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**SEMMELWEIS
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Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

Contributed by: Tamás Freund, Zsolt Liposits, Zoltán Nusser, László Acsády, Szabolcs Káli, József Haller, Zsófia Maglóczky, Nórbert Hájos, Emilia Madarász, György Karmos, Miklós Palkovits, Anita Kamondi, Lóránd Eröss, Róbert Gábel, Zoltán Kisvárdai, Zoltán Vidnyánszky

Wake-sleep cycle

Imre Kalló & György Karmos

Pázmány Péter Catholic University, Faculty of Information Technology

- I. The circadian rhythm
- II. Physiological characteristics of the sleep stages
- III. Brain mechanisms responsible for the wake-sleep cycle
- IV. Sleep disturbance

Physiology of the wake-sleep cycle

- The circadian rhythm
- Physiological characteristics of the sleep stages
- Brain mechanisms responsible for the wake-sleep cycle
- Sleep disturbance

Rhythmic functions of the living organisms: heart beat, respiration, brain waves, periods, reproductive cycle, migration cycle, etc.

Internally or externally driven rhythms :

circadian rhythm, lunar rhythm, seasonal rhythm

Internal clock-driven, synchronised rhythm (Zeitgeber)

Circadian fluctuations of human physiology

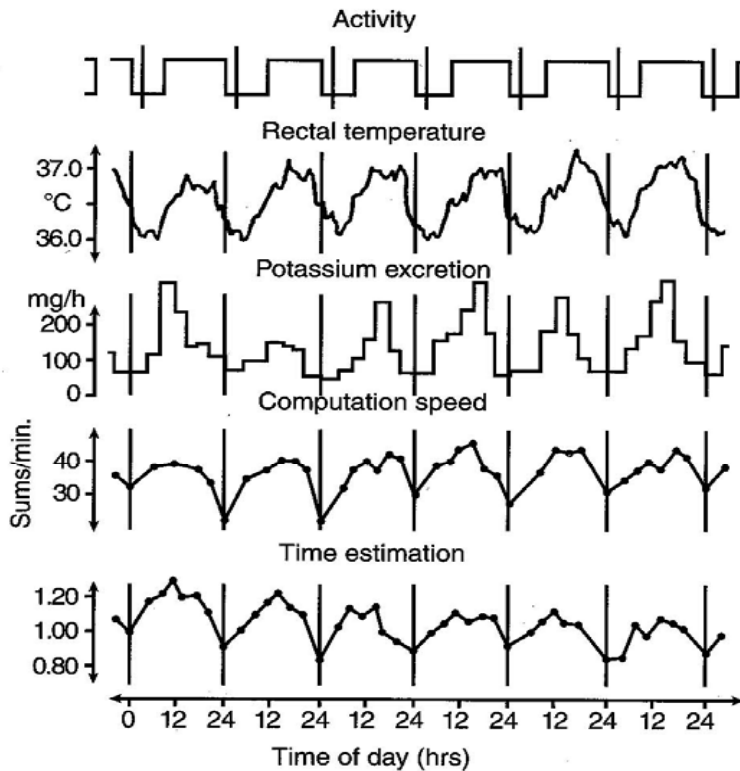


FIGURE 45.1 Daily rhythms in rest-activity, body temperature, potassium excretion, computation speed (number of computations performed per minute), and time estimation (accuracy with which short intervals of time are assessed). From Wever¹ with permission.

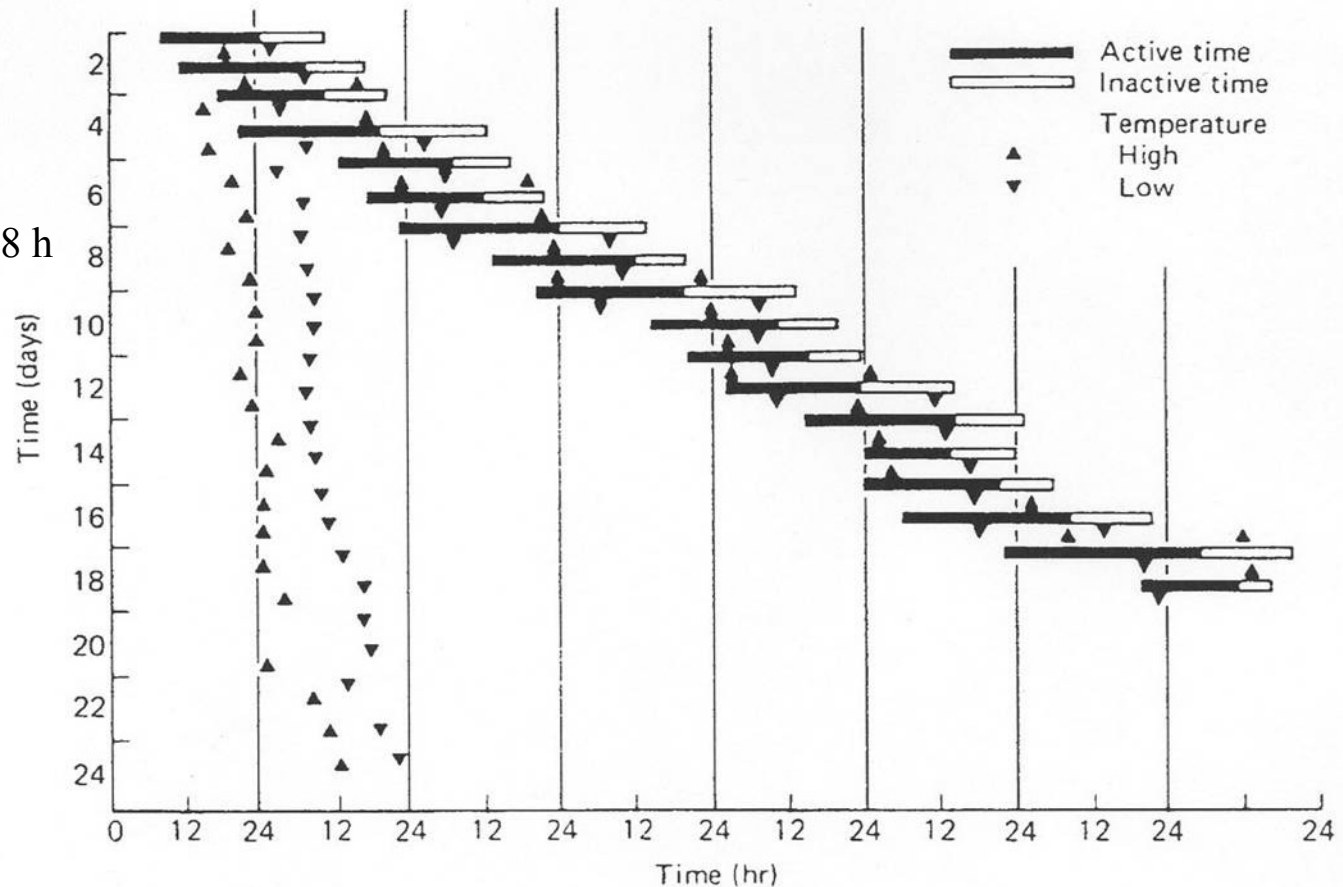
CIRCADIAN RHYTHM

Synchronising factor:
light-dark cycle

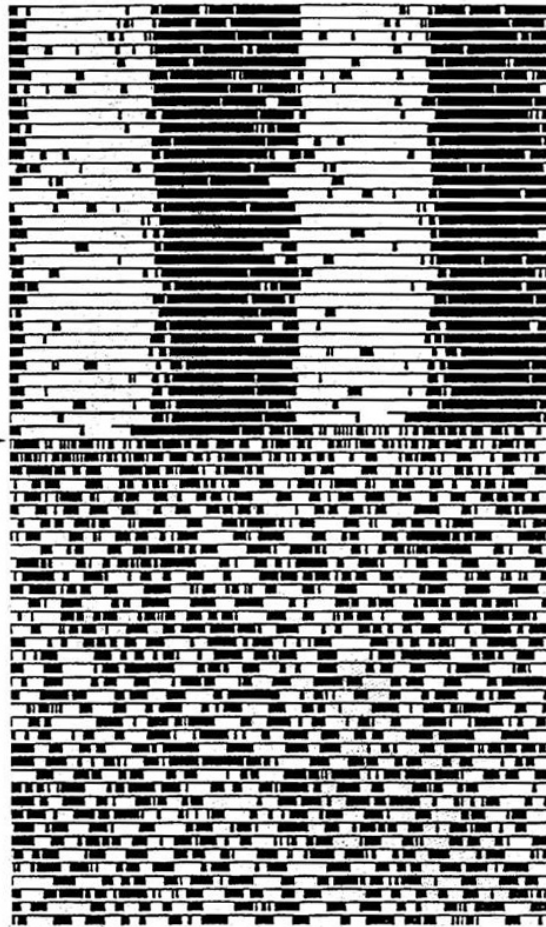
Circadian rule:

diurnal animals: light intensity increase, wake/sleep ratio increases
nocturnal animals: light intensity increase, wake-sleep ratio decrease

Shift of the human circadian rhythm in isolated environment

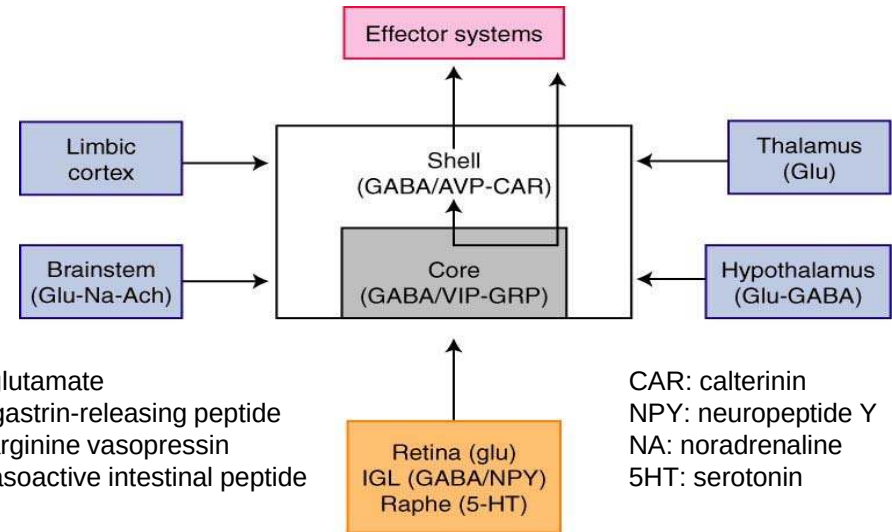
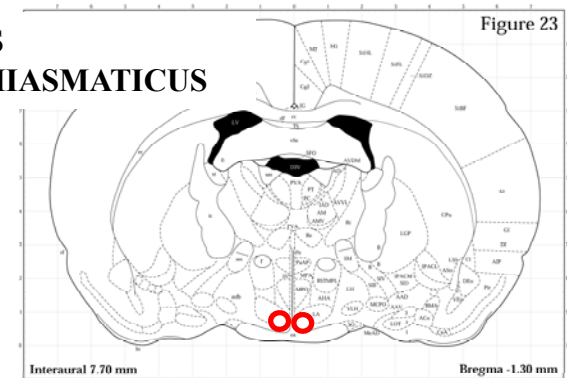


