Comparative physiology and pharmacology of sleep

Circadian rhythms
Circadian and homeostatic aspects of sleep regulation and their interaction

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Learning objectives

At the end of the lecture you should be able to understand:

- the principles of circadian rhythms
- the importance of circadian rhythms for sleep
- the interaction of circadian and homeostatic processes
- their relevance for sleep-wake regulation

Circadian rhythms

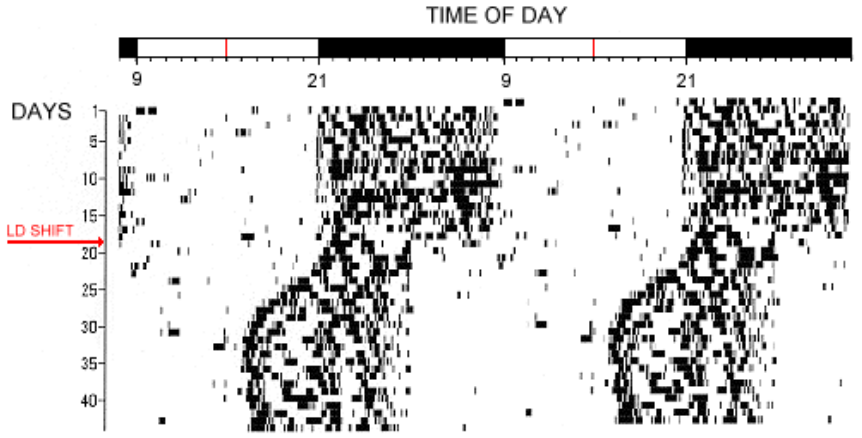
Long-term recordings of rest and activity in rats and mice

Running wheel

Infrared sensors

The rest-activity rhythm is an important marker of circadian rhythms in animals

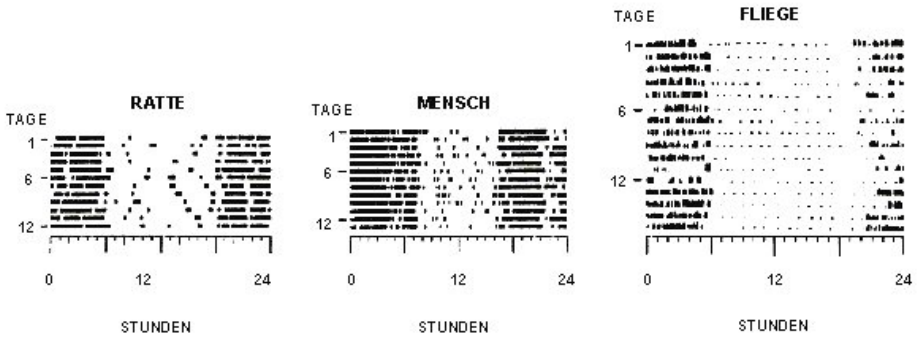
Effect of a shift of the light-dark cycle on activity (“jet-lag”)



Running wheel activity of a rat

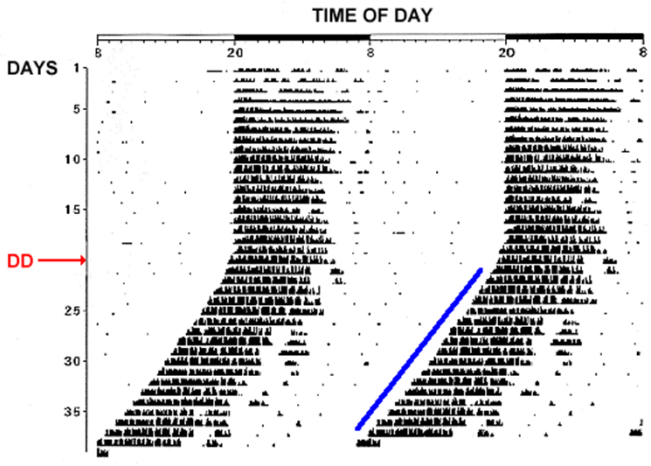
The light-dark cycle of our environment is the most important *synchronizer (“Zeitgeber”)* of circadian rhythms

