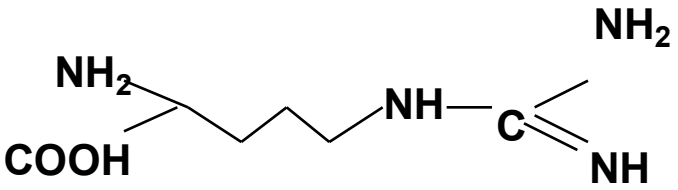
# Non-traditional Neurotransmitters

# Nitric Oxide




Arginine

Nitric Oxide Synthase
(NADPH, THB)

Citrulline

NO

- NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase

**NOS-1 (nNOS)**

Constitutive
Neuronal
$Ca^{++}$ -dependent

**NOS-2 (iNOS)**

Inducible
Mostly Glial
$Ca^{++}$ -independent
Pro-inflammatory

**NOS-3 (eNOS)**

Constitutive/Inducible
Vascular endothelium
$Ca^{++}$ -dependent

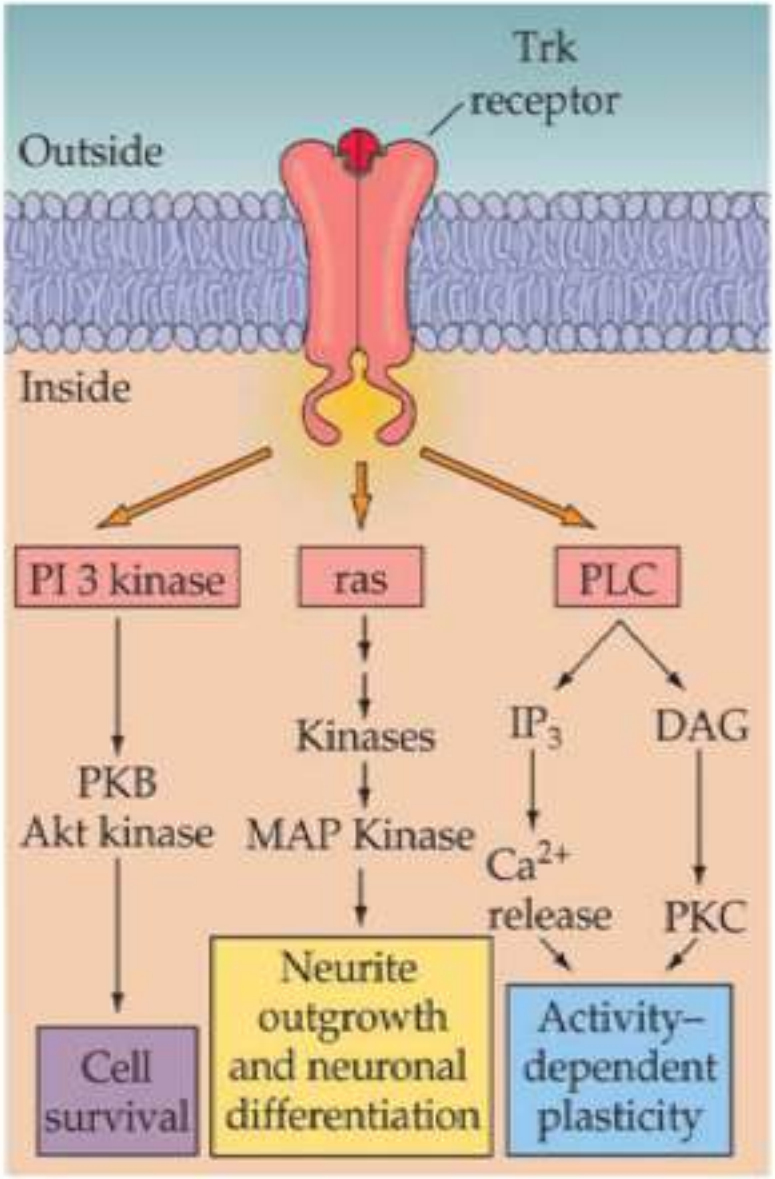
# Nitric Oxide (NO)

- NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase
- NO is widely distributed in brain and peripheral tissues
- NO is not stored and synthesis is regulated by the enzyme activity

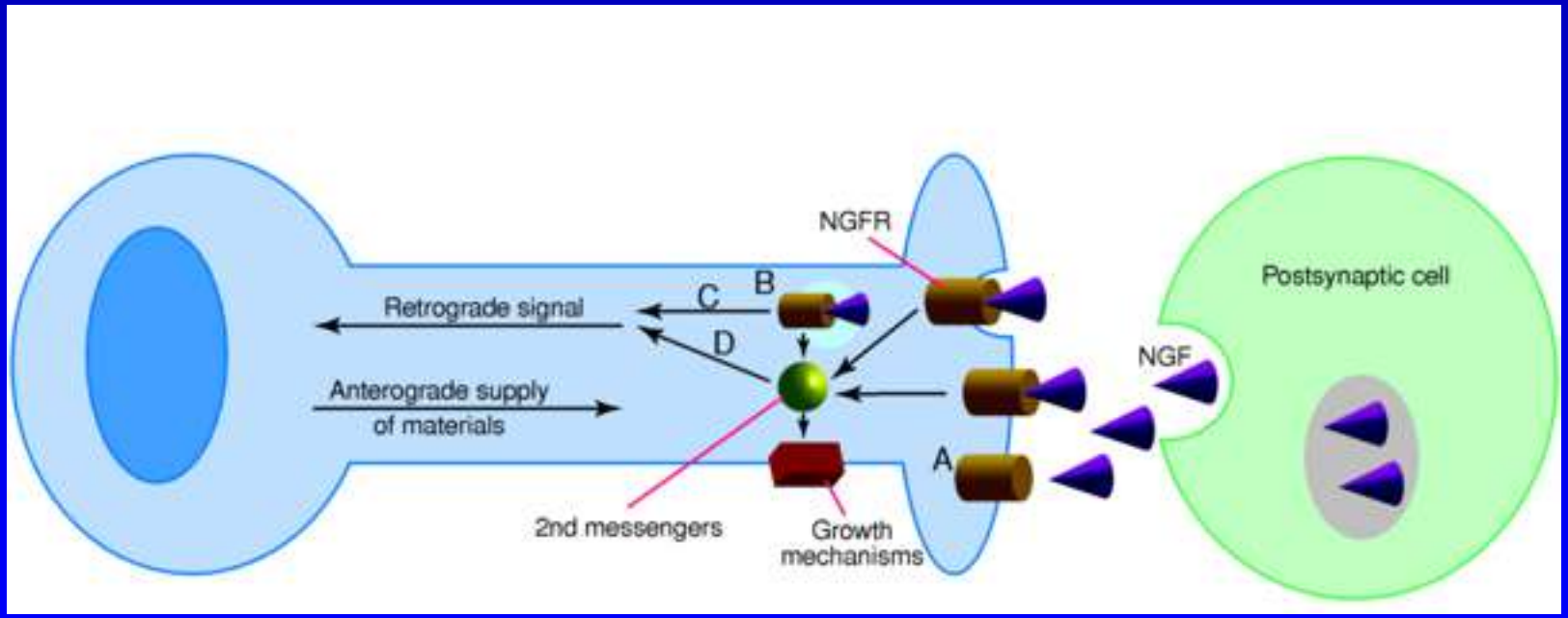
# Nitric Oxide

- Regulation of blood flow - Neuron-derived NO plays a major role in the regulation of blood flow, vasodilation and increased blood flow
- At the cellular level, NO  can changes intracellular metabolic functions that modify neuronal excitability and influence neurotransmitter release
- In the brain, NO acts as a neuromodulator to control behavioral activity, influence memory formation, and intensify responses to painful stimuli
- May be responsible for glutamate induced neurotoxicity

# Brain-derived neurotrophic factor "BDNF"


Trk
receptor
Outside
Inside
PI 3 kinase
ras
PLC
PKB
Akt kinase
Kinases
MAP Kinase
$IP_3$
DAG
$Ca^{2+}$
release
PKC
Cell
survival
Neurite
outgrowth
and neuronal
differentiation
Activity–
dependent
plasticity

# Transport of NGF



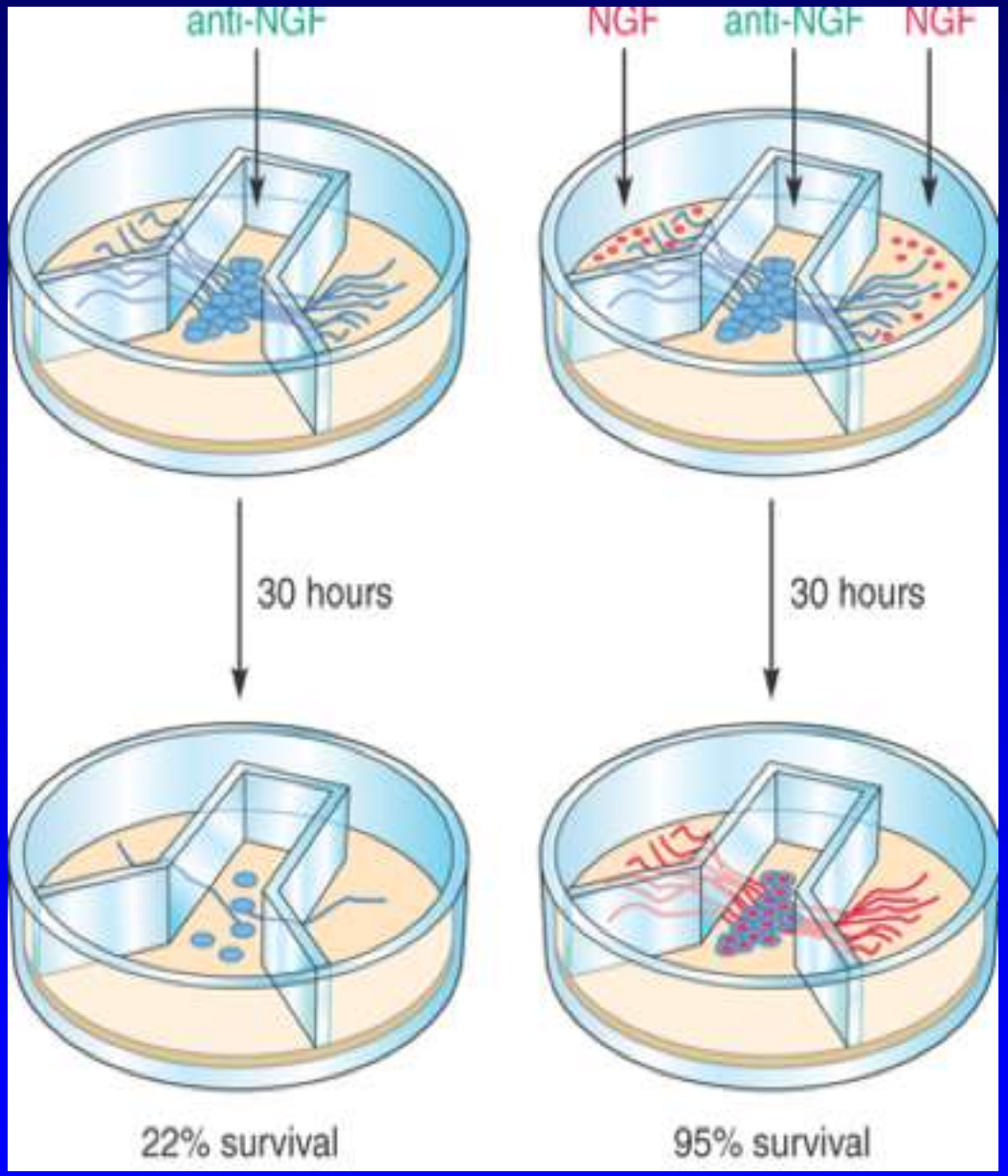
## NGF signal can be transduced at the tips of growing neuronal processes

Sympathetic neurons were placed in a TC system that allowed the somas and neurites to be bathed in different media.

