Why Focus on Sleep Hygiene in the Perioperative and Critical Care Settings

Dr Mervyn Maze MB ChB, FRCP, FRCA, FMedSci
William K Hamilton Distinguished Professor in Anesthesia
Department of Anesthesia and Perioperative Care,
University California San Francisco

Questions to be Addressed

- How does Sleep Restore Cognitive Processing?
- Do Sedative-hypnotics produce Sleep?
- What effect does Sleep Disruption have on Cognitive Function
  - Sleep deprivation?
  - Sleep fragmentation?
- What effect does Sleep Disruption have on Immune Function?
- What effect do Sedative-hypnotics have on
  - Cognitive Function?
  - Immune Function?

Potential Conflicts of Interest

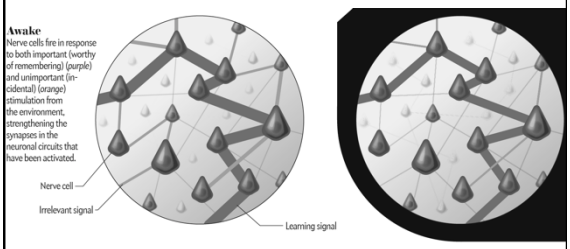
- Patented dexmedetomidine for use as sedative-hypnotic in1987 with Mika Scheinin
- Reassigned rights to patent
  - Farmos (Orion)
    - Abbott Labs
    - Hospira
  - $250K to Lab at Stanford University
- Accrued no other financial benefit

Questions to be Addressed

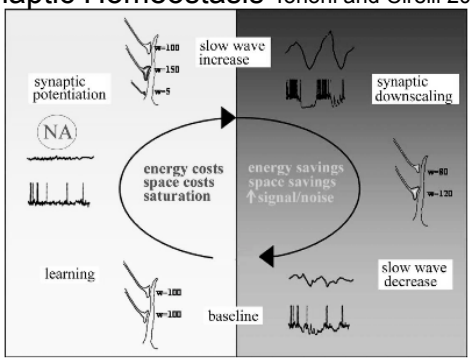
- How does Sleep Restore Cognitive Processing and prevent Delirium?

Synaptic Homeostasis Theory of Sleep and Cognition

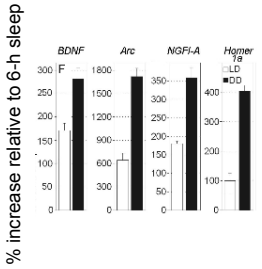
Tononi and Cirelli, 2006



Synaptic Homeostasis Tononi and Cirelli 2006

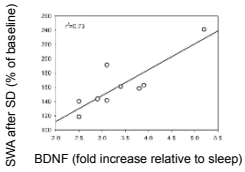


Wakefulness Increases Expression of Plasticity-related Genes Huber *et al*, Sleep 2007



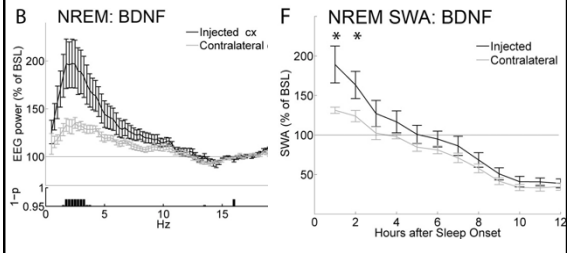
Wakefulness-induced BDNF is positively correlated with duration of SWA

Huber *et al* Sleep 2007



Exogenously administered BDNF increases NREM and SWA Sleep

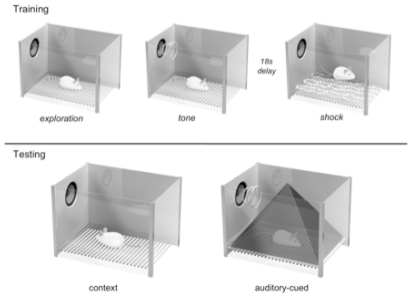
Faraguna *et al* J Neurosci 2008



Questions to be Addressed

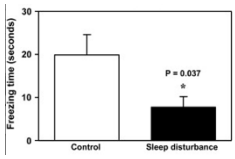
- What effect does Sleep Deprivation and Sleep Disruption have on Cognitive Function?