In all organisms rest-activity rhythms are synchronized with the “zeitgeber” light



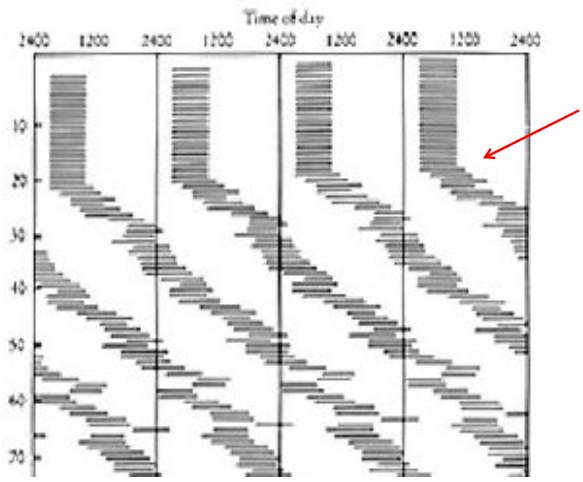
What happens in the absence of the light-dark cycle as a synchronizer?

Free-running activity rhythm of a mouse



Circadian rhythm: endogenous?

Free-run period: Aschoff Bunker, Andechs, Germany



No time information
= time free environment

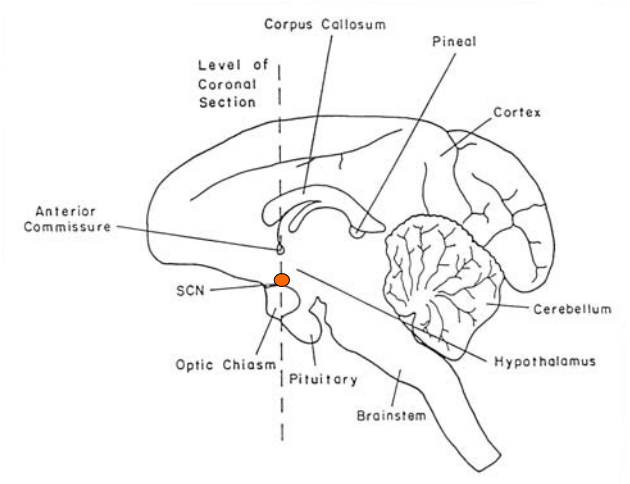
Self selected light-dark cycle

Period ≈ 25 h
Body temperature
Sleep-wake rhythm

Aschoff & Wever

Where is the "clock" located?

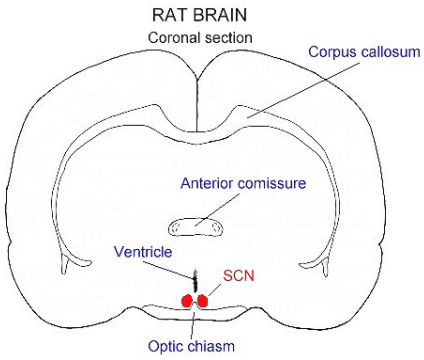
Brain anatomy of a squirrel monkey (median sagittal section)