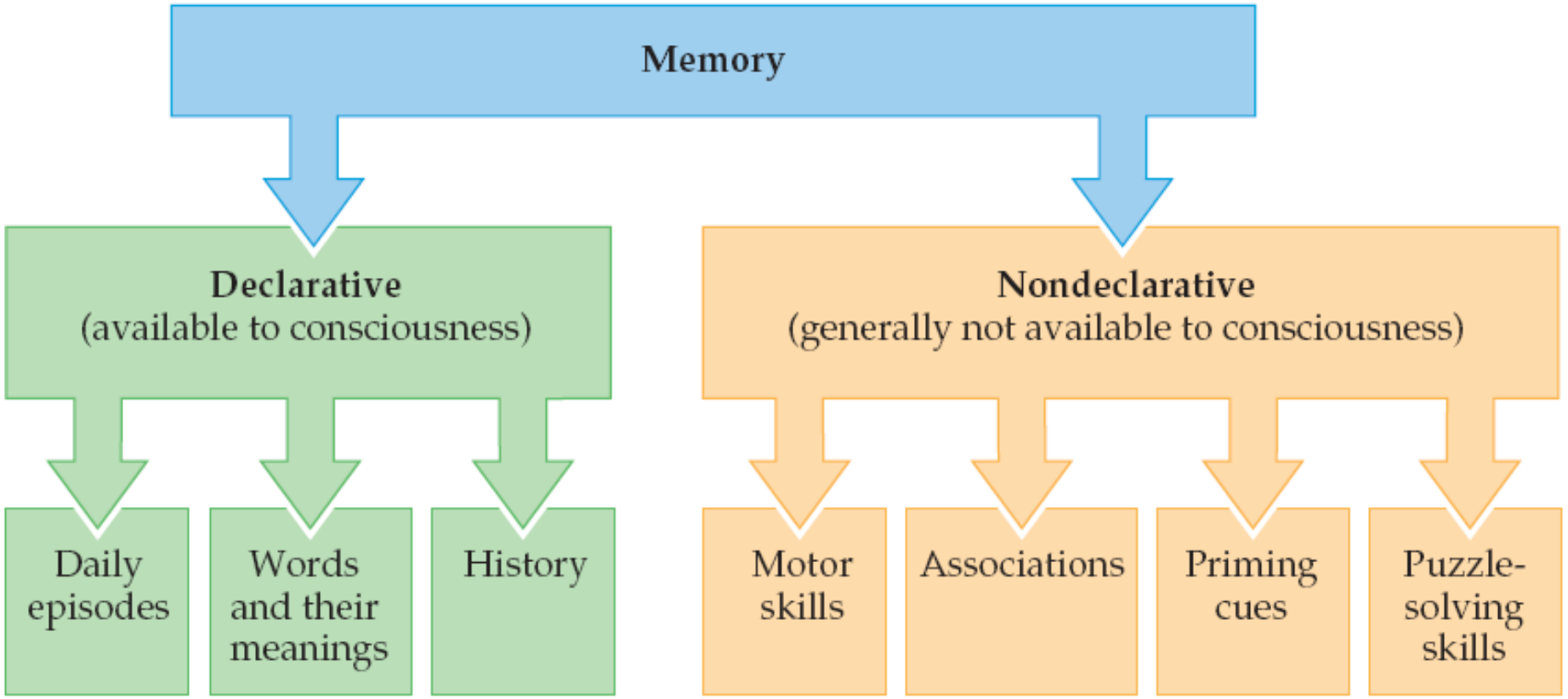
L: Most neurons die when grown without NGF for 30 hr.

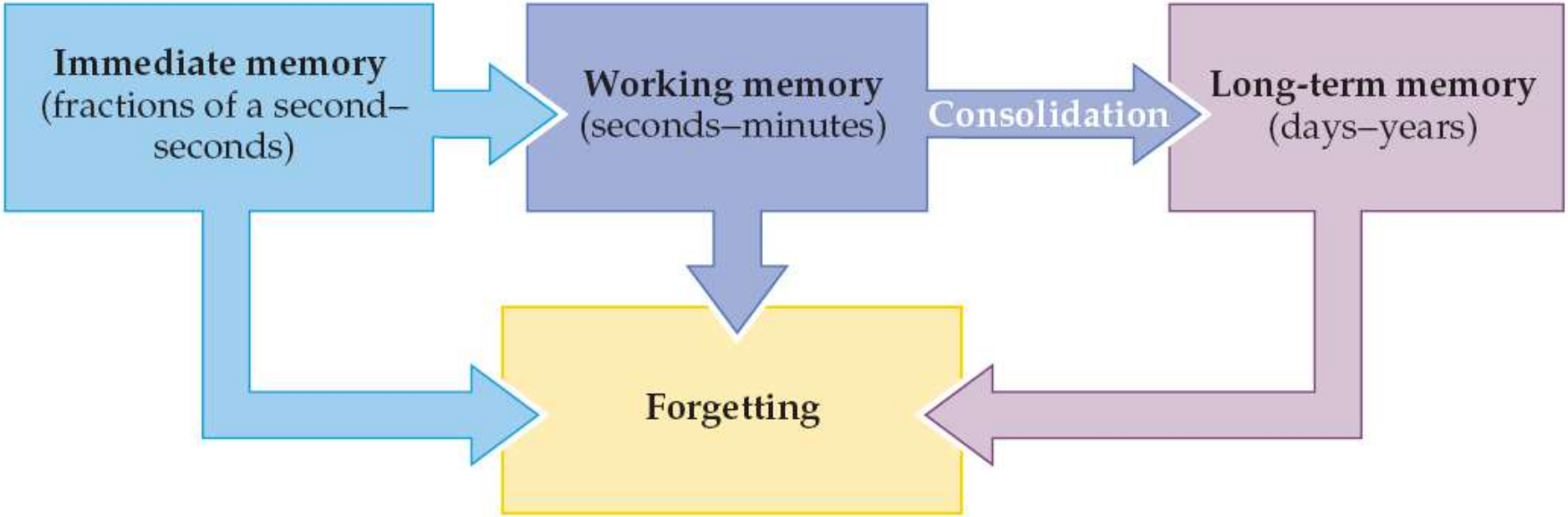
R: Neurons can be kept alive by adding NGF only to the compartments with growing neurites.

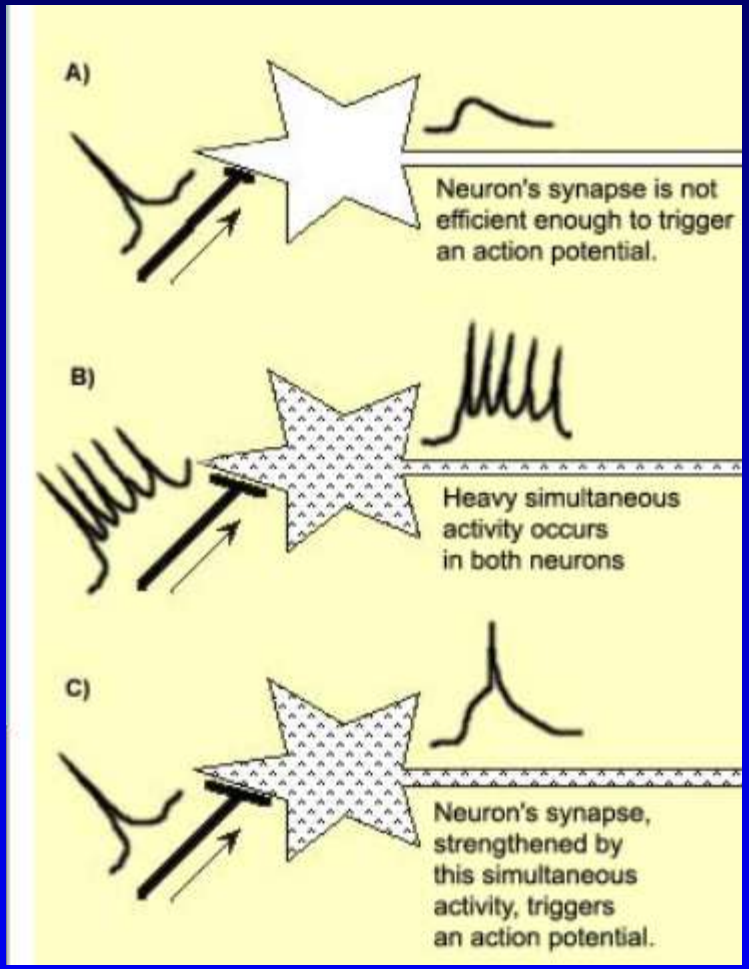
In both cases, anti-NGF prevented TrkA activation in the central compartment.



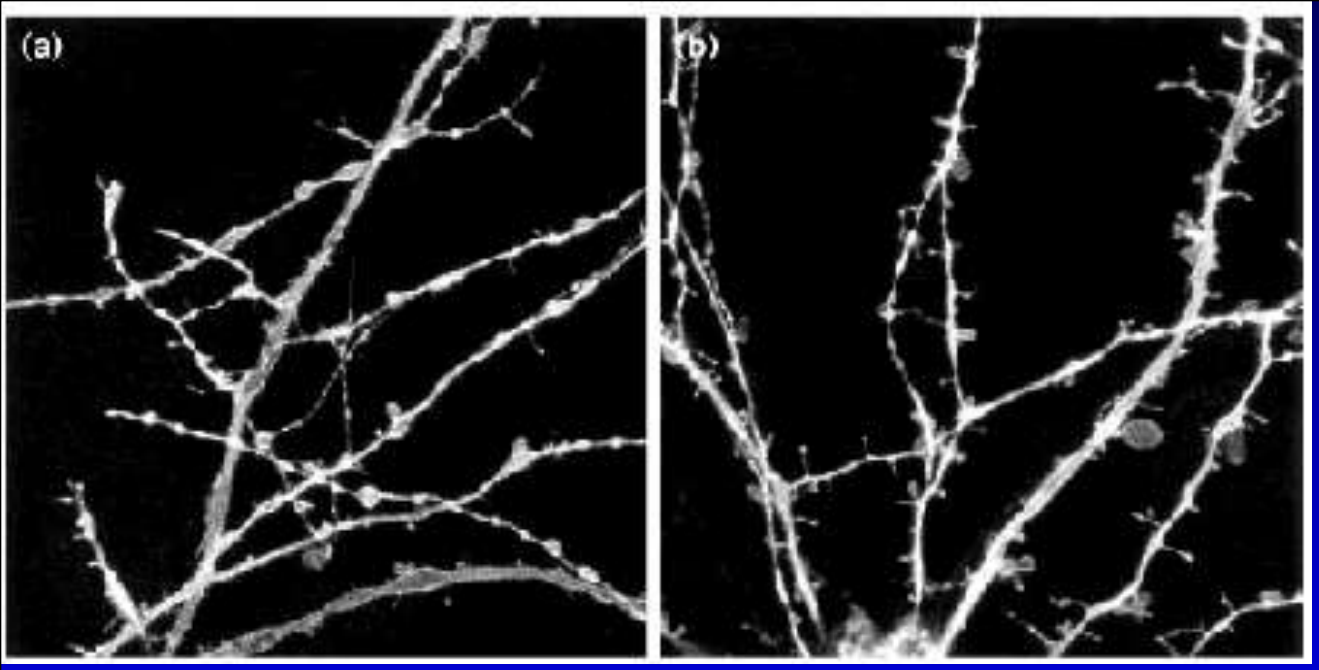
# Memory


Memory
Declarative
(available to consciousness)
Nondeclarative
(generally not available to consciousness)
Daily episodes
Words and their meanings
History
Motor skills
Associations
Priming cues
Puzzle-solving skills

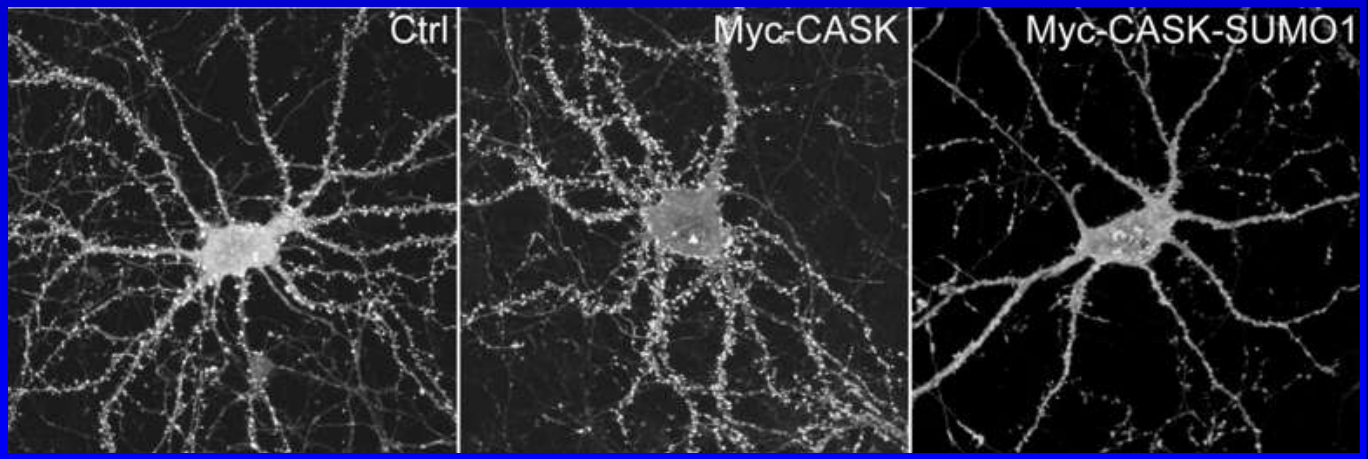

Immediate memory
(fractions of a second–seconds)
Working memory
(seconds–minutes)
Consolidation
Long-term memory
(days–years)
Forgetting

