De flexibele circadiane klok:
aangepast aan de natuur, maar niet aan de moderne samenleving.

Illustratie: Merlijn van Bijsterveld

prof.dr.
Roelof Hut

Chronobiologie, GELIFES
Rijksuniversiteit Groningen
r.a.hut@rug.nl

Ritmiek in de Natuur:

		interne representatie klok/oscillator
Populatie cycli	~4 jaar of langer	
Jaar/seizoens cyclus	1 jaar	circannuele klok
Maan cyclus	~29.5 dagen	circalunaire klok
Menstruatie cyclus	21-42 dagen	
Ovulatie cyclus	3-365 dagen	
Getijden cyclus	~12.42 uur	circatidale klok
Dag/nacht cyclus	24 uur	circadiane klok
Snelle rust/activiteit cyclus	3-4 uur	ultradiane klok
Non-REM / REM cyclus	1.5 uur	
Neuro-endocrine cycli	0.5-6 uur	
Neuronale depolarisatie	0.001-1 sec	

circadian** = latin ***circa (about) + ***dies*** (day)*

Uit examen programma Biologie:

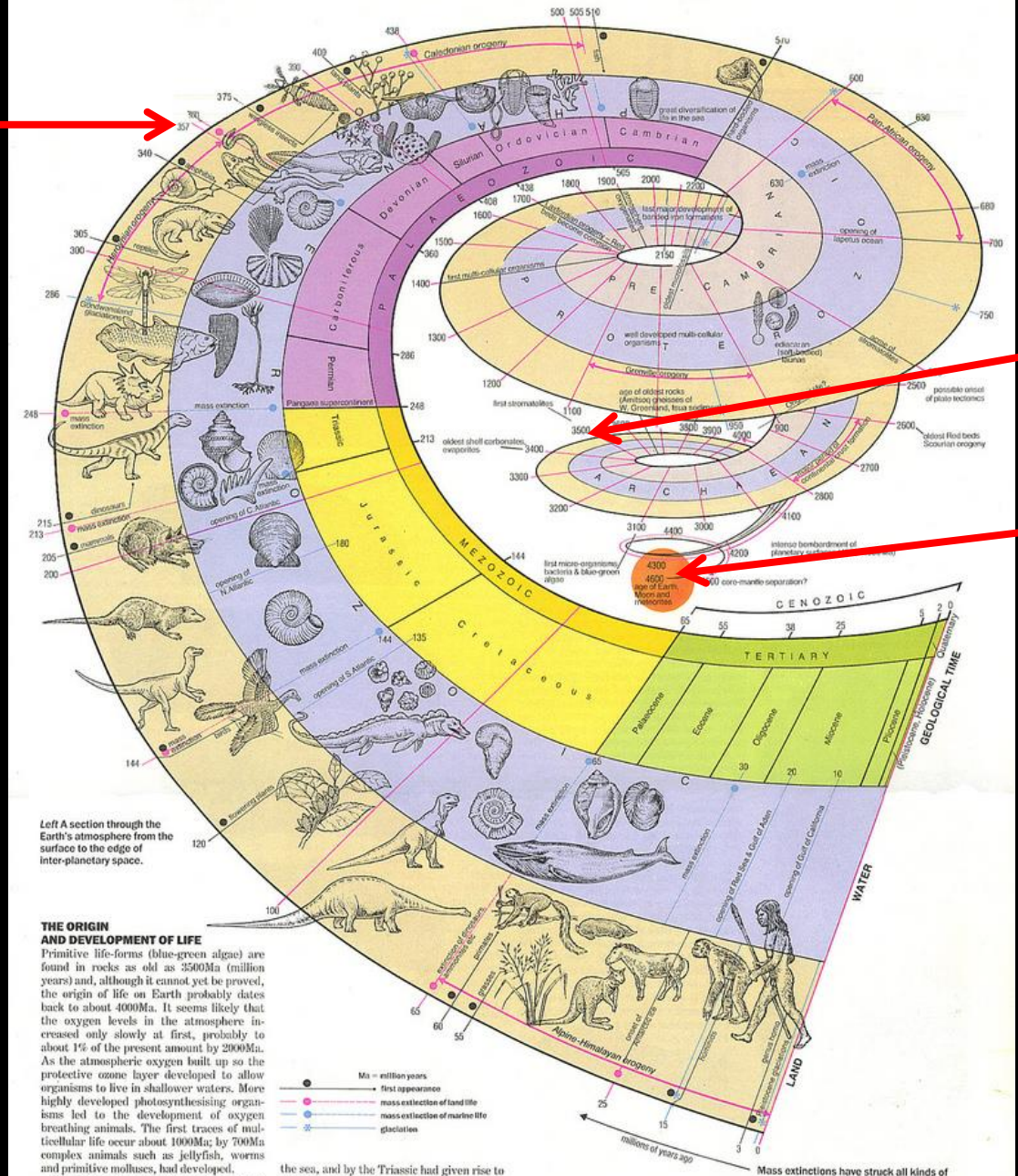
Domeinen:
- Molecuul en cel
- Orgaan en organsime
- Populatie en eco systeem

Denkvaardigheden:
- Systeem denken
- Evolutionair denken
- Ecologisch denken

terrestrische vertebraten 360 mya

Eerste levensvormen: (cyanobacteria) 3.8 bya

Onstaan van de Aarde 4.5 bya



Left A section through the Earth's atmosphere from the surface to the edge of inter-planetary space.

THE ORIGIN AND DEVELOPMENT OF LIFE

Primitive life-forms (blue-green algae) are found in rocks as old as 3500Ma (million years) and, although it cannot yet be proved, the origin of life on Earth probably dates back to about 4000Ma. It seems likely that the oxygen levels in the atmosphere increased only slowly at first, probably to about 1% of the present amount by 2000Ma. As the atmospheric oxygen built up so the protective ozone layer developed to allow organisms to live in shallower waters. More highly developed photosynthesising organisms led to the development of oxygen breathing animals. The first traces of multicellular life occur about 1000Ma; by 700Ma complex animals such as jellyfish, worms and primitive molluscs, had developed.

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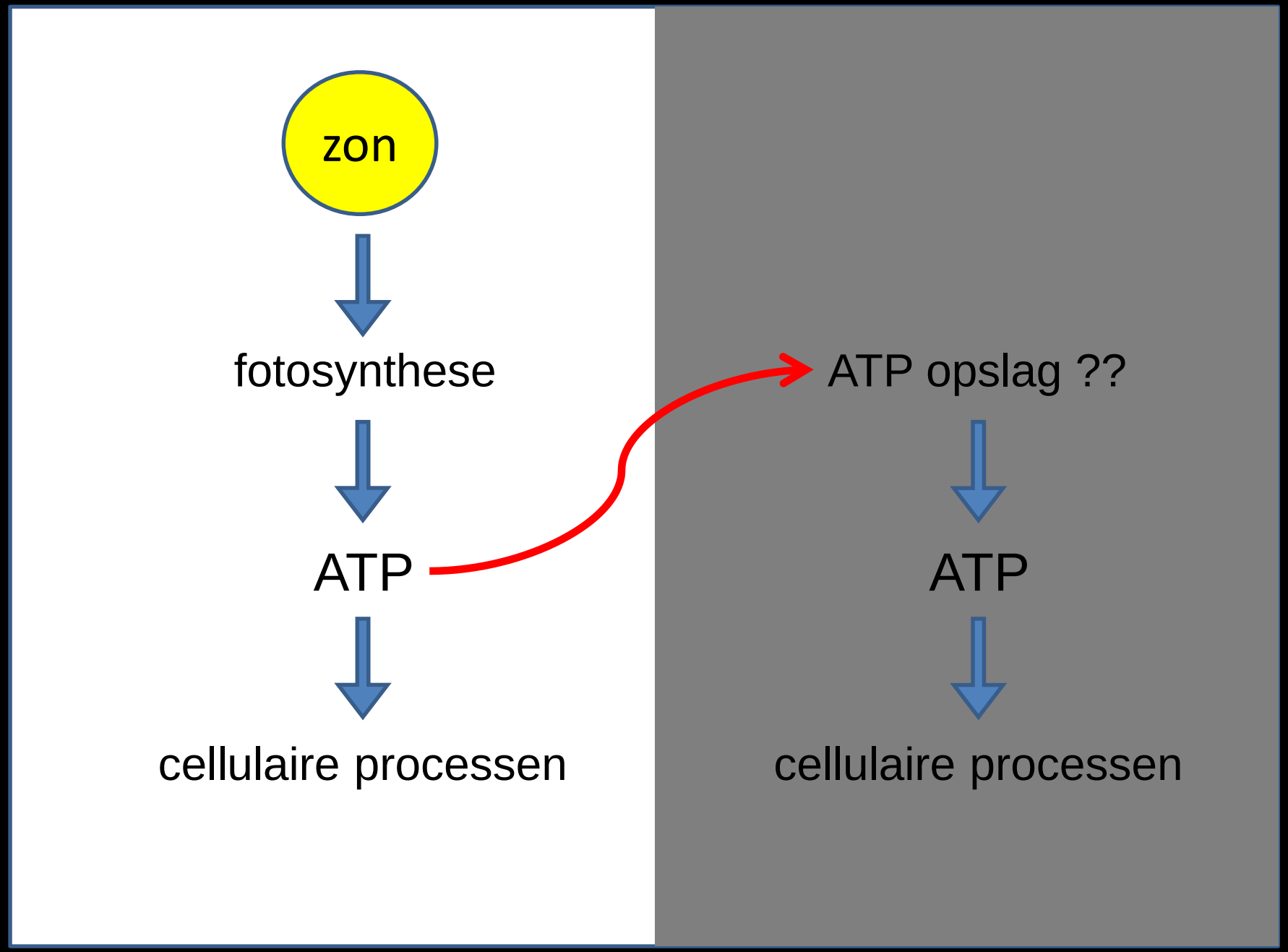
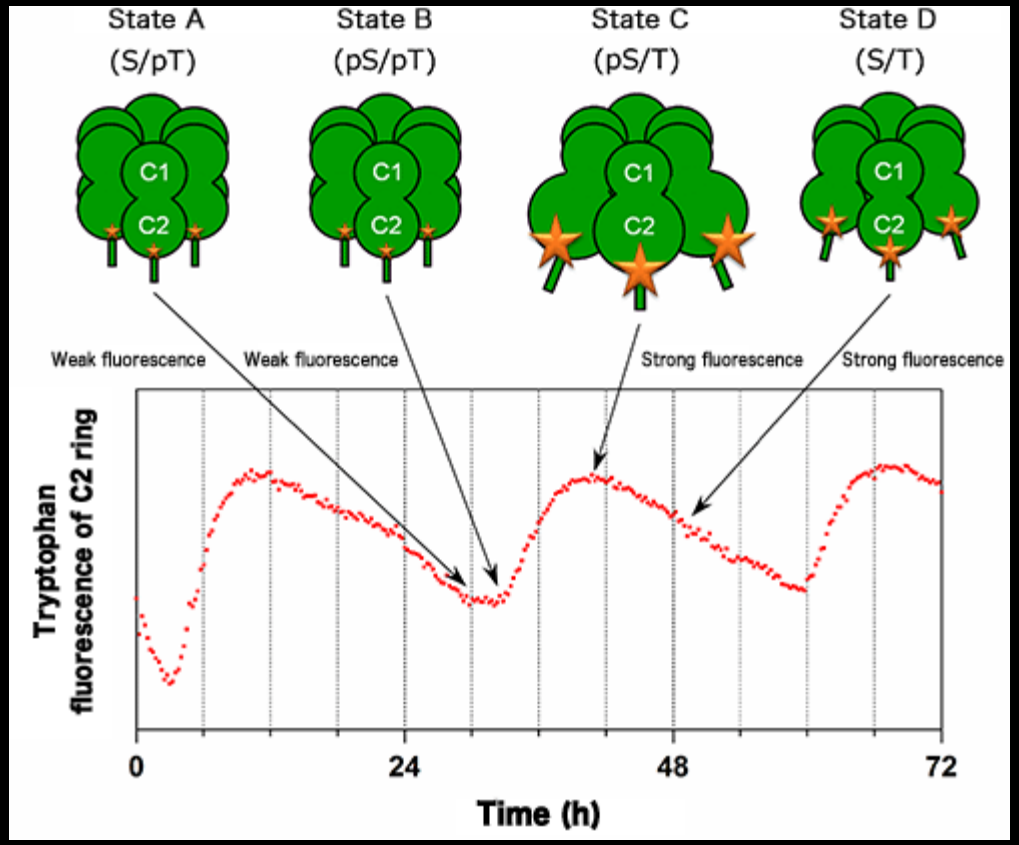
Mass extinctions have struck all kinds of marine life over the past 700 million years, from single-cell algae and plankton to huge swimming reptiles and whales. At the end of the Cretaceous period 65 million years ago most marine species became extinct. At about the same time the dinosaurs became extinct on land. In some cases an animal or plant group has been able to recover after a crisis and evolve a new species; in other cases the entire group has vanished.

Stromatolieten – de eerste vroegste restanten van leven

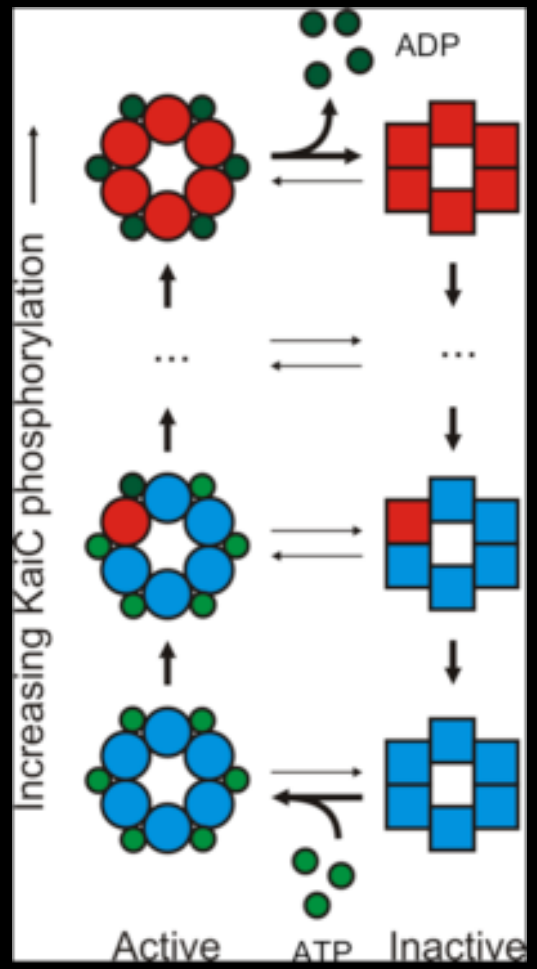
Cyanobacteria – Synechococcus sp.


