

Slaap/Waak ritme
&
HartVaat ziekten

Andries Kalsbeek

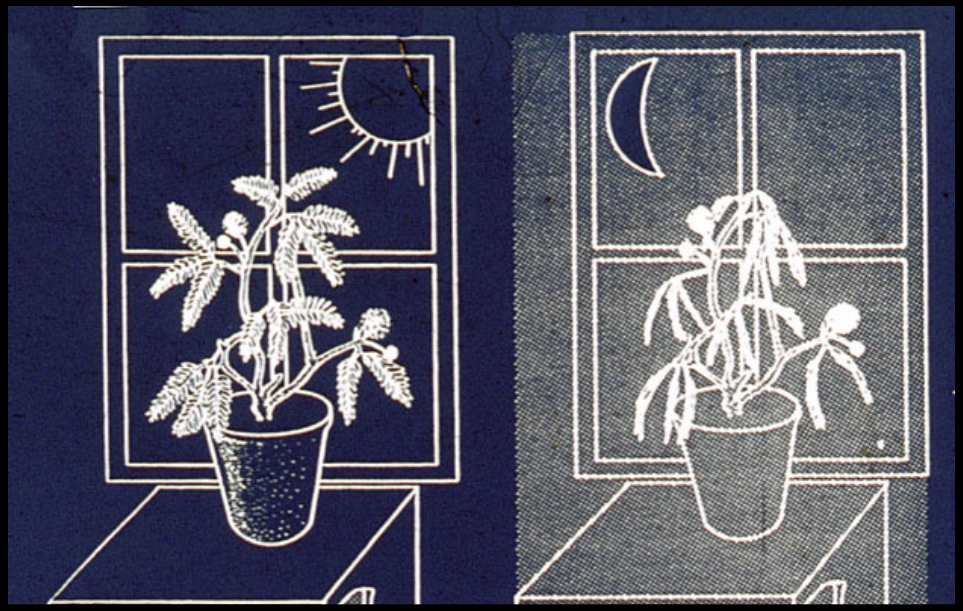
Nederlands Inst voor Neurowetenschappen (NIN), Amsterdam



Amsterdam Universitair Medische Centra (AUMC), Afd Endocrinologie en Metabolisme, Amsterdam

De Mimoso plant van Jean-Jacques de d'Ortous de Mairan in 1729

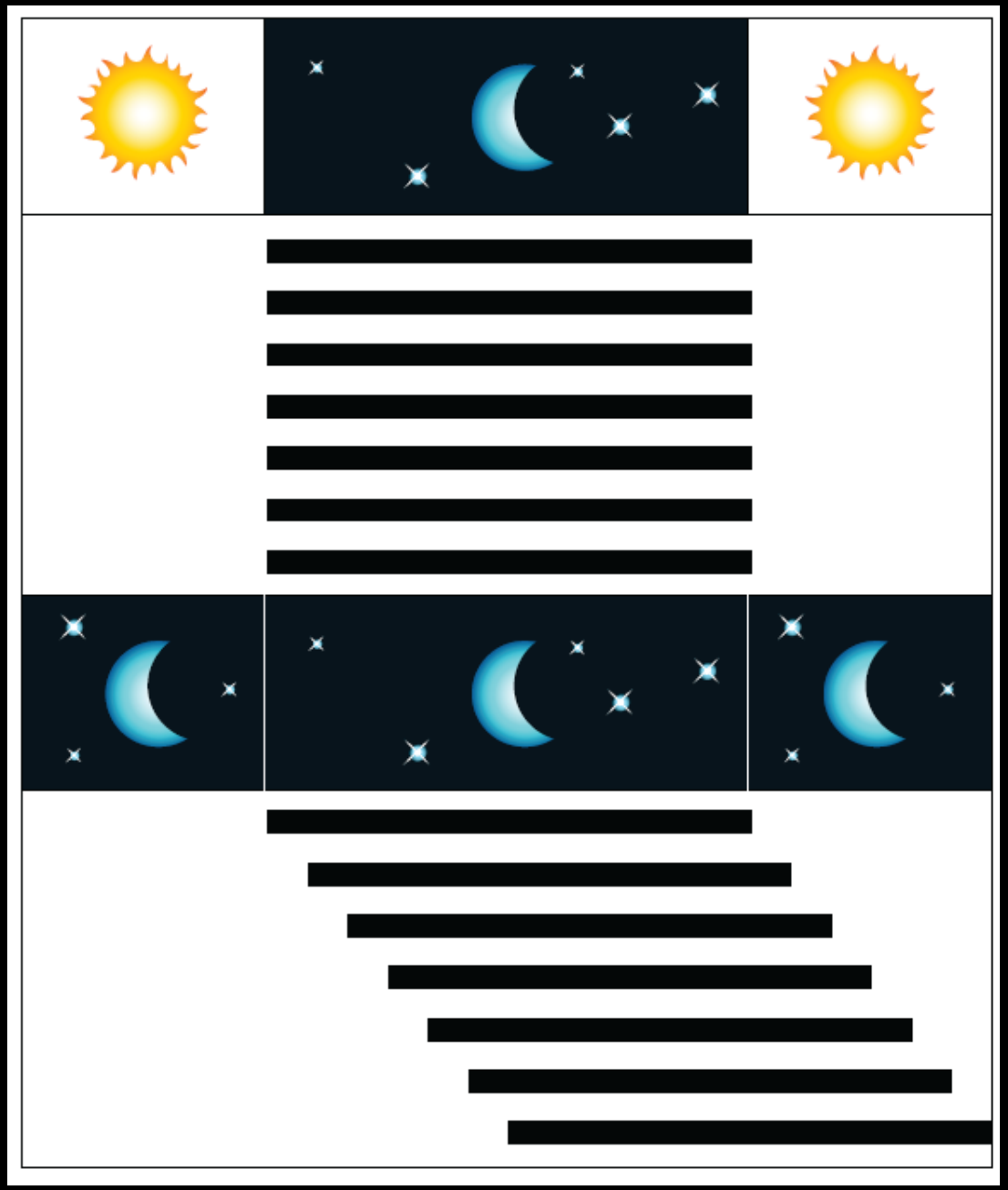




Michel Siffre in de grotten van Clamouse



Een klok met een periode van ongeveer 24 uur





Spaanse vrouw die ruim vijfhonderd dagen onder de grond zat komt boven

Door onze nieuwsredactie

14 apr 2023 om 16:16
Update: 12 dagen geleden

147 reacties

Een vijftigjarige Spaanse vrouw leefde anderhalf jaar in afzondering in een grot in een gebergte aan de Spaanse kust. Beatriz Flamini deed mee aan een onderzoek naar slaap- en waakritmes en het menselijk brein.

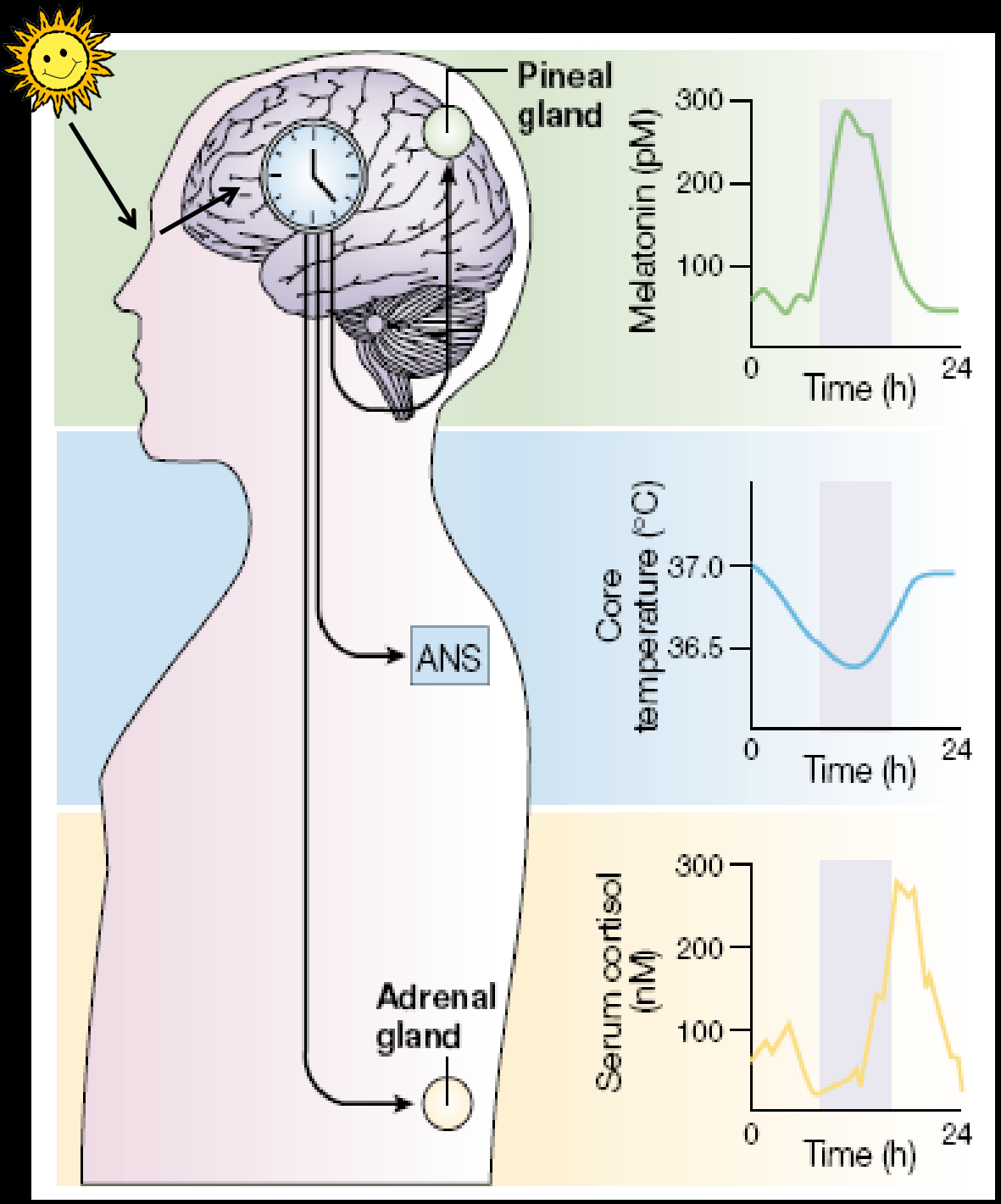
Flamini is bergbeklimmer, atlete en grotonderzoeker. Ze zat 510 dagen in een grot van 70 meter diepte waar ze geen daglicht zag. De grot was wel bewoonbaar gemaakt en voorzien van een waterleiding en elektriciteit. Er was ook een nooduitgang aangelegd.

Op 21 november 2021 ging Flamini de grot in. Sindsdien las ze zeker zestig boeken. Flamini had geen telefoon of horloge bij zich. Zonder daglicht verloor

Een klok met een periode van ongeveer 24 uur



....noemen we een circadiane klok
van de Latijnse woorden *circa* en *dies*
wat ongeveer een dag betekent



Onze biologische klok reguleert vele ritmes in ons lichaam

Hastings et al, 2003

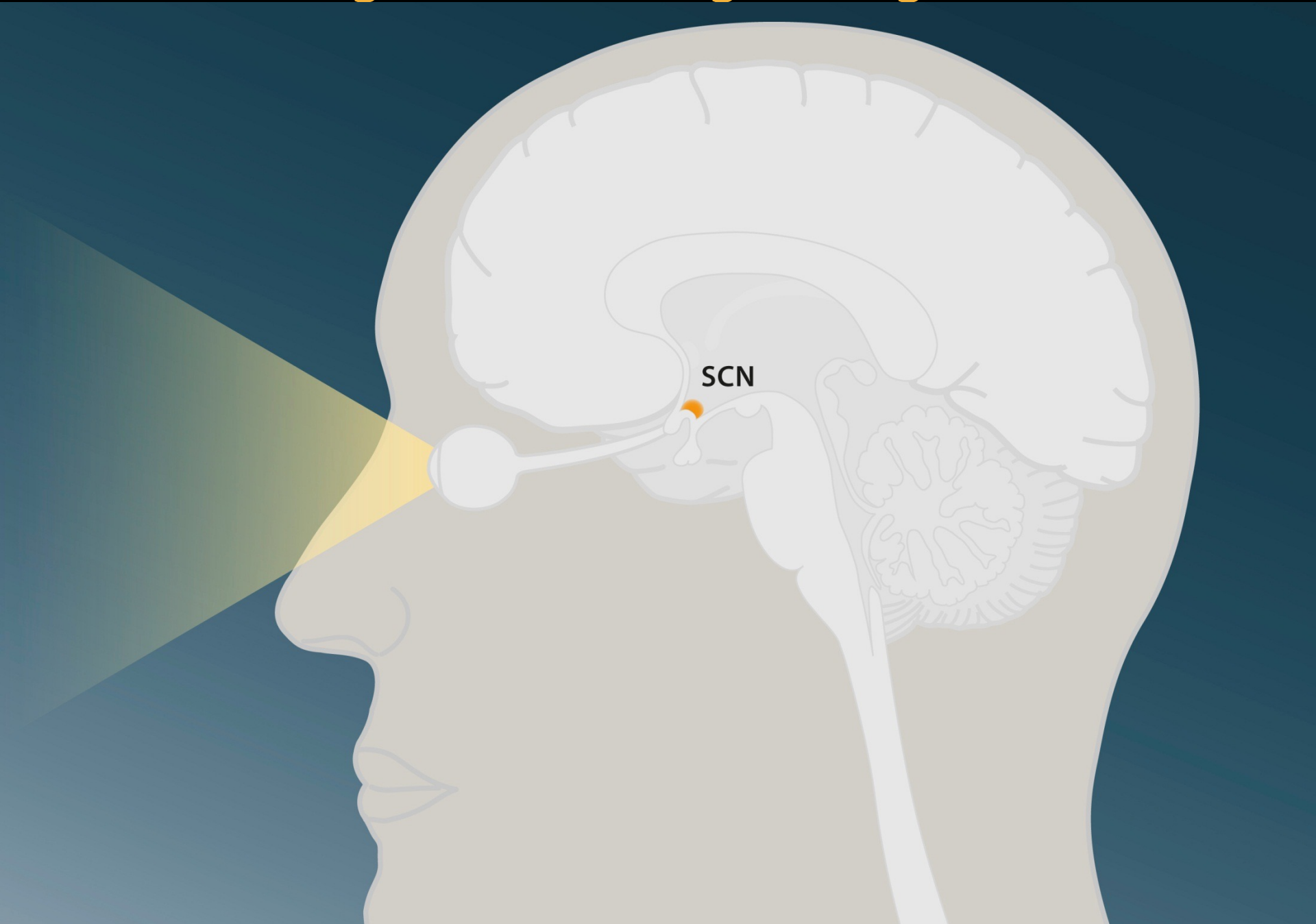


De hypothalamus

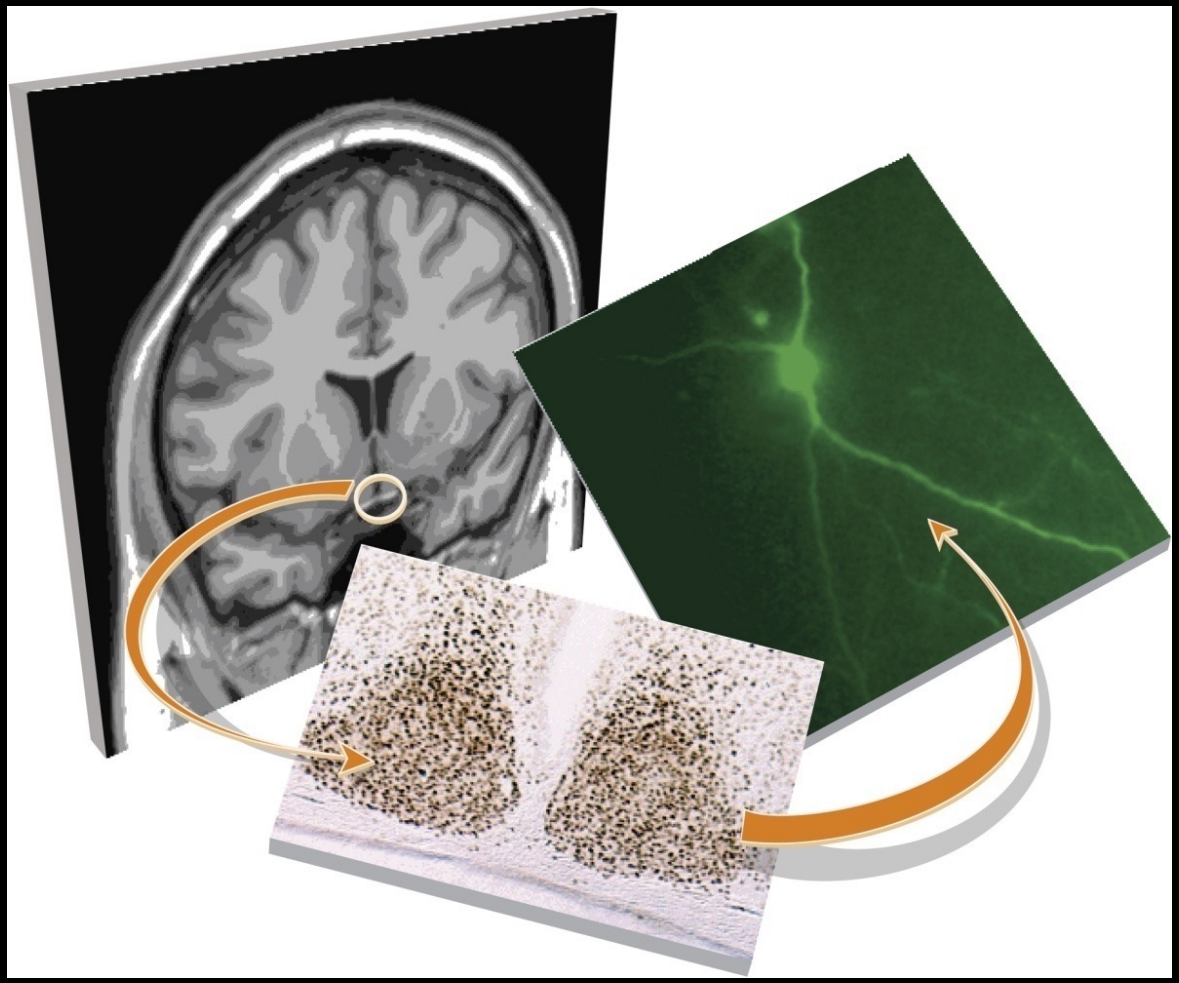
De biologische klok in de hypothalamus



De biologische klok is gevoelig voor licht

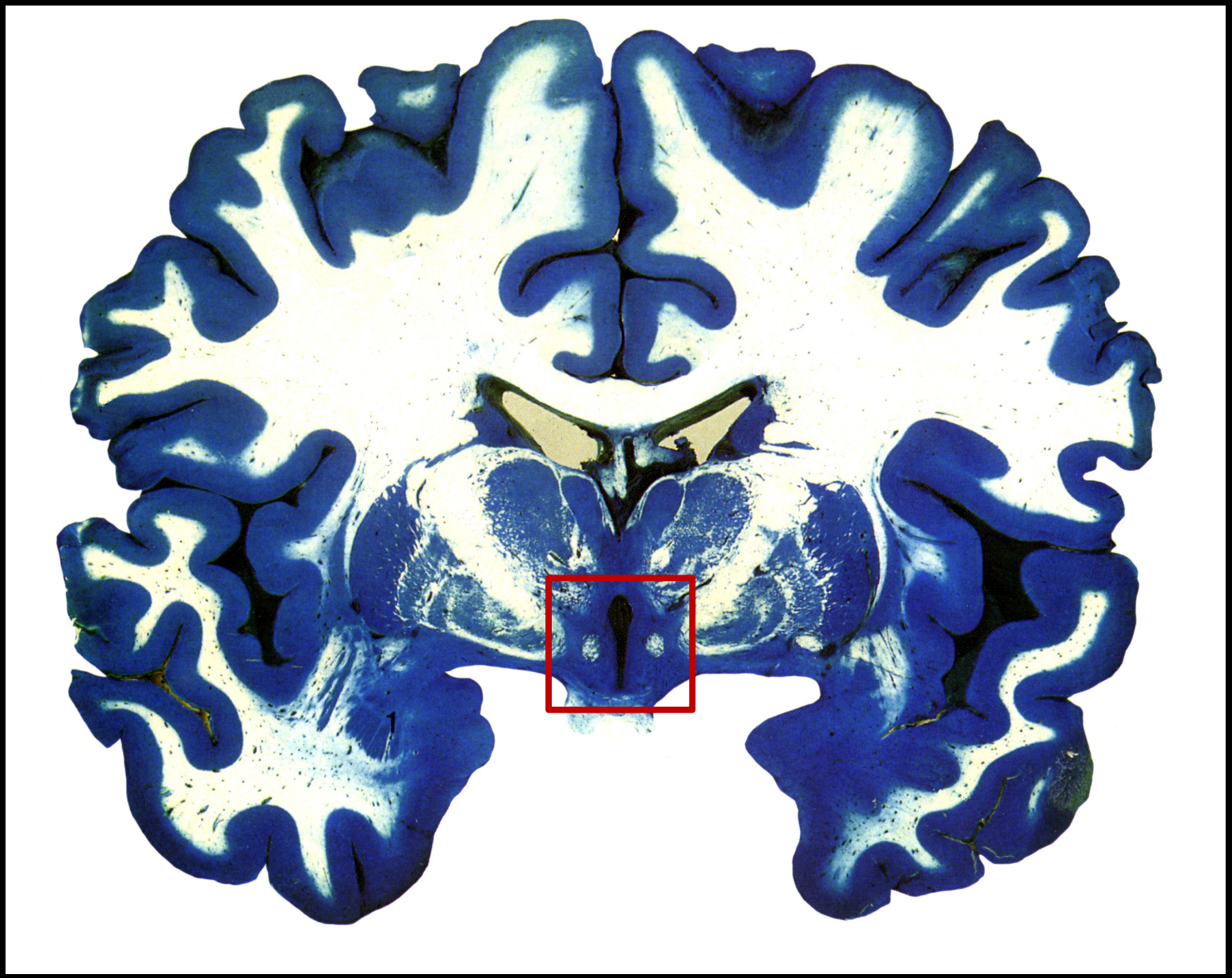


De Suprachiasmatische Nucleus (SCN)

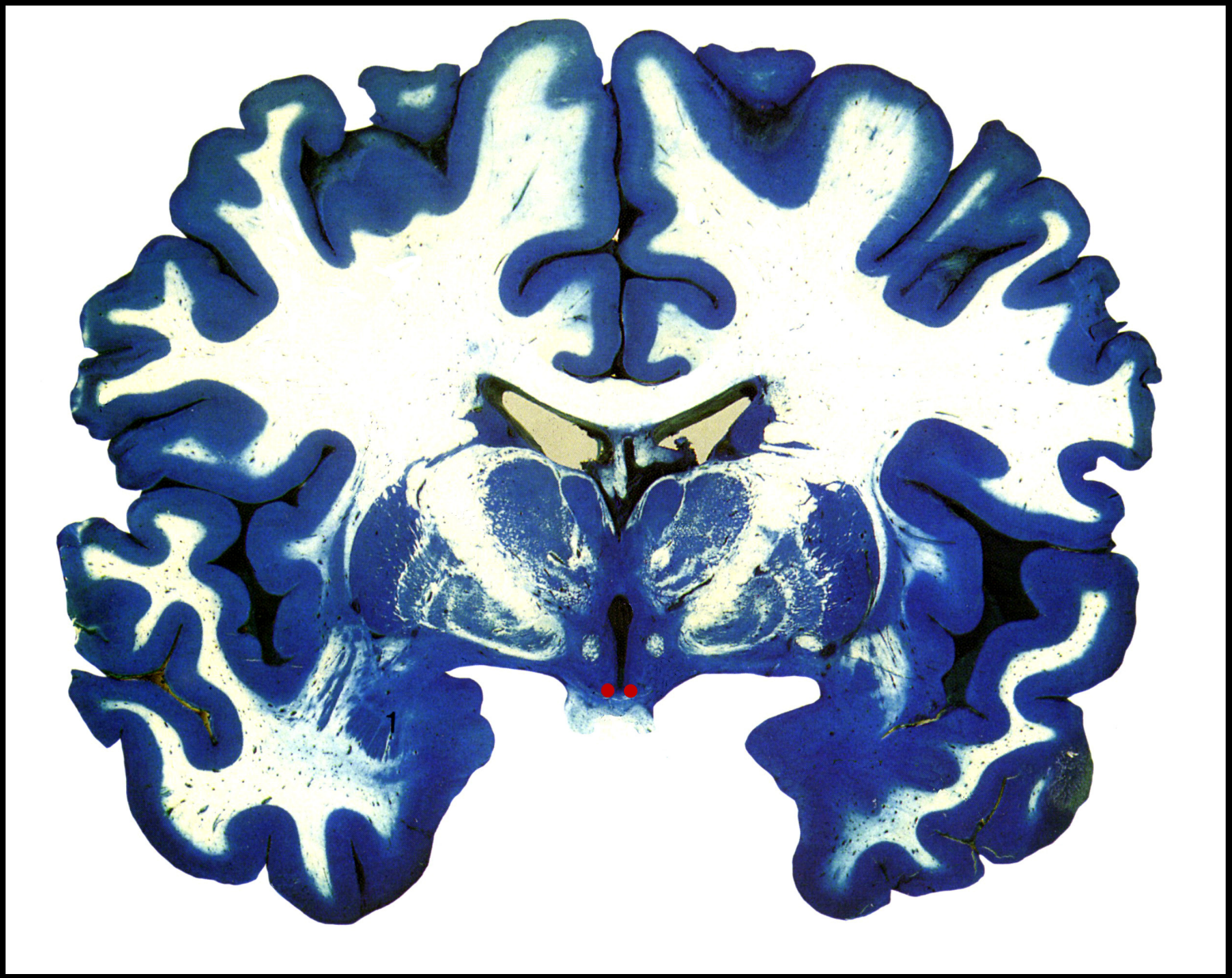


….of te wel:
“de kern die bovenop de kruising van de oogzenuw ligt”

