Circadian rhythms: sleep-waking cycle

Biological rhythms

(periodic physiological fluctuations)

Types of rhythms

1. Ultradian (Basic Rest-Activity Cycle)
2. Circadian (sleep-wake cycle)
3. Infradian (menstrual cycle)
4. Circannual (annual breeding cycles)

All rhythms allow us to time events and anticipate change!

Circadian Function

- Circadian (circa diem) rhythms
  - regular bodily rhythms that occur on a 24 hour cycle
- Internal biological clock(s)?
  - Pacemaker cells; cryptochrome proteins; clock genes
  - Fruit fly clock
    - 4 regulatory proteins that interact to give the clock periodicity
    - 2 proteins (CLOCK* and CYCLE) bind and increase production of PER (period) and TIM (timeless) – which accumulate over several hours
    - When enough PER and TIM are made they inactivate CLOCK-CYCLE complex

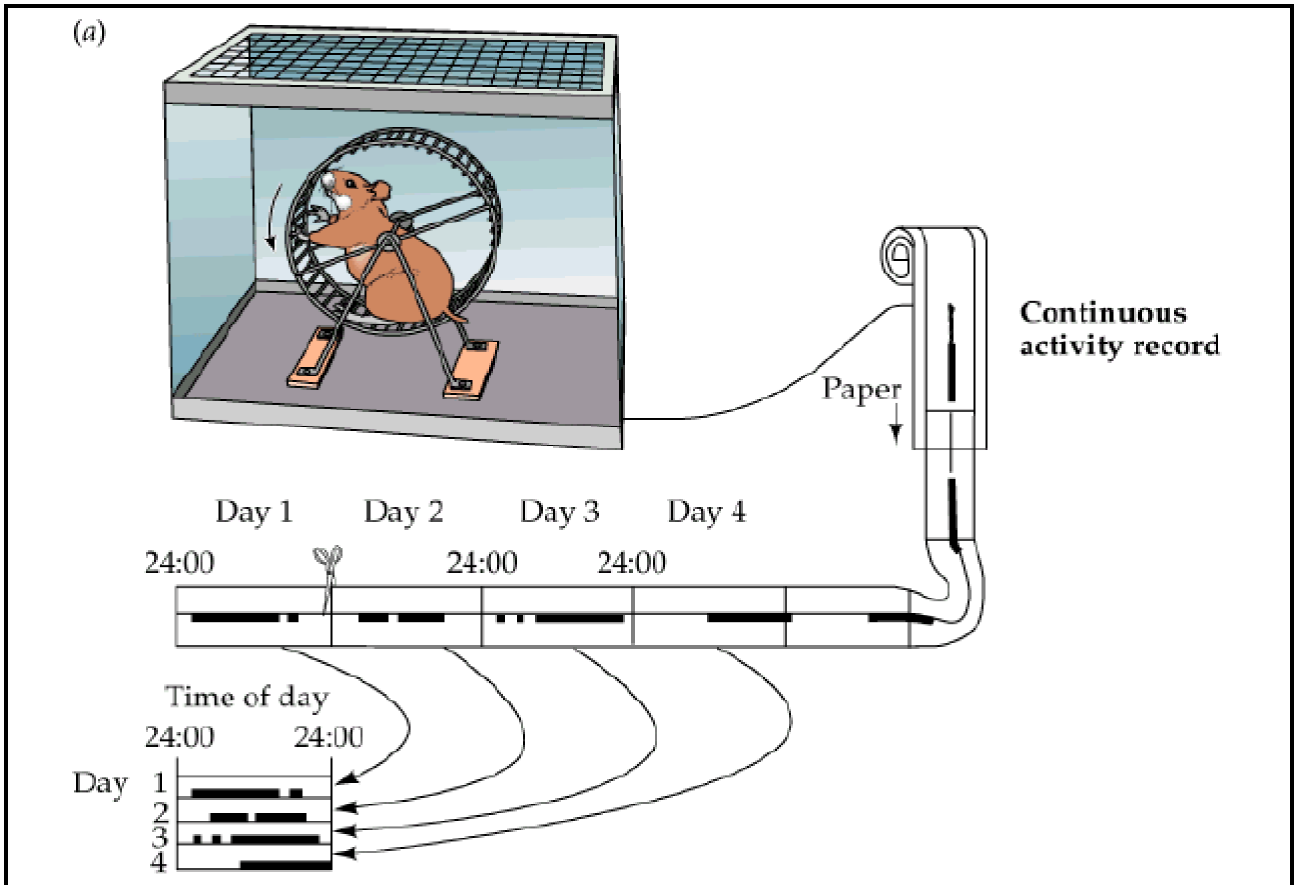
* Circadian locomotor output cycles kaput

Human Clocks

- Cave Studies and free-running clocks (24 hrs 11 min)
  - Why is this advantageous?
- Zeitgeber = External cue that helps to set the clock.
  - Light/dark; temperature, social interactions, activity
  - Entrainment/synchronization
  - whether a cycle advances, is delayed, or remains unchanged differs depending on the phase in the cycle at which it is presented

REM and BRACS = Basic Resting Activity Cycles (approx. 90 minutes)

Measuring biological rhythms



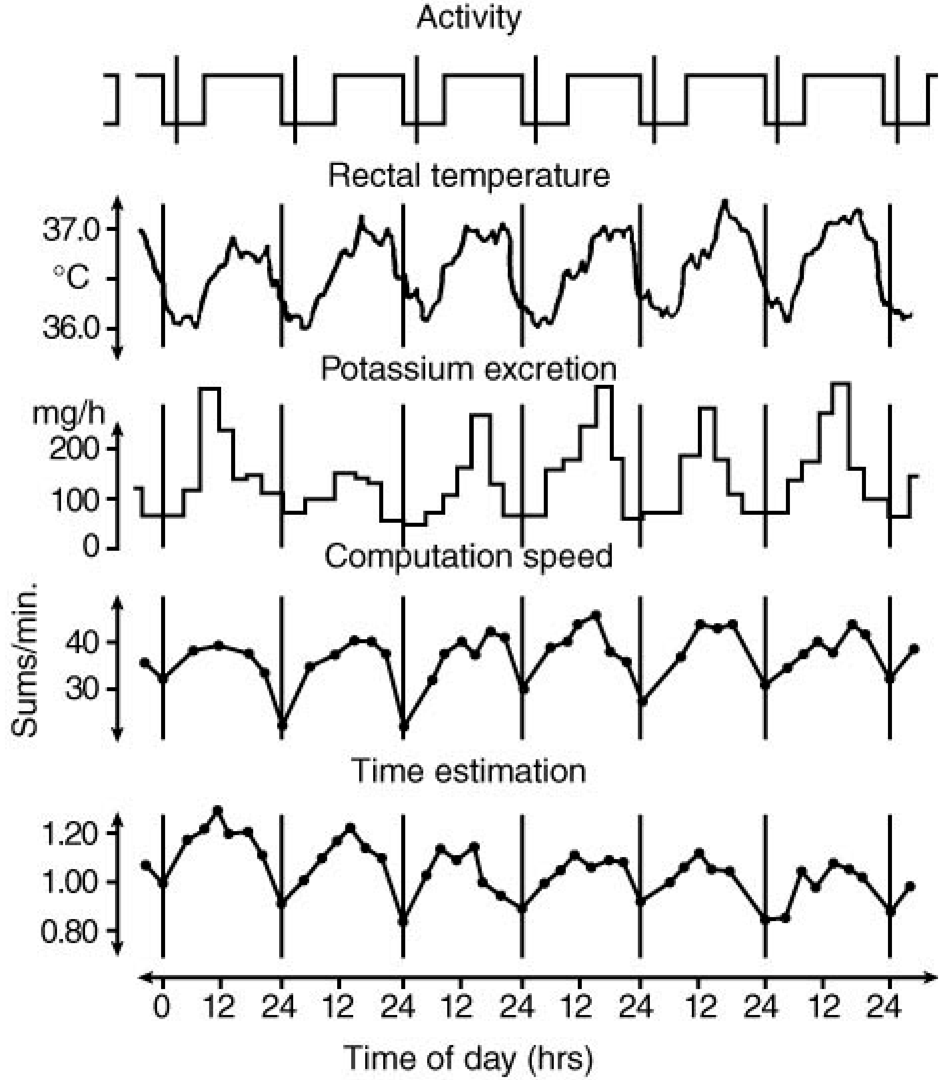
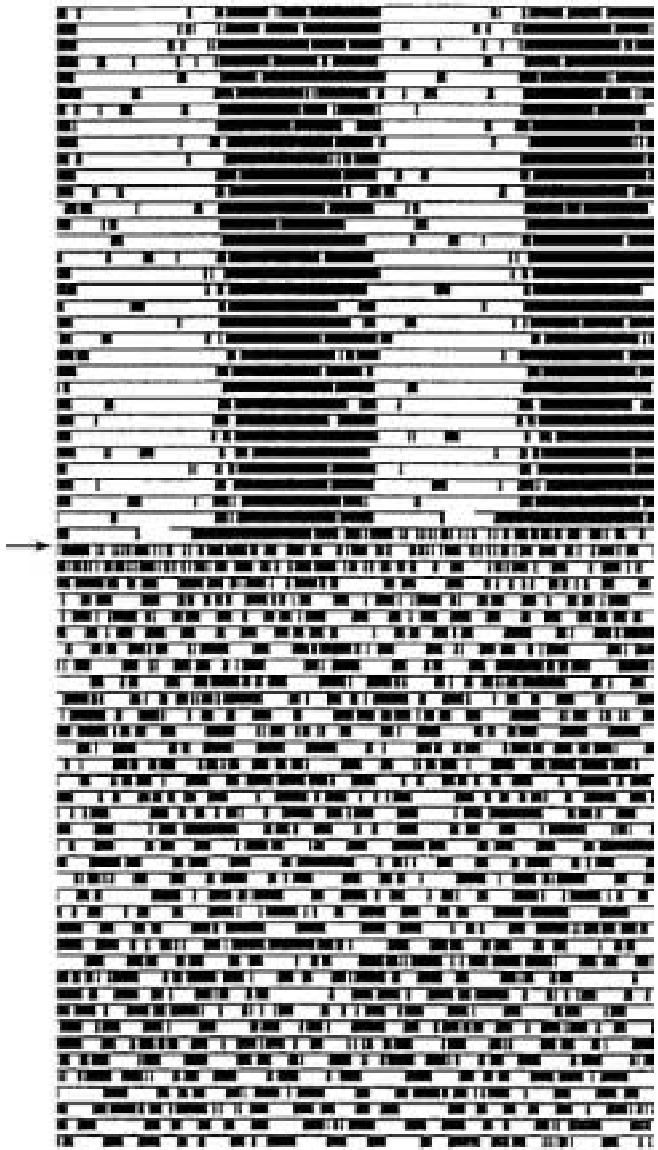


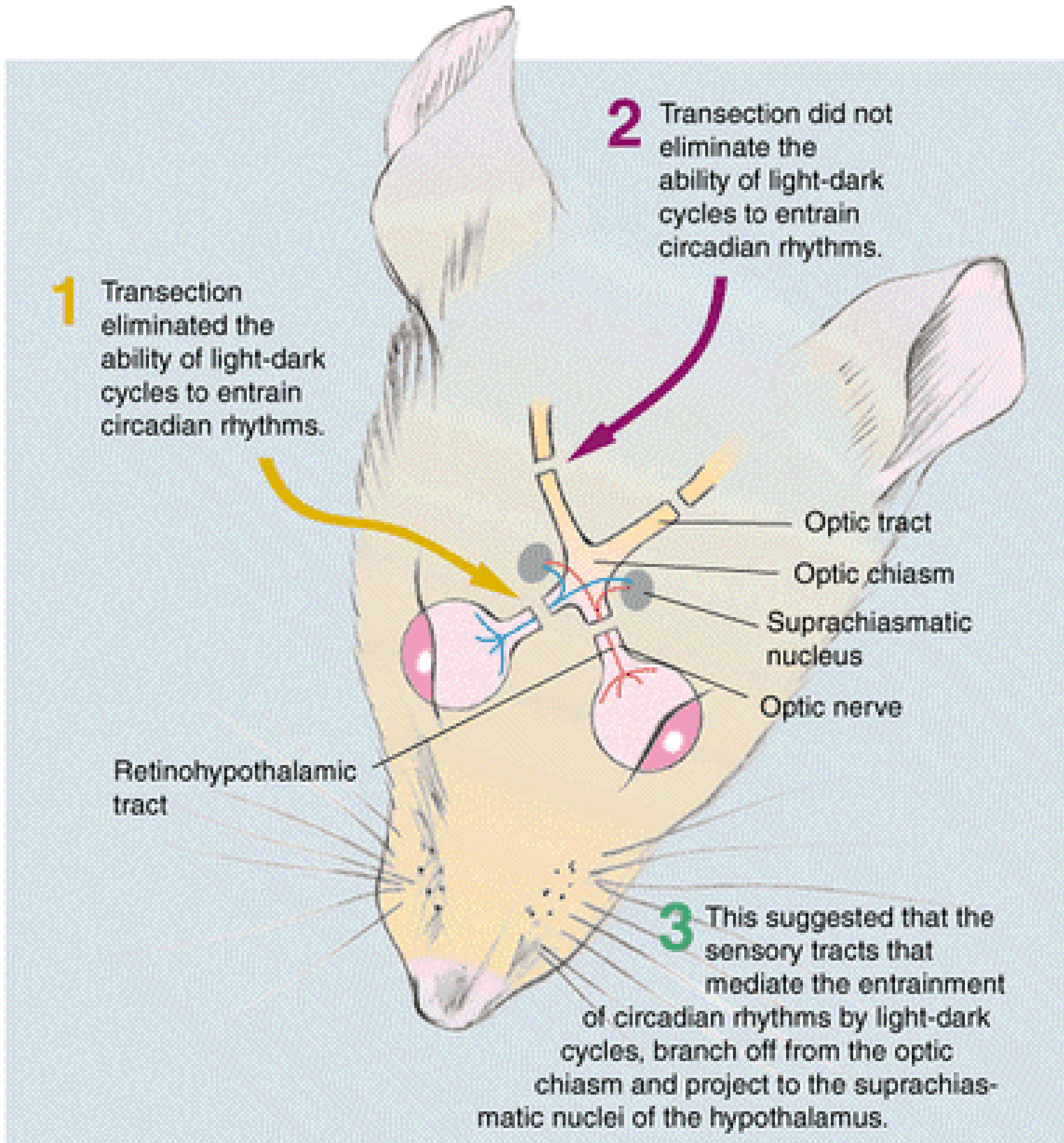
FIGURE 1 Daily rhythms in rest–activity, body temperature, potassium excretion, computation speed (number of computations performed per minute), and time estimation (accuracy with which short intervals of time are assessed). From Wever (1974) with permission.

