Human Sleep
Psychopharmacology
Laboratory

Modul BIO 406

"Experimentelle Humanstudien"

Frühlingssemester 2011, 12.5. – 3.6.2011

Physiologie des Schlafs und circadianer Rhythmen

12. Mai 2011

Hans-Peter Landolt
Institut für Pharmakologie & Toxikologie
Universität Zürich-Irchel

Raum 17-H-68
Tel. 01 - 635 59 53

Lernziele

- Prinzipien der Regulationsmechanismen und der neurochemischen Grundlagen der Schlaf-Wachsysteme
- Circadiane Rhythmen beim Menschen
- Pharmakologie von Schlaf-Wachstörungen

„Cargo ship crashes into Japanese neighborhood; captain fell asleep“

World News
Sep 04, 2004

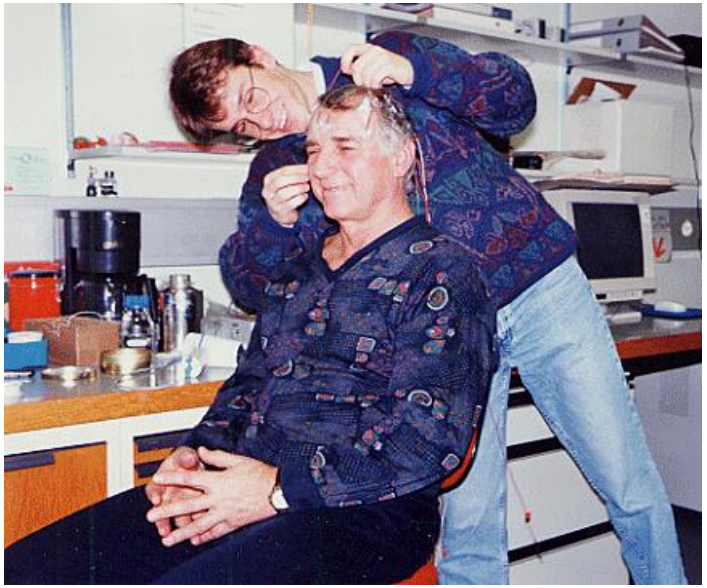
Catastrophes and accidents associated with lack of sleep:

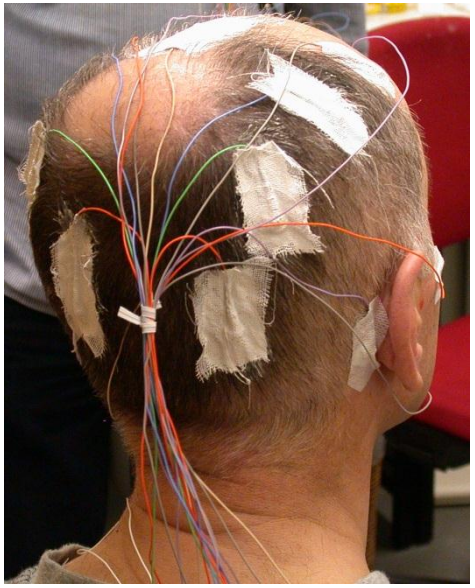
Bhopal, 1984

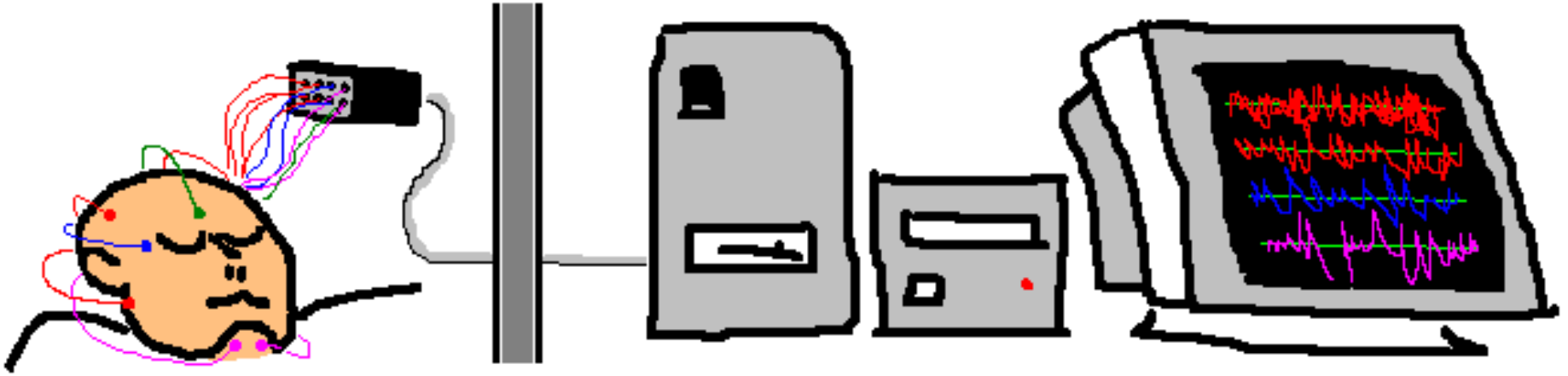
Exxon Valdez, 1989

Three Mile Islands, 1979

Tschernobyl, 1986







aus: Borbély, Tobler, Achermann & Geering, ***Bits of Sleep*** ®, 1998.

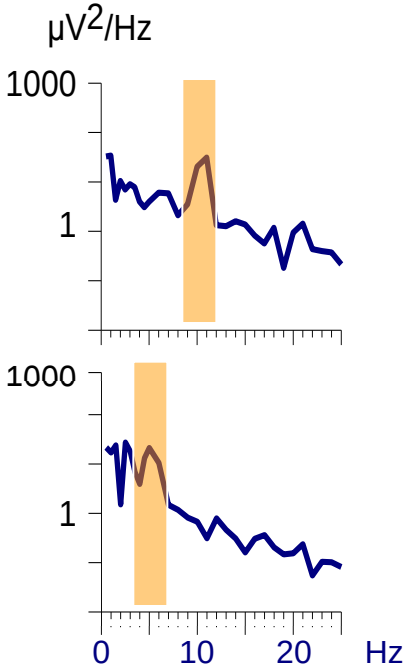
Theta activity reflects increasing “sleep need”

Raw EEG signal

Wakefulness

Sleepiness (awake)

Power spectra



alpha: 8-12 Hz

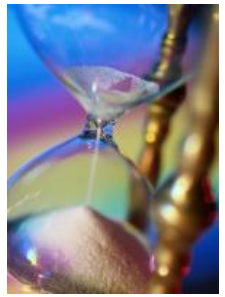
theta: 4-8 Hz

circadian clock

sleepiness

Time

hour glass



"sleep need"

Time

Day 1

Day 2

Theta activity (%)

150

125

100

n = 22

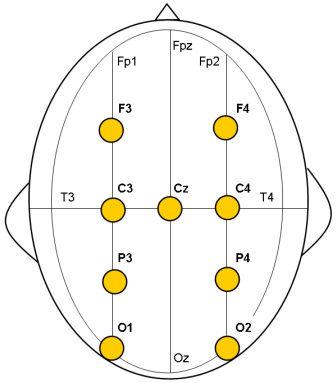
11 17 23 5 11 17 23

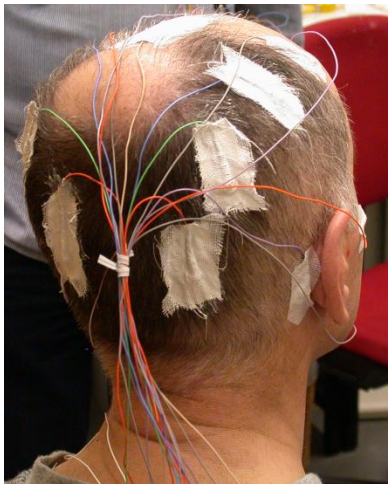
Clock time

Time course of theta activity

The EEG can be recorded also during sleep

10/20 system

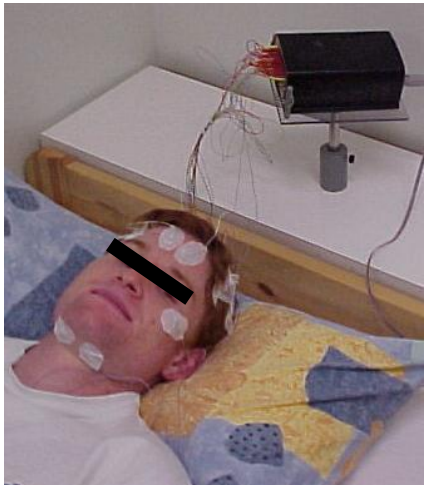




Waking EEG

3’ eyes closed
5’ eyes open

Sleep EEG



all-night recording

Electroencephalogram (EEG)

Electrooculogram (EOG)

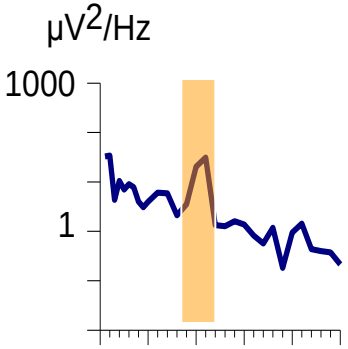
Electromyogram (EMG)

Tiefschlaf wird durch Deltawellen charakterisiert

Rohsignal

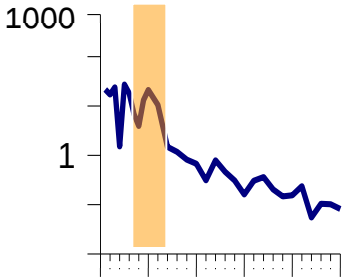
Leistungsspektrum

Wach



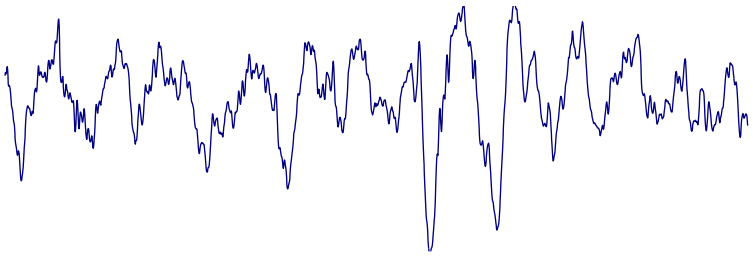
alpha: 8-12 Hz

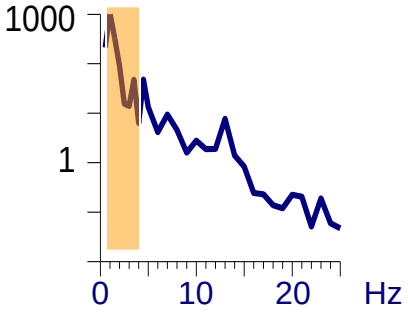
Schläfrig (wach)



