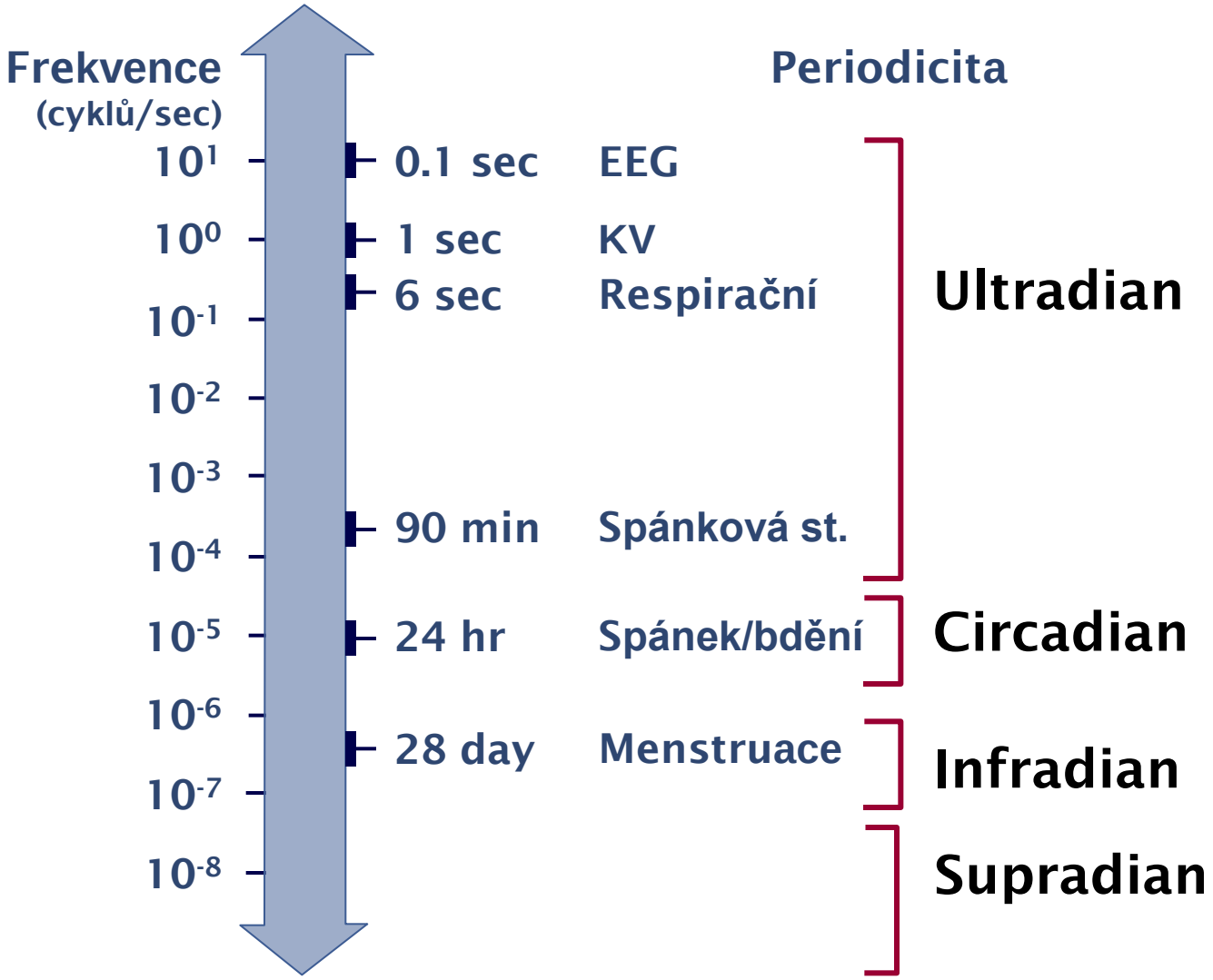
CIRKADIÁNNÍ RYTMY VE ZDRAVÍ A V NEMOCI

Martin ANDERS

Psychiatrická klinika 1. LF UK a VFN v Praze

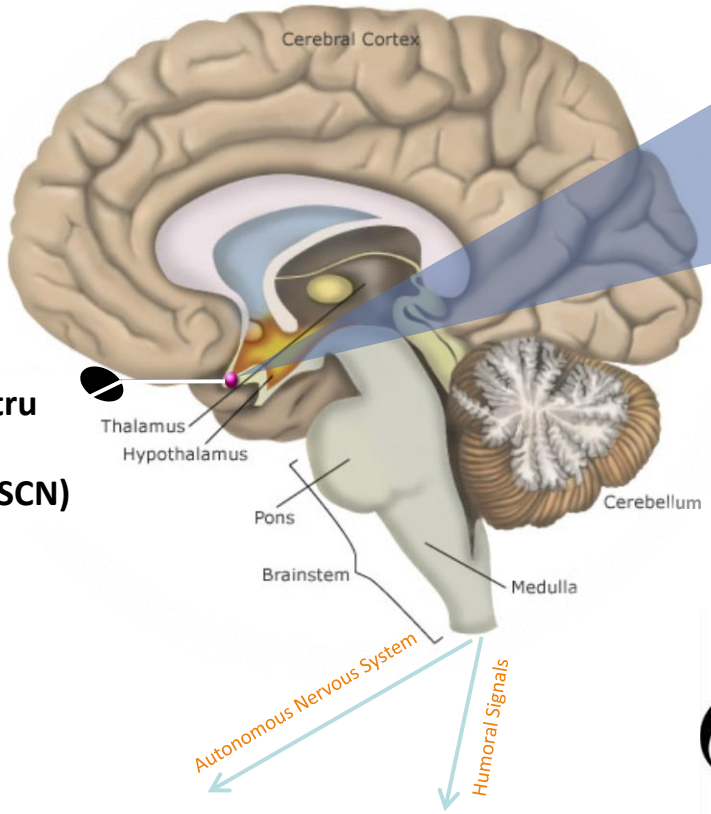
Podpořeno RVO-VFN 64165

Biologické rytmy se liší délkou cyklu

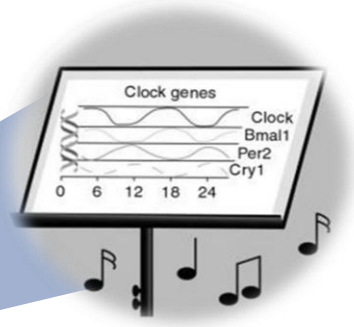


Moore-Ede et al., 1982

Cirkadiánní orchestr

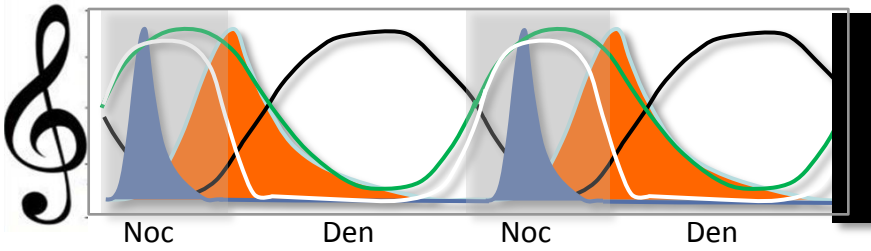


„Dirigent“ orchestru nucleus suprachiasmaticus (SCN)



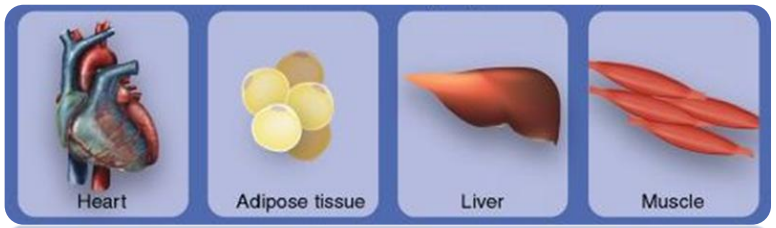
Partitura (hodinové geny)

Melodie (cirkadiánní rytmus)

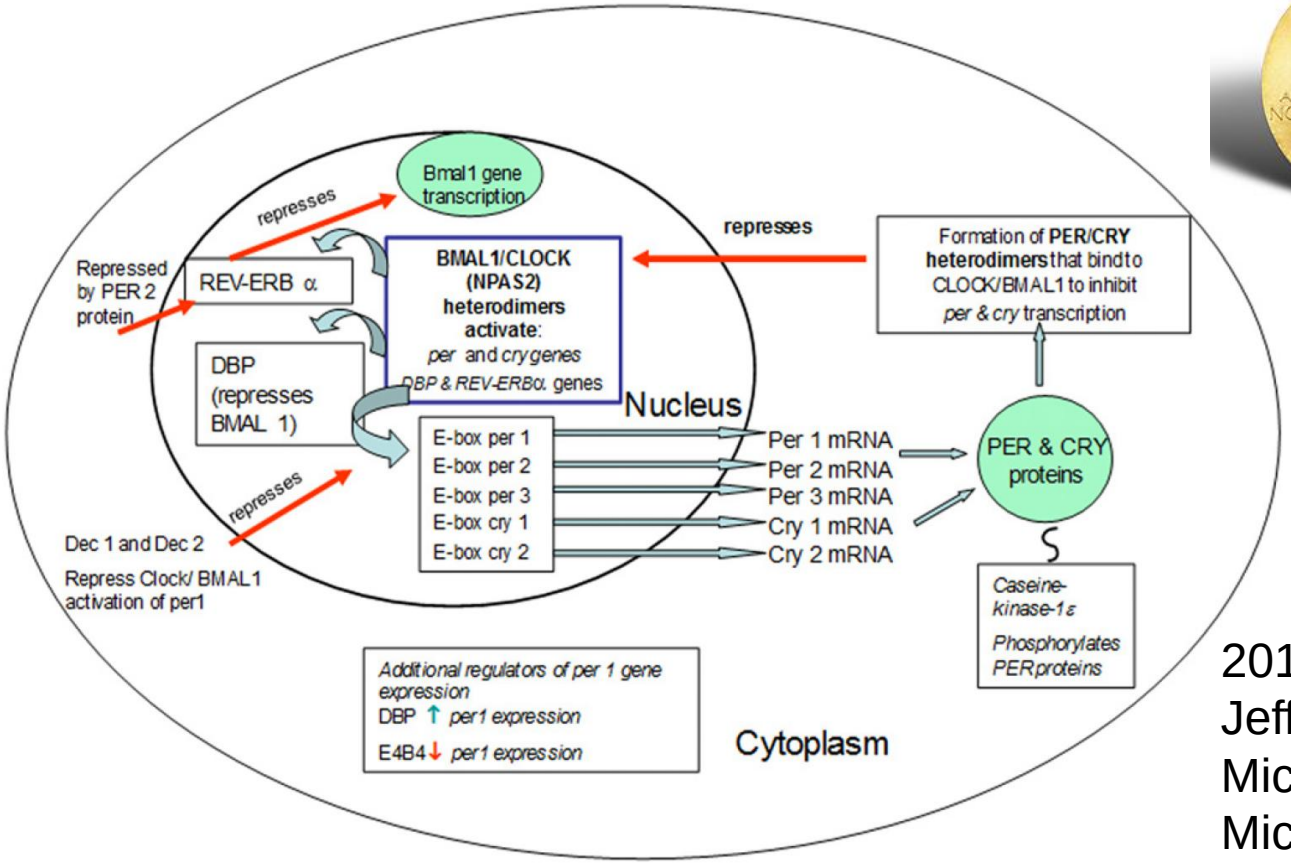


Melatonin
Kortizol
Růstový hormon
Leptin
Tělesná teplota

„Nástroje“ orchestru (peripheral clocks)



