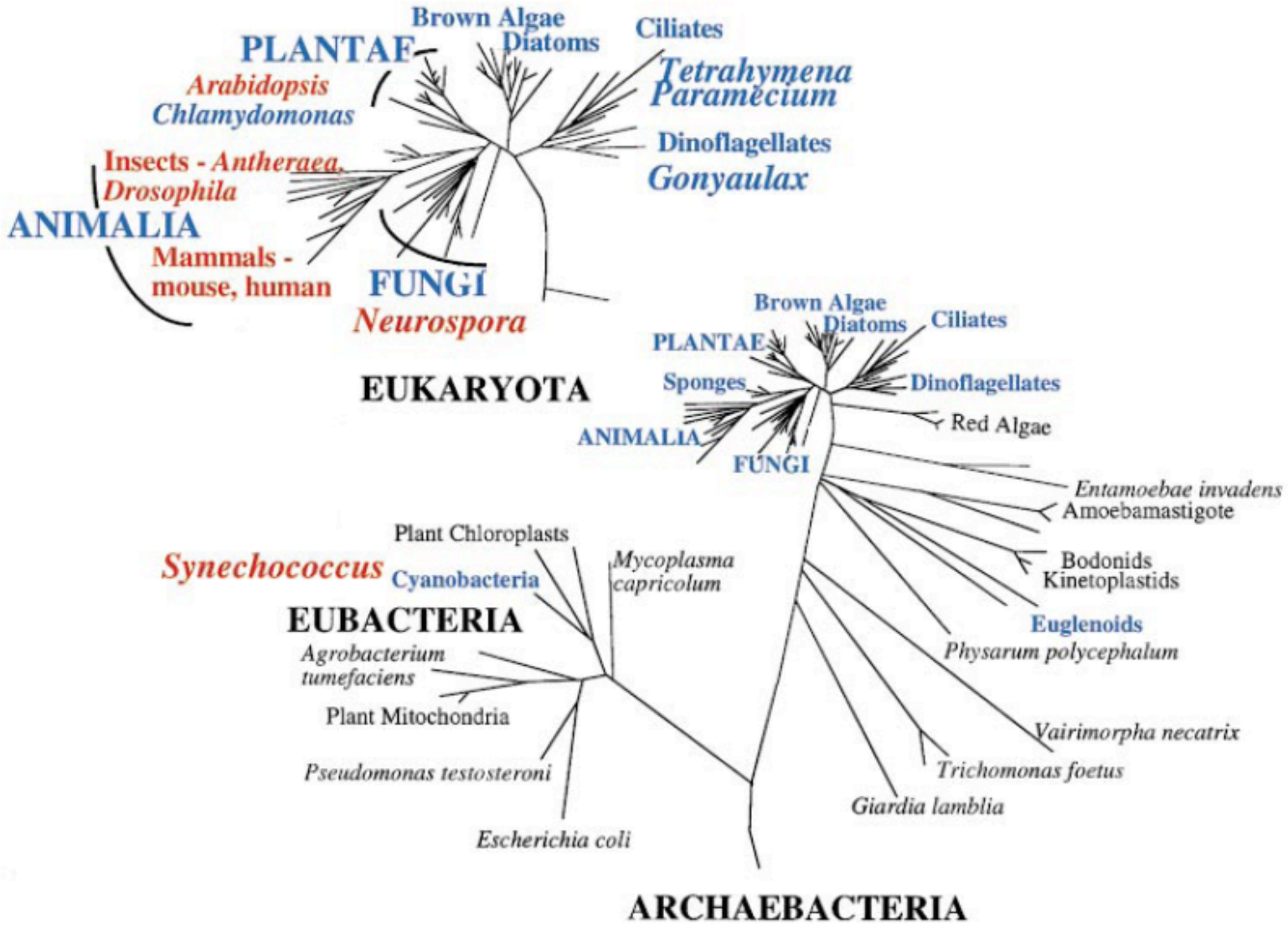
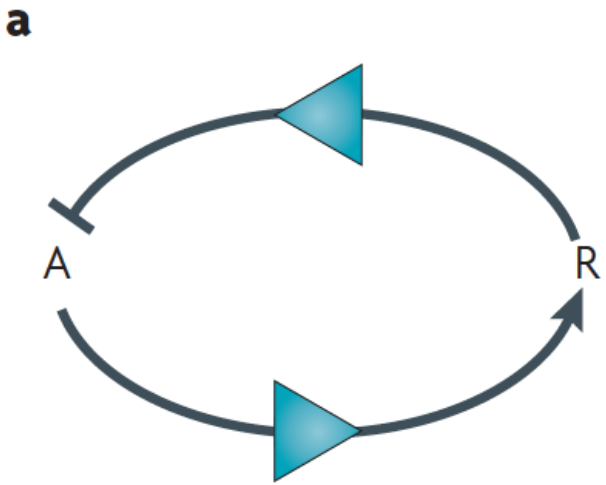

SHP Neuroscience
Week 11
Sleep

Circadian rhythms in the tree of life

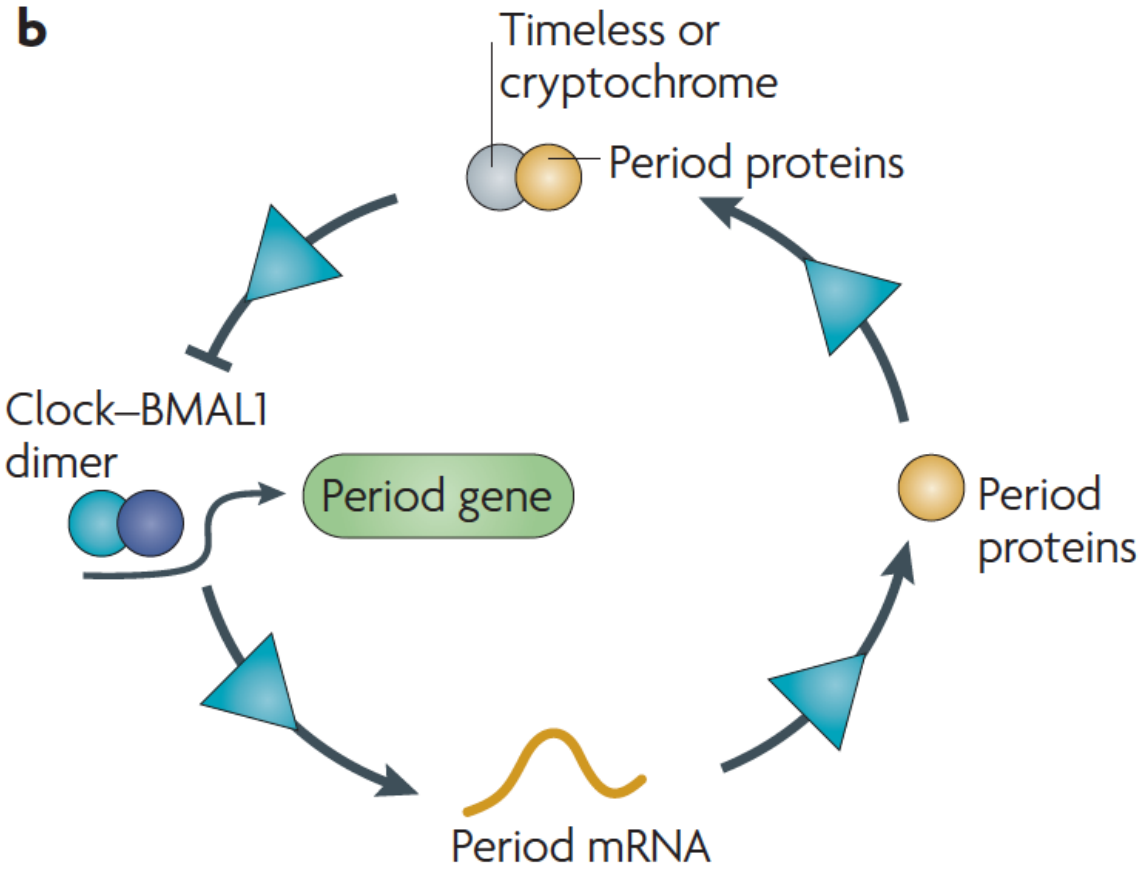


Blue : circadian rhythms have been described
Red : we know a lot about circadian rhythms in these species

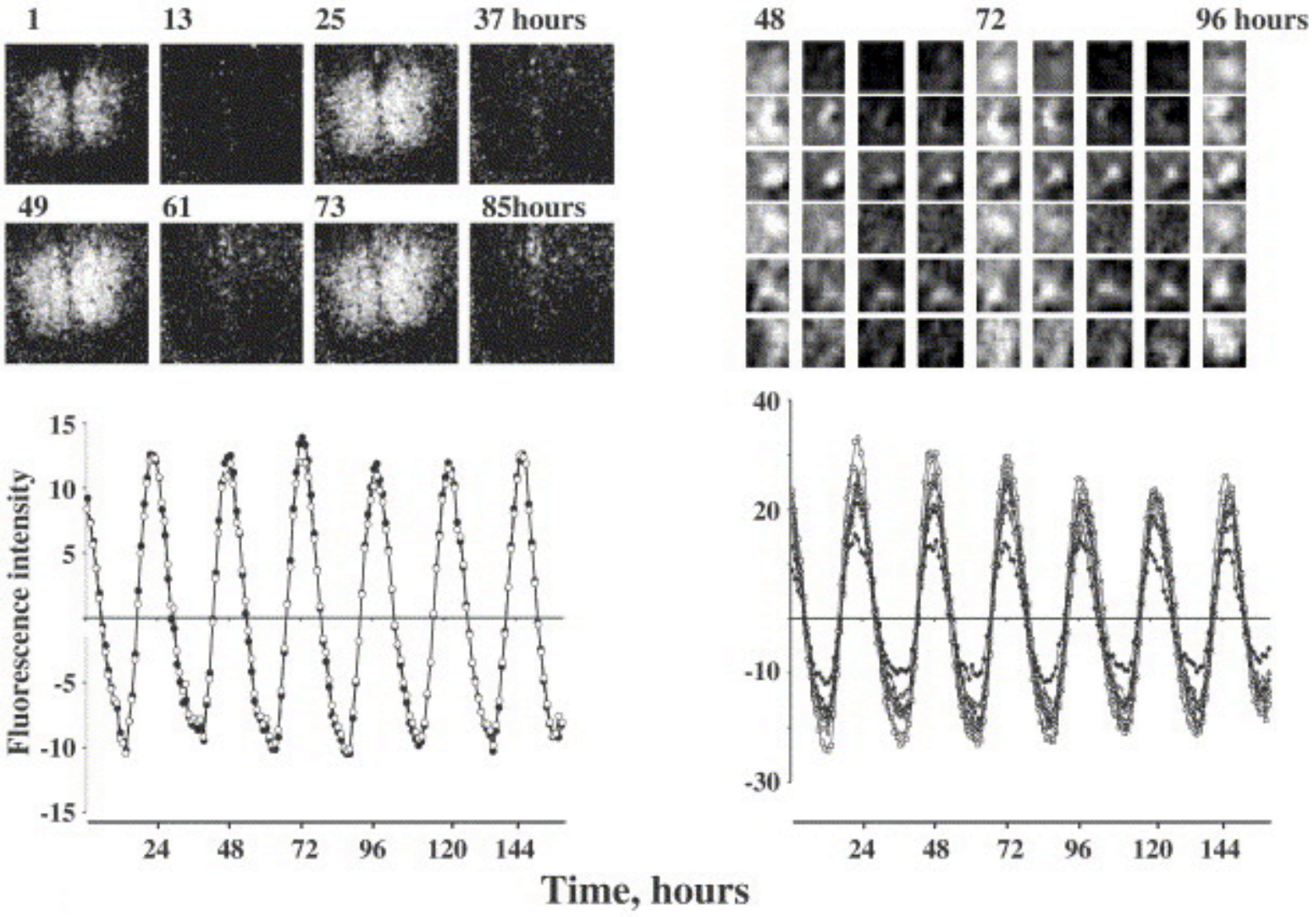
Can cells ‘tell time’?



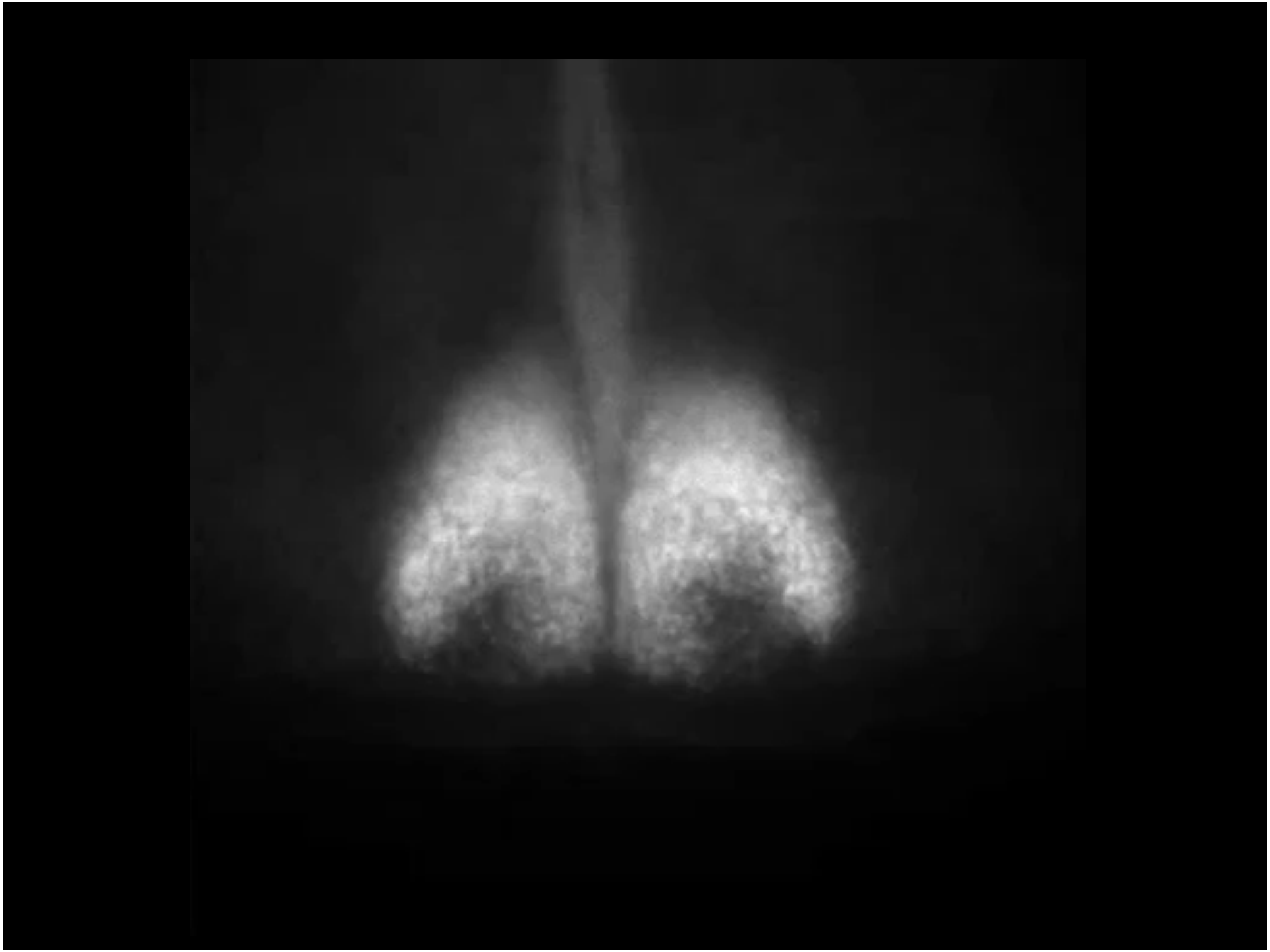
feedback loop



fluorescence coupled to *Per* gene

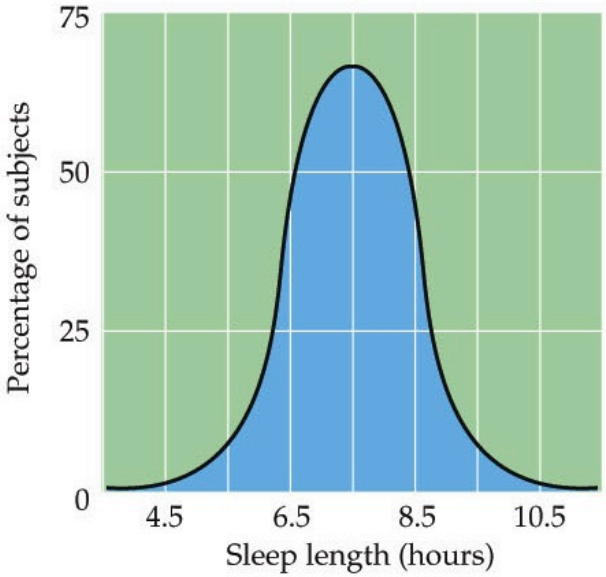


Maywood *et al.* 2006

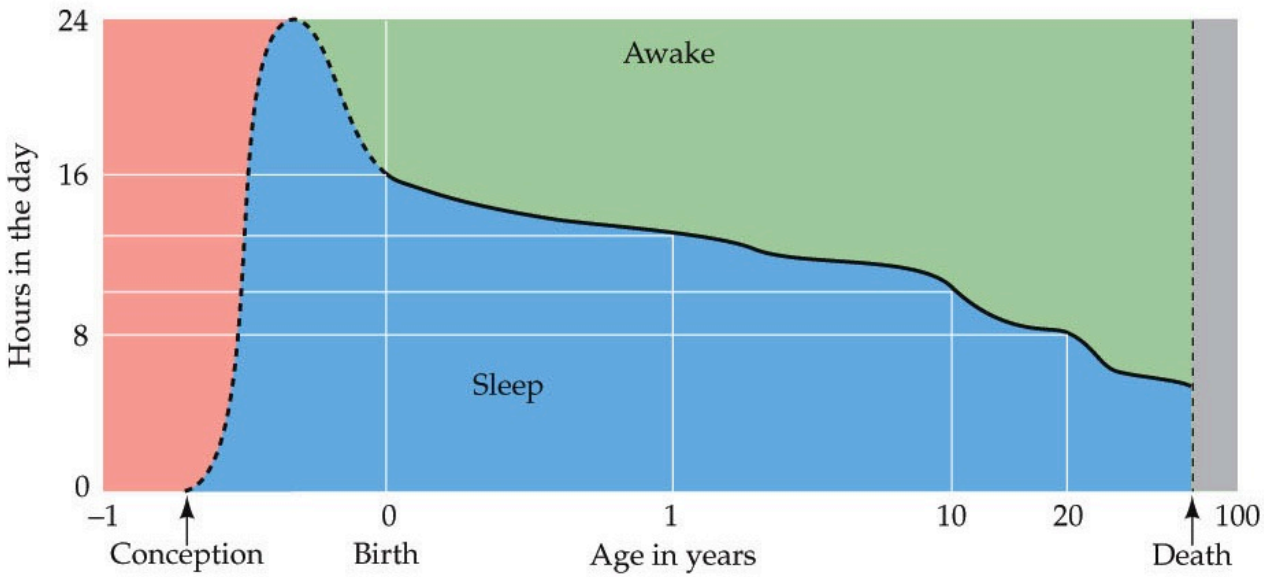


Onto human sleep…

Average ≈ 7-8 hrs/night



Sleep requirements change throughout lifespan

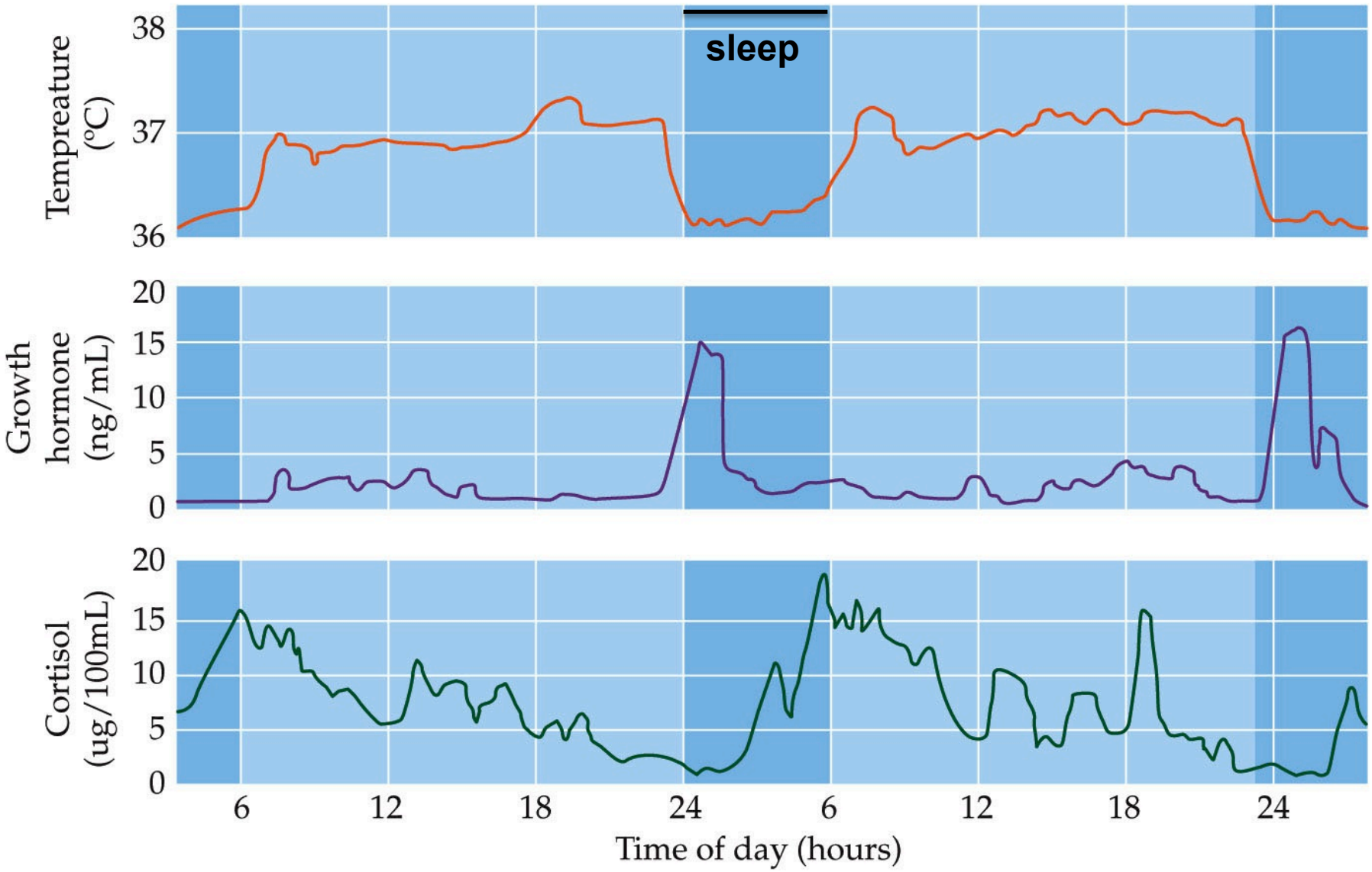


Infants: 17 hours

Teenagers: 9 hours

Elderly: sleep less at night

Body temperature and hormones follow a circadian rhythm



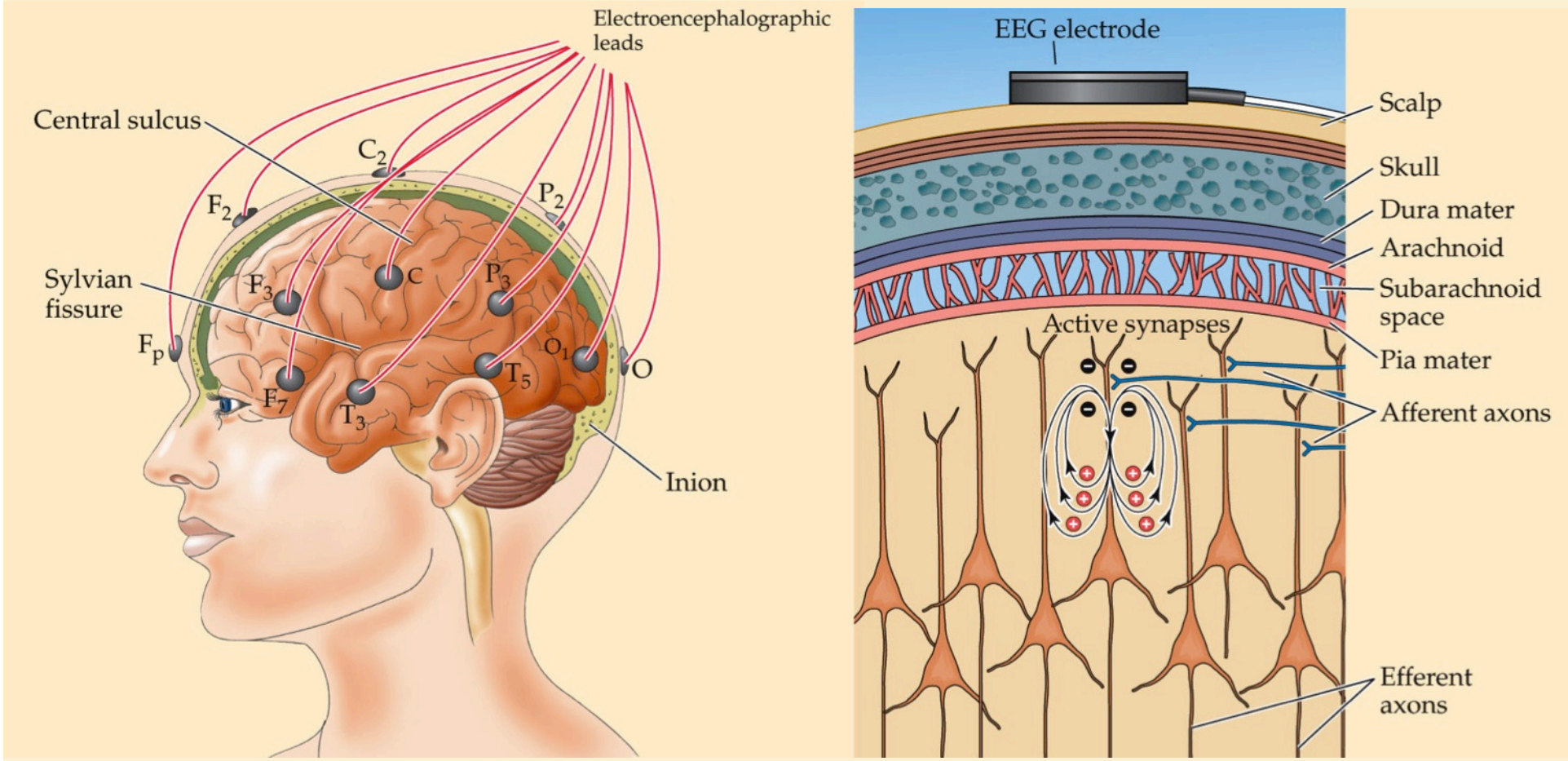
How do we know that the sleeping brain is different than the waking brain?

Answer:

electroencephalogram (**EEG**)

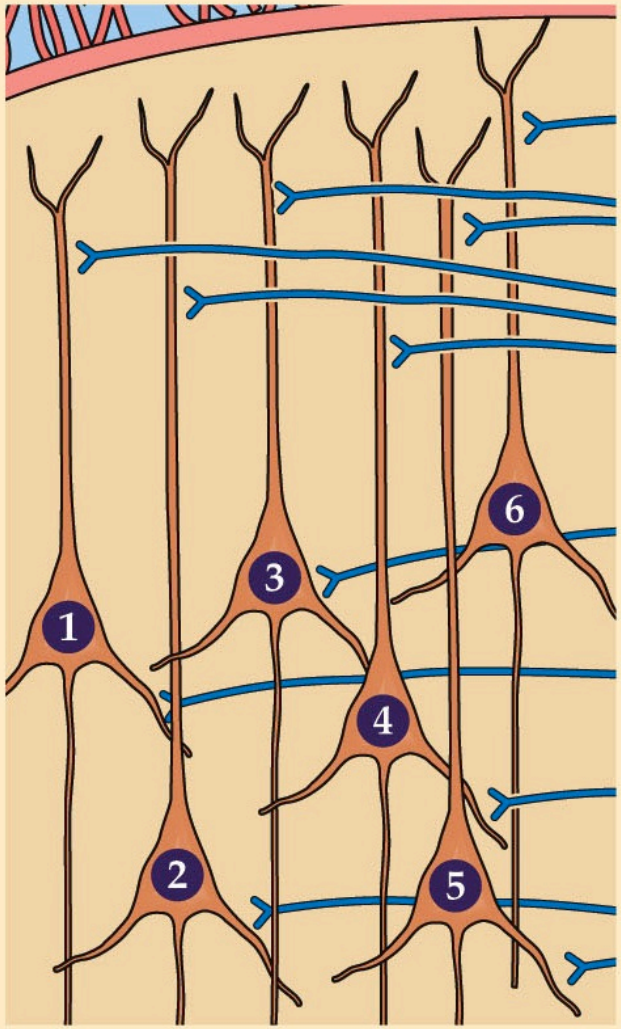


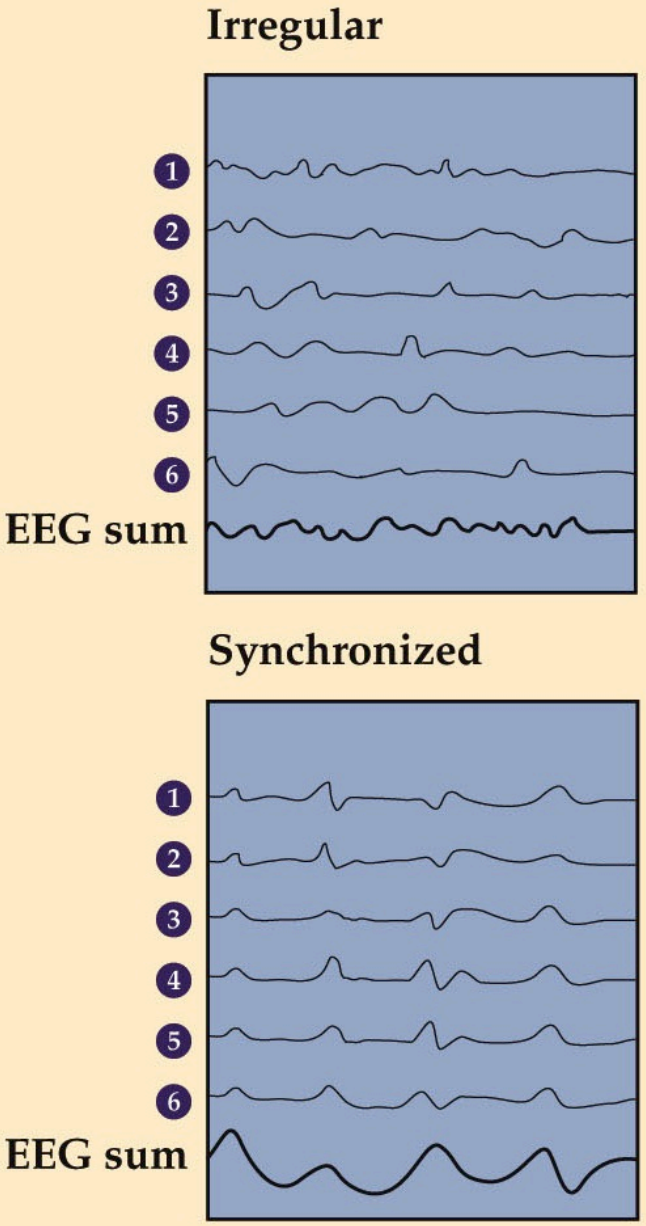
EEG


Electroencephalographic leads
Central sulcus
Sylvian fissure
C_2
F_2
P_2
F_3
C
P_3
F_p
O_1
O
T_5
F_7
T_3
Inion
EEG electrode
Scalp
Skull
Dura mater
Arachnoid
Subarachnoid space
Pia mater
Active synapses
Afferent axons
Efferent axons

EEG

↑ Amplitude = ↑ Synchrony





EEG

How synchronized the neurons are in a particular brain area (a few cm)

Can tell us the frequency at which neurons are activated

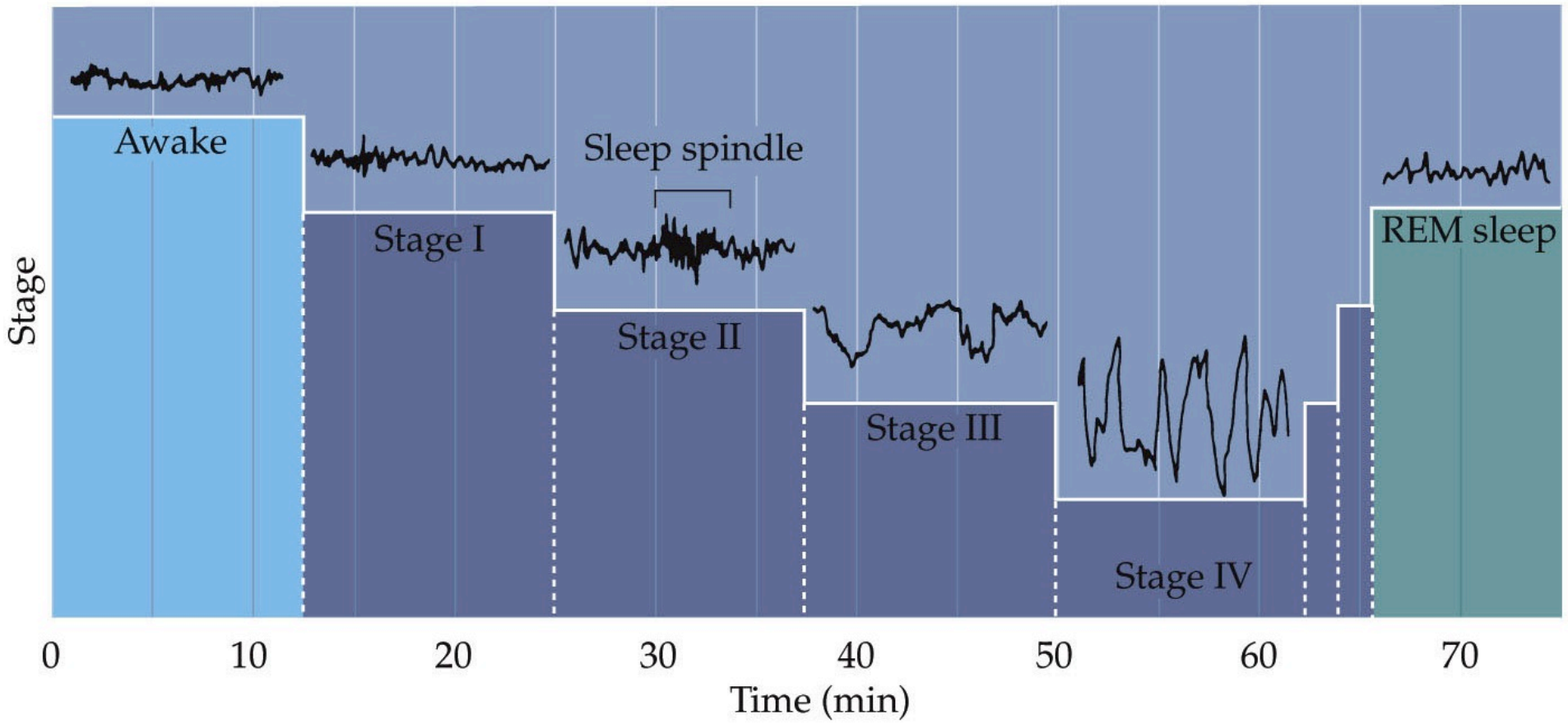
but,

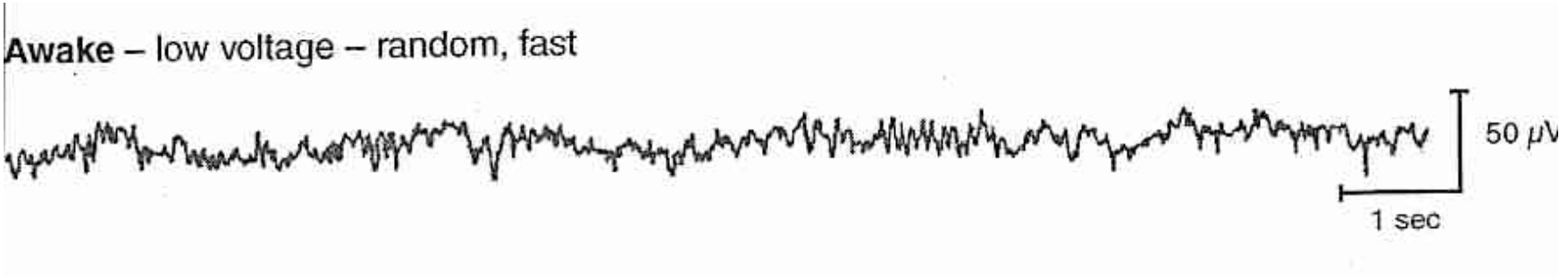
Only tells us the average behavior over a relatively large area
(difficult to interpret what's actually occurring in the circuit)

