Sleep and the circadian rhythm

Do you get enough sleep?

(7-9 hours per night)

(unless you are part of the 1%)

25% chance that you’re not

- https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-adults-getting-enough-sleep-infographic.html

Negative health outcomes associated with chronic insufficient sleep

- Greater risk for heart disease, stroke, asthma, arthritis, depression, diabetes
- 20% of car crashes are attributed to drowsy driving
- Likely carcinogenic, conferring risk similar to HPV infection
- Decreased sperm counts, decreased circulating testosterone, and testicular shrinkage in males

Why don’t we get enough sleep?

- When you have a lot to do, do you sometimes stay up late or wake up early?
- Do you put reducing sleep duration in the same category as skipping meals or exercise?

What is sleep?

- Decrease in physical activity
- Decoupling from external inputs
- Changes in brain wave activity (recall from Chap 6: How are brain waves measured?)

Phases of sleep

- Rapid eye movement (REM) sleep
- Non-REM (NREM) sleep
  - NREM1
  - NREM2
  - NREM3

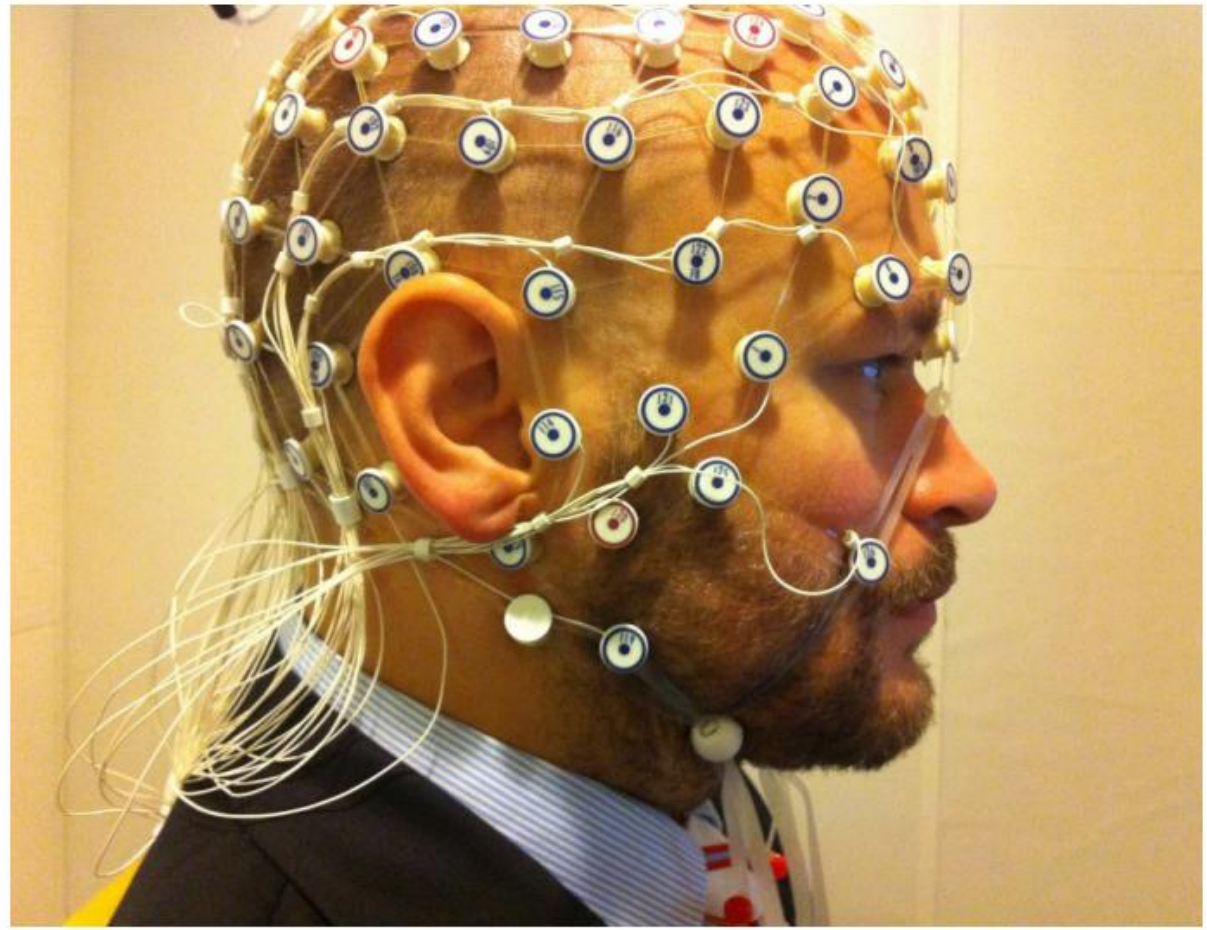


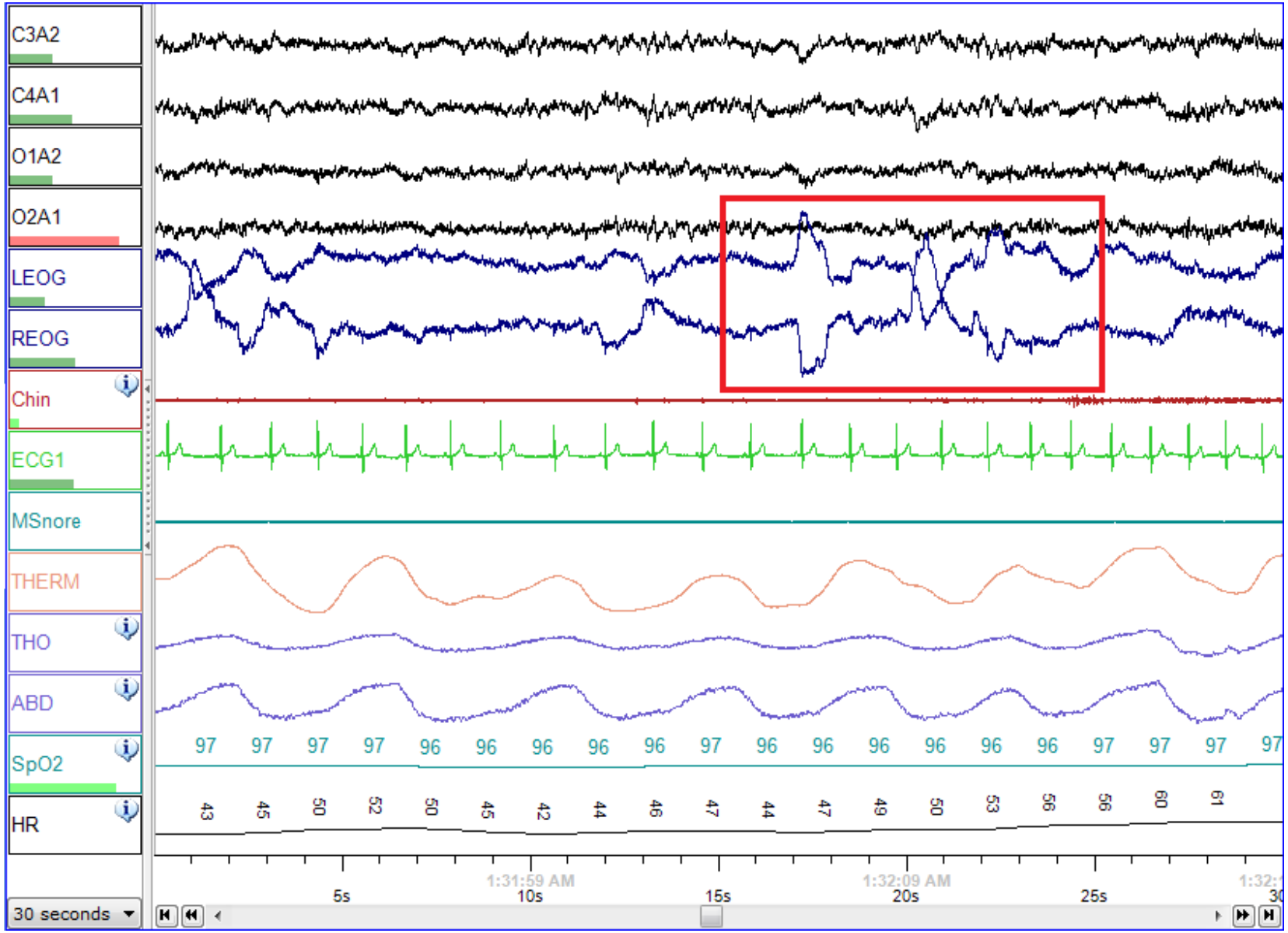
Figure 12.2 In an EEG, electrodes are placed on the head that can detect and record neuronal activity of the cortex.