► A Typical Free-Running Circadian Sleep-Wake Cycle

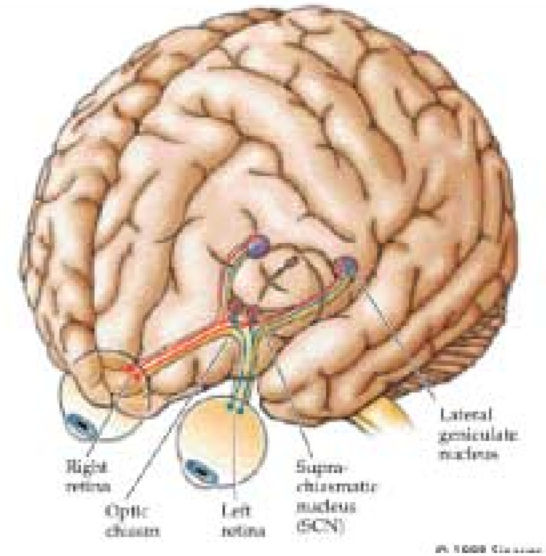


Source: Adapted from Wever, 1979, p. 30.

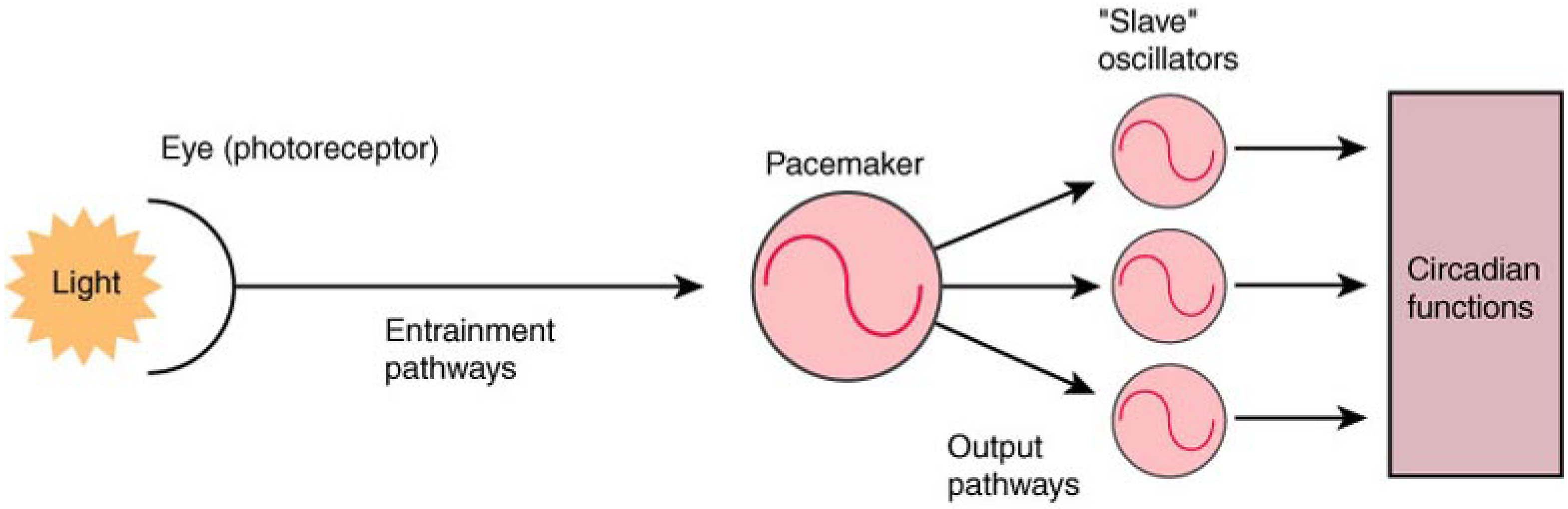
► Discovery of the Retinohypothalamic Tracts



Suprachiasmatic nucleus is master pacemaker

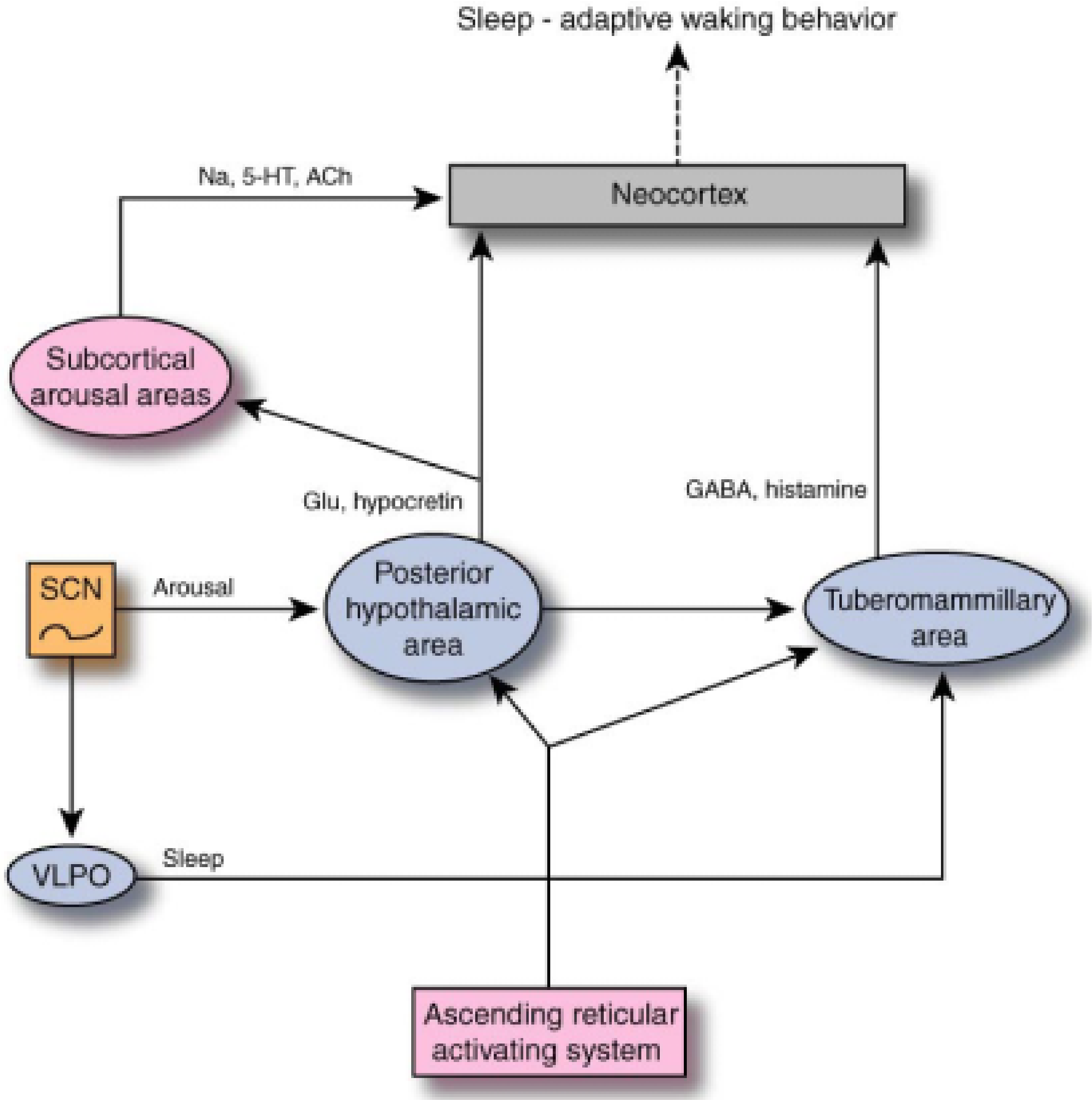


1. Activity in suprachiasmatic nucleus correlates with circadian rhythms
2. Lesions of suprachiasmatic nucleus abolish free-running rhythms
3. Isolated suprachiasmatic nucleus continues to cycle
4. Transplanted suprachiasmatic nucleus imparts rhythm of the donor on the host

