

# Timekeepers of the Brain: Circadian Regulation in Health and Disease

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# Disclosures

No disclosures

# Objectives

Participants will be able to apply circadian principles when evaluating patients with neurological conditions

Participants will be able to evaluate the role of circadian dysfunction in chronic disease and overall health

# Preventive Neurology

- “Brain health”: covers various domains of brain function
- Sleep and circadian rhythms play a central role in optimization of performance
- “Sleep diplomacy”
- Primary prevention: neurologists can contribute to public health education

- Sleep and wakefulness are part of the more basic functions of the brain
- Sleep and circadian rhythms may serve a similar critical role in our health and well-being
- Circadian clocks regulate body temperature, hormone secretion, appetite, alertness, and most basic body functions

- Sleep—enough of it, good quality, and at the right time—is a core determinant of brain health, yet is routinely underrecognized in neurological practice

# AHA suggests 7-9 hrs of sleep for optimal cardiovascular health



- 7-9 hours for adults
- 8-10 hours for ages 13-18 years
- 9-12 hours for ages 6-12 years
- 10-16 hours for ages 5 and younger

# Sleep deficiency:

- You don't get enough sleep (sleep deprivation)
- You sleep at the wrong time of day
- You don't sleep well or get all the different types of sleep your body needs
- You have a sleep disorder that prevents you from getting enough sleep or causes poor-quality sleep

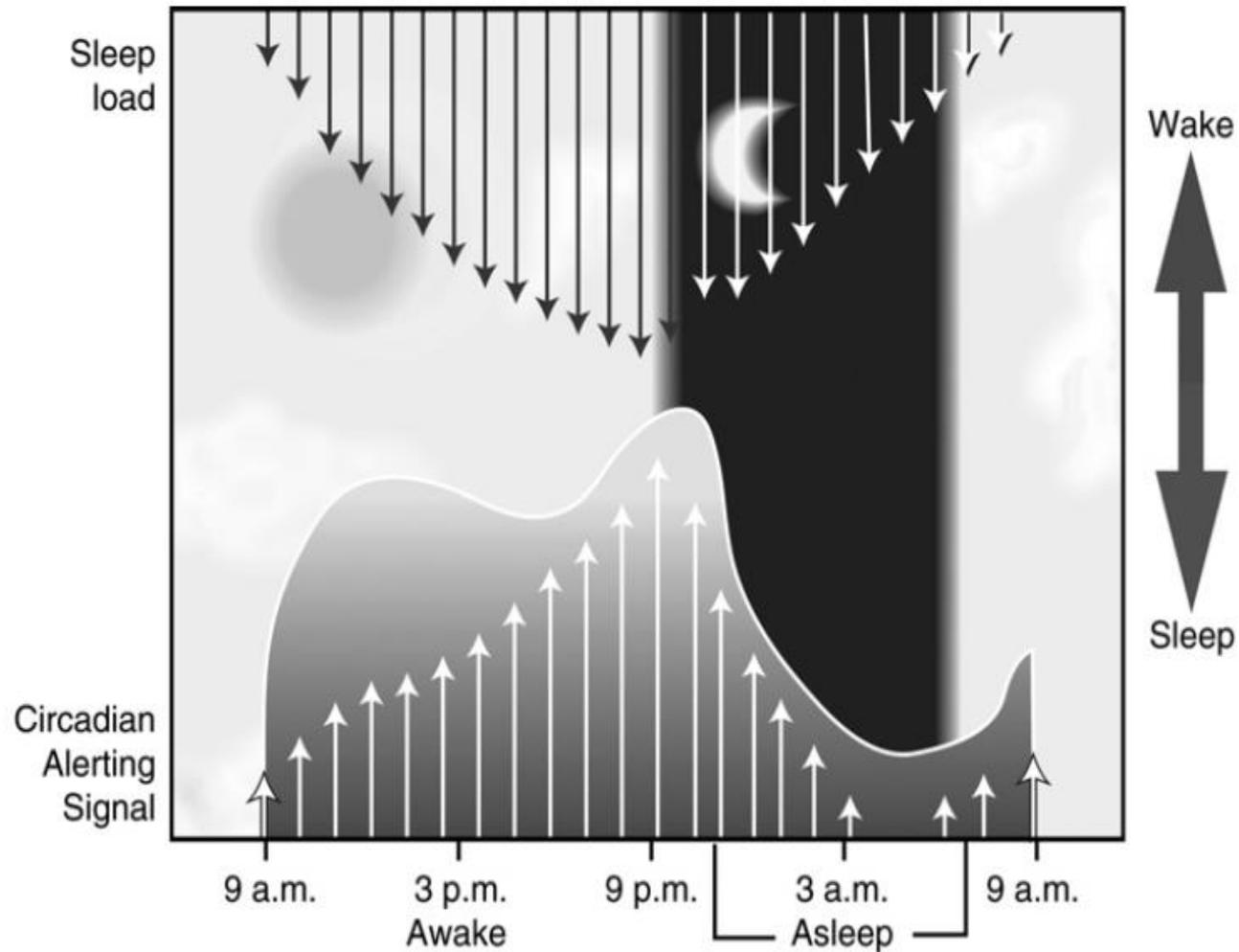
<https://www.nhlbi.nih.gov/health/sleep-deprivation>