Activity rhythm of rats before and after SCN lesion

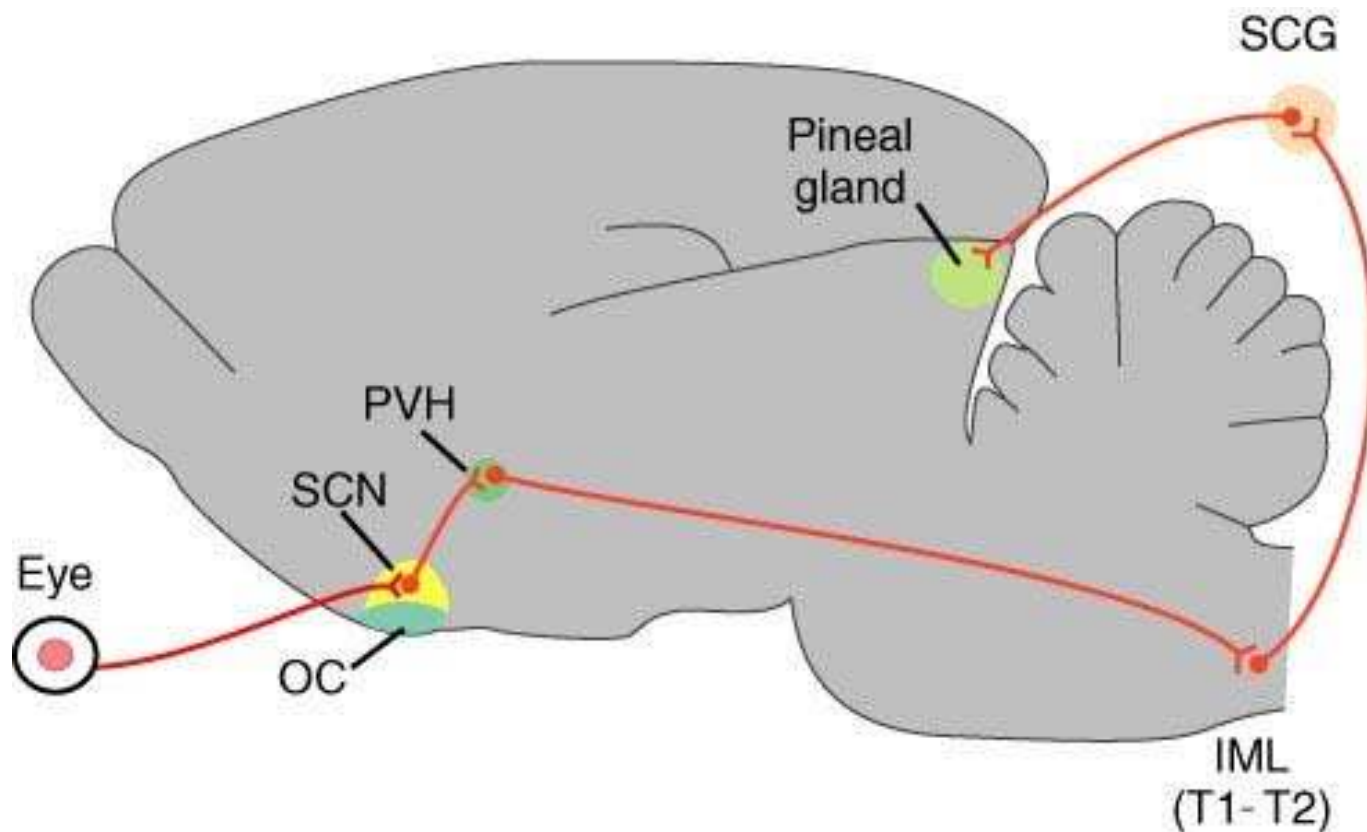


SCN lesion →

NUCLEUS SUPRACHIASMATICUS



Regulation of melatonin secretion in rat

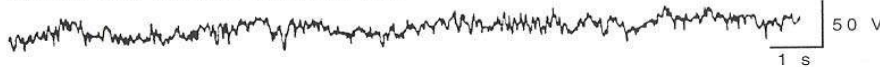


Physiology of the wake-sleep cycle

- The circadian rhythm
- **Physiological characteristics of the sleep stages**
- Brain mechanisms responsible for the wake-sleep cycle
- Sleep disturbance

Sleep stages on the EEG

Awake: low voltage-random, fast



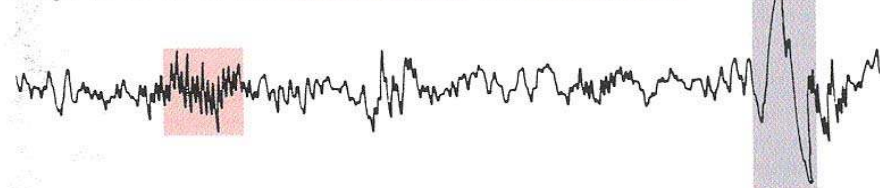
Drowsy: 8 to 12 cps- alpha waves



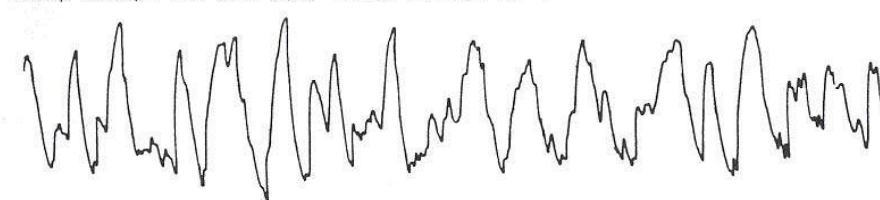
Stage 1: 3 to 7 cps- theta waves



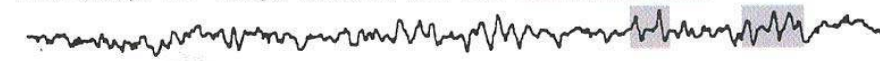
Stage 2: 12 to 14 cps- sleep spindles and K-complexes



Deep sleep: 1/2 to 2 cps- delta waves >75 μ V



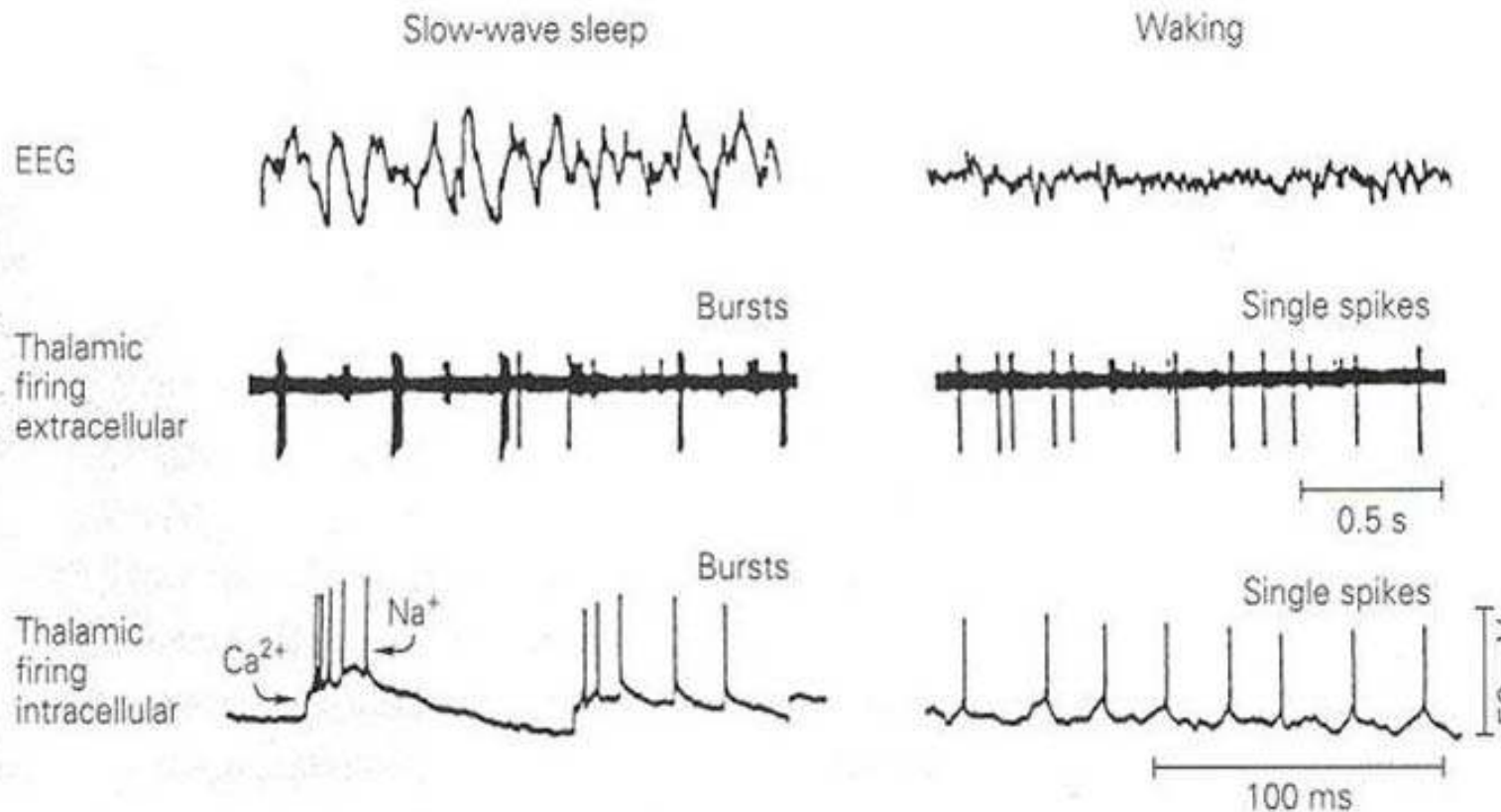
REM sleep: low voltage-random, fast with sawtooth waves



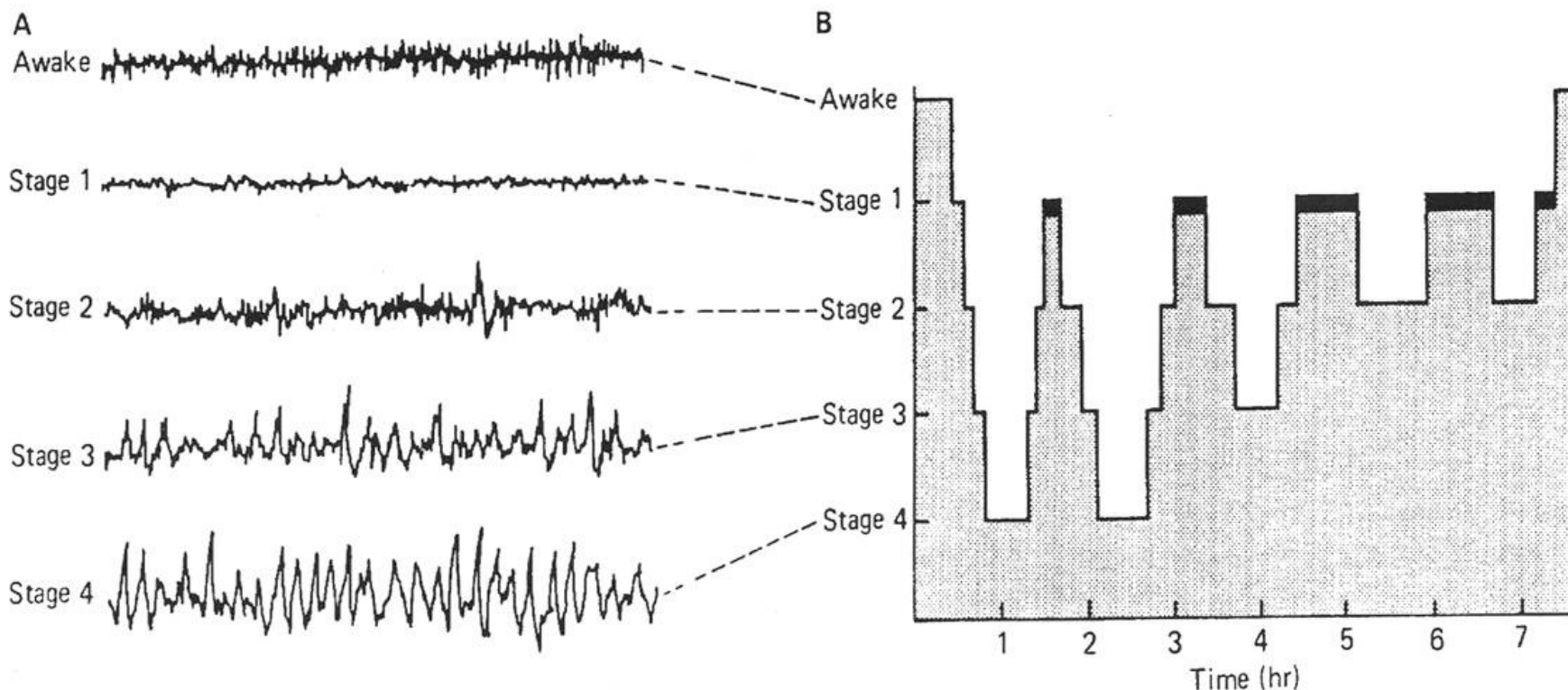
Stages of slow wave sleep:

1. stage: low amplitude, fast activity, with a few theta wave
2-5% of sleeping time
2. stage: theta waves, 10-14 Hz sleeping spindles
45-55% of sleeping time
3. stage: high amplitude theta and delta waves, 20-50% of waves >75 μ V
5-10% of sleeping time
4. stage: high amplitude delta waves, 20% of waves >75 μ V
15-20% of sleeping time

