World Congress of Neurology
TC 47: Sleep Disorders
Vienna, September 25, 2013

Circadian disorders for neurologists

No conflicts of interest related to this talk

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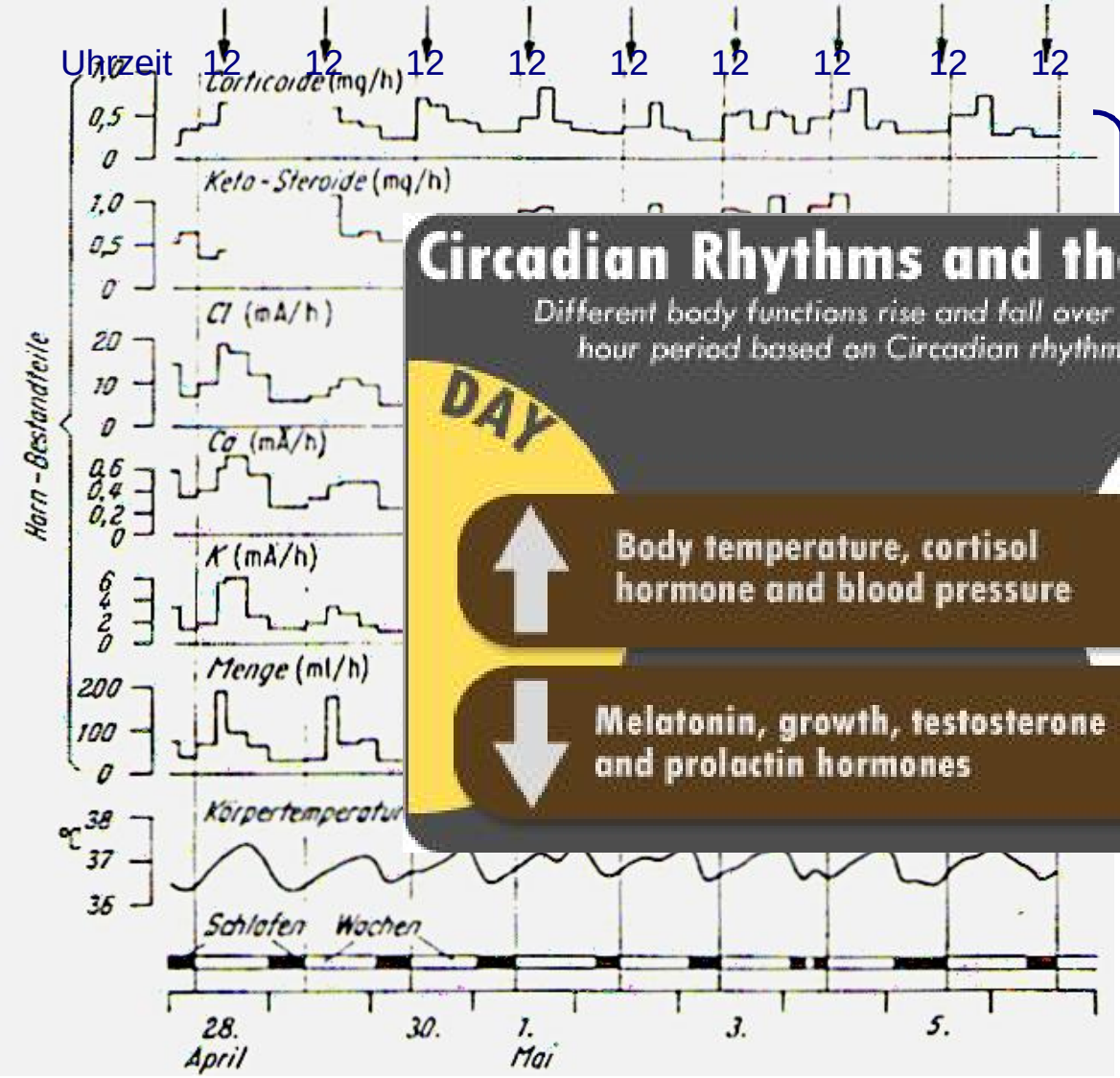
Circadian biology
Circadian disorders
Neurology and circadian biology

Circadian biology

Circadian disorders

Neurology and circadian biology

Circadian physiological variations



hormones

ions

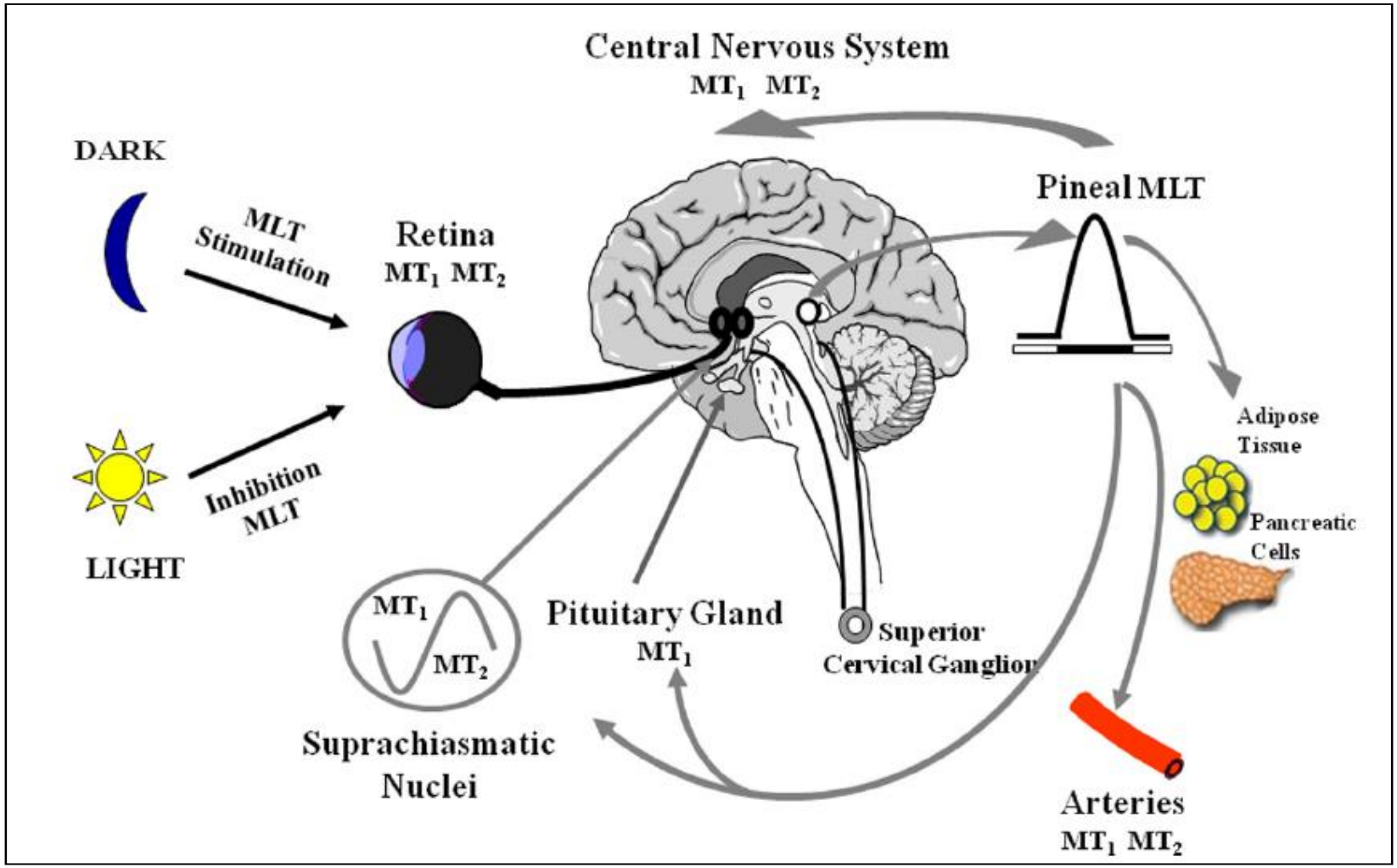
volume

Body temperature

Sleep-wake behavior

Aschoff & Wever, Naturwissenschaften, 1962

Circadian clock, melatonin, light



Dubocovich, 2010

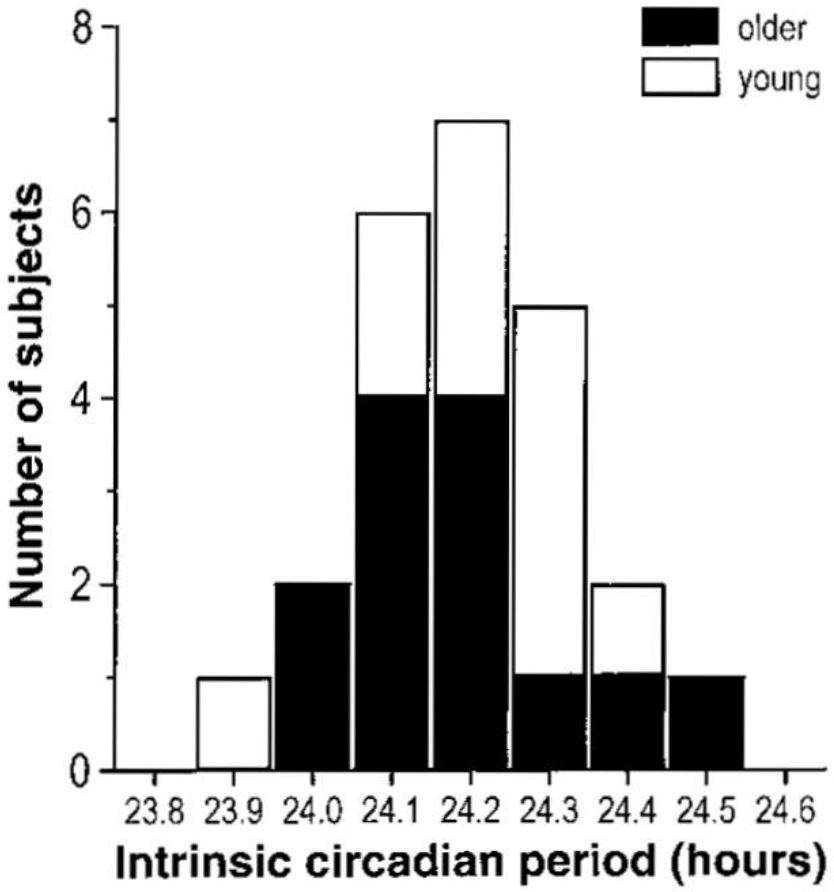
Light versus Melatonin

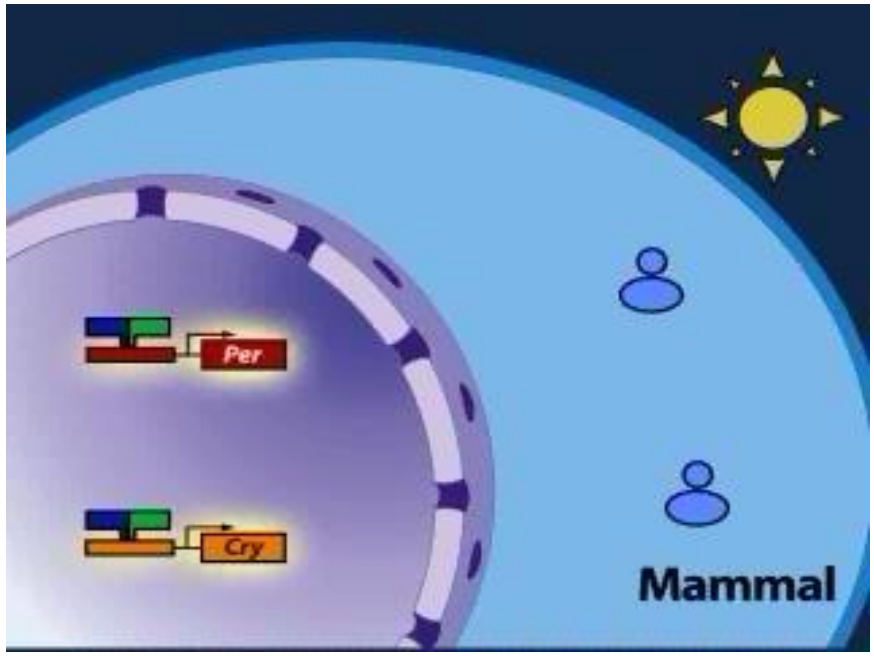
- „Zeitgeber“: evening: phase delays; morning: phase advances
- Alerting properties
- Mood enhancing
- Melatonin suppression
- Cortisol suppression
- Sleep latency ?Y
- Slow-wave activity ?8