By Rklawton via CC BY-SA 4.0

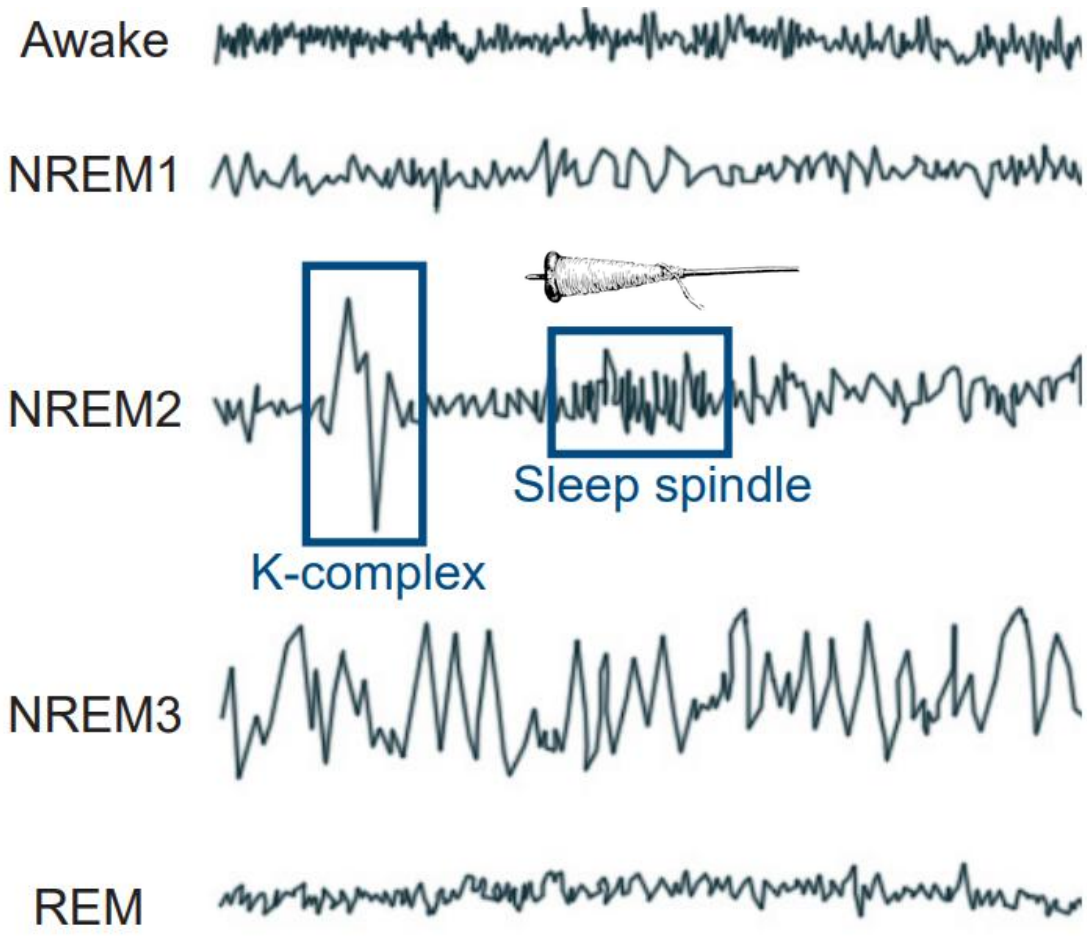
By Kuyohong via CC BY-SA 4.0

Polysomnography

- Multi-parameter sleep study
- Diagnostic tool in sleep medicine
- Measure eye movements (EOG), skeletal muscle activation (EMG), heart rhythm (ECG), respiratory airflow, respiratory effort, pulse oximetry, and EEG



By NascarEd - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=24506939



Beta (13-30 Hz)

Alpha (8-13 Hz) and theta (4-8 Hz)

Theta (4-8 Hz) + K-complexes and sleep spindles

Delta (1-4 Hz)

Beta waves (13-30 Hz)

Figure 12.3 Throughout the night, the EEG shows that the brain cycles through different patterns of activity.

Spindle is from public domain
https://commons.wikimedia.org/wiki/File:History_of_Inventions_USNM_29_Spindle.png