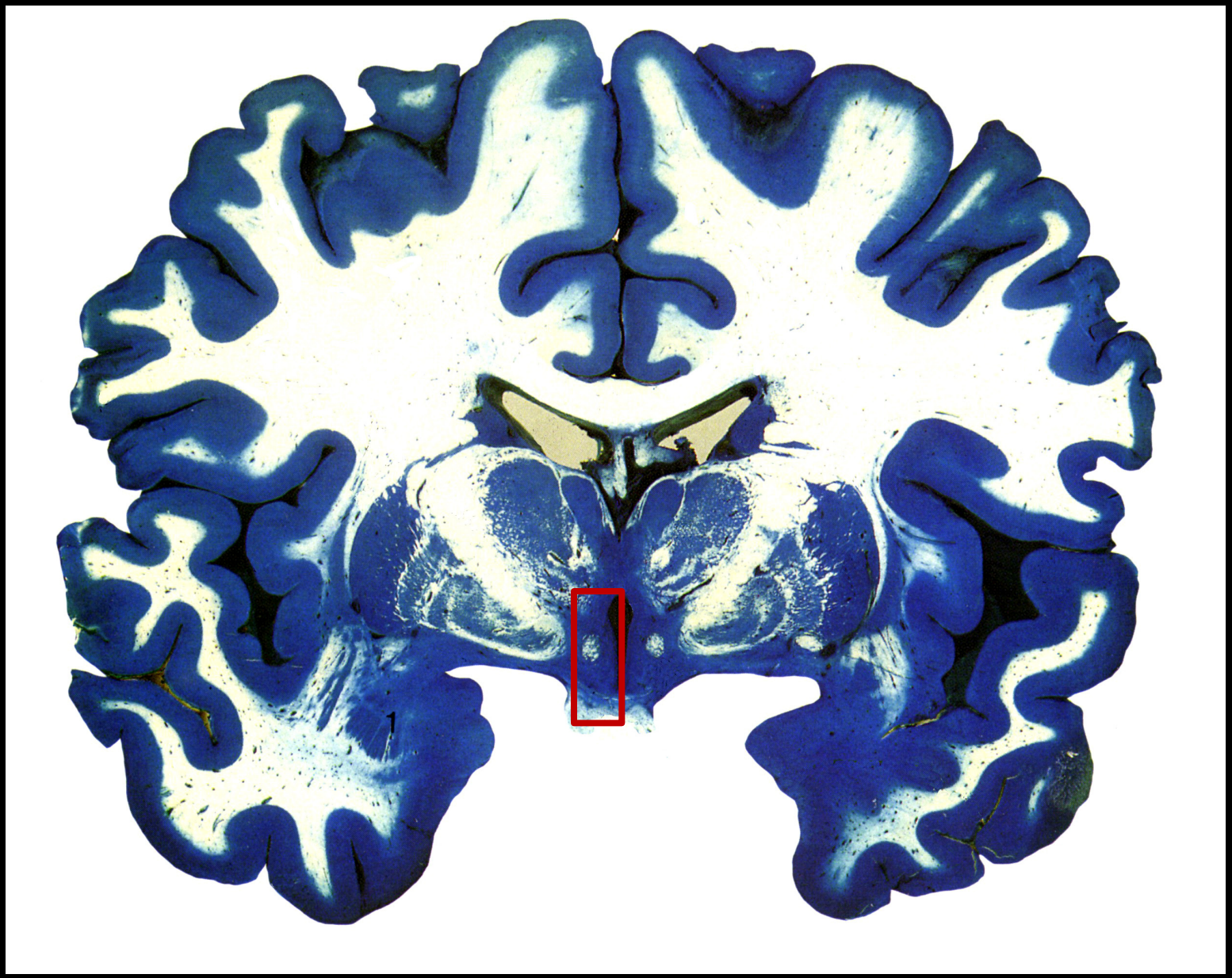
De hypothalamus



Onze biologische klok in de SCN



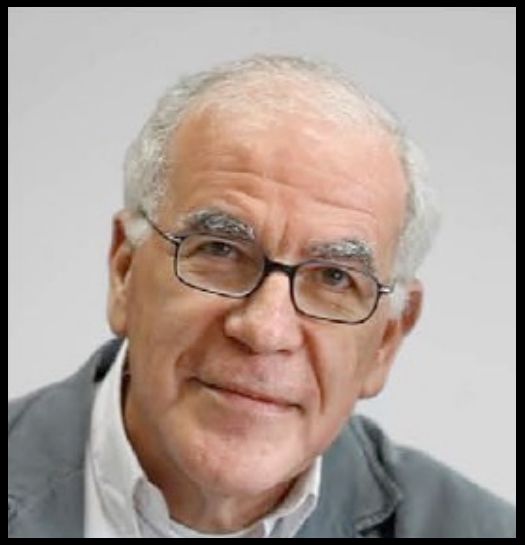
De hypothalamus

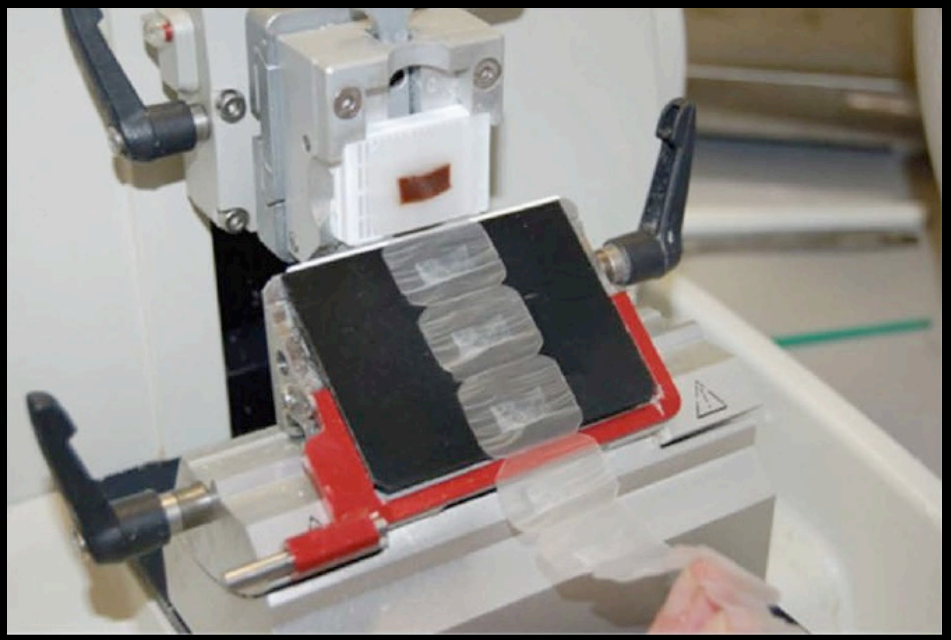


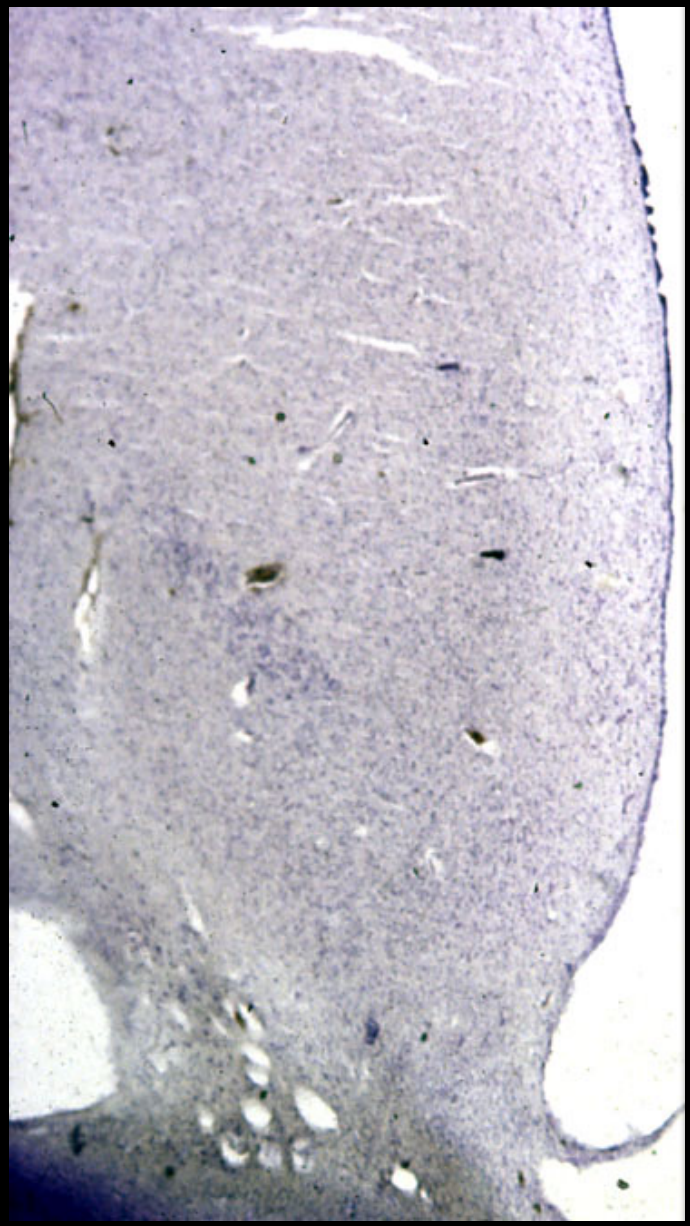
NETHERLANDS BRAIN BANK

De hypothalamus bevat ook onze biologische klok





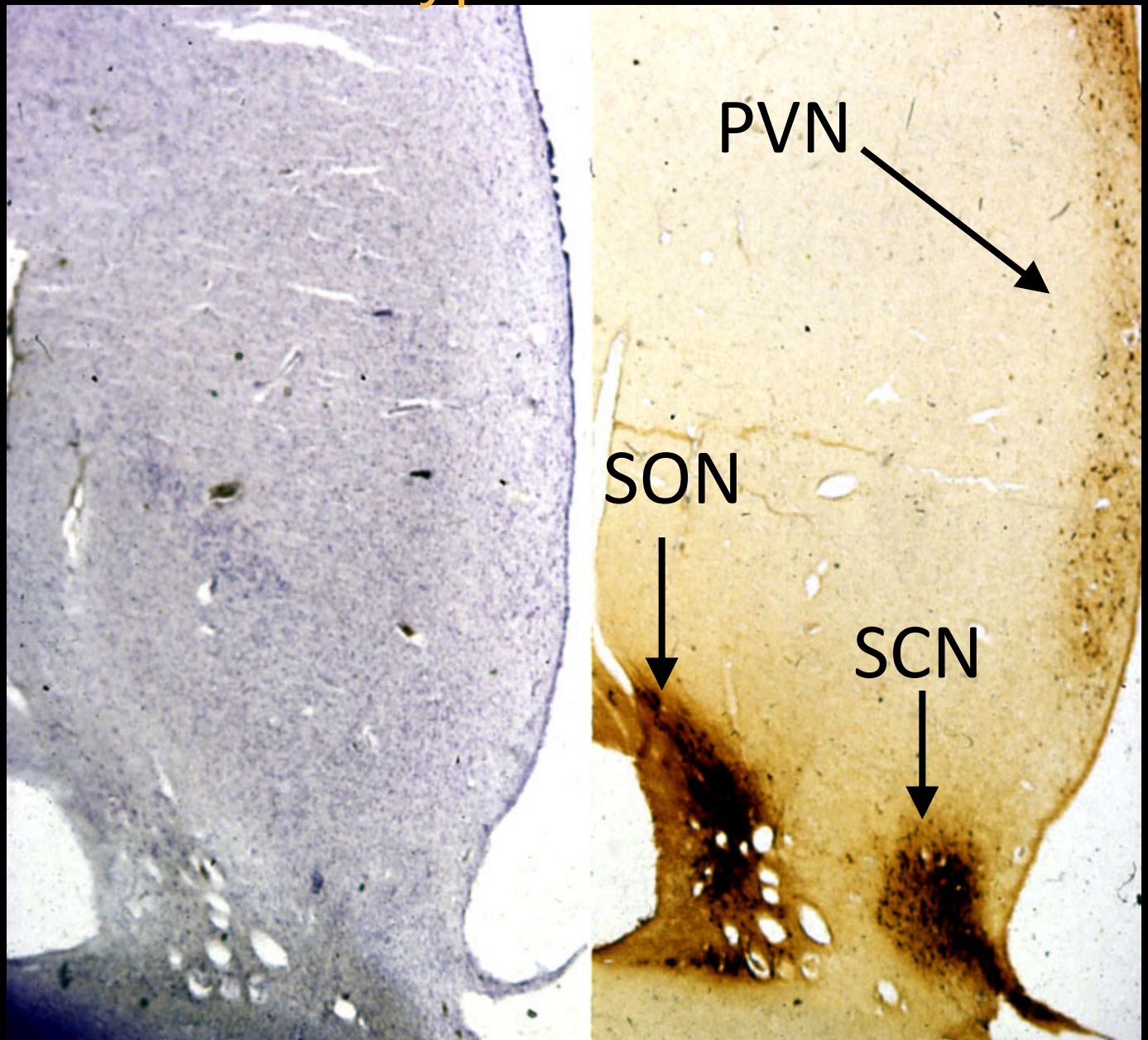




Een dwarsdoorsnee van de humane hypothalamus

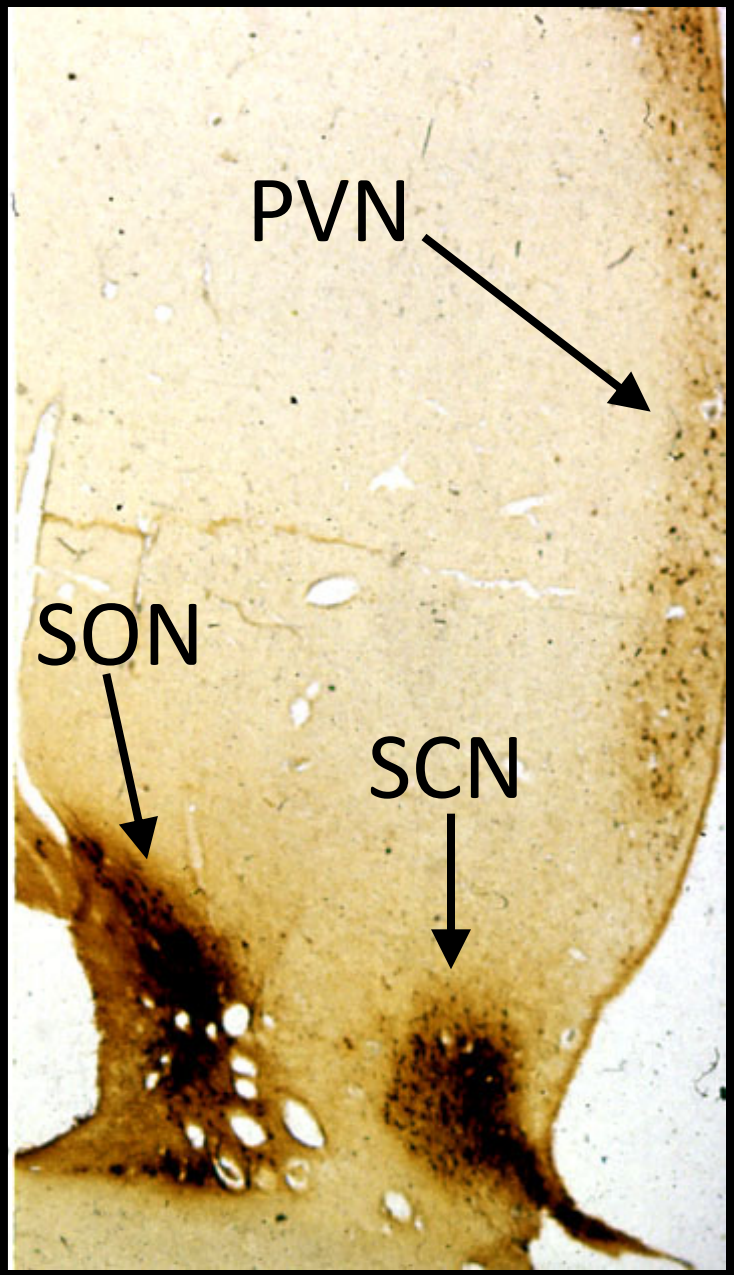
Alle neuronen

Vasopressine neuronen

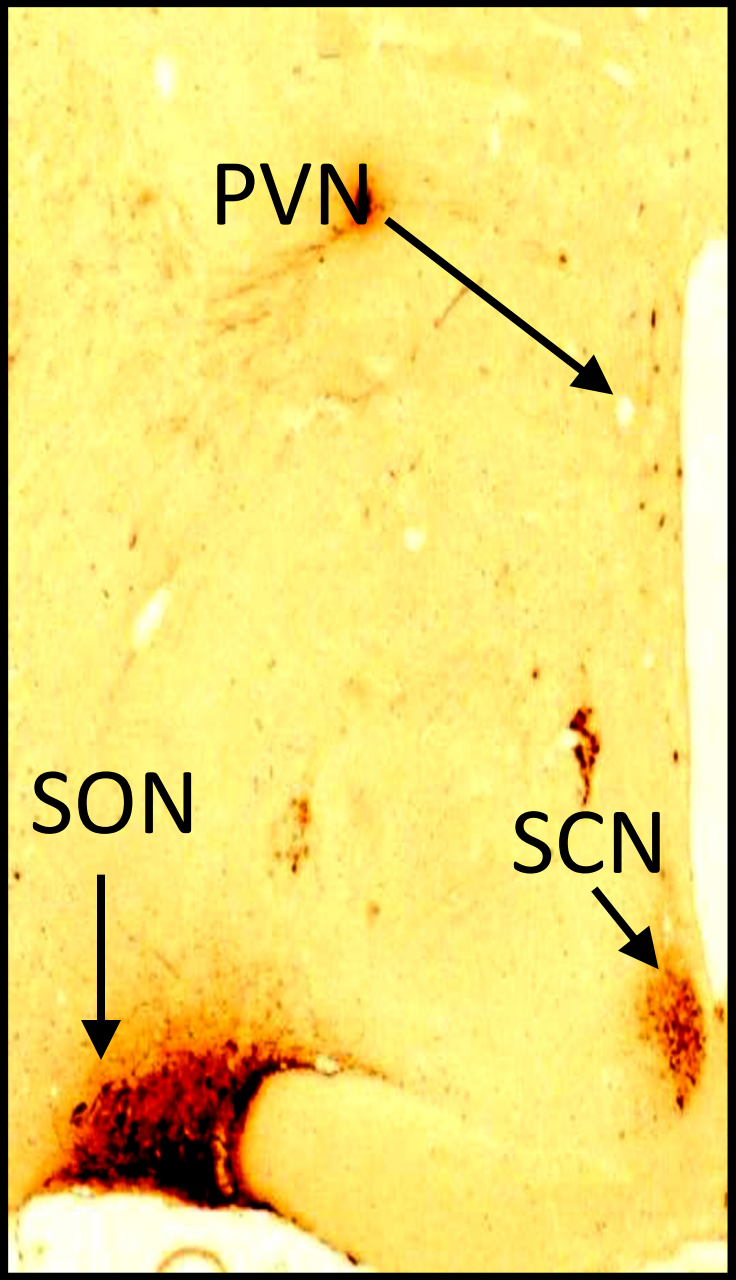


Vasopressine in de hypothalamus

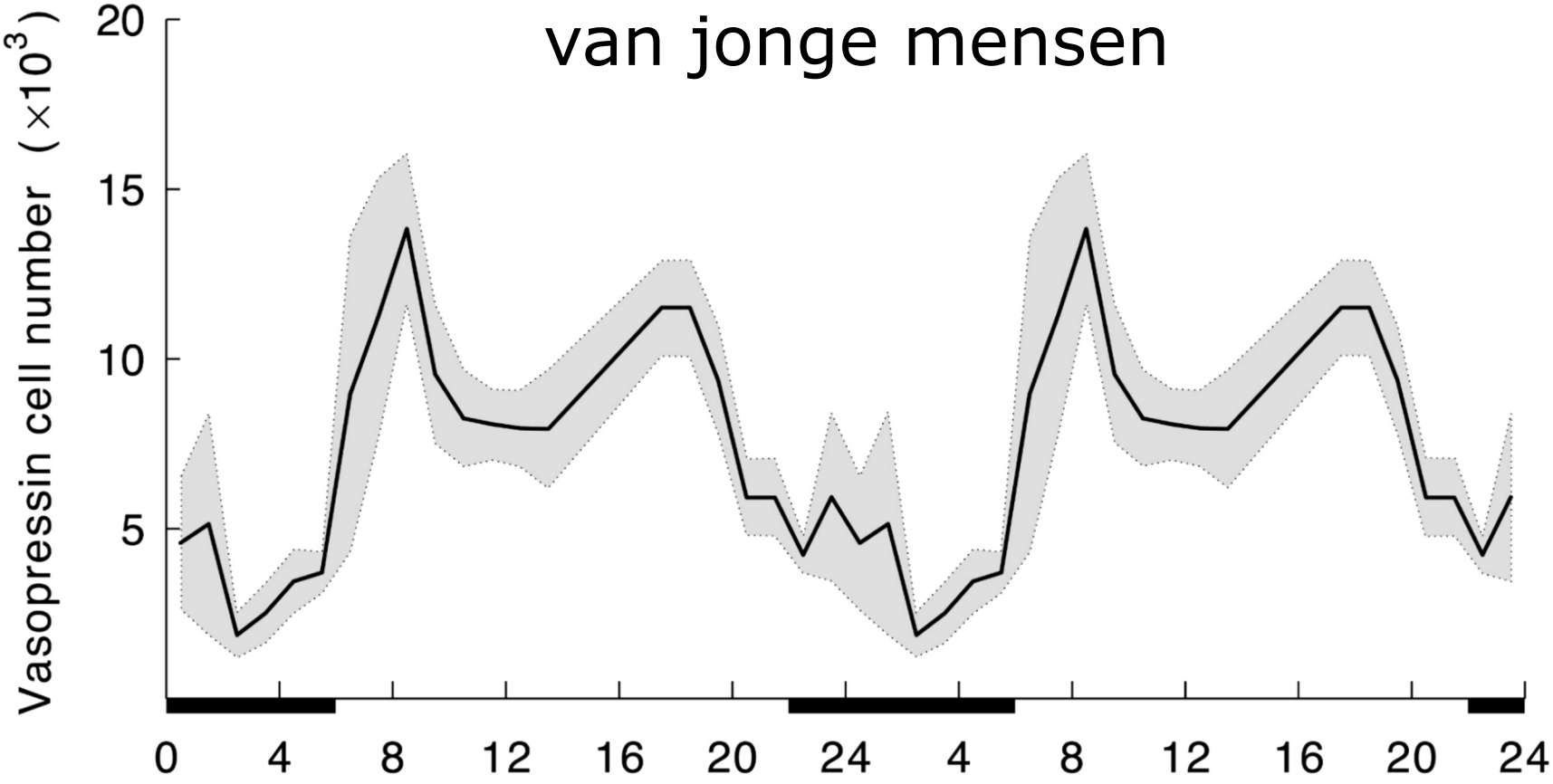
Mens



Rat

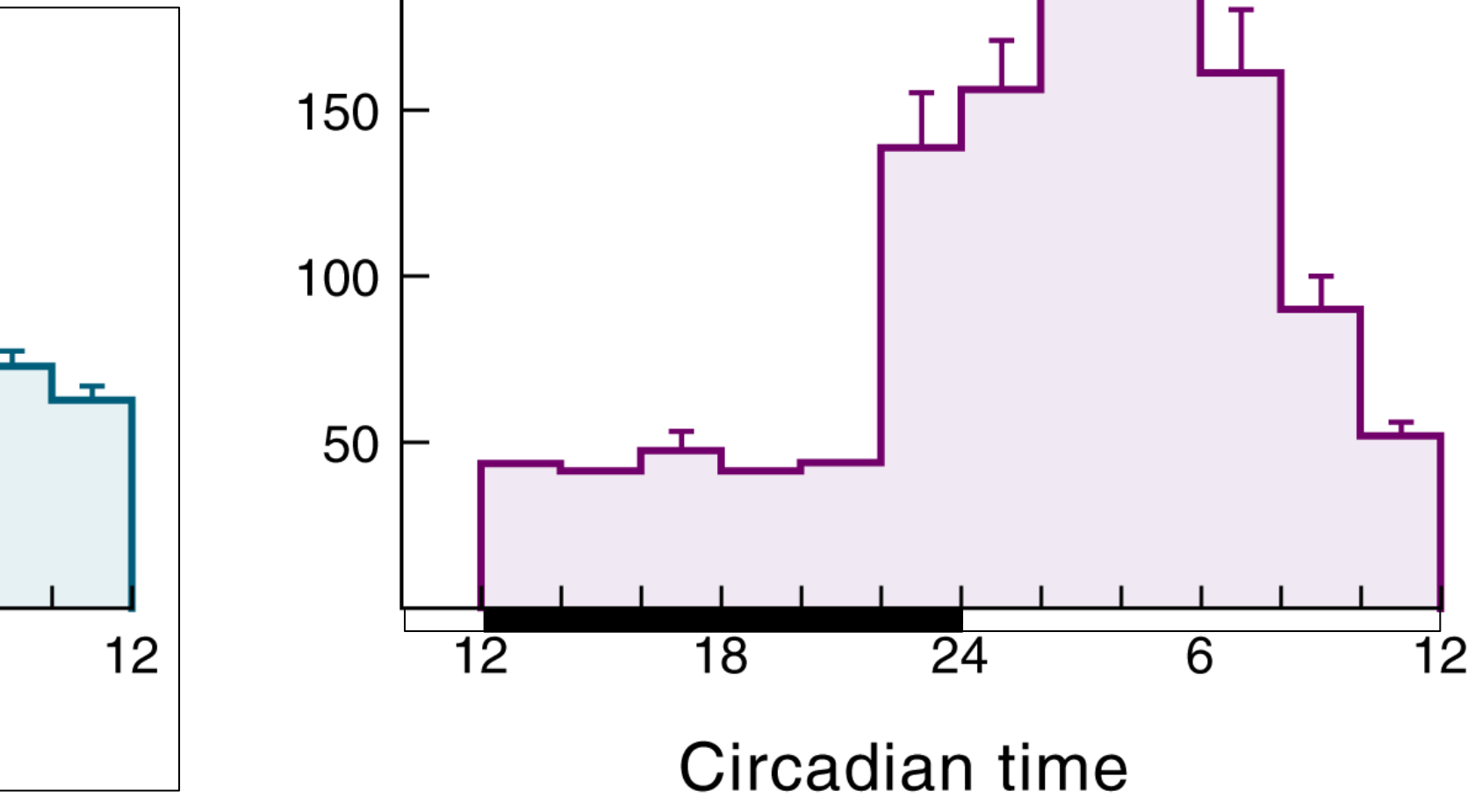


Vasopressine cellen in de SCN van jonge mensen

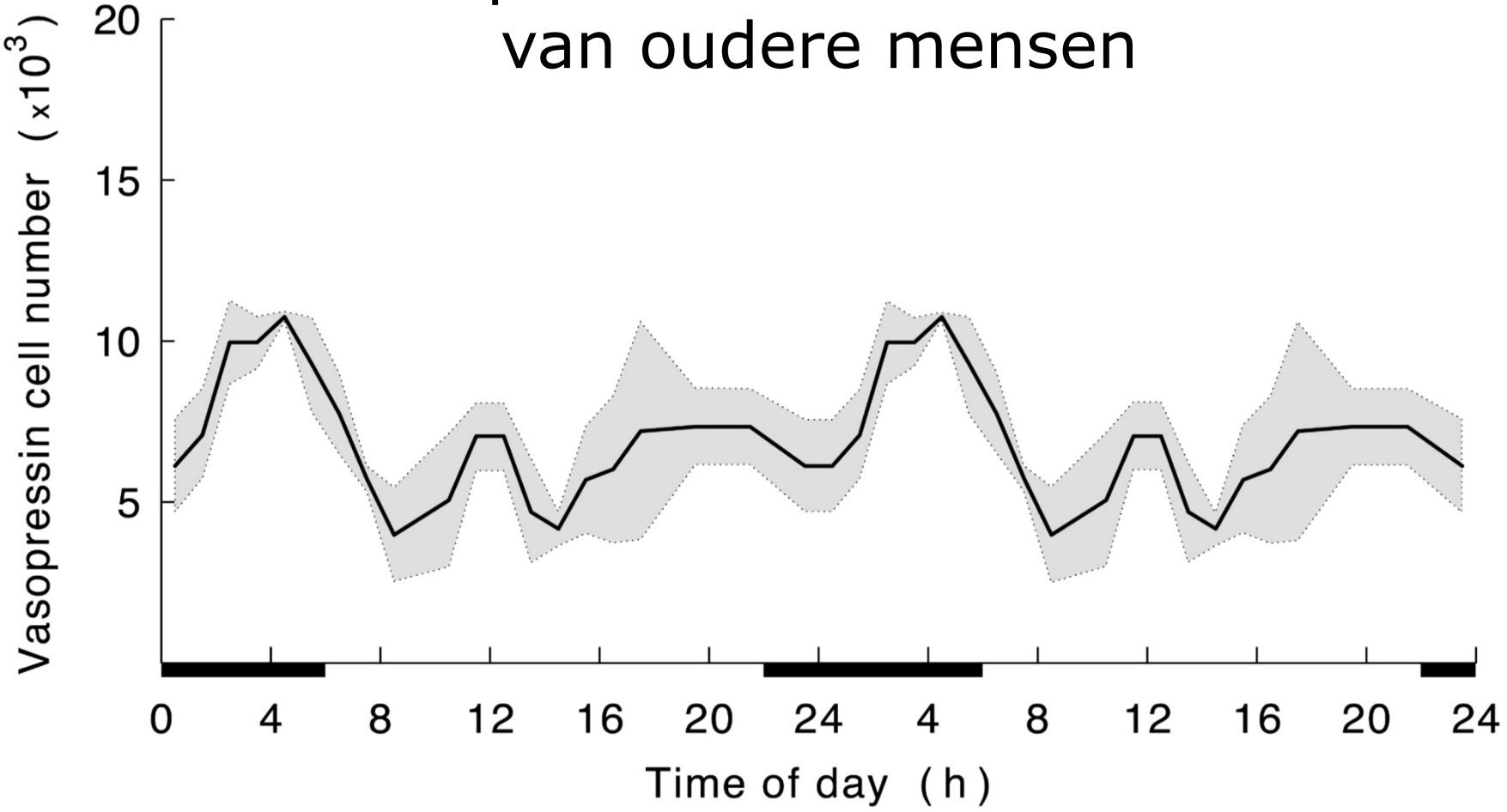


Hofman et al., Brain Res. 1994

Een dag/nacht ritme van vasopressine in het CSF van de rat



Vasopressine cellen in de SCN van oudere mensen



Hofman et al., Brain Res. 1994

Onze klok & HartVaat ziekten



Circadian Variation in Cardiovascular Events

James E. Muller

AJH 1999;12:35S–42S

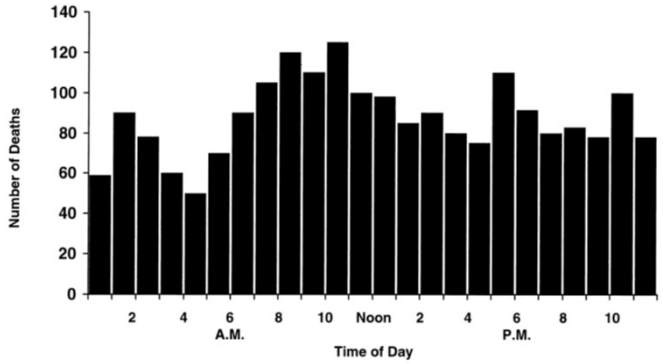


FIGURE 2. *Time of day of out-of-hospital SCD (≤1 h from onset of symptoms to death) for 2203 persons who died in Massachusetts during 1983. A statistically significant ($P < .001$) diurnal variation is evident, with a primary peak between 7 and 11 AM. Adapted with permission from Muller et al: Circadian variation in the frequency of SCD. Circulation 1987;75:131–138.*[2]