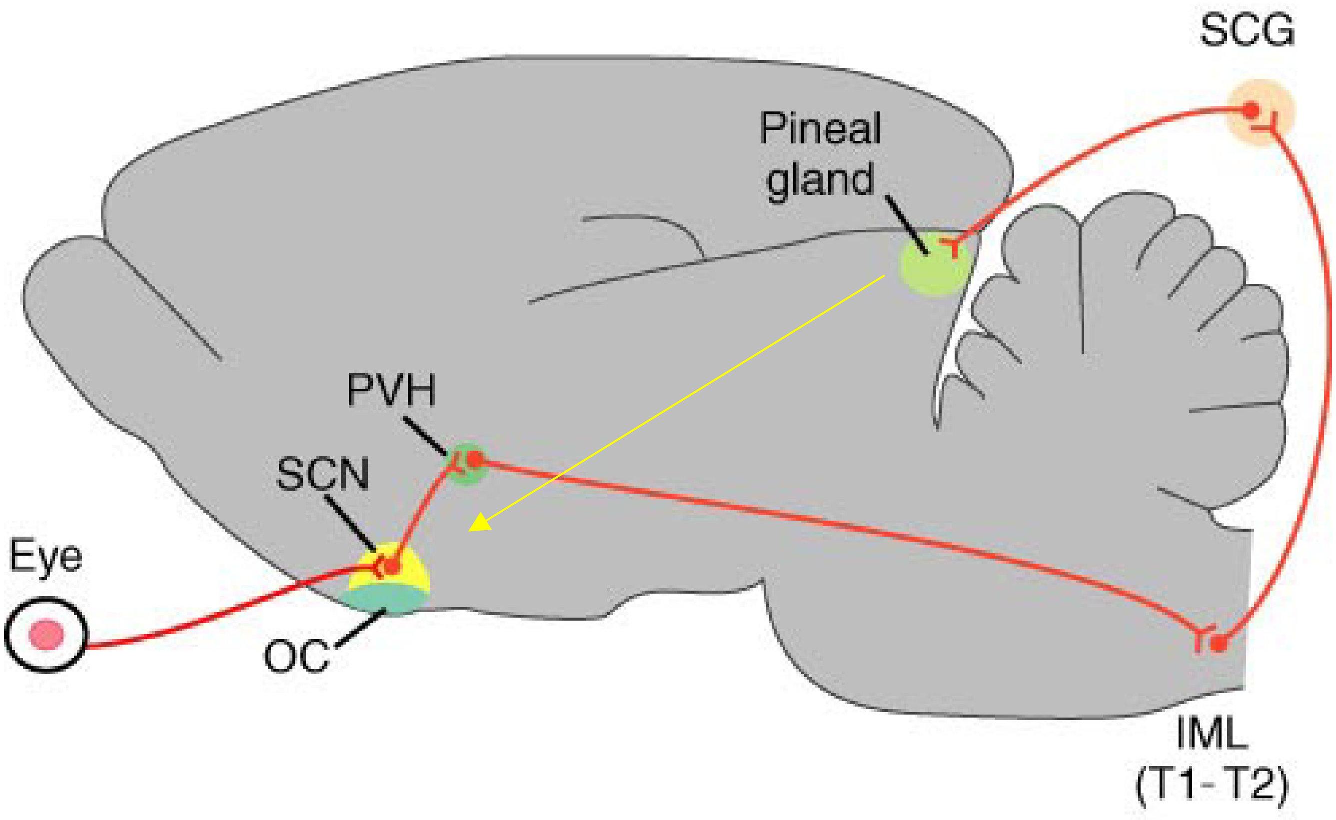


A Model proposed to explain circadian function

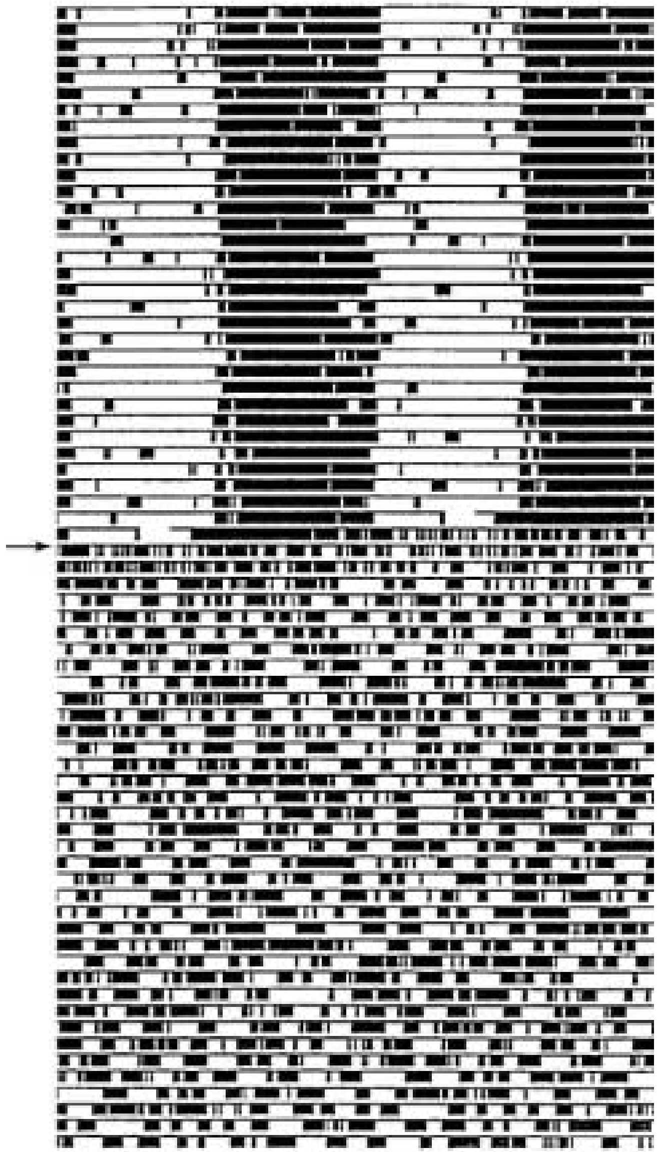
An anatomical route for regulating circadian function



Regulation of "The Clock"

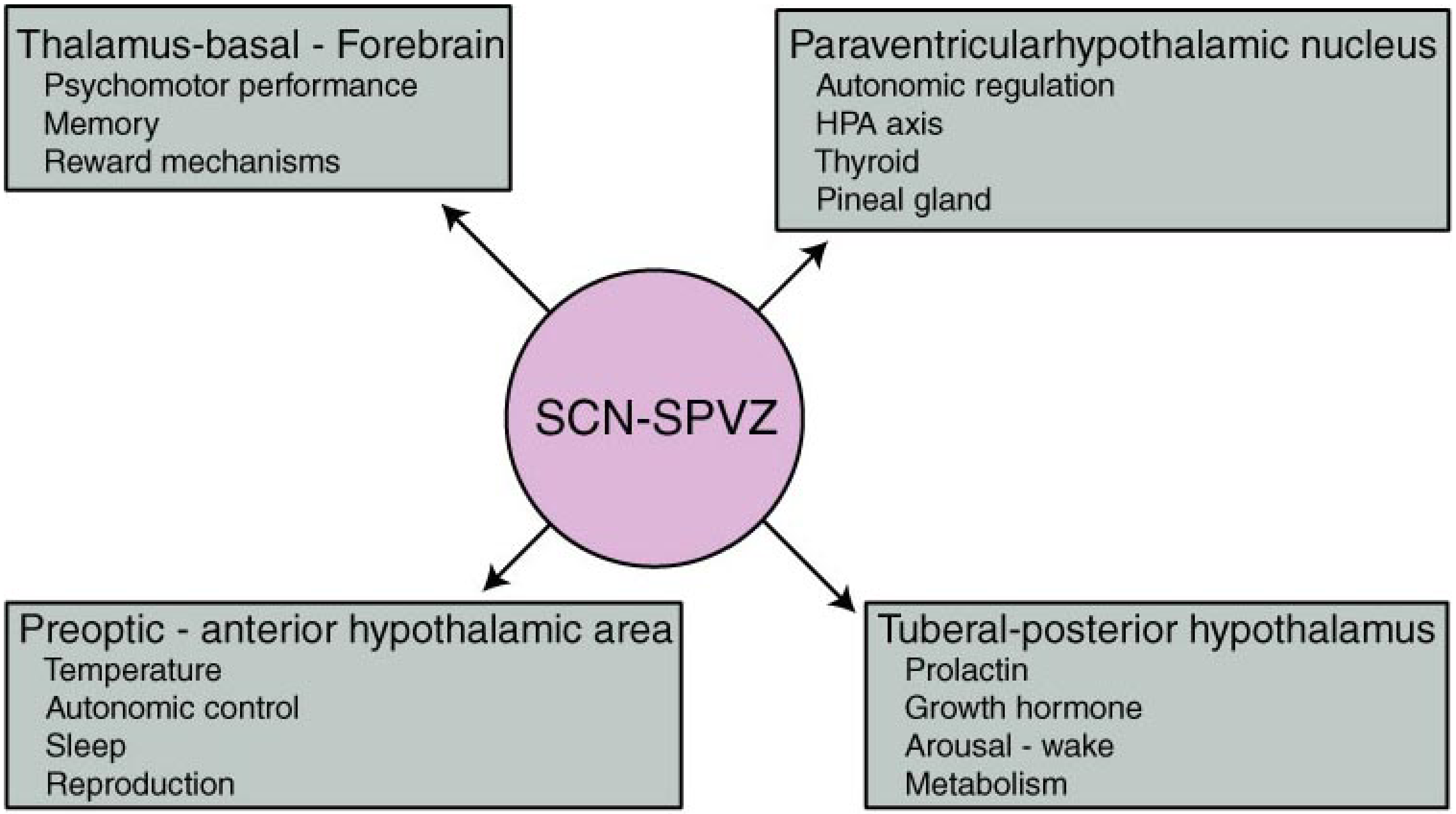


A map of Activity Cycles in a Rat



Pre SCN Ablation

Post SCN Ablation



Subparaventricular zone is thought to reinforce or overlap function of the SCN. Many of the projections are duplicate.

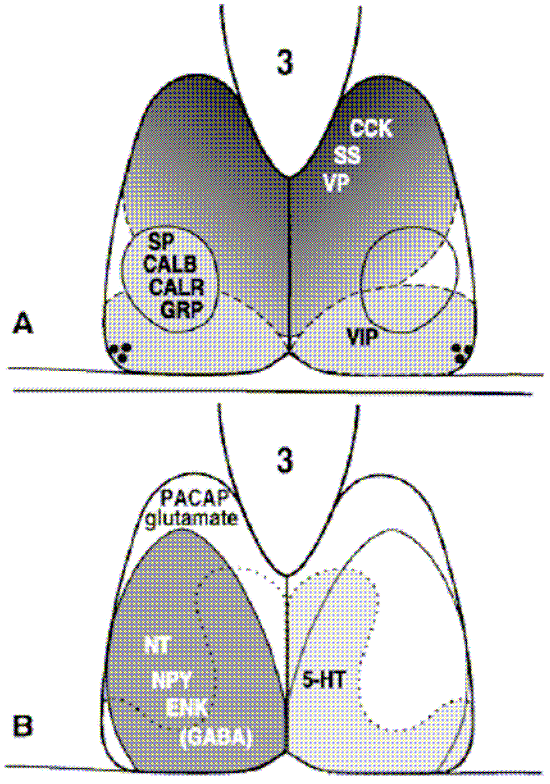
Note: Consider effects across the listed categories

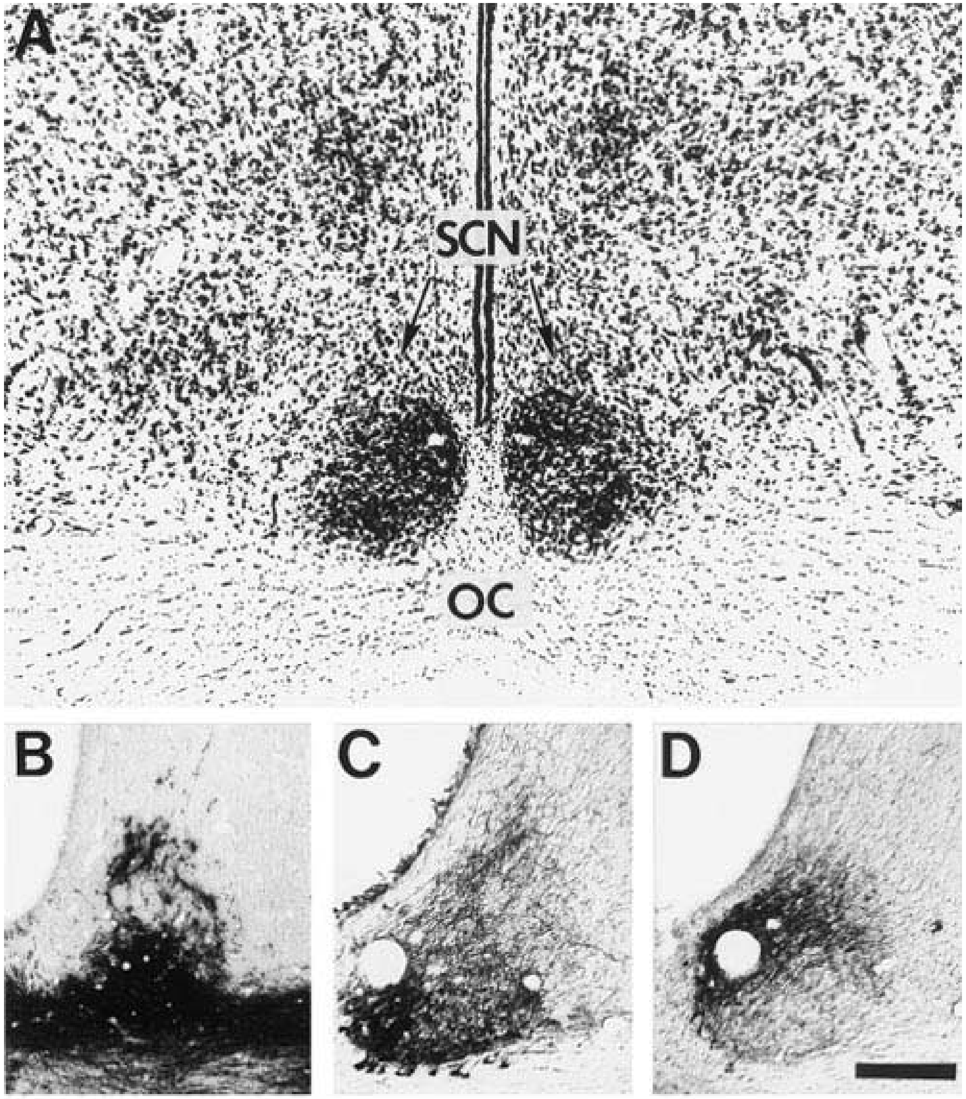
New Findings

- The existence of photoreceptors not specialized for visual functioning
  - Regulate photoperiodism
  - Entrainment of circadian rhythms
- Melanopsin-containing cells found in monkey retinal ganglion cell layer (Provencio et al., 2000)
  - Most likely comprise the retinohypothalamic tract
  - Sensitive to wavelengths in the 484-500 nm (blue light)

SCN

- Rat SCN is divided into
  - Dorsomedial (shell; nonvisual?)
    - Vasopressin neurons
  - ventrolateral (core; visual?)
    - VIP neurons
    - Geniculohypothalamic tract (GHT)
    - Retinal afferents
  - Overlapping area containing
    - Calretinin, Calbindin, gastrin-releasing peptide, substance P and enkephalin neurons

