Circadian Rhythms and Sleep in Aging

Vancouver Summer Program

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Outline

9:00 – 10:30 AM	**Overview of sleep and circadian rhythms**
10:30 – 10:45 AM	**Break #1**
10:45 – 11:25 AM	**How do sleep and circadian rhythms change with age?**
11:25 – 11:30 AM	**Break #2**
11:30 – 12:00 PM	**Improving sleep and circadian rhythms in older adulthood**

Overview of Sleep and Circadian Rhythms

Defining Sleep Quality


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Why do we sleep?

Growth

Restoration and Recovery

Immune Function

Brain Health

- Memory processing
- Consolidation of learning
- Restoration and recovery of neural tissue

What is the cost of poor sleep?

Poor sleep quality is linked to

- Obesity
- Increased mortality risk
- Cardiovascular Disease
- Alzheimer's Disease

Animal models of complete sleep loss show progressive neurological and physiological dysfunction:

- Movement disorders
- Increased food intake
- 20% weight loss
- Increased energy expenditure (~2x normal)
- Early death

What is sleep quality?

Sleep quality is not easily defined (multi-dimensional construct)

The National Sleep Foundation has defined several different measures of sleep quality:

1. **Sleep Efficiency:** The ratio of time spent sleeping vs. time spent trying to sleep
2. **Sleep Latency:** Length of time (in minutes) it takes to fall asleep
3. **Sleep Duration:** Total time spent sleeping
4. **Awakenings:** Number of times a person wakes after initiating sleep
5. **Wake After Sleep Onset (WASO):** Time spent awake after sleep has been initiated before final awakening
6. **Sleep Architecture:** The basic structural organization of sleep

Sleep Fragmentation

Practice Question

William starts trying to sleep at 10 PM (22:00) and gets out of bed the next morning at 6 AM (6:00). During the night, he spends 7.5 hours actually asleep and is awake for 0.5 hours. What is William's:

1. **Sleep Duration?**

2. **Sleep Efficiency?**

3. **Wake After Sleep Onset?**

Answers

1. **Sleep Duration**= 7.5 hours

2. **Sleep Efficiency**= (7.5 hours spent sleeping) / (8 hours spent trying to sleep)= 93.75%

3. **Wake After Sleep Onset**= 0.5 hours

Sleep Architecture

Sleep Architecture is the basic structural organization of sleep

There are 2 structural types of sleep:

- Rapid Eye-Movement (REM) Sleep
- Non-Rapid Eye-Movement (NREM) Sleep

NREM is further divided into stages 1, 2, 3, and 4, representing a continuum of relative depth

Non-REM Sleep

Light Sleep

Deep Sleep

Slow Wave Sleep (SWS)

REM Sleep

Cortex

Right

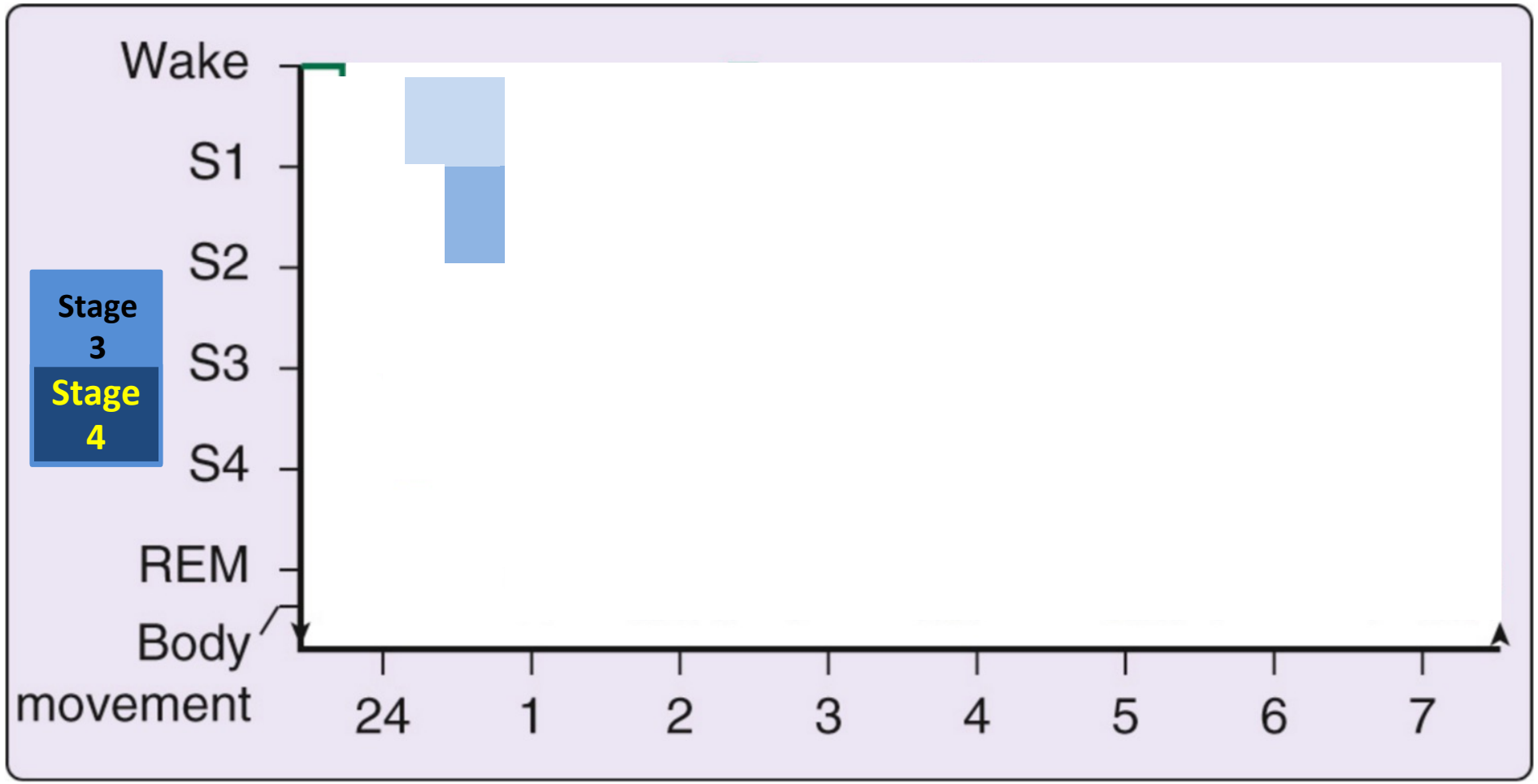
Eyes

Left

Chin

Citation:
Principles & Practice of Sleep Medicine, p. 16

Sleep Architecture



Citation:
Principles & Practice of Sleep Medicine, p. 19

Sleep Architecture Across the Sleep Window

Stage 1 = 2 to 5% (~30 minutes)
- A transitional stage

Stage 2 = 45 to 55% (~4 hours)
- Dominates NREM in 2nd half of sleep

Slow Wave Sleep (i.e., Stage 3 and 4) = 10 to 20% (~90 minutes)
- Dominates NREM in 1st half of sleep
- Stage 4 is the dominant stage of Slow Wave Sleep

REM = 20 to 25% (~2 hours)
- Dominates the 2nd half of the sleep window

Measuring Sleep Quality

Objective Methods

1. Polysomnography (PSG)- “The Gold Standard”
2. Electrical Encephalography (EEG)
3. Apnea-Hypopnea Index
4. Accelerometry

Subjective Methods

1. Self-reported sleep quality (e.g., Pittsburgh Sleep Quality Index)
2. Sleep diary

Measuring Sleep Quality

It is important to measure sleep quality using **both** objective and subjective methods.

Objective and subjective tools measure different aspects of sleep quality (Landry et al., 2016)

- Objective measures are not strongly associated with subjective measures of sleep quality

		Pittsburgh Sleep Quality Index Measured					
		Sleep Latency	Sleep Efficiency	Sleep Duration	Sleep Disturbances	Sleep Quality	Total Score
Accelerometer Measured	Sleep Latency	0.21	0.03	0.04	-0.02	0.02	0.08
	Sleep Efficiency	-0.11	-0.03	0.07	0.08	-0.18	-0.09
	Sleep Duration	0.12	-0.11	0.29**	0.23**	-0.1	0.03
	Sleep Fragmentation	0.05	-0.01	0.02	-0.03	0.05	0.02

Practice Question

1. What is the best method for measuring sleep quality?
   a) Polysomnography
   b) Self-Report
   c) Accelerometry
   d) Sleep-Diary
   e) There is no one best method

Summary

Sleep quality is a complex construct and has both *physiological* and *psychological* components

- Multiple different measures of sleep quality

Sleep architecture is the structural organization of sleep (measured by polysomnography)

- NREM Sleep (Stages 1, 2, 3, 4)
- REM Sleep (Dreaming)

Measuring sleep quality requires objective and subjective methods

Overview of Sleep and Circadian Rhythms

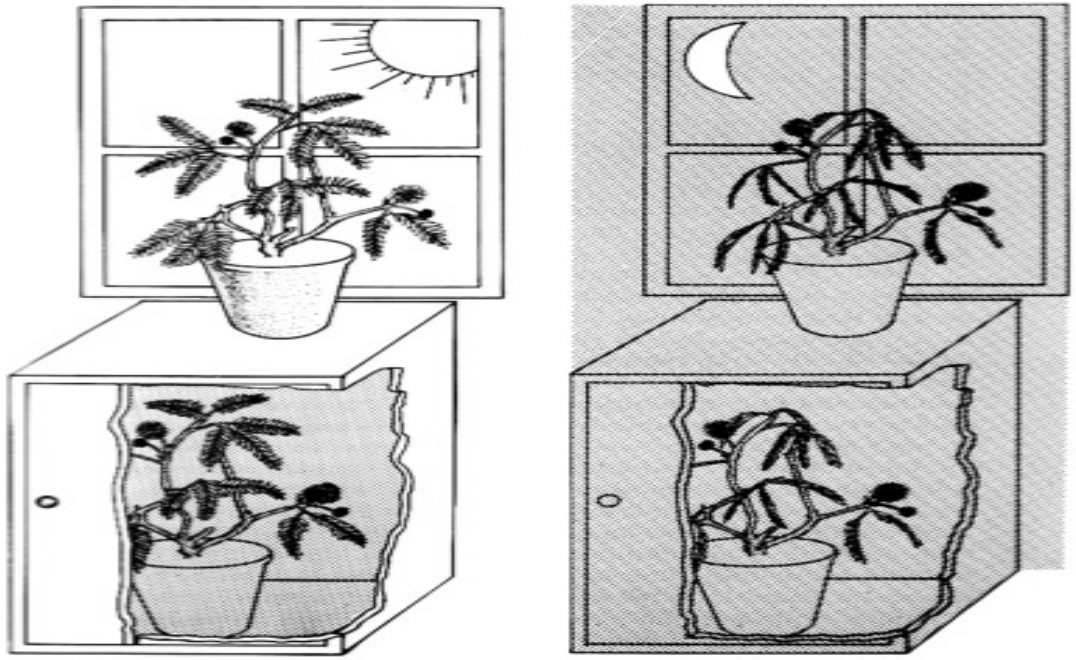
Defining Circadian Rhythms

What are Circadian Rhythms?

Circadian rhythms are ~24-hour cyclic changes in physiology and behaviour that are governed by various endogenous biological clocks in coordination with the solar light-dark cycle (Golombek & Rosenstein, 2010).

Key features of circadian rhythms:

1. Synchronizing effect of light-dark cycles
2. Persistence of rhythmicity in constant darkness
3. “Negative Masking” by light

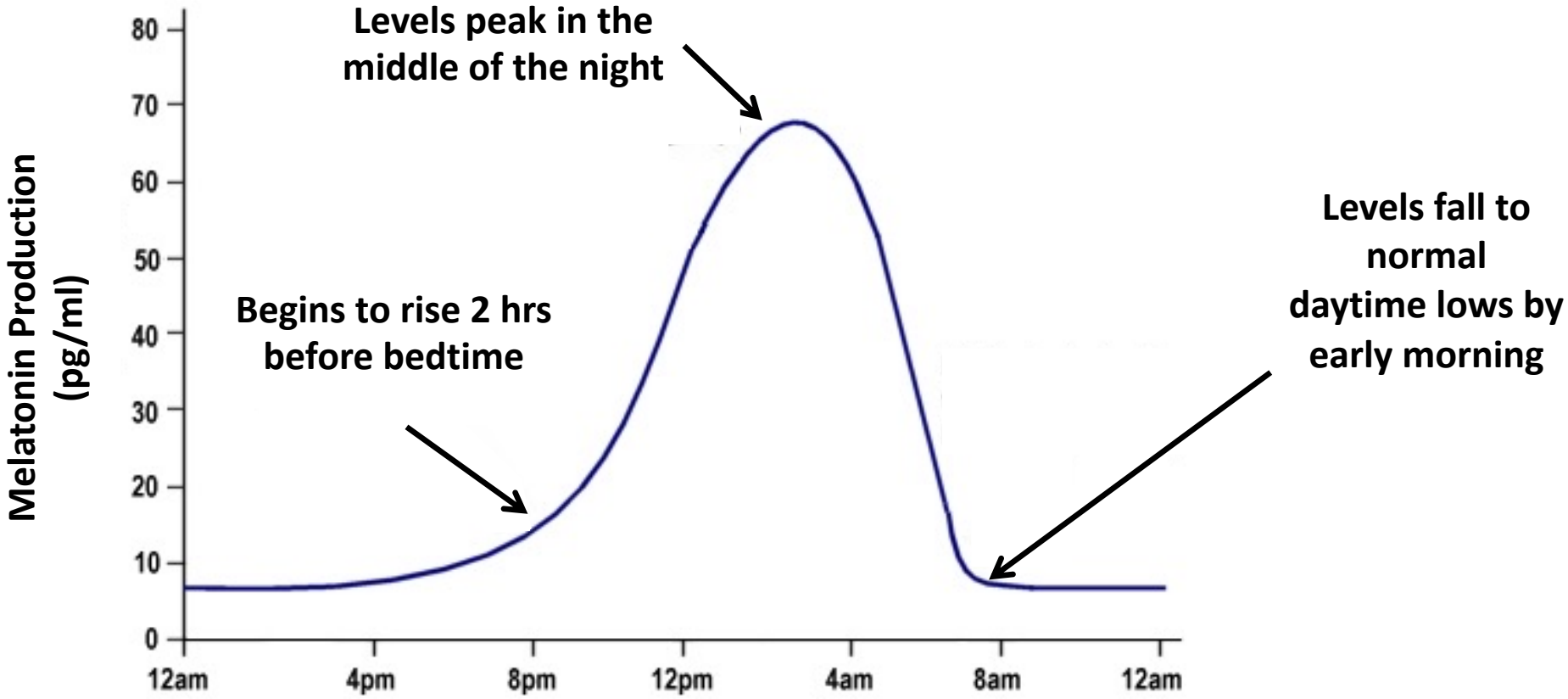


What are Circadian Rhythms?

