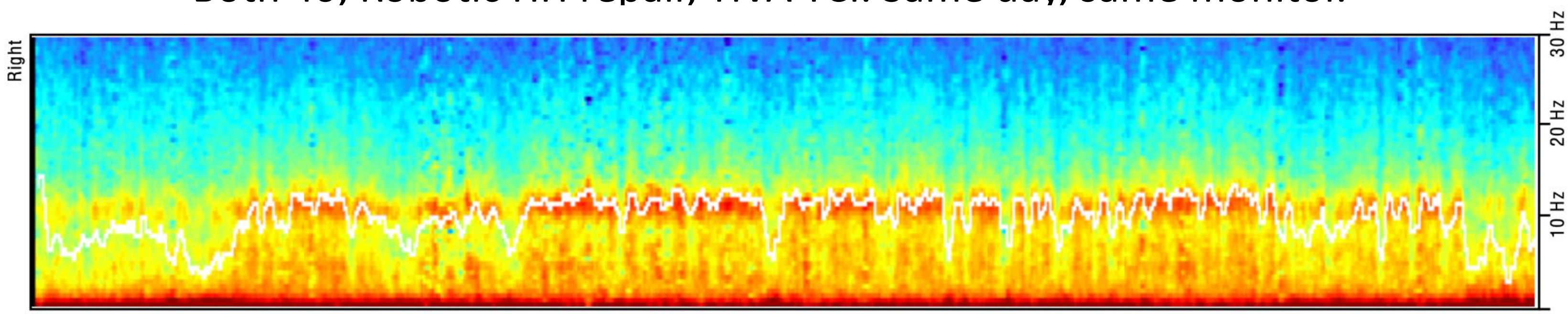
Giattino, C., Gardner, J., Sbahi, F., (2017) **Intraoperative Frontal Alpha-Band Power Correlates with Preoperative Neurocognitive Function in Older Adults.**
https://doi.org/10.3389/fnsys.2017.00024

A tale of two brains



Both 40, Robotic HH repair, TIVA TCI. Same day, same monitor.



Brain age is physiological, not just chronological

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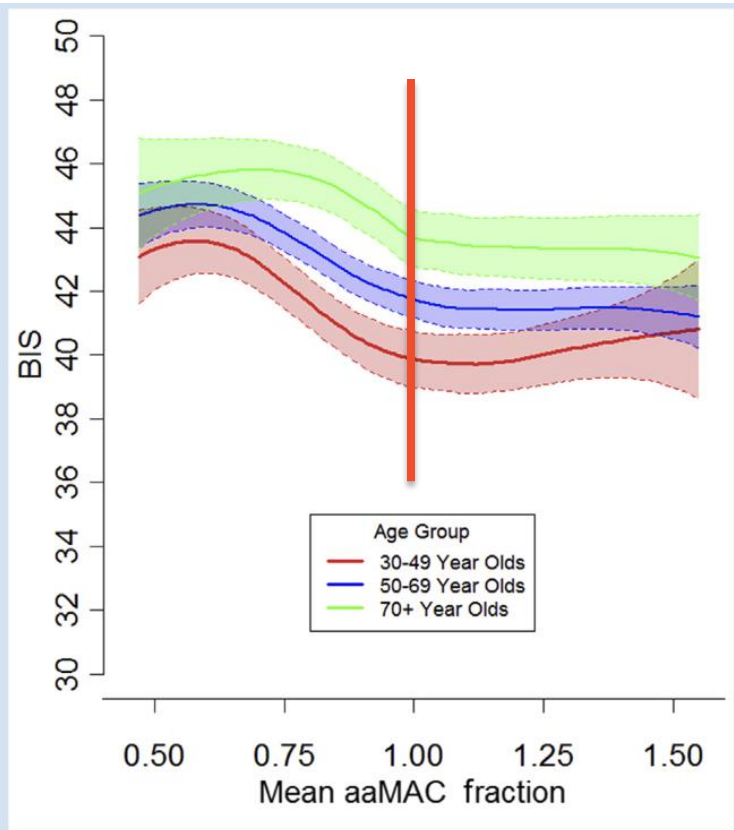
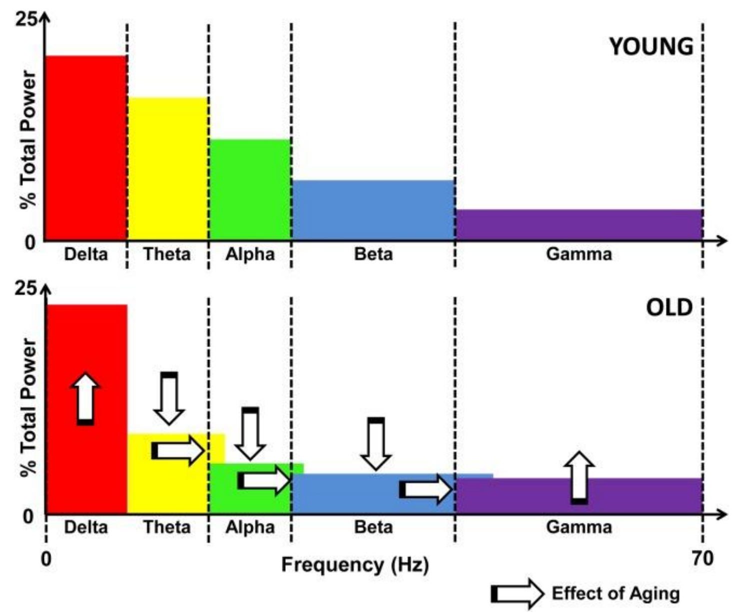
Ageing brain