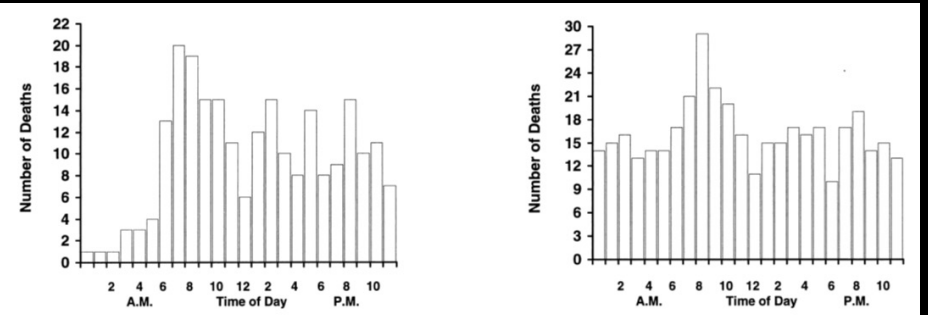


FIGURE 1. **Left:** *Time of day of definite SCD (n = 264). The decrease in incidence from 9 AM to 1 PM, compared with the morning peak, occurs during an interval in which observation is likely to be constant.* **Right:** *Time of day of definite or possible SCD (n = 429). The hourly risk of SCD is approximately 70% higher from 7 to 9 AM than the mean risk during the remaining 22 h of the day. Adapted with permission from Excerpta Medica Inc. from Willich et al: Circadian variation in the incidence of SCD in the Framingham Heart Study Population. Am J Cardiol 1987;60:801–806.*[1]

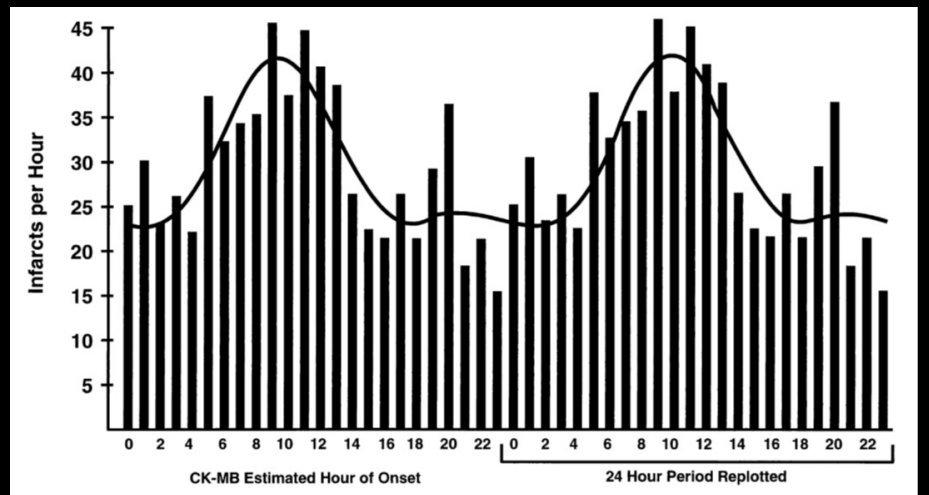


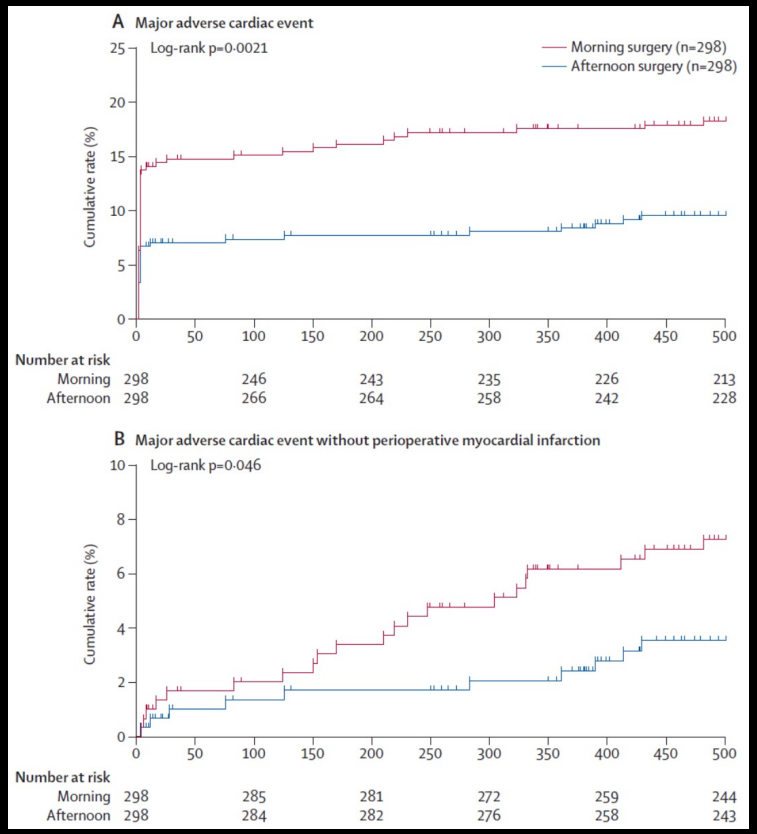
FIGURE 3. *The number of infarctions (in the MILIS database) beginning during each hour of the day is plotted at* **left**. *At* **right**, *the identical findings are plotted again to display the relationship between the end and beginning of the day. A two-harmonic–regression equation for the frequency of onset of MI has been fitted to the data (ie, curved line). A pronounced circadian variation is evident, with a primary peak frequency of MI at 9 AM and a secondary peak at 8 PM. Adapted with permission from Muller et al: Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–1322.*

Cardiovascular events after aortic valve replacement in either the morning or afternoon

Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbα antagonism: a single-centre propensity-matched cohort study and a randomised study

Lancet 2018; 391: 59–69

David Montaigne, Xavier Marechal, Thomas Modine, Augustin Coisne, Stéphanie Mouton, Georges Fayad, Sandro Ninni, Cédric Klein, Staniel Ortmans, Claire Seunes, Charlotte Potelle, Alexandre Berthier, Celine Gheeraert, Catherine Piveteau, Rebecca Deprez, Jérome Eeckhoute, Hélène Duez, Dominique Lacroix, Benoit Deprez, Bruno Jegou, Mohamed Koussa, Jean-Louis Edme, Philippe Lefebvre, Bart Staels



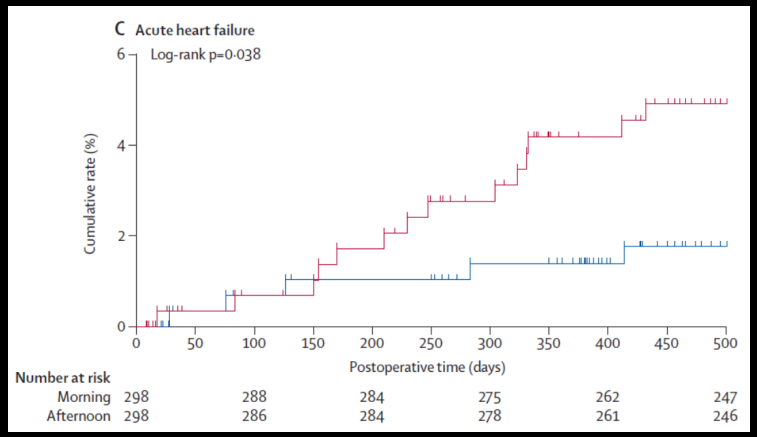
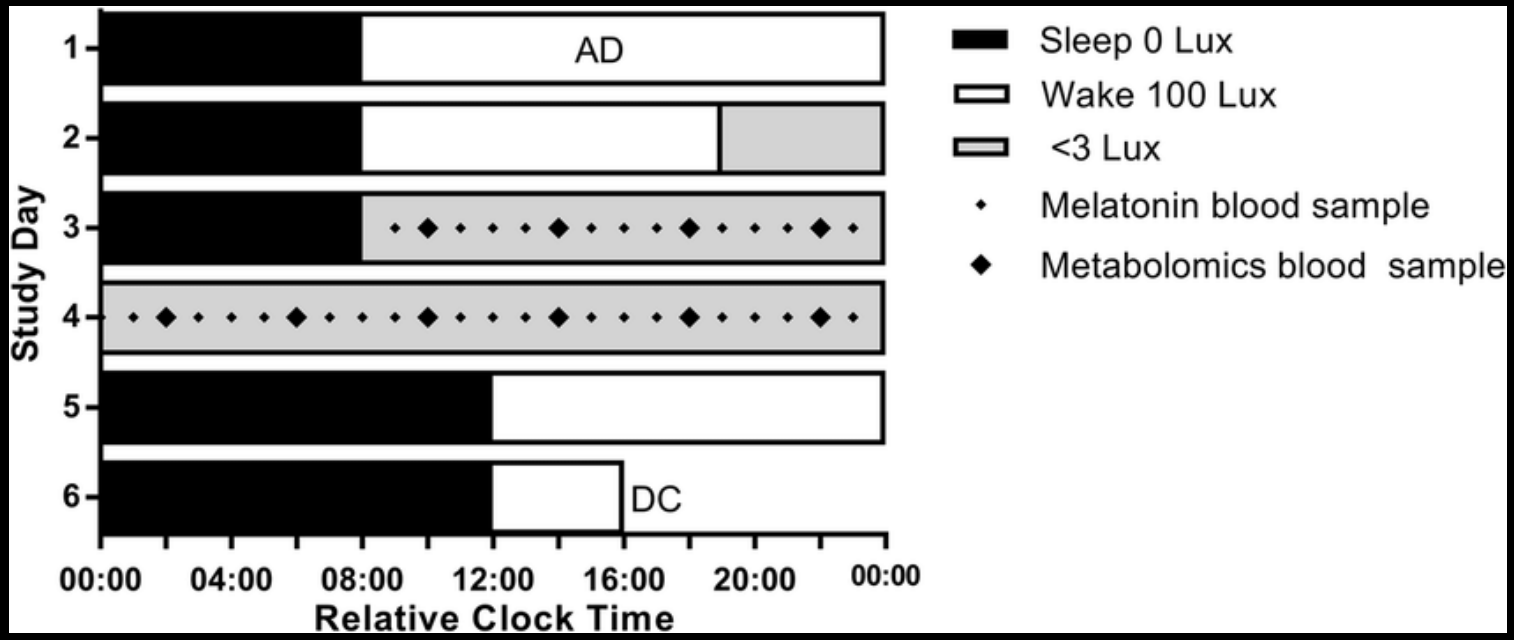


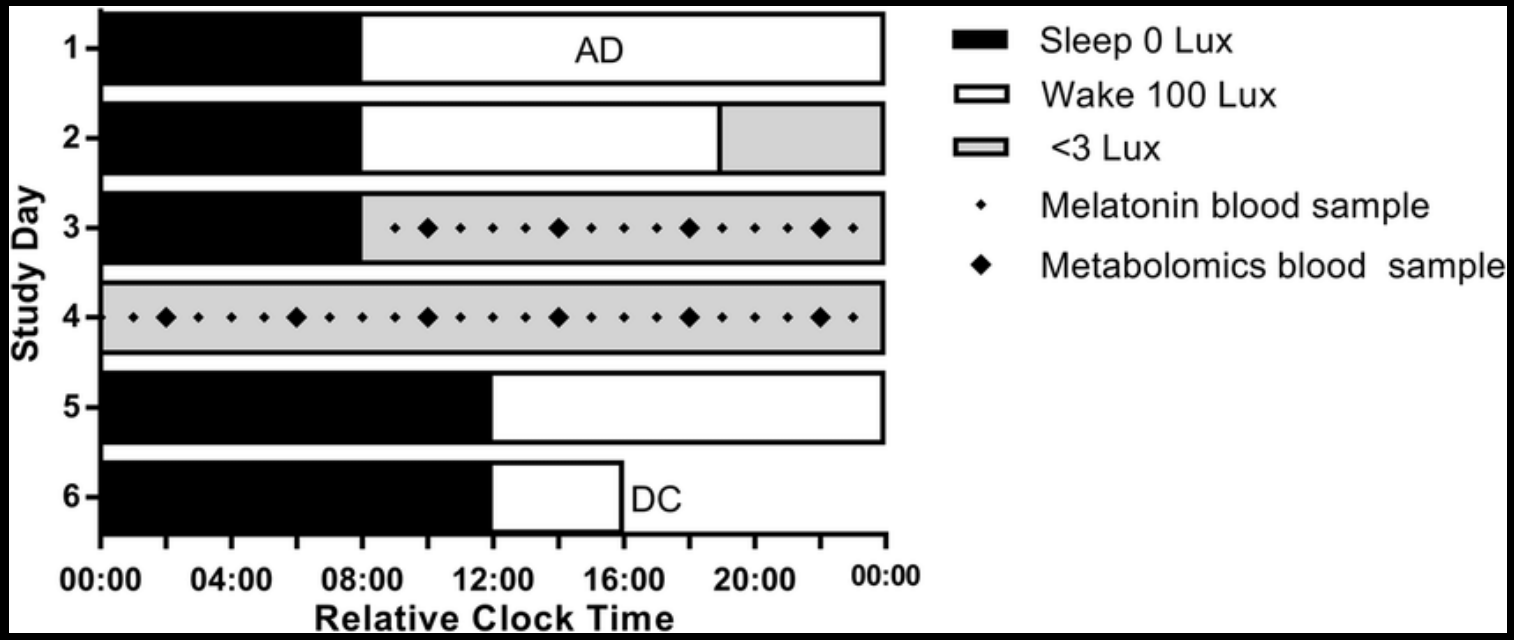
Figure 1: Cardiovascular events after aortic valve replacement surgery according to time of the day of surgery in the matched cohort population

(A) Major adverse cardiac events (ie, cardiovascular death, myocardial infarction, and acute heart failure). (B) Major adverse cardiac events without perioperative myocardial infarction. (C) Acute heart failure. p values were calculated by log-rank test.