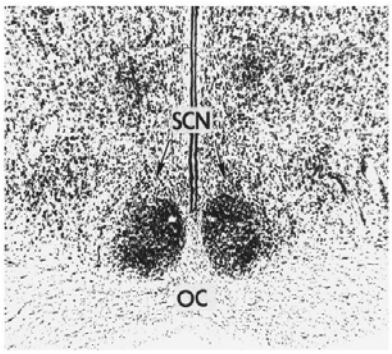


Moore-Ede, Sulzman and Fuller, 1982

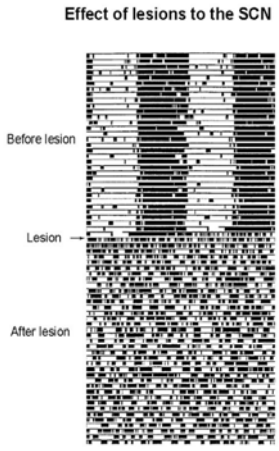
Circadian pacemaker in the brain

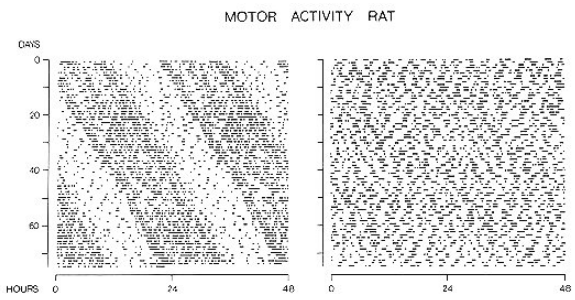
Suprachiasmatic nuclei





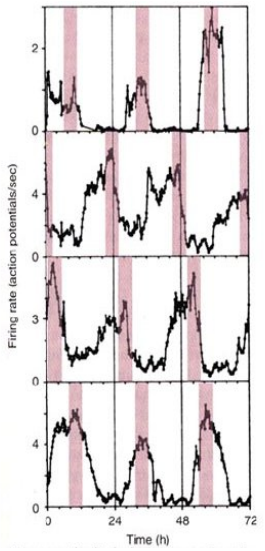
Lesion of the SCN leads to complete loss of rhythmicity





Circadian pacemaker – *in vitro* property

- SCN slices as well as SCN neurons still show rhythmic circadian activity *in vitro*

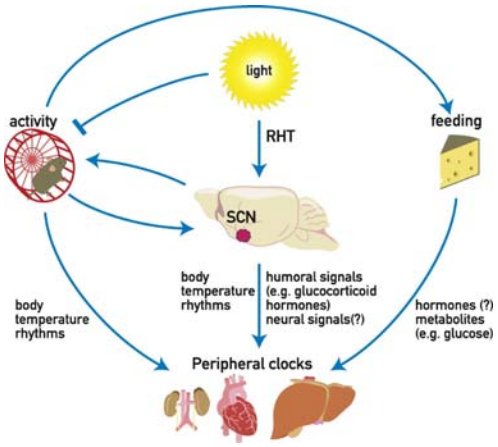


Welsh et al., Neuron, 1995

Evidence that the SCN is the «clock» in the brain:

- Lesion leads to loss of circadian rhythms
- circadian activity also *in vitro*
- SCN transplantation experiments (rhythm of donor is established)

Circadian clocks not only in the brain!



Circadian rhythmicity also in fibroblasts and liver cells: peripheral oscillators in cell cultures of peripheral cells

