

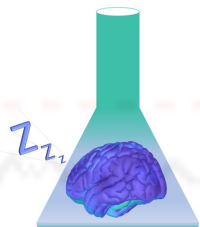
# Disrupted Sleep and Delirium

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NIDUS Webinar on Sleep and Circadian Rhythms  
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# Relevant Disclosures

- I have a patent on control of anesthetic state modulation, but with no income.
- I have an agreement with Elemind to lease equipment for non-pharmacologic potentiation of EEG slow waves, with no income to me.
- All relevant financial relationships have been mitigated.
- Funding Acknowledgements:



# Objectives

- Appreciate the importance of high-quality sleep in maintaining normal physiologic and cognitive functions.
- Understand the electroencephalographic and phenotypical changes associated with delirium that implicate disrupted sleep processes.
- Appreciate associations between disrupted sleep and delirium risk.
- Consider pharmacologic and non-pharmacologic approaches for modulating sleep structure in future delirium research.



# Delirium: Significance and Impact

**Costly**



**Common**



**Cognitive Decline?**



**Poor Prognostic Sign**



# Delirium: Core Features

**Awareness**



**Attention**



**Cognition**



**Fluctuating**



# Comparisons of Delirium and Sleep Deprivation

| Delirium (CAM-S)                  | Sleep Deprivation                             |
|-----------------------------------|---|
| Fluctuating over minutes to hours | Relatively constant but can fluctuate         |
| Inattention                       | Reduced psychomotor vigilance                 |
| Disorganized Thinking             | Impaired executive function & decision-making |
| Altered Level of Consciousness    | Drowsiness                                    |
| Disorientation                    | Disorientation                                |
| Memory Impairment                 | Impaired working memory                       |
| Perceptual Disturbances           | Visual misperceptions or hallucinations       |
| Psychomotor Agitation             | Irritability & paranoia                       |
| Psychomotor retardation           | Reduced reaction time                         |
| Altered Sleep/Wake Cycle          | Microsleeps during wakefulness                |