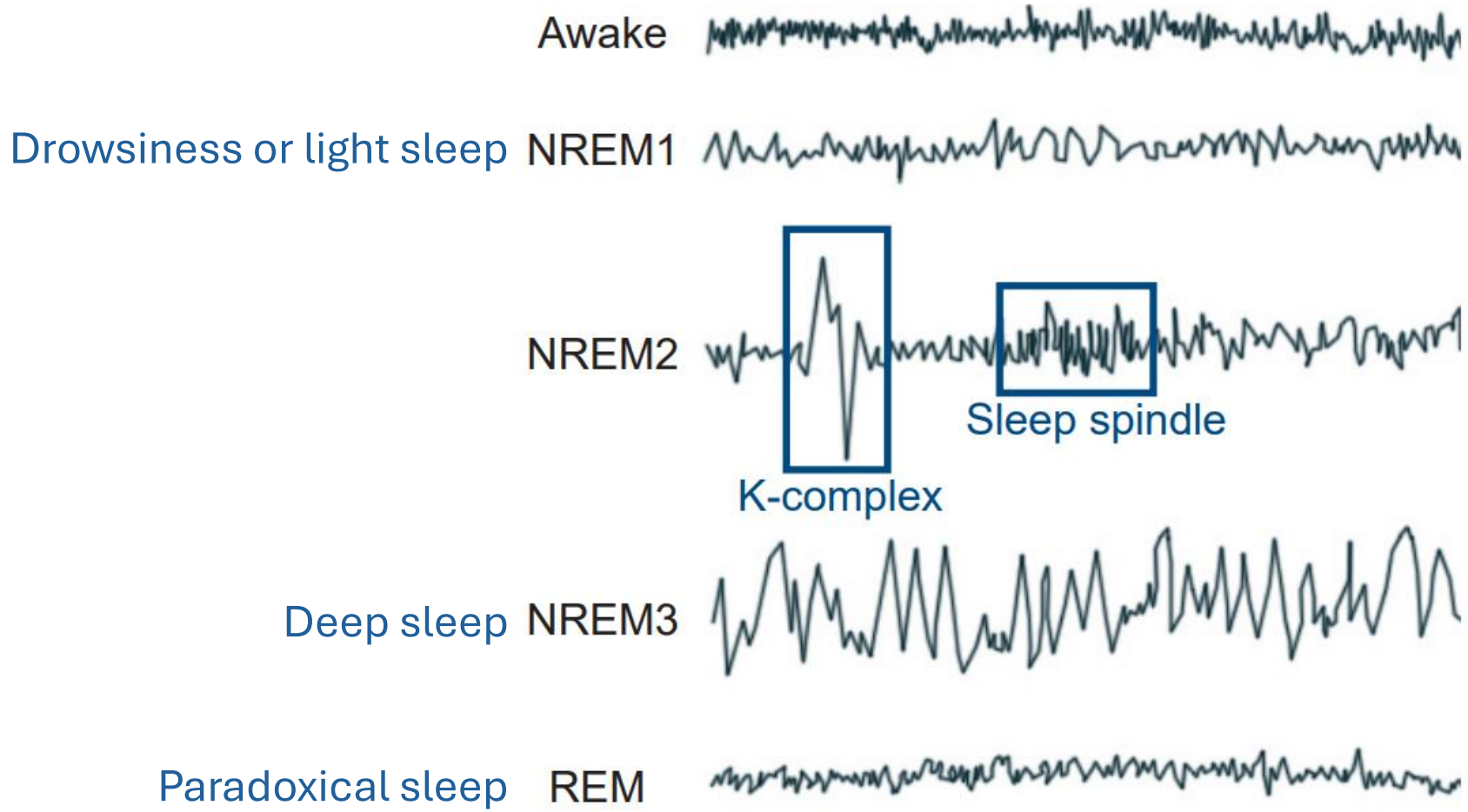
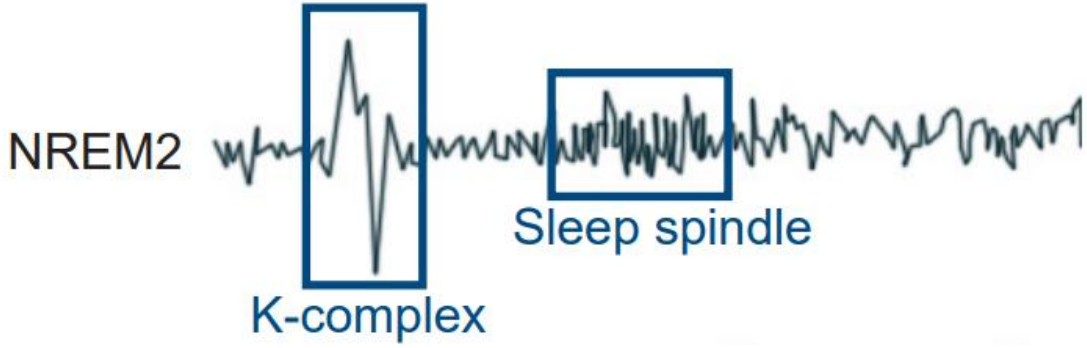


Figure 12.3 Throughout the night, the EEG shows that the brain cycles through different patterns of activity.

What are k-complexes and sleep spindles?

- K-complexes are the largest amplitude event on a healthy human EEG
- Sleep spindles follow k-complexes
- Sleep spindles are high frequency bursts of rapid neural activity in the low beta range
- Sleep spindle function
  - May be related to memory processes
  - May help minimize perception of outside stimuli to help you stay asleep



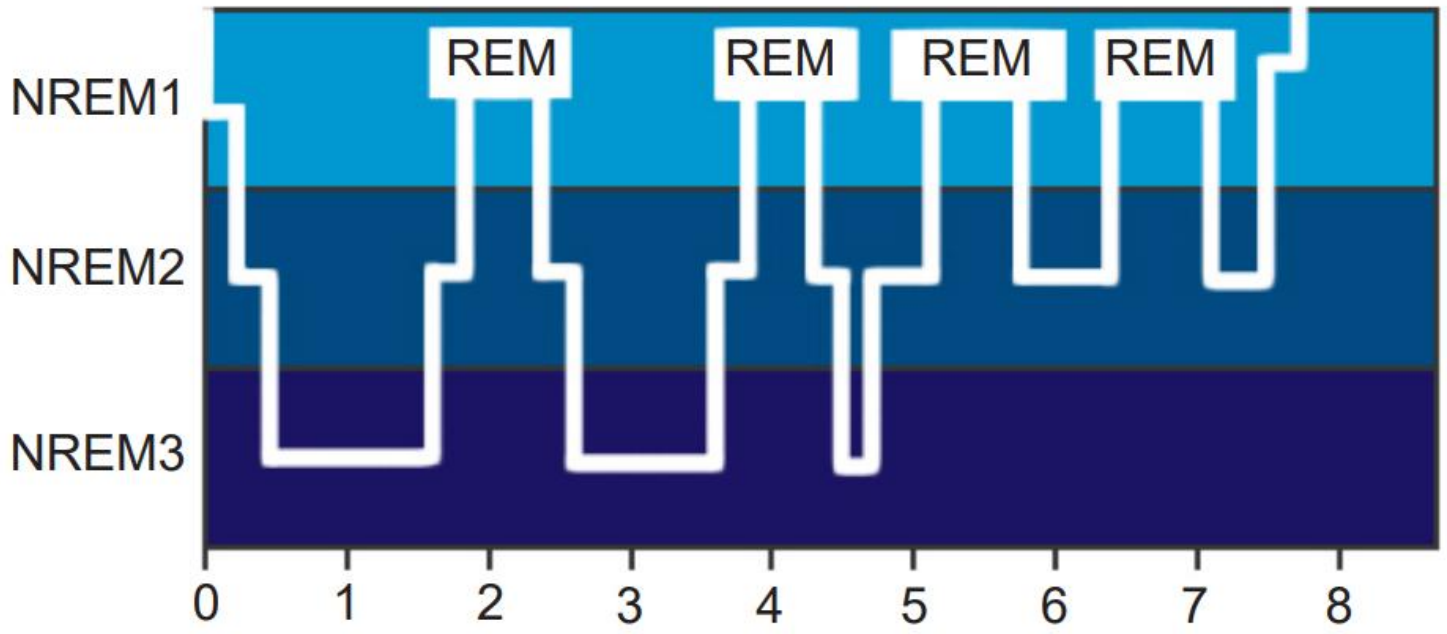


Figure 12.4 A hypnogram can be used to visualize the time spent in each phase of sleep over the night.

Predictable

Varies over the night

The discovery of REM sleep

- Nathaniel Kleitman, the father of sleep research
- Born in what is now Moldova to a Jewish family
- Forced to flee to Palestine
- Moved to the US at age 20 with nothing
- By age 28 had earned a PhD from the University of Chicago, went on to become faculty there
- Died in 1999 at the age of 104

Nathaniel Kleitman in 1948. Credit: University of Chicago Photographic Archive

Ovaltine

- Makers of Ovaltine sponsored Kleitman's early research
- They hoped to promote Ovaltine as a treatment for insomnia
- https://en.wikipedia.org/wiki/Ovaltine

Kleitman and his grad student, Eugene Aserinsky

Aserinky hooked sleepers up to an EEG

Recorded 800 m worth of data each night

Observed REMs for the “first” time (but remember… they are visible to anyone watching someone sleep!)

https://www.gettyimages.ca/detail/video/1960s-black-and-white-close-up-machine-generating-stock-video-footage/868-74

Why do we sleep?