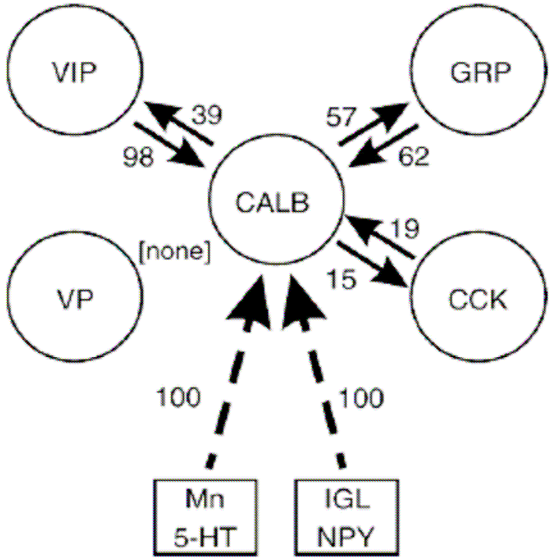


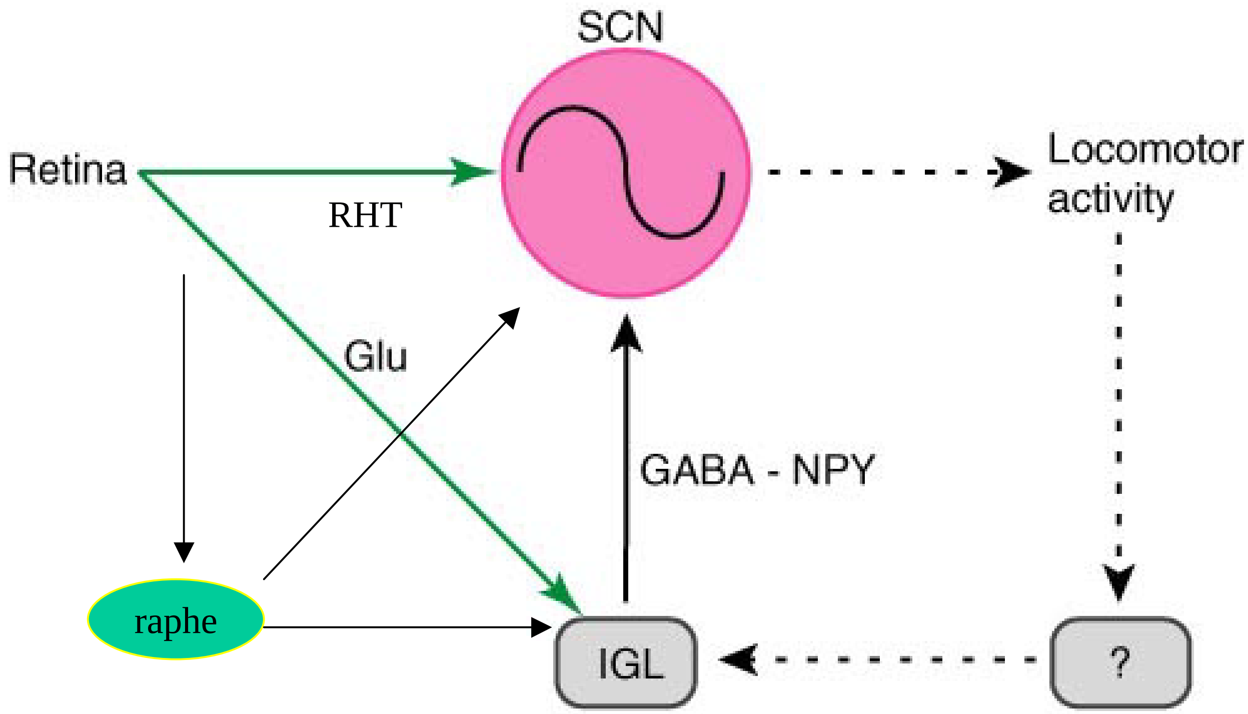


B: Retinohypothalamic Tract
C: VIP in the ventrolateral or “core” of the SCN
D: Vasopresin in the dorsomedial or “shell” of the SCN

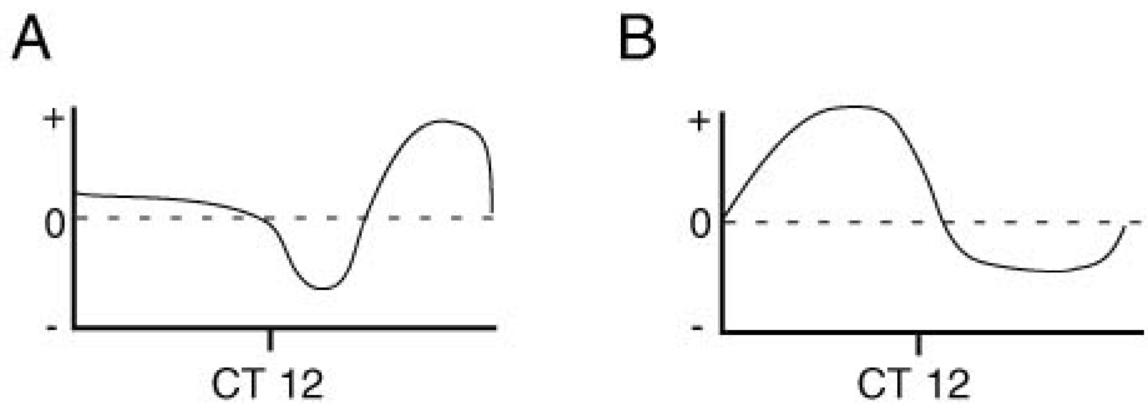
Interconnectivity in SCN

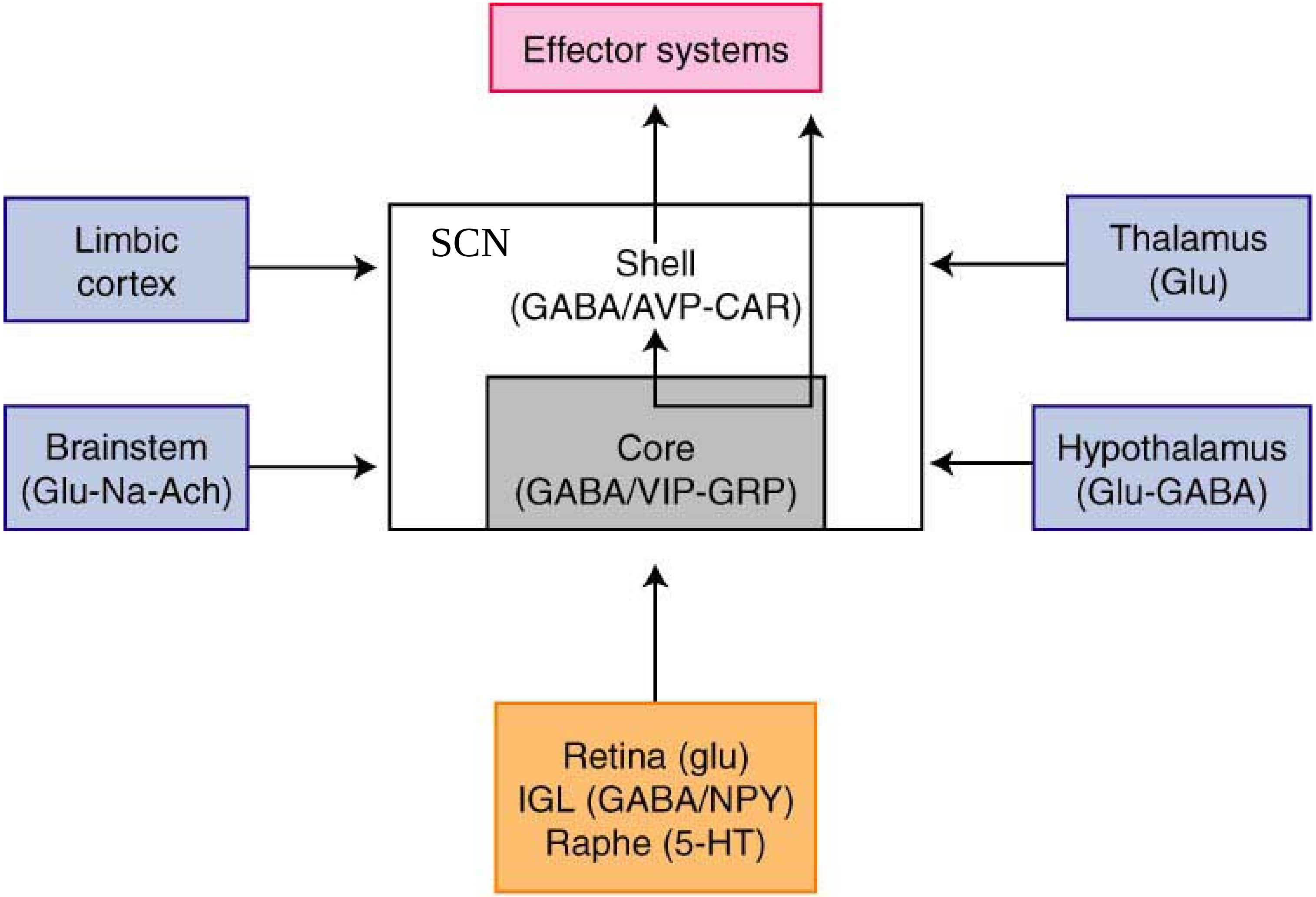
- 40-70% of SCN neurons are GABAergic





IGL = Intergeniculate Leaflet, a subdivision of the LGN





Herzog's 2007 study: VIP provides synchrony signal

Problems for SCN as a Pacemaker?

SUPPORT

- Lesion SCN → loss of cycles
- Transplant SCN → resume cycles in animals

PROBLEM?

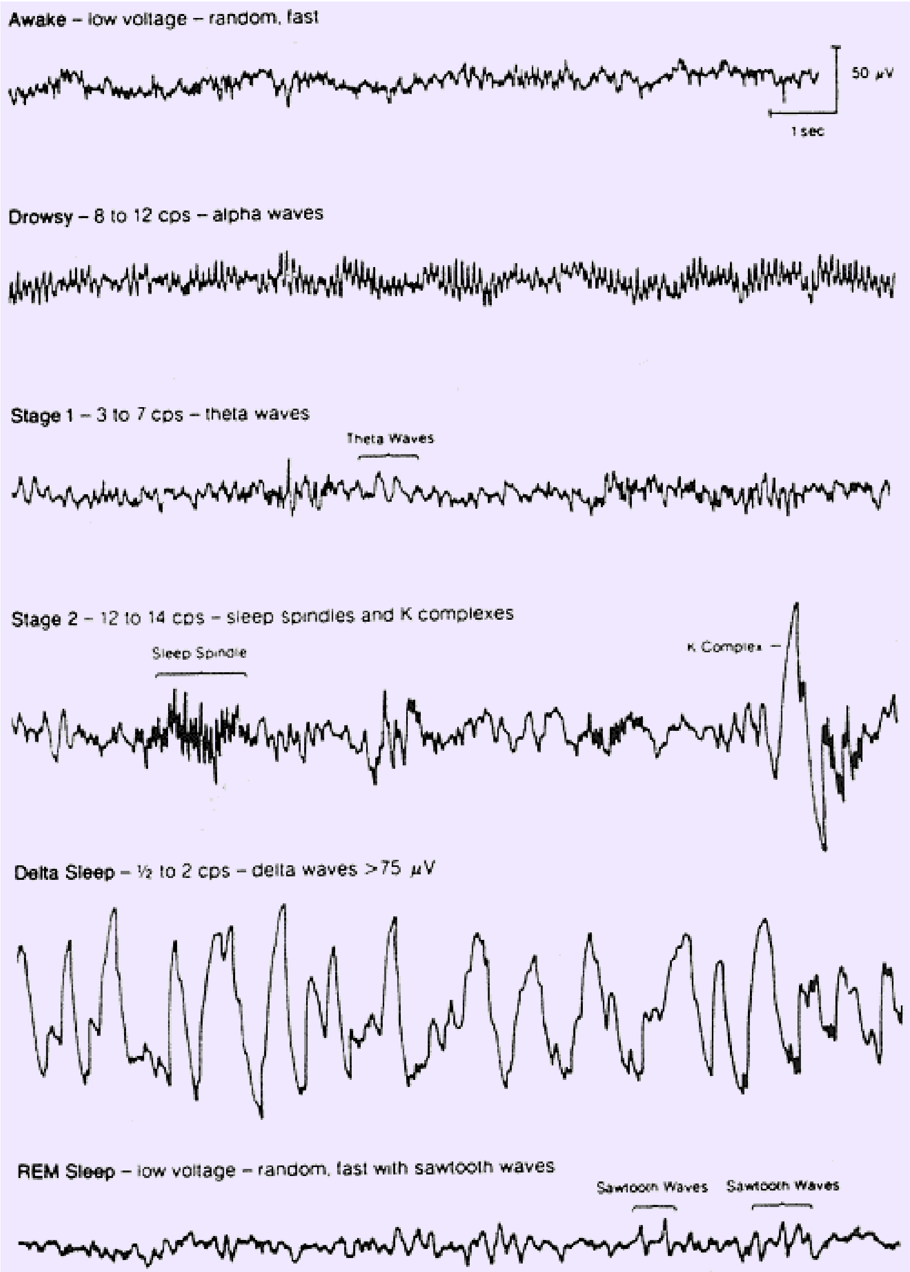
- Connectivity of the transplant does not seem necessary for recovery.
- Other agents important: a peptide (prokineticin) appears important for transmitting info.
- What is the spatial distribution of SCN neurons exhibiting clock-like behavior? Are all SCN cells pacemakers?
- Do all pacemaker cells in the SCN oscillate at the same phase?