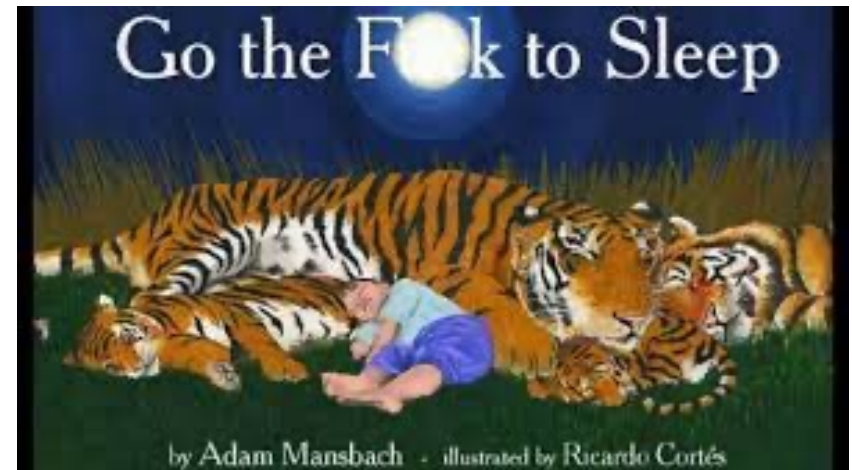
Inouye, *Ann Internal Med*, 2013

Alhola et al., *Neuropsychiatr Dis Treat*, 2013

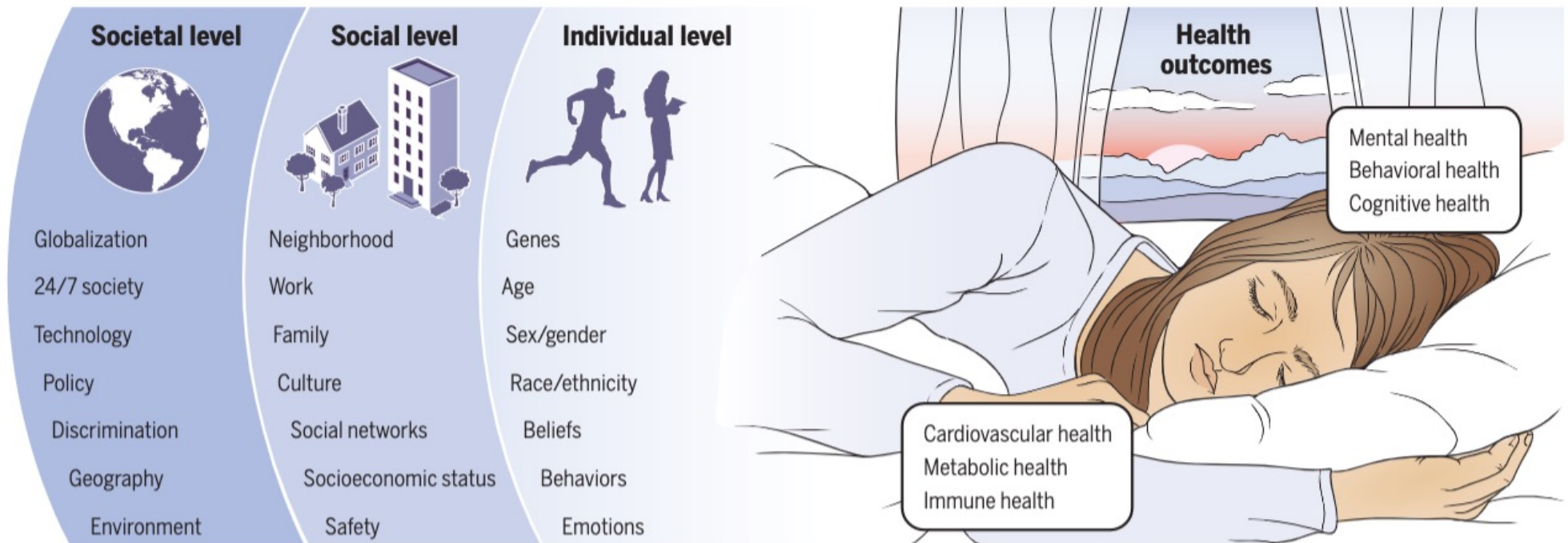


# Reasons to Study Sleep in Elucidating Delirium Pathophysiology

- Critical for maintaining consciousness and cognition
- Common
- Incompletely understood
- **Clinically relevant**
- **Modifiable**



# Importance of Sleep Health with Modifiers Across Societal Levels

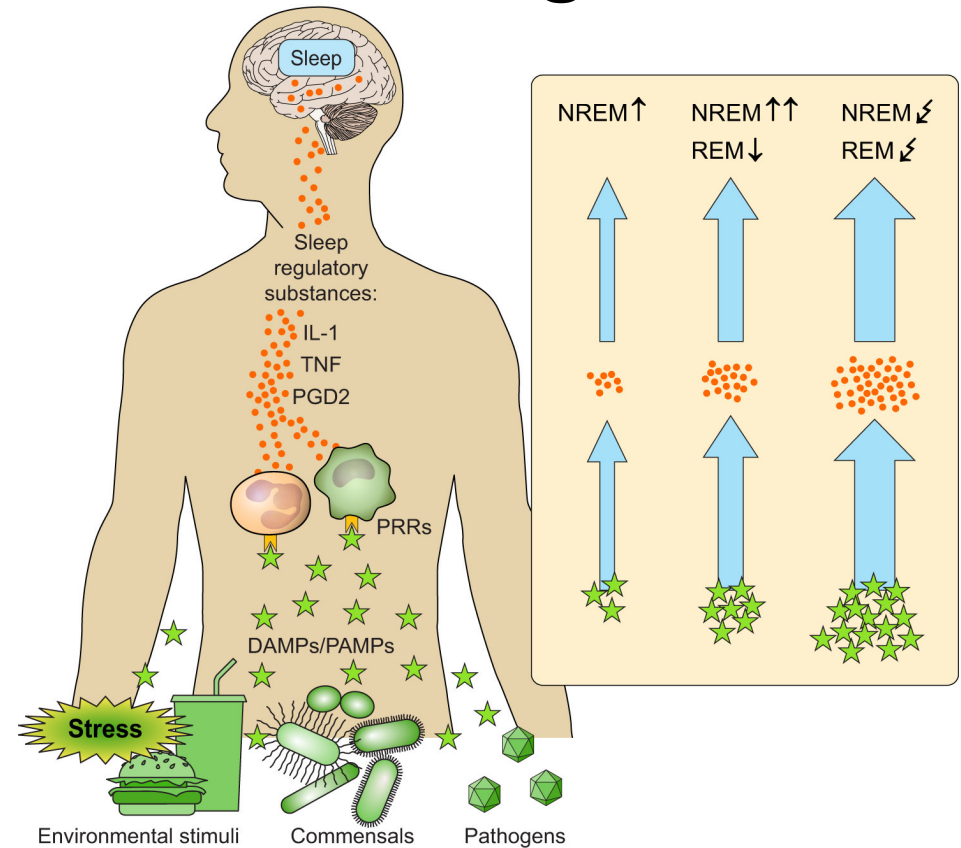
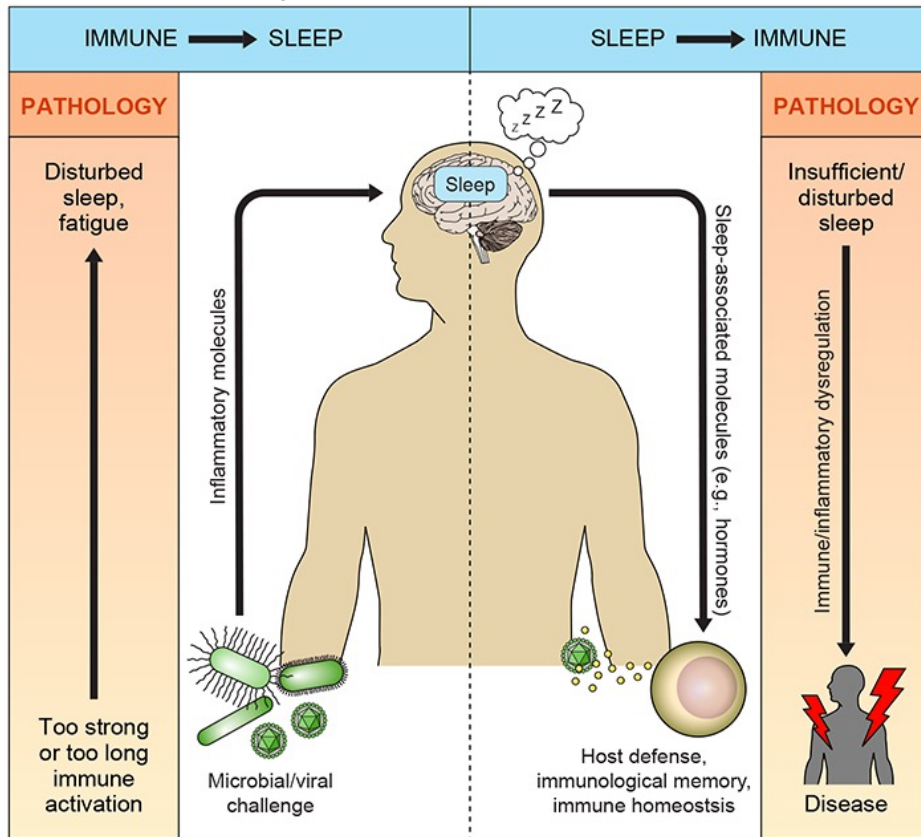