theta: 4-8 Hz

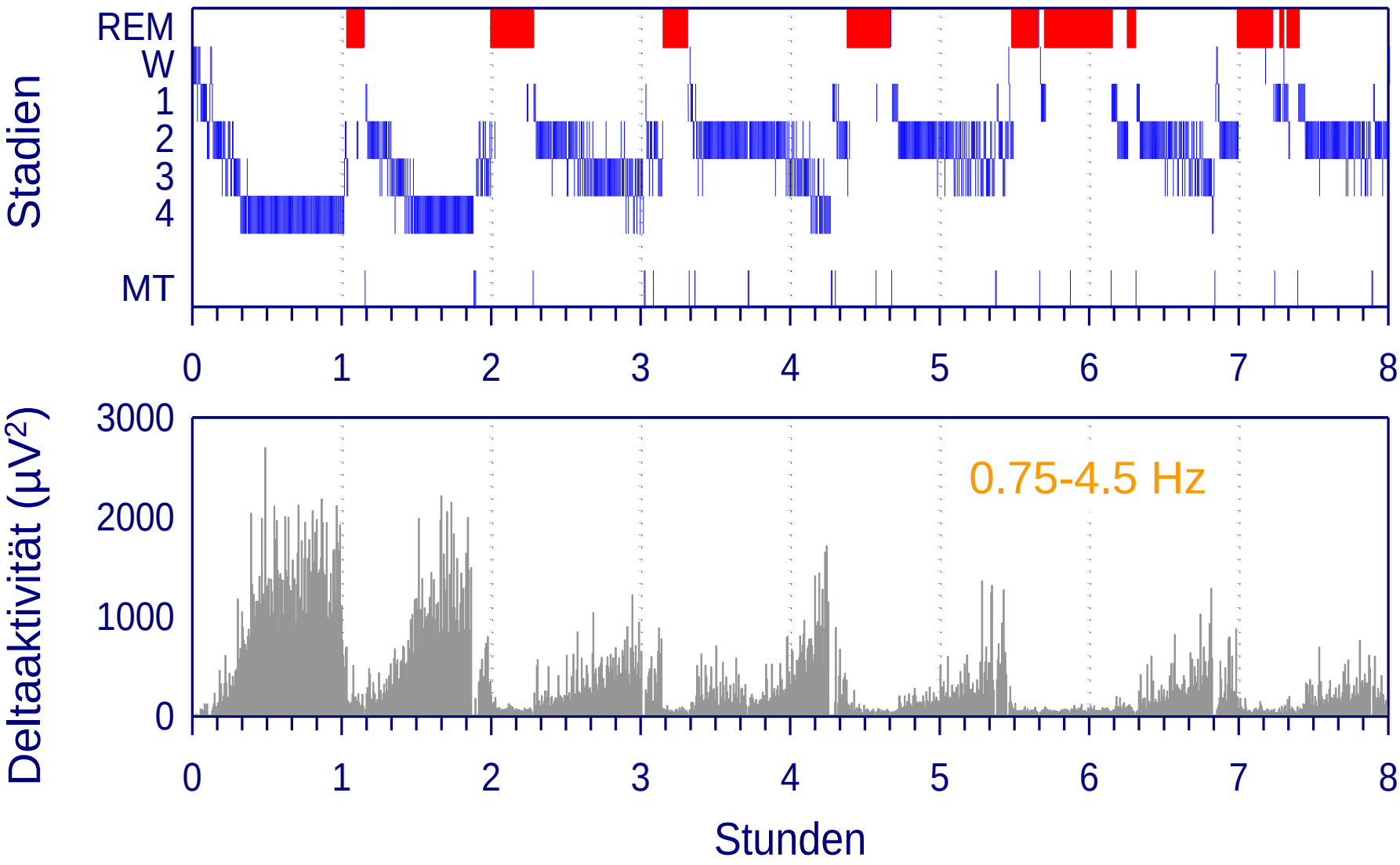
Tiefschlaf



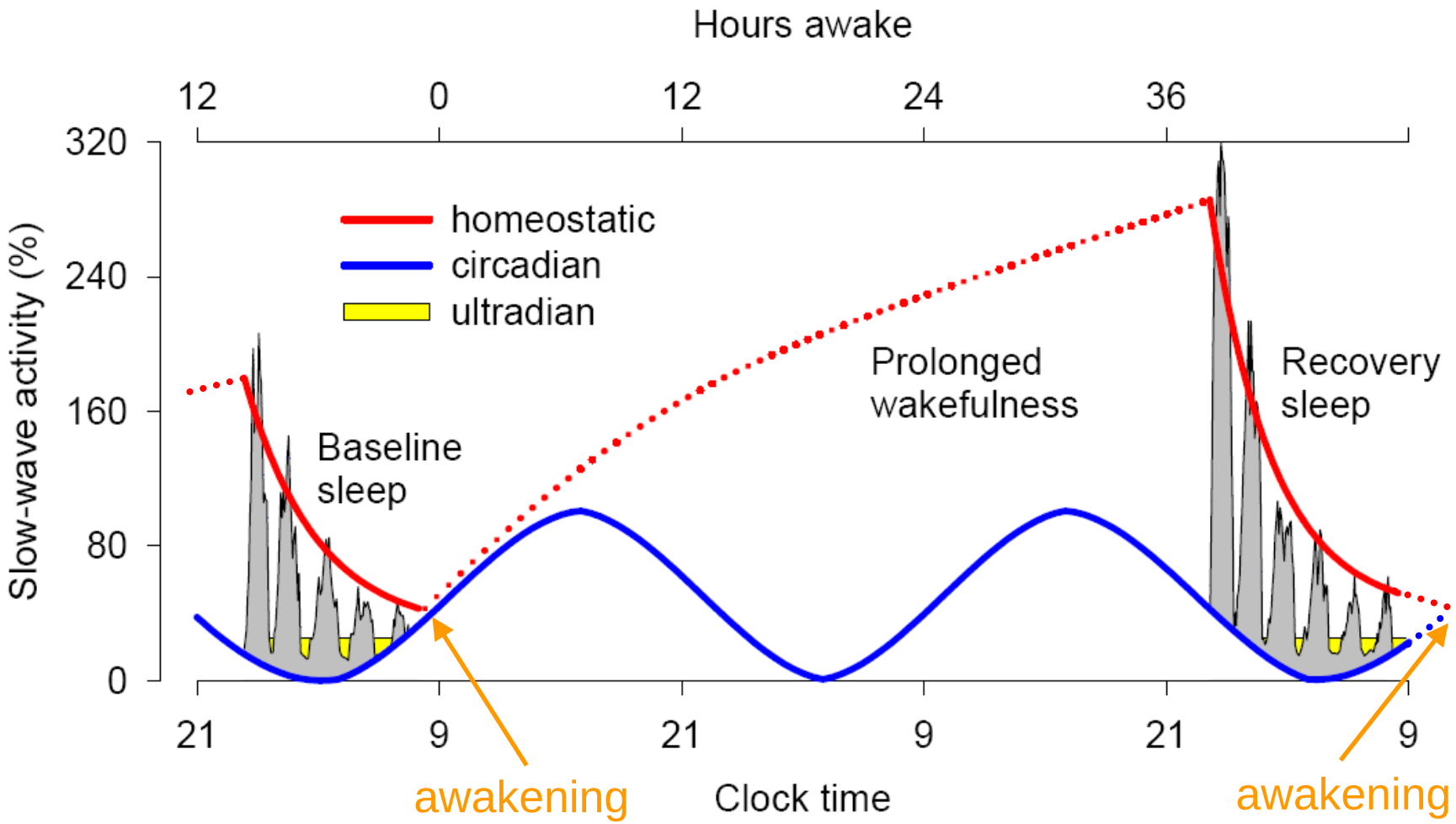


delta: < 4 Hz

Die Deltaaktivität widerspiegelt die Schlaftiefe



Physiological increase of sleep intensity and sleep duration after prolonged wakefulness



Homöostase als allgemeines Konzept in der Physiologie

"La fixité du milieu intérieur est la condition d'une vie libre et indépendante"

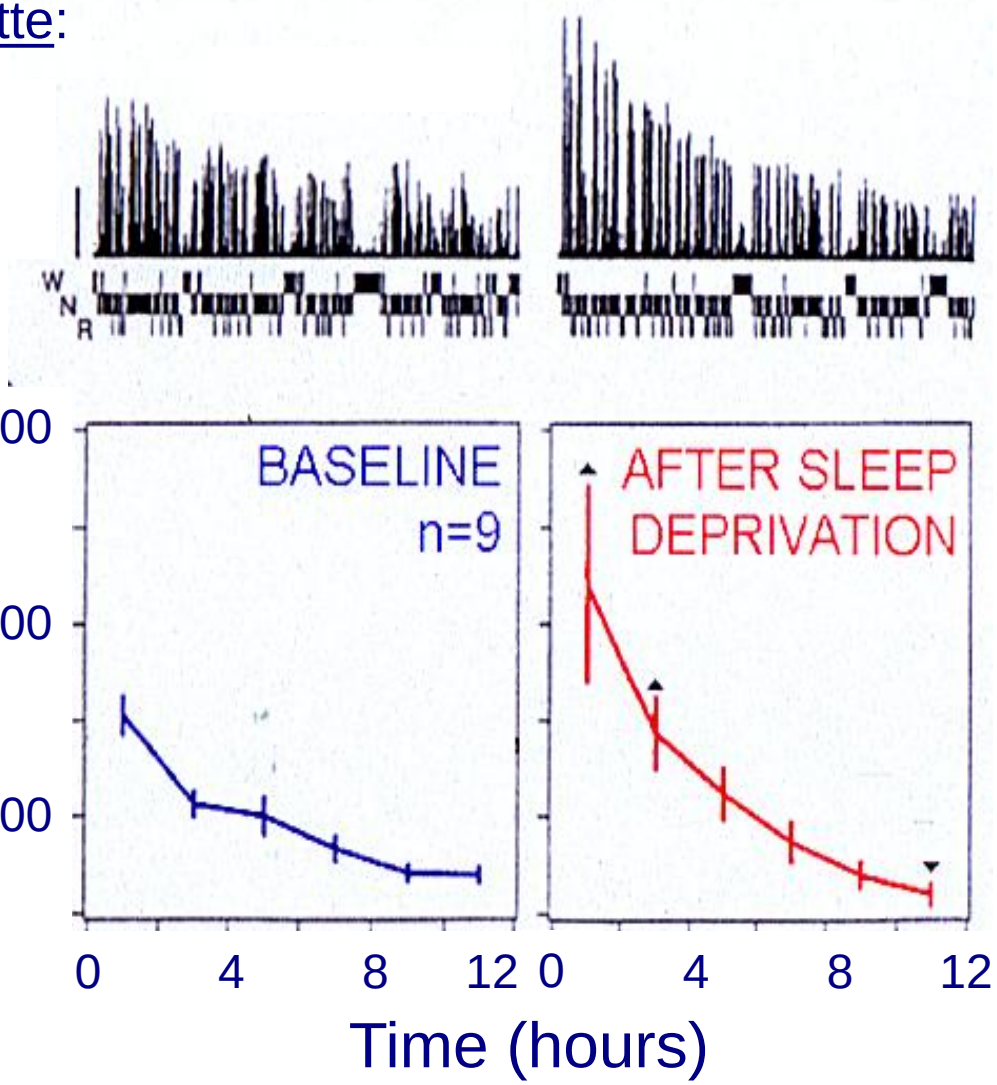
Claude Bernard. *Leçons sur les Phénomènes de la Vie Communs aux Animaux et aux Végétaux* (1878-1879)

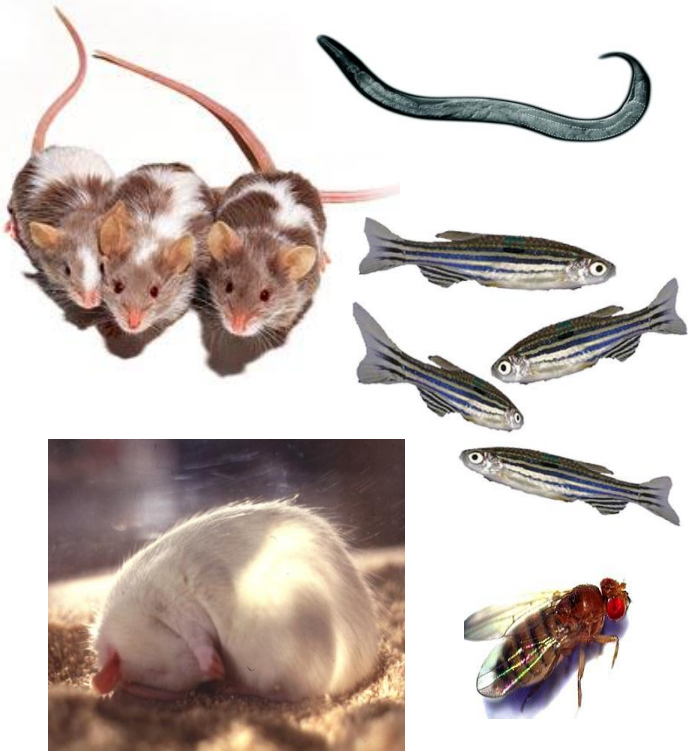
"coordinated physiological processes which maintain steady states in the organism […] – that I have suggested a special designation for these states, homeostasis"

Walter Bredford Cannon. *The Wisdom of the Body* (1932)

Schlaf-Homöostase ist allgemeines Prinzip

Ratte:





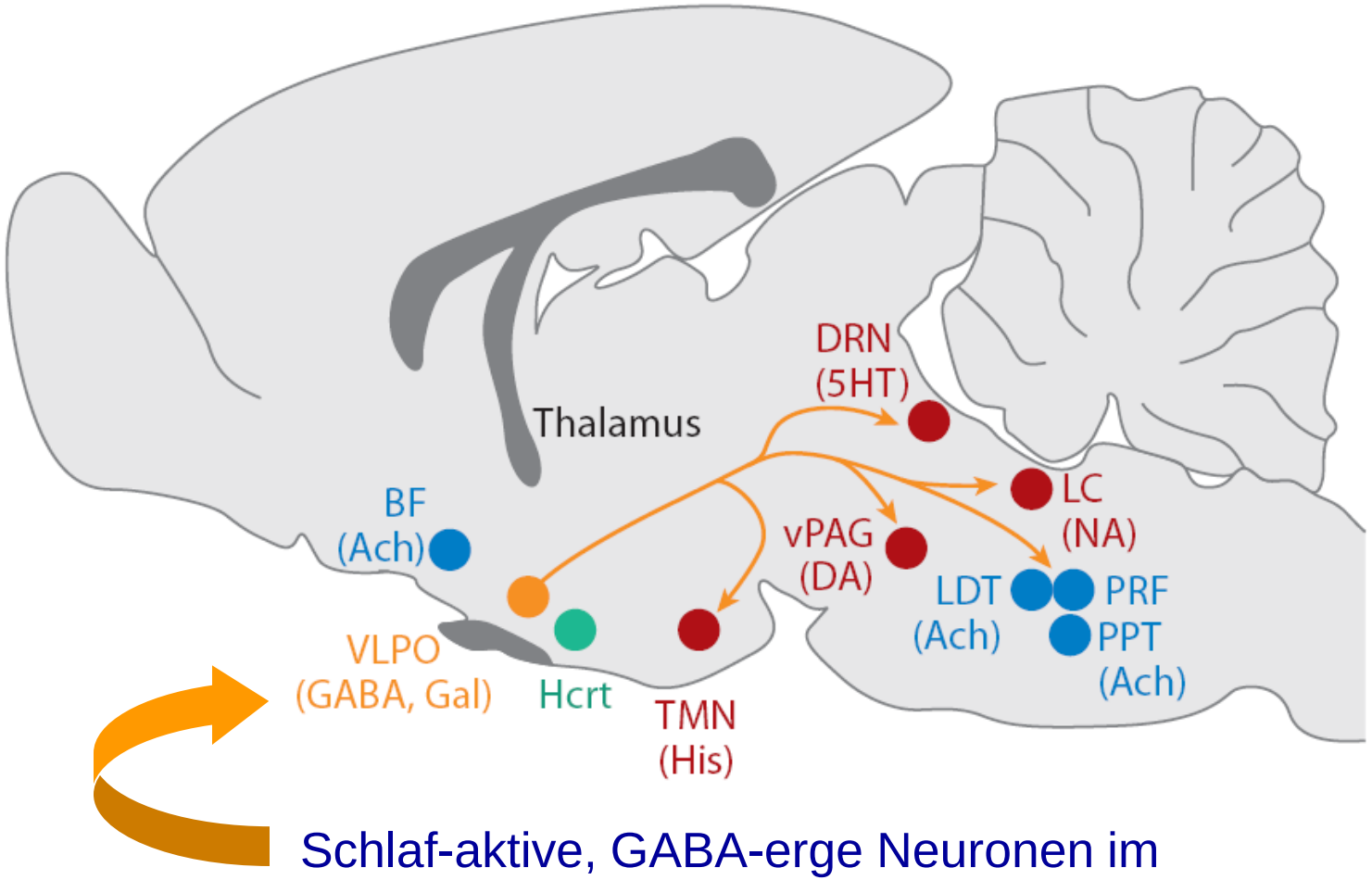
Schlaf-Homöostase

- wichtigster Aspekt der Schlafregulation
- "Geschichte" von Wach und Schlaf
- zuverlässige physiologische Marker (EEG)
  - Theta-Aktivität (~ 5-8 Hz) im Wachzustand
  - Delta-Aktivität (~ 1-4 Hz) im nonREM Schlaf

