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Beyond the Symptom: The Biology of Fatigue

September 27 – 28, 2021

Circadian rhythms and fatigue

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Disclaimer and Disclosures

Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

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

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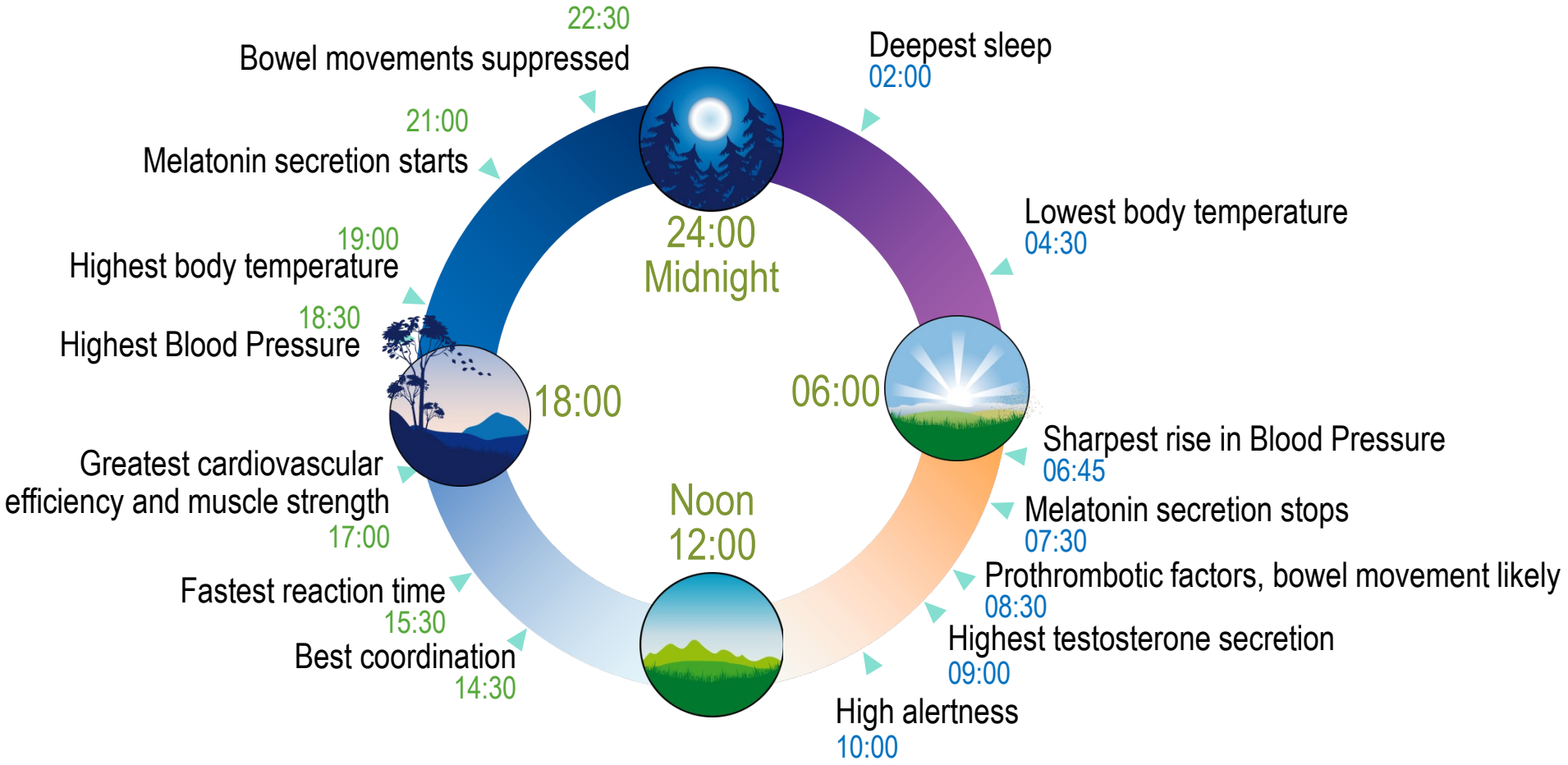
Sleep and Circadian Rhythms
Daily Changes in Physiology and Behavior



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?

