Circadian rhythms and fatigue

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Disclosure
This certifies that I, Elizabeth B Klerman, have the following financial relationships that may be relevant to the subject matter of this presentation.

For 2019-present:
Consulting: Circadian Therapeutics, National Sleep Foundation, Sanofi-Genzyme
Other: Partner owns Chronsulting
Sleep and Circadian Rhythms

Daily Changes in Physiology and Behavior

- Deepest sleep: 02:00
- Lowest body temperature: 04:30
- Sharpest rise in Blood Pressure: 06:45
- Melatonin secretion stops: 07:30
- Prothrombotic factors, bowel movement likely: 08:30
- Highest testosterone secretion: 09:00
- High alertness: 10:00
- Fastest reaction time: 15:30
- Best coordination: 14:30
- Greatest cardiovascular efficiency and muscle strength: 17:00
- Highest Blood Pressure: 18:30
- Highest body temperature: 19:00

Adapted from: Smolensky M, Lamberg L. The Body Clock Guide to Better Health. Courtesy of Dr. Phyllis Zee
Roles in Physiology and Pathophysiology

Sleep or circadian rhythms can be a(n)....

- **Exposure**: sleep/wake state and endogenous circadian rhythms cause changes in hormone levels, alertness level, feeding/fasting, posture
- **Moderator**: sleep and endogenous circadian rhythms moderate response to vaccines, medications or other stimuli, and relative timing of events (e.g., labor/delivery, heart attacks)
- **Mediator**: sleep mediates learning
- **Outcome**: exposure to caffeine reduces sleep

- Is sex/gender an exposure, moderator, and/or mediator of circadian and sleep effects/outcomes?
- Are health disparities an exposure, moderator, mediator, and/or outcome of circadian and sleep effects/outcomes?
Sleep duration and timing affect results

• Short sleep duration (immediate or long-term) or shiftwork:
  • Increased metabolic, cardiovascular, neurodegeneration, mood disturbances
  • Increased errors and accidents
  • Poor performance
  • Expected increased fatigue

• Sleep timing
  • Nighttime vs daytime sleep
Circadian rhythms affect results

- Rhythms in Control condition
- Intervention level at one time is same as Control level at another time.
- Intervention has different magnitude of result at different times
- If intervene during Dark, may not see differences between groups (i.e., no Intervention effect)
- If intervene at all times (Light and Dark), result may be affected by relative # of samples at each Timepoint
  -> Affects sample size required

Data from a study of Intervention and Control conditions
Note: Dark is ACTIVE time of rodents
Caveat: Circadian vs. Diurnal distinction

- Most studies of “circadian” rhythms are actually of diurnal rhythms.
- Circadian: endogenous ~24-hour rhythms/oscillations
- Diurnal: circadian plus evoked/masked from:
  - Activity/rest
  - Wake/sleep
  - Posture
  - Eating/fasting
  - Social interactions
  - Light levels
- Behaviors and associated changes may affect peripheral oscillators (e.g., in liver, heart)

Czeisler & Klerman Recent Prog Horm Res 1999
Two major determinants of physiological function *

1. Biological time of day (circadian rhythms)

2. Sleep/wake homeostasis:
   - Consecutive waking hours (short-term homeostasis)
     ➢ Includes sleep inertia
   - Multi-night sleep duration (long-term homeostasis)
   - + Non-linear interaction with circadian system

* approx. hourly timescales
A Protocol to separate Endogenous (circadian) and Exogenous (sleep/wake) Effects on Observed Rhythms

Forced desynchrony (FD) protocol

- Imposed desynchrony between sleep-wake schedule and output of the circadian pacemaker
- Sleep and wakefulness are be distributed evenly over the entire circadian cycle
- Analyze relative to circadian timing and relative to length of time awake or asleep

Dijk & Czeisler Neurosci Lett 1994
Non-linear interactions of circadian and homeostatic (sleep or wake dependent) measures on amount of Wake within a sleep episode

Dijk and Czeisler Neurosci Lett. 1994
Fatigue related mood scales from a FD protocol

• Healthy participants
  • No medications with no sleep disorders
  • Ages 18-35

• Forced desynchrony protocols
  • 3 different cycle lengths: 20 hr, 28 hr, 42.84 hr
  • 2 different wake: sleep ratios: 1:2 (8 hrs sleep/24 hrs); 1:3.3 (5.6 hr sleep/24 hours)

• Visual analog scales given ~ 2 hourly when participant awake
  • Four scales have some “fatigue” related words
Sleepy-Alert

**Homeostatic**

**Circadian**

- 20.0 hr
- 28.0 hr
- 42.85 hr

Wake Duration (hr)

0 = CBT min = ~5 am in entrained conditions

Circadian Time (hr)
Sleepy Alert in 3D

Early morning

Late afternoon

T=42.85, 1:3.3 ratio
Other fatigue related Mood measures; Homeostatic and Circadian
Conclusions:

• Self-reported fatigue in normal young adults depends on:
  • Length of time awake
  • Circadian time (phase)
  • Non-linear interaction of these two
  • -> consider night/shift workers (e.g., healthcare, security)

• May be different
  • Pharmaceuticals involved
    • Caffeine or other alertness promoting
      • Wyatt et al SLEEP 2004. Caffeine group reported MORE sleepy than Control group
    • Sleep promoting
    • Prescription meds
• Older individuals
• Specific pathophysiologies
Strong Recommendations for ALL future work

- Time of events recorded:
  - Intervention (e.g., questionnaire)
  - Sample taken

- Time of events included in study design
  - Nocturnal vs diurnal animals
  - Intervention/samples at all time of day

- Time of events included in analyses
  - If not in study design, check for bias in data collection.

- Sleep metrics include duration, timing, sleep disorders (presence, severity), chronotype

- Sleep metrics recorded:
  - Timing/duration
    - of prior sleep episode (may not be at night)
    - Habitual (may vary across days)
  - Length of time awake before intervention/sample taken

- Sleep metrics included in study design
  - Sleep duration/timing – recorded? Controlled?
  - Sleep disorders – screened/recorded?

- Sleep metrics in analyses
  - If not in study design, check for bias in data collection.