Grandner and Fernandez, *Science*, 2021



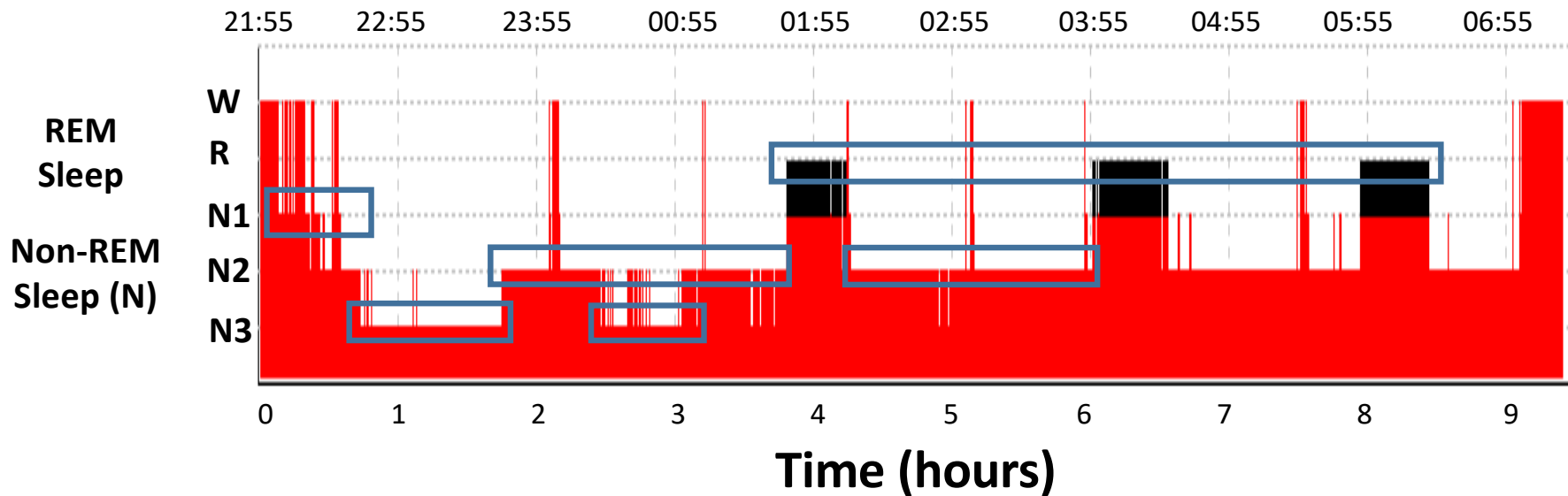


# Bidirectionality of Sleep and Immunity: Likely Contributor to Delirium Pathogenesis



Besedovsky et al., *Phys Rev*, 2019

# Normal Overnight Sleep Macrostructure



N1: Transition from wakefulness to sleep, ~5% TST

N2: Bulk of sleep, 50% TST

**N3: Slow Wave Sleep, 20% TST (declines with age)**

REM: Rapid Eye Movement Sleep, ~25% TST



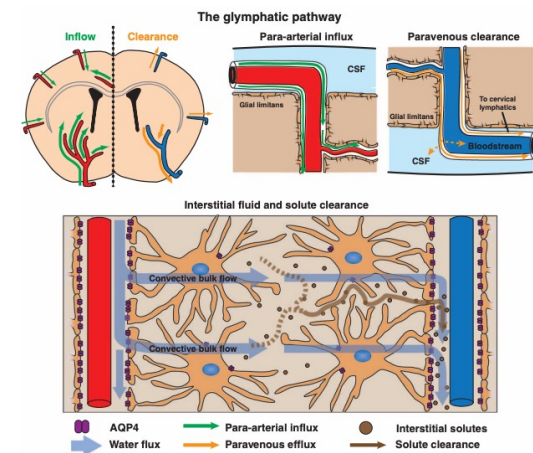
# States of Sleep May Aid in Clearance of AD Pathology

A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid  $\beta$

Jeffrey J. Iliff<sup>1,\*</sup>, Minghuan Wang<sup>1,2</sup>, Yonghong Liao<sup>1</sup>, Benjamin A. Plog<sup>1</sup>, Weiguo Peng<sup>1</sup>, Georg A. Gundersen<sup>3,4</sup>, Helene Benveniste<sup>5...</sup>