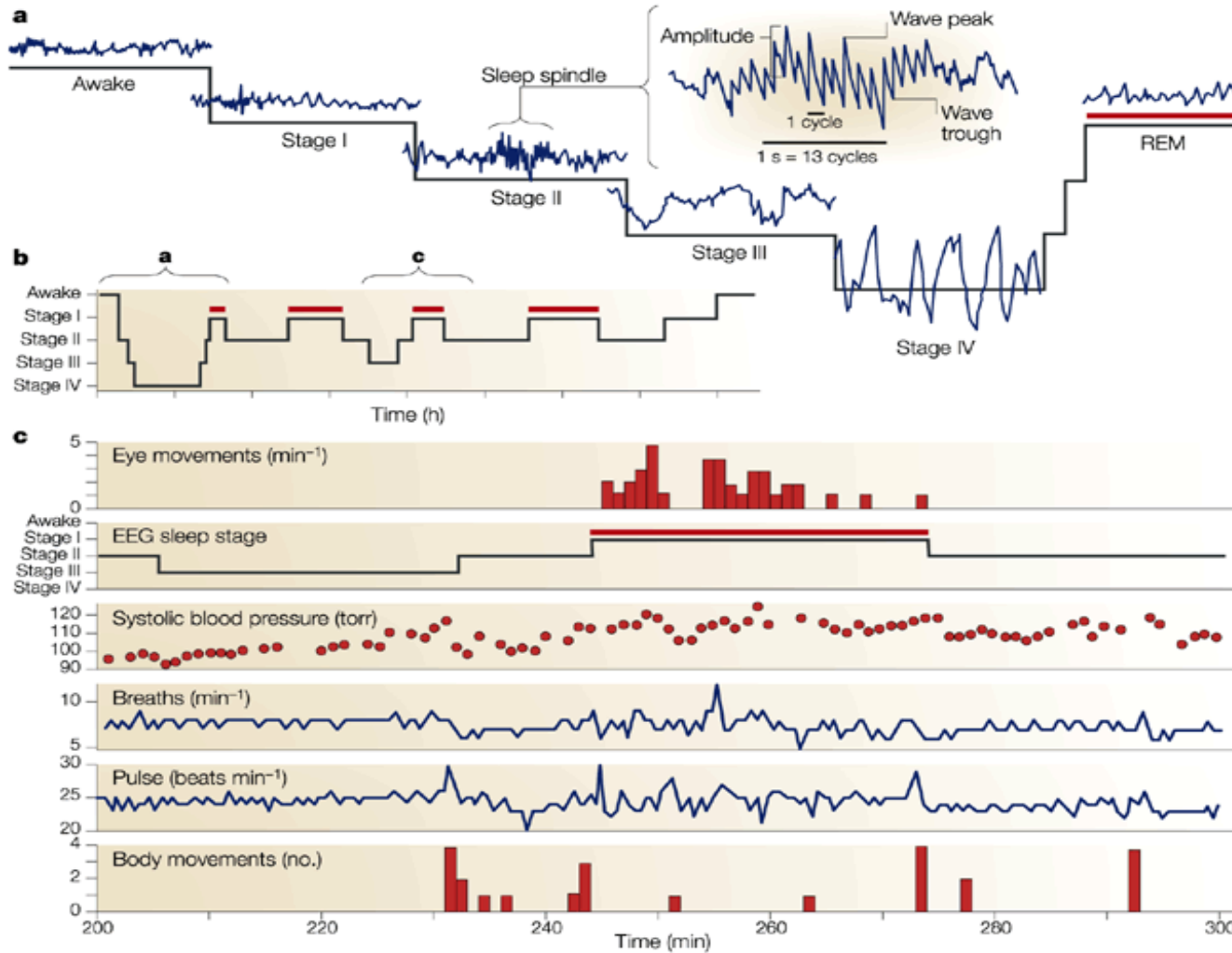
Operational pattern of thalamic „relay” cells in awake state and during slow-wave sleep



Stages of sleep during night sleep



Characteristics of NREM and REM sleep



Typical sleep phases in the cat



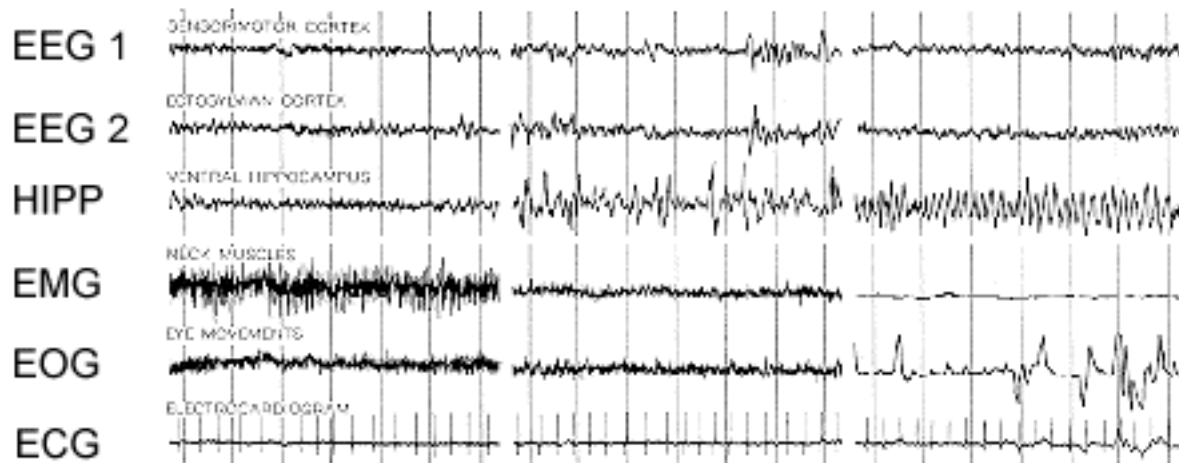
Waking



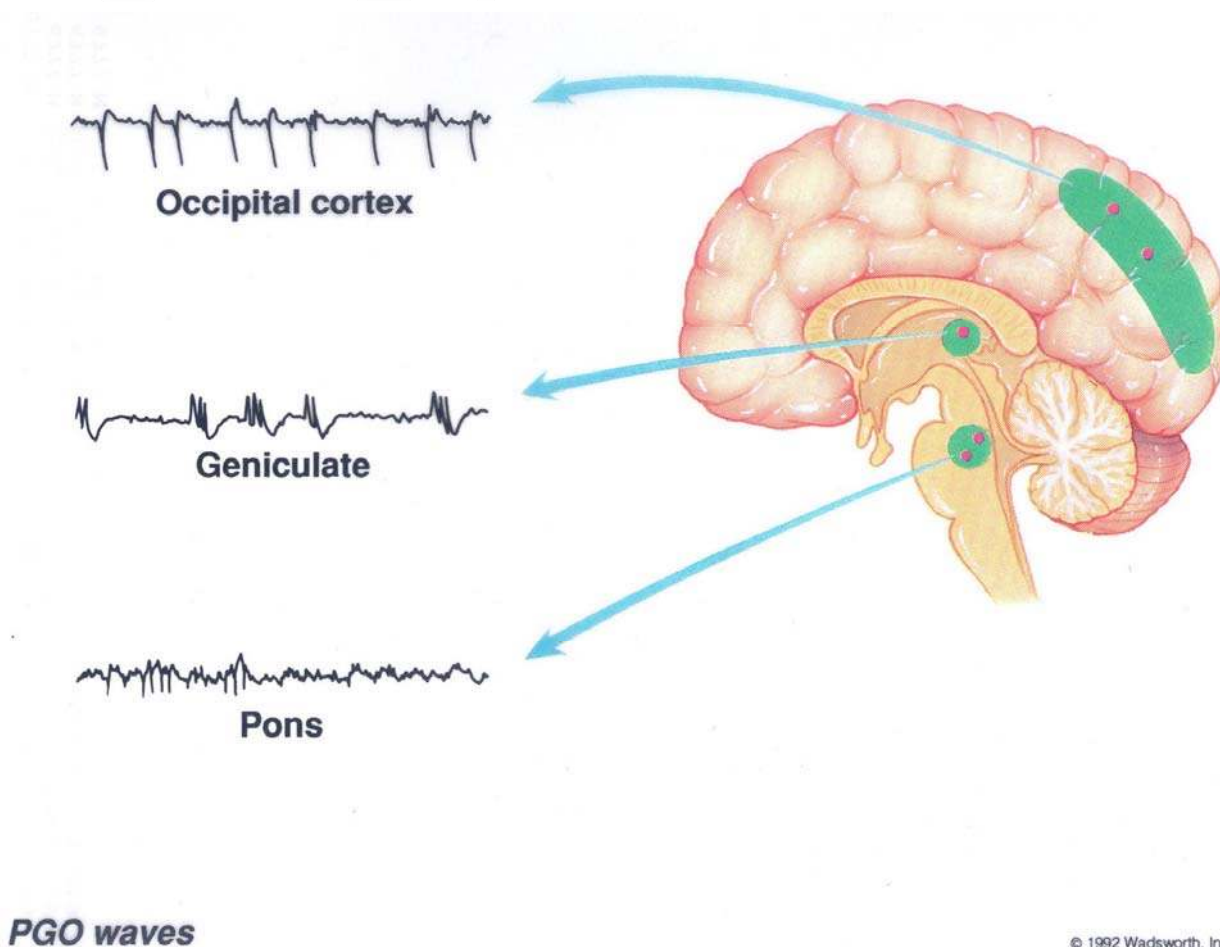
nonREM sleep



REM sleep

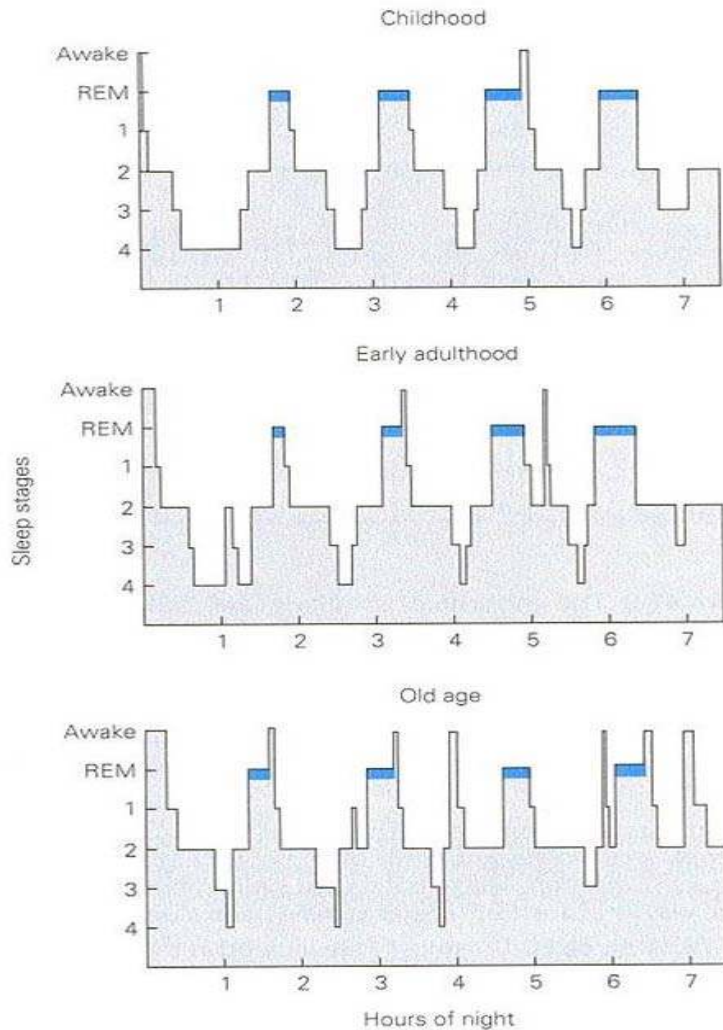


Ponto-Geniculo-Occipital (PGO) waves in REM sleep



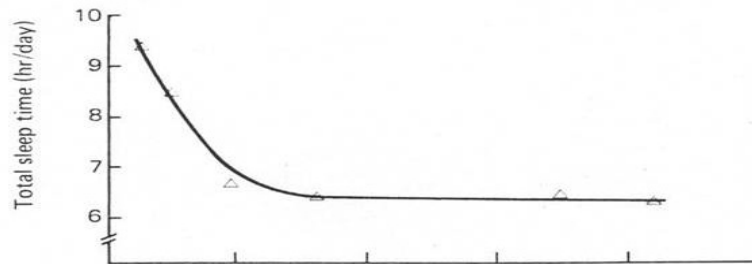
© 1992 Wadsworth, Inc.