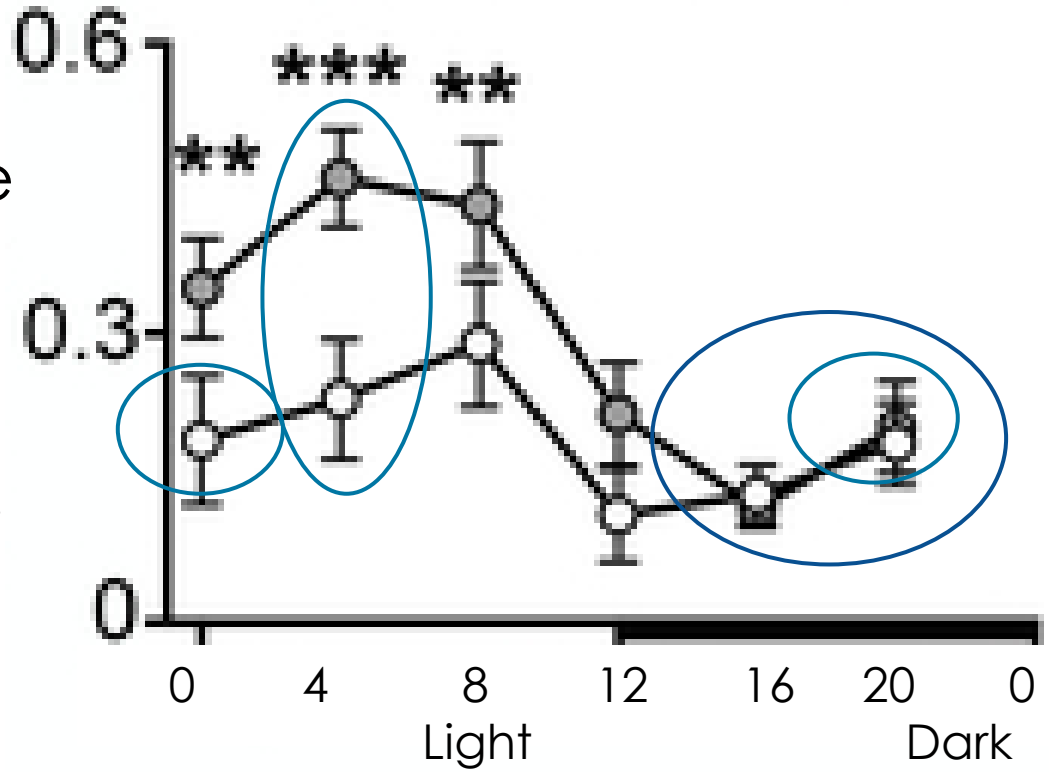
Sleep duration and timing affect results