+ See all authors and affiliations

*Sci Trans Med*, 2012

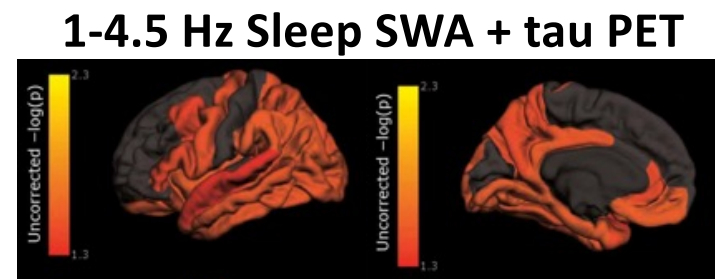


Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer's disease

Brendan P. Lucey<sup>1,2\*</sup>, Austin McCullough<sup>3</sup>, Eric C. Landsness<sup>1</sup>, Cristina D. Toedebusch<sup>1</sup>, Jennifer S. McLeland<sup>1</sup>, Aiad M. Zaza<sup>3</sup>, Anne M. Fagan<sup>1,2,4</sup>, Lena McCue<sup>5</sup>, Chengjie Xiong<sup>5</sup>, John C. Morris<sup>1,2,4</sup>, Tammie L. S. Benzinger<sup>3,4</sup>, David M. Holtzman<sup>1,2,4\*</sup>

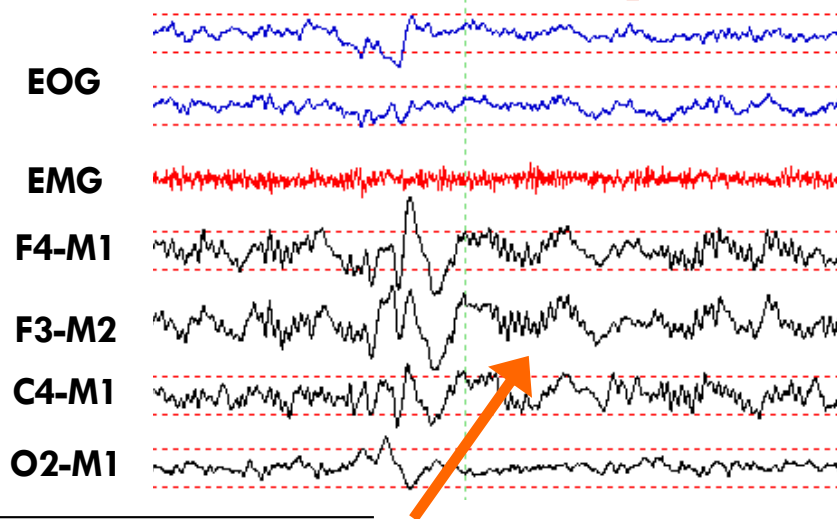


*Sci Trans Med*, 2019



# Sleep: Microstructure and Physiologic Roles

## N2 Sleep

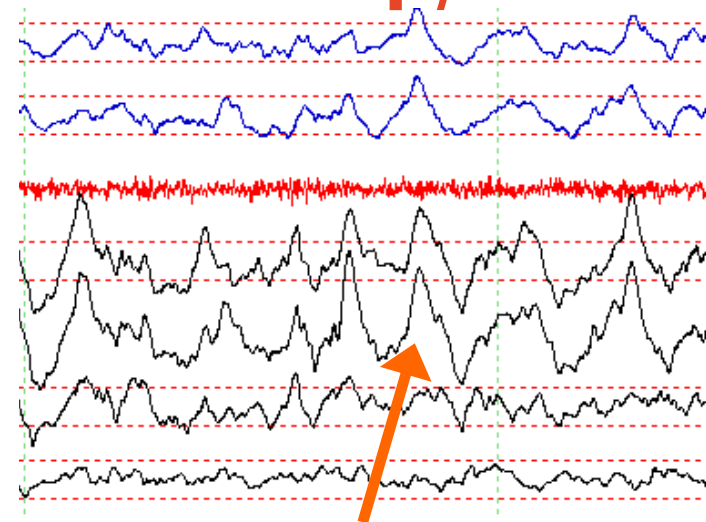


5 seconds

### Sleep Spindles

- Learning and memory
- Facilitate deeper sleep

## N3 Sleep/SWS



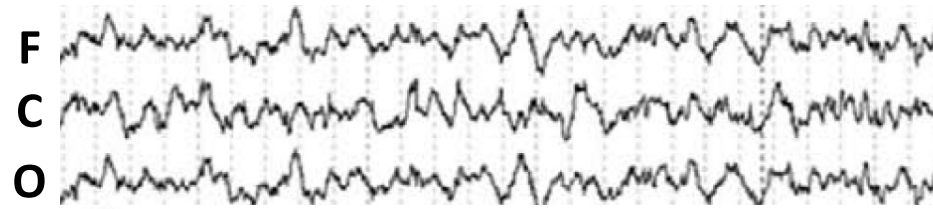
### Delta Waves

- Resetting of synapses
- Neurohumoral homeostasis
- Release of growth hormone
- Glymphatic system function

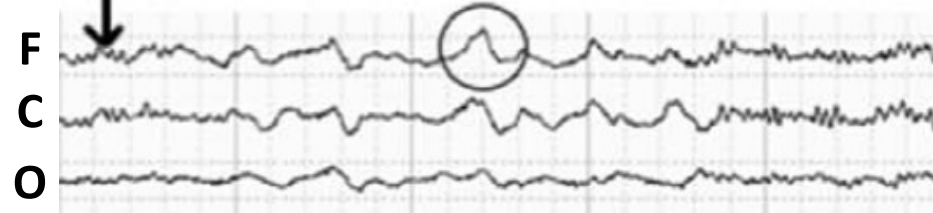


# Pathologic Wakefulness / Atypical Sleep?

“Pathologic Wakefulness”

