NORMAL SLEEP AND CIRCADIAN PHYSIOLOGY IN CHILDREN

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

Dr Alan Rechtshaffen

OVERVIEW

Introduction	Neural Control of Sleep	Sleep Stages
• Sleep architecture • Changes in sleep with age	• Neurobiology • Homeostasis • Circadian rhythm	• Physiology • Measurement • Scoring

INTRODUCTION

- Sleep architecture
- Changes in sleep with age

SLEEP

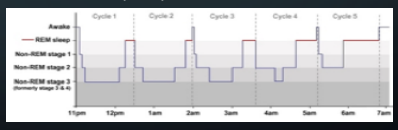
- Sleep is a 'state' of consciousness that we have no knowledge of being in until we wake up – Rapidly reversible state
- Sleep is a dynamic and regulated set of behavioral and physiological states during which many processes vital to health and well-being take place.
- Sleep is a physiologic drive similar to hunger or thirst
- All phases of normal sleep are under ***homeostatic control***, i.e., deprivation of a stage leads to rebound
- Purpose
  - Energy conservation, Restoration, Memory consolidation,
  - *House-keeping*

SLEEP ARCHITECTURE

- 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 paralysed body
  - *'Refresh the brain'*

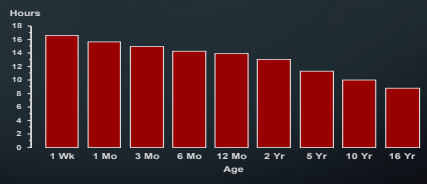
SLEEP ARCHITECTURE

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



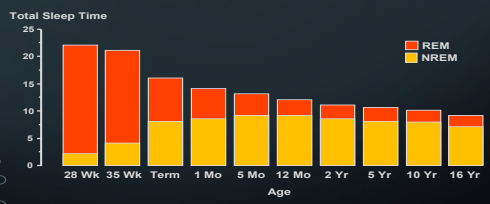
Kryger, Roth and Dement, 2017

TOTAL SLEEP DURATION CHANGE WITH AGE



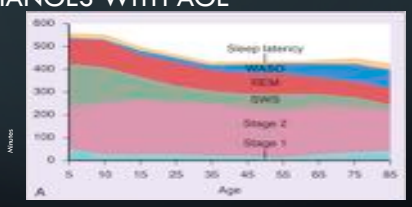
Modified from FERBER R.: Solve your child's sleep problems. New York. Simon & Shuster, 1985, p19

ONTOGENY OF REM AND NREM SLEEP



Sheldon SH, Spire J-P, Levy HB: Pediatric Sleep Medicine. Philidelphia. WB Saunders. 1992, p24

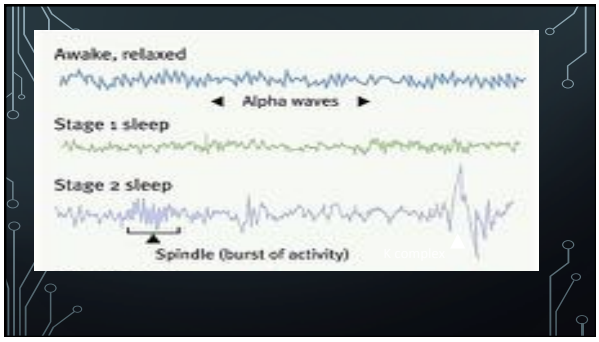
CHANGES WITH AGE



Ferber et al, 1995
Kryger, Roth and Dement, 2017

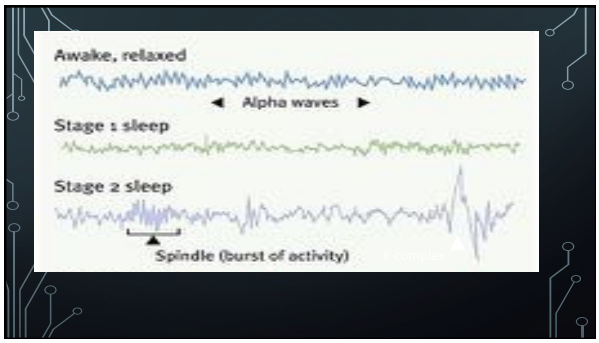
LIGHT SLEEP - STAGE 1

- 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)