zon
fotosynthese
ATP
cellulaire processen
ATP opslag ??
ATP
cellulaire processen

KaiC als energie (ATP) opslag in cyanobacteria
de eerste circadiane klok

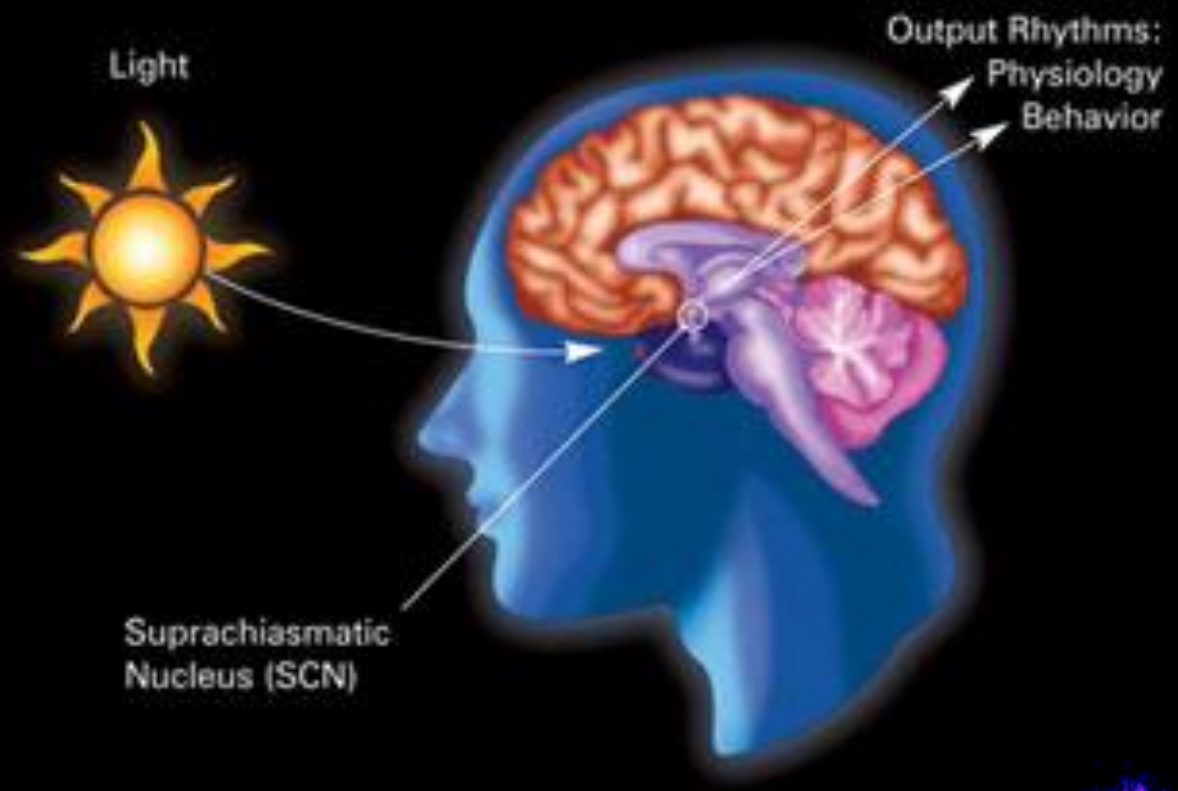


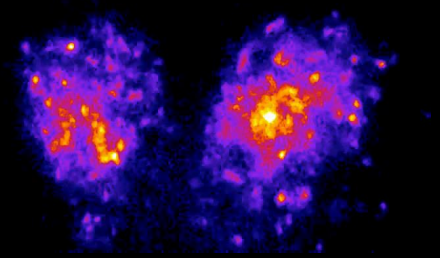
Kondo et al.

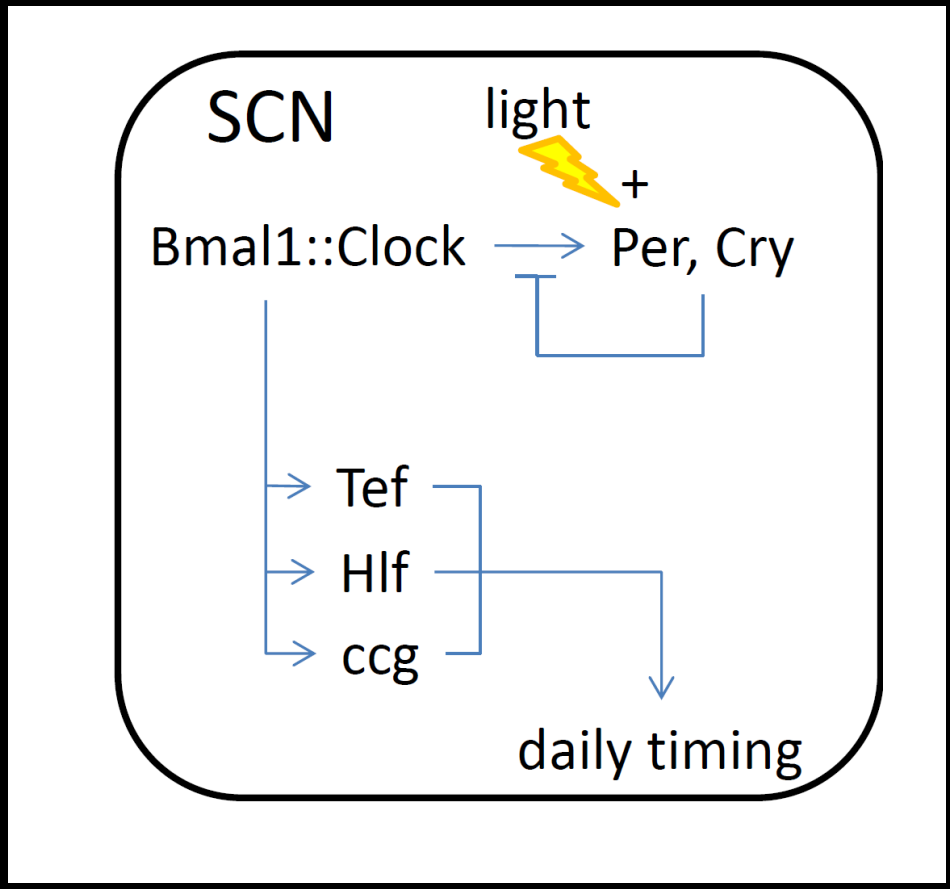


Ten Woude et al.

Het moleculaire mechanism van de circadiane klok:
De TTFL - transcriptie-translatie terugkoppeling (feedback loop)

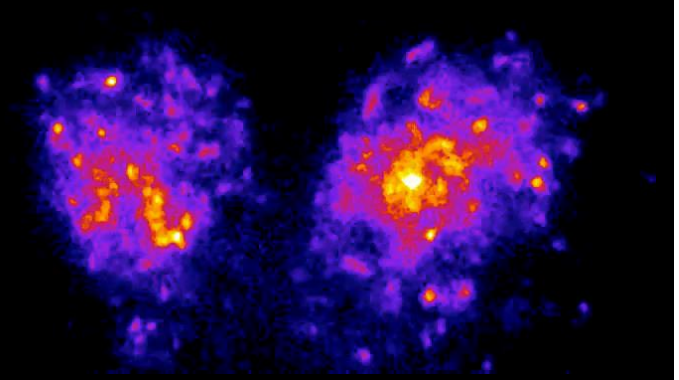




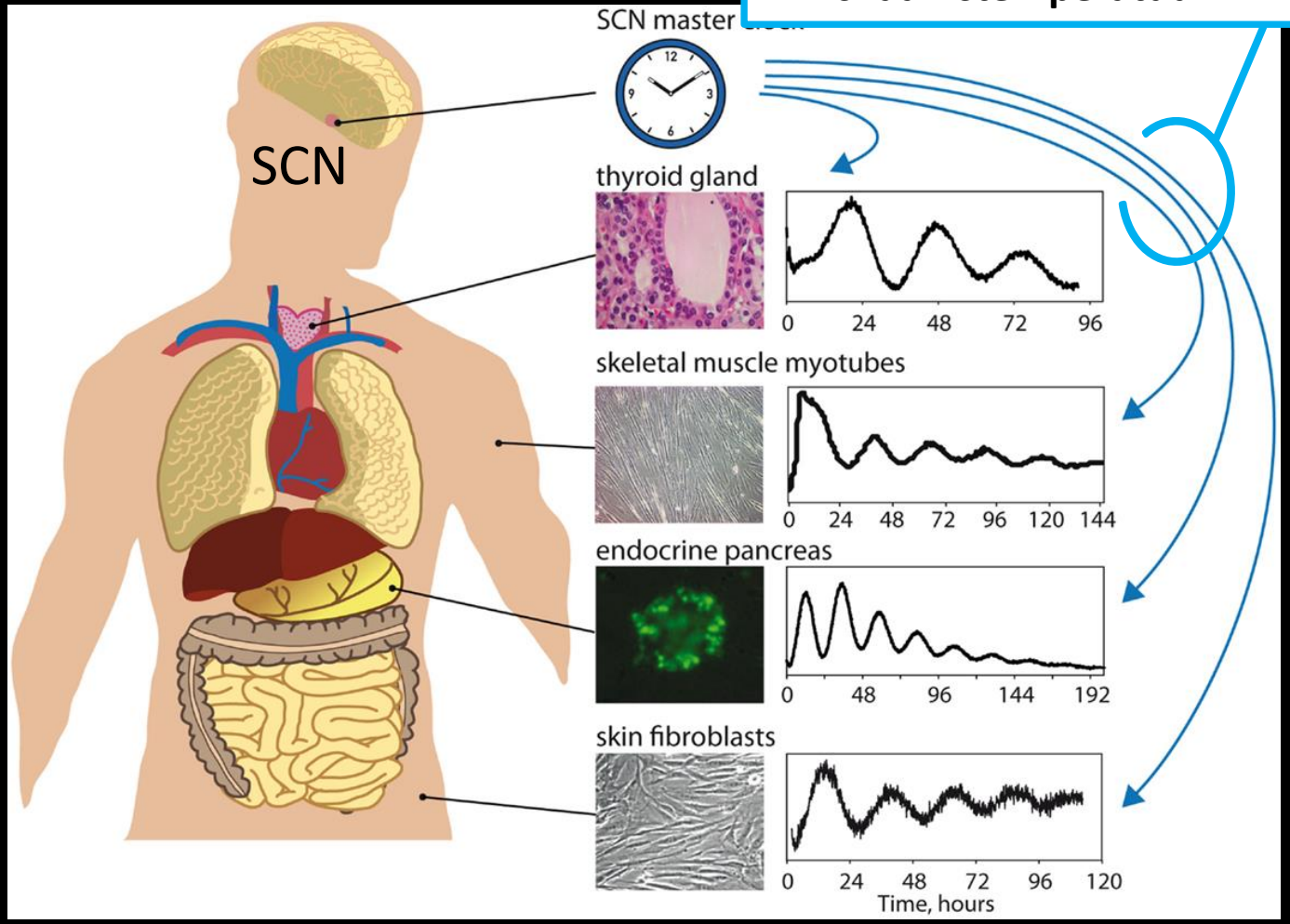


De circadiane klok in de hypothalamus is de suprachiamsatishce nucleus (SCN)
deze klok is een oscillator die circadiane klokken in andere weefsels synchroniseert

Pijnappelklier -> Melatonine
Autonoom Zenuwstelsel -> Bijnier -> Cortisol
Lichaamstemperatuur

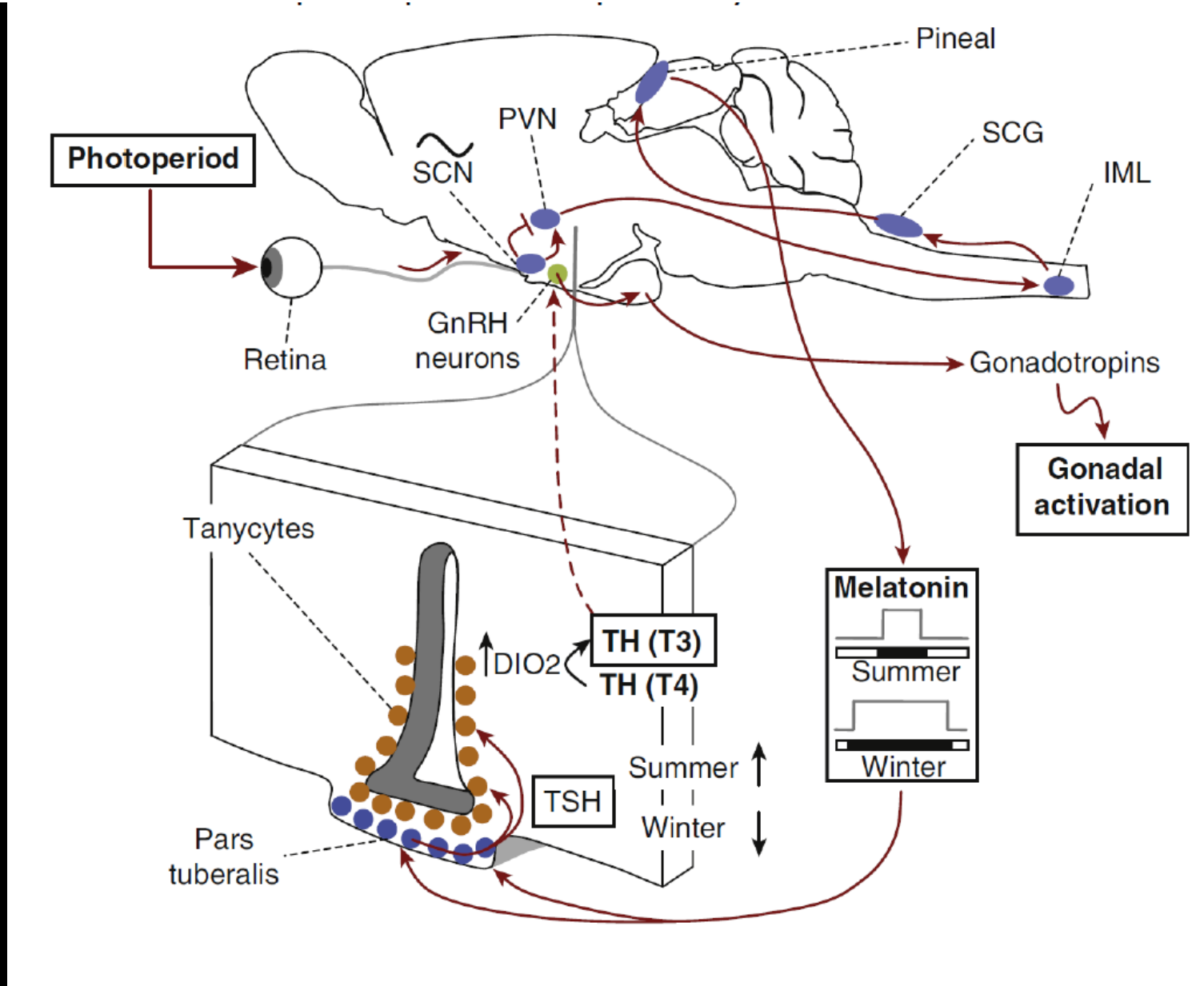


The main circadian clock: Suprachiasmatic nucleus (SCN)



Saini et al FrontNeurol 2015

Melatonine is bij zoogdieren een interne representatie van *nachtlengte* en synchroniseert *circannuele klok* in de *Pars tuberalis*



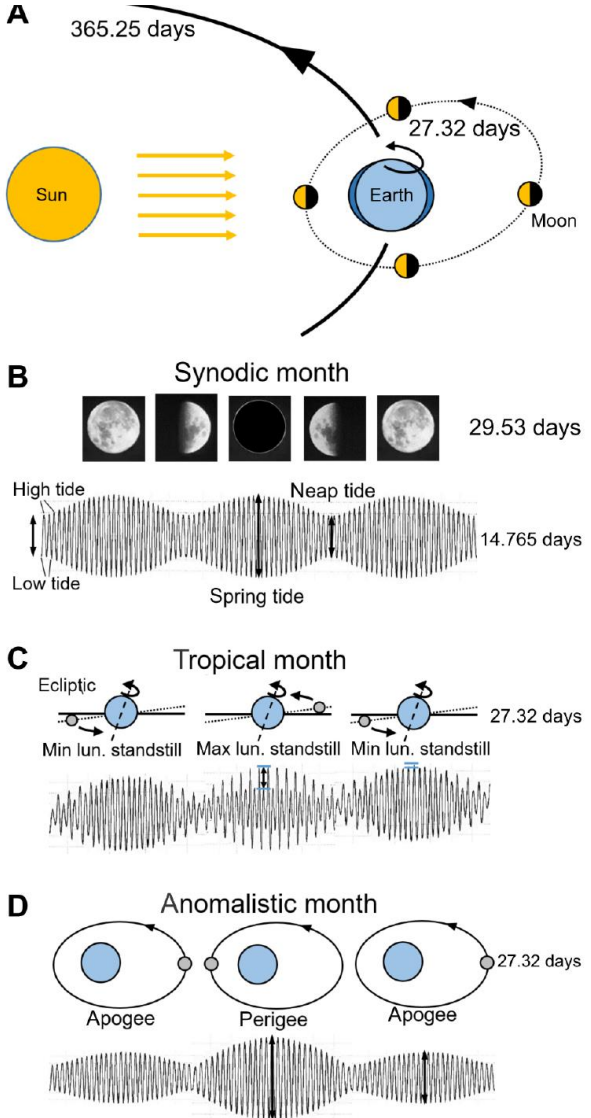
SCIENCE ADVANCES | RESEARCH ARTICLE 2021