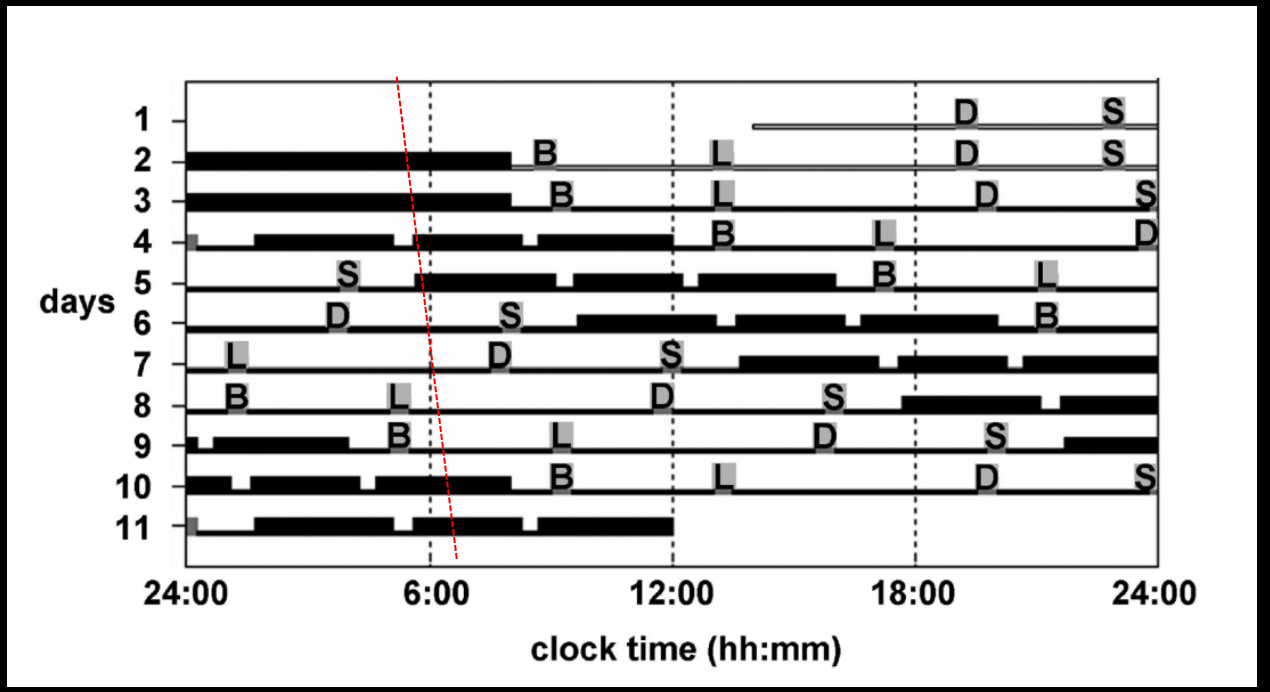
Constant Routine Protocol

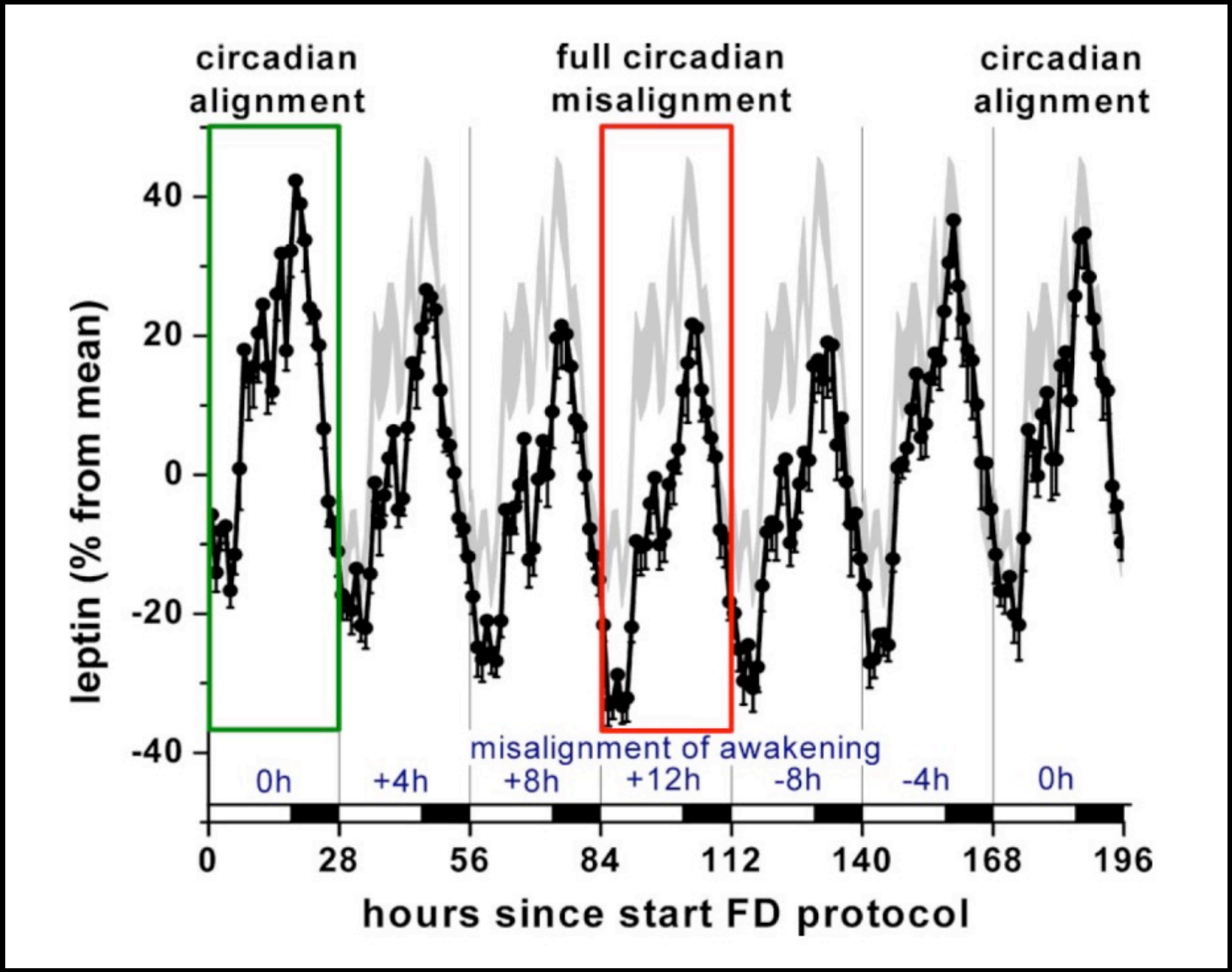


Constant Routine Protocol

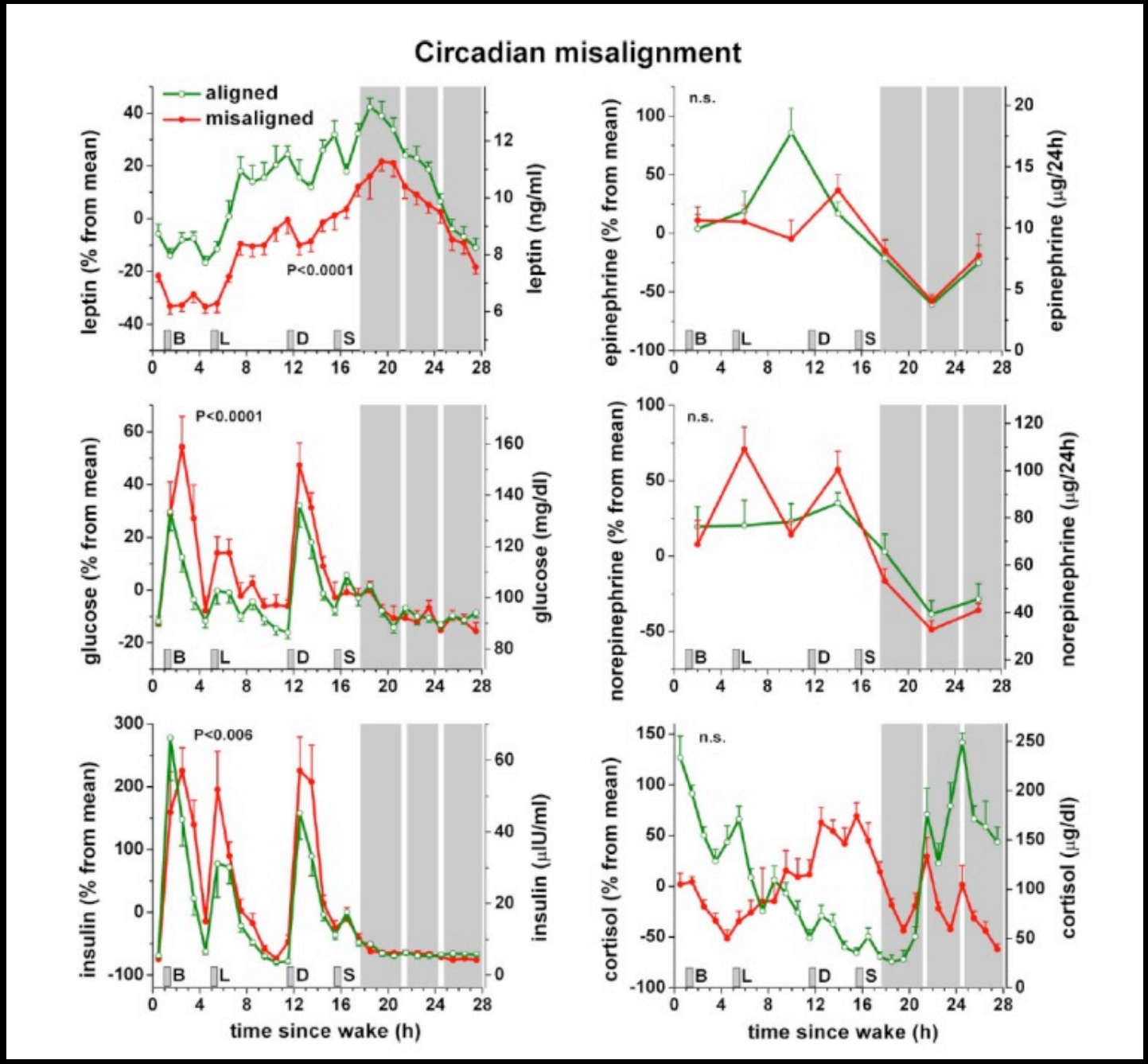


Forced Desynchrony Protocol



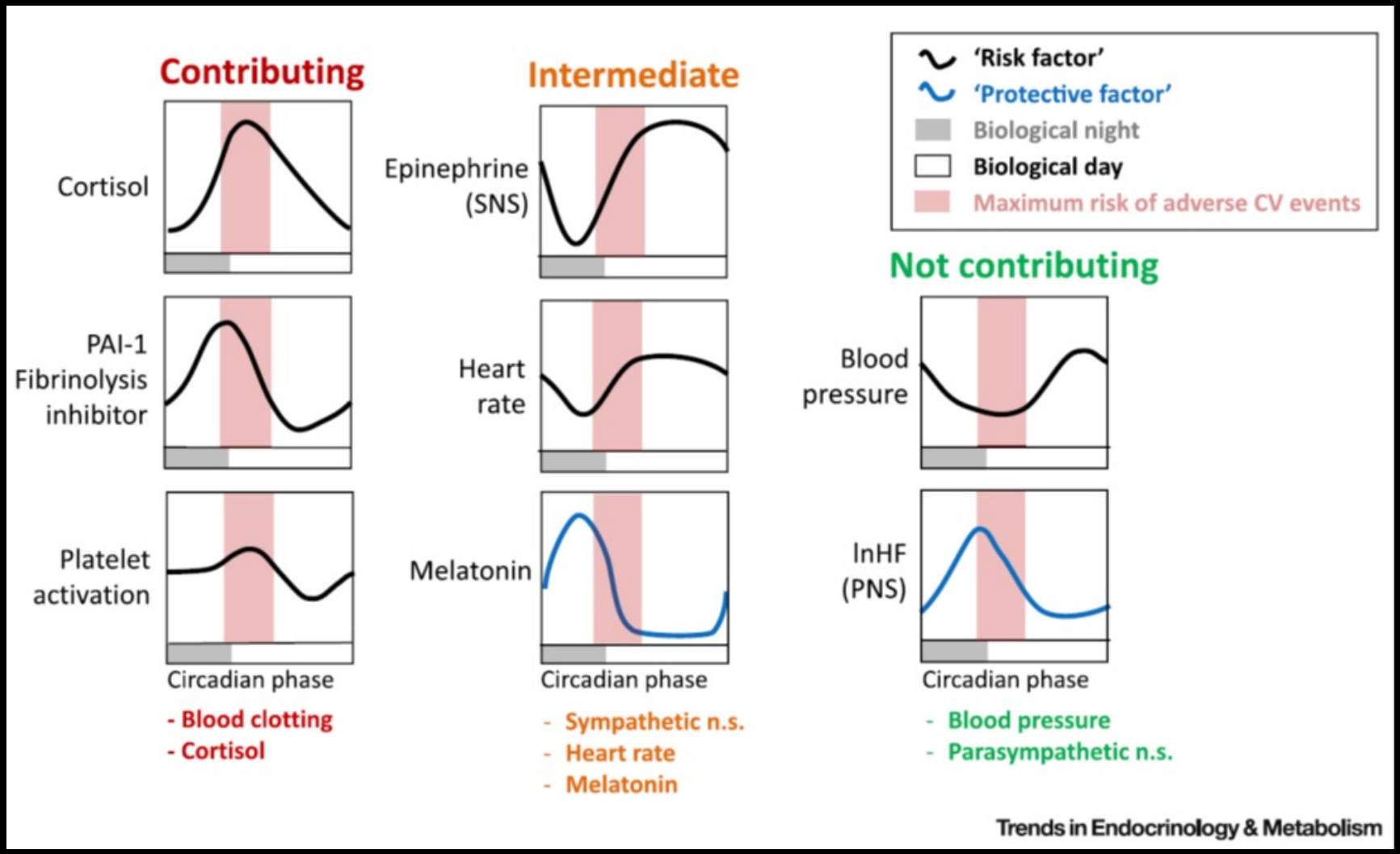


Scheer et al., 2009

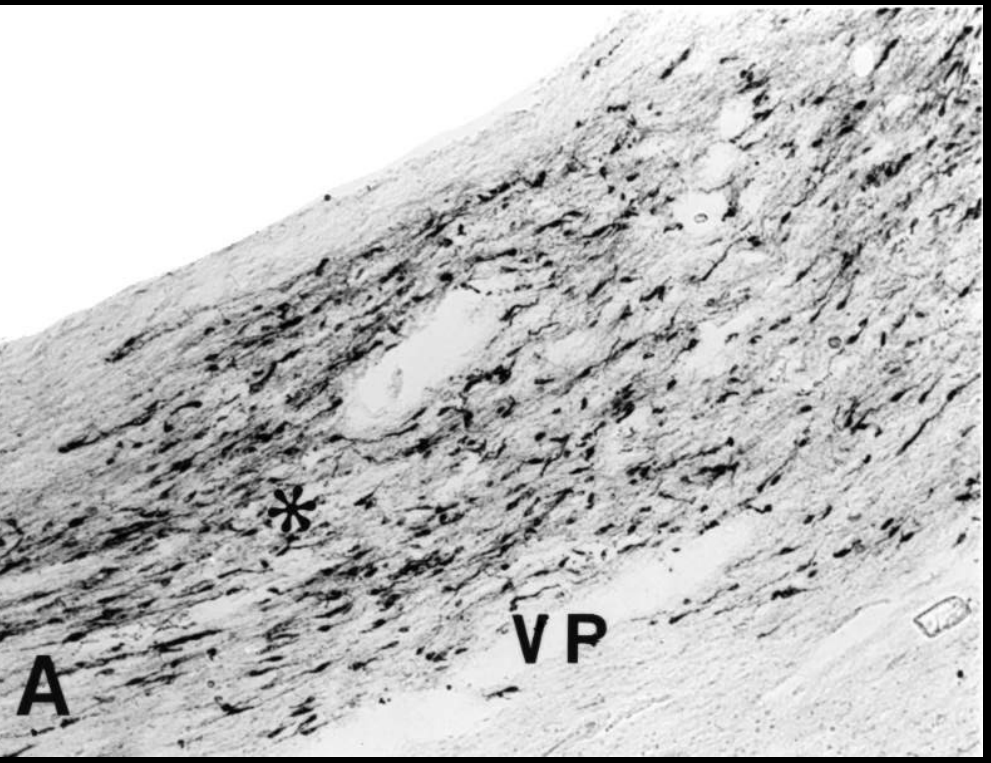


Scheer et al., 2009

Impact of circadian disruption on cardiovascular function



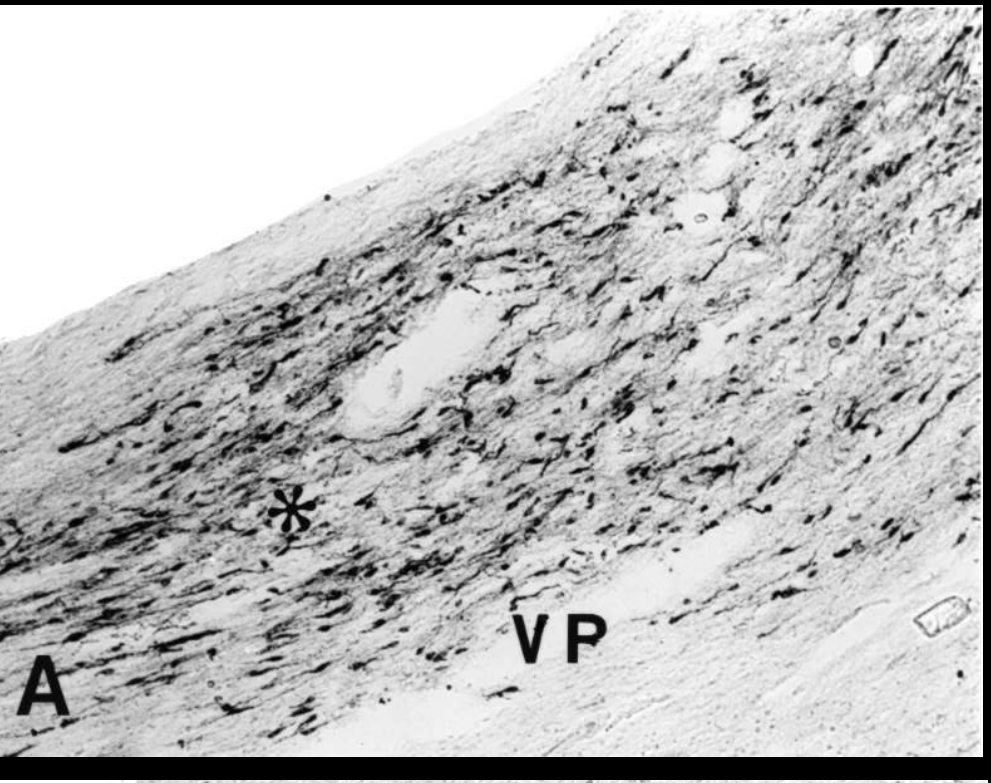
Chellappa et al., Tr Endo Metab, 2019



Humane hypothalamus met vasopressine (VP) kleuring

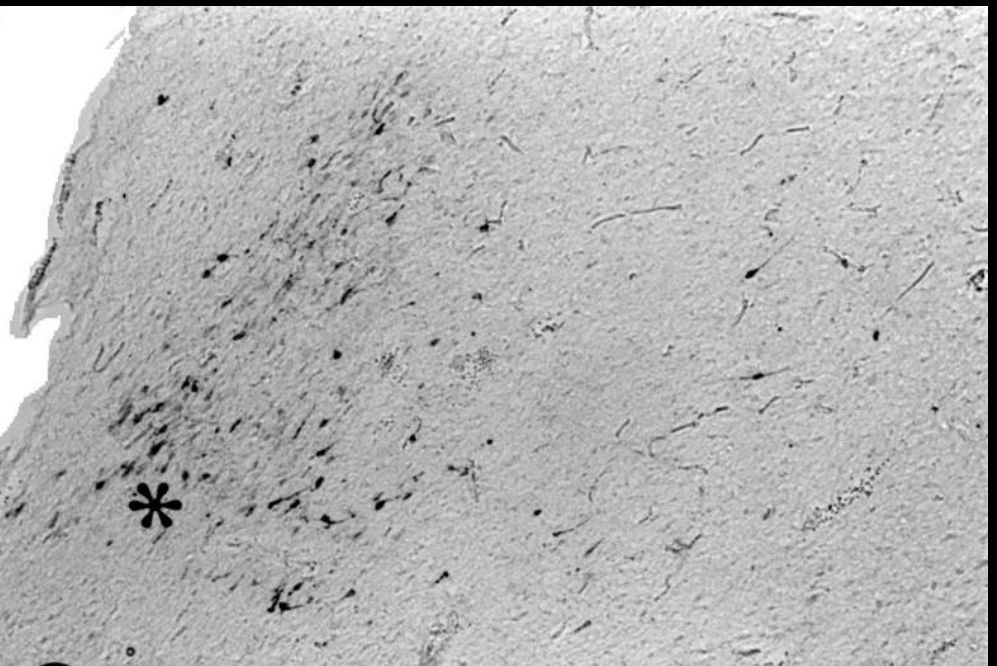
- Controle SCN

Goncharuk et al., J Comp Neurol, 2002



Humane hypothalamus met vasopressine (VP) kleuring

- Controle SCN

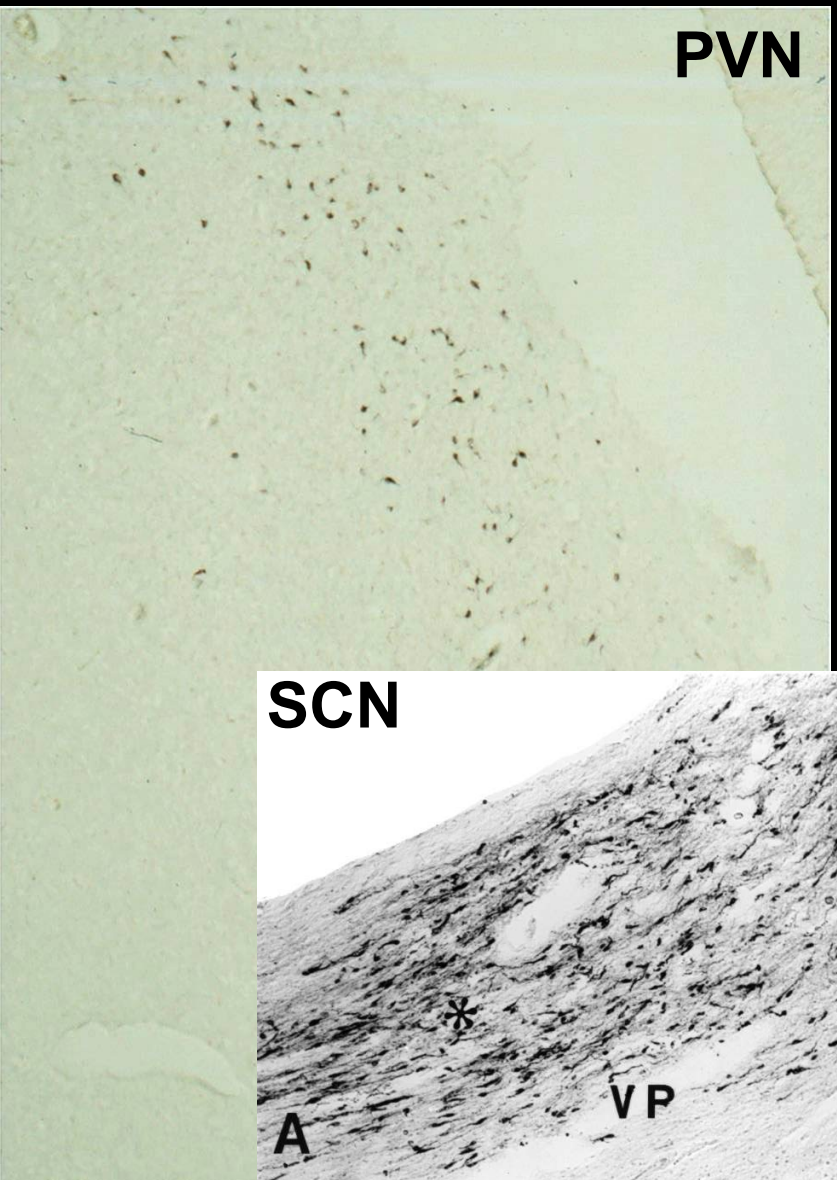


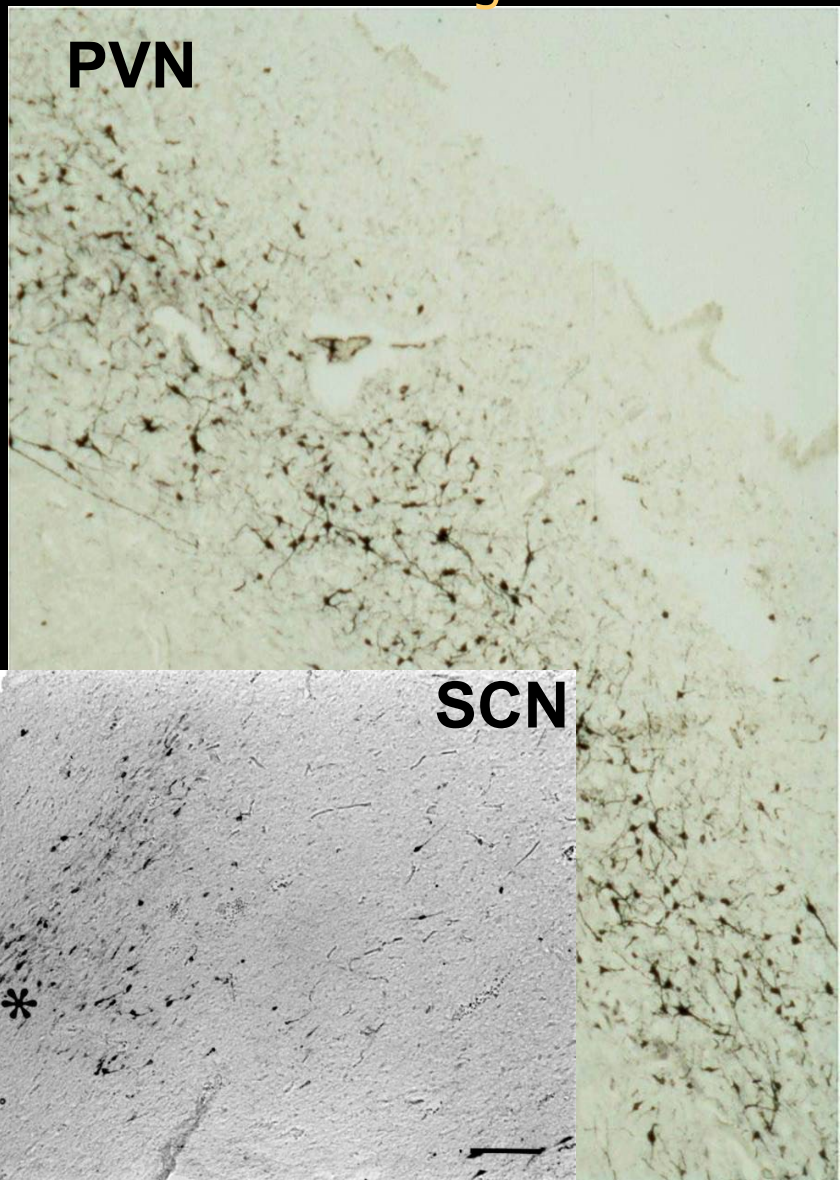
- Hoge bloeddruk SCN

Dezelfde humane hypothalamus gekleurd voor het stress hormoon (CRH)

Controle

Hoge bloeddruk





Autonoom zenuwstelsel of HPA – as?

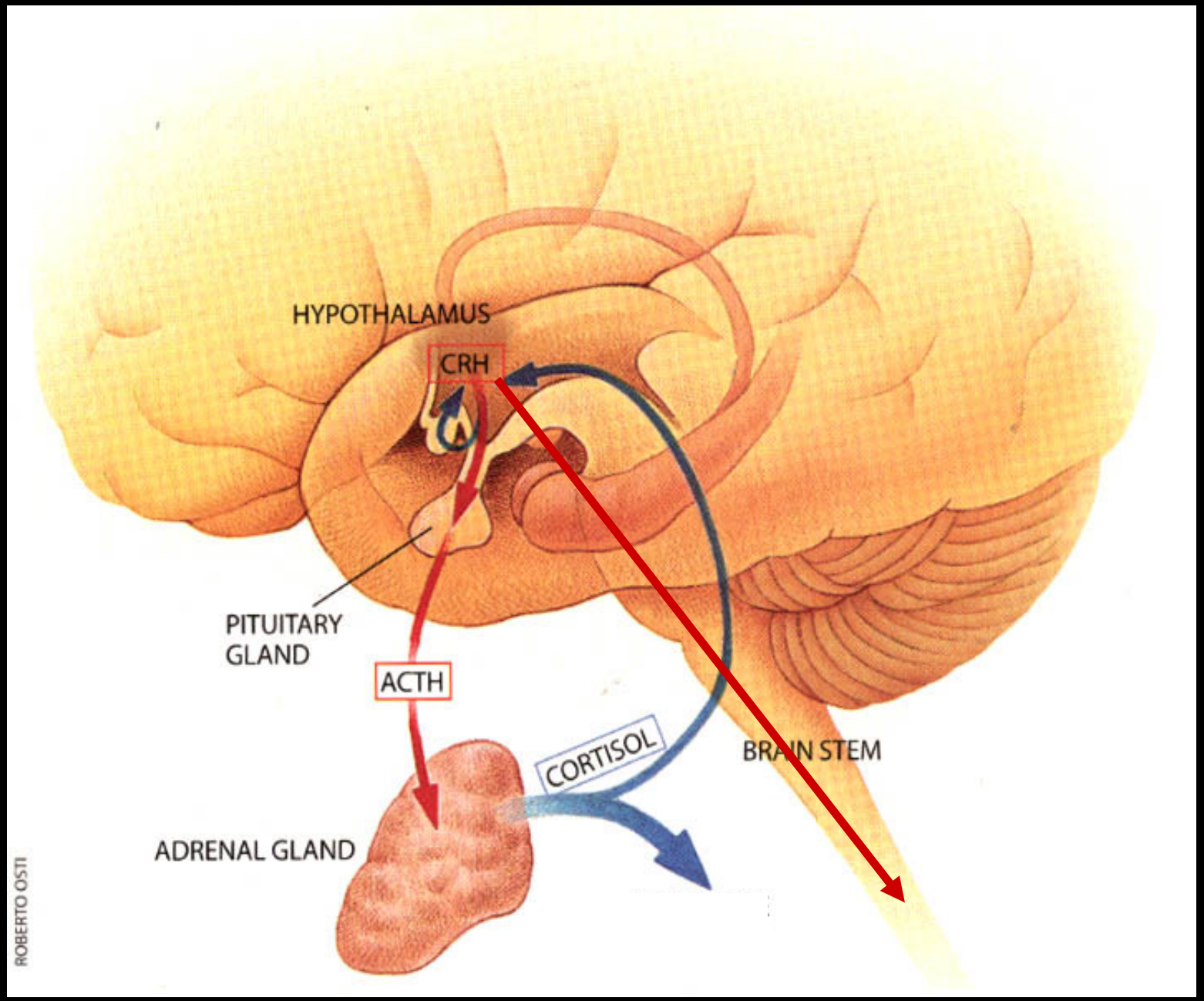
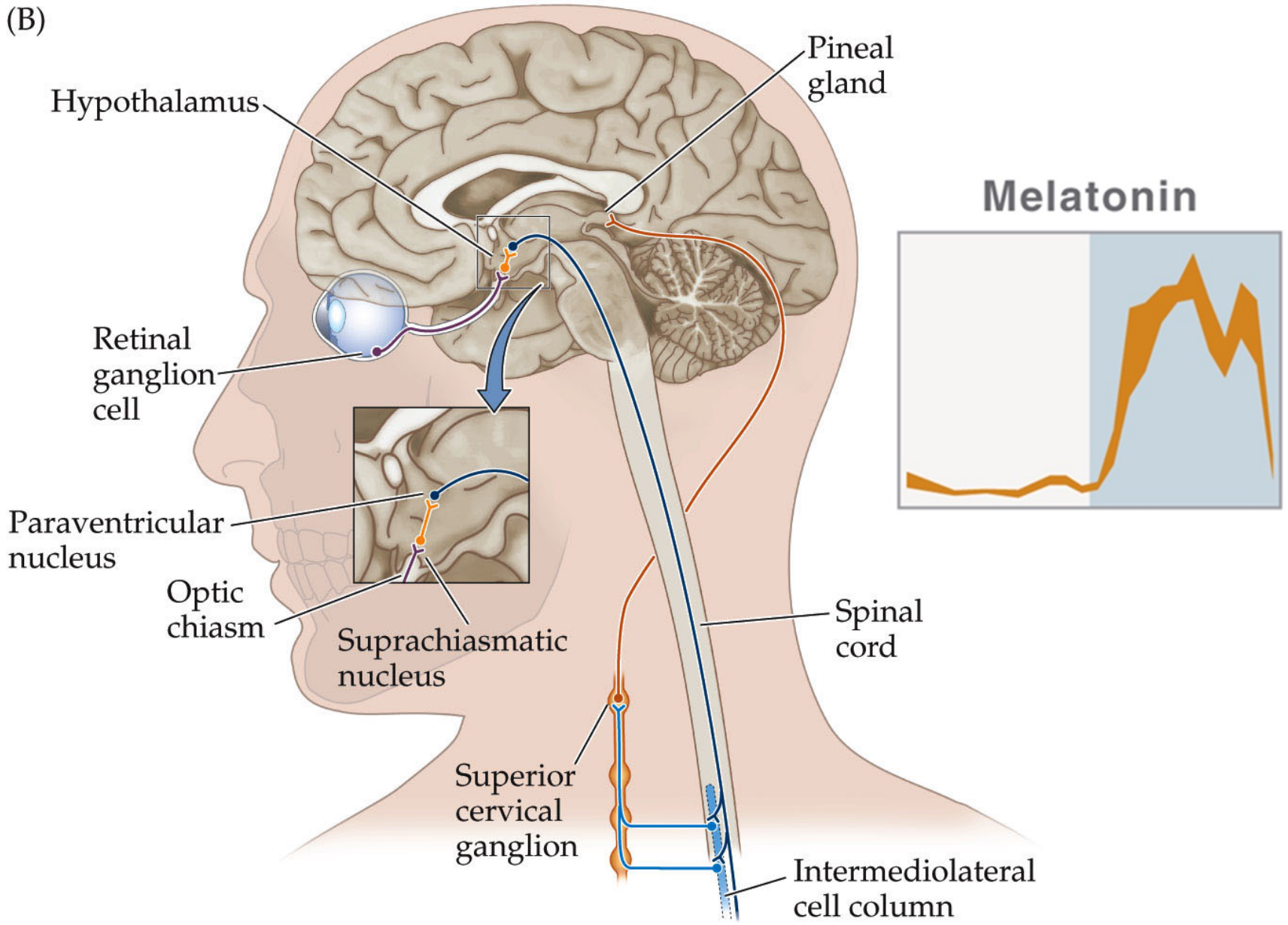


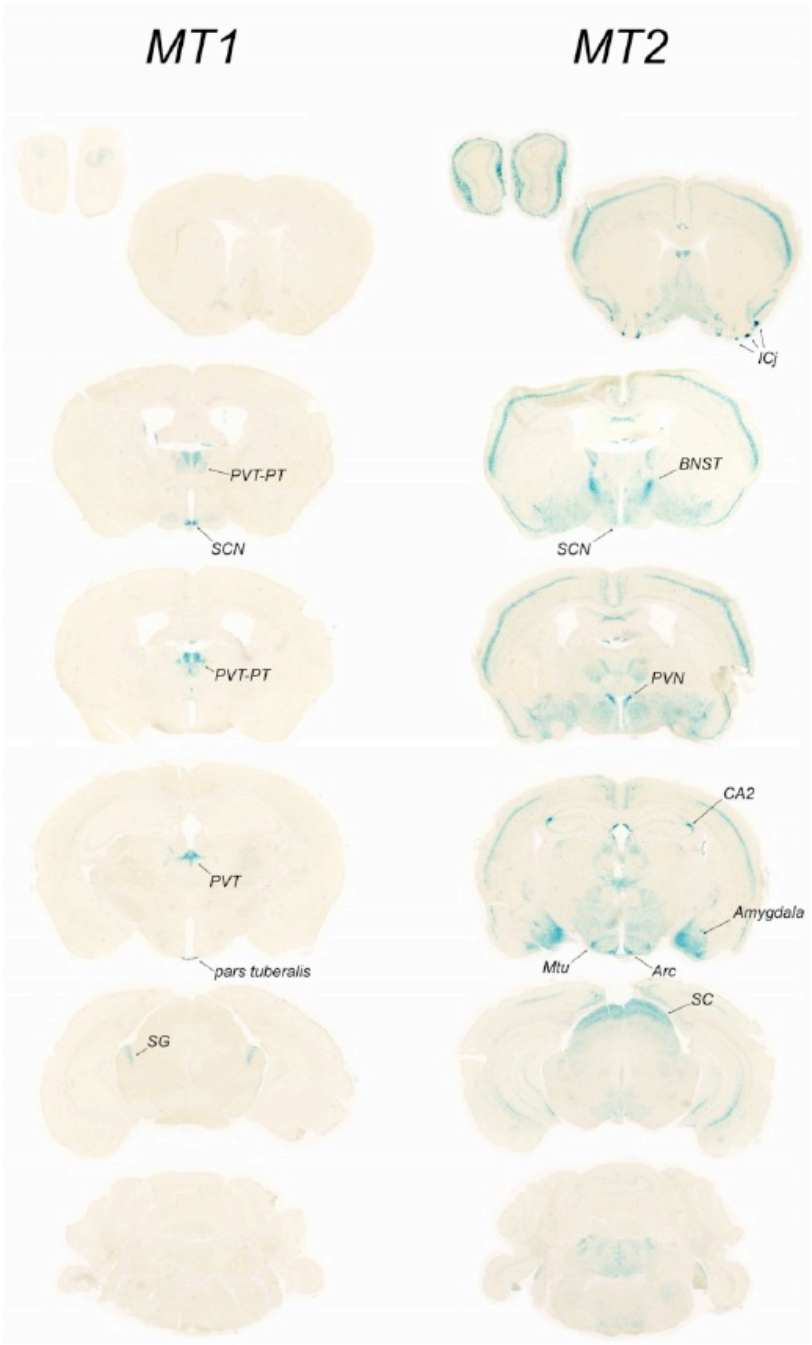
Figure 28.5 Photoreceptors responsible for signaling circadian light changes (Part 2)



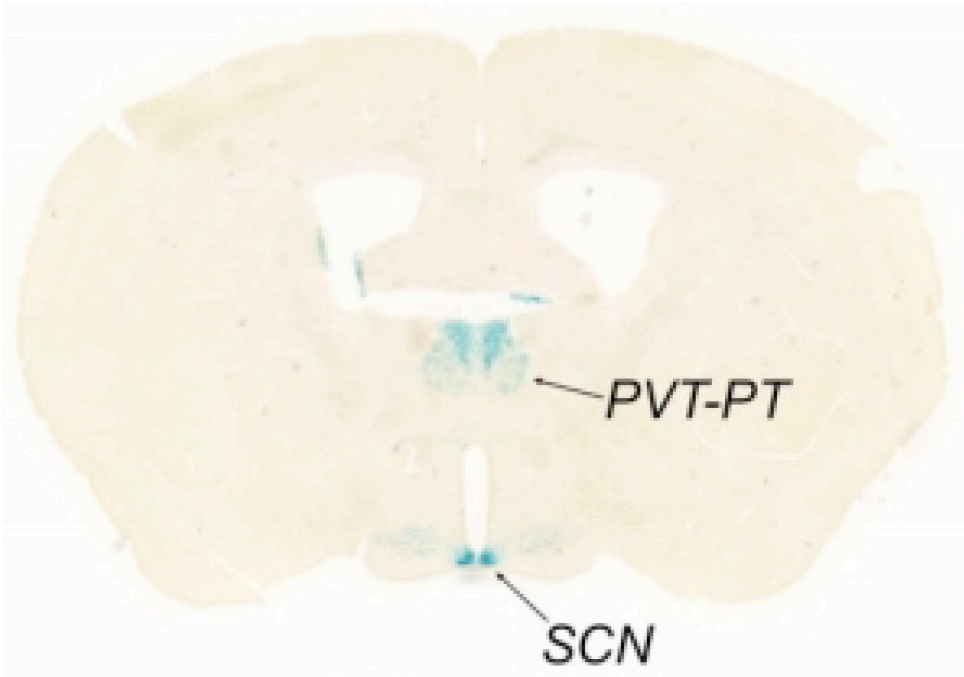
NEUROSCIENCE, *Fourth Edition*, Figure 28.5 (Part 2)

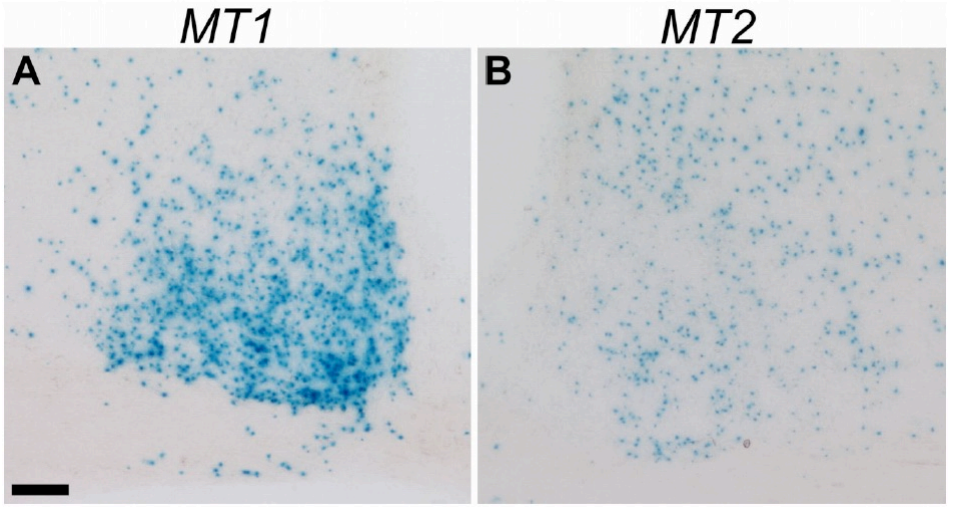
© 2008 Sinauer Associates, Inc.

