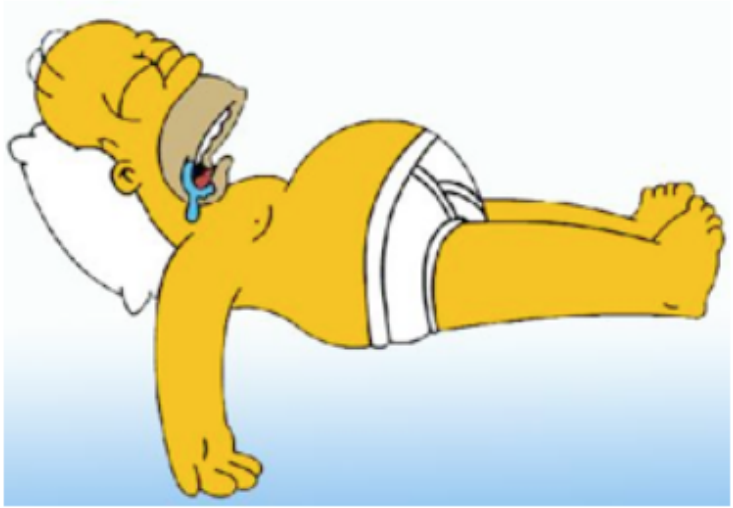
- **Sleep** defined by four criteria:
  - –reduced motor activity
  - –diminished responses to external stimuli
  - –stereotyped posture (in humans, lying down with eyes closed
  - –relatively reversible
    - distinguishes sleep from *coma* and *hibernation*



THE SLEEP CYCLE(S) - CIRCADIAN / ULTRADIAN RHYTHMS

- The cycle of activity and rest can be found in every living organism down to single celled organisms
- sequential phases of responsiveness and unresponsiveness are the primordia of waking and sleeping
- This cycle is one of <u>many</u> endogenous "circadian" rhythms in the adult human body that operate in a ~24 hour period under normal conditions

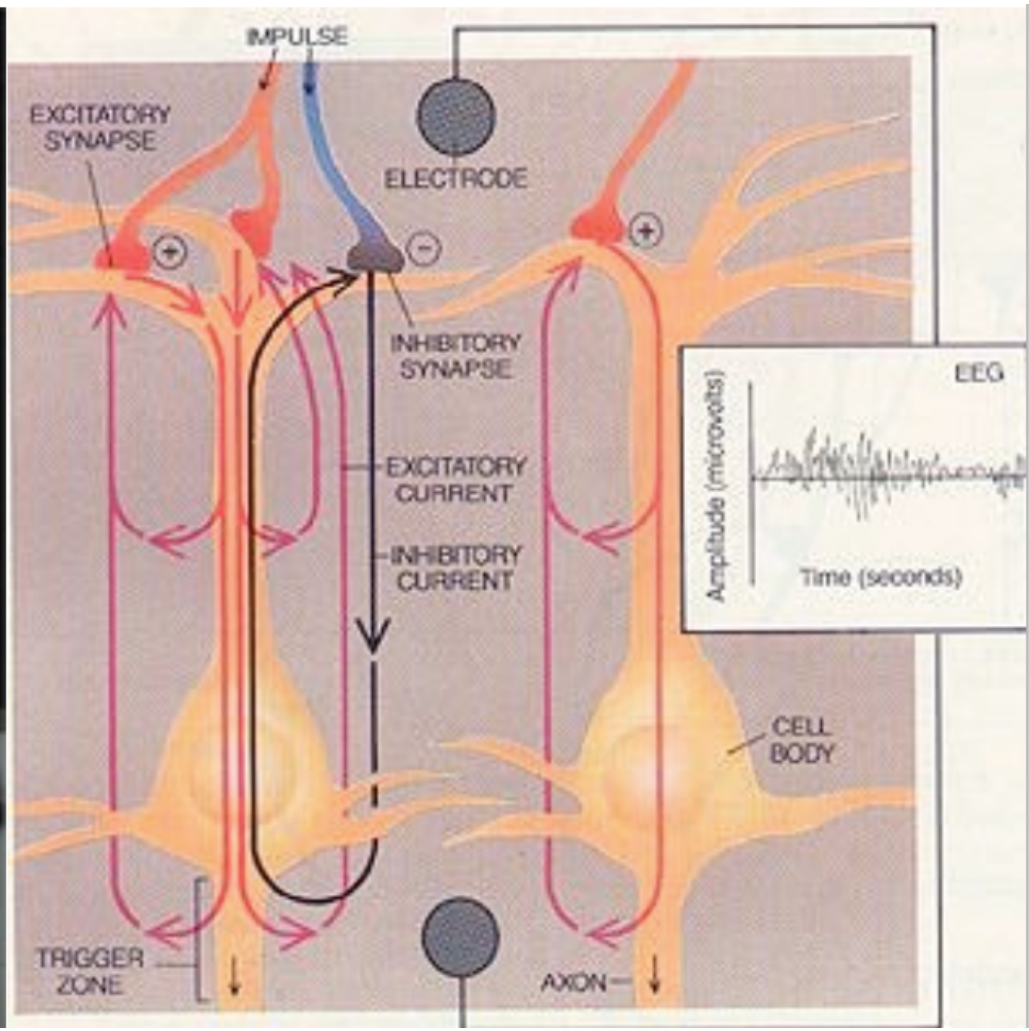
THE SLEEP CYCLE(S) - CIRCADIAN / ULTRADIAN RHYTHMS

- Daily life usually divided into 3 distinct periods for most animals (terrestrial placental mammals and marsupials):
  - "Double axis" of consciousness: Awake vs. asleep / Presence vs. absence of thoughts
    - Awake with thoughts ("normal" consciousness)
    - Asleep with thoughts ("fast-wave" / "REM" / paradoxical sleep)
      - highest recall of dreams
    - Asleep without thoughts ("slow-wave" / "non-REM sleep)
      - not totally devoid of dreaming (recall is much lower)
  - *Awake without thoughts ("transcendental" consciousness - can be cultivated)*

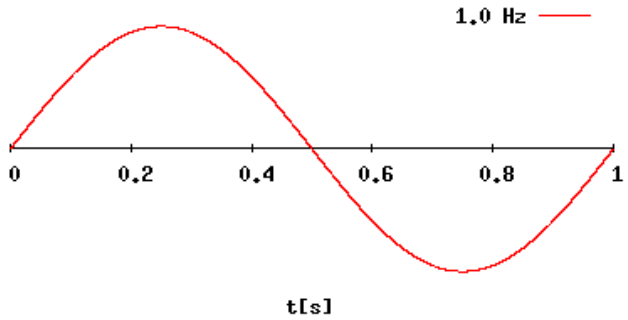
Characterizing Sleep

- 5 stages of sleep:
  - Slow wave 1, 2, 3, and 4 + REM
- each stage has unique characteristics
  - measured by:
    - EMG (muscles)
    - EOG (eye muscles)
    - EEG (brain)

- Sleep Stages - based on EEG and / or dreaming
- EEG (electroencephalogram)
  - Electrodes over scalp measure summed electrical activity (EPSPs / IPSPs) of millions of pyramidal neurons under the small scalp electrodes

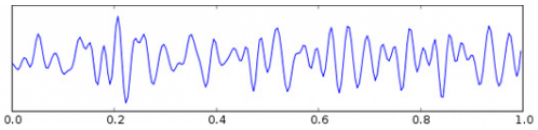


- EEG records cortical oscillations:

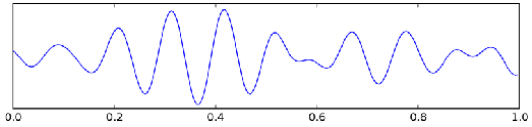


- distinguished by frequency (~1-30 Hz) / amplitude ranges (~20-100 μv) from the highest to the lowest frequency, and lowest to highest amplitude:

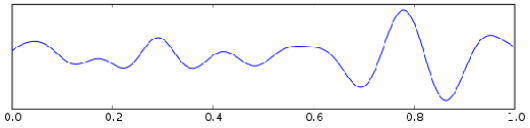
» beta



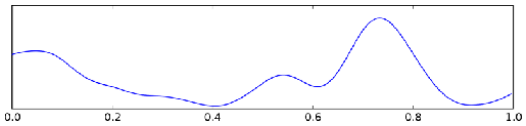
» alpha



» theta

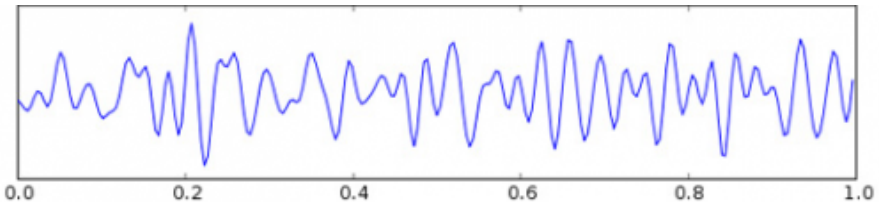


» delta

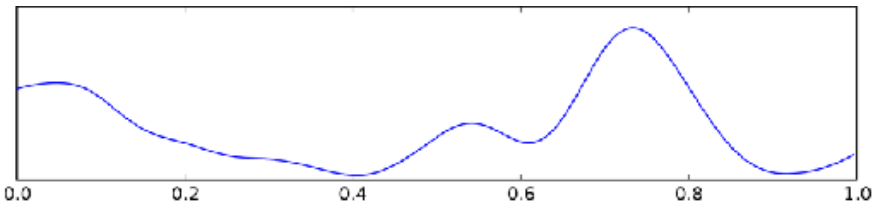


- brain always generates more than one brainwave pattern at a time
  - seldom in "just" beta for example
  - fluctuates between states, sometimes emitting different waves simultaneously, with one of them being predominant

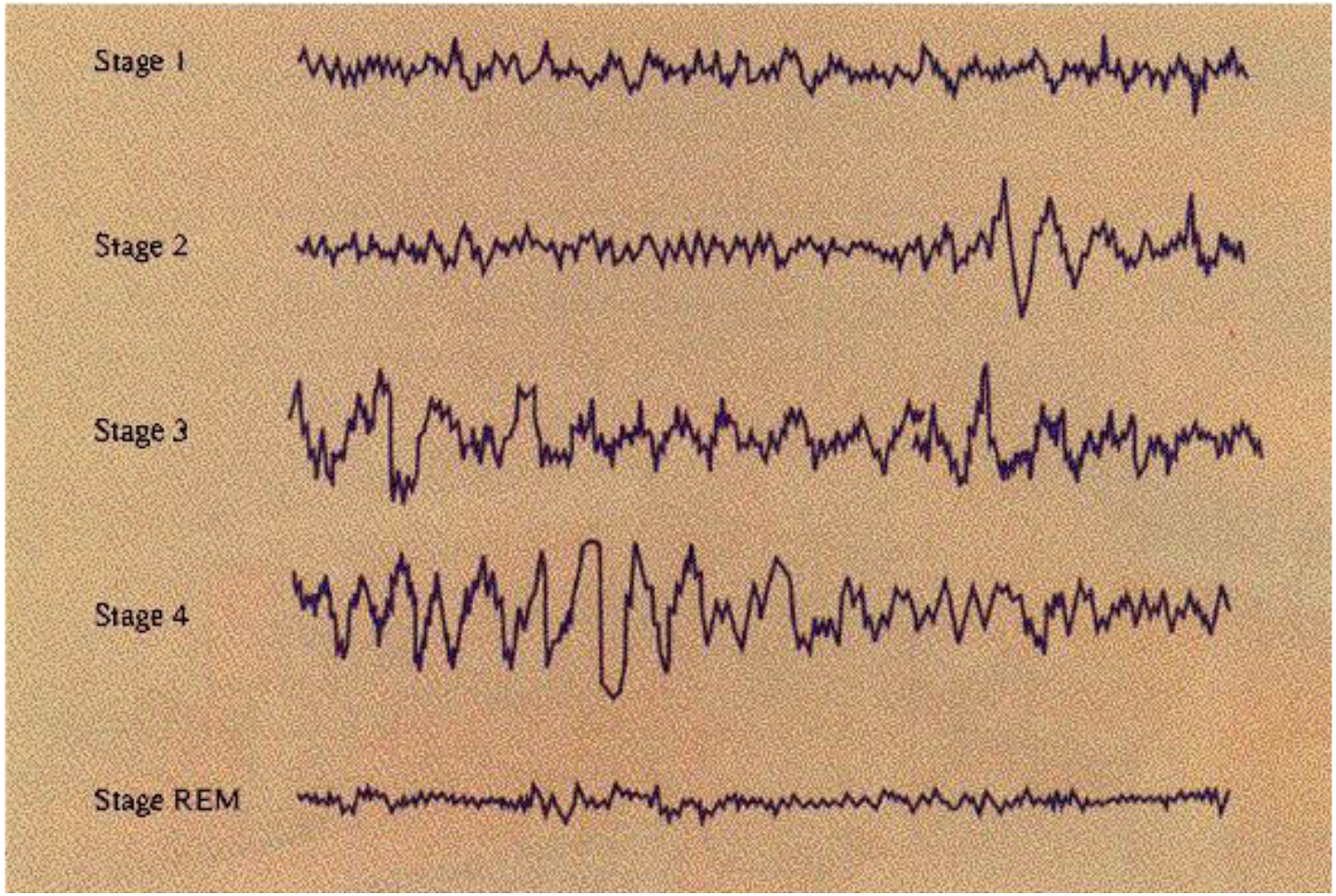
- Waking is characterized by an EEG waves with low amplitude and high frequency
- Fast-wave / REM - desynchronized EEG activity during sleep, at which time dreaming, rapid eye movements, and muscular paralysis occur