- „Zeitgeber“: evening: phase advances; morning: phase delays
- Soporific properties
- No effects (exception: agomelatine)
- Melatonin increase
- -
- Sleep latency ?B
- Sleep spindle activity during daytime sleep ?£

Endogenous circadian rhythm/Clock genes

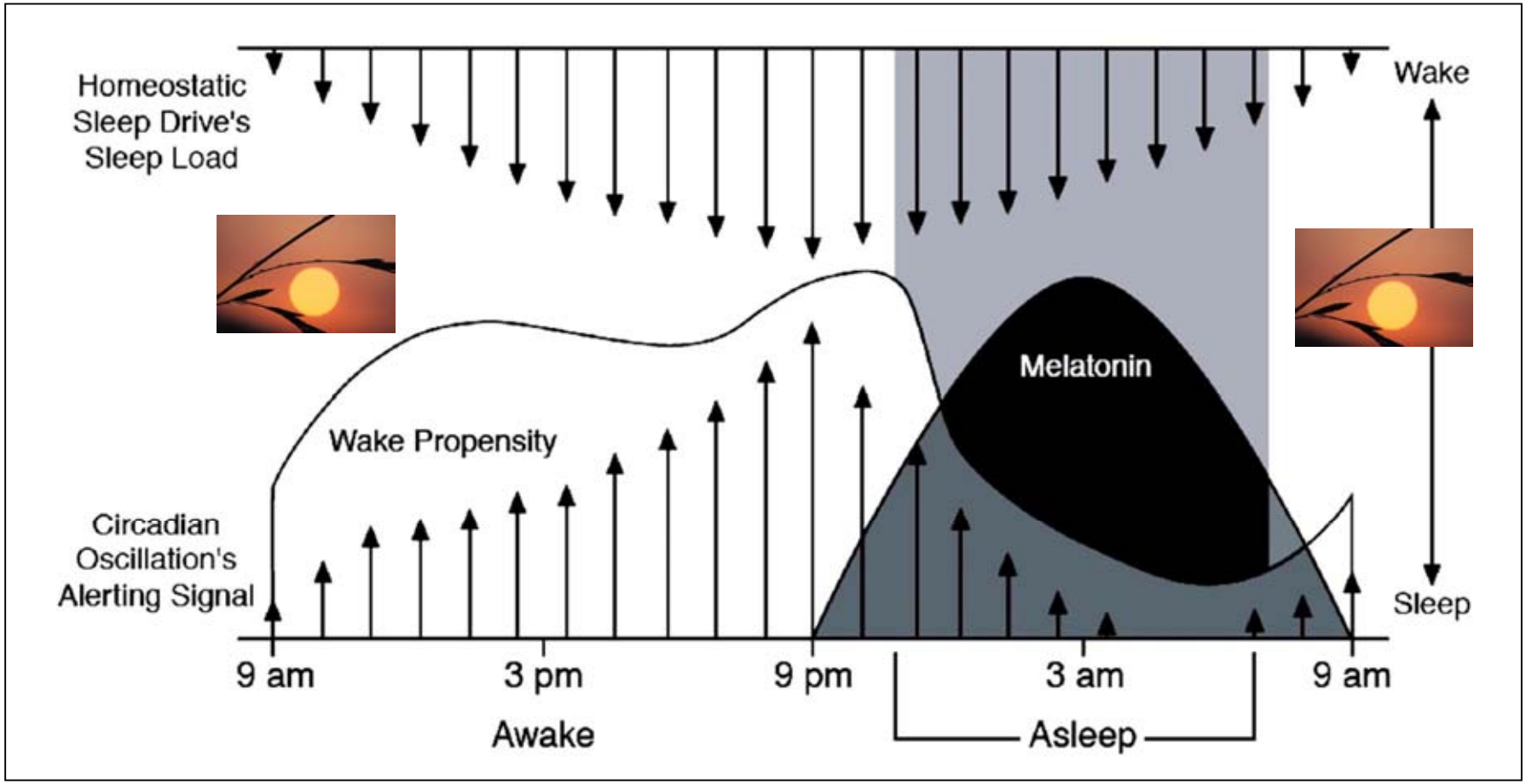
Median ≈ 24.2 hours





Czeisler, Science 1999

Sleep-wake regulation



Circadian biology

Circadian disorders

Neurology and circadian biology

Circadian disorders: Classification

- Delayed sleep phase syndrome
- Advanced sleep phase syndrome
- Non 24-hour sleep-wake type

- Shift work sleep disorder
- Jet lag syndrome

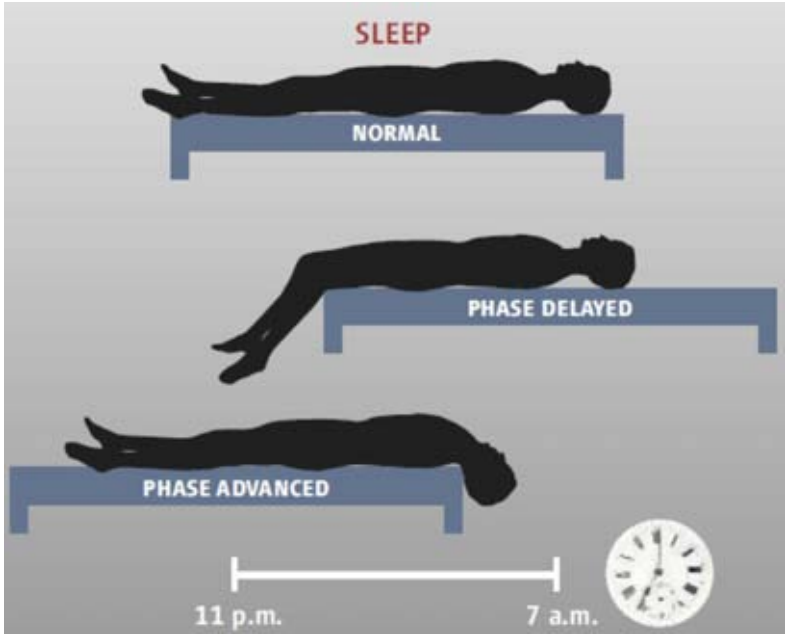
Advanced Sleep Phase Syndrome

"Early Birds"

Normal

"Night owls"

Delayed Sleep Phase Syndrome



Circadian disorders: Clinical features

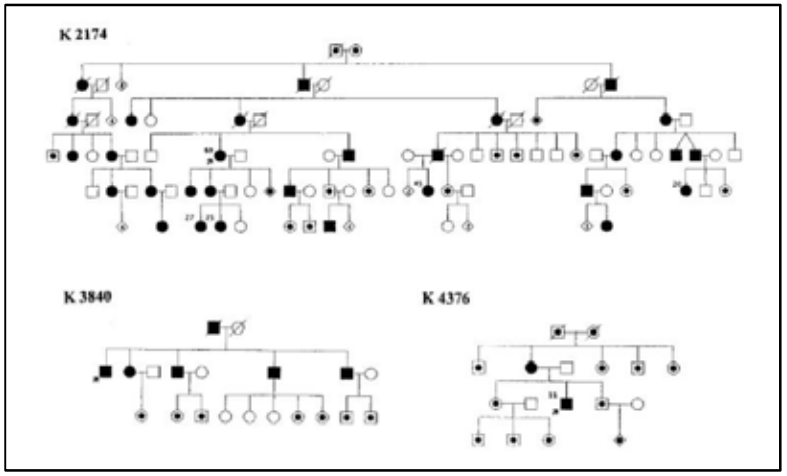
- Insomnia
- Excessive daytime sleepiness

- Gastrointestinal symptoms
- Other somatic symptoms (headache,...)
- Accidents
- Impairment of social, occupational functioning
- Increased cardiovascular risk (?)

Circadian disorders: Etiopathogenesis

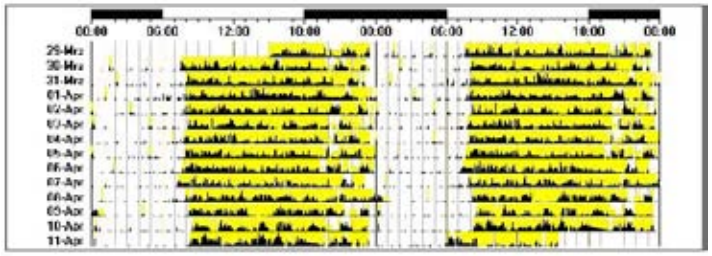
- Alteration of circadian clock
- Misalignment (circadian clock vs timing of sleep)

- Genetic factors
- Psychological factors
- Environmental factors

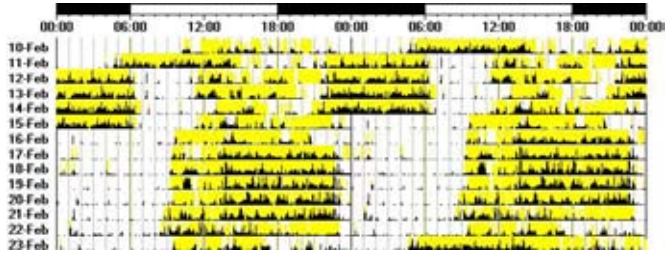


Circadian disorders: Diagnosis

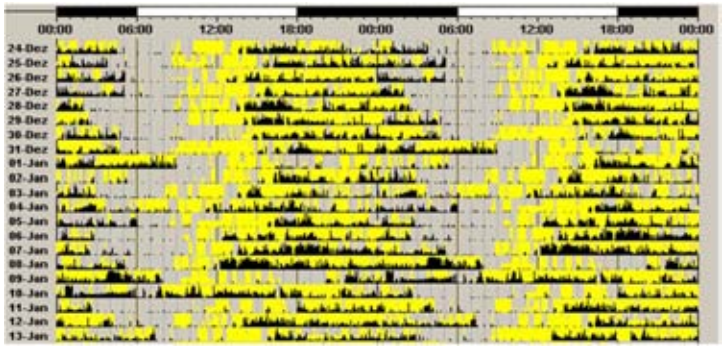
- Sleep diaries
- Actigraphy
- Saliva melatonin measurements (DLMO)
- Genetics