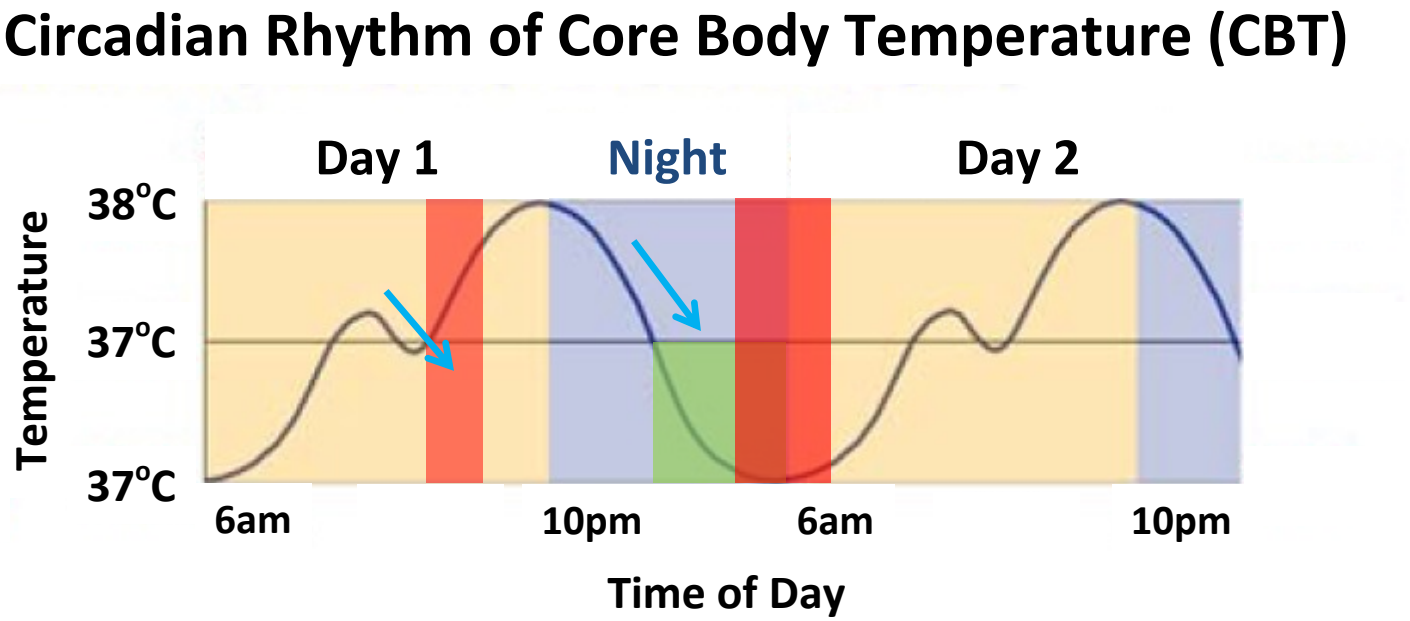
Circadian rhythms help to control:

- Sleep-Wake Cycle
- Hunger
- Growth
- Melatonin
- Body Temperature
- Cognitive Function

Melatonin Rhythm



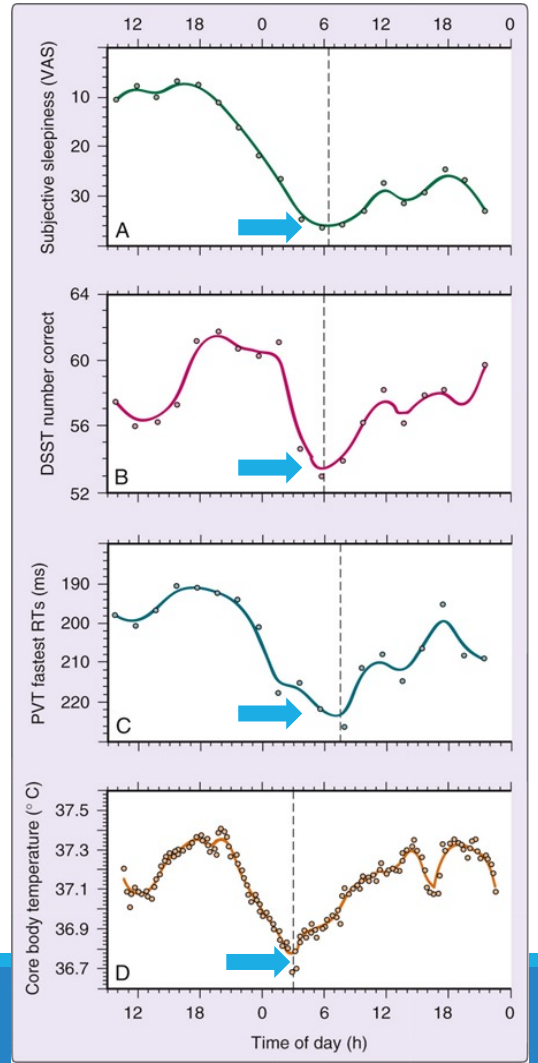
Body Temperature Rhythm



Core body temperature rhythm is tightly linked to:

- Sleep drive (i.e., the urge to sleep)
- REM sleep (concentrated in the 2nd half)
- Cognitive function (lowest after CBT bottoms out)

Cognitive Performance Rhythm



Subjective Sleepiness:

- Increases as CBT decreases
- Peak sleepiness just before habitual wake-time

Working Memory:

- Peaks just before habitual bedtime
- Lowest point just after the CBT minimum (CB_{Tmin})

Attention:

- Peaks just before habitual bedtime
- Lowest point just before habitual wake-time

Core Body Temperature (CBT):

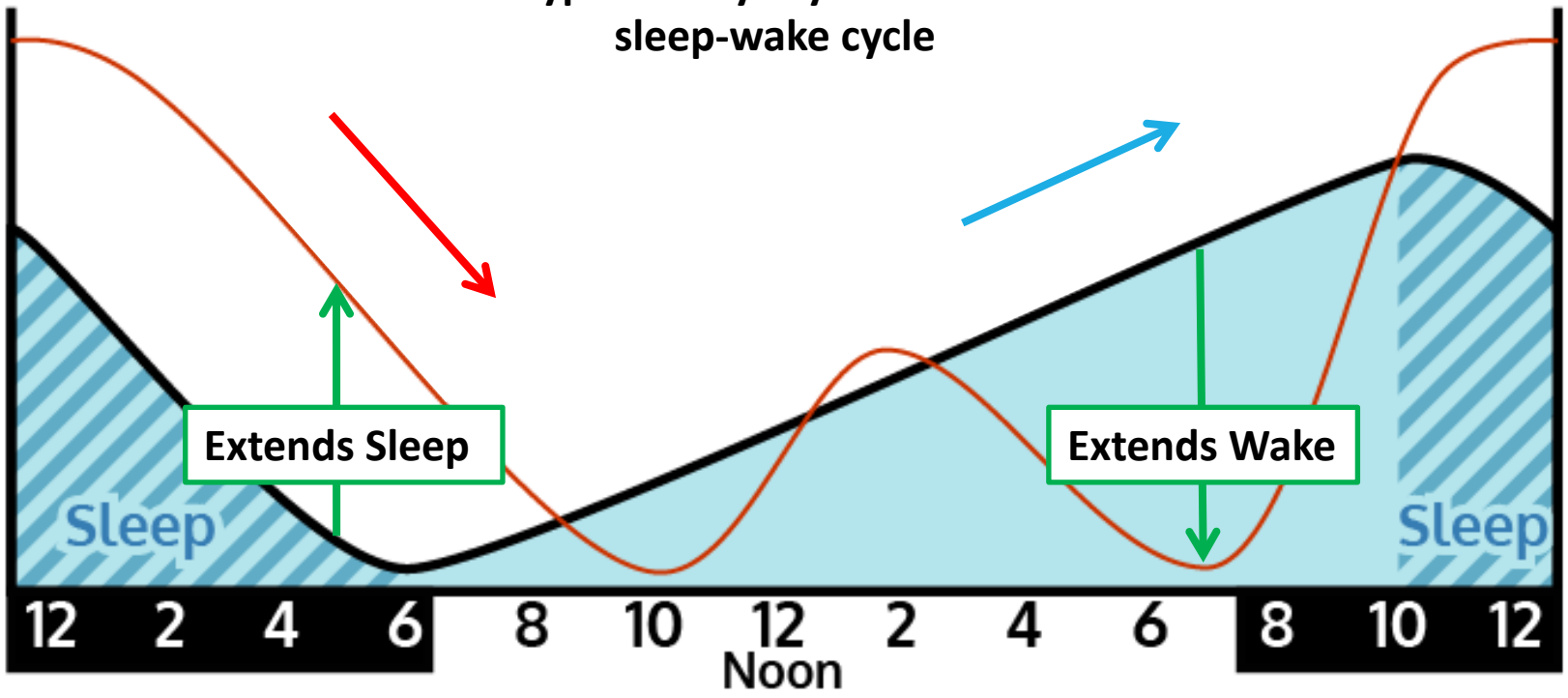
- Peaks just before habitual bedtime
- Lowest point 2-3 hours before habitual wake-time

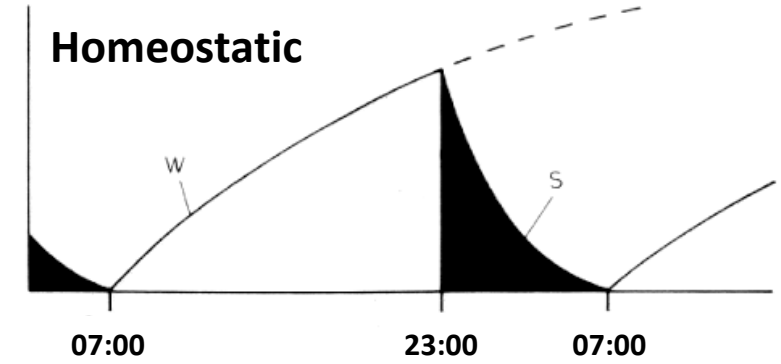
Sleep-Wake Rhythm

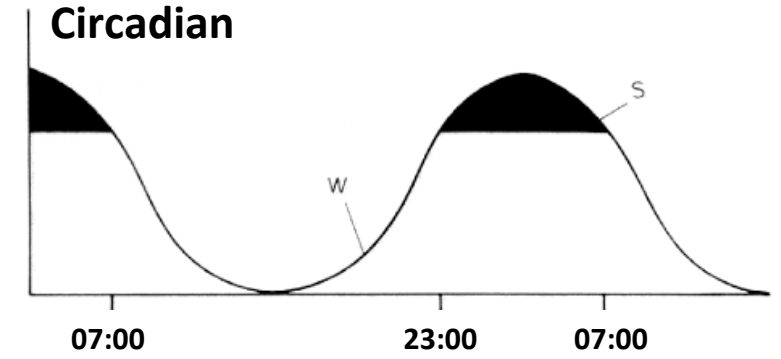
The paradoxical relationship between sleep need and sleep urge:

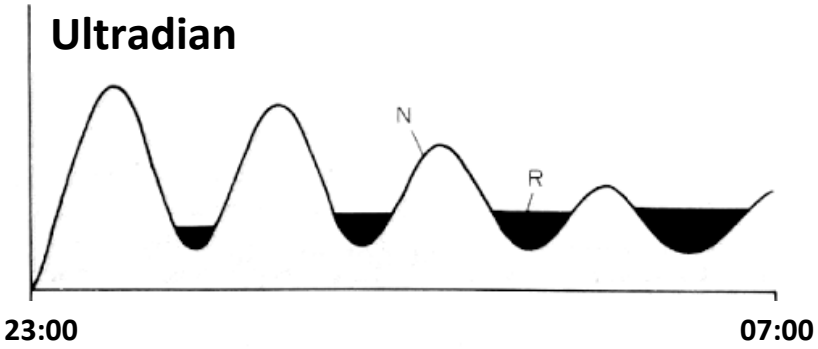
- Homeostasis drives sleep need
- Circadian regulation drives sleep urge
- Circadian drive opposes homeostasis

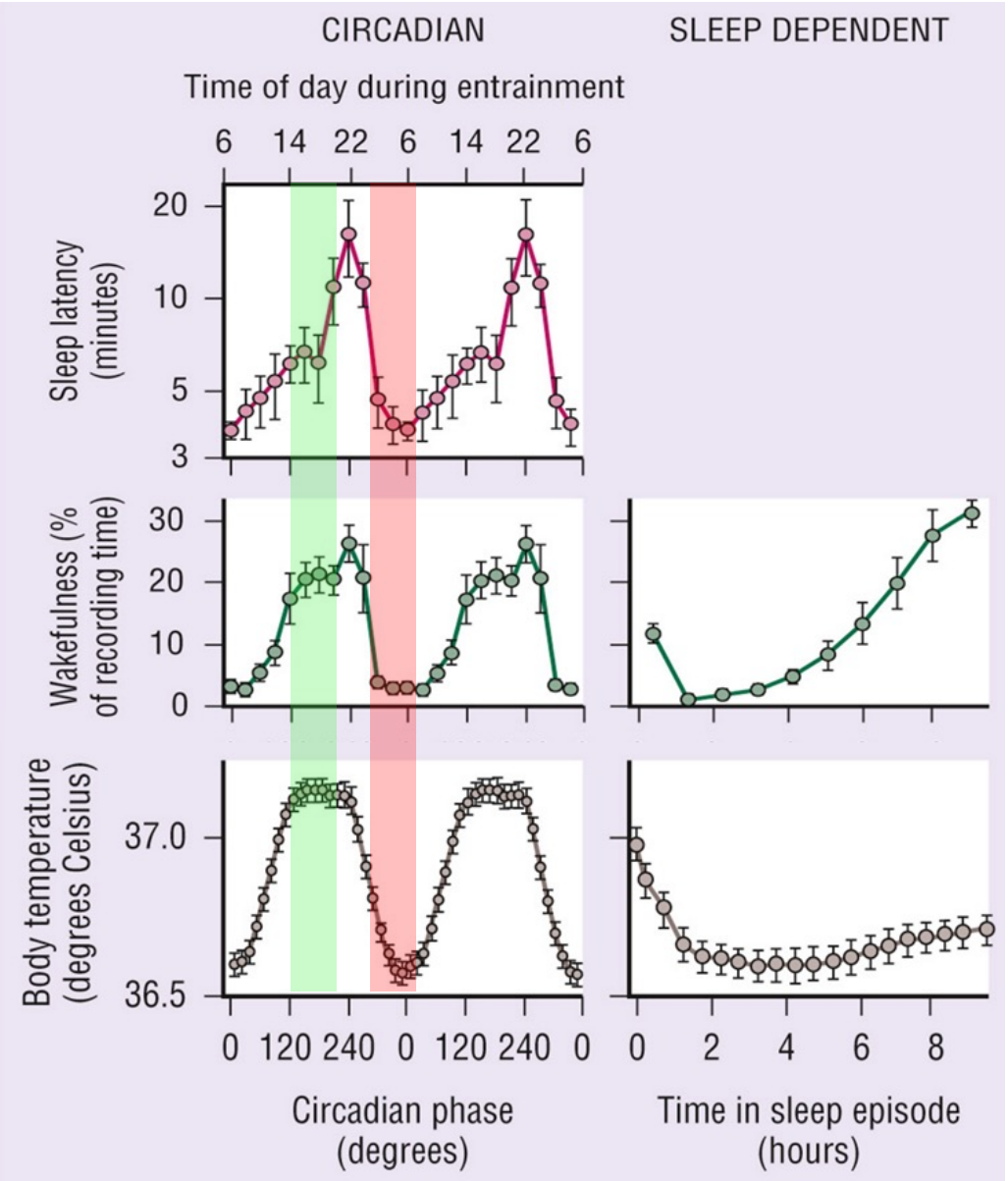
Typical daily rhythm of the sleep-wake cycle

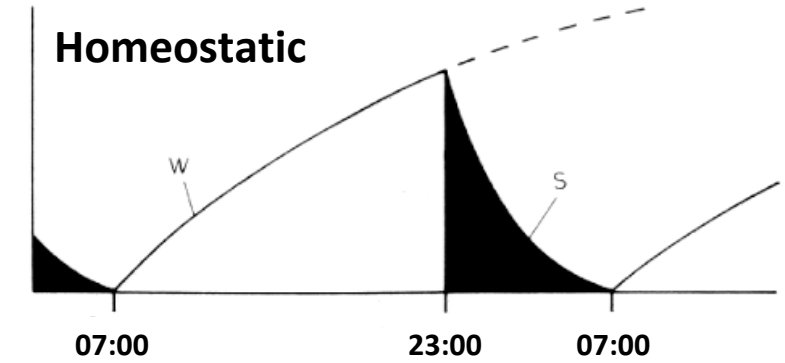



Homeostatic
W
S
07:00
23:00
07:00


Circadian
S
W
07:00
23:00
07:00


Ultradian
N
R
23:00
07:00


CIRCADIAN
SLEEP DEPENDENT
Time of day during entrainment
6 14 22 6 14 22 6
Sleep latency (minutes)
20
10
5
3
Wakefulness (% of recording time)
30
20
10
0
Body temperature (degrees Celsius)
37.0
36.5
0 120 240 0 120 240 0
Circadian phase (degrees)
0 2 4 6 8
Time in sleep episode (hours)