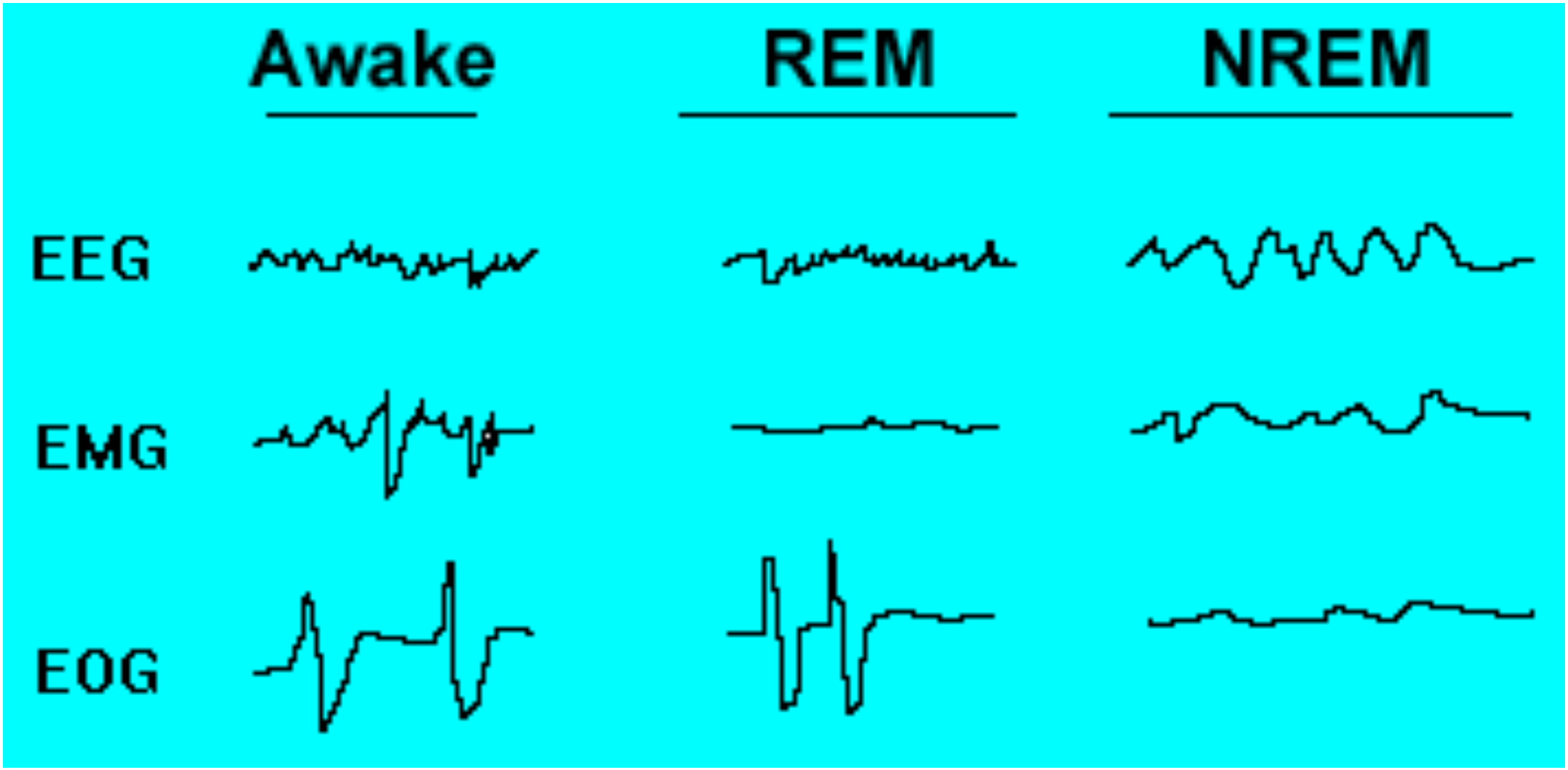


- Compared with waking and REM sleep, slow-wave sleep is characterized by EEG waves with greater amplitude and lower frequency
- From the time you fall asleep to the time you reach the deepest slow-wave sleep (~90 min), the amplitude of these waves increases continuously, while their frequency diminishes



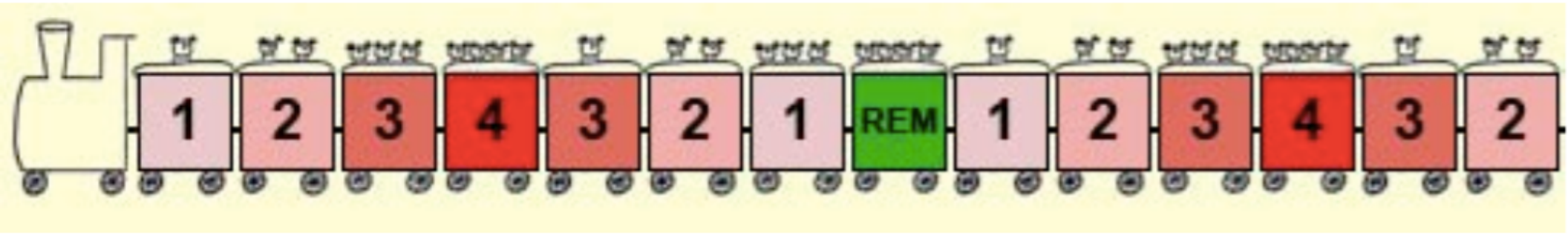
- EEG Patterns:
  - excited awake (beta / desynched / high freq / low amp)
  - relaxed (alpha / more synched / lower freq / higher amp) - specialized case of waking EEG (awake, but very relaxed)
  - drowsy (even more synched / lower freq / higher amp)
  - asleep (theta - even more synched)
  - deep sleep (delta - very synchronized)



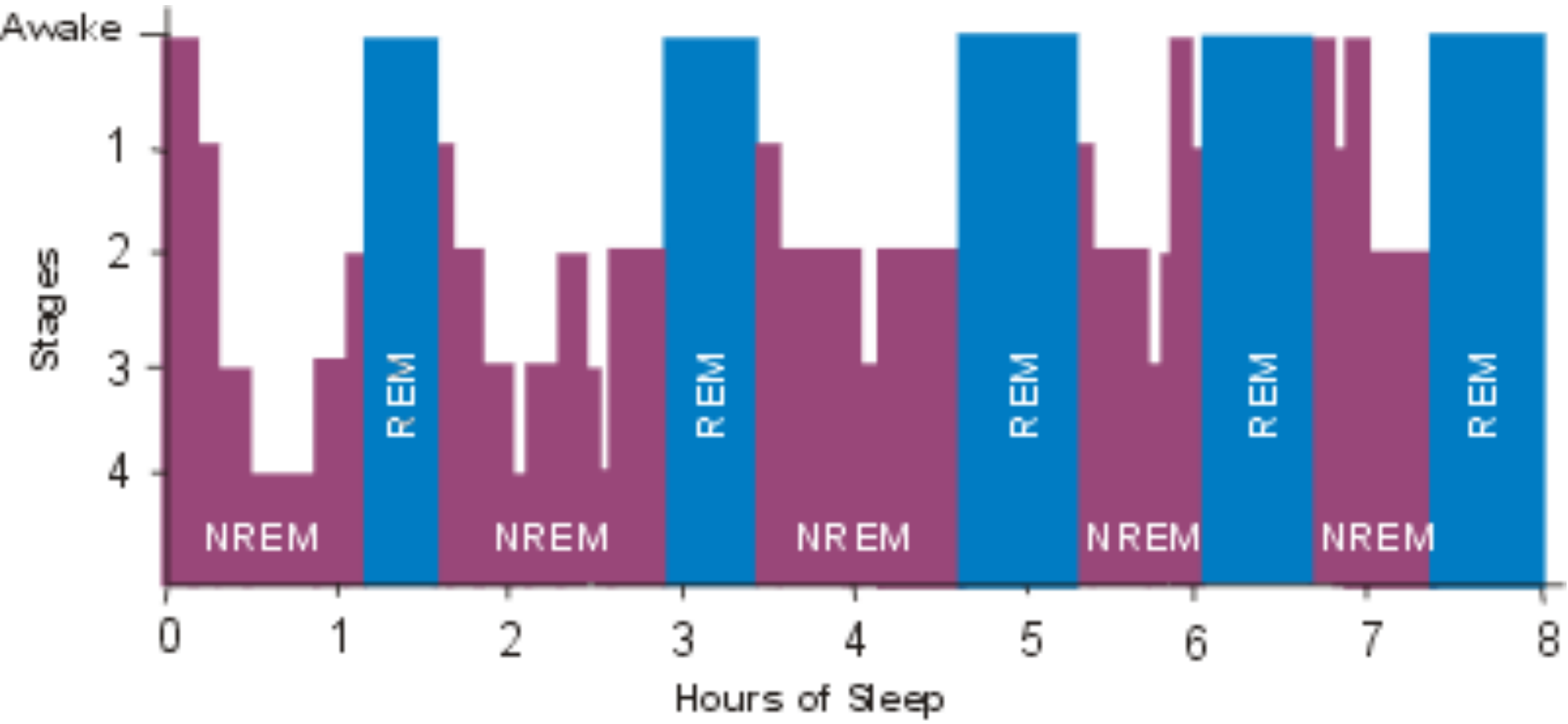

Awake
REM
NREM
EEG
EMG
EOG

Basic sleep cycle

- Falling into a deeper and deeper sleep as the night progresses is actually a gradual, continuous process, but categorizing into stages provides a convenient framework
- recurrent cycles in which the various stages of sleep follow one another, somewhat like a series of waves (4 or 5 of these cycles in one night's sleep)
  - each cycle lasts about 1.5 to 2 hours
  - each descent into deep non-REM sleep is followed by a climb back up directly into a period of REM sleep
- Deep slow-wave sleep (Stages 3 and 4) predominates earlier in the night
- pattern reverses toward the end of the night - fast-wave sleep predominates