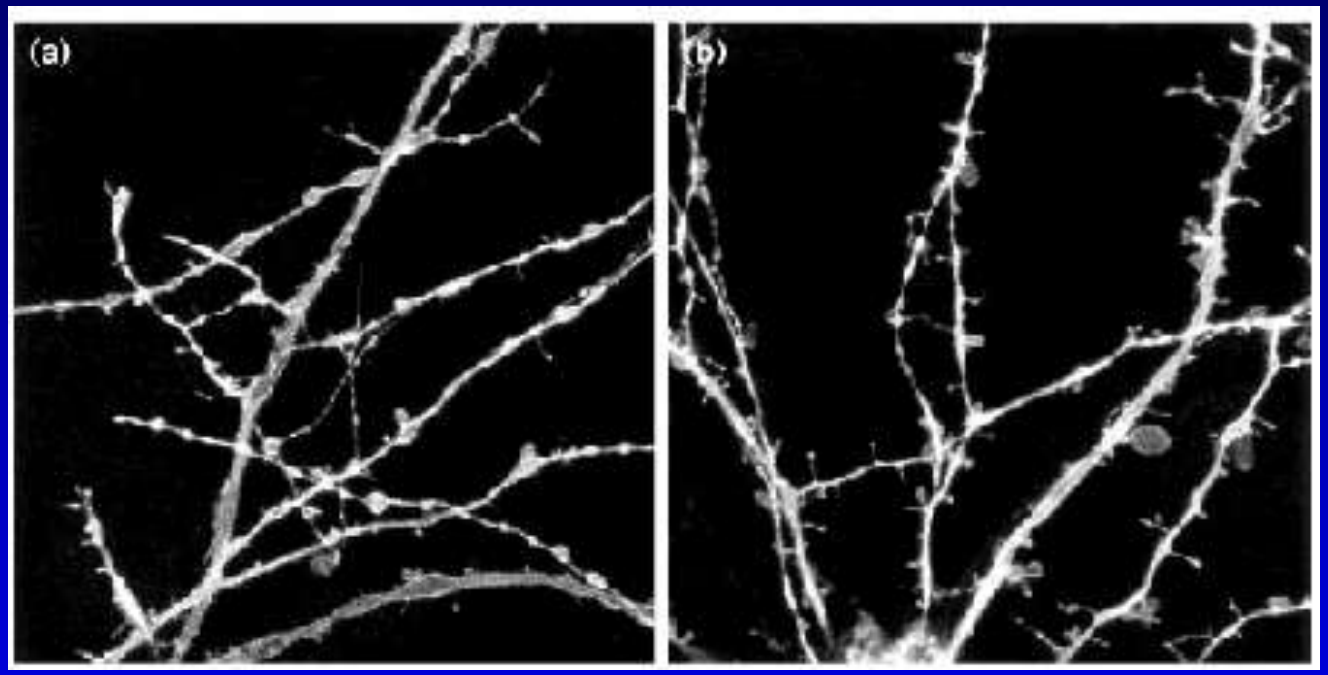



- Long term potentiation LTP , and LTD

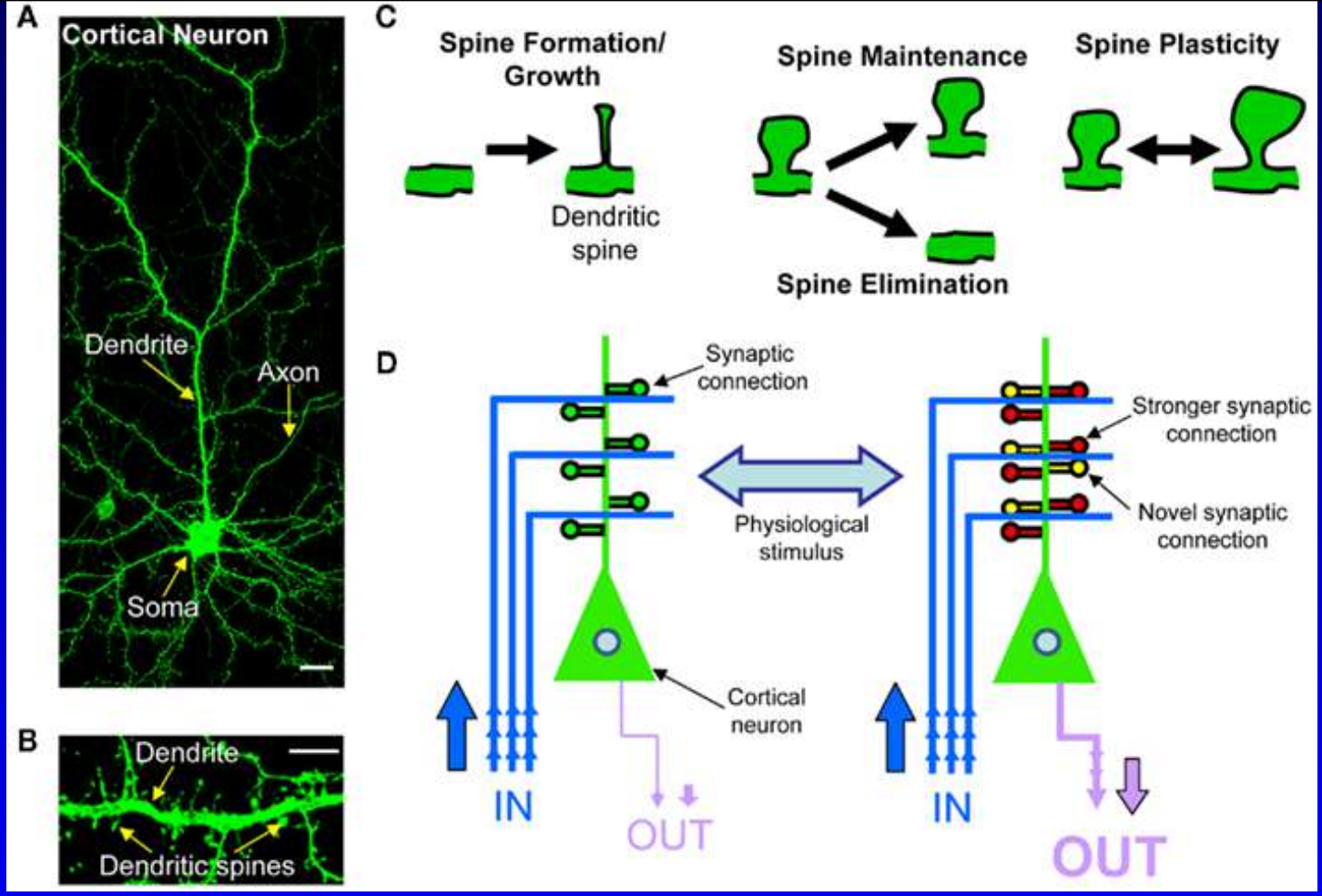



- Spines





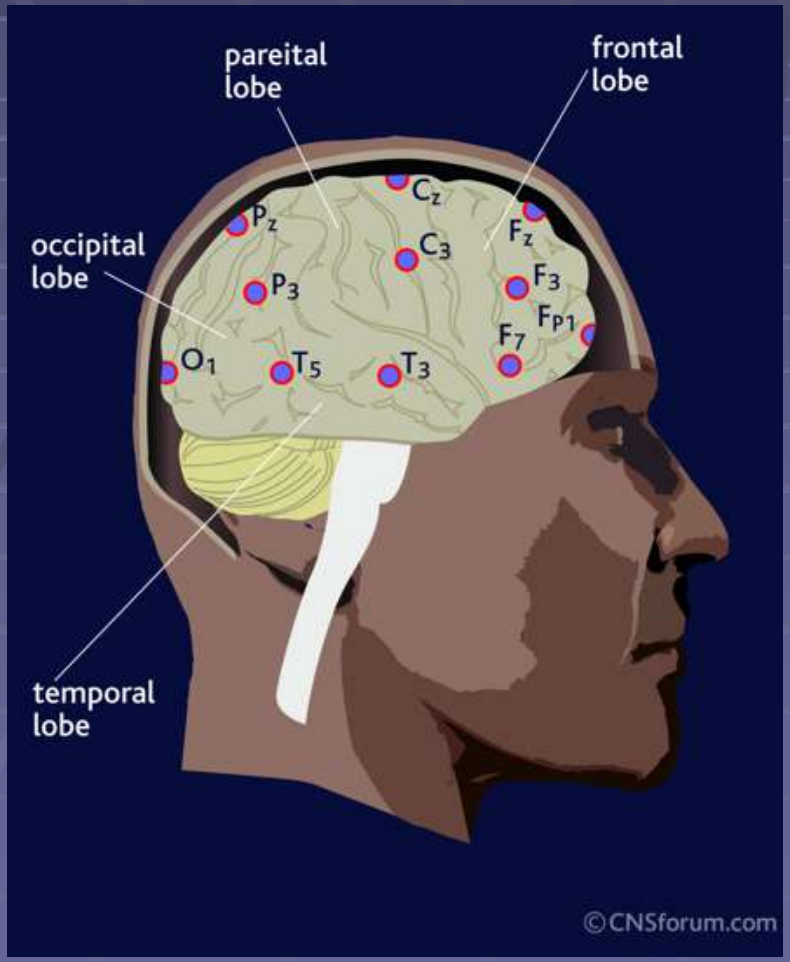

- Spines
- Long term potentiation LTP and LTD
- The glutamate receptor (NMDA)

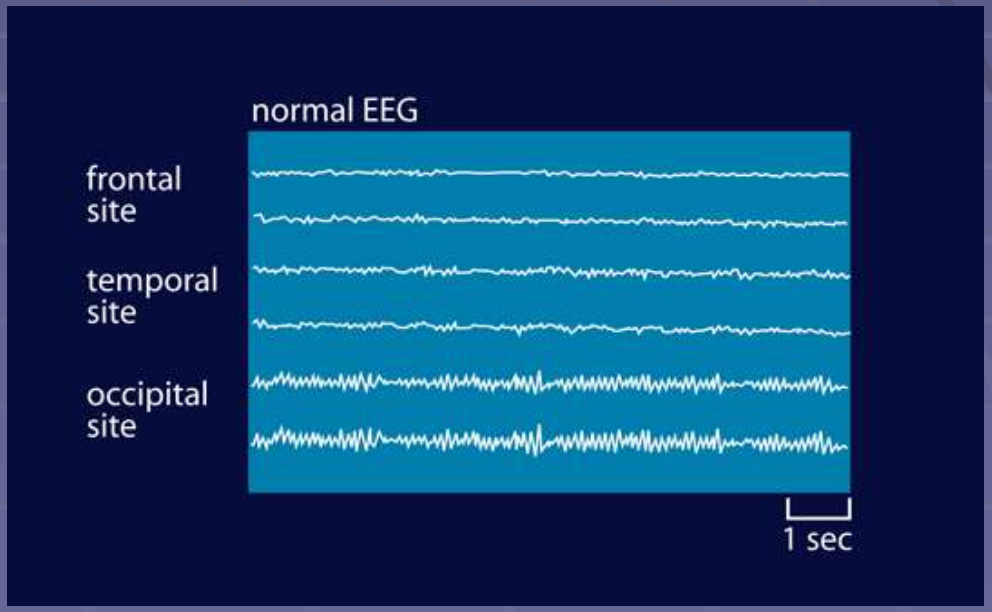



- Spines
- Long term potentiation LTP and LTD
- The glutamate receptor (NMDA)
- neuromodulators “NO, 5HT, norepinephrine”

# EEG waves

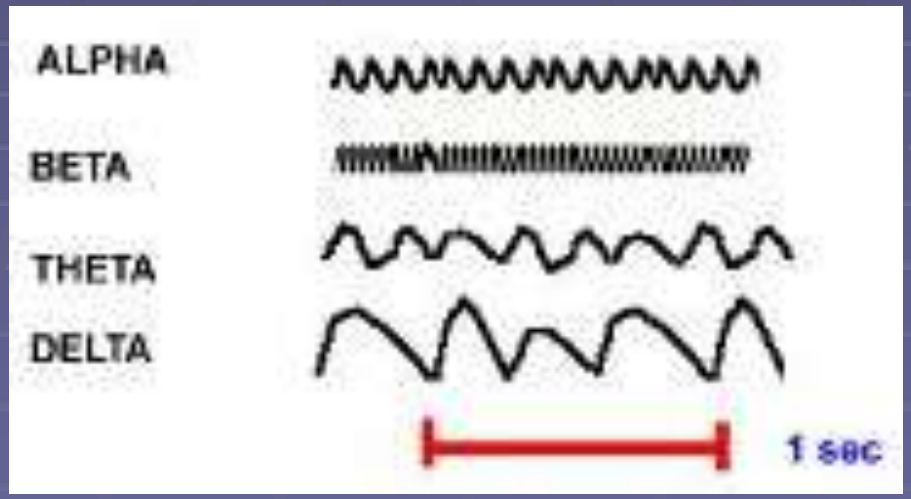
# EEG Electrode Placement



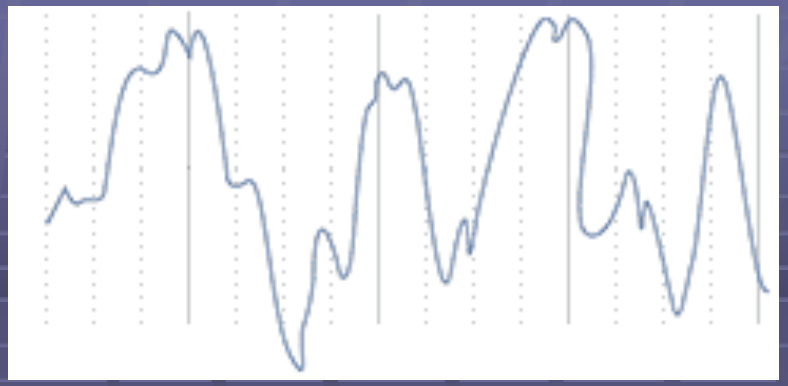
# Classifying EEG brain waves

- Frequency: the number of oscillations/waves per second, measured in Hertz (Hz)
  - reflects the firing rate of neurons
  - alpha, beta, theta, delta