What is sleep?

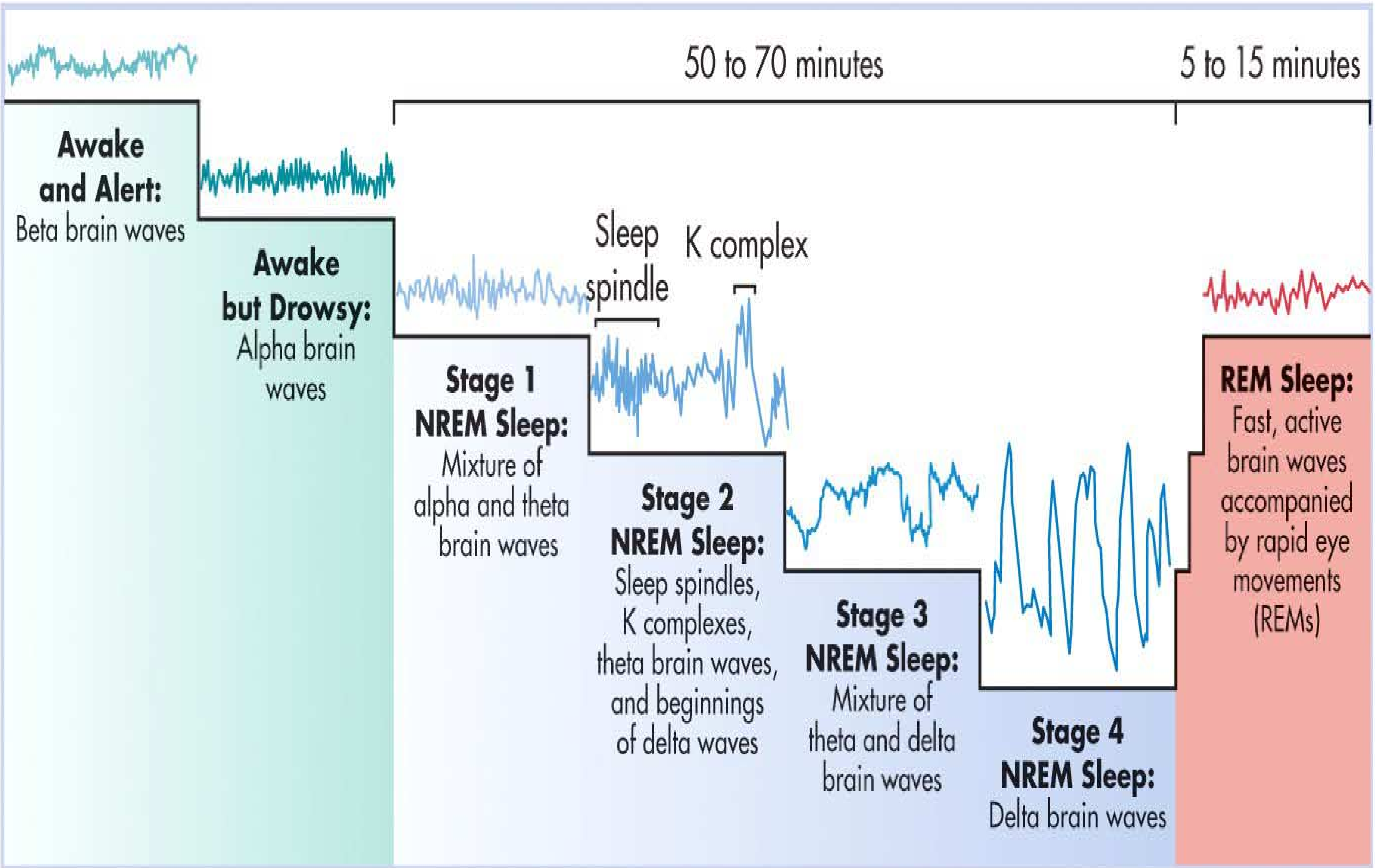
"Natural periodic state of rest for the mind and body, in which the eyes usually close, *and consciousness is completely or partly lost*, so that there is a decrease in bodily movement or external stimuli."

- – Not the absence of waking
- – Not due to lack of sensory input
- – An active process

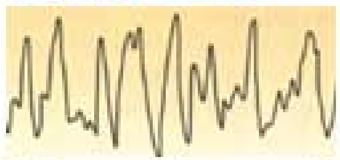
Nathaniel Kleitman and the first sleep lab (1950s)

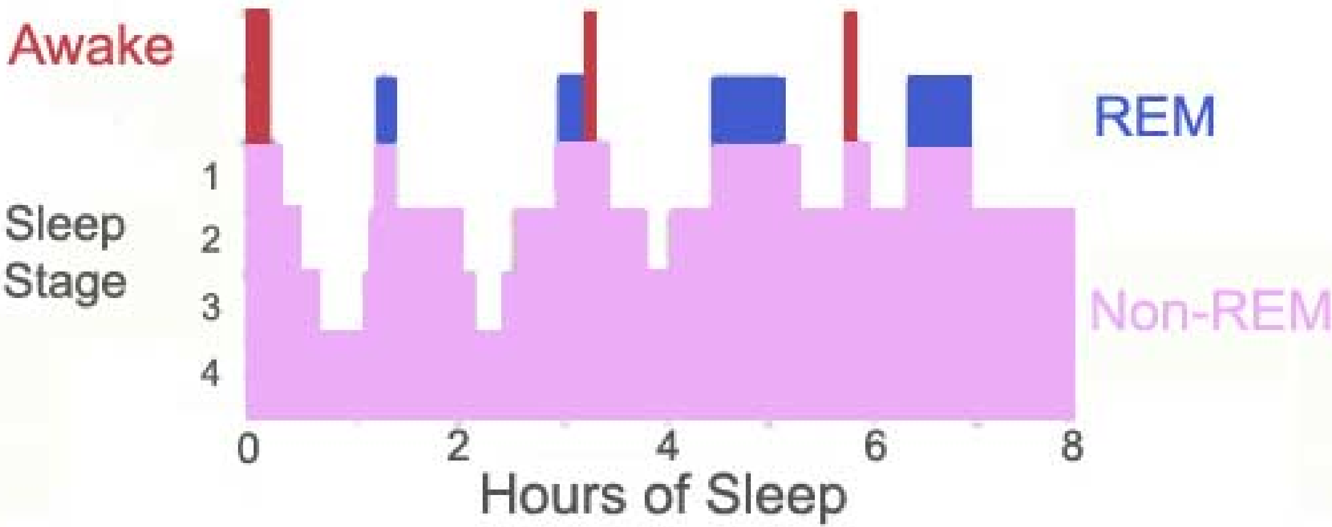


Single Cycle of Sleep

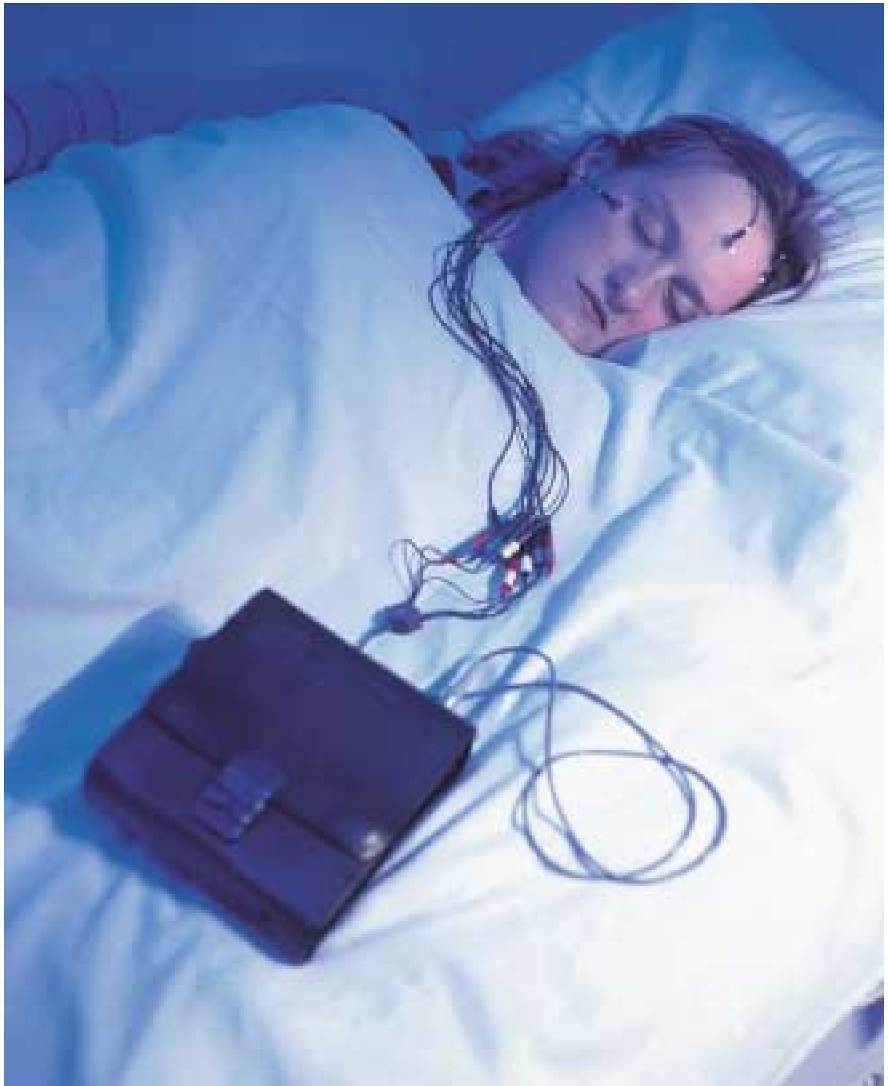


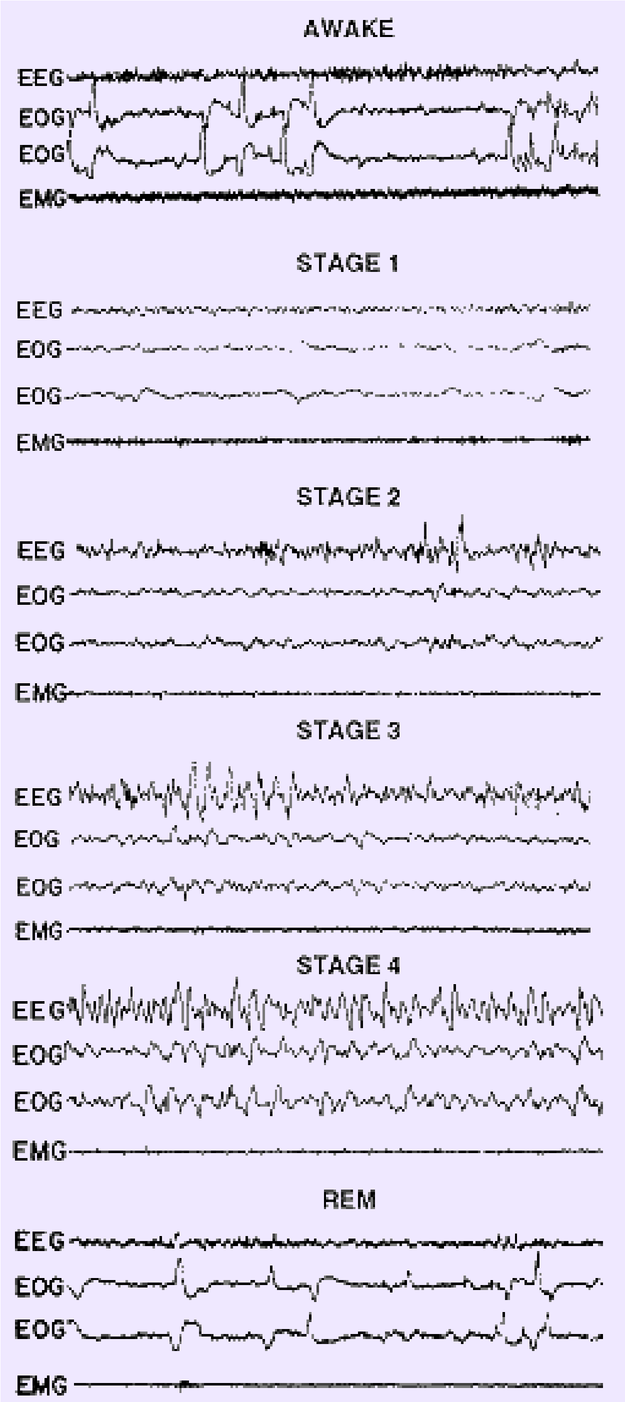
Characteristics of N-REM and REM

Non-REM	REM (Paradoxical)
Slow EEG	EEG similar to awake person
	
Muscular activity	No movement
Dreaming rare	Dreaming common
Easily awakened	Hard to arouse easily
80% of sleep time	20% of sleep time



Getting the whole picture….

