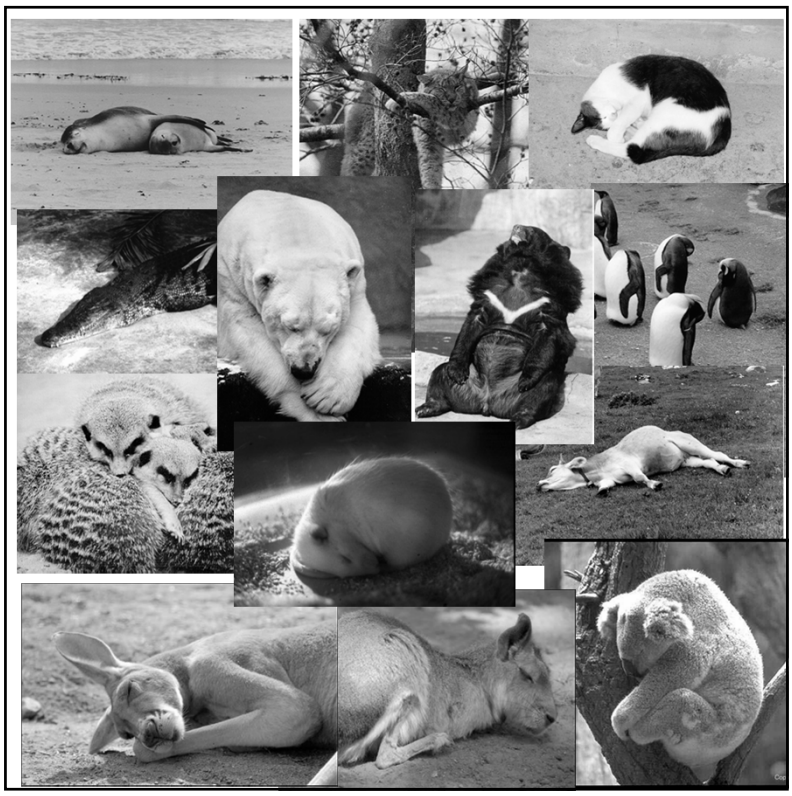
Regulation of Sleep and Wakefulness



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Definition of sleep

- rest-activity NOT= sleep-wakefulness
- general criteria of sleep
  - lack of movements
  - elevated sensory threshold
  - full reversibility
  - stereotypic posture
  - specific resting place
  - circadian organization
  - homeostatic regulation: deprivation – rebound
- mammals (and birds) - polygraphic criteria

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Stages in human sleep

- Berger 1929: arousal level is related to EEG patterns: δ, θ, α, β, later γ
- Loomis 1937: 5 stages of the sleep-wakefulness – 1 W and 4 SWS
- Aserinsky and Kleitman 1953: discovery of paradoxical sleep related to dreaming
- Rechtschaffen-Kales criteria
  - NREM1: 2-7 Hz, slow eye movements, <20 μV
  - NREM2: spindles, K-complexes, slow waves at low amplitude
  - NREM3: <2 Hz >75 μV waves 20-50%
  - NREM4: <2 Hz >75 μV waves >50%
  - REM: cortical activation, lack of muscle tone, rapid eye movements, twitches

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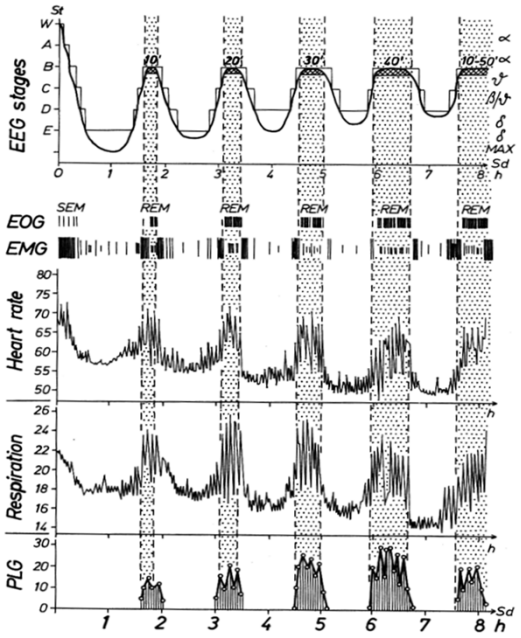
Physiological variables in sleep



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REM sleep in humans

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Why do we sleep?