Neurochemie der Schlaf-Wachregulation

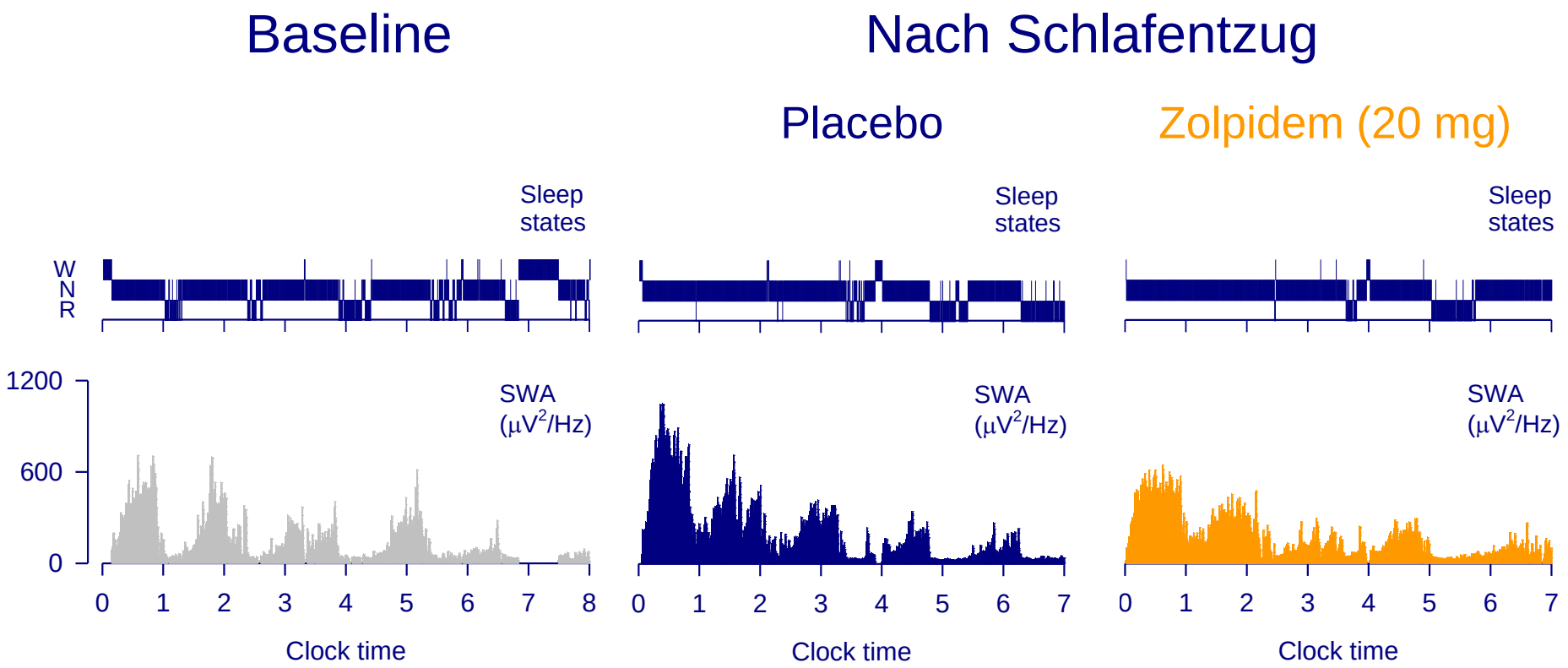
γ-Aminobuttersäure (GABA)

= wichtigster hemmender Neurotransmitter



Schlaf-aktive, GABA-erge Neuronen im ventro-lateralen, prä-optischen Hypothalamus

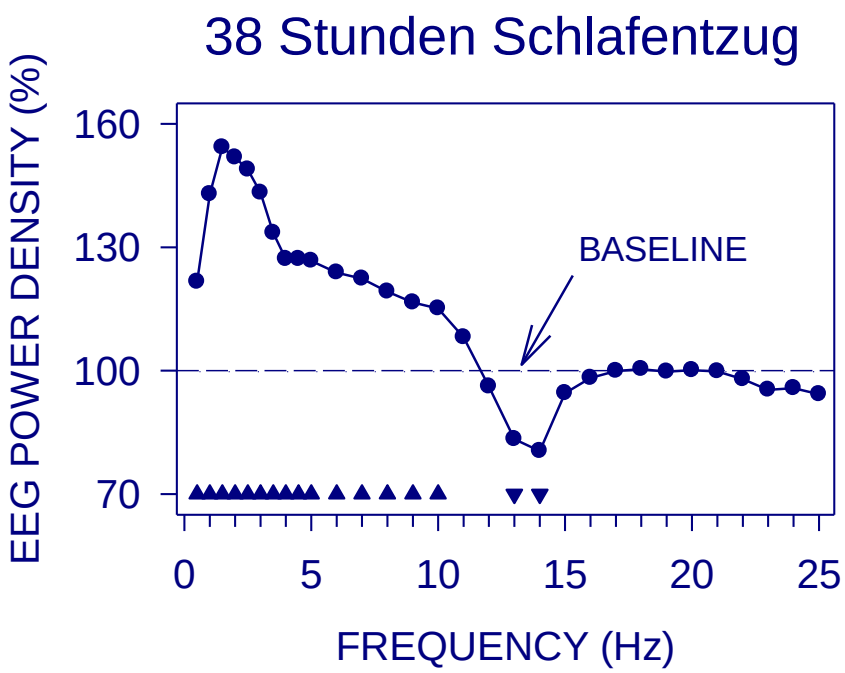
Agonistische $GABA_A$-Rezeptor Modulation bewirkt keinen physiologischen Schlaf

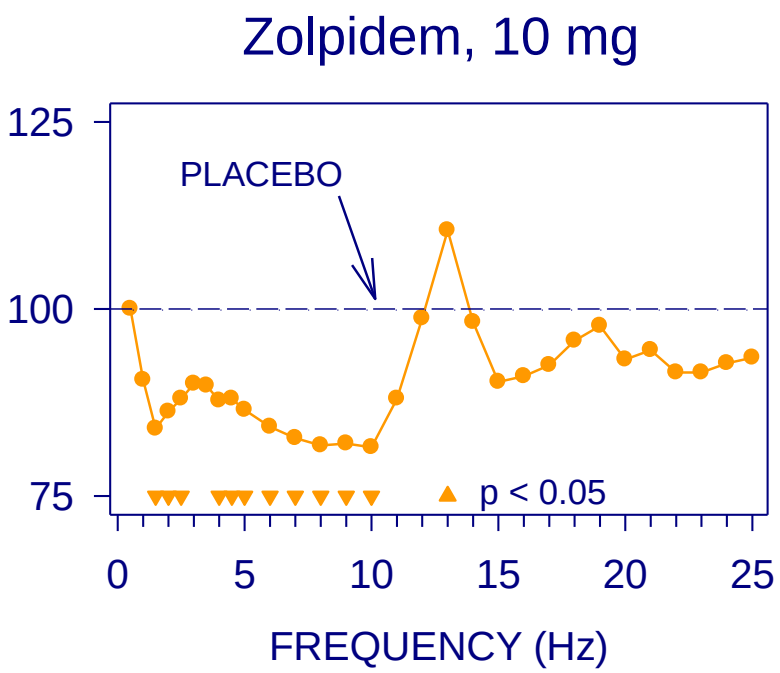


Landolt *et al.*, J Sleep Res (2000)

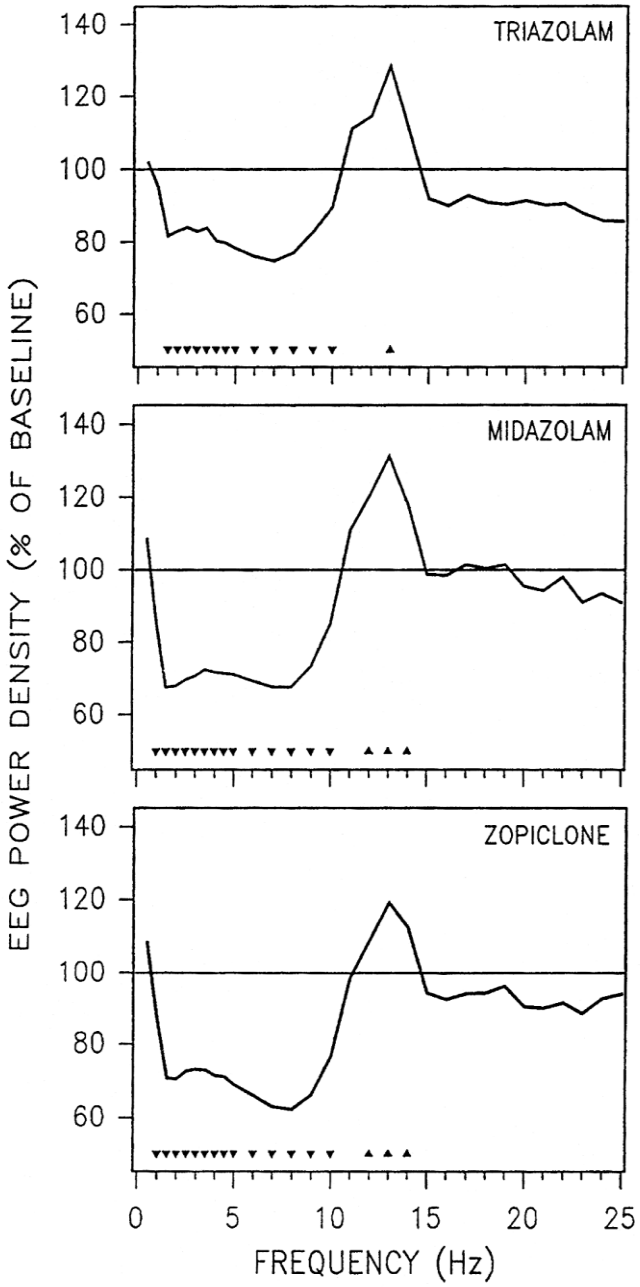
Schlafentzug *vs.* „GABA-erge Schlafmittel“

→ entgegen gesetzte Effekte auf EEG im nonREM Schlaf

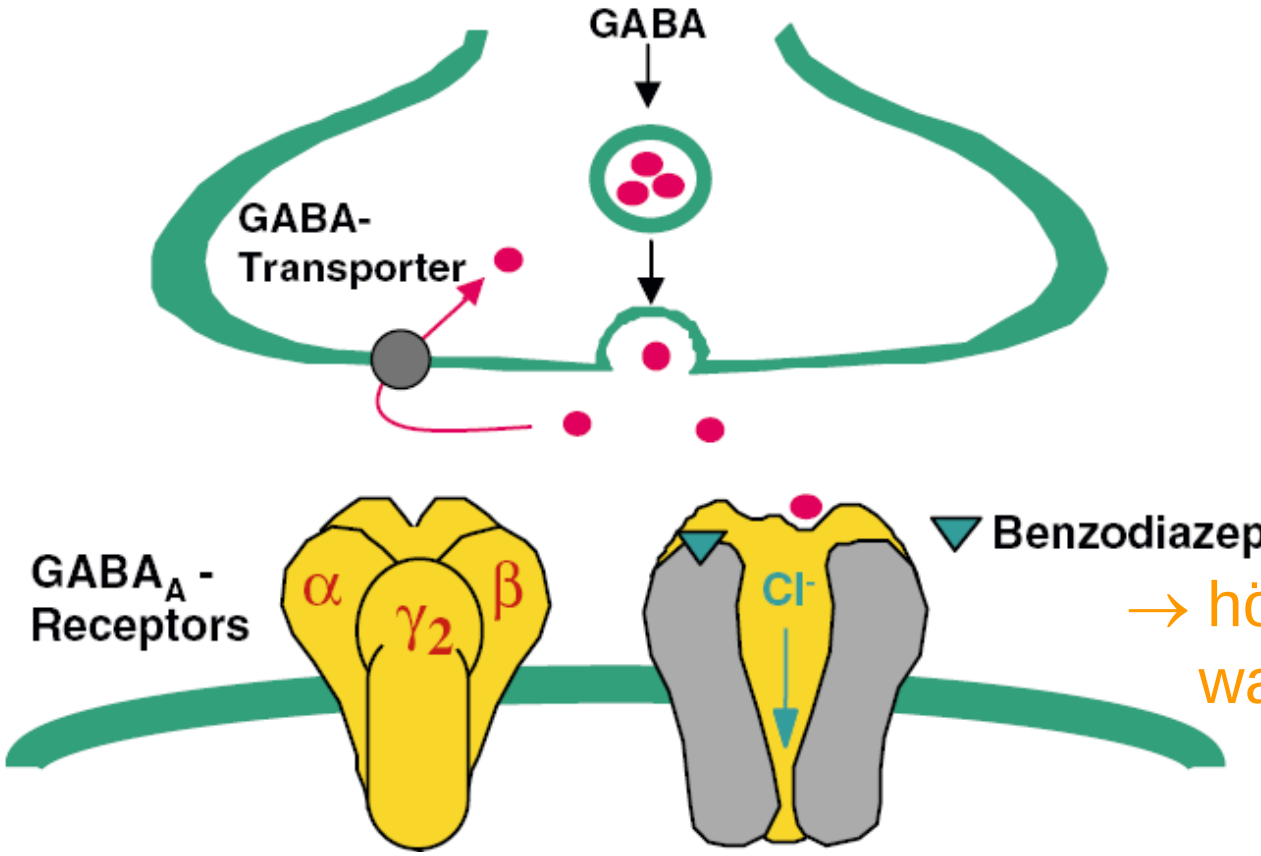




Spektrale Benzodiazepin „Signatur“



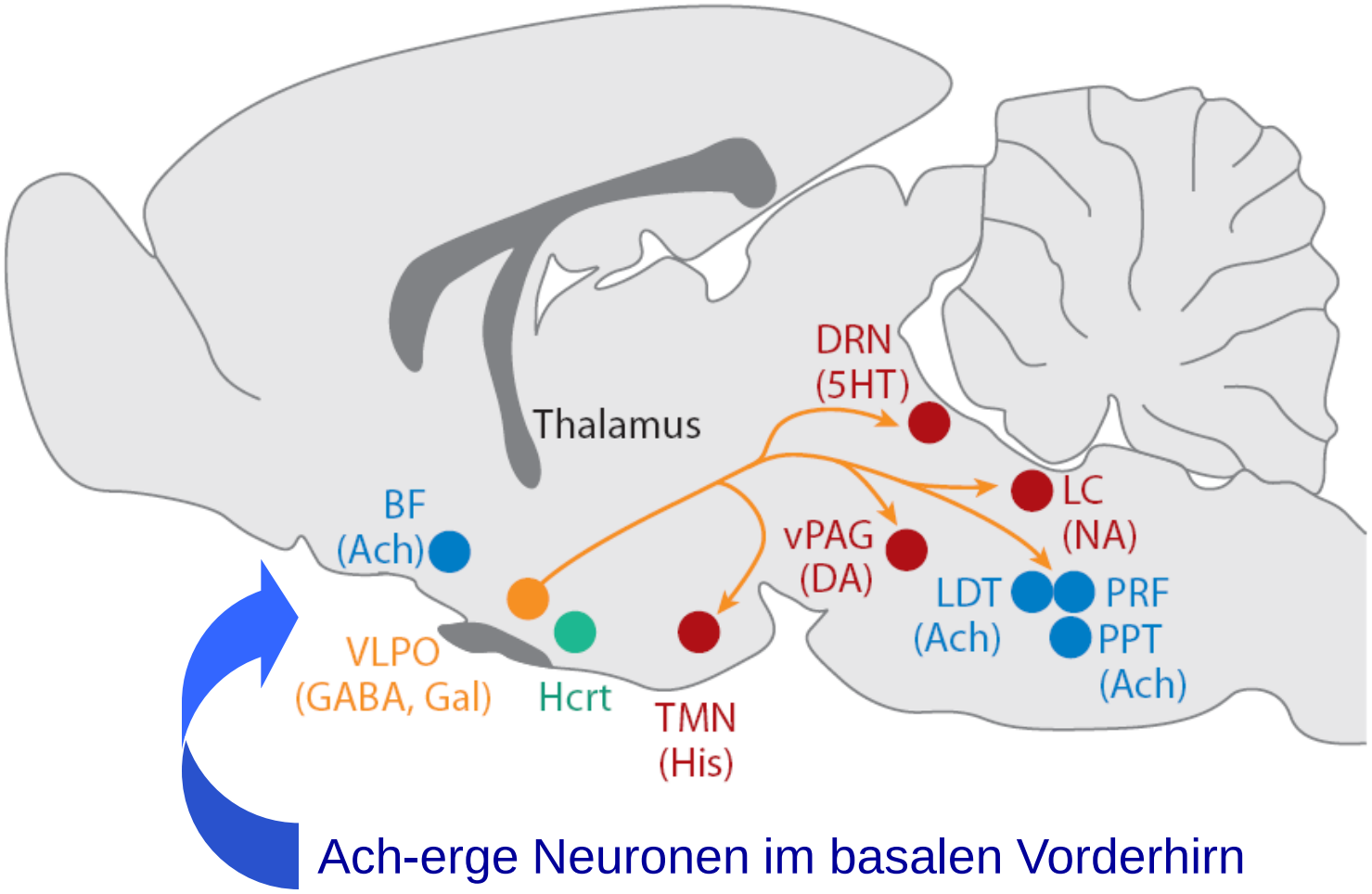
Wirkungsmechanismus der Benzodiazepine



→ höhere Öffnungs-
wahrscheinlichkeit

Möhler, Cell Tissue Res (2006)