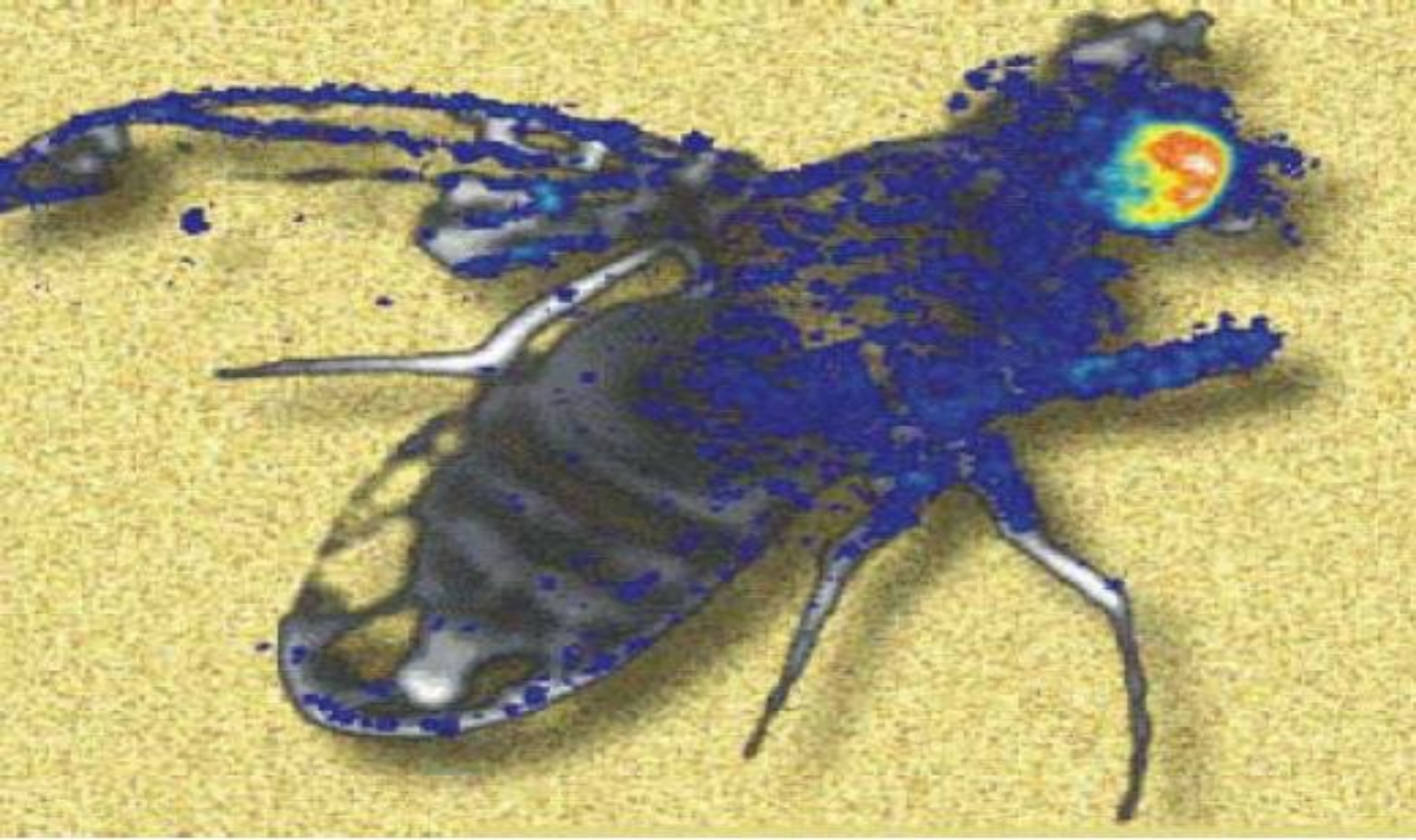
Clock genes machinery (20 000 neuronů)



2017:
Jeffry C. Hall
Michael Rosbash
Michael W. Young

Figure 1. Simplified model of mammalian clock gene machinery. The intracellular clock gene machinery involves complex multiple interlocking transcriptional/translational loops containing positive and negative transcription factors to adjust rhythms to an approximate 24-hour cycle. Note that BMAL1/CLOCK and enhancer boxes (E-boxes) comprise a central core component. Clock signals from the suprachiasmatic nucleus modulate output pathways including sleep, hormones, core body temperature, and mood. CRY, cryptochrome; mRNA, messenger RNA; PER, period.

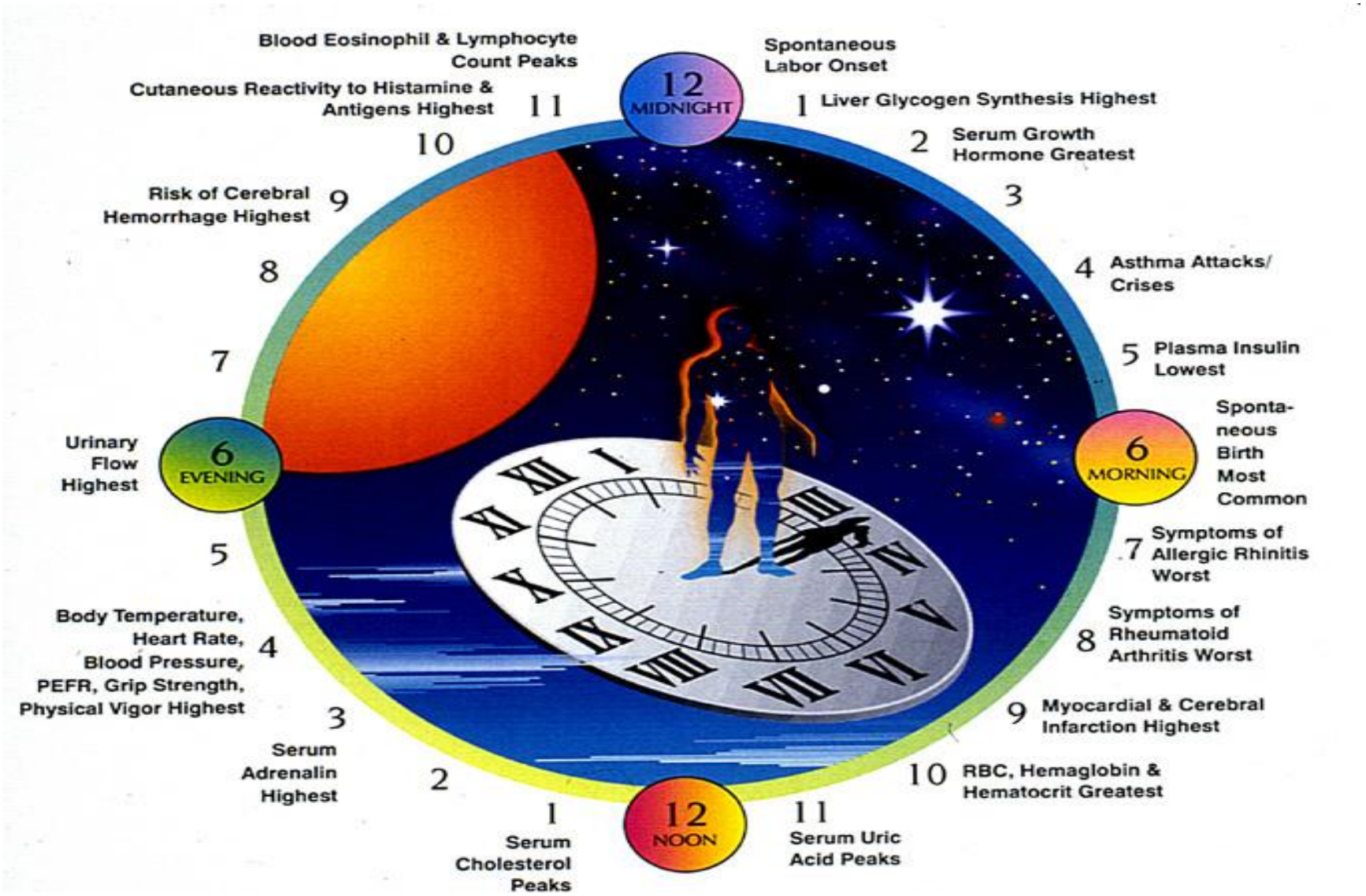
Bunney a Bunney 2013



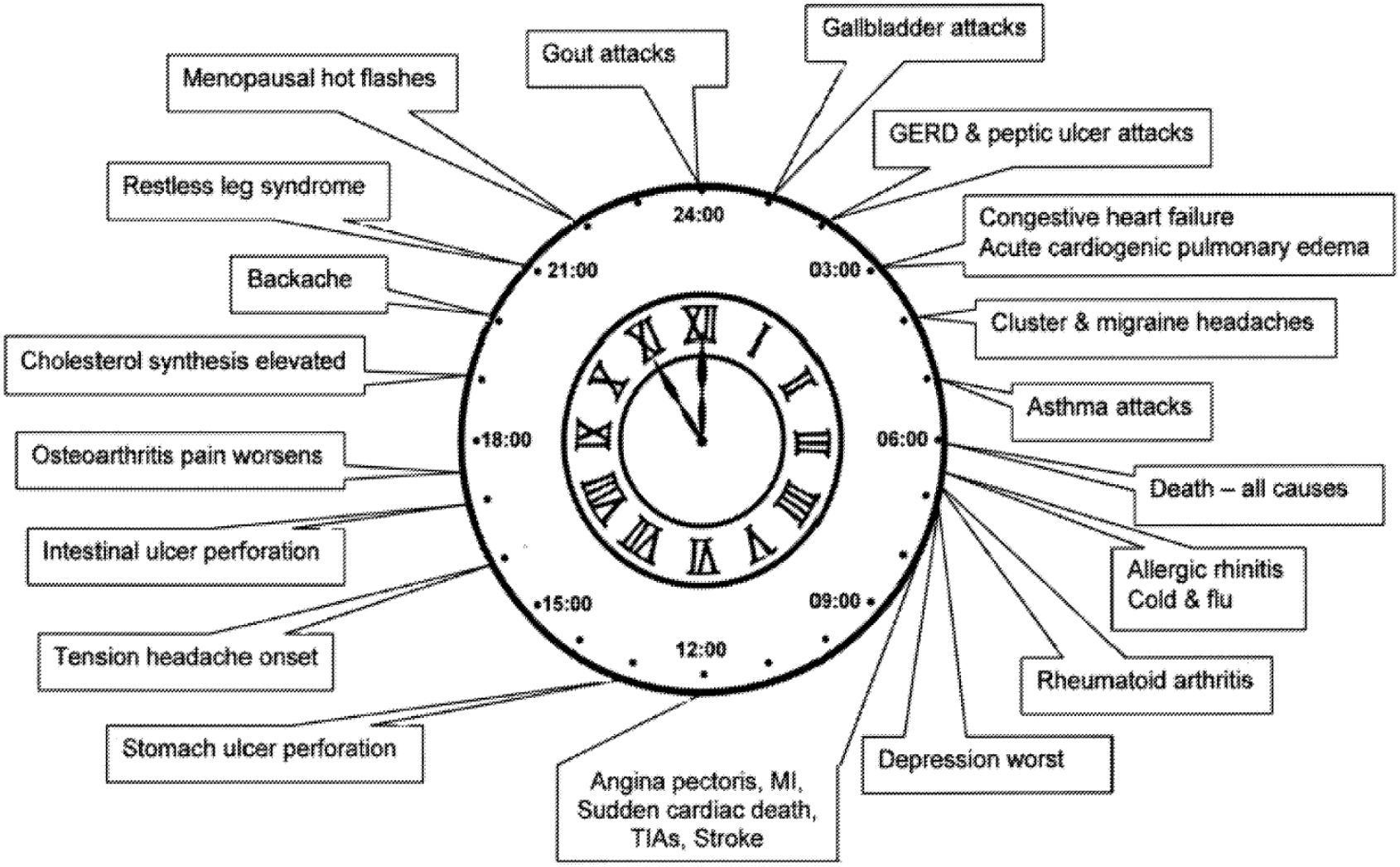
Genes that code for the clock protein, PER, glow in the head and other body parts of a fruit fly. Researchers made the clocks glow by engineering transgenic strains of flies in which the same genes that illuminate a jellyfish and a firefly's tail are attached to PER. The gene for *luciferase*, the enzyme that glows intermittently in fireflies, was expressed along with PER to reveal when the clock protein was being produced. Flies were also molecularly altered to brightly mark the clock sites with Green Fluorescent Protein, which glows constantly in jellyfish. *Source: Jeffrey Plautz, Ph.D., Stanford University; Steve Kay, Ph.D., The Scripps Research Institute*®

Střídání cyklů,
obecná vlastnost organismu
ve zdraví i v nemoci?