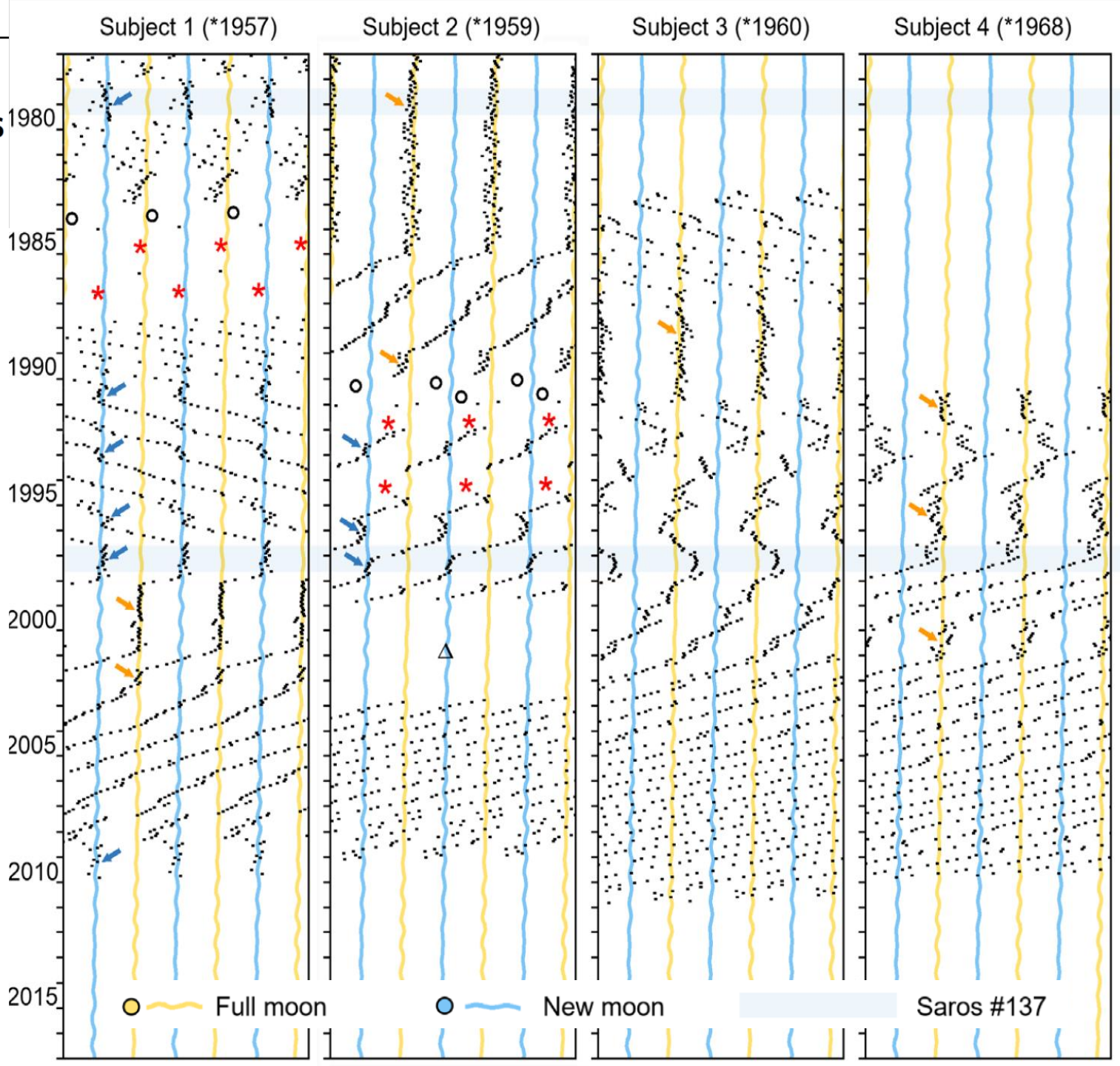
PHYSIOLOGY

Women temporarily synchronize their menstrual cycles with the luminance and gravimetric cycles of the Moon

C. Helfrich-Förster[1]*, S. Monecke[2], I. Spiousas[3], T. Hovestadt[4], O. Mitesser[5], T. A. Wehr[6]

Charlotte Helfrig-Förster





Wat is zijn functies van de circadiane klok?

Externe functie *(relatie met de omgeving):*

Synchronisatie van gedrag en fysiologie met de omgeving (b.v. licht, temperatuur, luchtvochtigheid)

- Optimalisatie van fotosynthese (primaire productie in ecosystemen!)
- Anticipatie dag/nacht veranderingen (b.v. predatiekans, thermoregulatie, metabolisme)
- Anticipatie seizoensveranderingen (circadiane klokken meten de daglengte)

Interne functie *(relatie met fysiologie):*

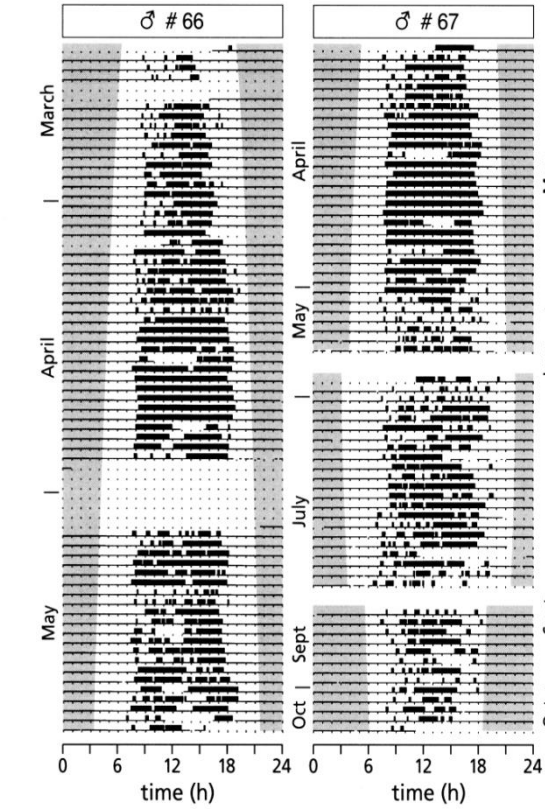
Synchronisatie van weefsels en organen en gedrag

- Synchronisatie van spijsvertering met gedrag (b.v. lever metabolisme en maaltijd)
- Synchronisatie van fysiologisch functies met gedrag (b.v. slaap > immuun functie)
- Synchronisatie van weefsels en hormonen (b.v. GnRH piek > LH piek > ovulation)

variatie in gedragsritmiek

dagactief

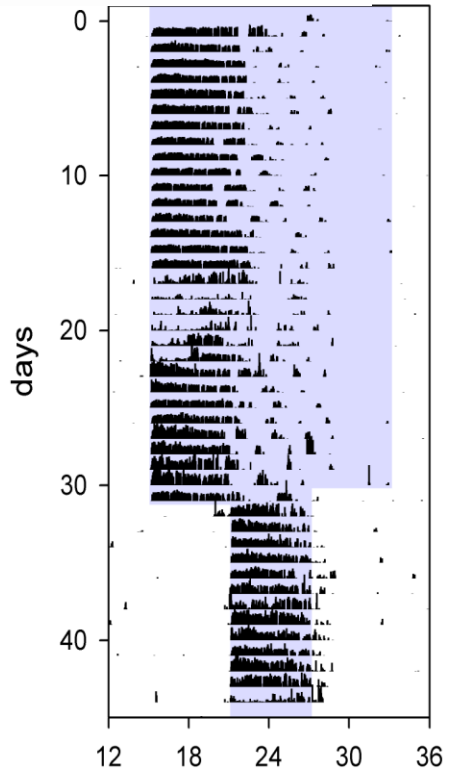
ground squirrel



Hut et al. JBiolRhythms 1999

nachtactief

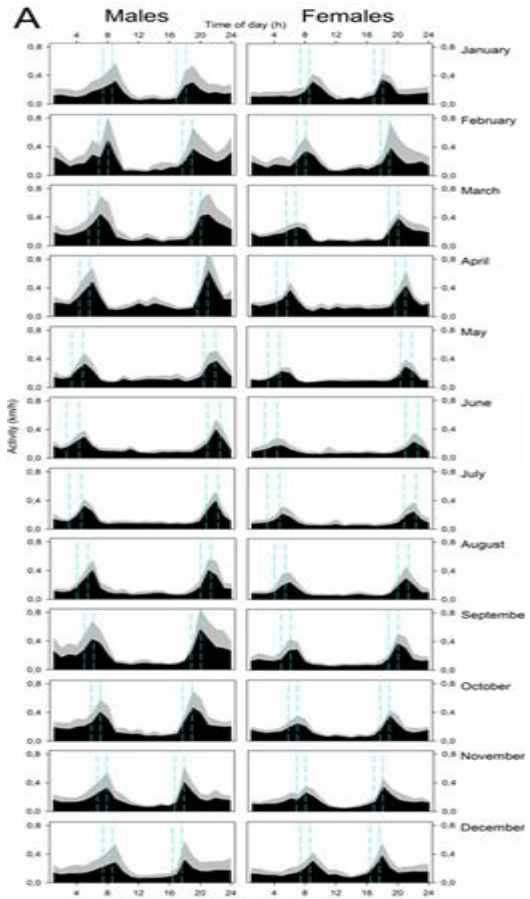
house mouse



Comas & Hut JBiolRhythms 2009

schemeractief (crepusculair)

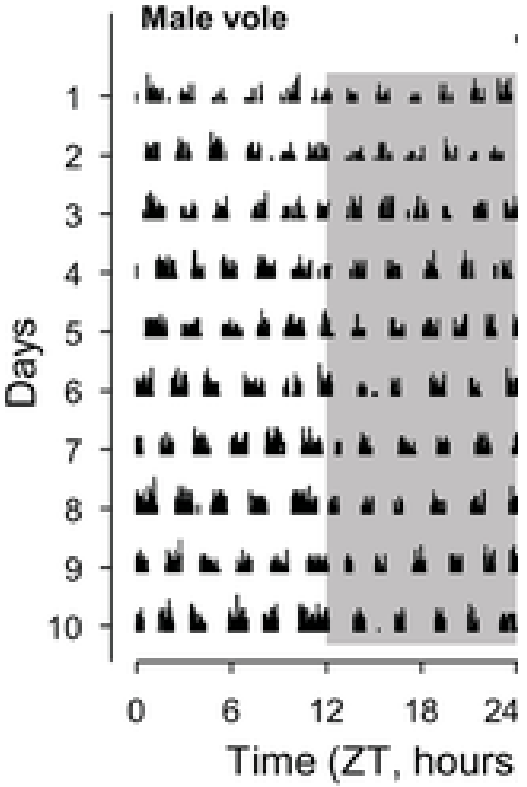
red deer



Ensing et al *PLoS ONE 2014*

ultradian

vole



Psomas et al FASEB *2023*

terrestrische vertebraten 360 mya

archosauriers 260 mya

zoogdieren 200 mya

nocturnal bottleneck

uitsterven dinosauriërs 65 mya

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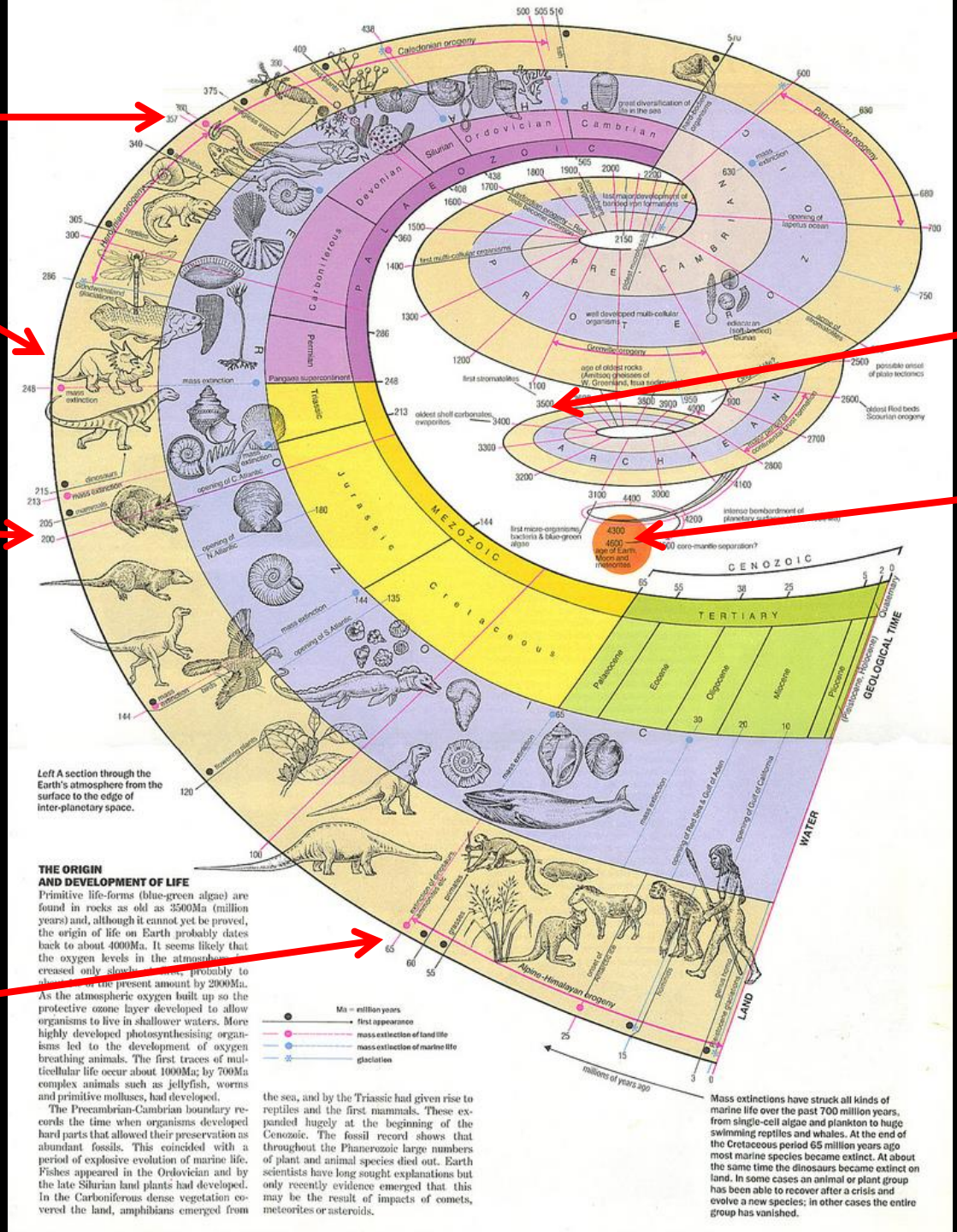
Onstaan van de Aarde 4.5 bya



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Evolution of homeothermy in mammals

A. W. Crompton, C. Richard Taylor & James A. Jagger

Museum of Comparative Zoology, Harvard University, Cambridge, Massachusetts 02138

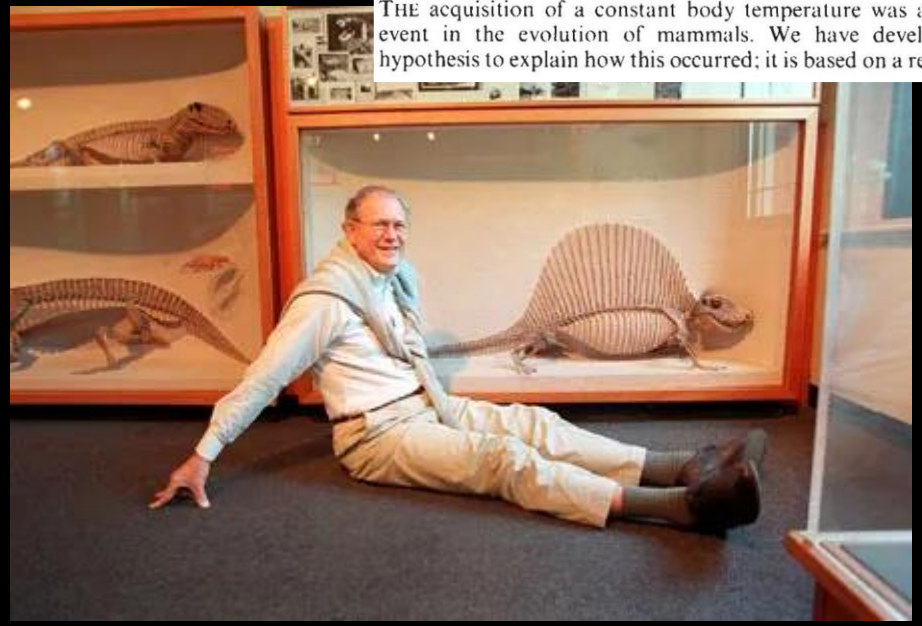
Nature 1978

We propose that mammalian homeothermy was acquired in two steps. The first step enabled mammals to invade a nocturnal niche without an increase in resting metabolic rate. The second step enabled them to invade a diurnal niche and involved the acquisition of higher body temperatures and metabolic rates.