- We don’t know!
- Three popular theories:
  - Recuperation theory
  - Evolutionary adaptation theory
  - Brain plasticity theory

Recuperation theory

- Being awake is stressful and exerts a physically demanding toll on the body
- The body therefore needs a period of time when energy usage decreases and the body's natural repair system can work without disruption
- Sleep "resets" the body

Evidence for the recuperation theory

- Enhanced metabolic cleaning during sleep
  - The glymphatic system
- Immune system function improves with sleep
  - Transmissible illness susceptibility
  - Vaccine effectiveness
- Growth hormone production increases during sleep
  - GH is produced and released by the hypothalamus
  - Largest wave occurs early in the night during NREM3 sleep

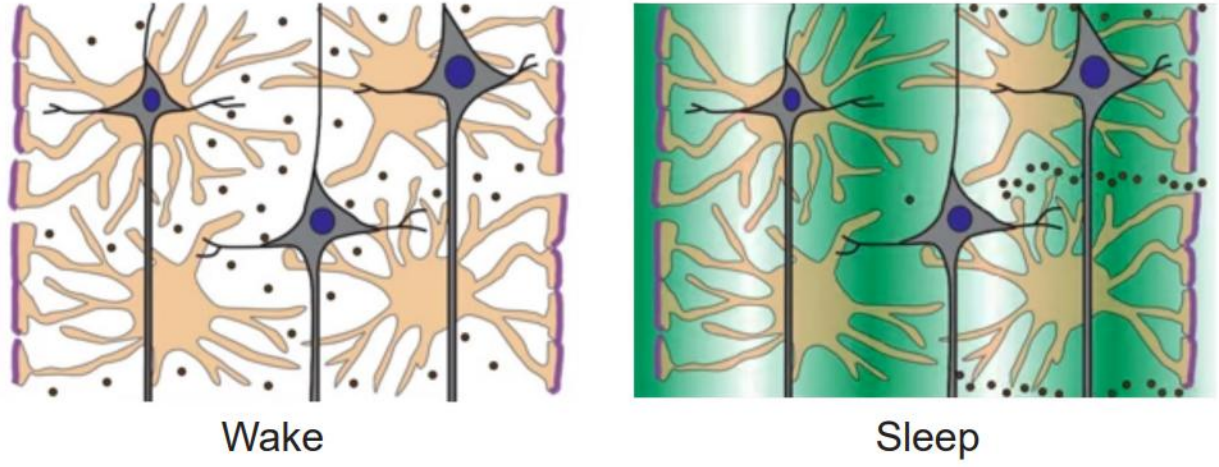


Figure 12.5 During sleep, the glymphatic system increases flow of CSF (green waves) that are able to wash out the amyloid-beta protein (black dots) from the interstitial space.

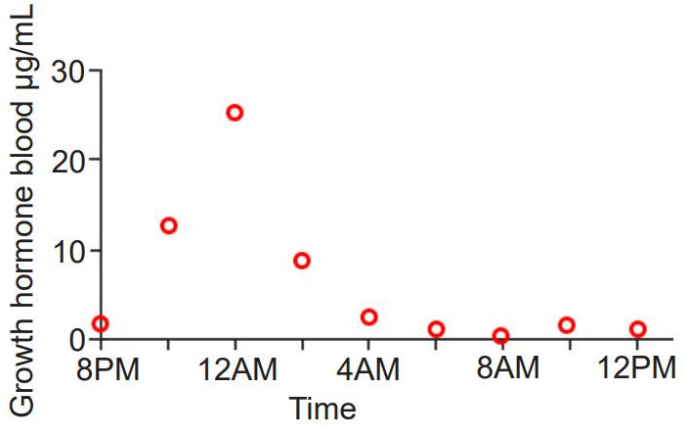


Figure 12.6 Growth hormone levels peak early in the night during deep sleep.

Sleep deprivation

- After total sleep deprivation for several days, humans experience
  - No dramatic physiological changes
  - Sleepiness
  - Mood disturbances
  - Difficulty maintain vigilance
  - Microsleeps
  - Decreased executive function

Peter Tripp

NYC radio DJ raising $ for charity

Sat inside a glass booth in Times Square, stayed awake for 201 hours while broadcasting

Severe psychological symptoms, including paranoia and hallucinations

Later involved in a bribery scandal, lost his job, and got divorced (long term impacts?)

NPR: Randy Gardner

“Decades ago, Randy Gardner stayed awake for 11 days. He broke a record in the process, but the teenage stunt has come back to haunt him. At 71, he offers wisdom about staying up past your bedtime.”

https://www.npr.org/2017/12/27/573739653/the-haunting-effects-of-going-days-without-sleep

The Guinness Book of World Records no longer allows people to try to break the record for longest period of wakefulness

Evolutionary adaptation theory

- Animal sleep patterns are different across species in a manner that benefits each animal
- Humans sleep when it is dark to avoid wandering off a cliff
- Dolphins sleep with half their brain at a time to watch out for predator during sleep
- Tigers are the top predator of their niche and sleep 20 hours/day
- Weakness: sleep involves a period during which the organism is drastically less able to detect approaching predators

Brain plasticity theory

- Sleep is a period of time during which critical changes can occur
- Circuits undergo consolidation processes that are important for memory formation
- Evidence
  - Academic performance and examination grades worsen as a person's nightly sleep decreases
  - NREM3 sleep important for declarative memory
  - REM sleep important for procedural memory
  - Newborns sleep 70% of the day

Dreaming

Myth or fact?

External stimuli are incorporated into dreams	
Dreams run in real-time	
Not everybody dreams	
Penile/clitoral erections indicate dreams with sexual content	
Sleep talking and somnambulism (sleep walking) are the acting out of dreams	

Hypothesis: REMs are associated with dreaming

Tested (by Kleitman in the 1950s) by waking participants up during various stages of sleep and asking them if they had been dreaming

- 80 percent of awakenings from REM sleep led to dream reports
- 7 percent of awakenings from non-REM-sleep stages led to dream reports

More recently, we have found that dreaming during non-REM is more common than previously thought

Antidepressant drugs can reduce REM sleep without affecting dream recall

Cortical lesions can abolish dreaming without affecting REM sleep

Sleep and the circadian rhythm

The circadian rhythm

- Almost every living organism we know of on Earth exhibits a cyclic pattern of activity that closely matches the rising and setting of the sun
- First documented in 1729 in a plant
- Heliotropism: light-seeking movements (e.g., opening leaves in the daytime to capture sunlight)
- Heliotropism occurs even when plants are placed in a dark room