N.P., 44y (Nr. 1220)
normal subject



N.N., 34y (Nr. 1646)
shift-worker

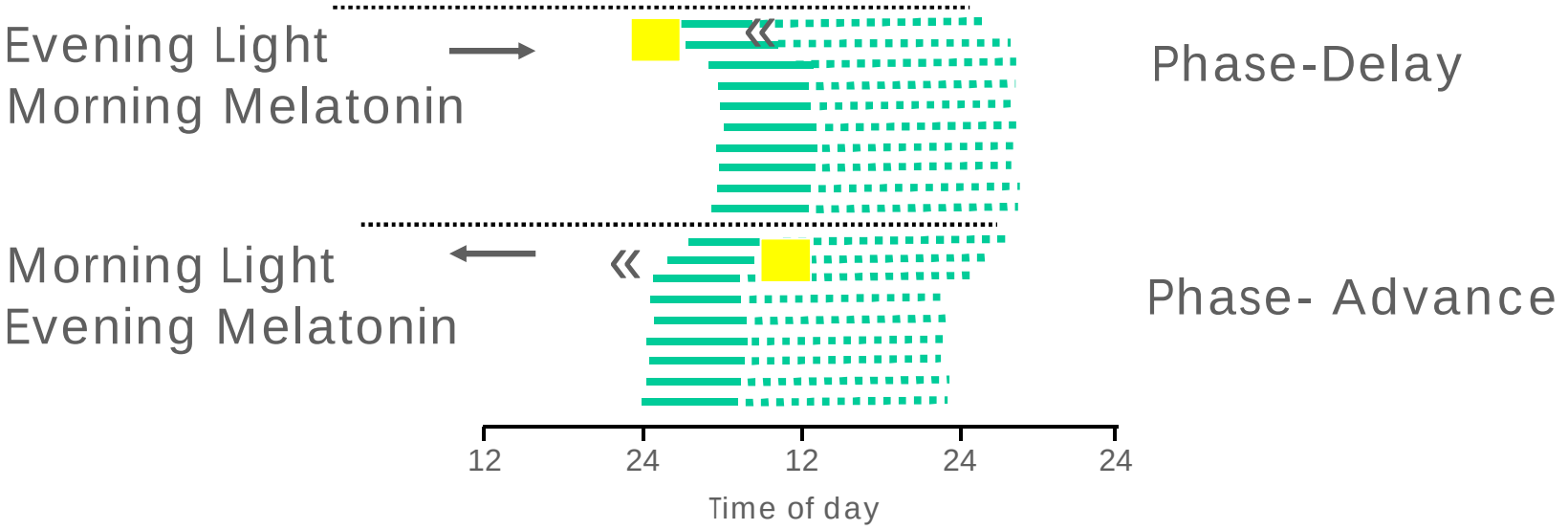


R.S., 24y (Nr. 1170)
delayed sleep phase
syndrome

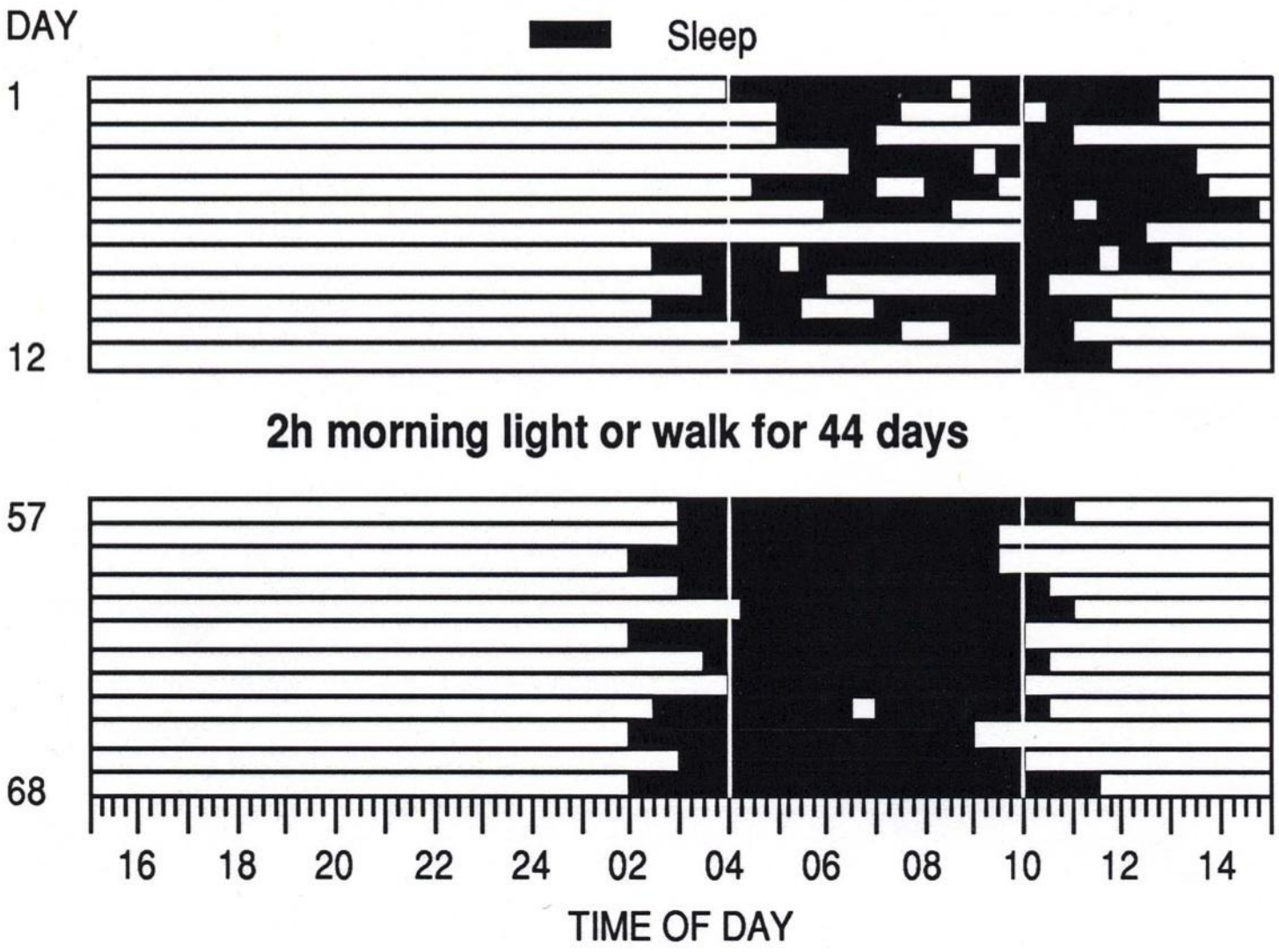
Circadian disorders: Treatment

- Bright light
- Melatonin
- Sleep hygiene
- Behavioral interventions

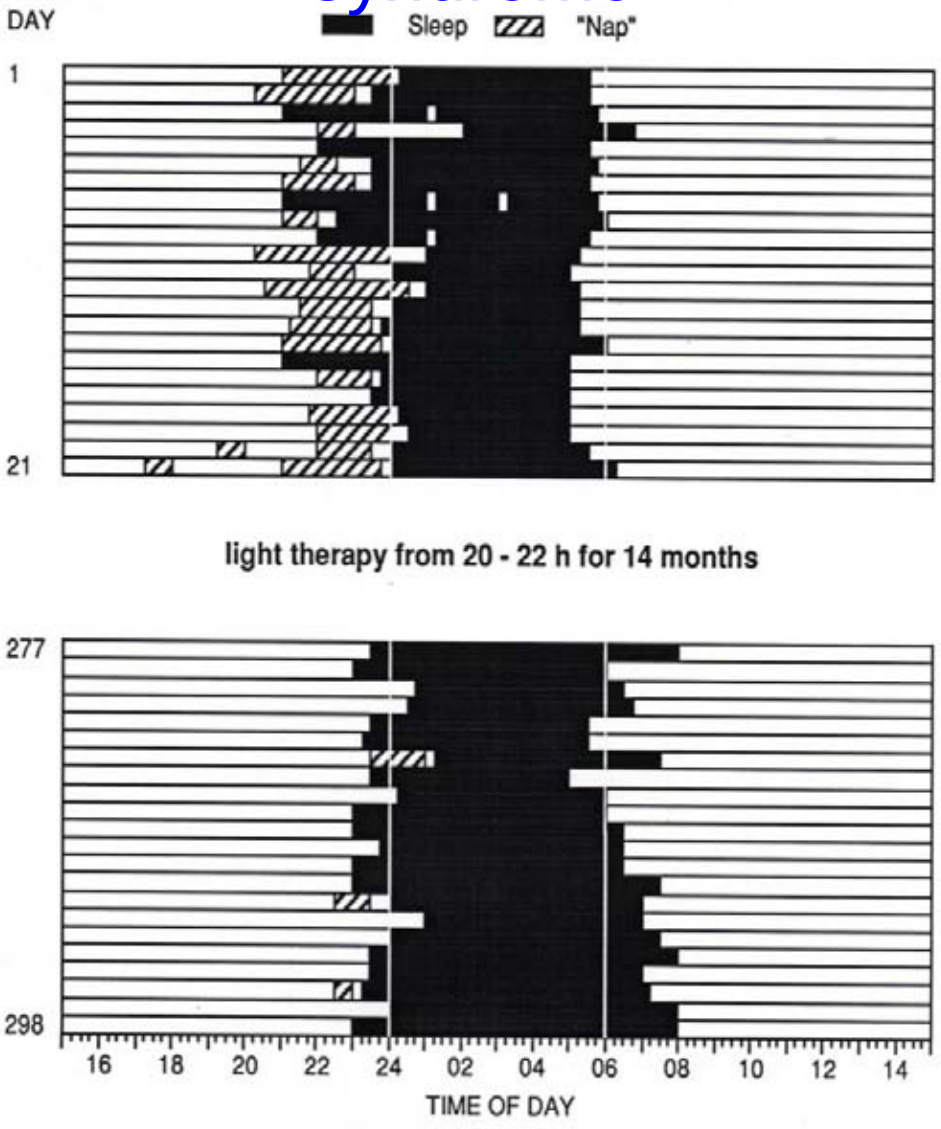
Light and Melatonin as Zeitgeber



Delayed sleep phase syndrome



Advanced sleep phase syndrome



Circadian biology
Circadian disorders
Neurology and circadian biology

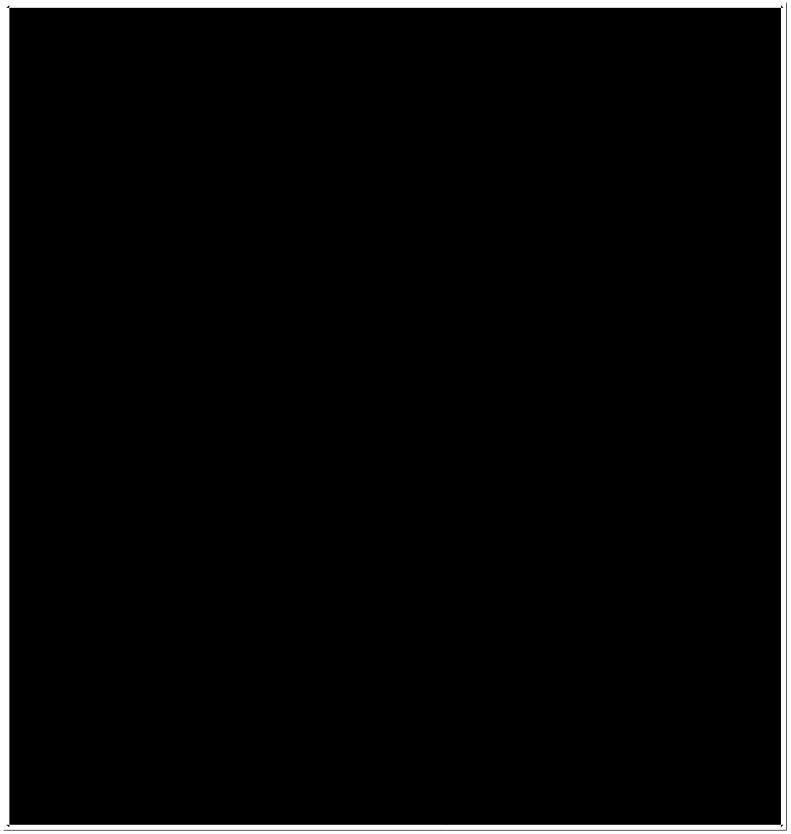
Neurology and circadian biology

- Restless legs syndrome
- Stroke
- Epilepsy
- Parkinson
- Aging/dementia
- Others (headache, spinal cord disorders, syncope,...)