THE acquisition of a constant body temperature was a major event in the evolution of mammals. We have developed a hypothesis to explain how this occurred; it is based on a review of the fossil record and a comparison of the energetics of insectivores, monotremes and marsupials.

Hypothesis

Our hypothesis is as follows. Homeothermy enabled the first mammals to invade a temporally wide nocturnal niche that had previously not been exploited fully by small insectivores. The body temperature of these first homeotherms was about 10 °C lower than the 38–40 °C found in most present day mammals. These first mammals could maintain their lower constant body temperature without the high resting metabolic rate typical of most living mammals. The loss of visual information in a



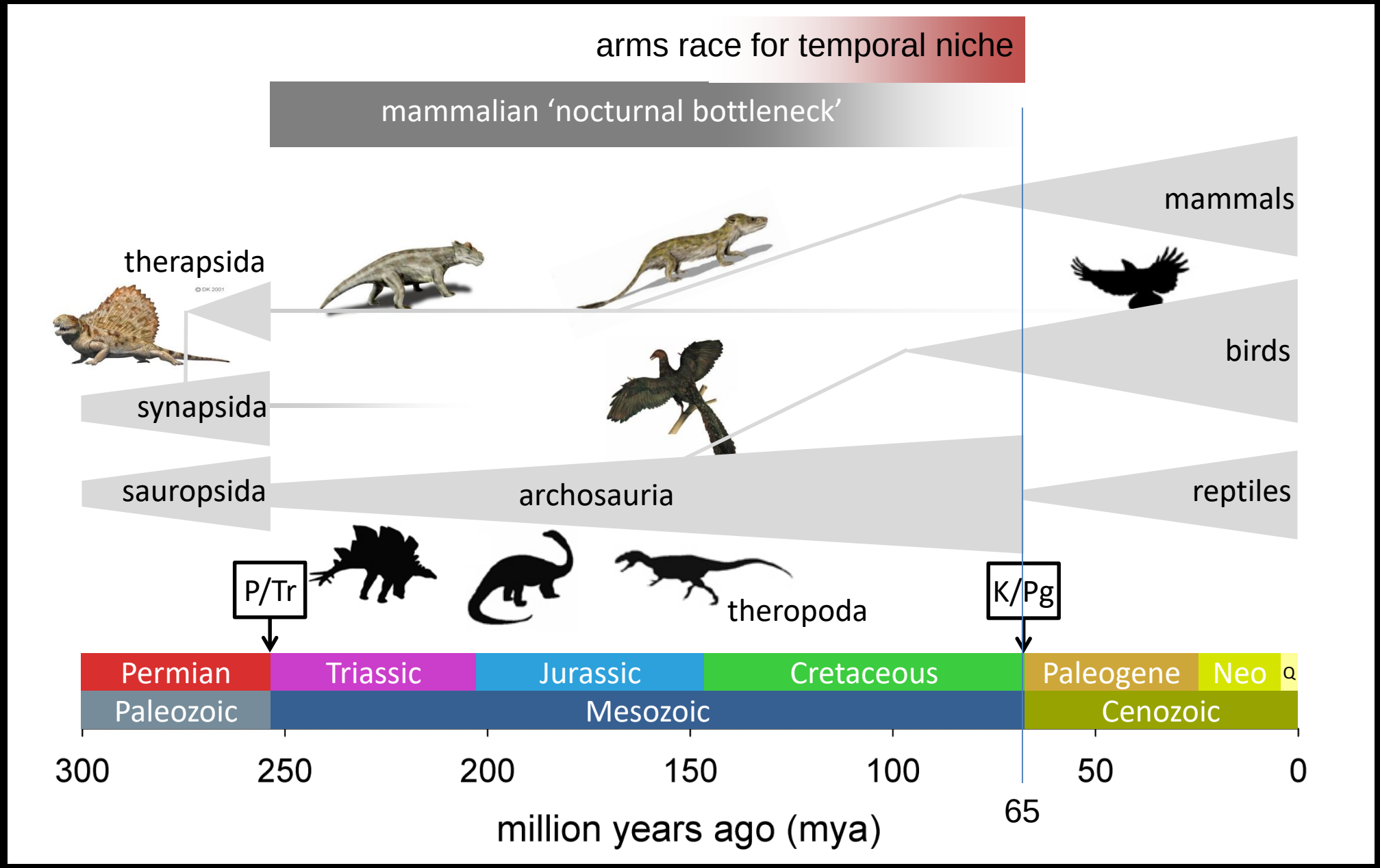
Fuss Crompton with a **Therapsid** fossil
at the Museum of Comparative Zoology, Harvard,
of which he was the director.

Alfred ‘Fuss’ Crompton
Born 1927

Megazostrodon (~200MYa)

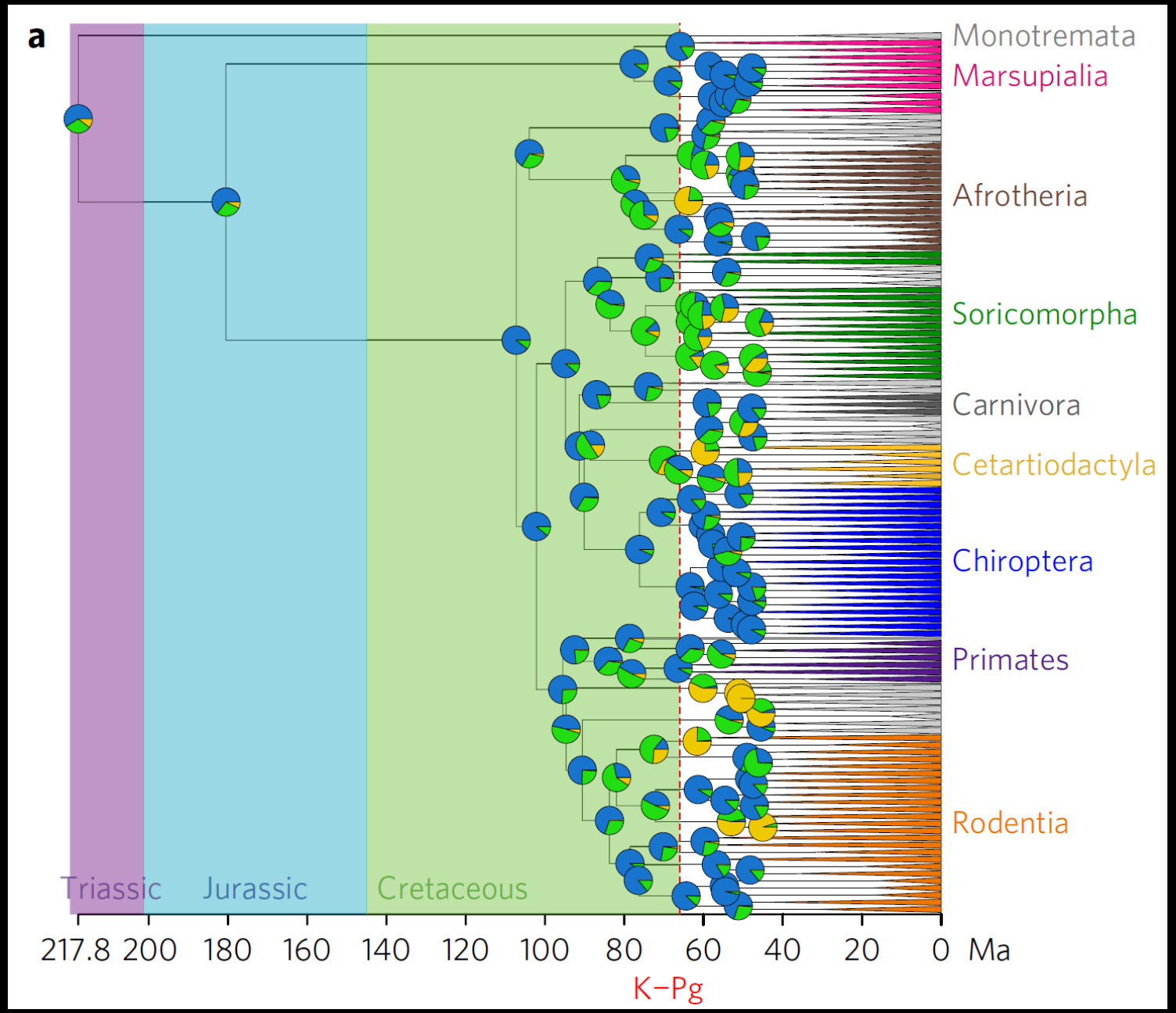
Fig. 1 Reconstruction of one of the earliest known mammals (*Megazostrodon rudnerae*) from the late Triassic, about 200 Myr ago.

De wapenwedloop voor de dagactieve / nachtactieve ecologische niche begon al voordat de Dino's uitstierven



Gerkema, Davies, Foster, Menaker, Hut (2013) ProcRoySocB

Phylogenetische evolutie van zoogdieren

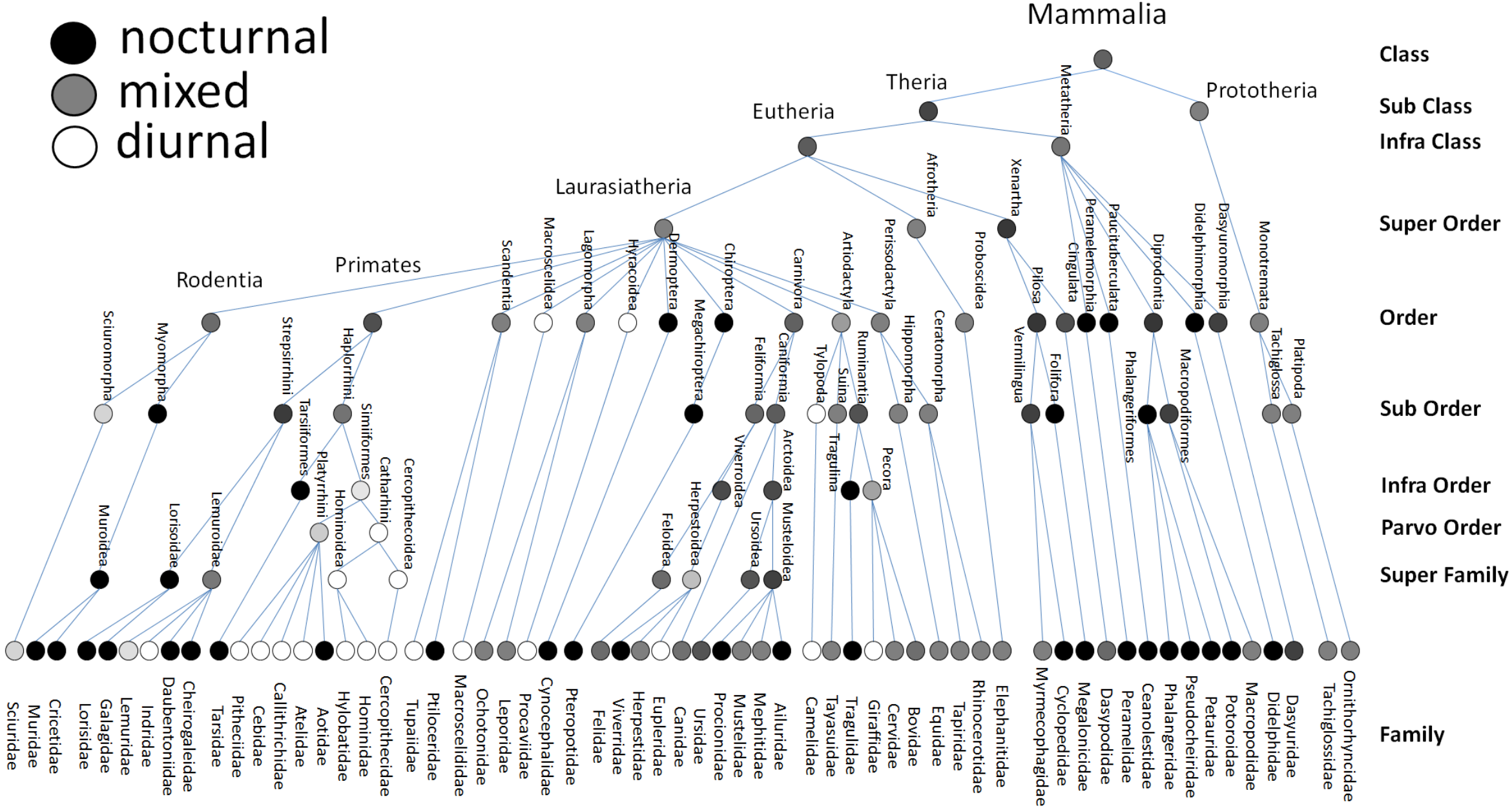


Dagactiviteit (geel)
ontstond **voor** K-Pg.

Schemeractiviteit (groen)
ontstond **lang voor** K-Pg

Maor et al 2017 Nature Ecol & Evol

Activity Patterns of the mammalian lineage



Nachtactiviteit vs. Dagactiviteit

De ‘nocturnal-bottleneck’ tijdens het mesosoicum
is de wapenwedloop tussen dino’s (dagactief) en zoogdieren (nachtactief)

Dit heeft mogelijk geleid tot diversificatie bij de zoogdieren (al voor het uitsterven van de dino’s!)
en een selectie voordeel voor plasticiteit van activiteits ritmiek.

Zien we hiervan iets terug bij huidige zoogdieren?

