Circadian and Sleep Science

Ravi Allada, M.D.
Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td></td>
</tr>
<tr>
<td>Speakers’ Bureaus</td>
<td></td>
</tr>
<tr>
<td>Financial support</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1. 
2. 
3.
Overview

• Sleep in pre-industrial societies
• Sleep in unlearning social biases
• β-amyloid/NREM/hippocampal memory
• REM sleep circuits
• Neuronal firing rate homeostasis
• Bicycle model for circadian clock neuron output
• Circadian clocks and insulin release
• Caffeine and clock phase shifts to light
• Cannabinoids and sleep
Does modern day artificial light exposure affect our sleep?

Theory: Artificial light impairs sleep

Are we actually getting less sleep?

- Actiwatch monitor
  - light, acceleration data
- Finger and abdominal temperature recorded

Dijk and Skeldon. Nature 2015

Yetish et al. Current Biology 2016
Sleep duration is only 6-7 h

- Sleep duration is season-dependent
- Sleep onset is dependent on temperature
- Sleep offset corresponds to light and temperature
- Average time asleep only 5.7–7.1 hr
Pre-industrial societies sleep levels are equivalent to industrial ones

- Sleep in industrial societies is delayed continuing after sunset
- Sleep persists to the end of the night during periods of lowest ambient temperature
- Sleep in industrial societies is not below the level in (some?) pre-industrial societies
- Sleeping out of sync with circadian clocks.....circadian disruption?
- See also Moreno et al, 2015 access to electric light in Amazon reduces sleep
Can “replay” during sleep facilitate unlearning of social biases?

• Cueing selectively activates memory during sleep and facilitates memory consolidation (Oudiette et al 2013, Anthony et al 2012)
• Social biases are inherent and can be unlearned
• Can memory reactivation during sleep contribute?


Hu et al. Science 2015
Unlearning implicit social biases during sleep

Xiaoqing Hu,1,2 James W. Antony,1,3 Jessica D. Creery,1 Iliana M. Vargas,1 Galen V. Bodenhausen,1 Ken A. Paller1*

- 360 face-word pairs, with 180 counter-stereotype target pairs in each type of training
- Correct responses to targets followed by sound-A (gender) or sound-B (race)

Example target pairs:

Math
Counter Gender Bias Training

Sunshine
Counter Racial Bias Training

Hu et al. Science 2015
Cued memory reactivation during sleep increases consolidation of social bias unlearning

Effect is correlated with sleep duration
Effects of cueing persist 1 week later

Hu et al. Science 2015
β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation

Bryce A Mander1, Shawn M Marks2, Jacob W Vogel2, Vikram Rao1, Brandon Lu3, Jared M Saletin1, Sonia Ancoli-Israel4, William J Jagust2,5 & Matthew P Walker1,2

26 cognitively normal older (~75 y) adults receive PIB-PET

Perform word pair memory task

PIB=Pittsburgh compound B for Abeta plaque

1 night of polysomnographically recorded sleep

Repeat word-pair task while in fMRI next day
Levels of PIB in medial prefrontal cortex correlate with less SWA and poor memory retention

Path analysis shows that Aβ effects on SWA mediate memory effects

DVR= Distribution Volume Ratio

Brainstem REM sleep circuitry

- Pons studied extensively (Lu et al 2006)
- Medulla has REM-active neurons (Sapin et al 2009)
  - Causal?

Saper et al. Neuron 2010
Control of REM sleep by ventral medulla GABAergic neurons

Franz Weber¹, Shinjae Chung¹, Kevin T. Beier², Min Xu¹, Liqun Luo² & Yang Dan¹

Is activation of GABAergic neurons in medulla sufficient to induce REM sleep?

A light-sensitive protein from algae

This protein is an ion channel that opens in response to blue light

Take the gene for this protein...

... and insert the DNA into specific neurons in the brain

Neurons communicate by “firing.” This is an electrical signal created by opening & closing ion channels.

So now you can cause neurons to fire just by flashing blue light!

mostlyscience.com  stanford.edu

SLEEP 2016

© Associated Professional Sleep Societies, LLC
Activation of ventral medulla GABAergic neurons activates REM sleep

Neuronal Firing Rate Homeostasis Is Inhibited by Sleep and Promoted by Wake

Authors
Keith B. Hengen, Alejandro Torrado Pacheco, James N. McGregor, Stephen D. Van Hooser, Gina G. Turrigiano

Sleep is gating or counteracting homeostatic plasticity?