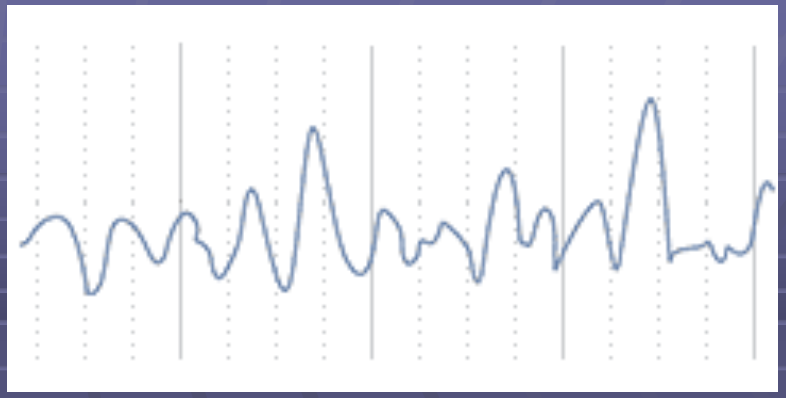

- Amplitude: the magnitude of brain waves, measured in millivolts (mV), gives an indication of the wave's "power".
  - The number of neurons firing in synchrony & the distance between the neurons and the recording electrode

# Delta Waves



- **Slowest frequency waves: 1 – 3 Hz**
- **Associated tasks & behaviors:**
  - deep, dreamless sleep, not moving, not attentive, sleeping

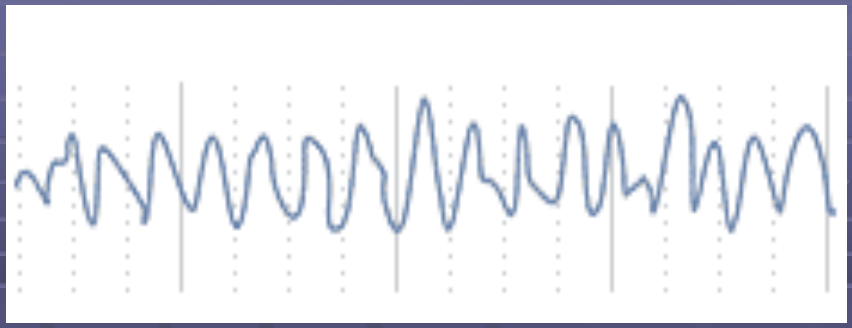
# Theta Waves



- **Slow wave frequency: 4 – 8 Hz**

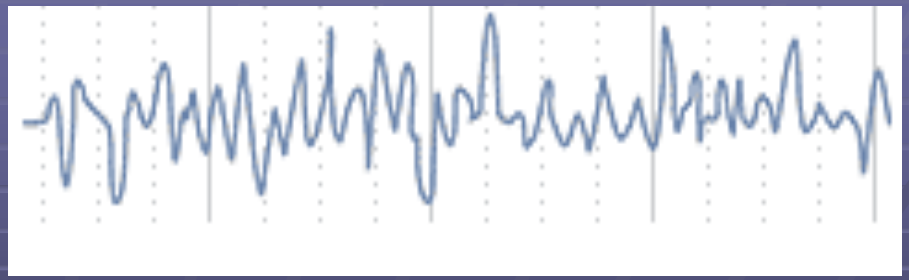
- **Associated tasks & behaviors:**
  - State between wakefulness and sleep "Drowsy"
  - during sleep, meditation, internal focus, and prayer; subconsciousness.

# Alpha Waves



- Mid wave frequency: 8 - 13 Hz
- Parietal and occipital lobes
- Associated tasks & behaviors:
  - Relaxing, watching television, light reading (e.g., novel), eyes closed.

# Beta Waves



- **High wave frequency: 12 - 35 Hz**
  - The “normal” dominant rhythm \
  - mostly on temporal and frontal lobe
- **Associated tasks & behaviors:**
  - listening and thinking during analytical problem solving, judgment, decision making, processing information,

# EEG Waveforms

- Alpha
  - 8-13 Hz
  - Parietal and occipital prominent
  - Relaxed wakeful
- Beta
  - 13-30 Hz
  - Frontal prominent
  - Intense mental activity
- Delta
  - 0.5-4 Hz
  - Drowsiness/early SWS
- Theta
  - 4-7 Hz
  - Drowsiness/early SWS

# Sleep

# Why Do We Need Sleep?

## Adaptive Evolutionary Function

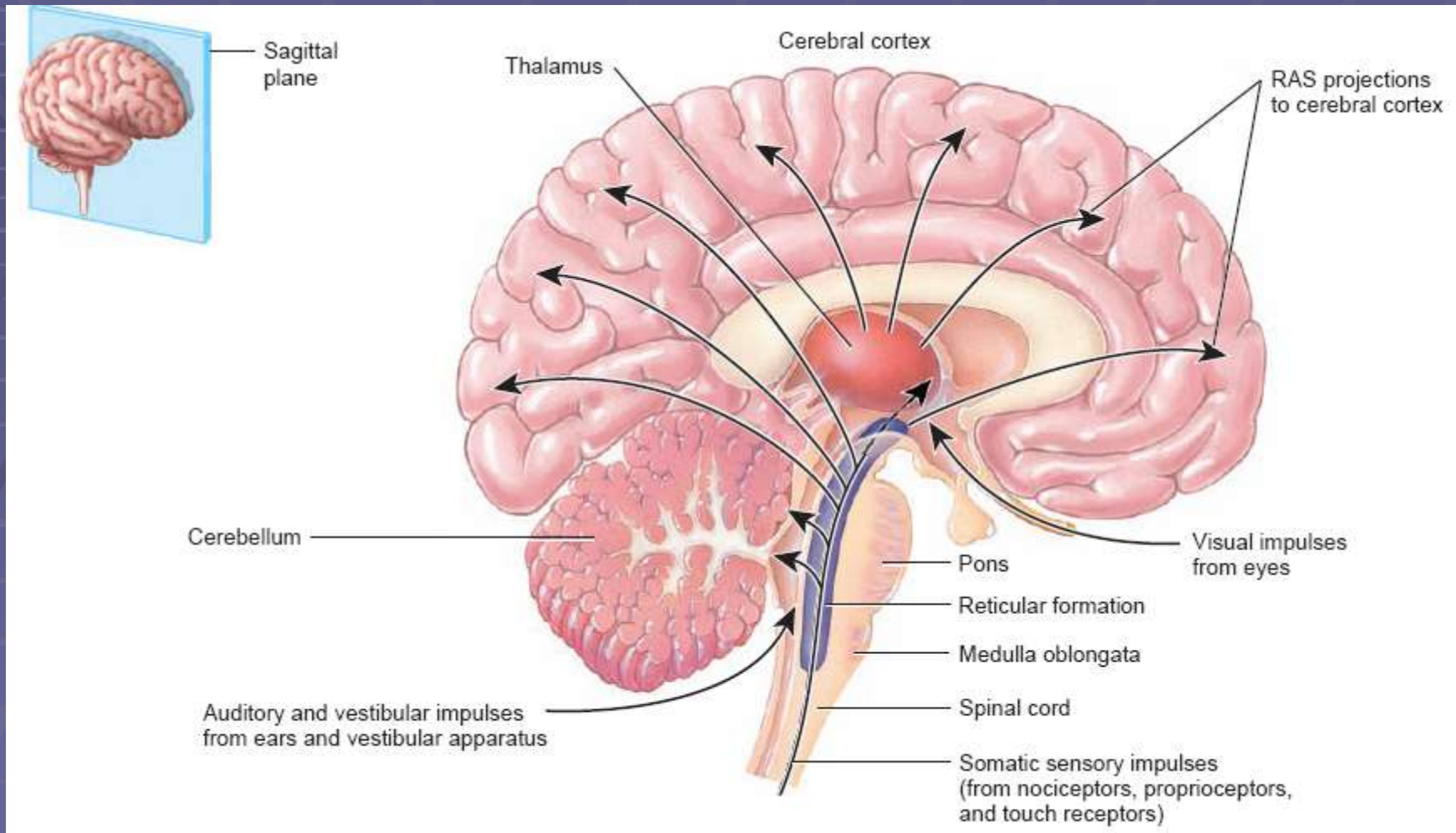
- safety
- energy conservation/ efficiency