Schibler and Sassone-Corsi, Cell, 2002

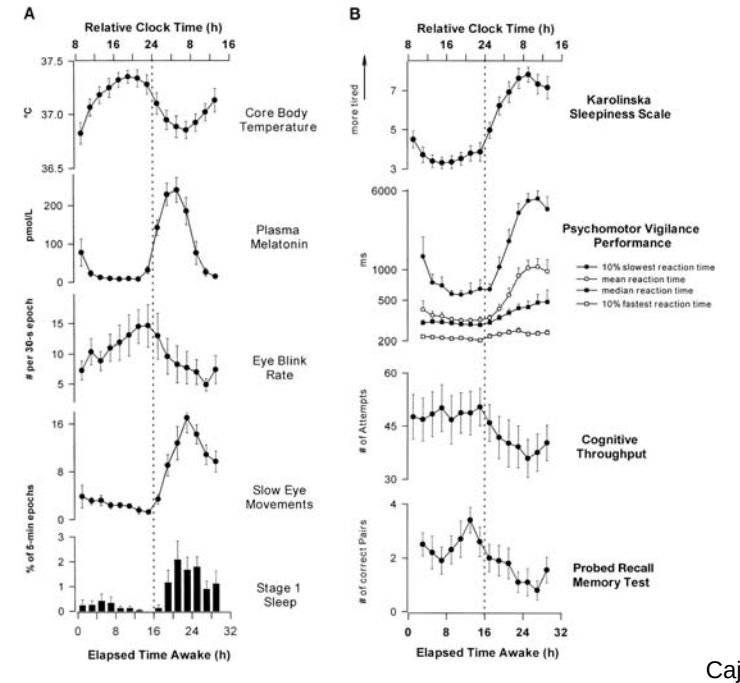
Circadian rhythms are ubiquitous

- animals
- plants
- monad organisms

Question of mechanism and function

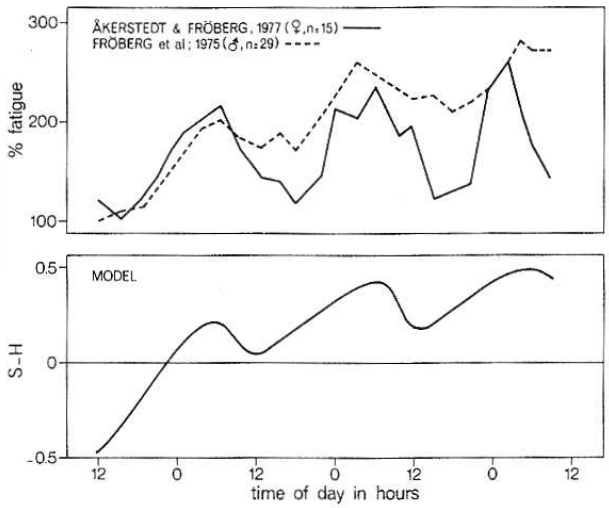
- relation to 24-h light-dark cycle of the environment
- anticipation
- coordination of all body rhythms
- seasonal change in photoperiod

Circadian and homeostatic aspects of sleep regulation and their interaction



Cajochen et al., 1999

Circadian influence on fatigue



Daan et al., 1984

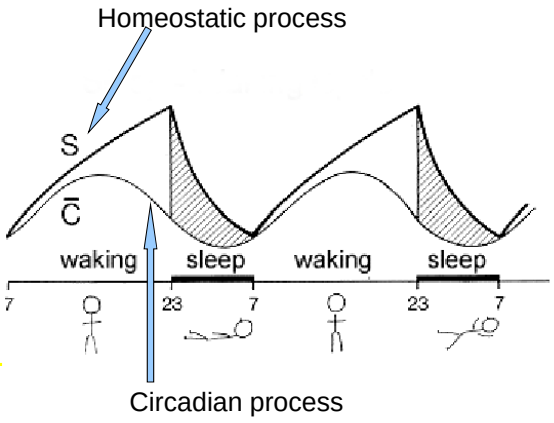
Sleep homeostasis

- Sleep-wake dependent aspect of sleep regulation
- Sleep propensity
  - **augmented** when sleep is curtailed or absent
  - **reduced** in response to excess sleep

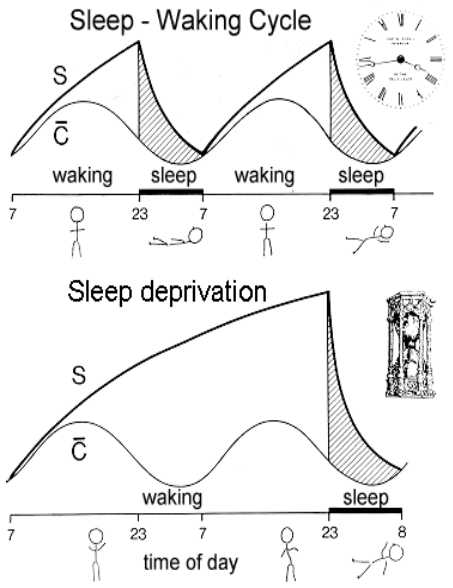
Circadian rhythms

- Relation to 24-h light-dark cycle
- Anticipation
- Coordination of all body rhythms
- Seasonal changes in photoperiod