- Because it is nighttime
  - circadian regulation
- Because I am sleepy
  - homeostatic regulation
- Because the lecture is boring
  - luxury sleep – effects of internal-external stimuli

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Types of biological rhythms

- what do we call rhythm in a living organism? – physiological events occurring at approximately regular times
- internally controlled rhythms: breathing, heart beat, gut motility, brain waves, etc.
- externally determined rhythms: singing in certain birds, tulips, etc.
- rhythms controlled by an internal clock that is synchronized to the environment by Zeitgebers (synchronizing factors) – when these are missing: free-running rhythm

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External-internal rhythms

Credit: National Library of Medicine

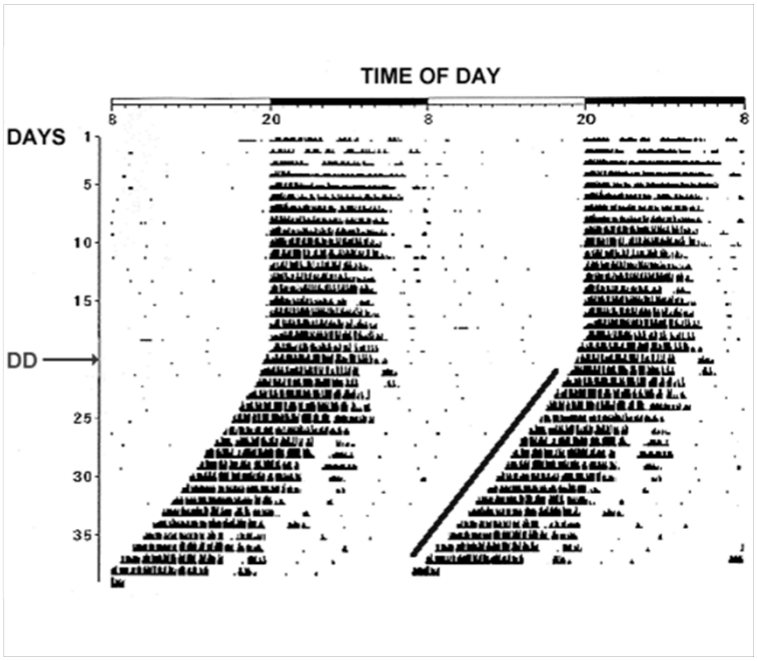
DES SCIENCES. 35

OBSERVATION BOTANIQUE.

- De Mairan (1729): leaf movement of mimosa continues in darkness

10/34

Circadian rhythm in hamster



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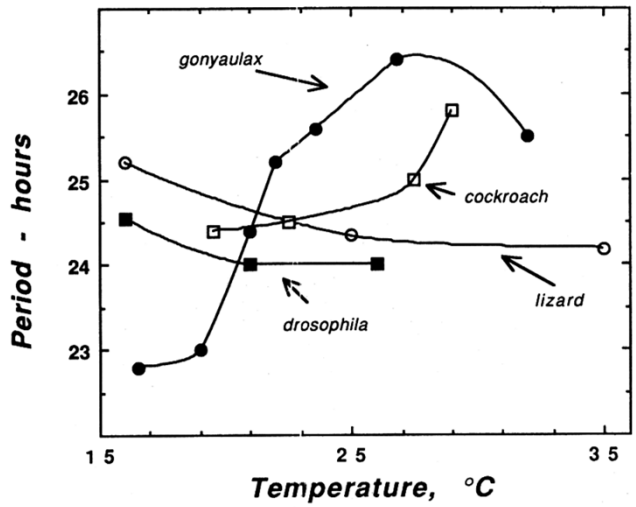
Temperature dependency of circadian rhythms



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Light effects

- circadian period (T) of diurnal and nocturnal animals change in opposite direction in constant light (LL) :
  - Aschoff's rule:
    diurnal animal: T decreases with light intensity
    nocturnal animal: T increases with light intensity
  - circadian rule:
    diurnal animal: wake/sleep ratio increases with light intensity
    nocturnal animal: wake/sleep ratio decreases with light intensity
- the strong physiological effect of light is also shown by persistent oestrus
- short light impulses can change the phase of circadian rhythms