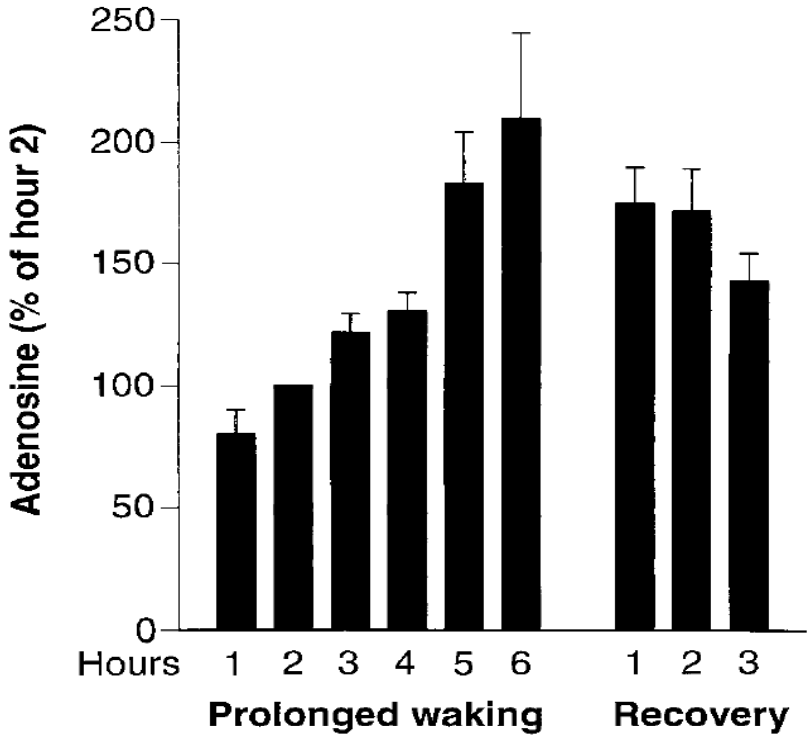
Adenosin



Ach-erge Neuronen im basalen Vorderhirn

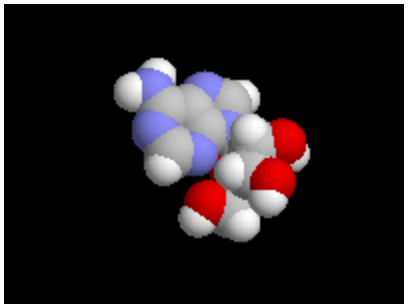
⇒ Hemmung durch Adenosin (Rainnie *et al.*, Science, 1994)

Chemisches Korrelat der Schlaf-Homöostase?



n = 6 Katzen

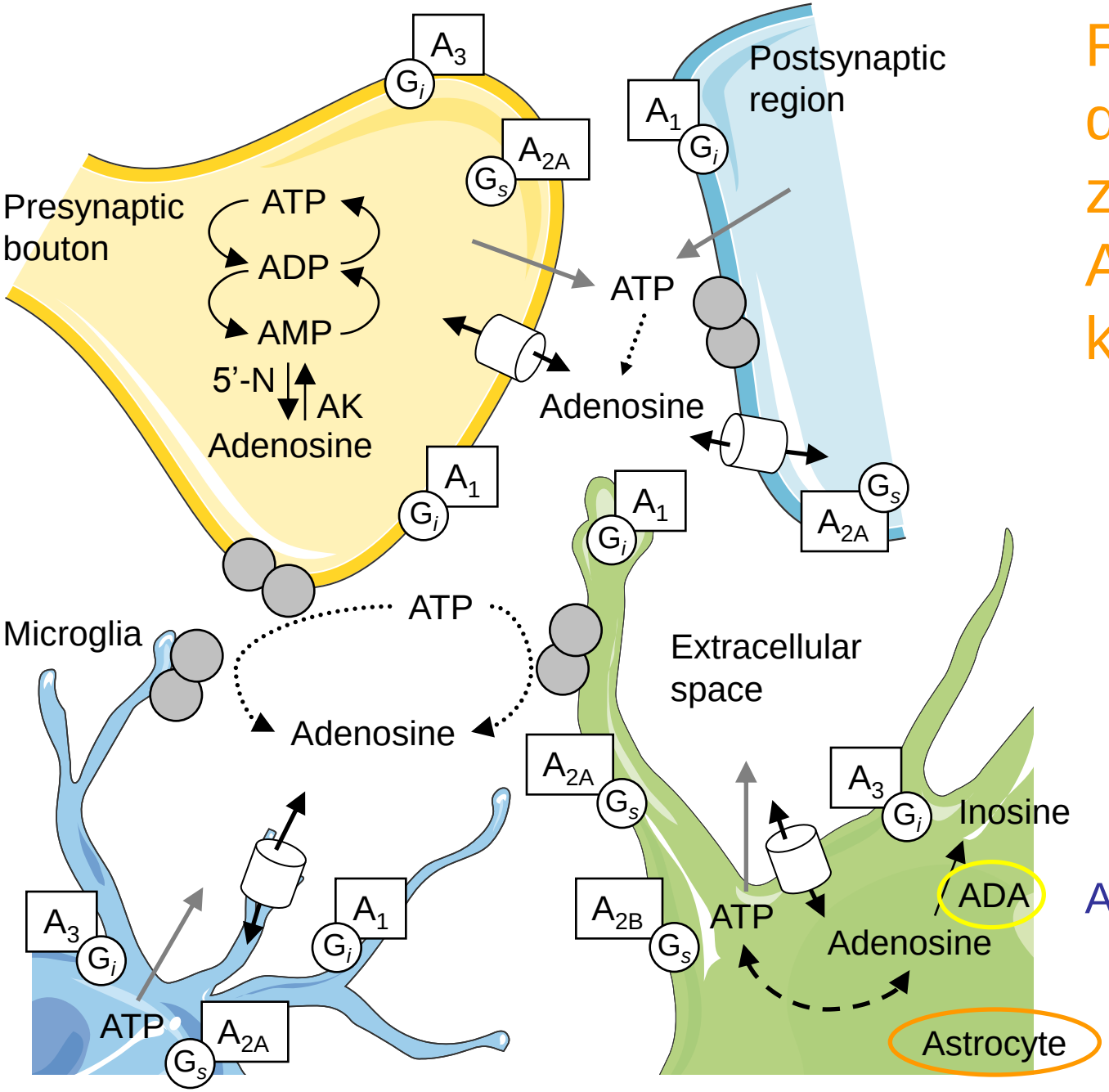
Adenosin



$[Adenosin]_{ext}$: ↑ Schlafentzug, ↓ Erholungsschlaf

Porkka-Heiskanen *et al.*, Science (1997)

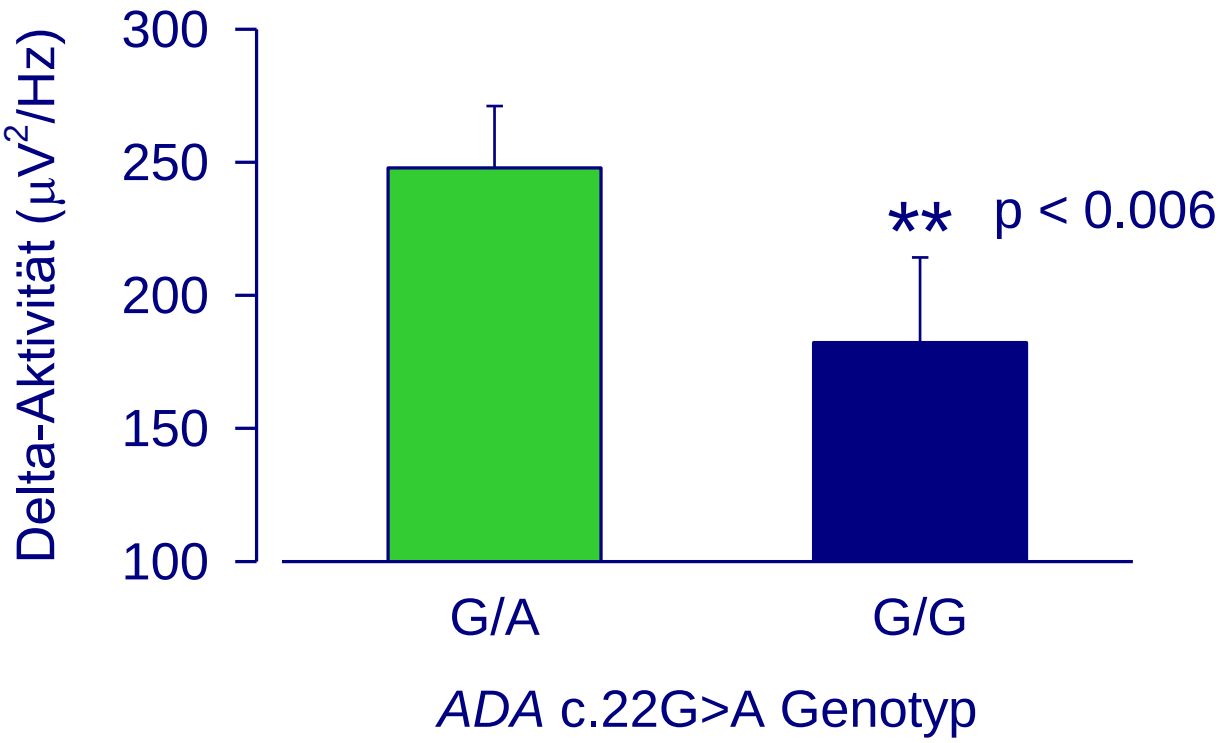
Regulation der extra-zellulären Adenosin-konzentration



ADA = Adenosin-desaminase

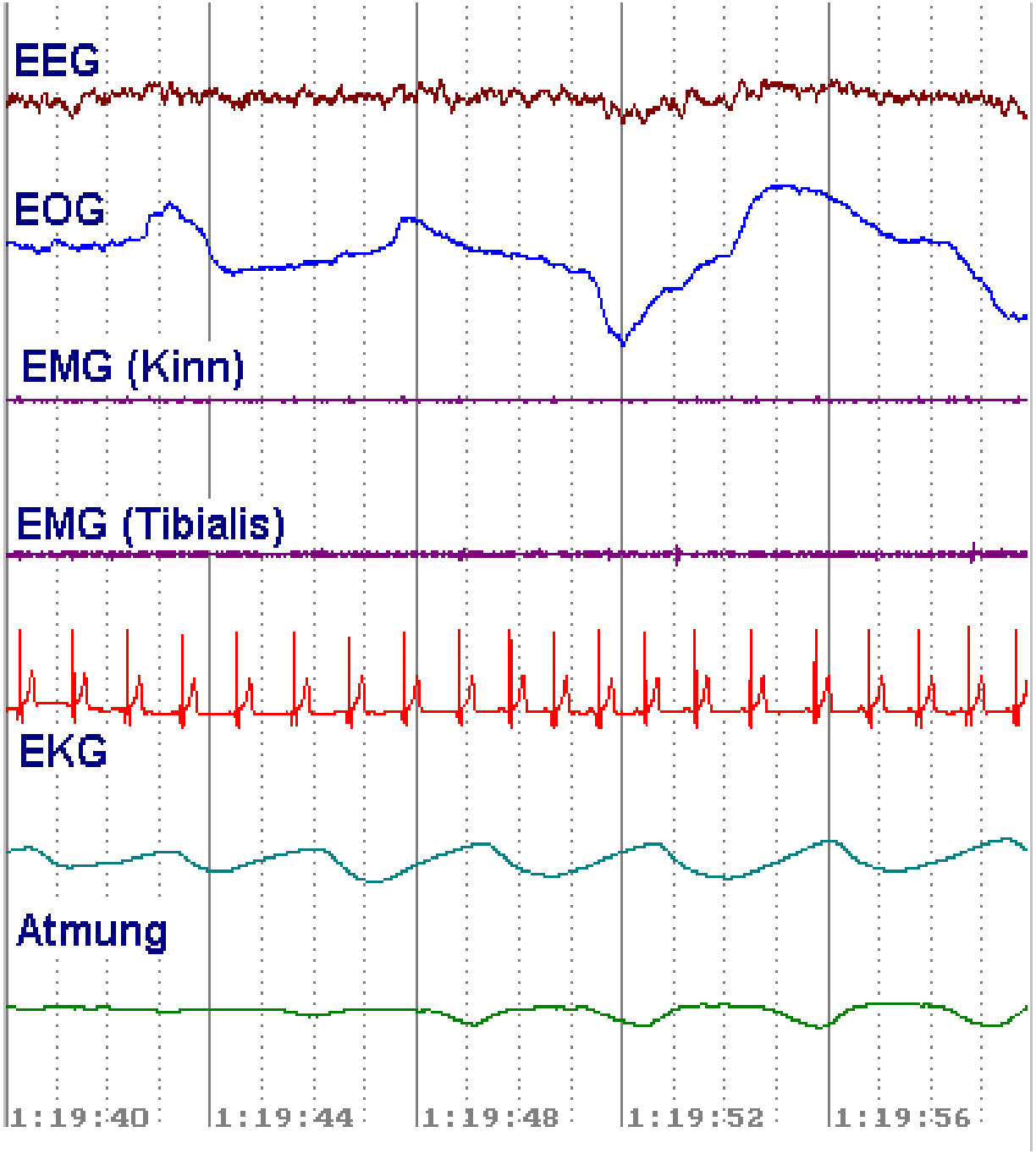
Landolt (2008)

