

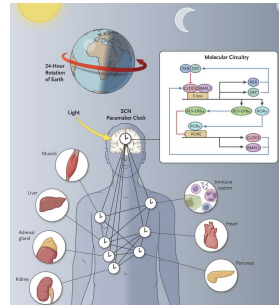


chronobiology: the basics and the clinical implications

Rodolfo Costa & Sara Montagnese




the circadian timing system as an adaptation to cyclic environmental changes



Allada & Bass, NEJM 2021

talk outline

- the discovery of the first clock gene
- circadian, infradian and ultradian clocks
- a model for the circadian clock system
- the evolution of circadian rhythmicity
- adaptive significance of circadian programs
- the mammalian circadian clock system
- genetic variability in clock genes

the first clock mutants in the fruit fly



Proc. Nat. Acad. Sci. USA
Vol. 68, No. 9, pp. 2112-2116, September 1971

Clock Mutants of *Drosophila melanogaster*

(eclosion/circadian/rhythm/X chromosome)

RONALD J. KONOPKA AND SEYMOUR BENZER

Division of Biology, California Institute of Technology, Pasadena, Calif. 91109
Contributed by Seymour Benzer, July 8, 1971

ABSTRACT Three mutants have been isolated in which the normal 24-hour rhythm is drastically changed. One mutant is arrhythmic; another has a period of 19 hr; a third has a period of 28 hr. Both the eclosion rhythm of a population and the locomotor activity of individual flies are affected. All these mutations appear to involve the same functional gene on the X chromosome.

1984 - *period* controls circadian rhythmicity

P-Element Transformation with period Locus DNA Restores Rhythmicity to Mutant, Arrhythmic *Drosophila melanogaster*

Wilson A. Zdzienicka, David A. Wheeler, Christiane Rosbash, Michael W. Young, Michael Rosbash, and Jeffrey C. Hall

per⁰ arrhythmic fly

per⁰ transformed with *per⁺* gene rhythmic fly

Restoration of circadian behavioral rhythms by gene transfer in *Drosophila*

Michael A. Rosbash, J. Ash Jackson, & Michael W. Young

Proceedings of the National Academy of Sciences, Vol. 81, No. 12, June 1984, pp. 3618-3622

2017 Nobel prize in Physiology or Medicine

2017 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Jeffrey C. Hall
Michael Rosbash
Michael W. Young

"For their discovery of molecular mechanisms controlling the circadian rhythm"



all these organisms have a circadian clock

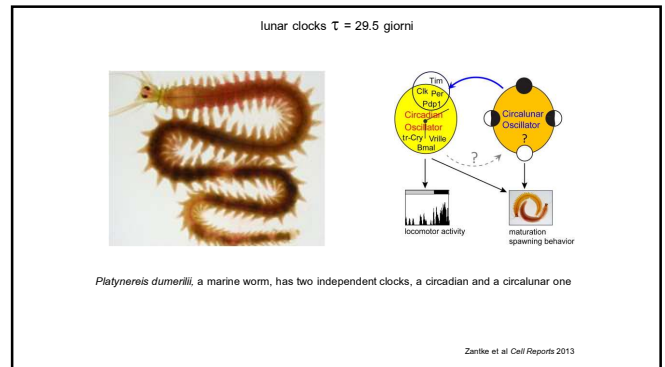
<p>Cyanobacteria</p>	<p>Drosophila</p>	<p>Arabidopsis</p>
<p>Neurospora</p>	<p>Mouse</p>	<p>Human</p>