Střídání a pravidelnost ve zdraví

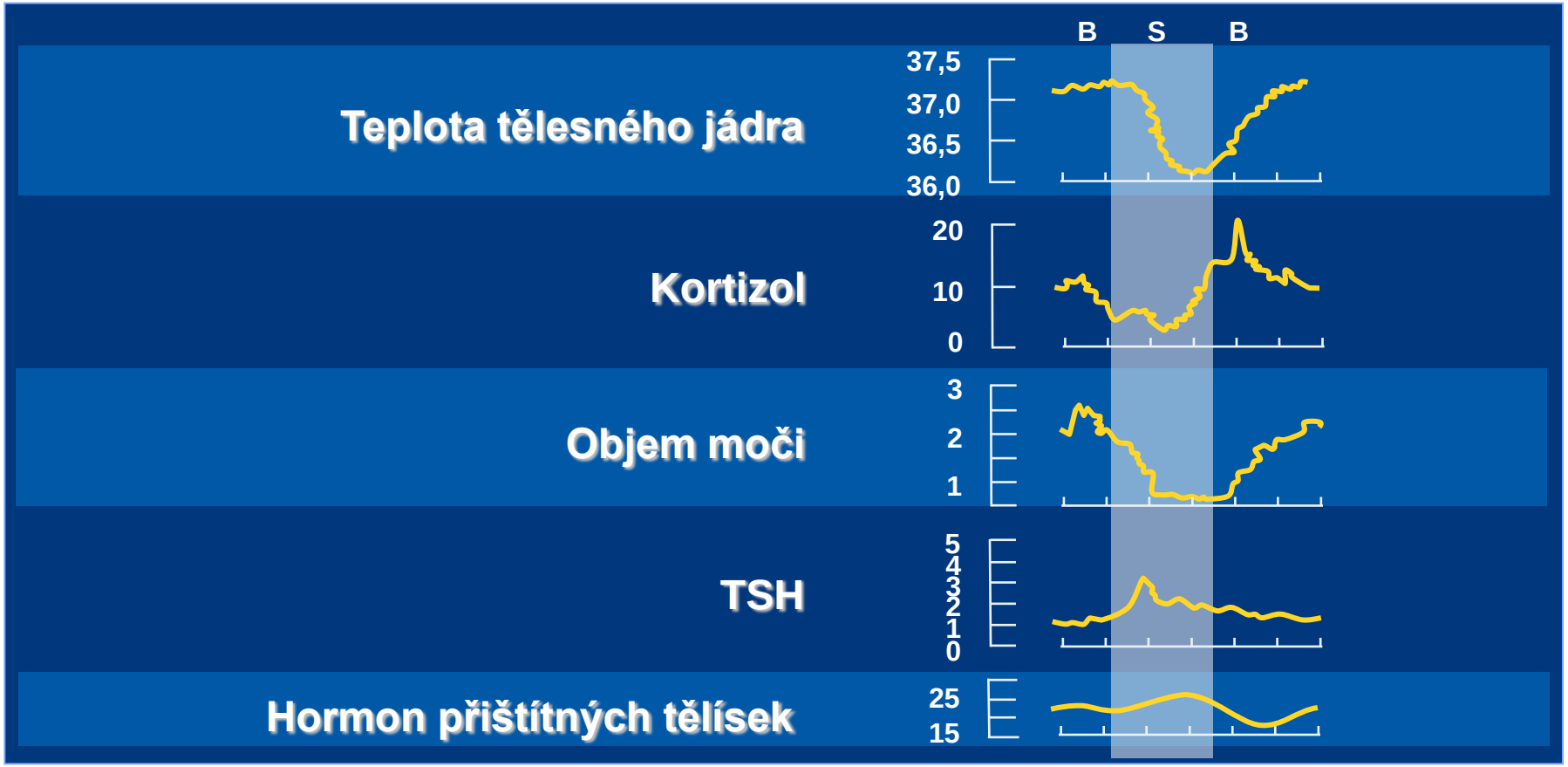


Střídání a pravidelnost v nemoci



Frijlink HW 2003

Cirkadiánní rytmus biologických markerů

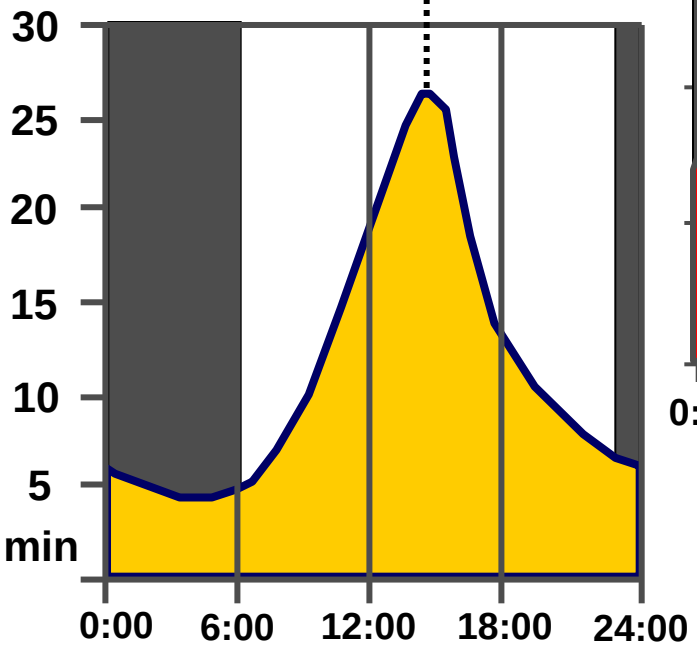


Czeisler and Khalsa, 2000

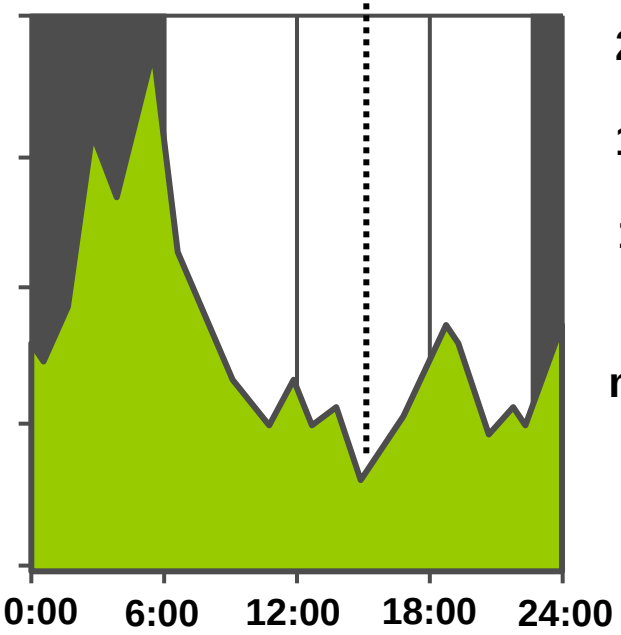
Lidský život je podmíněn cirkadiánní rytmicitou

14:00 – 15:00

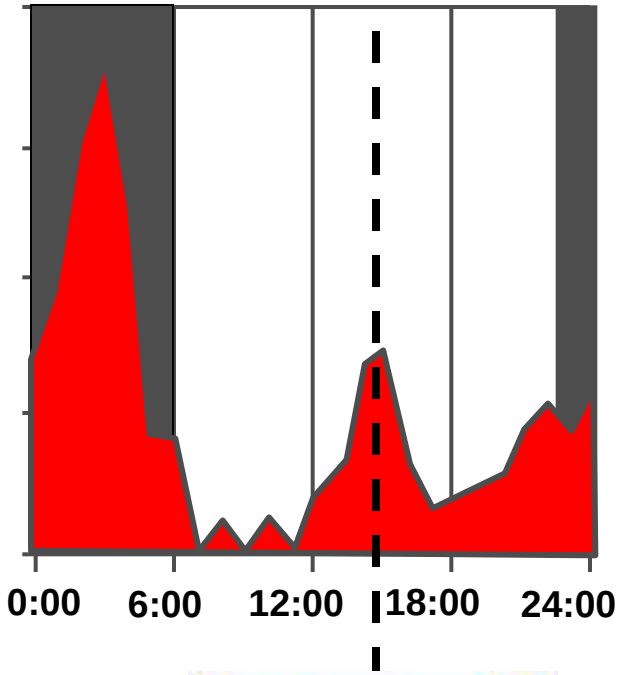
Trvání anestezie



Bolest



Chybovost



Cirkadiánní rytmus a somatické poruchy

- **kardiovaskulární onemocnění**
  - cirka-annuální kolísání mortality
  - cirkadiánní výskyt srdečních příhod
  - agregace trombocytů
  - kolísání TK

Phillips a kol. 2005

- **astma a plicní onemocnění**

- **nádorová onemocnění**
  - cirkadiánní rytmus a metastazování
  - vliv směnného režimu?

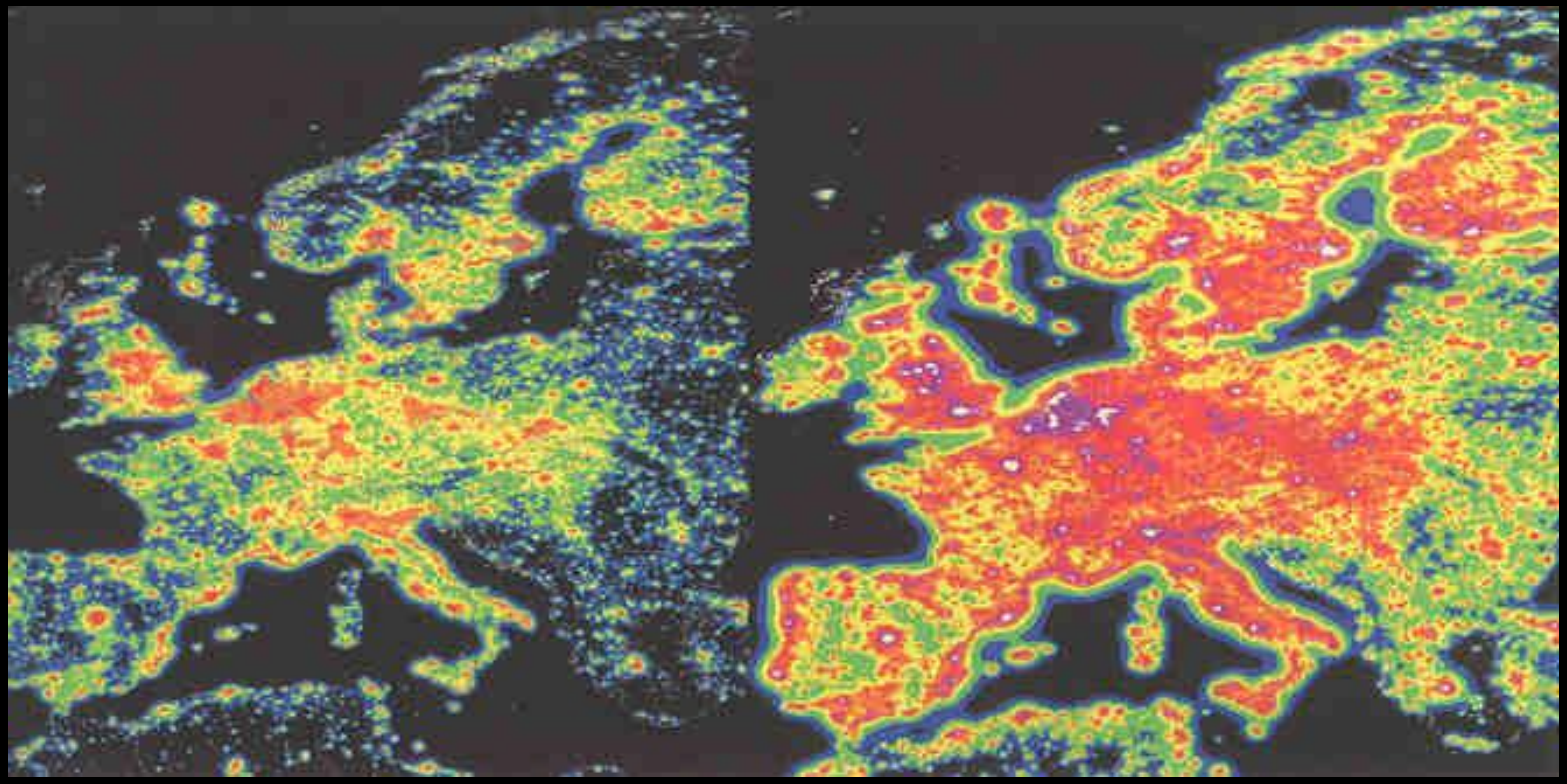
Civilizační onemocnění (disease of modernity)

- Zvýšení rizika chronických a často komorbidních onemocnění v mladších věkových skupinách
- Ateroskleróza
- Hormonální poruchy
- Nádory gastrointestinálního traktu
- Osteroporóza
- Diabetes mellitus II.typu
- Depresivní poruchy….