Trace Fear Conditioning (TFC)



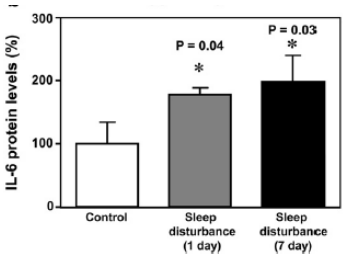
Sleep Deprivation Decreases Contextual Memory in TFC

Zhu *et al* Neurobiology of Disease 2012



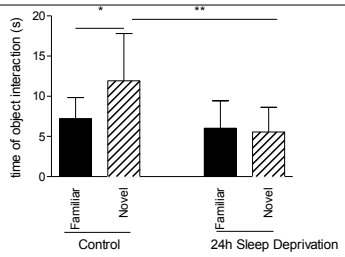
Sleep Deprivation Induces Neuroinflammation in Hippocampus

Zhu *et al* Neurobiology of Disease 2012



Sleep Fragmentation Decreases Memory in Novel Object Recognition Test

Vacas *et al* Submitted 2014



Sleep Fragmentation Increases Inflammatory Cytokines in Hc

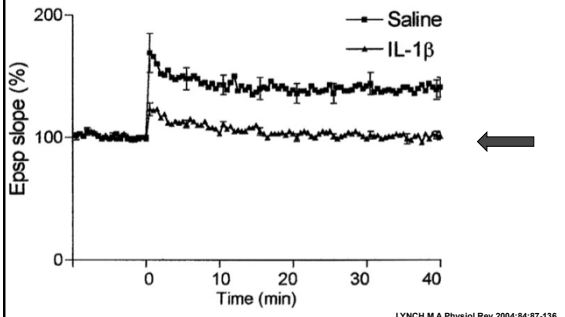
Vacas *et al* Submitted 2013

TNF mRNA	avg. ΔCT	SD	RQ	p value
Control n=4	16,95	0,69	1	<0,001
24h SD n=5	14,52	0,58	**5,4**	

IL1b mRNA	avg. ΔCT	SD	RQ	p value
Control n=4	14,18	1,79	1	0,1188
24h SD n=5	12,85	0,58	**2,5**	

IL6 mRNA	avg. ΔCT	SD	RQ	p value
Control n=4	15,31	0,75	1	0,2874
24h SD n=5	14,98	0,94	**1,3**	

IL-1β disrupts LTP and memory formation

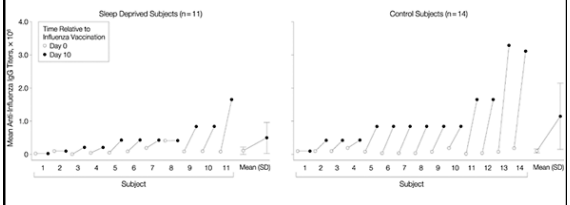


LYNCH M A Physiol Rev 2004;84:87-136

Questions to be Addressed

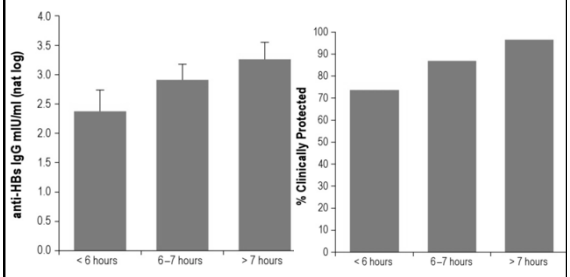
- What effect does Sleep Deprivation have on Immune Function?

Effect of Sleep Deprivation (12h) on Antibody Response to FluVaccination



Spiegel, K. et al. JAMA 2002;288:1471

Duration of sleep affects antibody response to Hepatitis B virus vaccination Prather *et al* 2012