Homeostatic
W
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07:00
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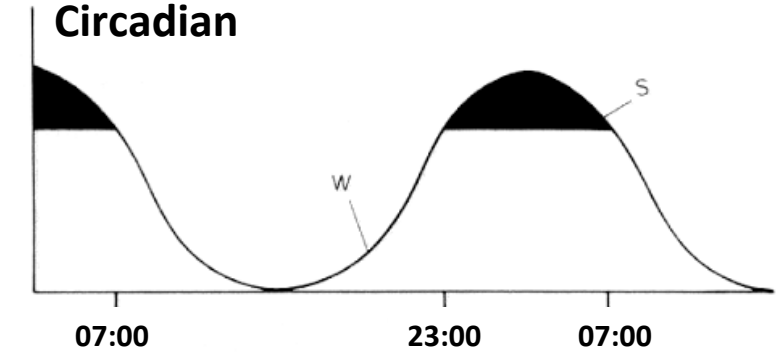
Circadian
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07:00
23:00
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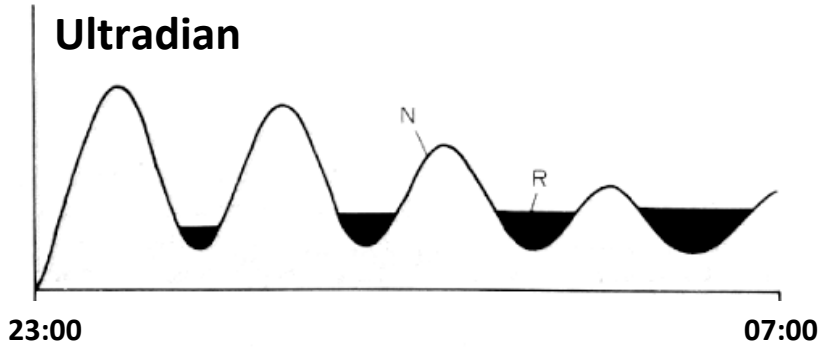
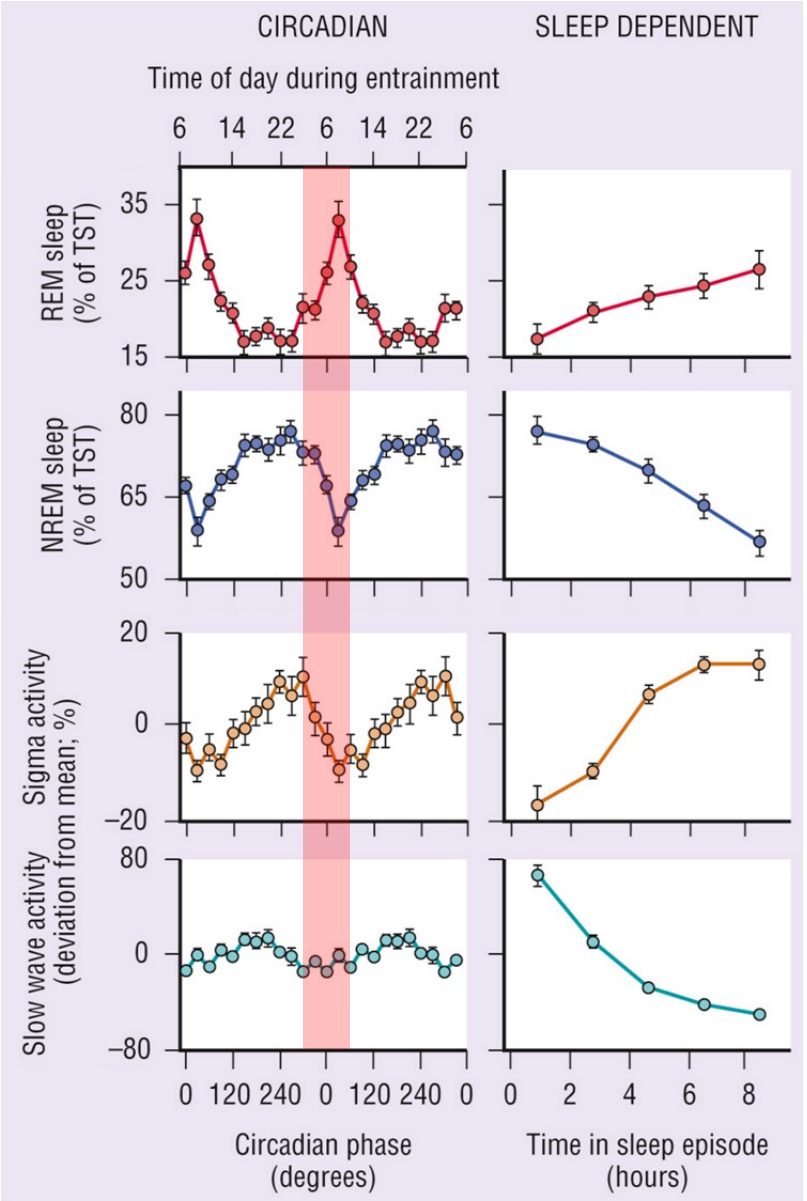
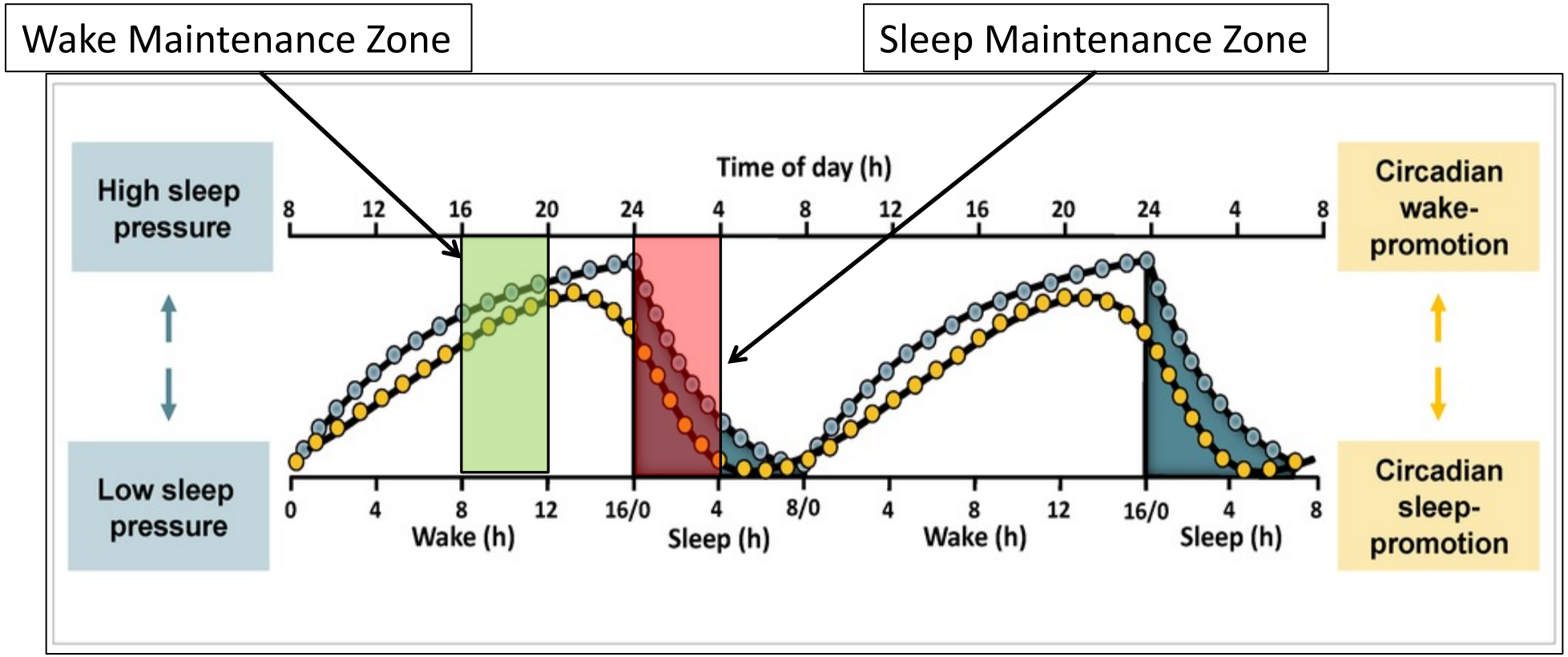

Ultradian
N
R
23:00
07:00

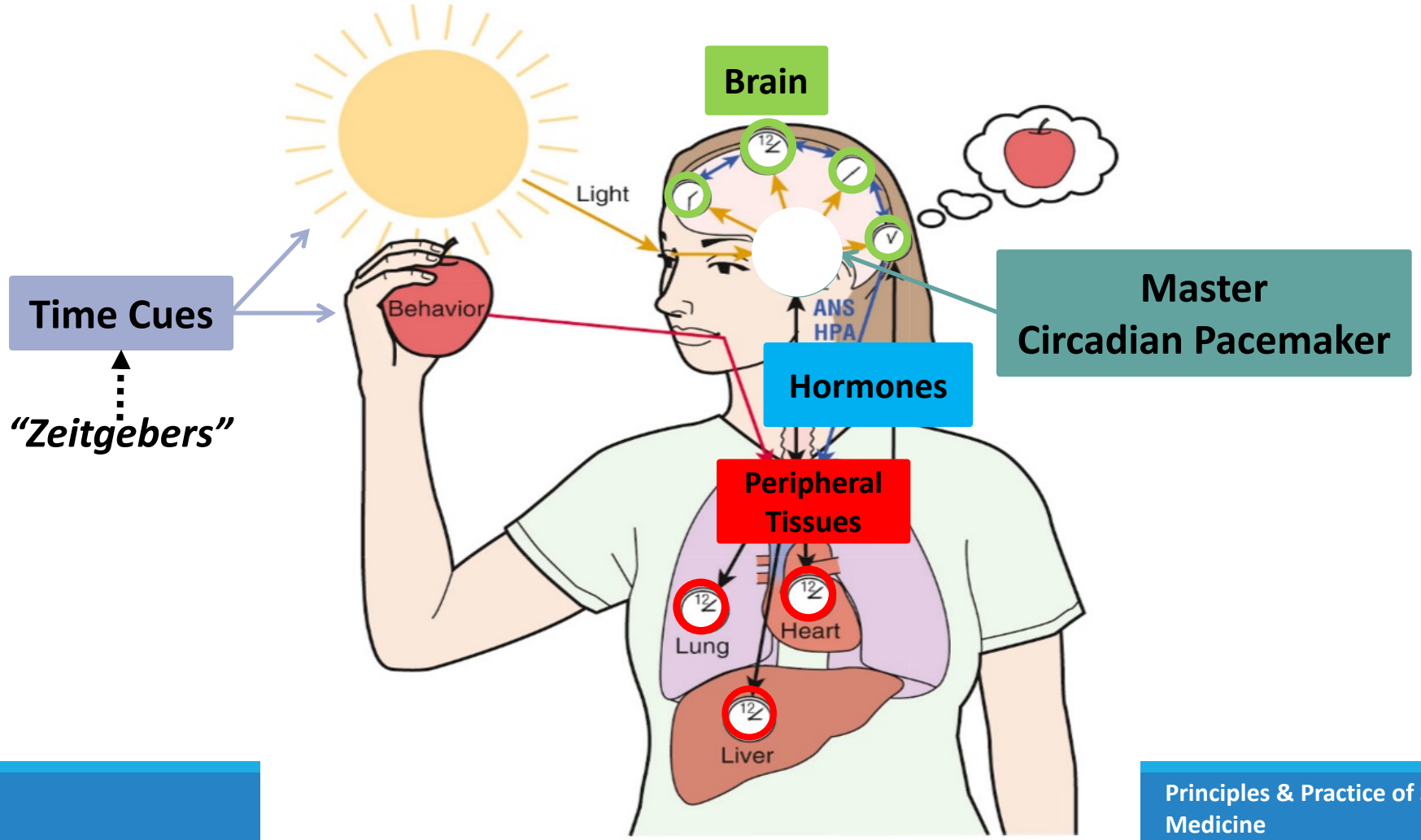

CIRCADIAN
SLEEP DEPENDENT
Time of day during entrainment
6 14 22 6 14 22 6
REM sleep (% of TST)
35
25
15
NREM sleep (% of TST)
80
65
50
Sigma activity (deviation from mean; %)
20
0
−20
Slow wave activity
80
0
−80
0 120 240 0 120 240 0
Circadian phase (degrees)
0 2 4 6 8
Time in sleep episode (hours)

Mechanisms that drive Sleep



Circadian Physiology 101

How do Circadian Rhythms Work?



Circadian Physiology 101

What are Zeitgebers?

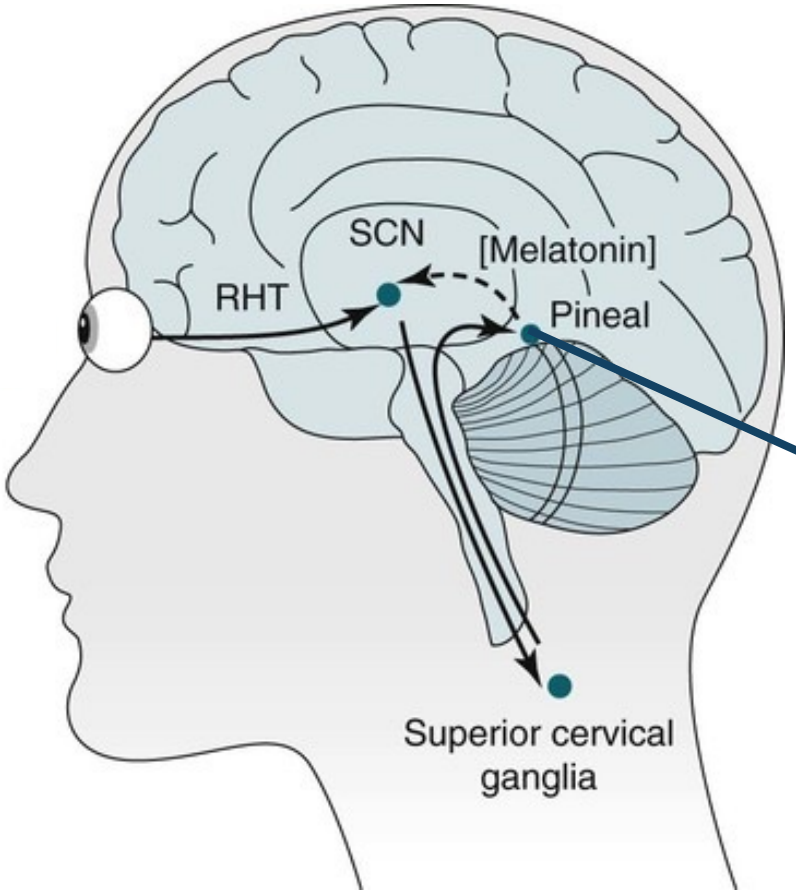
External time cues

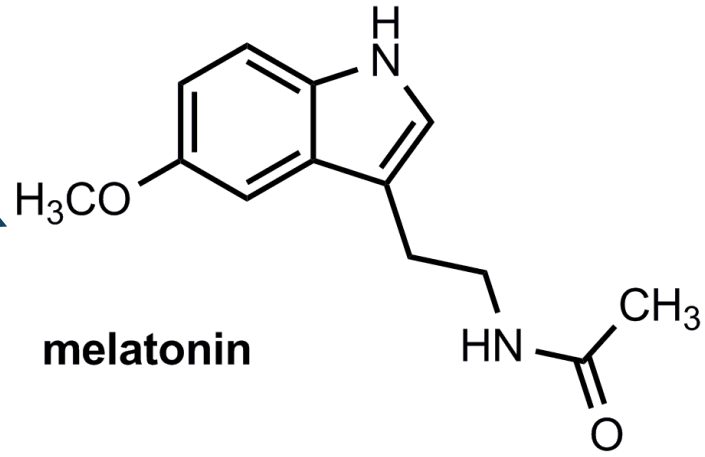
"Entrainment"

Internal clock time

Circadian Physiology 101

How does light entrain the human biological clock?

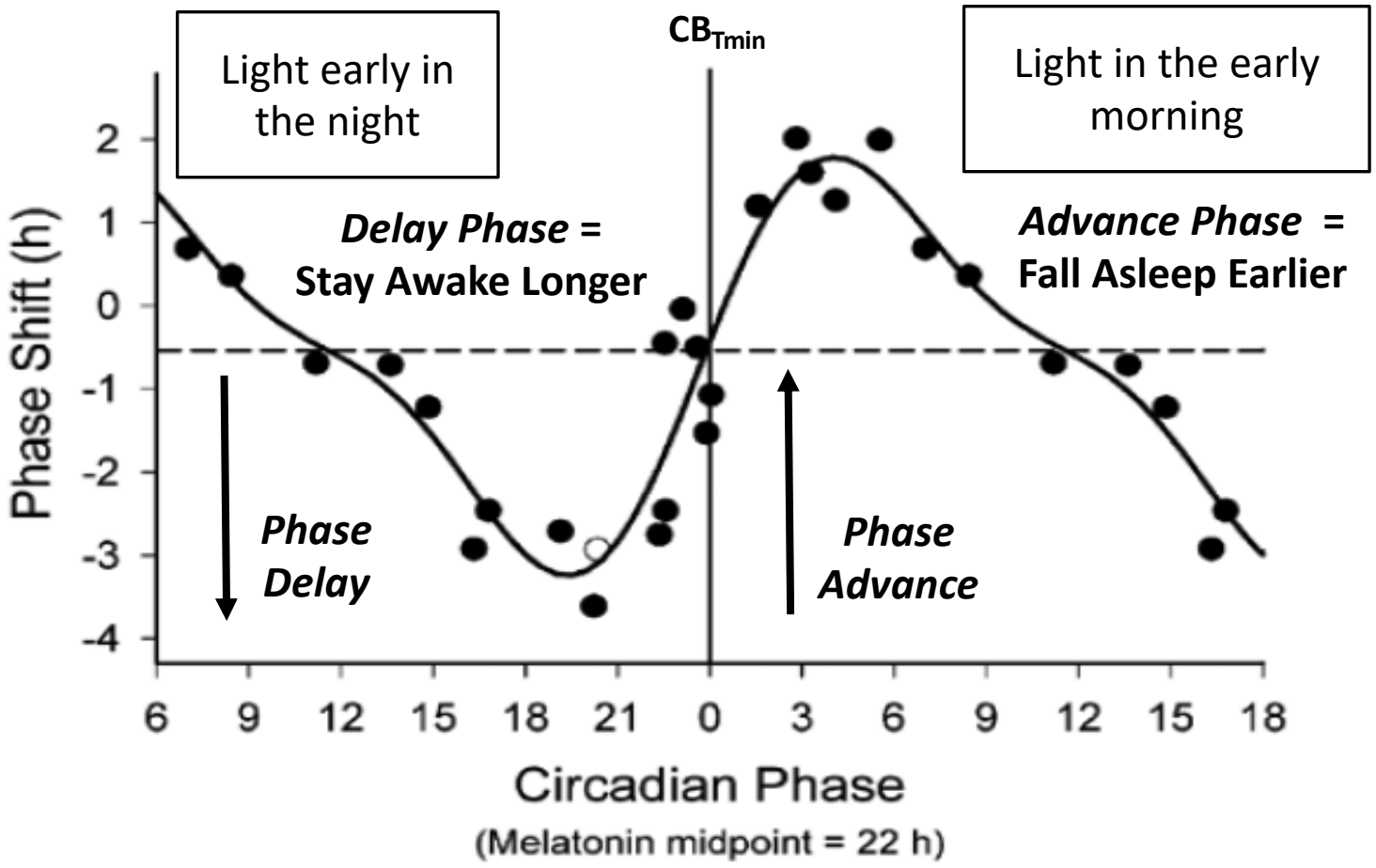




melatonin

Circadian Physiology 101

How does light entrain the biological clock?