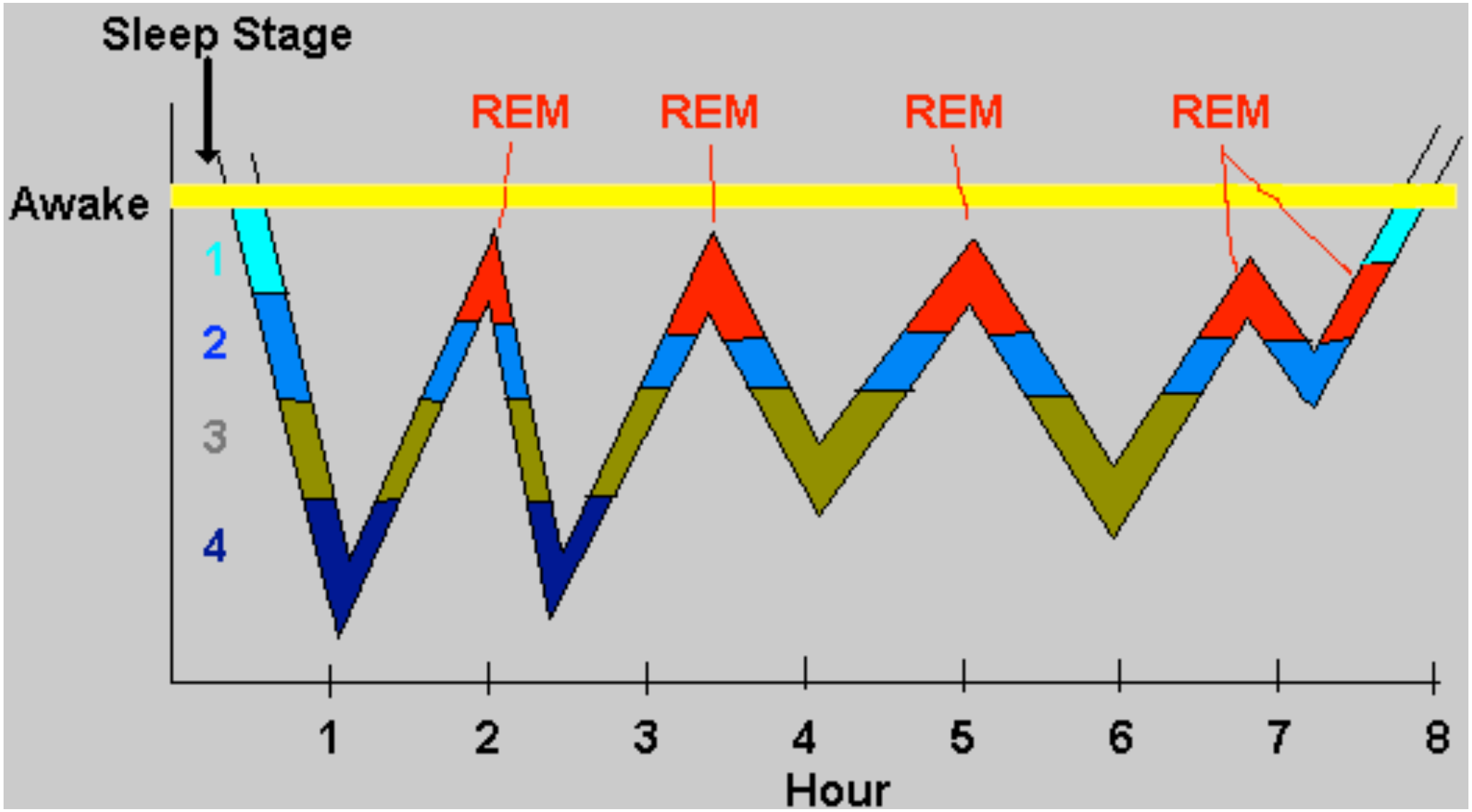


Basic sleep cycle

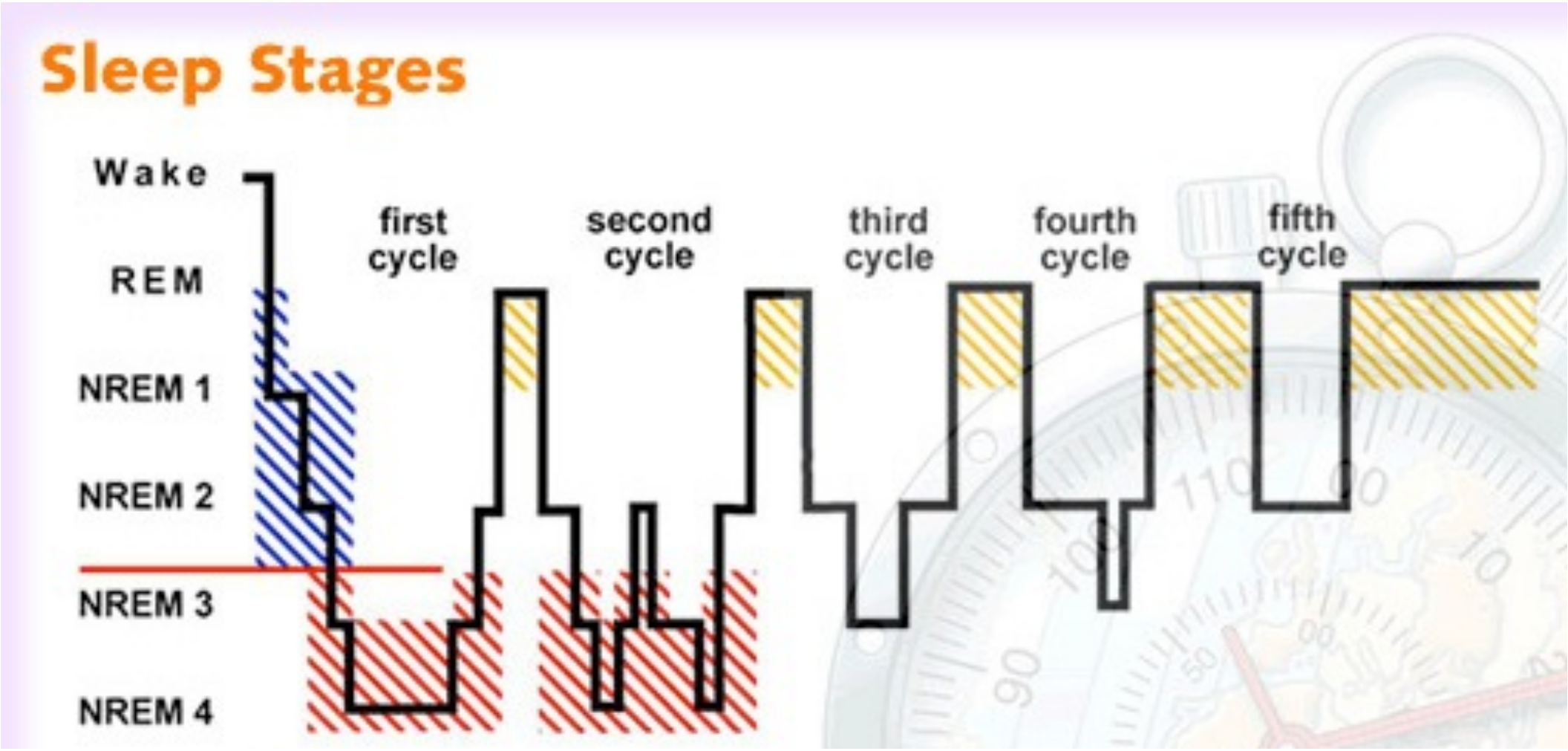


Sequences of states and stages of sleep on a typical night

Basic sleep cycle



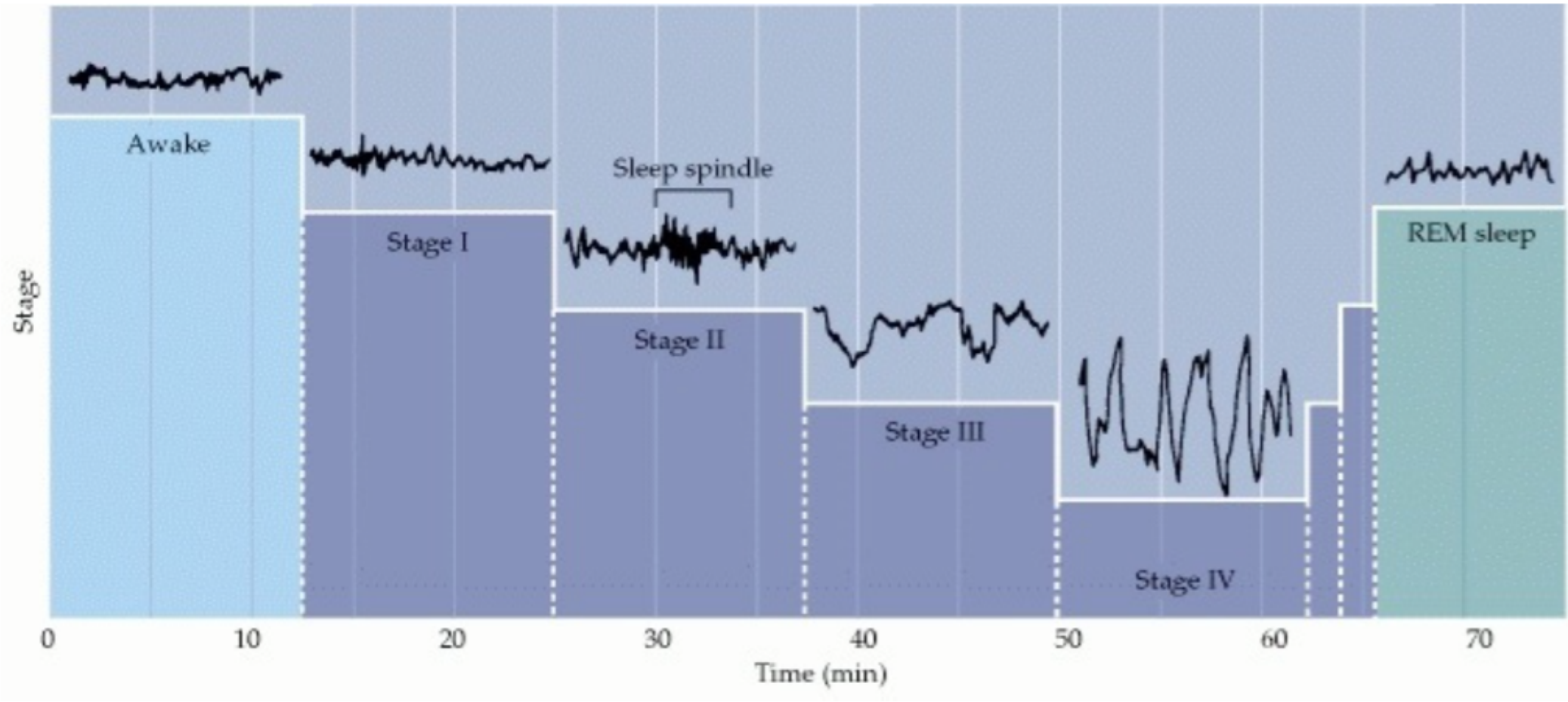
Basic sleep cycle