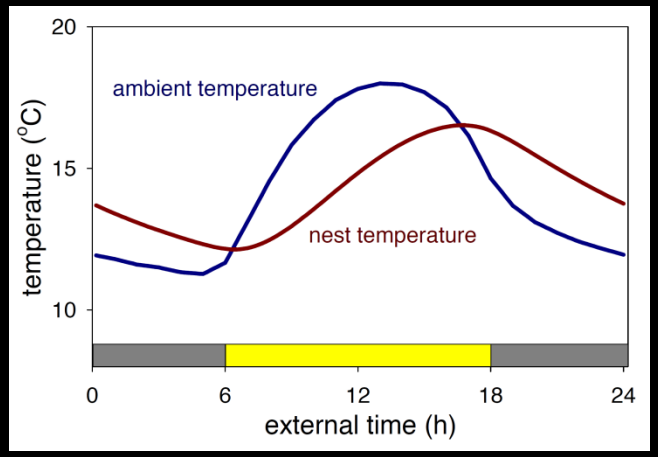
de Circadiane Thermo-Energetica hypothese

Hut et al. 2011 PLoS ONE
Hut et al. 2012 Progress in Brain Research
Van der Vinne et al 2014 PNAS
Van der Vinne et al 2015 JExpBiol
Riede et al 2017 JExpBiol
Van der Vinne et al 2019 EcolLett
Van Rosmalen et al. 2021 J. Biol. Rhythms
Van Rosmalen et al. 2024 CellReports
Van Rosmalen et al. 2024 CellMetabolism

Omgevingstemperatuur geeft energetisch voordeel voor dagactiviteity

Vincent van der Vinne

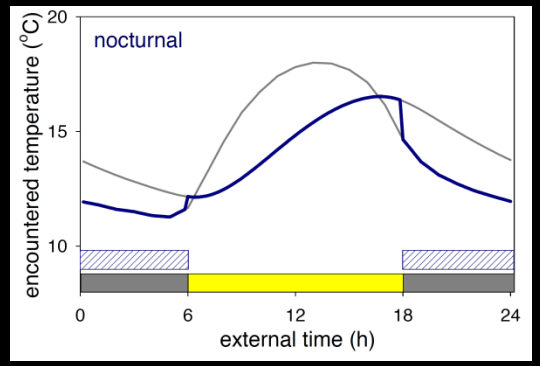
Newtonian cooling of a mouse nest

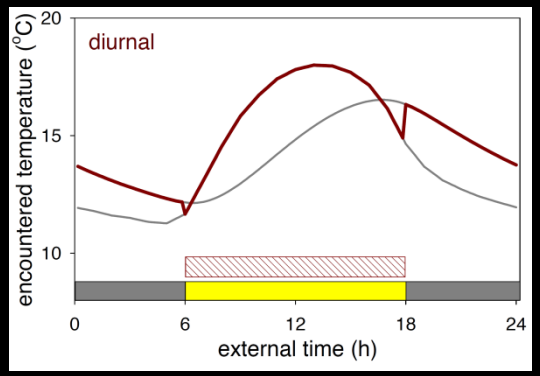


Modeleren van zoogdier energetica:

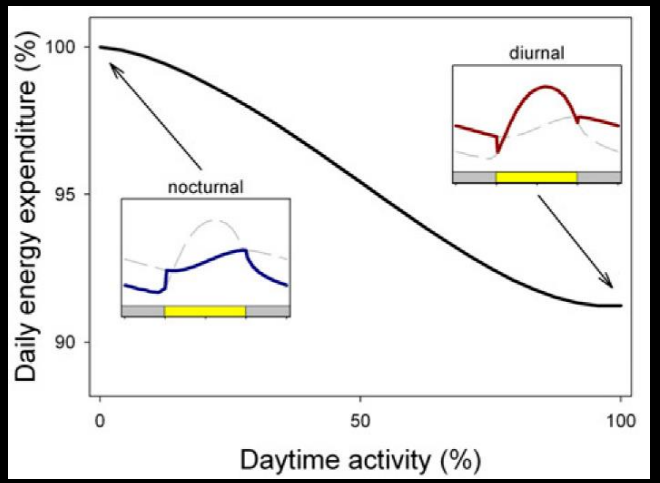
Nachtactiviteit kost energie!

T_a voor nacht / dag actief





Dagactiviteit is ~10% goedkoper



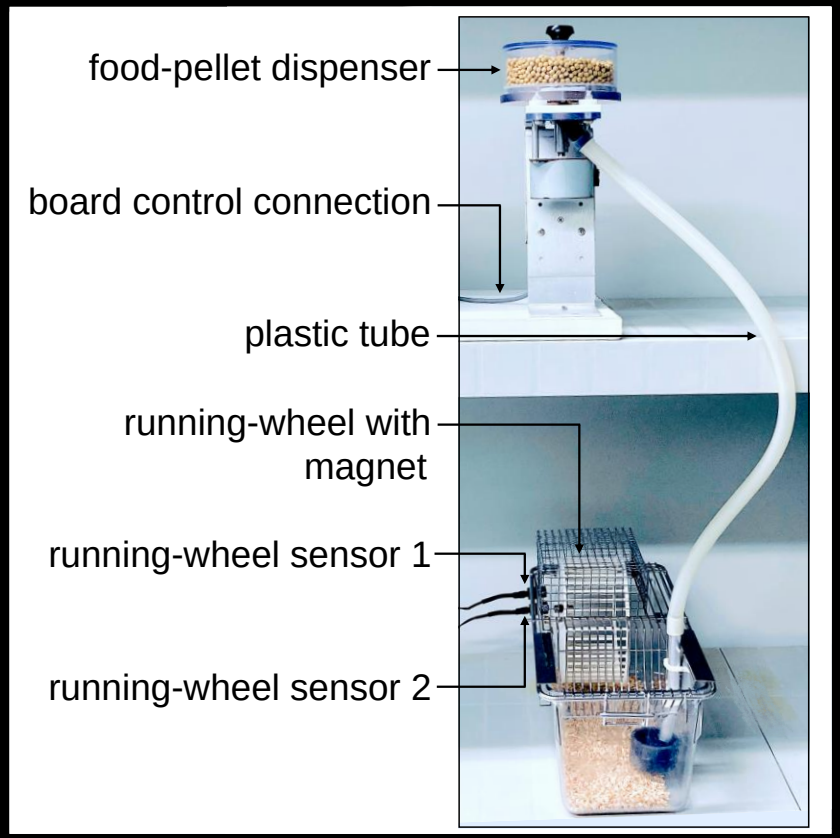
Van der Vinne et al 2014 PNAS

Hoe reageren kleine nachtactieve zoogdieren op lage voedsel dichtheid en lage temperatuur?

Common vole

House mouse

Het ‘Werken voor Voedsel’ protocol



Van Rosmalen et al. 2022 Neuromethods 186
Hiroti et al. (eds) doi:10.1007/978-1-0716-2577-4_9

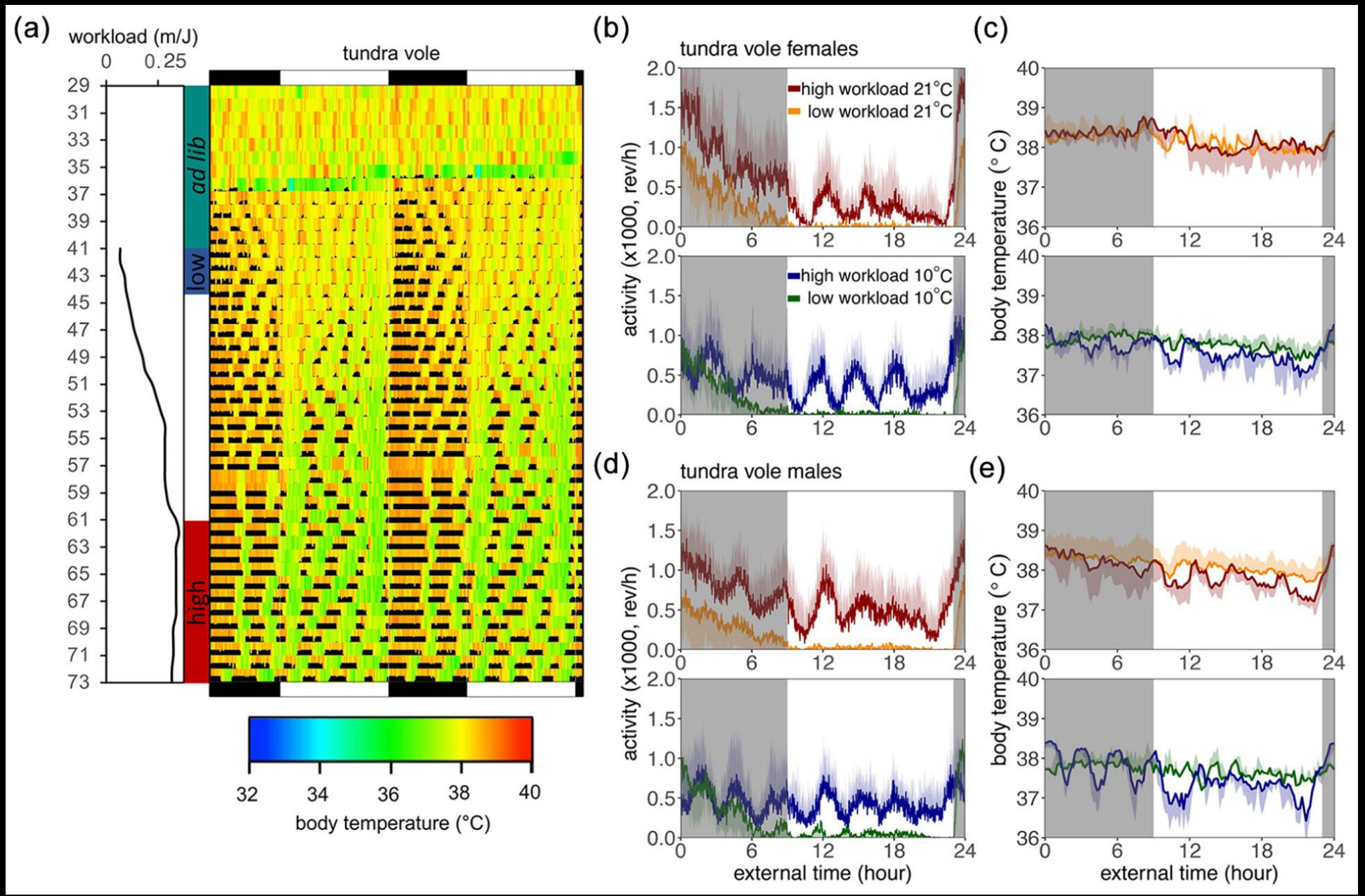
Violetta Pilorz

Vincent van der Vinne

Sjaak Riede

Laura van Rosmalen

‘Werken voor Voedsel’ protocol (negative energy balance) induceert ultradiaane dag&nacht activiteit in veldmuizen

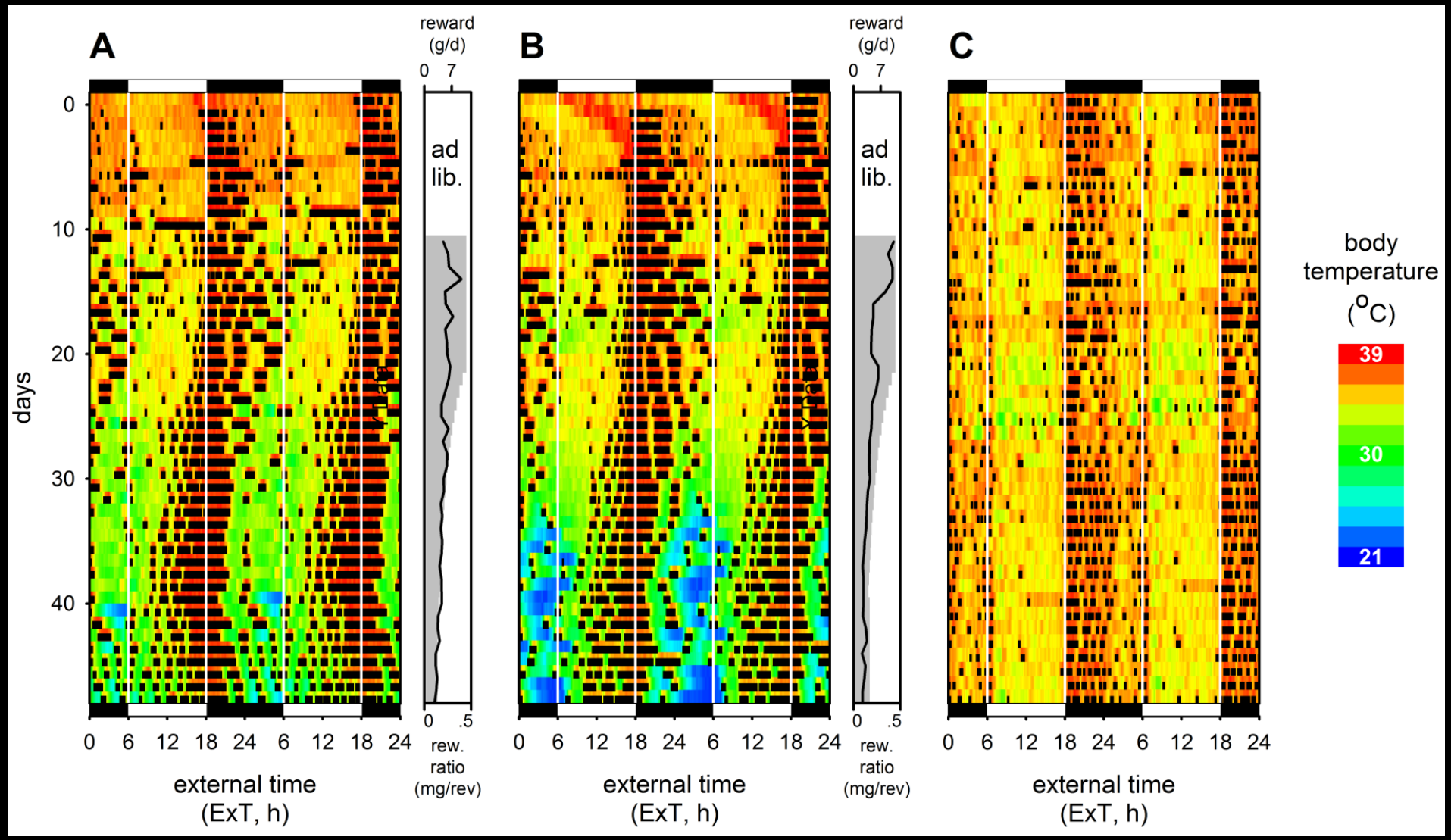


Tundra vole

Laura van Rosmalen

Van Rosmalen & Hut JBR 2021

‘Werken voor Voedsel’ protocol:
Negatieve energie-balans maakt nachtactieve muizen dagactief!