- 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

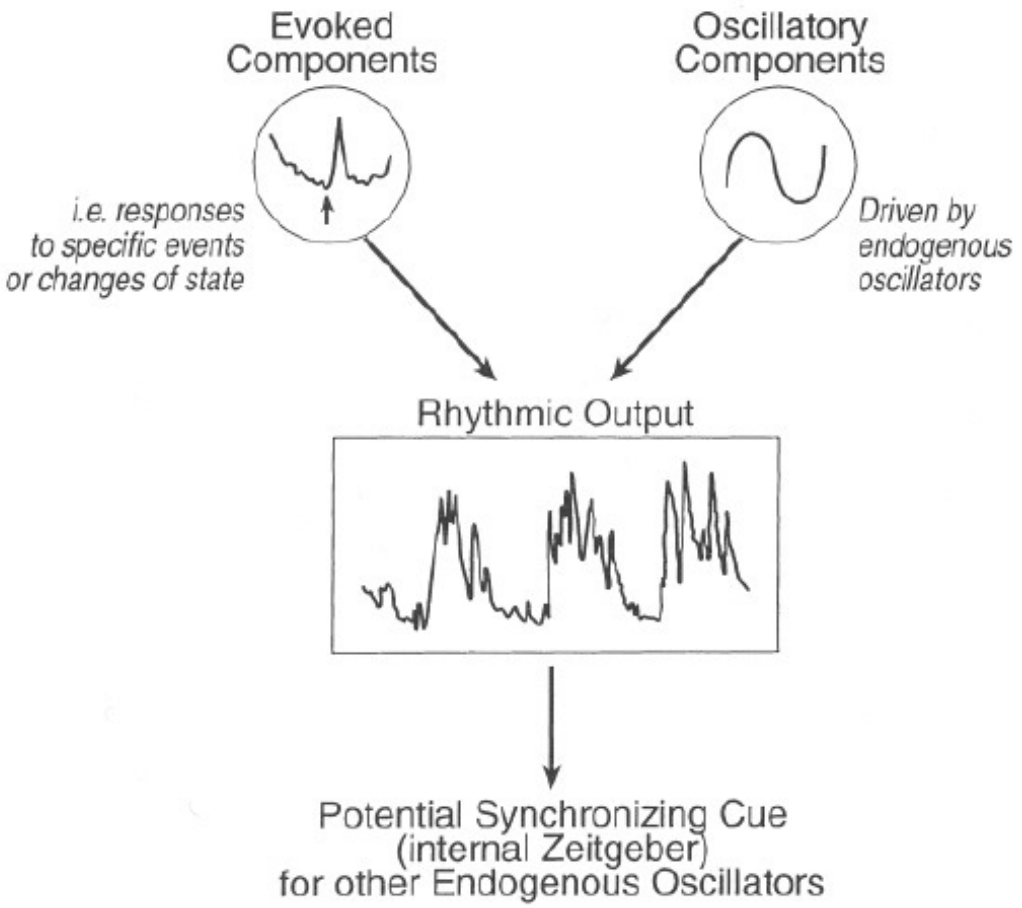


Adapted from McAlpine *Nature* 2019

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)



Endogenous Circadian
+
Evoked
Components

Observed (Diurnal) Output

Czeisler & Klerman *Recent Prog Horm Res* 1999

Two major determinants of physiological function *

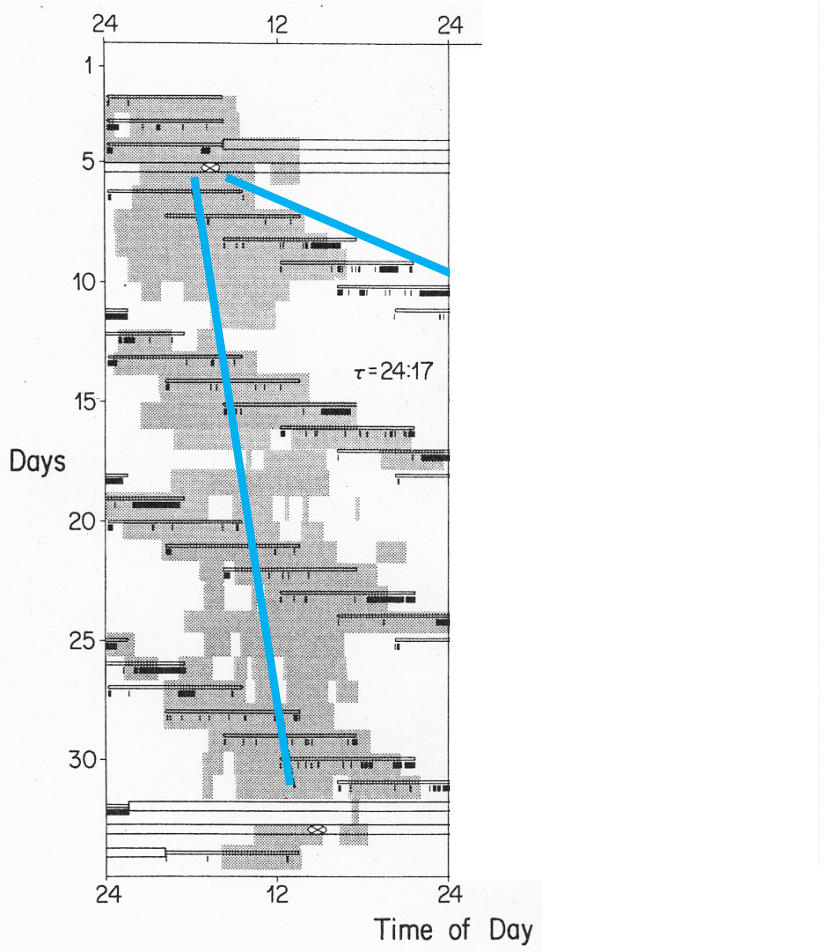
1. **Biological time of day (circadian rhythms)**
2. **Sleep/wake homeostasis:**
   - Consecutive waking hours (short-term homeostasis)
     - ➢ Includes sleep inertia
   - Multi-night sleep duration (long-term homeostasis**)**
   - + Non-linear interaction with circadian system