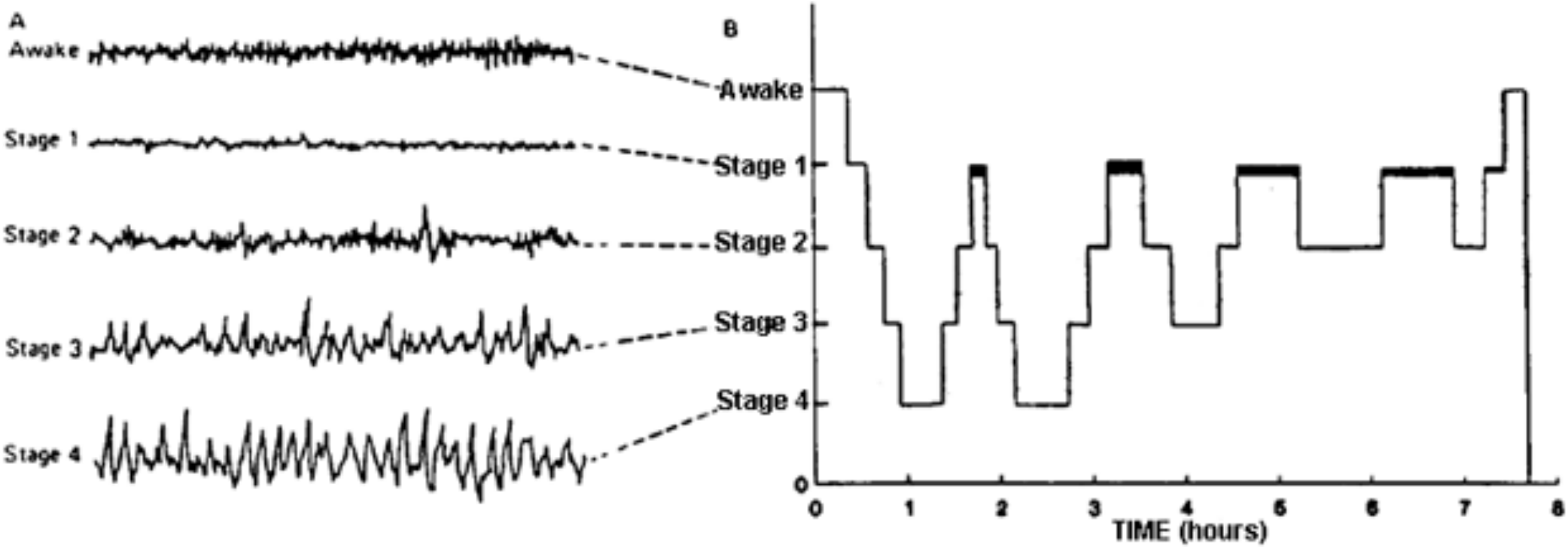
red – slow wave, yellow – “dreaming”

Stage	EEG Rate (Frequency)	EEG Size (Amplitude)
Awake	8-25 Hz	Low
1	6-8 Hz	Low
2	4-7 Hz Occasional "sleep spindles" Occasional "K" complexes	Medium
3	1-3 Hz	High
4	Less than 2 Hz	High
REM	More than 10 Hz	Low