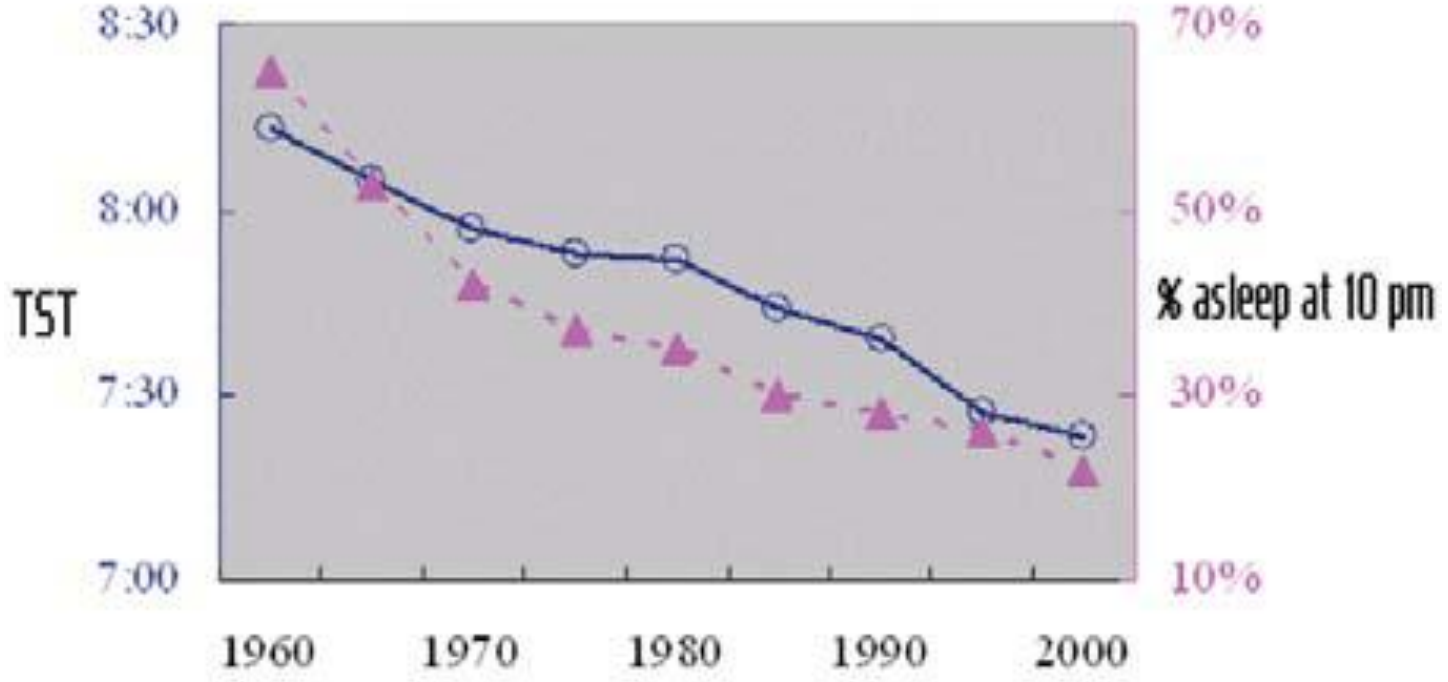
Civilizační onemocnění (disease of modernity)

- spojeny s počátky zemědělství
- industrializací
- urbanizací
- zrychlováním technologických změn
- změnami sociální kultury
- nárůstem počtu závislostí

Sky brightness at night in Europe
1998 and 2025



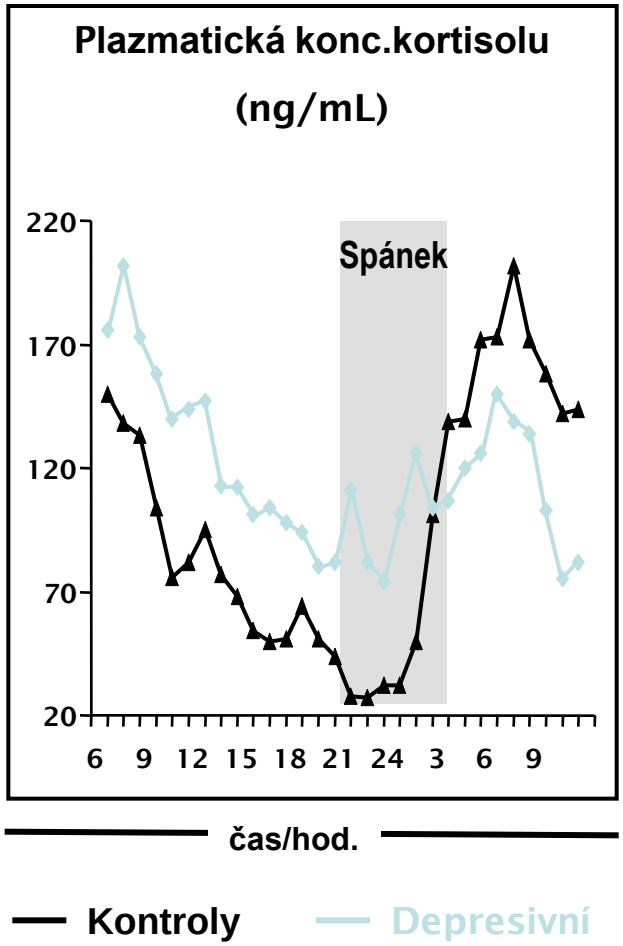
Civilizační trend či pandemie zkracování spánku



- Změny cirkadiánního schématu
- Pozdější usínání a vstávání
  Směnný a/nebo nepravidelný režim
- Více rušivých vlivů v okolí
- Neklidný (akční a workoholický) životní styl
- Poruchy spánku
- Závislosti na stimulačně působících látkách a alkoholu

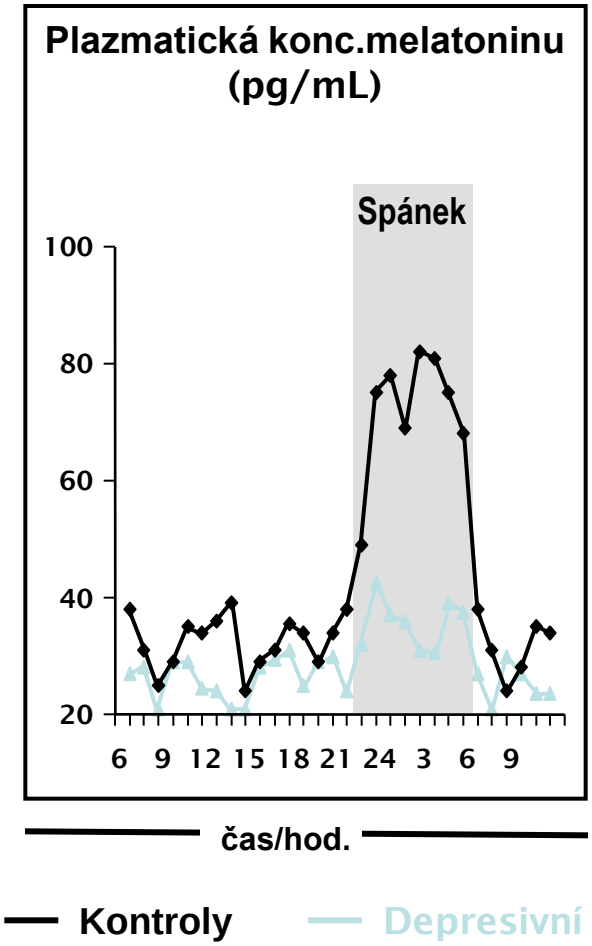

GEOGRAFICKÁ VARIABILITA
VÝSKYTU RAKOVINY
106
113
100
106
76
73
23
40
76
95
Věkově standardizovaná úmrtnost na rakovinu za rok
na 100 000 obyvatel
(WHO Cancer Mortality Bank)

Circadiánní rytmy u depresivních nemocných plazmatická koncentrace kortizolu



Souetre et al., *Am J Psychiatry* 1988; 145(9):1133-7; *Psychiatry Res* 1989; 28(3):263-78

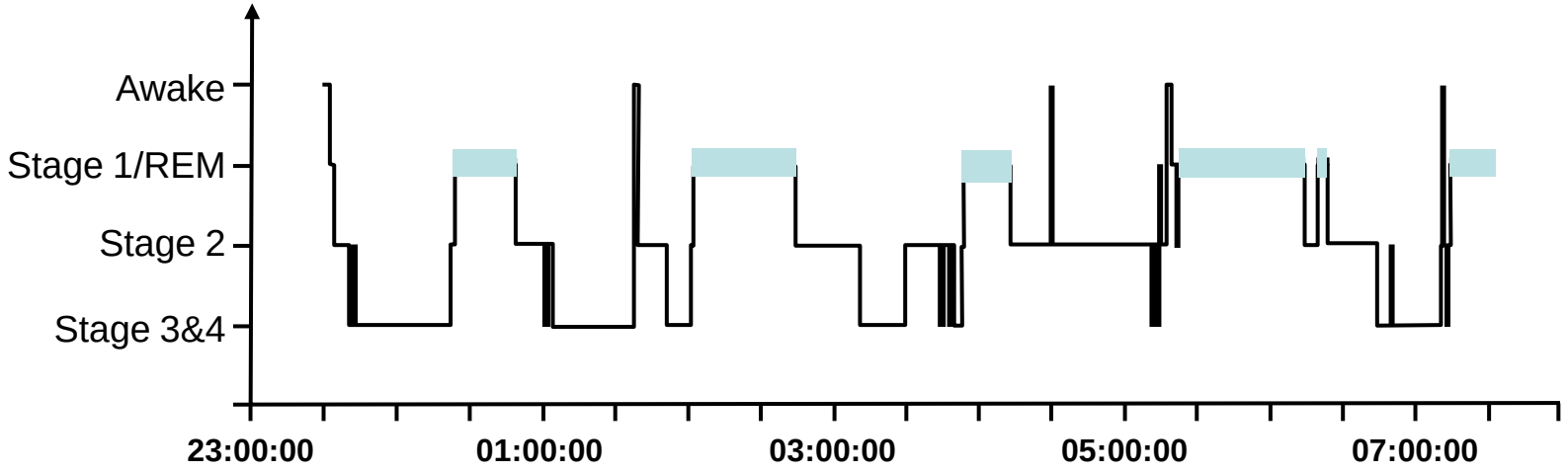
Circadiánní rytmy u depresivních nemocných plazmatická koncentrace melatoninu



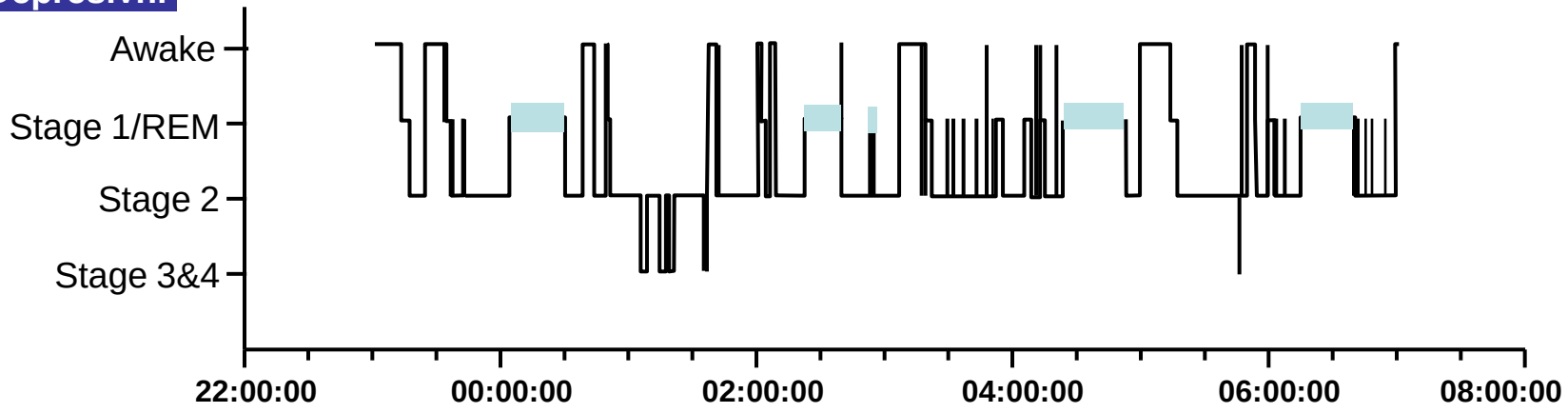
Souetre et al., *Am J Psychiatry* 1988; 145(9):1133-7; *Psychiatry Res* 1989; 28(3):263-78