Age-dependent characteristics of sleep cycles

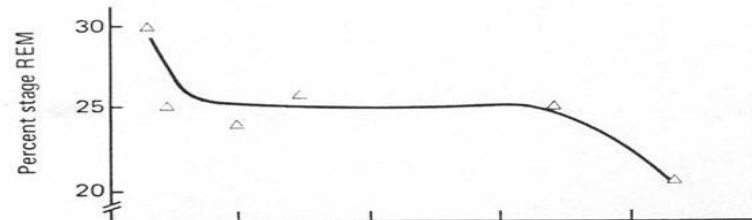


Age-dependent characteristics of sleep cycles

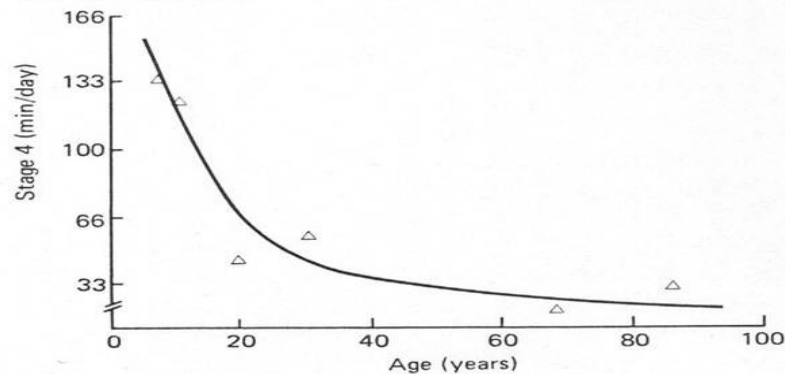
A Total sleep time



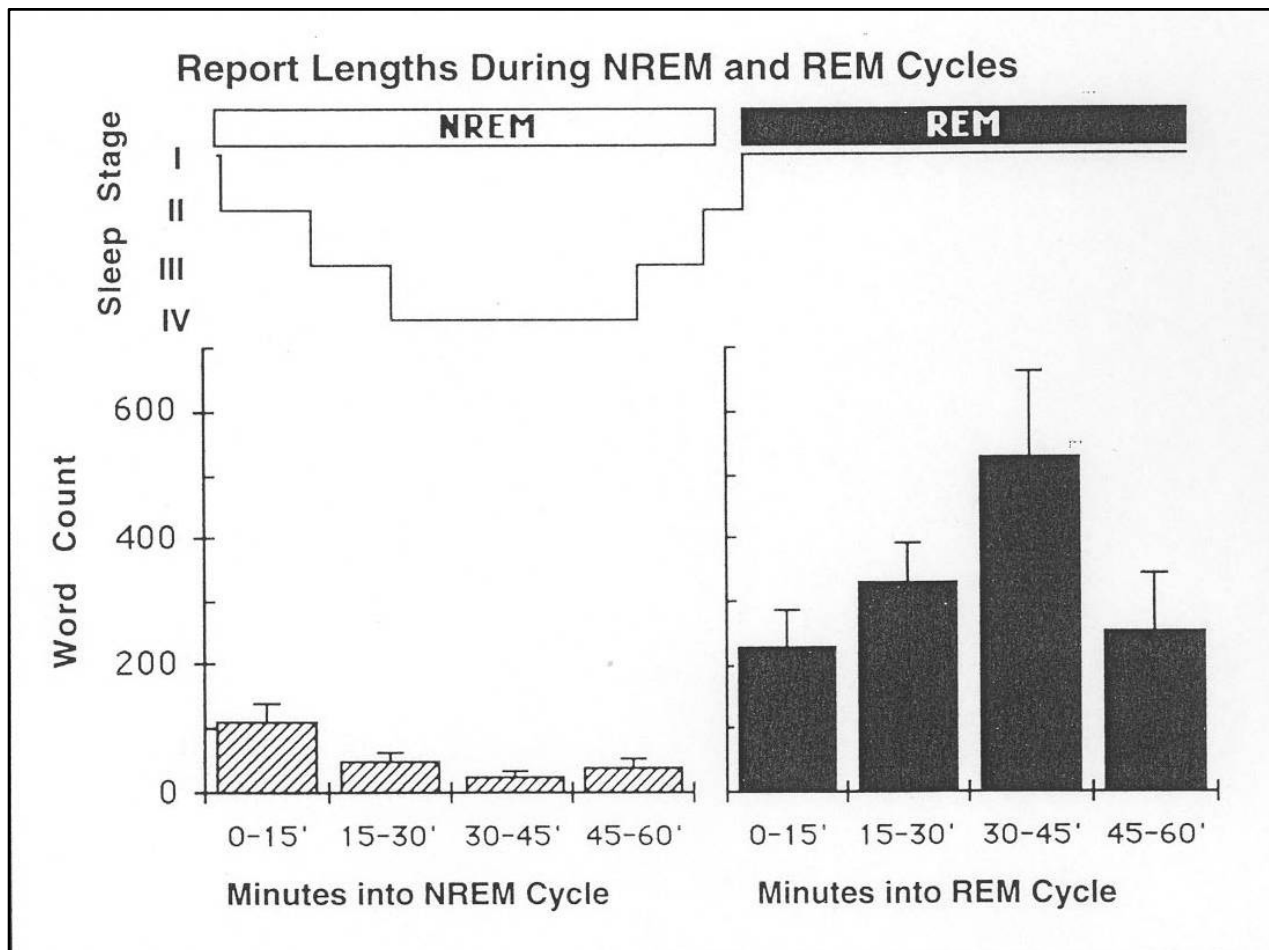
B Stage REM



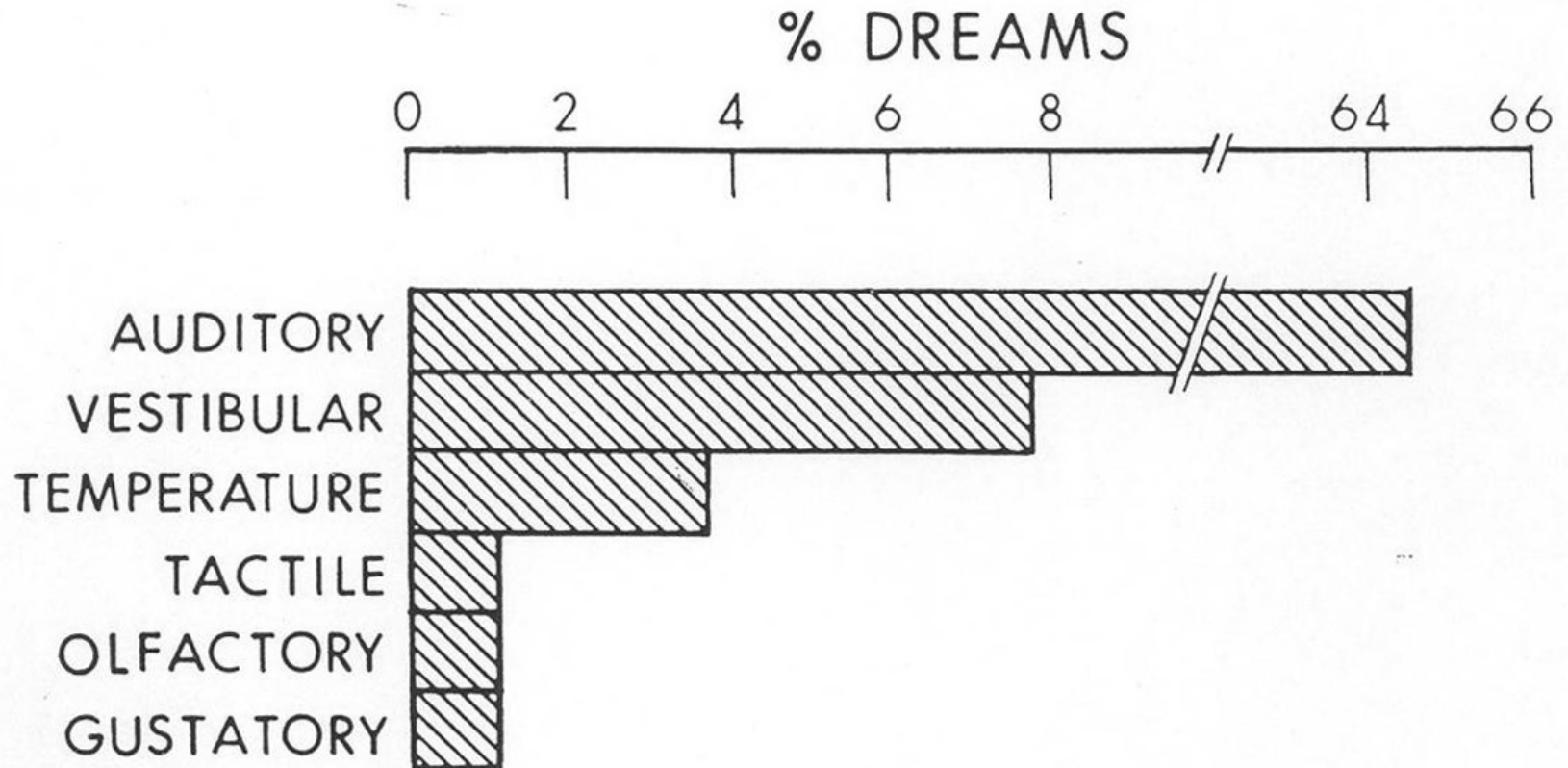
C Stage 4 non-REM



Dream report-lengths during NREM and REM phases



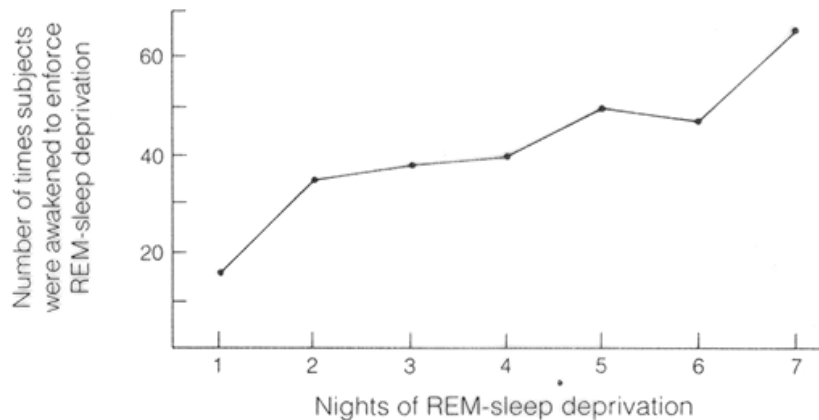
Proportion of sensory modalities in dream reports



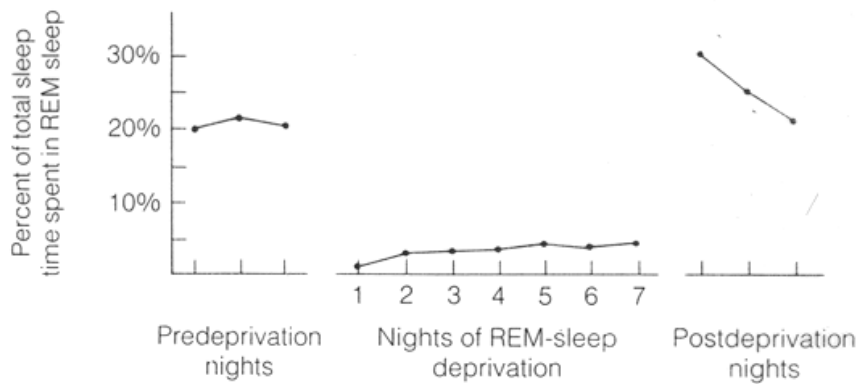
VISION = 100%

Effect of deprivation of REM sleep

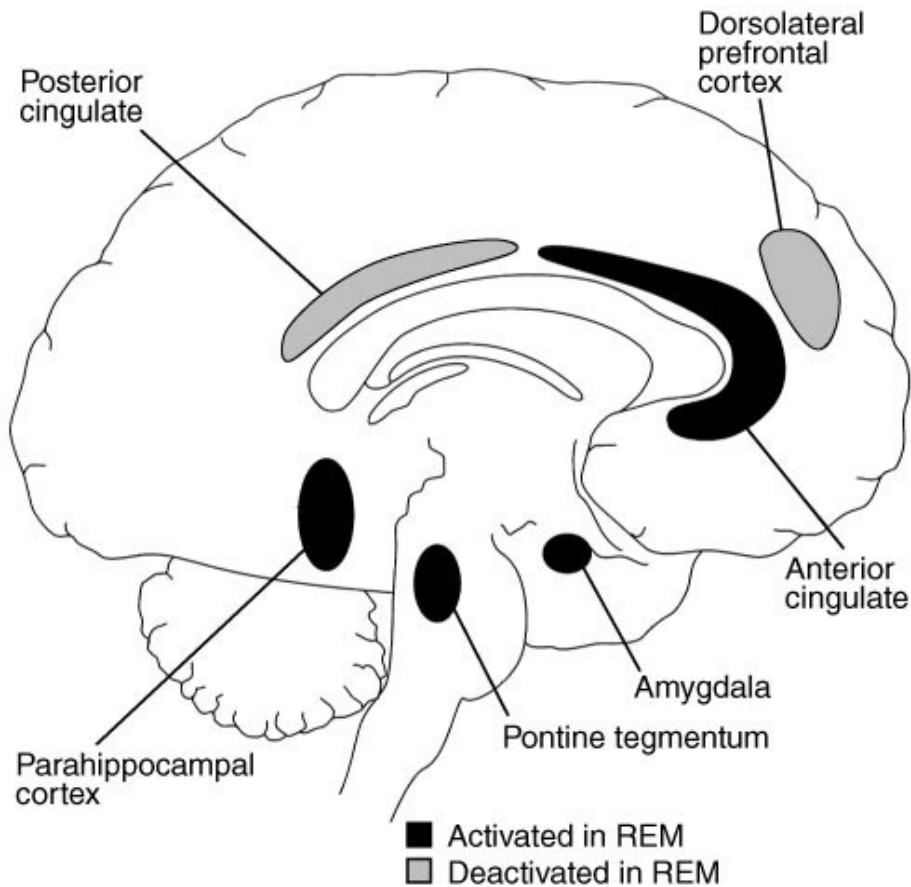
The number of awakenings required to deprive a subject of REM sleep increases as the period of deprivation ensues



After a period of REM-sleep deprivation, subjects spend a greater than usual portion of their sleep time in REM sleep



Active and inactive brain regions in REM sleep: results of PET studies



Physiology of the wake-sleep cycle

- The circadian rhythm
- Physiological characteristics of the sleep stages
- **Brain mechanisms responsible for the wake-sleep cycle**
- Sleep disturbance

Theories of wake-sleep regulation

Passive hypothesis – basic state is sleep – must find a waking center

Active hypothesis – basic state is awake, which is inhibited – must find a sleeping center

Chemical factors (adenosine, interleukin-1, $\text{TNF}\alpha$)