Practice Question

Beyoncé has a concert in China so she flies to Beijing from Los Angeles. Her 13-hour flight leaves at 10:00 AM and arrives in Beijjing at 2 PM (14:00) local time. When she lands in China, it will be 1:00 AM in Los Angeles.

Why does Beyonce feel “jet-lagged”? Is her circadian clock *phase-advanced*, *phase-delayed,* or *phase-neutral* based on local time?

Answer: Beyoncé feels jet-lagged because her circadian clock is currently un-aligned with the solar light-dark cycle. Her circadian clock is telling her it is time for sleep, although it is 2 PM (14:00) local time. When she lands in China, she is therefore phase-advanced.

How do we measure circadian rhythms?

Objective Methods

- Melatonin levels in urine or saliva
- Core body tempature
- Clock gene expression from hair follicle cells
- Activity from accelerometry

Subjective Methods

- Self-report (e.g., Munich Chronotype Questionnaire, Morning-Eveningness Questionnaire)

Summary

Circadian rhythms are ~24-hour cyclic changes in physiology and behaviour that are governed by endogenous biological clocks in coordination with the solar light-dark cycle

- Circadian rhythms are critical for regulation of the sleep-wake cycle

Entrainment is the process by which the biological clock synchronizes with the solar light-dark cycle.

- Entrainment is accomplished through external stimuli called *zeitgebers*. The principle *zeitgeber* is light.
- *Zeitgebers* can either “advance” or “delay” the circadian clock

Circadian rhythms can be measured both objectively and subjectively


Pause

How Do Sleep and Circadian Rhythms Change with Age?

Practice Question

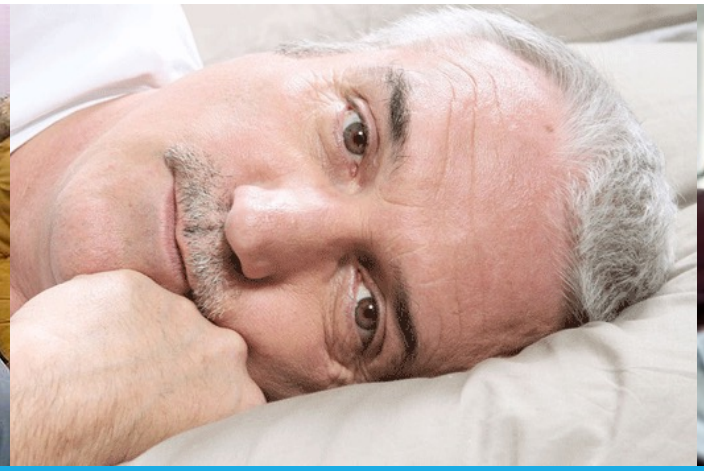
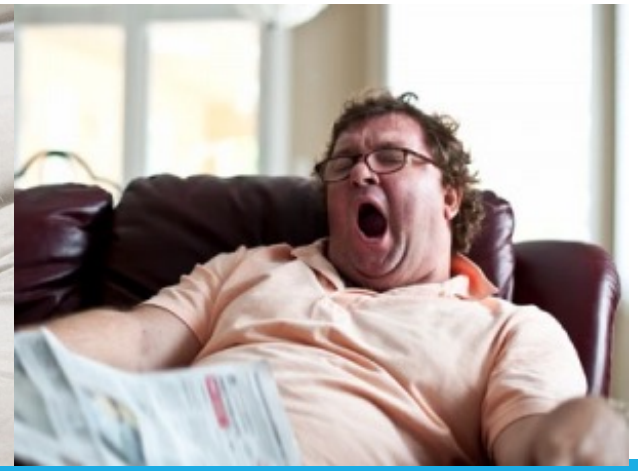
What parts of sleep quality do you think change as people age?

What are some of the reasons why sleep quality might change as people age?

Sleep & Aging

Normal changes include decreased:

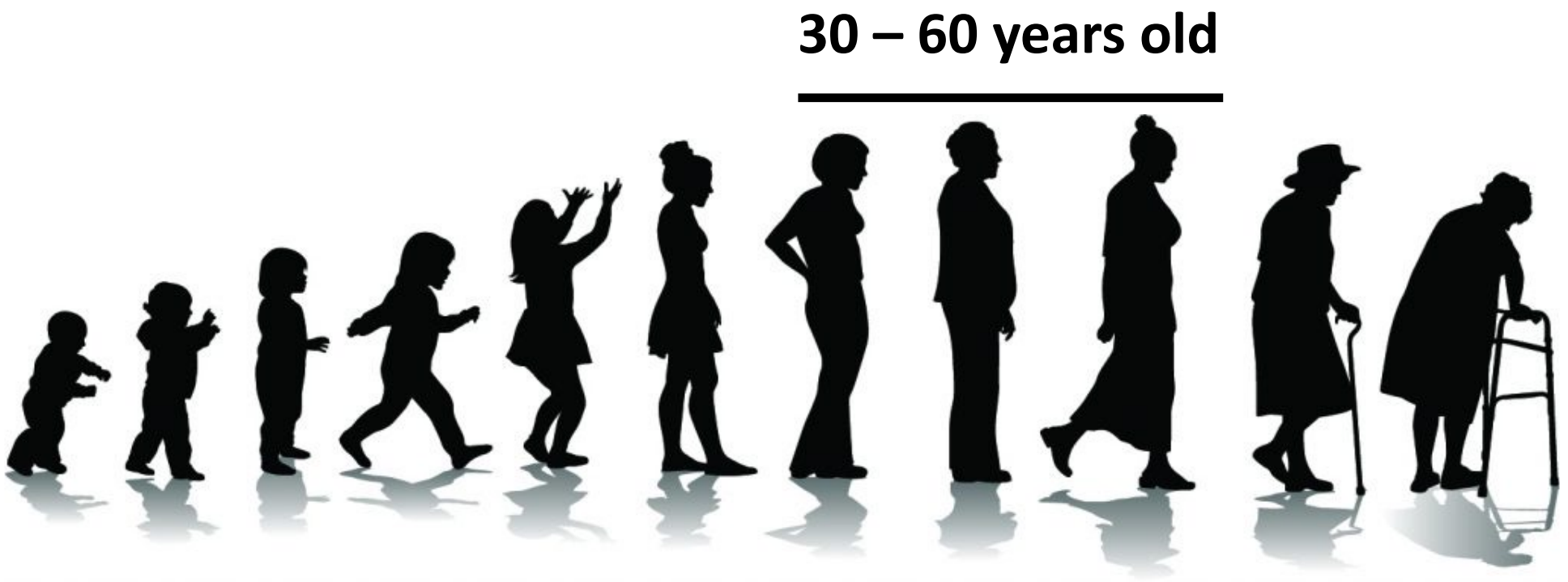
- Quantity
- Quality
- Consolidation
- Efficiency

Foley, 1995 *Sleep* 18(6): 425-432
Phillips, 2001 *Sleep Medicine* 2: 99-114

When does this change begin?

Age-related changes in sleep quality begin in the middle years:



Sleep Architecture & Aging

Variable	Older (mean ± S.E.M.)	Young (mean ± S.E.M.)	*P*
Sleep latency (min)	11·2 ± 2·1	14·0 ± 4·4	0·4525
REM latency (min)	56·0 ± 6·9	77·4 ± 10·7	0·0970
TRT (min)	478·3 ± 2·3	479·2 ± 1·4	0·7369
Wakefulness (min)	107·3 ± 11·4	39·5 ± 4·8	0·0001
TST (min)	370·8 ± 11·6	433·1 ± 5·0	0·0002
Sleep efficiency (%)	77·5 ± 2·4	90·4 ± 0·9	0·0001
Stage 1 (%)	18·0 ± 2·8	7·7 ± 1·5	0·0046
Stage 2 (%)	49·6 ± 3·0	53·2 ± 2·2	0·3634
Stage 3 (%)	8·6 ± 1·7	6·4 ± 0·9	0·2421
Stage 4 (%)	4·6 ± 2·0	13·0 ± 1·7	0·0043
SWS (%)	13·2 ± 2·7	19·4 ± 1·8	0·0792
REM sleep (%)	19·1 ± 1·1	19·6 ± 1·6	0·8006

Dijk, 1999

Circadian Rhythms and Aging

Younger Adulthood

Older Adulthood

Circadian Rhythms and Aging

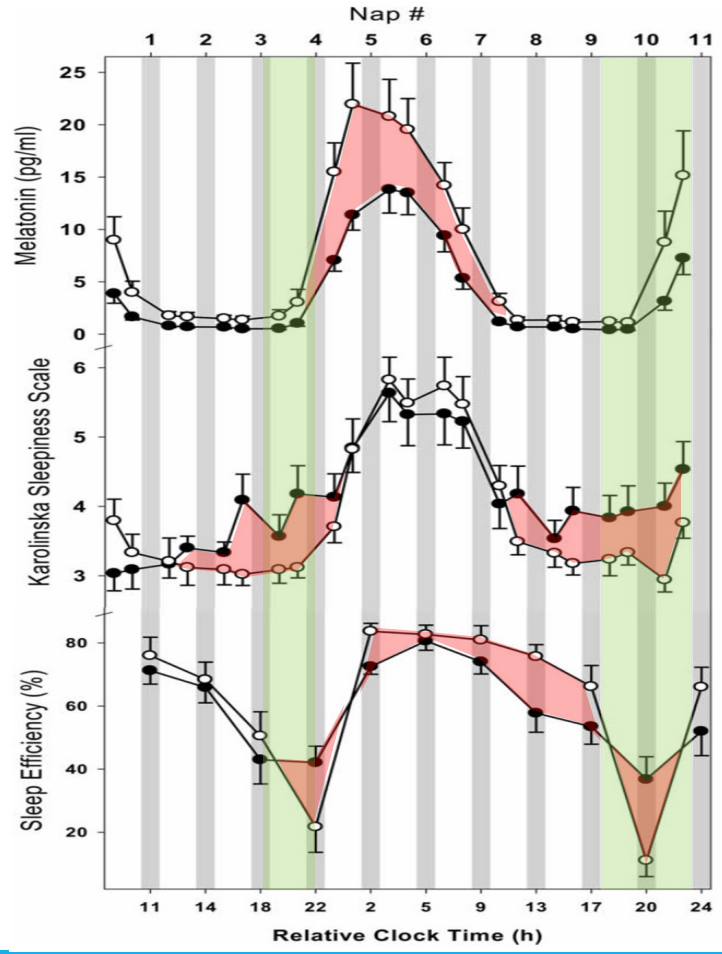
Compared to younger adults, older adults have:

1) Weakened wake maintenance zone

2) Increased daytime sleepiness

3) Decreased Melatonin amplitude

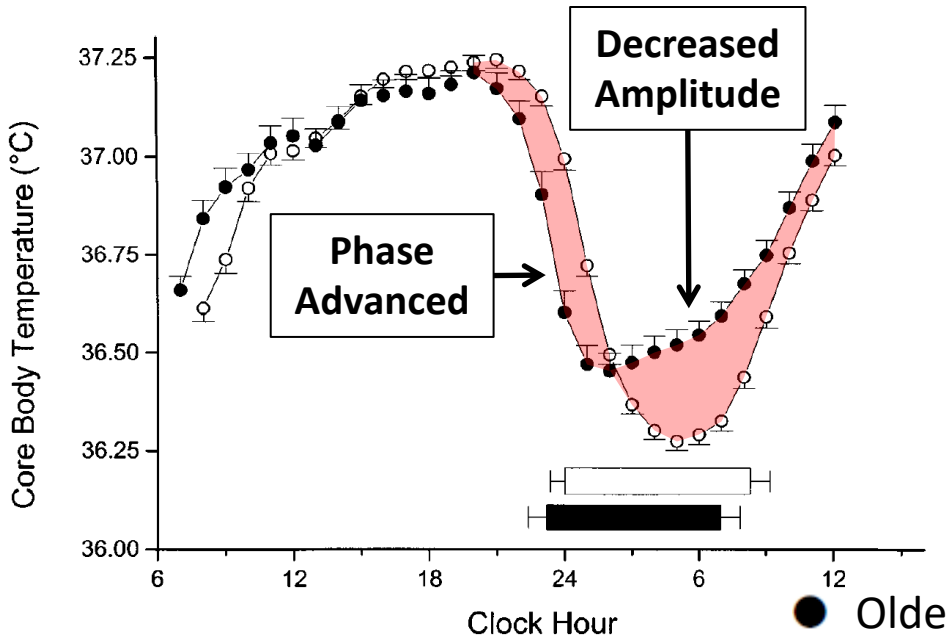
4) Reduced Sleep Efficiency



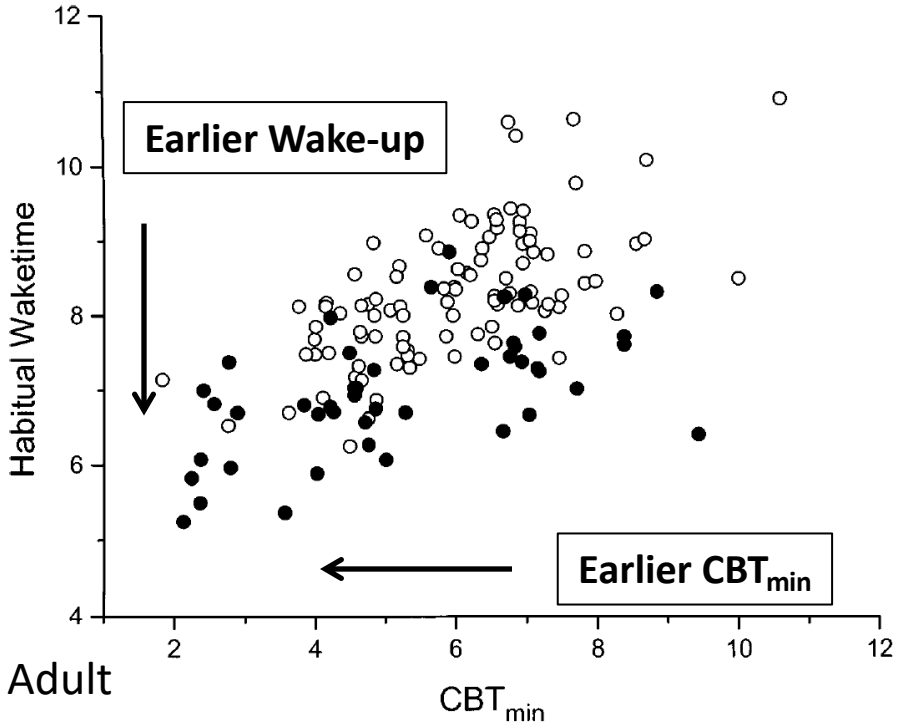
Cajochen et al., 2006

Circadian Rhythms and Aging

Core Body Temperature Rhythm



Habitual Wake Time



Older Adult

Young Adult

Duffy et al., 1998

Circadian Rhythms and Aging

Age-related changes in circadian rhythms from mouse models

A. Decreased running activity

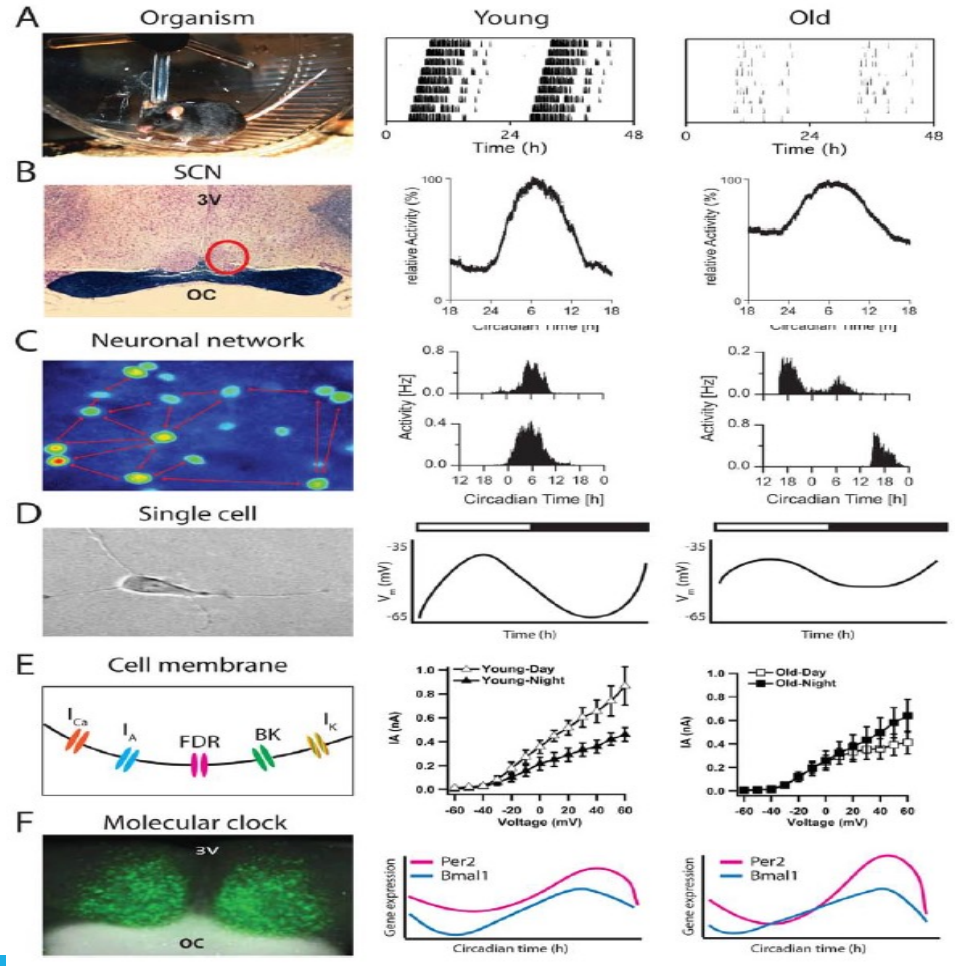
B. Decreased amplitude – SCN level

C. Altered timing of neuronal networks

D. Decreased amplitude – Single cell

E. Cell membrane changes

F. Down-regulation of clock genes



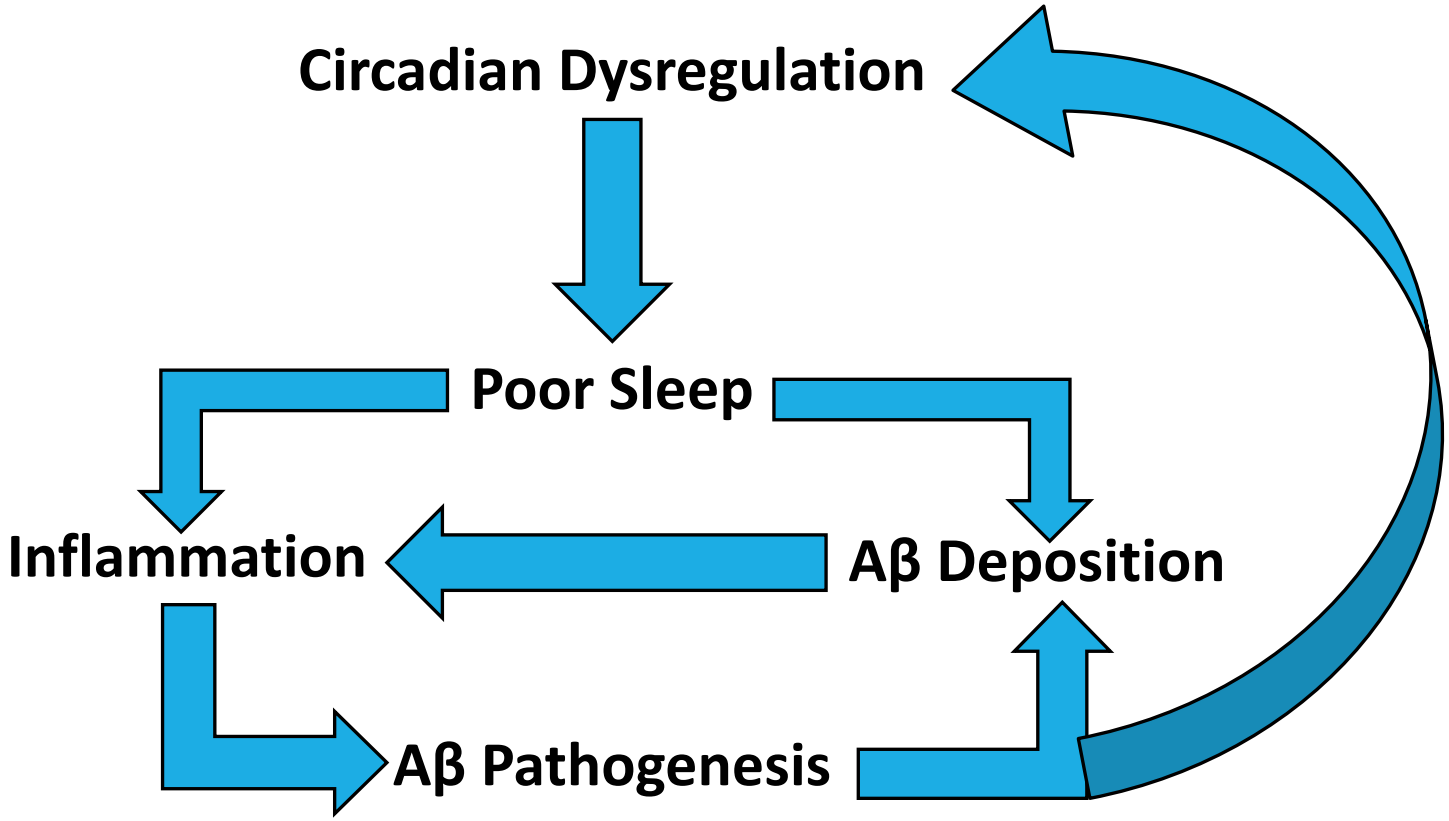
Cornelissen and Otsuka, 2017

Practice Question

What are some of the circadian reasons for why older adults have poorer sleep quality than younger adults?

Answer: Older adults have decreased melatonin amplitude and reduced core body temperature minimum. These changes in older adult physiology can make older adults fall asleep earlier than they would like, and wake up earlier than they would like.

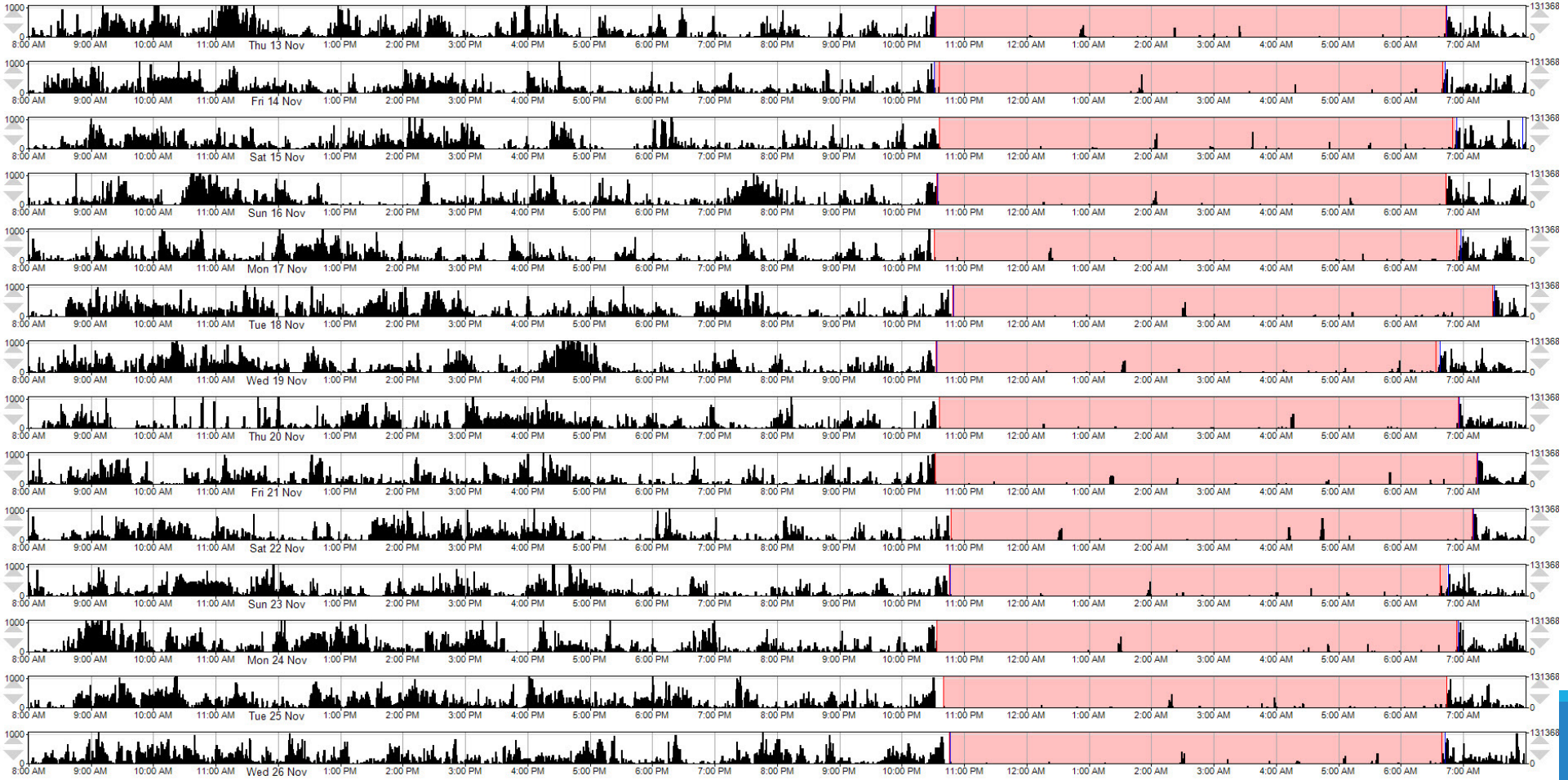
Circadian Rhythms and Cognitive Health



Landry and Liu-Ambrose, 2014

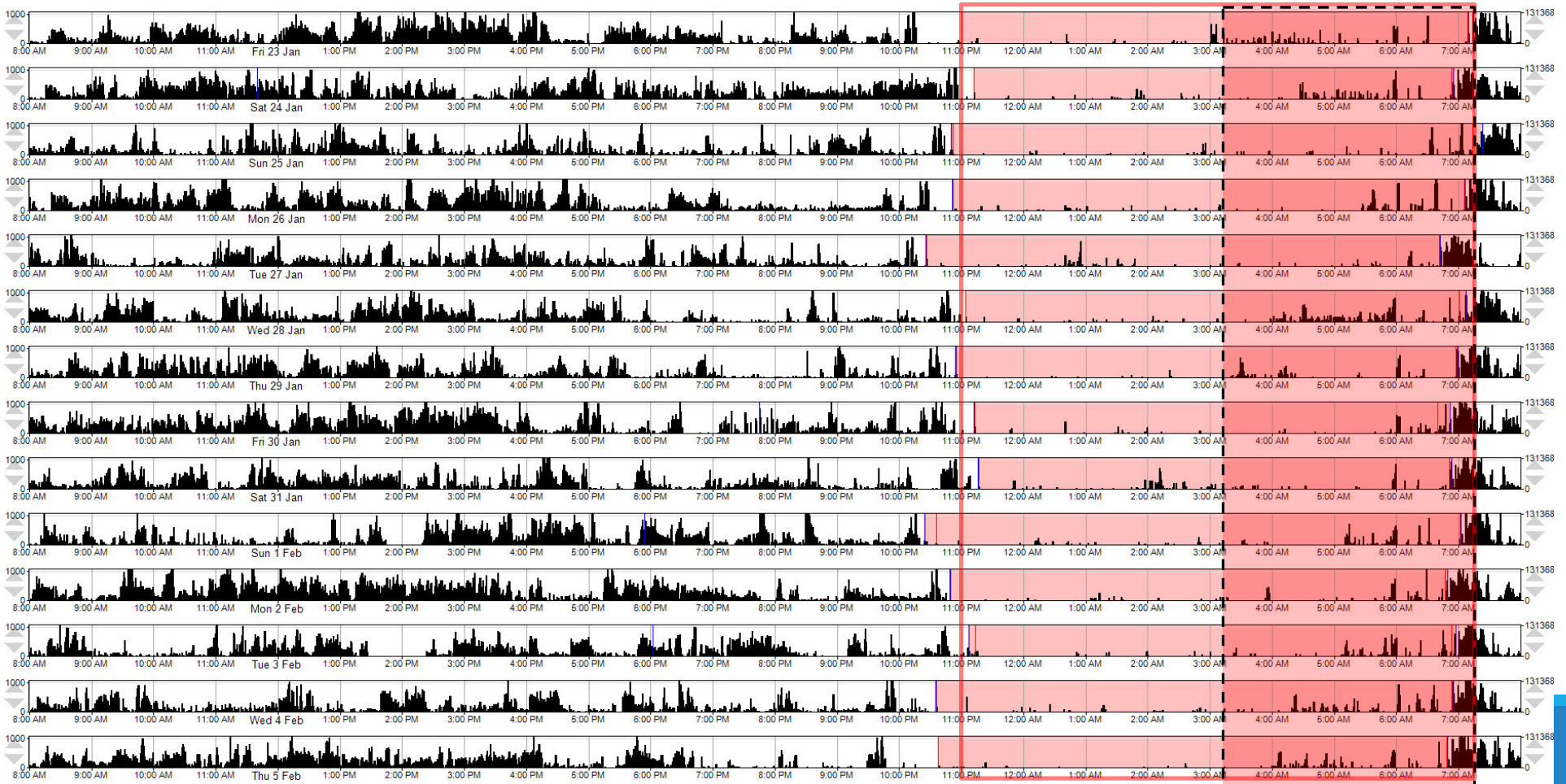
An Example of Good Sleep Quality

69 year old woman: Duration = 461 min; Efficiency = 93.1%; Fragmentation = 14.9



An Example of Poor Sleep Quality

73 year old woman: Duration = 368 min; Efficiency = 75.7%; Fragmentation = 41.0



Common Sleep Disorders in Aging

- Insomnia
- Obstructive Sleep Apnea
- Delayed Sleep Phase
- Narcolepsy
- Restless Legs Syndrome
- Periodic Limb Movements

Insomnia

Common causes of insomnia

- Shift Work
- Circadian Dysregulation
- Poor Sleep Hygiene
- Normal aging
- Stress
- Anxiety
- Depression
- Medications

Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by repetitive disruptions to the upper airway during sleep, resulting in decreased oxygenation and a variety of metabolic disturbances.