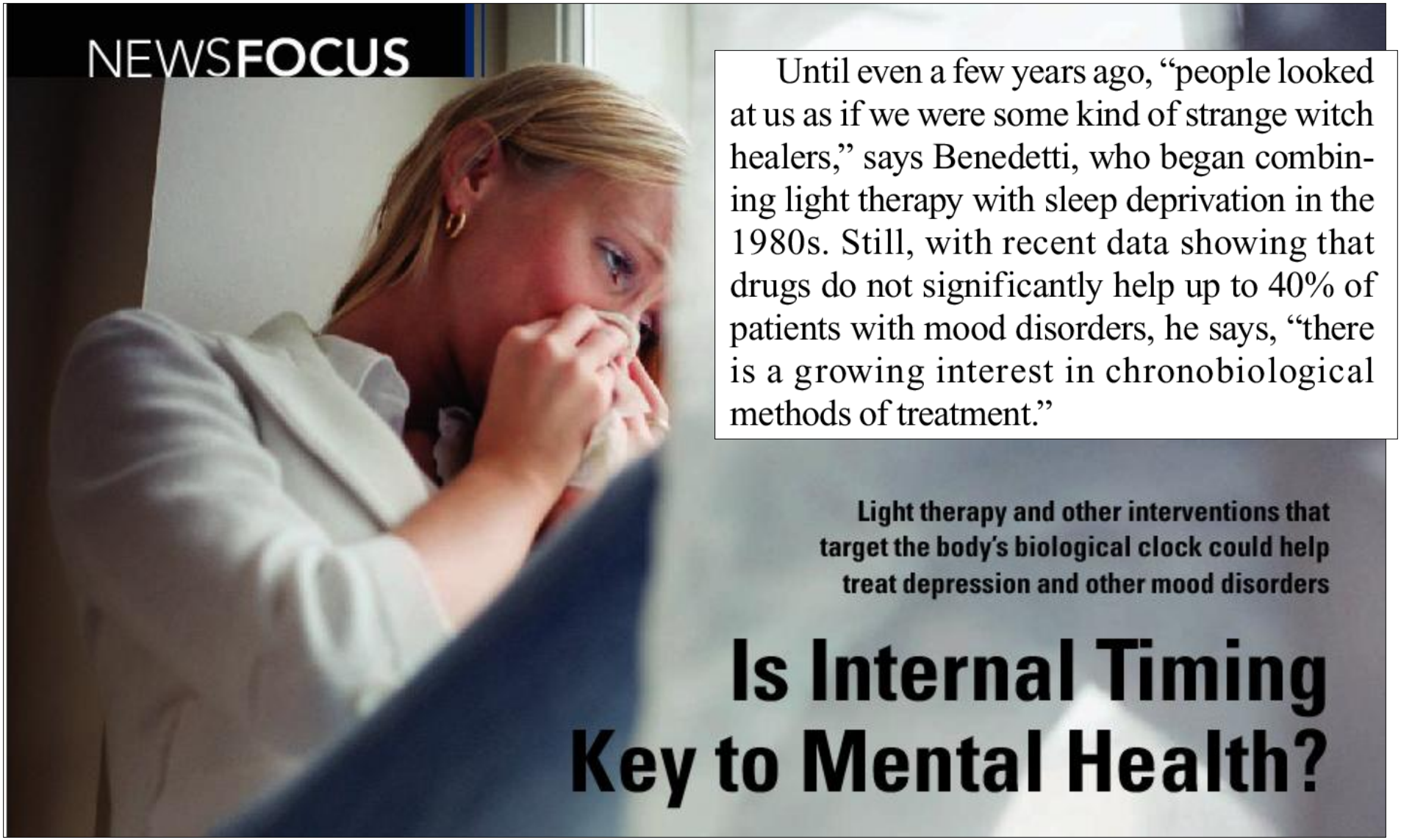
Spánková architektura ve zdraví a depresi

Spánková stádia



Depresivní





Until even a few years ago, "people looked at us as if we were some kind of strange witch healers," says Benedetti, who began combining light therapy with sleep deprivation in the 1980s. Still, with recent data showing that drugs do not significantly help up to 40% of patients with mood disorders, he says, "there is a growing interest in chronobiological methods of treatment."

Light therapy and other interventions that target the body's biological clock could help treat depression and other mood disorders

Is Internal Timing Key to Mental Health?

–YUDHIJIT BHATTACHARJEE

14 SEPTEMBER 2007 VOL 317 **SCIENCE**

Sociální jet lag a kardiometabolické riziko

ORIGINAL ARTICLE

EASE: JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Social Jetlag, Chronotype, and Cardiometabolic Risk

Patricia M. Wong, Brant P. Hasler, Thomas W. Kamarck, Matthew F. Muldoon, and Stephen B. Manuck

Department of Psychology (P.M.W., T.W.K., S.B.M.), University of Pittsburgh, Pittsburgh, Pennsylvania 15213; and Department of Psychiatry (B.P.H.) and Department of Heart and Vascular Institute (M.F.M.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

Context: Shift work, which imposes a habitual disruption in the circadian system, has been linked to increased incidence of cardiometabolic diseases, and acute circadian misalignment alters various metabolic processes. However, it remains unclear whether day-to-day circadian dysregulation contributes to these risks beyond poor sleep and other behavioral characteristics.

Objective: Individuals differ in circadian phase preference, known as chronotype, but may be constrained by modern work obligations to specific sleep schedules. Individuals experience social jetlag (SJL) due to a habitual discrepancy between their endogenous circadian rhythm and actual sleep times imposed by social obligations. Here, we examined whether chronotype and/or SJL associate with components of cardiovascular disease risk beyond the known effects of sleep disturbances, poor health behaviors, and depressive symptomatology.

Design: Participants were healthy, midlife adults who worked part- or full-time day shifts (n = 447; mean age, 42.7 [range, 30–54] y; 53% female; 83% white). Chronotype was assessed with the Composite Scale of Morningness. SJL was quantified as the difference (in minutes) between the midpoints of actigraphy-derived sleep intervals before work vs non-workdays.

Results: Multiple regression analyses showed that SJL related to a lower high-density lipoprotein-cholesterol level, higher triglycerides, higher fasting plasma insulin, insulin resistance, and adiposity ($P < .05$), even after adjustment for subjective sleep quality, actigraphy-derived sleep characteristics, depressive symptomatology, and health behaviors. Evening chronotype associated with lower high-density lipoprotein-cholesterol after adjustment for covariates.

Conclusion: Our findings suggest that a misalignment of sleep timing is associated with metabolic risk factors that predispose to diabetes and atherosclerotic cardiovascular disease. (***J Clin Endocrinol Metab*** **100: 0000–0000, 2015)**

Chronotypy a mortalita?

CHRONOBIOLOGY INTERNATIONAL
https://doi.org/10.1080/07420528.2018.1454458

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Associations between chronotype, morbidity and mortality in the UK Biobank cohort

Kristen L. Knutson [a] and Malcolm von Schantz [b]

[a]Center for Circadian and Sleep Medicine, Department of Neurology, Northwestern University, Chicago, IL, USA; [b]Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK

ABSTRACT

Later chronotype (i.e. evening preference) and later timing of sleep have been associated with greater morbidity, including higher rates of metabolic dysfunction and cardiovascular disease (CVD). However, no one has examined whether chronotype is associated with mortality risk to date. Our objective was to test the hypothesis that being an evening type is associated with increased mortality in a large cohort study, the UK Biobank. Our analysis included 433 268 adults aged 38–73 at the time of enrolment and an average 6.5-year follow-up. The primary exposure was chronotype, as assessed through a single self-reported question-defining participants as definite morning types, moderate morning types, moderate evening types or definite evening types. The primary outcomes were all-cause mortality and mortality due to CVD. Prevalent disease was also compared among the chronotype groups. Analyses were adjusted for age, sex, ethnicity, smoking, body mass index, sleep duration, socioeconomic status and comorbidities. Greater eveningness, particularly being a definite evening type, was significantly associated with a higher prevalence of all comorbidities. Comparing definite evening type to definite morning type, the associations were strongest for psychological disorders (OR 1.94, 95% CI 1.86–2.02, $p = < 0.001$), followed by diabetes (OR 1.30, 95% CI 1.24–1.36, $p = < 0.001$), neurological disorders (OR 1.25, 95% CI 1.20–1.30, $p = < 0.001$), gastrointestinal/abdominal disorders (OR 1.23, 95% CI 1.19–1.27, $p = < 0.001$) and respiratory disorders (OR 1.22, 95% CI 1.18–1.26, $p = < 0.001$). The total number of deaths was 10 534, out of which 2127 were due to CVD. Greater eveningness, based on chronotype as an ordinal variable, was associated with a small increased risk of all-cause mortality (HR 1.02, 95% CI 1.004–1.05, $p = 0.017$) and CVD mortality (HR 1.04, 95% CI 1.00–1.09, $p = 0.06$). Compared to definite morning types, definite evening types had significantly increased risk of all-cause mortality (HR 1.10, 95% CI 1.02–1.18, $p = 0.012$). This first report of increased mortality in evening types is consistent with previous reports of increased levels of cardiometabolic risk factors in this group. Mortality risk in evening types may be due to behavioural, psychological and physiological risk factors, many of which may be attributable to chronic misalignment between internal physiological timing and externally imposed timing of work and social activities. These findings suggest the need for researching possible interventions aimed at either modifying circadian rhythms in individuals or at allowing evening types greater working hour flexibility.

ARTICLE HISTORY
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informa
healthcare

Associations of Chronotype and Sleep With Cardiovascular Diseases and Type 2 Diabetes

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In this study, the authors analyzed whether chronotypes, sleep duration, and sleep sufficiency are associated with cardiovascular diseases and type 2 diabetes by using the National FINRISK Study 2007 data (N = 6258), being a representative sample of the population aged 25 to 74 living in five areas of Finland. Health status assessments and laboratory measurements from the participants (N = 4589) of the DILGOM substudy were used for the detailed analysis of chronotype. Evening types had a 2.5-fold odds ratio for type 2 diabetes ($p < .01$) as compared with morning types, the association being independent of sleep duration and sleep sufficiency. Evening types had a 1.3-fold odds ratio for arterial hypertension ($p < .05$ after controlling for sleep duration or sleep sufficiency), a faster resting heart rate and a lower systolic blood pressure (both $p < .01$), and lower levels of serum total cholesterol and low-density lipoprotein cholesterol (both $p < .0001$) than morning types. There were significant 1.2- to 1.4-fold odds ratios for arterial hypertension among those with long or short sleep durations or reduced sleep sufficiency. To conclude, the behavioral trait towards eveningness is suggested to predispose individuals to type 2 diabetes in particular, whereas compromised sleep is robustly associated with arterial hypertension. (Author correspondence: ilona.merikanto@helsinki.fi)

Keywords: Chronotype, Circadian, Diurnal, Eveningness, Glucose tolerance, Morningness, Waist circumference

Treatment of Hypertension With Chronotherapy: Is It Time?

Annals of Pharmacotherapy
1–12

DOI: 10.1177/1060028014563535
aop.sagepub.com
SAGE

Paul M. Stranges, PharmD[1,2], Amy M. Drew, PharmD[1,3], Patricia Rafferty, PharmD[1,4], Jerrica E. Shuster, PharmD[1,2], and Amie D. Brooks, PharmD[1,4]

Abstract

Objective: To review evidence for dosing antihypertensives at bedtime and possible cardiovascular risk reduction. **Data Sources:** A PubMed, EMBASE, and Cochrane Controlled Trials database literature search (1990-September 2014) limited to human subjects was performed using the search terms *hypertension, chronotherapy, ambulatory blood pressure, morning administration, evening administration*, and *antihypertensives.* Additional references were identified from literature citations. **Study Selection:** All prospective studies assessing cardiovascular outcomes or comparing morning to evening administration of antihypertensives were selected. **Data Synthesis:** Compared with morning administration, dosing one or more antihypertensive medications at bedtime helps induce a normal circadian blood pressure pattern and reduces the risk of cardiovascular disease morbidity and mortality in individuals with hypertension. Similar results have been reported in high-risk individuals with diabetes, chronic kidney disease, and resistant hypertension. A lack of diversity among studied populations and reliance on subgroup analyses are among the limitations of these data. All antihypertensive medications have not been studied in chronotherapy and do not uniformly achieve desired results. The most substantial evidence exists for medications affecting the renin-angiotensin-aldosterone system. **Conclusions:** Despite growing evidence and promise as a cost-effective strategy for reducing cardiovascular risk, chronotherapy is not uniformly recommended in the treatment of hypertension. Careful selection of patients and antihypertensives for chronotherapy is required. Further investigation is needed to evaluate the definitive impact of chronotherapy on cardiovascular outcomes.