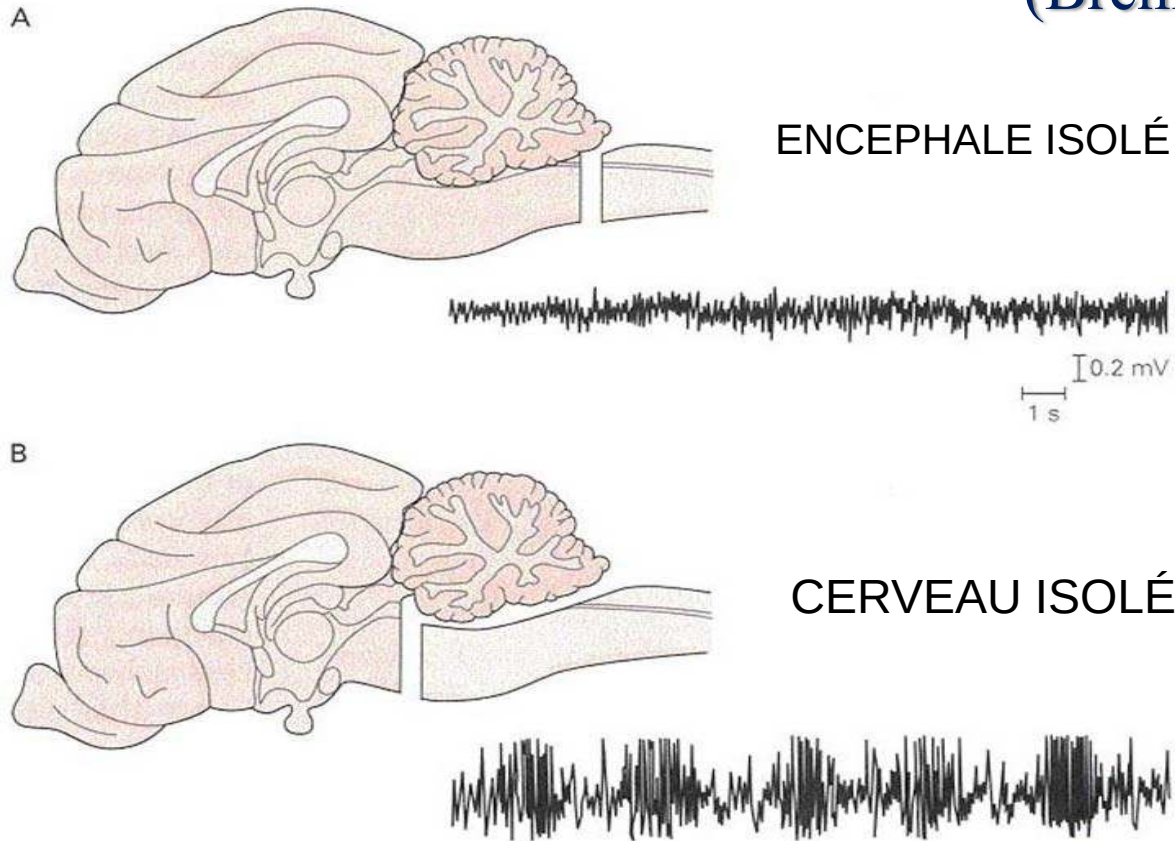
Center – theories

Effect of sleep deprivation

NREM 15-22 days

REM 16 hours

EEG effects of brainstem transections (Bremer 1935-37)



Sleep evoked by low frequency stimulation of the thalamus



Walter Rudolf Hess
1881-1973

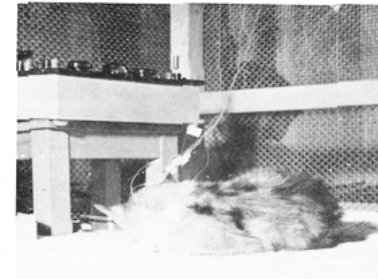
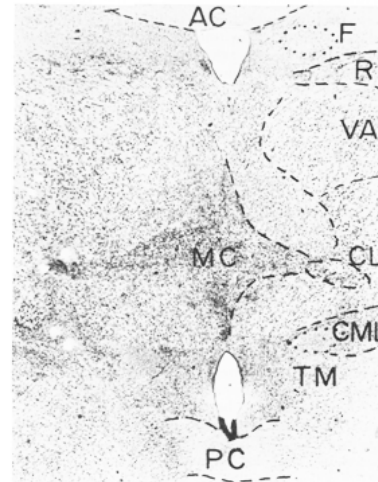
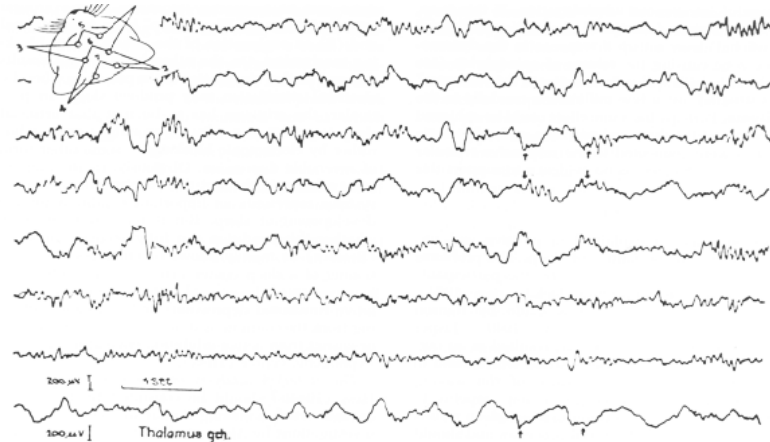
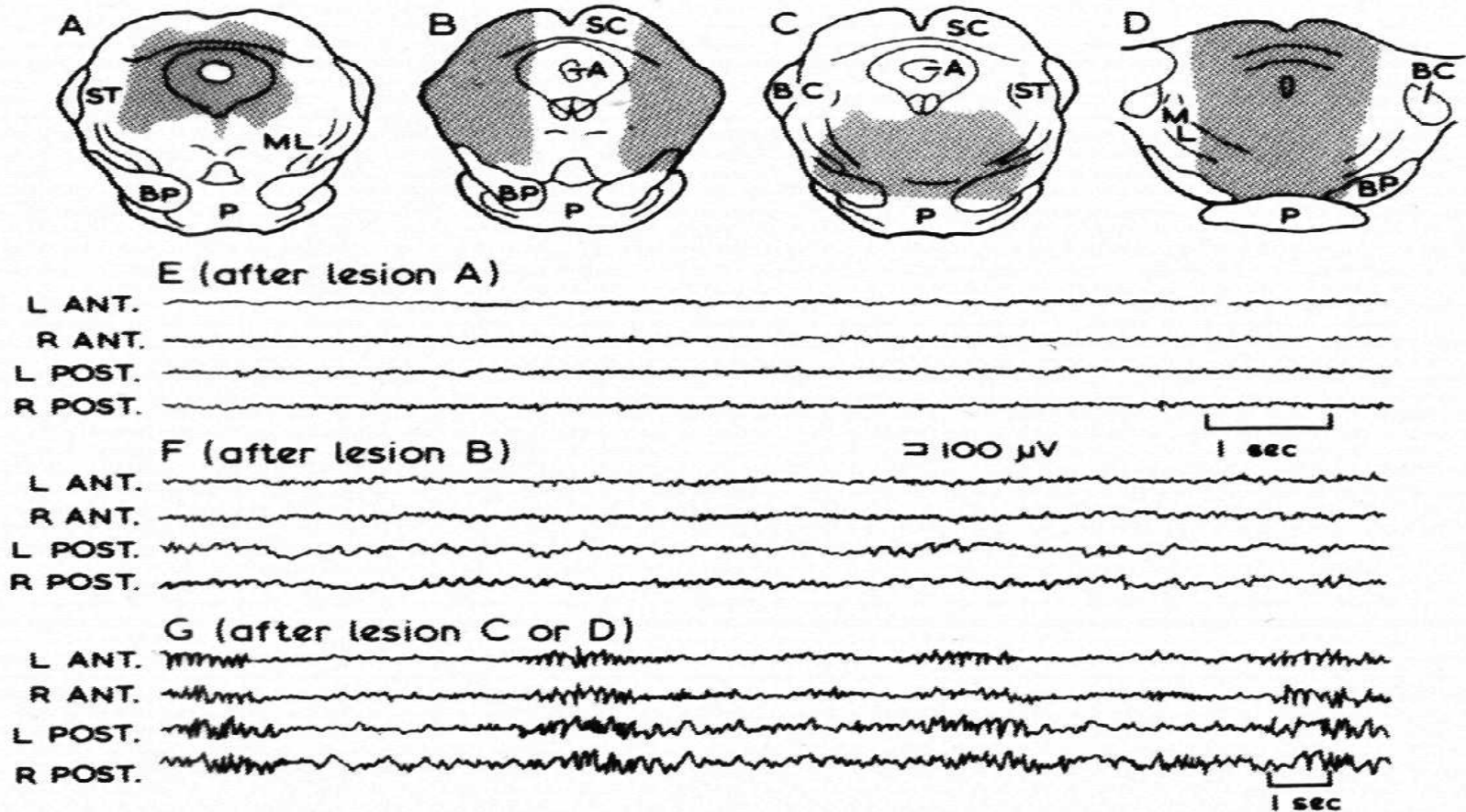
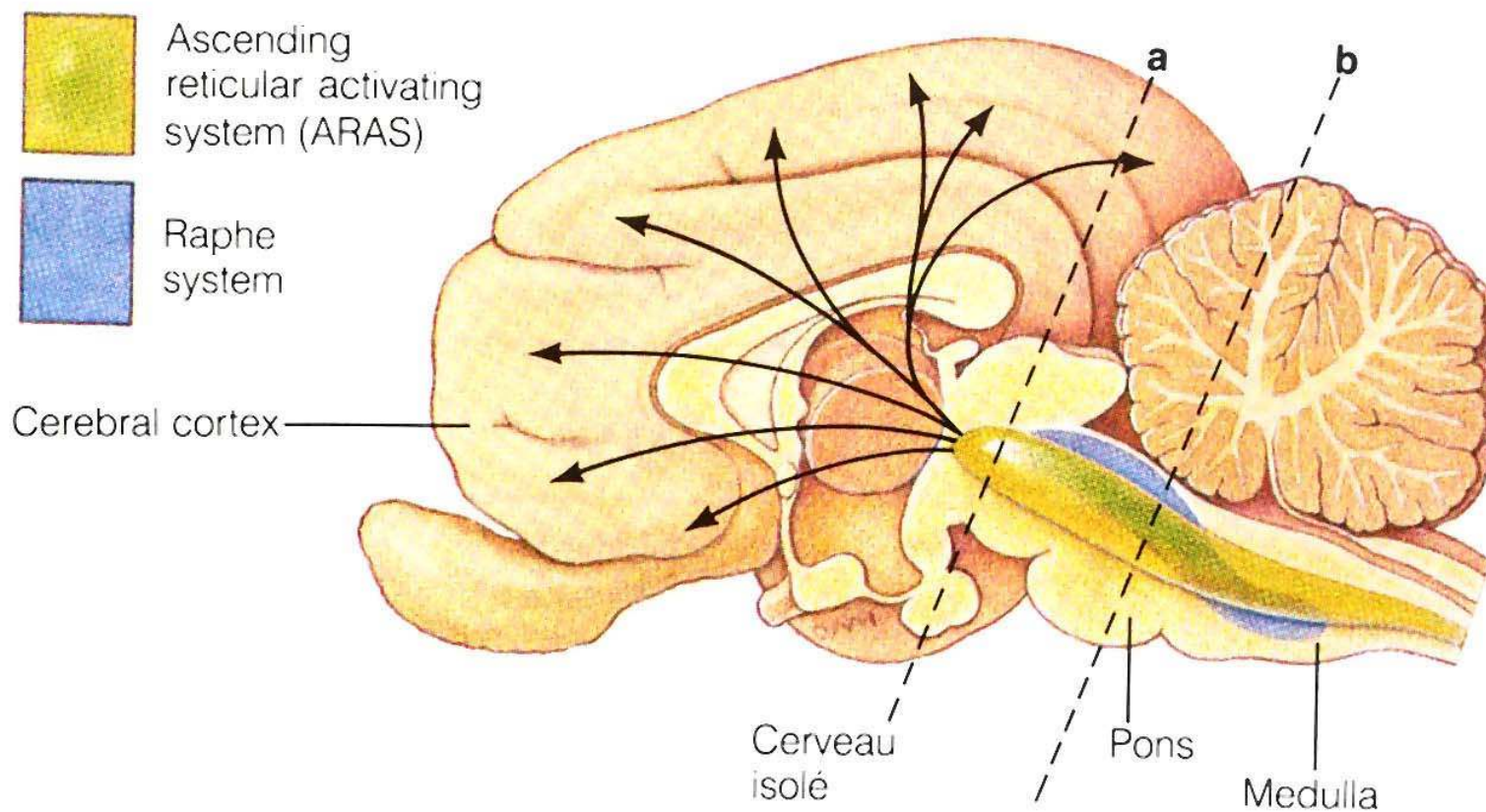


Fig. 20.13. Sleep produced by electrical stimulation of the intralaminar region of the thalamus. The EEG, localization of stimulating electrodes, and behavior of the same animal, cat 462, are shown. *EEG*: The record of spindle and delta wave activity in cortex and thalamus was taken during an interval between two stimulation periods, while the animal was sleeping. *Localization*: The tracks (region of the bare tips) of three twin needles are visible in the left thalamus (horizontal section passing through the anterior and posterior commissures). The sleep effect was produced by repeated