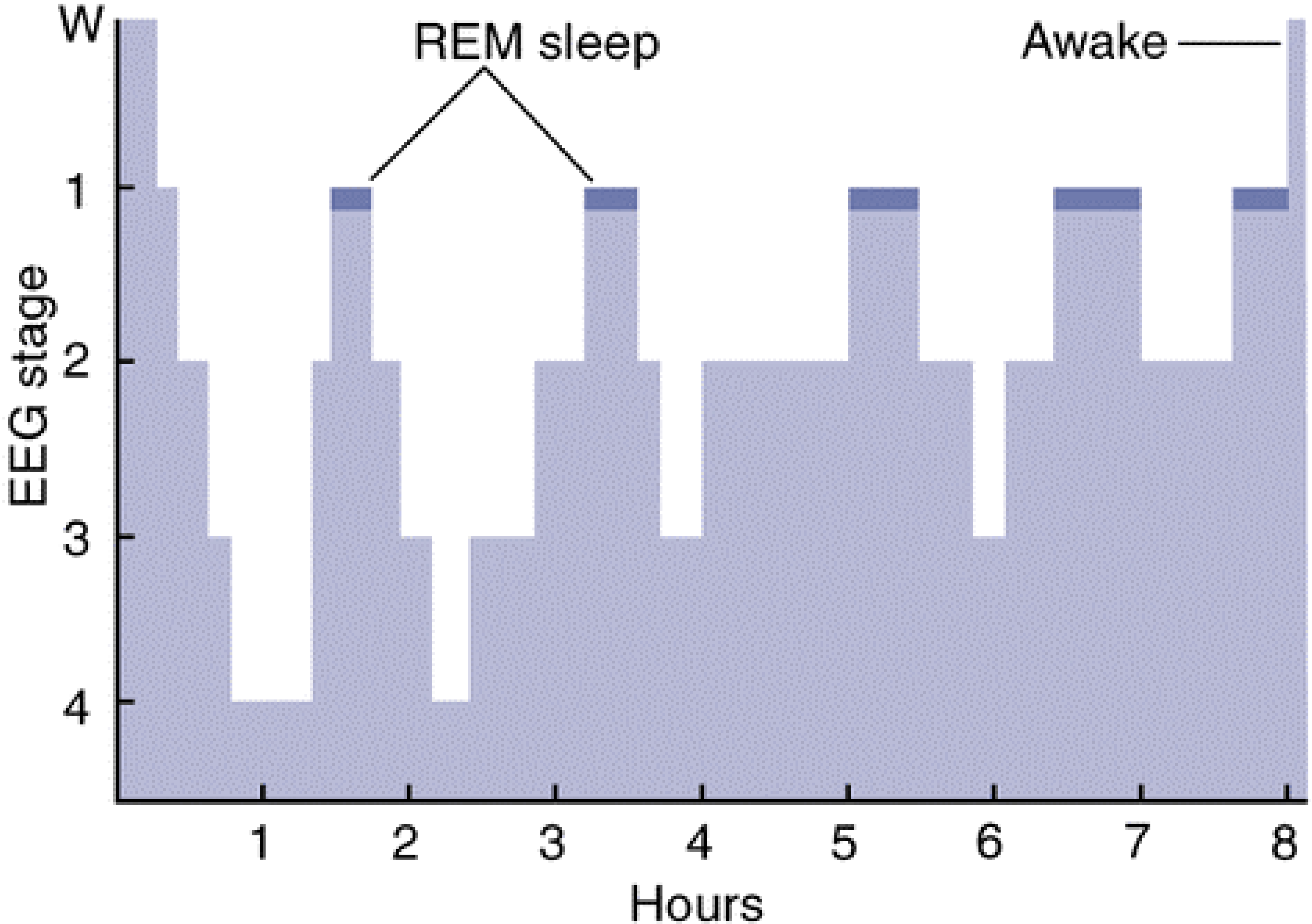




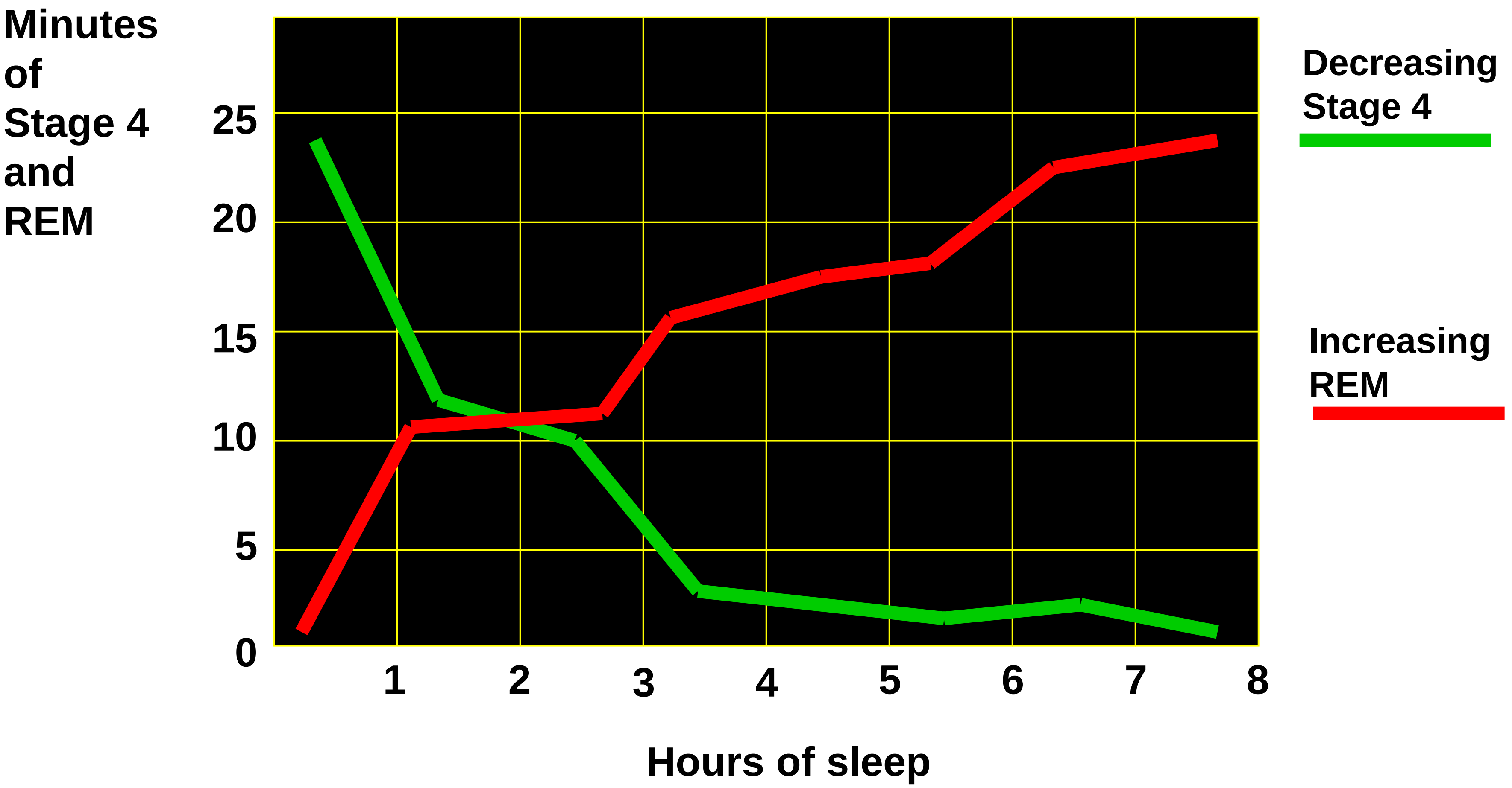
Sleep Stages

- <u>Stage 1</u>(initial)- low voltage, fast wave
- <u>Stage 2</u>- higher voltage, slower wave
  - K complexes, sleep spindles
- <u>Stage 3</u>- some delta waves
- <u>Stage 4</u>- delta waves predominate
- <u>Stage 1</u> emergent-
  - low muscle tone
  - REM sleep

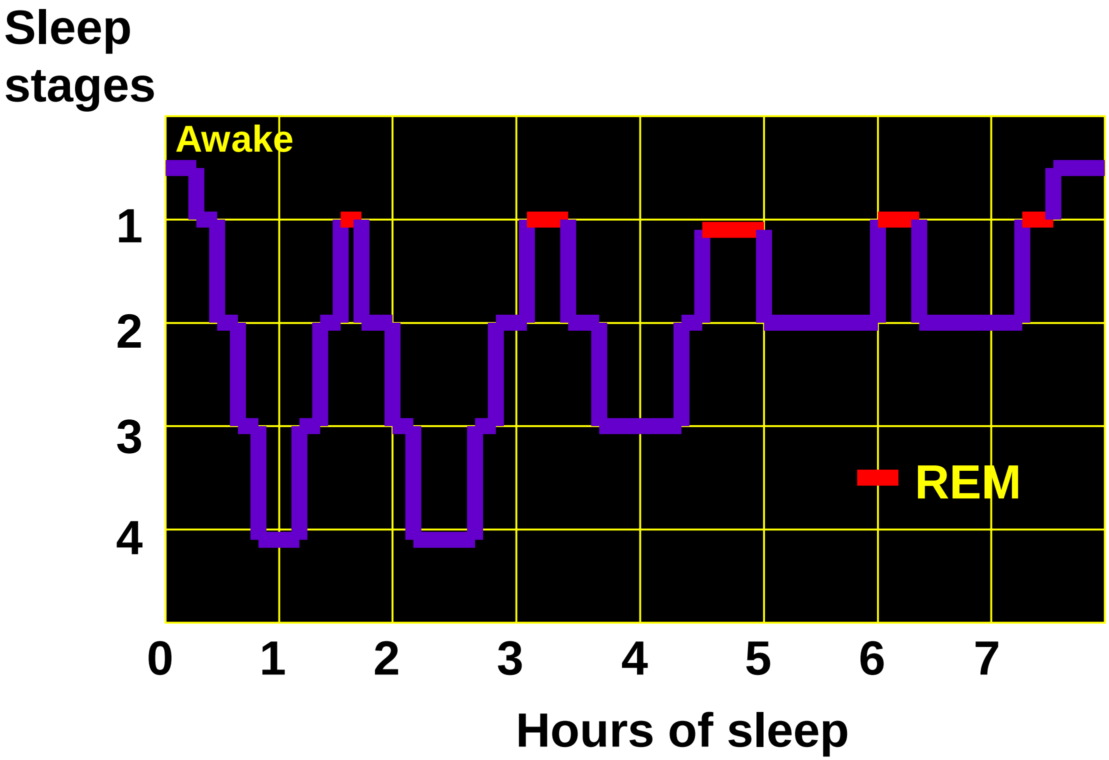
► **Typical Pattern of the Stages of Sleep During a Single Night**