RLS and circadian biology

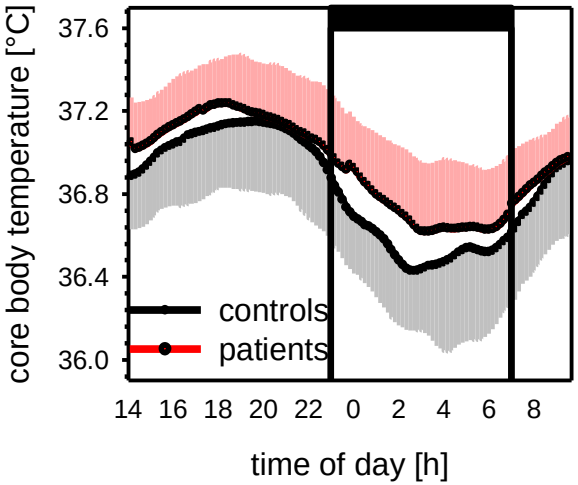
Circadian distribution of symptoms

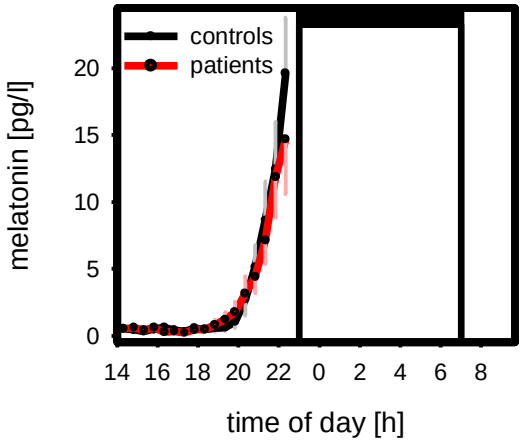
No evidence for circadian disturbances

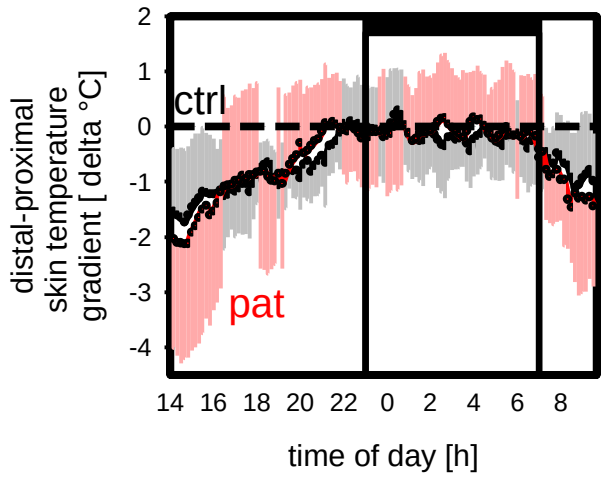


Trenkwalder, Ann Neurol 2004

Circadian parameters in RLS





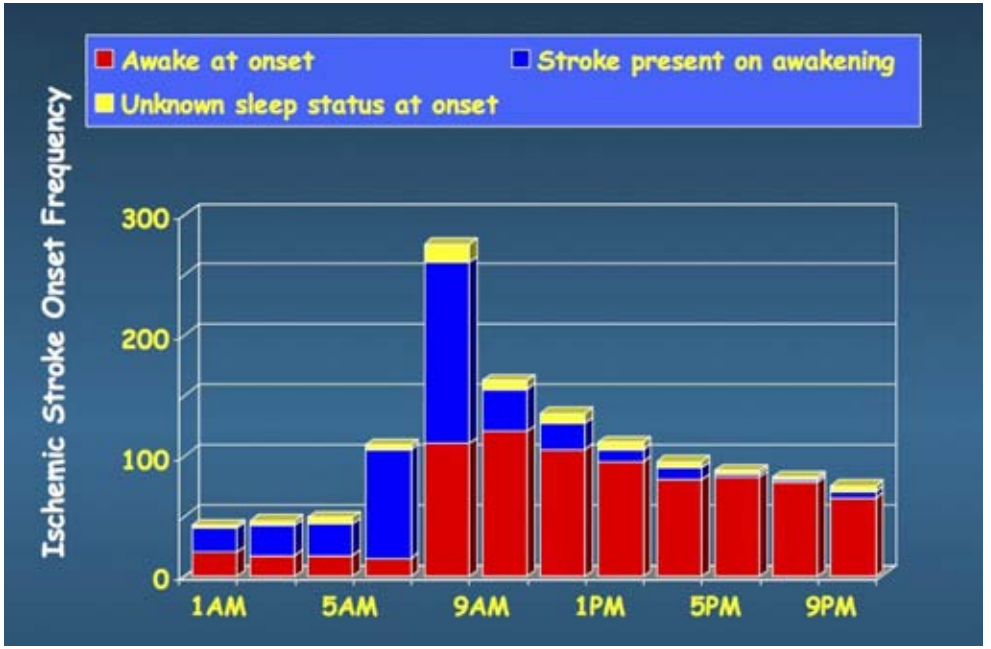


Clavadetscher, JSR 2002

Stroke and circadian biology

Circadian distribution of stroke onset

Marler, Stroke 1989
Muller, NEJM 1985



Sleep-wake inversion in acute stroke

Bassetti, Hdb Neurol 2011

Shift work and stroke risk

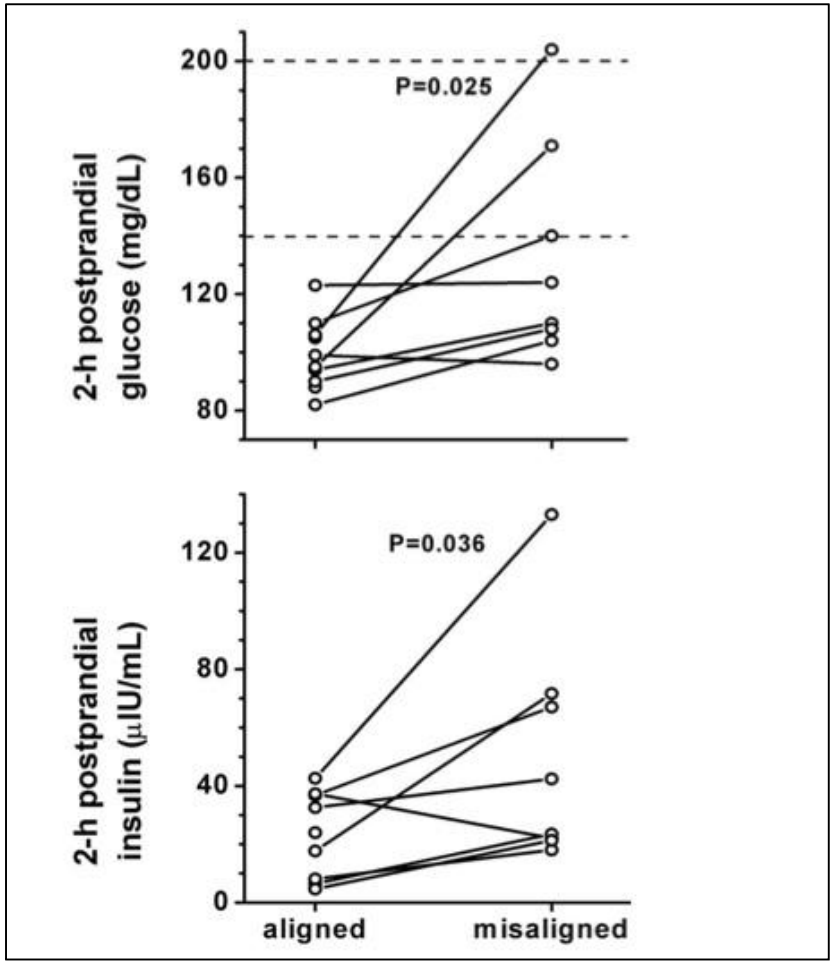
Brown, Am J Epidemiol 2009

Adverse metabolic and cardiovascular consequences of circadian misalignment

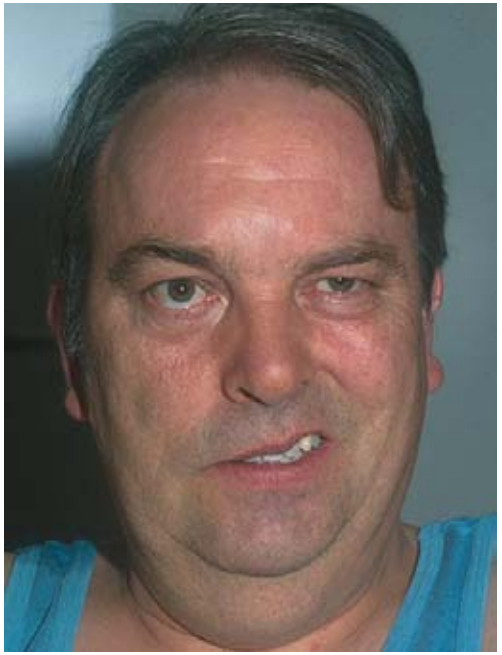
Frank A. J. L. Scheer[a,b,1], Michael F. Hilton[a,2], Christos S. Mantzoros[b,c], and Steven A. Shea[a,b]

[a]Division of Sleep Medicine, Brigham and Women's Hospital, Boston, MA 02115; [b]Harvard Medical School, Harvard University, Boston, MA 02115; and [c]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215

PNAS, 2010



Predictors of sleep disordered breathing in stroke patients



F.M., 54y

TABLE 6. Independent Predictors of AHI

	Wald's Statistic	*P* Value	Odds Ratio
Age	14.722	0.000	1.069
Diabetes	6.056	0.014	4.269
[redacted]			

Logistic regression analysis, dependent variable: AHI.
Nagelkerke $r^2=0.295$.
*Onset of stroke between 9:01 PM and 6.00 AM, 25%; between 6:01 AM and 9:00 PM, 75%.

