




The Role of Sleep Disturbances on Neuroinflammation in the Developing Brain

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- Society for Anesthesia & Sleep Medicine
- Multi-institutional T32 in Sleep and Genetics
- FAER Research in Fellowship Grant
- Institutional K12
- Johns Hopkins Sommer Scholar Award



I ASKED SANTA FOR A RESEARCH GRANT.



YOU STILL BELIEVE IN RESEARCH GRANTS?

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Principle Concepts: Sleep and Brain Development


Sleep is necessary for:

- Neurosensory development
- Preservation of brain plasticity
- Learning and long term memory



Principle Concept

Evolution of sleep reflects the complex brain maturational process during infancy, childhood and adolescence

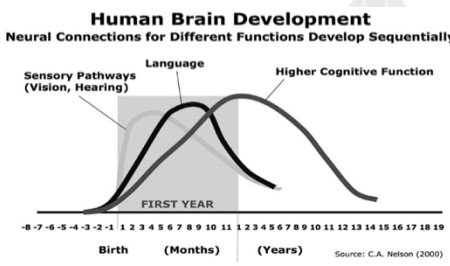


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Sleep and the Developing Brain

Human Brain Development

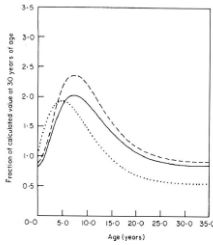
Neural Connections for Different Functions Develop Sequentially



Source: C.A. Nelson (2000)

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Synaptic density, CMRO₂ and delta wave amplitude: parallels



Gamma distribution model of growth in childhood and decline in adolescence

- synaptic density
- delta wave amplitude
- ___ cerebral metabolic rate

Changes in delta power are a reflection of synaptic pruning, brain maturation and reorganization

Feinberg et al, 1990. Journal of Theoretical Biology

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Sleep and Cognition

- Very little research on sleep and cognition in children w/o OSA before school-age period

Child Development, September/October 2013, Volume 84, Number 5, Pages 1940-1950

Sleep and Cognition in Preschool Years: Specific Links to Executive Functioning

Annie Bernier, Mikael H. Beauchamp, and Andréanne Bouvette-Torres
University of Montreal Stephanie M. Carlson
University of Minnesota


Infant sleep at 10 months of age as a window to cognitive development

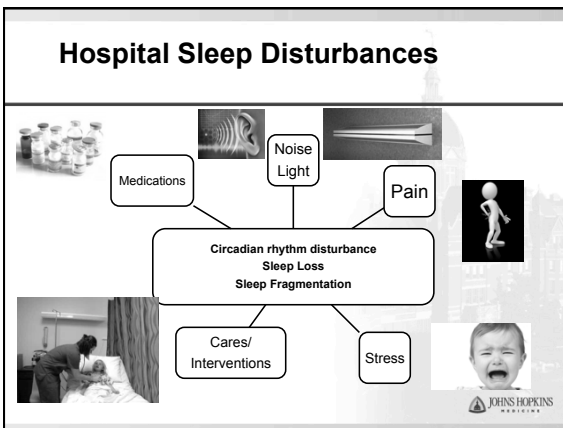
Anat Scheer*

SLEEP-WAKE CONSOLIDATION AND LANGUAGE DEVELOPMENT



Associations Between Sleep-Wake Consolidation and Language Development in Early Childhood: A Longitudinal Twin Study

Walter D'Esposito, PhD¹, Leslie Truitt, PhD², Nadine Fogel, PhD³, Daniela Poff, PhD⁴, Robert E. Trembly, PhD^{1,2,3,4}, Joseph T. Nguyen, MD^{1,2,3,4}, Nicole Biron, PhD^{1,2}





Are they sleeping?




Pediatric Intensive Care and Sleep: Is it a priority?

Sedation, Sleep Promotion, and Delirium Screening Practices in the Care of Mechanically Ventilated Children: A Wake-Up Call for the Pediatric Critical Care Community



Sagar B. Kudchadkar, MD¹; Shresh Yasthi, MD¹; Saanchi M. Parashik, MD¹

- Surveyed 341 pediatric intensivists internationally
- <15% of intensivists in North America aware of any efforts made to optimize sleep of critically ill children in their unit including any of following:
 - Noise reduction
 - Lighting
 - Earplugs/eyemasks
- Opioids and benzos used by 85% for sedation
- <2% screen for delirium


Kudchadkar et al. 2014, Crit Care Med.




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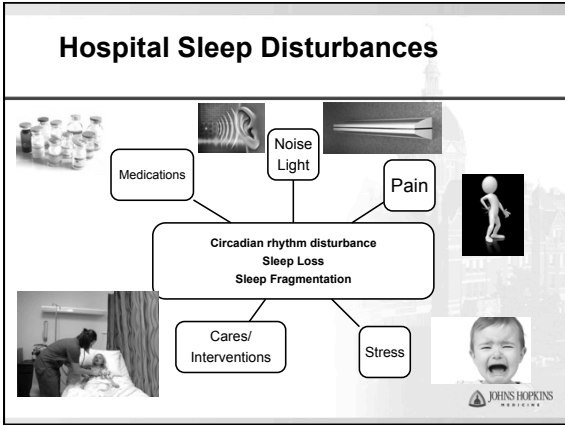