Hengen et al. Cell 2015

Mrsic-Flogel et al. Neuron 2007
How Are 24 h Circadian Clocks Coupled to the Control of Pacemaker Neurons that Govern Sleep-Wake Cycles

Cell

A Conserved Bicycle Model for Circadian Clock Control of Membrane Excitability

Authors
Matthieu Flourakis, Elzbieta Kula-Eversole, Alan L. Hutchison, ..., Casey O. Diekman, Indira M. Raman, Ravi Allada

Locomotor activity

Morning peak

Evening peak

ZT0  ZT12

Days

DL  DD

50

SLEEP 2016

© Associated Professional Sleep Societies, LLC
Conservation of Circadian Sleep-Wake Behavior Between Flies and Humans: *period* Gene

**Mutation**
- *PER (S589N)*
- *PER2 (S662G)*

**Normal**
- Wake 6am
- Wake 8am
- Wake 6pm
- Wake 3am
- Wake 7am

**FASPS**
- Wake 6pm
- Wake 3am
- Wake 7am

*per* gene

Graph showing the comparison of sleep patterns between different conditions.
Morning sodium and evening potassium conductances drive membrane potential rhythms

Flourakis et al. Cell 2015
Evolution of Neural Substrates of Sleep-Wake Behavior

Raible and Arendt, 2004
Circadian rhythms operate in the periphery driving insulin release

Lamia and Evans. Nature 2010

Marcheva et al. Science 2010
Pancreatic β cell enhancers regulate rhythmic transcription of genes controlling insulin secretion

Rhythmic Insulin Exocytosis in β Cells

Cycling Genes from β Cells Using RNA seq

Perelis et al. Science 2015
Rhythmic insulin secretion is driven by cycling RNAs

Perelis et al. Science 2015
Caffeine well known for promoting wake

Caffeine also lengthens period in organisms from fungi, flies, to human cells—what about humans?

Protocol
- 13 days of monitoring
- black bars= sleep period
- Grey hashed bars- constant routine
- Sun- exposure to 3000 lux (evening bright light)
- Day 11 received caffeine (double shot of espresso) or 3 hours before bedtime
- Examined melatonin rhythm phase

Burke et al. Science Translational Medicine 2015
Caffeine phase delays the melatonin rhythm

- Bright light phase delays melatonin rhythms
- Caffeine+bright light not different (saturating?)

Burke et al. Science Translational Medicine 2015
Conclusion: Maybe you shouldn’t have another cup

- Caffeine exposure shifts the clock in humans
- Exacerbates phase issues in those (e.g., teens) with delayed phase

Adapted from MedicalDaily.com
Impaired sleep increases appetite and food intake

Impact of sleep loss on appetite similar to cannabinoids
Endogenously produced and can affect the brain

Sleep Restriction Enhances the Daily Rhythm of Circulating Levels of Endocannabinoid 2-Arachidonoylglycerol

Erin C. Hanlon, PhD; Esra Tasali, MD; Rachel Leproult, PhD; Kara L. Stuhr, BS; Elizabeth Doncheck, BS; Harriet de Wit, PhD; Cecilia J. Hillard, PhD; Eve Van Cauter, PhD

--------- 24 h blood sampling  v Hunger, appetite, vigor, affect questionnaires
\downarrow Carbohydrate rich meals  \downarrow Ad lib buffet  \longrightarrow Snacks available in room

<table>
<thead>
<tr>
<th>Normal Sleep (NS)</th>
<th>Restricted Sleep (RS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HABITUATION NIGHT</strong></td>
<td><strong>HABITUATION NIGHT</strong></td>
</tr>
<tr>
<td>NS 1</td>
<td>RS 1</td>
</tr>
<tr>
<td>NS 2</td>
<td>RS 2</td>
</tr>
<tr>
<td>NS 3</td>
<td>RS 3</td>
</tr>
<tr>
<td>NS 4</td>
<td>RS 4</td>
</tr>
</tbody>
</table>

Clock Time

Hanlon et al. Sleep 2016
Sleep deprivation amplifies and extends rhythms in endocannabinoids

Red = restricted sleep; Black = normal sleep; Closed arrows = carbohydrate rich food; Open arrows = acrophase of normal sleep condition

Hanlon et al. Sleep 2016
You Can Now Blame Eating an Entire Pizza on Lack of Sleep

It's science.

Could Sleep Deprivation Be Giving You the Munchies?

Insomnia is a bit like marijuana, reveals study

Not Getting Enough Sleep Can Cause The Munchies, Just Like Smoking Weed
References