Violetta Pilorz

Huismuis

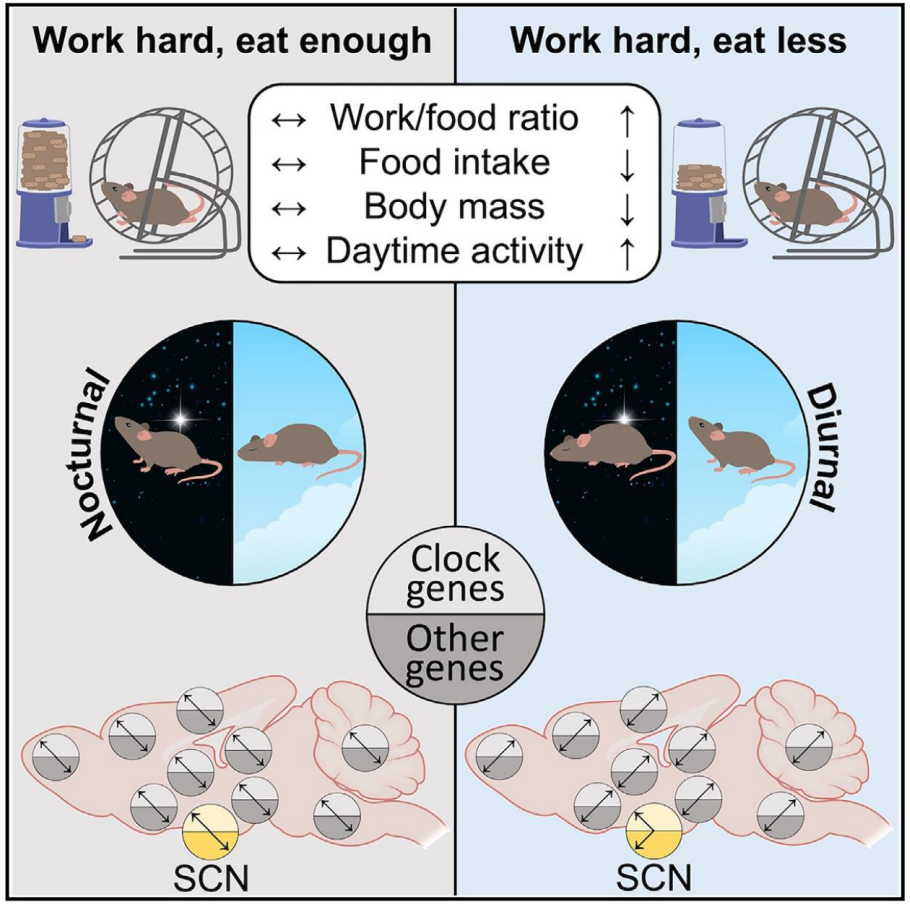
Hut, Pilorz et al. 2011 PLoS ONE

Cell Reports

Resource

Energy balance drives diurnal and nocturnal brain transcriptome rhythms

Graphical abstract



Authors

Laura van Rosmalen, Shaunak Deota, Geraldine Maier, ..., Ramesh K. Ramasamy, Roelof A. Hut, Satchidananda Panda

Correspondence

r.a.hut@rug.nl (R.A.H.), satchin@salk.edu (S.P.)

In brief

van Rosmalen et al. present a rhythmic transcriptome atlas of 21 tissues, including 17 brain regions, from nocturnal and diurnal mice. A distinct set of rhythmic genes is linked to the temporal niche. The habenula emerged as the most affected tissue, suggesting a role in the observed nocturnal-diurnal switch.

Satchin Panda

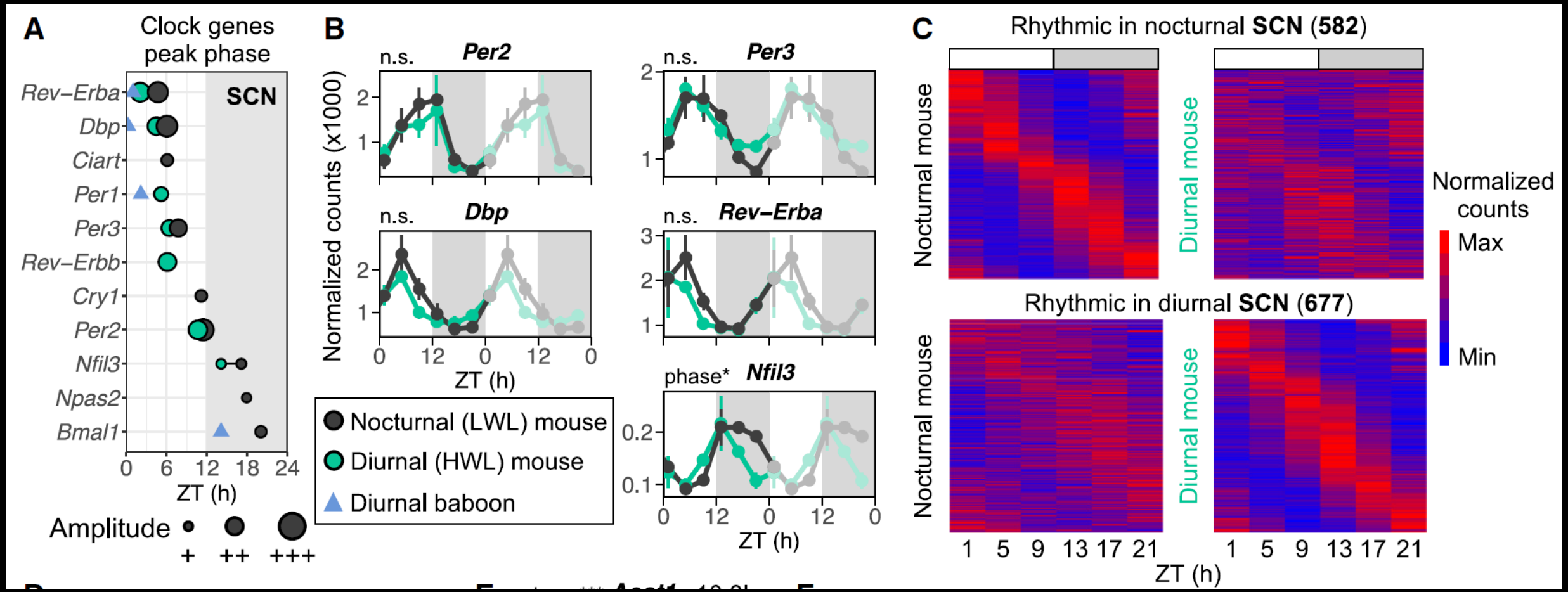
Laura van Rosmalen

Highlights

- The SCN clock is resistant to a behavioral nocturnal-diurnal switch
- Extra-SCN clocks adapt to a behavioral nocturnal-diurnal switch
- Nocturnal and diurnal phenotypes are associated with specific sets of rhythmic genes
- The habenula is most affected, implying a role in driving nocturnal-diurnal switches

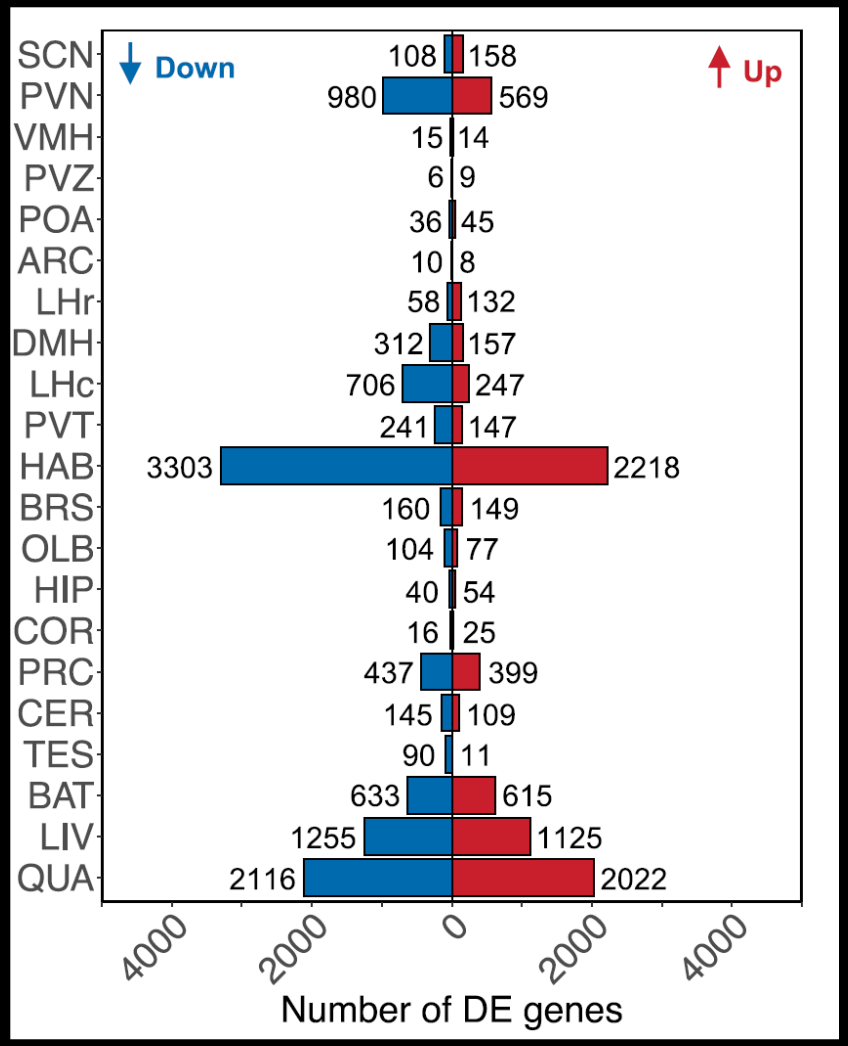
Van Rosmalen et al 2024 Cell Reports

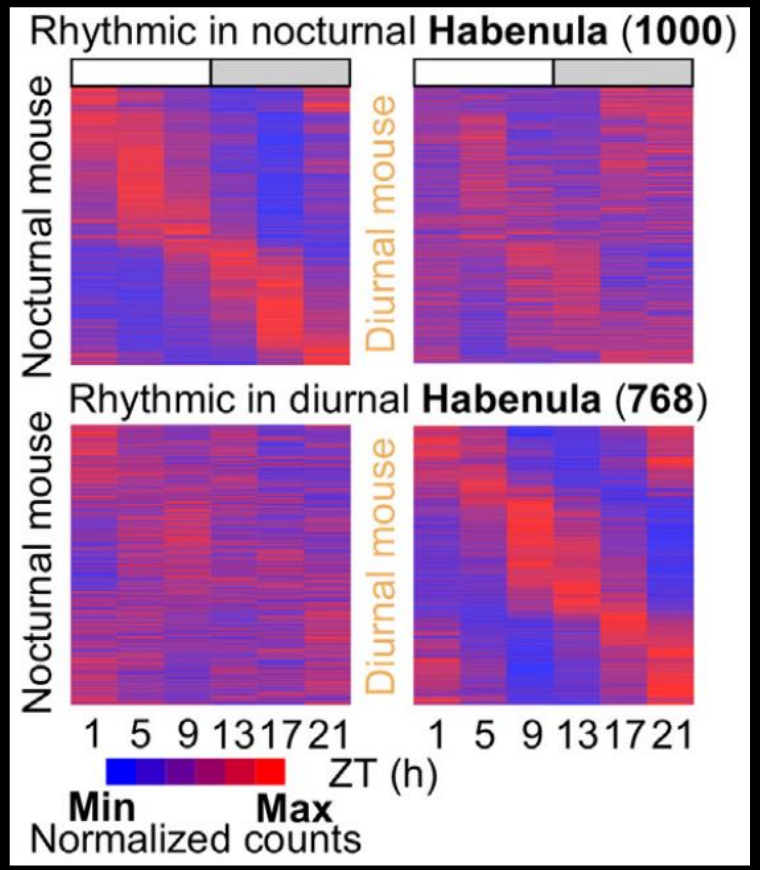
The composition of rhythmic (output) genes in the SCN changes, but not the clock genes!

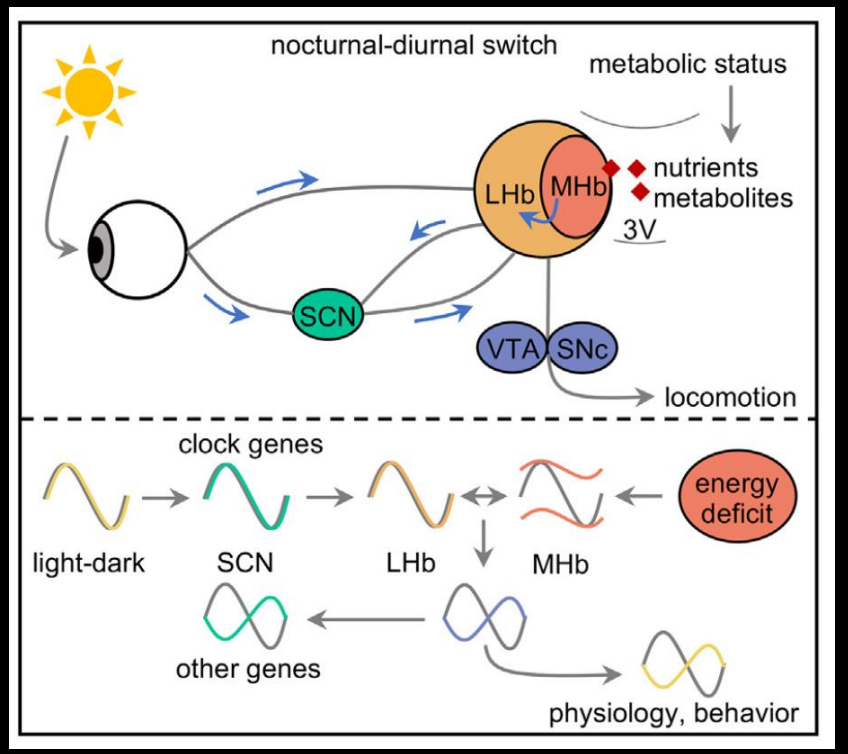


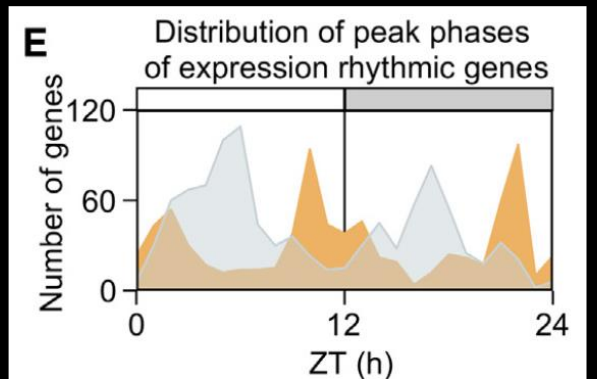
Van Rosmalen et al 2024 Cell Reports

Most changes in gene expression and rhythmic gene expression are in habenula
The (medial) Habenula may contain the nocturnal/diurnal switch in mice







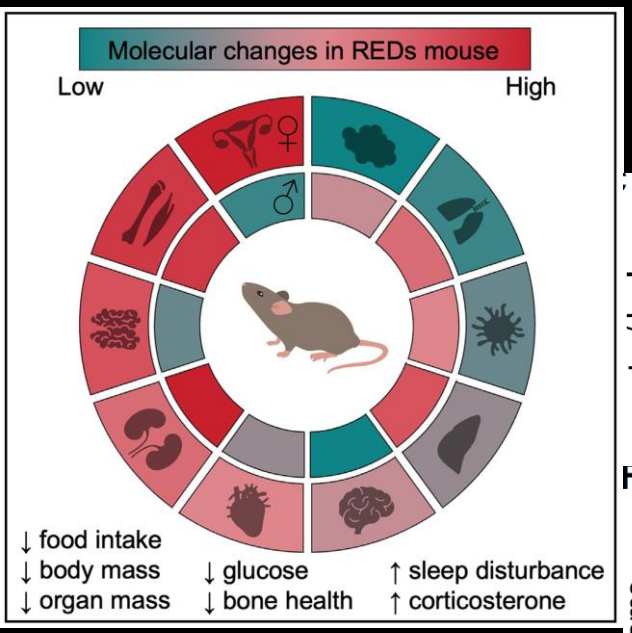


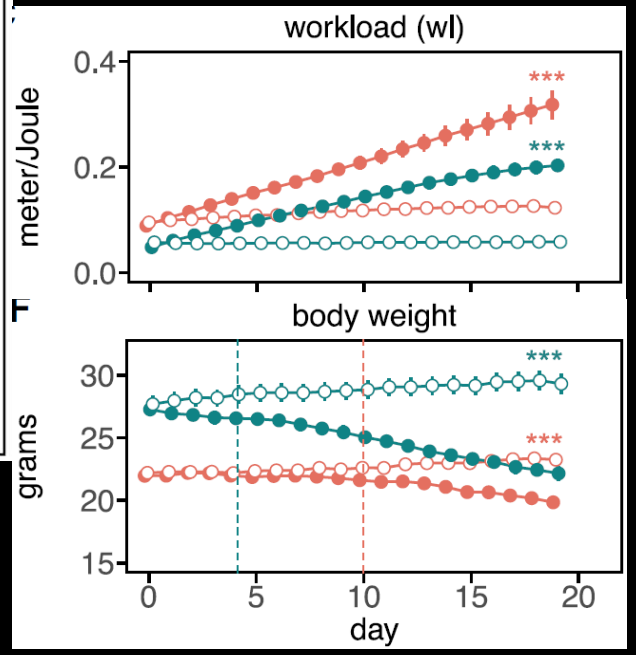
Van Rosmalen et al 2024 Cell Reports

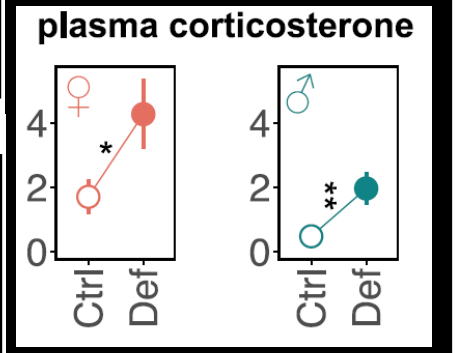
Cell Metabolism

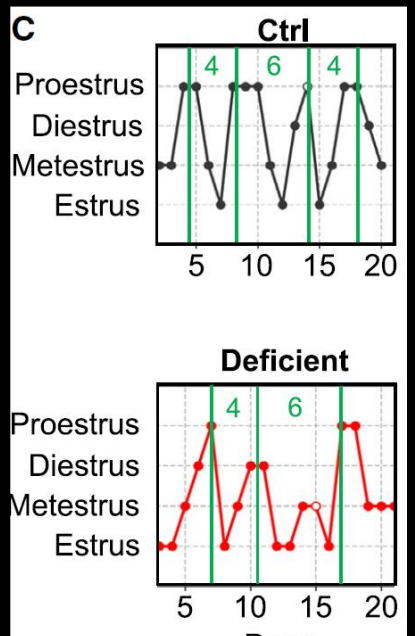
Multi-organ transcriptome atlas of a mouse model of relative energy deficiency in sport (REDs)