* approx. hourly timescales

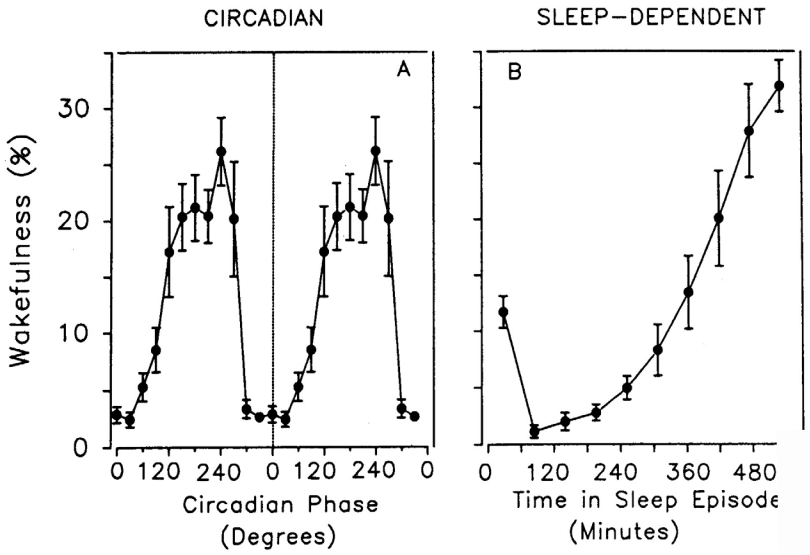
A Protocol to separate Endogenous (circadian) and Exogenous (sleep/wake) Effects on Observed Rhythms

Forced desynchrony (FD) protocol

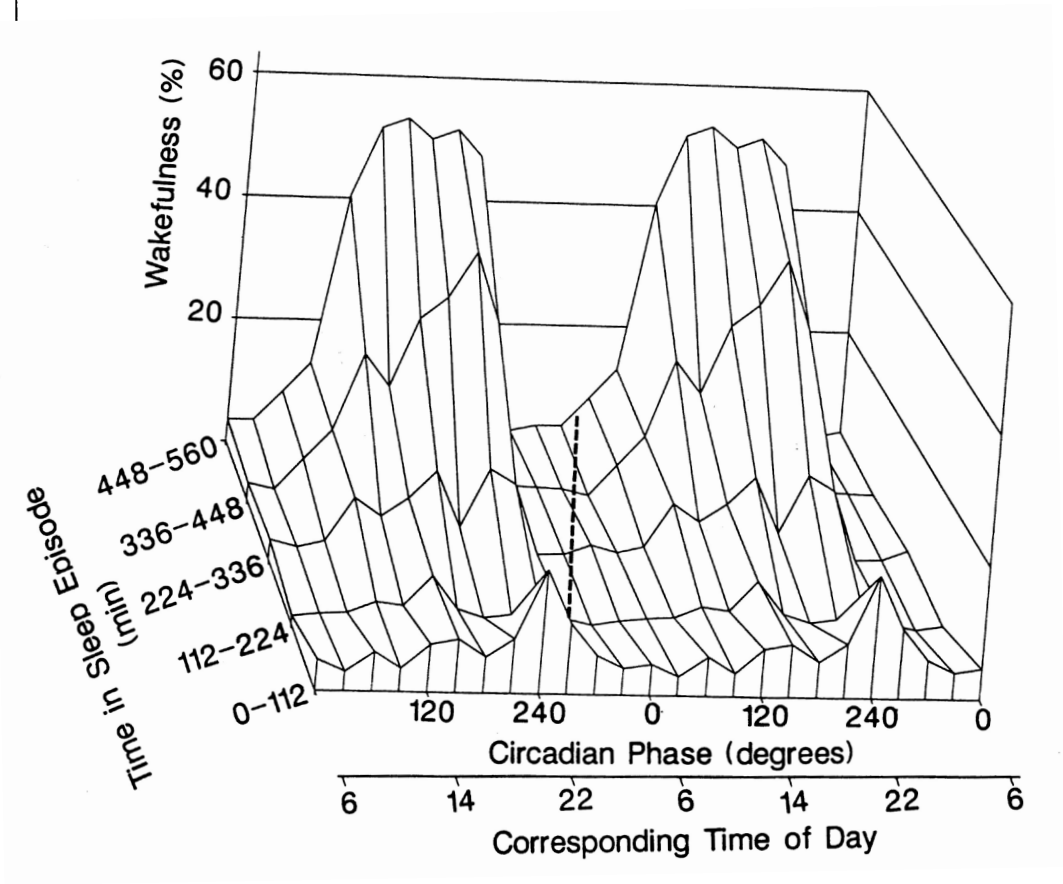
- Imposed desynchrony between sleep-wake schedule and output of the circadian pacemaker
- Sleep and wakefulness are be distributed evenly over the entire circadian cycle
- Analyze relative to circadian timing and relative to length of time awake or asleep