Brain distribution of melatonin receptors



Suprachiasmatic nucleus (SCN)





Plasma melatonin concentrations in hypertensive patients with the dipping and non-dipping blood pressure profile

M. Zeman[a,*], K. Dulková[b], V. Bada[b], I. Herichová[a]

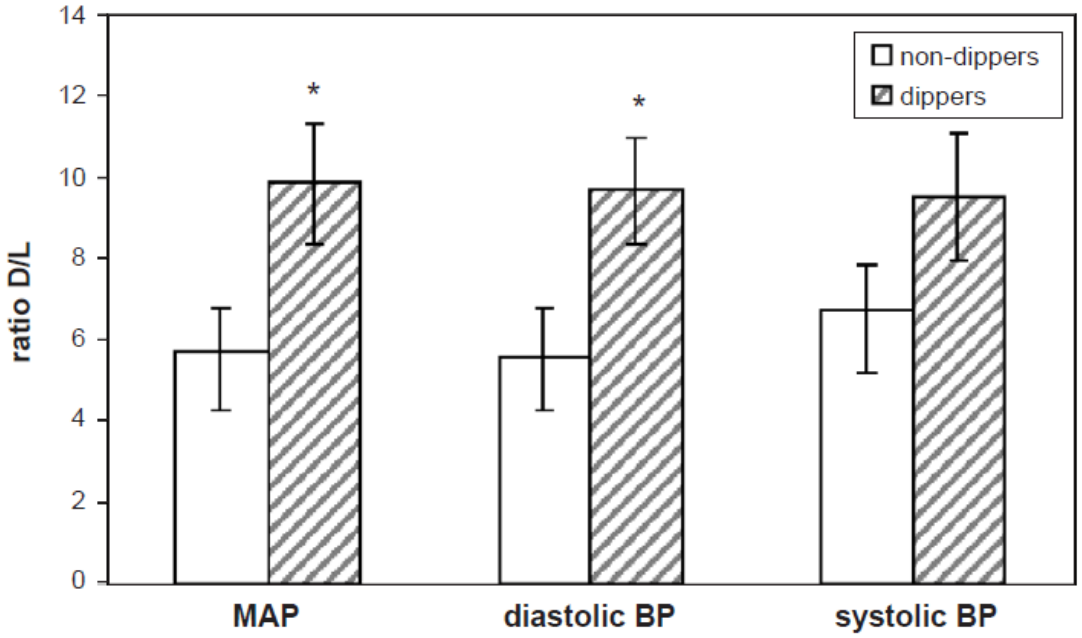


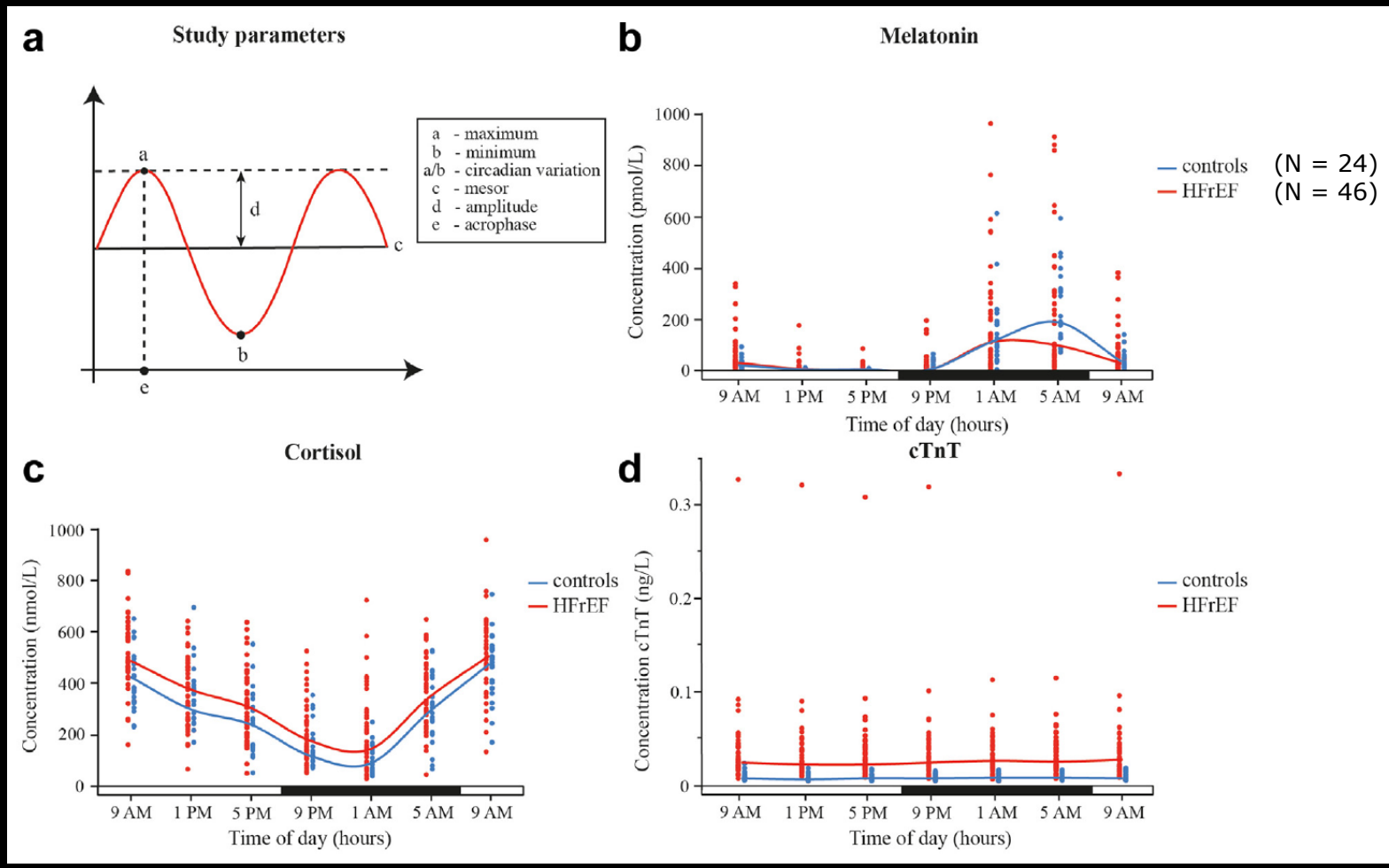
Fig. 2. Ratio of night-time and day-time melatonin levels (D/L) in plasma of patients assorted into groups of non-dippers (white columns) or dippers (dashed columns) according to the diurnal index (DI) counted on the basis of mean arterial blood pressure (MAP), diastolic blood pressure (diastolic BP) or systolic blood pressure (systolic BP). For details see Fig. 1 legend; asterisk indicates significant differences between dipping and non-dipping group * $P < 0.05$.

Zeman et al., 2005, Life Sci

The circadian clock remains intact, but with dampened hormonal output in heart failure

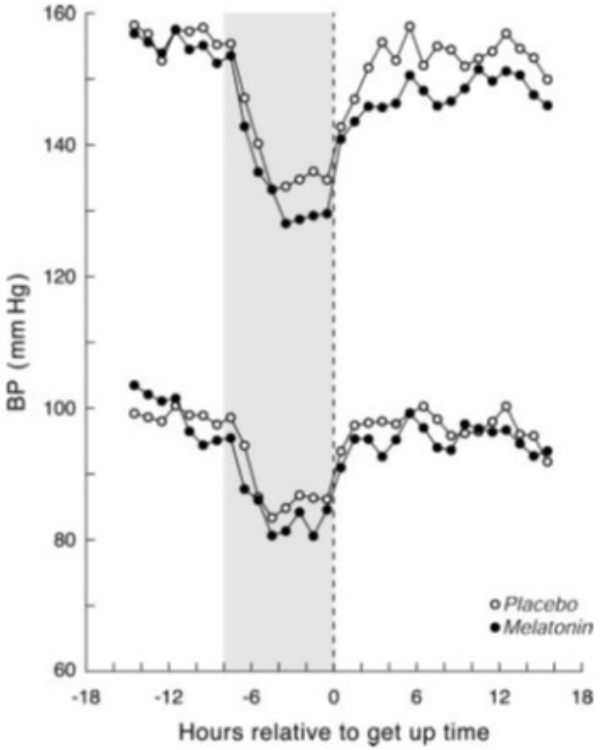
eBioMedicine
2023;91: 104556

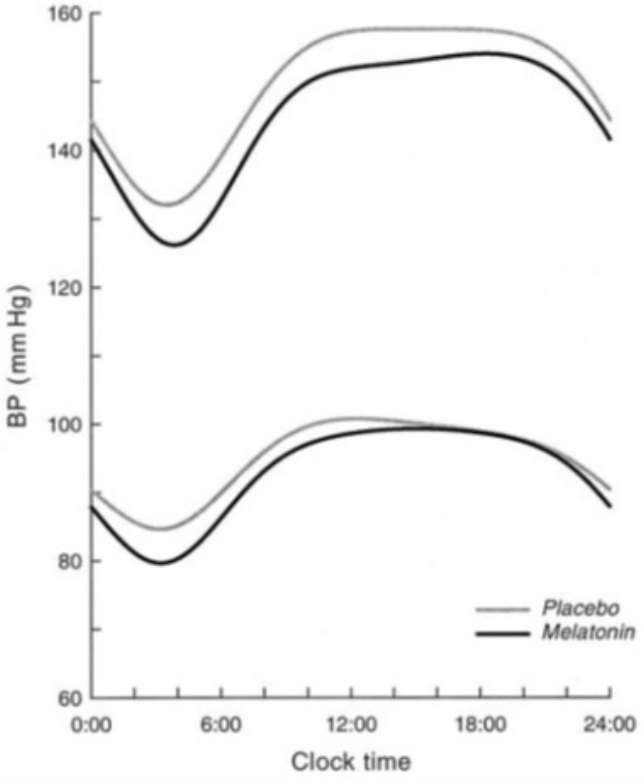
Sandra Crnko,[a,b,p] Markella I. Printezi,[a,p] Peter-Paul M. Zwetsloot,[a] Laurynas Leiteris,[b] Andrew I. Lumley,[c] Lu Zhang,[c] Isabelle Ernens,[c] Tijn P. J. Jansen,[d] Lilian Homsma,[e] Dries Feyen,[f] Martijn van Faassen,[g] Bastiaan C. du Pré,[h] Carlo A. J. M. Gaillard,[i] Hans Kemperman,[j] Marish I. F. J. Oerlemans,[a] Pieter A. F. M. Doevendans,[a,k,l] Anne M. May,[m] Nicolaas P. A. Zuithoff,[n] Joost P. G. Sluijter,[a,b,o] Yvan Devaux,[c,q] and Linda W. van Laake[a,b,q,*]



Daily Nighttime Melatonin Reduces Blood Pressure in Male Patients With Essential Hypertension

Frank A.J.L. Scheer, Gert A. Van Montfrans, Eus J.W. van Someren, Gideon Mairuhu, Ruud M. Buijs





3. Hourly means of ambulatory BP after repeated mela-

Scheer et al., Hypertension, 2004

De Suprachiasmatische Nucleus (SCN)





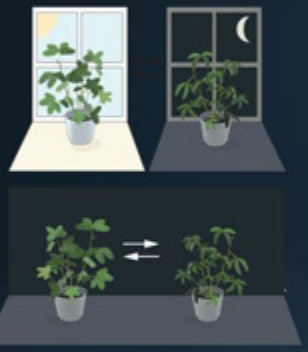
The Nobel Prize in Physiology or Medicine 2017



What makes us tick?

The 2017 Nobel Prize in Physiology or Medicine has been awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young **for their discoveries of molecular mechanisms controlling the circadian rhythm.**

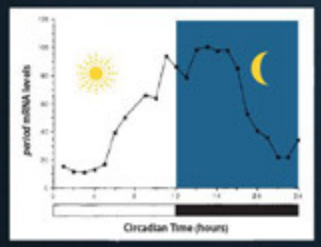
Life on Earth is adapted to the rotation of our planet. Living organisms prepare their physiology for the fluctuations between night and day. These daily rhythms are known as "circadian", from the Latin *circadien*, meaning "around a day". The circadian rhythm is regulated by an inner biological clock in our cells. This year's Nobel laureates were able to peek inside our biological clock and elucidate its inner workings.





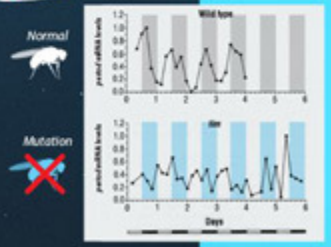
An internal biological clock

In the 18th century, the astronomer Jean Jacques d'Ortous de Mairan studied mimosa plants, whose leaves open during daytime and close at dusk. When he placed the plant in constant darkness, the leaves continued to follow their normal daily oscillation independent of daily light. Plants seemed to have an inner biological clock.



The *period* gene

The Nobel Laureates isolated a gene called *period*, which is required for the circadian rhythm in fruit flies. The gene encodes the PER protein. Jeffrey Hall and Michael Rosbash showed that the *period* gene activity (mRNA levels) followed a 24-hour rhythm.

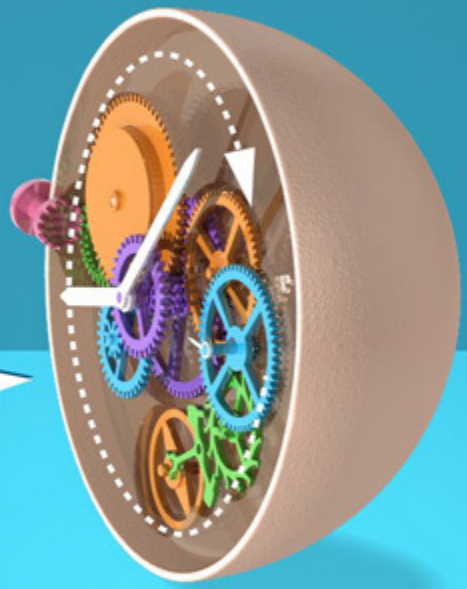


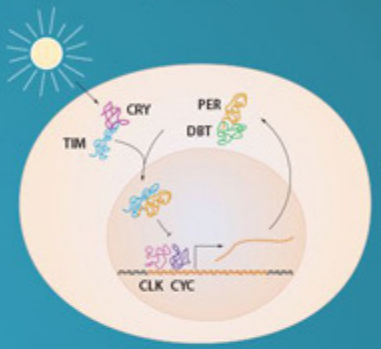
The *timeless* gene

Michael Young identified a second gene, called *timeless*, encoding the TIM protein. He showed that TIM is essential for a normal circadian rhythm and that TIM is required for the oscillation of *period* mRNA levels.

Cogs and wheels of the biological clock

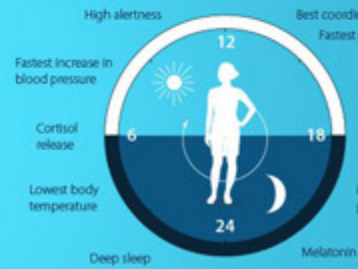
The paradigm-shifting discoveries by the laureates established the key mechanistic principles for the biological clock in fruit flies. The PER protein prevents its own synthesis by blocking the *period* gene and thereby regulates its own level in a continuous, cyclic rhythm. To block the *period* gene, PER needs to reach the cell nucleus. TIM binds to PER, enabling entry into the cell nucleus where the two proteins inhibit *period*. Additional proteins are required to stabilize PER (DBT), activate the *period* gene (CLK and CYC), and to calibrate the clock by light (CRY).





The circadian clock in humans

Biological clocks function by the same principles in other multicellular organisms, including humans. A large proportion of our genes are regulated by the biological clock and, consequently, a carefully calibrated circadian rhythm anticipates and adapts our physiology to the different phases of the day. A precisely calibrated clock regulates many processes including sleep, feeding, hormone levels, blood pressure and body temperature. Since the seminal discoveries by the three laureates, circadian biology has developed into a vast and highly dynamic research field, with implications for our health and wellbeing.



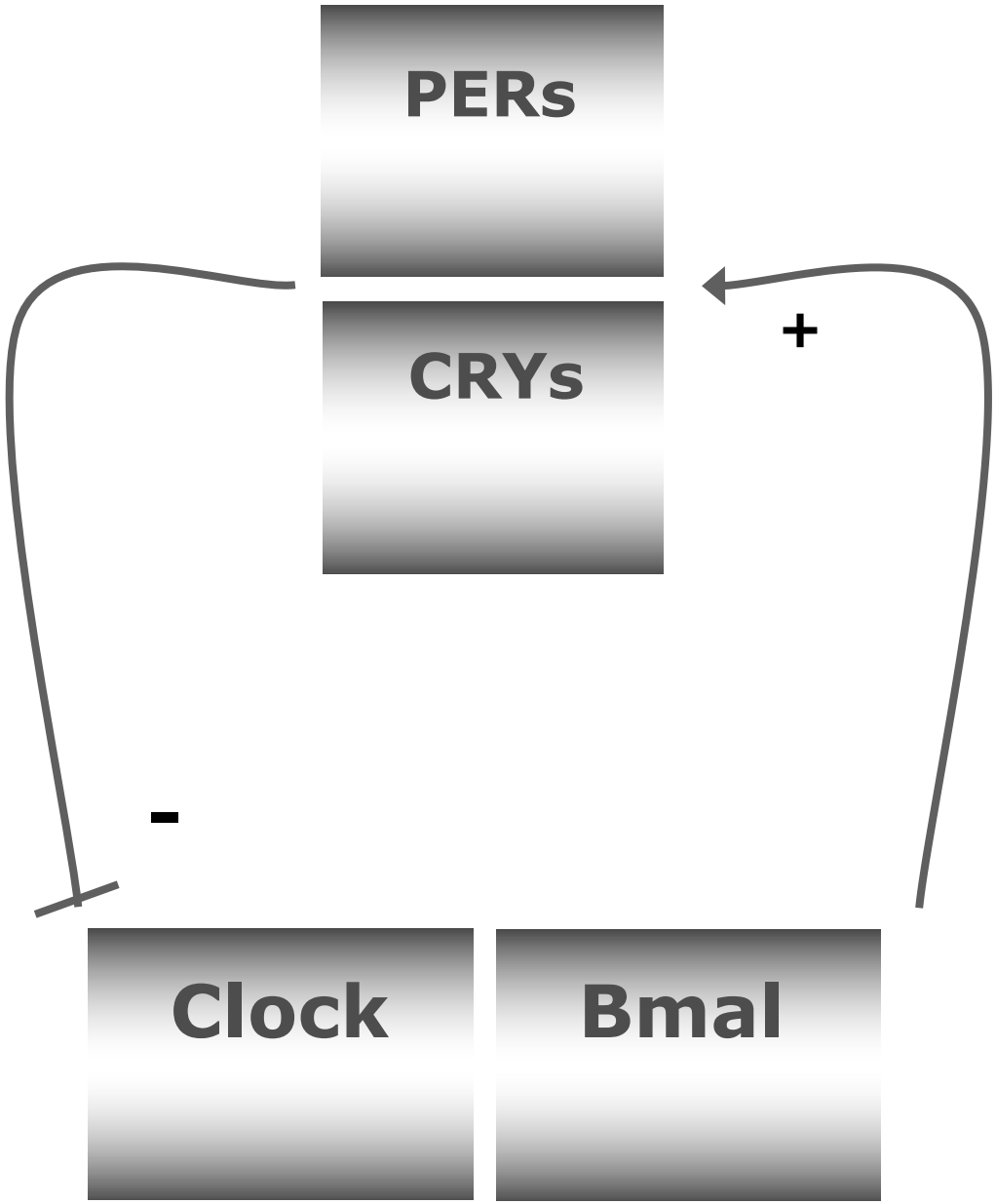
Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

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Text and scientific advise: The Nobel Committee for Physiology or Medicine
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De moleculaire klok







Dus de endogene (of circadiane) meester klok bevindt zich in de hypothalamus, maar door onze Nobelprijs winnaars weten we nu dat er……



. . overal in ons lichaam klokken zijn!

Schibler et al., 2005

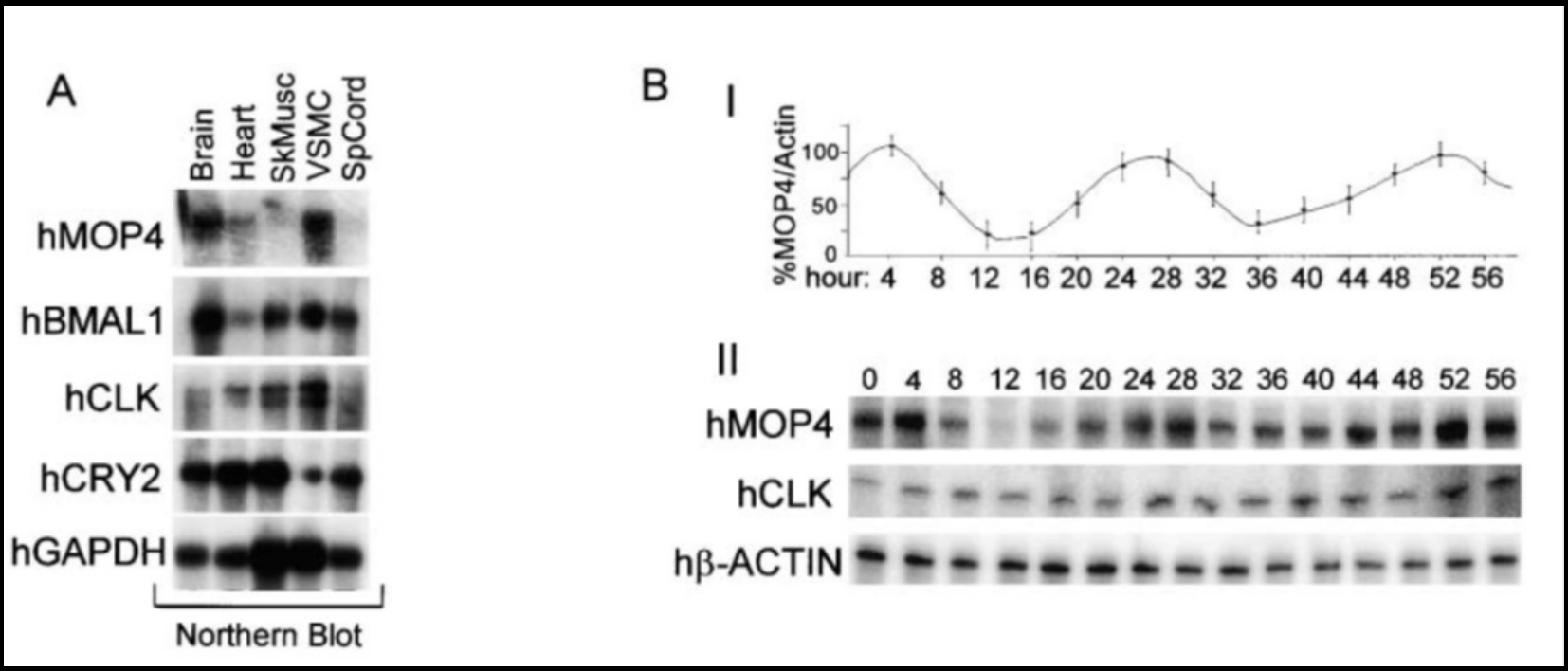
First evidence of a circadian clock in mouse aorta in 2001

Cell, Vol. 105, 877–889, June 29, 2001, Copyright ©2001 by Cell Press

Regulation of CLOCK and MOP4 by Nuclear Hormone Receptors in the Vasculature: A Humoral Mechanism to Reset a Peripheral Clock

Peter McNamara,[1] Sang-beom Seo,[2] Radu Daniel Rudic,[1] Amita Sehgal,[3] Debabrata Chakravarti,[2] and Garret A. FitzGerald[1,2,4]

quently, complexes of mPER and mCRY proteins enter the nucleus, where they shut off CLOCK:BMAL1-mediated transcription. At the same time, mPER2 up-regulates levels of *Bmal1* RNA through an as yet unchar-

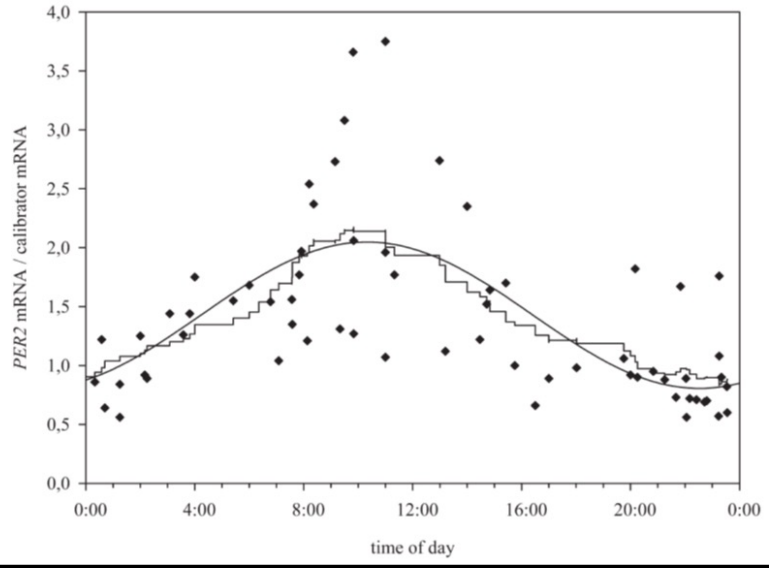


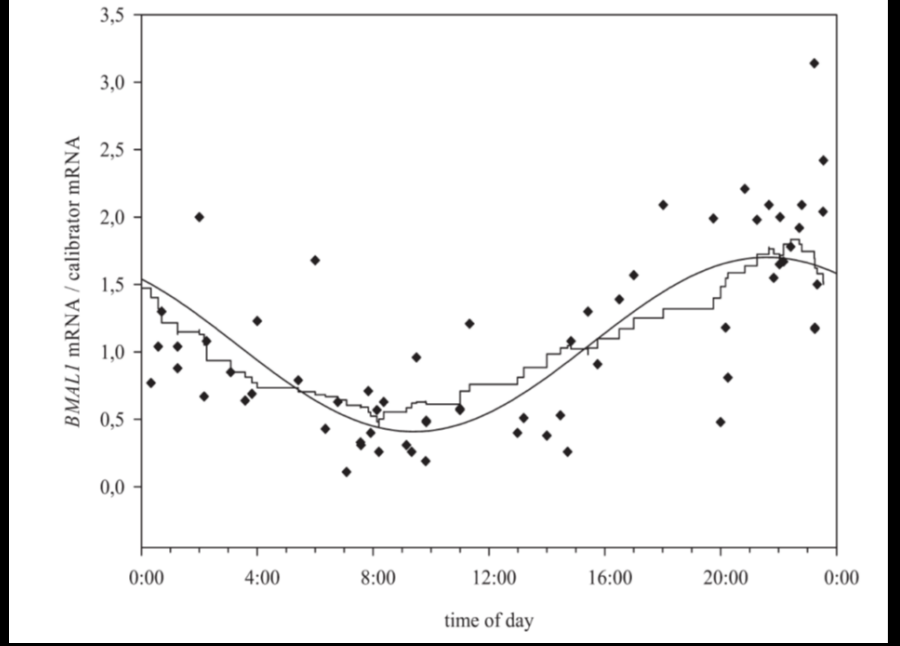
Chronobiology International, 26(4): 621–636, (2009)
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ISSN 0742-0528 print/1525-6073 online
DOI: 10.1080/07420520902924939