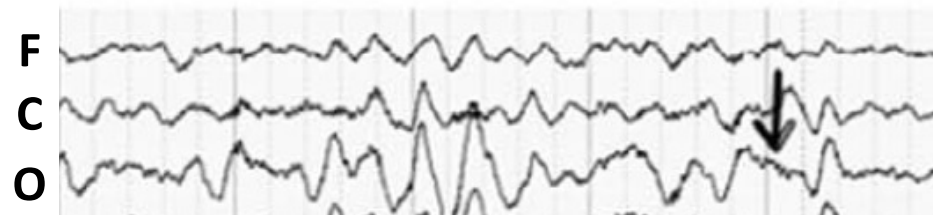


A<sub>t</sub>1

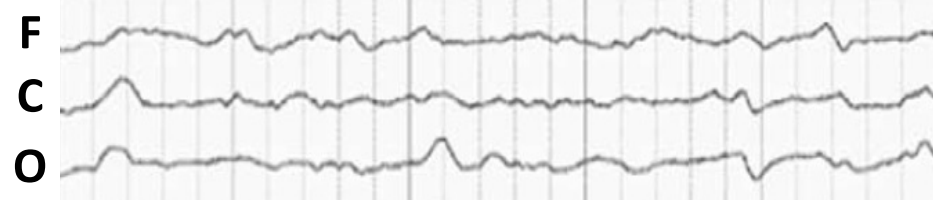


“Atypical Sleep”

A<sub>t</sub>2



A<sub>t</sub>3



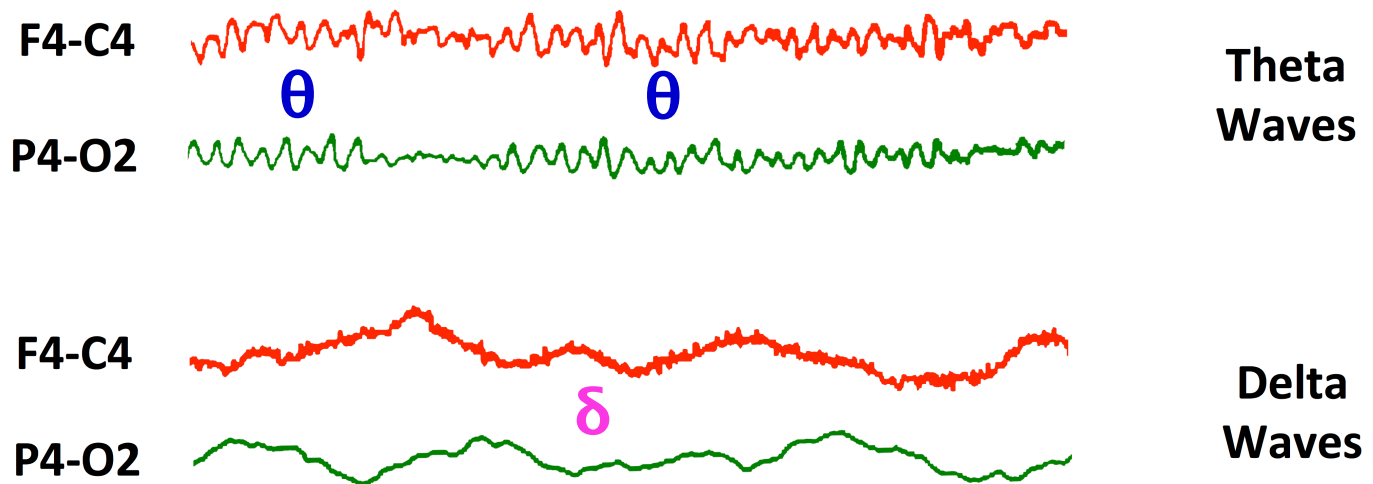
5 sec



Watson et al., 2013

# Do EEG Changes During Delirium Reflect Damage or a Healing Process?"

Escalating  
Severity of Sepsis  
Encephalopathy



*Palanca et al. BJA 2017, Modified Young et al., Clin Invest Med 1990*

# Markers of Sleep Pressure During Wakefulness Are Associated with Delirium Features

**Table. Consistency in Relationships Among Clinical Features of Delirium and Eyes-Closed Relative Alpha Power and Eyes-Open Relative Theta Power**

|                                   | Alpha, eyes closed |         | Theta, eyes open |         |
|-----------------------------------|--------------------|---------|------------------|---------|
|                                   | Occipital          | Frontal | Occipital        | Frontal |
| Delirium presence/<br>absence     | a                  | a       |                  |         |
| Delirium severity                 | b                  | a,c     | b                |         |
| Inattention                       | b                  | b       | b                | b       |
| Disorganized thinking             |                    |         | b                |         |
| Altered level of<br>consciousness |                    |         |                  | d       |
| Recovery over time                | a,c                |         |                  | b       |

*Guay et al., Anest Analg 2022*

Awake Theta:  
**Sleep pressure**

Occipital Alpha:  
**Posterior Dominant Rhythm**



The background of the slide features a faint, light gray ECG (heart rate) line. Overlaid on this are several horizontal red dashed lines, creating a grid-like appearance. The text is centered on the slide.

## Is Delirium a Disorder of Sleep and Wakefulness?

Does delirium consist of intrusions of sleep  
processes into wakefulness to heal ischemic,  
metabolic, or inflammatory insults?