Rhythms in the Human Brain

α rhythm	8-13 Hz	visual cortex, eyes closed
β rhythm	14-60 Hz	visual cortex, eyes open
δ rhythm	< 4 Hz	drowsiness, sleep (or pathological conditions)
θ rhythm	4-7 Hz	

Sleep Stages defined by cortical rhythms

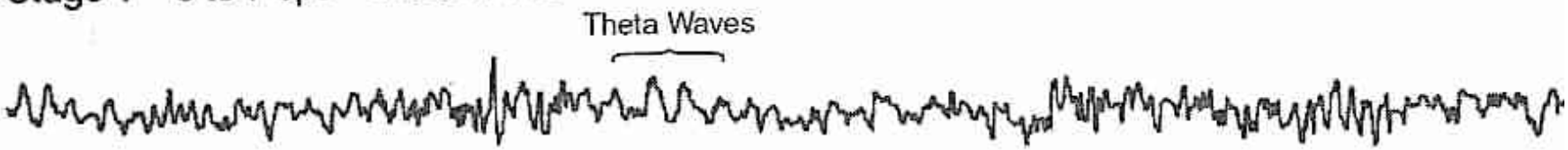


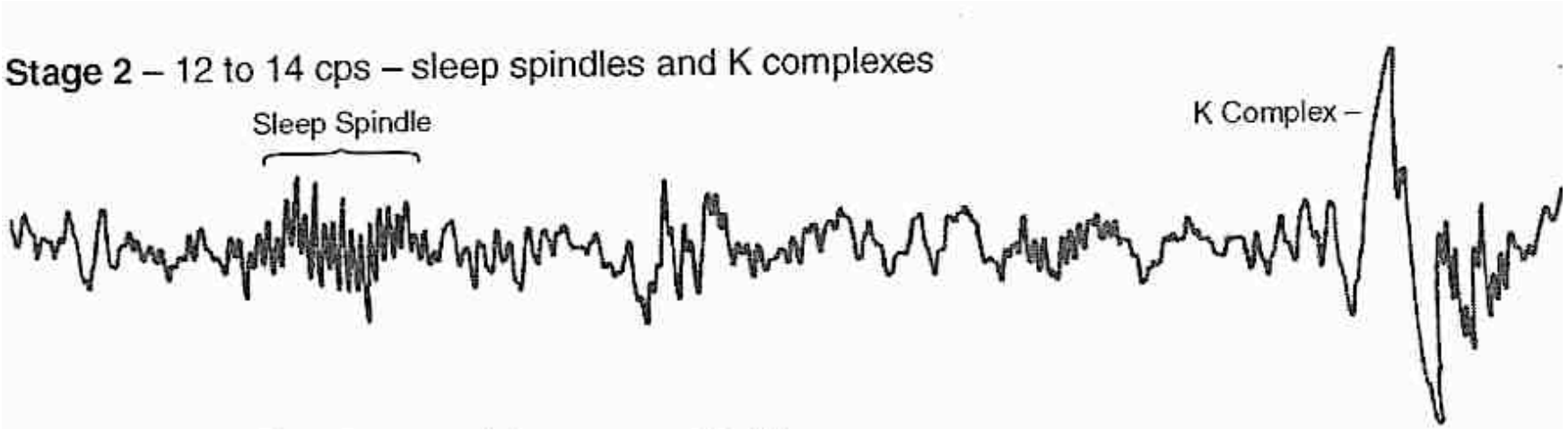

Awake – low voltage – random, fast
50 μV
1 sec

Drowsy – 8 to 12 cps – alpha waves

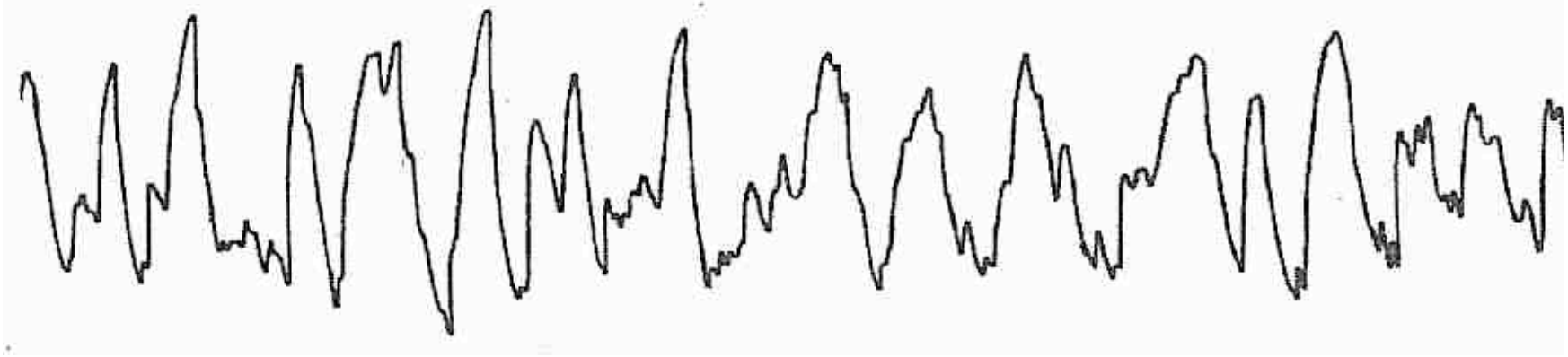


Stage 1 – 3 to 7 cps – theta waves

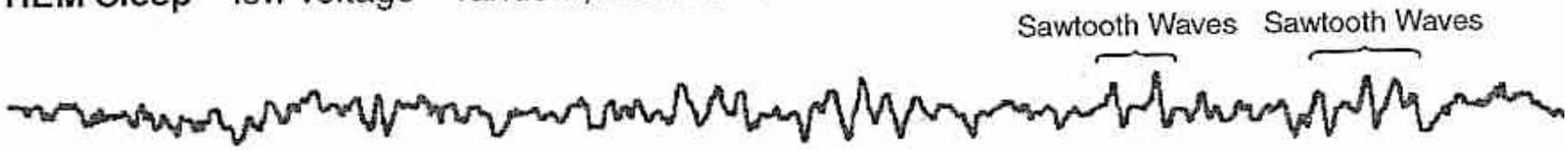



Stage 2 – 12 to 14 cps – sleep spindles and K complexes
Sleep Spindle
K Complex –

Delta Sleep – 1/2 to 2 cps – delta waves >75 μV



REM Sleep – low voltage – random, fast with sawtooth waves

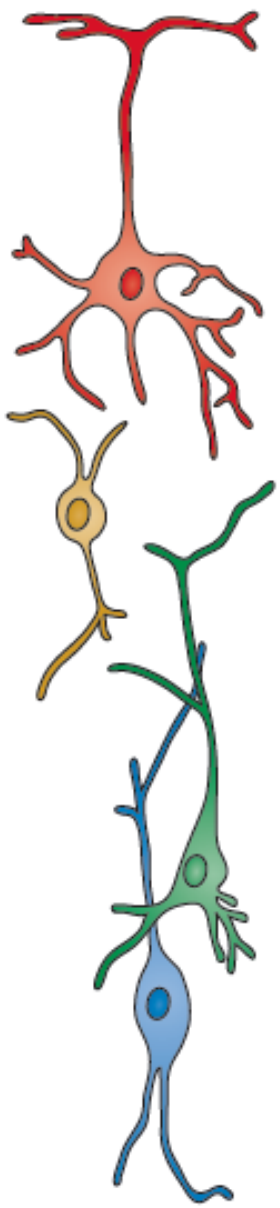


Awake – low voltage – random, fast

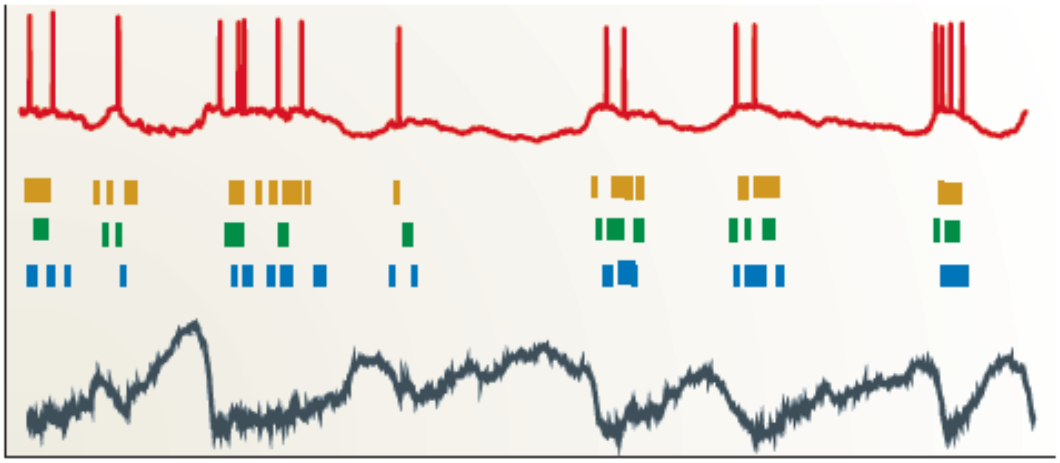


Sleep Waves

Awake	15-60 Hz	30 μV	high frequency, low amplitude
Stage I	4-8 Hz	50-100 μV	
Stage II	10-12 Hz	50-150 μV	
Stage III	2-4 Hz	100-150 μV	
Stage IV	0.5-2 Hz	100-200 μV	delta (δ) or slow-wave sleep low frequency, high amplitude
REM	high frequency, low amplitude (similar to awake)		



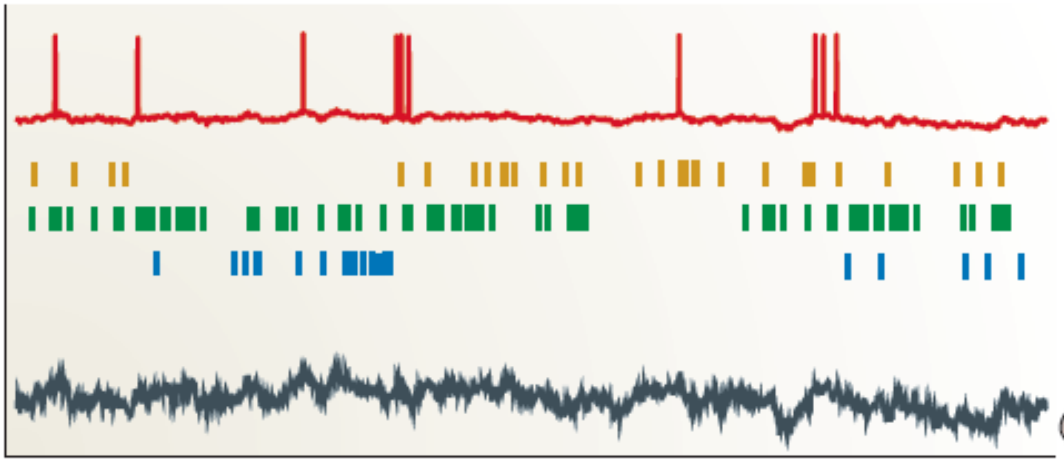
a Sychronized state



Sleeping
Quiescent (at rest)



b Desychronized state



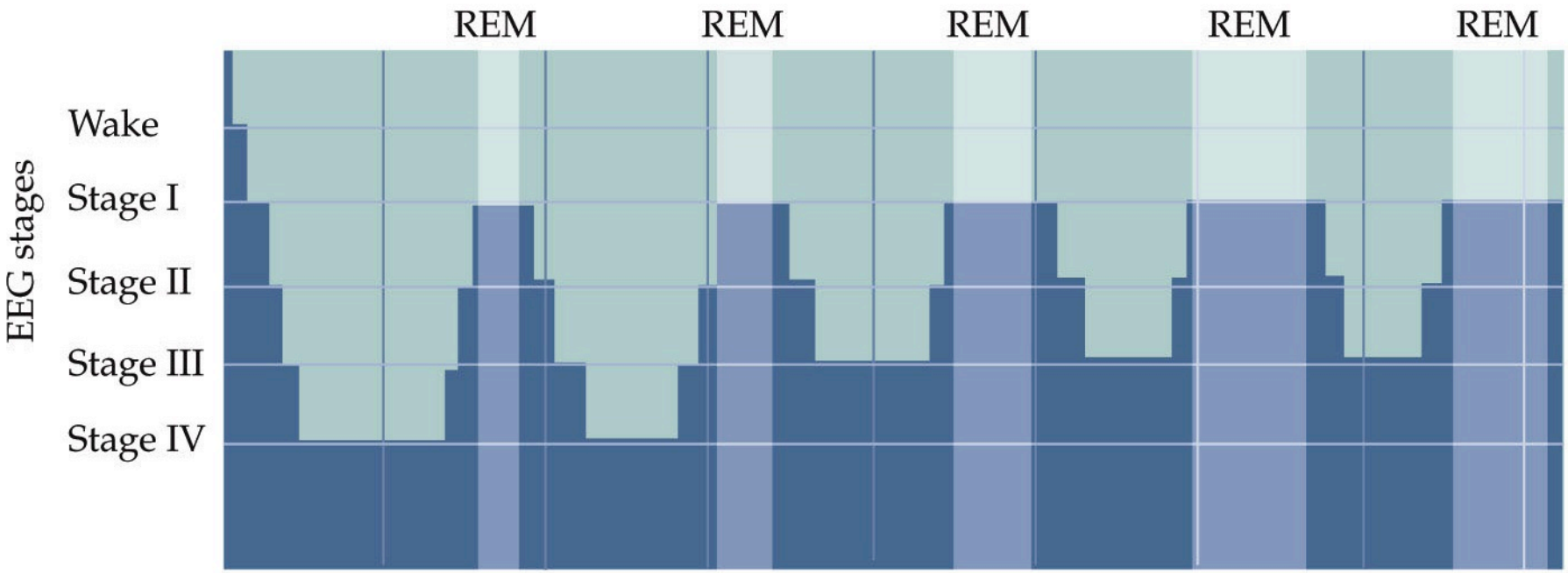
Awake, behaving



Harris & Thiele, 2011

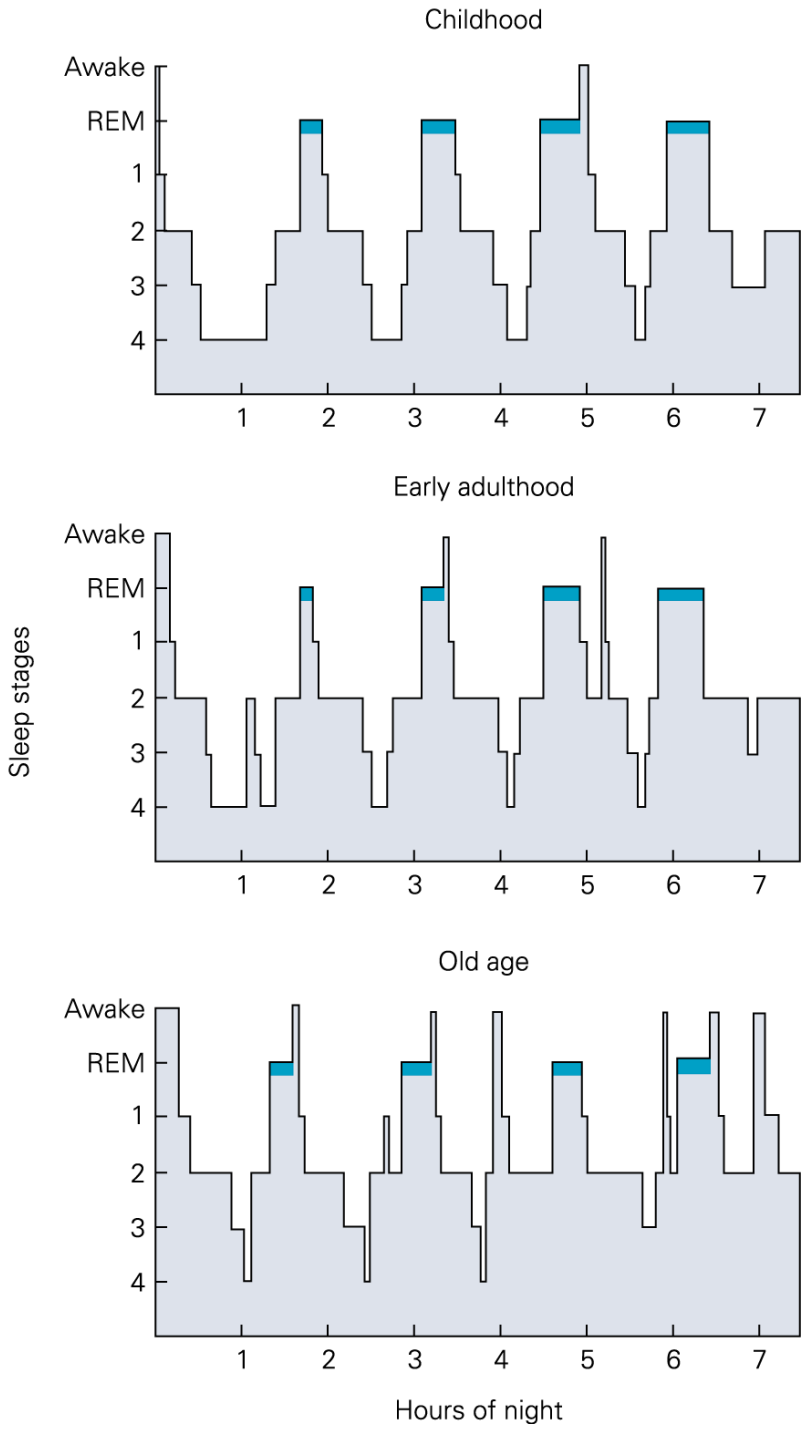
Sleep Structure

hypnograms

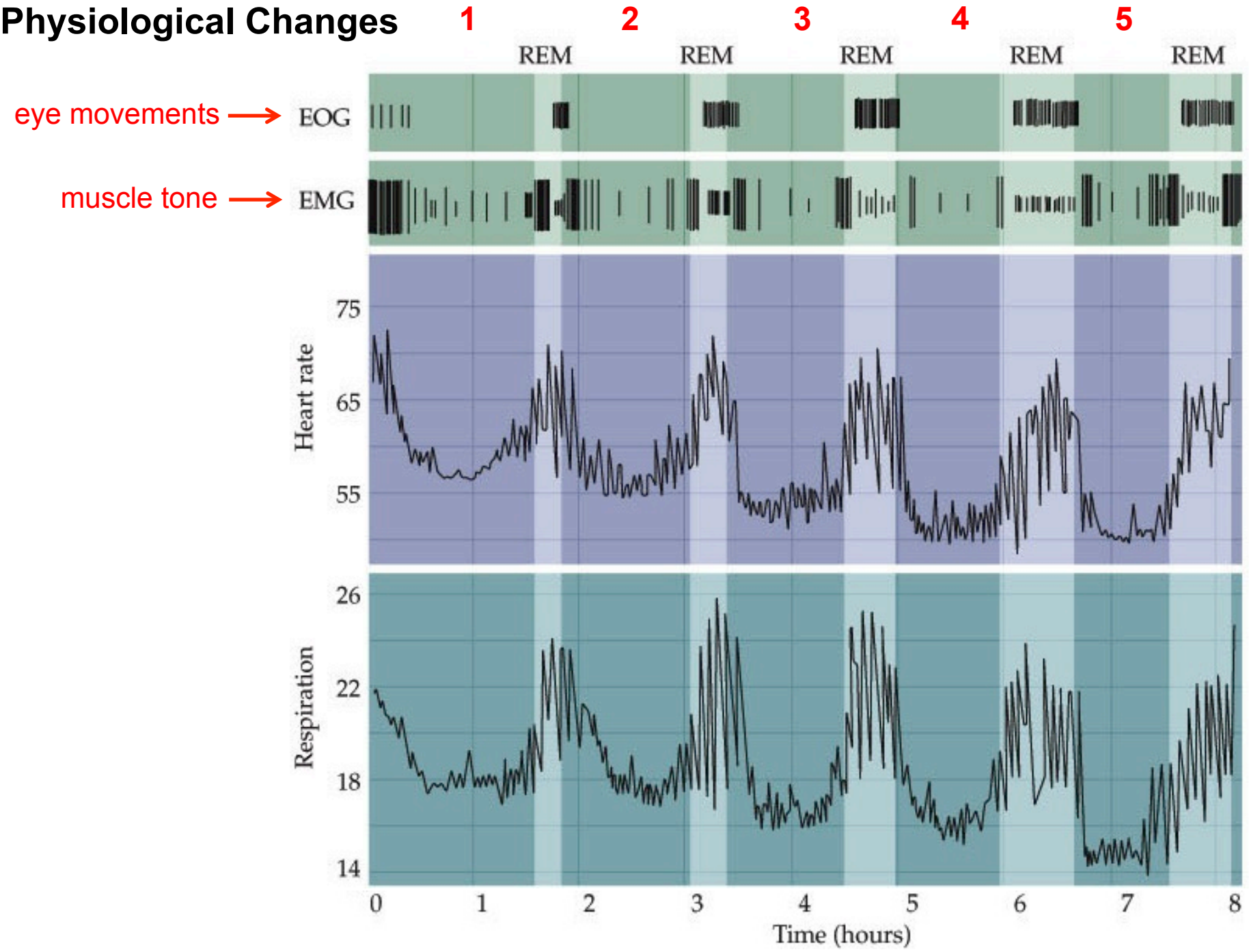


Sleep Structure

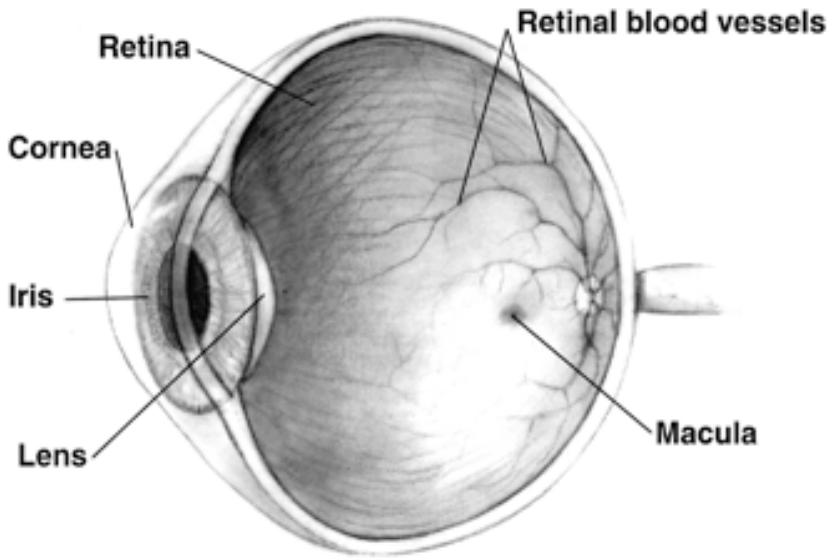
hypnograms

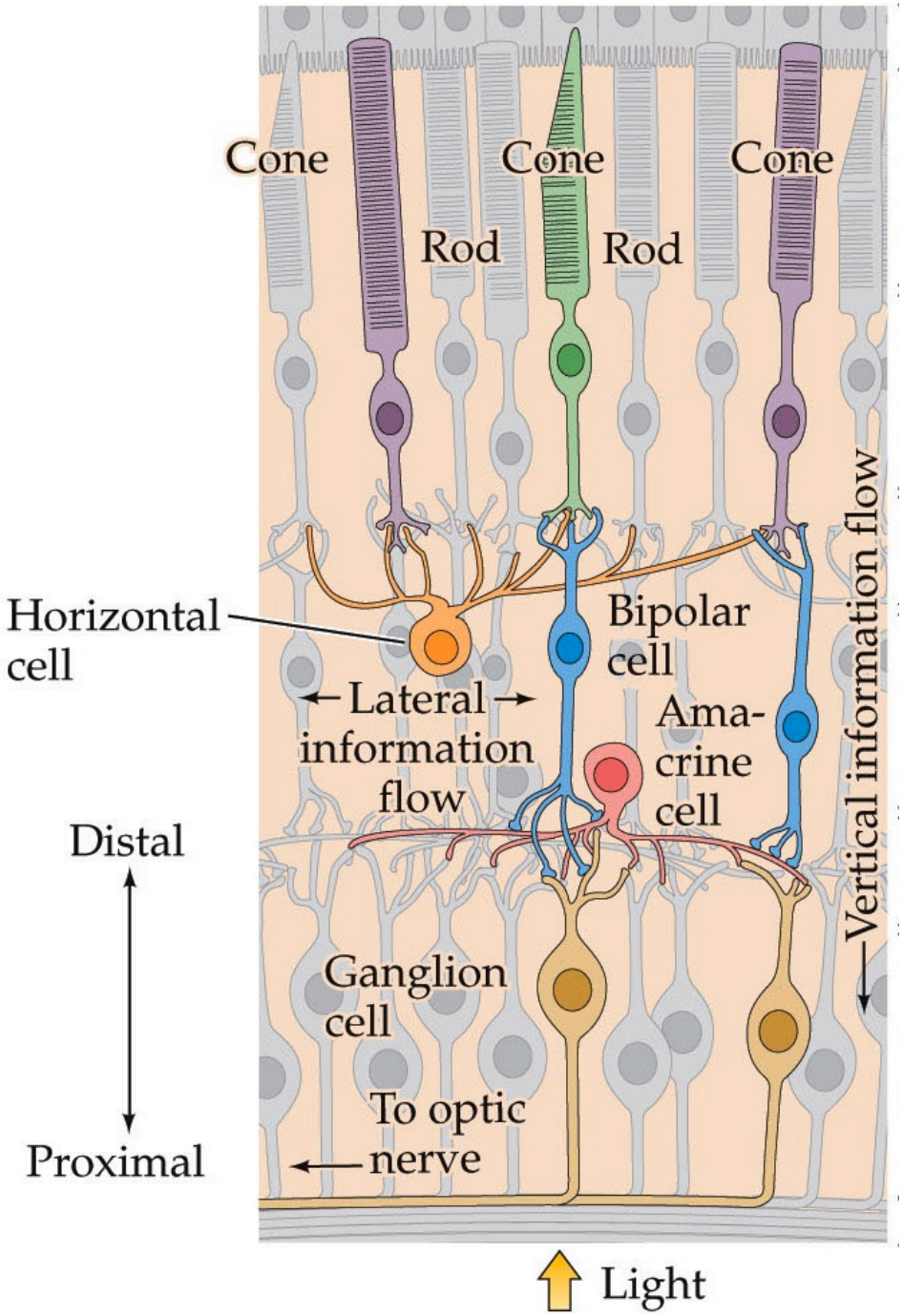


Physiological Changes



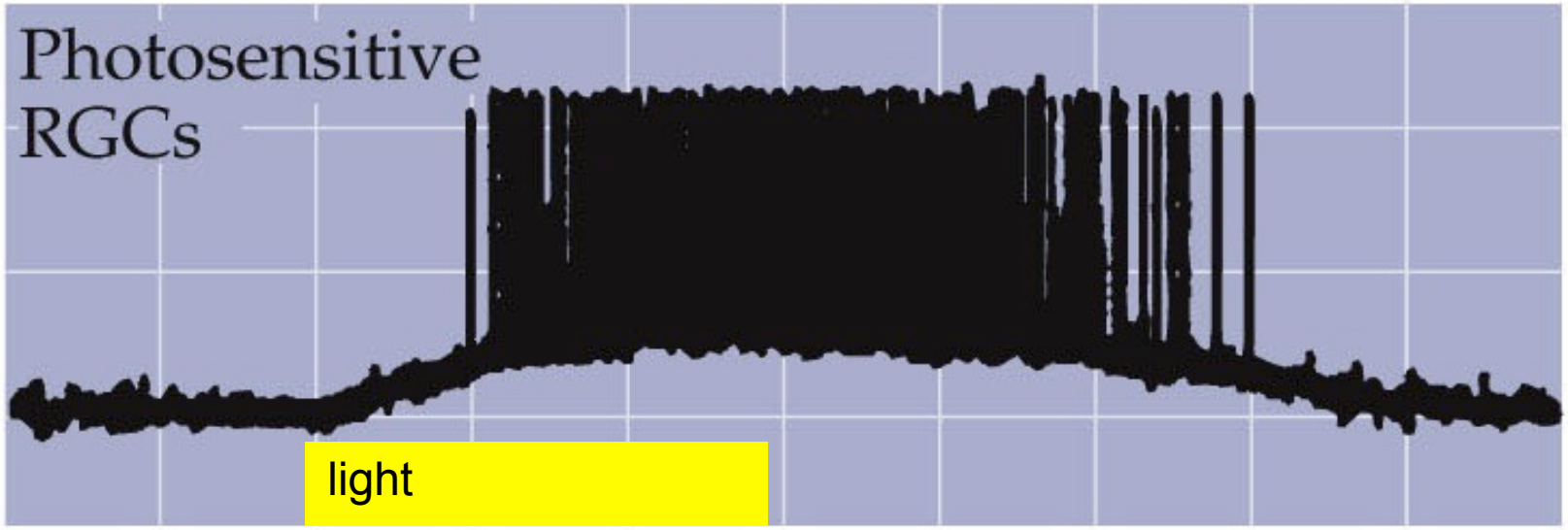
What makes us sleep?





What makes us sleep?

Some retinal ganglion cells are directly photosensitive



What makes us sleep?