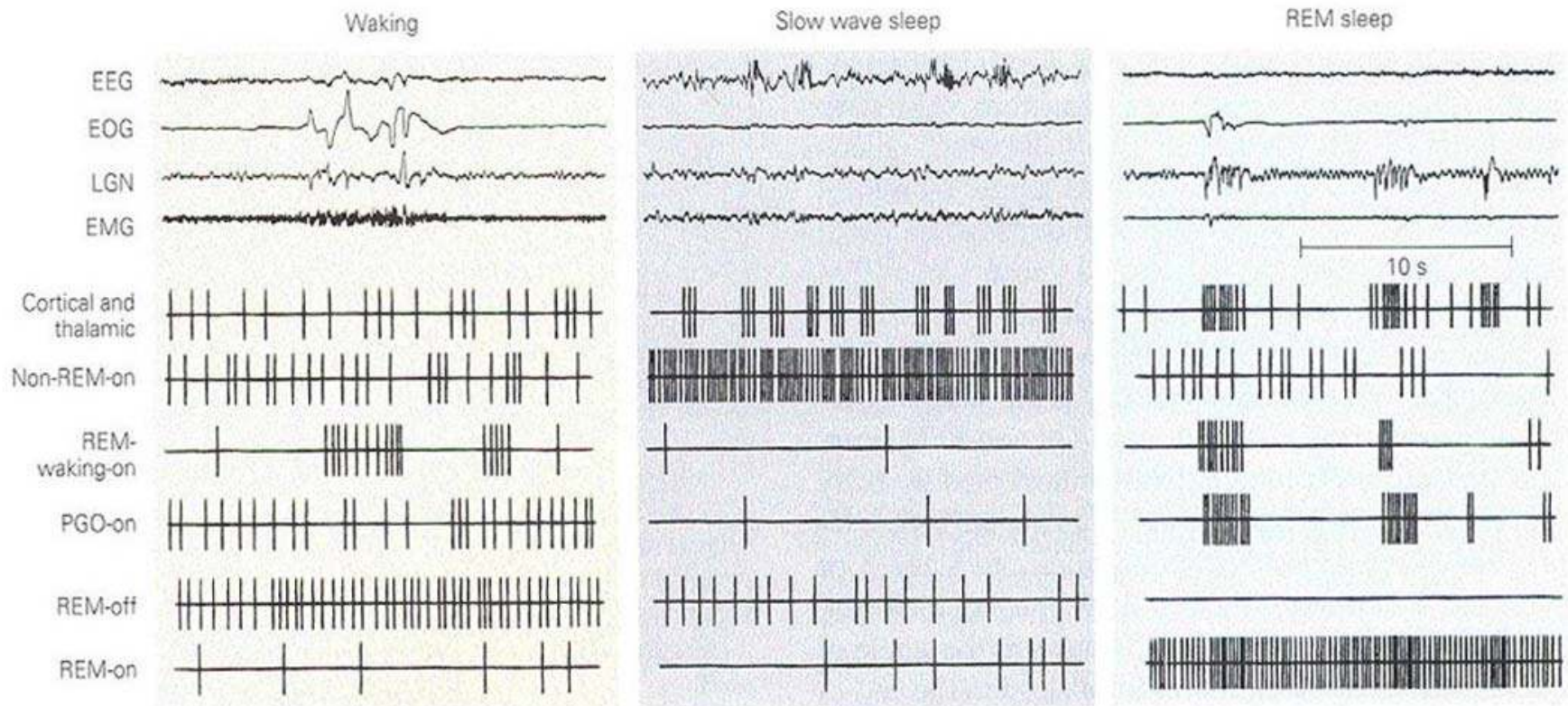
Effect of brainstem lesions (Moruzzi and Magoun, 1949)



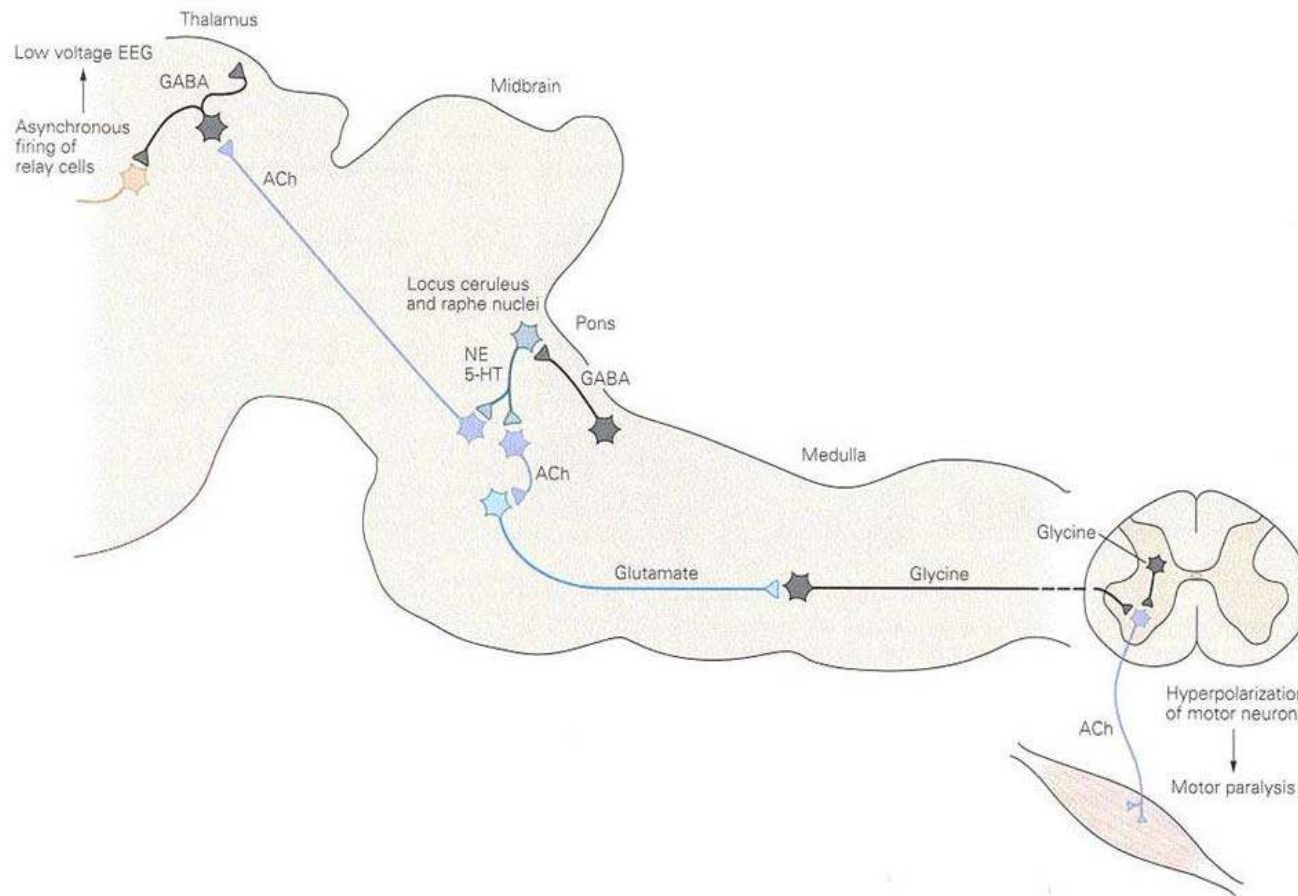
Reticular activating system



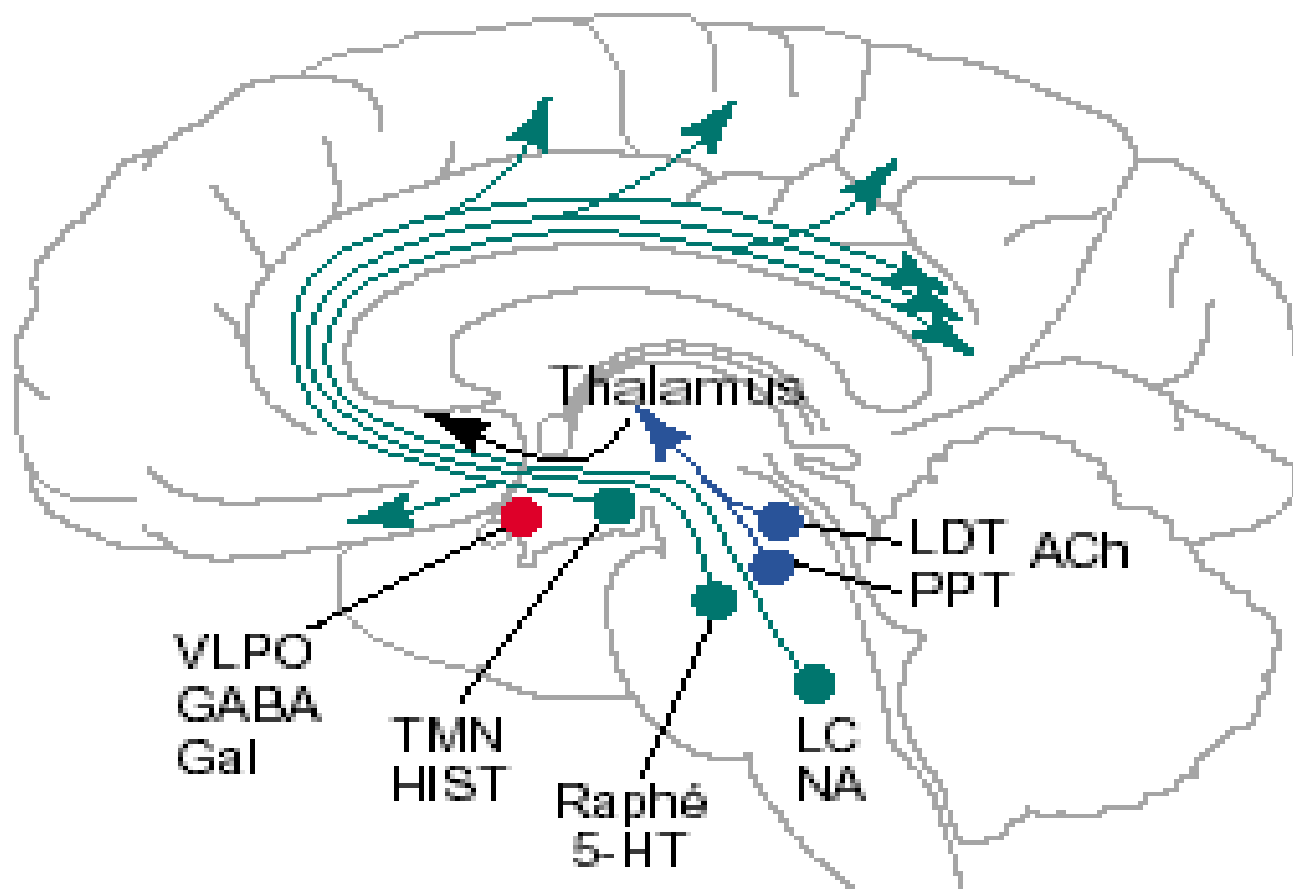
Deep brain single cell activities during sleep phases