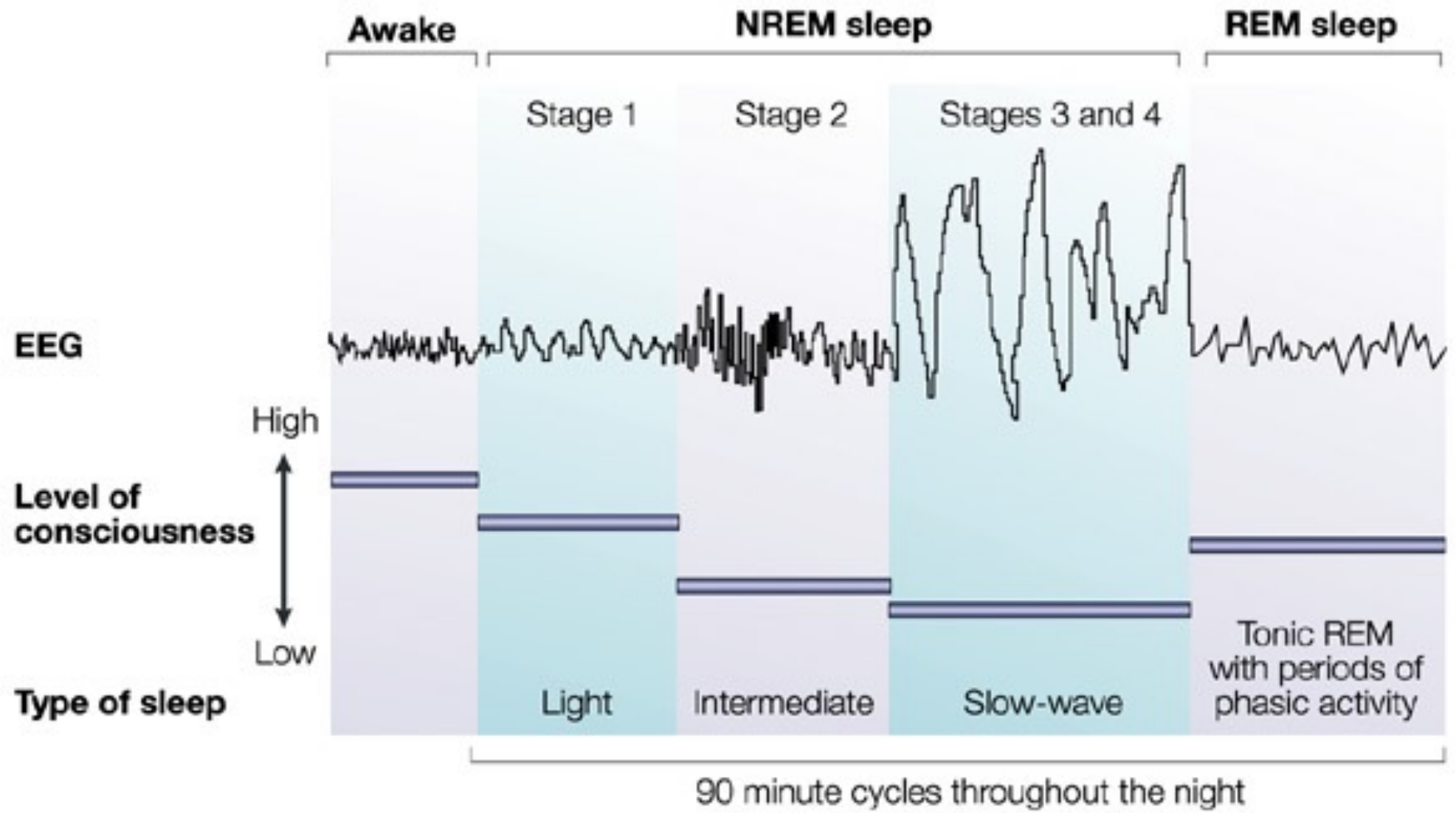
Basic sleep cycle



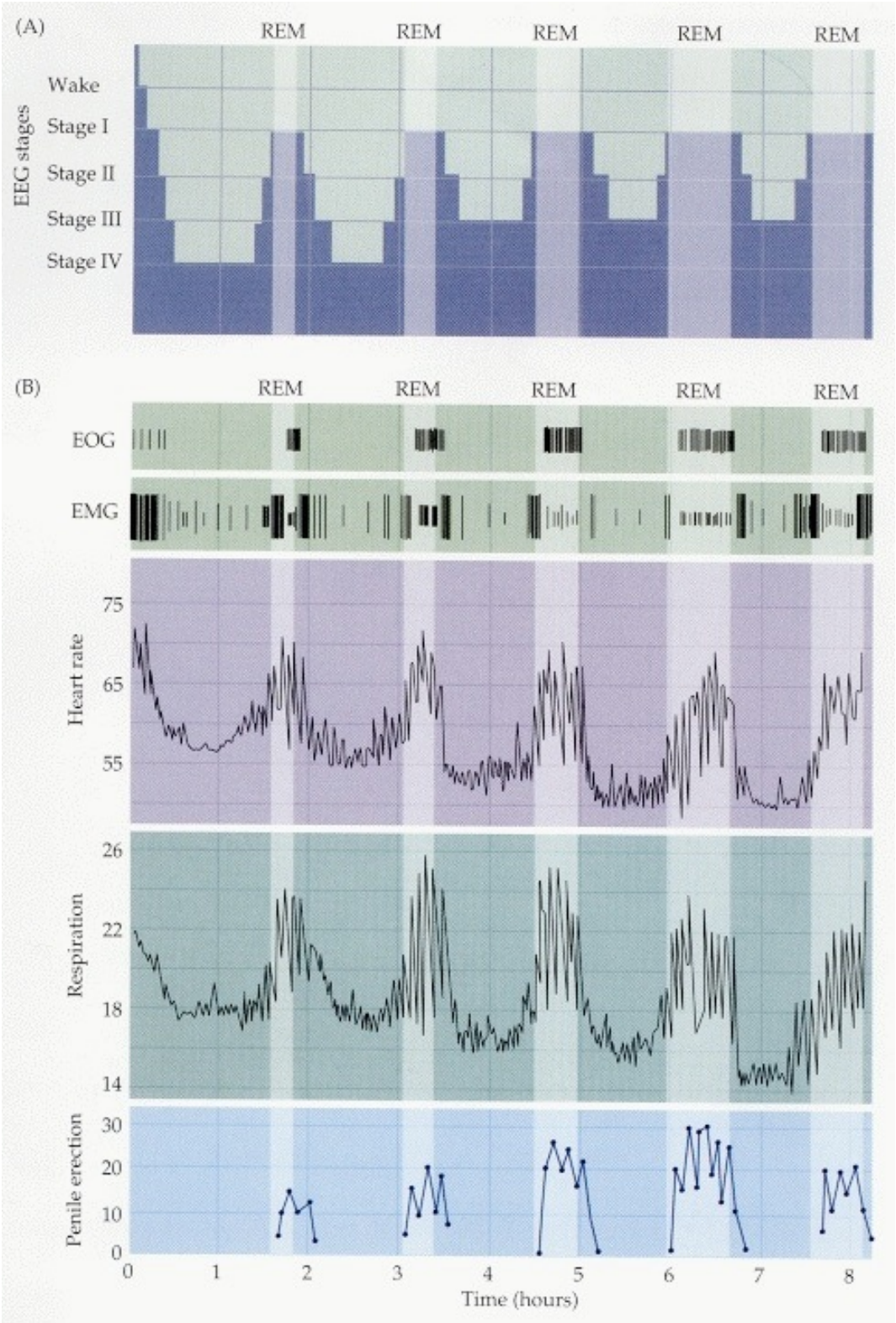
Basic sleep cycle



Stages of Sleep

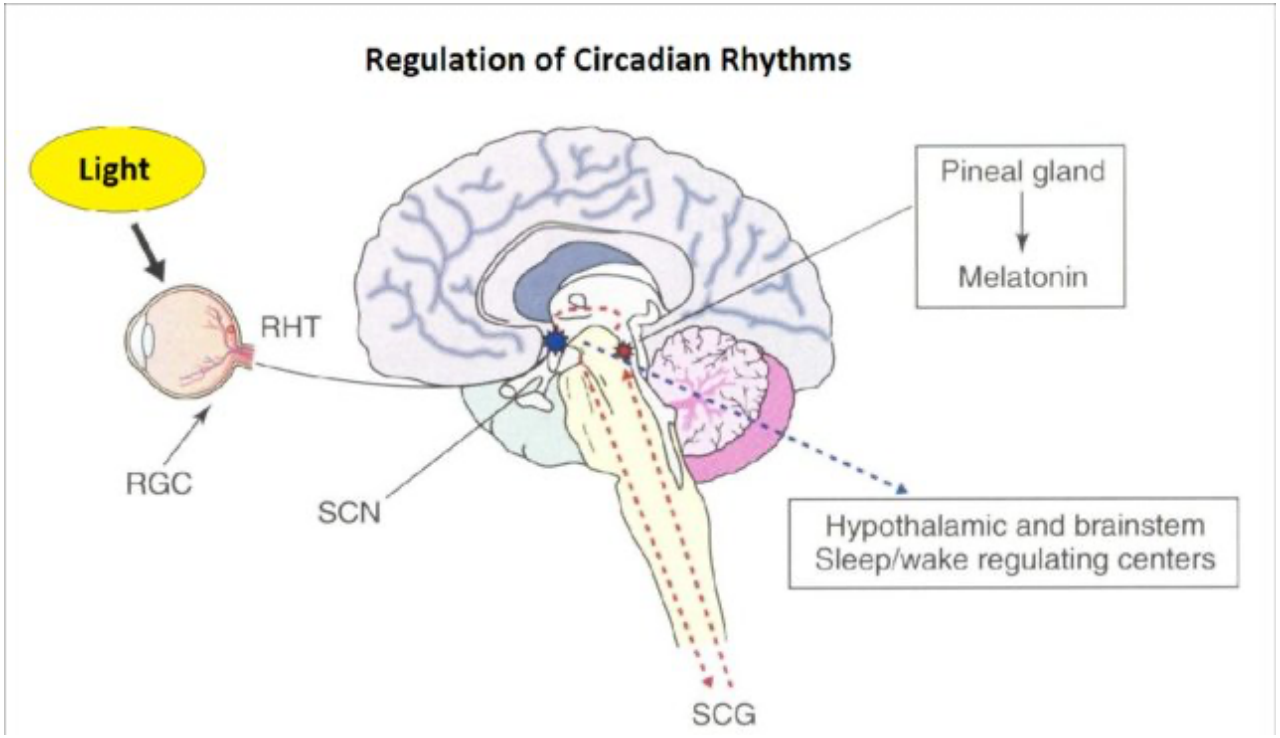


Nature Reviews | Immunology


(A)
REM
REM
REM
REM
REM
EEG stages
Wake
Stage I
Stage II
Stage III
Stage IV
(B)
REM
REM
REM
REM
REM
EOG
EMG
Heart rate
75
65
55
Respiration
26
22
18
14
Penile erection
30
20
10
0
0
1
2
3
4
5
6
7
8
Time (hours)

Anatomy of Sleep

- Suprachiasmatic nucleus of the hypothalamus serves as the "biological clock" for the wake / sleep cycle
  - direct connections w/ retina
    - light entering the retina serves to entrain endogenous rhythms to light cycle
    - lesions of the area disrupt this entrainment and can result in insomnia
- Light inhibits production of melatonin, which inhibits orexin neurons in the hypothalamus
  - So orexin neurons are active during daylight hours



Anatomy of Sleep

- Interplay of at least 4 neurotransmitter systems (NE / 5-HT / ACh / GABA)
  - brainstem aminergic neurons (NE / 5-HT)
  - “basal forebrain” cholinergic neurons (ACh)
  - thalamic neurons (GABA)

- maintenance of the active waking state requires modulatory systems of the upper brainstem:
  - Locus ceruleus (norepinephrine / NE)
  - Dorsal raphe nucleus in the periaqueductal gray (serotonin / 5-HT)
    - Both fire maximally during alert waking
    - also inhibits cholinergic neurons, so ACh cells only fire in response to a strong stimulus
- During waking, the aminergic and cholinergic systems exhibit out-of-phase reciprocal activity

Anatomy of Sleep

- During states of drowsiness these NE / 5-HT / ACh signals decrease
  - Results in reduced responsiveness to afferent signals

- The EEG spindling pattern which marks the transition from waking to slow-wave sleep is caused by the activation of the thalamocortical "oscillation mode”