Two process model of sleep regulation

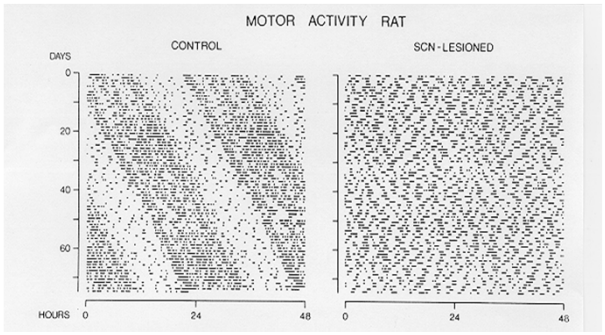


Borbély, Human Neurobiol,1982
Daan et al., Am J Physiol, 1984

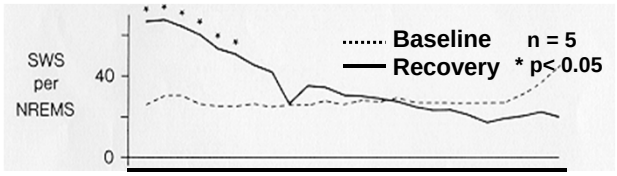


- Circadian rhythms: nuclei in the anterior hypothalamus, SCN
- Sleep: no specific center, involvement of different brain regions, networks

Circadian and homeostatic regulation of sleep can be dissociated in mammals



Effect of 24 h sleep deprivation



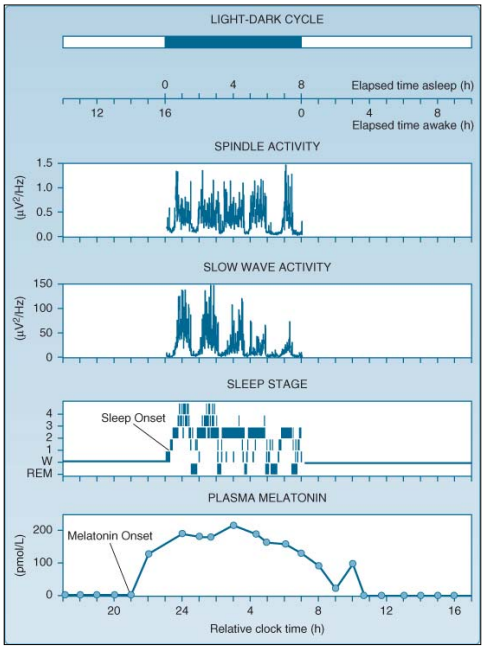
Tobler, Borbély, Groos, Neurosci Letters 42, 1983; Mistlberger et al, Sleep 6, 1983; Trachsel et al, Brain Res., 1992

- Increase of SWA after sleep deprivation in rats with SCN lesion
- Intact homeostatic regulation in the absence of a circadian sleep-wake rhythm
- Sleep homeostasis and circadian aspects can be dissociated (rat)

- How is the association between circadian and homeostatic aspects of sleep in humans?