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

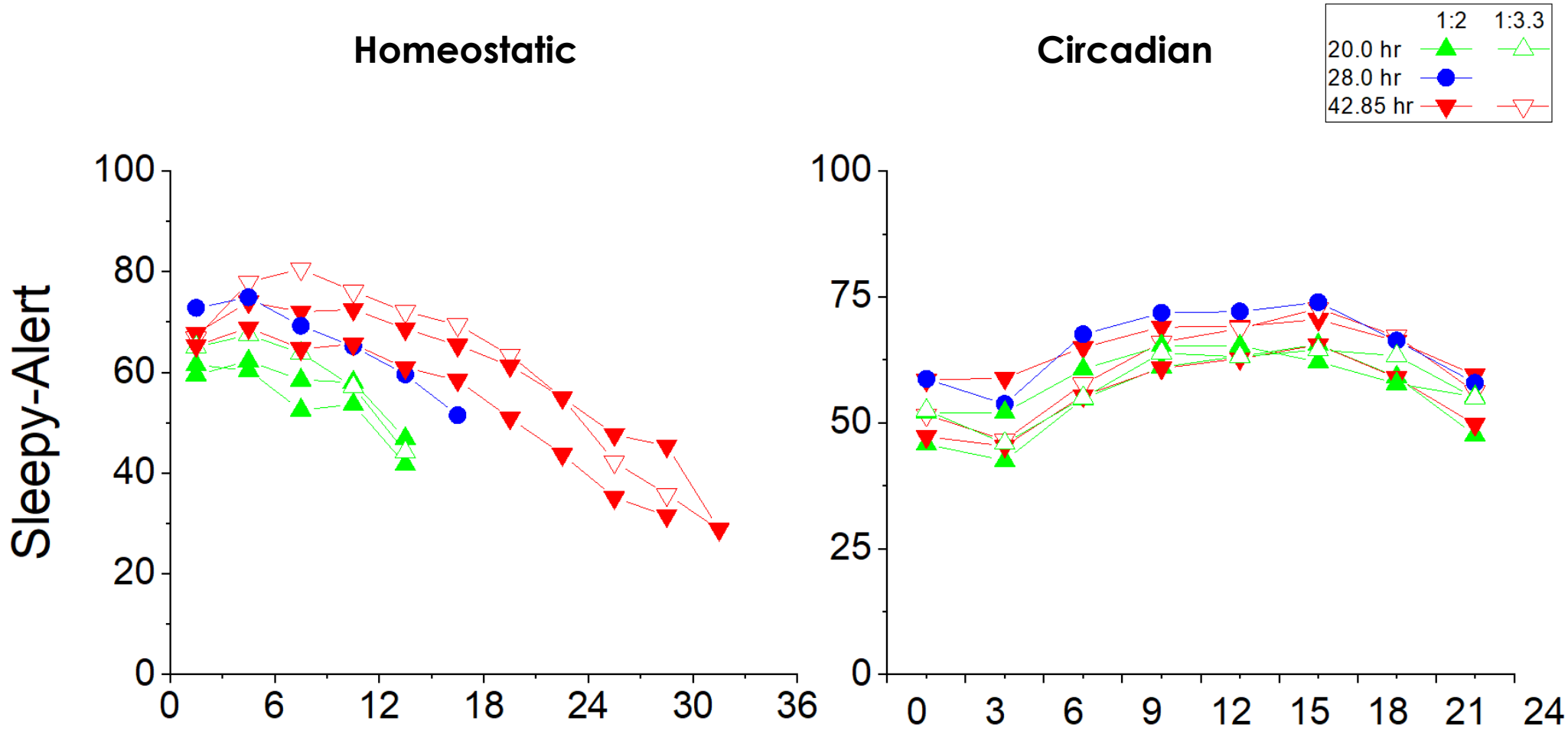


Dijk and Czeisler *Neurosci Lett*. 1994