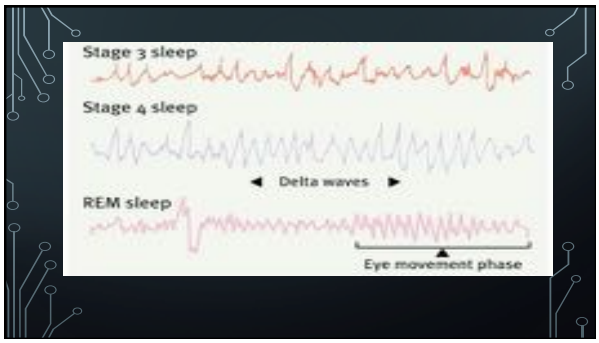
LIGHT SLEEP- STAGE 2

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



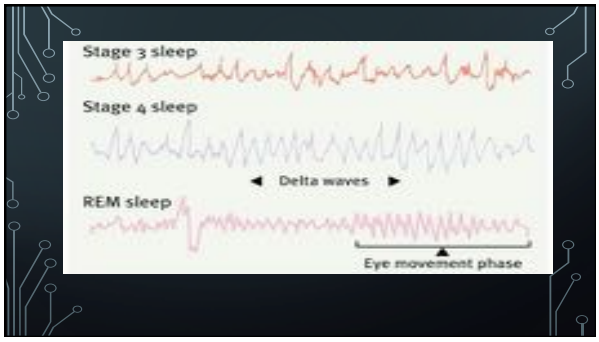
DEEP SLEEP – STAGE 3

- 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

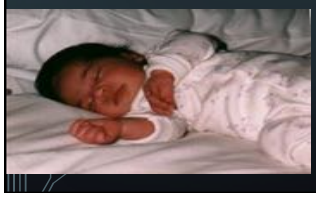


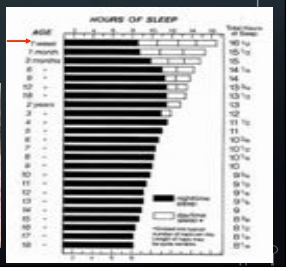
SLEEP DEVELOPMENT

- 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

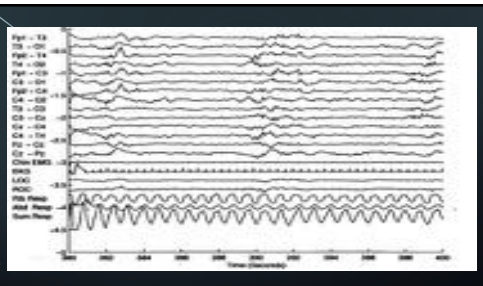
Wake transitions to Active sleep

Active sleep

- 50% of sleep time
- Eyes closed, eye movements
- Respiration uneven
- Corresponds to REM
- Newborns enter sleep through Active/REM sleep

SLEEP DEVELOPMENT: NEWBORN QUIET SLEEP

- Quiet sleep
  - 20% of sleep time
  - Eyes closed, no movements
  - Respiration slow and regular
  - A tonic level of muscle tone exists
  - Trace Alternans (high voltage bursts on low frequency background)
  - Corresponds to NREM
- Indeterminate Sleep (mixed state)
  - 30% of sleep time



Tracé alternant 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)

Spindle

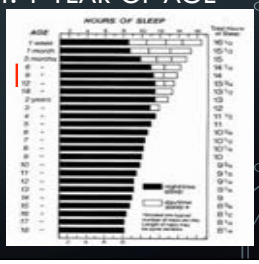
K-complex

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:
  - Total sleep time 13-14h
  - Sleeping through the night (70-80% at 9/12)
  - Have 2 naps /day

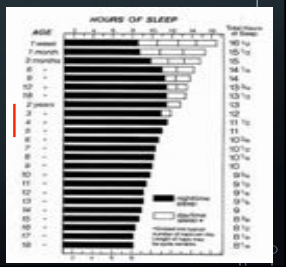
SLEEP DEVELOPMENT: 1 YEAR OF AGE

- Well defined EEG for Sleep Staging
- Sleep architecture
- Total sleep time (TST)
- Sleep latency
- Sleep efficiency
- Arousals
- Awakenings



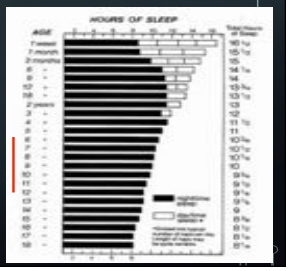
SLEEP DEVELOPMENT: TODDLERS AND EARLY CHILDHOOD (2-5 YEARS)

- 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



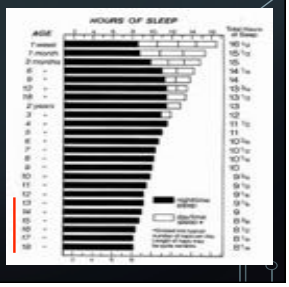
SLEEP DEVELOPMENT: MIDDLE CHILDHOOD (6-12 YEARS)