# Circadian Health

- Consens, FB. Circadian Rhythm Sleep-Wake Disorders, Continuum. 2023 Aug 1;29(4):1149-1166
- <https://nigms.nih.gov/education/fact-sheets/Pages/circadian-rhythms.aspx#:~:text=Circadian%20rhythms%20are%20physical%2C%20mental,the%20study%20of%20circadian%20rhythms.>

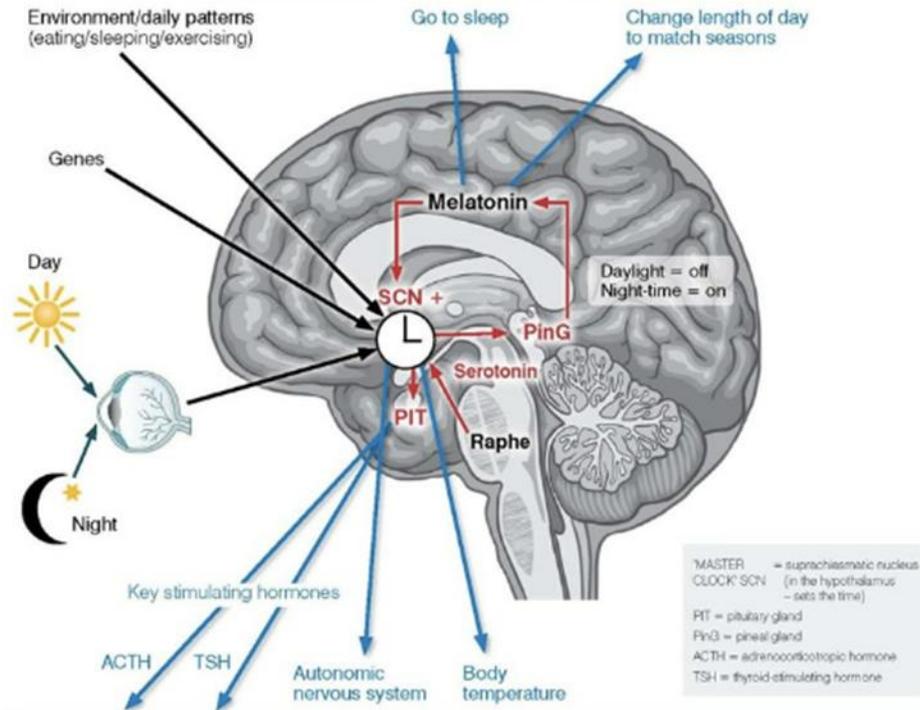
# Public Health

- Circadian rhythm disruption is ubiquitous in our society, as jet lag, social jet lag, shift work, fueled by light pollution
- 99% is affected by light pollution
- 70% works indoor
- 15% works night shift
- African American and Hispanics are twice as likely to be working night shift compared to whites



**Fig. 2.** Two-process model of sleep regulation. (Data from Edgar DM, Dement WC, Fuller CA. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* 1993;13:1065–79.)