Fatigue related mood scales from a FD protocol

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

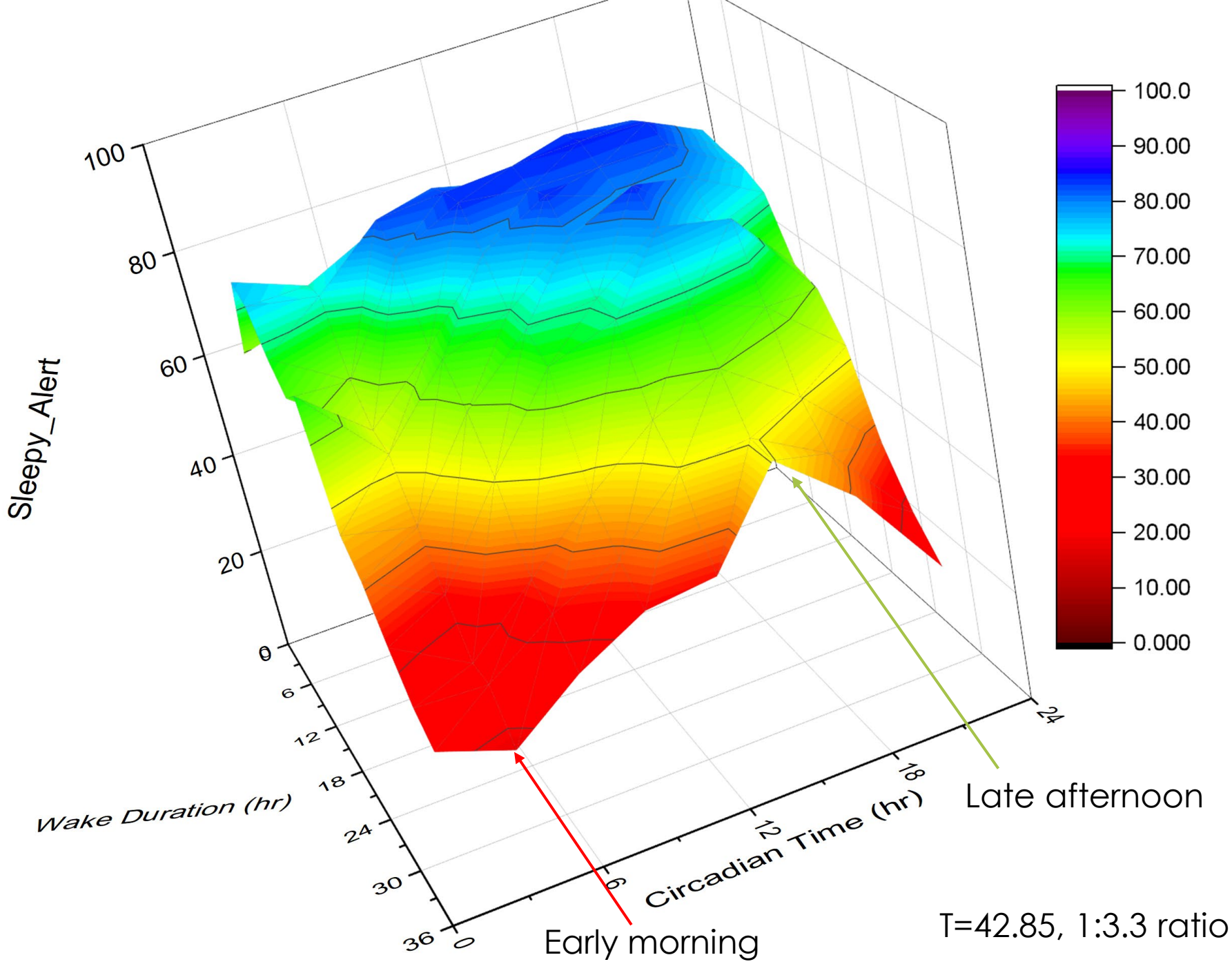


Wake Duration (hr)