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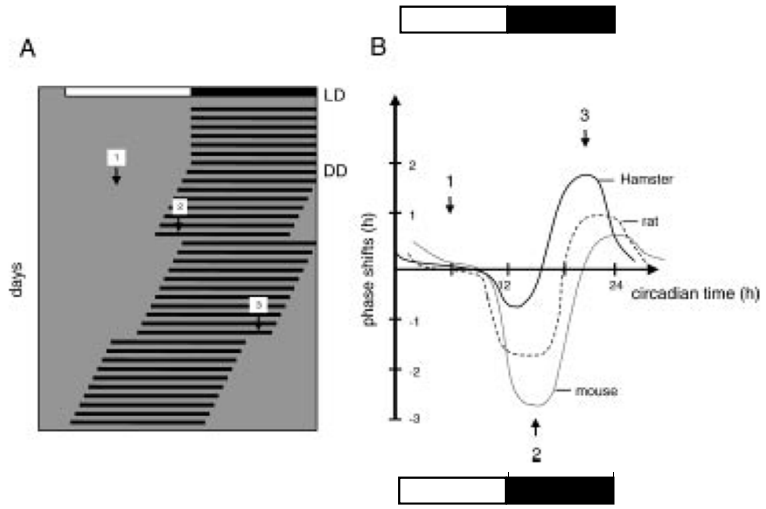
Phase-response curve I. (PRC)



Hannibal, Cell & Tissue Res. 309:73,2002

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Master clock of daily rhythms

- daily rhythms can be examined the most easily and probably they are the most important
- master clock was sought along the optic pathway lesioning various neuron groups
- two teams, independently, but simultaneously located the master clock:
  - Stephan and Zucker, 1972
  - Moore and Eichler, 1972
- it is the tiny, paired nucleus in the anterior hypothalamus, above the crossing of the optic tract: the nucleus suprachiasmaticus (SCN)
- in non-mammalian species, clock is also associated with the optic pathway

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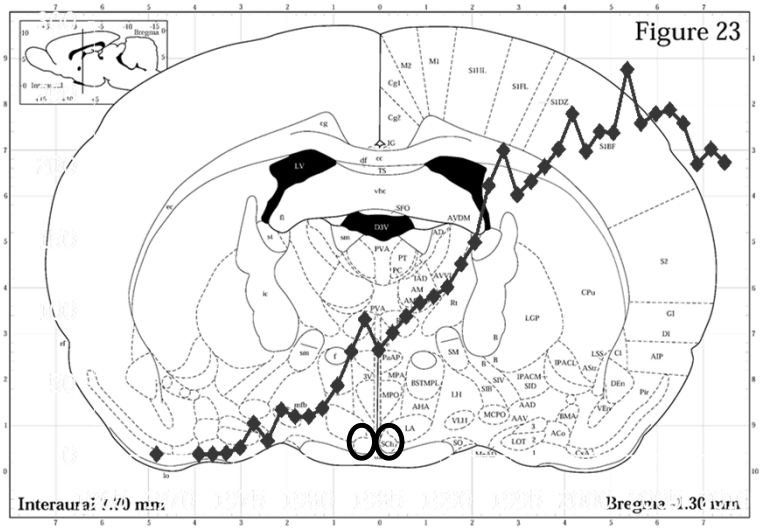
Pulvinar projections to the SCN



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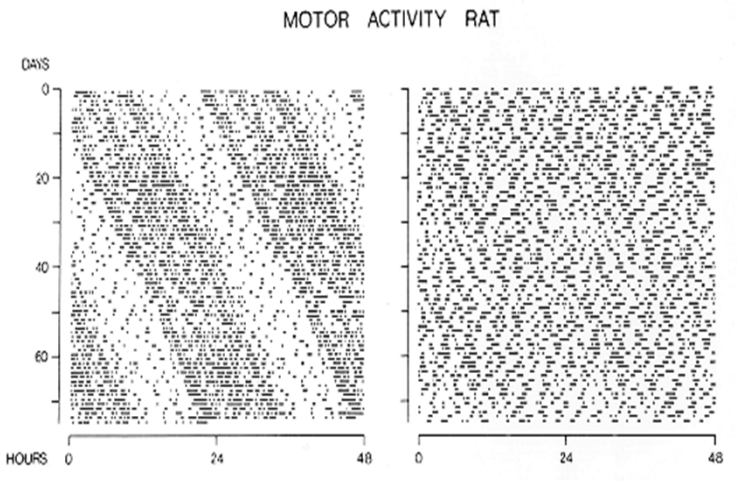
Effect of SCN ablation in rats