  - The GABAergic neurons of the thalamus, which are inhibited by cholinergic projections during waking, begin firing as these influences decrease
    - This sets up cycles of inhibition / excitation that oscillate at 7-14 Hz
      - resulting in the synchronous firing of large groups of cells

- As slow-wave sleep progresses, the inhibitory influences of the aminergic systems on the cholinergic cells declines
  - The cholinergic cells develop a spontaneous bursting pattern because of this disinhibition. This provides the thalamus with strong pulses of cholinergic modulation, leading to the onset of REM sleep
    - during REM - frontal cortex is “off”, while sensorimotor / emotion / memory are active…. the “warden” has left the building

Why Sleep?

WHY SLEEP?

- 2 possible processes - sleep is passive or active
- Until the late 1950's, sleep was viewed as a passive process
  - i.e, the brain lapses into sleep only when insufficient sensory stimulation exists to keep it awake

Why Sleep?

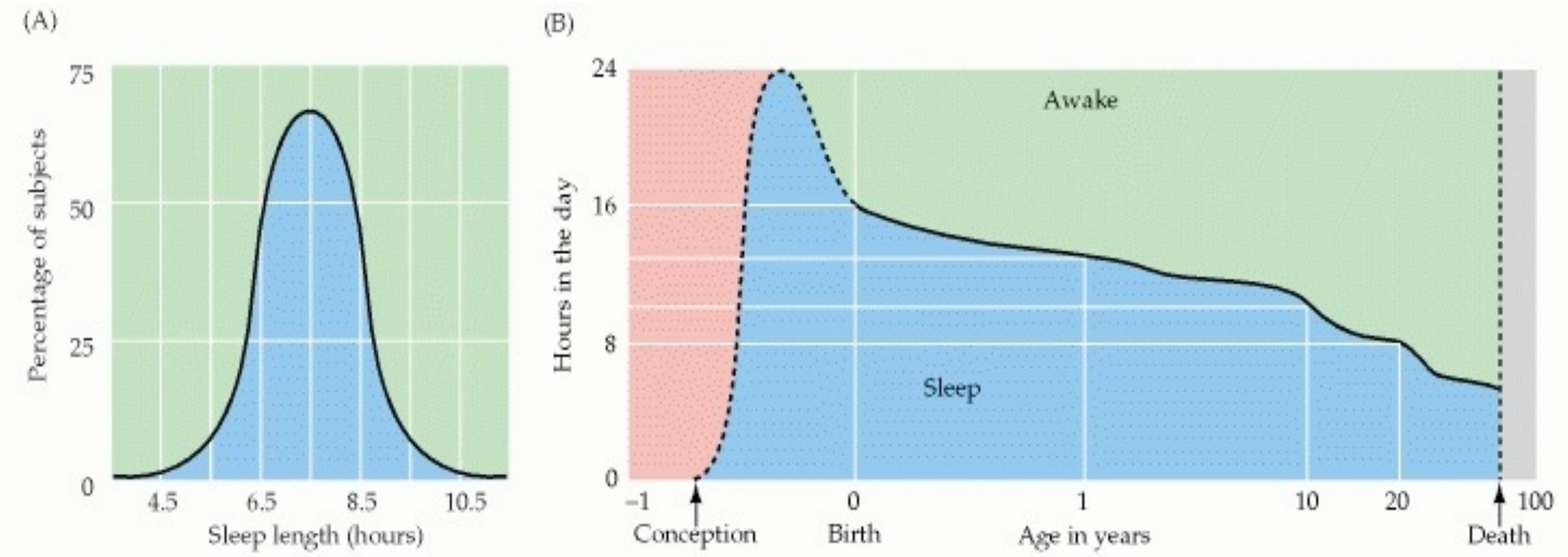
- must be VERY IMPORTANT for evolution to allow 1/3 of our lives to be defenseless and unproductive
- Restorative: helps the body recover from all the work it did while an animal was awake.
  - the more physical exercise an animal does, the more NREM an animal will have
  - if people are deprived of NREM by waking them up each time they get to stage 4 sleep, then they complain of being physically tired
  - If people are deprived of REM sleep by waking them up each time the have REM type EEG patterns, they can get anxious and irritable
  - If animals are deprived of REM for several days and then allowed to get an undisturbed period of sleep, animals will go into "REM rebound"
  - important for memory and learning (babies sleep more)
- Adaptive: need of animals to protect themselves. In general, animals that serve as food for other animals sleep the least.