# Approaches to Probe Relationships Between Delirium and Sleep Relationships



Micro Motionlogger Watch  
Leung et al., *J Clin Sleep Med*, 2021



Actigraph GT3XBT  
Maybrier et al., *J Clin Sleep Med*, 2019



Dreem  
Smith et al., *BMJ Open*, 2020

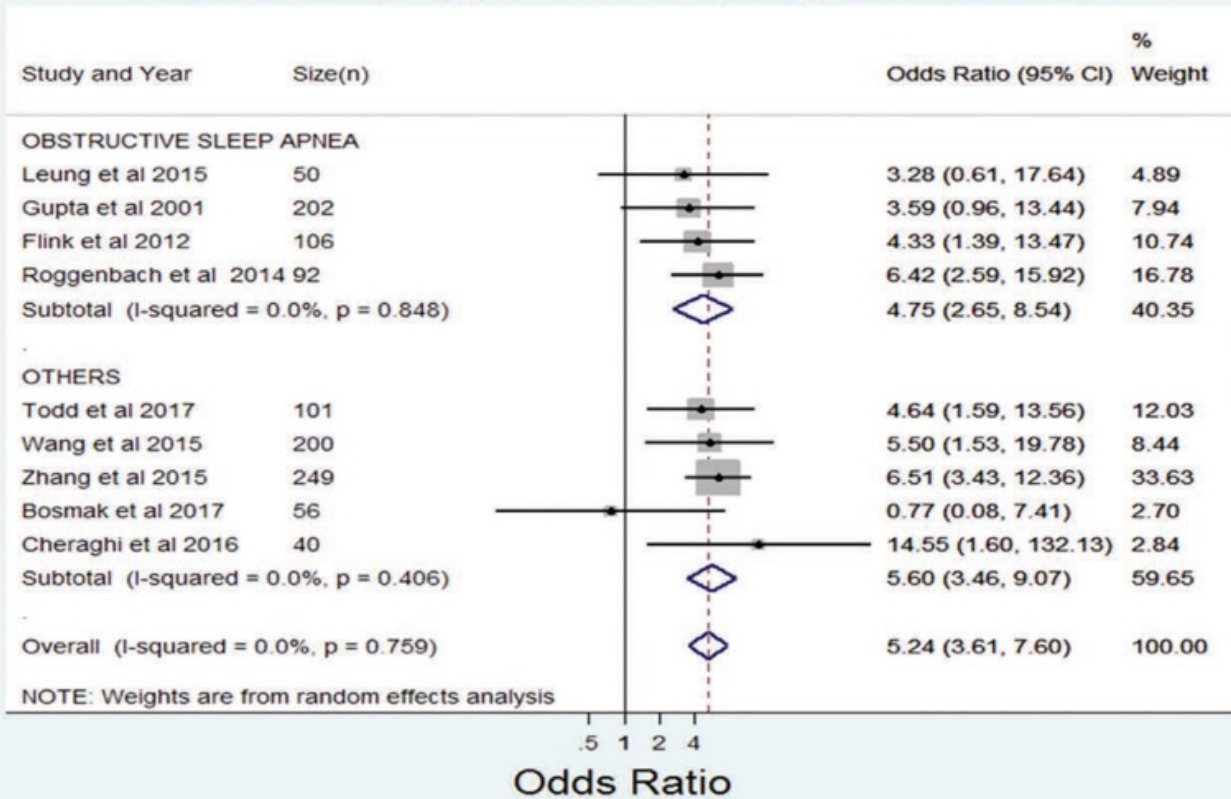


Trackit Sleep Walker  
Oldham et al., *Gen Hosp Psychiatry*, 2021



# Associations Between Sleep Disturbances on Delirium

## A Grouped by Type of Sleeping Disturbance

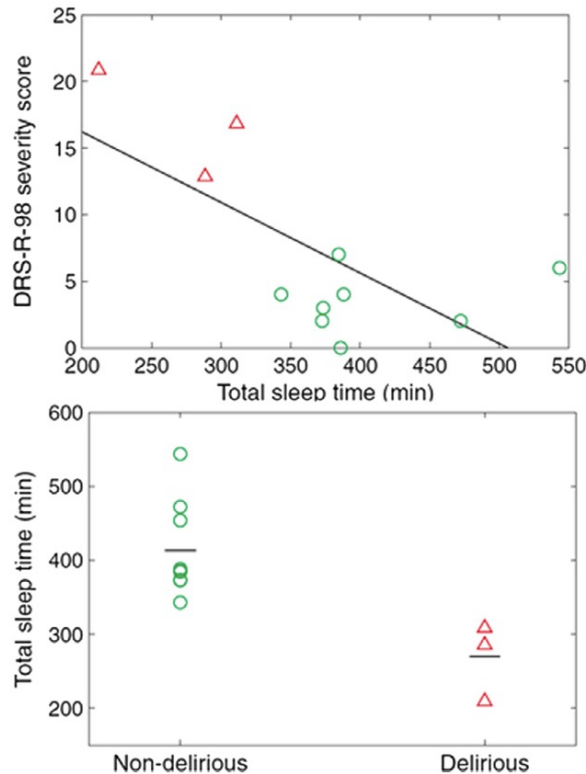


**Preoperative Sleep  
Disturbance:  
~3-5X Risk of Delirium**



# Sleep Structural Measures and Delirium Outcomes

Total  
Sleep  
Time

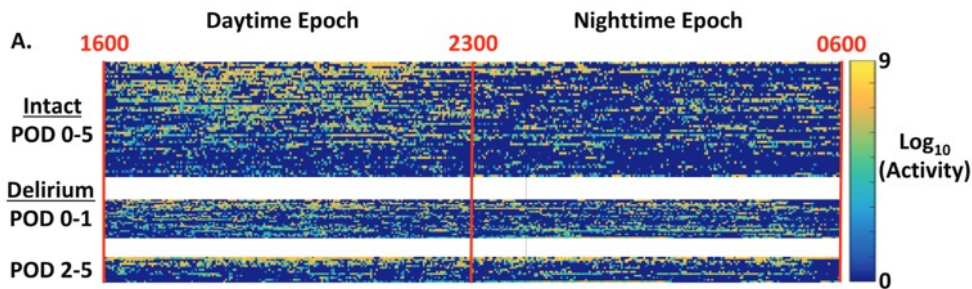


POD 1 after orthopedic surgery. N = 12  
Evans et al., *Clin Neurophysiol*, 2017

Preoperative sleep before surgical AVR. N = 15  
Oldham et al., *Gen Hosp Psychiatry*, 2021