BIS values **3.44** points higher between 30-49 year old and 70+ at aaMAC.

BIS may over read a little in older patients.
-potential for increased volatile dosing.



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Ni, K., Cooter, M., Gupta, D., et al (2019). **Paradox of age: older patients receive higher age-adjusted minimum alveolar concentration fractions of volatile anaesthetics yet display higher bispectral index values.** https://doi.org/10.1016/j.bja.2019.05.040

A vision of the future…

A "one size fits all" pEEG monitor, which works for any anaesthetic agent, and across all ages, including EEG measures of nociception.

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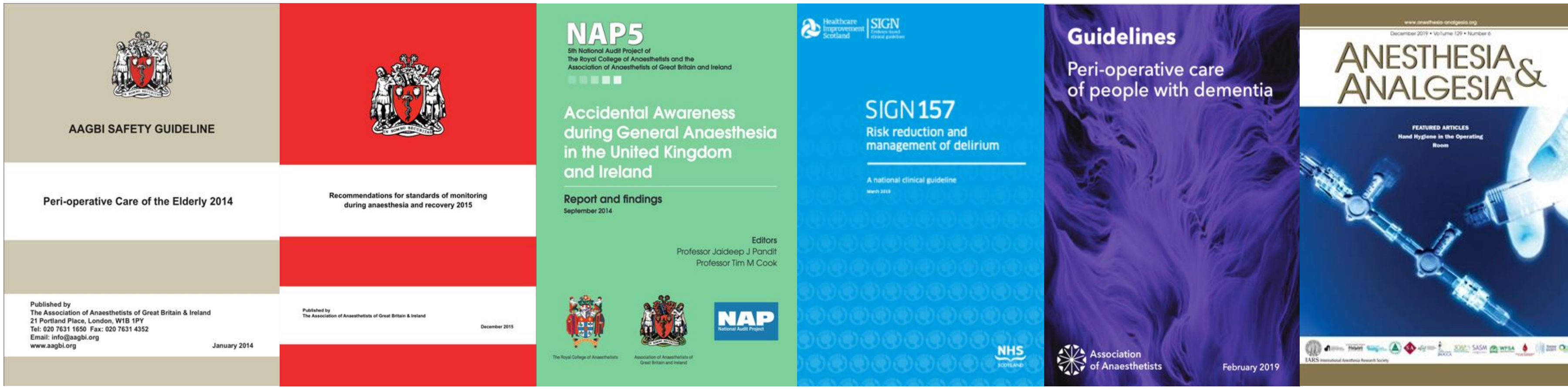
Ramaswamy, S., *Kuizenga, M.*, *Weerink, M.*, *Vereecke, H.*, *Struys, M.*, & *Nagaraj, S.* (2019). **Novel drug-independent sedation level estimation based on machine learning of quantitative frontal electroencephalogram features in healthy volunteers**. https://doi.org/10.1016/j.bja.2019.06.004

Jensen, E., Valencia, J., López, A., Anglada, T., Agustí, M., Ramos, Y., Serra, R., Jospin, M., Pineda, P., & Gambus, P. (2014). **Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia** https://doi.org/10.1111/aas.12359

All those in favour…



R Depth of anaesthesia should be monitored in <u>all patients aged over 60 years</u> under general anaesthesia for surgery expected to last for more than one hour, with the aim of avoiding excessively deep anaesthesia.