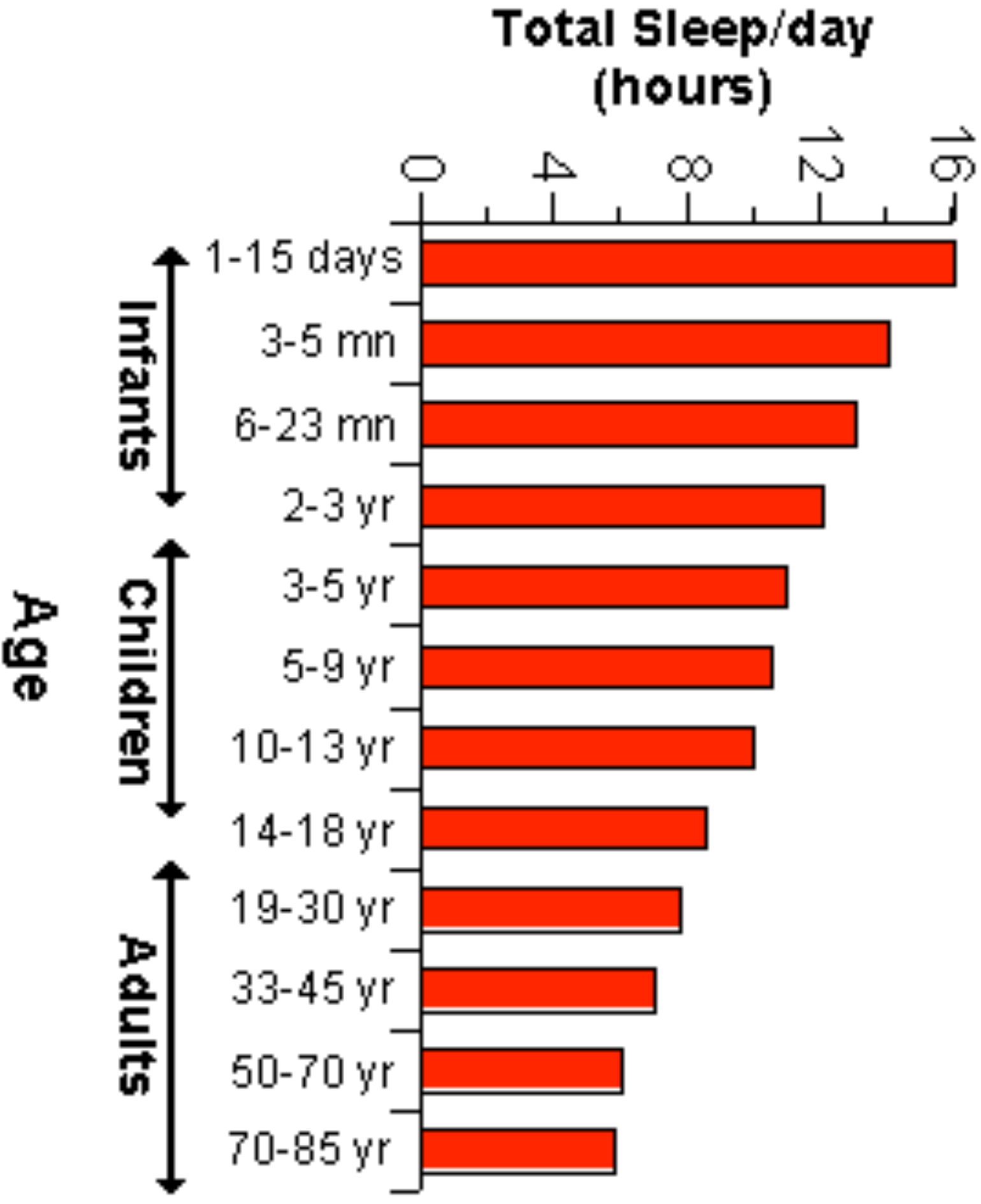
Sleep and Development / Aging:

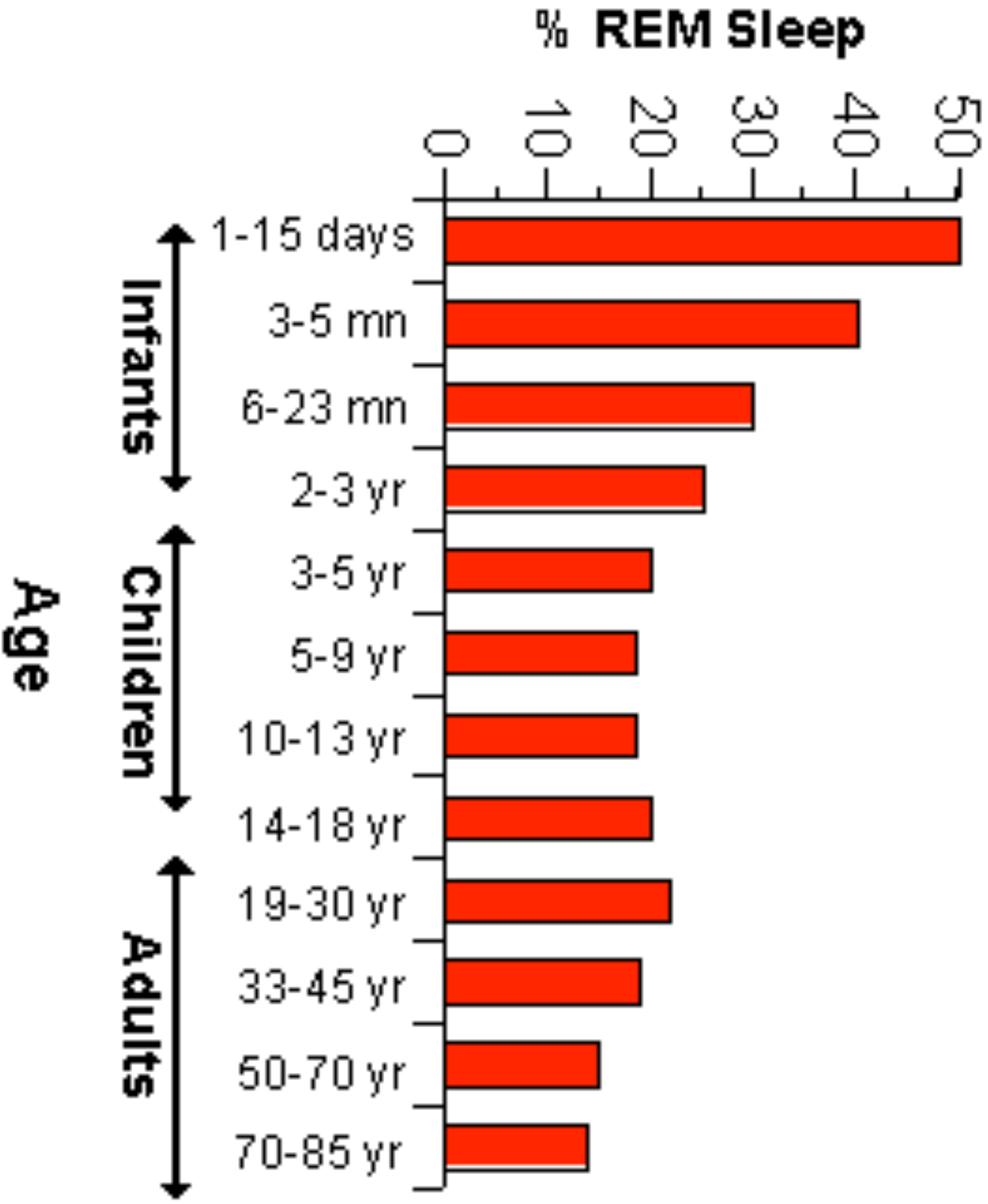
- REM and stage 4 change the most over the lifetime
  - REM:
    - preterm 80-60% of total sleep time
    - fullterm 50%
    - 2 years 30-35%
    - 10-80 years 25% (1-2 hours day)
    - 80+ years 20%
  - stage 4:
    - early childhood 20% (2 hours / day)
    - progressive decline w/ age
    - 60+ none (spontaneous waking / naps compensate)

- in REM sleep, nature has provided the nervous system w/ activity for development to promote growth
  - nervous system may be “exercising” during sleep?
    - hippocampal patterns replayed 20x faster
    - learning a skill - after sleep, it can improve up to 20-30%

Stages of Sleep though Development




Total Sleep/day
(hours)
0
4
8
12
16
Age
Infants
Children
Adults
1-15 days
3-5 mn
6-23 mn
2-3 yr
3-5 yr
5-9 yr
10-13 yr
14-18 yr
19-30 yr
33-45 yr
50-70 yr
70-85 yr


% REM Sleep
0
10
20
30
40
50
Age
Infants
Children
Adults
1-15 days
3-5 mn
6-23 mn
2-3 yr
3-5 yr
5-9 yr
10-13 yr
14-18 yr
19-30 yr
33-45 yr
50-70 yr
70-85 yr

Glymphatic system