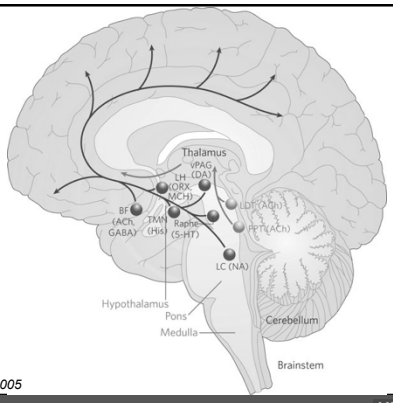


Recap

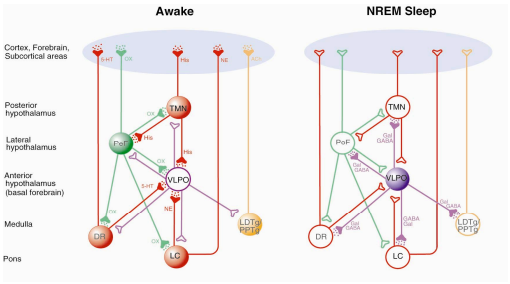
- Slow wave activity sleep downscales synaptic potentiation required to enable “space” for new memory formation.
- BDNF accumulates during wakefulness and drives Slow Wave Activity (0.5 – 4.5 Hz) sleep (nREM stages 3-4), and synaptic downscaling
- BDNF, SWA, and downscaling are required for normal cognitive processing
- Sleep deprivation induces neuroinflammation and impairs cognition
- Sleep Deprivation impairs immunological function
  - acquired

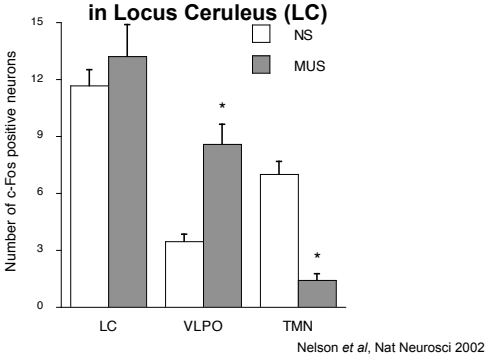
Questions to be Addressed

- Do Sedative-hypnotics produce natural “sleep?”



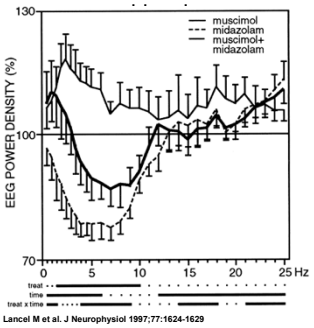
Saper *et al*, *2005*





Nelson *et al*, Nat Neurosci 2002

EEG power densities within non-REM sleep over the 6-h recording period of muscimol, midazolam, and muscimol

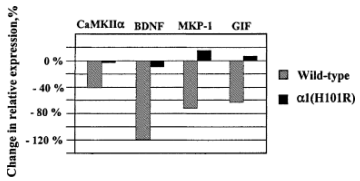


Lancel M et al. J Neurophysiol 1997;77:1624-1629

Journal of Neurophysiology

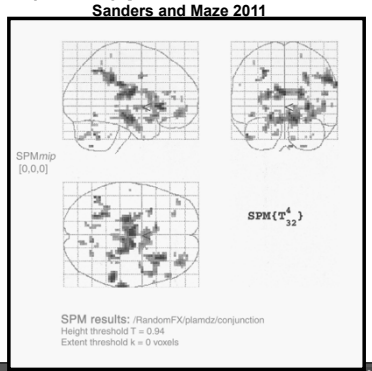
BDZ decrease Trophic Protein Expression by signaling through $\alpha 1$ subunit of the $GABA_AR$

J Neurochem 2004

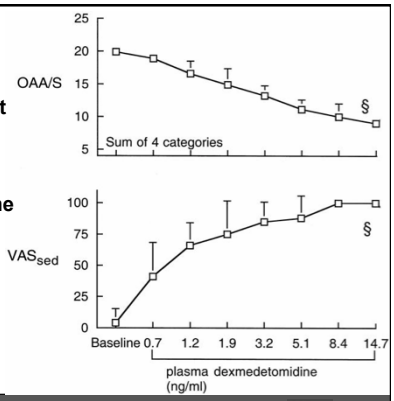


fMRI (BOLD) placebo – midazolam

Sanders and Maze 2011



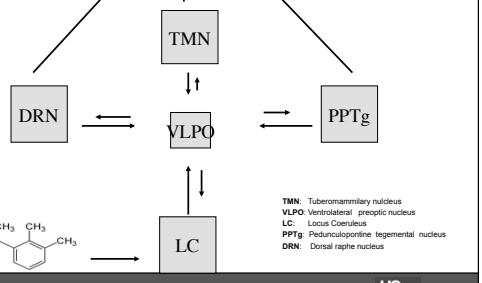
Dose-dependent Loss of wakefulness by Dexmedetomidine In Volunteers