## Setting the 24-hour circadian rhythm



ORGAN LEVEL							
Adrenal gland	Thyroid gland	Heart	Pancreas	Liver	Fat	Muscle	Gut
cortisol	thyroid hormone		insulin	glycogen	lipid metabolism		

Food and activity

### DAY

#### Muscle

- Fatty acid uptake
- Glycolytic metabolism

#### Fat

- Lipogenesis
- Adiponectin production

#### Liver

- Glycogen synthesis
- Cholesterol synthesis
- Bile acid synthesis

#### Pancreas

- Insulin secretion

### NIGHT

#### Muscle

- Oxidative metabolism
- Lipid catabolism
- Leptin secretion

#### Liver

- Gluconeogenesis
- Glycogenolysis
- Mitochondrial biogenesis

#### Pancreas

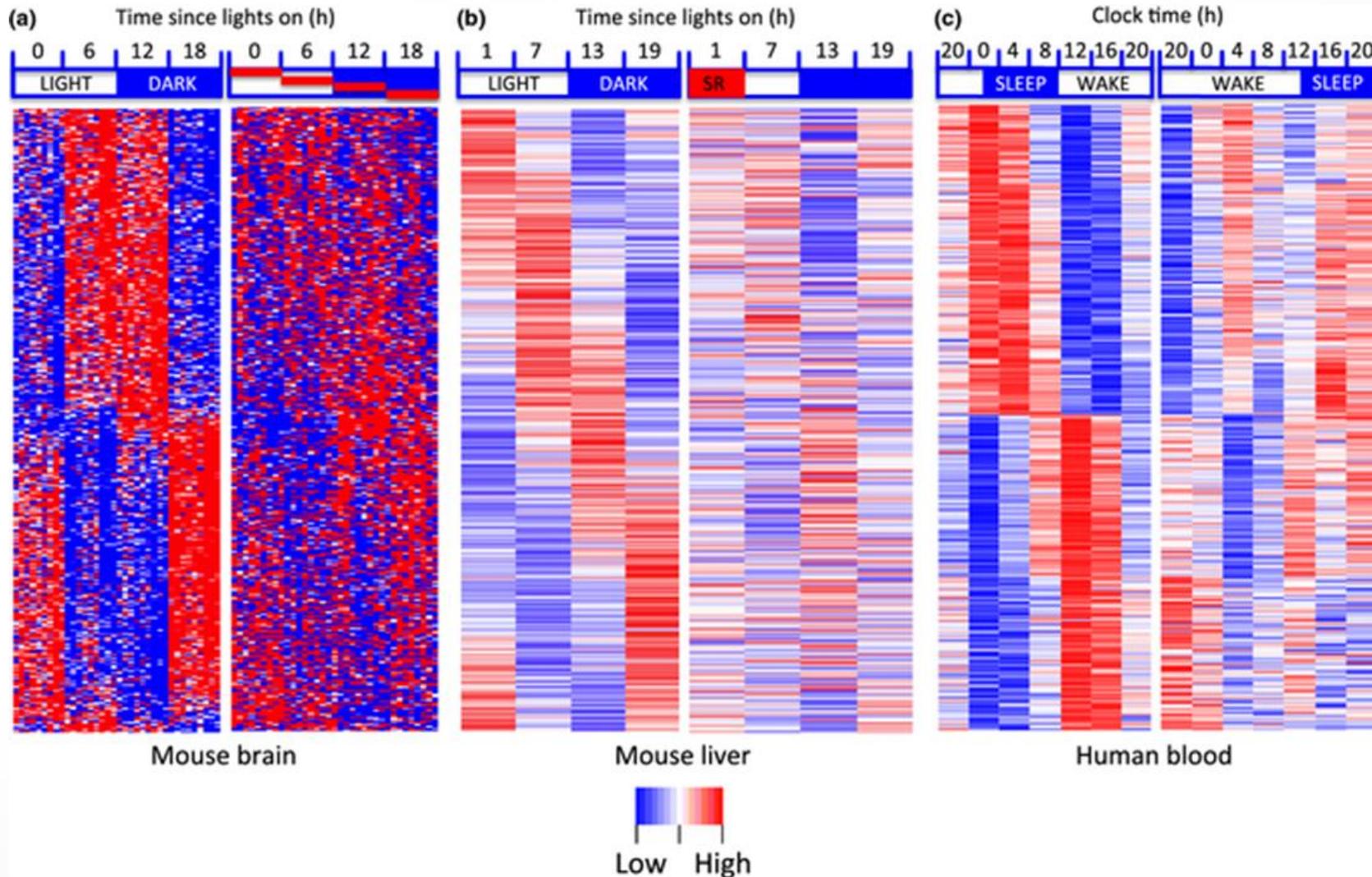
- Glucagon secretion



# Zeitgebers (“time givers”)

- Include light (the main zeitgeber), temperature, exercise, food intake and timing, and social activities
- Those inputs have different oscillations in individual tissues: the external stimuli involved in reprogramming include sleep deprivation, aging, the timing of food, and a high-fat diet