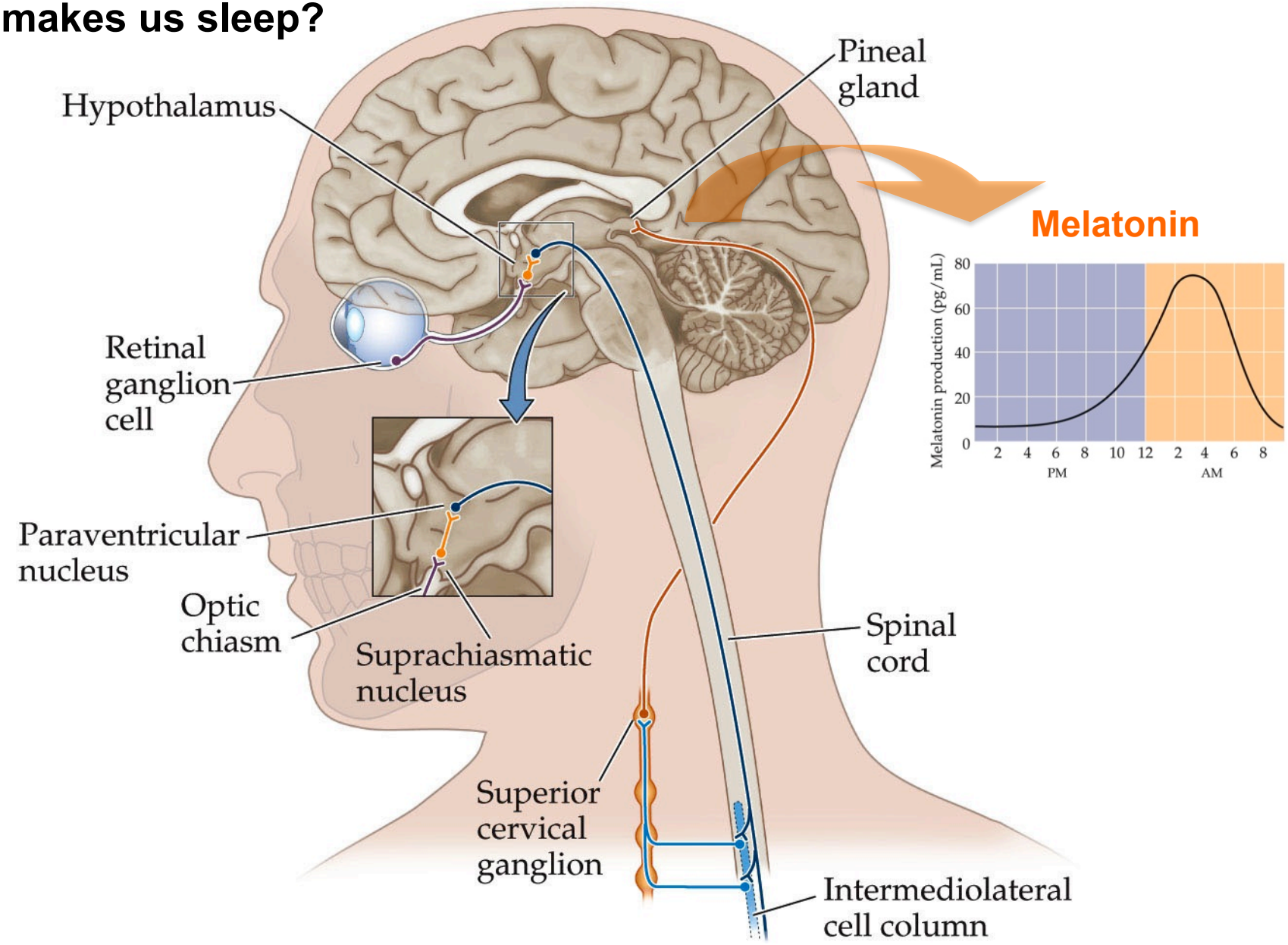
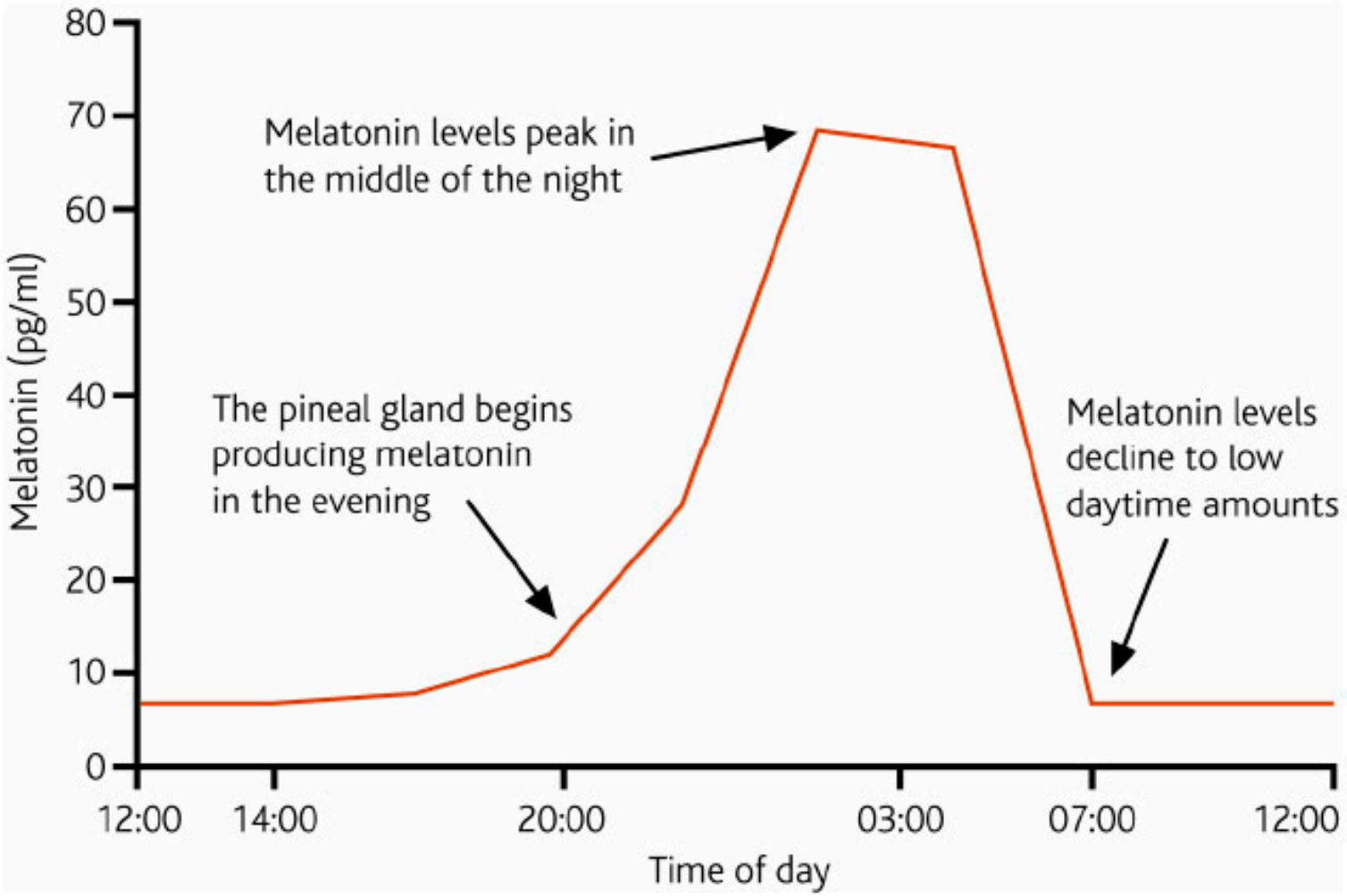


Figure 1: Fluctuation in melatonin levels over a 24-hour period



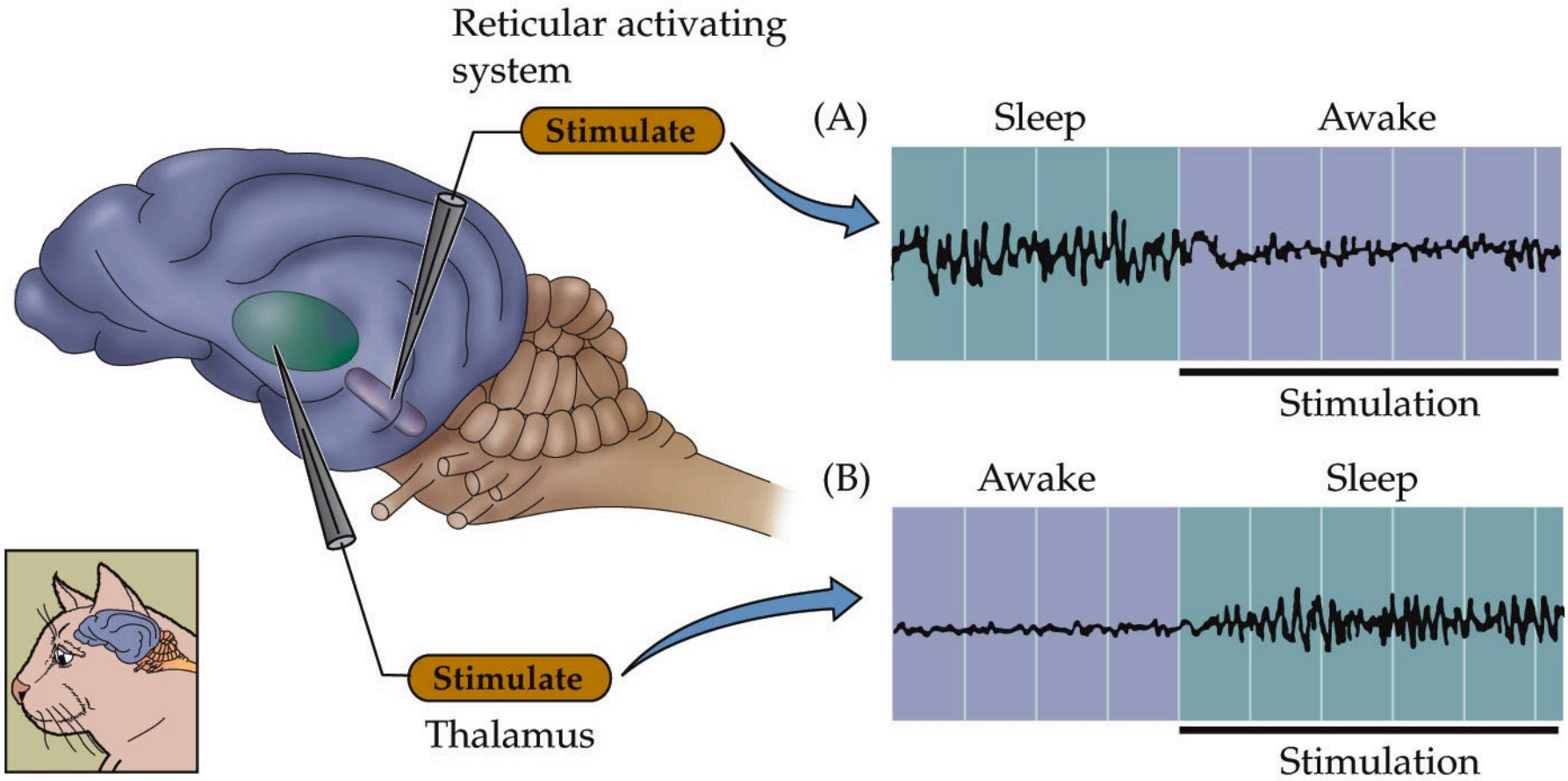
Setting the clock

Zeitgebers:

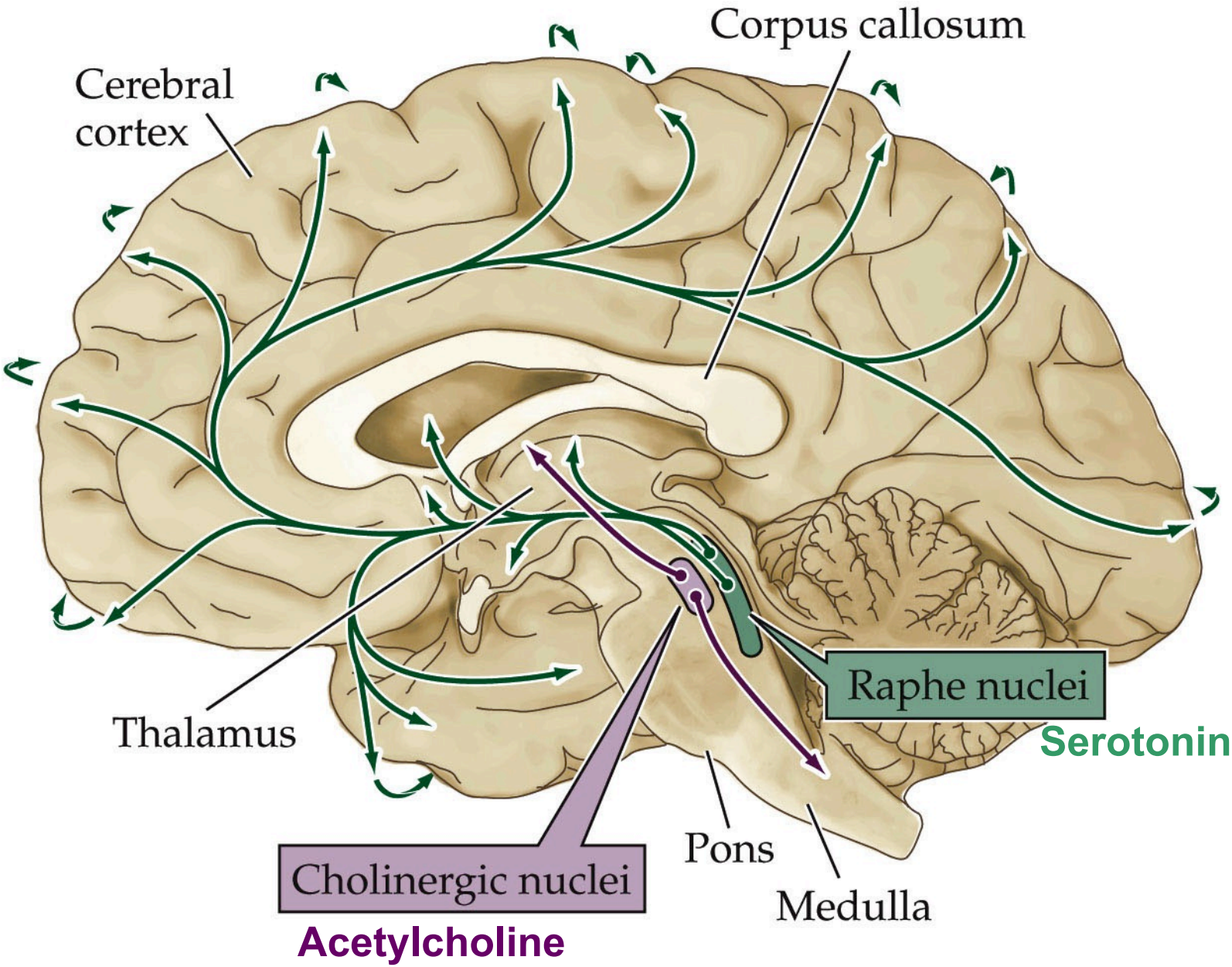
light
odor
sound
temperature change
anything periodic…

Master Regulators of Sleep

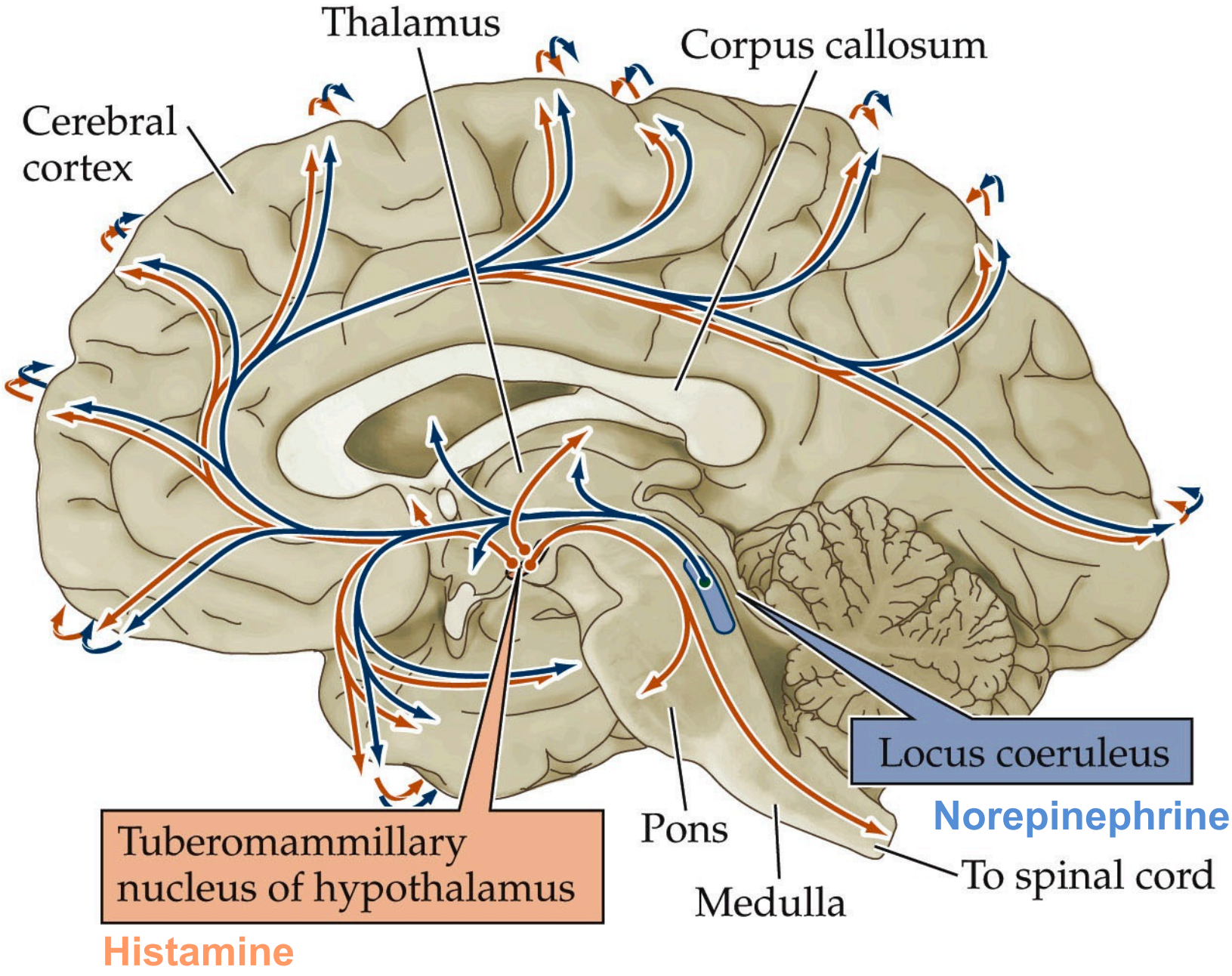
Reticular activating system = **cholinergic neurons**

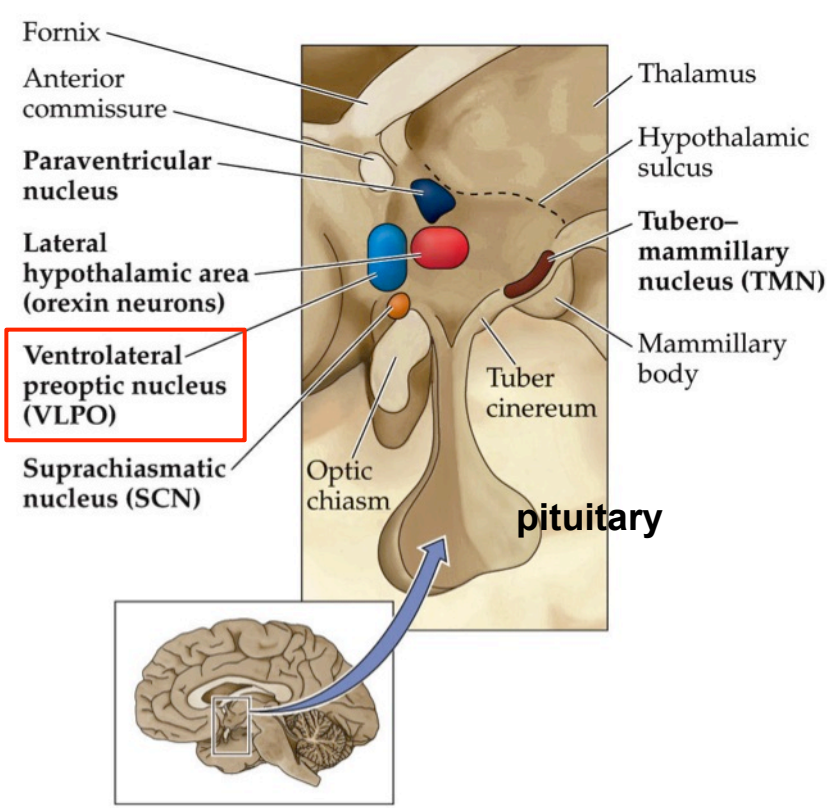


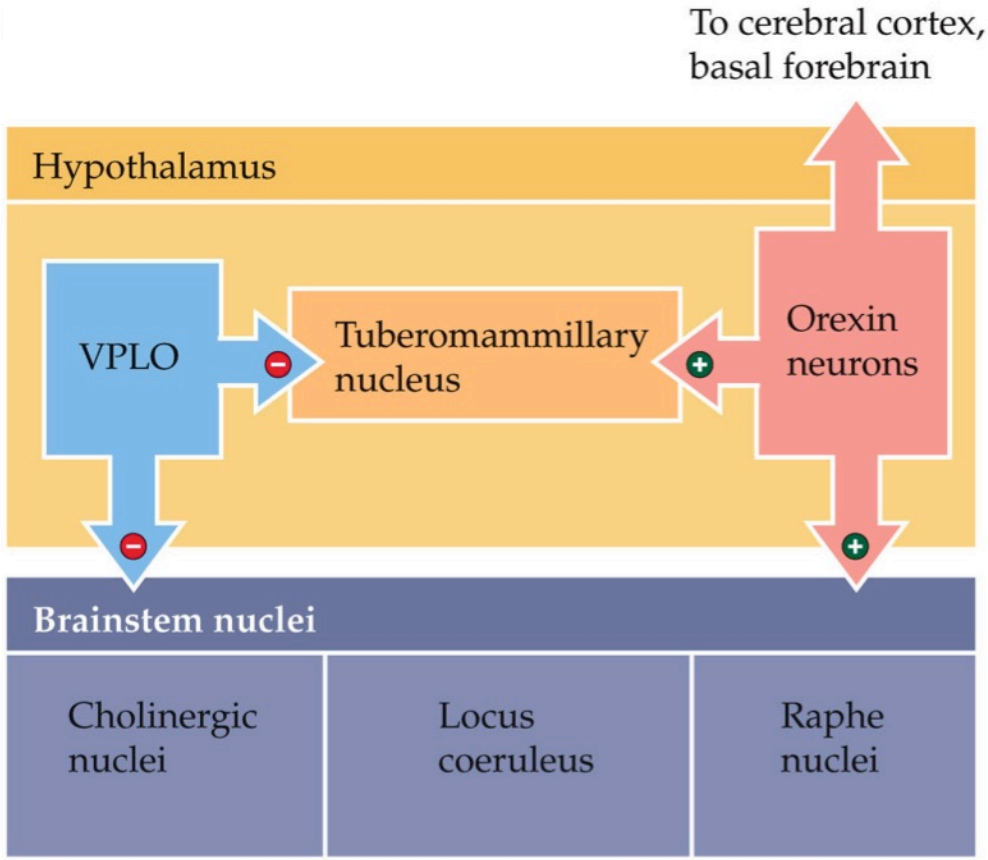
Brainstem Regulators of Sleep



Brainstem Regulators of Sleep



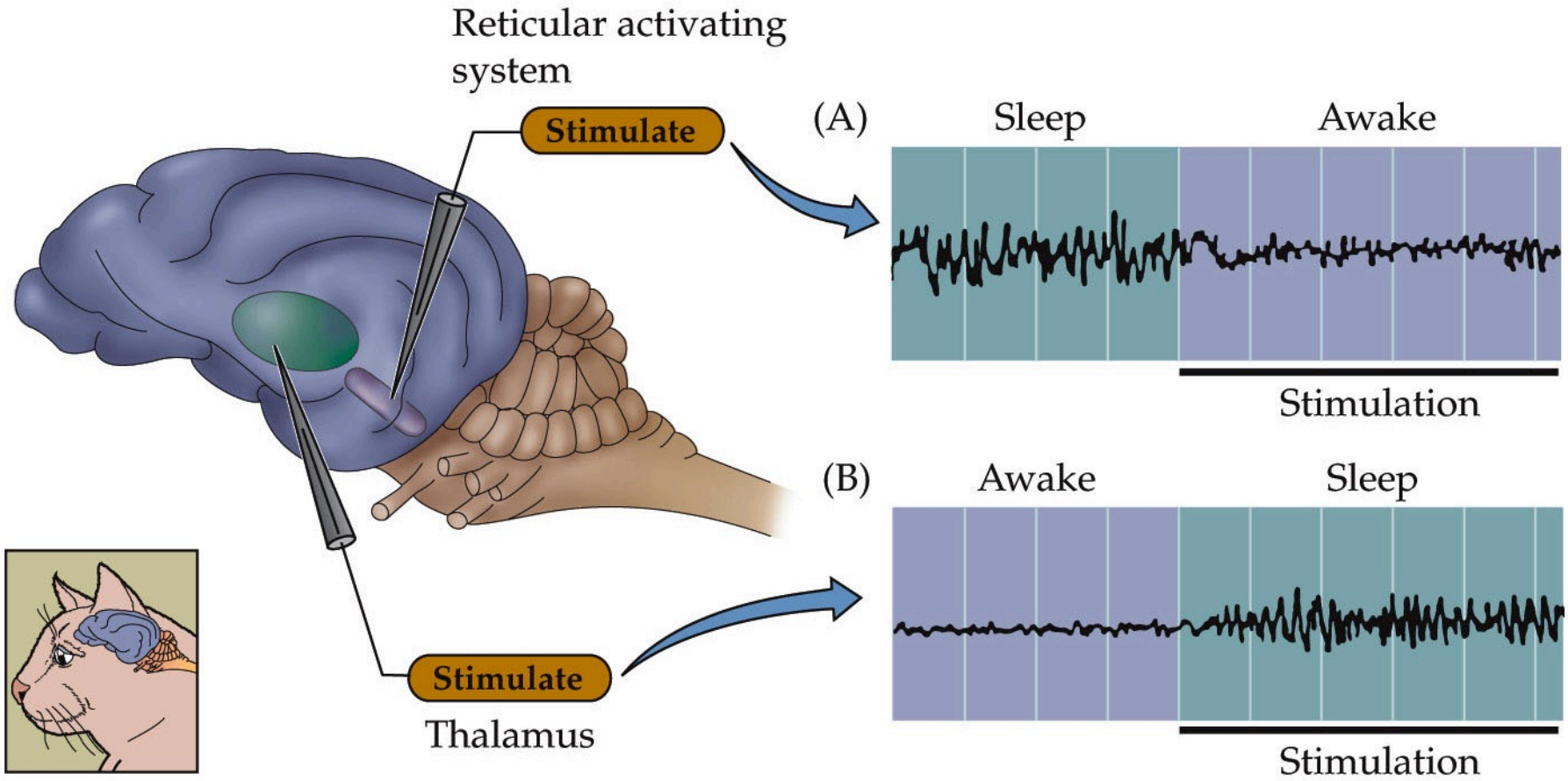


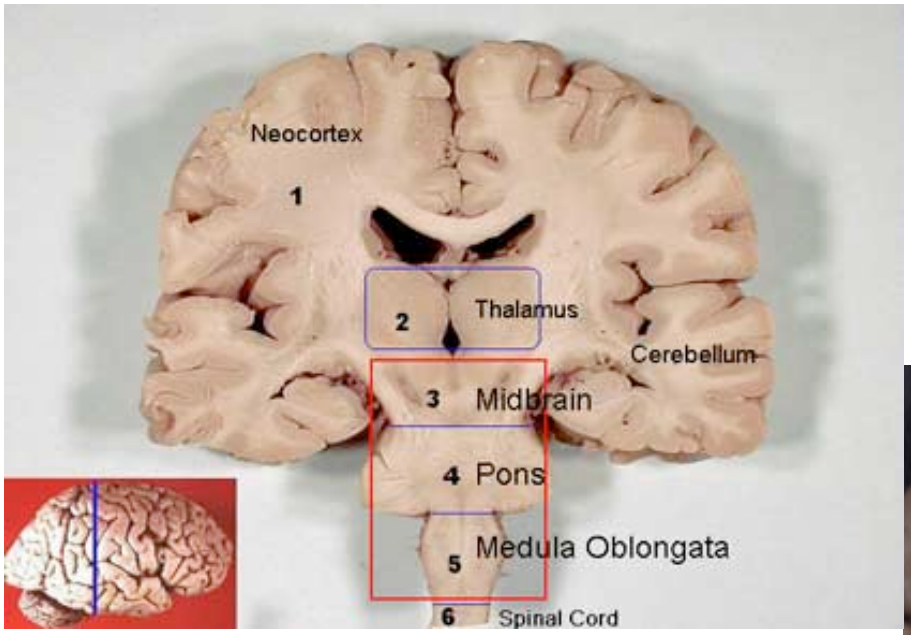


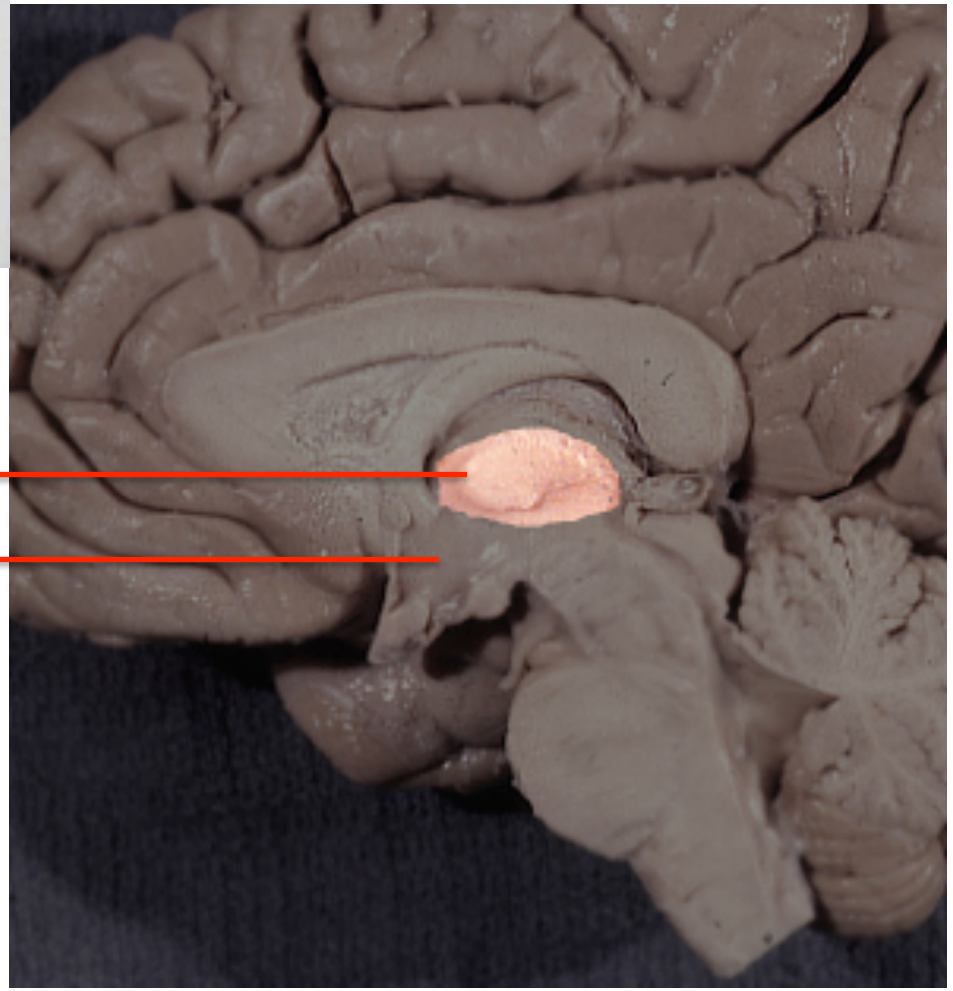
VLPO periodically inhibits the brainstem arousal centers

Master Regulators of Sleep

Reticular activating system = **cholinergic neurons**



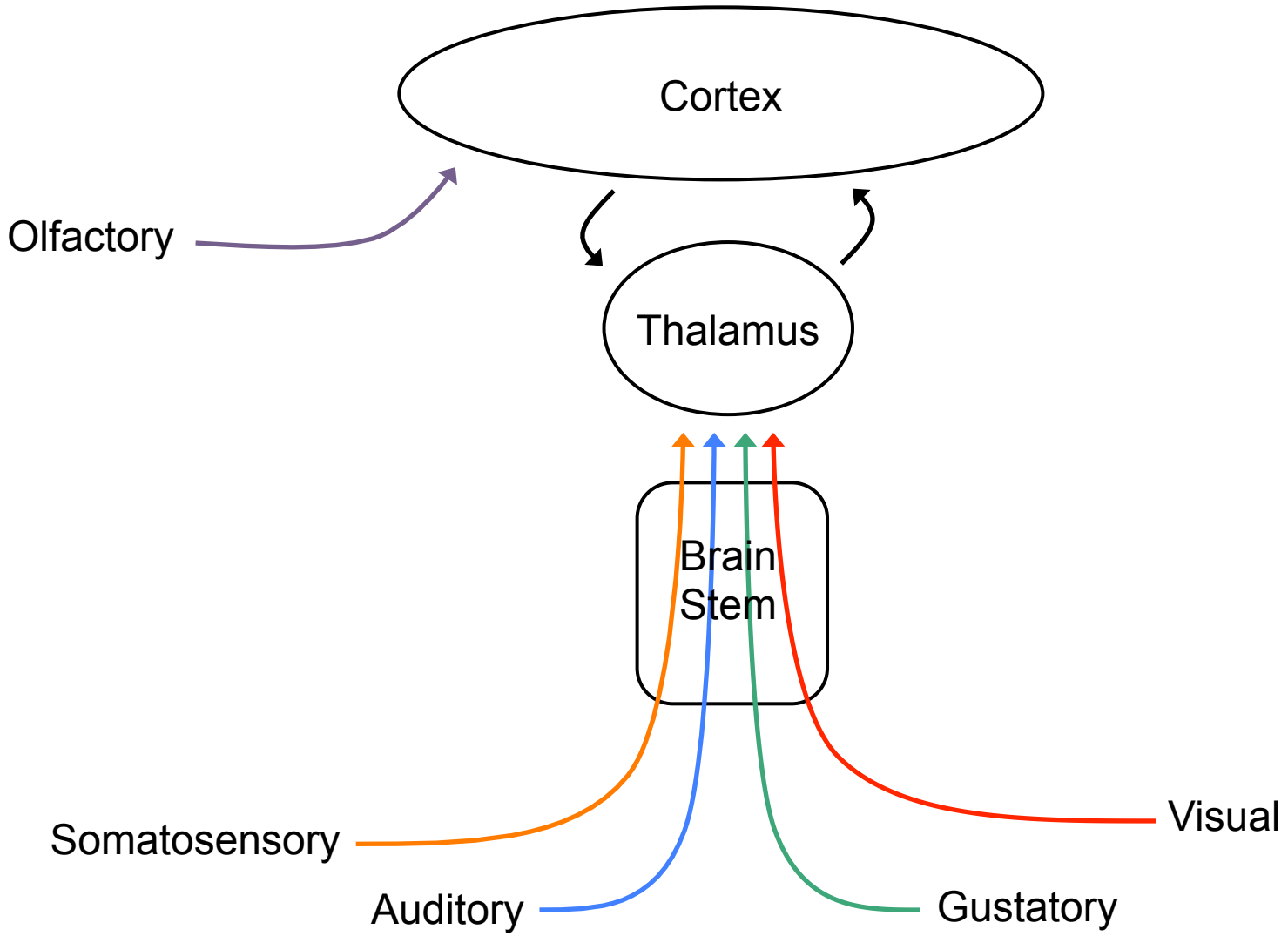




Thalamus

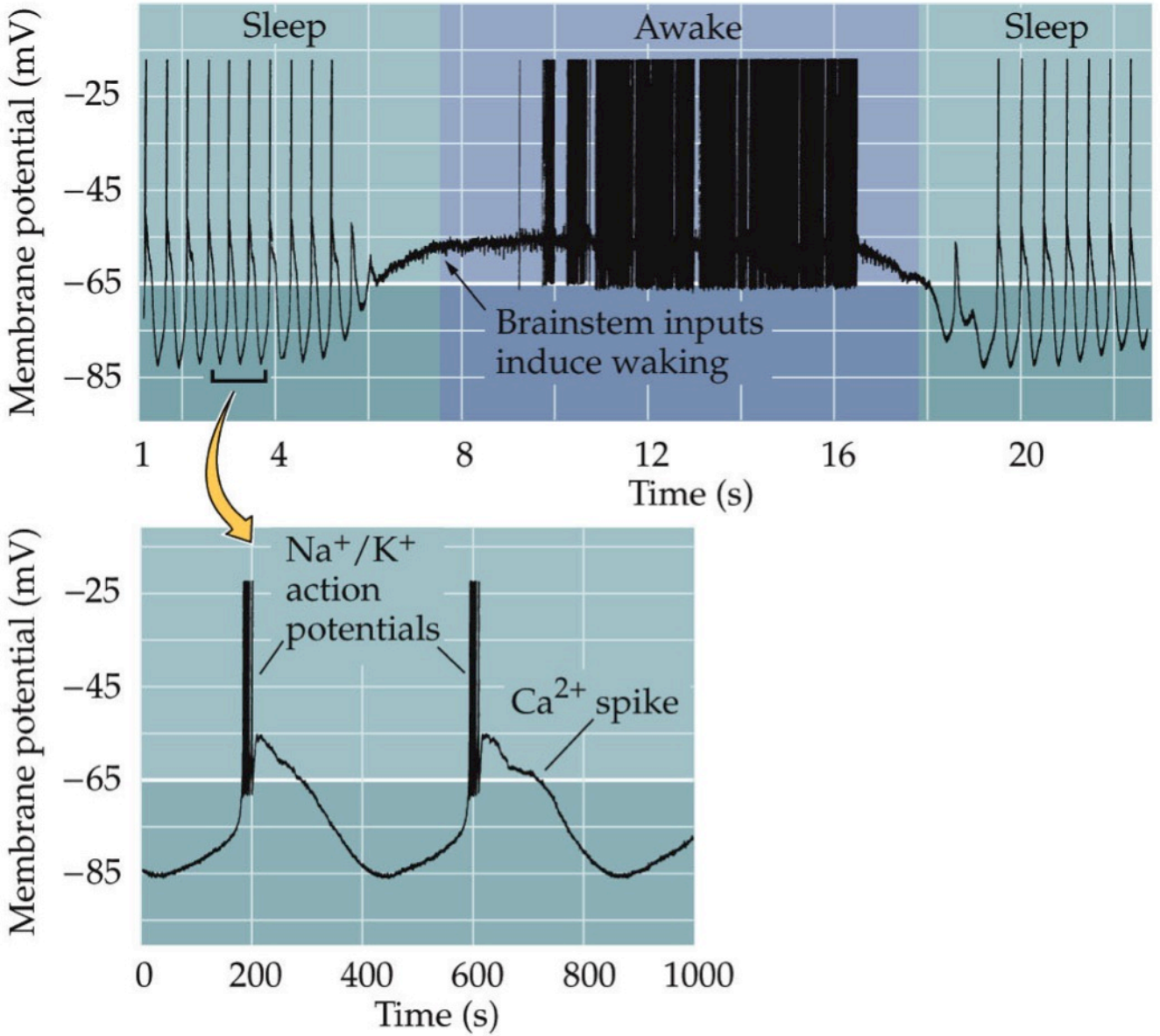
Hypothalamus

Thalamus Sensory “gate” to cortex

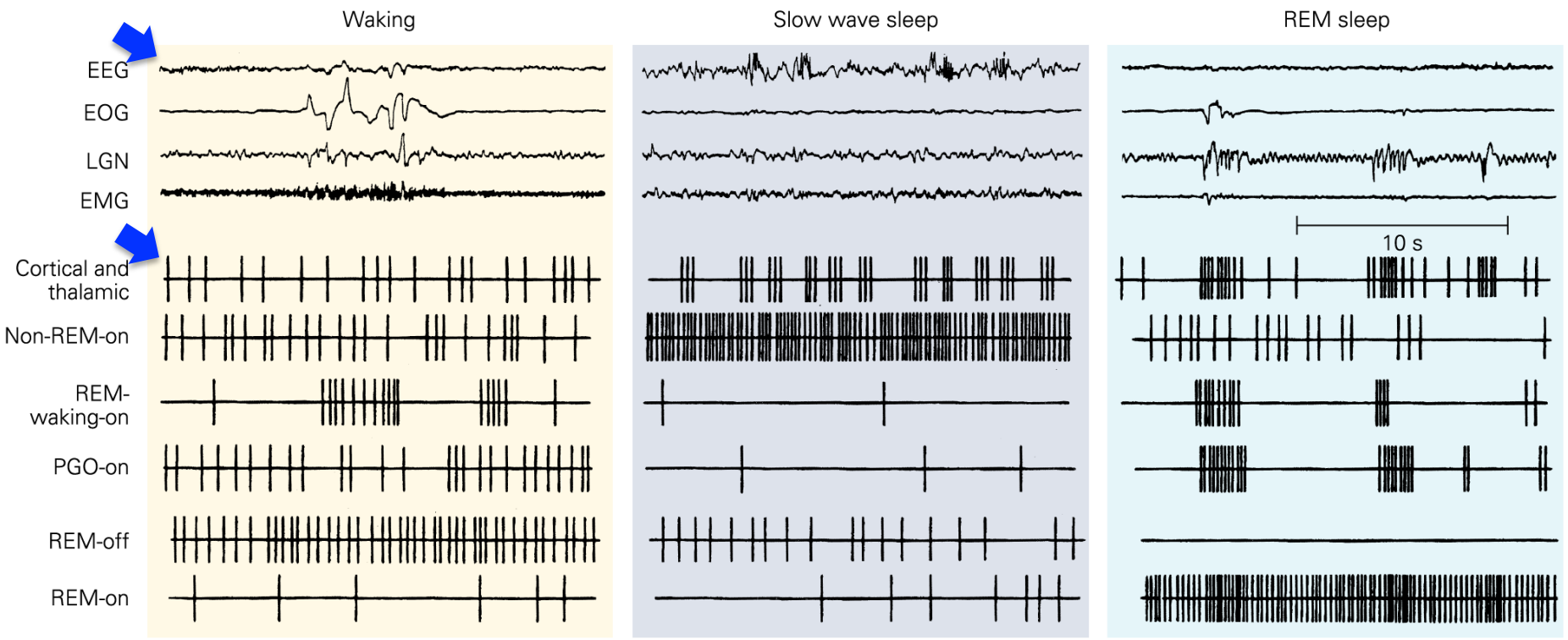


Sleep is an *uncoupling* of cortex from sensory inputs

Thalamic neurons can fire in 2 modes:

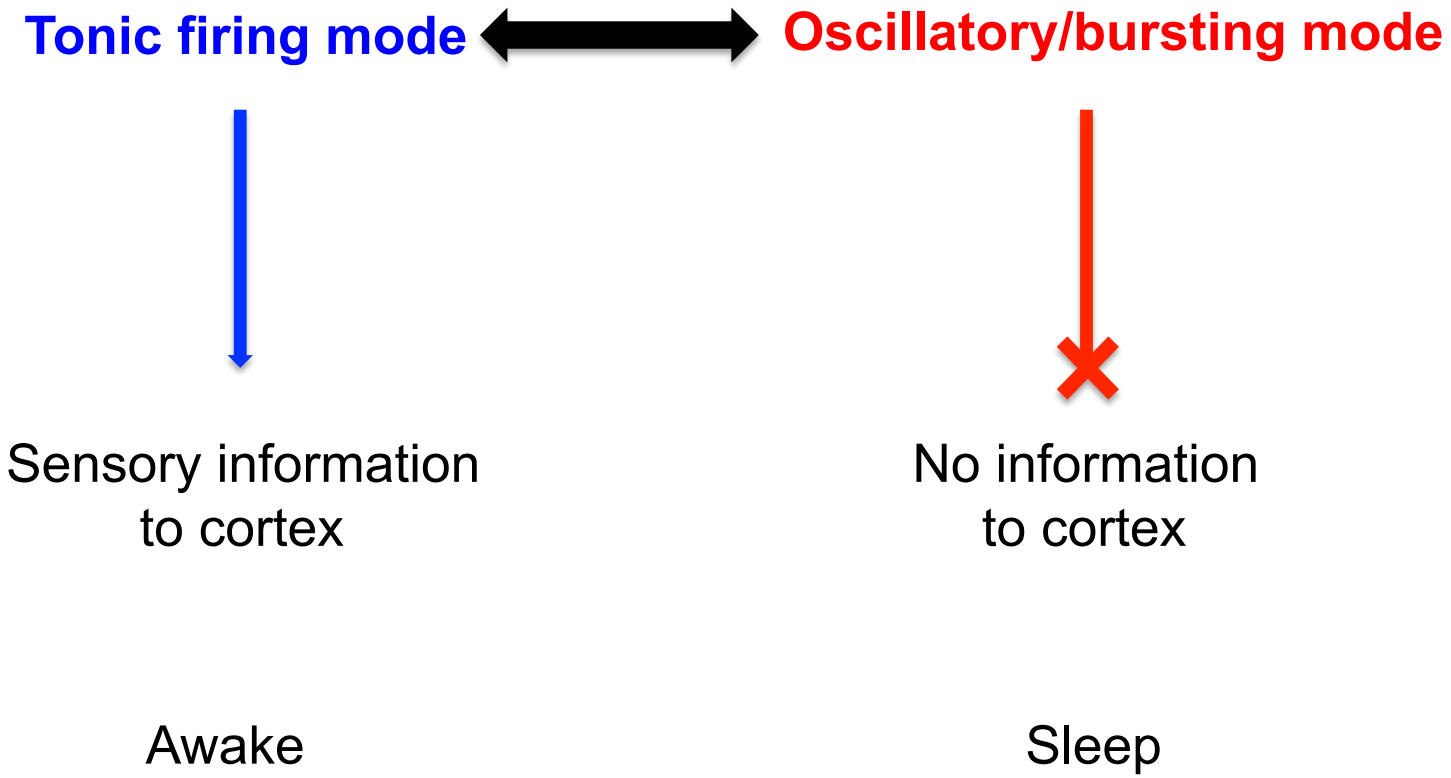


Sleep is an *uncoupling* of cortex from sensory inputs

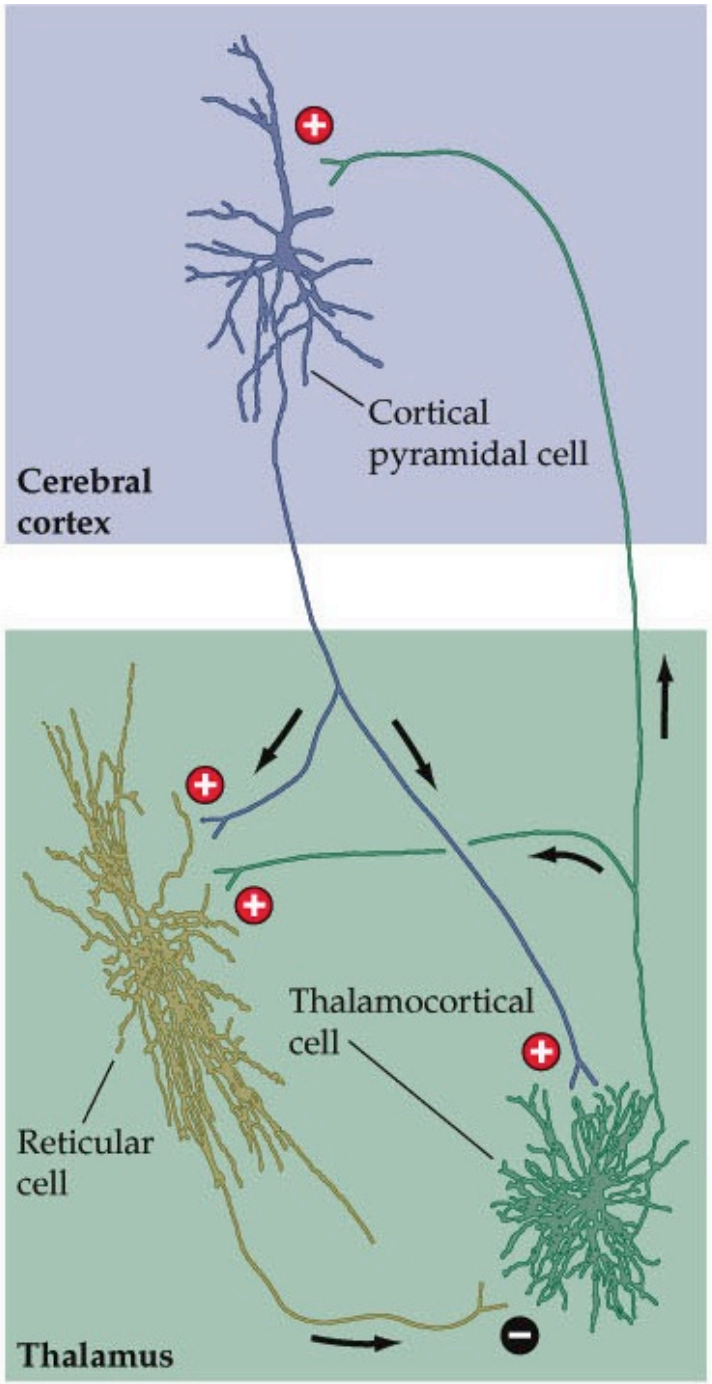


Sleep is an *uncoupling* of cortex from sensory inputs

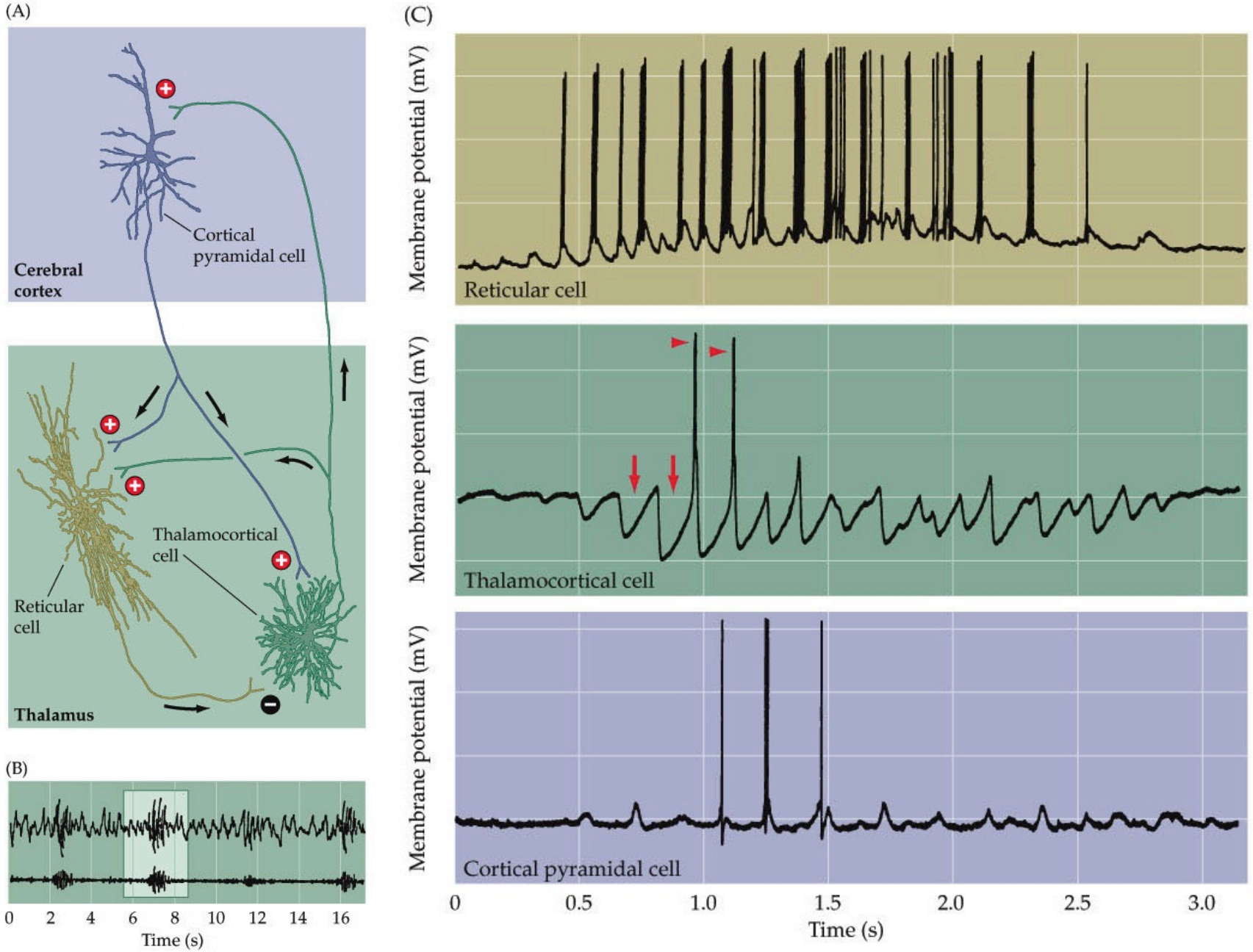
Thalamic neurons can fire in 2 modes:

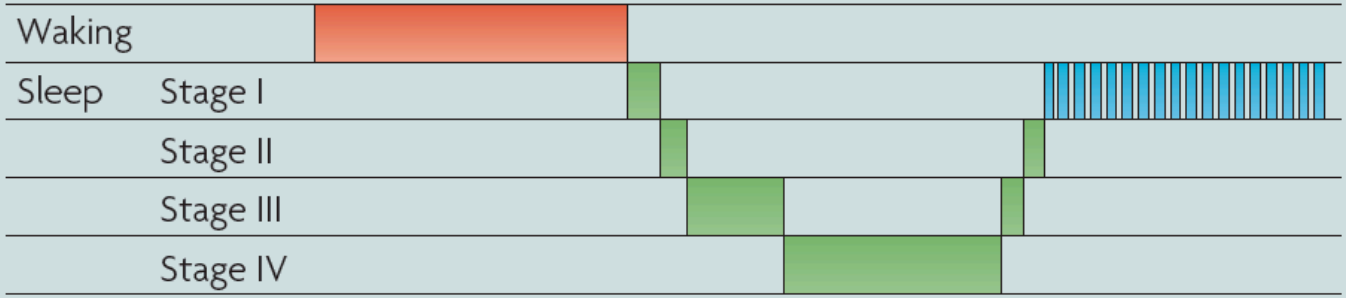
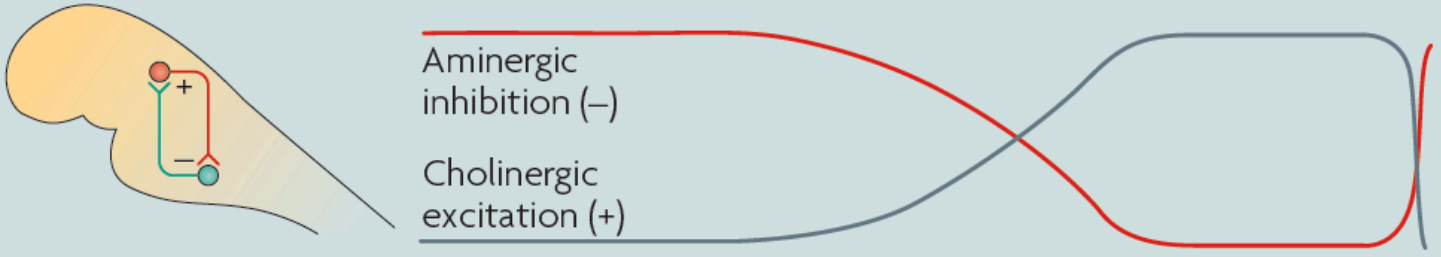


‘falling’ asleep



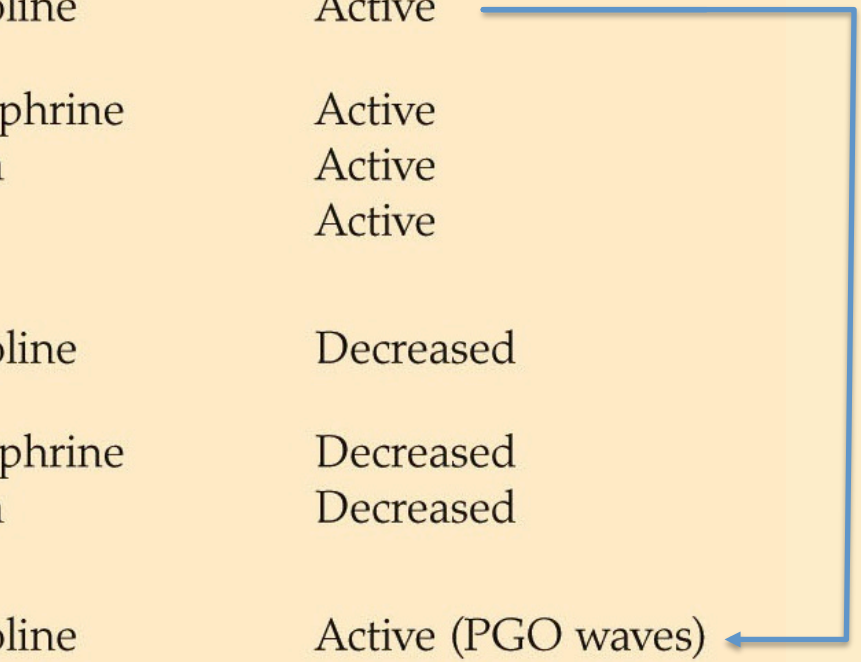
Sleep spindles are an indication of this uncoupling

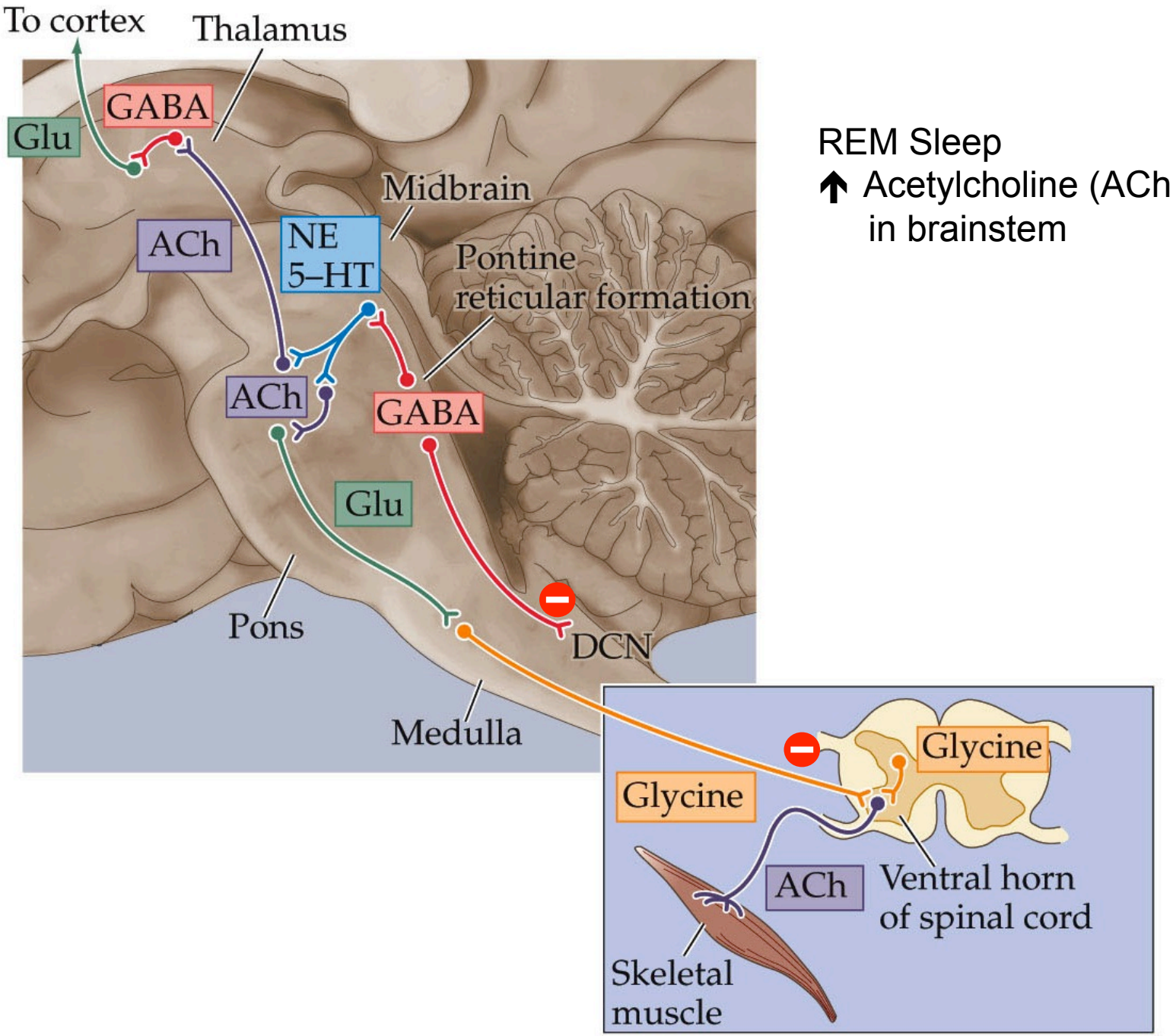


State	Waking	NREM sleep	REM sleep
Behaviour			
Polygraph			
Sensation and perception	Vivid, externally generated	Dull or absent	Vivid, internally generated
Thought	Logical and progressive	Logical and perseverative	Non-logical and bizzare
Movement	Continuous and voluntary	Episodic and involuntary	Commanded but inhibited
Neuronal model			

Hobson, 2009

Brainstem nuclei responsible	Neurotransmitter involved	Activity state of the relevant brainstem neurons
Wakefulness		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active
Locus coeruleus	Norepinephrine	Active
Raphe nuclei	Serotonin	Active
Tuberomammillary nuclei	Orexin	Active
Non-REM sleep		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Decreased
Locus coeruleus	Norepinephrine	Decreased
Raphe nuclei	Serotonin	Decreased
REM sleep on		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active (PGO waves)
Raphe nuclei	Serotonin	Inactive
REM sleep off		
Locus coeruleus	Norepinephrine	Active

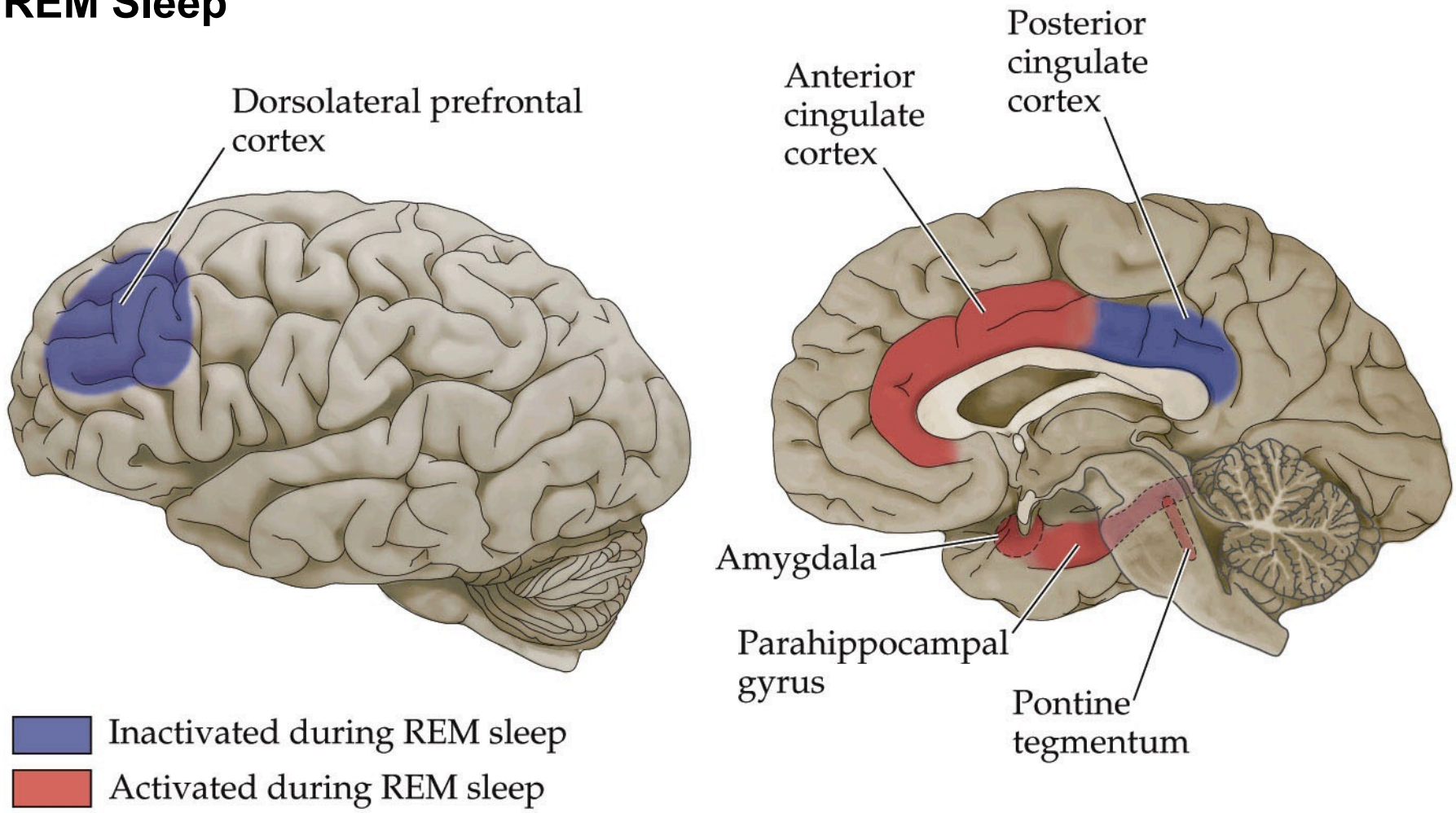




REM Sleep

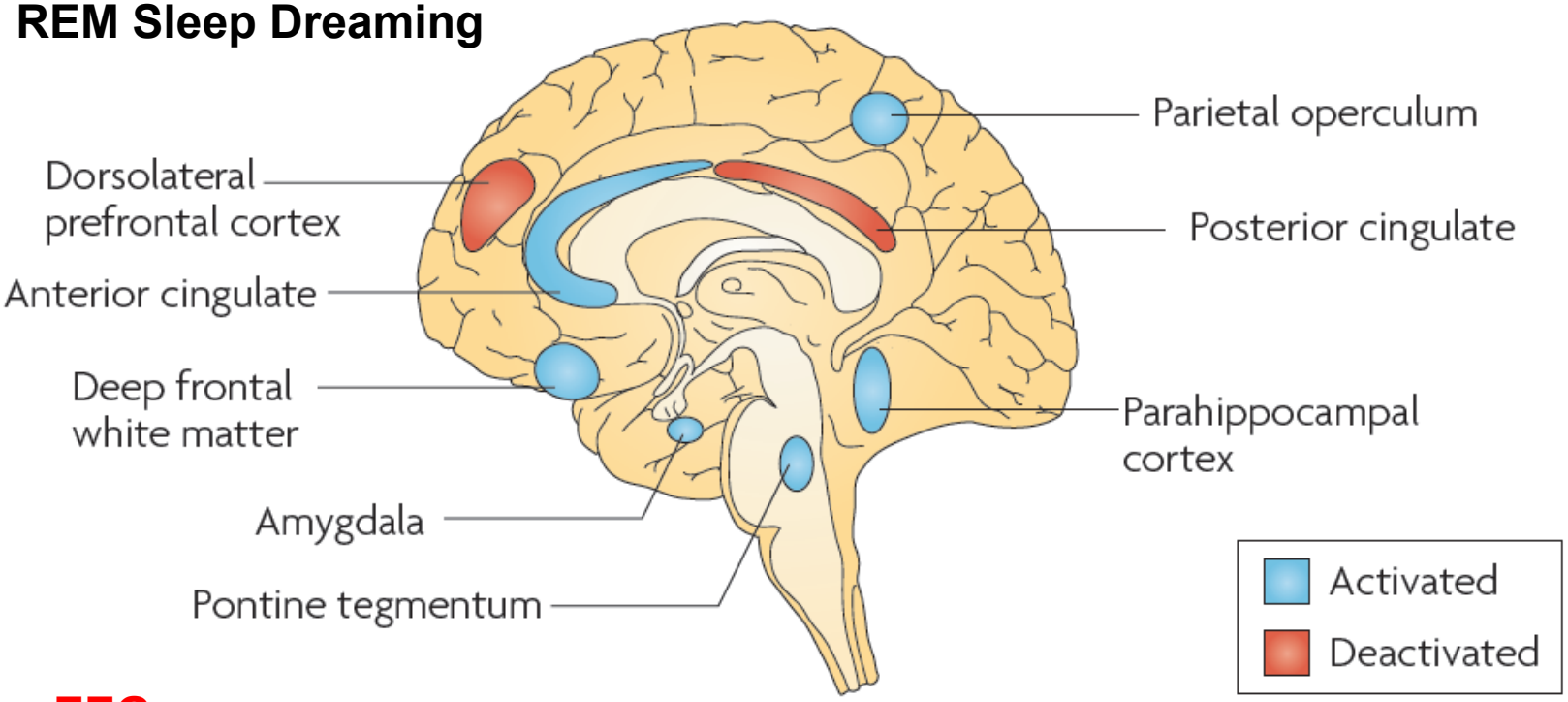
↑ Acetylcholine (ACh) in brainstem

REM Sleep

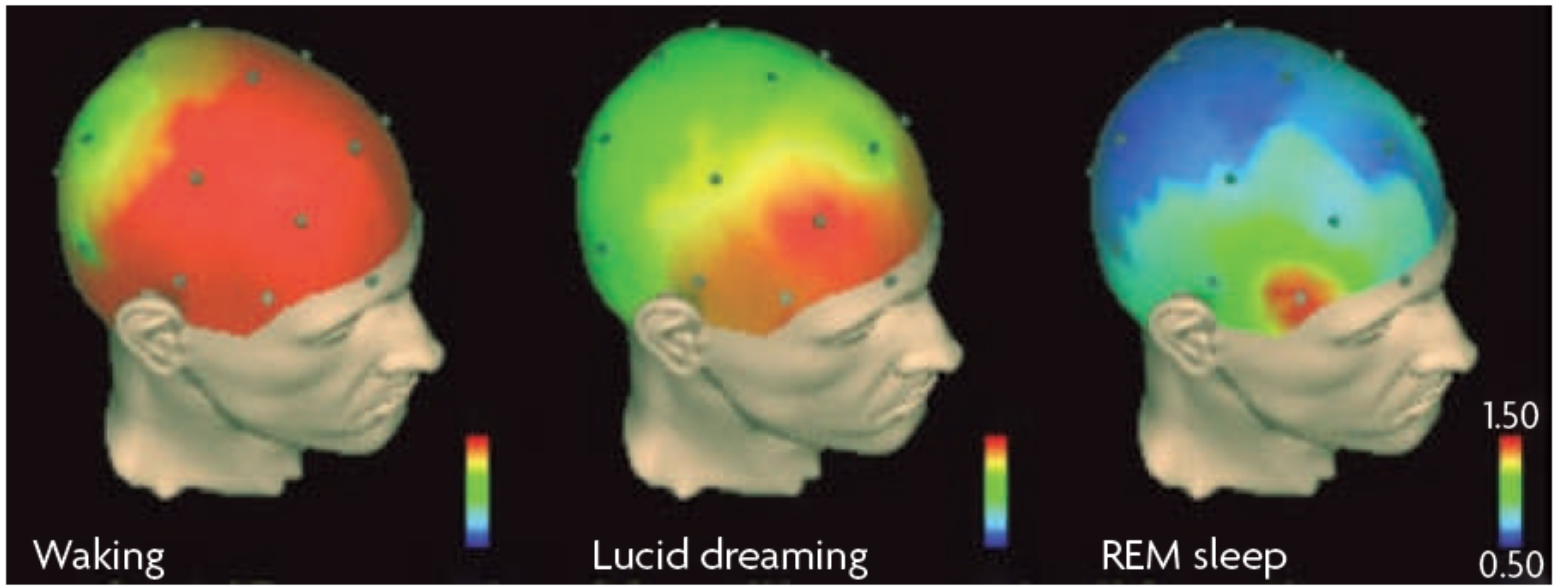


REM dreams = emotional, inappropriate social content
Late stage dreams = lucid, logical