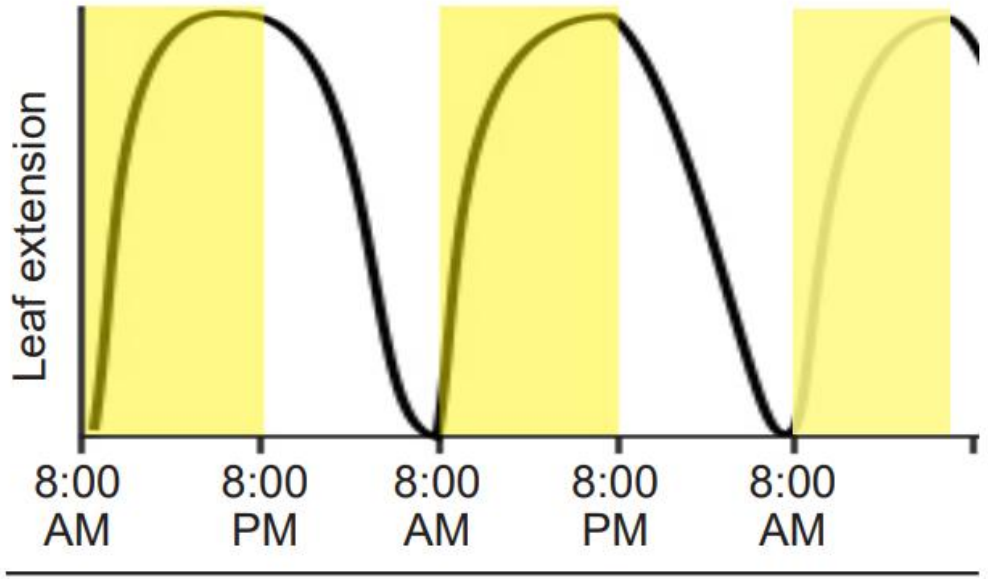


Figure 12.10 The leaves of the *Mimosa pudica* plant open and close their leaves in time with the 24-hour cycle of sun rising and setting, even in complete darkness.

Chronobiology

- The study of day-night dependent periodic phenomena in living things

Circadian rhythms

- Any behaviour or physiological measure that intrinsically cycles on a 24-hour pattern is said to be a circadian rhythm
- Circa = around
- Diem = day
- Ultradian rhythms: faster than 24 hours (e.g., human sleep phases)
- Infradian rhythms: slower than 24 hours (e.g., human menstrual cycle)

Examples of circadian rhythms

- Blood pressure (peaks at 11 AM)
- Body temperature (dips in the evening)
- Withdrawal reflexes (peak around midnight)
- Hunger-driving hormone production (rises before lunch and dinner)
- Attention (highest in the morning)
- Nitrogen fixing of cyanobacteria (even though their lifespan is ~6 hours)

Zeitgebers

- German word for “time givers”
- Environmental or social cues that entrain circadian rhythms
- E.g., sunlight
- Entrainable rhythms: rhythms that change in response to a stimulus
- In the lab: Entrain rhythms by setting the cues (e.g., light in the lab)
  - Was thought that we could entrain rhythms to different periods but not too different (e.g., 22 hours but not 20 hours) – but see Harrison et al., 2016

Jetlag

- When you fly a long distance, your circadian rhythms take time to entrain to the new rhythm of the zeitgeber (i.e., new time zone)
- Increases in melatonin are entrained to occur at nighttime
- Taking oral melatonin can help reduce jetlag duration

Free-running circadian rhythms

- In the absence of zeitgebers, rhythms will free-run
- In lab studies, free-running sleep-wake rhythm estimated to be about 26 hours in humans (e.g., fall asleep and wake up two hours later each day)
- Non-24-hour sleep-wake disorder (Wikipedia article needs work but we did not have a subscription to a journal with a good review article)
  - Impacts majority of individuals with total blindness but also some individuals with sight
  - Can be treated with a melatonin agonist
- International Space Station
  - 16 sunsets & sunrises per 24 hour period (one “day” every ~90 min)
  - Bright blue LEDs during “daytime” and red-shifted wavelengths during evening help induce astronaut sleepiness

Circadian rhythms on the molecular level

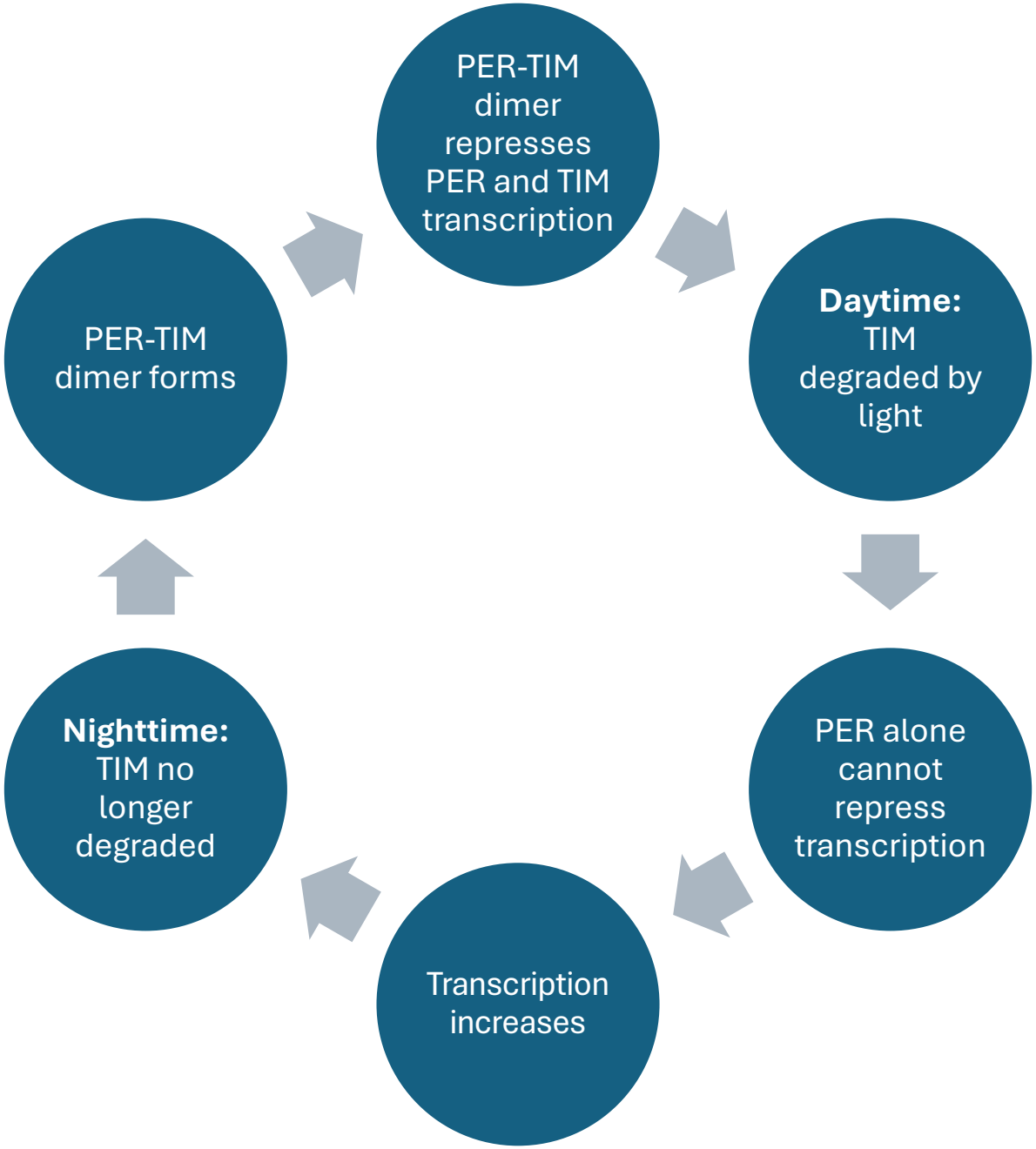
Genome (blueprint for organism) is housed in the nucleus of a cell and is made up of genes

Genes get transcribed into proteins

Proteins do many things (e.g., ion channels, enzymes, etc.)

