“If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process ever made.”

Dr Alan Rechtschaffen
Sleep is organized in stages:
- About every 90 or 100 minutes we pass through 4 stages of sleep.
- Two distinct states:
  - Non-rapid eye movement (NREM) and rapid eye movement (REM)
  - NREM
    - Relatively inactive brain in a movable body
    - Comprised of N1, N2, and N3
    - 'Rest the body'
  - REM
    - Activated brain in a paralyzed body
    - 'Refresh the brain'

As night progresses:
- Increased REM per cycle
- Decreased N3 per cycle

Changes with age:
- Body movement decreases
- Spontaneous waking may occur
- Rolling of eyeballs
- Brain wave frequency drops from alpha waves (8-12 Hz) to theta waves (3-7 Hz)
**LIGHT SLEEP - STAGE 2**

- Brain waves slow down (theta waves predominate)
- Bursts of brain activity - 'Sleep Spindles'
- K complexes

**DEEP SLEEP – STAGE 3**

- Deep sleep sets in – hard to wake up
- Brain waves slow (delta sleep/slow wave sleep 0.5-2 Hz) and large in amplitude
- Breathing becomes rhythmic (chemical breathing) and muscles remain relaxed.
- 30-40 min initially, becomes shorter later

**REM SLEEP - RAPID EYE MOVEMENT**

- REM – lasts 20 – 30 minutes
- Motor cortex is active
- Heart rate rises, breathing rapid, irregular “like wake”
- Sweating reduces/ceases
- Eyes rapidly move around
- Dream sleep
- Muscles so relaxed “essentially paralyzed” - EMG reduces in amplitude
SLEEP DEVELOPMENT

- Newborn Sleep
- Infant sleep
- Toddler and preschool
- Middle childhood
- Adolescence

SLEEP DEVELOPMENT: NEWBORN

- Newborns sleep 16-18h a day
- 8 hours of night sleep and 8 hours of daytime sleep
- 4 naps: 2 h each

SLEEP DEVELOPMENT: NEWBORN ACTIVE SLEEP

- Wake transitions to Active sleep followed by 50% of sleep time
- Eyes closed, eye movements
- Respiration uneven
- Corresponds to REM

SLEEP DEVELOPMENT: NEWBORN QUIET SLEEP

- Quiet sleep
- 20% of sleep time
- Eye closed, no movements
- Respiration clear and regular
- No muscle tone
- Trace Alternans (high voltage bursts on low frequency background)
- Corresponds to NREM

- Indeterminate Sleep (mixed state)
- 30% of sleep time

Track alternating quiet sleep characterized by alternating broad band bursts of activity with intermittent epochs of relative EEG quiescence.
SLEEP DEVELOPMENT: INFANTS (0-6 MONTHS)
• As maturation occurs in brain, specific EEG changes are noted, and sleep reorganization occurs
• Spindles (12-14 Hz) appear at 2-6 months (stage 2, NREM)
• K-complexes 4-6 months (stage 2, NREM)

SLEEP DEVELOPMENT: 6 MONTHS TO 1 YEAR
• By 6 months of age:
  • Active sleep (now REM) decreases from 50% → 30%
  • Quite sleep (now NREM) sleep increases from 20% → 60%
• Well defined NREM stages 2 and 3
• Loss of sleep onset REM
• By 1 year of age:
  • Sleep onset REM 1.5 h
  • Sleeping through the night (50%-60% at 11/12)
  • Near age 3: day

SLEEP DEVELOPMENT: 1 YEAR OF AGE
• Well defined EEG for Sleep Staging
• Sleep architecture
• Total sleep time (TST)
• Sleep latency
• Sleep efficiency
• Anxieties
• Awakenings

SLEEP DEVELOPMENT: TODDLERS AND EARLY CHILDHOOD (2-5 YEARS)
• Total sleep time 11-12h
• Naps decrease to 1/d and at 4 years cease
• REM decreases from 30% → 20% of total sleep time
• Slow wave sleep (stage 3) consolidates in the first third of the night

SLEEP DEVELOPMENT: MIDDLE CHILDHOOD (6-12 YEARS)
• 9-11 h
• Sleep patterns stable
• Low levels of daytime sleepiness

SLEEP DEVELOPMENT: ADOLESCENT
• Behavioral changes
• Psychosocial demands
• Endocrine changes
• Phase delay
• Evening alertness
• Decrease SWS (stage 3)
NEURAL CONTROL OF SLEEP

- Wake promoting mechanisms
- Sleep promoting mechanisms
- Sleep – wake switch
- Homeostasis
- Circadian Rhythm

NEUROBIOLOGY

WAKE PROMOTING MECHANISMS

- Ascending arousal system
  1. Ventral tegmental area
  2. Brainstem, hypothalamus, basal forebrain and cerebral cortex

- Kryger, Roth and Dement, 2017
- Schwartz and Roth, 2008

WAKE PROMOTING MECHANISMS

- ENS on
  - Acetylcholine
  - Dopamine
  - Glutamate

- Posterior hypothalamus
  - Melanin-concentrating hormone (MCH) neurons and GABA
  - Role in both NREM and REM sleep initiation and maintenance