## Restorative Function

- body rejuvenation & growth

## Brain Plasticity

- enhances synaptic connections
- memory consolidation

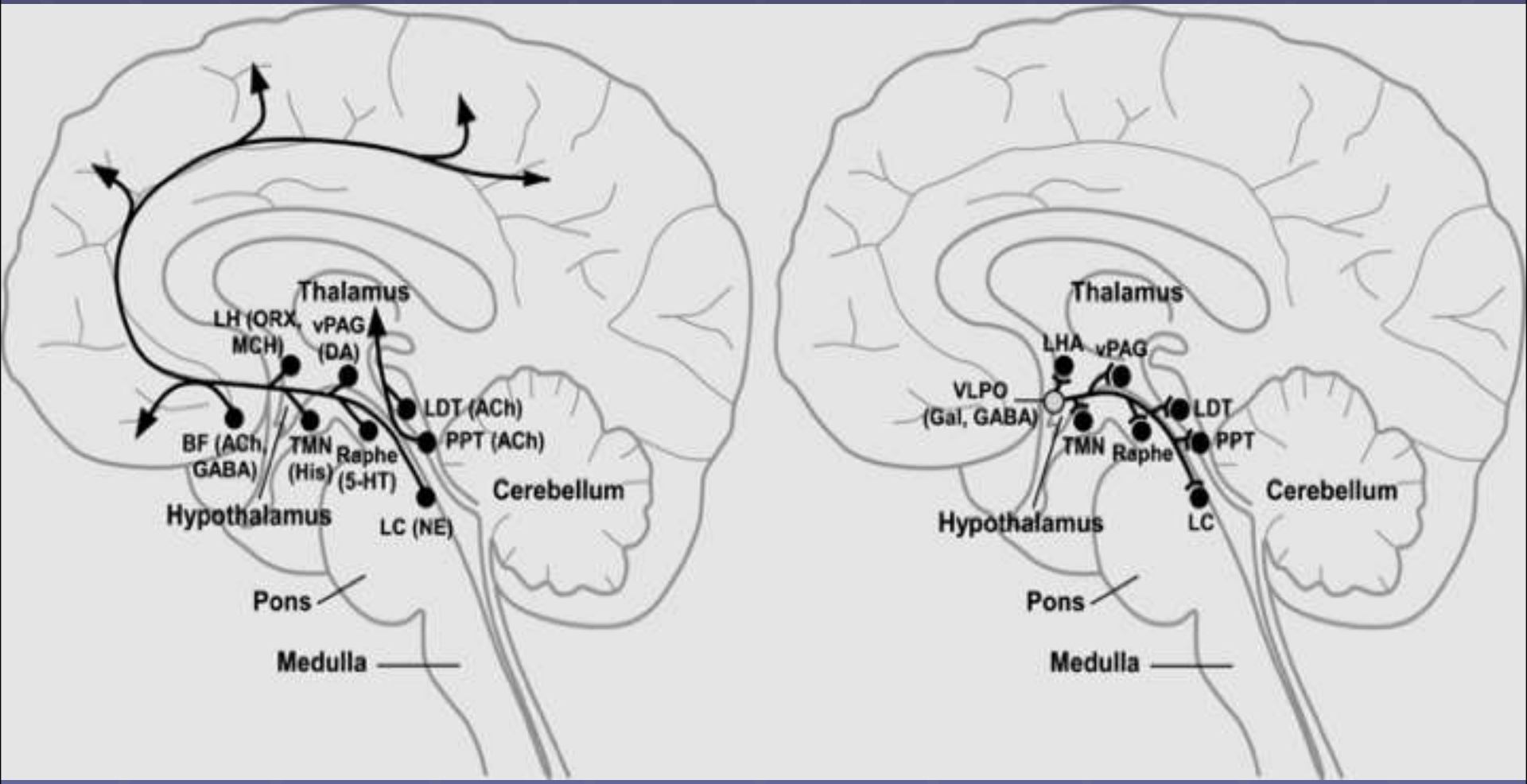



Sagittal section through brain and spinal cord

# The ascending arousal system promotes wake

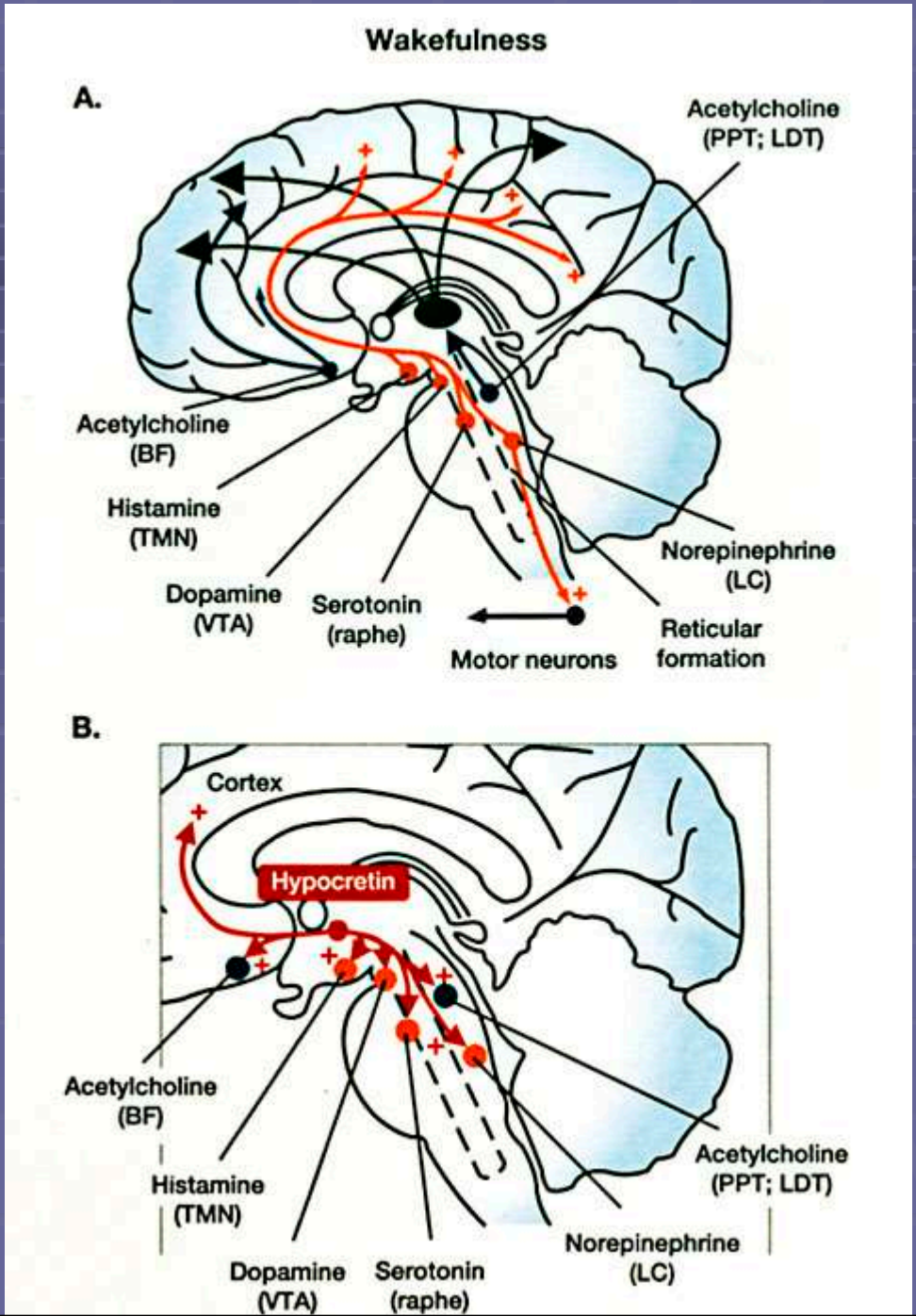
A.

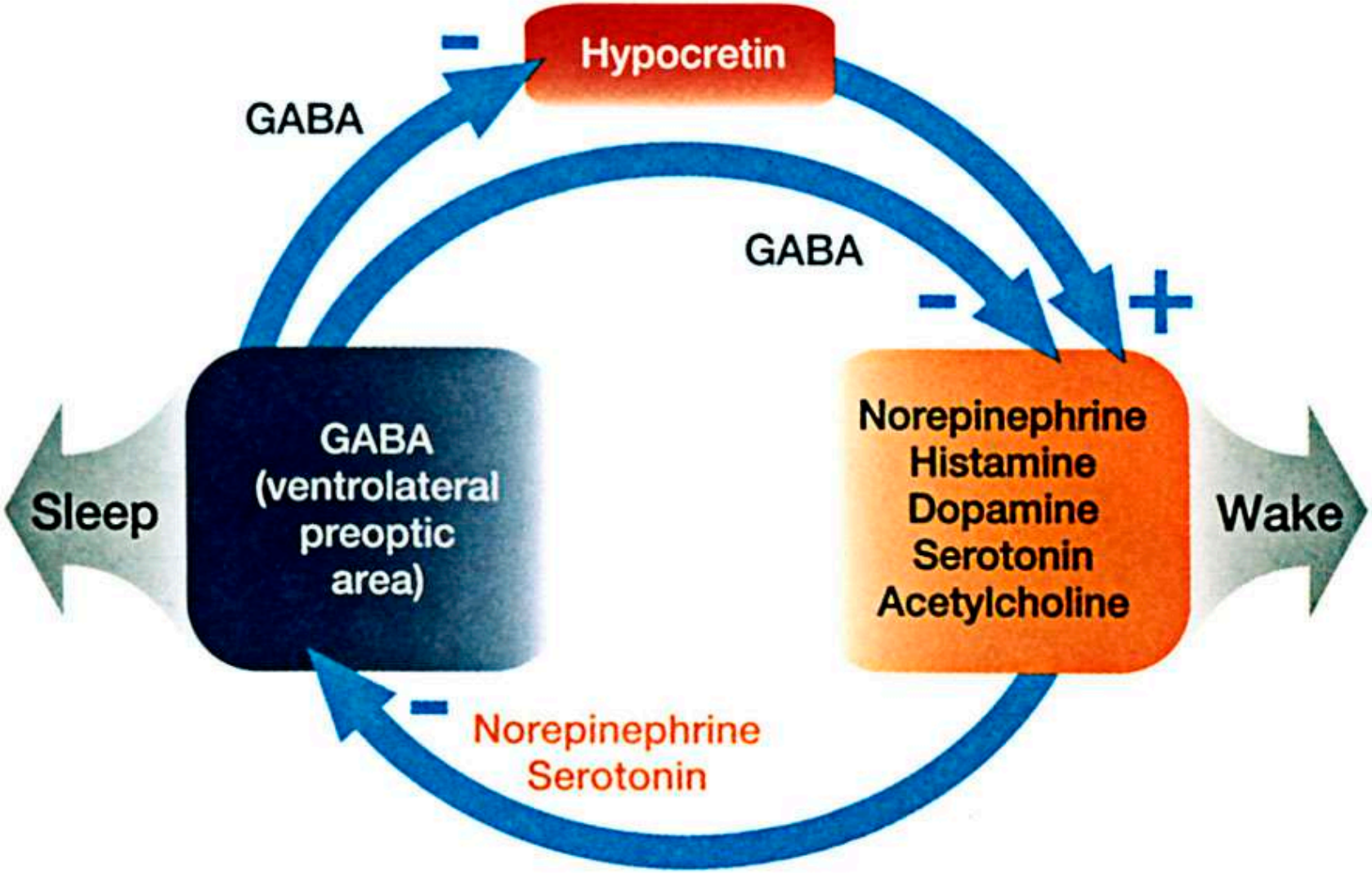
B.



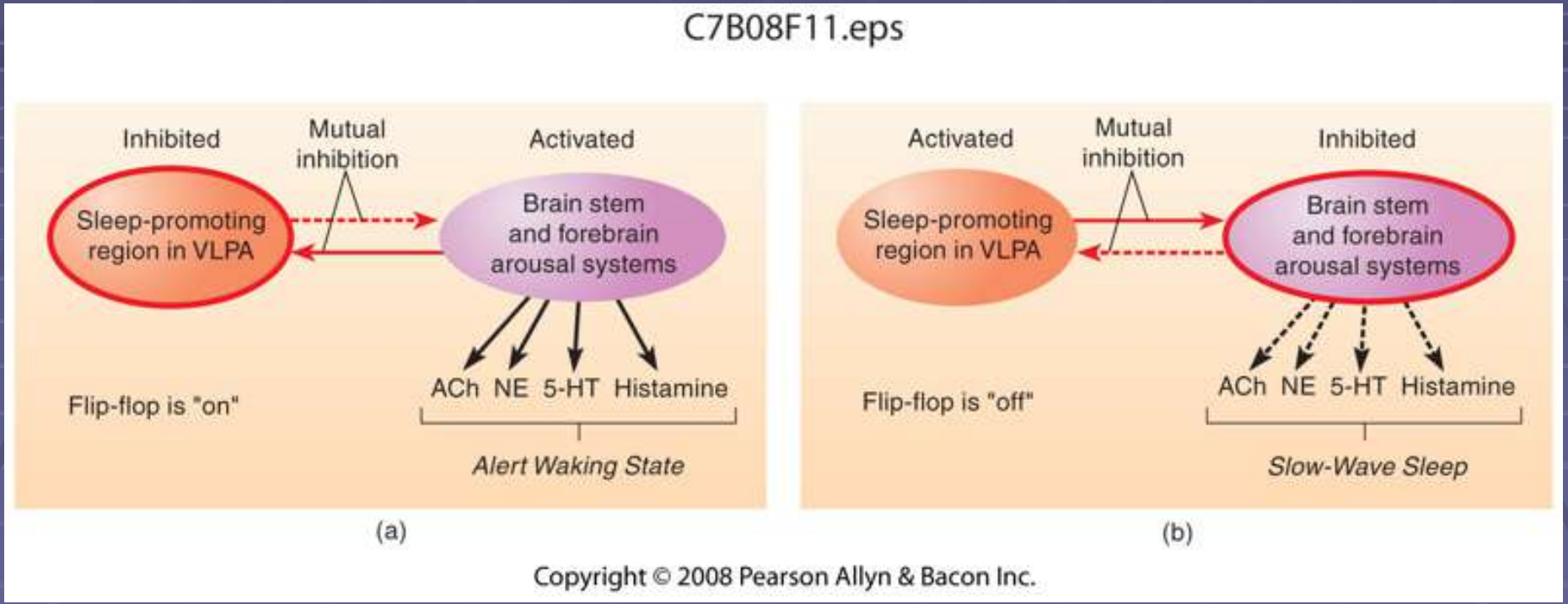

*Modified from Fuller et al., J Biol Rhythms, 2006*

# Hypocreatin (orexin)

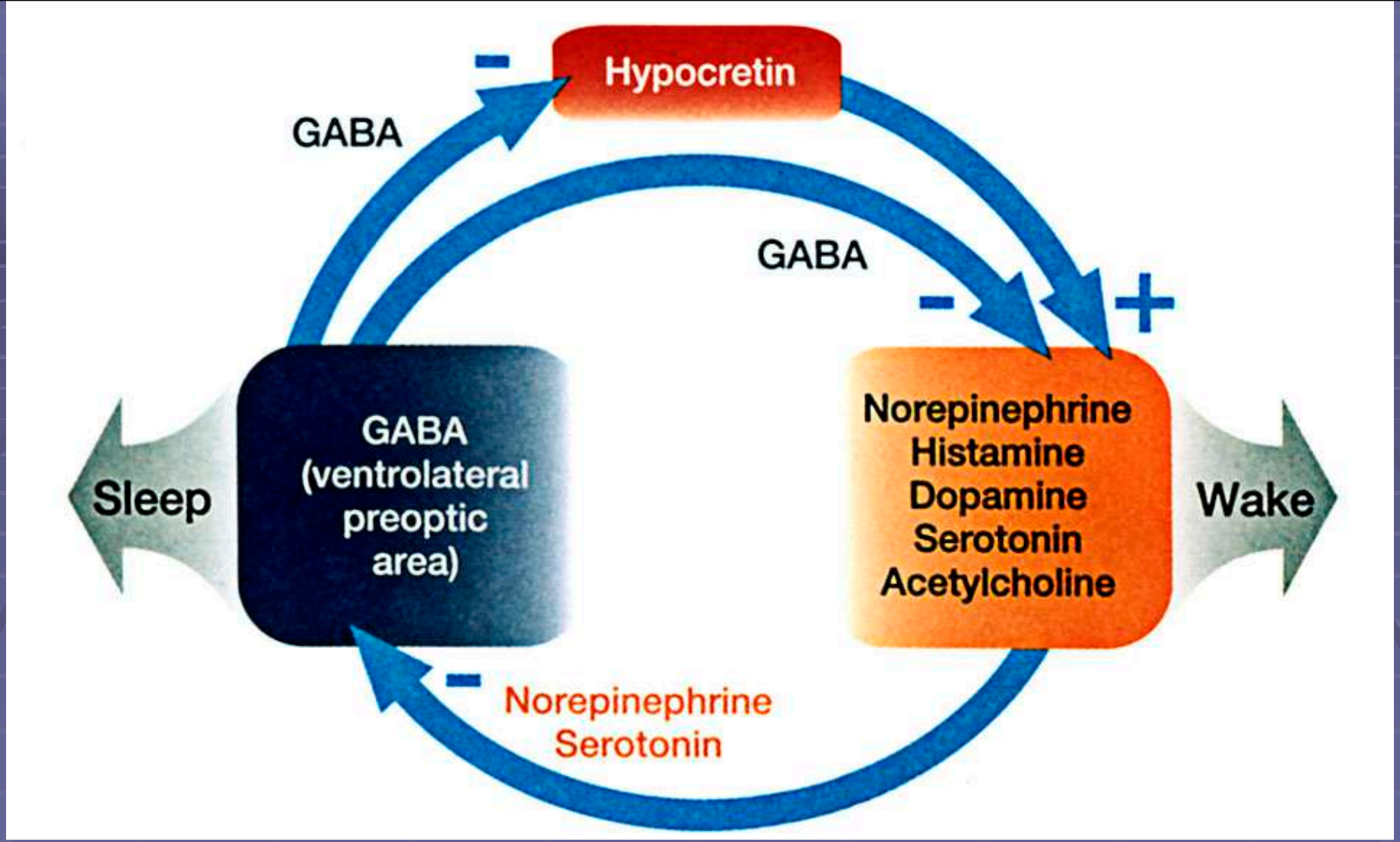



Hypocretin
GABA
GABA
Sleep
GABA
(ventrolateral
preoptic
area)
Norepinephrine
Histamine
Dopamine
Serotonin
Acetylcholine
Wake
Norepinephrine
Serotonin