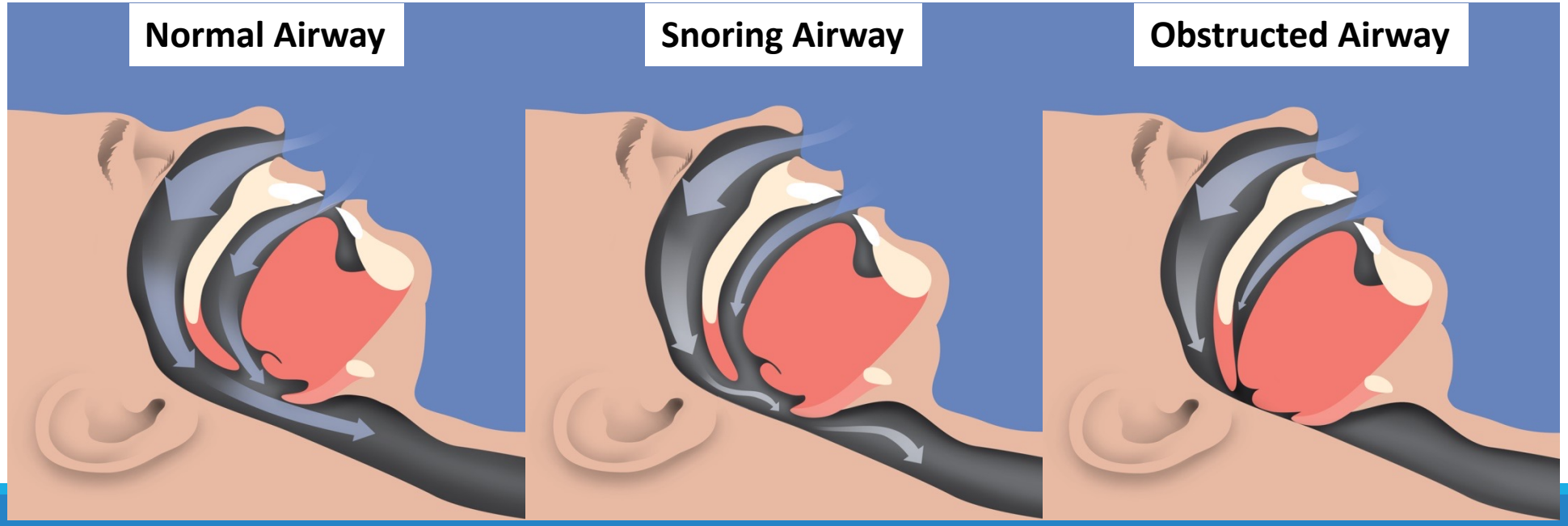
Obstructive Sleep Apnea:

Symptoms

Snoring, gasping, or choking

Excessive daytime sleepiness

Pauses in breathing while sleeping



Obstructive Sleep Apnea:

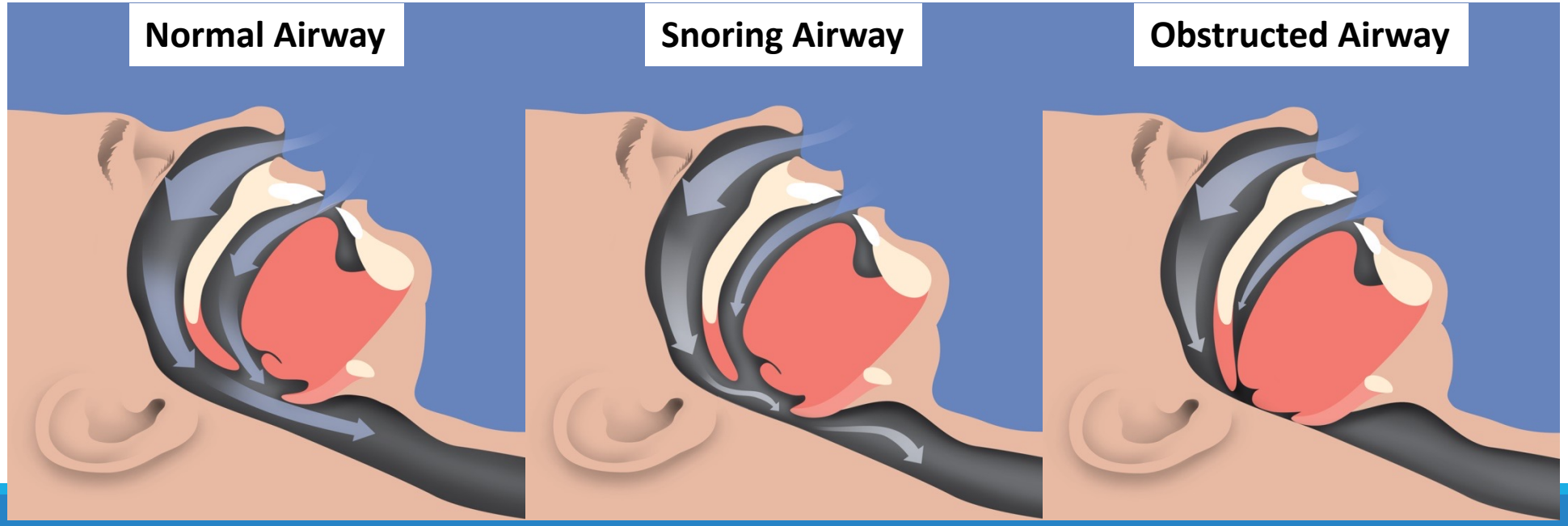
Risk Factors

Body Mass Index >30 kg/m^2

Large neck size (>43 cm for men; >41 cm for women)

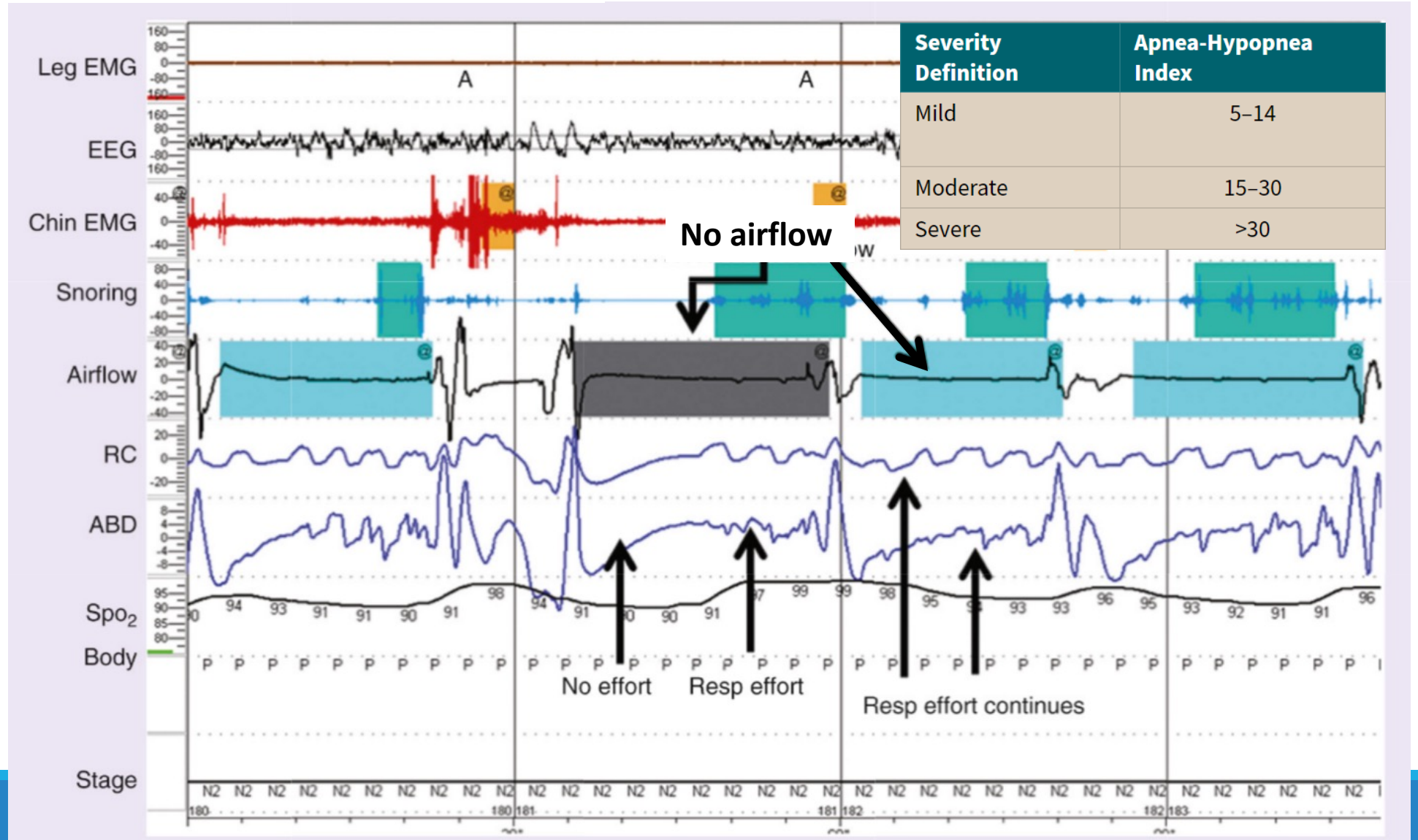
Ability to fall asleep anywhere, at any time

Frequent urination during sleep window



Principles & Practice of Sleep Medicine, p. 750-756; 1110-1124

OSA Diagnosis



Severity Definition	Apnea-Hypopnea Index
Mild	5–14
Moderate	15–30
Severe	>30

Obstructive Sleep Apnea as a Risk Factor

Obstructive sleep apnea increases the risk of

- Type 2 Diabetes Mellitus
- Cardiovascular Disease
- Metabolic Syndrome
- Stroke
- Alzheimer's Disease

Delayed Sleep Phase

Narcolepsy

A sleep disorder characterized by excessive daytime sleepiness and abnormal transitions to REM sleep

Clinical features:

- Excessive daytime sleepiness
- Sudden unwanted sleep episodes
- Cataplexy: an abrupt loss of muscle tone
- Sleep paralysis and hallucinations upon sleep onset
- Fragmented sleep at night

Restless Legs Syndrome

- Strong urge to move
- Uncomfortable or painful
- Intensifies during inactivity
- Activity relieves symptoms, but disrupts sleep
- Symptoms are worse in the evening or during the night

Periodic Limb Movements

Occur during NREM sleep

Repeated every 20-40 seconds

Symptomatic of RLS, but without excessive daytime sleepiness

Summary

Sleep quality changes in terms of quality and quantity throughout life.

Older adults have shorter sleep duration, poorer sleep efficiency, and different sleep architecture than younger adults

Changes in older adult sleep quality may be due to changes in circadian rhythms with age


Pause

Improving Sleep and Circadian Rhythms in Older Adulthood

Common Therapies for Improving Sleep

Medication

Cognitive Behavioural Therapy
- Sleep Hygiene

Treatments for Obstructive Sleep Apnea
- Continuous Positive Air-Pressure, Snore-guard, Exercise

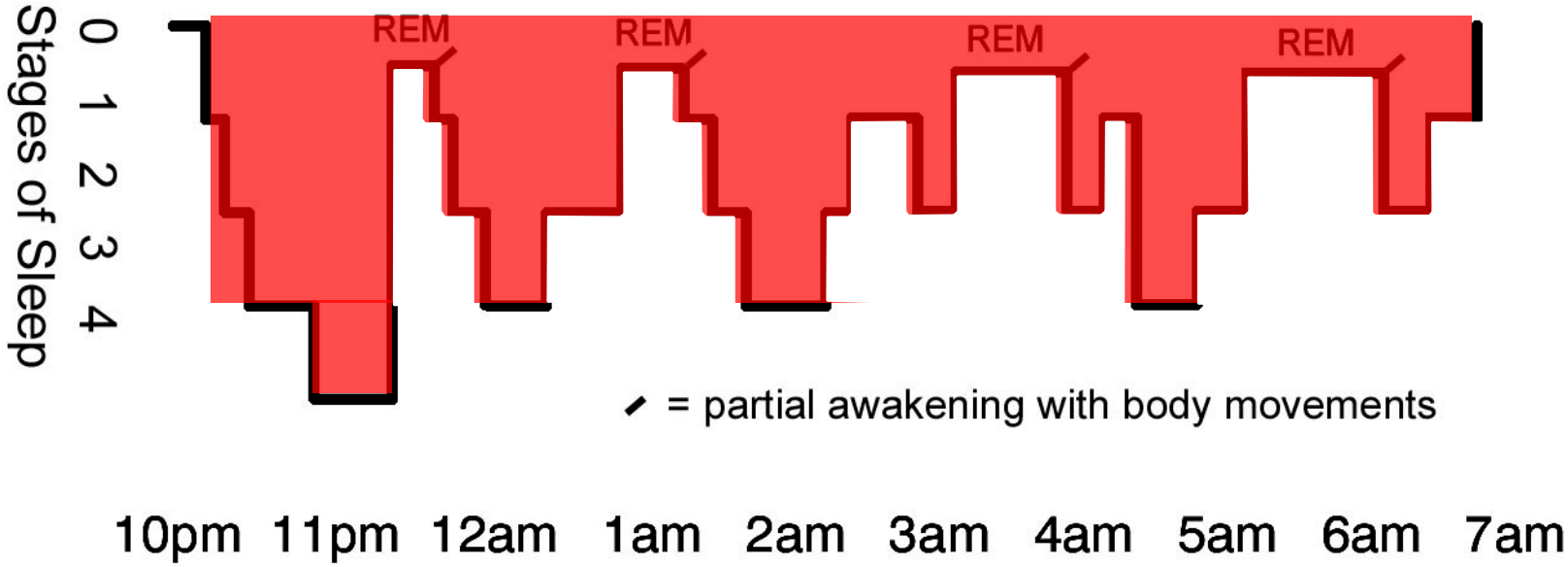
Physical Activity and Exercise

Chronobiotics

Treatments for Improving Sleep:
Medication

Benzodiazepines, Zolpidem (Ambien), Zopiclone (Imovane) and other sleep aids induce “pharmacological” sleep

At present, there is no drug which can mimic or induce a proper “physiological” sleep



Note: Other medications used for sleep include serotonin antagonist re-uptake inhibitors (e.g. Trazadone), and antipsychotics (Seroquel). The effects of these medications are different than other over-the-counter sleep aids.

Treatments for Improving Sleep:
Medication

Most common form of treatment

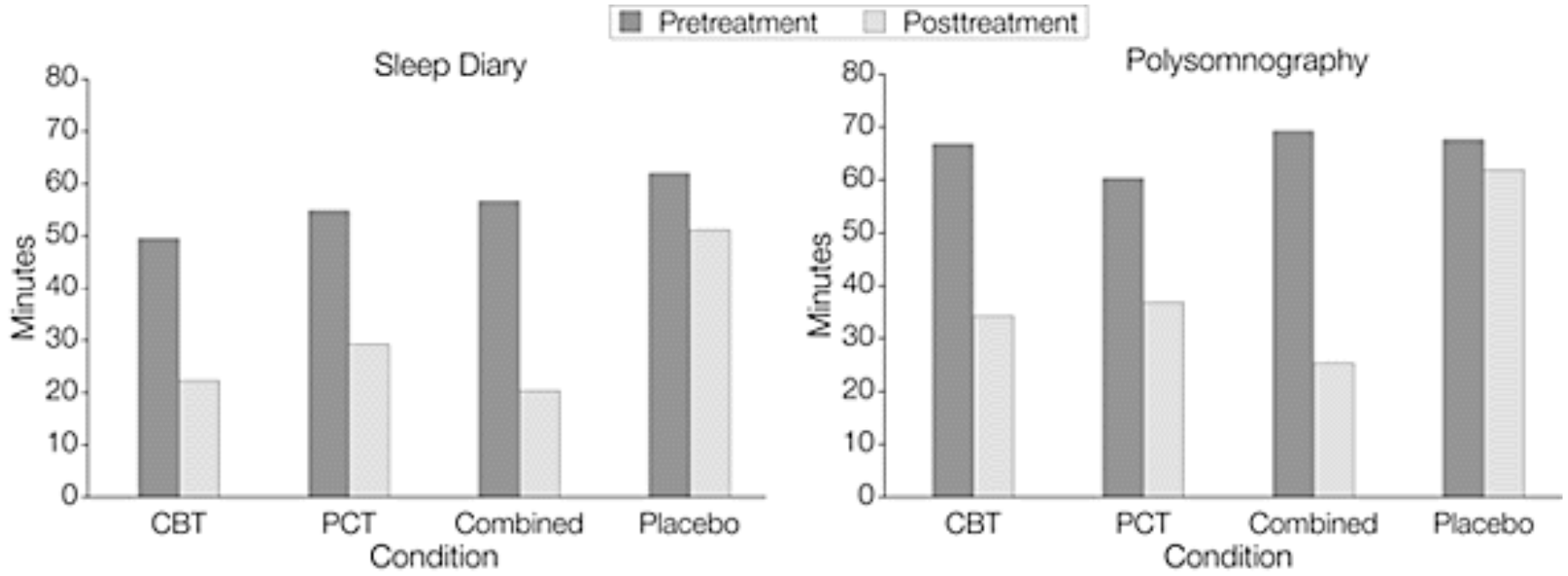
Effective for short-term problems

Sleeping pills are associated with a much higher risk of mortality

Mortality risk of **30** sleeping pills per month was equal to risk associated with smoking one pack of cigarettes per day (Kripke et al., 1998)

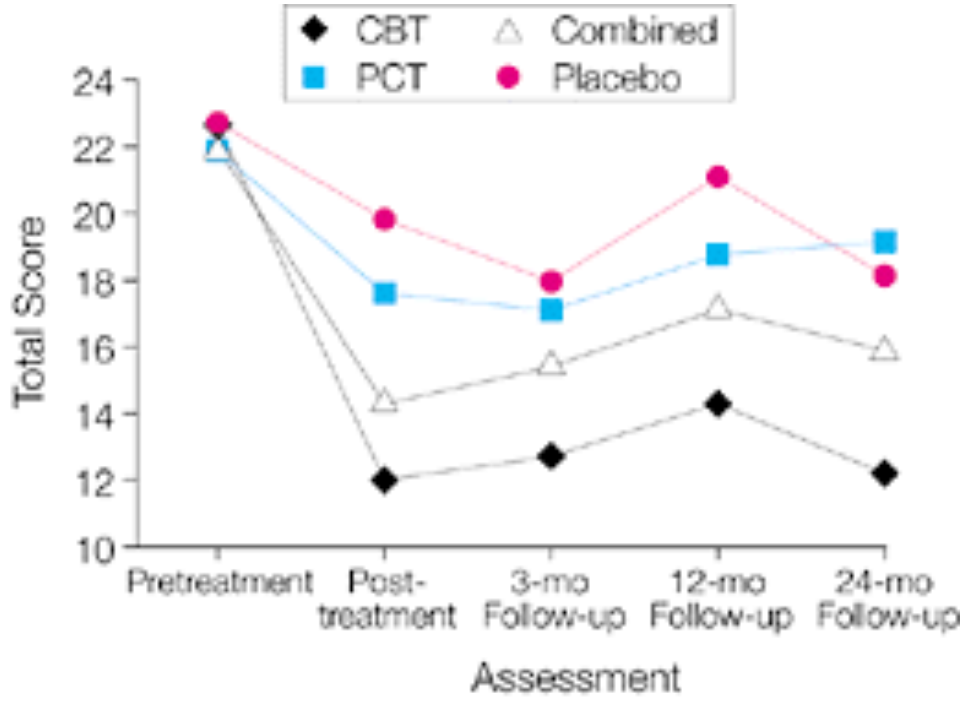
Pills/Month	Risk Ratio
0	1.0
1-29	1.8
30	3.2

Treatments for Improving Sleep:
Cognitive Behavioural Therapy



Changes in Wake After Sleep Onset in CBT, PCT, and combined PCT and CBT vs. Control
CBT: Cognitive Behavioural Therapy; PCT: Pharmacological Therapy

Treatments for Improving Sleep:
Cognitive Behavioural Therapy



Changes in sleep impairment score for CBT, PCT, and Combined PCT and CBT vs. control
CBT: Cognitive Behavioural Therapy; PCT: Pharmacological Therapy

Treatments for Improving Sleep:
Cognitive Behavioural Therapy

Cognitive behavioural therapy is highly effective, but not often used to improve sleep.