- Cortical sleep-active neurons
  - Less well described
  - Neuronal nitric oxide synthase (nNOS) and GABA
  - Unclear if primary or secondary (i.e. disinhibition) role in sleep

SLEEP PROMOTING MECHANISMS

- Pre-optic area (POA) of hypothalamus:
  1. Ventrolateral nuclei (VLPO)
  - Activated by adenosine
  2. Median nuclei (MnPO)
  - Activated by time awake and warmth

- Cortical sleep-active neurons
  - Less well described
  - Neuronal nitric oxide synthase (nNOS) and GABA
  - Unclear if primary or secondary (i.e. disinhibition) role in sleep

SLEEP – WAKE BALANCE

- Strong reciprocal inhibition
- Bi-directional stable sleep-wake switch
- Intermediate states are resisted
- Changes are infrequent and rapid
- Homeostatic and circadian drive switch

Saper 2005
- Schwartz and Roth, 2008
OREXIN
- Lateral hypothalamus
- Innervates major nuclei involved in arousal
- Provides stability to sleep-wake balance
- Differs from other wake promoting mechanisms
  - Knockout does not lead to excess sleep
  - Rather, creates dysfunctional switching

Kryger, Roth and Dement, 2017
Schwartz and Roth, 2008

REGULATION OF SLEEP
- What drives the switch to change?
  - The two process model
    1. Homeostatic sleep drive
    2. Circadian arousal drive
- Process S
- Process C

HOMEOSTATIC SLEEP DRIVE
- Process S (Sleep)
- General model of sleep homeostasis
  - Extended wakefulness → Increased sleep pressure → Mediates switch to sleep
  - Sleep → Reduced levels of sleep pressure → Maintenance of wakefulness
- Adenosine appears to be key component

Schwartz and Roth, 2008

WAKEFULNESS
- During the later part of the waking day the circadian pacemaker opposes the increasing drive for sleep by an increasingly stronger drive for waking
- A couple of hours before bedtime, the pineal gland releases the sleep promoting hormone melatonin into the bloodstream.

TRANSITION TO SLEEP
- Melatonin receptors on the SCN then suppress the firing of SCN neurons
- Melatonin may serve to quiet the wake-promoting signal facilitating sleep after the peak of the circadian drive for wakefulness
- Melatonin secretion is suppressed by exposure to bright light

SLEEP AND AWAKENING
- SCN promotes sleep most strongly just before habitual wake time, after many hours of sleep have dissipated sleep pressure
- The peak in the circadian rhythm of sleep propensity is just before wake time
- The other period of propensity to sleep is in the afternoon when there is a circadian dip
**Entrainment**

- Entrainment: Phase and period control of one oscillating process by another.
- External clock controls the circadian internal clock by cues/markers.
- Important to keep the internal phase same as environmental.
- Keeps body in sync with sunrise and sunset shifts.
- Light is the strongest cue.

**Zeitgebers**

- Zeitgebers: “Time-givers” are environmental cues that assist in entrainment.
- Light (sunrise, sunset).
- Physical activity.
- Melatonin from the pineal gland.
- Social cues.
- Free-running rhythm: The rhythm observed when all environmental cues are removed.

**Circadian Rhythm**

- Process C (Circadian).
- Master clock = suprachiasmatic nucleus (SCN) of the anterior hypothalamus.
- Cellular mechanism: Transcriptional feedback loops.

**Circadian Rhythm: Drivers**

- Light:
  - Single most important cue.
  - Stimulates SCN via retino-hypothalamic tract (RHT).
  - Shorter wavelength (blue) = greatest effect.
  - Increase Per transcription.
- Melatonin:
  - Secreted by pineal gland.
  - Inhibits SCN.
  - Production inhibited by RHT pathway.
- Intergeniculate leaflet (IGL) of the thalamus:
  - Stimulates SCN in response to light, exercise, appetite and others.

**Circadian Rhythm Outputs**

- Indirectly connects with arousal systems and NREM.
- Modulates brainstem monoaminergic neurons.
- Modulates cardiovascular rhythm.
- Circadian peripheral clocks.
- SCN has role in anxiety/panic disorders.

**Waking Up to Sleep Science**

- Nobel Prize in Physiology or Medicine 2017.
- Jeffrey C. Hall, Michael Rosbash, and Michael W. Young.
- Insights into the circadian rhythms.
OVERVIEW

Introduction
• Sleep architecture
• Changes in sleep with age

Neural Control of Sleep
• Neurobiology
• Homeostasis
• Circadian rhythms

Sleep Stages
• Physiology
• Measurement
• Scoring

SUMMARY
• Sleep is composed of many ultradian cycles
• Sleep is a homeostatic drive
• Sleep characteristics evolve from infancy to adolescence
• Alertness is a balance of the circadian drive and the homeostatic sleep drive
• Individuals have sleep duration requirements and circadian periods that cannot be changed