Circadian rhythms on the molecular level

- Mutations in “period” gene changes sleeping habits of fruit flies
  - Codes for protein PER
  - Mutated PER associated with sleep-wake cycles of 29 hours, 19 hours cycles, or no predictable patterns at all
- “timeless” gene
  - Codes for protein TIM, which interacts with PER by forming a dimer
- TIM-PER dimer enters nucleus, binds to genome, prevents further transcription of PER and TIM
  - Negative feedback


PER-TIM dimer represses PER and TIM transcription
Daytime: TIM degraded by light
PER alone cannot repress transcription
Transcription increases
Nighttime: TIM no longer degraded
PER-TIM dimer forms

Neurochemical signals

- Many neurotransmitters impact sleep
  - Glutamatergic signaling is heightened during awake state
  - Many glutamatergic neurons increase activity during REM sleep
  - Drugs that increase action of GABA are used as sedatives and sleep aids
  - Norepinephrine upregulates sympathetic nervous system to enhance alertness

- We are going to focus on adenosine, melatonin, and histamine

Adenosine

- One of the four main building blocks of DNA (which makes up genes)
- Involved in inflammation, immune response, and heart rate modulation
- Part of ATP molecule (stores energy)
  - ATP gets broken down to release energy
  - Increase in adenosine throughout the day as a result
  - Higher adenosine = more sleepy

Chemically blocking adenosine reduces sleepiness

- Caffeine is the world's most popular unregulated psychostimulant drug
- Theobromine and theophylline also block adenosine and are found in tea and chocolate

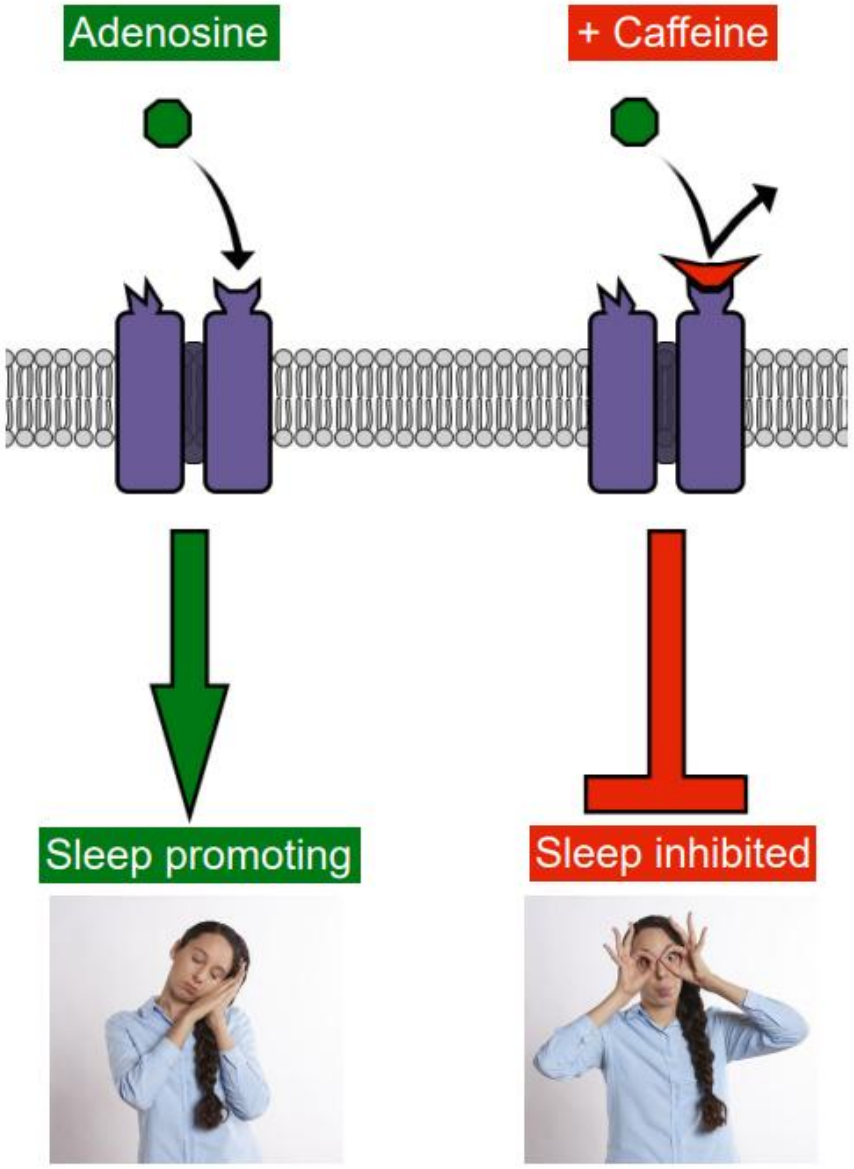


Figure 12.14 Caffeine acts as an antagonist for adenosine signaling.

Caffeine is an adenosine ....

A) agonist

B) partial agonist

C) inverse agonist

D) antagonist

Melatonin

- Hormone that helps regulate the sleep-wake cycle
- Produced by the pineal gland
  - Tryptophan -> melatonin
  - Recall: What other neuroactive chemical is tryptophan converted to?

Control of melatonin production

- Recall: Visual information goes from photoreceptors through the optic tract to the brain
- Information about whether it is daytime goes from photosensitive ganglion cells through the retinohypothalamic tract to the brain
- RHT axons synapse on the suprachiasmatic nucleus (SCN) of the hypothalamus
- SCN neurons inhibit pineal gland, reducing melatonin production during the day

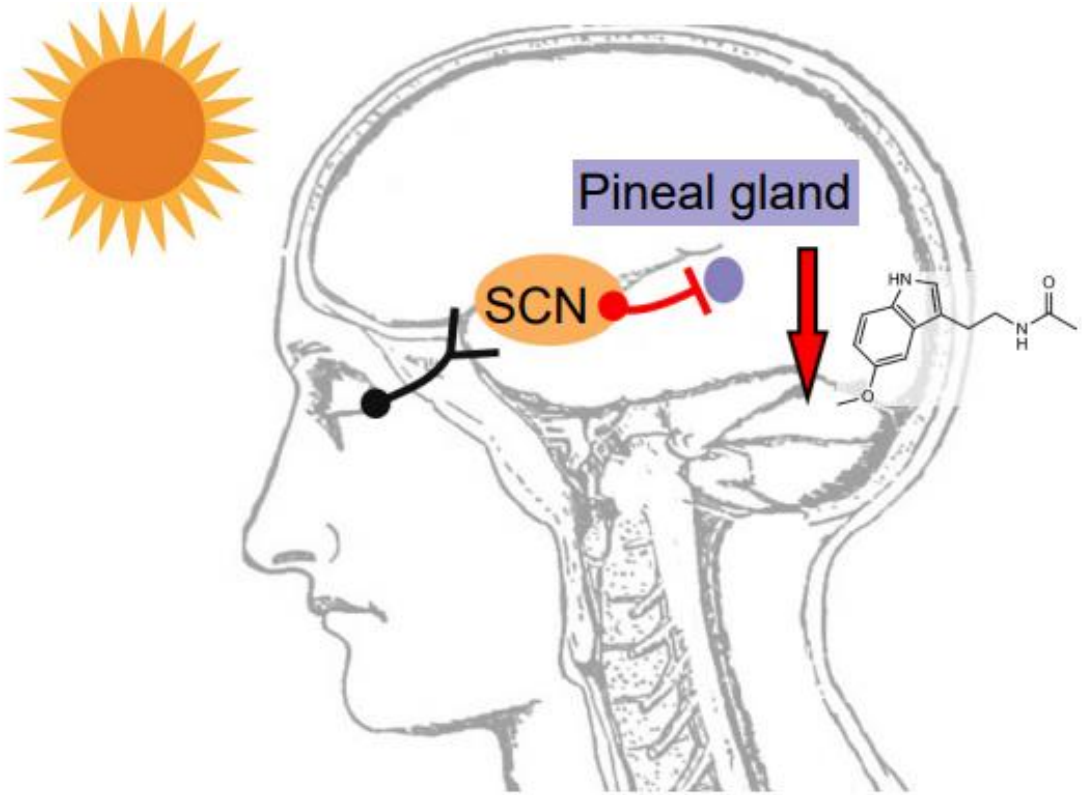


Figure 12.15 Exposure to light sends information via the retinohypothalamic tract and signals to the suprachiasmatic nucleus of the hypothalamus, which inhibits pineal gland production of melatonin.