Bassetti, Stroke 2006

Epilepsy and circadian biology

Circadian distribution of seizures

Loddenkemper, Neurology 2011

TABLE 1.1 Proportion of Patients with Diurnal, Nocturnal, and Diffuse Epilepsy in Early Clinical Observational Studies

Author	No. of patients	Diurnal epilepsy (%)	Nocturnal epilepsy (%)	Diffuse epilepsy (%)
Gowers, 1865	84	42	21	37
Langdon-Down and Brain, 1929	66	43	24	33
Patry, 1931	750	45	19	36

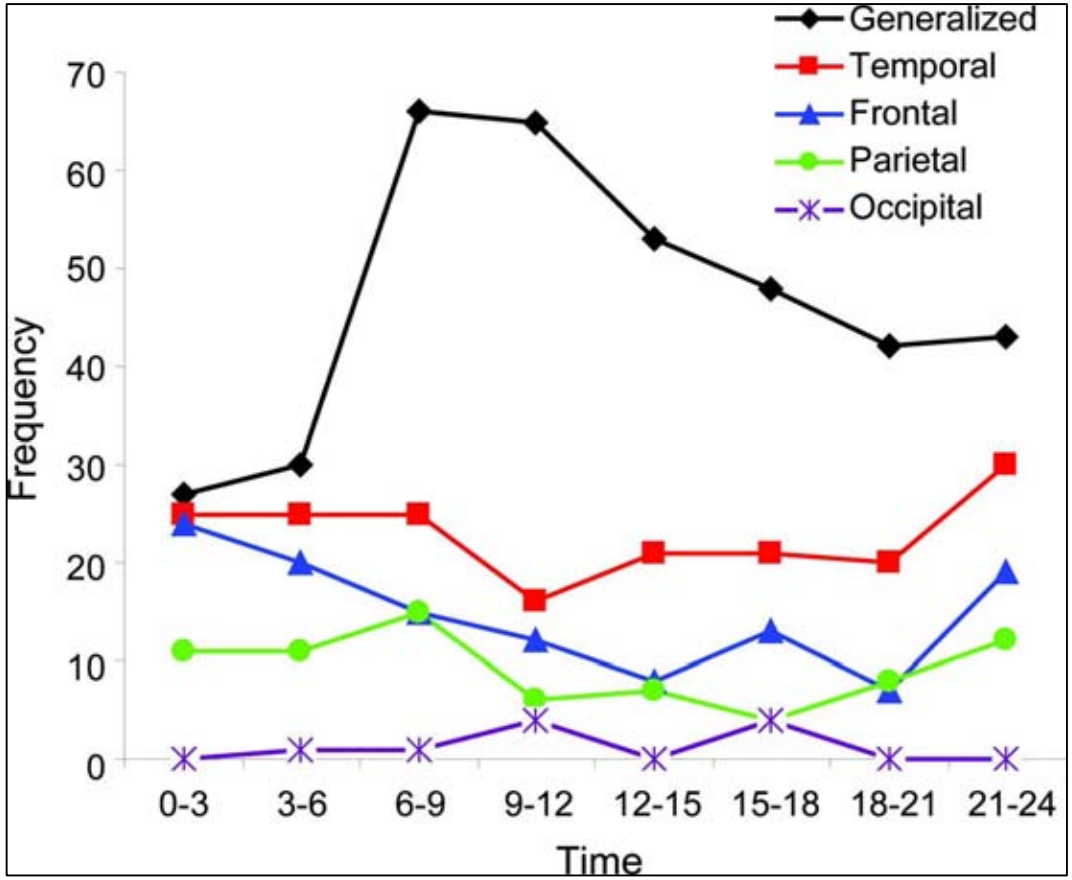
Chronopharmacotherapy

Ramgopal, Curr Neurol Neurosci Rep 2013

Melatonin/bright light for febrile seizures, epilepsy

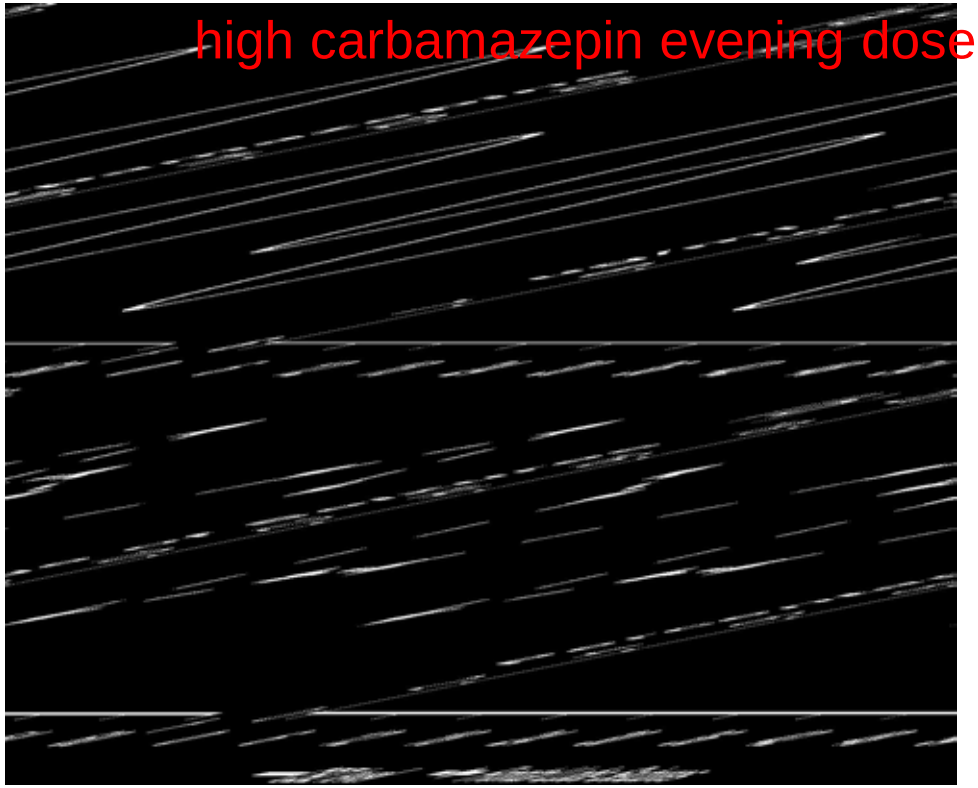
Sanchez-Barcelo, Int J Pediatr 2011

Circadian distribution of pediatric seizures



Loddenkemper, Neurology 2011

Chronopharmacology



Ramgopal, Curr Neurol Neurosci Rep 2013

Parkinson and circadian biology

Phase advance

Bordet, Clin Pharmacol 2003
Videnovic, Exper Neurol 2012

Melatonin treatment of RBD

Boeve, Sleep med 2003

Sleep benefit

Bateman, JNNP 1999
Högl, Neurology 1998

and Parkin/PINK1 mutations

Wiley, Mov Dis 2004
Bonifati, Neurology 2005

Bright light for motor/non motor disturbances

Willis, Chronobiol Int 2007
Paus, Mov Dis 2007
Terman, Sleep Med Rev 2007

Sleep benefit in Parkinson disease

Answers to questionnaire regarding medication, Hoehn and Yahr stage, the presence of motor fluctuations, and sleep benefit in 113 patients with Parkinson's disease related to sleep benefit determined by ADL scores of "worst"-"best" (w−b> 12=sleep benefit)

	No of patients	*Sleep benefit (w−b>12)*	*No of patients (%)*
Levodopa treatment	105		
Dopamine agonists (bromocriptine)	23		
Selegiline	61		
Artane or other anticholinergic	42		
Hoehn and Yahr (mean daily on):			
Stage 1	30	6	20
Stage 2	37	21	57
Stage 3	24	12	50
Stage 4	19	10	53
Stage 5	3	0	
Motor fluctuations	80	43	54
		Confirmed by ADL scores	
Subjective sleep benefit	66	40/66	
No sleep benefit	23	4/14 (no forms nine patients)	
Uncertain regarding sleep benefit	24	5/24 SB present	

[redacted]

Bateman, JNNP 1999

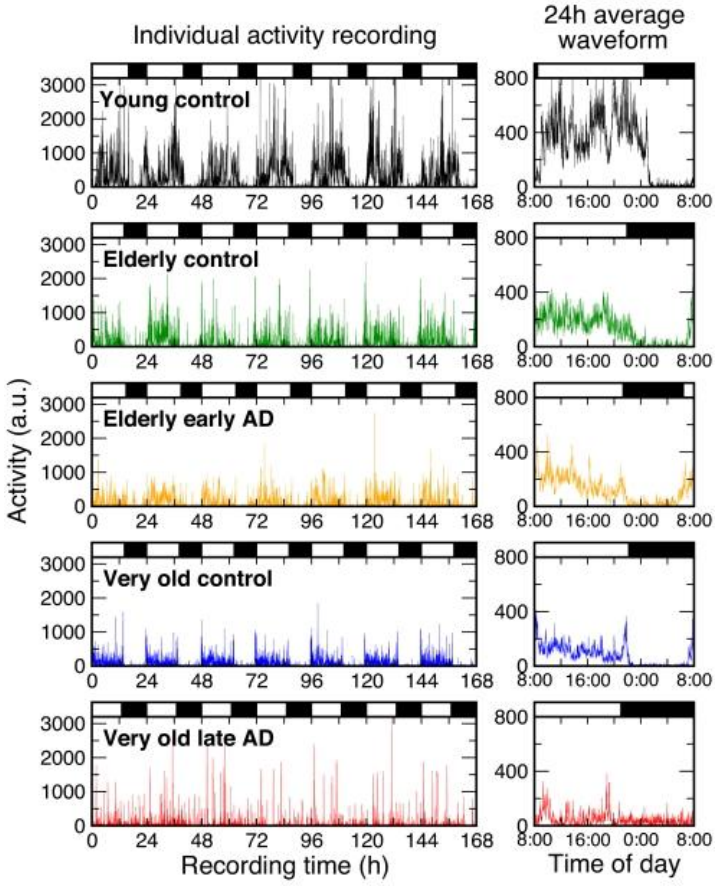
Dementia and circadian biology

Aging/dementia associated with decreased SCN activity and melatonin deficienvy

Garfinkel, Lancet 1995
Volicer, Am J Psychiat 2001
Hu, PNAS 2009

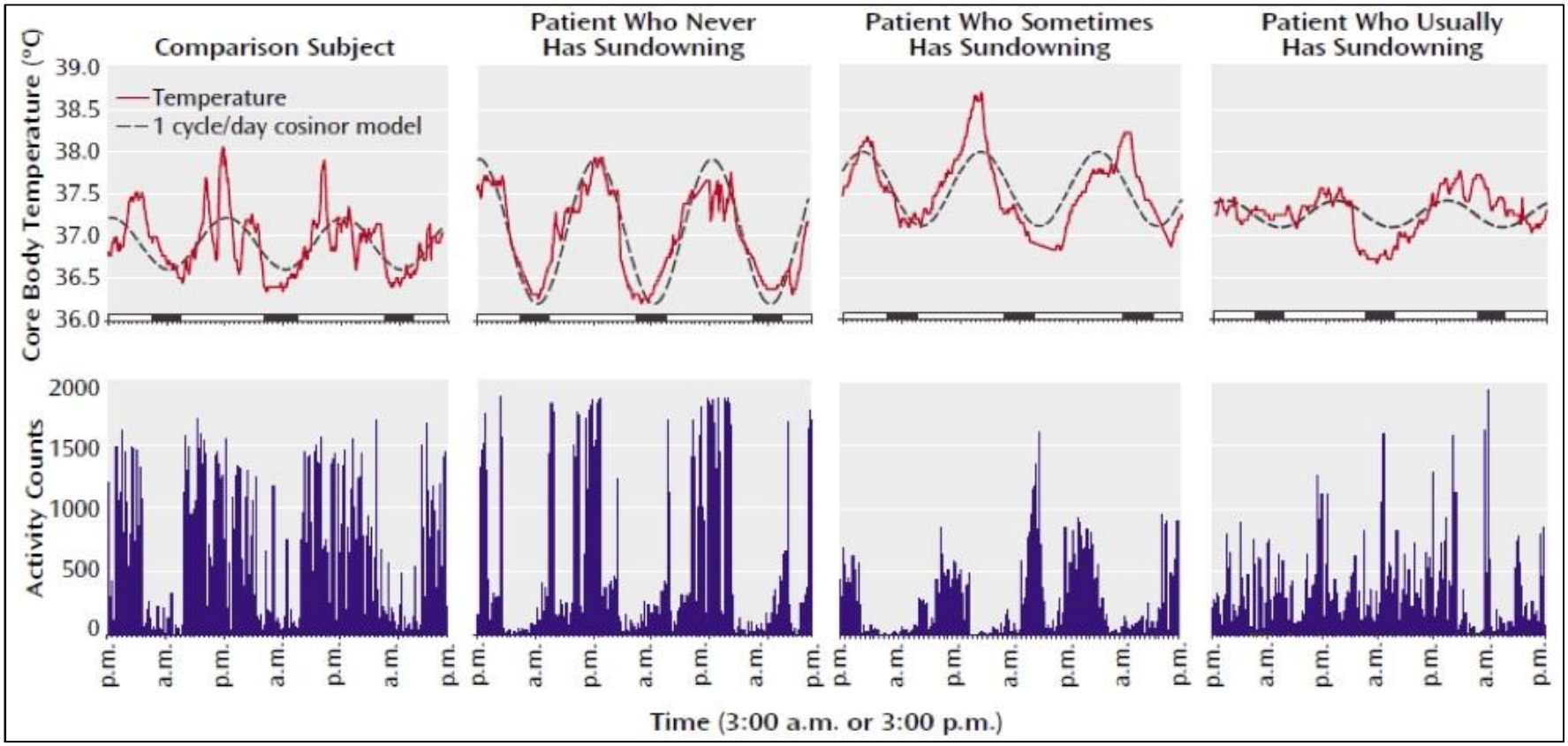
Sundowning/cognition improved by bright light