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CLOCK GENES DISPLAY RHYTHMIC EXPRESSION IN HUMAN HEARTS

Valentin Leibetseder,[1,2] Susanne Humpeler,[1,2] Martin Svoboda,[1] Diethart Schmid,[1] Theresia Thalhammer,[1] Andreas Zuckermann,[3] Wolfgang Marktl,[1,2] and Cem Ekmekcioglu[1,2]





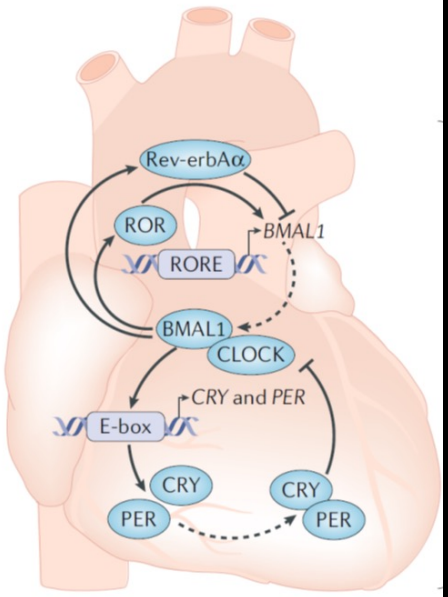


Fig. 1 | **Overview of the core molecular clock**

Table 1 | **Clock mechanism disturbance: insights from animal studies**

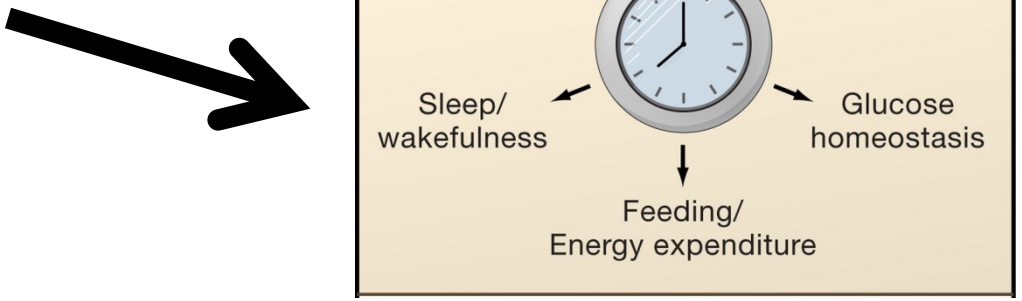
Method of clock disturbance	Effects	Refs
Bmal1-knockout mice	Loss of physiological rhythms in heart rate and blood pressure	48
Per2-knockout mice	Endothelial dysfunction	47
Csnk1e-mutant mice (rodents have a genetic (circadian) rhythm of 22 h living in 24-h environment)	Cardiomyopathy, cardiac and renal fibrosis, impaired cardiac contractility and renal disease	60
Cardiomyocyte-specific *Clock*-mutant mice (dominant negative overexpression of CLOCK specifically in cardiomyocytes)	Disruption of physiological variation in 10% of the transcriptome; bradycardia, disruption of normal heart rate and rhythm, and mitochondrial dysfunction	54
Bmal1-knockout mice and *Clock*-mutant mice	Vascular injury, endothelial dysfunction and pathological vascular remodelling	171
$Dbp^{-/-}Hlf^{-/-}Tef^{-/-}$ mice (knockout of three major transcription factors leading to clock dysfunction)	Cardiomyopathy, cardiac hypertrophy, left ventricular dysfunction and low aldosterone levels	172
Cardiomyocyte-specific *Clock*-mutant mice	Decreased tolerance to ischaemia–reperfusion injury	103
Cardiomyocyte-specific *Clock*-mutant plus cardiomyocyte-specific *Bmal1*-knockout mice	Drug-induced hypertrophic cardiomyopathy	173
Klf15-knockout mice (transcription of *Klf15* is regulated by the molecular clock)	Loss of physiological rhythm in ventricular repolarization duration and increased susceptibility to ventricular arrhythmias	63
Bmal1-knockout mice	Dilated cardiomyopathy (thinning of the myocardial walls, dilatation of the left ventricle and decreased systolic function)	62
Mice with inducible, cardiomyocyte-specific disruption of *Bmal1*	Bradycardia, prolonged QRS duration and ventricular arrhythmias	174
Cardiomyocyte-specific *Clock*-mutant mice	Disruption of physiological variation in 8% of the proteome	116
Cardiomyocyte-specific *Bmal1*-knockout mice	Disruption of physiological variation in 10% of the transcriptome; cardiac metabolism changes, dilated cardiomyopathy and premature death	64
Vascular-smooth-muscle-cell-specific *Bmal1*-knockout mice	Diminished 24-h rhythm in blood pressure and change in timing of blood pressure peak	175

CLOCK, circadian locomotor output cycles protein kaput.

Crnko et al., Nat Rev Cardiology, 2019

Het oude circadiane systeem

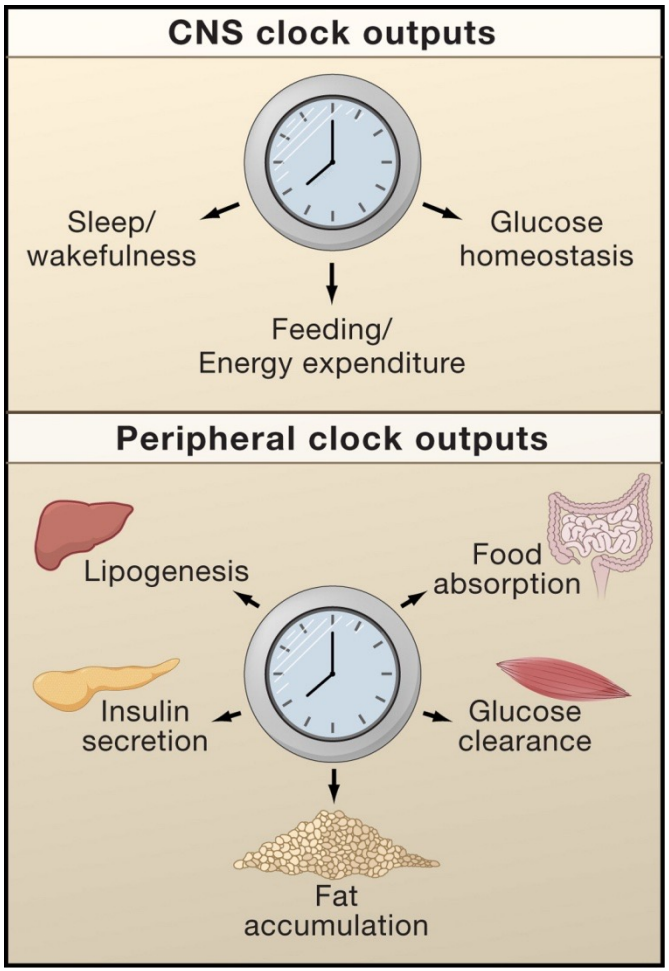




Green et al. Cell 2008

Het nieuwe circadiane systeem

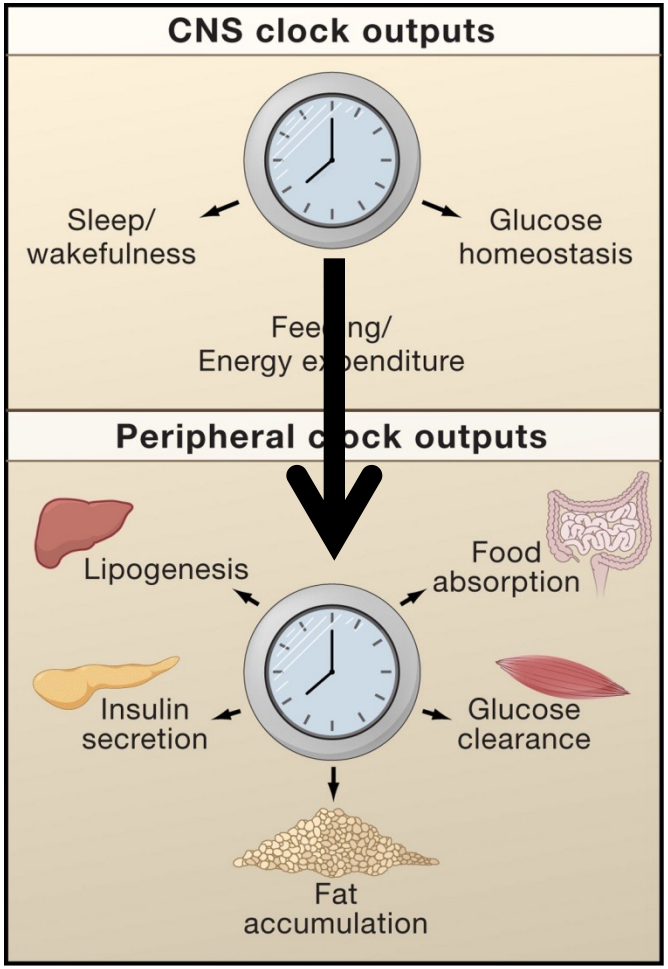




Green et al. Cell 2008

Het nieuwe circadiane systeem



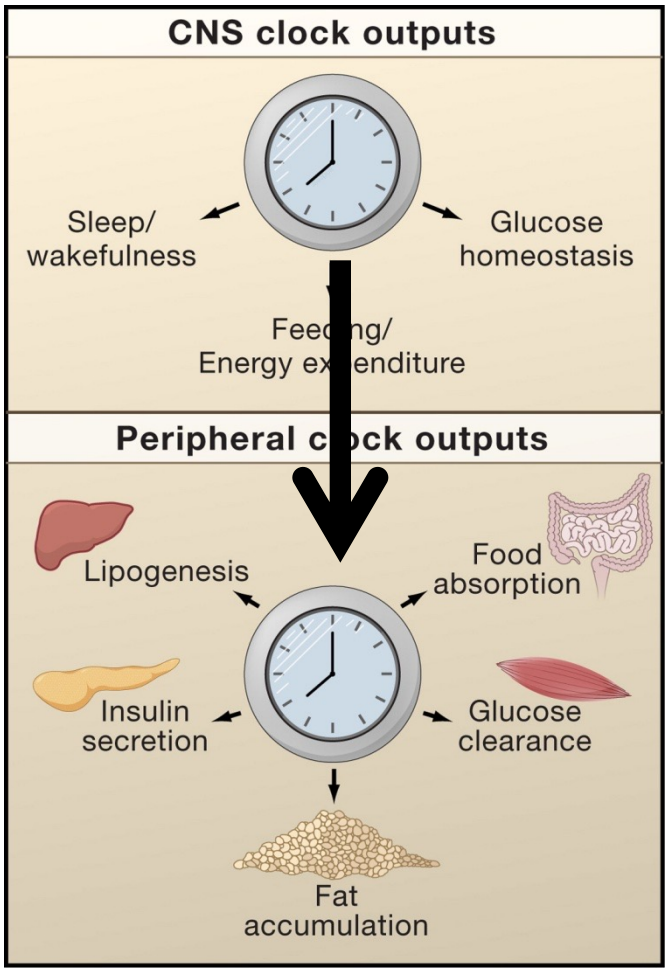


Green et al. Cell 2008

Het nieuwe circadiane systeem







Green et al. Cell 2008

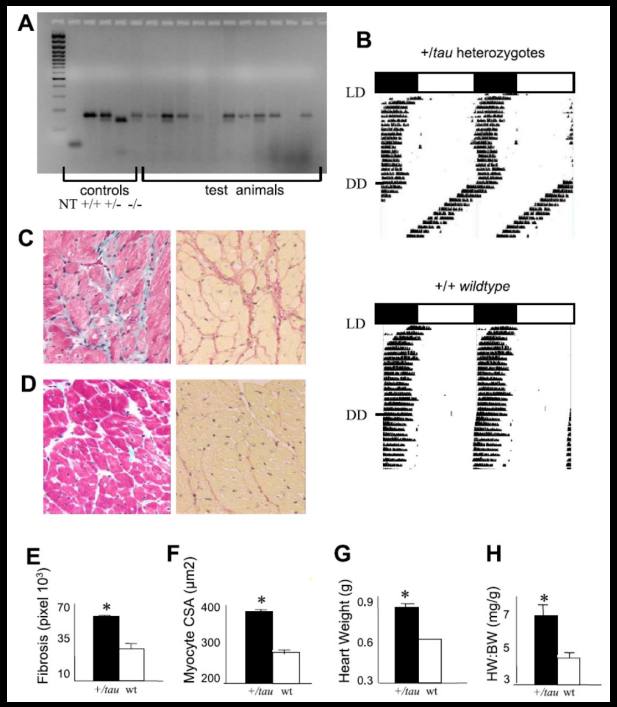
Desynchronization of external, central and peripheral clocks results in cardiovascular disease

Am J Physiol Regul Integr Comp Physiol 294: R1675–R1683, 2008.
First published February, 13, 2008; doi:10.1152/ajpregu.00829.2007.

Circadian rhythm disorganization produces profound cardiovascular and renal disease in hamsters

Tami A. Martino,[1,2,3] Gavin Y. Oudit,[1,2] Andrew M. Herzenberg,[1] Nazneen Tata,[1] Margaret M. Koletar,[3,4] Golam M. Kabir,[2] Denise D. Belsham,[1,3] Peter H. Backx,[2,3] Martin R. Ralph,[3,4] and Michael J. Sole[1,2,3]

[1]University Health Network, Toronto, Ontario; [2]Heart and Stroke/Richard Lewar Centre for Cardiovascular Excellence, [3]Departments of Physiology, Medicine, and Psychology, and [4]Centre for Biological Timing and Cognition, University of Toronto, Ontario, Canada



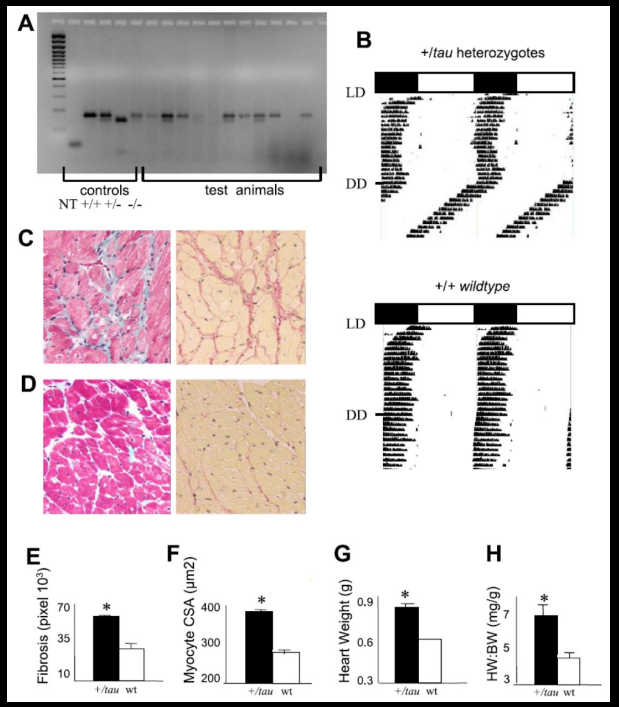
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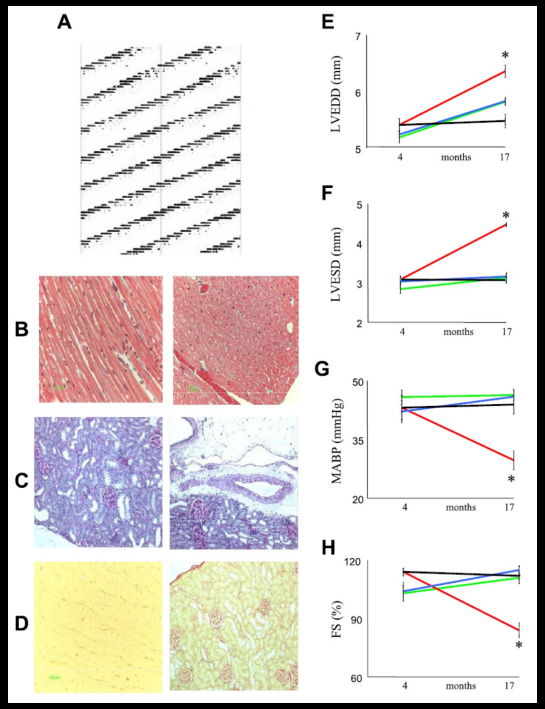
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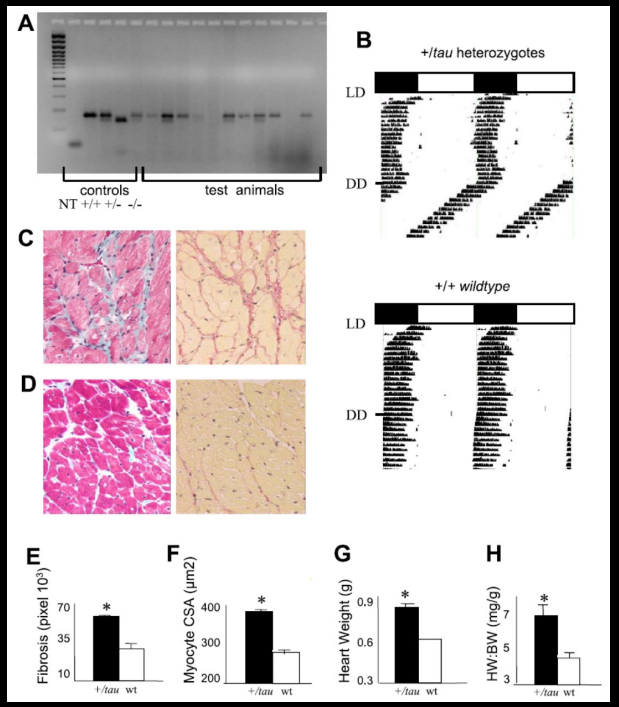
Desynchronization of external, central and peripheral clocks results in cardiovascular disease

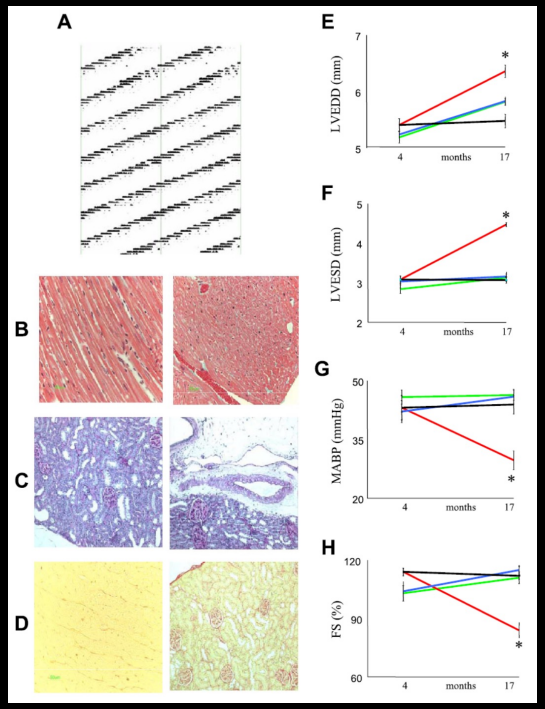
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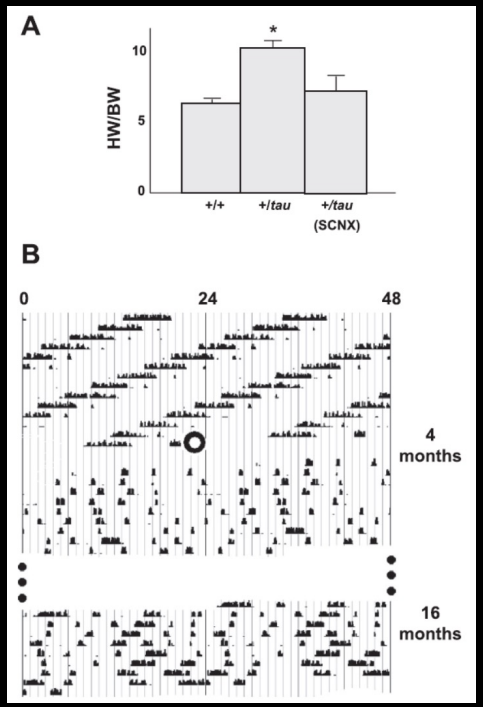
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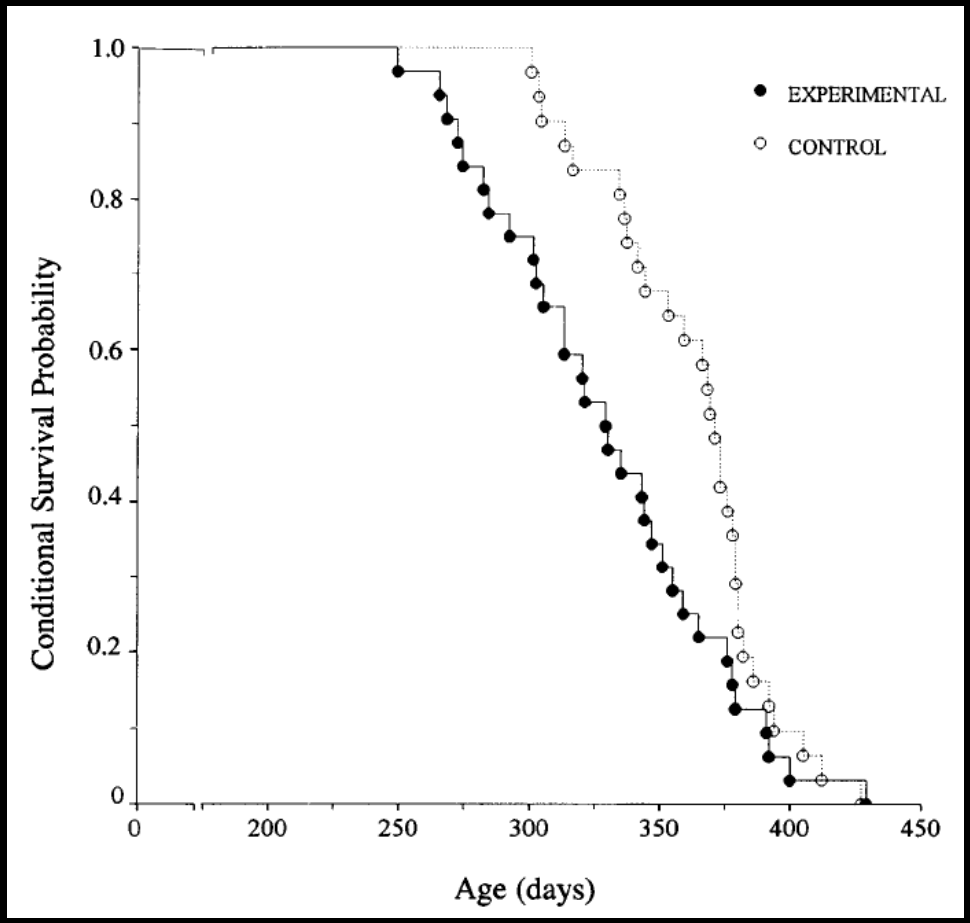






Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease

PLAMEN D. PENEV,[1,2] DANIEL E. KOLKER,[1], PHYLLIS C. ZEE,[1,2] AND FRED W. TUREK[1,2]
[1]*Center for Circadian Biology and Medicine, Department of Neurobiology and Physiology, Northwestern University, Evanston, Illinois 60208 and* [2]*Department of Neurology, Northwestern University Medical School, Chicago, Illinois 60211*



Penev et al., Am J Physiol, 1998

Verwarde klokken







In Nederland zijn er meer dan 1 miljoen mensen die regelmatig in ploegendiensten werken

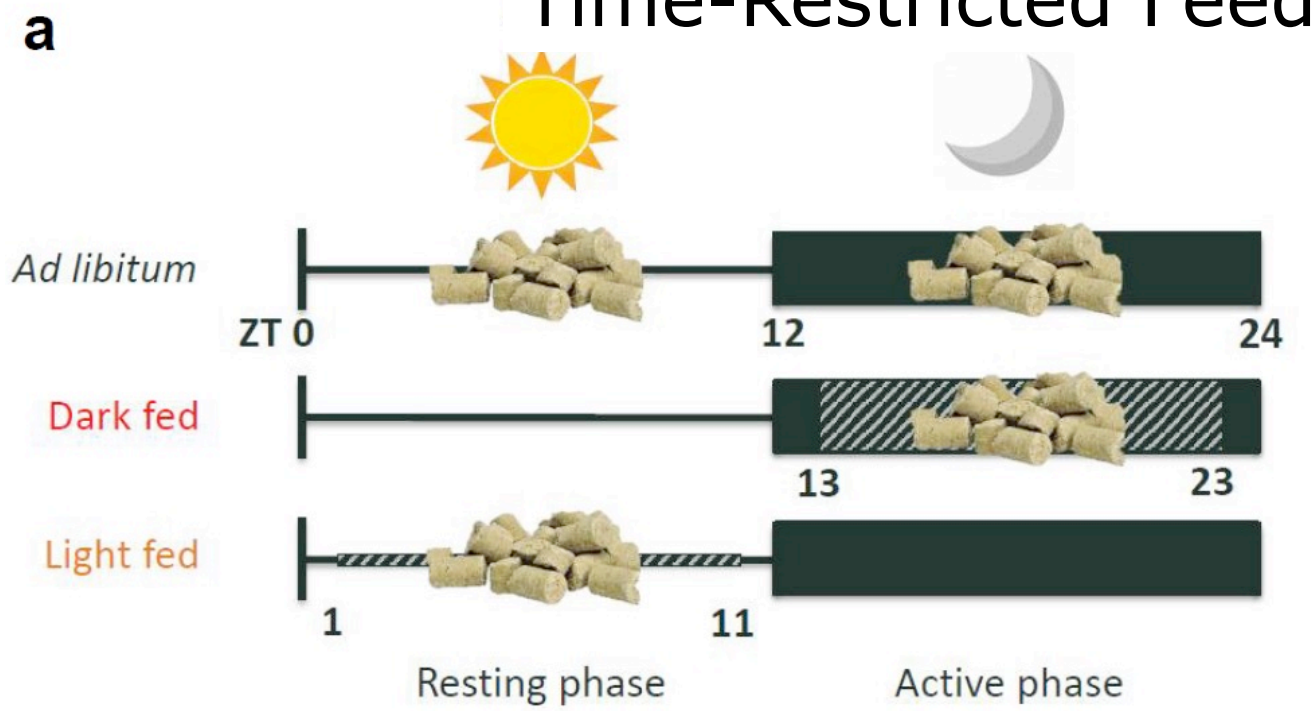
64% van de werkenden werkt regelmatig buiten kantoor uren
1 op 5 werkenden doet nacht diensten

40% van de ploegendienst werkers meldt gezondheidsproblemen binnen 2 – 3 jaar na de start van de ploegendienst