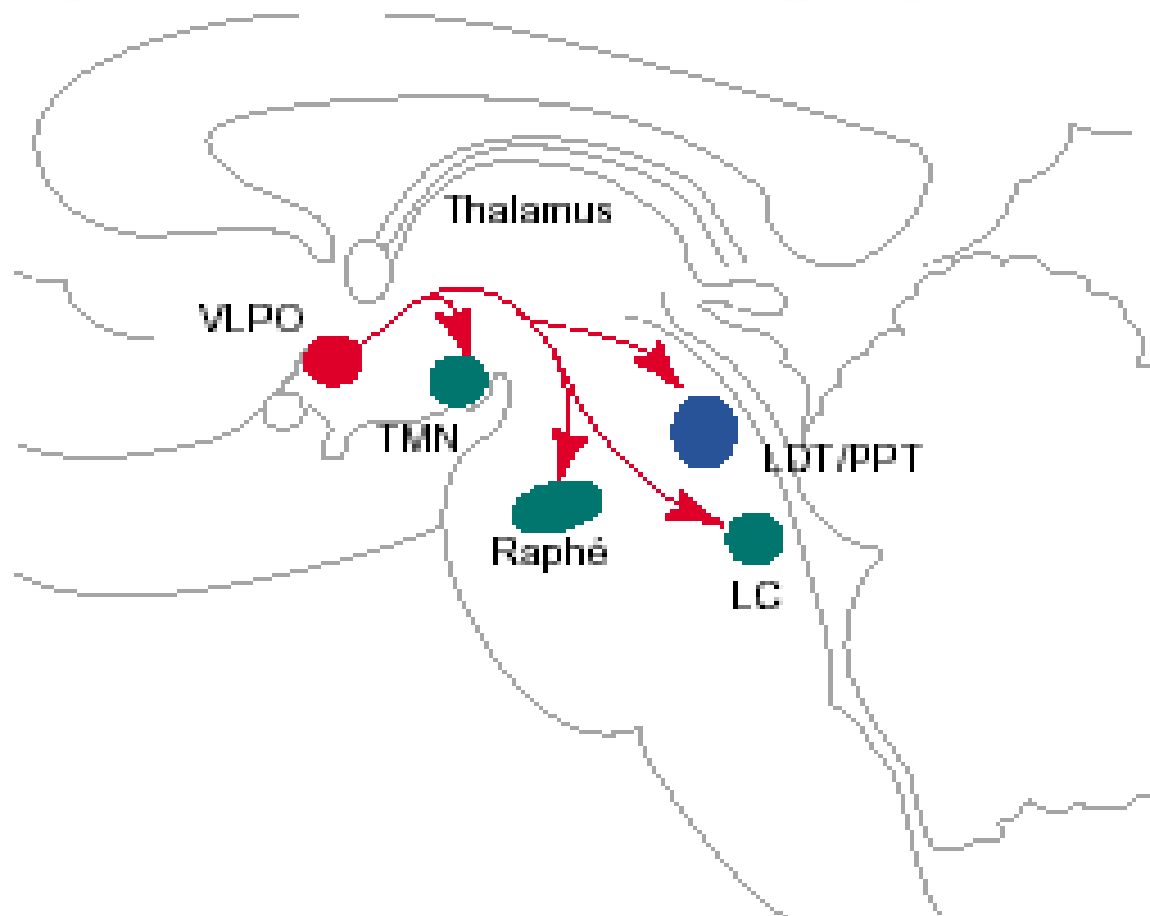
Postulated mechanism of REM atonia



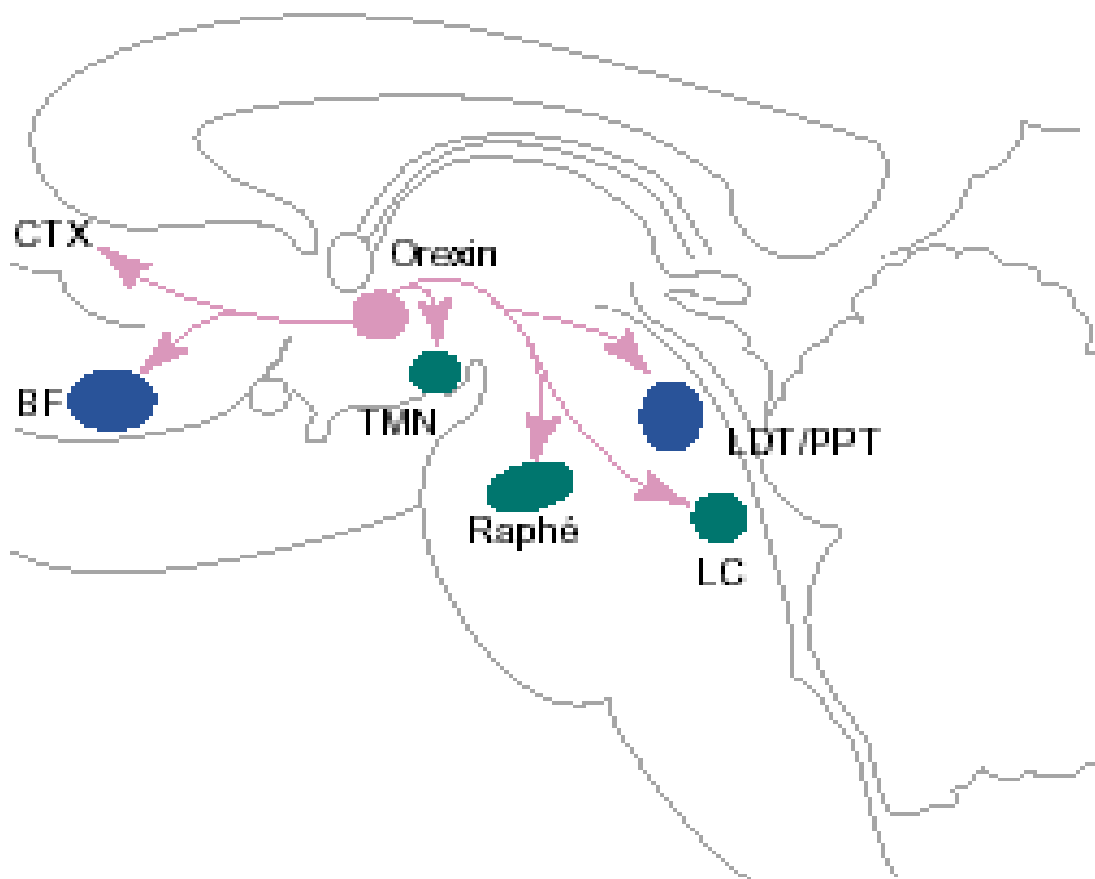
Elements of the brainstem activating system



Projections of the ventrolateral preoptic nucleus



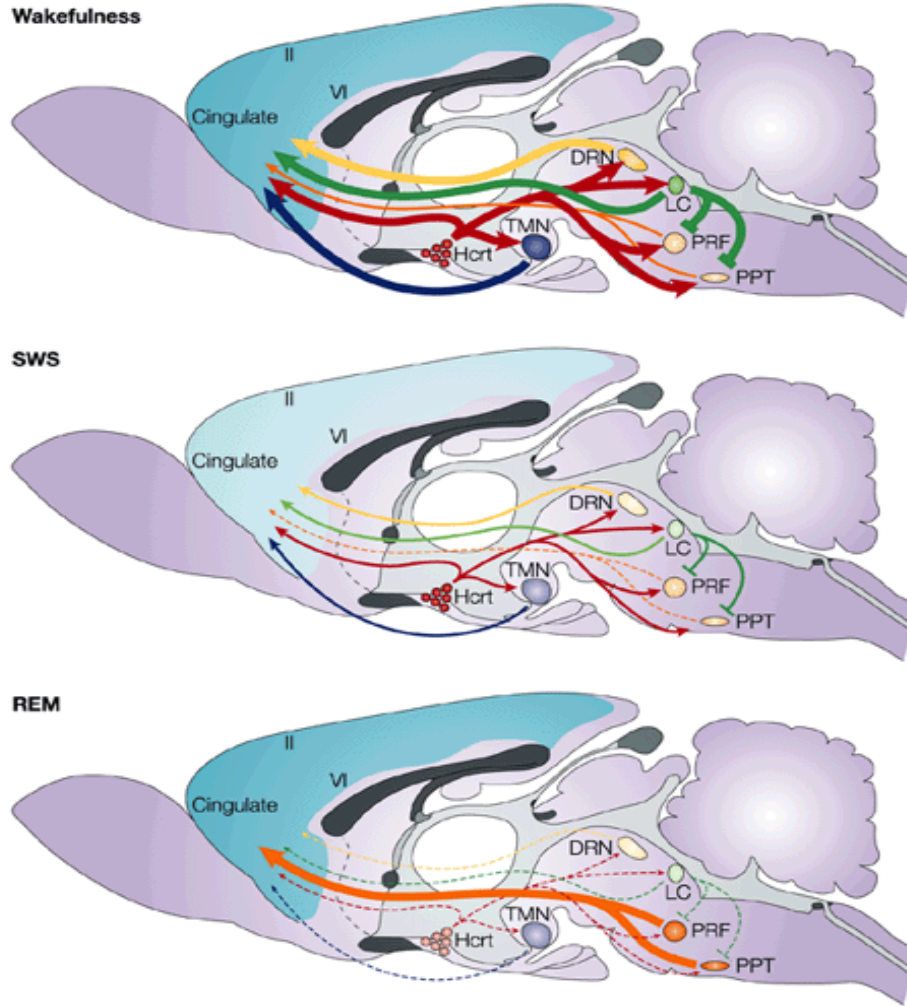
Projections of the orexin neurons



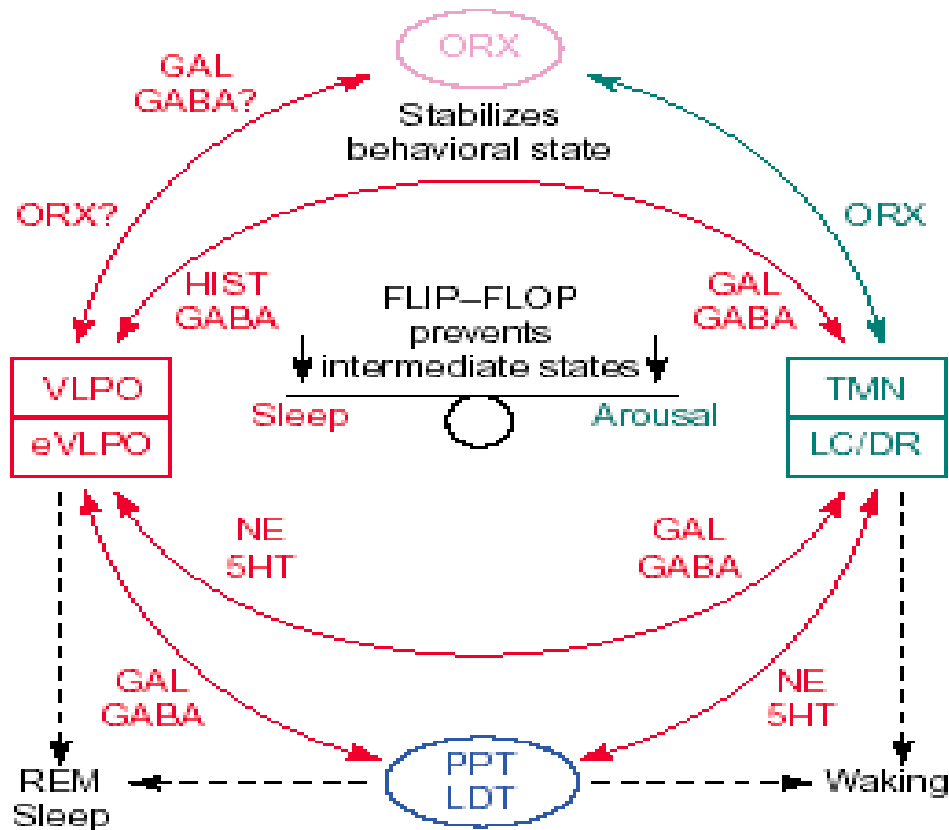
Function of the neurons participating in the regulation

	Wakefulness	NREM sleep	REM sleep
EEG	Fast, low voltage	Slow, high voltage	Fast, low voltage
Eye movement	Vision related	Slow, infrequent	Rapid
Muscle tone	↑↑	↑	0
LDT/PPT	↑	0	↑↑
LC/DR/TMN	↑↑	↑	0
VLPO cluster	0	↑↑	↑?
VLPO extended	0	↑?	↑↑
Orexin/hypocretin	↑↑	0?	0?
*Firing rates are as follows: two arrows = rapid firing, one arrow = slower firing, 0 = little or no firing. Question marks represent hypothesized firing patterns for which there is as yet no firm evidence. Abbreviations: DR, dorsal raphe nucleus; EEG, electroencephalogram; LC, locus coeruleus; LDT, laterodorsal tegmental nuclei; NREM, nonrapid eye movement; PPT, pedunculopontine tegmental nuclei; REM, rapid eye movement; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.			

Transmitter systems participating in the regulation



Model of the wake-sleep regulation



Physiology of the wake-sleep cycle

- The circadian rhythm
- Physiological characteristics of the sleep stages
- Brain mechanisms responsible for the wake-sleep cycle
- Sleep disturbance

Dyssomniák

Intrinsic alvászavarok
 Psychophysiológiai insomnia
 Insomnia objektív alvászavarok nélkül (sleep state misperception)
 Idiopathiás insomnia
 Narcolepsia
 Recurrens hypersomnia
 Idiopathiás hypersomnia
 Posttraumás hypersomnia
 Obstruktív alvási apnoe-syndroma
 Centralis alvási apnoe-syndroma
 Centralis alveolaris hypoventilatio-syndroma
 Periodikus lábmozgászavar
 „Nyugtalan láb”-syndroma

Extrinsic alvászavarok

Inadequat alvási hygiene
 Környezeti eredetű alvászavar
 Magassági insomnia
 Alkalmazkodási alvászavar
 Elégtelen alvás-syndroma
 Alvással kapcsolatos életrend kialakulatlanágából származó insomnia
 Kondicionáló tényezők hiányából származó insomnia
 Ételallergia okozta insomnia
 Éjszakai evés- (ivás) syndroma
 Altatószer-függőség okozta alvászavar
 Alkoholfüggőség okozta alvászavar
 Méregzéshez társuló alvászavar

A cirkadián ritmus zavara által

okozott alvászavarok
 Időzónaváltás-syndroma (jet lag)
 Váltott műszakos munka melletti alvászavar
 Szabálytalan alvás-ébredés mintázat

Késleltetett alvásfázis-syndroma
 Siettetett alvásfázis-syndroma
 Nem 24 órás alvás-ébredés ritmus

Parasomniák

Ébredési zavarok
 Ébredési zavartság
 Alvajárás
 Éjszakai félelmes felriadás

Az alvás-ébredés átmenet zavarai

Ritmusos mozgászavarok
 Alváskezdeti rángások
 Alvás alatti beszéd
 Éjszakai lábgyörcsök

REM-alvással kapcsolatos

parasomniák
 Lidércnyomás
 Alvási paralysis
 A peniserektio alvással kapcsolatos zavara
 Alvás alatti fájdalmas erectio
 REM-alvásban jelentkező asystolia
 REM-alvásban megjelenő magatartászavar

Egyéb parasomniák

Alvási bruxismus (fogcsikorgatás)
 Enuresis nocturna
 Nyelési reflex alvás alatti hiányából adódó aspiratio
 Nocturnalis paroxysmalis dystonia
 Hirtelen (magyarázat nélküli) éjszakai halál-syndroma
 Horkolás
 Csecsemőkori alvási apnoe
 Congenitalis centralis hypoventilatio-syndroma
 Hirtelen csecsemőhalál-syndroma
 Benignus újszülöttkori alvási myoclonus