"EEG monitoring should be considered as part of the vital organ monitors to guide anesthetic management".

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Chan, M., Hedrick, T., Egan, T., et al (2019). **American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes** https://dx.doi.org/10.1213/ane.0000000000004502

Conclusions

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Chan, M., Hedrick, T., Egan, T., et al (2019). **American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes** https://dx.doi.org/10.1213/ane.0000000000004502

Questions

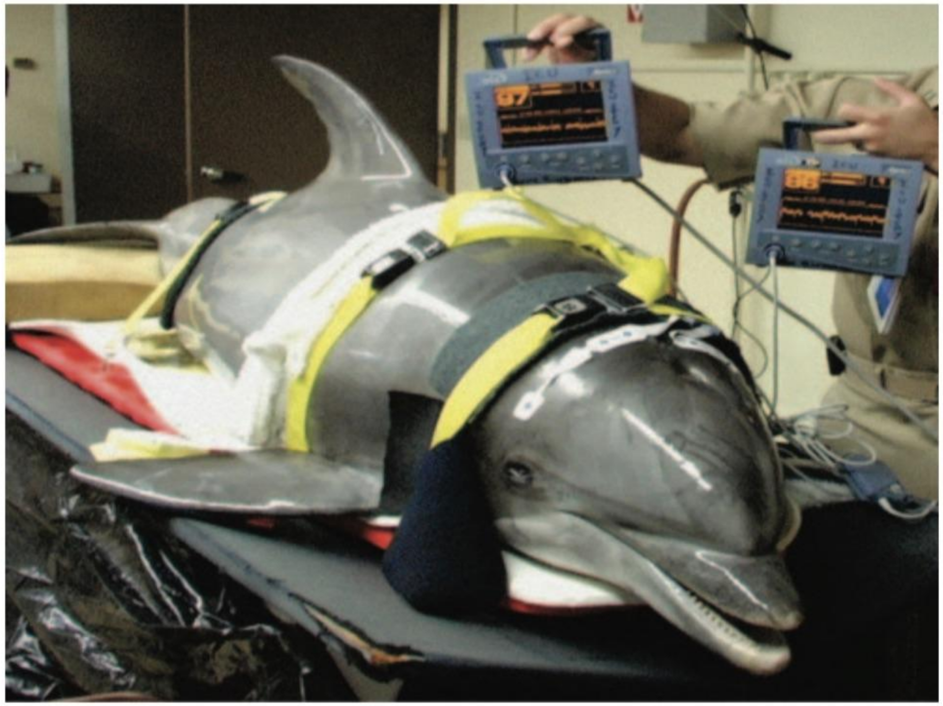

Figure 1. Photograph showing the montage of the bispectral index (BIS) monitor leads on a dolphin. Right BIS = 97, left BIS = 86. Narrow, tall spikes seen on the electroencephalogram displays are an electrocardiogram effect.

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Further learning

eLearning
https://icetap.org

http://eristest2.partners.org/education/

http://eegforanesthesia.iars.org/ [CPD Certificate]

Avoiding too deep anaesthesia (ESA) [CPD Certificate]

Review papers

Purdon, P., Sampson, A., Pavone, K., Brown, E. (2015). Clinical Electroencephalography for Anesthesiologists Part 1: Background and Basic Signatures https://dx.doi.org/10.1097/aln.0000000000000841

Bennett, C., Voss, L., Barnard, J., Sleigh, J. (2009). Practical Use of the Raw Electroencephalogram Waveform During General Anesthesia; The Art and Science https://dx.doi.org/10.1213/ane.0b013e3181a9fc38

Hagihira, S. (2015). Changes in the electroencephalogram during anaesthesia and their physiological basis. https://dx.doi.org/10.1093/bja/aev212