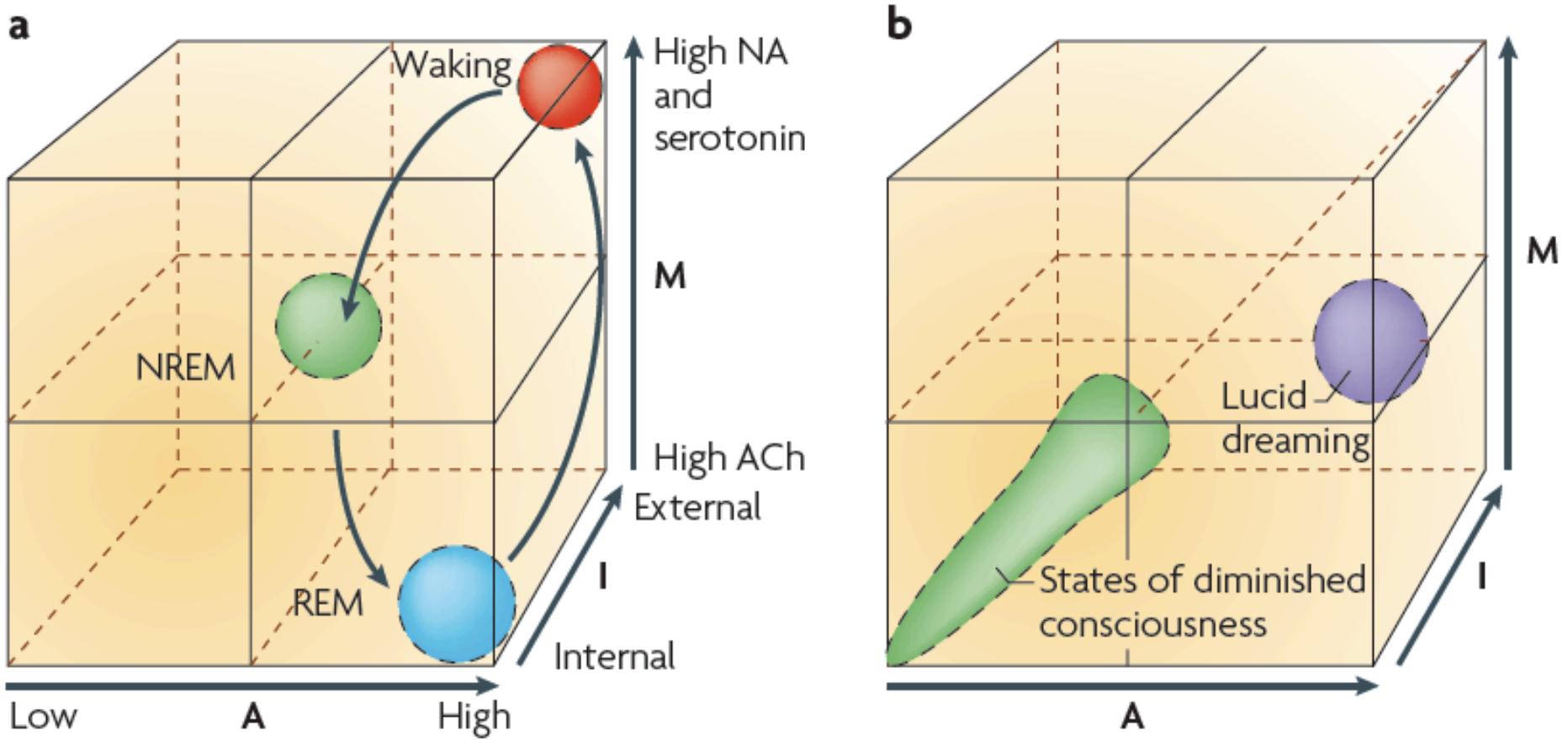
a **REM Sleep Dreaming**



b **EEG**



Hobson, 2009



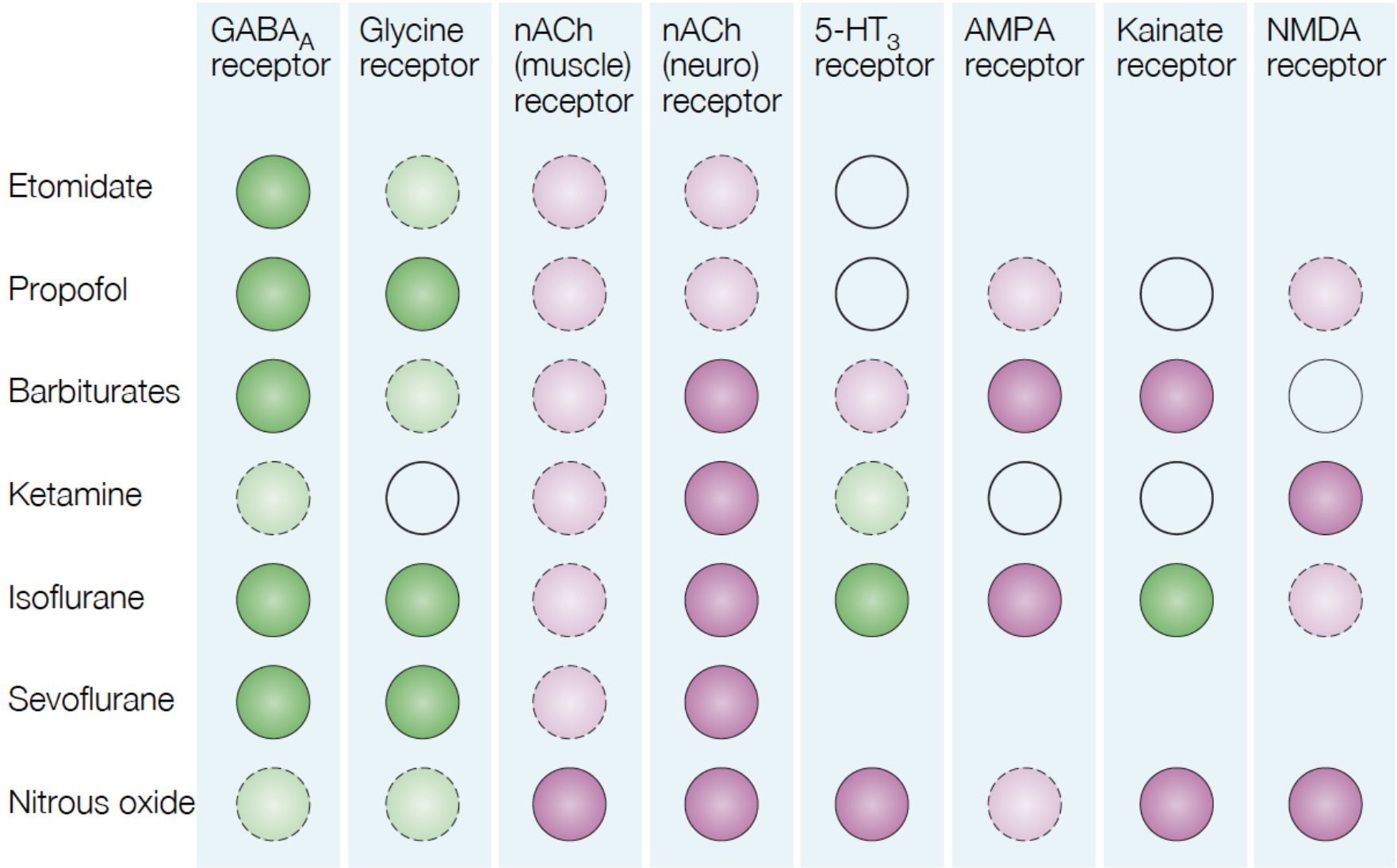
A neural activation

I input-output gating (thalamus)

M modulation (acetylcholine vs. norepinephrine/serotonin)

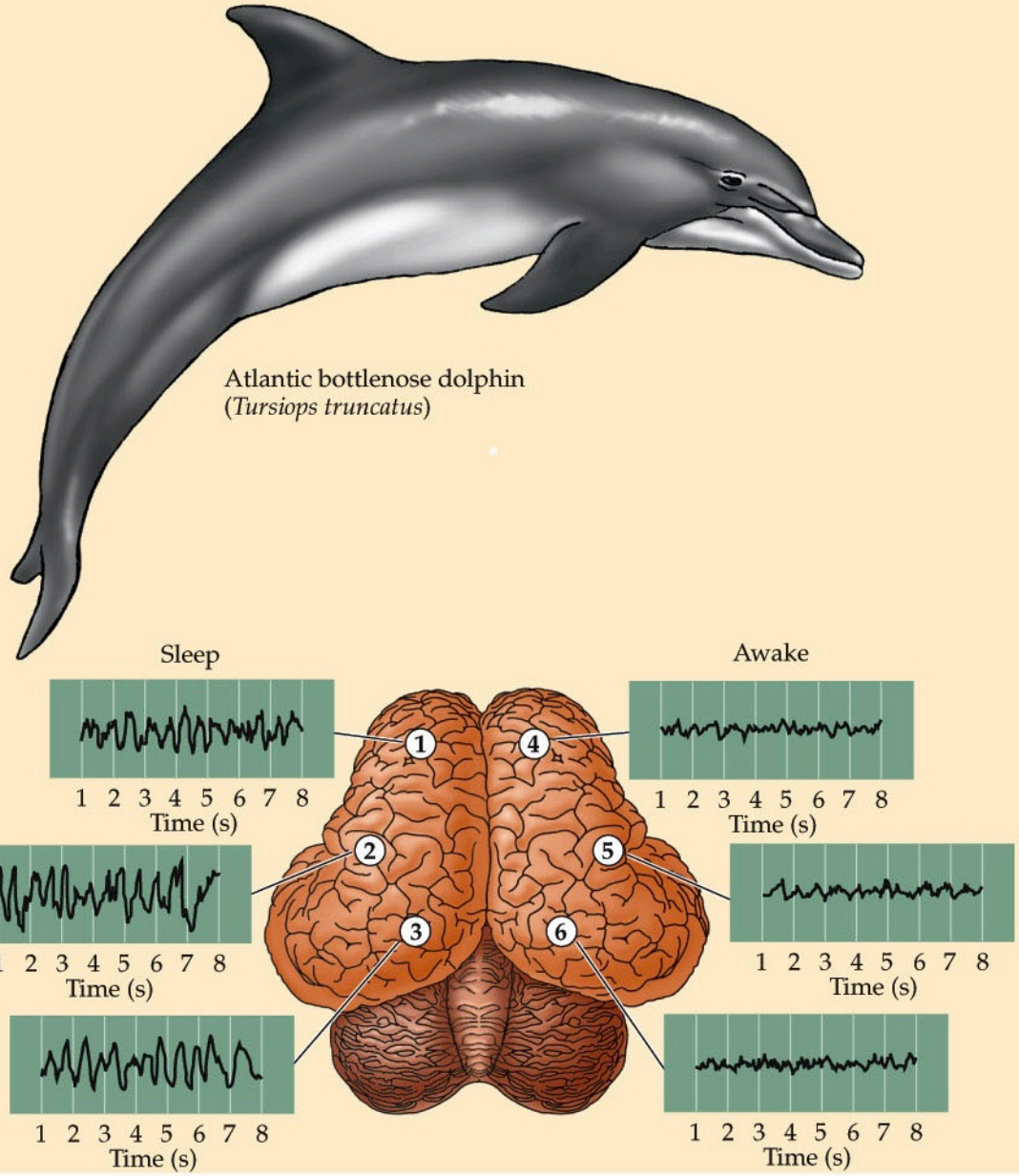
Hobson, 2009

General Anesthesia is *not* sleep



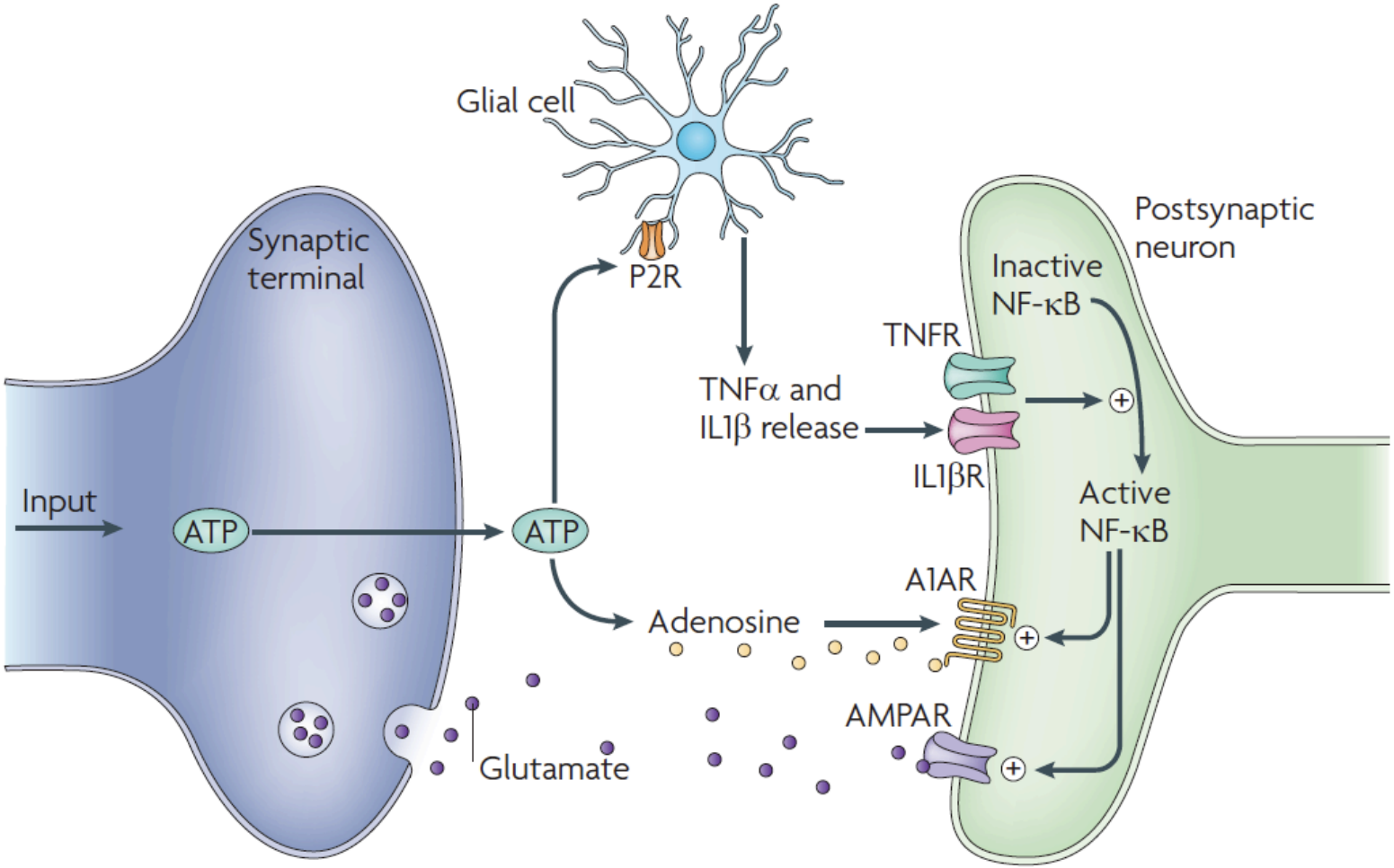
Green = agonist
Purple = antagonist

Unilateral Sleep



Local Sleep

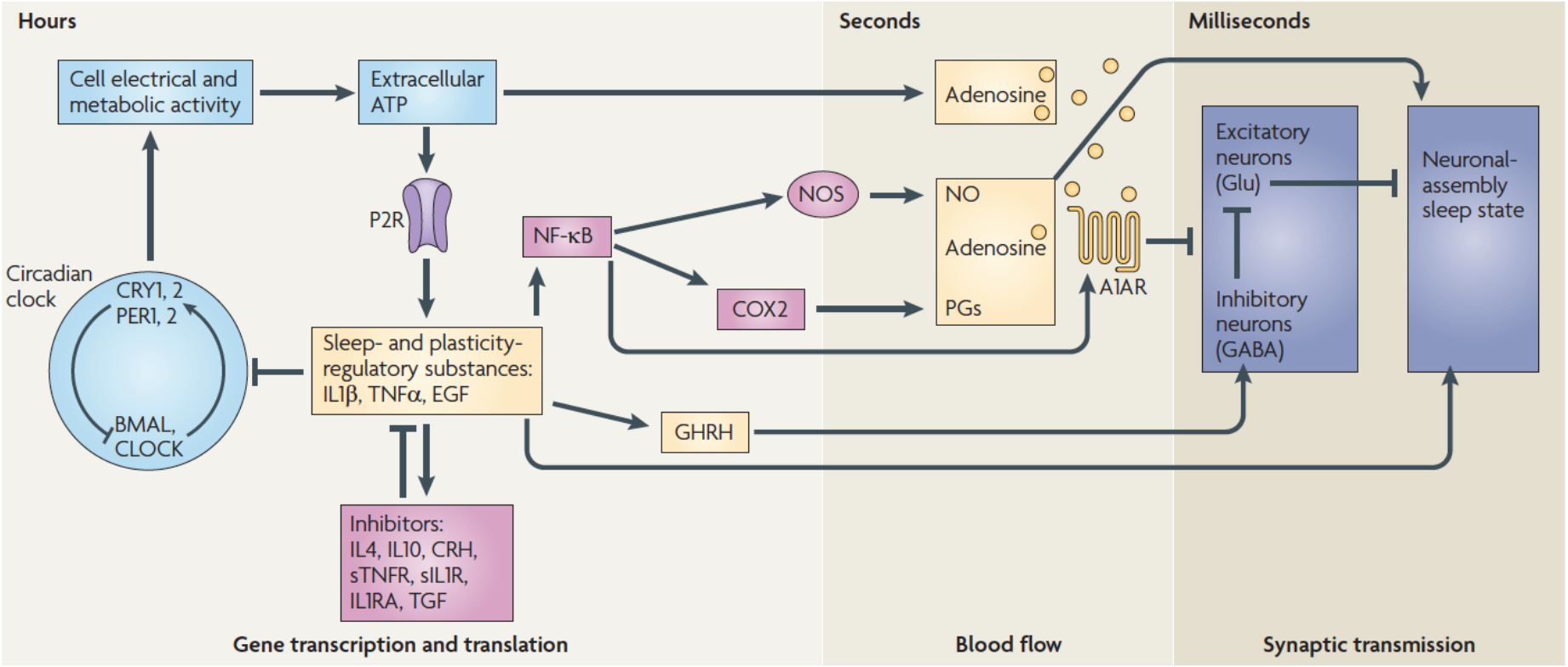
Can *neurons* or groups of neurons sleep without the rest of the brain?



Sleep is dependent on past neural activity

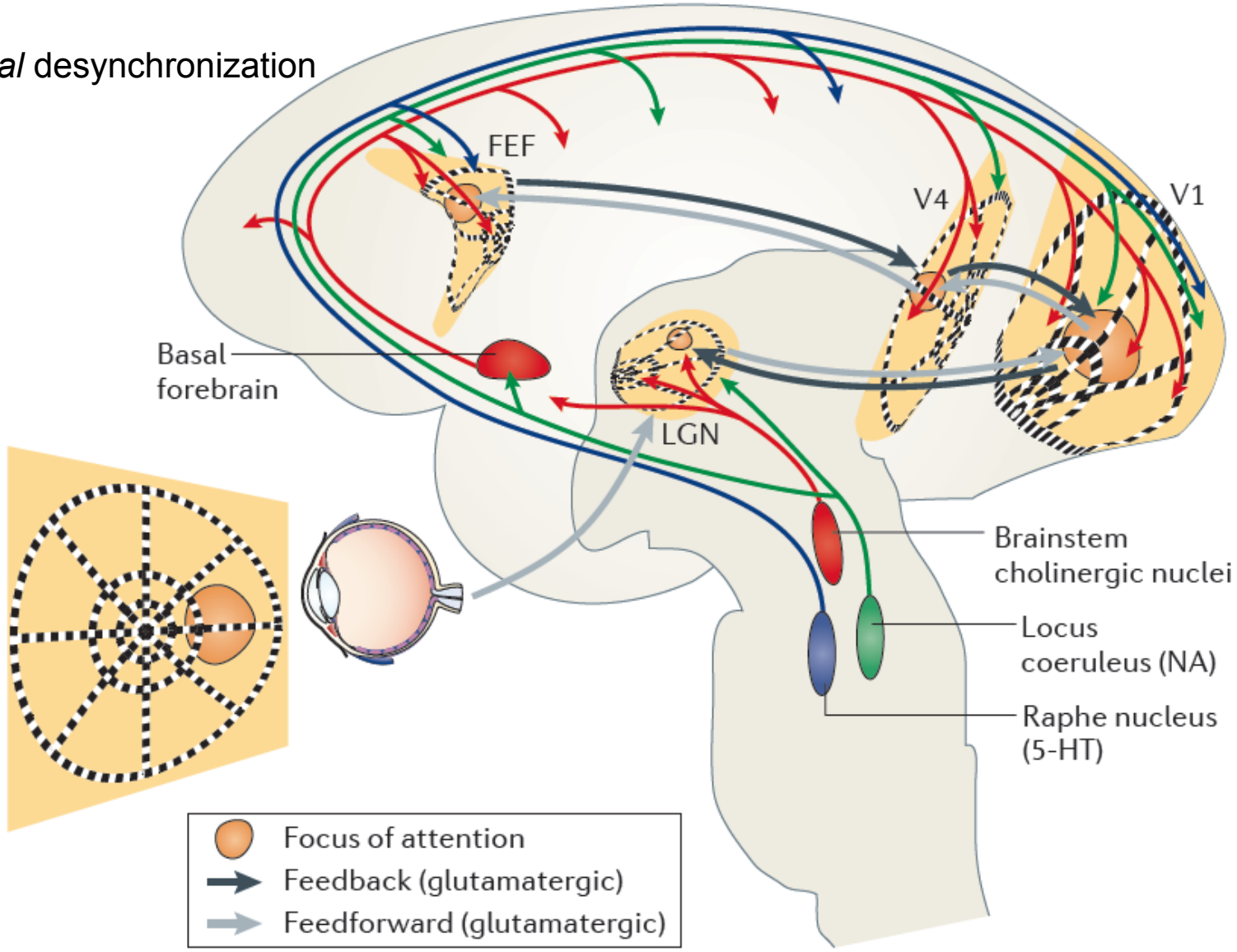
Can *neurons* or groups of neurons sleep without the rest of the brain?

sleep molecules interact with the immune system



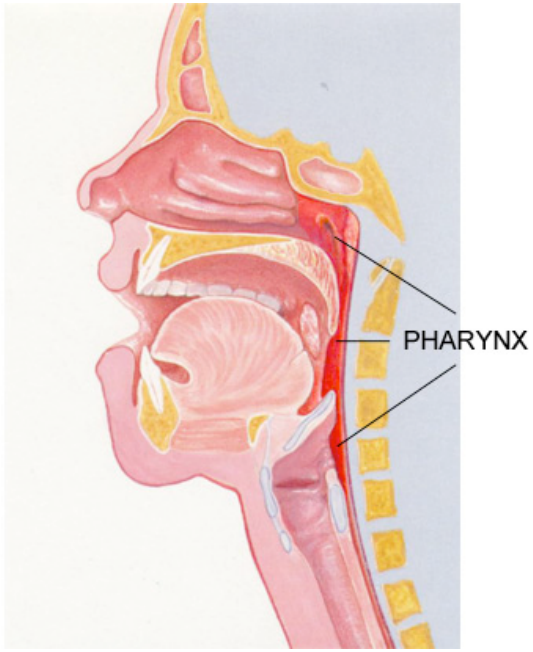
Can *neurons* or groups of neurons be ‘more awake’ than the rest of the brain?

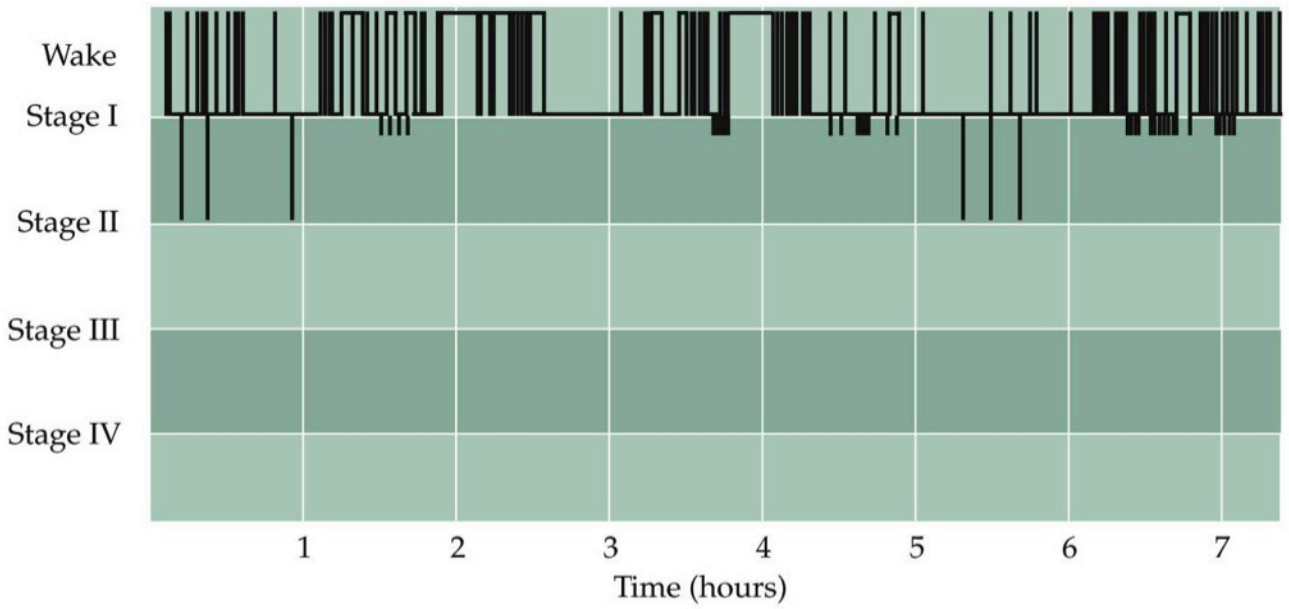
attention is a *local* desynchronization



Harris & Thiele, 2011

Sleep Apnea


PHARYNX


Wake
Stage I
Stage II
Stage III
Stage IV
1
2
3
4
5
6
7
Time (hours)

Narcolepsy

auto-immune response against neurons that produce **orexin**

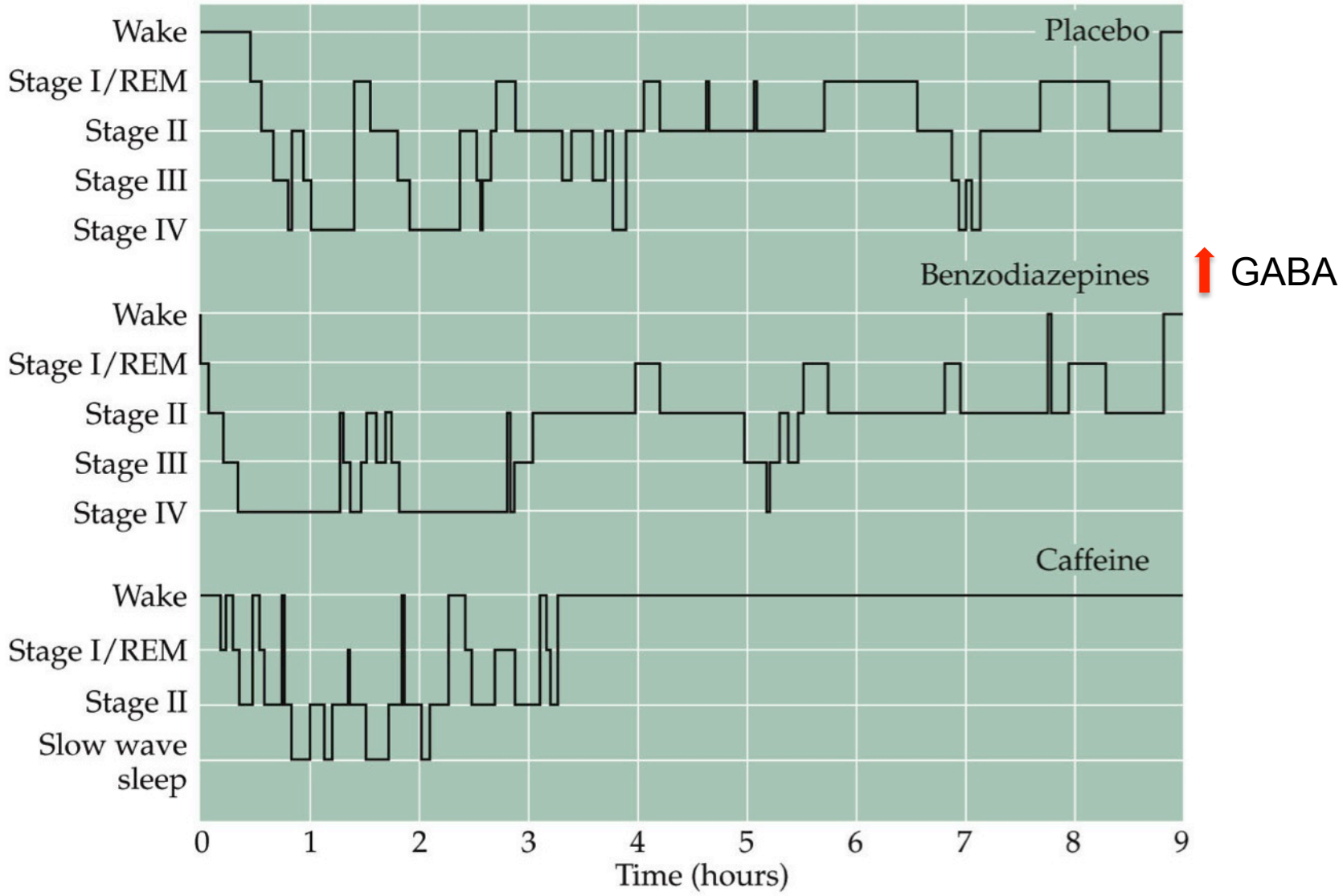
- cataplexy
- sleep paralysis
- hypnagogic hallucinations
- excessive daytime sleepiness

Fatal Familial Insomnia

PRNP gene mutation → prion protein

(similar to Creutzfeldt-Jakob disease)

Drugs and Sleep



Drugs and Sleep drugs that promote sleep

barbiturates (-barbital)
benzodiazepines (-pam)

zolpidem (Ambien)
zaleplon (Sonata)
eszopiclone (Lunesta)

GABA receptor agonists

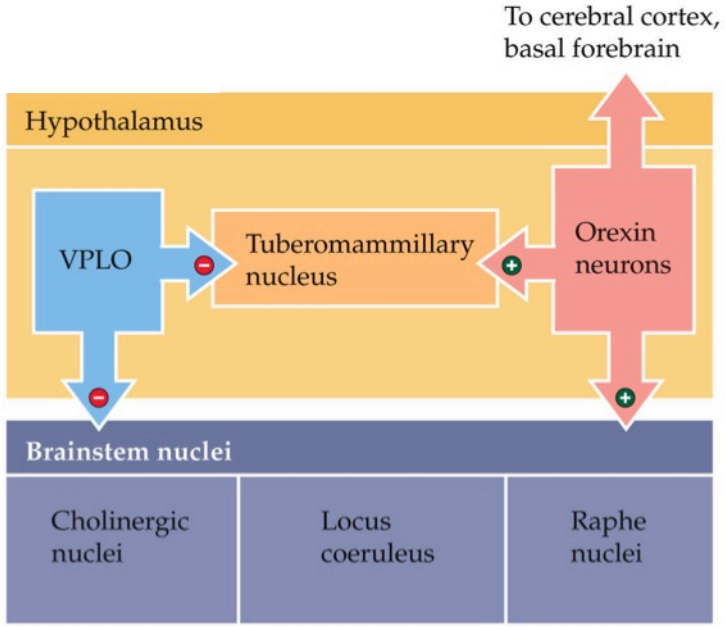
- amnesia
- fugue states
- hallucinations

Drugs and Sleep drugs that promote wakefulness

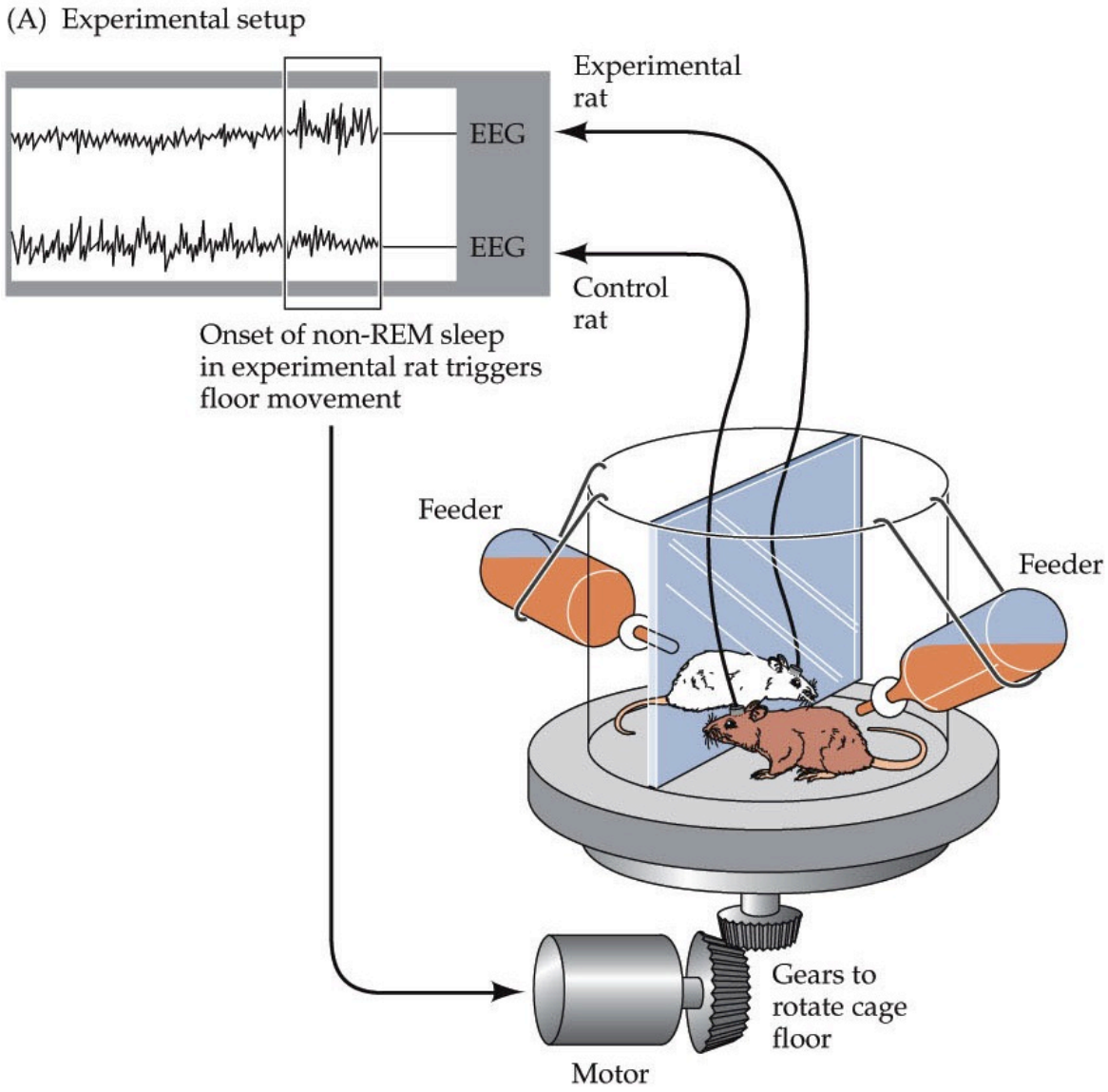
modafinil (Provigil) ⬆ norepinephrine
⬆ histamine (via hypothalamus)

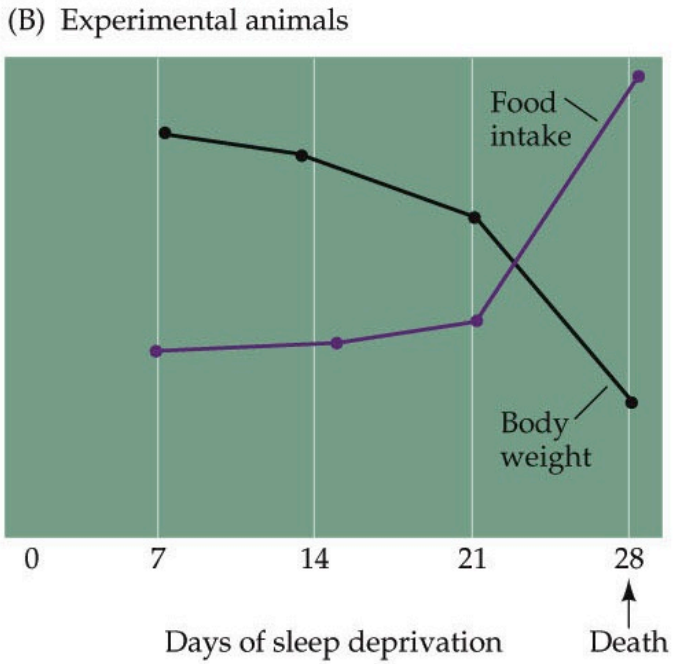
orexin A (nasal spray)

development funded by DARPA
reverses negative cognitive functions of sleep loss



Do we really need to sleep?