Belgyógyászati/psychiatriai

betegségekkel társuló alvászavarok
 Elmebetegségek
 Psychosisok
 Hangulat-zavar
 Szorongásos zavar
 Pánikbetegség
 Alkoholizmus

Neurológiai betegségek

Agyi degeneratív megbetegedések
 Dementia
 Parkinsonismus
 Fatális familiaris insomnia
 Alváshoz társuló epilepsia
 Alvás alatti elektromos status epilepticus
 Alvással kapcsolatos fejfájások

Egyéb belgyógyászati betegségek

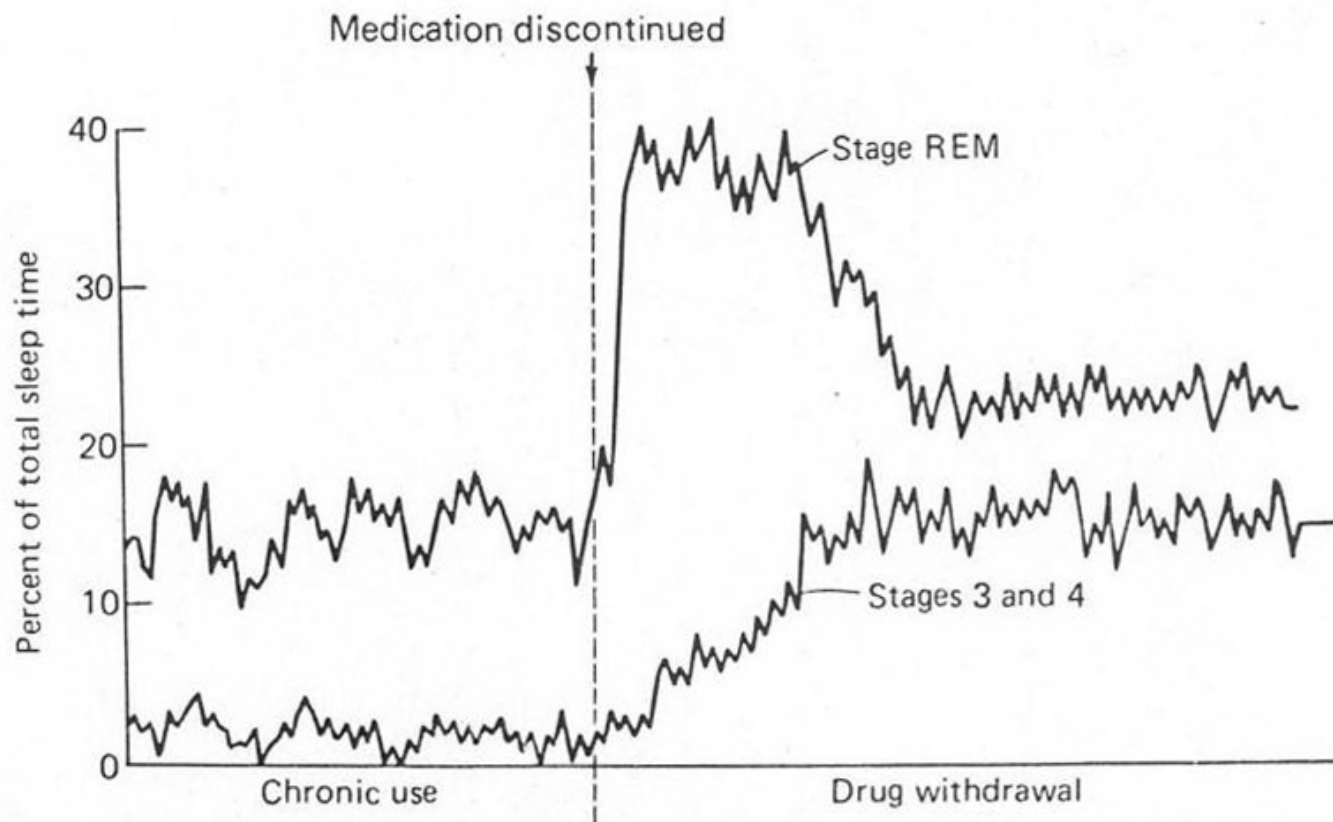
Alomkór
 Éjszakai cardialis ischaemia
 Chronikus obstruktív tüdőbetegségek
 Alvással kapcsolatos asthma
 Alvással kapcsolatos gastroesophagealis reflux
 Gyomor-, nyombéllelkegy
 Fibrositis-syndroma

Feltételezett alvászavarok

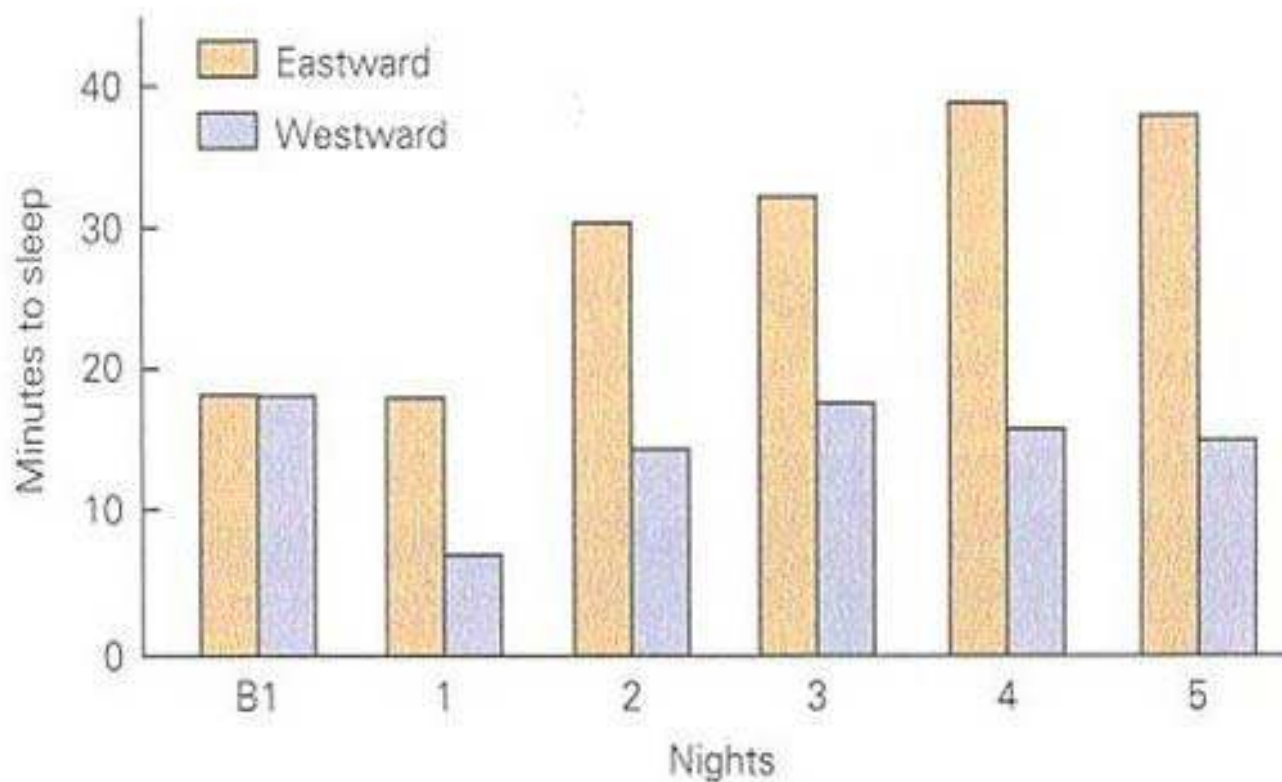
Kis alvási igényűek (rövid alvók)
 Nagy alvási igényűek (hosszú alvók)
 Éberségi szint fenntartási zavara
 Abortív myoclonus
 Alvási hyperhidrosis
 Menstruációhoz társuló alvászavar
 Terhességhez társuló alvászavar
 Félelmes hypnagog hallucinációk
 Alvás alatti neurogen tachypnoe
 Alvás alatti laryngospasmus
 Alvás alatti fulladás-syndroma

International classification of sleep disturbances

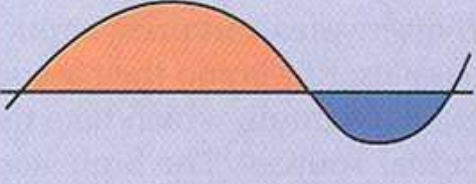
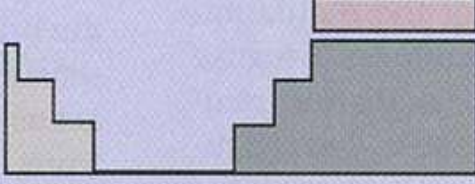
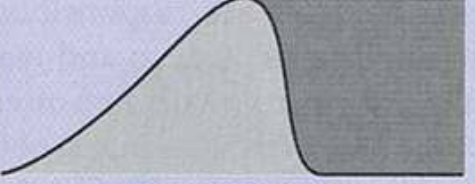
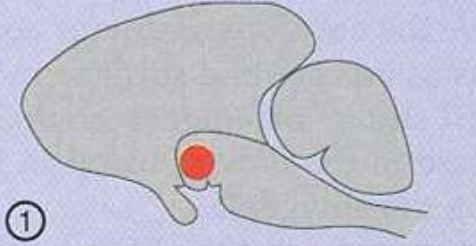
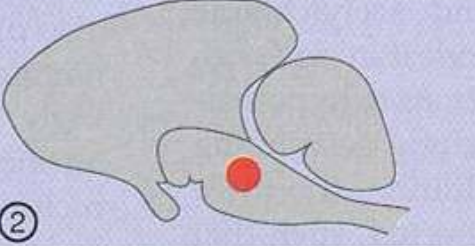
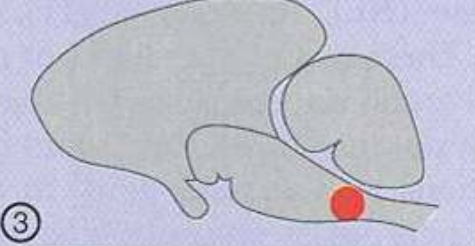
Effect of sleep pill deprivation

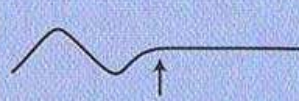
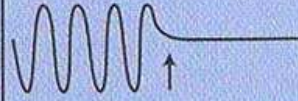
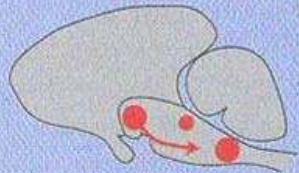
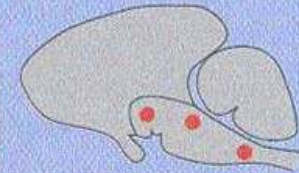
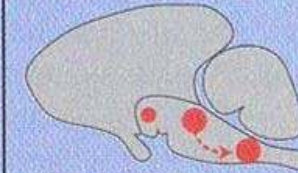
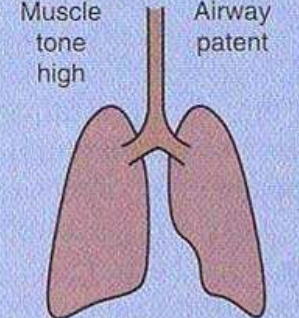
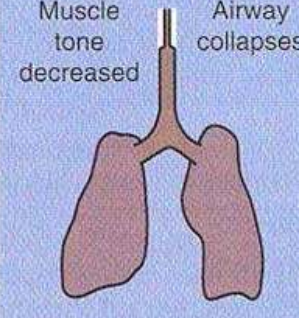
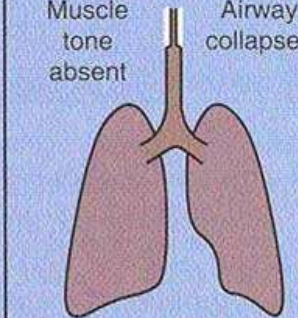


Effect of travelling through several time zones



Biological rhythms and the brainstem biological clocks

	Activity / rest	NREM / REM	Inspiration / expiration
Phases			
Period	24 - 25 hours	90 - 100 minutes	3 - 4 seconds
Brain locus of clock			
Cellular mechanism	Unknown, suprachiasmatic nucleus implicated	Reciprocal interaction of cholinergic and aminergic neurons	Reciprocal inhibition of respiratory and expiratory neurons
Function	Synchronizes internal rhythms with external forces	Sets "state" of organism	Regulates gas exchange

Wake	NREM sleep	REM sleep
Eupnea / hyperpnea  ↑ Voluntary or metabolic response	Hypopnea / apnea  Obstruction	Hyperpnea / apnea  Desynchronization of respiratory oscillator
 Strong tonic neural drive	 Decreased tonic neural drive	 Increased tonic and phasic neural drive
Muscle tone high Airway patent 	Muscle tone decreased Airway collapses  Forced expiration	Muscle tone absent Airway collapses 

Relationship between sleep and respiration

**OBSTRUCTIVE SLEEP APNEA SYNDROME
OSAS**

**Continuous Positive Airway Pressure
CPAP**