Typical Nightly Sleep Stages

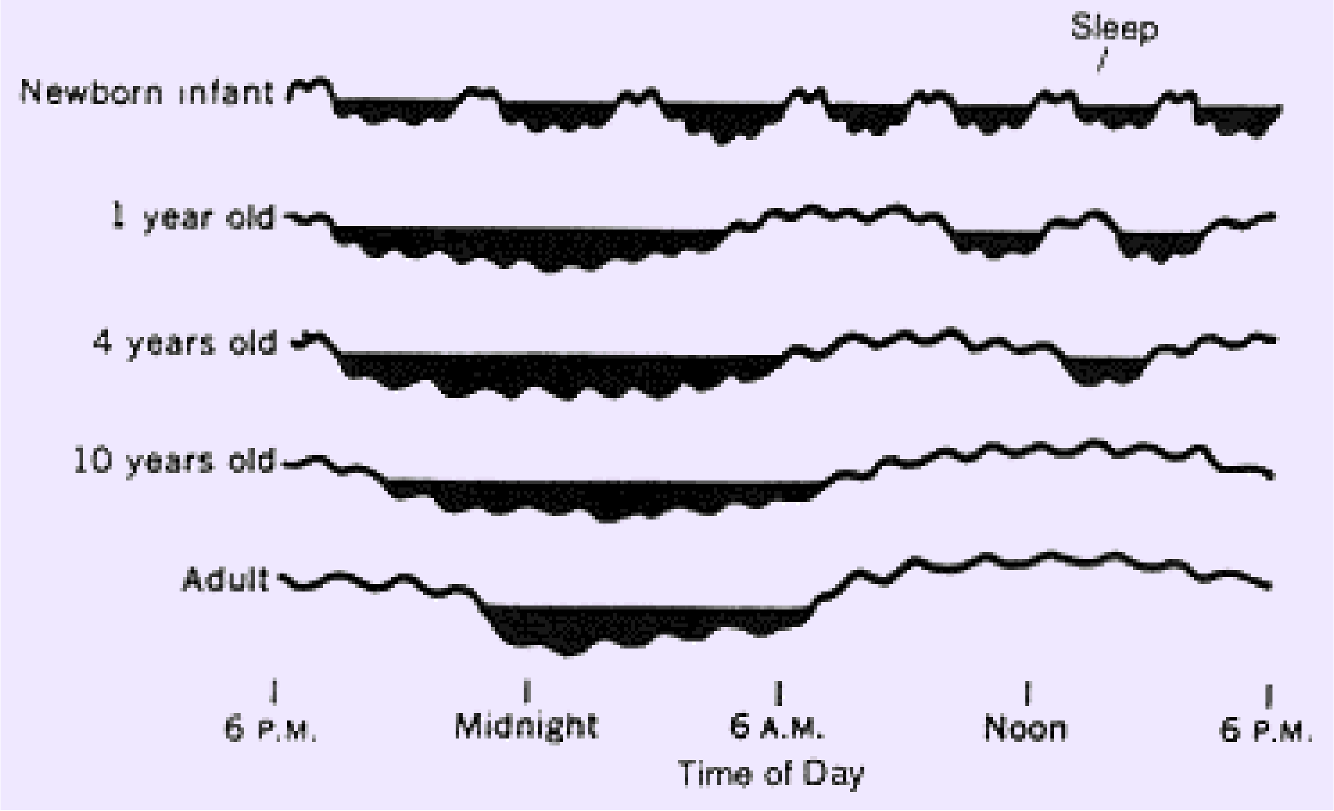


Night Terrors and Nightmares

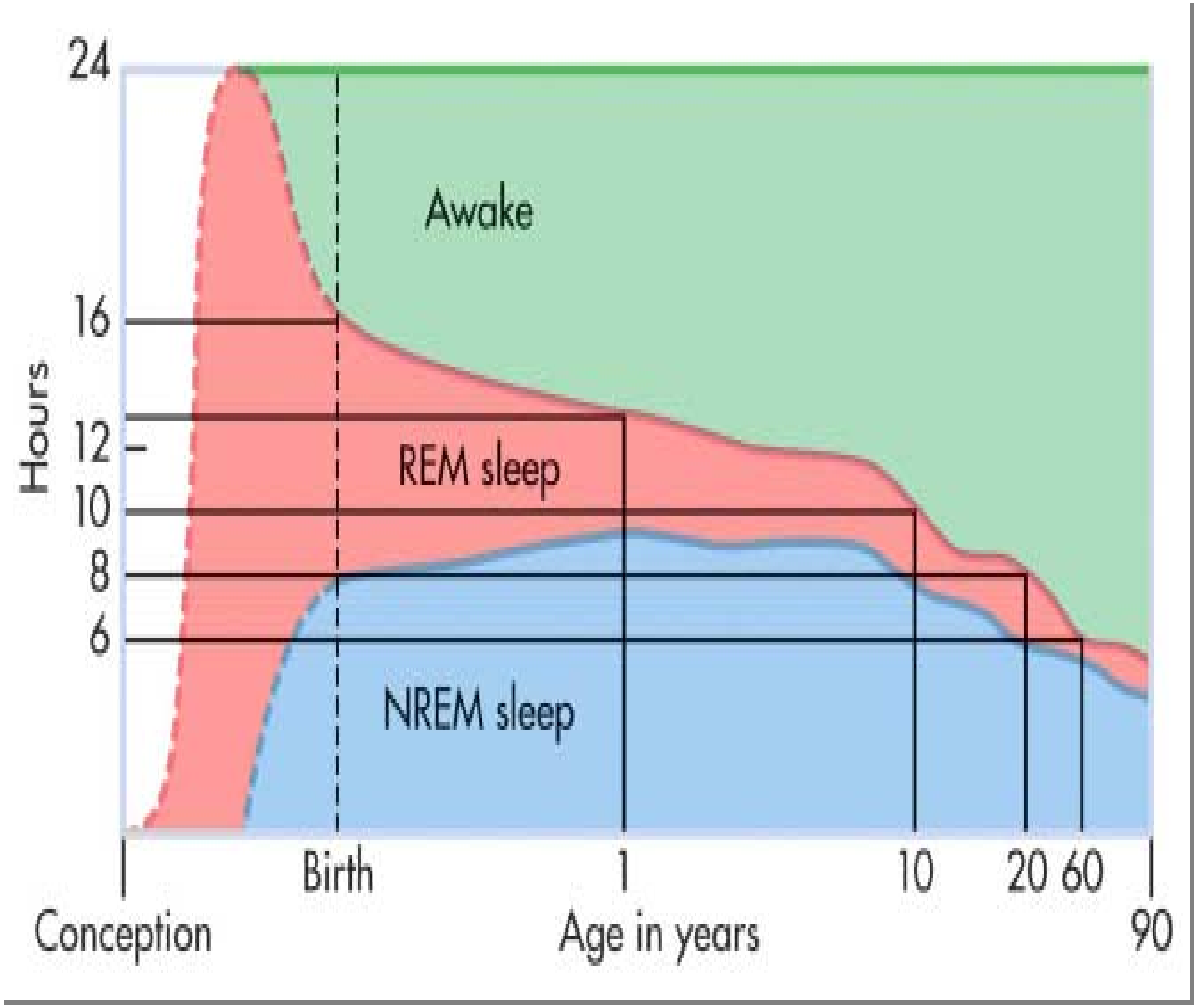


- Night Terrors
  - occur within 2 or 3 hours of falling asleep, usually during Stage 4
  - high arousal- appearance of being terrified
- Nightmares
  - occur towards morning
  - during REM sleep

Sleep over the lifespan - early sleep patterns



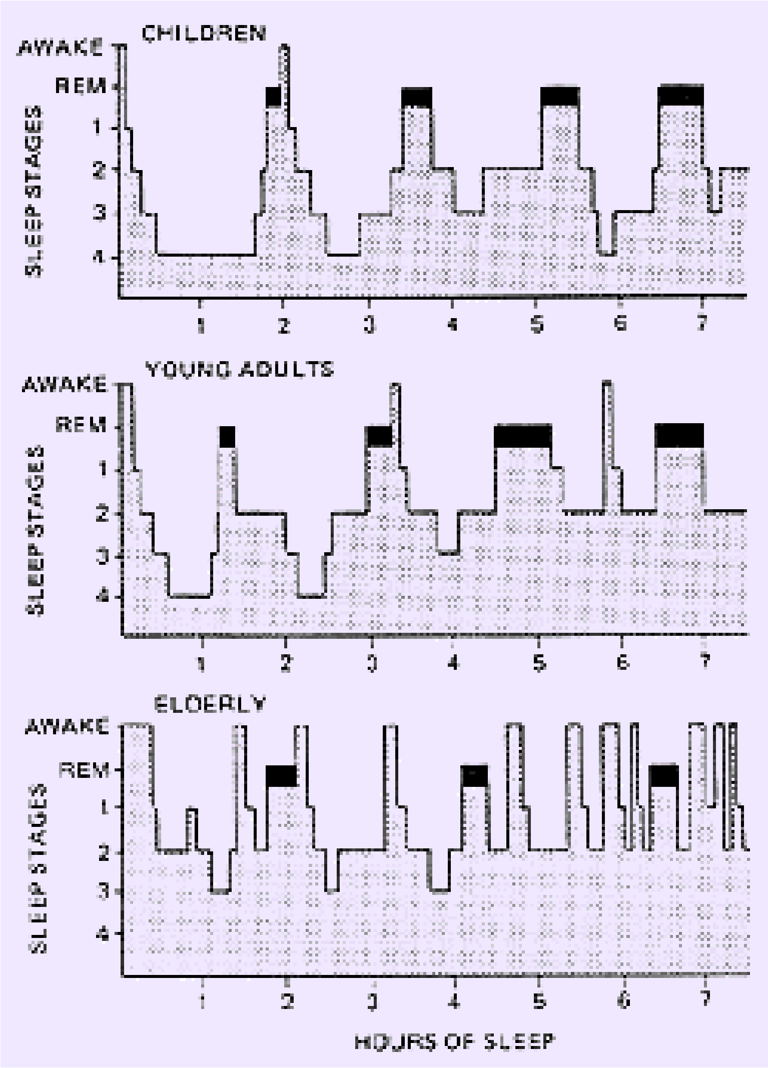
Sleep changes over the lifespan



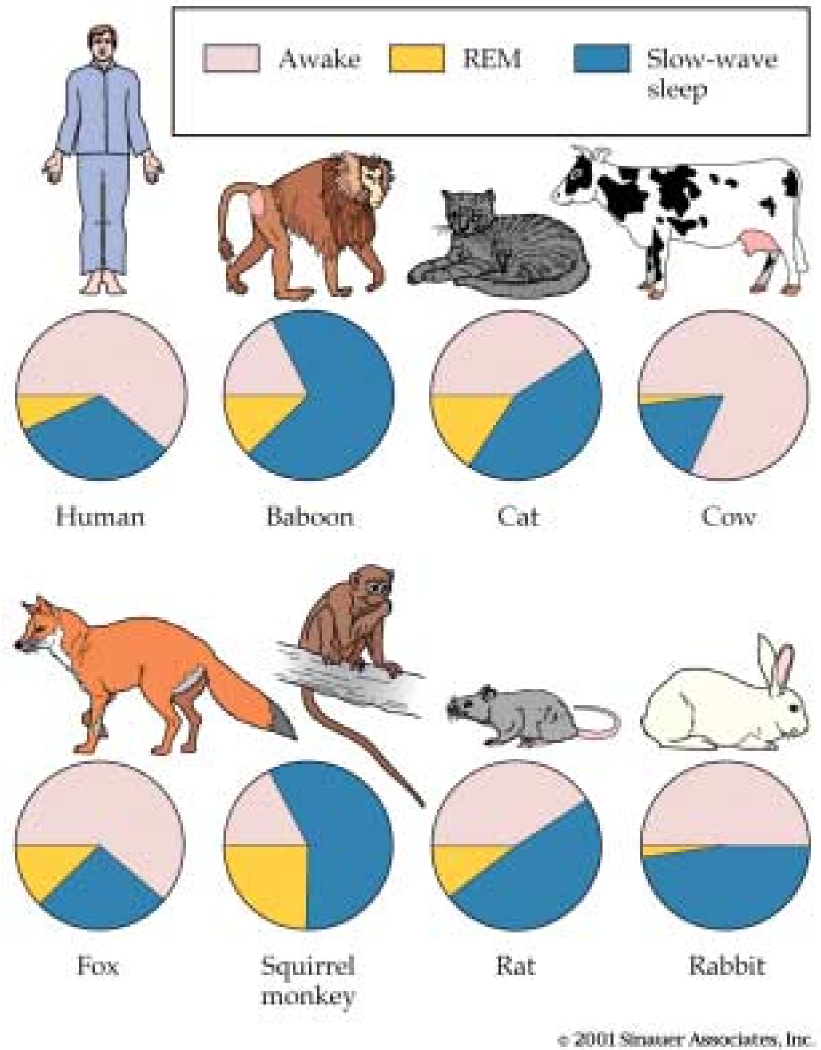
- Continuous REM in gestation
- Sleep quality changes with age:

Amount of time in slow wave and REM sleep decreases with age

Sleep architecture over the lifespan



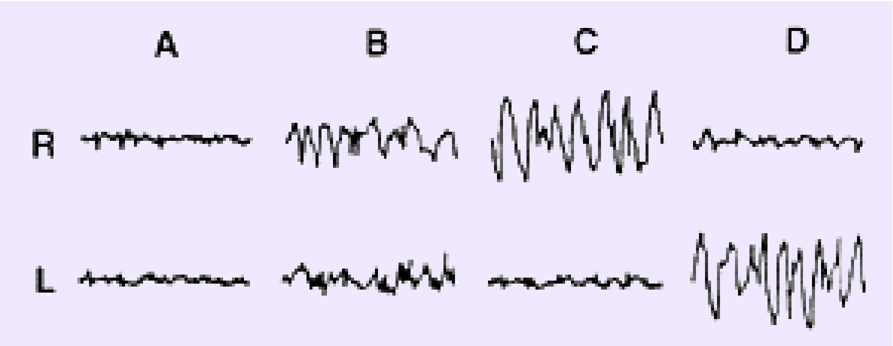
Comparative Sleep Patterns



- Virtually all animals sleep
- Birds have short NREM and REM (9 seconds)
  - waterfowl can sleep while swimming
  - transoceanic migrators can sleep while flying
- Reptiles have no REM
  - homeothermy? (but echidna * have no REM either)
- Smaller body size, more sleep → regulation of body temp?
- Longer life, less sleep