Sleep EEG in critically ill children



Kudchadkar et al., J Clin Sleep Med 2015

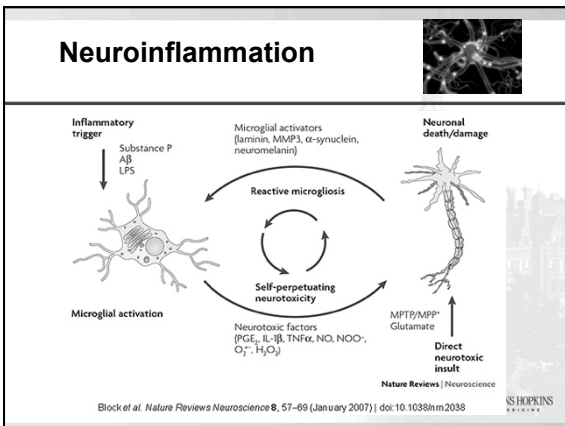




So how do we proceed?

- Sleep is important
- Sleep changes and evolves during infancy and childhood
- Sleep disturbances during infancy and childhood may have negative effects on neurocognitive outcomes

A small image of a brain section showing cellular structures. The Johns Hopkins University logo is in the bottom right corner.




Sleep Disturbance and Neuroinflammation

- Could the negative effects of sleep disturbances during early development be mediated through neuroinflammation?


Sleep disturbance induces neuroinflammation and impairment of learning and memory

Biao Zhu^{1,2}, Yuanlin Dong¹, Zhipeng Xu¹, Heinrich S. Gompf³, Sarah A.P. Ward¹, Zhanggang Xue², Changhong Miao², Yiyang Zhang¹, Nancy L. Chamberlin⁴, and Zhongcong Xie¹

Neurobiol Dis. 2012 December



Sleep and Neuroinflammation




- Sleep disturbance in adults leads to:
 - Microglial activation
 - Altered cytokine expression
 - Impaired performance on vigilance and attentional tasks
 - Learning and memory impairment
- Inflammation compromises the immune privilege of the CNS, and may affect critical phases of brain development.

The role of inflammation in perinatal brain injury



Nat Rev Neurol 2015

Henrik Hagberg, Carina Mallard, Donna M. Ferrero, Susan J. Vannucci, Steven W. Levison, Zinab S. Vester and Pierre Gressens



Neonatal rabbit model of sleep fragmentation

- Why rabbits?
 - Rabbits exhibit human timing of perinatal brain white matter maturation when compared to rodent models
 - Synaptogenesis
 - Microglial presence
 - Myelination

Hypothesis

KEEP CALM AND TEST YOUR HYPOTHESIS

Neonatal sleep disturbances lead to microglial activation and altered cytokine profiles in the neonatal brain when compared to controls.

November 4, 2015

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Sleep fragmentation: Methods

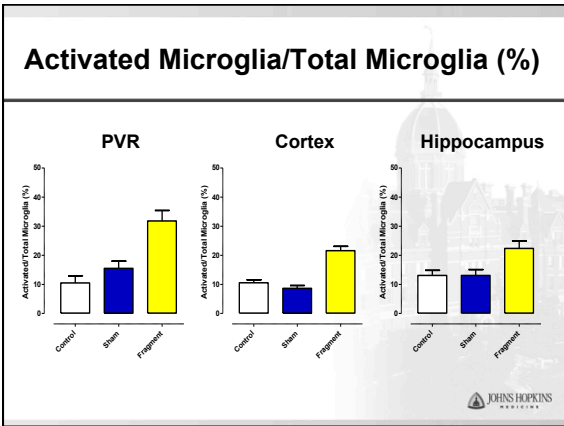
- P3 NZW Rabbits: Control, sham, sleep frag
 - Exhibit human timing of perinatal brain white matter maturation, synaptogenesis, and microglial presence.
- Orbital shaker method
 - 30s on, 90s off; 100 rpm
- Hand fed 3X daily

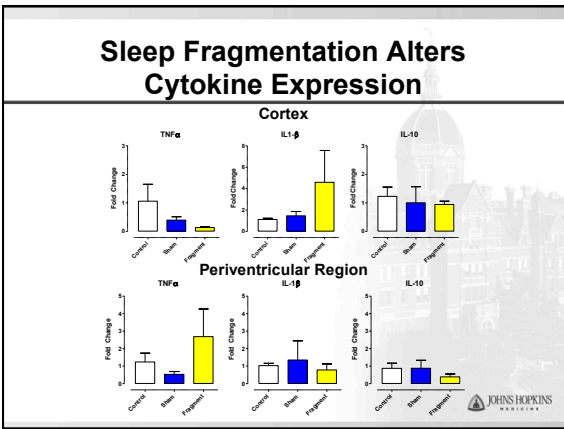
Validation of a novel method to interrupt sleep in the mouse
Christopher M. Sinton^{1*}, Della Kovakkattu², Randal S. Friese³

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Sleep fragmentation activates microglia

	PVR	Cortex	Hippocampus
Fragmented			
Sham			








Conclusions and Future Directions

- Sleep fragmentation at an early age results in microglial activation and altered cytokine expression in the cortex and PVR.
- EEG and spectral analysis will be used to validate the model
- Behavioral analyses will be used to assess neurocognitive function following sleep fragmentation.
- Next steps include evaluation of myelination and potential macrophage infiltration.

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Thank you!

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