Teaches individual to recognize and change beliefs that affect ability to sleep.
- Used to help control or eliminate negative thoughts and worries which keep person awake

Helps develop good sleep habits and avoid behaviours that keep individual from sleeping well

Cognitive Behavioural Therapy techniques include
- Stimulus control therapy
- Sleep restriction
- Sleep hygiene
- Relaxation training
- Paradoxical intention (Passive awakeness)
- Biofeedback

Treatments for Improving Sleep:
Sleep Hygiene

Set of habits and behavioural practices which can improve sleep quality

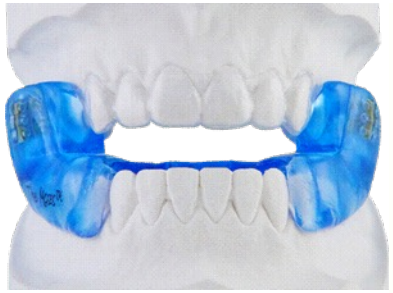
- A part of cognitive behavioural therapy

Good sleep hygiene includes:

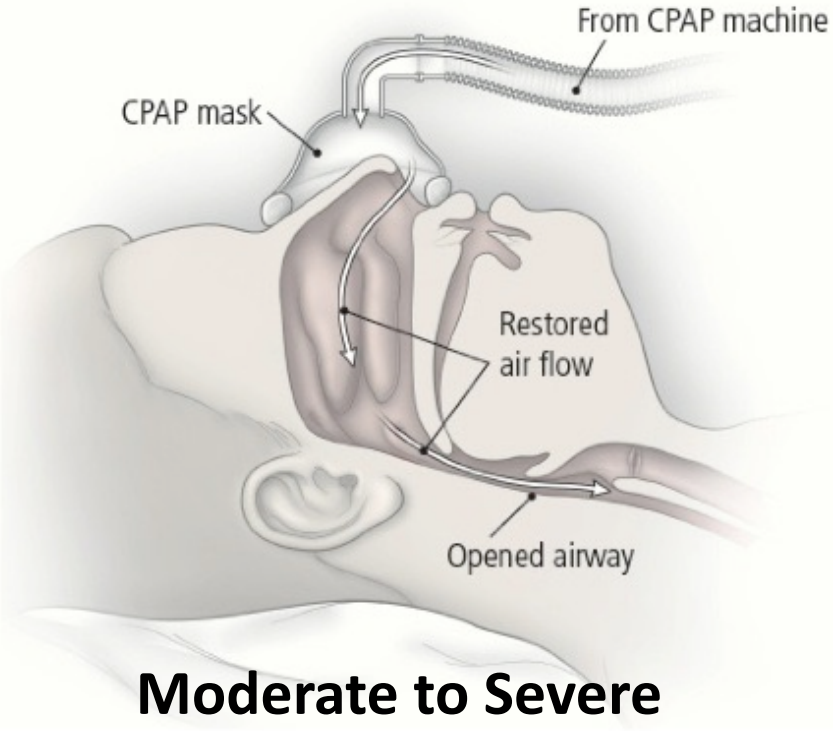
- A sleep friendly environment (temperature, light, sound, bed comfort, etc.)
- A sleep inducing routine
- Avoiding electronics at night

Treatments for Improving Sleep:

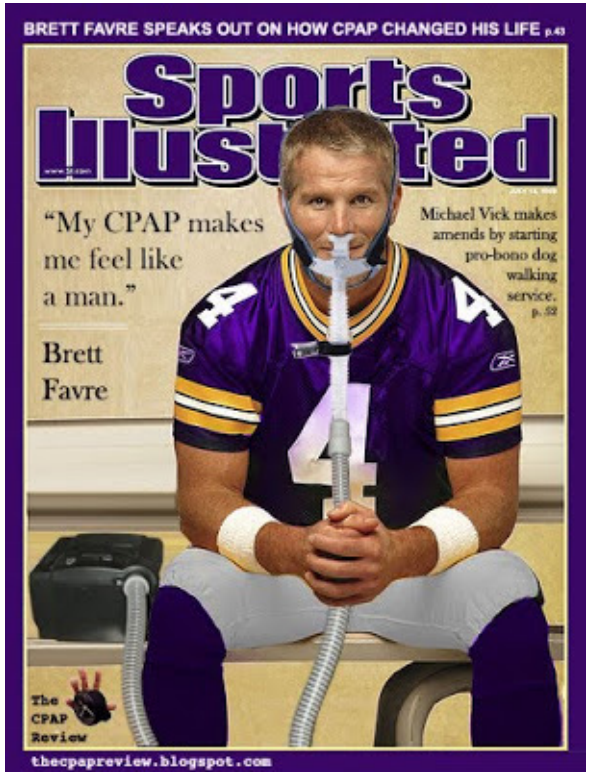
Obstructive Sleep Apnea Treatments



Mild



Moderate to Severe



Treatments for Improving Sleep:
Physical Activity and Exercise

Physical activity and exercise can impact both acute and chronic sleep quality (Kredlow et al., 2015)

Acute Changes

- Small benefits on sleep duration, sleep latency, sleep efficiency, stage 1 sleep, and slow wave sleep
- Moderate benefit on WASO
- Small improvements in REM sleep

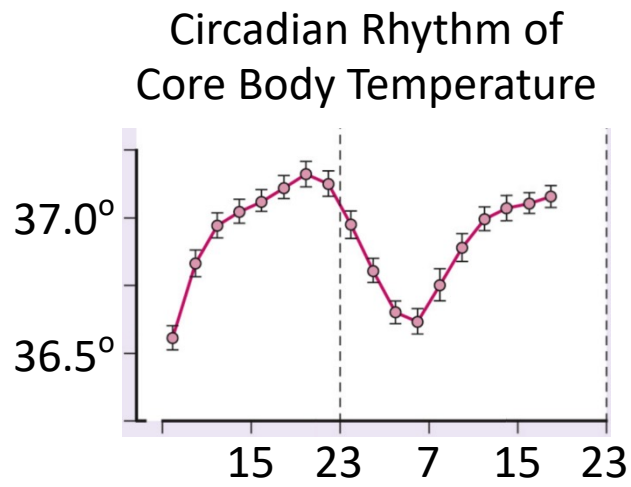
Chronic Changes

- Small benefit on sleep duration, sleep efficiency,
- Small-to-medium benefits on sleep latency and subjective sleep quality

The effects of exercise and physical activity on sleep quality appear to weaken with age

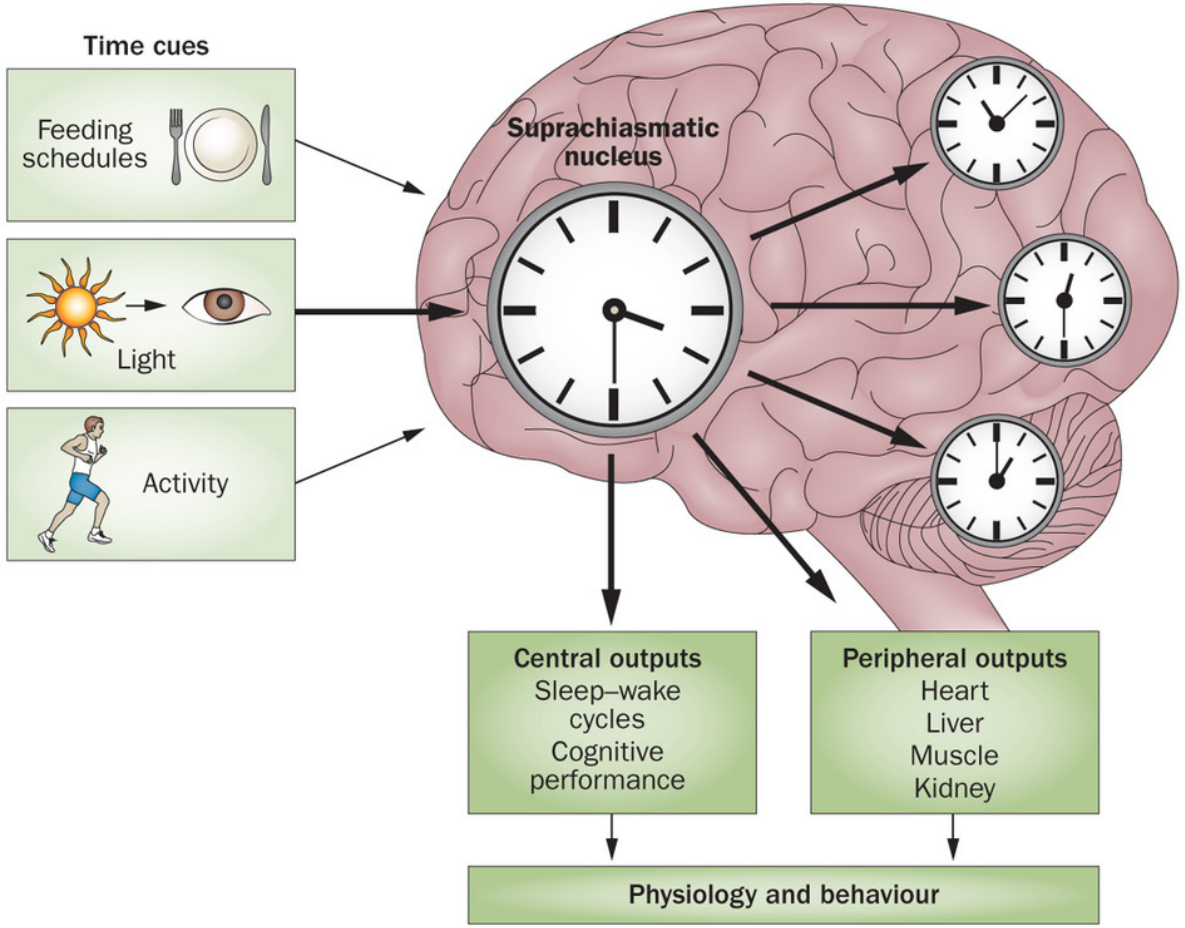
Treatments for Improving Circadian Rhythms

Chronobiotics



Chronobiotic:

- **Any environmental time cue capable of entraining circadian rhythms**
- **These time cues are called Zeitgebers (i.e., time giver, in German)**



Treatments for Improving Circadian Rhythms

Chronobiotics

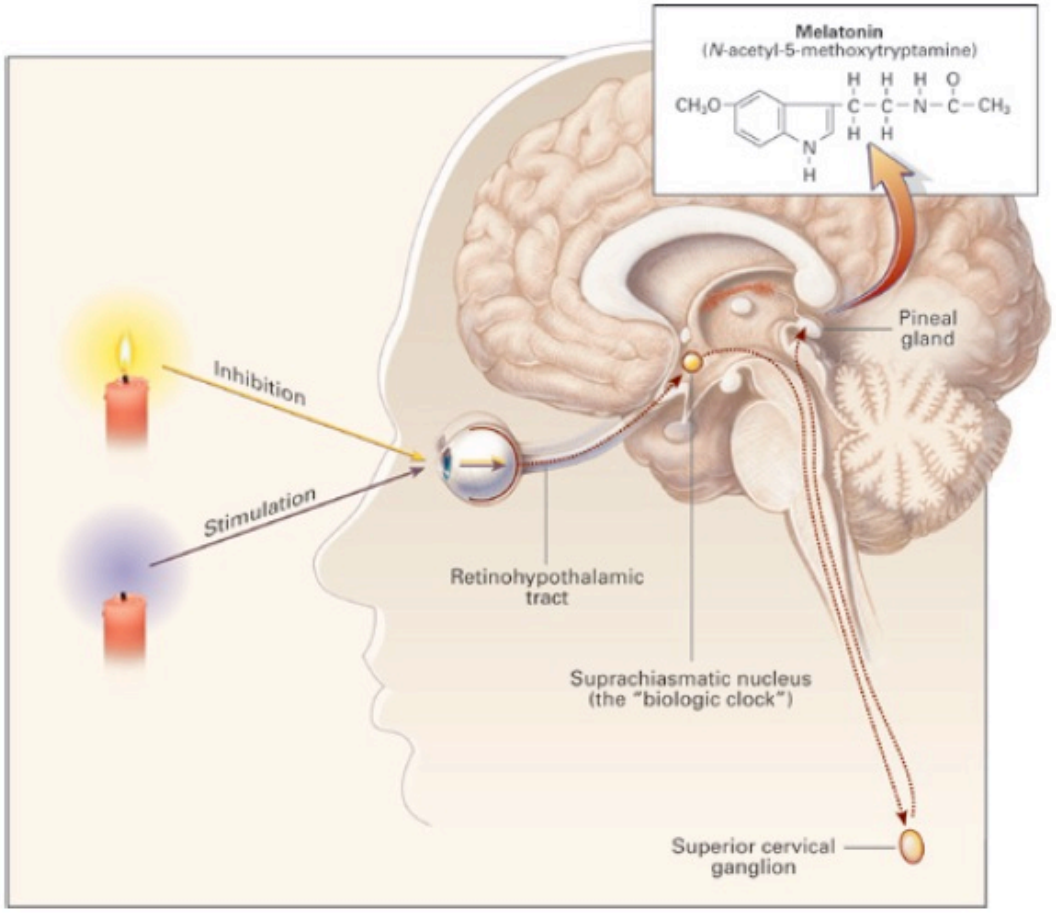
External time cues

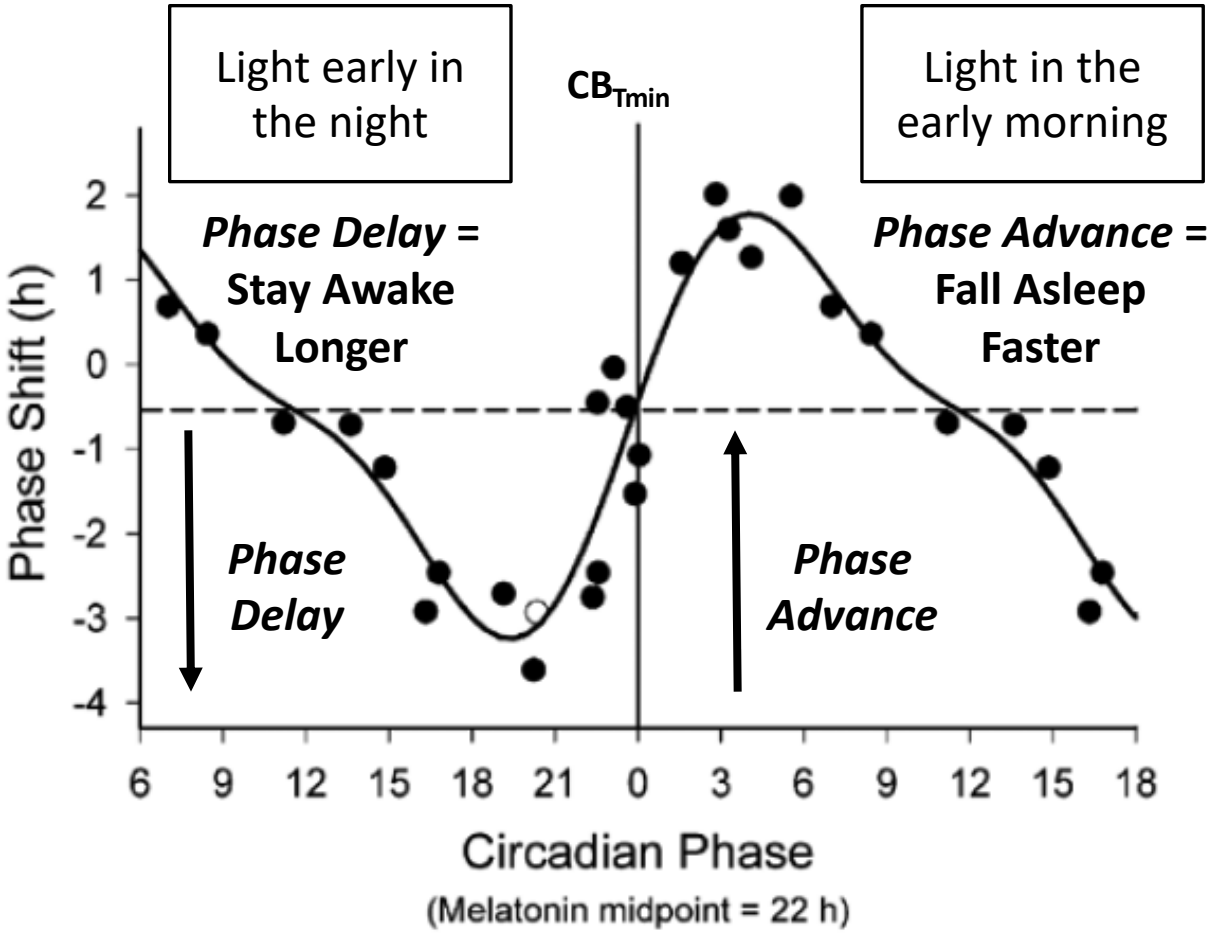
"Entrainment"