Population (n)	(Mean)	Mean	Admin	Admin	Admin	Admin	Admin	edtime Admin	Morning Admin	Bedtime Admin	Reference
								e r	Composite CVD Outcome[a] (%)		
Essential HTN (2201)	5.6 Years	130.6/78.5	9.4/7.2	8.9/6.5	6.6/5.2	11.8[b]/7.9[b]	61.6	34.4[b]	17.2	6.3[b]	Hermida et al[6]
Type 2 diabetes (448)	5.4 Years	133.4/74.3	8.3/6.1	9.1/6.3	6.1/4.6	14.2[b]/9.1[b]	76.3	49.5[b]	29.3	10.6[b]	Hermida et al[7]
CKD (661)	5.4 Years	134.7/78.4	9.4/6.9	8.1/5.7[b]	6.4/4.9	12.0[b]/7.8	71.1	41.0[b]	31.3	10.6[b]	Hermida et al[8]
Resistant HTN (776)	5.4 Years	130/74.7	5.4/4.2	7.3/5.1	2.7/2.5	12.6[b]/7.8[b]	74.7	39.2[b]	26	10.6[b]	Ayala et al[22]

Abbreviations: Admin, administration; BP, blood pressure (reported as systolic blood pressure/diastolic blood pressure in mm Hg.); CKD, chronic kidney disease; HTN, hypertension.
[a]Composite CVD outcome: all-cause death, myocardial infarction, angina pectoris, coronary revascularization, heart failure, acute arterial occlusion of the lower extremities, rupture of aortic aneurisms, thrombotic occlusion of the retinal artery, hemorrhagic stroke, ischemic stroke, and transient ischemic attack.
[b]Statistically significant between treatment groups.

RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

Glucocorticoids and chronotherapy in rheumatoid arthritis

Maurizio Cutolo

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► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2015-000203).

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ABSTRACT

It is evident that the morning symptoms of rheumatoid arthritis (RA) are linked to the circadian abnormal increase in night inflammation, favoured by inadequate cortisol secretion under conditions of active disease. Therefore, exogenous glucocorticoid treatment is recommended in RA at low doses since it may partially act like a 'replacement therapy'. The prevention/treatment of the night upregulation of the immune/inflammatory reaction (and related flare of cytokine synthesis) has been shown to be more effective when exogenous glucocorticoid administration is obtained with a night-time-release formulation. Large-scale trials documented that modified-release prednisone has greater efficacy then morning prednisone for long-term low-dose glucocorticoid treatment in patients with RA, showing at least a more significant reduction in morning joint stiffness. Interestingly, despite a considerably higher cost than conventional prednisone, chronotherapy with night-time-release prednisone was recognised as a cost-effective option for patients with RA not on glucocorticoids who are eligible for therapy

Key messages

What is already known about this subject?

- Morning clinical symptoms of rheumatoid arthritis are linked to circadian abnormal increase of night inflammation, favoured by inadequate cortisol secretion.

What does this study add?

- Several evidences now seem to confirm that the treatment of the night up-regulation of the immune/inflammatory reaction at lest in rheumatoid arthritis, is more effective when exogenous glucocorticoid administration is obtained with nighttime-release chronotherapy.

How might this impact on clinical practice?

- Treatment of rheumatoid arthritis is starting to include the concept of chronotherapy also for the use of conventional DMARDs and NSAIDs.

Antidepresiva a SCN

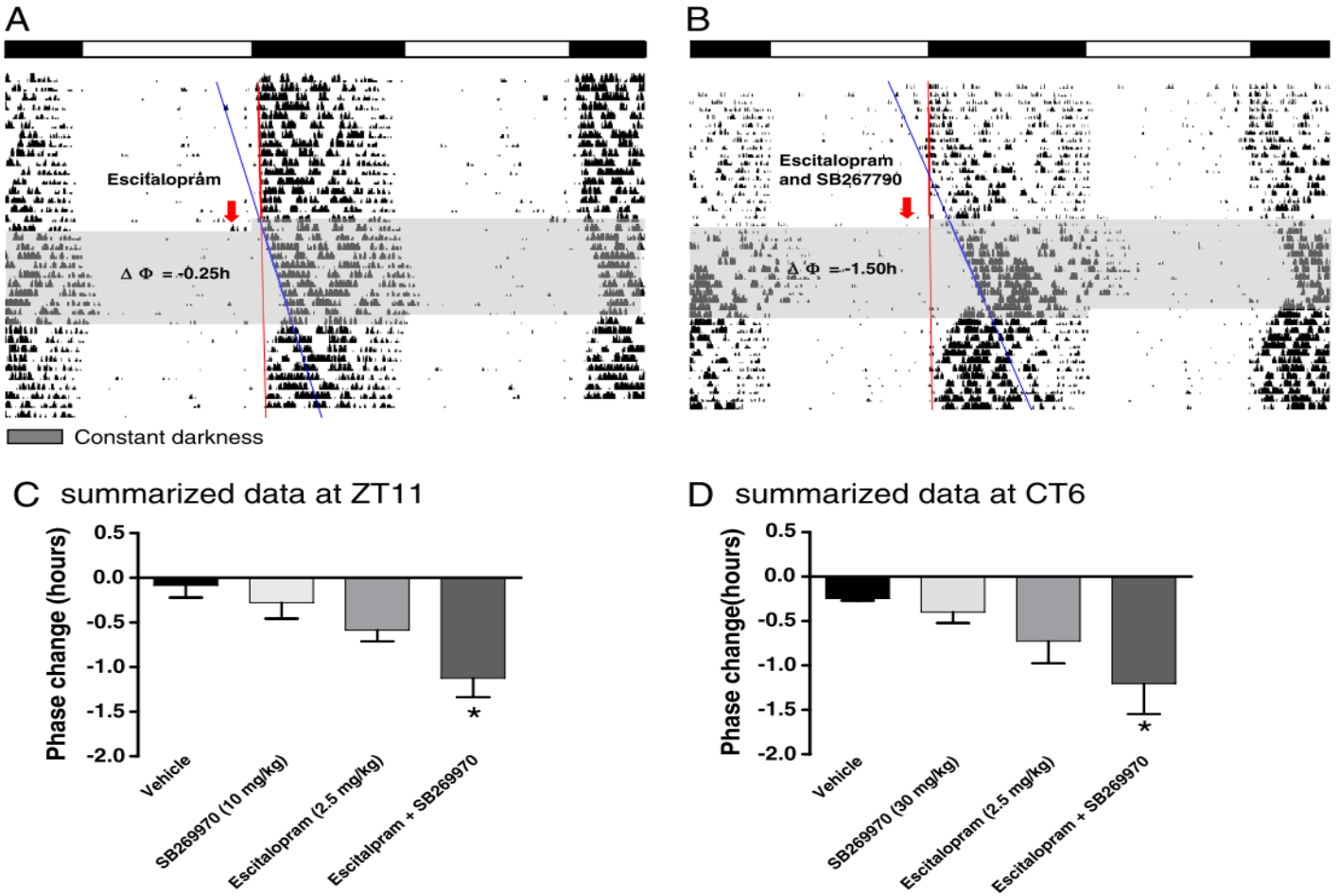
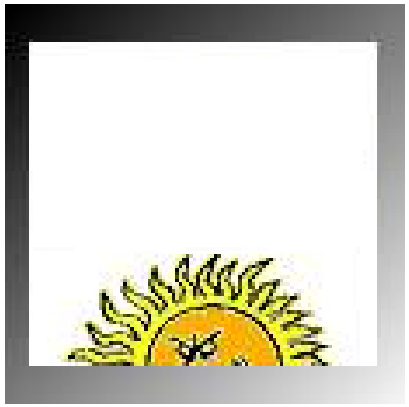


Fig. 3. Combined dosing of a selective serotonin reuptake inhibitor (SSRI) and a 5-HT_7 receptor antagonist on daily running wheel behavior as revealed in double-plotted actograms. (A) Representative actogram showing the effect of a single acute injection of escitalopram (2.5 mg/kg s.c.) at ZT11 (zeitgeber time 11 or 11 h after lights-on or 1 h before lights-off in a 12:12 light:dark (LD) cycle) following entrainment to the LD cycle as calculated by extrapolation of activity onsets in constant darkness (DD) back to the time of dosing (change in phase ($\Delta\Phi$) = −0.25 h); (B) effect of combined doses of escitalopram (2.5 mg/kg s.c.) and SB269970 (10 mg/kg s.c.) at ZT11, yielding a more substantial phase change in activity onsets ($\Delta\Phi$ = −1.50 h); (C) summarized data with all injections occurring at ZT11 and revealing a significantly greater phase delay following combined dosing with escitalopram and SB269970 (mean ± SEM; ANOVA, [$F(3, 21) = 7.797$, $p = 0.0011$]; *$p < 0.001$ vs. vehicle; < 0.05 vs. all other treatment groups); (D) summarized data with all injections occurring at CT6 (circadian time 6, during DD but 6 h after lights-on would have normally occurred) (mean ± SEM; ANOVA, $F(3, 12) = 3.950$, $p = 0.0358$; *$p < 0.05$ vs. vehicle and SB269970 alone).