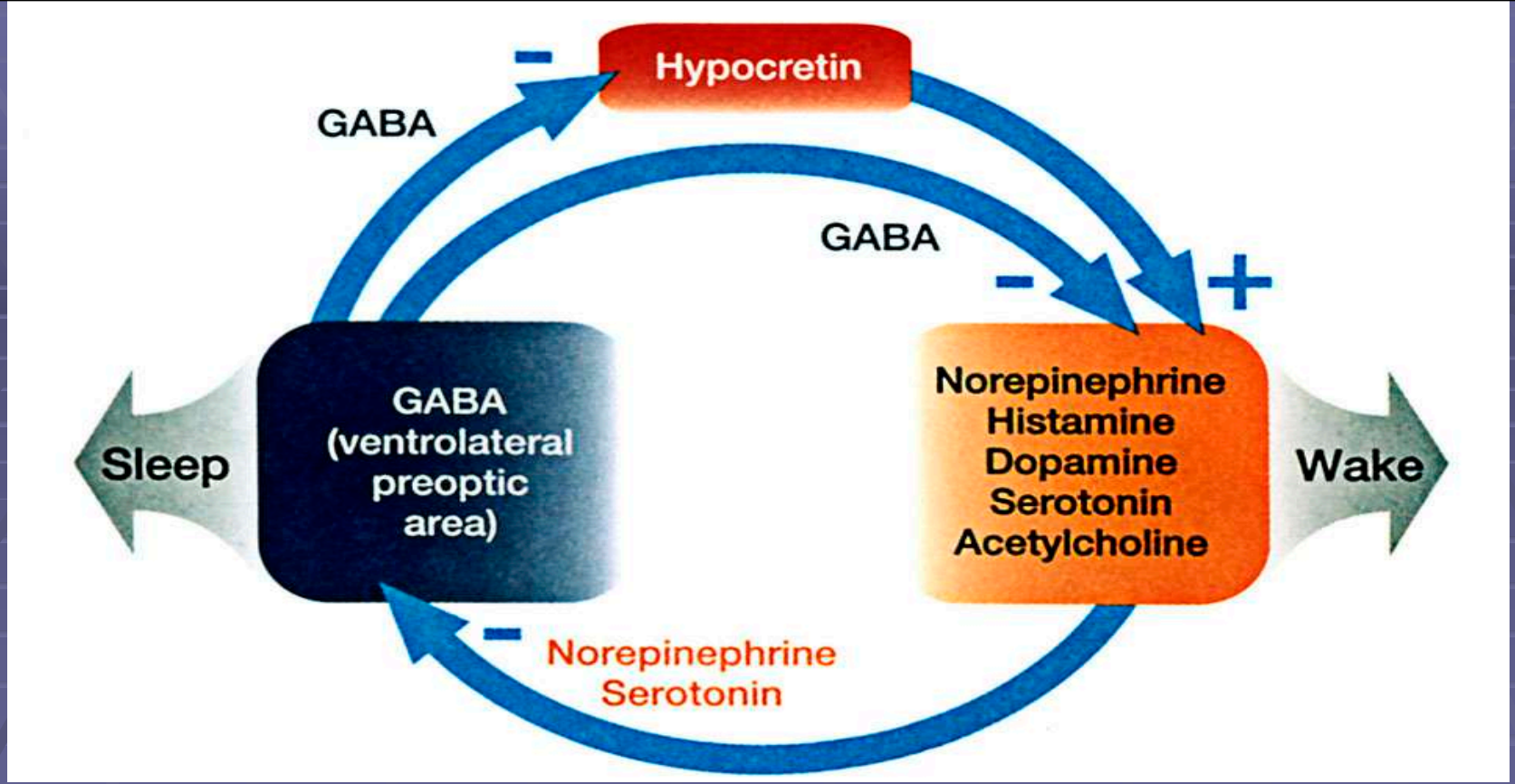
# Sleep/Waking "Flip-Flop"



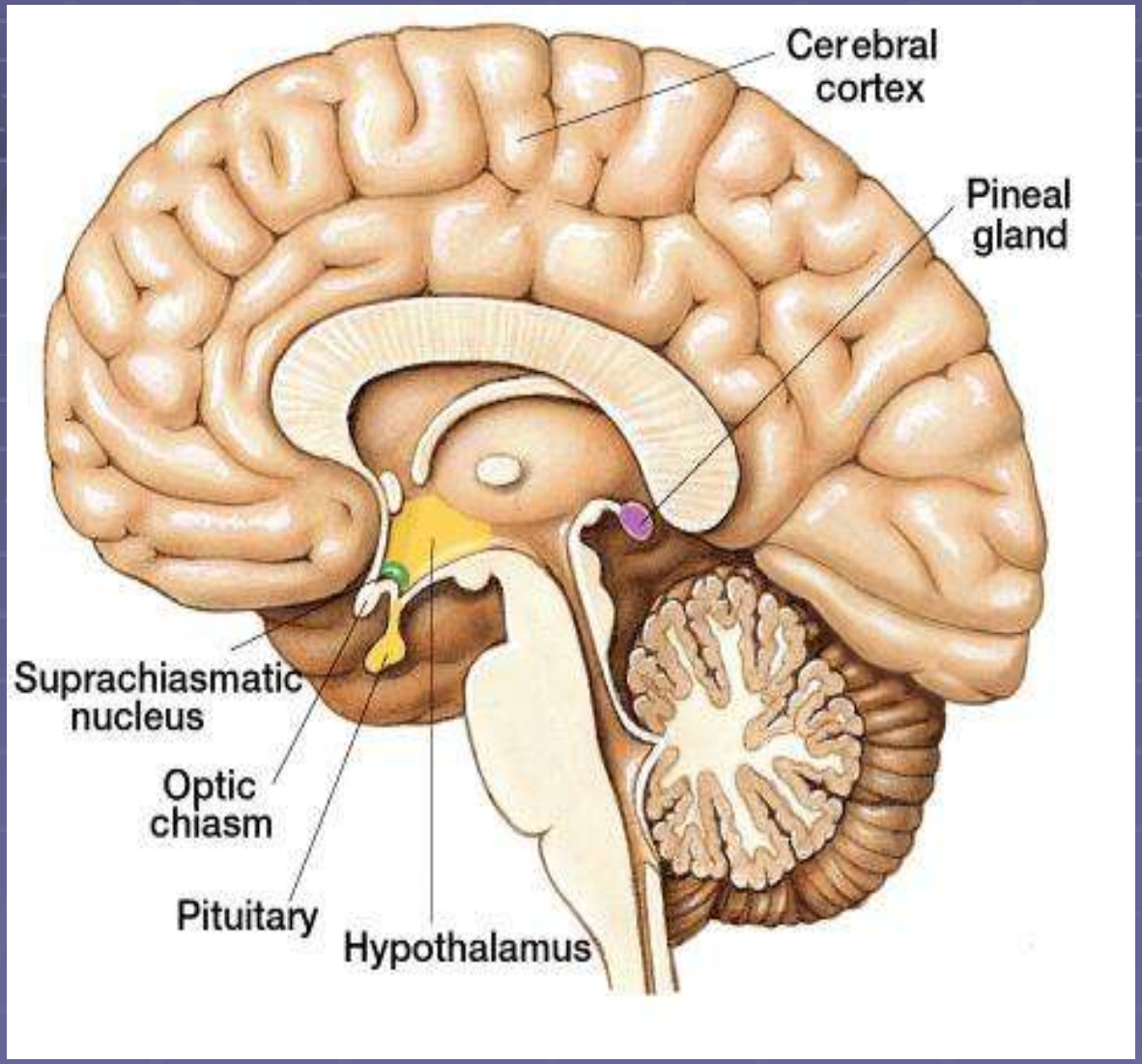

**vlPOA= ventrolateral preoptic area**
**ACh = acetylcholine**
**NE = norepinephrine**
**5-HT = serotonin**




Narcolepsy VS Insomnia

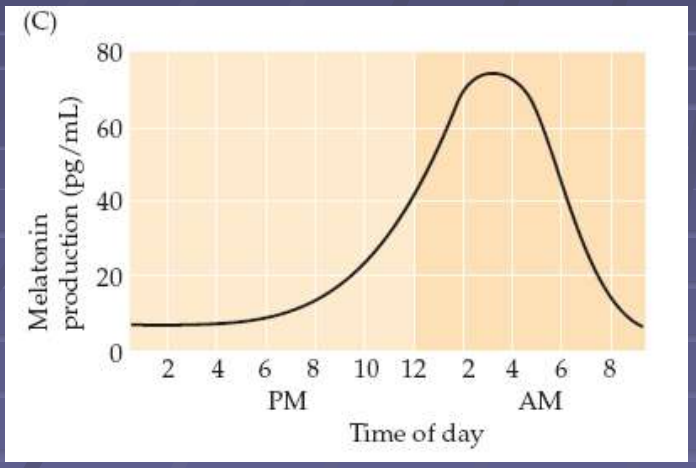


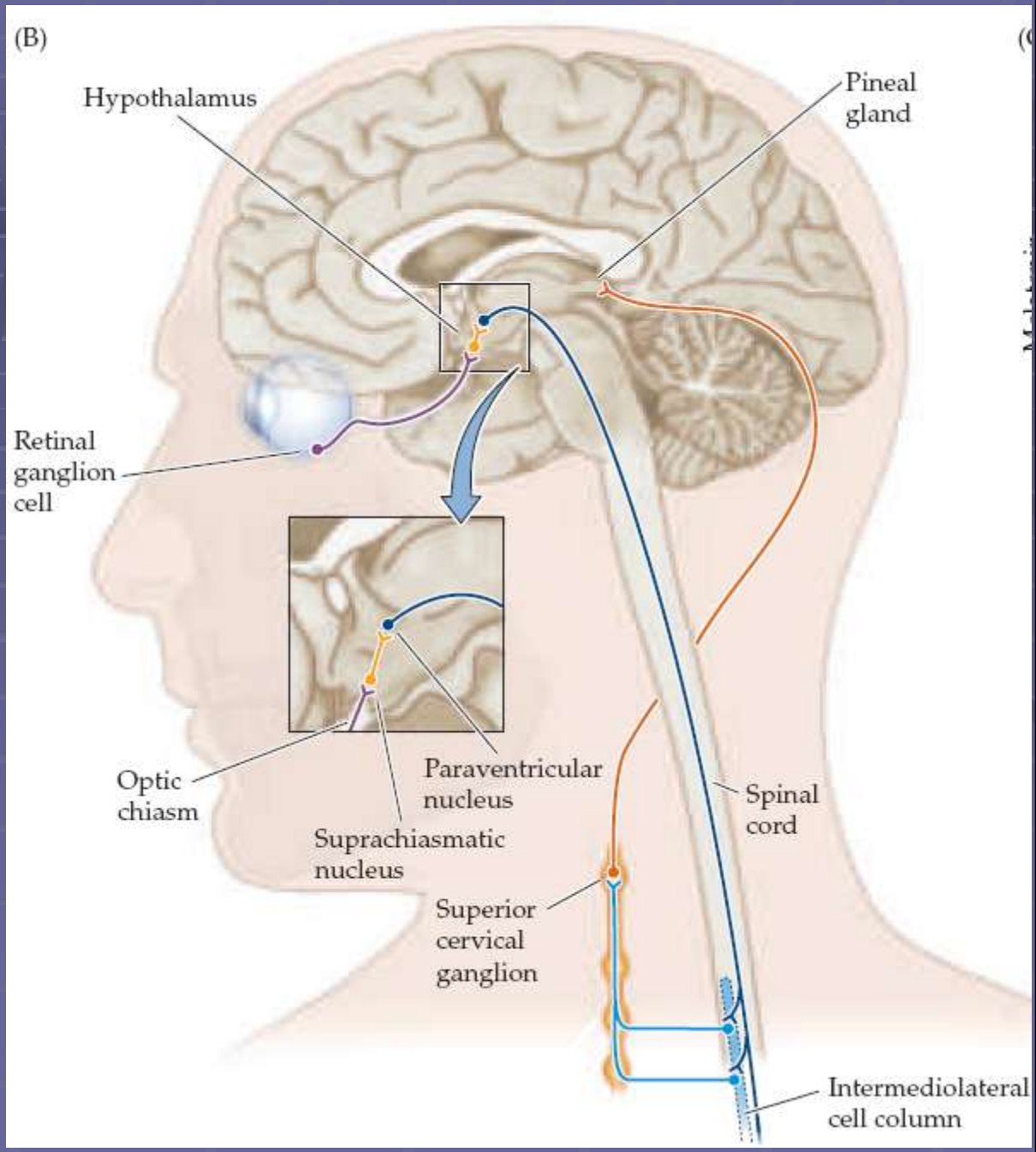

Melatonin: Produced by pineal gland, released at night-inhibited during the day (circadian regulation); initiates and maintain sleep; treat symptoms of jet lag and insomnia