Impact of light wavelength

- Violet-blue light (e.g., LED lighting, digital screens) are more effective at activating the retinohypothalamic tract and inhibiting melatonin than yellow-red light

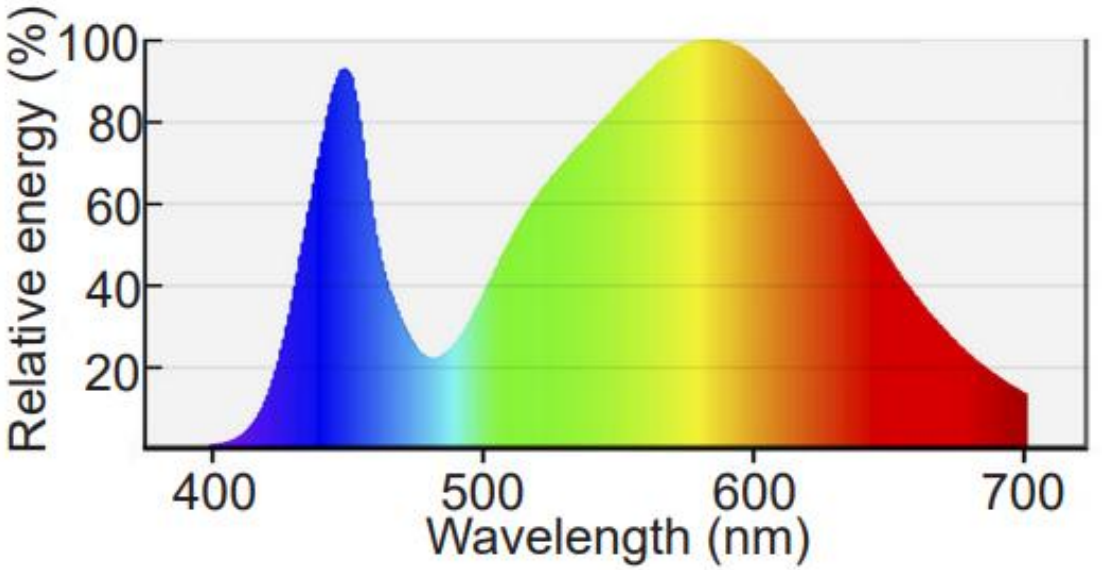


Figure 12.17 Production of melatonin is most strongly suppressed by blue wavelenghts of light, which are emitted by the LEDs that backlight digital devices like computer or cellphone screens.

Histamine

- Small signaling molecule (hormone, neurotransmitter)
- Pro-wakefulness
- Older anti-histamines (for allergies) promote sleepiness

Brain structures involved in sleep

The electrical activity of which brain structures are measured with EEG?

EEG is most sensitive to post-synaptic potentials generated in superficial layers of the cortex, on the crests of gyri directly abutting the skull, producing currents radial to the skull.

Post-synaptic potentials originating deeper in the cortex, inside sulci, in midline or deep structures, or producing currents that are tangential to the skull, make far less contribution to the EEG signal.

(from https://en.wikipedia.org/wiki/Electroencephalography)

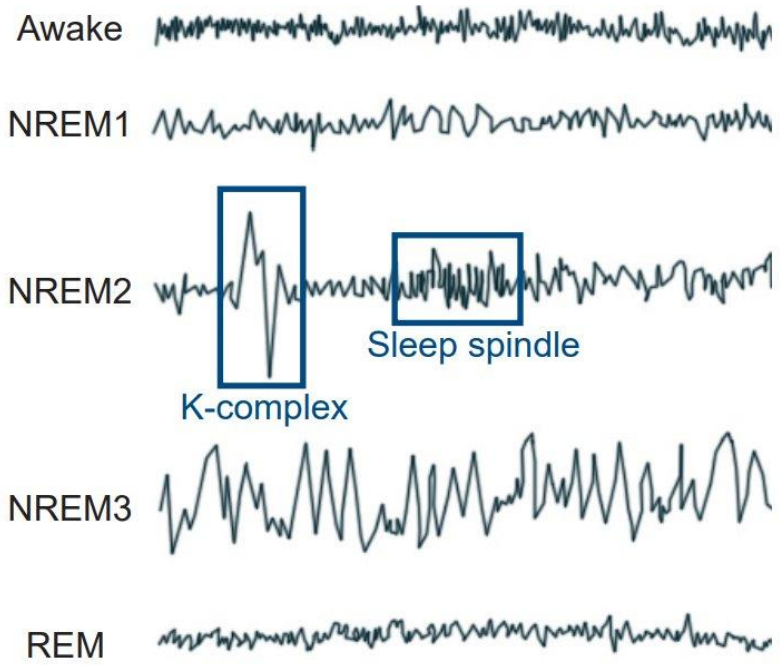


Figure 12.3 Throughout the night, the EEG shows that the brain cycles through different patterns of activity.