- 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. Brainstem → Thalamus
   - Primarily acetylcholine
   - REM ON
2. Brainstem, hypothalamus, basal forebrain and cerebral cortex
   - Multiple Neuropeptides
   - REM OFF
- Chronic elimination of a single component often has little impact on wakefulness

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

NEUROBIOLOGY
WAKE PROMOTING MECHANISMS

- REM on
  - Acteylcholine — Thalamic nuclei, basal forebrain
  - Dopamine — Substantia nigra, hypothalamus
  - Glutamate — Widespread
- REM off
  - Serotonin — Dorsal and median raphe
  - Noradrenaline — Locus coeruleus
  - Histamine — Tuberomammillary nucleus
  - Orexin — Lateral hypothalamus

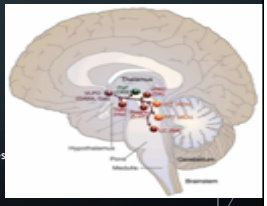
Kryger, Roth and Dement, 2017
Schwartz and Roth, 2008

NEUROBIOLOGY
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

- GABA and Glycine are principle neuropeptides



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

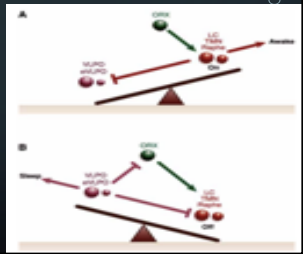
NEUROBIOLOGY
SLEEP PROMOTING MECHANISMS

- 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

Kryger, Roth and Dement, 2017

SLEEP – WAKE BALANCE

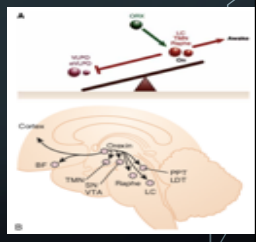
- Strong reciprocal inhibition
- Bi-directional stable sleep wake switch
  - Intermediate states are resisted
  - Changes are infrequent and rapid
- Homeostatic and circadian drive switch



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

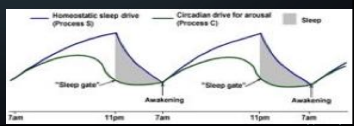


Kryger, Roth and Dement, 2017
Schwartz and Roth, 2008

REGULATION OF SLEEP

- What drives the switch to change?
- The two process model

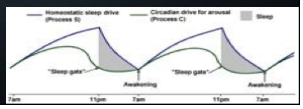
1. Homeostatic sleep drive
   - Process S
2. Circadian arousal drive
   - Process C



Schwartz and Roth, 2008

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**

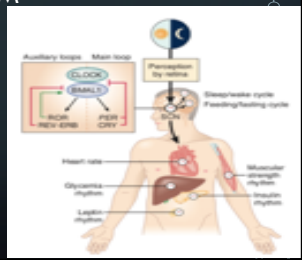
ZEITGEBERS

- **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 clues are removed

CIRCADIAN RHYTHM

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

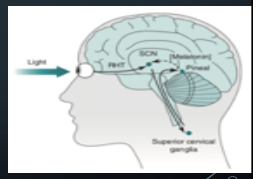
Kryger, Roth and Dement, 2017



CIRCADIAN RHYTHM - DRIVERS

- Light
  - Single most important cue
  - **Stimulates** SCN via retino-hypothalamic tract (RHT)
  - Shorter wave length (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

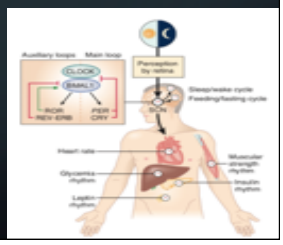
Kryger, Roth and Dement, 2017
Berry, 2012



CIRCADIAN RHYTHM
SCN OUTPUTS

- Indirectly connects with arousal systems and VLPO
  - via sub-paraventricular zone (SPZ) to the dorsomedial nucleus of hypothalamus (DMH)
- 'Conducts' peripheral clocks
  - SCN has a role in maintaining synchrony in many sites with an independent circadian rhythm

Kryger, Roth and Dement, 2017
Berry, 2012



WAKING UP TO SLEEP SCIENCE

OVERVIEW

- Introduction
  - Sleep architecture
  - Changes in sleep with age
- Neural Control of Sleep
  - Neurobiology
  - Homeostasis
  - Circadian rhythm
- 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