Höhere Schlaftiefe bei Probanden mit genetisch reduzierter ADA-Aktivität



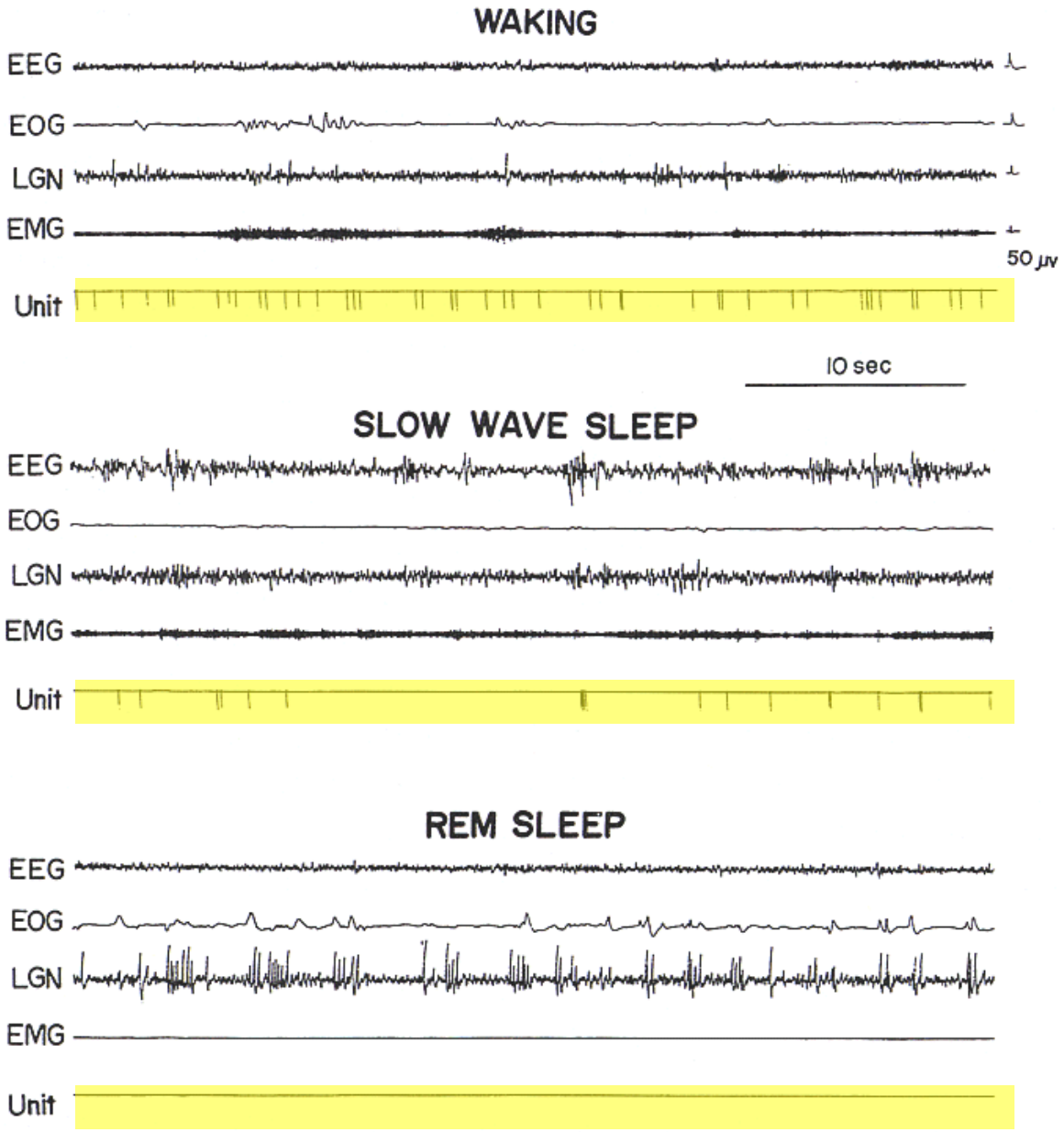
n = 7 pro Gruppe

Rétey *et al.*, Proc Natl Acad Sci USA (2005)



Rapid-eye movement (REM) Schlaf

Aktivität serotonerger Neurone im N. raphe dorsalis



am aktivsten im Wachzustand

Abnahme der Aktivität im nonREM Schlaf

vollkommen ruhig im REM Schlaf

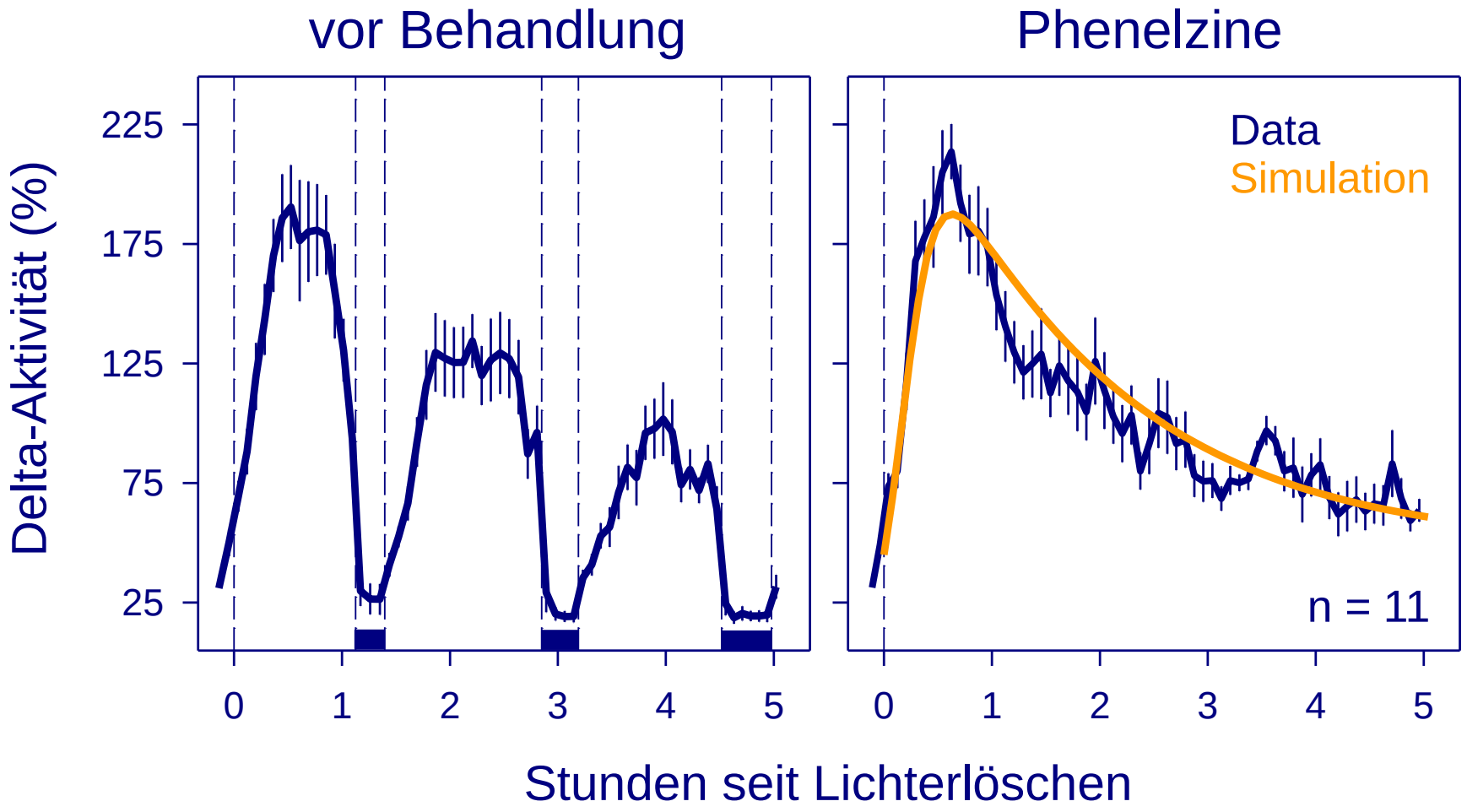
Monoamin-Oxidase (MAO) Hemmer

↑ Serotonin

↑ Norepinephrin

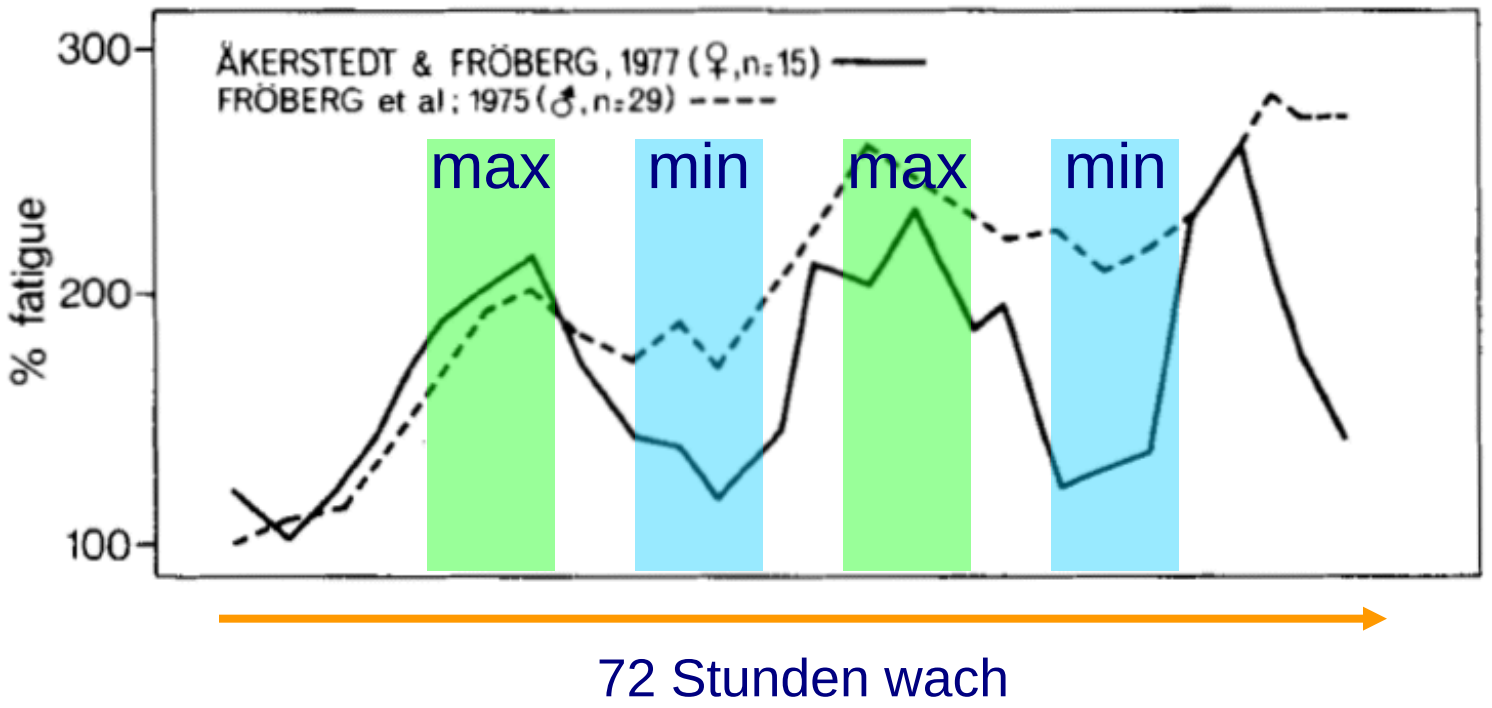
↑ Dopamin

Elimination des REM Schlafs mit MAO-Hemmer



Landolt *et al.*, Arch Gen Psychiatry (2001)

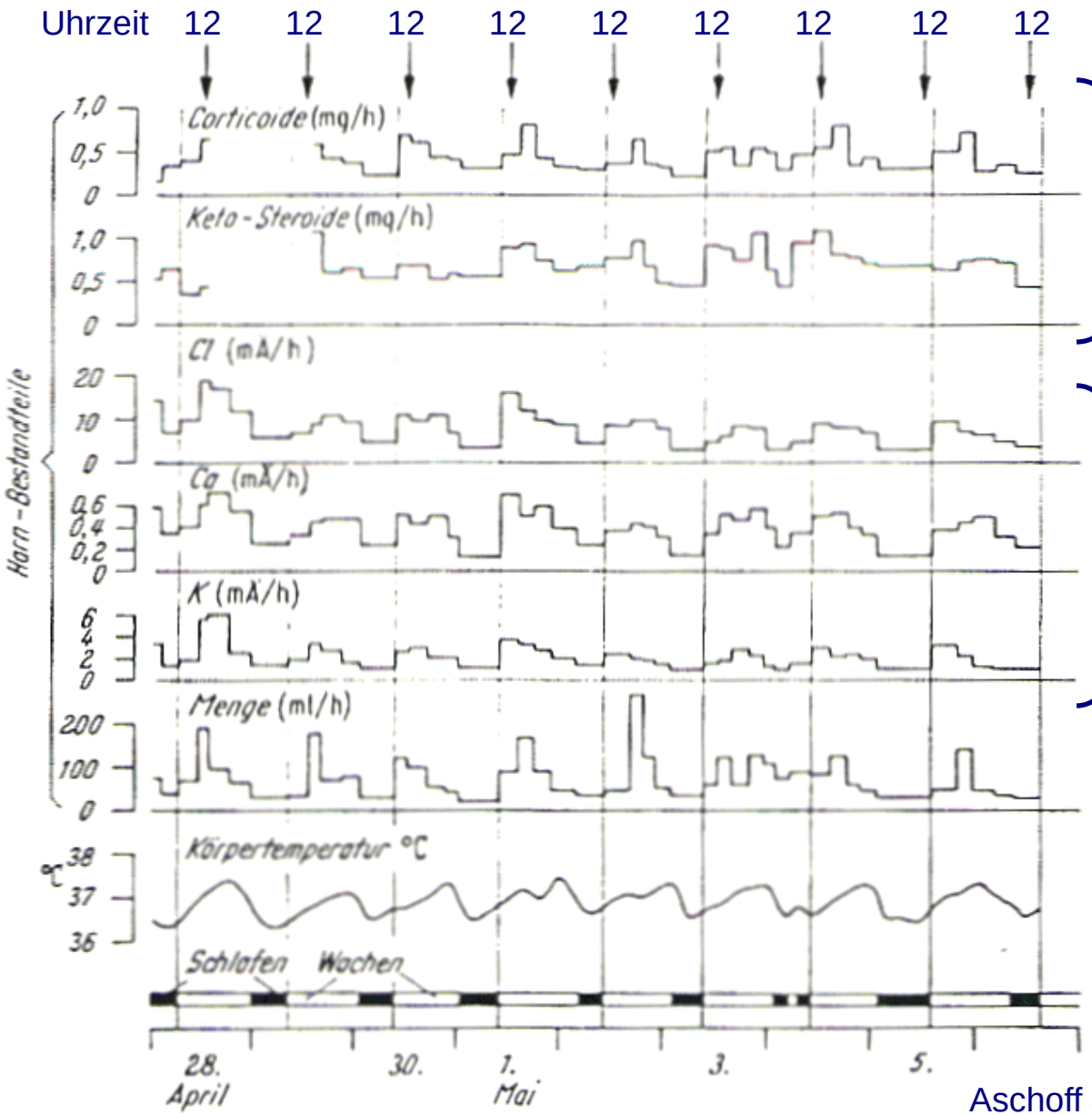
Verlauf der Schläfrigkeit bei Schlafentzug