Lujpen, Rev Neurosci 2003
Riemersma-van der Lek, JAMA 2008



Hu, PNAS 2009

Sundowning and dementia

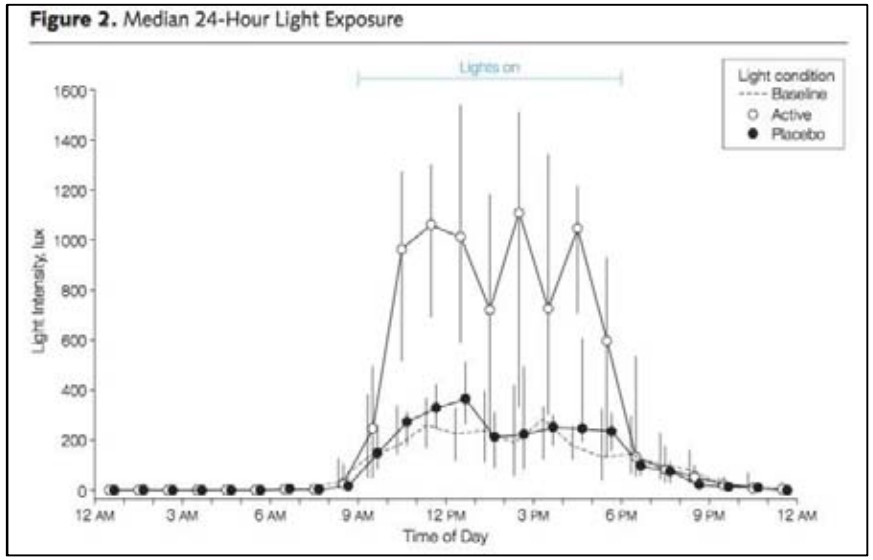


Volicer, Am J Psychiat 2001

Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities

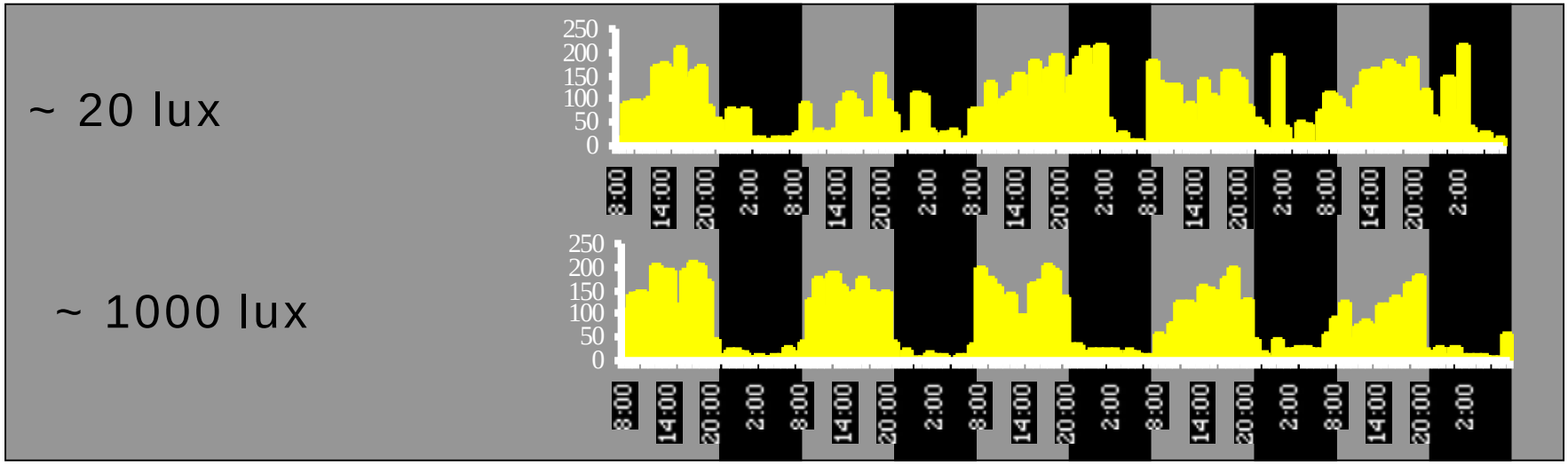
A Randomized Controlled Trial

JAMA 2008



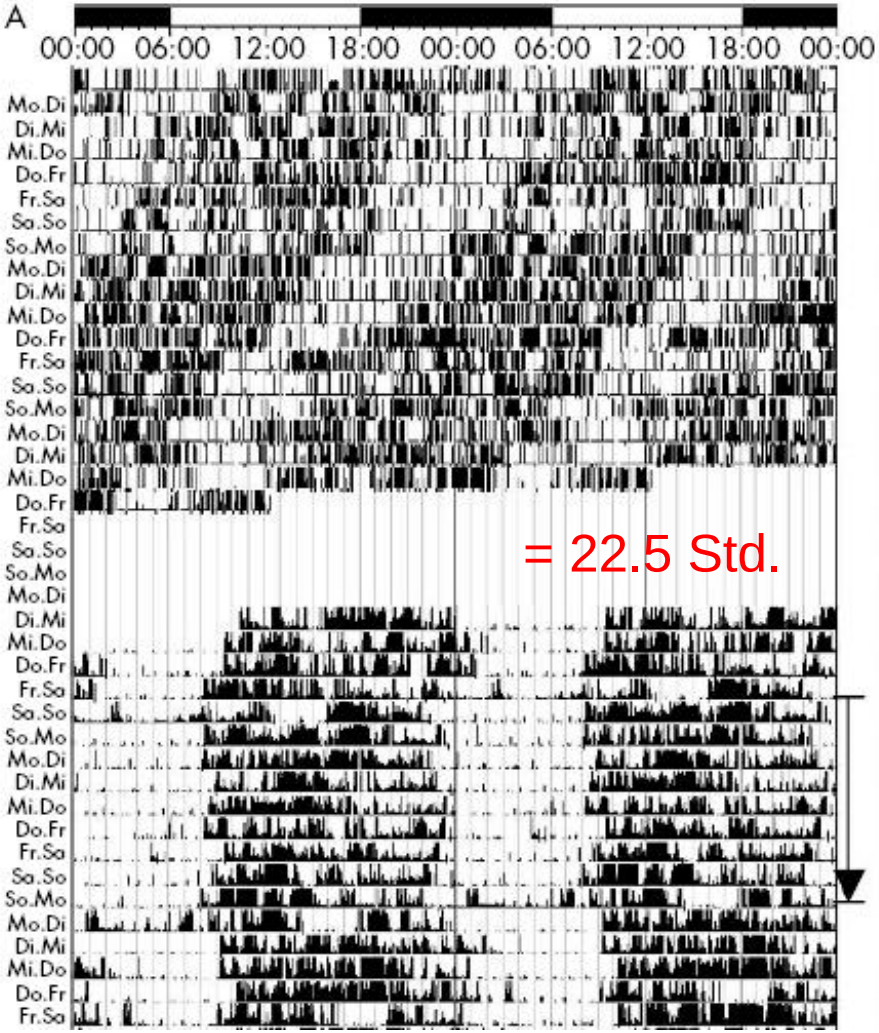
In conclusion, the simple measure of increasing the illumination level in group care facilities ameliorated symptoms of disturbed cognition, mood, behavior, functional abilities, and sleep. Melatonin improved sleep, but its long-term use by elderly individuals can only be recommended in combination with light to suppress adverse effects on mood. The long-term application of whole-day bright light did not have adverse effects, on the contrary, and could be considered for use in care facilities for elderly individuals with dementia.