EEN DIERMODEL VOOR HET WERKEN IN PLOEGENDIENST



Time-Restricted Feeding = TRF

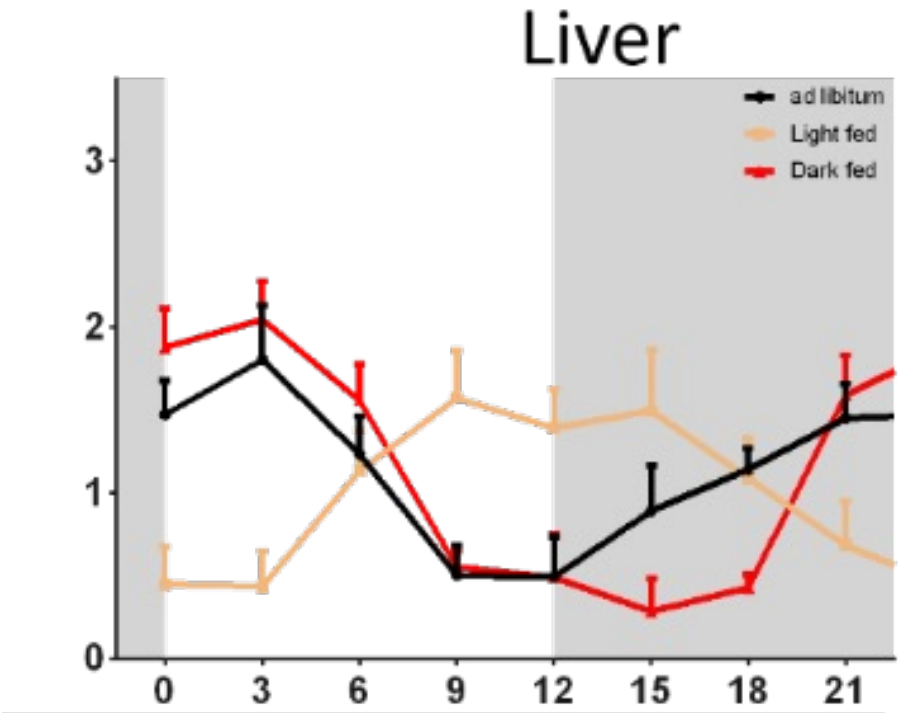




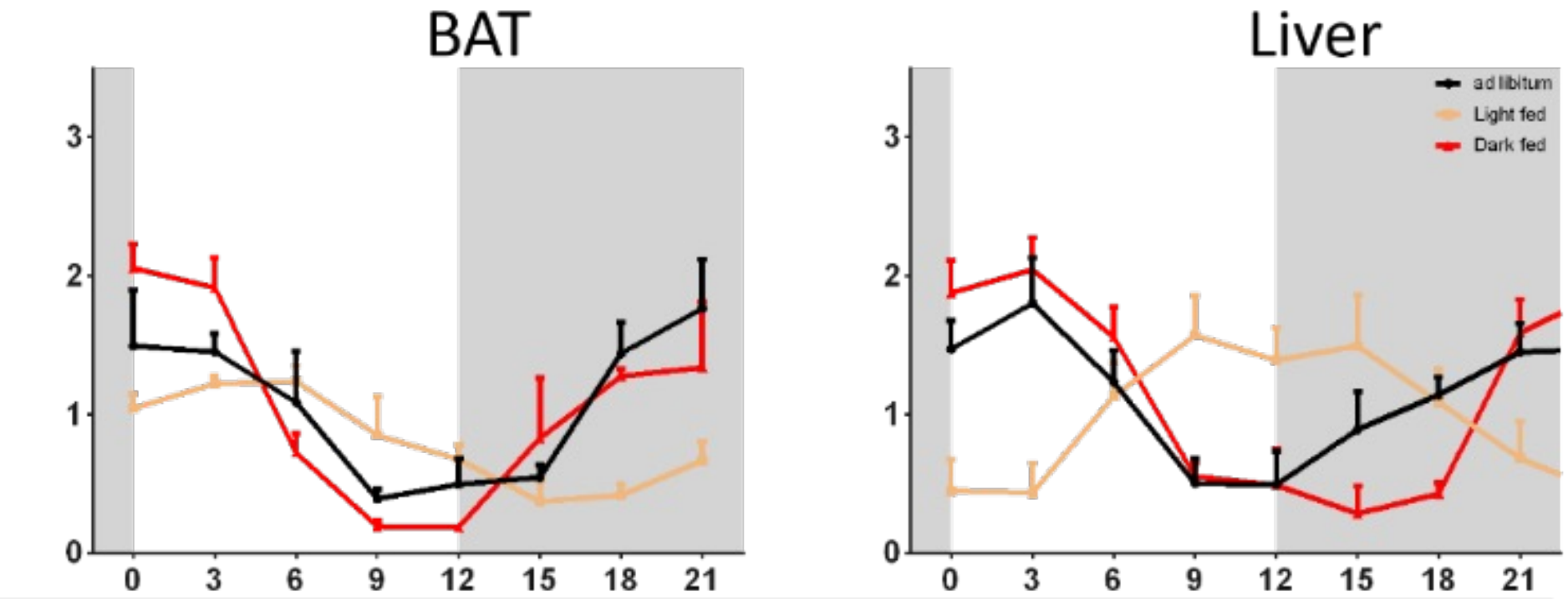
4 weeks



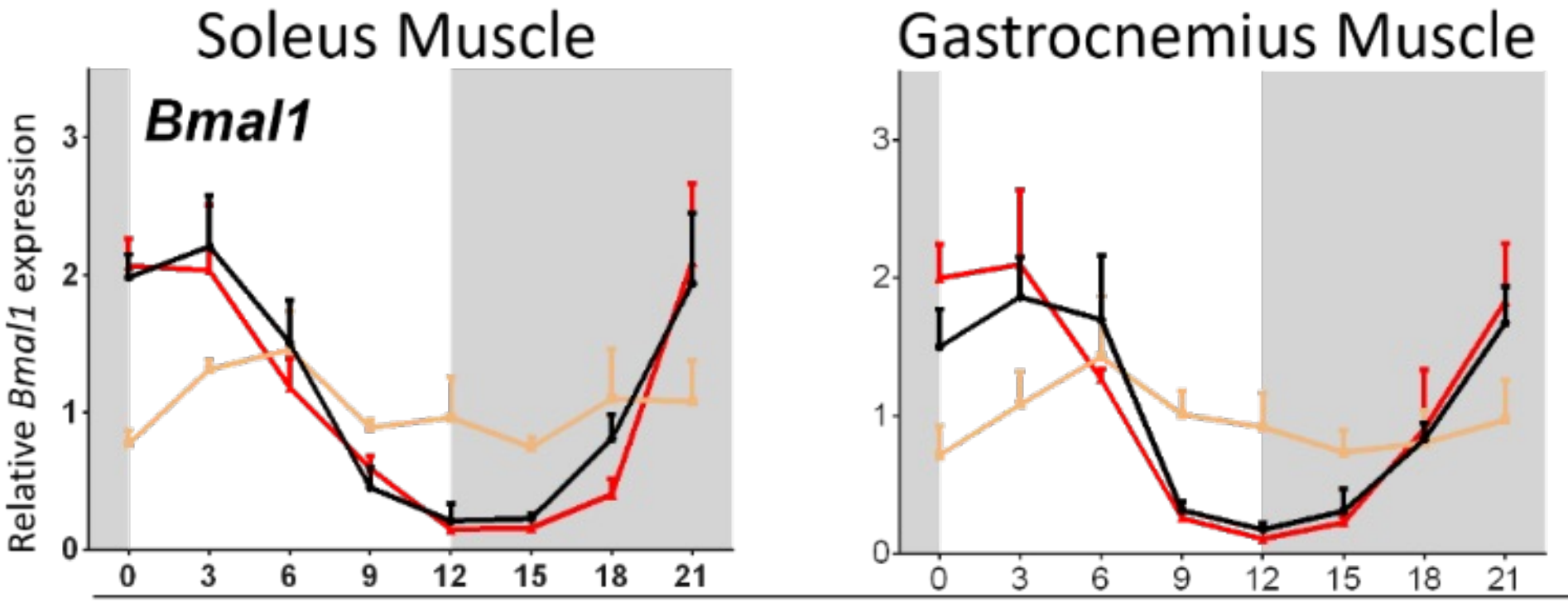
TRF effecten op perifere klokken



TRF effecten op perifere klokken



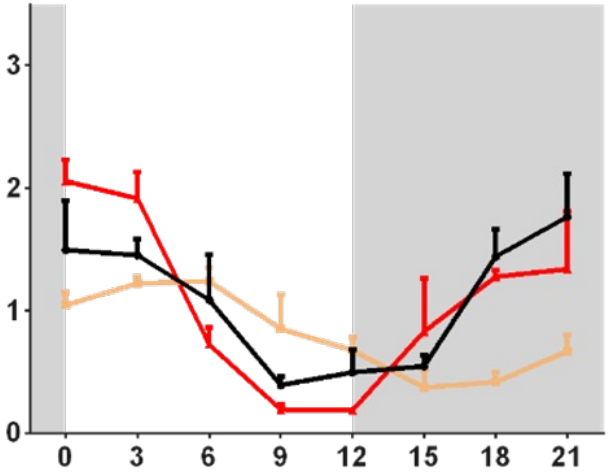
TRF effecten op perifere klokken



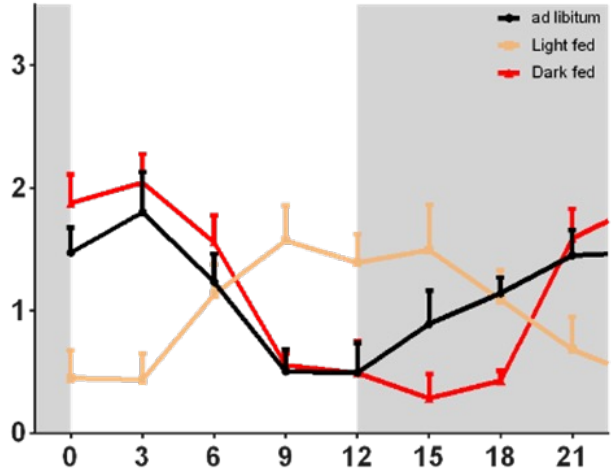
.....DUS DE VERSCHUIVING
VERSCHILT PER ORGAAN



BAT

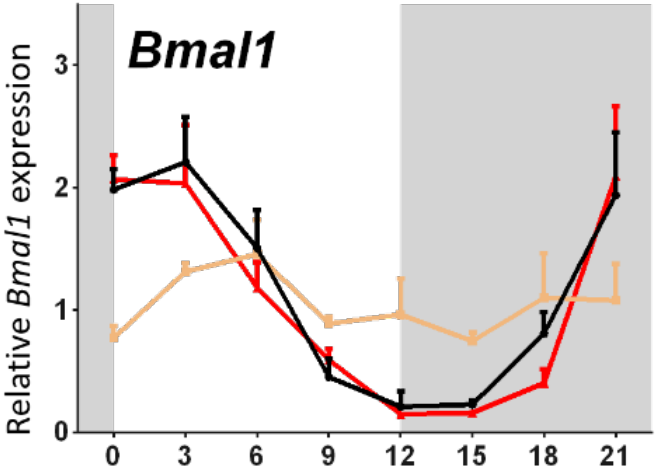


Liver

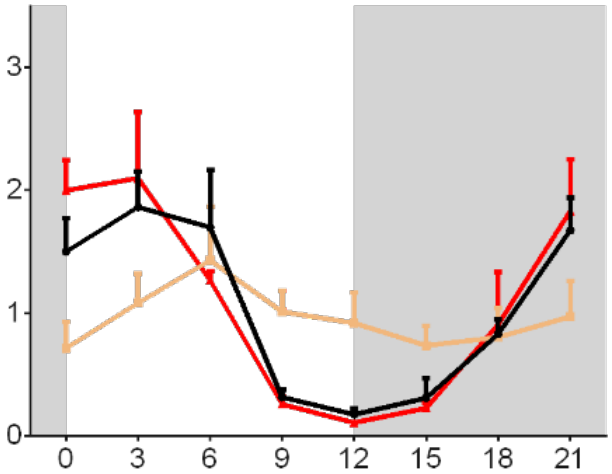




Soleus Muscle



Gastrocnemius Muscle



European Journal of Preventive Cardiology

ESC European Society of Cardiology

Full research paper

European Journal of Preventive Cardiology
2018, Vol. 25(12) 1293–1302
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SAGE

Shift work and risk of cardiovascular disease morbidity and mortality: A dose–response meta-analysis of cohort studies

Dongming Wang[1,2], Wenyu Ruan[3], Zhenlong Chen[2], Ying Peng[4] and Wenzhen Li[5]

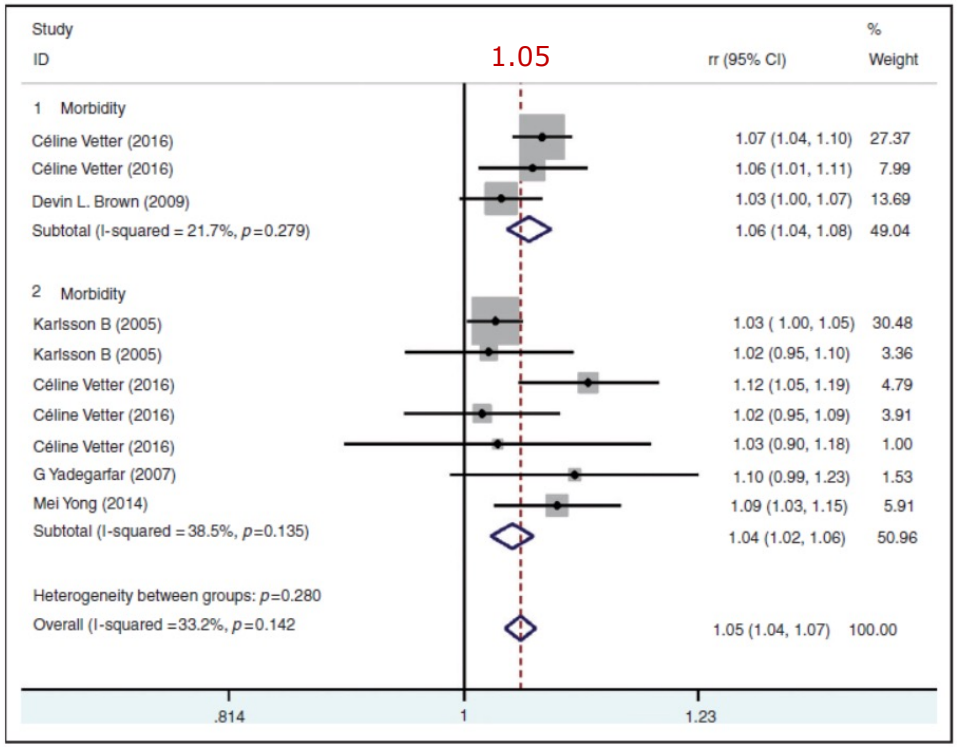


Figure 1. Forest plot of the summary relative risk of cardiovascular disease risk for an increase of 5 years of shift work.

European Journal of Preventive Cardiology
ESC European Society of Cardiology
Full research paper

Shift work and risk of cardiovascular disease morbidity and mortality: A dose–response meta-analysis of cohort studies

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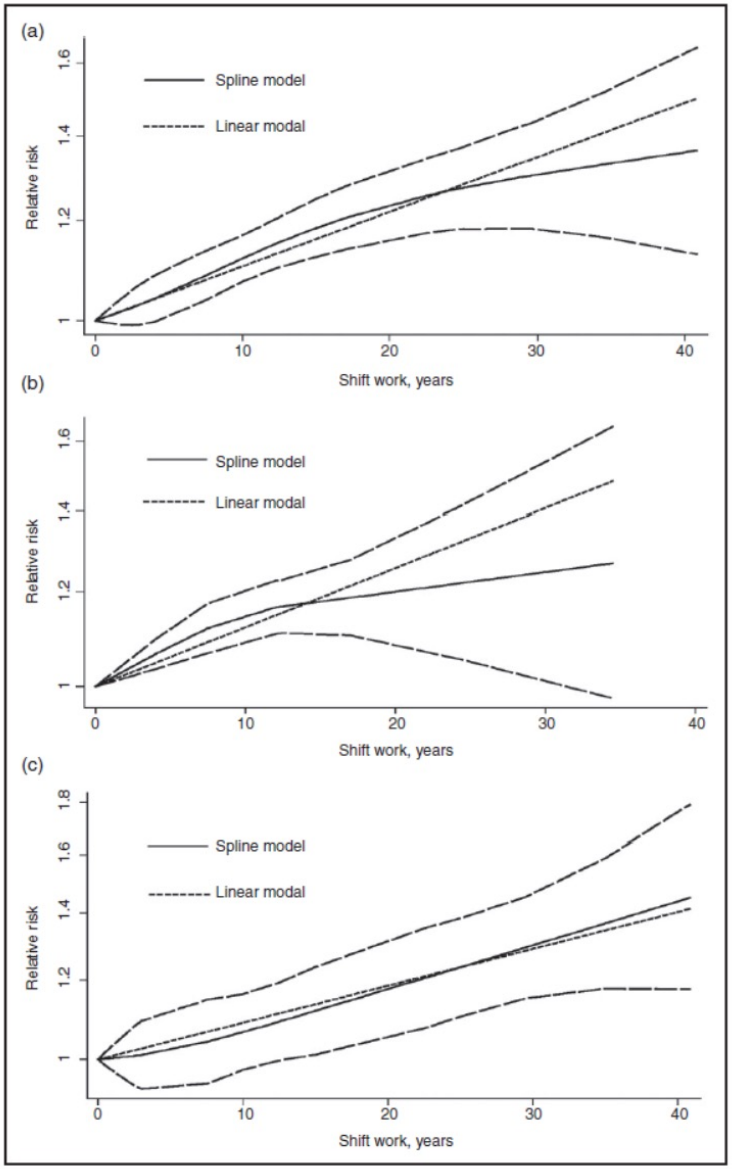


Figure 2. Dose–response relationship plot between duration of shift work and risk of cardiovascular disease (CVD); (a) CVD risk; (b) CVD morbidity risk; and (c) CVD mortality risk.

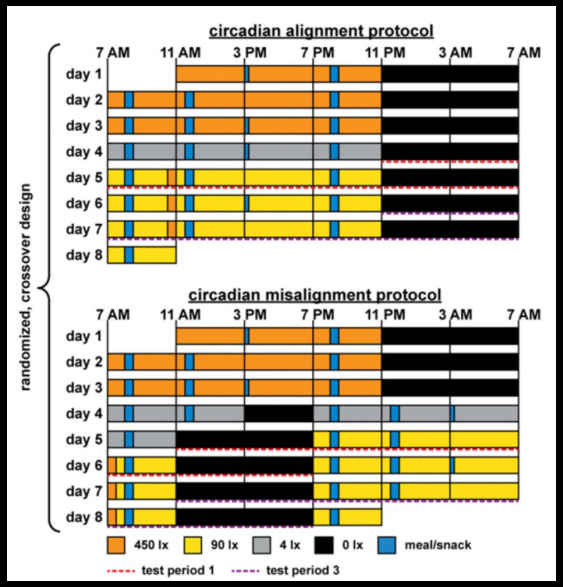
Circadian misalignment increases cardiovascular disease risk factors in humans

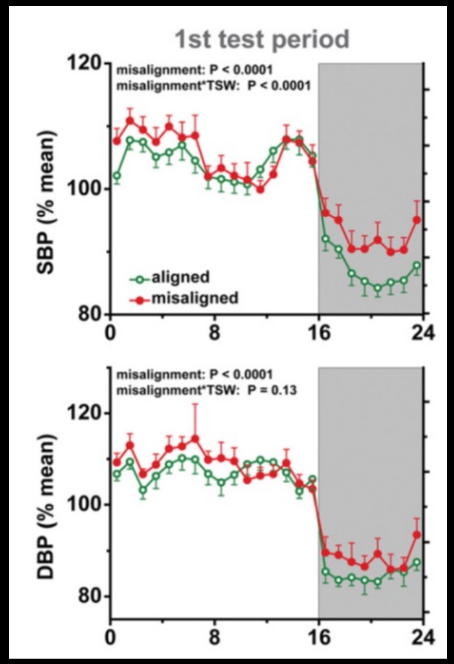
Christopher J. Morris[a,b,1], Taylor E. Purvis[a], Kun Hu[a,b], and Frank A. J. L. Scheer[a,b,1]

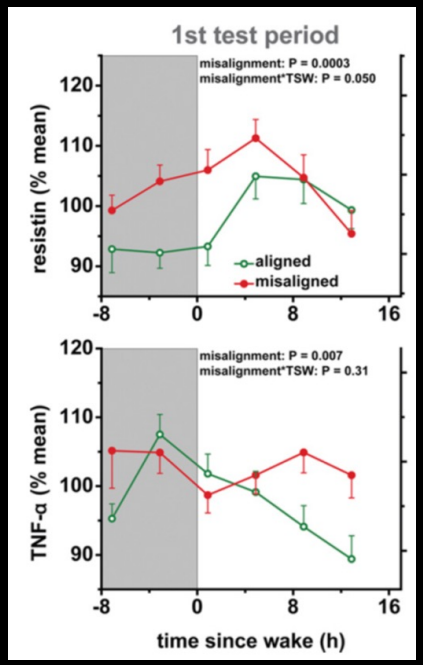
[a]Medical Chronobiology Program, Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA 02115; and [b]Division of Sleep Medicine, Department of Medicine, Harvard Medical School, Boston, MA 02115

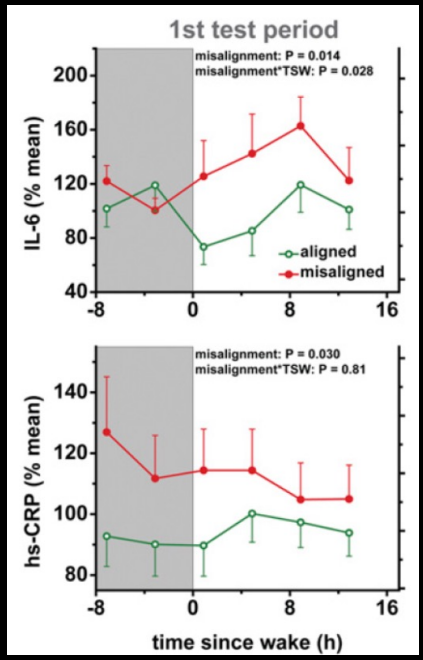
Edited by Joseph S. Takahashi, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, and approved January 6, 2016 (received for review August 25, 2015)

Shift work is a risk factor for hypertension, inflammation, and misalignment on sleep blood pressure, which is a better predictor





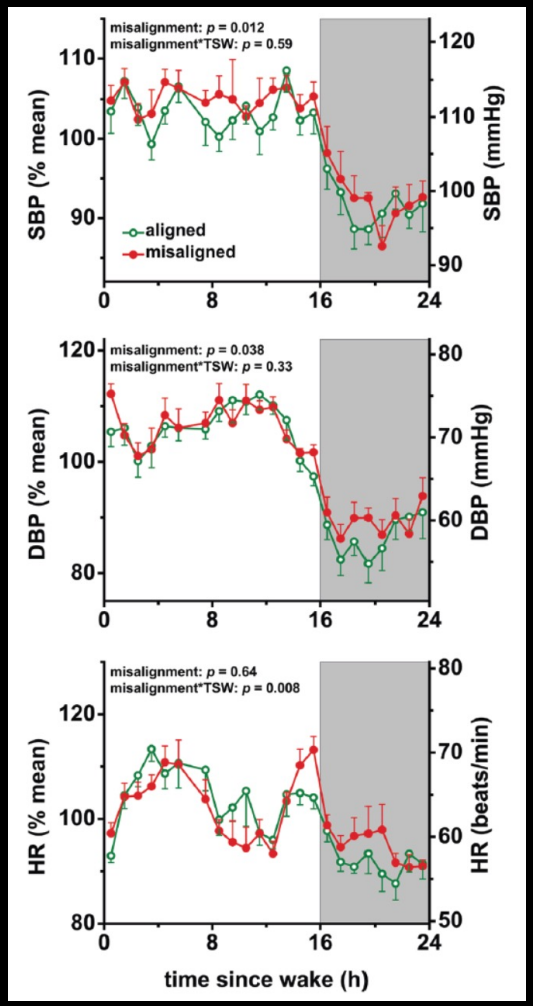


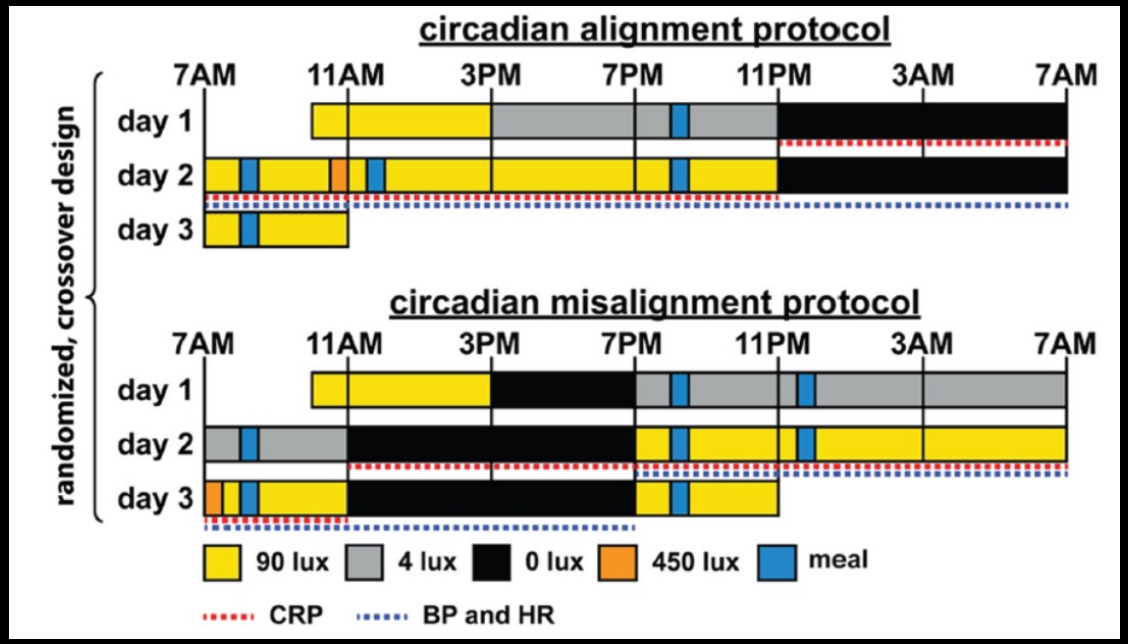


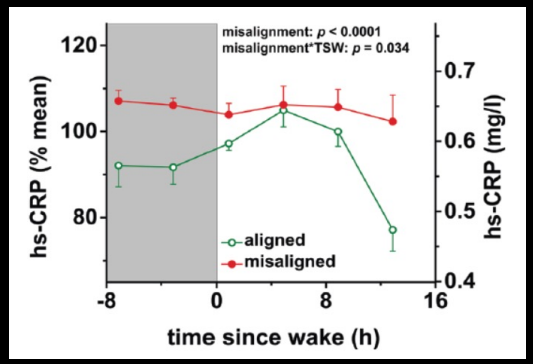
Circadian Misalignment Increases C-Reactive Protein and Blood Pressure in Chronic Shift Workers

Christopher J. Morris,[*,†,1] Taylor E. Purvis,[*] Joseph Mistretta,[*] Kun Hu,[*,†] and Frank A. J. L. Scheer[*,†,1]