⇒ nicht nur homöostatische, sondern auch circadiane Einflüsse regulieren Schlaf und Wachzustand

Daan *et al.*, Am J Physiol (1984)

Die menschliche Physiologie ist circadian



Hormone im Urin

Ionen im Urin

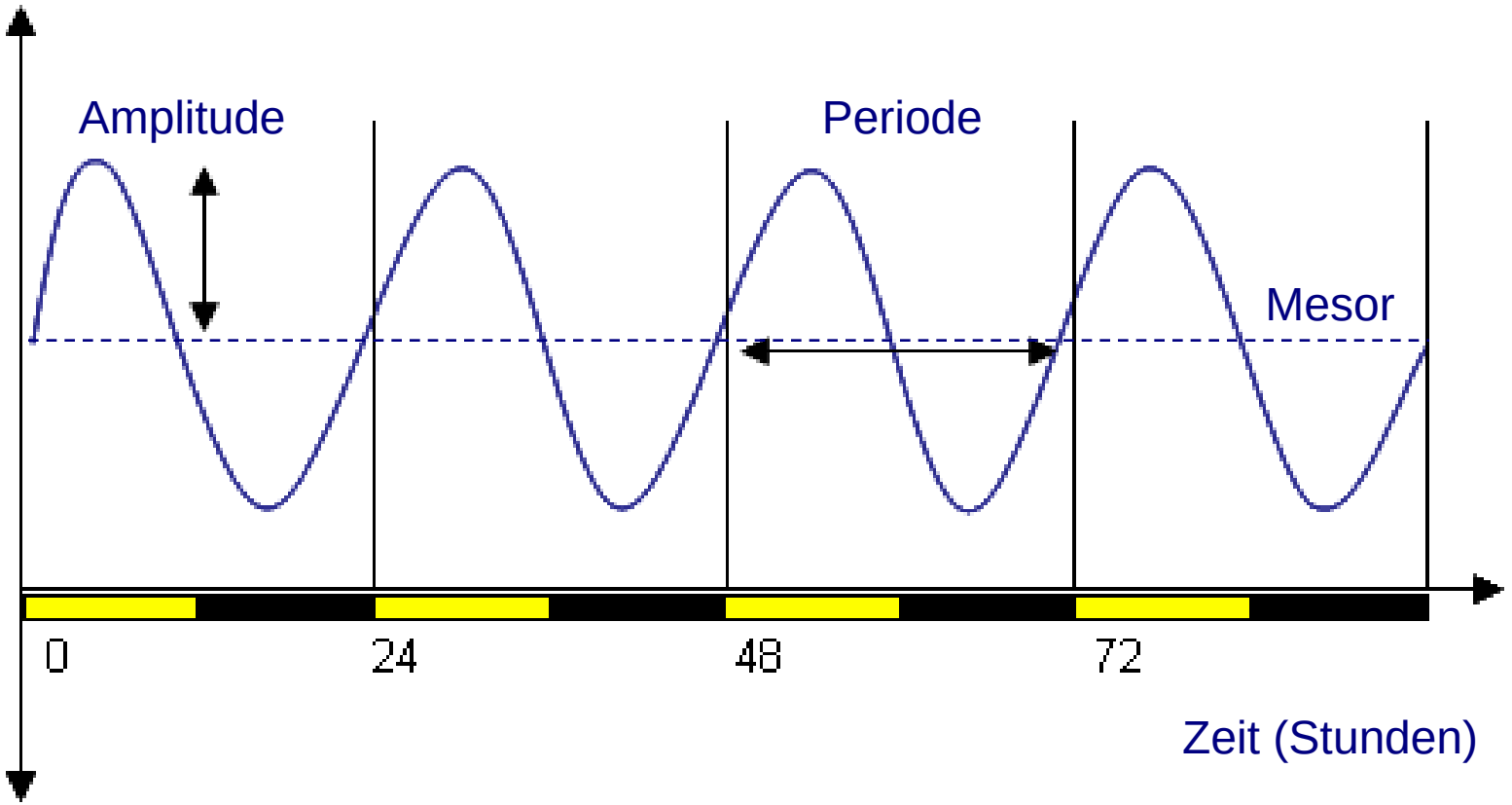
Harnvolumen

Körpertemperatur

Schlaf-Wachverhalten

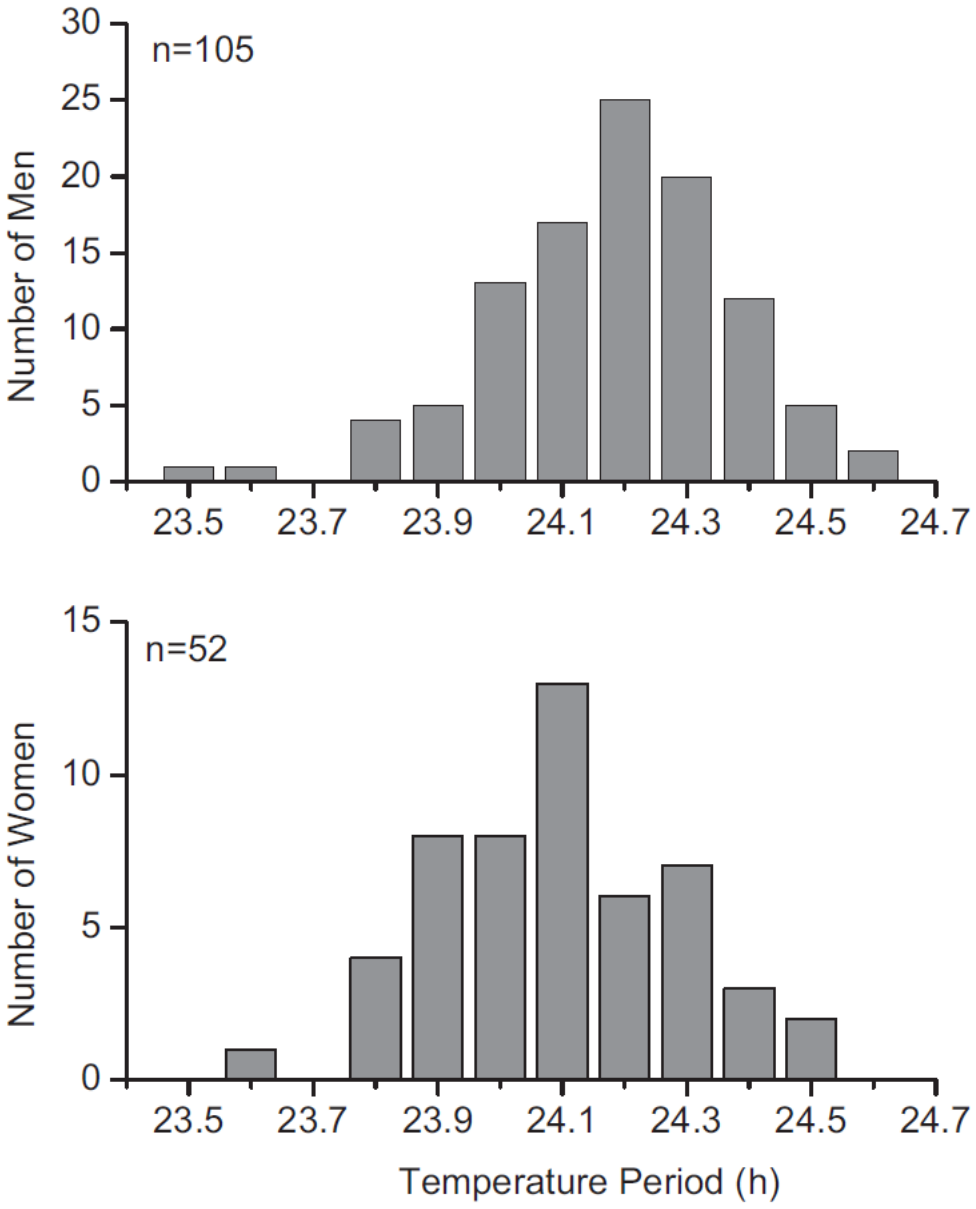
Aschoff & Wever, Naturwissenschaften (1962)

Charakterisierung circadianer Rhythmen



Periode	Periodendauer τ (ca. 24 Std.)
Amplitude	“Grösse” des Rhythmus
Mesor	angepasster 24-Std. Mittelwert

Stabile circadiane Periode beim Menschen



Männer:

$\tau \approx$ 24 h 11 min ± 12 min

Mittelwert:

$\tau \approx$ 24 h 9 min ± 12 min

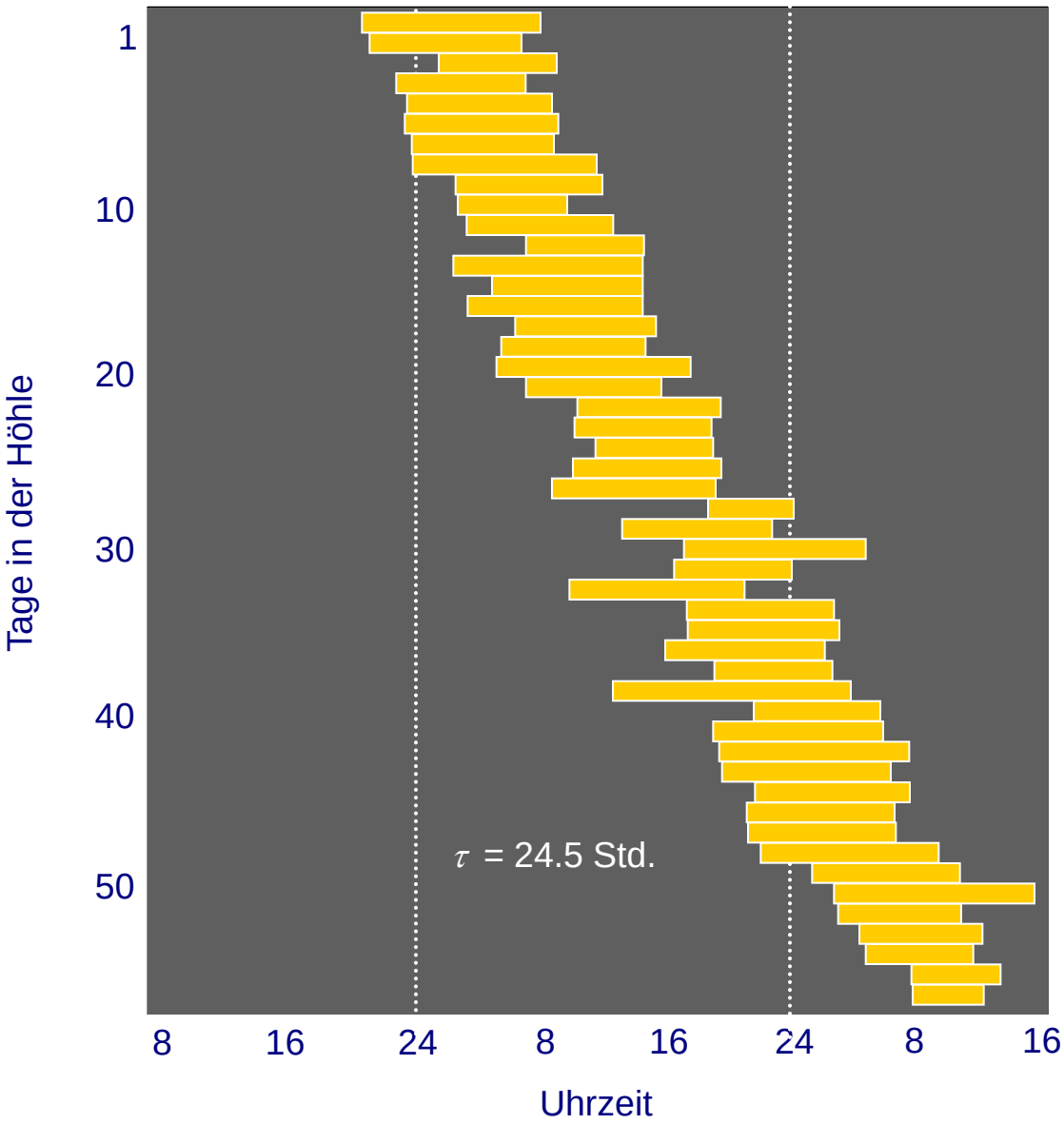
(Rhythmus der Körpertemperatur)

Frauen:

$\tau \approx$ 24 h 5 min ± 12 min

Duffy *et al.*, Proc Natl Acad Sci USA (2011)