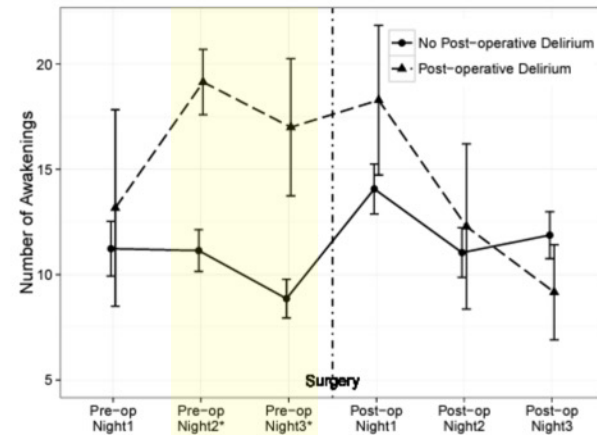


# Actigraphy Measures and Postoperative Delirium Outcomes

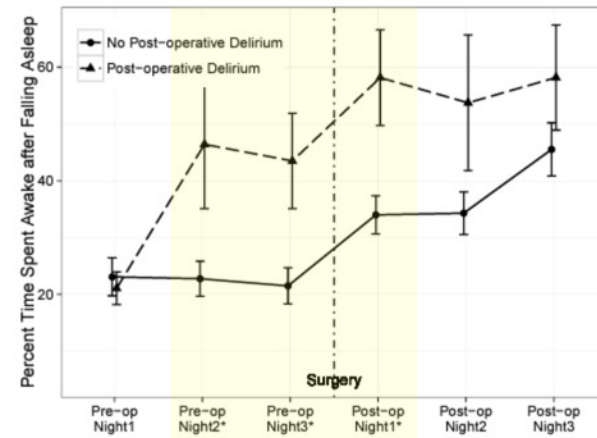


Intact/No Delirium had **greater movement during day relative to night** compared to those with hypoactive delirium

N = 88, postoperative sleep  
Maybrier et al., *J Clin Sleep Med*, 2019



# Awakenings



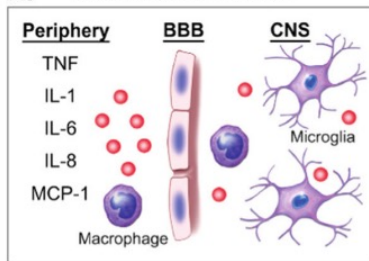
Wakefulness After Sleep Onset (WASO)

Non-Cardiac surgery. N = 50  
Leung et al., *J Clin Sleep Med*, 2021

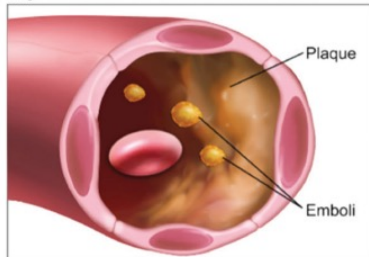


# Contributions of Obstructive Sleep Apnea Revisited

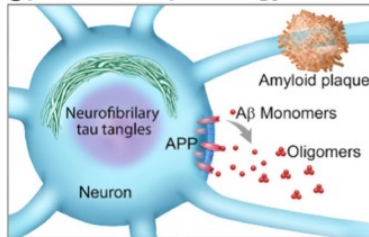
## A. BBB Breakdown and Neuroinflammation



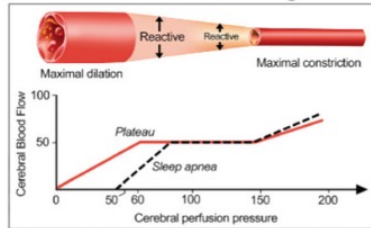
## B. Cerebrovascular Disease



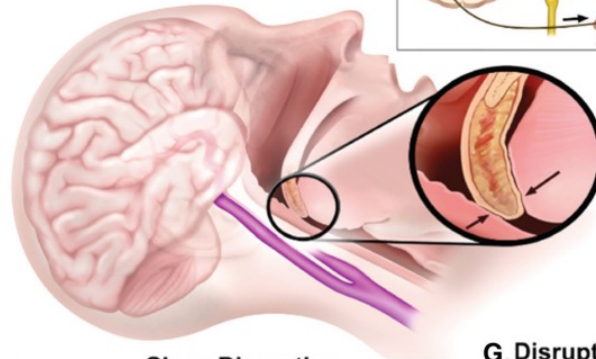
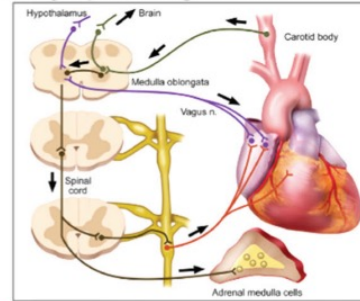
## C. Alzheimer's Disease Neuropathology