Cerebral cortex
Pineal gland
Suprachiasmatic nucleus
Optic chiasm
Pituitary
Hypothalamus

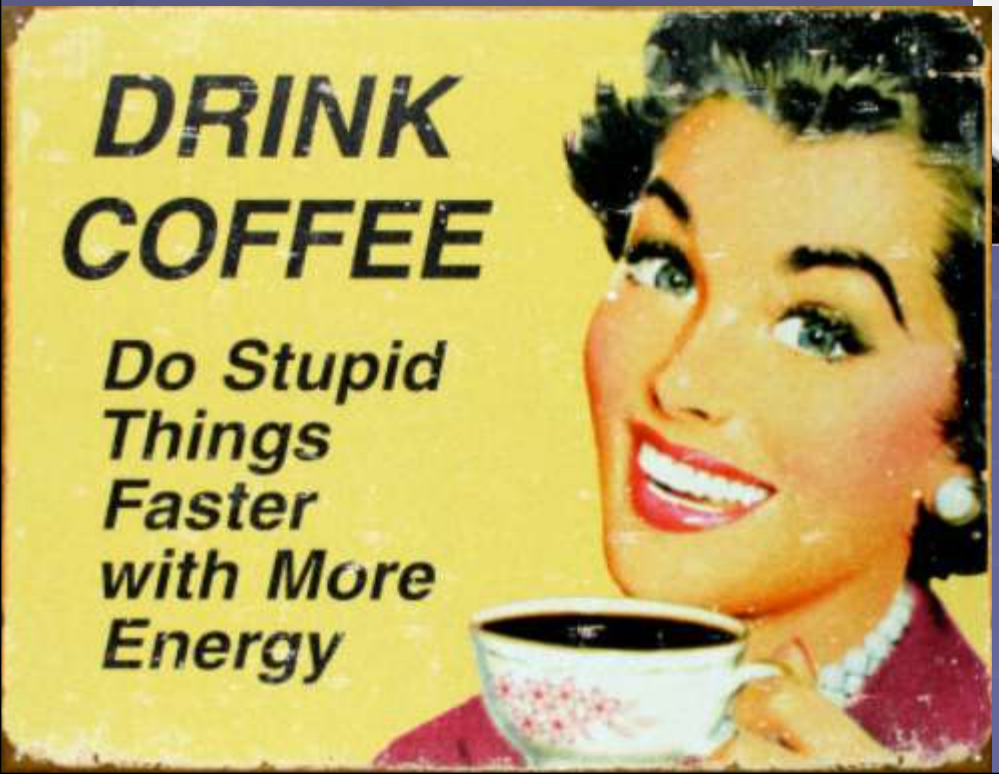
# Biological Clocks

- Suprachiasmatic nucleus
  - A nucleus situated atop the optic chiasm responsible for organizing circadian rhythms.
- Pineal gland
  - A gland attached to the dorsal tectum; produces melatonin and plays a role in circadian and seasonal rhythms.


(C)
Melatonin production (pg/mL)
80
60
40
20
0
2 4 6 8 10 12 2 4 6 8
PM
AM
Time of day

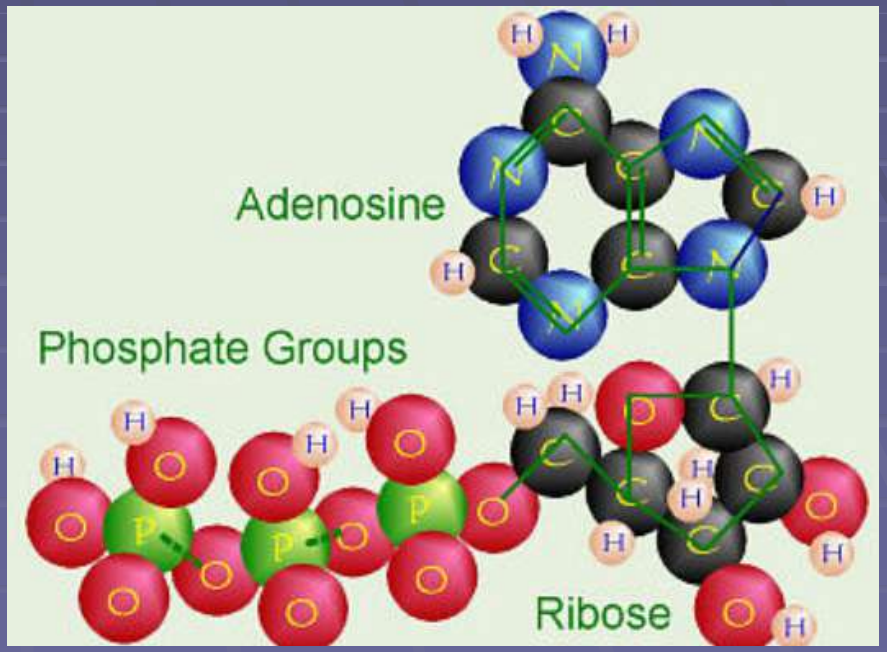

(B)
Hypothalamus
Pineal gland
Retinal ganglion cell
Optic chiasm
Paraventricular nucleus
Suprachiasmatic nucleus
Spinal cord
Superior cervical ganglion
Intermediolateral cell column

# Coffee



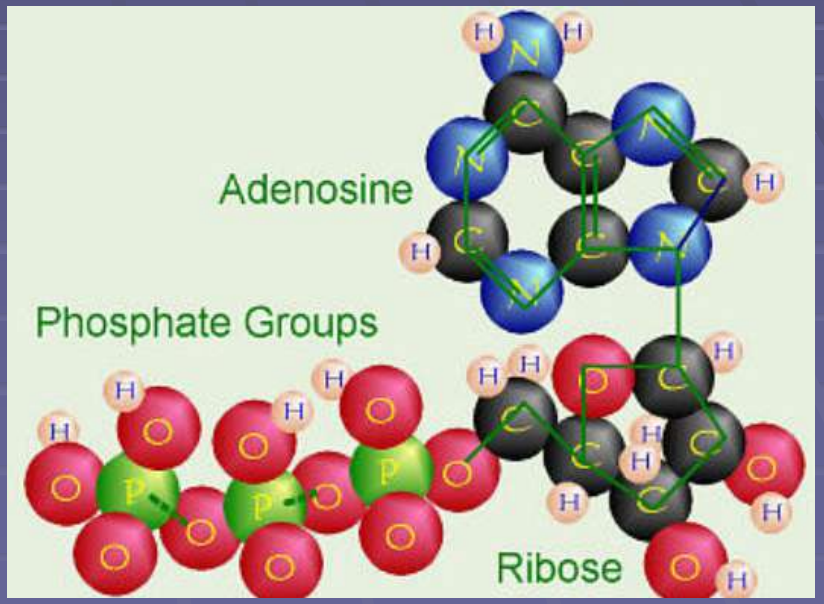
# Coffee

- During waking, brain consume ATP



# Coffee

- During waking, brain consume ATP
- ↑ adenosine



# Coffee

- During waking, brain consume ATP
- ↑ adenosine
- Adenosine bind to A1 receptor
- Inhibit acetylcholine neurons

# Coffee

- During waking, brain consume ATP
- ↑ adenosine
- Adenosine bind to A1 receptor
- Inhibit acetylcholine neurons
- Caffeine and Theophylline are A1 antagonist

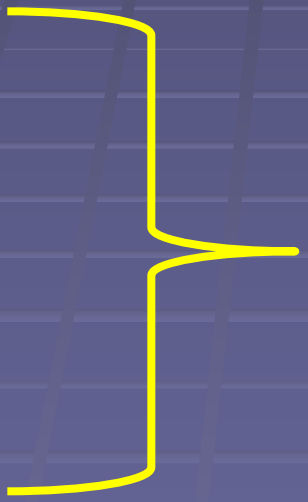
# Sleep stages

- **Awake**
- ***Stage 1***
- ***Stage 2***
- ***Stage 3***
- ***Stage 4***

Slow wave sleep

# Sleep stages

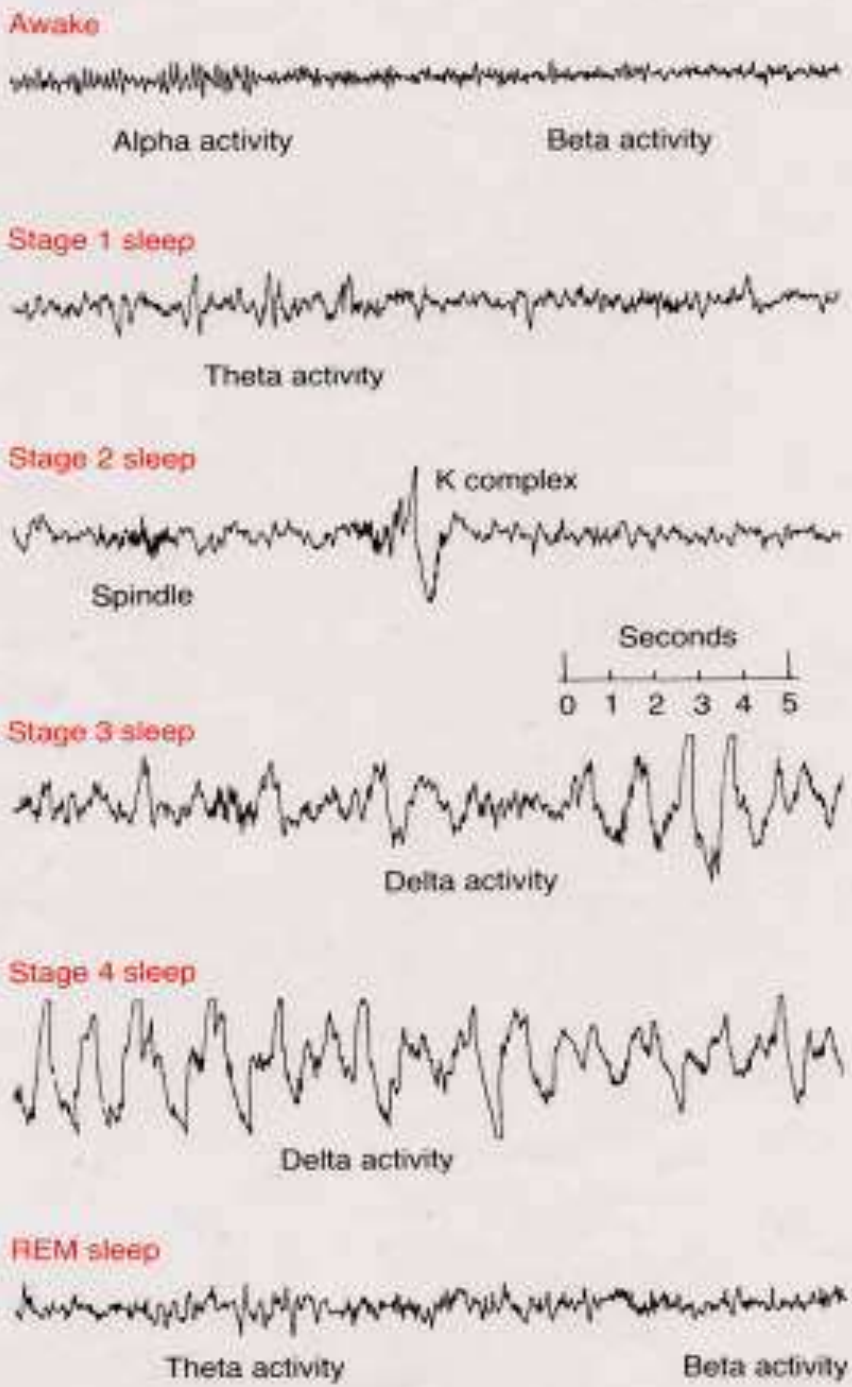
- **Awake**
- ***Stage 1***
- ***Stage 2***
- ***Stage 3***
- ***Stage 4***
- **Rapid eye movement sleep (REM)**



Slow wave sleep (NREM)