# How sleep and wakefulness influence circadian rhythmicity: effects of insufficient and mistimed sleep on the animal and human transcriptome



When sleep is displaced to the daytime:

- 97% of rhythmic genes become arrhythmic
- 1/3 of all genes show changes in temporal expression profiles

- Circadian misalignment increases CVD risk, and has been associated with increased risk of cancer, autoimmune disease, psychiatric disorders

- Multi-Ethnic Study of Atherosclerosis (MESA) examined circadian misalignment and cardio metabolic risk: increased perceived stress and depression, a higher 10-year risk of cardiovascular disease, greater risk for obesity, hypertension, and diabetes, and higher fasting glucose hemoglobin A1C levels

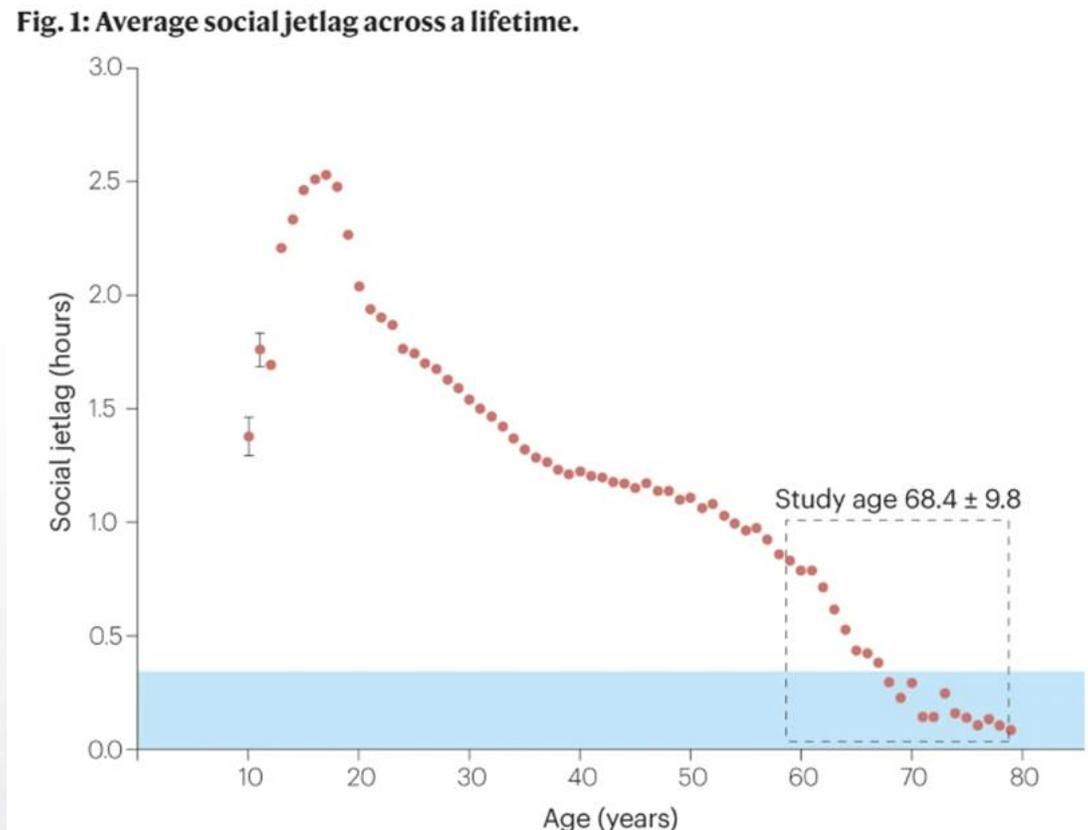
- Female nurses who worked night shifts for over 30 years displayed a 36% increased relative risk of breast cancer
- Men with a rotating shift schedule have a 20% higher risk of developing prostate cancer compared with those who have a fixed night shift schedule