* Spiny anteater—egg laying mammal

Half-sleep marine animals



- Either right or left side of the brain is in a sleep state
- Evidenced by EEG
- “Half-asleep” for 8 hours a day
- Therefore, never fully unconscious/unaware
- Advantageous to prevent predation and drifting away

The functions and neural bases of sleep

Sleep deprivation I

<u>Sleep deprivation stunts</u>

Peter Tripp -- radio DJ sleep deprived self for 260 hours

--> became psychotic

Randy Gardner -- sleep deprived for 264 hours under supervision of sleep researcher Dement

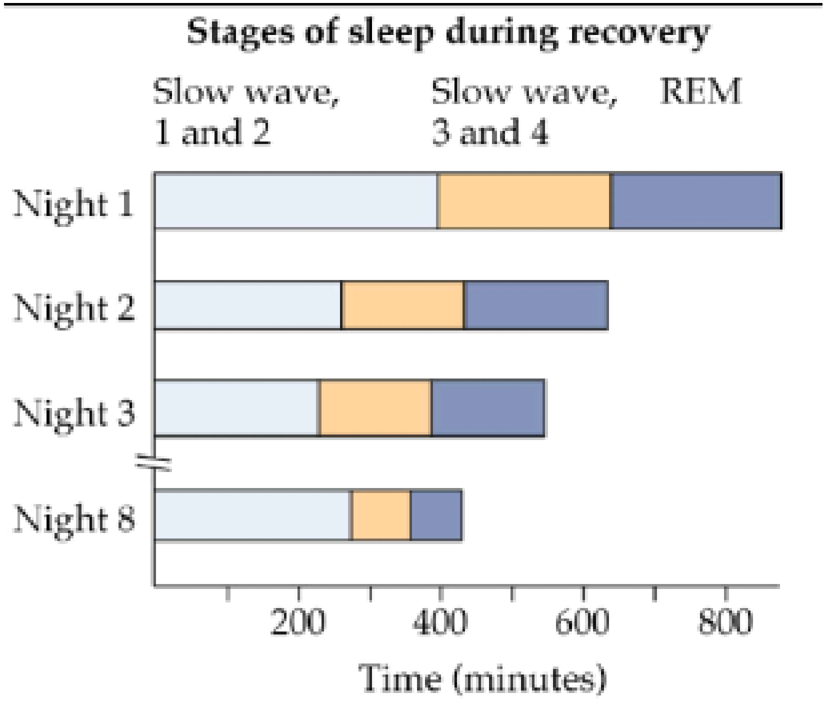
--> few reported ill-effects (played a mean game of pinball)

Sleep deprivation II

<u>Rebound phenomena</u>

- following sleep deprivation, we recover much of our lost sleep but there is some segregation of recovery of different types of sleep.

- following selective SWS or REM deprivation, there is selective recovery



Sleep deprivation III

Sleep deprivation MAY cause death

EXTREME sleep deprivation in animals will eventually cause death (thermoregulatory irregularities, loss of inflammatory responses, infection)

Fatal familial insomnia leads to death but actual cause of death is unknown

* there's a big stress confound here *

Theories of Sleep I

Sleep is adaptive (**Circadian Theory**)

- sleep forces us to be quiet at certain times of the day
- this allows us to share ecological niches with other species
- allows us to conserve energy (species with high metabolic demands sleep more, though metabolism is high during REM)
- allows us to avoid predators (rough correlation between predatory status and sleep properties, though many animals are predator AND prey
- thermoregulation (sleep may help keep us cool - alternating REM and SWS may prevent overcooling)

Theories of sleep function

2. Sleep is restorative (**Recuperation Theory**)

-sleep helps us to get back something we lose during waking
-growth hormone is only secreted during sleep (though not in kids under 4, not in adults over 60 and not in all animals)
-correlational studies not THAT convincing
    -small increase in SWS after ultramarathon
    -no decreases in sleep in quadraplegics

Theories of sleep function

3. Sleep promotes learning

-sleep deprivation can have small effects on ability to learn, but impossible to disentangle other effects of deprivation
- memory loss occurs when sleep is deprived on the same night after material has been learned
-some studies show a slight increase in REM after difficult cognitive tasks
-however, some people sleep little or not at all and show no obvious deficits in ability to learn

Theories of sleep function

No single theory of sleep function is completely satisfactory

Perhaps sleep is multifactorial -- originally served to keep us quiet and still but now other functions (those that work best when we're quiet and still?) piggy back onto the sleep state.

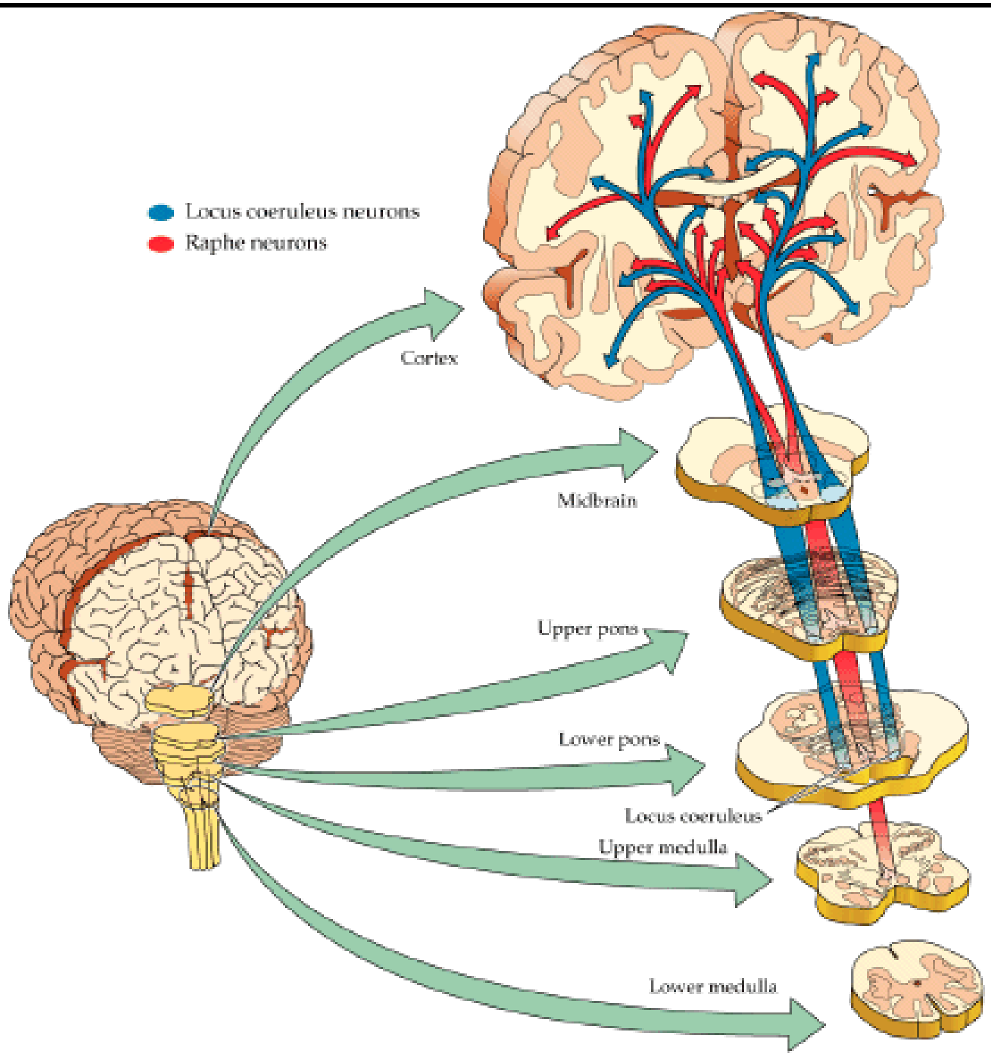
Neural Mechanisms of Sleep

- Reticular activating system
  - integrates sensory input and regulates arousal
  - Stimulating the system while the subject (usually a cat) is sleeping will awaken them.
  - destruction results in somnolence

- Raphe nuclei lesions lead to insomnia
  - Serotonin source
  - Normally promotes sleep
  - destruction results in insomnia
  - REM permanently inhibited

- Locus coeruleus:
  - dense nucleus of cells in brainstem
  - NE source
  - promotes wakefulness

- The control of sleeping and waking is distributed in multiple areas of the brainstem to control the entire nervous system
  - A balance and interaction between alert systems and rest systems

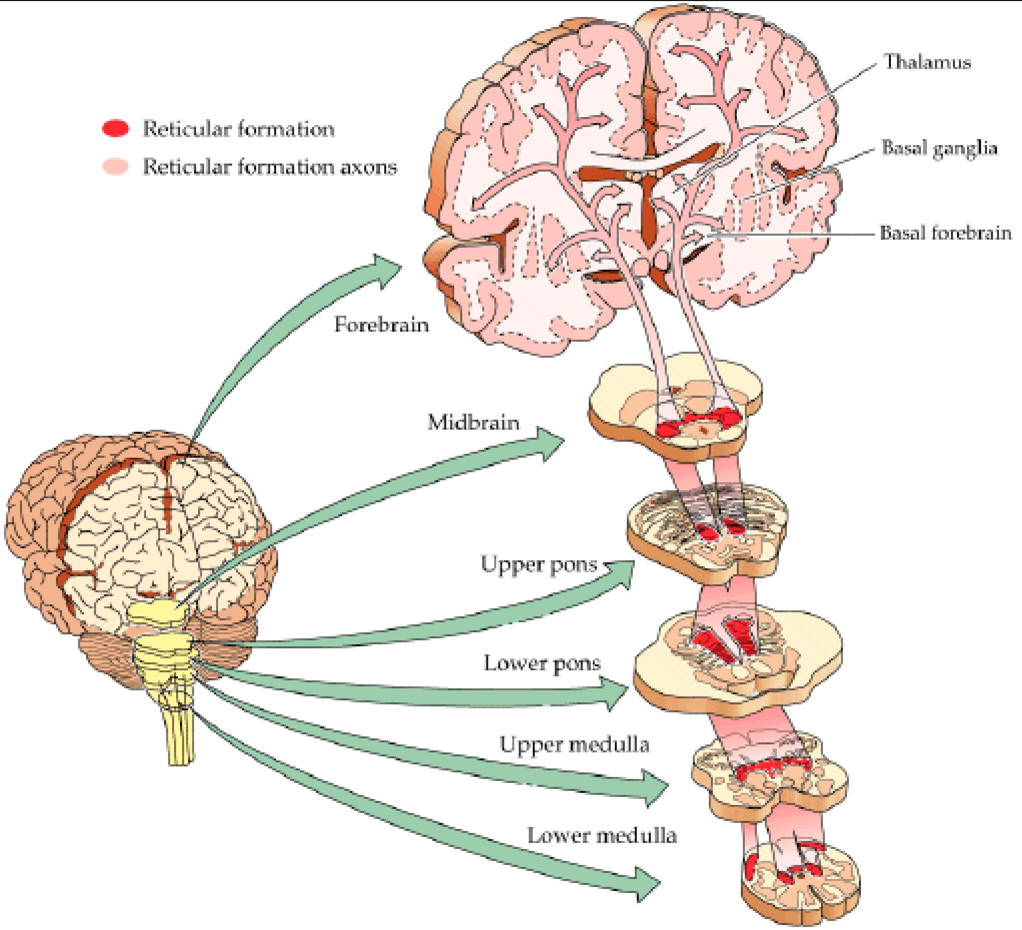


Raphe promotes sleep

Locus coeruleus promotes wakefulness

*so sleep control is distributed across centers

The reticular formation also promotes wakefulness



Narcolepsy

- Excessive daytime sleepiness
- Abnormal REM sleep
  - Sleep paralysis
- Hypnagogic hallucinations
- Cateplexy: sudden and transient paralysis triggered by high emotional arousal
  - e.g hysteric laughing
- Hypothesis: Cholinergic hyperactivity and monaminergic hypoactivity in the pons
- Single autosomal recessive genetic disorder (in canines)
  - Hypocretin…

Narcolepsy—Neurochemical Basis

- Narcolepsy has been studied since 1880
- Hyocretin protein and receptor was discovered in 1998 and shown to be from the hypothalamus
- Hypocretin was attributed to narcolepsy in 1999 in canines, in 2000 for humans
  - Greatly reduced levels of hypocretin peptides in CSF
  - No or barely detectable hypocretin-containing neurons in their hypothalamus
- Mouse knockout for hypocretin made in 1999 and is an effective model for narcolepsy
- Modafinal drug treatment

Narcolepsy—Neurochemical Basis

What does hypocretin do and how?

- Increases wakefulness
- Suppresses REM sleep

- Targets:
  - Dorsal raphe
  - Locus ceoruleus
  - Pons
  - Reticular formation
  - Basal forbrain
- 2 receptor types
  - Can have various effects
  - Metabotrophic