Circadian Time (hr)

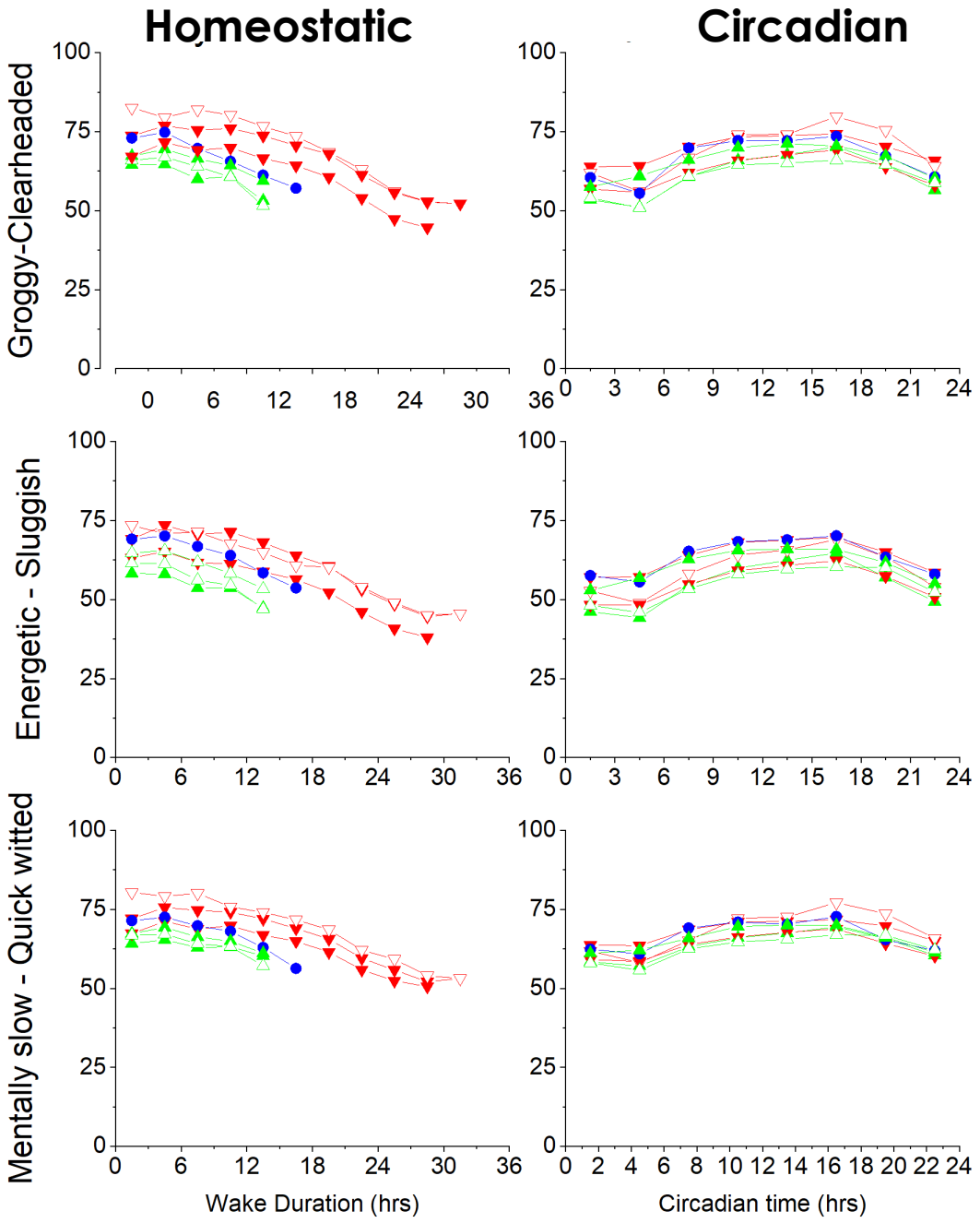
0=CBT min=~5 am in entrained conditions

Sleepy Alert in 3D



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.