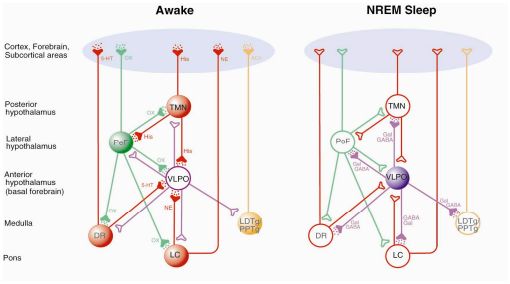
Ebert *et al*, 2000

Sedation by Dexmedetomidine

Nelson *et al* Anesthesiology 2003
Rabin *et al* Eur J Pharmacol 1996

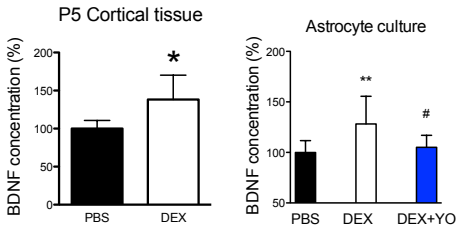


TMN: Tuberomammilary nulcleus
VLPO: Ventrolateral preoptic nucleus
LC: Locus Coeruleus
PPTg: Pedunculopontine tegemental nucleus
DRN: Dorsal raphe nucleus



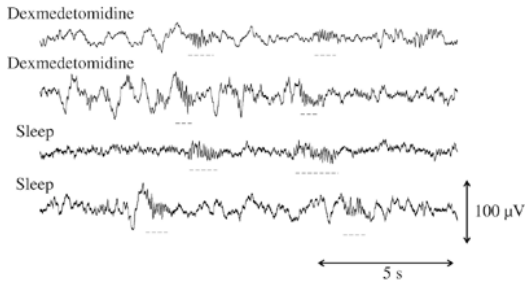
Dexmedetomidine increases BDNF expression through an α_2 adrenoceptor

Degos *et al* Anesthesiology 2013

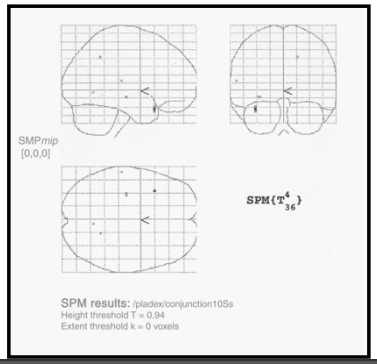


Sleep Spindles in Dex and Natural Sleep

Huuponen *et al* Acta Anaesth Scand 2010

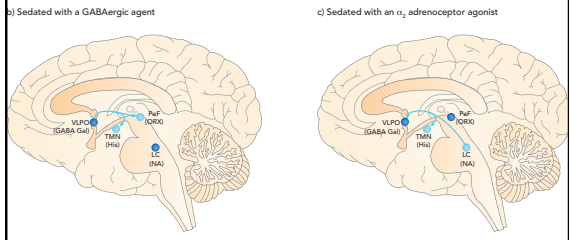


fMRI placebo – dexmedetomidine Sanders and Maze 2011



Neural substrates required for BDZ- *vs* α_2-sedation

Nelson *et al*, Nature Neuroscience 2002; Nelson *et al* Anesthesiology 2003
Zecharia *et al*, J Neuroscience, 2009



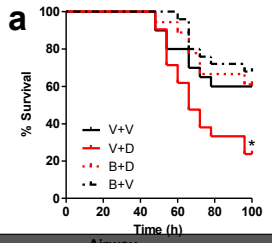
Differential Effects of Sedative-Hypnotics Data on Sleep Neurobiology

- Converge on Sleep Pathways
  - α_2 agonists in the brainstem
  - BDZs in hypothalamus
- EEG Sleep Pattern
  - α_2 agonists increase SWS activity
  - BDZs decrease SWS activity
- BDNF Response
  - α_2 agonists increase
  - BDZs decrease

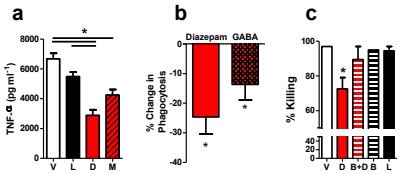
Questions to be Addressed

- What effects do Sedative-hypnotics have on immune function?