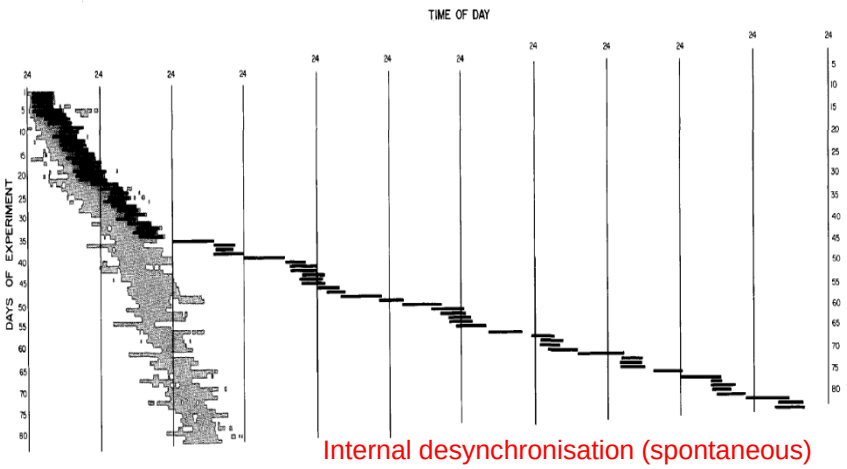
Problem:

- normal situation: both components change simultaneously



Dijk & Franken (2005) Principles and Practice of Sleep Medicine

Free-run study

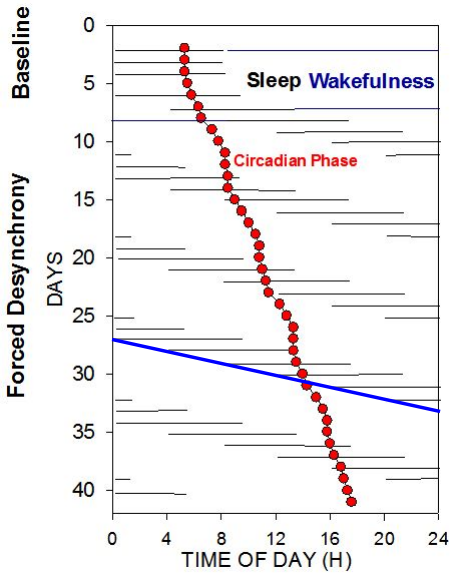


Internal desynchronisation (spontaneous)