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Discovery of clock genes

- 1985 – Martin Ralph – tau-mutant hamster
- short period in continuous dark (DD), Mendelian inheritance (20/22/24)
- breakthrough in 1994 using forward genetics – Vitaterna (PhD student)
- Clock mutant among the first 42 mice – abnormally long period, ceases in DD
- the mutation caused loss of a glu-rich region characteristic for bHLH type transcription factors
- conclusion: CLOCK is a transcription factor
- CLOCK also contains a PAS (Per-Arnt-Sim) domain – ability to form dimers with similar proteins

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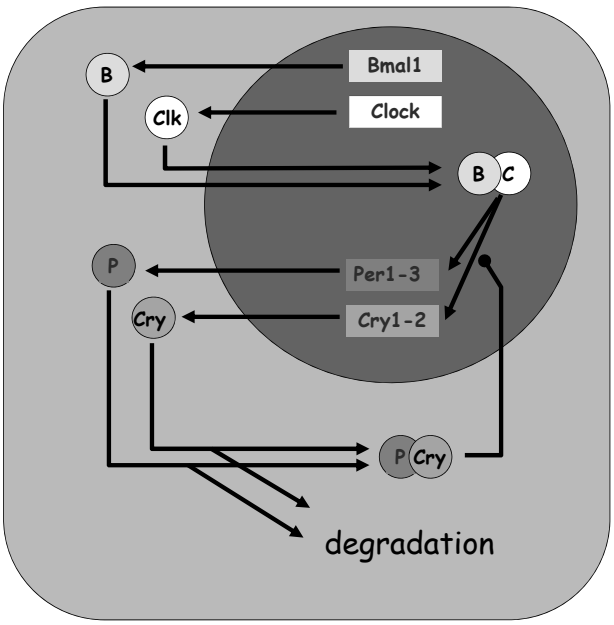
Clock mechanism (mammals)



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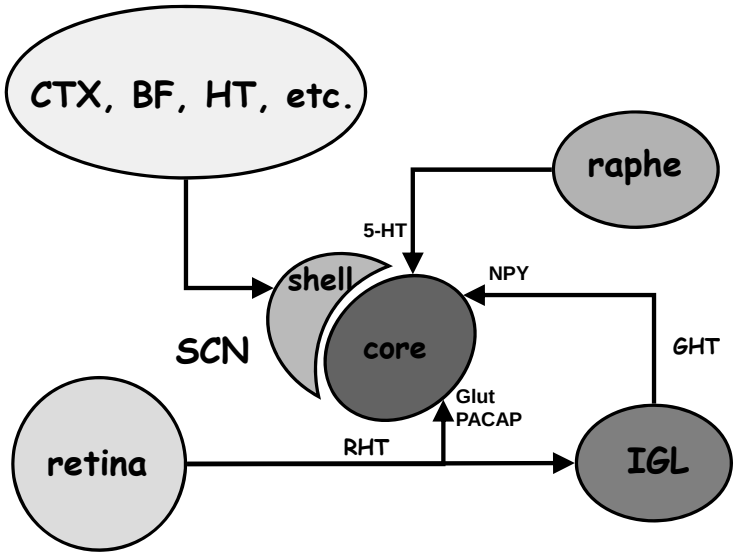
Inputs to the SCN



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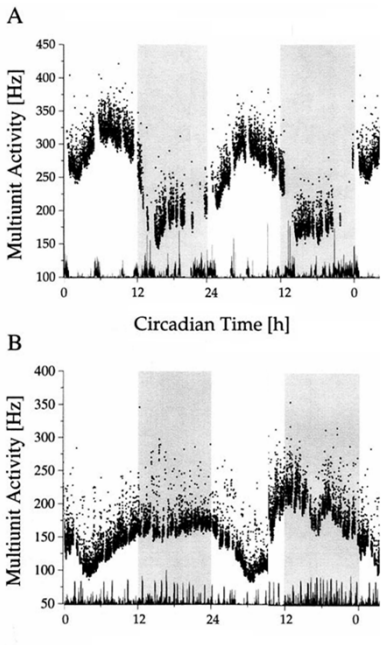
SCN activity in vivo