BDZs increase lethality from *Strep Pneumoniae* infection in mice through $GABA_A$ receptor Sanders *et al* CCM 2013



Diazepam inhibits macrophage function by inhibiting LPS-stimulated TNFα release and phagocytosis Sanders *et al* CCM 2013



Effect of Chronic BDZ use on occurrence of Community Acquired Pneumonia (CAP)

Exposure variable	Cases (n=4,964)	Controls (n=29,697)	Adjusted OR (95%CI)	P value
Benzodiazepines				
No	3,695 (74.44%)	25,071 (84.42%)	1.00	
Yes	1,269 (25.56%)	4,626 (15.58%)	**1.54 (1.42-1.67)**	<0.001

Obiora *et al* Thorax 2013

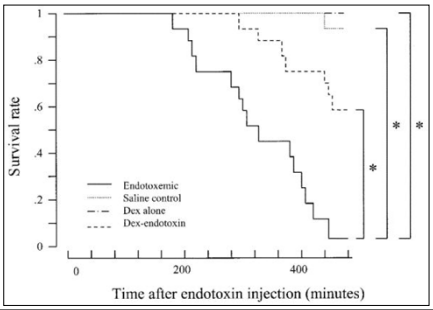
Effect of Chronic BDZ use on mortality from Community Acquired Pneumonia

Drug	Numbers dead at 30 days (%) (n=947)	30-day Adjusted Hazard Ratio [1] (95% CI)	P value	Long-term mortality (%) (n=1547)	Long-term mortality Adjusted Hazard Ratio[1] (95% CI)	P value
Benzodiazepine						
No	568 (15.4)	1.00		938 (25.4)	1.00	
Yes	379 (29.9)	**1.22 (1.06- 1.39)***	0.004	609 (48.0)	**1.32 (1.19-1.47)**	<0.001

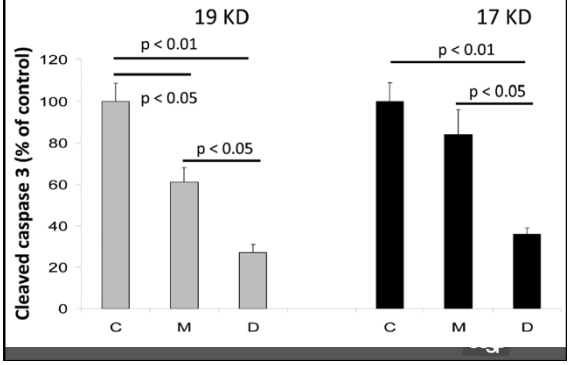
Obiora *et al* Thorax 2013

Dexmedetomidine reduces sepsis mortality

Taniguchi *et al* Critical Care Medicine 2004



Preservation of splenocytes by sedatives during sepsis Qiao *et al* Critical Care 2009

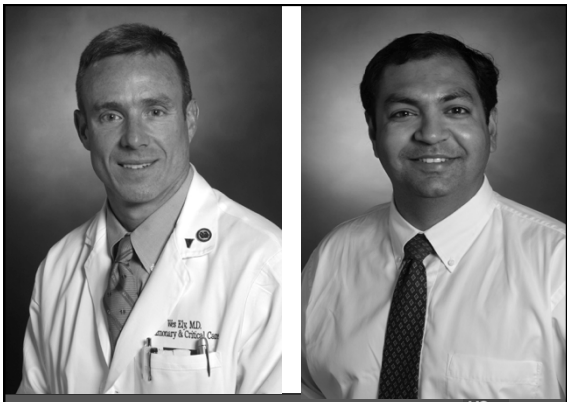


Differential Effects of Sedative-Hypnotics Data on Immunity

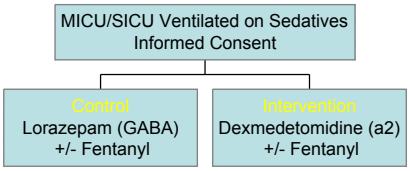
- Benzodiazepines
  - disable phagocytic function
  - increases mortality rate in sepsis
  - increase rate and MR from CAP
- α2 agonists
  - preserve vasoconstrictor response to pressors in experimental sepsis (DNS)
  - decrease mortality rate in sepsis
- α2 agonists > BDZs
  - preservation of splenocytes in sepsis