gray: body temperatur < mean
black: sleep

Czeisler et al., 1980

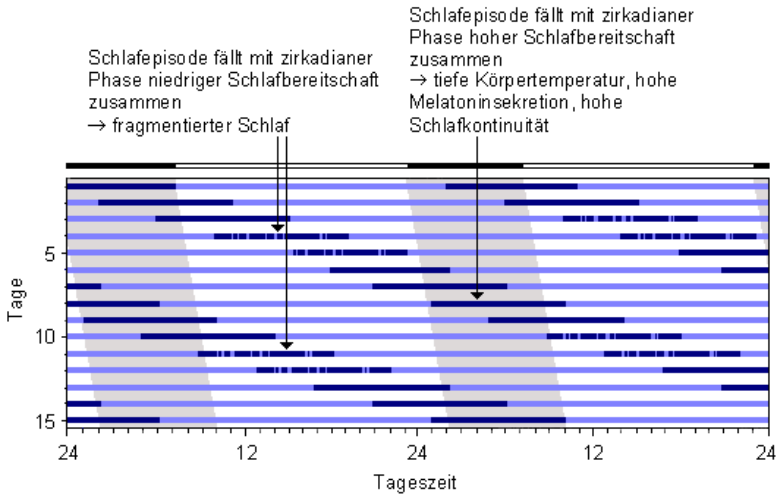
Forced desynchrony

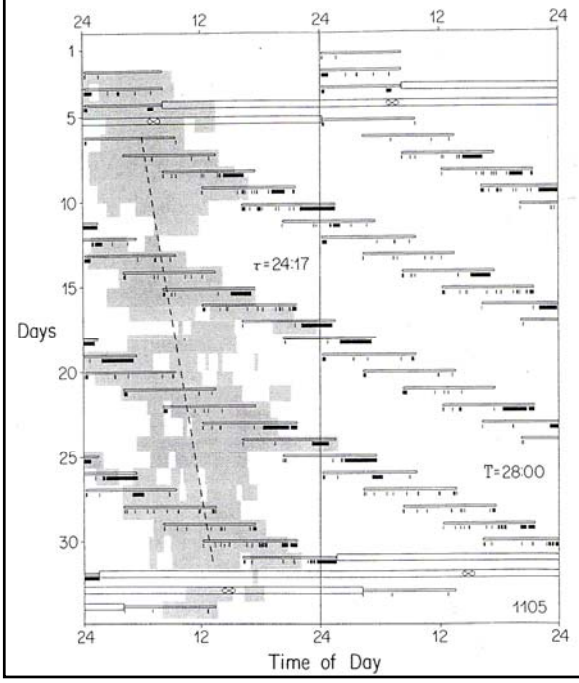


Dim light (< 10 Lux)
28h day; 1/3 sleep

Circadian period ≈ 24.2 h

sleep-wake (28 h)