Longest period without sleep: *18 days, 21 hours, 40 mins.
(during a rocking chair marathon)

hallucinations
paranoia
blurred vision
slurred speech
memory/concentration lapses

Slept longer than usual afterward, but no other consequences

*official Guiness record is 264 hours (~11 days)

Why sleep?

Theory 1: Metabolic Purposes

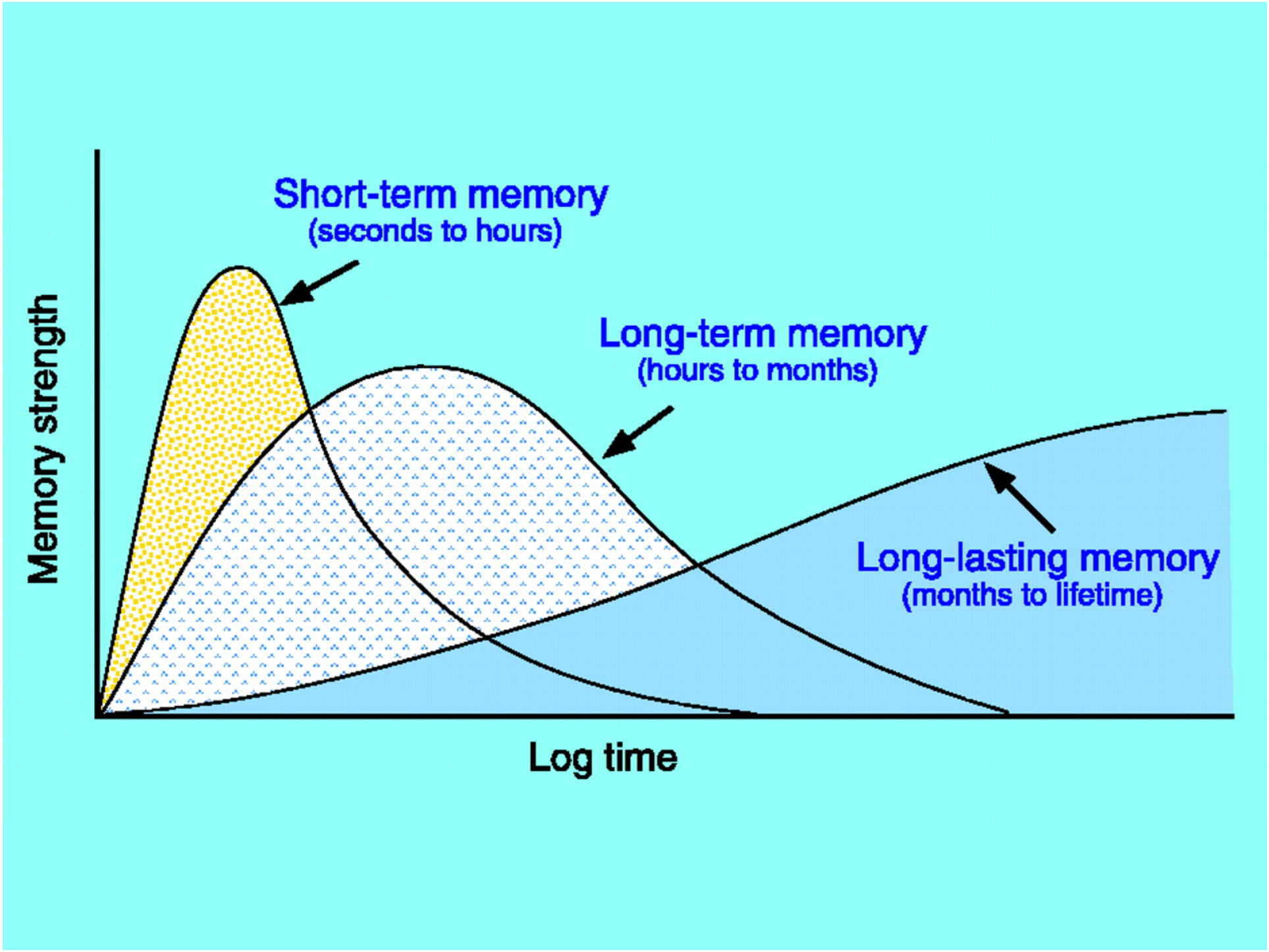
Metabolic Purpose of Sleep

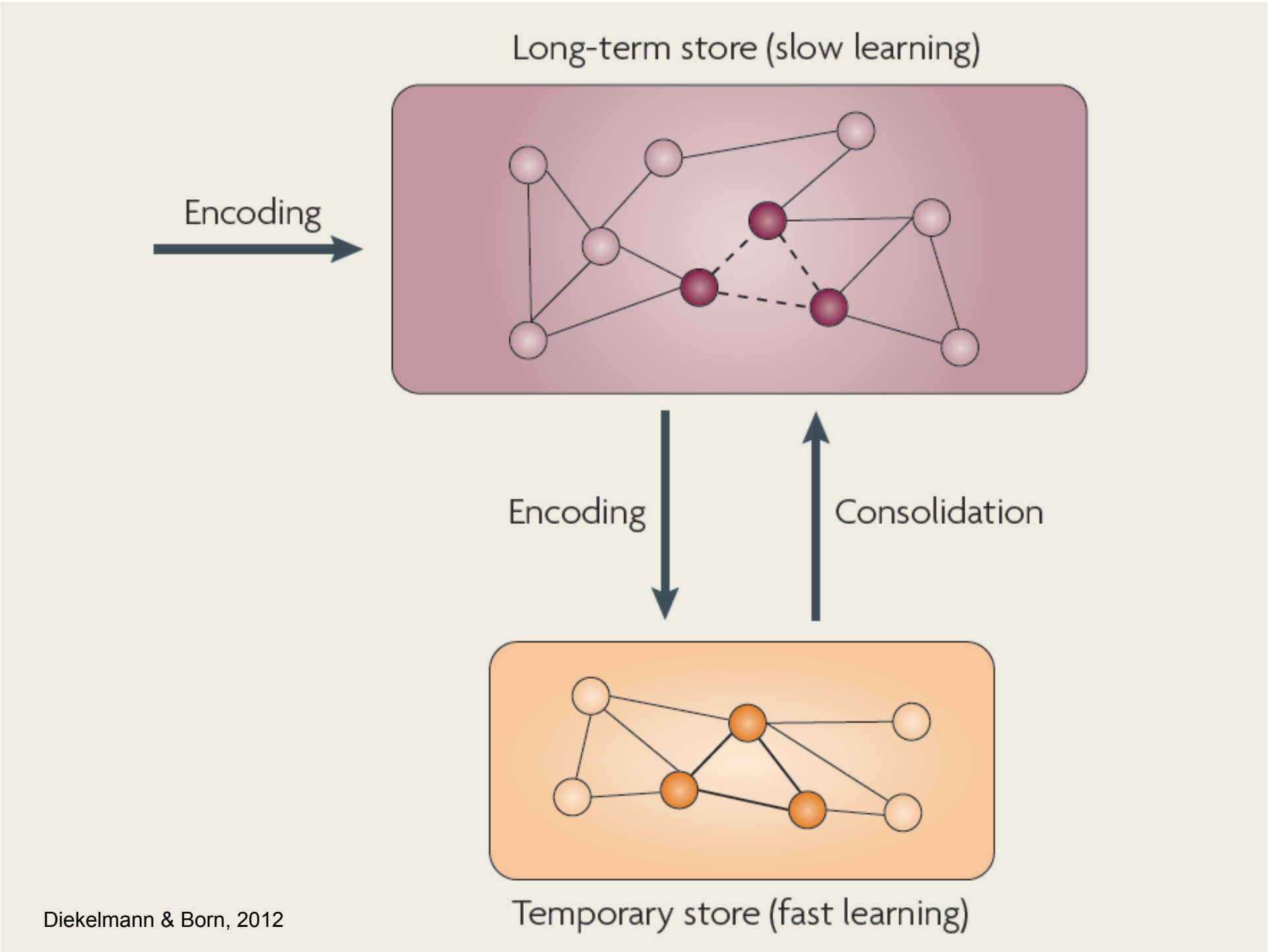
- Restore body and brain glycogen levels
- Reduce heat loss (body temperature falls during night)
- Oxygen consumption decreases during sleep

⬇ Metabolic rate (save energy)

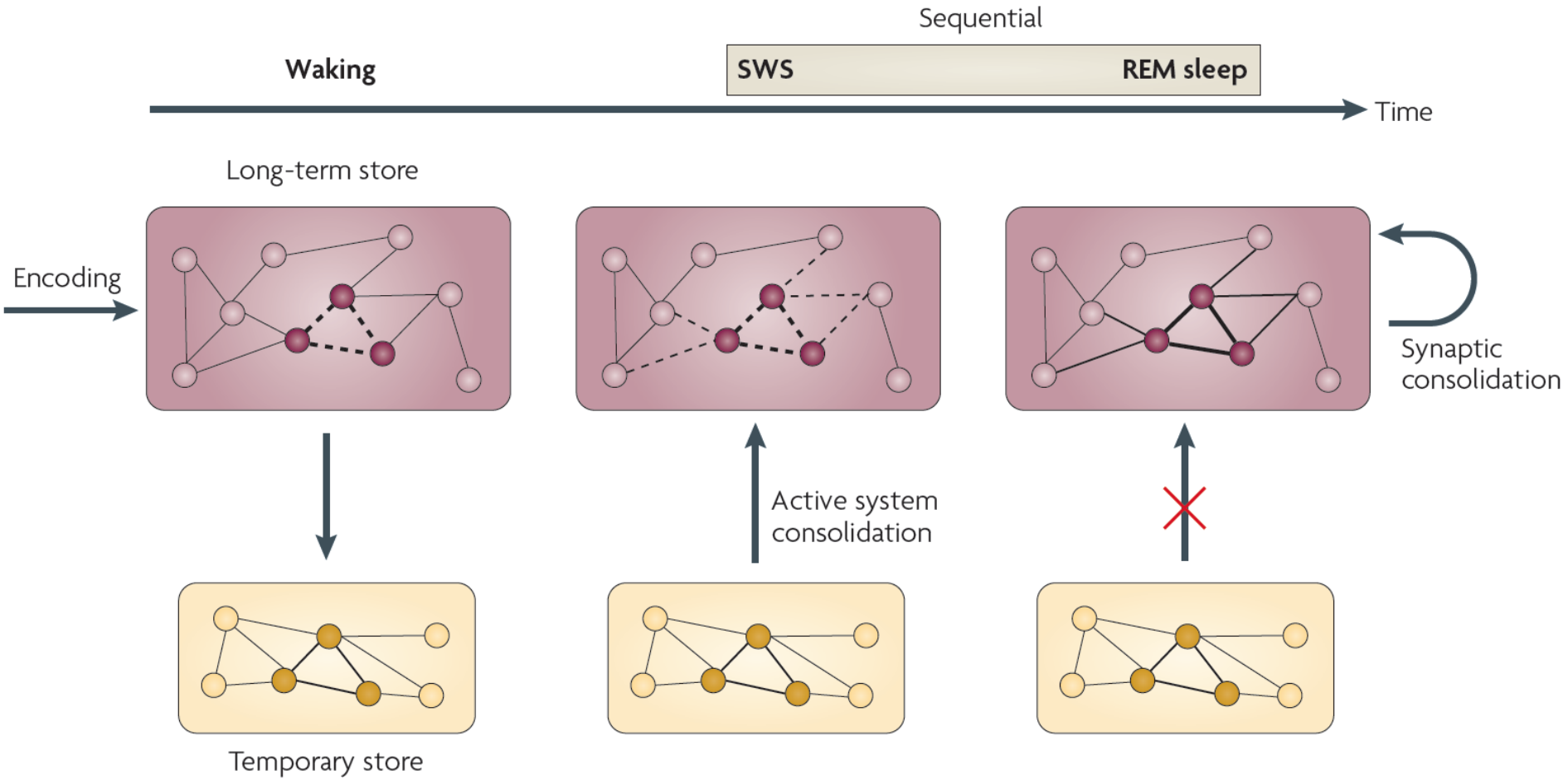
Why sleep?

Theory 2: Memory consolidation


Short-term memory
(seconds to hours)
Long-term memory
(hours to months)
Long-lasting memory
(months to lifetime)
Memory strength
Log time



Diekelmann & Born, 2012



Diekelmann & Born, 2012

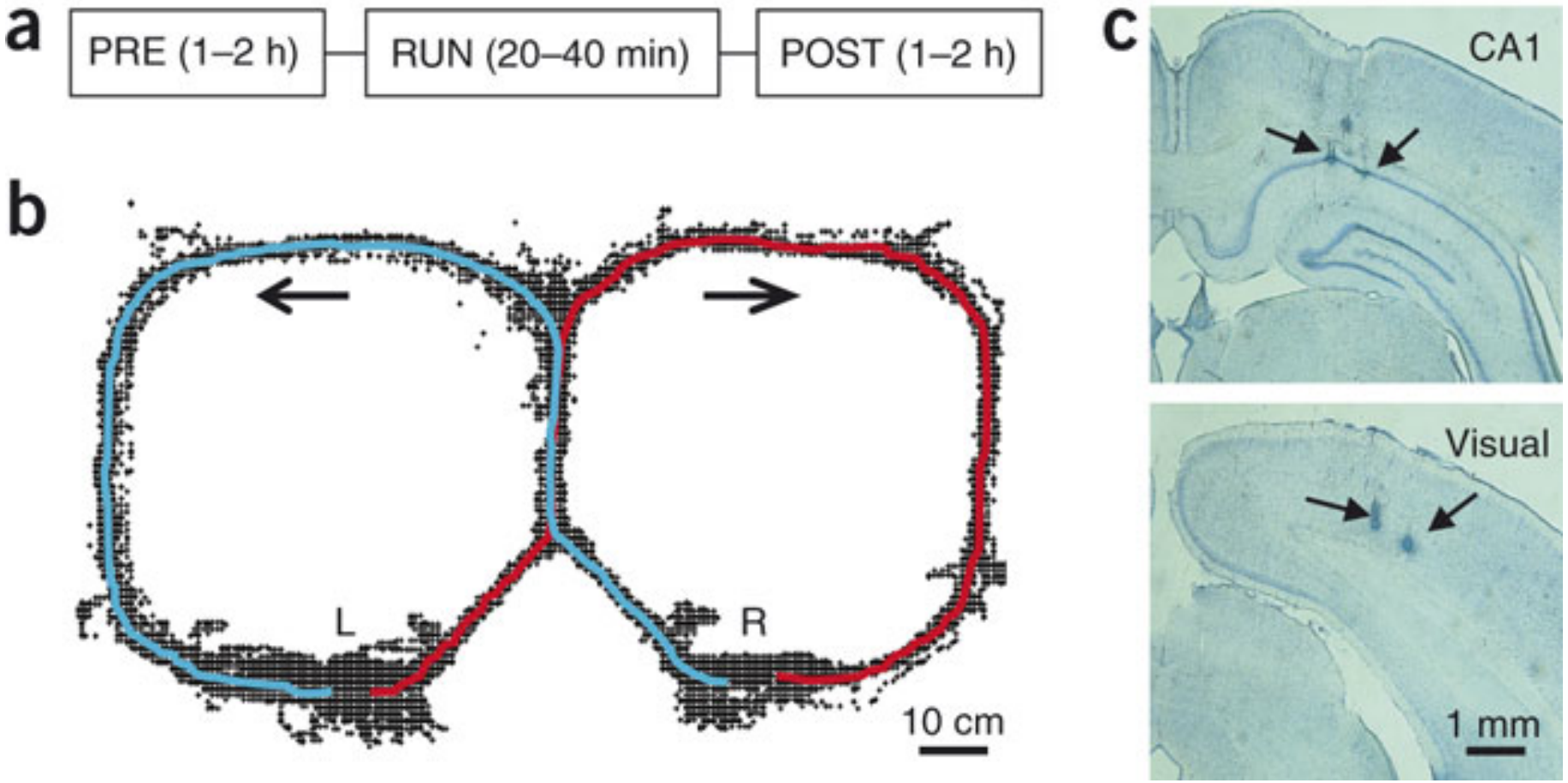
nature neuroscience

Coordinated memory replay in the visual cortex and hippocampus during sleep

Daoyun Ji & Matthew A Wilson

Sleep replay of awake experience in the cortex and hippocampus has been proposed to be involved in memory consolidation. However, whether temporally structured replay occurs in the cortex and whether the replay events in the two areas are related are unknown. Here we studied multicell spiking patterns in both the visual cortex and hippocampus during slow-wave sleep in rats. We found that spiking patterns not only in the cortex but also in the hippocampus were organized into frames, defined as periods of stepwise increase in neuronal population activity. The multicell firing sequences evoked by awake experience were replayed during these frames in both regions. Furthermore, replay events in the sensory cortex and hippocampus were coordinated to reflect the same experience. These results imply simultaneous reactivation of coherent memory traces in the cortex and hippocampus during sleep that may contribute to or reflect the result of the memory consolidation process.

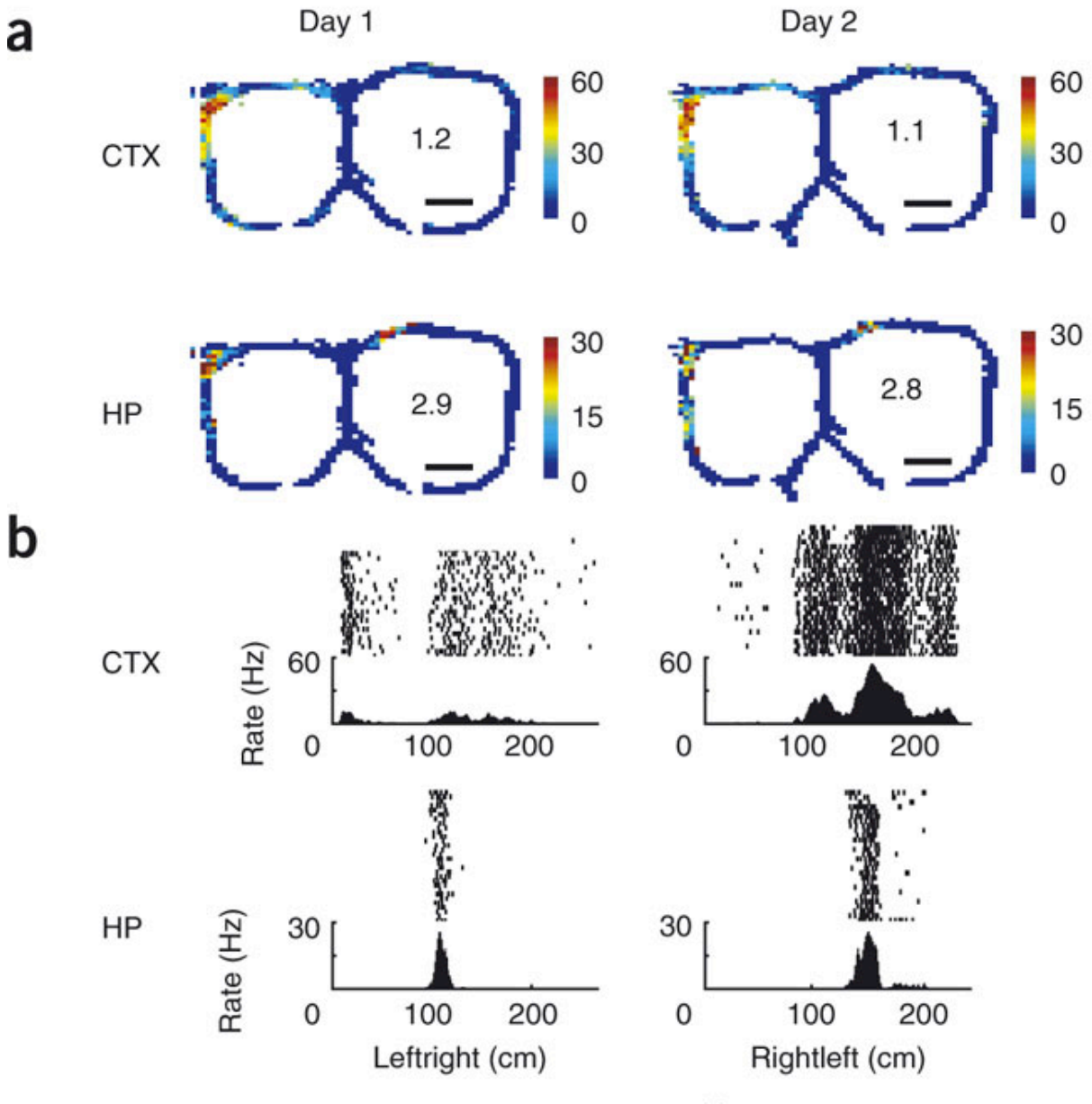
‘Replay’ of experience during sleep



1) Sleep 1 to 2 hours.
2) Run for 20-40 minutes: first left, then right, then left, etc.
3) Sleep again.

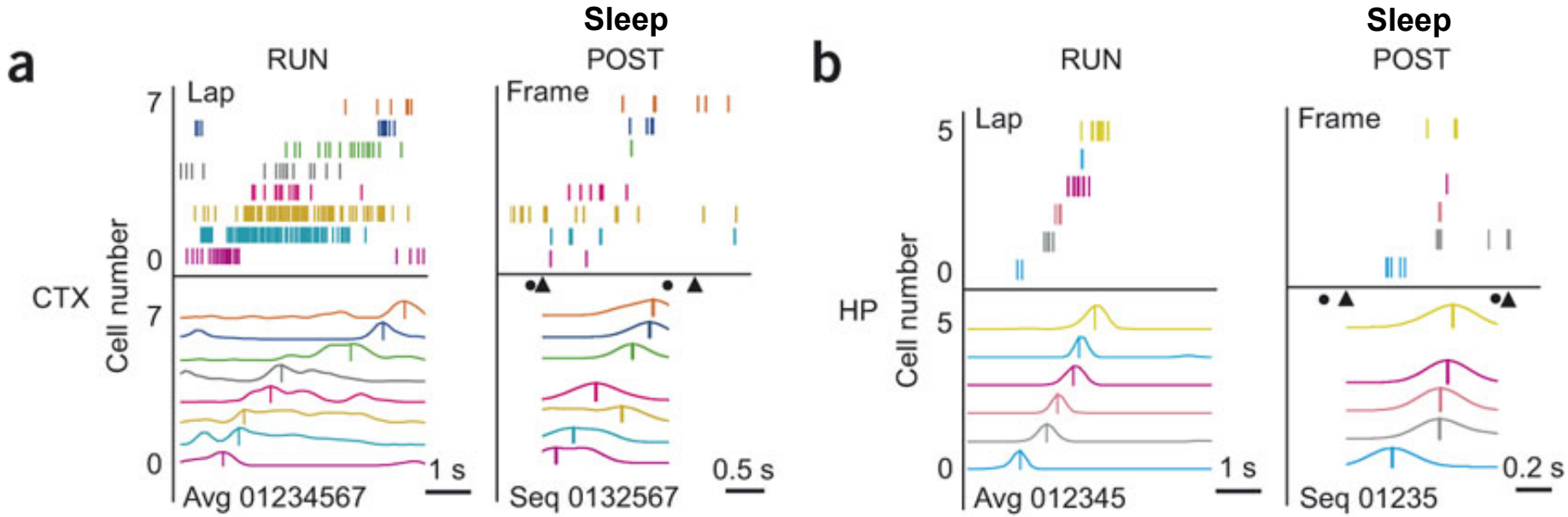
Ji & Wilson, 2007

Implant electrodes to record from the hippocampus and the cortex



Ji & Wilson, 2007

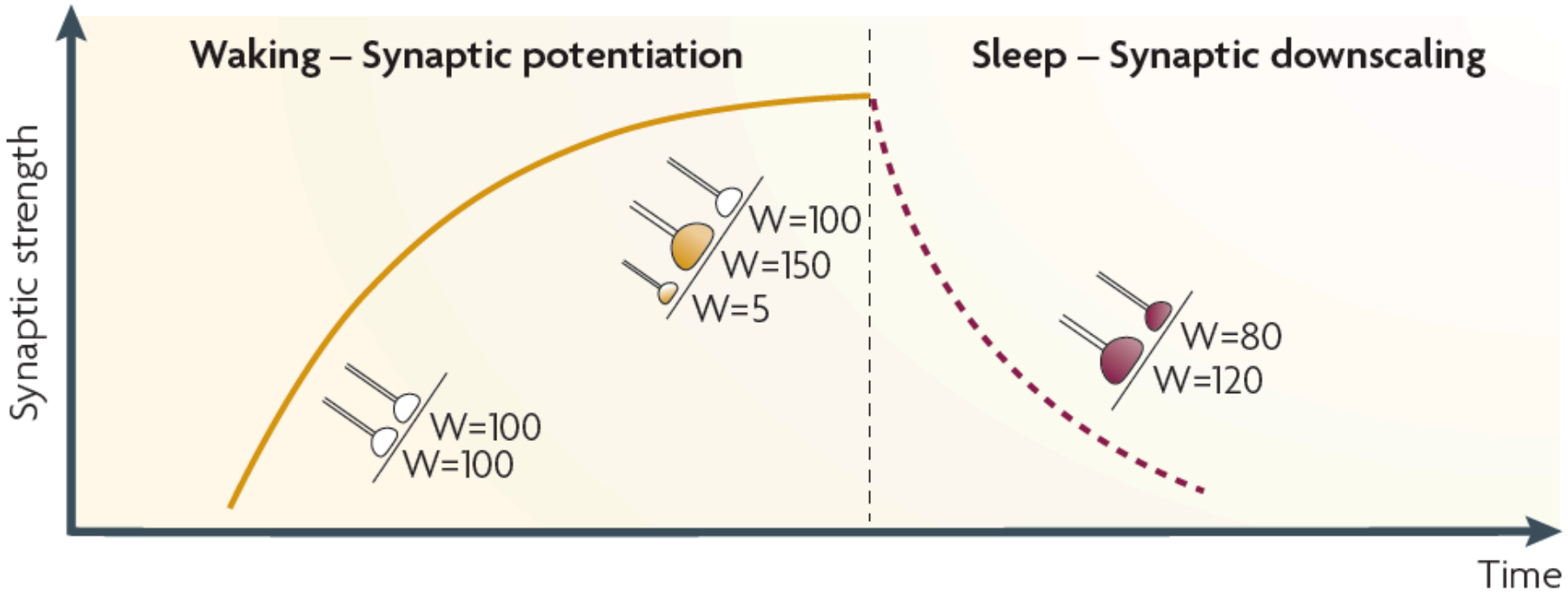
Cells fire in same pattern during running and then during sleep



Ji & Wilson, 2007

Why sleep?

Theory 3: Synaptic Homeostasis

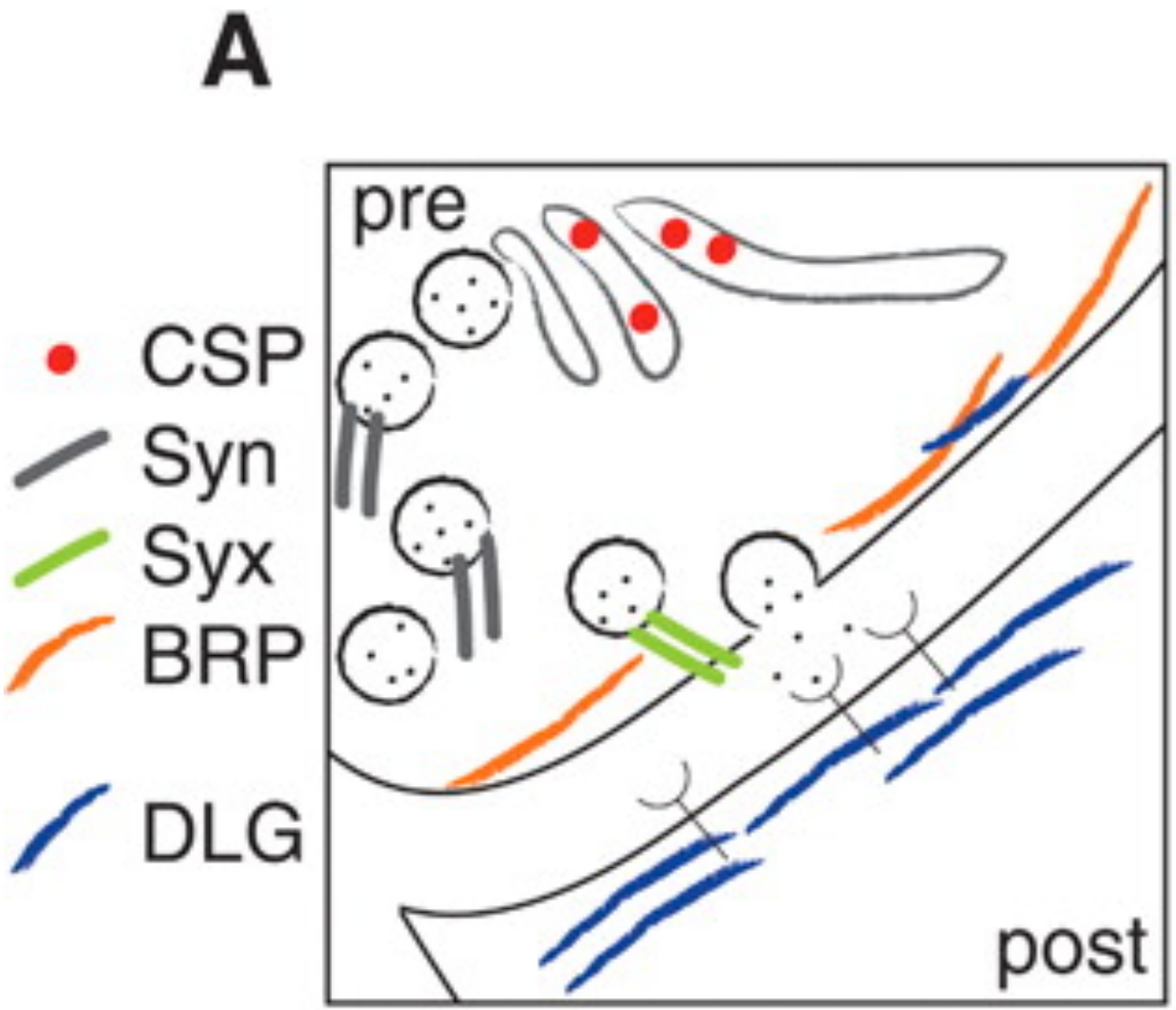


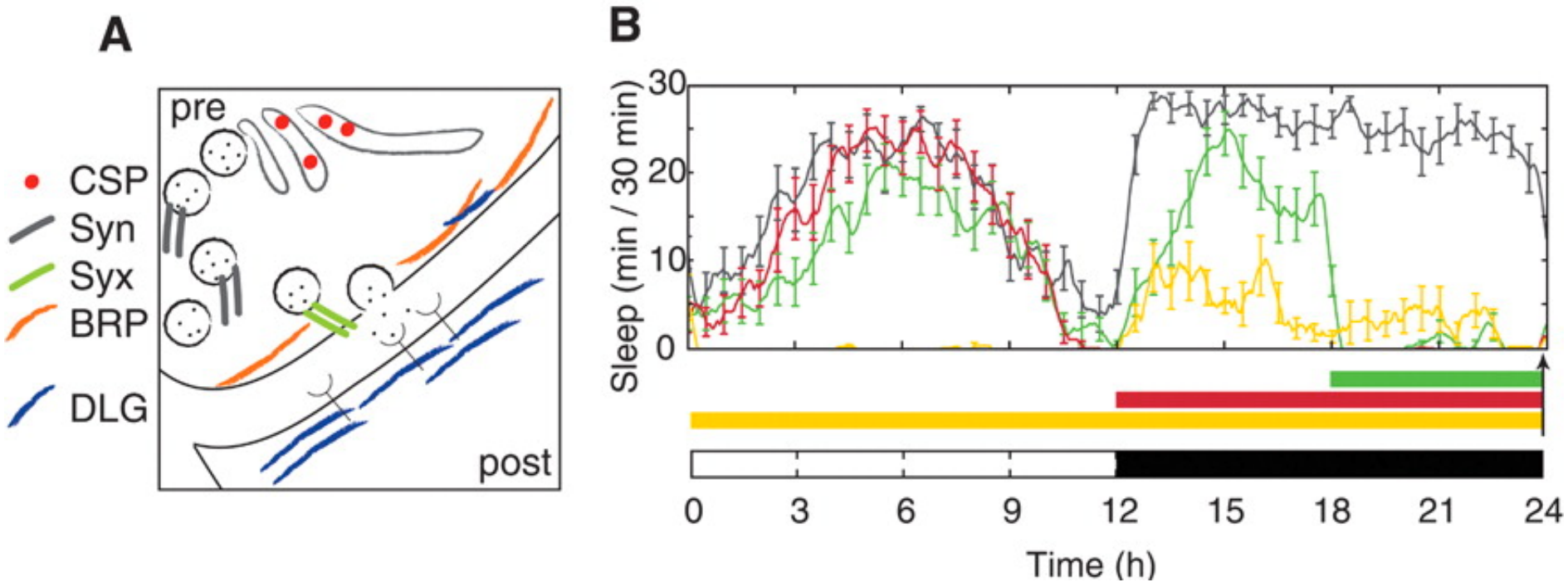
Diekelmann & Born, 2012

Widespread Changes in Synaptic Markers as a Function of Sleep and Wakefulness in *Drosophila*