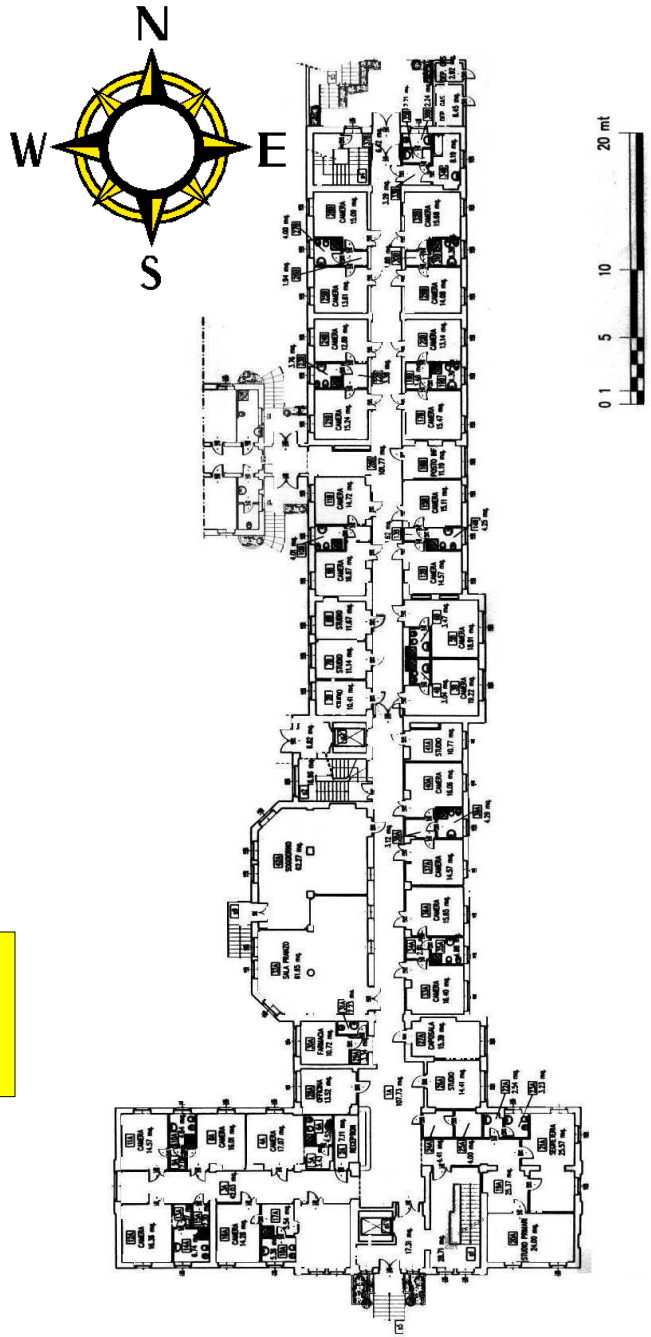
Westrich et al., 2012



West

Morning: 1400 lux

Afternoon: 3000 lux



East

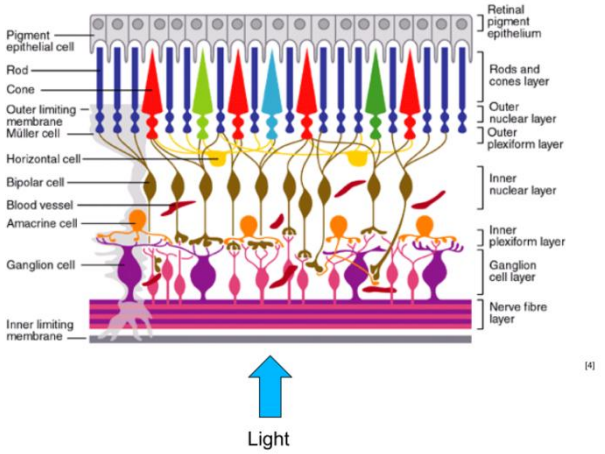
Morning: 15500 lux

Afternoon: 2700 lux

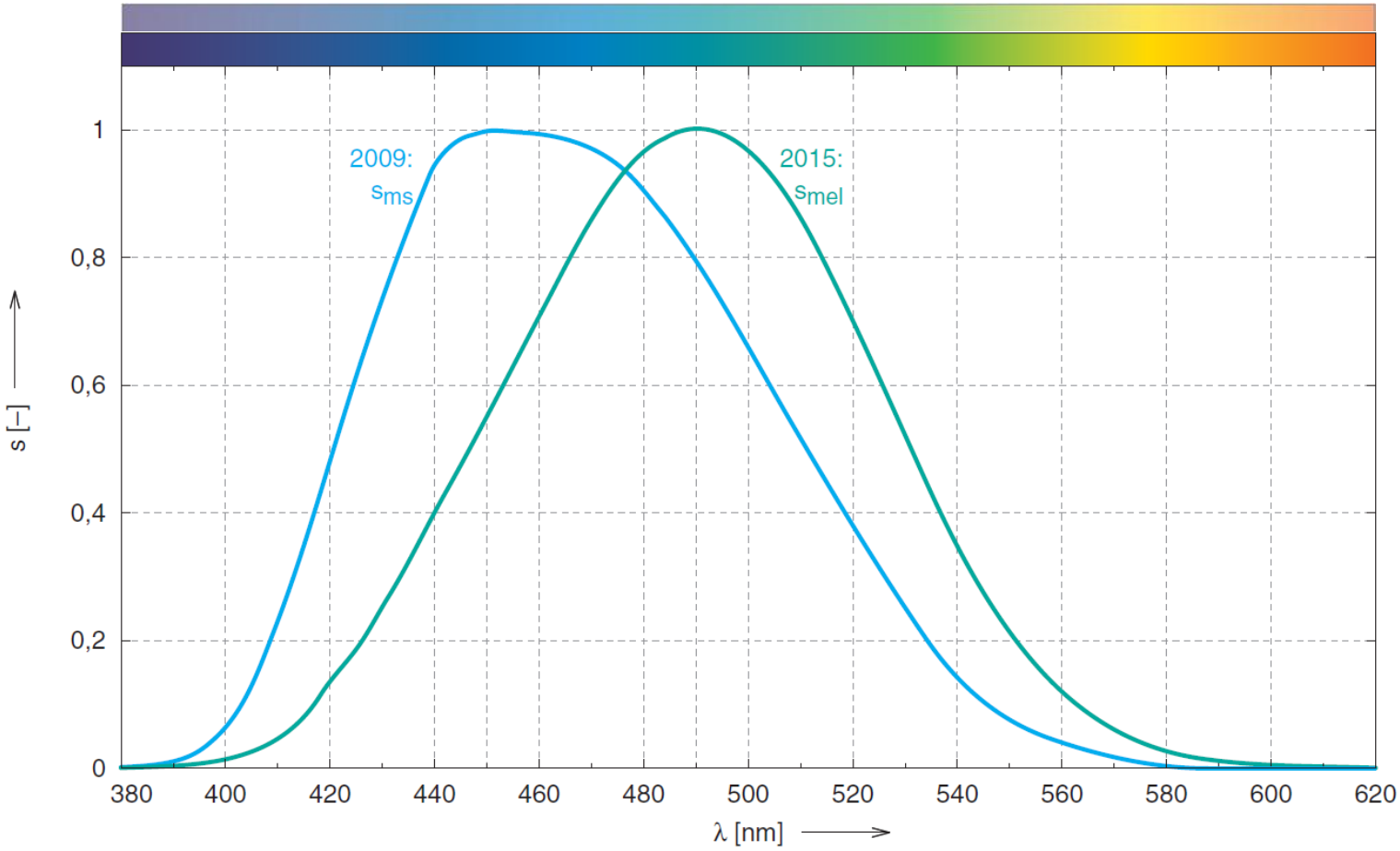
Světlocitlivé gangliové buňky (i)

- **ipRGCs** (max sensitivita 460-480nm)
  Intrinsically photosensitive Retinal Ganglion Cells

- 1923 (Keeler)
- 1991 (Foster, Provencio)
- 1998 (Provencio)
- 2002 (Hattar, Berson)
- 2007 (Zaidi, Zeisler, Foster)



Spektrální odezva ipRGCs



Data: DIN 5031-100


SPECTRUM
MODE
I-Time
100 ms
λp
477 nm
1
360 410 460 510 560 610 660 710 760
setting
home
save file


SPECTRUM
MODE
I-Time
439 ms
λp
749 nm
1
360 410 460 510 560 610 660 710 760
setting
home
save file


SPECTRUM
A
MODE
I-Time
251 ms
λp
759 nm
1
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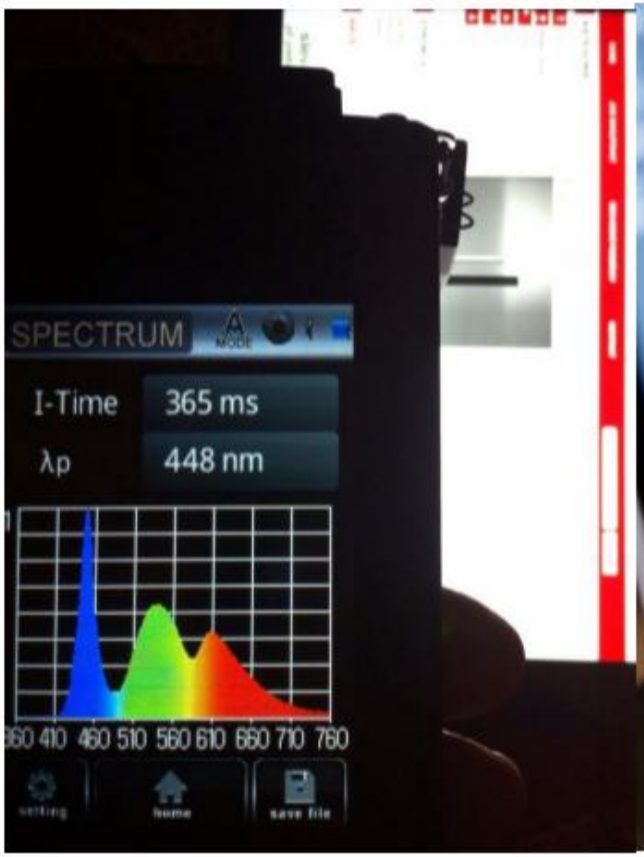
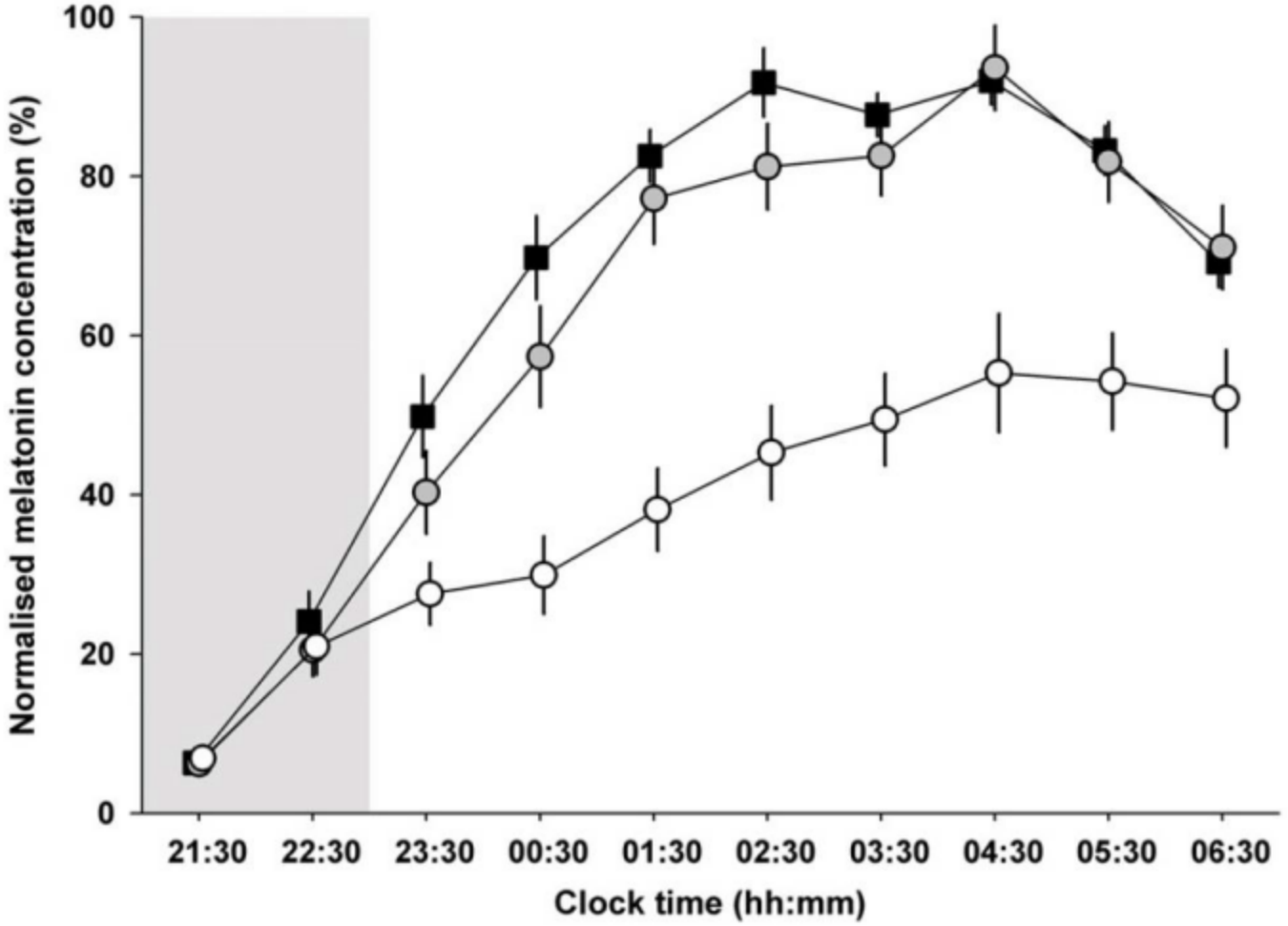
setting
home
save file


SPECTRUM
I-Time
365 ms
λp
448 nm
360 410 460 510 560 610 660 710 760
setting
home
save file



Van de Werken et al., 2013

- Melatonin supression

NREM:

- Lower amount of slow-wave (delta/theta) frontal activity
- Fewer sleep spindles (Cho et al., 2013)

REM:

- Longer onset latency
- Shorter REM phase (Munch et al., 2011)

Chang et al., 2015

- 4 hours of evening book reading
- „paper“ books vs e-books (from a tablet)

- 55% evening melatonin reduction
- 90 minut phase shift (later melatonin secretion the following day)
- Longer sleep latency (takes longer to fall asleep)
- 20% less REM sleep

Chronobiologická fototerapie

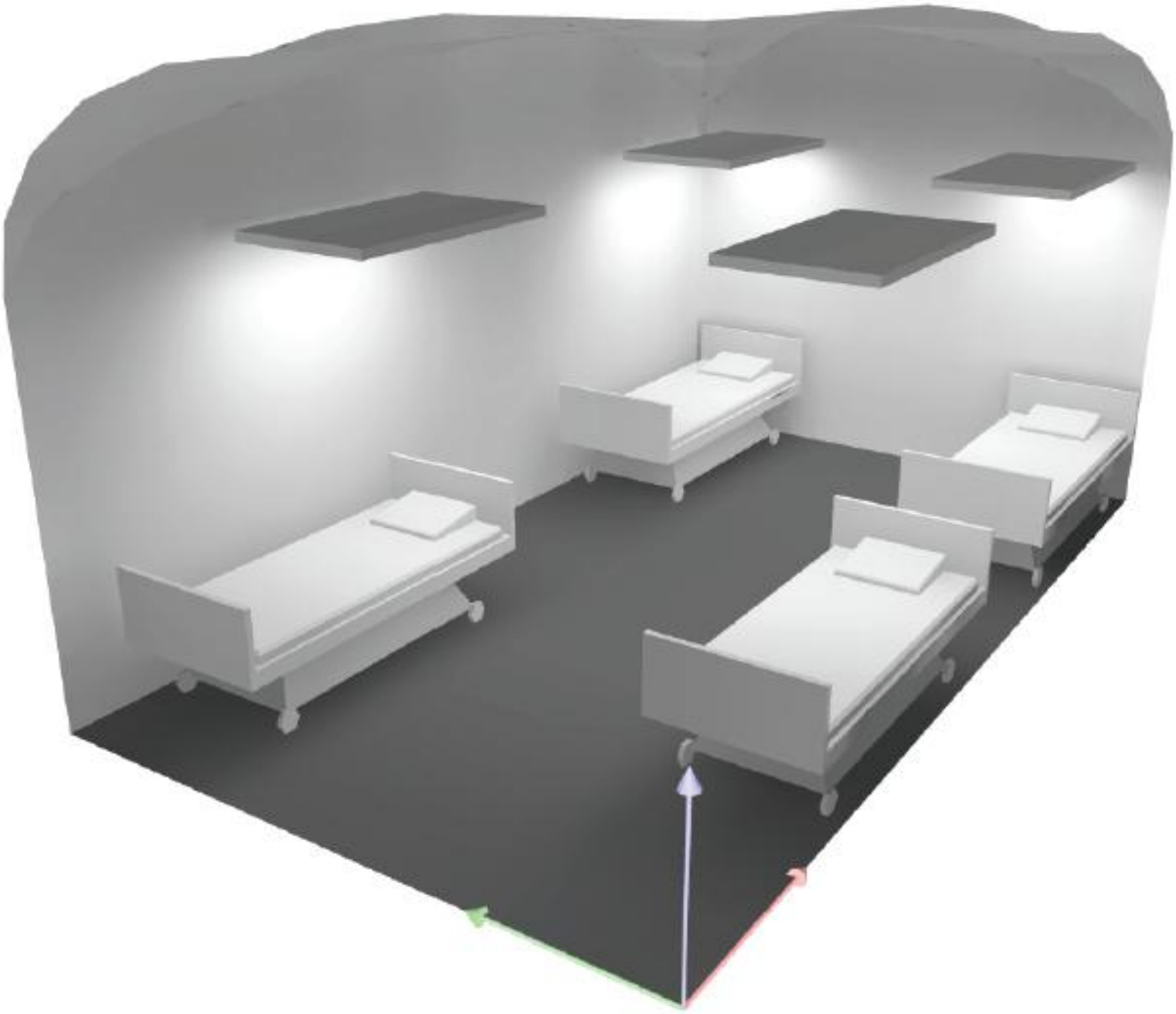
- Intenzita osvětlení očí. $E > 1000$ lx
- Podíl aktivující modré složky. $T_c > 5500$ K
- Délka aplikace. $t = 5\ klx \cdot h / E$
- Načasování aplikace v rámci dne. $t_{start}(MEQ)$