Sleep is controlled by a network of brain areas

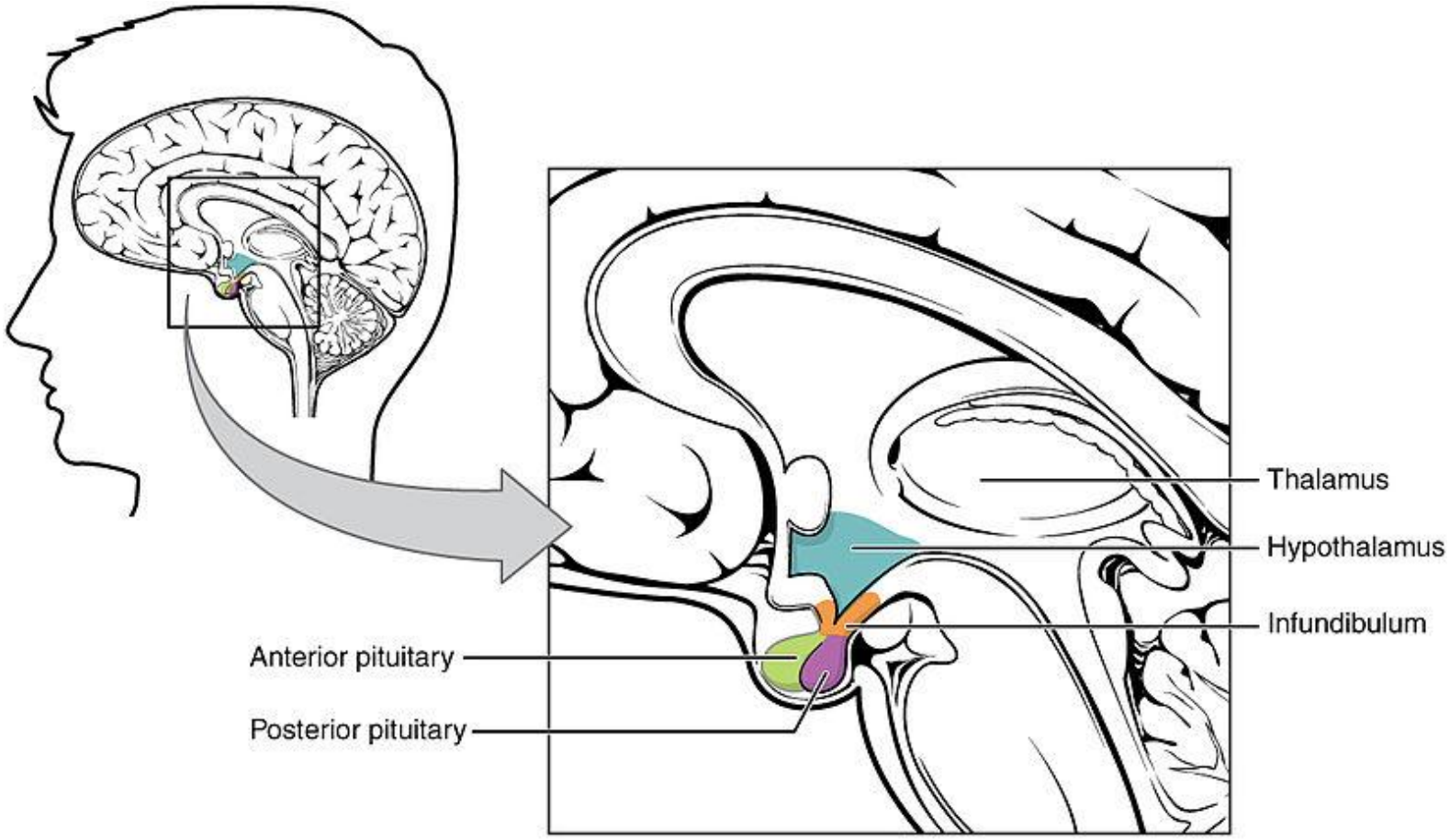
- Cells within evolutionarily older areas of the brain
- Hypothalamus
- Reticular formation

Encephalitis lethargica

- AKA sleeping sickness
  - Cause unknown, but thought to be related to Spanish flu pandemic around WWI
  - Progressive lethargy that started with drowsiness and ended in coma
  - Worldwide pandemic of 5 million (1916-1930)
  - 50% died, many others failed to fully recover
- Injuries found in the hypothalamus upon autopsy
  - Persistently sleepy patients had posterior hypothalamus damage
  - Patients with insomnia had anterior hypothalamus damage

Hypothalamus

- Anterior: sleep promoting
- Posterior: wakefulness promoting



Implication of von Economo's finding

- Sleep was previously thought of as an overall decrease in brain activity
- The finding that the anterior hypothalamus promoted sleep contradicted that view
- Later confirmed by EEG

More hypothalamus subregions

- SCN
  - Important for circadian rhythms via regulating melatonin release
- Lateral hypothalamus
  - Produces pro-wakefulness signaling molecule orexin
  - These neurons are lost in people with severe narcolepsy
- Tuberomammillary nucleus
  - Major site of neuronal production of wakefulness signal histamine

Reticular formation

- Found in the brainstem
- Large net of interconnected clumps of neurons
- Difficult to anatomically classify its individual structures and boundaries
- Contributes to alertness and consciousness
- Severe injuries result in coma
- Information flows upwards and downwards (latter is not involved in sleep)
- Ascending reticular activating system receives inputs from all sensory systems before sending wide projections across all areas of cortex

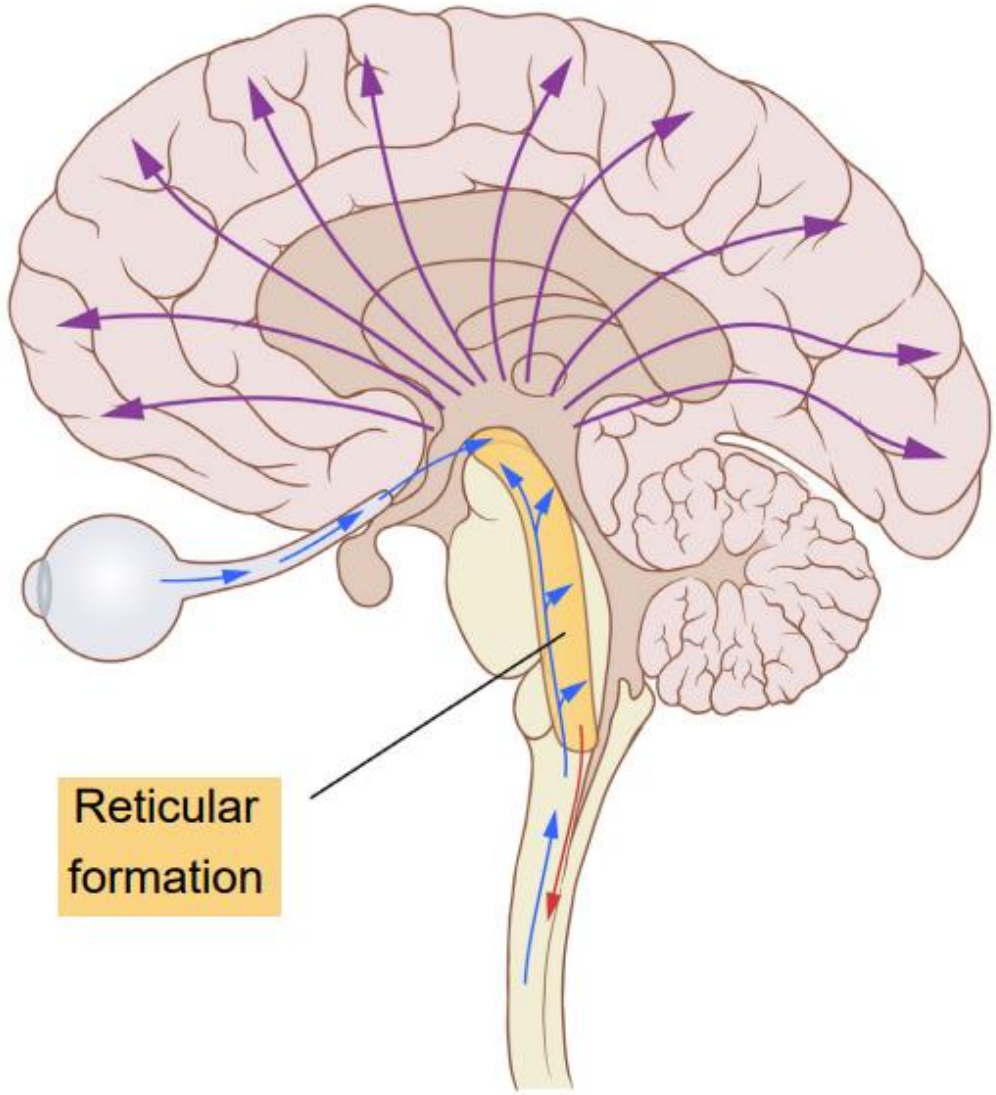


Figure 12.19 The reticular formation in the brain stem is a series of interconnected neurons that control some functions of consciousness.