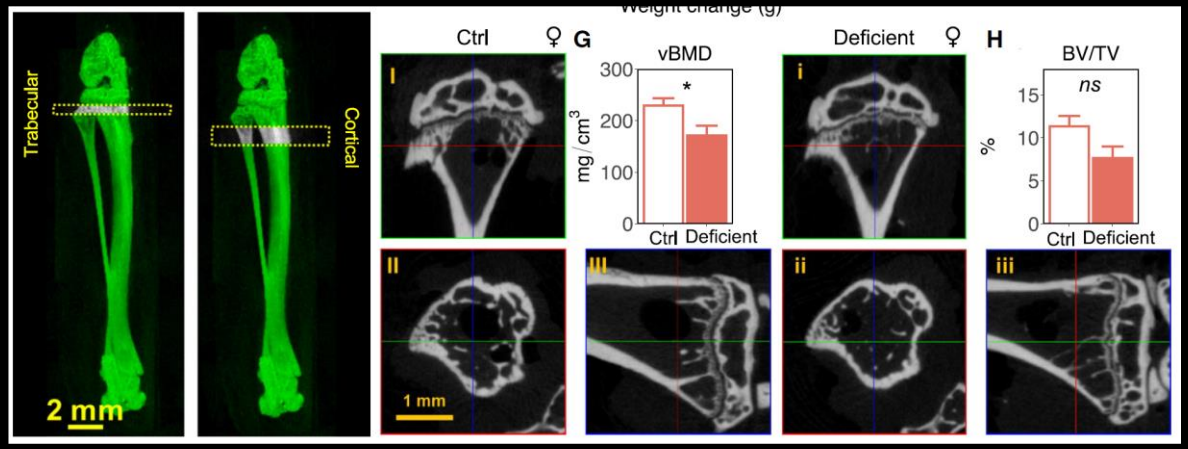
REDs voorheen
Female Athletic Triad

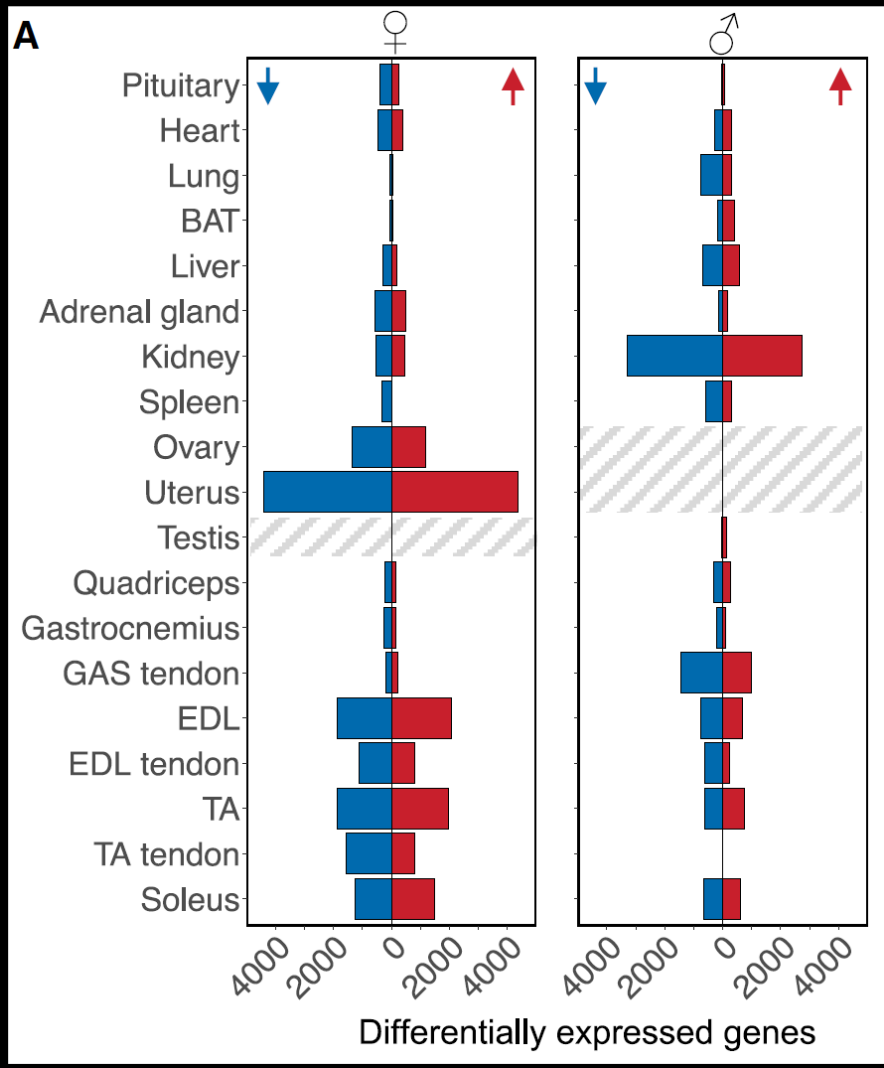








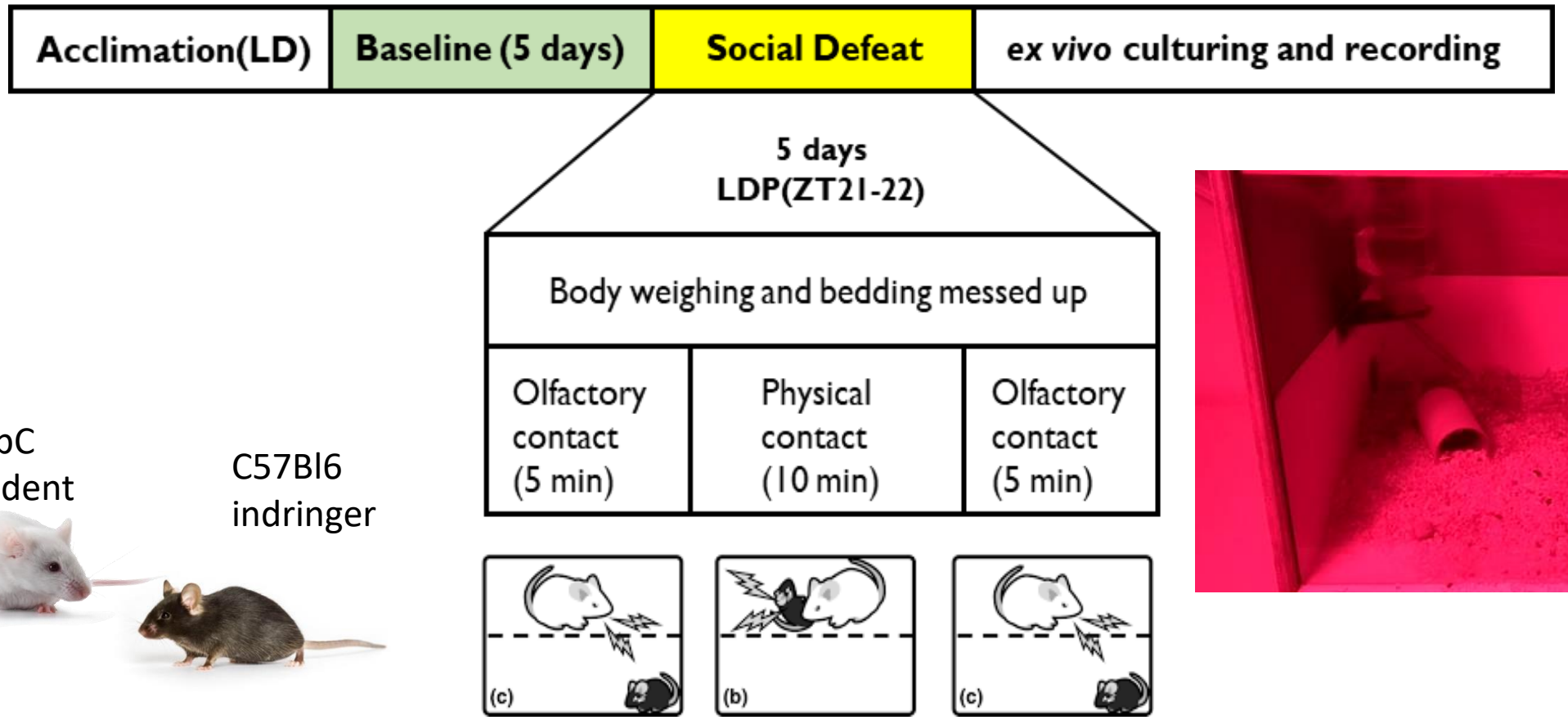




Van Rosmalen et al. 2024 Cell Metabolism

The social defeat stress protocol

1. Trunk blood collection
2. Tissue collection: lung, kidney, pituitary



BalbC resident

C57Bl6 indringer

Toyoda, *Animal Science Journal*, 2017

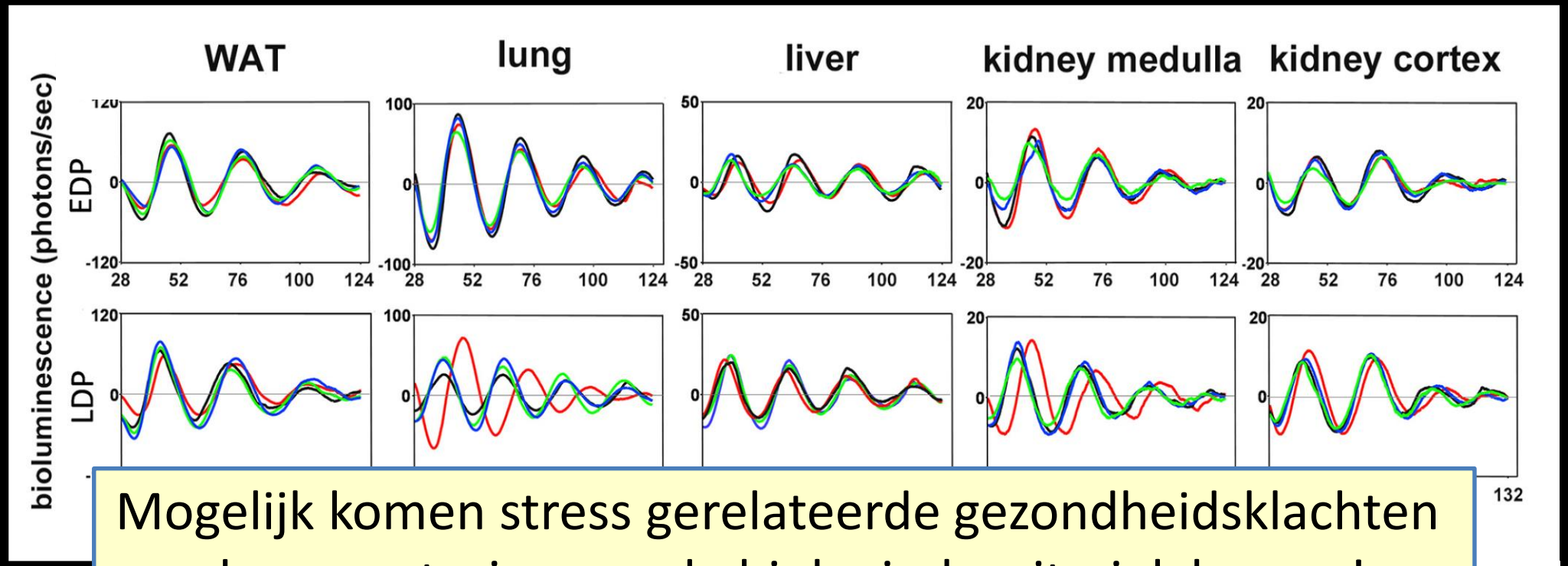
Koolhaas et al. 2013

Chronische stress kan het circadiaan ritme in organen verstoren,

vooral aan het eind van de activiteit/begin rust, als cortisol laag is

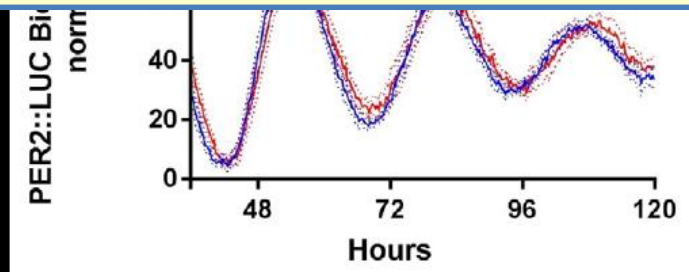
Simone Ota

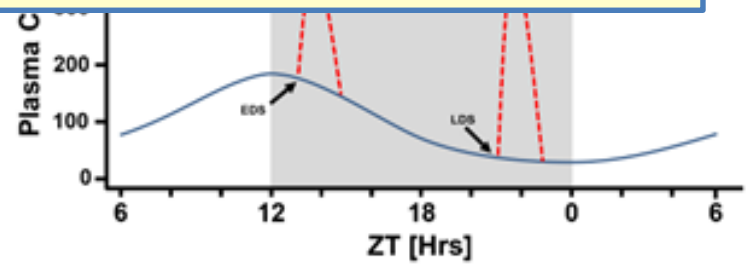
Xiangpan Kong



Mogelijk komen stress gerelateerde gezondheidsklachten door verstoring van de biologische ritmiek komen!

Circadiaan Syndroom ?!