Forced desynchrony

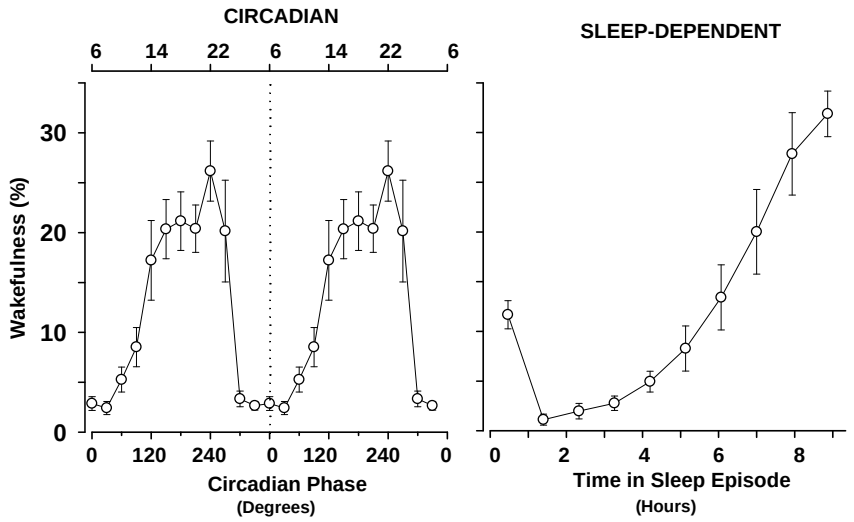
Dim light (< 10 Lux)
28h day; 1/3 sleep

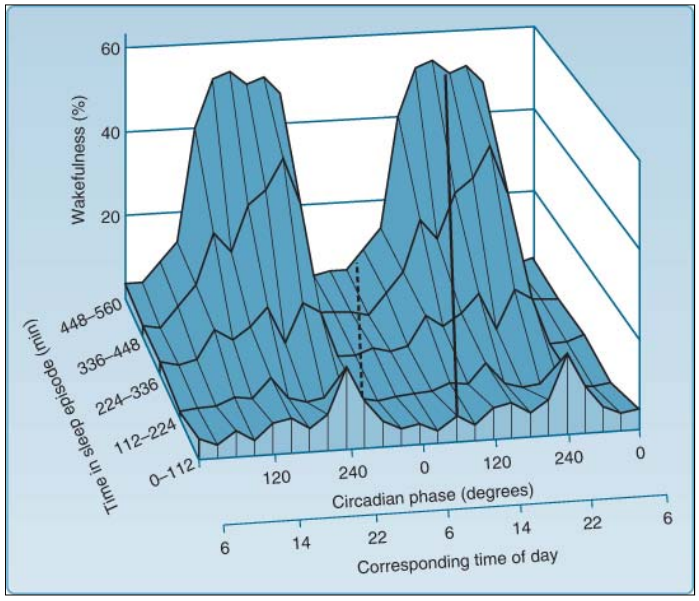
Circadian period ≈ 24.2 h

gray: body temperatur
< mean
black: wake

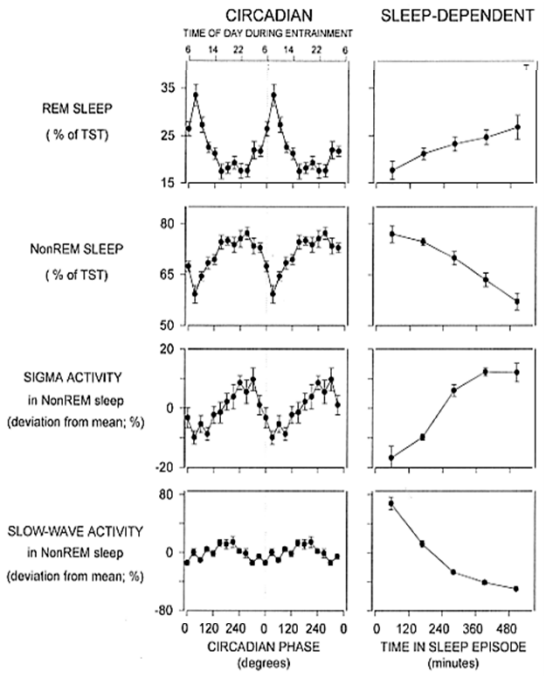
Dijk et al., 1992

Wakefulness during sleep: strong circadian and sleep dependent components





Dijk & Franken (2005) Principles and Practice of Sleep Medicine



REM sleep:

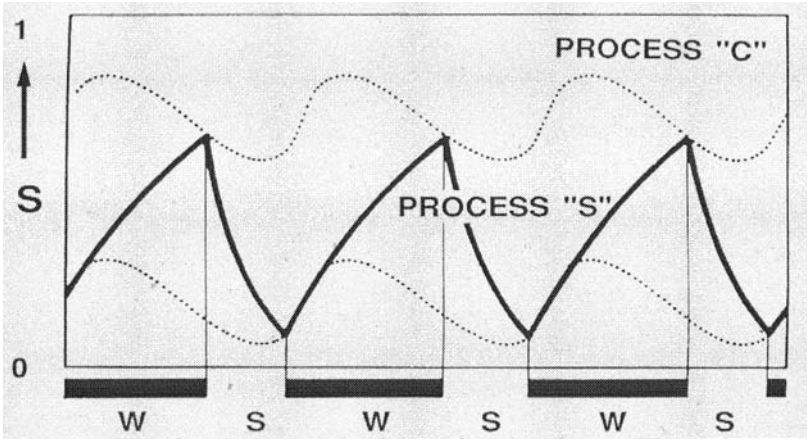
- circadian modulation
- sleep dependent disinhibition

Slow-wave activity:

- no circadian modulation
- homeostatic regulation

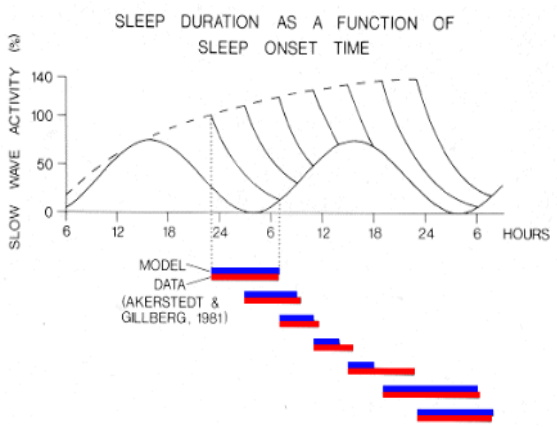
Dijk and Czeisler, 1995

"Two-process model" of sleep regulation



Daan, Beersma & Borbély, Am J Physiol 246, 1984

Circadian effects: displaced sleep



Borbély, 1982

Interaction of ***sleep homeostasis*** and ***circadian processes*** determine

- timing of sleep and wakefulness
- fatigue / alertness
- cognitive performance
- etc.

Additional factors:

- external influences (society, environment, etc.)
- decisions