Figure 5. Detrimental effect of circadian disruption on overall survival in patients with distinct cancer types at an advanced or metastatic stage. Actual survival rates at 2 years according to circadian robustness (white boxes) or disruption (grey boxes) based on circadian patterns in cortisol (three studies on the left) or rest-activity (two studies on the right). For each study, survival outcomes differed with statistical significance independently of other prognostic factors. Redrawn with data from (64,65,67,68,85,118). CRC = colorectal cancer; MBC = metastatic breast cancer; NSCLC = non-small-cell lung cancer; RCC = renal cell carcinoma.

# Social Jetlag

- Sleep patterns differ workdays/days off due to social life or work



- Circadian disruption increases the risk for neurologic disorders across the lifespan: has a negative effect on cerebrovascular disease, epilepsy, pain, migraine, multiple sclerosis, neurodegenerative disorders, and neurodevelopmental disorders

- Preclinical and clinical studies have correlated circadian disruption with the accumulation of neurotoxin proteins and neurodegeneration itself

- Less robust and delayed circadian rest/activity rhythms, measured with actigraphy, were associated with subsequent mild cognitive impairment and dementia in a study of older women

- the importance of good sleep in the context of glymphatic waste clearance has emerged as a novel therapeutic target for sustaining brain health

Mestre H, Mori Y, Nedergaard M. The Brain's Glymphatic System: Current Controversies. *Trends Neurosci.* 2020 Jul;43(7):458-466. doi: 10.1016/j.tins.2020.04.003. Epub 2020 May 15. PMID: 32423764; PMCID: PMC7331945.

- Greater N3 activity and higher sleep efficiency may protect against increases in brain A $\beta$  accumulation
- Less N3 sleep has been associated with smaller brain volumes
- More fragmented and rest/activity rhythms have been tied to brain A $\beta$  deposition and greater medial temporal lobe atrophy

# Interventions

- Professional sports:
- Association between the winning percentages and the number of time zones traveled for the away evening games, with a clear disadvantage for the teams travelling westward.
  - NBA ( $F_{2,5908} = 16.12, P < 0.0001$ )
  - NHL ( $F_{2,5639} = 4.48, P = 0.011$ )

# Interventions

- In Parkinson's, timed light therapy improved daytime sleepiness, sleep quality, daily physical activity levels, and Total Unified Parkinson's Disease Rating Scale score
- In AD, morning bright light therapy ( $\geq 2,500$  lux) improves consolidation of the rest/ activity rhythm, increases nighttime sleep and daytime wakefulness, and improves evening agitation

# Recommendations

- Go to sleep and wake up at the same time every day!
- NO light in the eyes before or during the night: set blue light filter on screens ahead of bedtime (or wear glasses)
- Be exposed to bright light in the morning

# Recommendations

- Don't forget to ask your patients about their sleep habits: quantity, quality and timing of sleep.. and don't forget to check on your own sleep health
- Don't forget to think how sleep/wake cycles and circadian rhythms could affect the results when reviewing a paper...

# Conclusions

- The misalignment of circadian clocks has deleterious consequences for our health
- Improvement and treatment of sleep and circadian rhythms problems could have a significant impact on your patient outcomes and health
- Advanced understanding of the role of circadian rhythms, including chronotherapeutic interventions, could have a tremendous potential to improve human health

# Educational resources

- American Academy of Sleep Medicine
- <http://sleepeducation.org/>
- <http://healthysleep.med.harvard.edu/healthy/getting/overcoming/tips>
- <https://www.nhlbi.nih.gov/health-topics/education-and-awareness/sleep-health>
- <https://www.cdc.gov/sleep/index.html>
- National Sleep Foundation <https://www.thensf.org/>



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# Questions