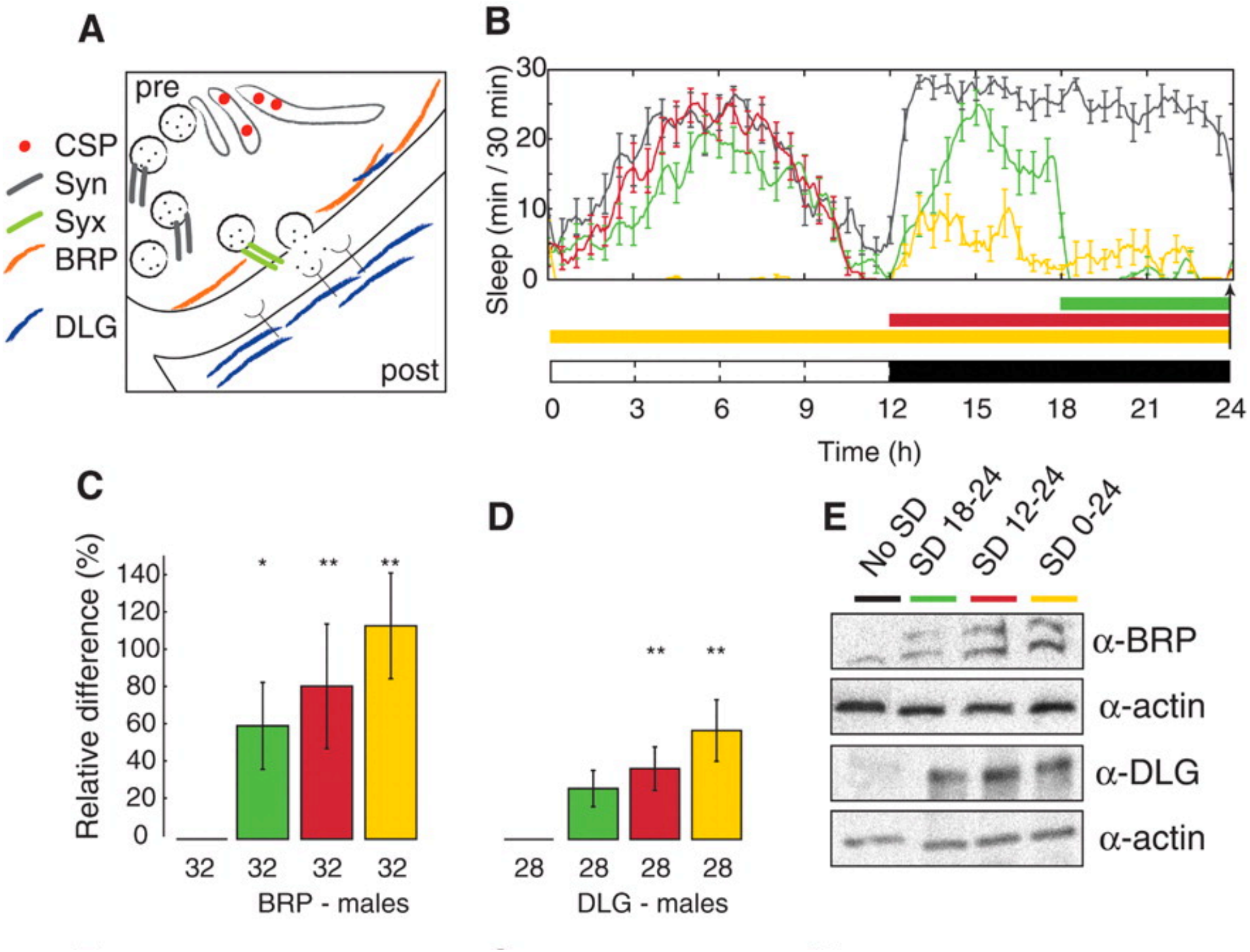
Giorgio F. Gilestro, Giulio Tononi,* Chiara Cirelli*

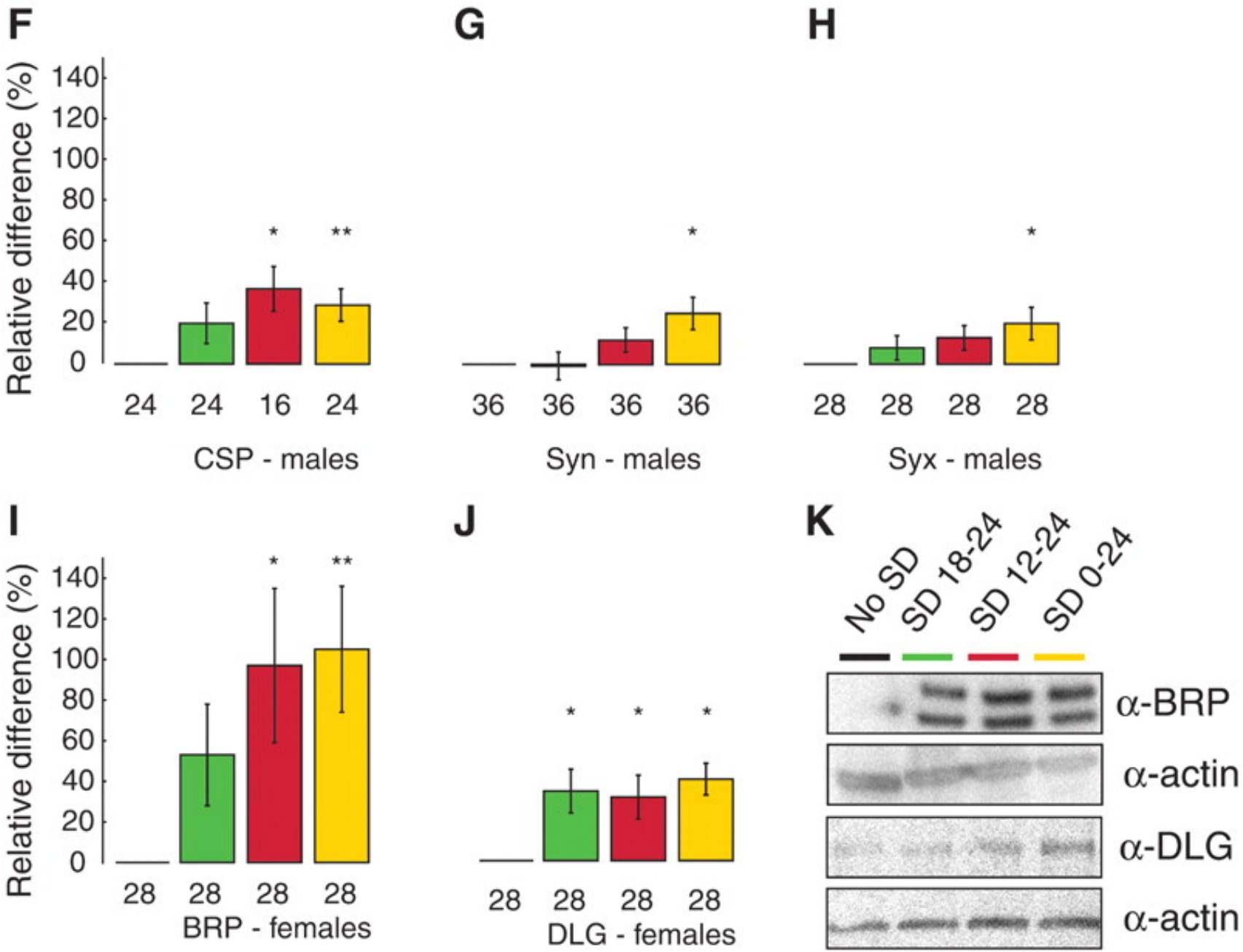
Sleep is universal, strictly regulated, and necessary for cognition. Why this is so remains a mystery, although recent work suggests that sleep, memory, and plasticity are linked. However, little is known about how wakefulness and sleep affect synapses. Using Western blots and confocal microscopy in *Drosophila*, we found that protein levels of key components of central synapses were high after waking and low after sleep. These changes were related to behavioral state rather than time of day and occurred in all major areas of the *Drosophila* brain. The decrease of synaptic markers during sleep was progressive, and sleep was necessary for their decline. Thus, sleep may be involved in maintaining synaptic homeostasis altered by waking activities.


A
pre
CSP
Syn
Syx
BRP
DLG
post

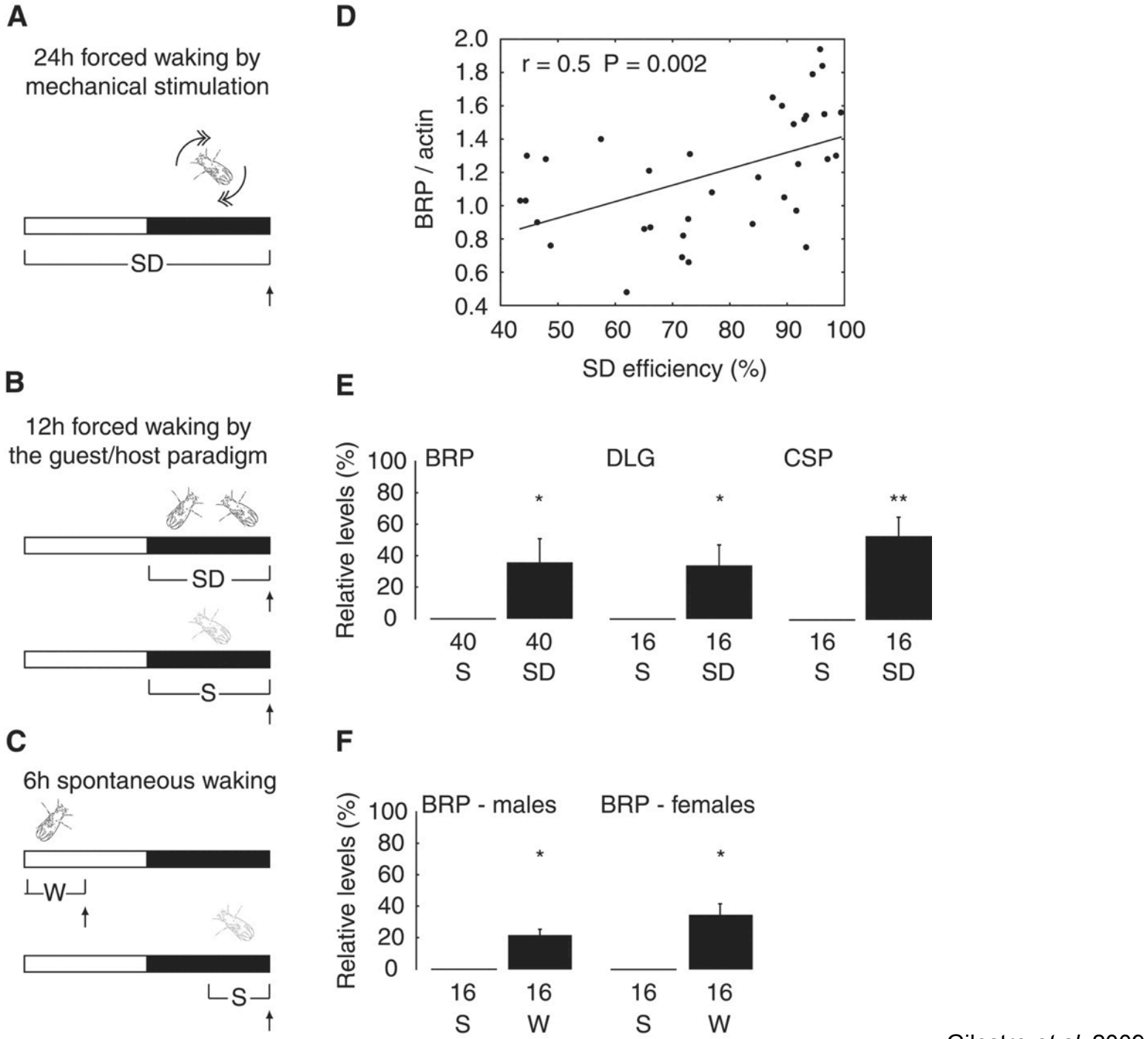


Gilestro *et al.* 2009

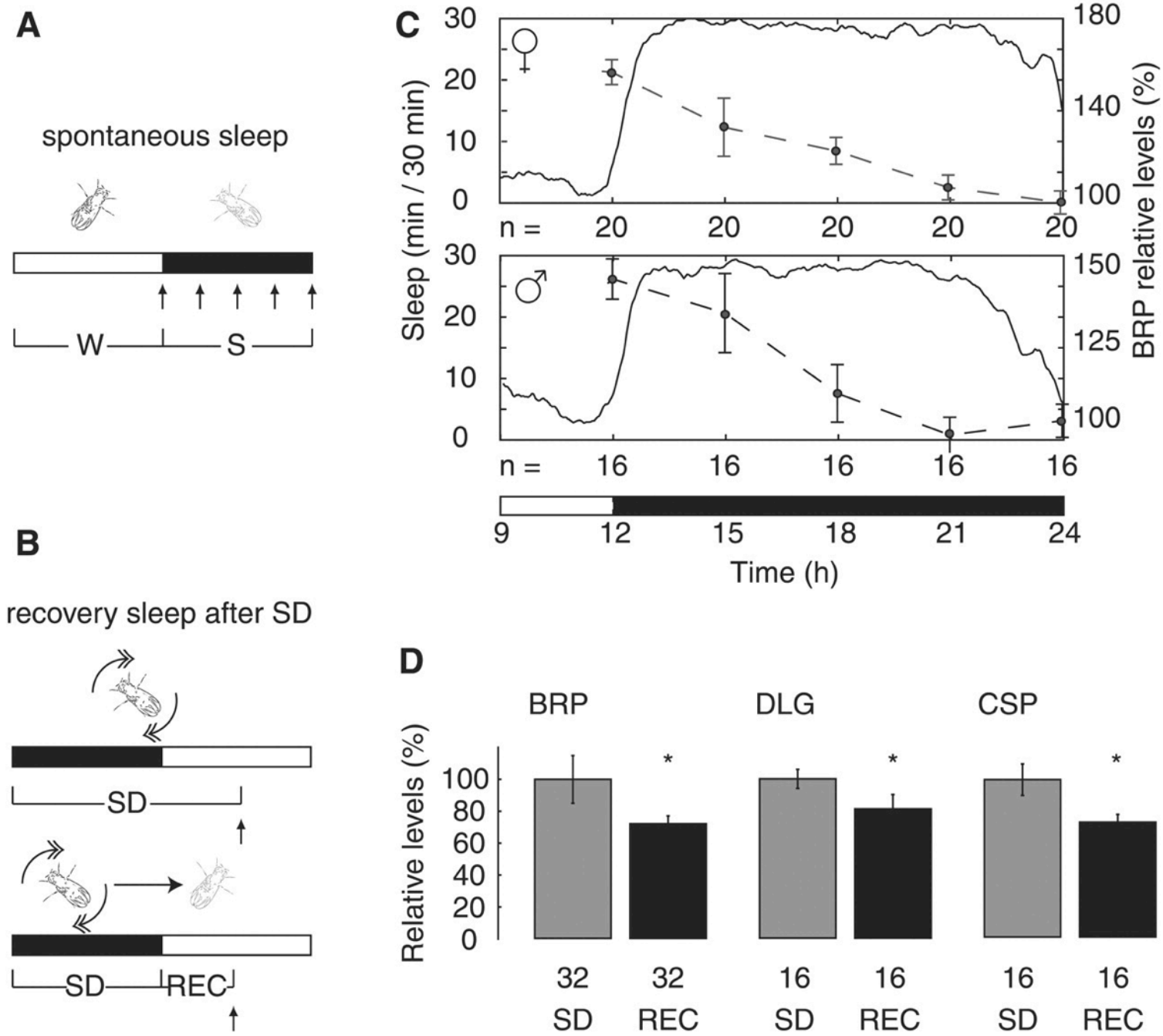

A
pre
post
CSP
Syn
Syx
BRP
DLG
B
Sleep (min / 30 min)
30
20
10
0
0
3
6
9
12
15
18
21
24
Time (h)
C
Relative difference (%)
140
120
100
80
60
40
20
0
*
**
**
32
32
32
32
BRP - males
D
**
**
28
28
28
28
DLG - males
E
No SD
SD 18-24
SD 12-24
SD 0-24
α-BRP
α-actin
α-DLG
α-actin



Gilestro *et al.* 2009

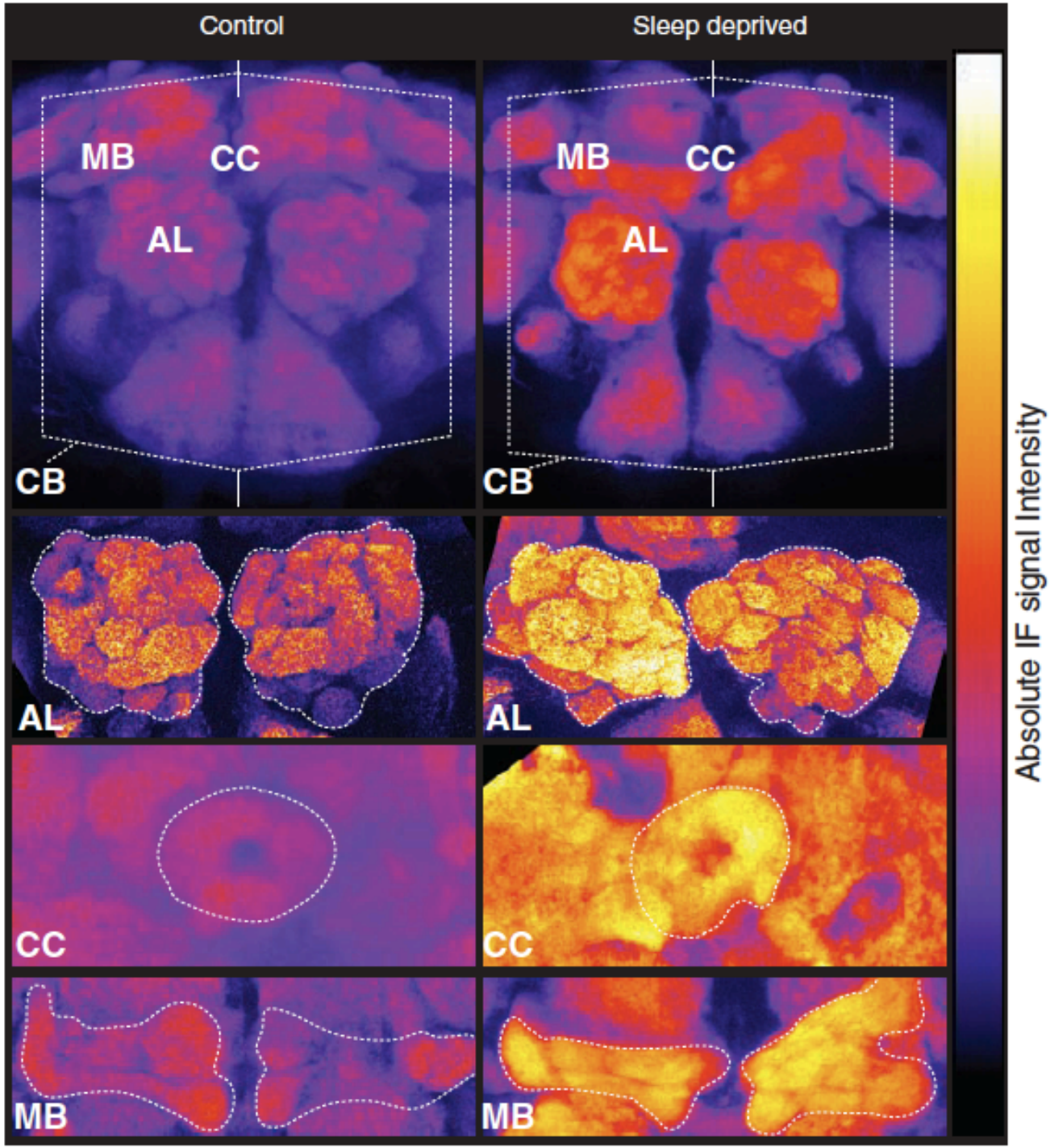


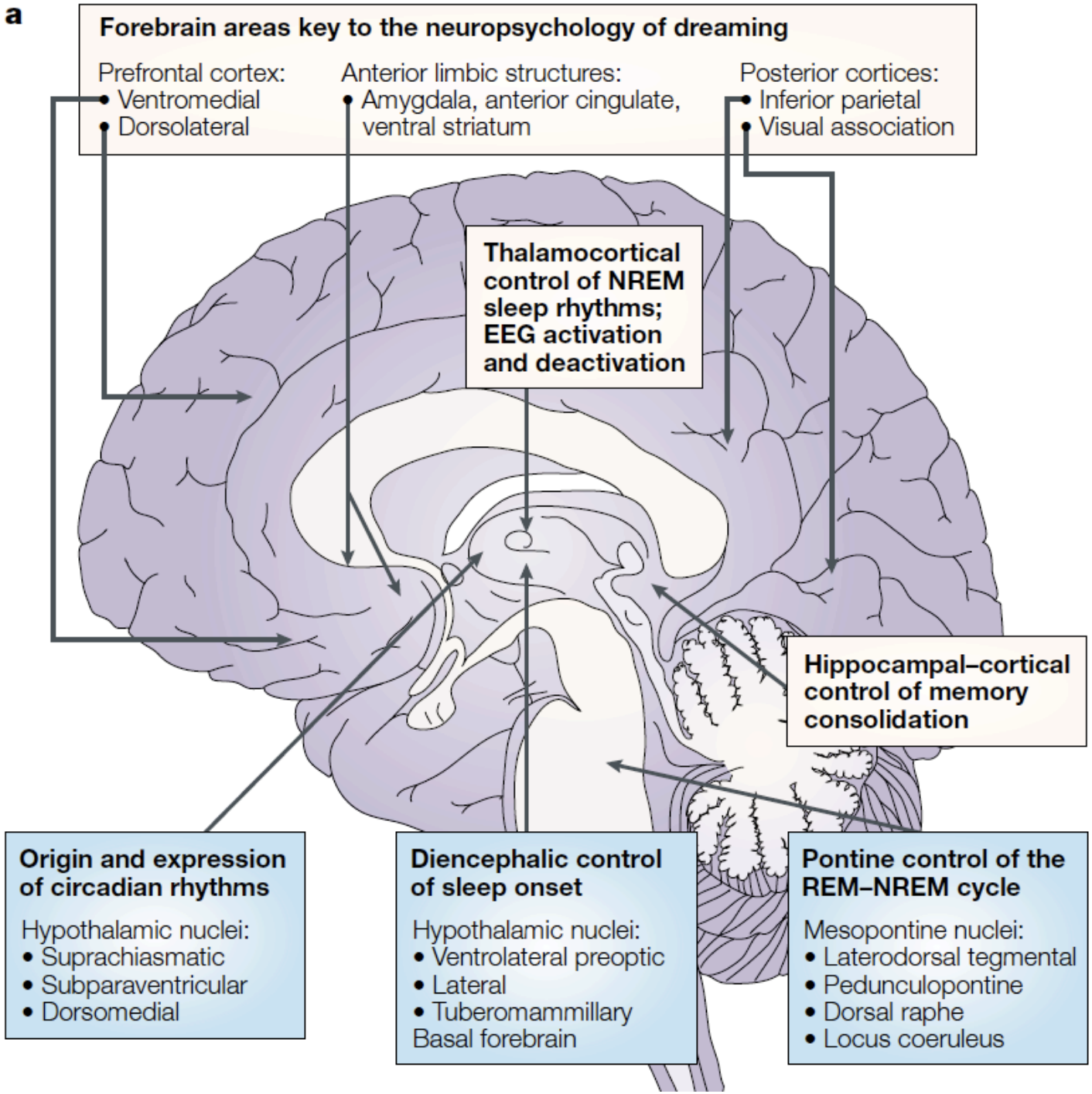
Gilestro *et al.* 2009

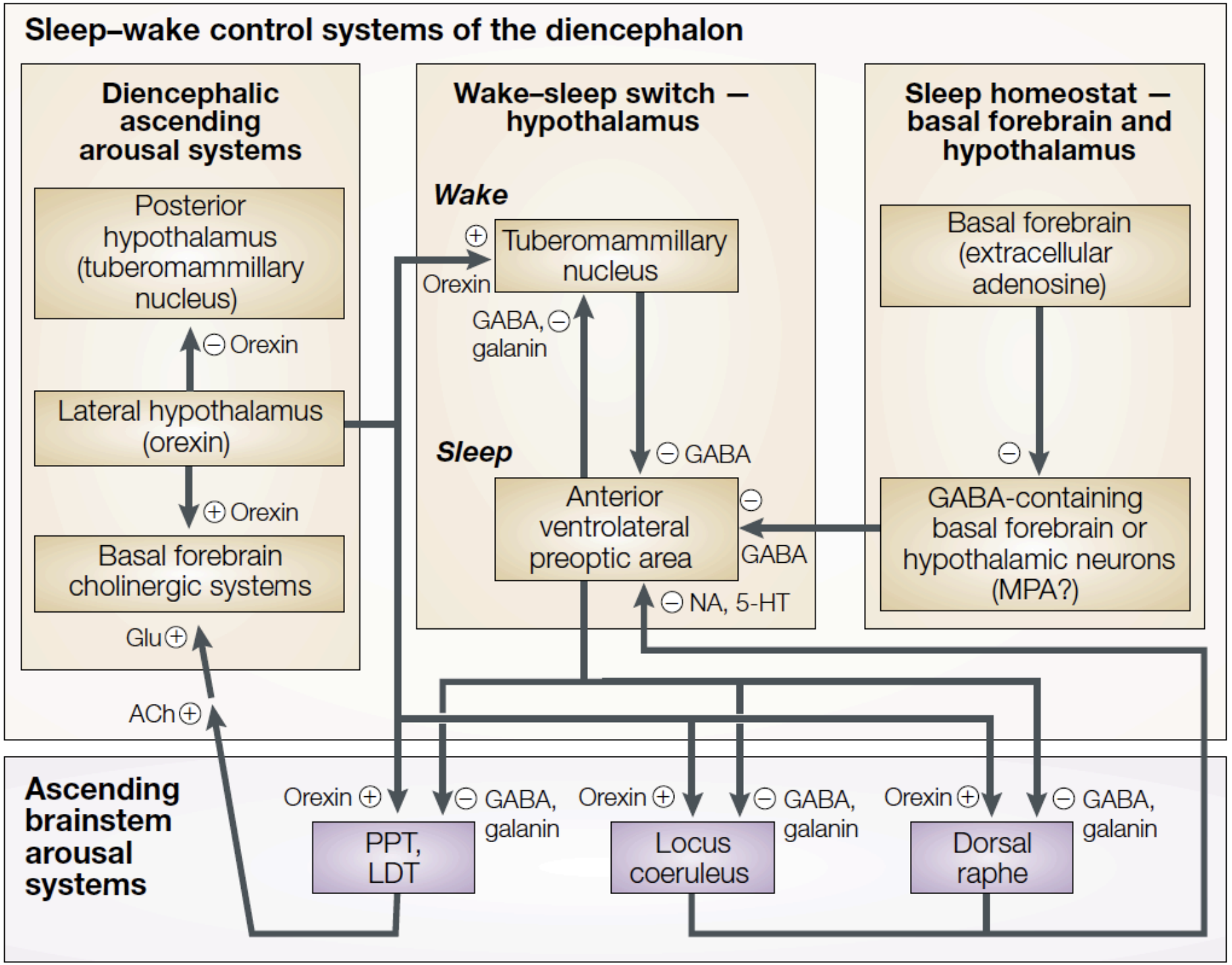


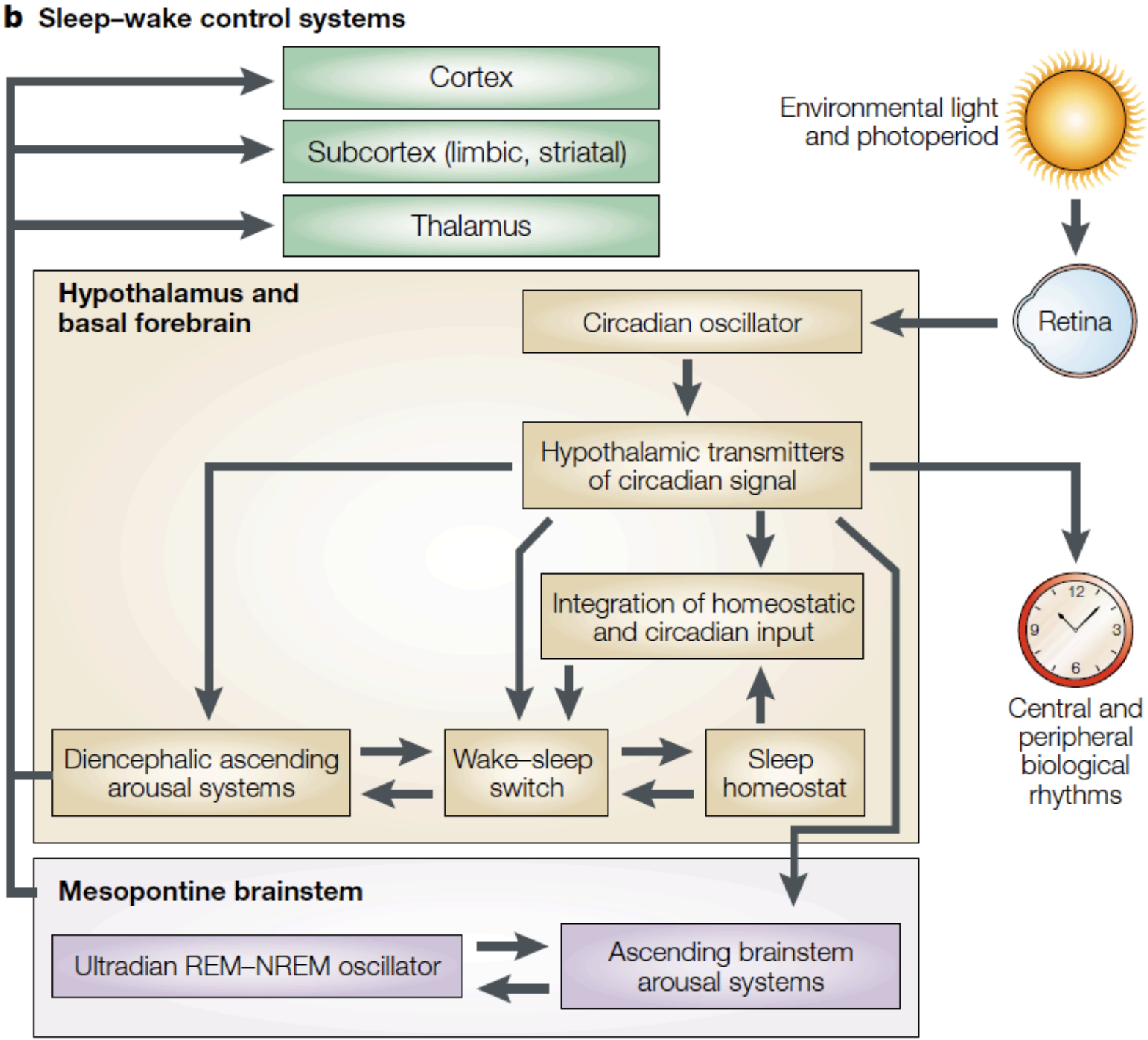
Gilestro *et al.* 2009

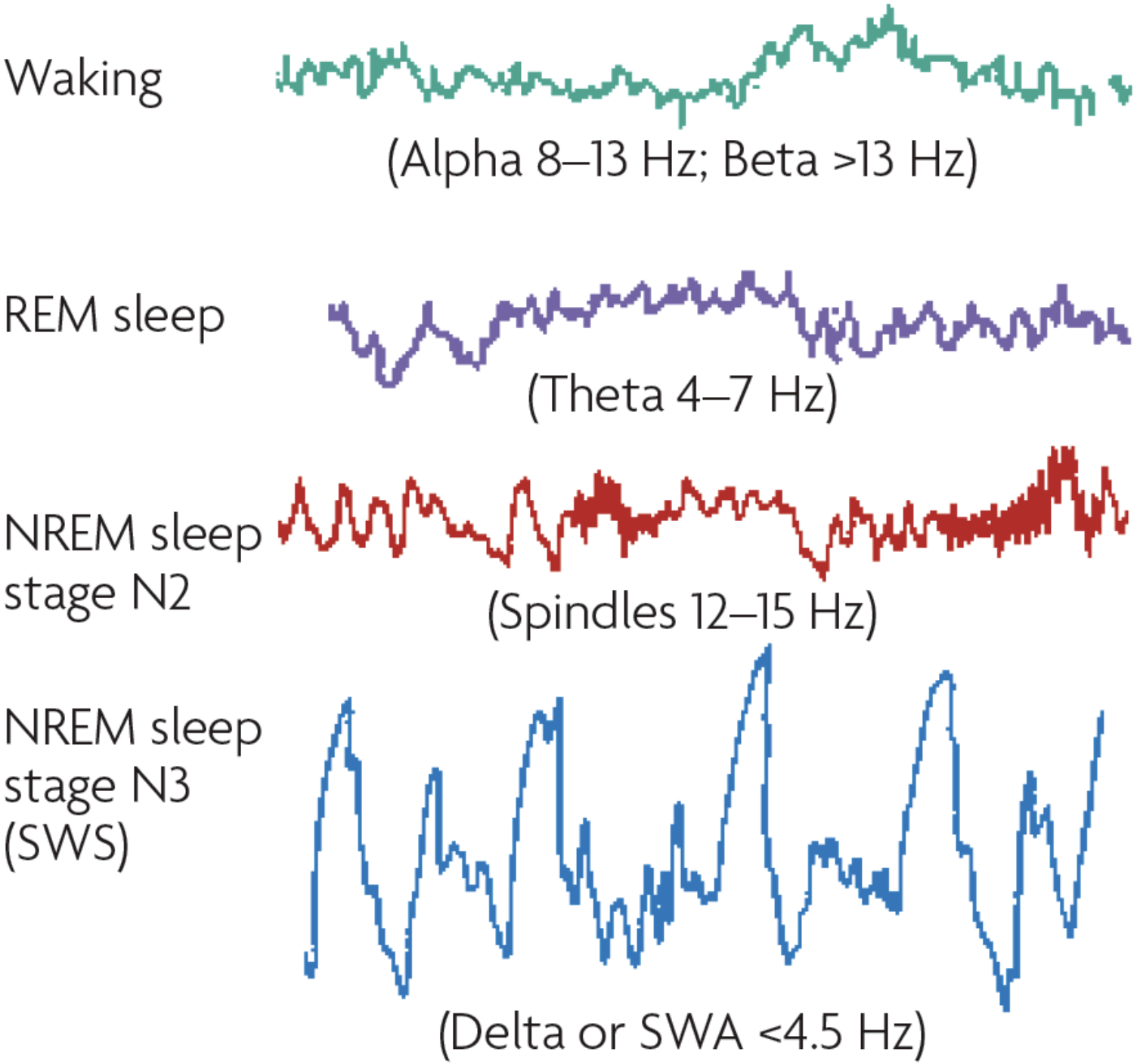
BRP Expression

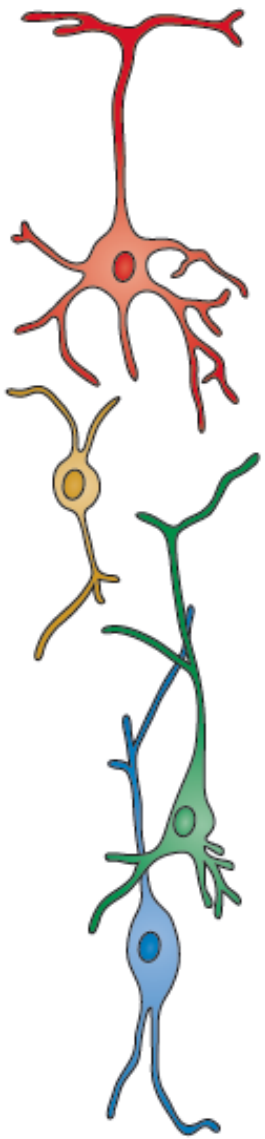



a
Forebrain areas key to the neuropsychology of dreaming
Prefrontal cortex:
• Ventromedial
• Dorsolateral
Anterior limbic structures:
• Amygdala, anterior cingulate, ventral striatum
Posterior cortices:
• Inferior parietal
• Visual association
Thalamocortical control of NREM sleep rhythms; EEG activation and deactivation
Hippocampal–cortical control of memory consolidation
Origin and expression of circadian rhythms
Hypothalamic nuclei:
• Suprachiasmatic
• Subparaventricular
• Dorsomedial
Diencephalic control of sleep onset
Hypothalamic nuclei:
• Ventrolateral preoptic
• Lateral
• Tuberomammillary
Basal forebrain
Pontine control of the REM–NREM cycle
Mesopontine nuclei:
• Laterodorsal tegmental
• Pedunculopontine
• Dorsal raphe
• Locus coeruleus