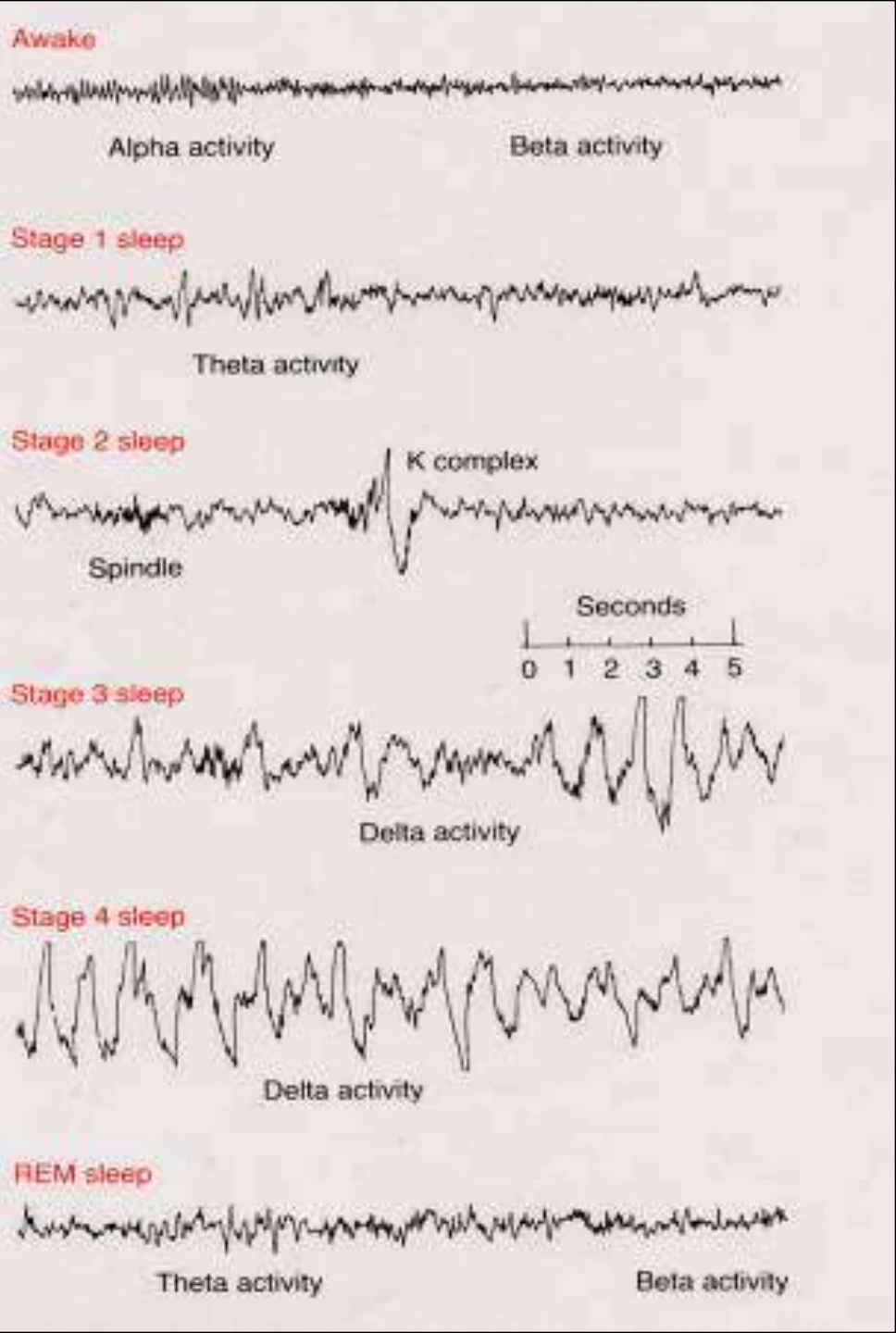
# Types and Stages of Sleep: NREM

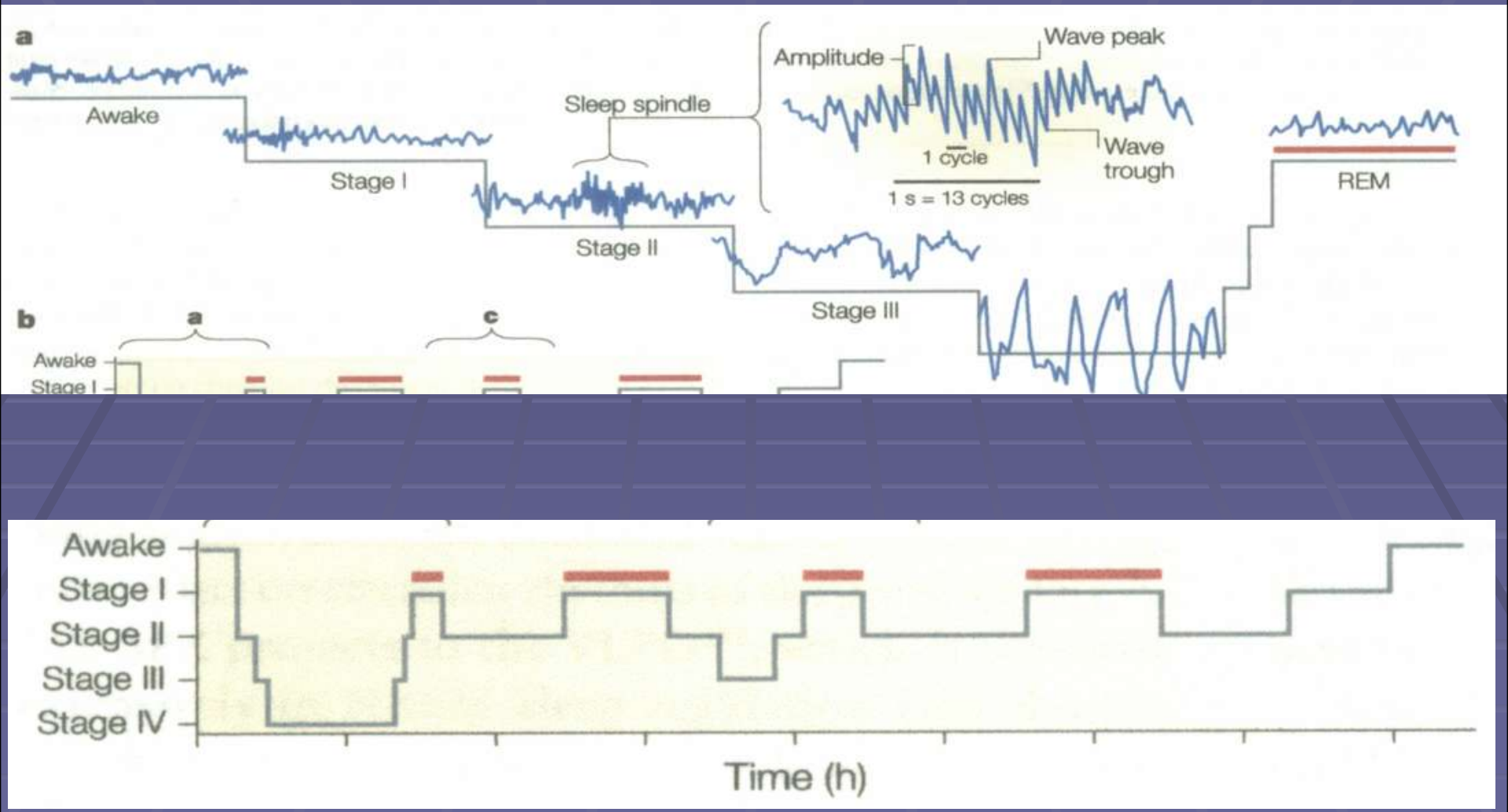
- Stage 1 – eyes are closed and relaxation begins; the EEG shows alpha waves; one can be easily aroused
- Stage 2 – EEG pattern is irregular with sleep spindles (high-voltage wave bursts); arousal is more difficult



–Stage 3 – sleep deepens;; theta and delta waves appear; vital signs decline; dreaming is common

–Stage 4 – EEG pattern is dominated by delta waves; skeletal muscles are relaxed; arousal is difficult



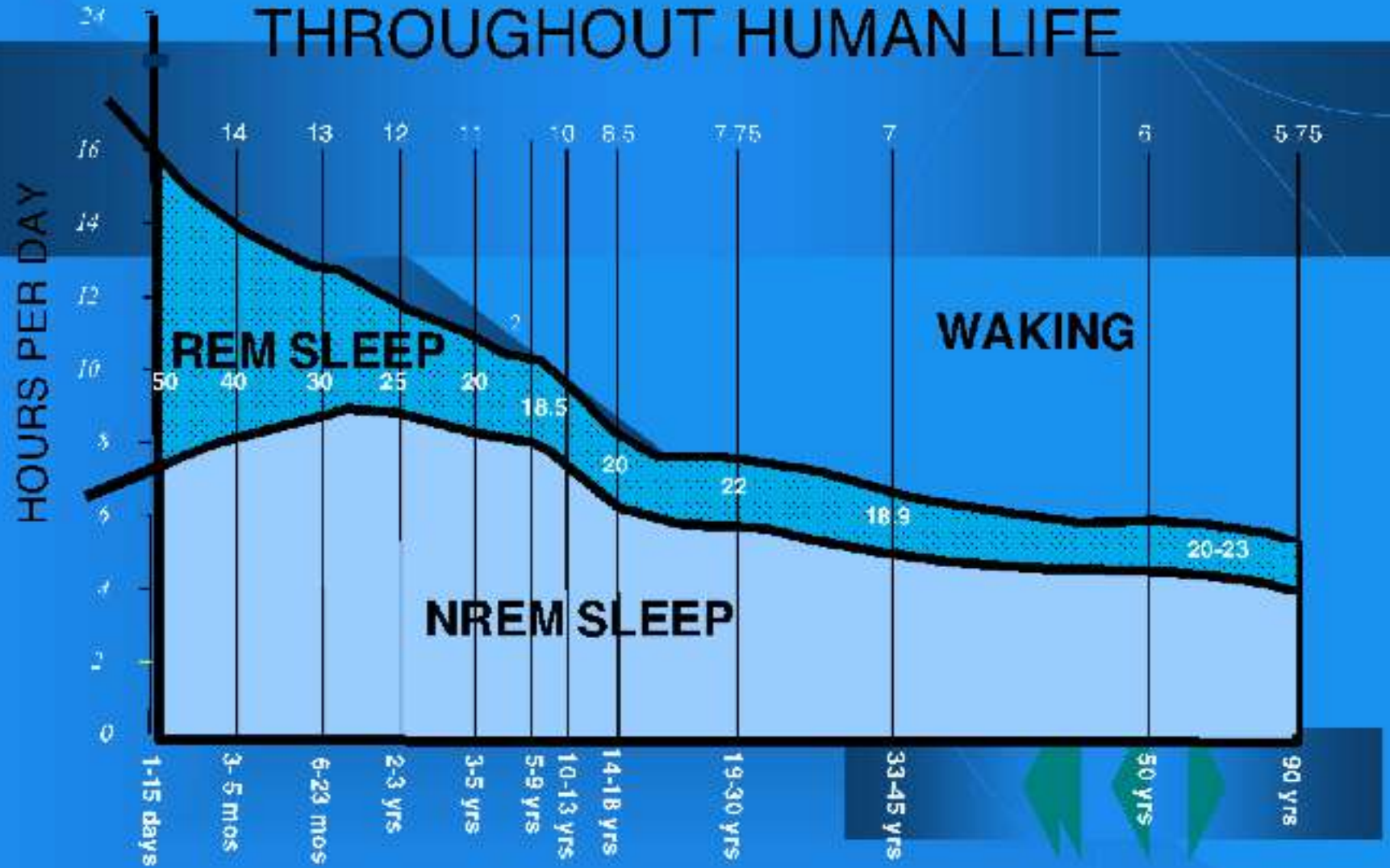

a
Awake
Stage I
Sleep spindle
Stage II
Stage III
REM
Amplitude
Wave peak
Wave trough
1 cycle
1 s = 13 cycles
b
a
c
Awake
Stage I


Awake
Stage I
Stage II
Stage III
Stage IV
Time (h)

# REM Sleep

- Presence of beta activity (desynchronized EEG pattern)
- Physiological arousal threshold increases
  - Heart-rate quickens
  - Breathing more irregular and rapid
  - Brainwave activity resembles wakefulness
  - Genital arousal
- Loss of muscle tone (paralysis)
- Vivid, emotional dreams
- May be involved in memory consolidation

# SLEEP AND WAKE THROUGHOUT HUMAN LIFE




AFTER ROFFWARG , MUZIO & DEMENT, *Science* (1966).

# REM Dreaming

- "vivid and exciting"
- ~3 per night
- Longer, more detailed
- Fantasy world
- nightmares

# NREM Dreaming

- "just thinking"
- Shorter, less active
- Logical, realistic

# Dream theories

- Activation synthesis theory
  - Sensory experiences are fabricated by the cortex as a means of interpreting signals from the PGO activity.
- Continual activation theory
  - Encoding of short term into long-term memories.
  - NREM sleep processes the conscious-related memory (declarative memory),
  - REM sleep processes the unconscious related memory (procedural memory).

# Sleep Disorders

- insomnia
- sleep walking, talking, and eating
- nightmares and night terrors
- narcolepsy
- sleep apnea

# Sleep Disorders

- Insomnia: persistent problems in falling asleep, staying asleep, or awakening too early
- Sleep Apnea: repeated interruption of breathing during sleep
- Narcolepsy: sudden and irresistible onsets of sleep during normal waking hours

# Sleep disorders

- **Nightmares**: anxiety-arousing dreams occurring near the end of sleep, during REM sleep
- **Night Terrors**: abrupt awakenings from NREM sleep accompanied by intense physiological arousal and feelings of panic

# Sleep Disorders

- Somnambulism…sleepwalking
  - 40% of children will have an episode, peaking at between 11-12 years of age;
  - Can be induced if arouse children during NREM;
  - associated with complete amnesia,
  - Occurs within 2 hours of falling asleep.. EEG..reveals both waking and sleep signals. Considered benign.

# Coma & Brain death

- Definition:
  - Greek in origin – “deep sleep or trance”
  - It refers to an unconscious state characterised by a lack of both arousal and responsiveness