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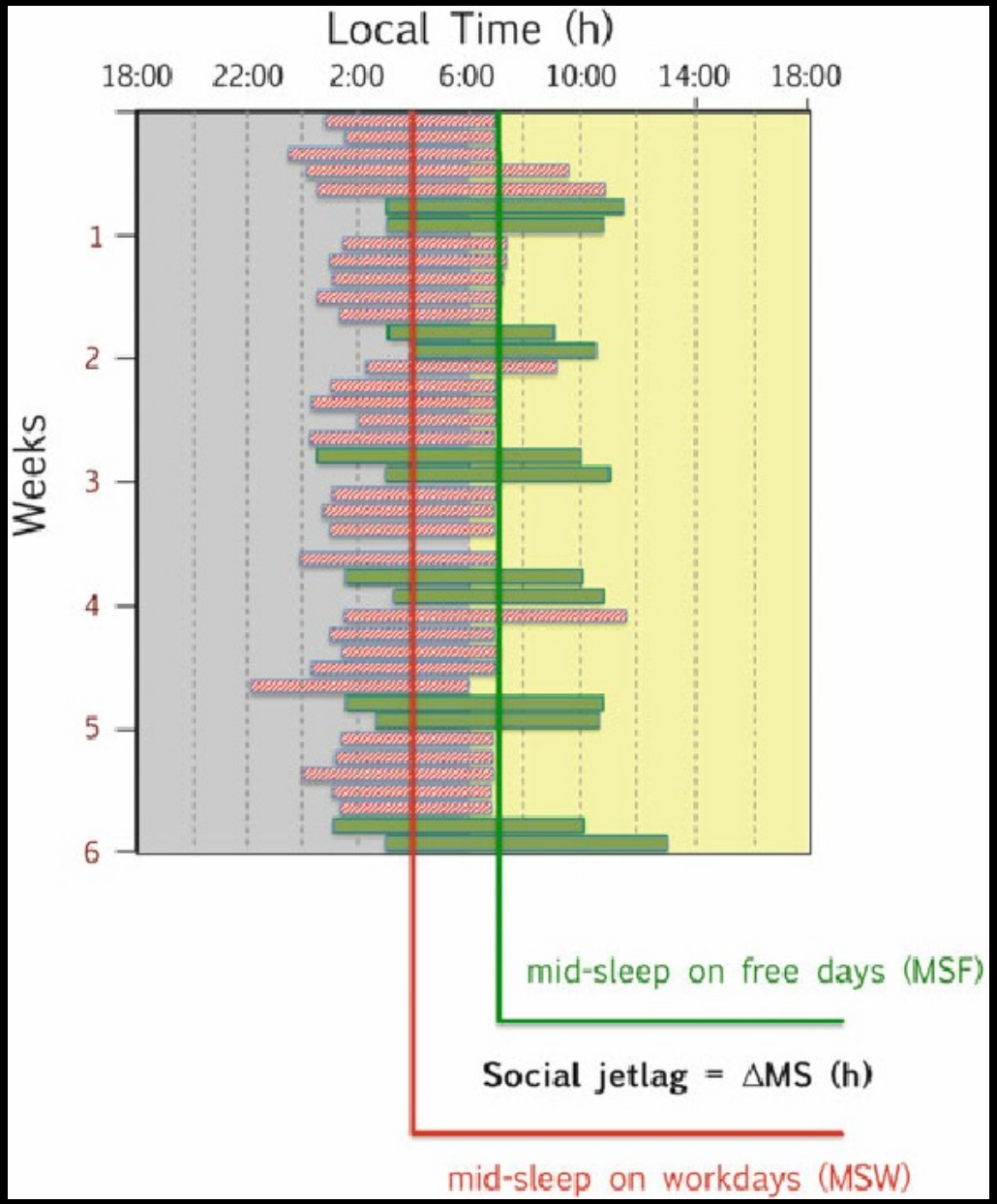






Morris et al., J Biol Rhythms, 2017

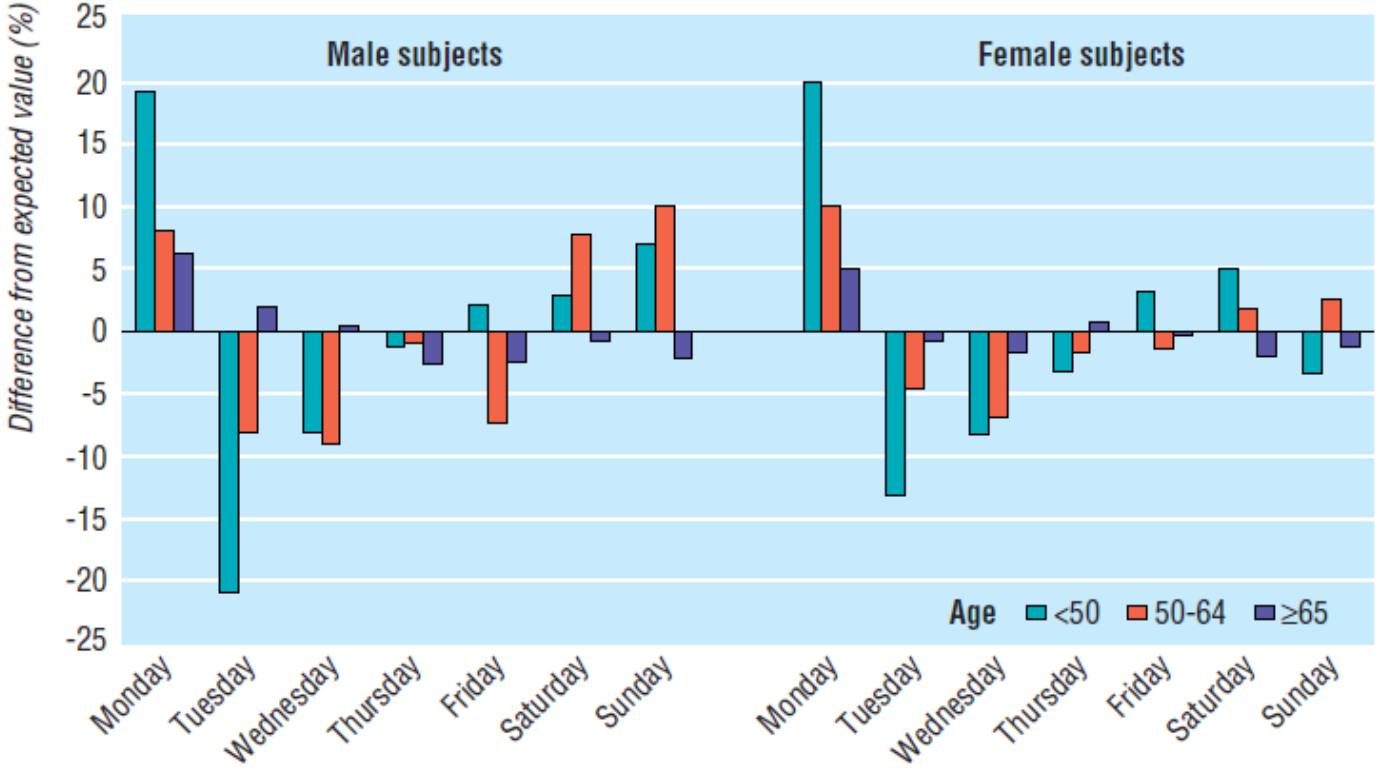
Sociale jetlag



Wittmann et al., Chronobiol Int, 2006

"I don't like Mondays"—day of the week of coronary heart disease deaths in Scotland: study of routinely collected data

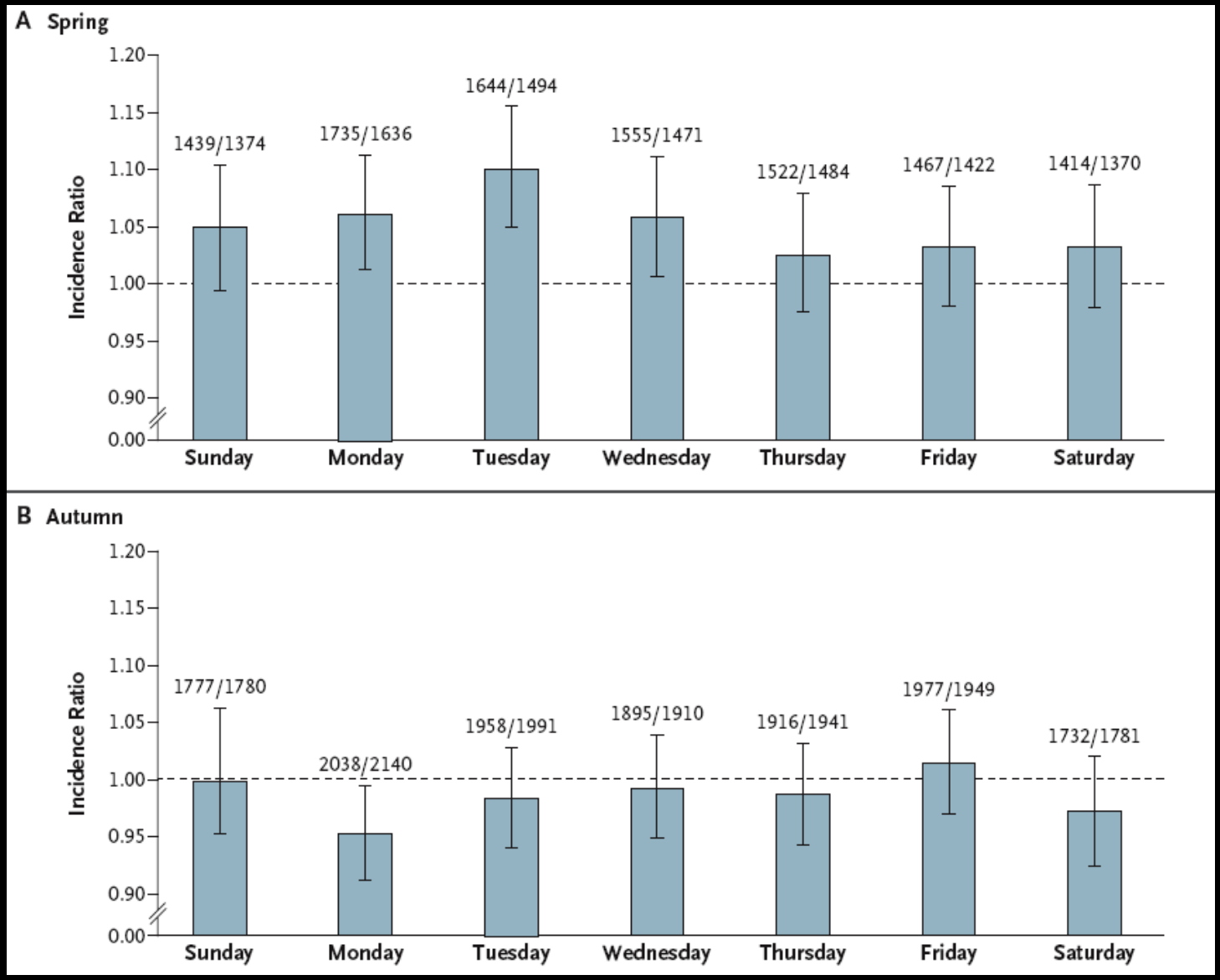
Christine Evans, James Chalmers, Simon Capewell, Adam Redpath, Alan Finlayson, James Boyd, Jill Pell, John McMurray, Kate Macintyre, Lesley Graham



Deaths from coronary heart disease occurring outside hospital, by day of week, in people with no previous admissions for coronary heart disease, Scotland, 1986-95: percentage difference from expected values

Evans et al, BMJ, 2000

Daylight saving time in spring and autumn



Janszky & Ljung, New Engl J Med, 2008





Ik zou ook best een ochtendmens kunnen zijn, tenminste... Als de ochtend om een uur of 12 zou beginnen.

CHRONOBIOLOGY INTERNATIONAL
2018, VOL. 35, NO. 8, 1045–1053
https://doi.org/10.1080/07420528.2018.1454458

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

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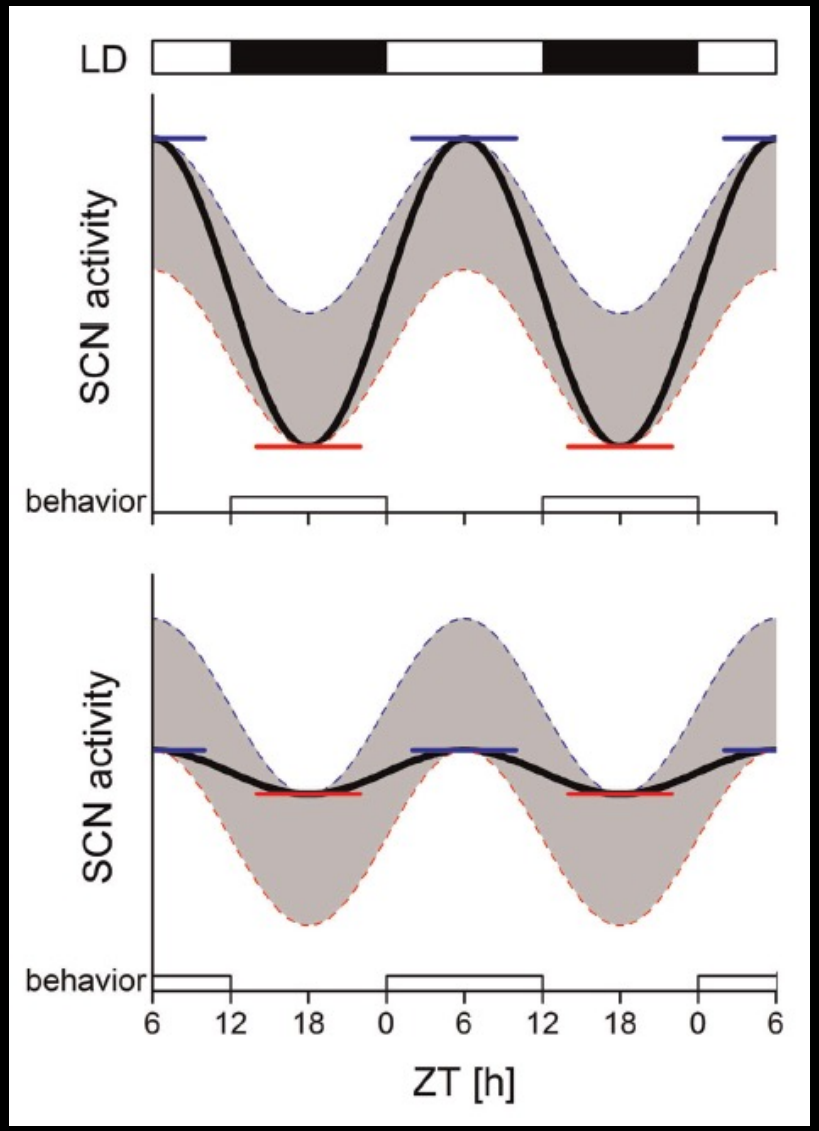
Table 2. Associations between chronotype and prevalent comorbidities adjusting for age and sex.

	Four-level chronotype (1 = Definite morning type to 4 = definite evening type)	Categorical variables			
Prevalent comorbidity	OR per level (95% CI)	Definite morning type	Moderate morning types OR (95% CI)	Moderate evening types OR (95% CI)	Definite evening type OR (95% CI)
CVD	1.01 (1.004, 1.02) $p = 0.002$	Ref	0.91 (0.90, 0.93) $p < 0.001$	0.97 (0.95, 0.99) $p = 0.001$	1.07 (1.04, 1.10) $p < 0.001$
Diabetes	1.06 (1.05, 1.08) $p < 0.001$	Ref	0.82 (0.80, 0.85) $p < 0.001$	0.98 (0.94, 1.01) $p = 0.20$	1.30 (1.24, 1.36) $p < 0.001$
Neurological	1.06 (1.05, 1.08) $p < 0.001$	Ref	1.02 (1.00, 1.04) $p = 0.20$	1.08 (1.05, 1.11) $p < 0.001$	1.25 (1.20, 1.30) $p < 0.001$
Endocrine	1.04 (1.03, 1.06) $p < 0.001$	Ref	0.98 (0.95, 1.02) $p = 0.34$	1.04 (1.01, 1.08) $p = 0.015$	1.17 (1.12, 1.23) $p < 0.001$
Renal	1.02 (1.004, 1.04) $p = 0.015$	Ref	1.01 (0.97, 1.05) $p = 0.65$	1.01 (0.97, 1.05) $p = 0.58$	1.10 (1.04, 1.16) $p = 0.001$
Respiratory	1.05 (1.04, 1.06) $p < 0.001$	Ref	0.94 (0.92, 0.96) $p < 0.001$	1.03 (1.01, 1.05) $p = 0.007$	1.22 (1.18, 1.26) $p < 0.001$
Musculoskeletal	1.04 (1.03, 1.05) $p < 0.001$	Ref	0.96 (0.94, 0.98) $p < 0.001$	1.05 (1.03, 1.07) $p < 0.001$	1.14 (1.11, 1.18) $p < 0.001$
Gastrointestinal/ Abdominal	1.07 (1.06, 1.08) $p < 0.001$	Ref	1.00 (0.98, 1.02) $p = 1.0$	1.12 (1.09, 1.14) $p < 0.001$	1.23 (1.19, 1.27) $p < 0.001$
Psychological	1.25 (1.23, 1.26) $p < 0.001$	Ref	1.07 (1.04, 1.11) $p < 0.001$	1.44 (1.40, 1.49) $p < 0.001$	1.94 (1.86, 2.02) $p < 0.001$

Chronotype was examined as both an pseudo-continuous four-level variable and as categorical variables with definite morning type as referent.

Doe de juiste dingen, op het juiste moment van de dag





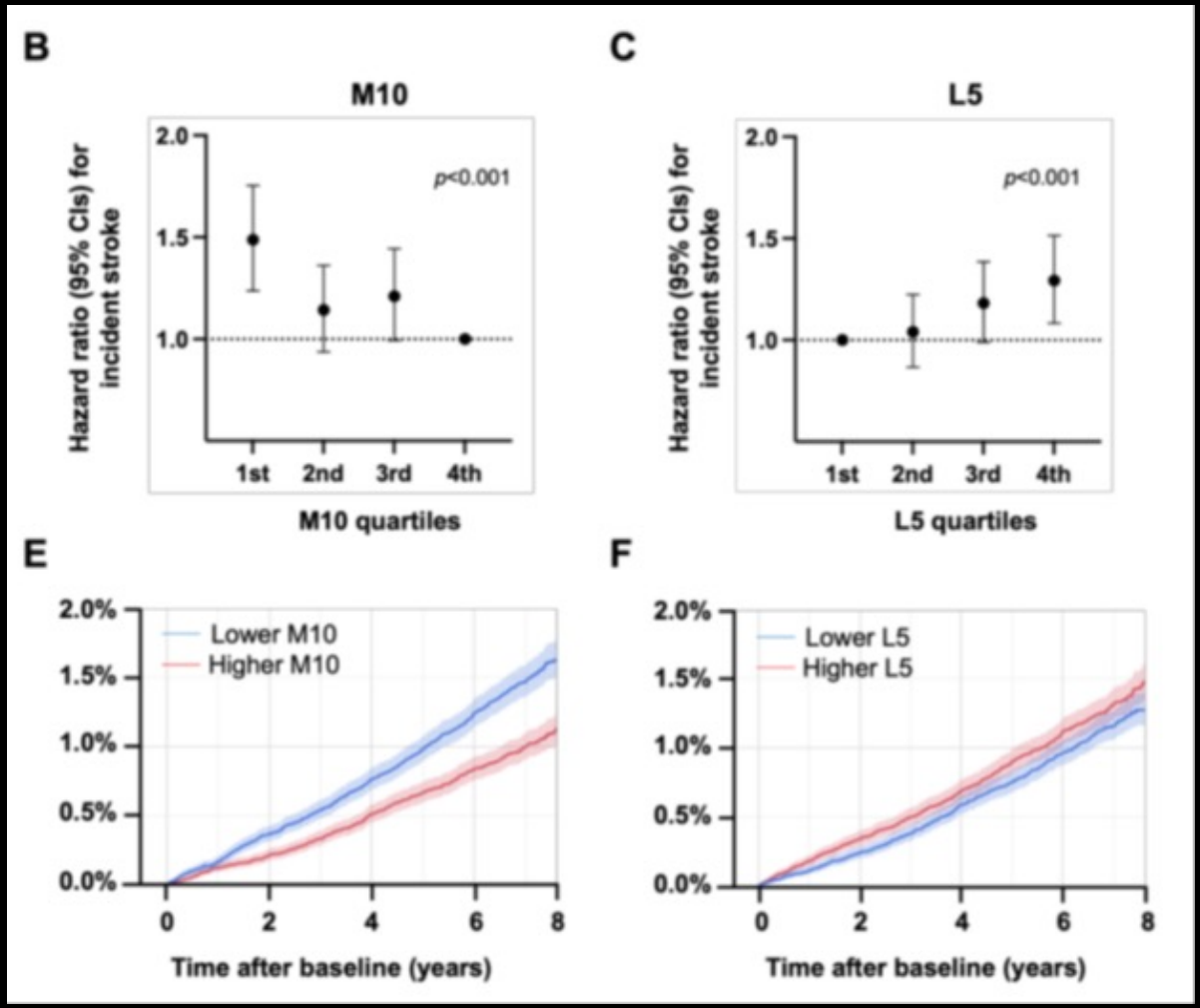






Van Oosterhout et al, 2012

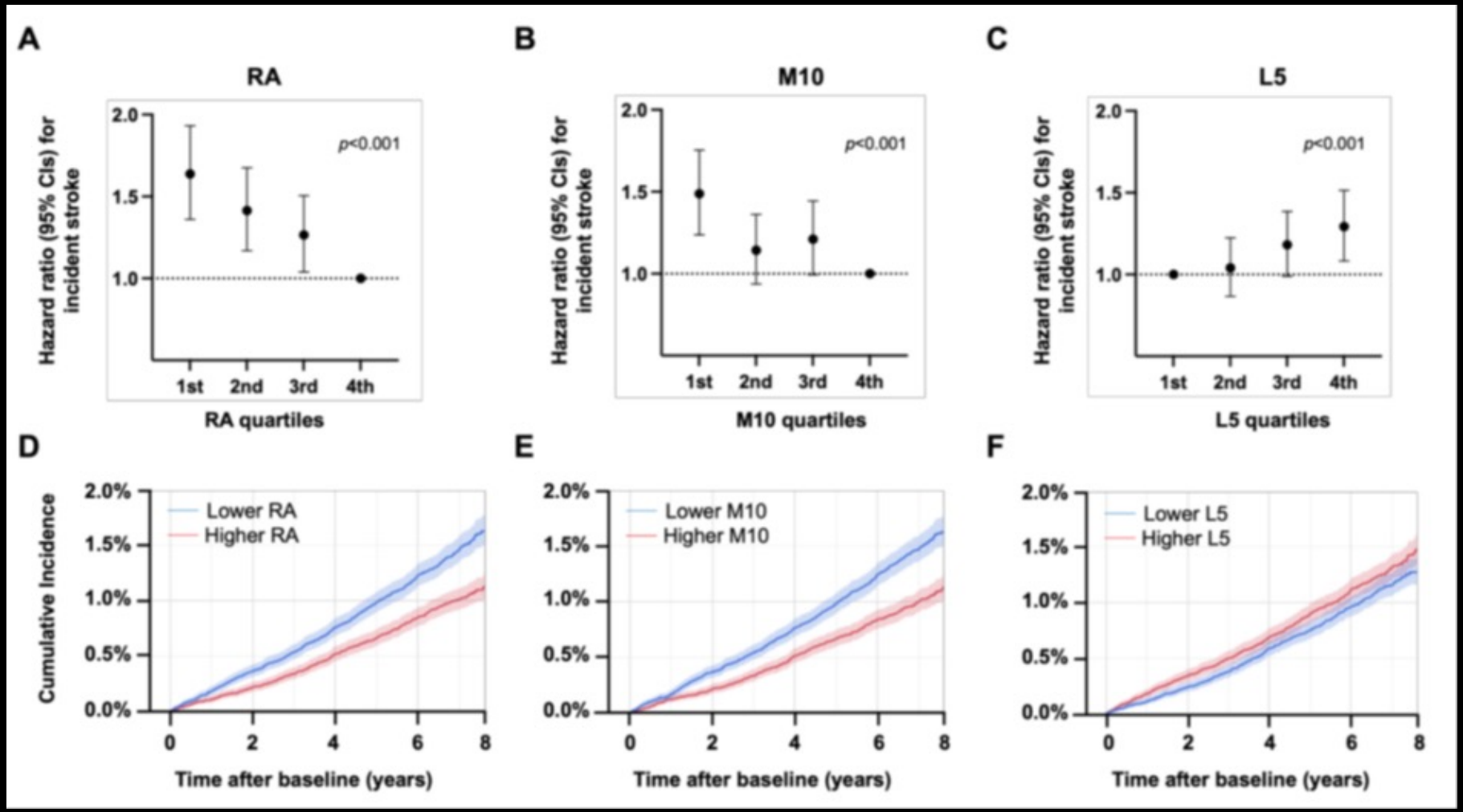
Associations of rest-activity rhythm disturbances with stroke risk and post-stroke adverse outcomes – A UK Biobank study



M10 = 10 hours with most activity
L5 = 5 hours with least activity

Gao et al., MedRxiv, 2023

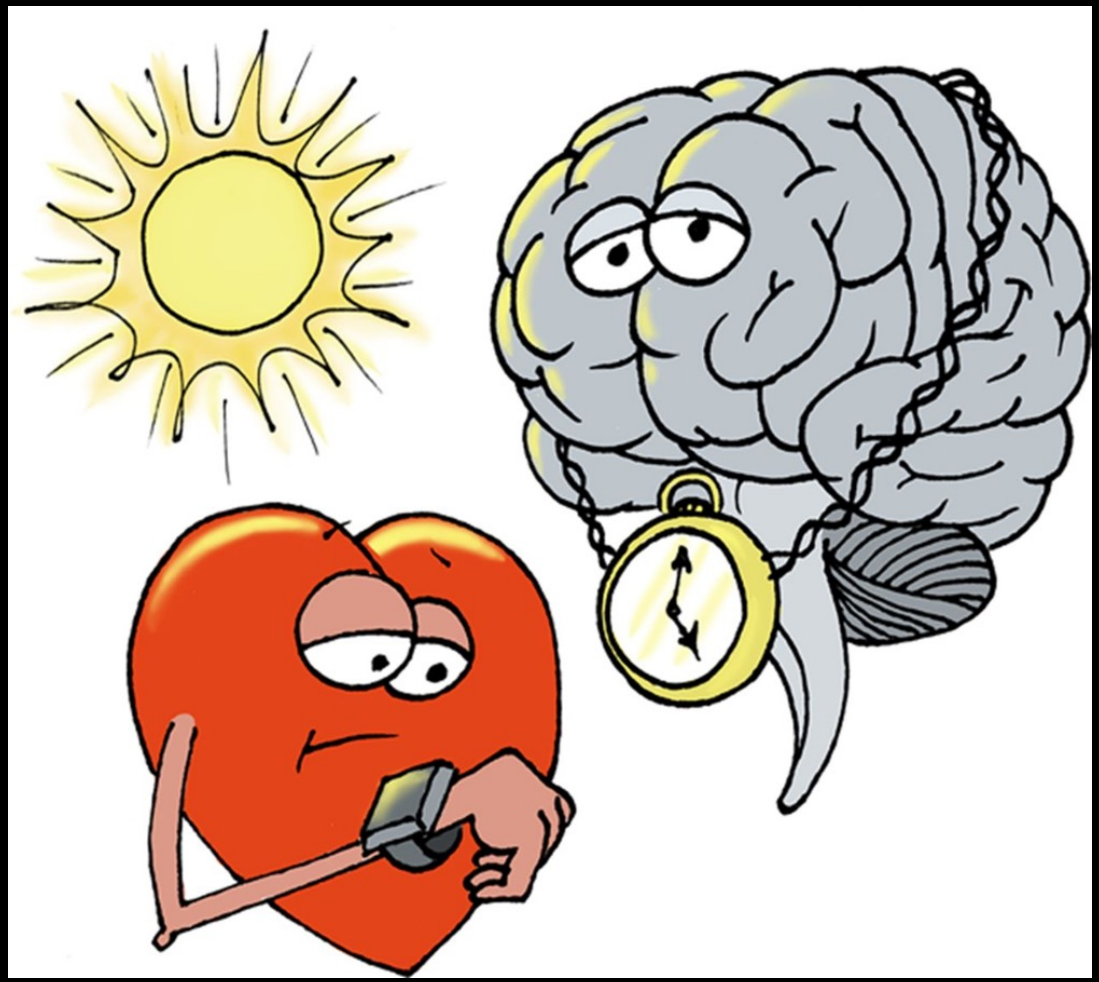
Associations of rest-activity rhythm disturbances with stroke risk and post-stroke adverse outcomes – A UK Biobank study



M10 = 10 hours with most activity
L5 = 5 hours with least activity
RA = Relative amplitude (M10-L5/M10+L5)

Gao et al., MedRxiv, 2023

..dank voor uw aandacht!!



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