SCN

HT



Meijer, J.H., Watanabe, K., Schaap, J., Albus, H., **Détári, L.**., J. Neurosci. 18(1998):9078

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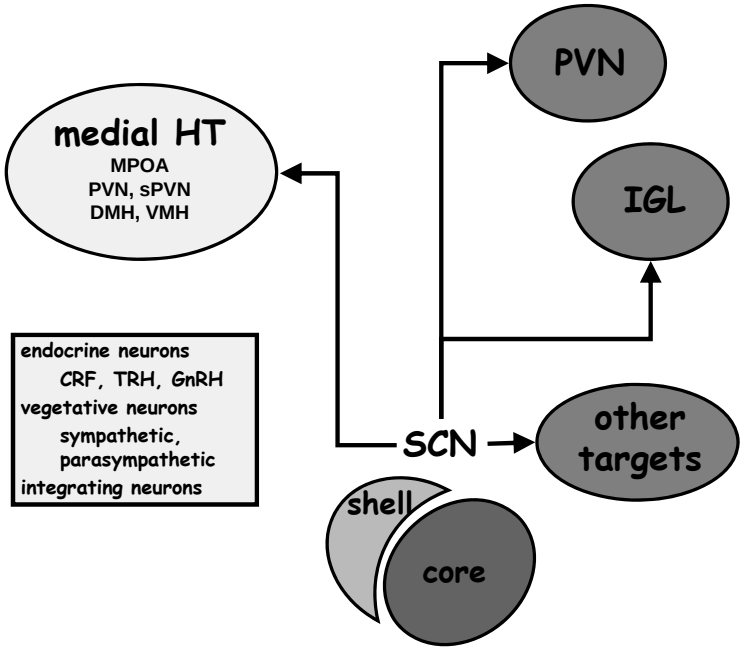
Outputs of the SCN



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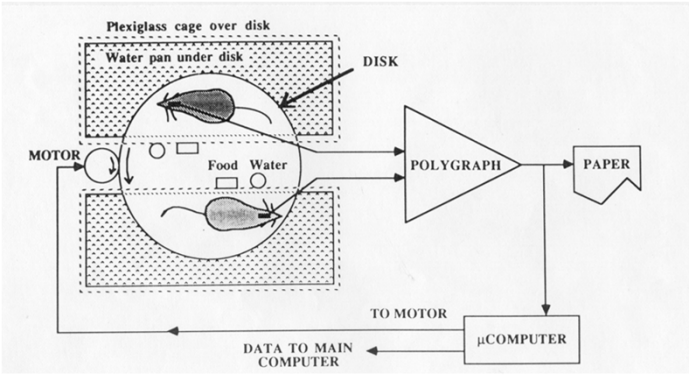
Humoral regulation of sleep

- closely related to homeostatic regulation
- something is being accumulated or used up
- sleep can be easily disturbed, but difficult to induce, appropriate control is a main issue

- two approaches:
  - harmful effects of sleep deprivation
    - stress is difficult to eliminate
    - motivation to sleep is almost as strong as motivation to avoid pain - torture
  - isolation of sleep factors
    - following sleep deprivation
    - during natural or experimentally evoked sleep
    - testing prospective signal molecules normally present in our body

24/34

Sleep deprivation



NREM deprivation: set-point of thermo-regulation increases
REM deprivation: heat dissipation increases
energy homeostasis becomes disturbed

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Sleep factors

- Ishimori, Pieron, ~1910: dogs kept awake by forced walking for 10 days – successful sleep transfer
- methodological problems – repeated with positive results in goat-rat experiments
- deprivation is not needed for the effect – collection of human urine
- end result: muramyl peptide from the bacterial cell wall
- Monnier sleep induced by thalamic stimulation in rabbits: DSIP (9 aa-s) – the best candidate
- but: these are not natural sleep factors
- natural signal molecules: GHRH, adenosine, interleukin-1, TNFa, PGD2

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Transfer of natural sleep

- parabiotic animals: Matsumoto, 1972 – higher synchronity of NREM and REM sleep than between animals joined by their skin only
- de Andres, 1976 – transplantation of an additional head to dogs – independent sleep, 108 h survival
- Siamese twins – independent sleep is possible, but contradicting results exist
- Mukhametov, 1985-87 sleep in dolphins – the two hemispheres can sleep separately
- described in other animals as well: birds, whale, etc. – complete decussation of the visual pathway is a prerequisite