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different endogenous clocks dictate time in different temporal domains

	type of rhythm	cycle length
<i>solar influence</i>		
	circadian	24 hours
	annual / seasonal	365 days
<i>lunar influence</i>		
	lunar	29.5 days
	semilunar	14.8 days
	tidal	12.4 hours



lunar influence on human reproductive behaviour remains controversial

SCIENCE ADVANCES | RESEARCH ARTICLE

PHYSIOLOGY

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

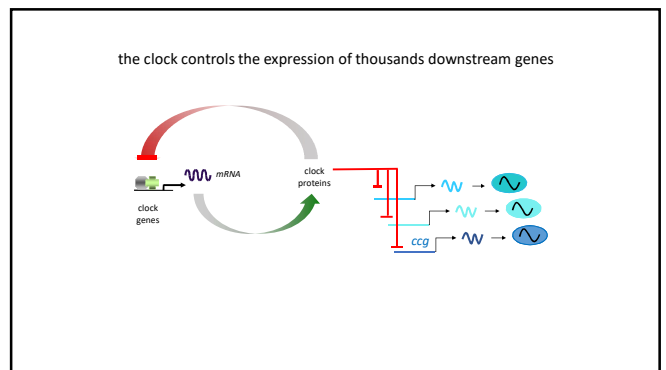
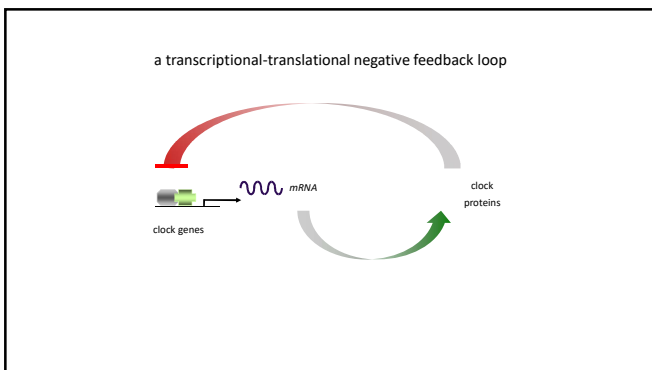
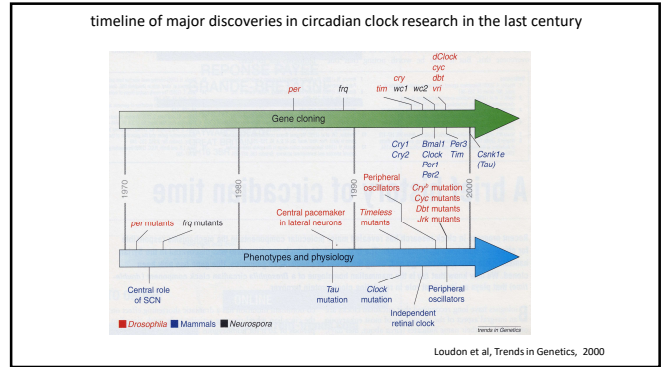
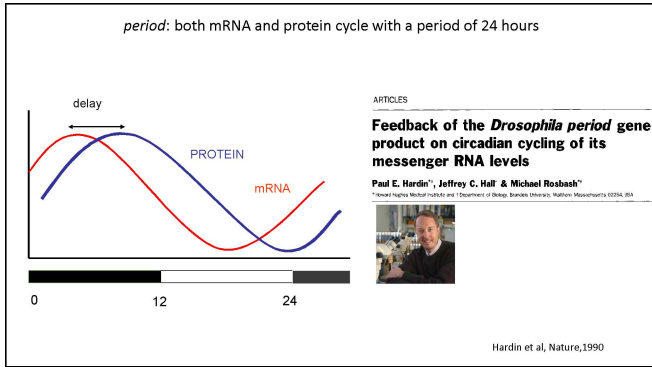
C. Helfrich-Förster^{1*}, S. Monecke², I. Splousas³, T. Hovestadt⁴, O. Mitesser⁵, T. A. Wehr⁶

- long records (up to 32 years) of menses onsets in 22 women
- the approach allows to investigate the possibility that lunar influence might be present intermittently and in different forms over a woman's life
- the study tests the influence of both moon gravity and moon luminance on menses onsets