Light and sleep-wake rhythms in elderly homes



Van Someren, 2002

Free runnning cycle and hypothalamic lesion

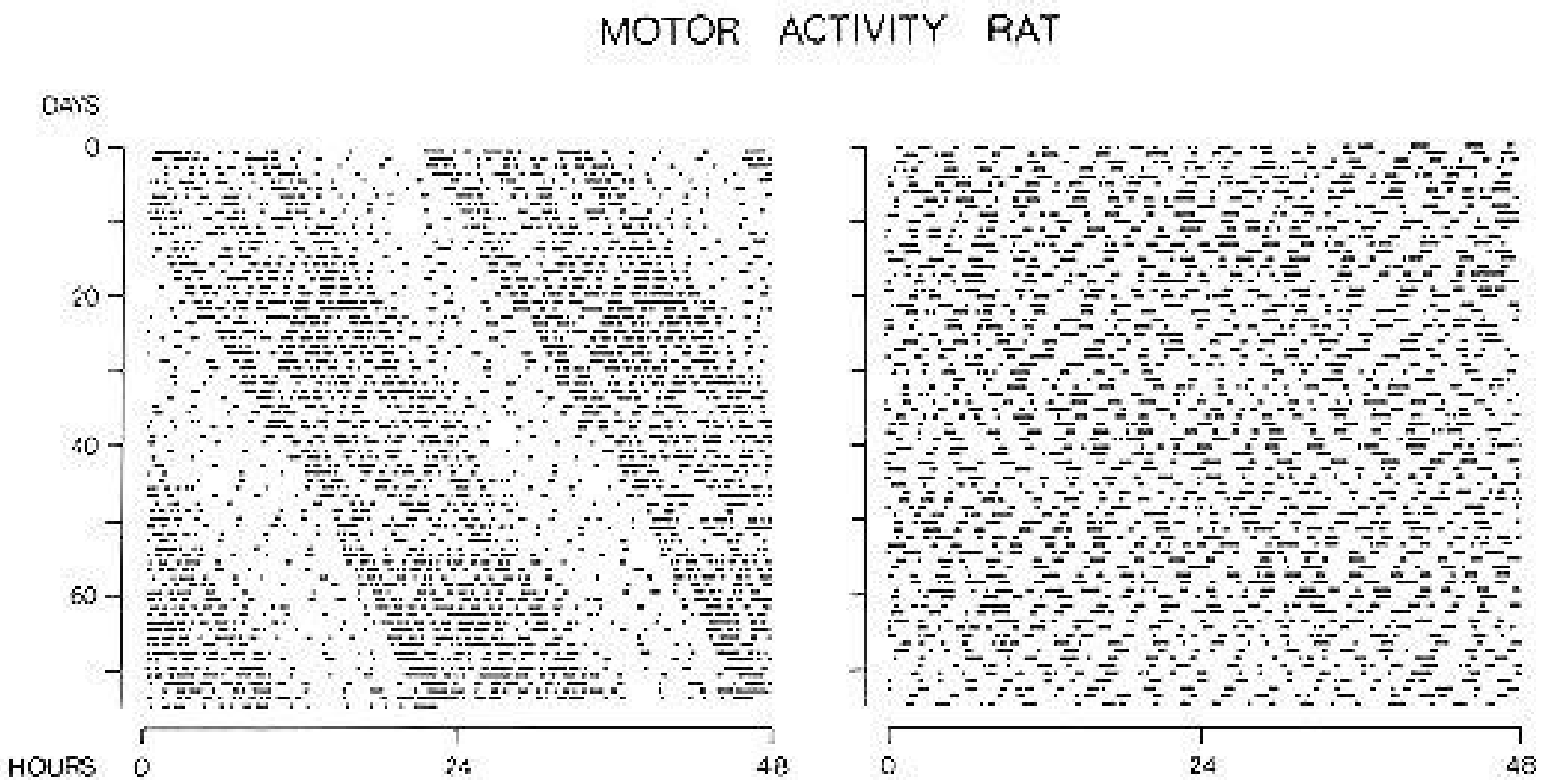


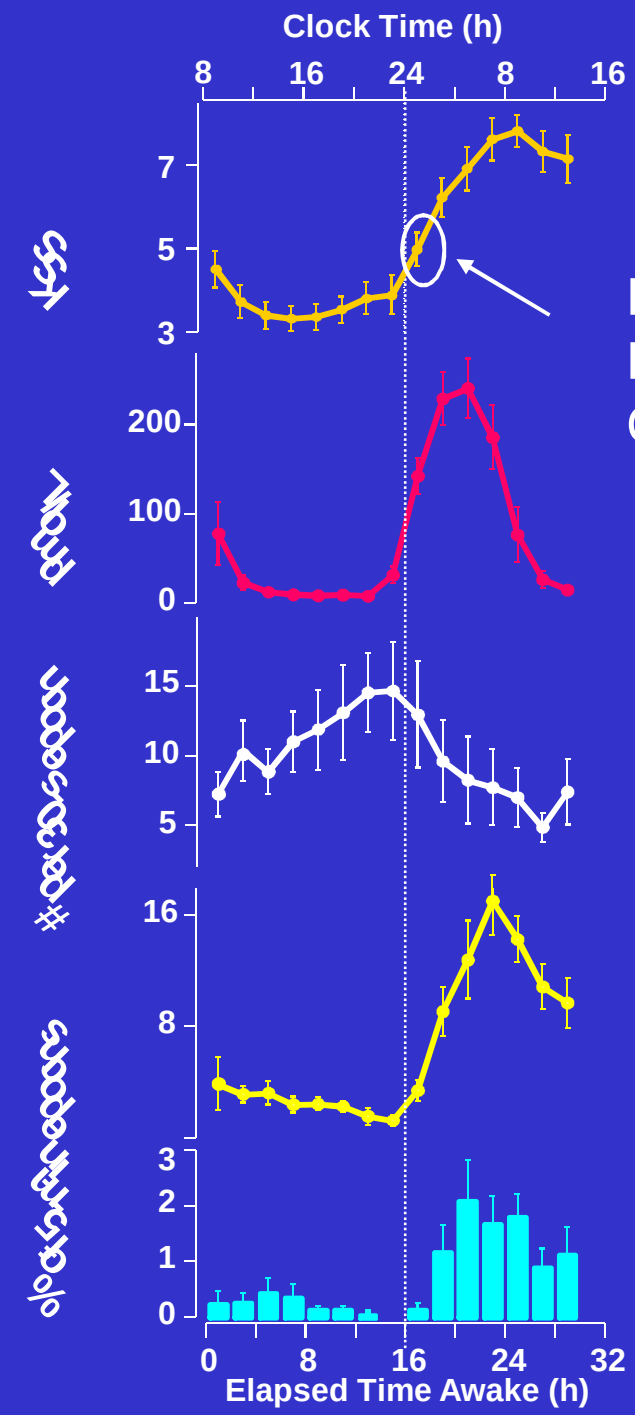
Resynchronisation via social zeitgeber

Bloch, JNNP 2005

Circadian biology
Circadian disorders
Neurology and circadian biology

Sleep-wake arrhythmia after SCN lesion





Karolinska Sleepiness Scale

Exon Valdes: *00:04 a.m.*
Bhopal: *00:40 a.m.*
Chernobyl: *01:23 a.m.*

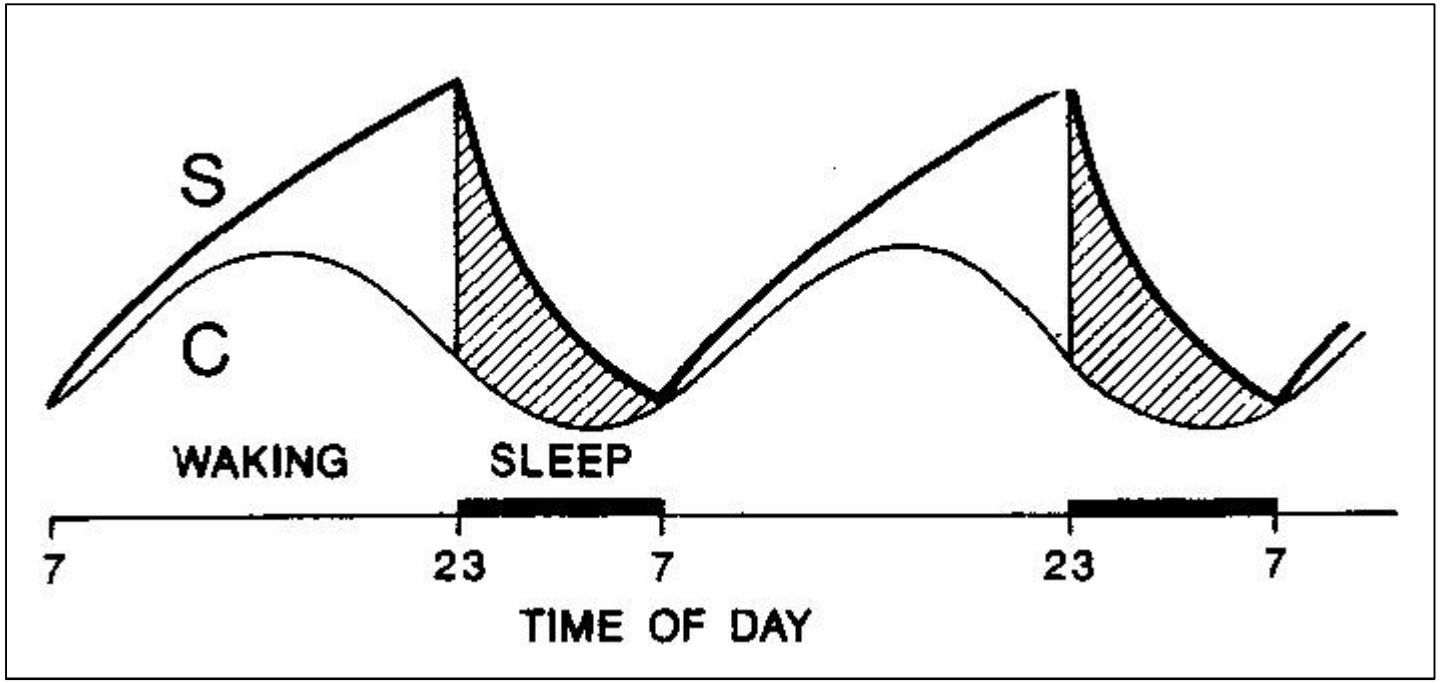
Plasma Melatonin

Eye Blink Rate

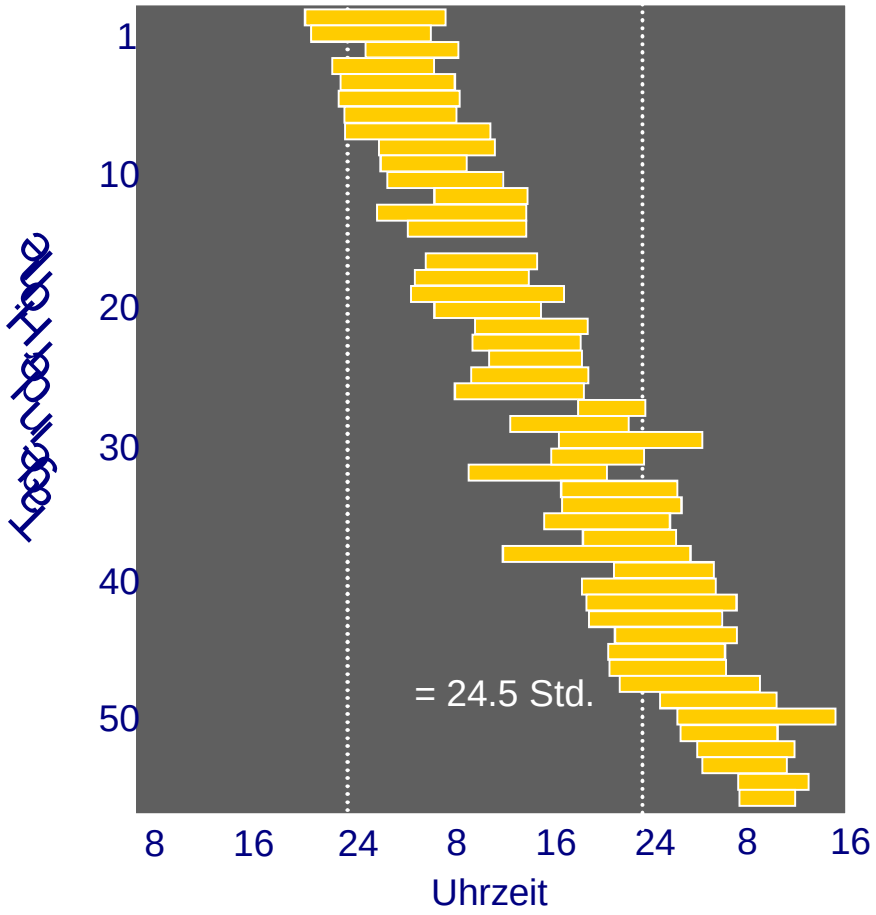
Slow Eye Movements

Incidental Sleep
Stage 1

Cajochen, Am. J. Physiol. 1999

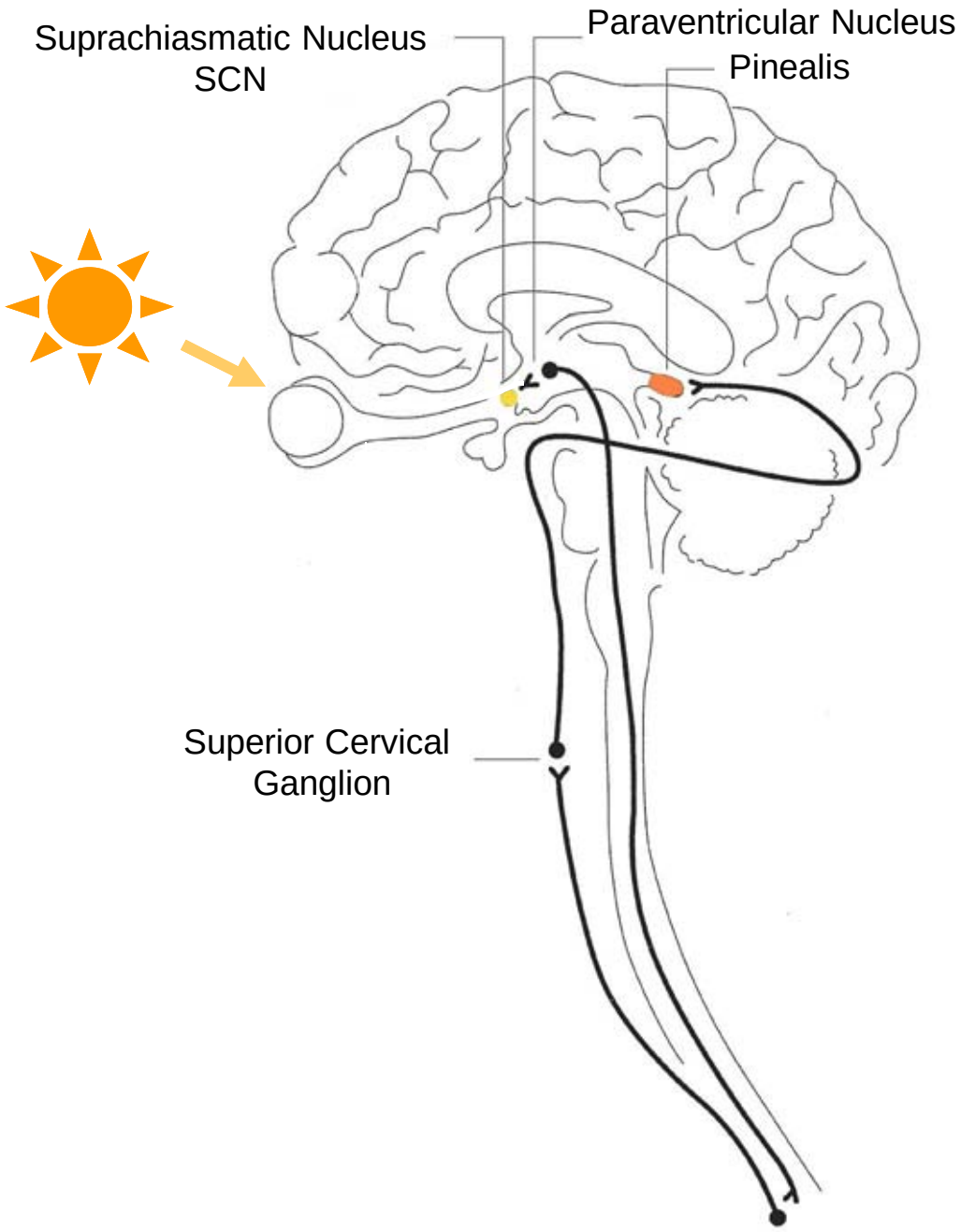

S
C
WAKING
SLEEP
7
23
7
23
7
TIME OF DAY

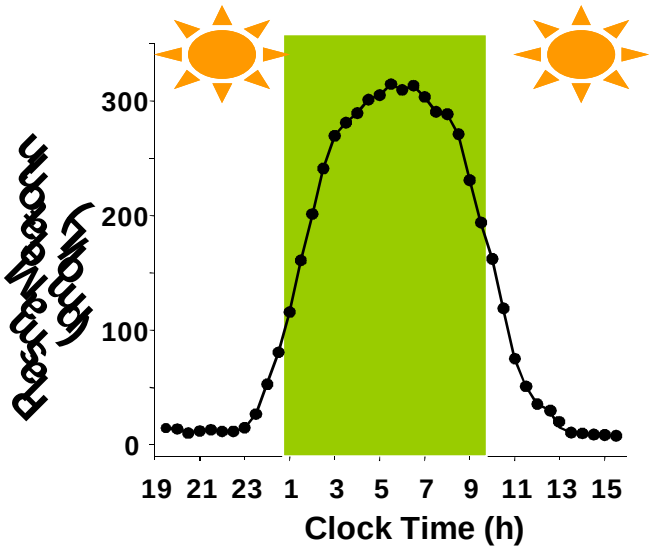