Ota et al. 2020 PhysBeh (DD)
Kong et al. 2022 JBR (LD)

Gezondheidsklacht:

Slaap

Cognitie

Spijsvertering

Cardio-vasculair

Metabolisch

Nier functie

Respiratoir

Kanker

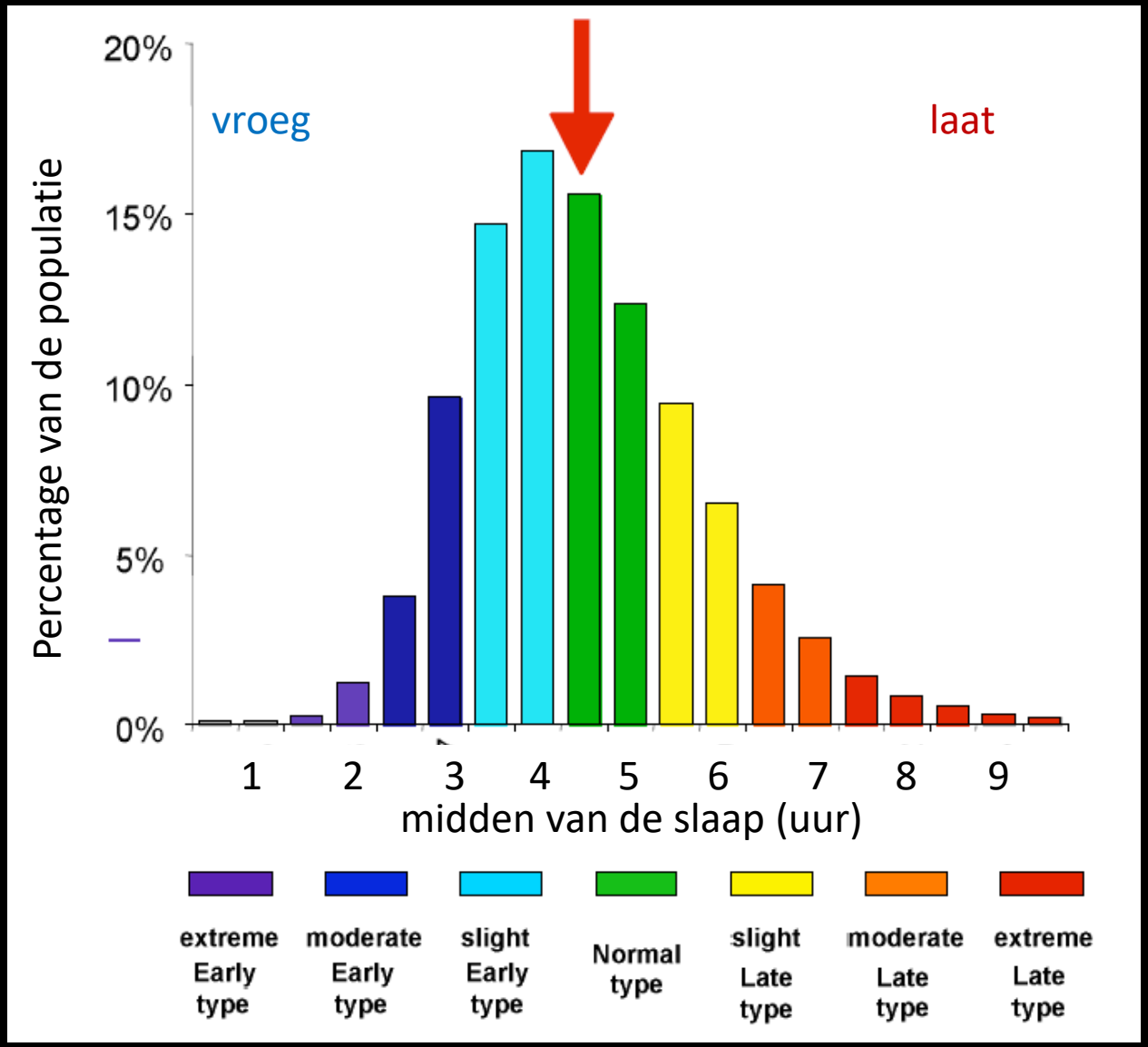
Hoofdpijn / Spierpijn

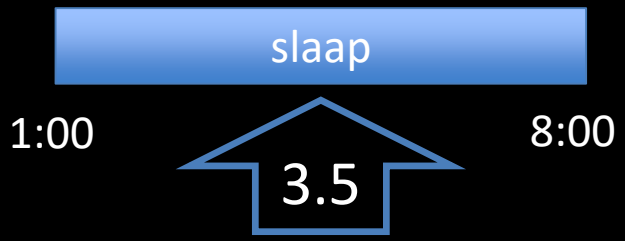
	STRESS		PLOEGENDIENST	
Health problems	**Stress**	**References**	**Shift Work**	**References**
Sleep related symptoms:				
Difficulty falling asleep	✓	(Kalmbach et al., 2018)	✓	(Omholt et al., 2017)
Poor sleep quality	✓	(Darwaj et al., 1977)	✓	(Reis et al., 2016)
Fatigue	✓	(Vandekerckhove et al., 2011)	✓	(Santos et al., 2004b)
Insomnia	✓		✓	(Chatterjee & Ambekar, 2017)
Cognitive symptoms:				
Impaired memory	✓	(Menard et al., 2017)	✓	(Kwak et al., 2020)
Decreased (motor) performance	✓	(de Souza-Talarico et al., 2011)	✓	(Roman et al., 2023a)
Anxiety, Depression	✓		✓	
Mood swings, Difficulties concentrating	✓		✓	
	✓		✓	
Gastrointestinal issues:				
Abdominal pain	✓	(Alonso et al., 2008)	✓	(Roman et al., 2023b)
Indigestion / digestive issues	✓	(Konturek et al., 2011)	✓	(Nojkov et al., 2010)
Constipation	✓	(Bhatia & Tandon, 2005)	✓	(Caruso et al., 2004)
Diarrhea	✓		✓	(Sveinsdóttir, 2006)
Bowel disorder	✓		✓	(Segawa et al., 1987)
				(Saberi & Moravveji, 2010)
				(Zhen Lu et al., 2006)
Cardiovascular issues:				
Increased heart rate	✓	(Azza et al., 2020)	✓	(Furlan et al., 2000)
Increased blood pressure	✓	(Manenschijn et al., 2013)	✓	(Fujiwara et al., 1992)
Metabolic issues:				
Diabetes	✓	(Harris et al., 2017)	✓	(Mukherji et al., 2019)
Fatty liver disease	✓	(Shea et al., 2021)	✓	(Lim et al., 2020)
Obesity	✓	(Tomiyama, 2019)	✓	
Endocrine disruption	✓		✓	
Renal issues:				
Chronic kidney disease	✓	(Bruce et al., 2015)	✓	(Charles et al., 2013)
Adrenal glands dysfunction	✓		✓	(Uhm et al., 2018)
Respiratory issues:				
Shallow breathing	✓	(Ritz & Kullowatz, 2005)	✓	(Omholt et al., 2017)
Impaired lung function	✓		✓	(Aquino-Santos et al., 2020)
				(Santos et al., 2004a)
Cancer:				
Breast cancer	✓	(Zheng et al., 2023) (Hou et al., 2013) (Dai et al., 2020)	✓	(Gehlert & Clanton, 2020)(Papantoniou et al., 2017)
Colon cancer	✓		✓	
Other physical symptoms:				
Headache	✓	(Ursin et al., 1988)	✓	(Lin et al., 2007)
Muscle pain	✓		✓	(Brum et al., 2015)
				(Appel et al., 2020)

Kan chronische stress tot circadiaan syndroom' leiden, vergelijkbaar met ploegendienst ?

Melenhorst & Hut *in prep*

Chronotype (midden van de slaap op vrije dagen)



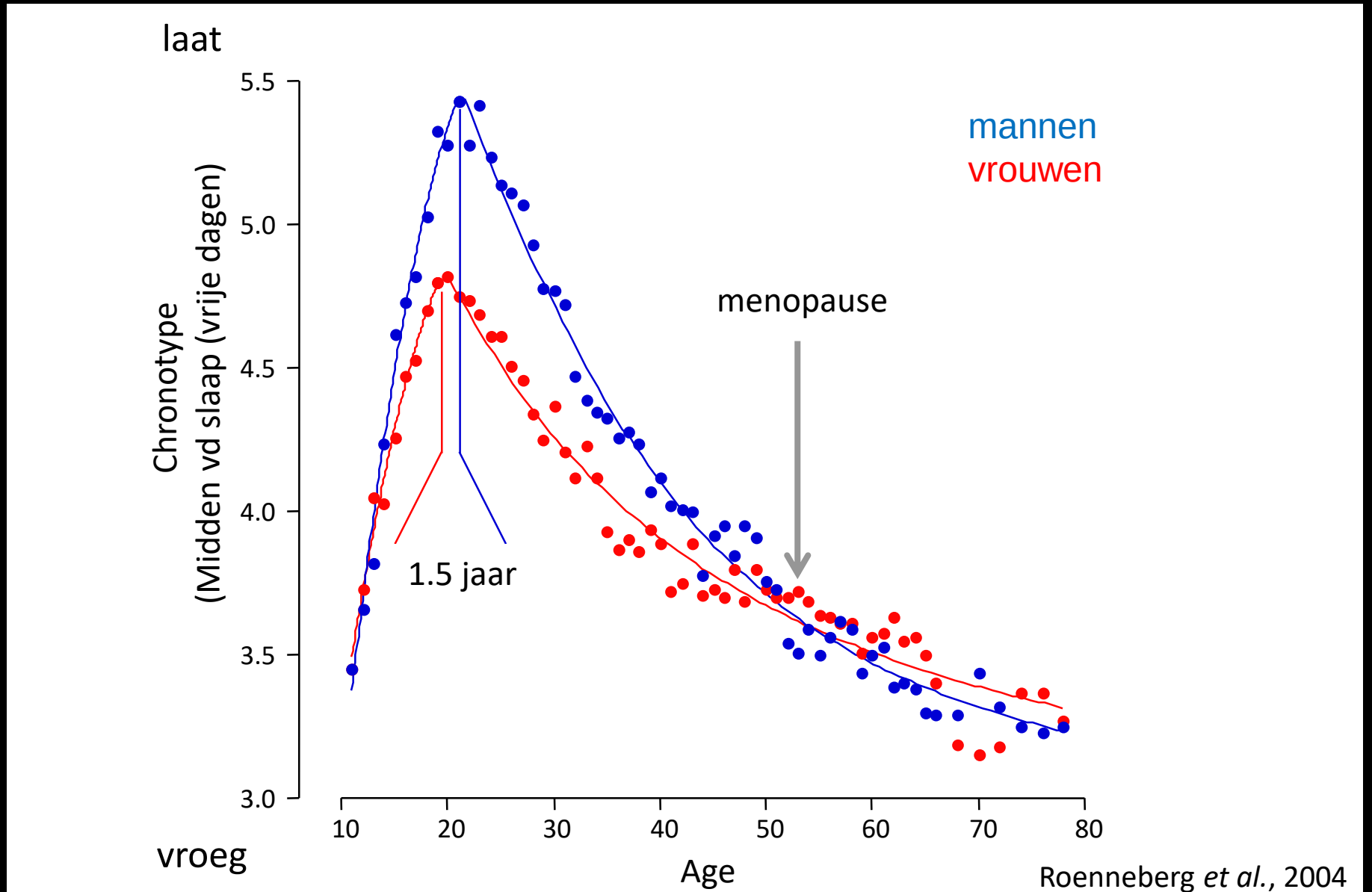


- Veel variatie tussen personen (vroege en late types !)
- Mensen slapen laat rond hun 20e
- Mannen zijn later dan vrouwen
- Late chronotypes hebben vaak SLAAP TEKORT!
- Late chronotypes presteren hierdoor slechter, zowel mental als fysiek!

N>150.000

Roenneberg et al. 2007

Chronotype hangt af van geslacht en leeftijd



Timing
externe stimulus

Licht-donker cyclus

voedsel

stress

fysieke inspanning

SCN

pijnappelklier

Brein

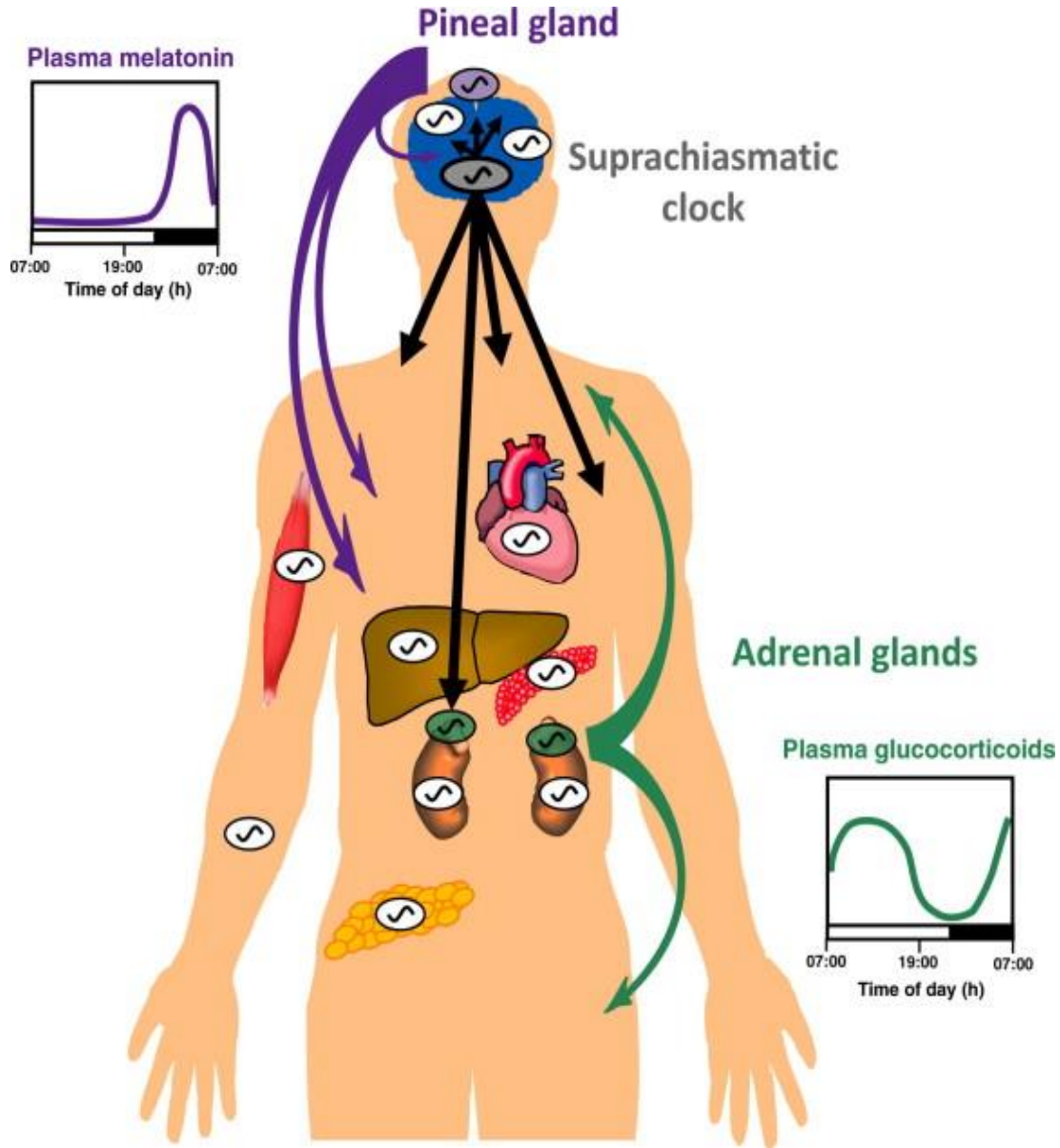
lever
spijsvertering

bijnier

long

hart

skelet spier



Hoe kunnen we social jetlag (= slaap tekort) en interne desynchronisatie voorkomen?

Regelmaat voor slaap en voeding!

Vroege chronotypes:
- ochtend: oranje bril
- middag: rust
- avond: fysieke training

Late chronotypes:
- ochtend: zonlicht
- middag: fysieke training
- avond: rust + oranje bril

Hoe staat de biologische klok van NIBI bezoekers afgesteld?

Kom langs bij BioClock in de koffiepauze & doe de test!

BIOKLOK.NL

Chronobiology unit 2024
University of Groningen

https://bioclockconsortium.org