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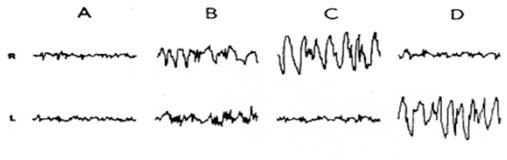
Unihemispheric sleep in dolphins



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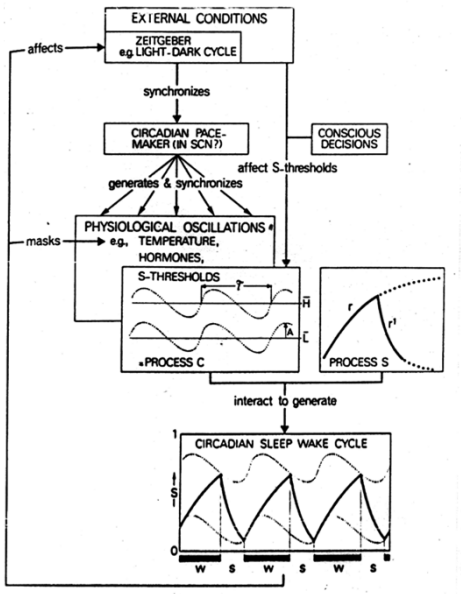
Synthesis



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Neuronal regulation of sleep

- active hypothesis – basal state: waking
  - Pavlov: irradiation of inhibition
  - search for sleep centers - criteria:
    - lesion – elimination of sleep
    - stimulation – induction of sleep
    - neuronal activity – correlated with sleep
  - von Economo: encephalitis outbrake – basal forebrain
  - midpontine pretrigeminal transsection - raphe – Jouvet, 1967
  - spindles - thalamus – Andersen and Anderson, 1968
- passive hypothesis – basal state: sleep
  - classical transsections of Bremer, 30's
  - Moruzzi and Magoun, 1959 - ARAS
  - Shute and Lewis, 1967 – supposed ACh pathways

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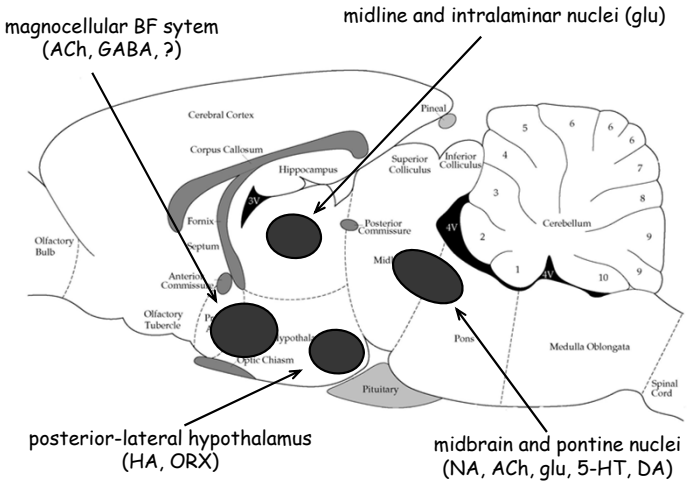
Arousing areas



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Role of the basal forebrain

- von Economo: BF-POA promotes sleep, posterior HT promotes wakefulness
- Sterman and Clemente 1962- lesion causes decreased or fragmented sleep
- stimulation – sleep (also at high frequency!)
- conditioned response to sounds
- warming, ACh crystals – sleep
- late 70's, early 80's – description of the cholinergic system
- cholinergic cells disappear or shrink in Alzheimer's disease
- electrical – excitotoxic – selective lesion
- corticopetal projection is not exclusively cholinergic
- SCN, thermoregulation, proximity of HT, VLPO, prefrontal cortex – high importance

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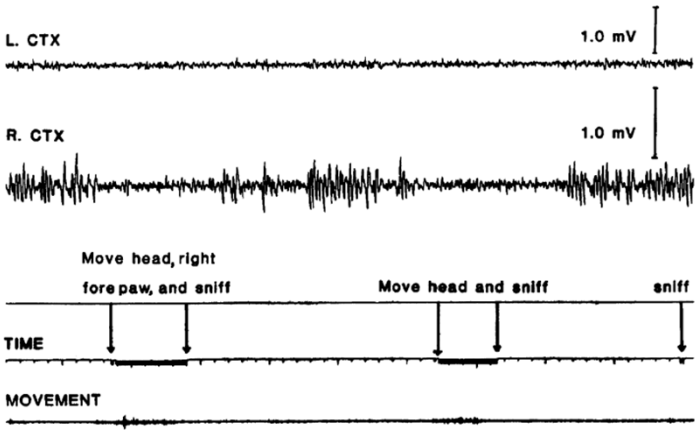
Unilateral lesion of BF I.