Schlafepisoden in dunkler Höhle

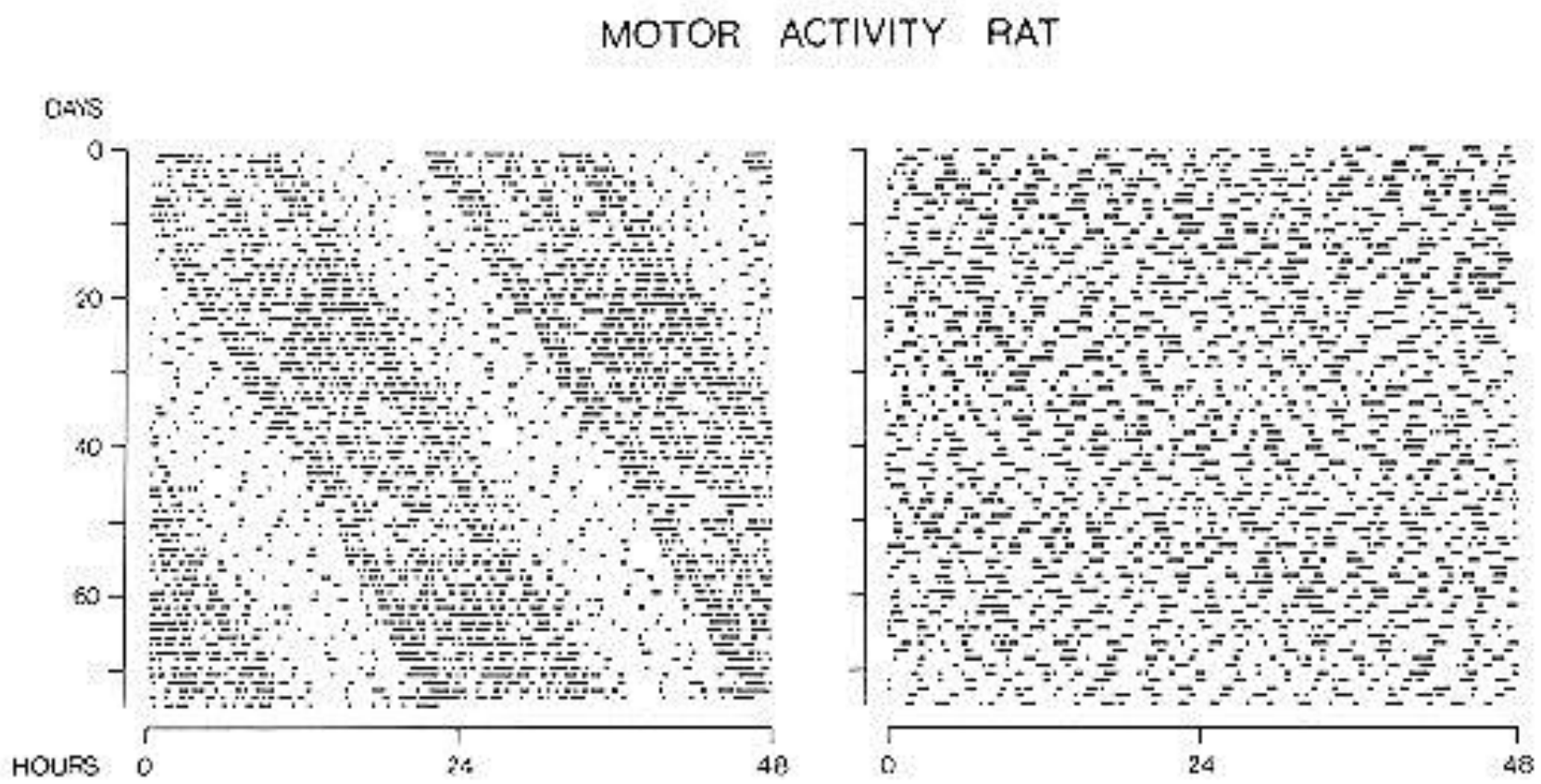


Michel Siffre

- lebte 62 Tage in Höhle in französischen Alpen
- kein Licht (Stirnlampe)
- 120 m tief, 0° C

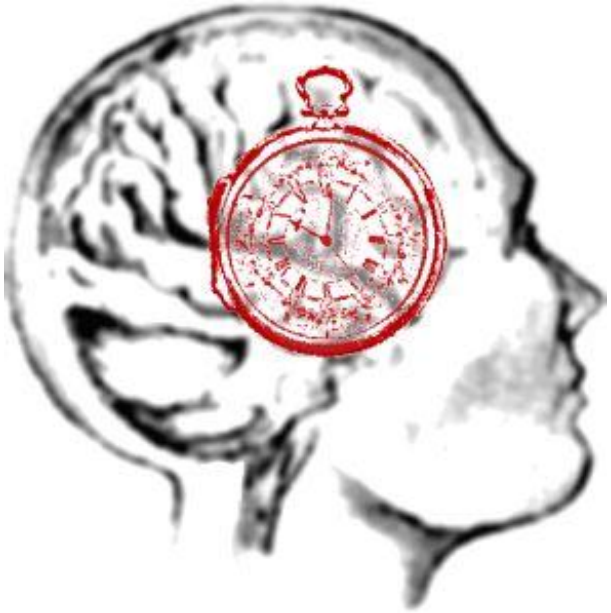
nach Siffre, *Hors du Temps* (1964)

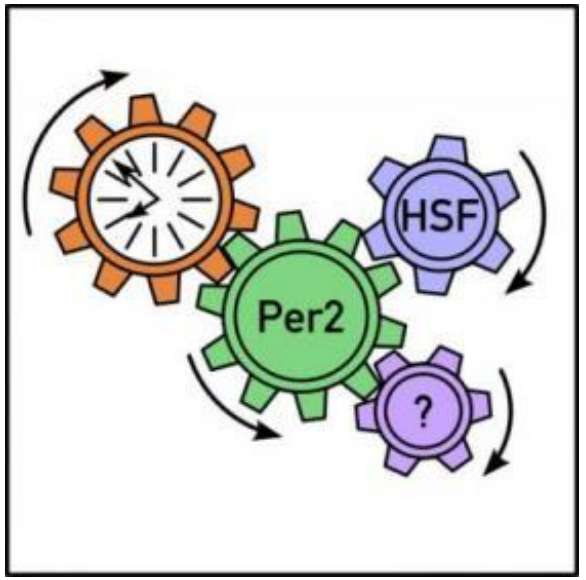
Arrhythmischer Ruhe-Aktivitätsrhythmus nach SCN-Läsion



Molekulare Regulation circadianer Rhythmen

Negative Rückkopplung und zeitliche Verzögerung



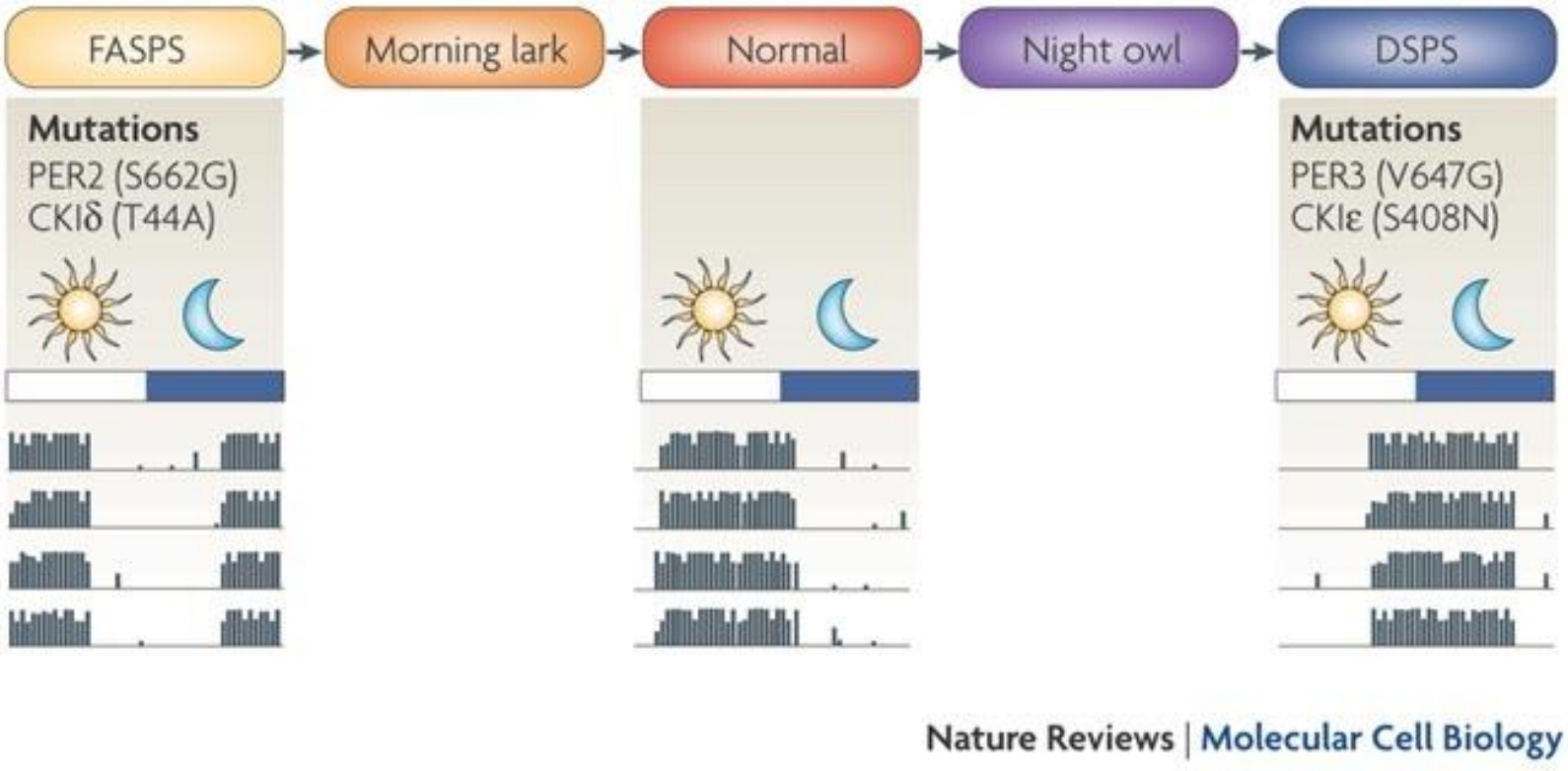


Positiver Arm
CLOCK, BMAL1

Negativer Arm
PER1, PER2,
CRY1, CRY 2

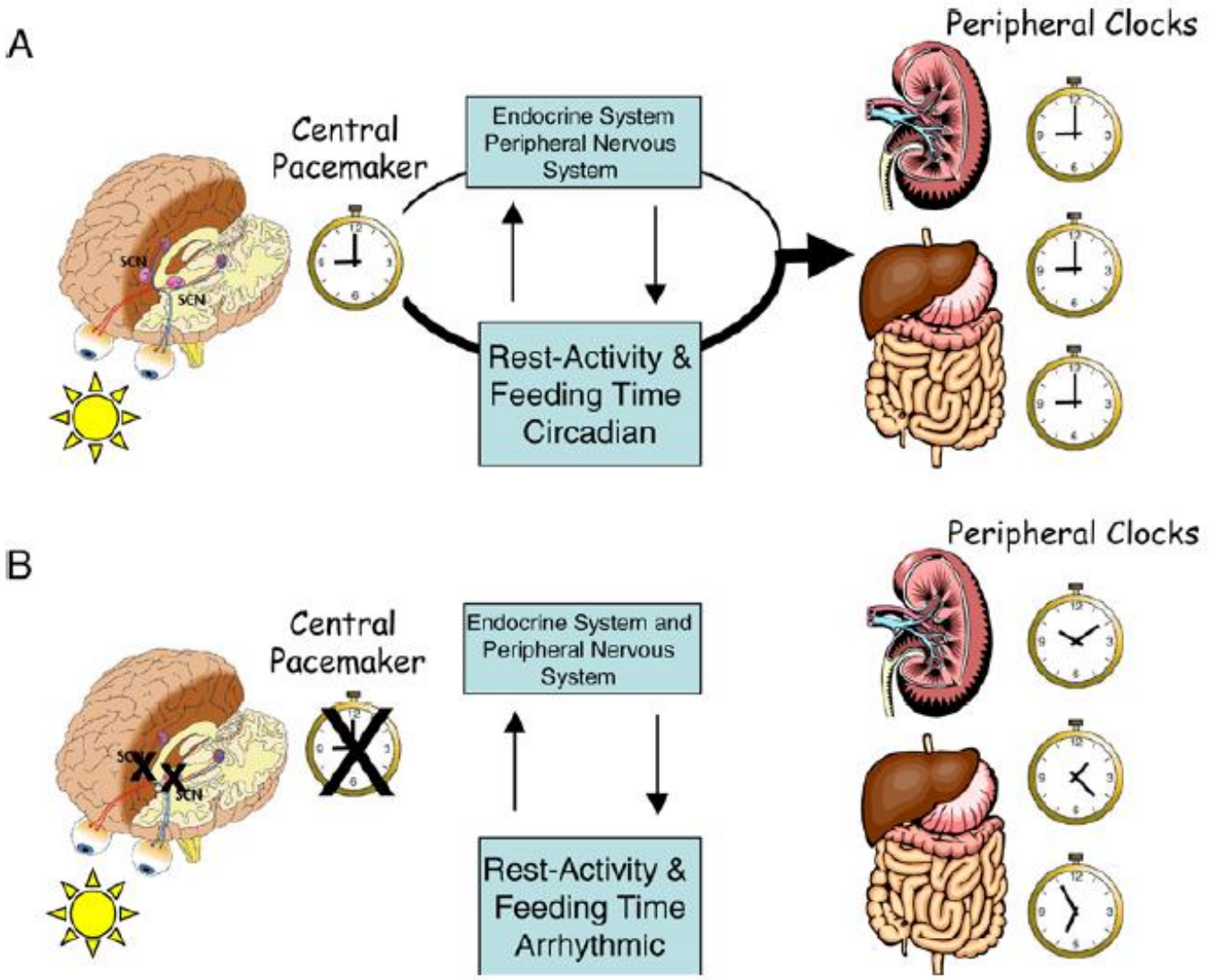
Zwei gekoppelte „feedback loops“

Mutationen bei "Uhrengenen" bewirken Phasenverschiebung des Schlaf-Wachrhythmus



Gallego & Virshup (2007)

Zentrale und periphere circadiane Uhren



Gachon *et al.*, Chromosoma (2004)

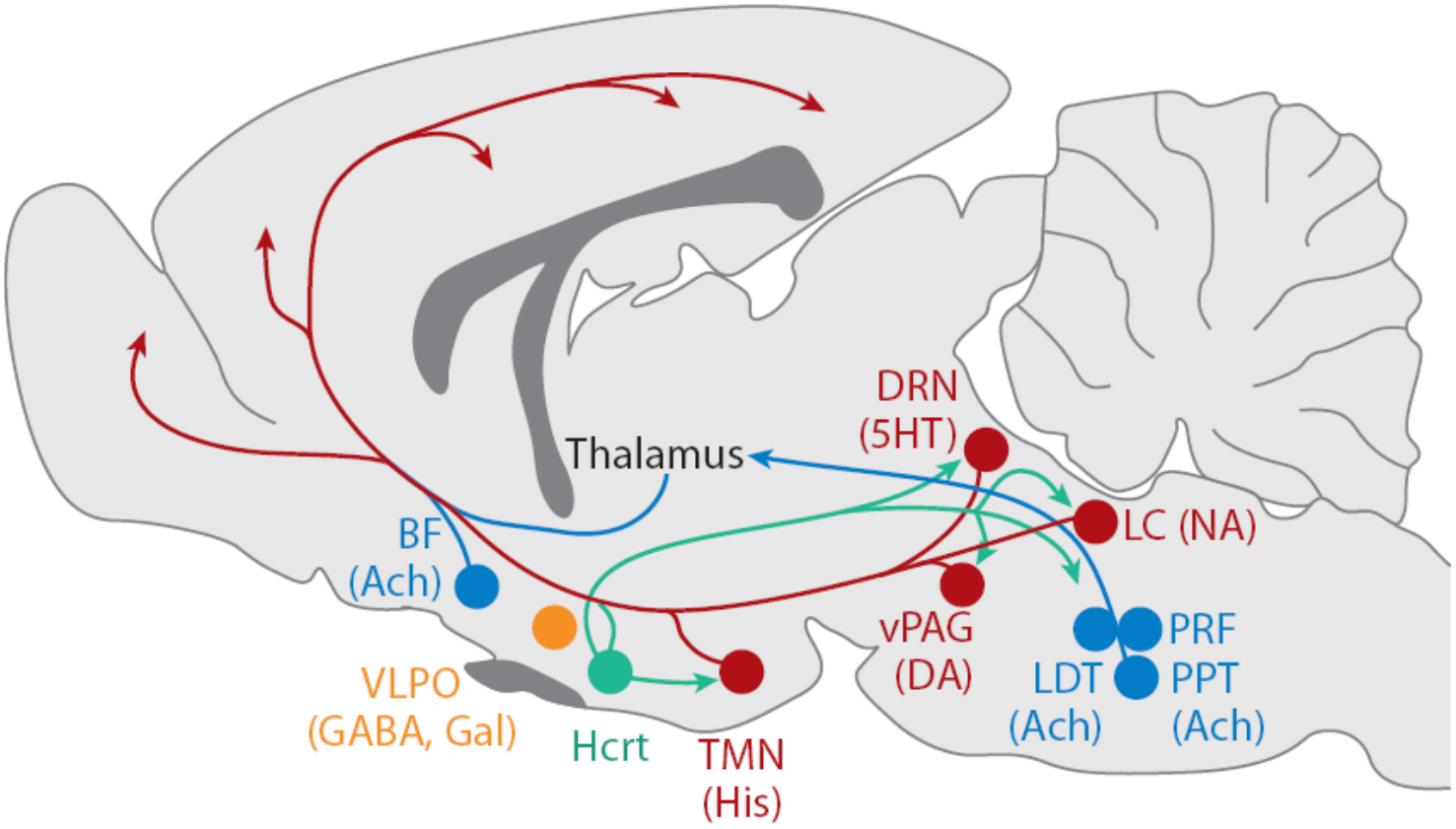
Circadiane Rhythmen

Wozu ?