Free-running sleep-wake cyclus



Siffre, Hors du Temps, 1964

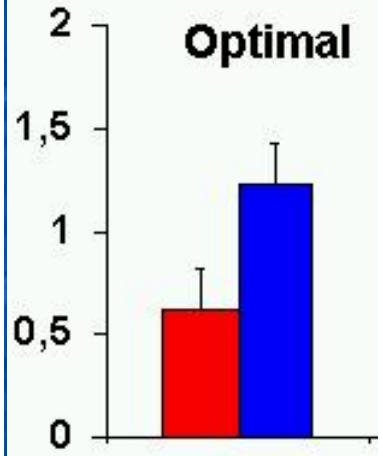
Circadian clock

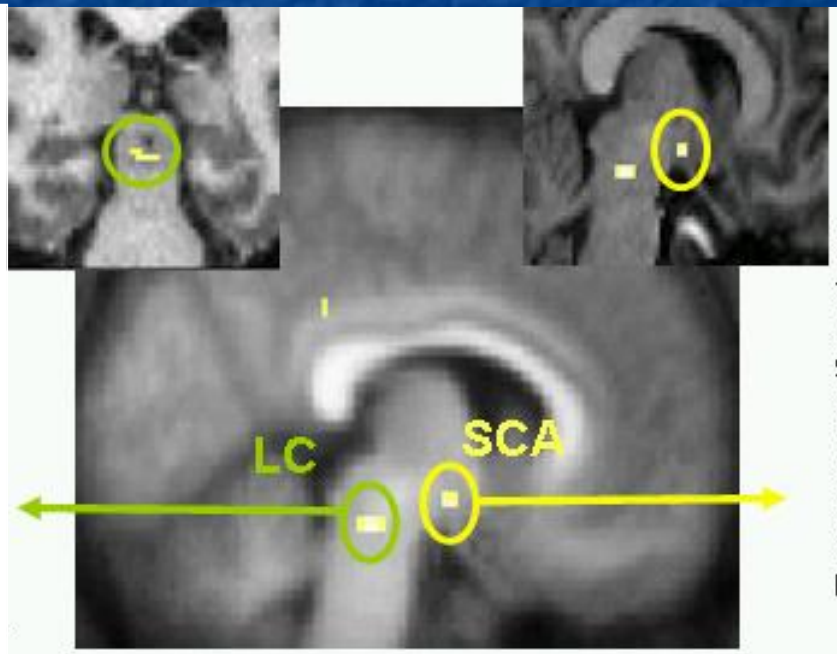


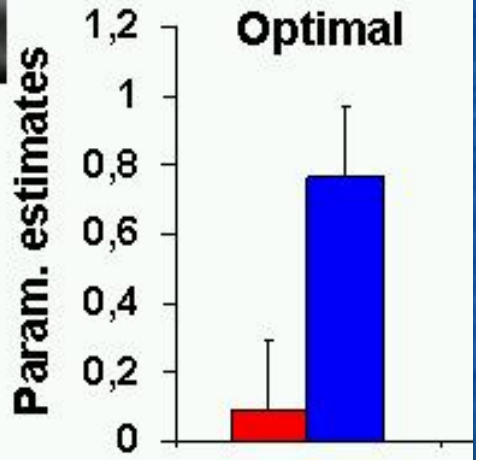


Activation of the SCN and LC during the wake-maintenance zone in the evening

Morning Types
Evening Types

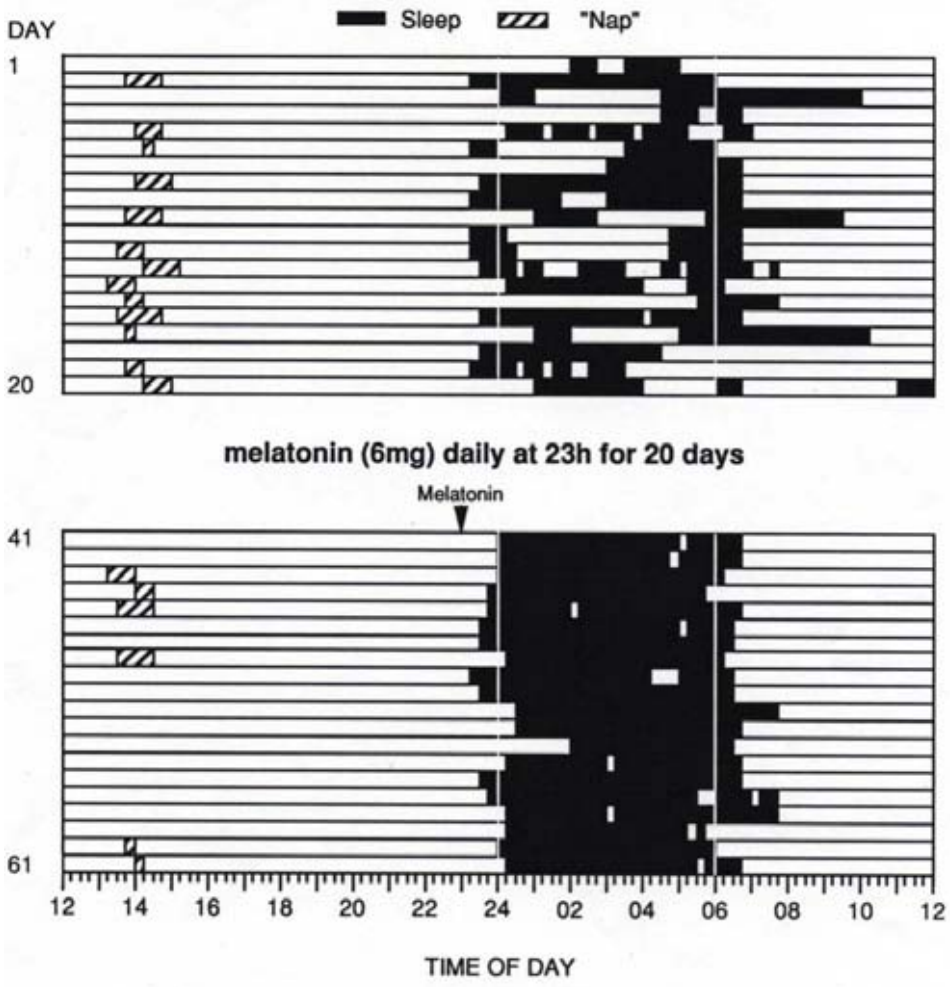






Schmidt, Science 2009

Blindness

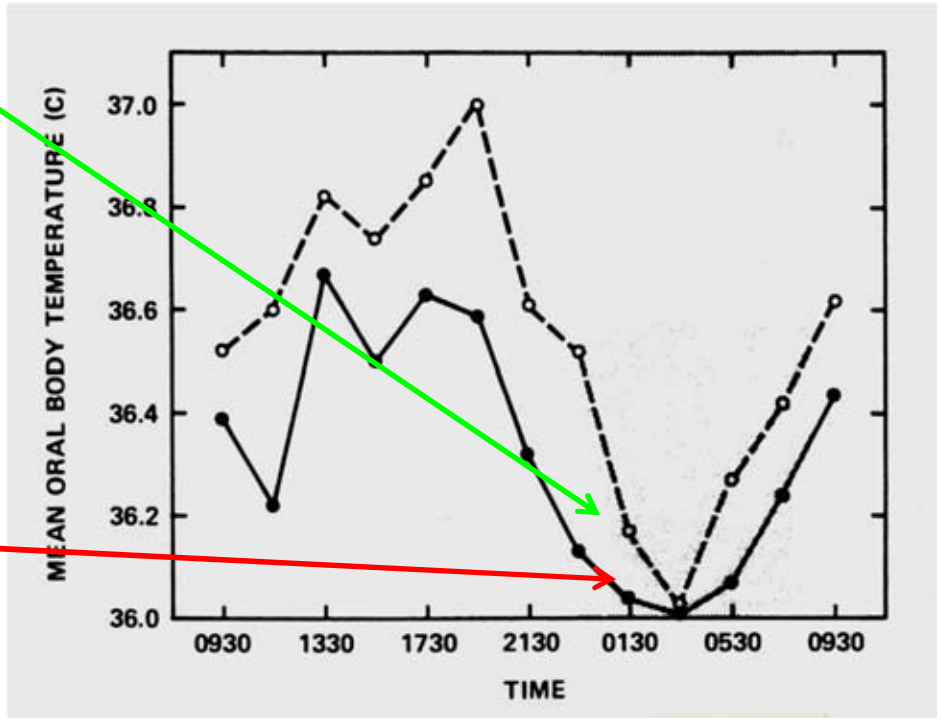

Sleep
"Nap"
DAY
1
20
melatonin (6mg) daily at 23h for 20 days
Melatonin
41
61
12
14
16
18
20
22
24
02
04
06
08
10
12
TIME OF DAY

Aging and altered circadian rhythm

(decreased amplitude, earlier/advanced phase)

young

old



SCN= suprachiasmatic nucleus

Bliwise, Normal Aging, In: Principles and Practice of Sleep Medicine, 2000