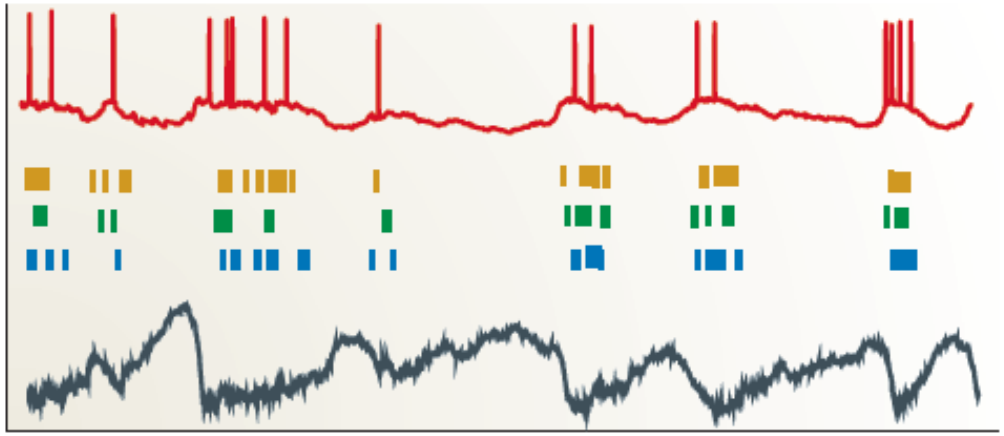

Sleep–wake control systems of the diencephalon
Diencephalic ascending arousal systems
Posterior hypothalamus (tuberomammillary nucleus)
⊖ Orexin
Lateral hypothalamus (orexin)
⊕ Orexin
Basal forebrain cholinergic systems
Glu ⊕
ACh ⊕
Wake–sleep switch — hypothalamus
Wake
⊕ Orexin
Tuberomammillary nucleus
GABA, ⊖ galanin
Sleep
⊖ GABA
Anterior ventrolateral preoptic area
⊖ GABA
⊖ NA, 5-HT
Sleep homeostat — basal forebrain and hypothalamus
Basal forebrain (extracellular adenosine)
⊖
GABA-containing basal forebrain or hypothalamic neurons (MPA?)
Ascending brainstem arousal systems
Orexin ⊕
⊖ GABA, galanin
PPT, LDT
Orexin ⊕
⊖ GABA, galanin
Locus coeruleus
Orexin ⊕
⊖ GABA, galanin
Dorsal raphe


b Sleep–wake control systems
Cortex
Subcortex (limbic, striatal)
Thalamus
Environmental light and photoperiod
Retina
Hypothalamus and basal forebrain
Circadian oscillator
Hypothalamic transmitters of circadian signal
Integration of homeostatic and circadian input
Diencephalic ascending arousal systems
Wake–sleep switch
Sleep homeostat
Central and peripheral biological rhythms
Mesopontine brainstem
Ultradian REM–NREM oscillator
Ascending brainstem arousal systems


Waking
(Alpha 8–13 Hz; Beta >13 Hz)
REM sleep
(Theta 4–7 Hz)
NREM sleep stage N2
(Spindles 12–15 Hz)
NREM sleep stage N3 (SWS)
(Delta or SWA <4.5 Hz)



a Sychronized state

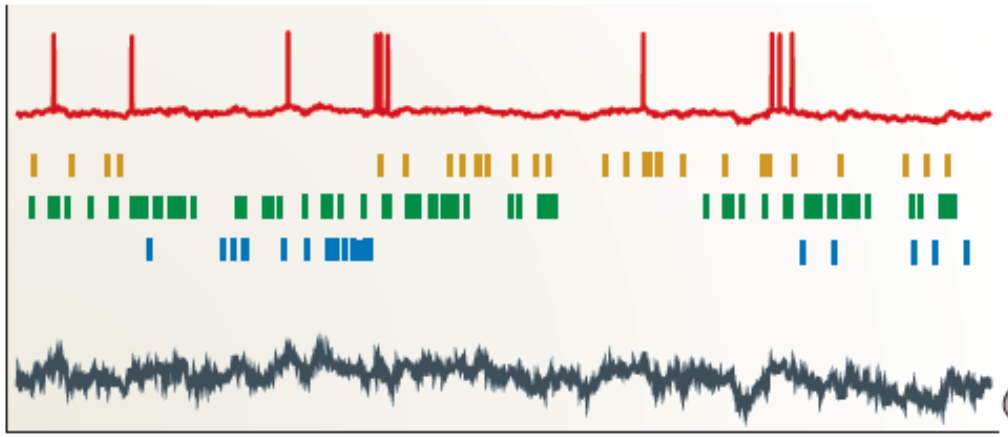


Time

Sleeping
Quiescent (at rest)



b Desynchronized state



Time

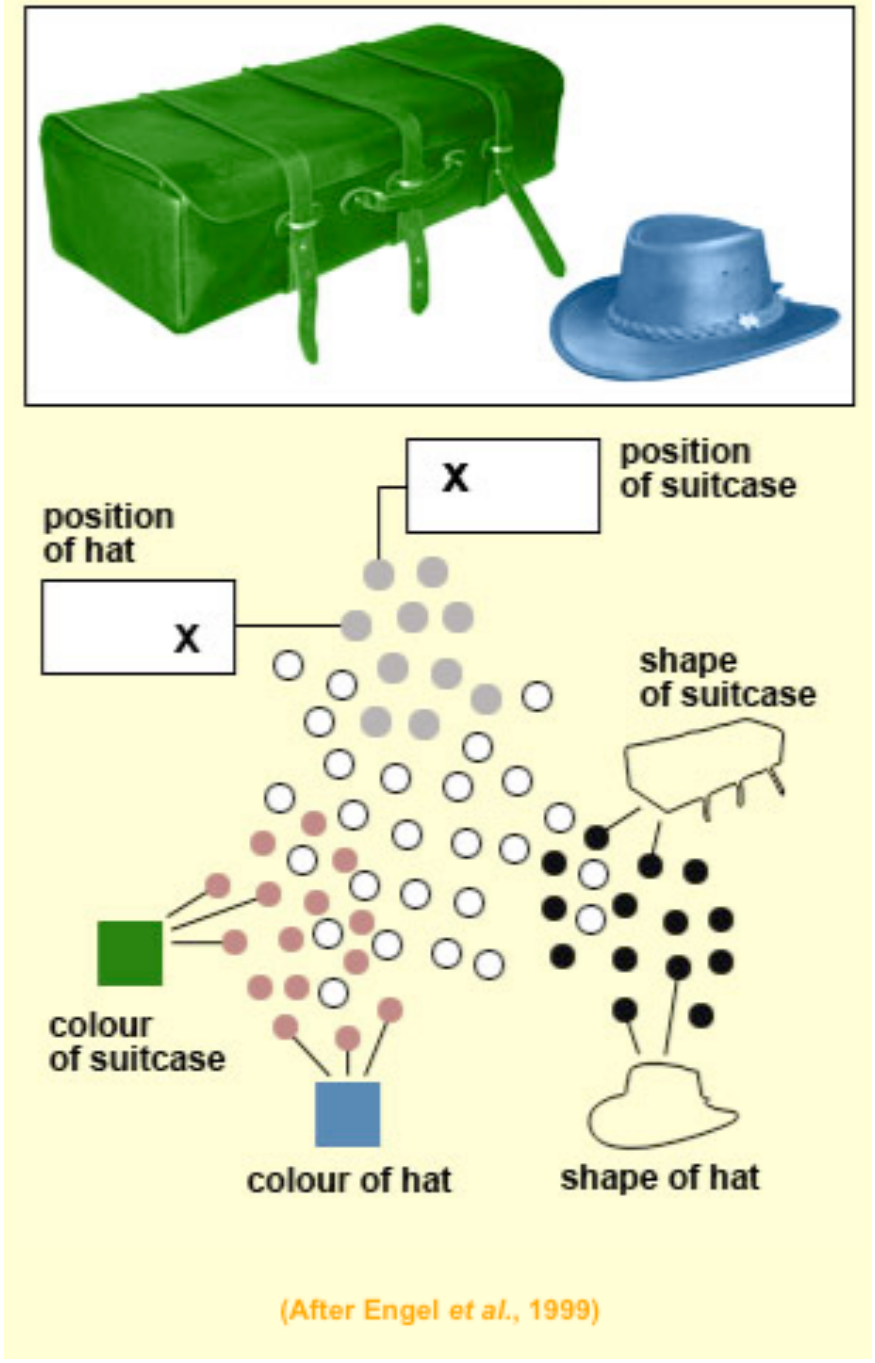
Awake, behaving



Harris & Thiele, 2011

Binding Problem

How can we have a conscious, coherent, unified perception of an object, given that its various attributes are processed in different parts of the brain?

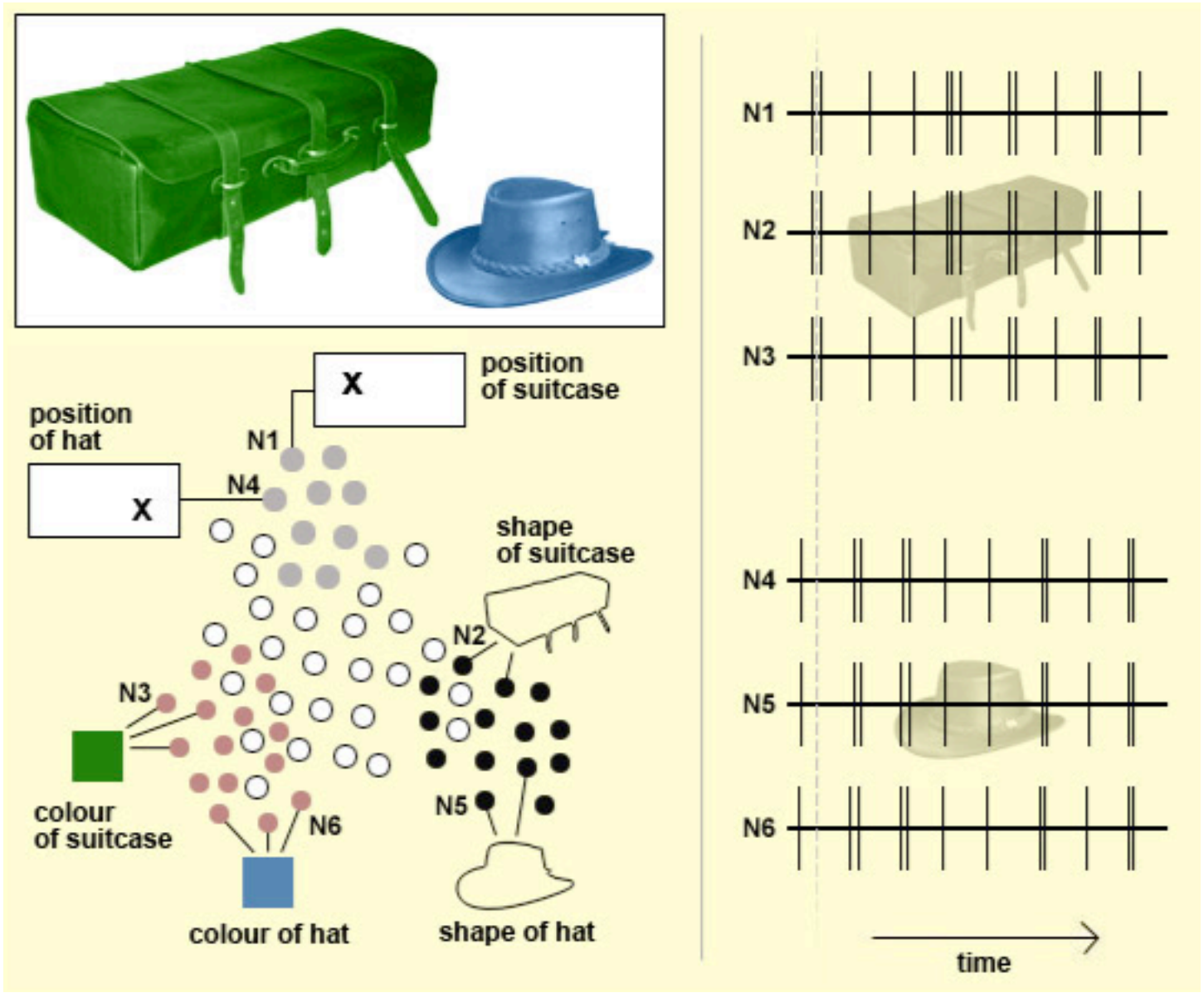


(After Engel *et al.*, 1999)

Time vs. Space

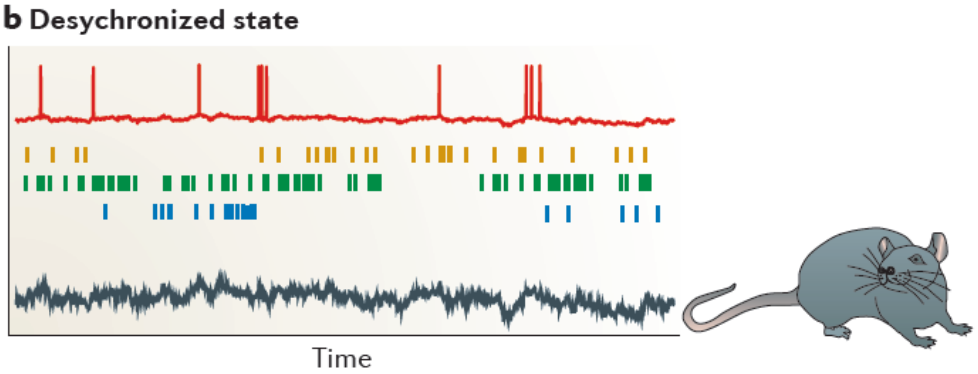
Does the brain provide an internal temporal “reference frame” to link all information together, rather than a specific brain area?

Synchronization of neural assemblies



Large groups of neurons (“cell assemblies”) can fire synchronously at 35-75 Hz

Gamma frequency oscillations (“40 Hz”)



Francis Crick & Christof Koch

two neurons oscillating synchronously in gamma range – part of same representation, conscious

two neurons oscillating synchronously outside gamma range – same representation, unconscious

two neurons asynchronous – not bound in an active representation

Rodolfo Llinas, 1990s

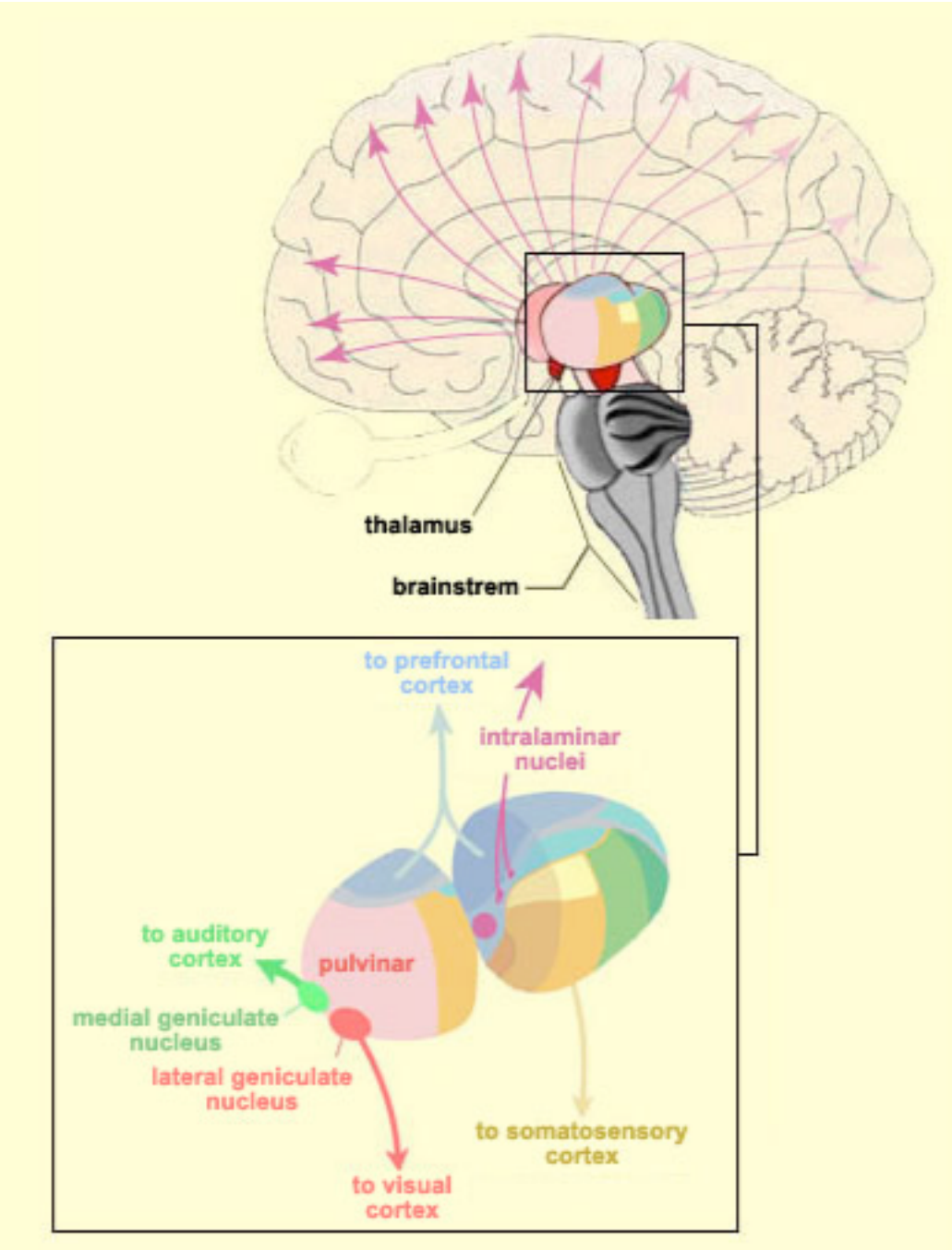
MEGs of Human Subjects

waves of neural activity proceding from anterior to posterior in cortex

12.5-ms of activity followed by
12.5-ms of quiescence
(*i.e.* total period of wave = 25 ms)

corresponds to 40-Hz gamma oscillation

“conscious” perception is neurons synchronous with each other and with an internal reference reference clock



Neural Darwinism

assemblies of neurons are constantly firing together, and the assembly that fires the strongest enters consciousness (winner-take-all competition)

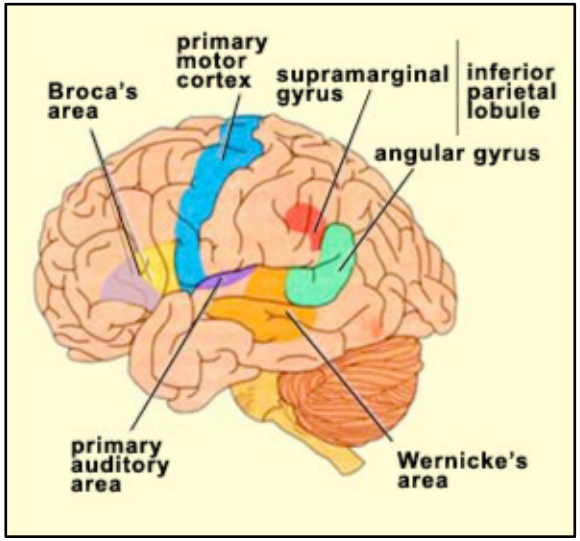
Metarepresentations

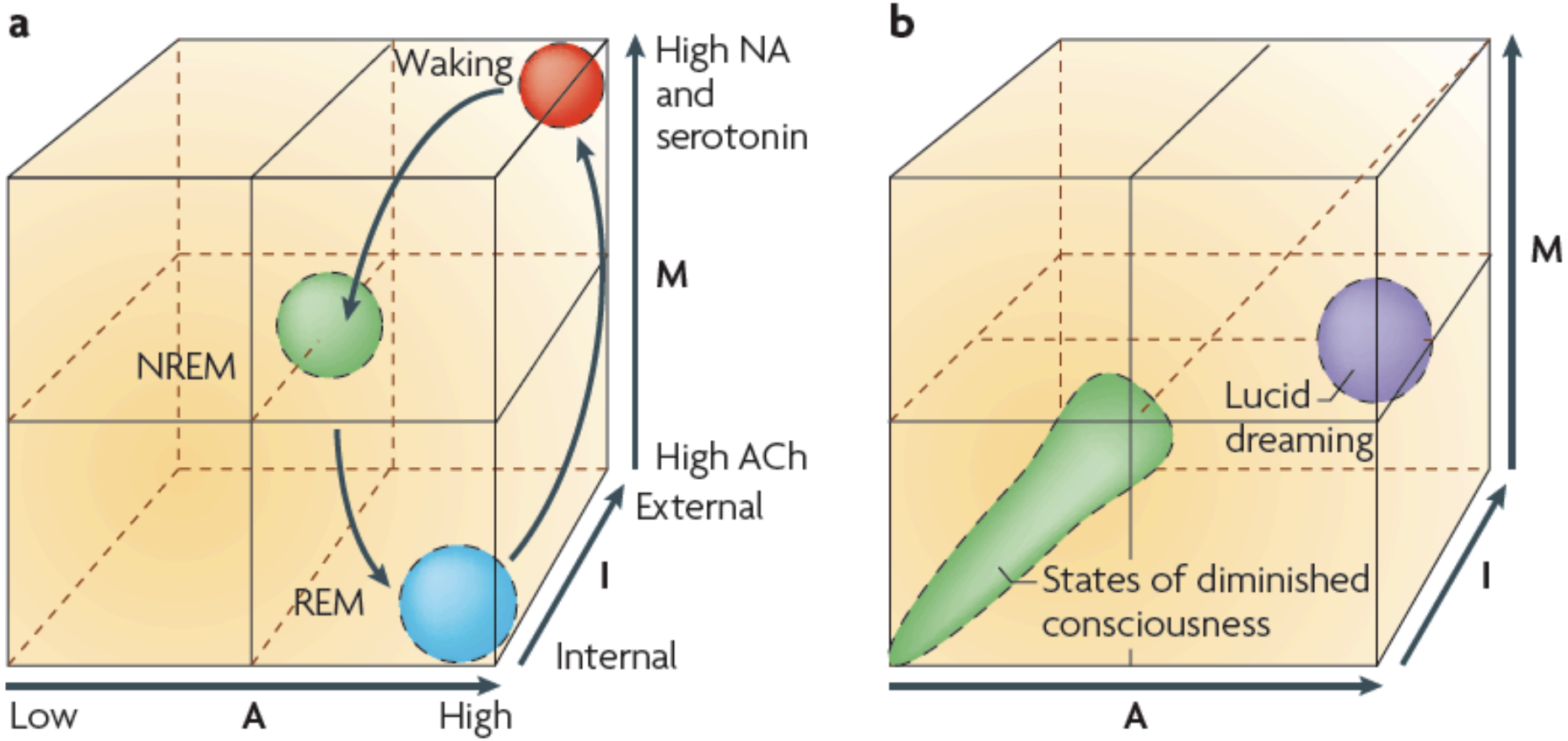
V.S. Ramachandran

brain has evolved ability to form representations of sensory representations

inferior parietal lobe
- angular gyrus
- supramarginal gyrus

anterior cingulate cortex





A neural activation

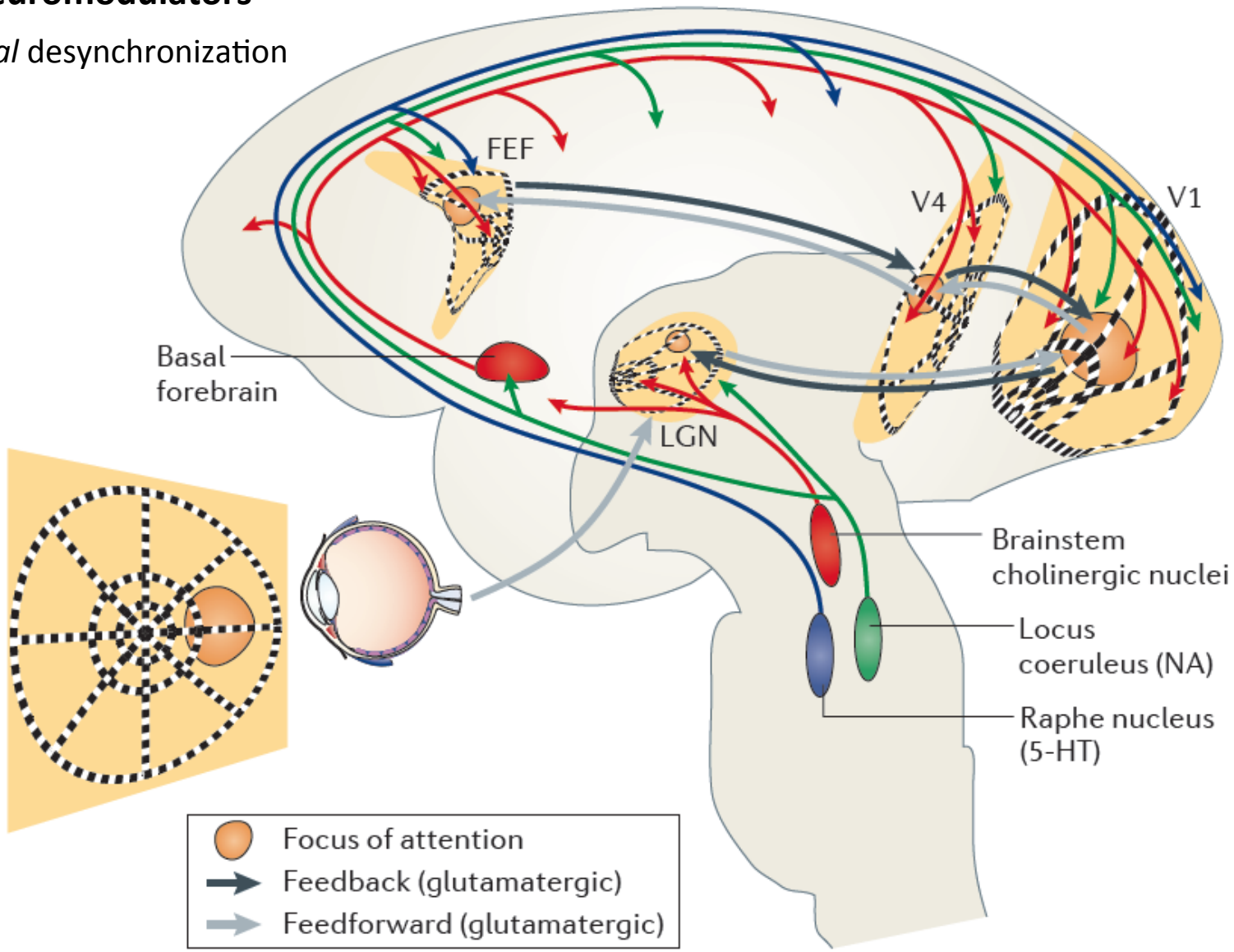
I input-output gating (thalamus)

M modulation (acetylcholine vs. norepinephrine/serotonin)

Hobson, 2009

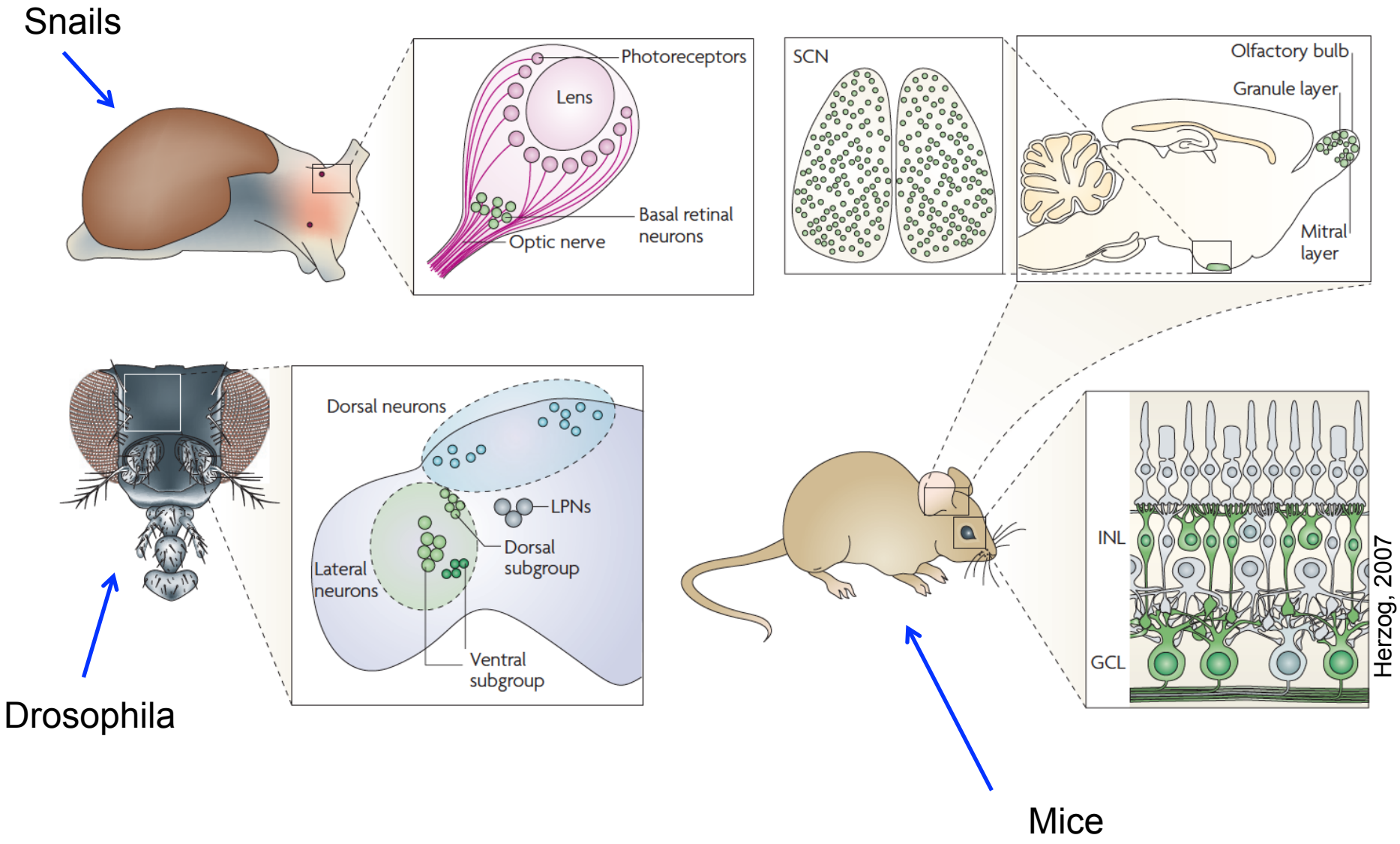
Attention & Neuromodulators

attention is a *local* desynchronization

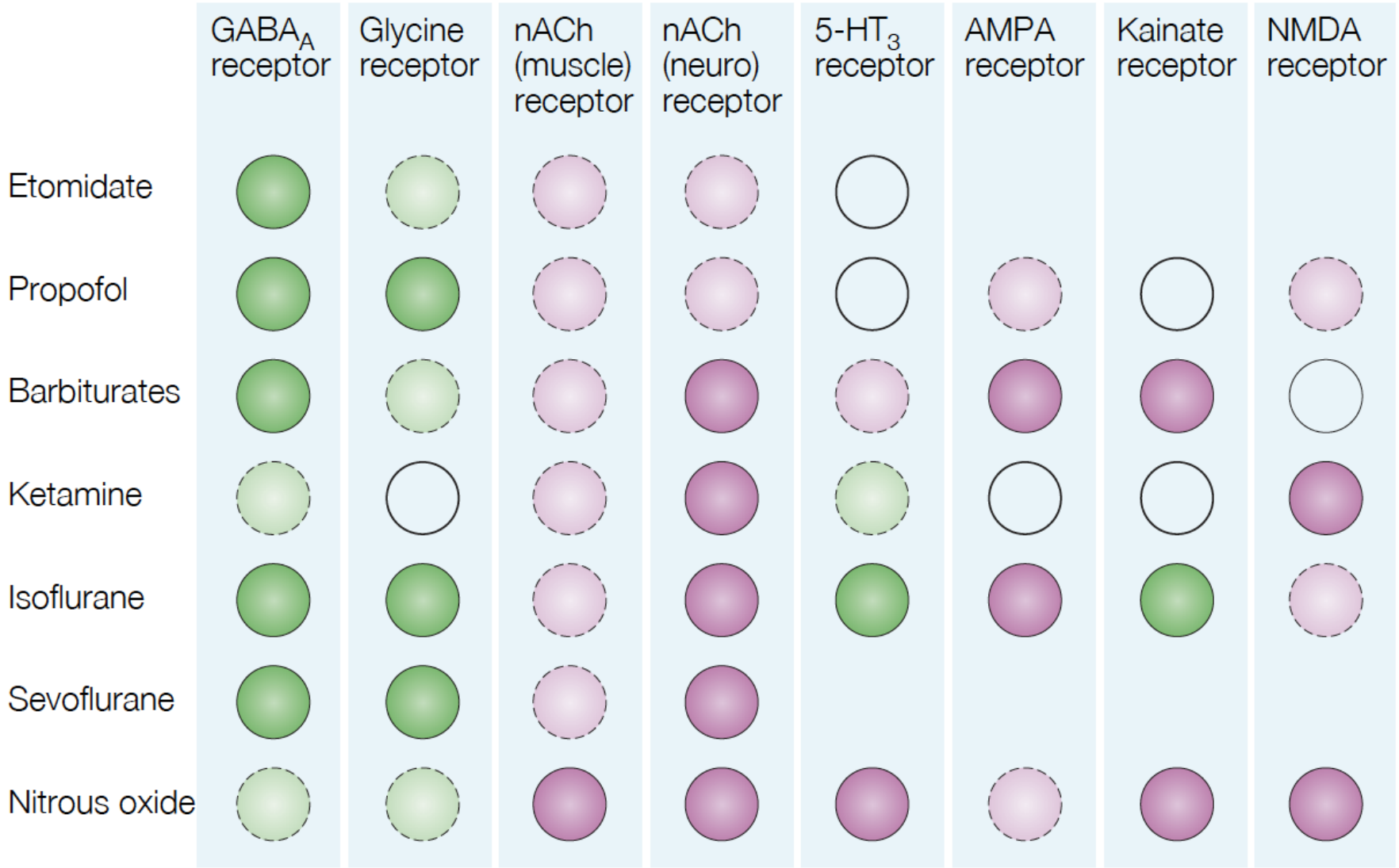


Harris & Thiele, 2011

Circadian rhythms in other animals



General Anesthesia



Green = agonist
Purple = antagonist