- Anpassung an den 24-Stunden Hell-Dunkel Rhythmus der Umgebung
- Koordination aller Körperrhythmen
- Antizipation
- Saisonale Änderung der Photoperiode

Neurochemie der Schlaf-Wachregulation

Schlüsselelemente des „ascending reticular arousal system“

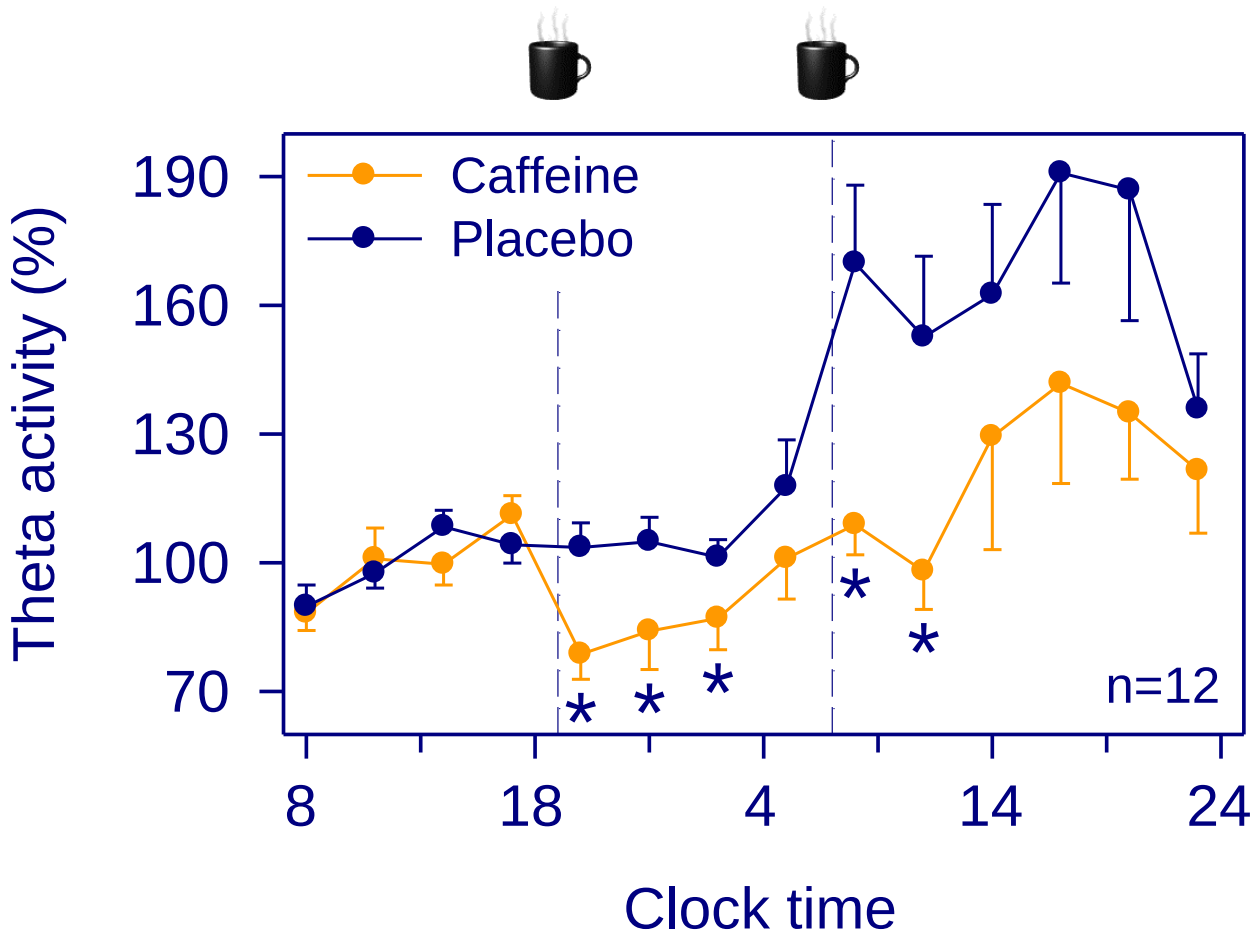


Andretic *et al.*, Annu Rev Genet (2008)

Wachstimulierende Agenzien

- Koffein
  - Adenosin-Rezeptor *Antagonist*

Caffeine attenuates build-up of sleep need during prolonged wakefulness



* $p < 0.05$

Landolt *et al.*, Neuropsychopharmacology (2004)

Wachstimulierende Agenzien

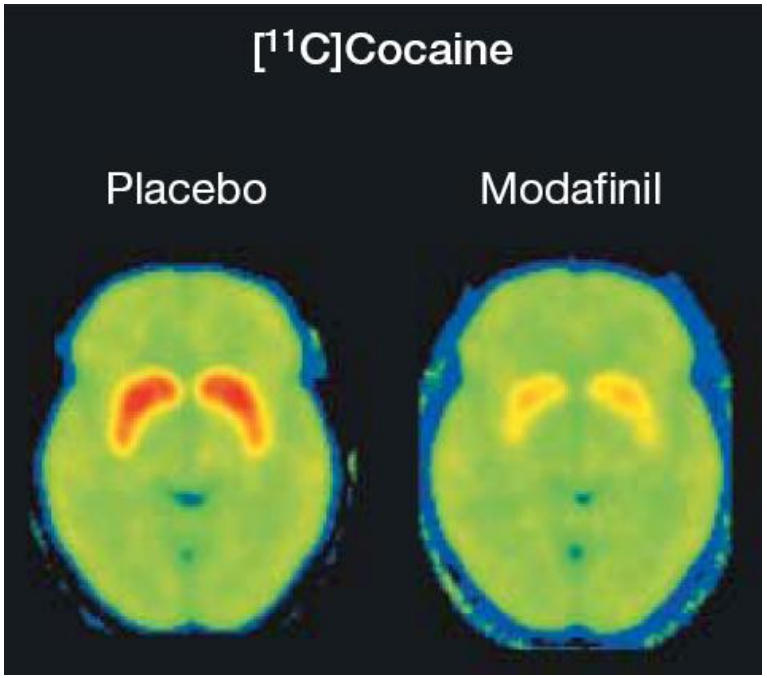
- Koffein
  - Adenosin-Rezeptor *Antagonist*

- Amphetamin
- Methylphenidat (Ritalin)
- Modafinil (Modasomil)
  - interagiert vermutlich auch mit noradrenergem System

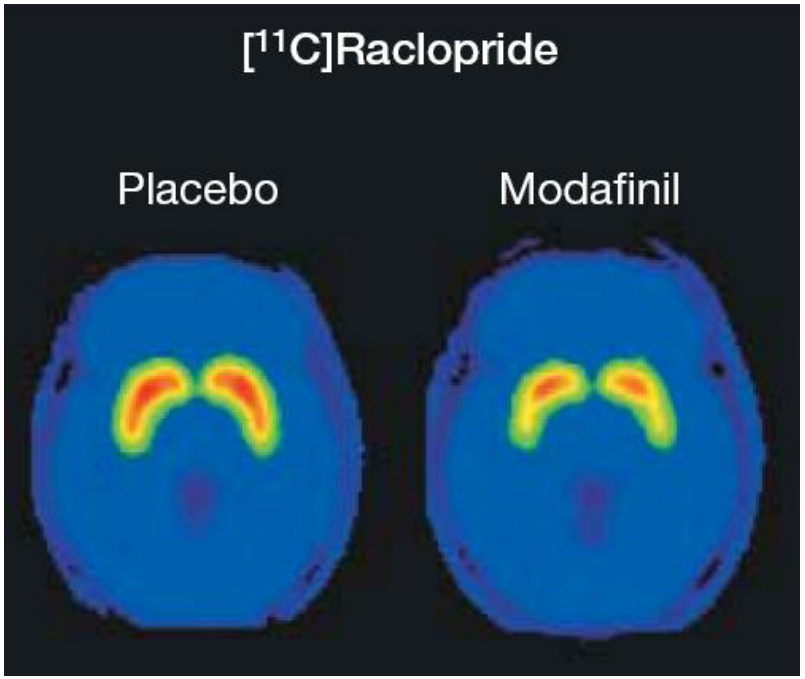
} hemmen Dopamin-Wiederaufnahme

Modafinil belegt Dopamintransporter und erhöht extrazelluläre Dopaminkonzentration

Dopamintransporter



Dopamin D_2/D_3 Rezeptor

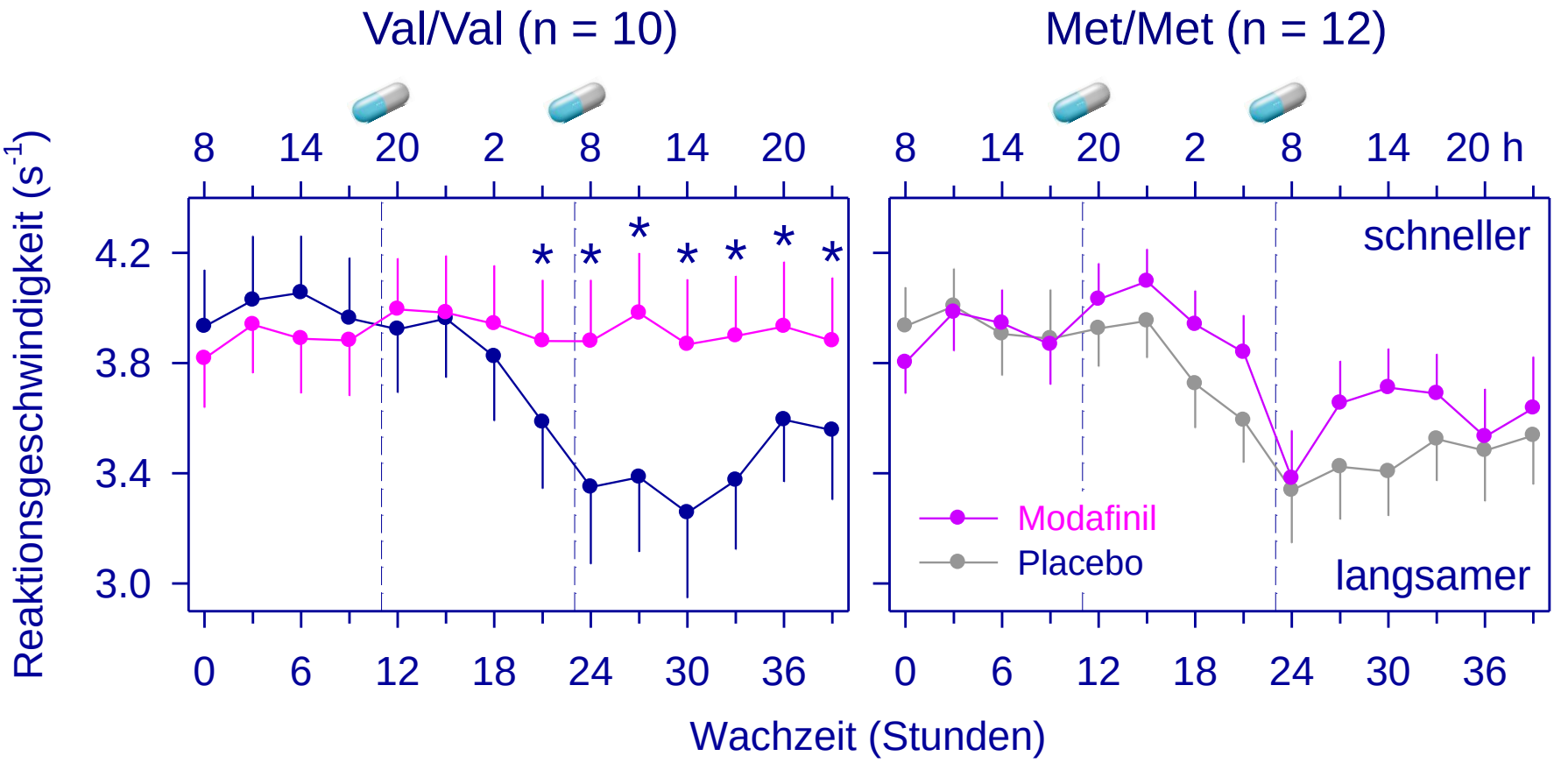


Volkow *et al.*, JAMA (2009)

Modafinil and COMT modulieren dopaminerge Neurotransmission

- Verstärkte dopaminerge Neurotransmission trägt zur stimulierenden Wirkung von Modafinil bei (Wisor *et al.*, 2001; Qu *et al.*, 2008; Volkow *et al.*, 2009)
- Catechol-O-methyltransferase (COMT) katalysiert Abbau von Dopamin im cerebralen Cortex
- Funktioneller COMT *Val158Met* Polymorphismus
  - Val/Val Genotyp $\Rightarrow$ tiefer dopaminerger Tonus
    Met/Met Genotyp $\Rightarrow$ hoher dopaminerger Tonus
  - moduliert Schläfrigkeit and Wirkung von Modafinil bei Narkolepsie (Dauvilliers *et al.*, 2001; Dauvilliers *et al.*, 2002)

Modafinil verhindert Abnahme der Reaktionszeit nach Schlafentzug nur beim Val/Val Genotyp



* $p < 0.05$

Bodenmann *et al.*, Clin Pharm Ther (2009)

Courbet, 1841