- Individuální faktory, věk, chronotyp. k(věk)
- Subj. přijatelnost a příjemnost světla. R_a, U, G

Zdroj světla

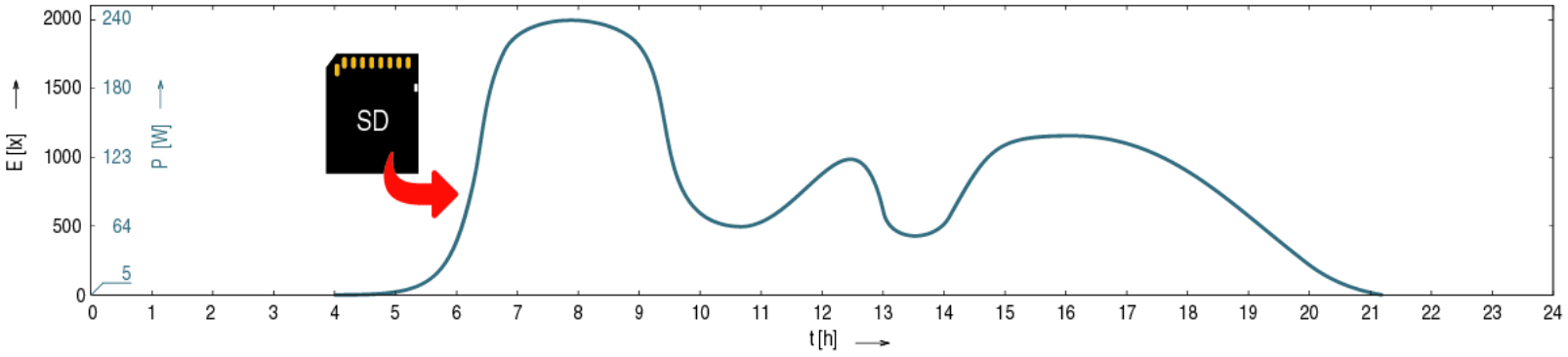
- Nad lůžko pacienta
- h = 2,35 m (1,8 m tr.)
- E = 0–2000 lx (2500 lx)
- T_c = 1800–6500 K

- Manuální a automatický mód
- VFN



Automatický mód svítidla

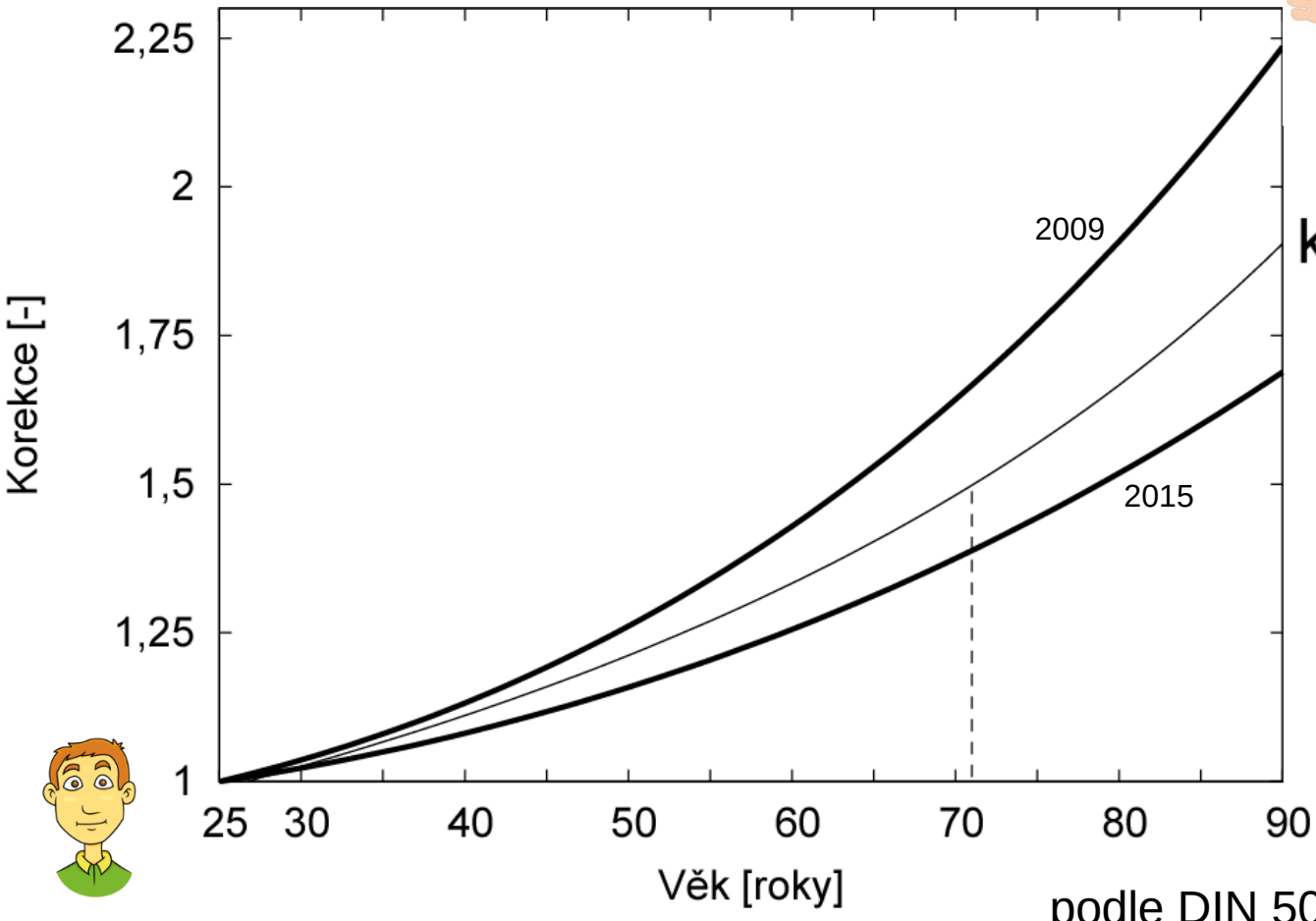
- **Maximální variabilita**
  - Program nahraje lékař na SD kartu.
  - Svítidlo automaticky mění intenzitu a tón světla podle programu a podle hodin.



Světlo a nemocní vyššího věku

In the Plejecentret Albertshøj care facility in Albertslund, Denmark, circadian lighting has been installed to assess the impact of such lighting on quality of life in elderly patients in comparison to regular lighting. *Source: Chromaviso*

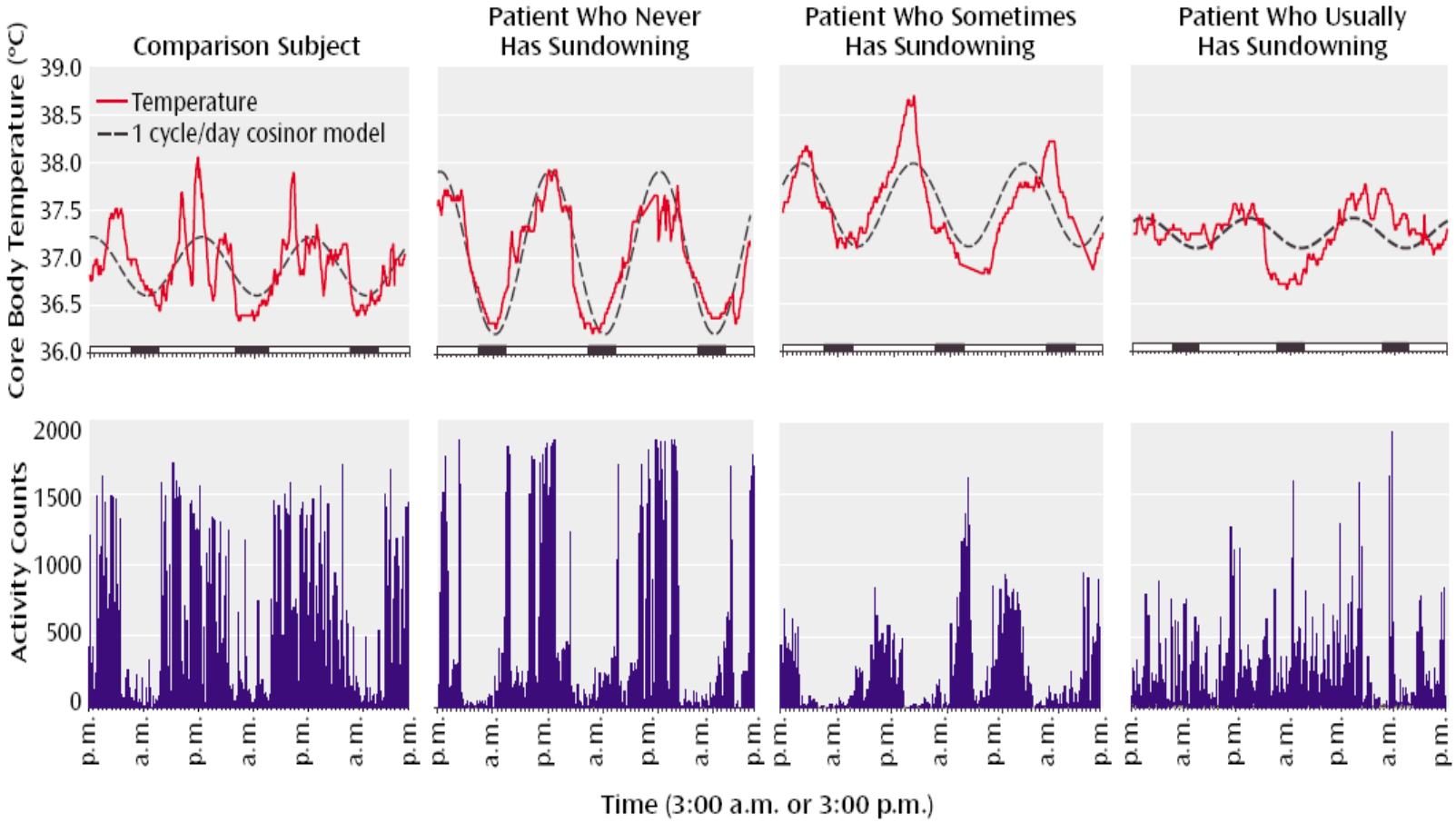
Korekce poklesu prostupnosti čočky



$$k \doteq \frac{100}{120\text{-}3/4\ V}$$

podle DIN 5036-1 a [6]

Alzheimerova choroba a cirkadiánní rytmy



Volicer et al., 2001

Gerontopsychiatrické oddělení - přízemí

- Stropní svítidla
- Pokoj a jídelna
- E = 30–3000 lx
- T_c = 6500 K

- VFN
- 2012

Světlo a rehabilitace po CMP

Automatic circadian lighting changes from early morning to late night are part of post-stroke patient care at the Central Hospital in Karlstad, Sweden. *Source: Chromaviso*


luminette®

Life „hangs“ on clock functions

⬇

Try to live with them !

Děkuji za pozornost!