Internal clock time

Chronobiotics

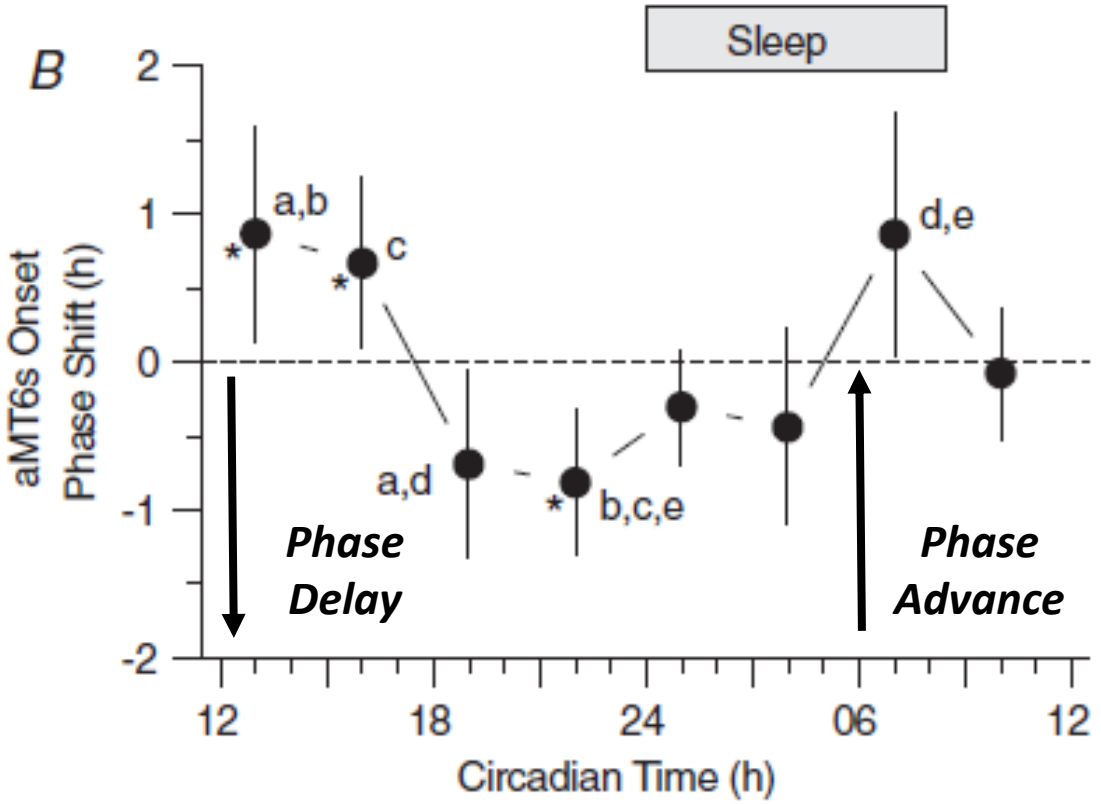
Bright Light Therapy: The most important chronobiotic





Chronobiotics

Physical Activity as a chronobiotic



Youngstedt et al., 2019

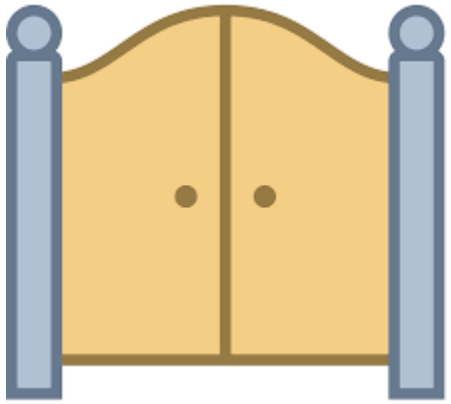
Chronobiotics

How does physical activity entrain the biological clock?

Physical activity performed in the morning or early afternoon does not appear to have a consistent effect on phase shifts (*Buxton et al., 2003; Baehr et al., 2003*)

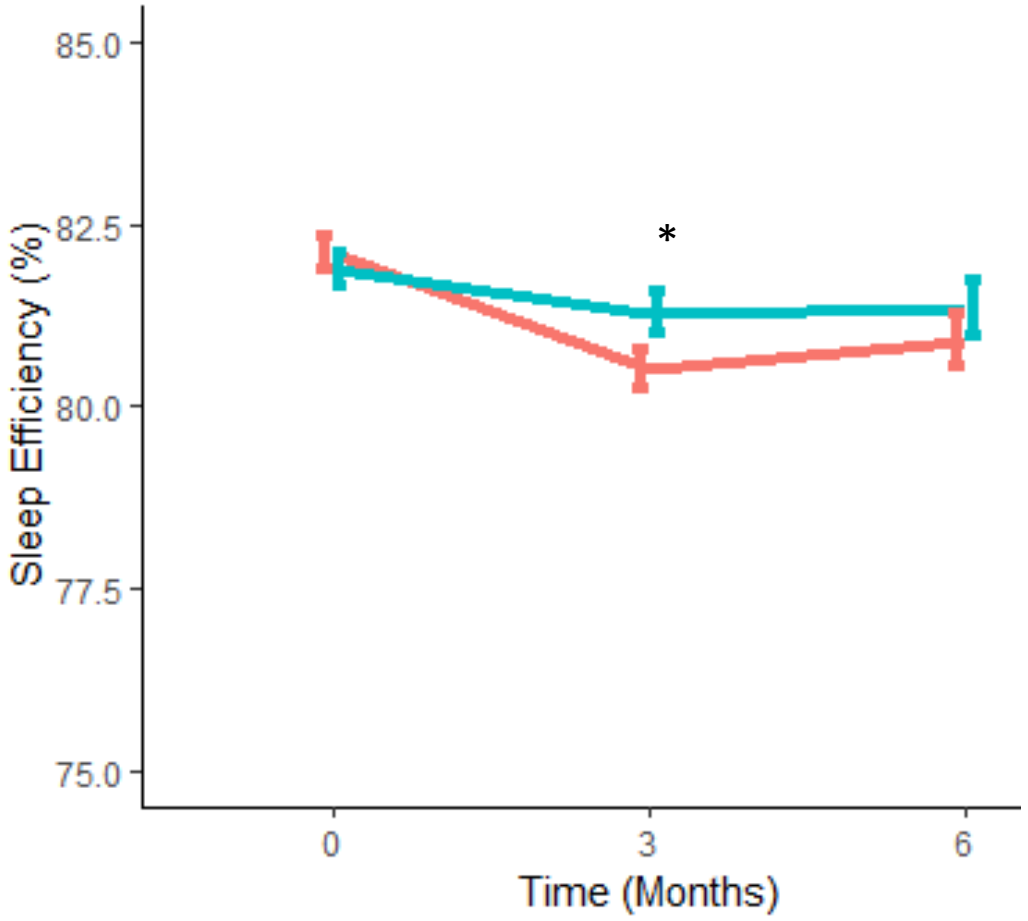
- Physical activity in the late afternoon causes a phase advance (i.e., fall asleep faster)
- Physical activity late at night causes phase delay (i.e., stay awake longer)

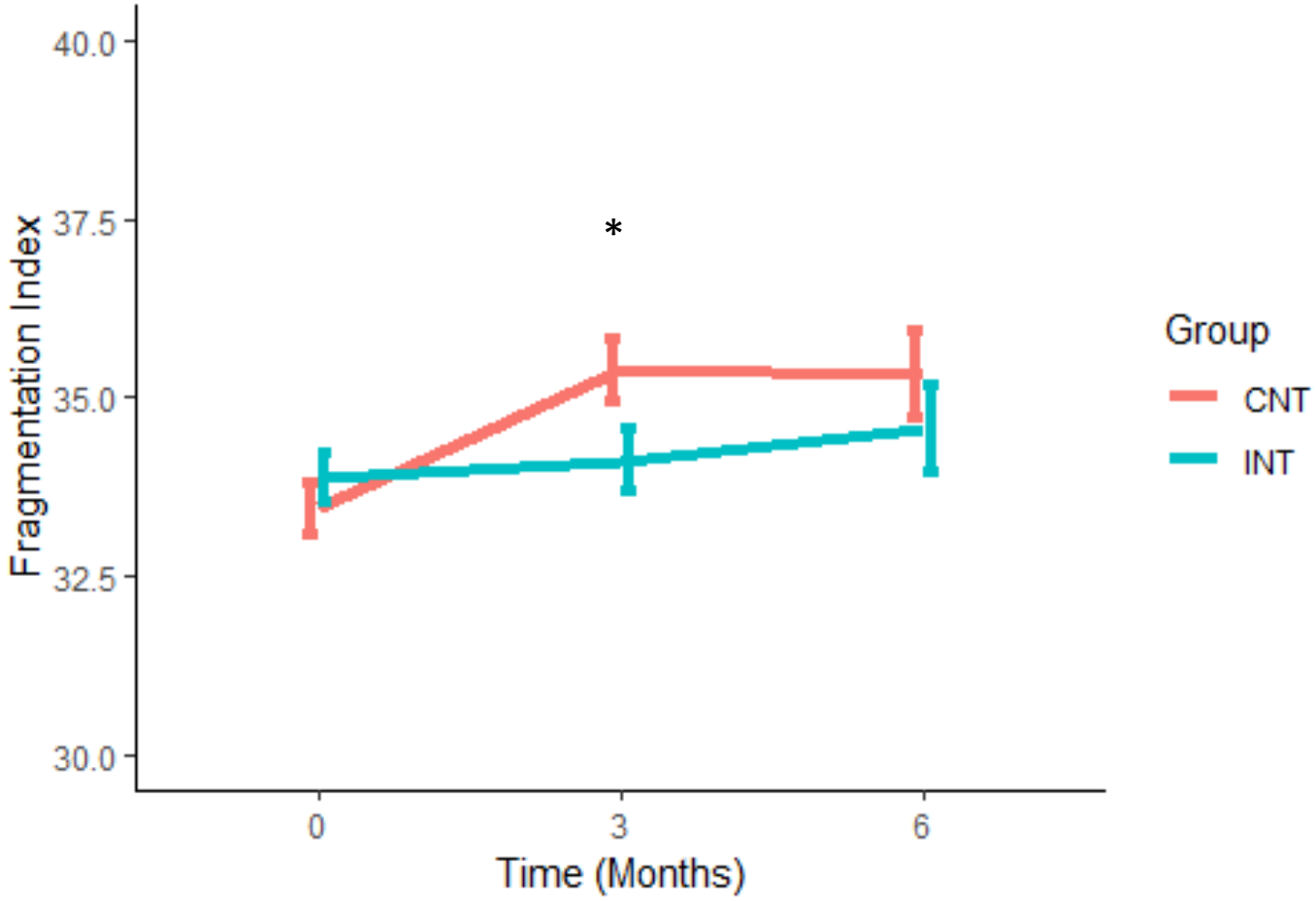
Time-based response to how physical activity impacts phase shifts may coincide with the “sleep gate” (*Dijk & Edgar, 1999*)



Chronobiotics

Personalized chronotherapy maintains sleep efficiency and fragmentation compared to usual care

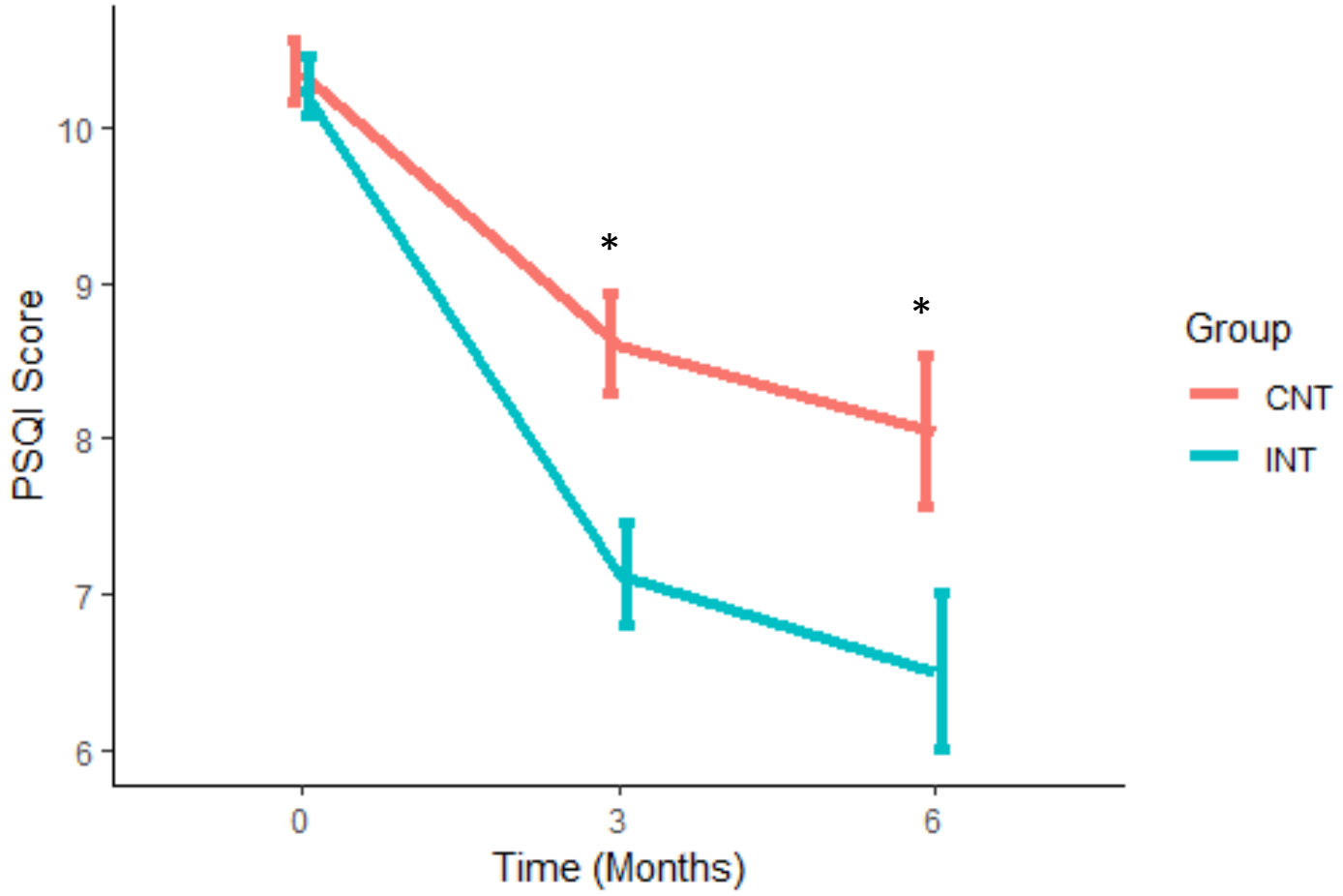




Note: Model Controls for Baseline Sleep Efficiency and STOP –BANG score

Chronobiotics

Personalized chronotherapy significantly improves subjective sleep quality compared to usual care



Note: Model Controls for Baseline PSQI Score and STOP –BANG score

Treatments for Improving Circadian Rhythms
Chronobiotics

Uses zeitgebers to re-align the biological clock

Can improve both circadian rhythms and sleep quality

Requires precise timing according to circadian cycle

Feasibility long-term is questionable

Practice Question

What is the best method for improving sleep quality?

What is the least effective method for improving sleep quality?

Answer: There is no one best method, or least effective method for improving sleep quality. Sleep is complicated, and improving sleep often requires a multi-faceted approach.

Summary

There are a number of treatments to improve sleep and circadian rhythms

- Pharmacological and behavioural strategies

The effects of these interventions tend to have a modest effect-size at best

Lifestyle and behavioural strategies may be the most healthy long-term, but it is dependent upon the individual person's needs

Questions