Problems with ICU Sedation

- Prolonged sedation provokes
  - difficulty in weaning from mechanical ventilation
  - increased length of stay in intensive care unit
- Precludes neurological examination
- Predisposes to infection
- Predisposes to delirium (cognitive dysfunction)

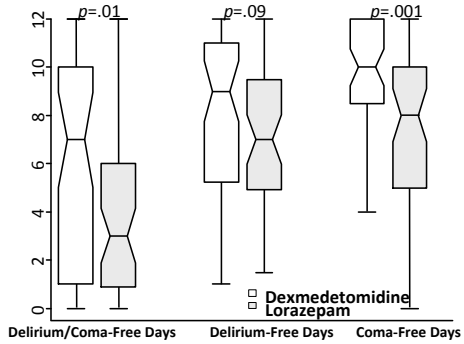


MENDS Study
Double blind randomized controlled trial

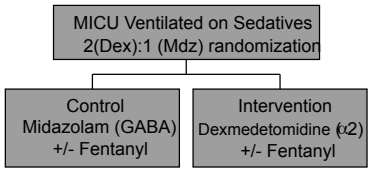


Pandharipande et al, JAMA 2007

Acute Brain Dysfunction in sedated ICU Patients



Dexmedetomidine *vs* Midazolam for ICU Sedation



Riker R. et al JAMA 2009

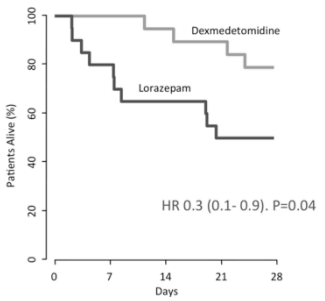
Dex Long-term study outcomes

Outcome	Midaz n=122	Dexmed n=244	P value
Time within -2 to +1 RASS	81%	80.8%	0.94
Baseline delirium	54.5%	56%	NS
Delirium during DBT	76%	55%	0.0004
Delirium duration (mean)	2.7	1.4	0.0001
Time to extubation (median)	138.4 h	93.8 h	0.02
ICU LOS	8	6.3	0.03
Infection	20%	10%	0.02

Riker et al JAMA 2009

Other Clinical Outcomes From MENDS I

Outcome	Loraz n=50	Dexmed n=51	P value
MV free days	18 (0,23)	22 (0,24)	0.22
ICU stay	9 (6,13.5)	7.5 (5,18)	0.31
Mortality (28 days)	27%	17%	0.18



Pandharipande *et al* Critical Care 2010

Effect of Sedatives in the ICU

- Benzodiazepines enhance likelihood of developing 'acute brain failure'
  - Induces hypnotic effect that
    - Lacks cognitive restorative effects of SWA
    - Enhances infection and death from Sepsis
- Dexmedetomidine may be beneficial
  - Induces sleep that enables
    - Restoration of Cognitive Function
    - Maintenance of immune system function

Questions Addressed

- Sleep Restores Cognitive Processing
- Sleep Disruption produces cognitive dysfunction
- Sleep Disruption produces immune dysfunction
- Benzodiazepines produce
  - chemical immobilization
  - Cognitive dysfunction
  - Immune dysfunction
- $\alpha 2$ agonists
  - Induced similar state to natural sleep
  - Preserves cognitive function
  - Prevents hyperinflammatory state

Further Questions to be Addressed

- How does propofol infusion compare with dexmedetomidine infusion?
- Is dexmedetomidine safe for sedation in the neonatal ICU

Acknowledgments

- Guo Tian-Zhi, Carla Coelho, Christiana Correa-Sales, Brad Rabin, Tina Reid, Frances Davies, Steve Shafer
- Nick Franks, Daqing Ma
- Pratik Pandharipande, Wes Ely
- Clif Saper, Lee Limbird
- Su Vacas, Laura Nelson, Rob Sanders, Anna Zecharia
- NIH
- MRC
- Wellcome Trust
- Hospira