Vanderwolf, C.H., *Int. Rev. Neurobiol.,* 30 (1988): 225-340

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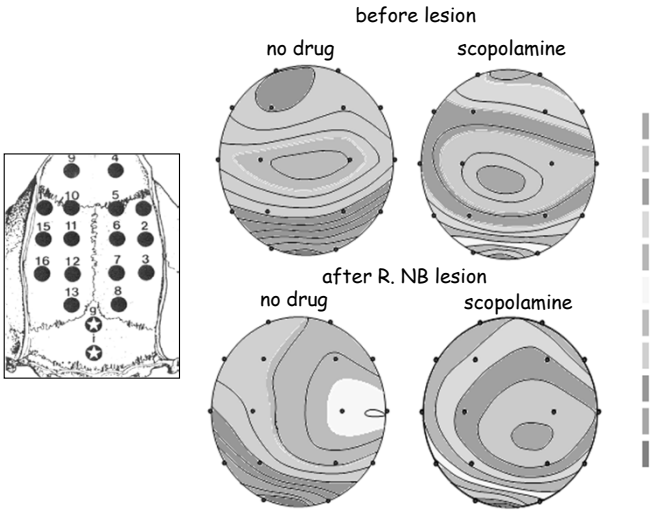
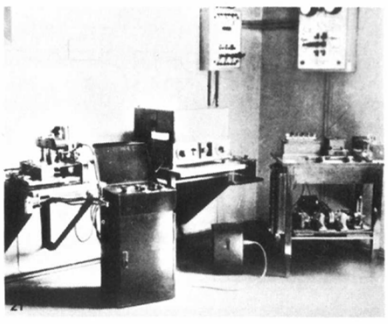
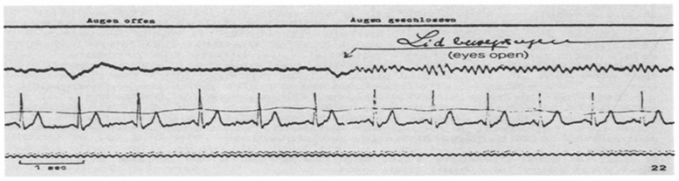
Unilateral lesion of BF II.



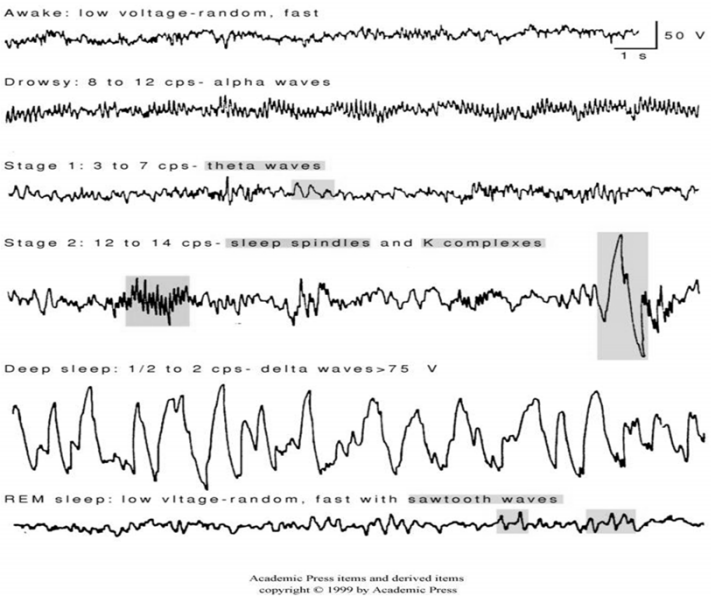
modified from Buzsáki et al., *J.Neurosci* 8 (1988): 4007-4026

Berger - 1929





Sleep stages



Brainstem transsections