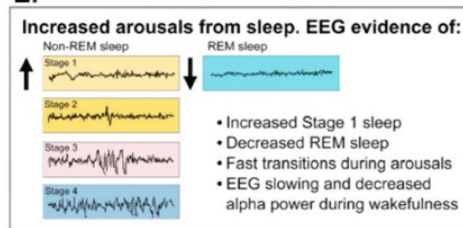
## D. Altered Cerebral Autoregulation



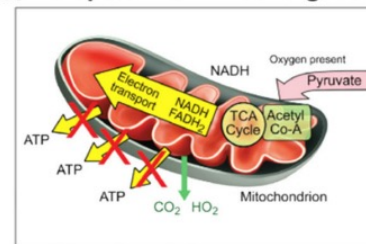
## F. Sympathovagal Imbalance



## E. Sleep Disruption



## G. Disrupted Brain Bioenergetics



“Seven studies have investigated the association between OSA and POD, with mixed results. **There is very limited evidence** that OSA plays a role in postoperative neurocognitive disorders because few studies have been conducted in the perioperative setting.”



# Non-pharmacologic and Pharmacologic Interventions Targeting Sleep

- **Sleep Hygiene** (Meta-analysis: Kamdar et al., 2016)
- **Melatonin/receptor agonists** (Uncertain: Hatta et al., 2014 and 2019; Ford et al., 2020; Oh et al., 2021; Wibrow et al., 2022)
- **Orexin receptor antagonists** (Uncertain: Hatta et al., 2017 and 2019; Jaiswal et al., 2019)
- **Dexmedetomidine** (Promising: Skrobik et al., 2018, Qu et al., 2022)
- **Sleep Slow Wave or Sleep Spindle promotion?**



# A Few of Many Outstanding Questions!

- Do deficiencies in preoperative sleep constitute risk factors for postoperative delirium across a broad population?
- What are the important measures of sleep that are protective factors for conferring protection and mitigating injury?
- What are molecules/neurons/circuits that are involved in delirium pathophysiology and sleep/immune system cross-talk? Can we intervene on sleep microstructure to disrupt the processes?



# Conclusions

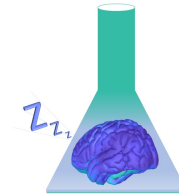
- Postoperative delirium is an important clinical problem.
- Sleep, a fundamental process for promoting healing, is a potential target for improving delirium outcomes. More work is needed to evaluate associations at a larger scale.
- Sleep microstructure has associated physiologic benefits.
- Pharmacologic and non-pharmacologic approaches to improve delirium outcomes through modulation of sleep structure are under development.



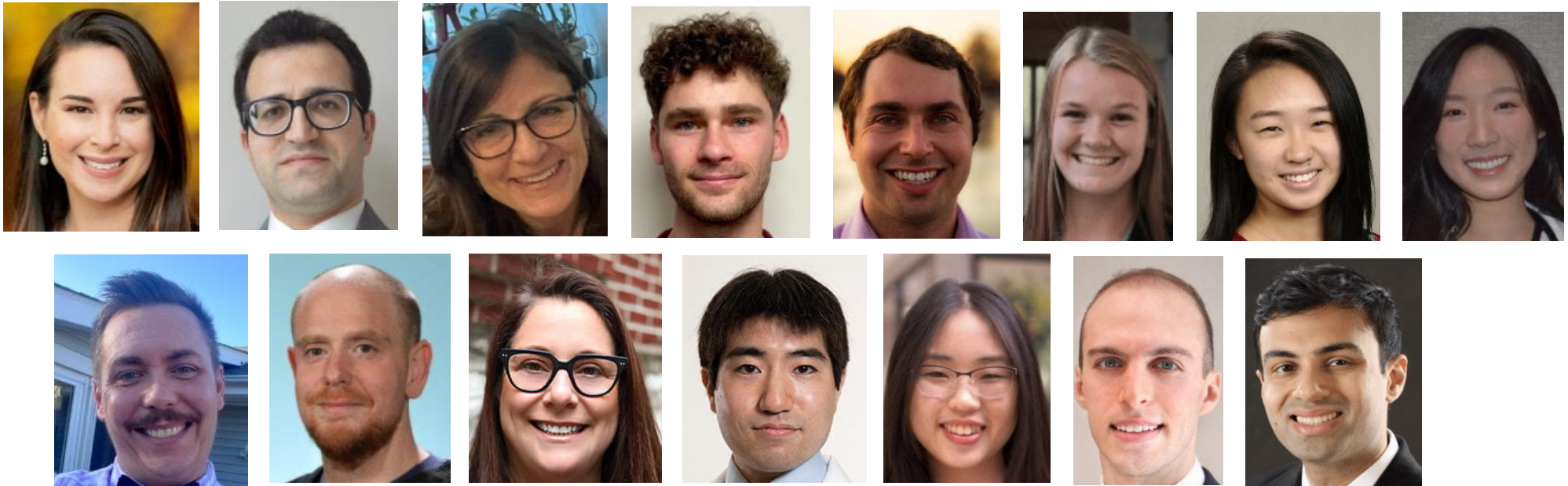


# Thank you! Join us!

*Good sleep = Good wakefulness*



## Sleep Brain Lab



**American Delirium Society SIG on Sleep and Circadian Rhythms?**  
**[palancab@wustl.edu](mailto:palancab@wustl.edu)**