Helfrich-Foerster et al Science Adv 2021

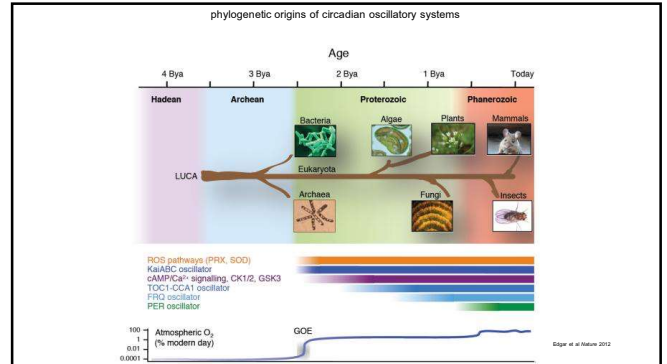
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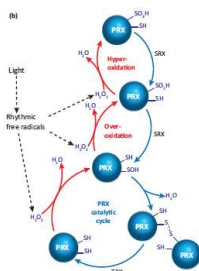


talk outline

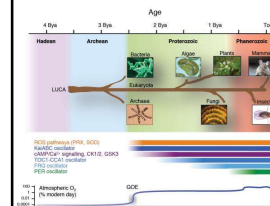
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non transcriptional time-keeping:
rhythmic production of peroxide (H₂O₂) drives rhythms in the oxidation level of peroxidorexin (PRX) proteins



a proto-clock based on kinases



peroxidorexins oxidation-reduction cycles are an indicator of time being kept by an unknown ancient timekeeper

while core clock gears are different in different life domains, it is always kinases - and the same type of kinases - that set the speed of the clock

two of these, Casein kinase 1 (CK1) and Glycogen synthase kinase 3 (GSK3) are also important in pacing peroxidorexin clocks

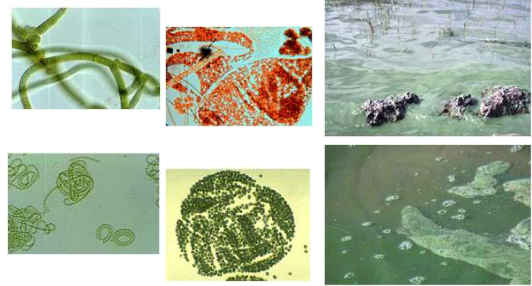
It is therefore possible that:

- kinases may have formed a simple ancestral timer leading to the features of the clocks we see today

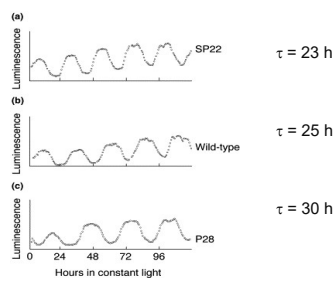
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adaptive significance of circadian programs in cyanobacteria

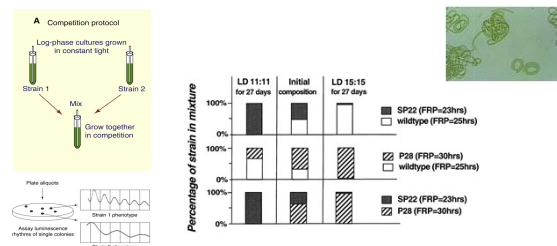


wild type and mutant strains exhibit different free running periods



Johnson et al., Trends Microbiol., 1998

competitive advantage when the period of the clock resonates with the environmental cycles



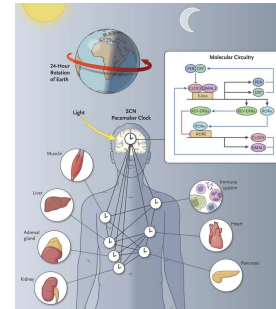
This is the first rigorous demonstration in any organism of an advantage conferred by a circadian system to fitness

Johnson et al., Trends Microbiol., 1998

talk outline

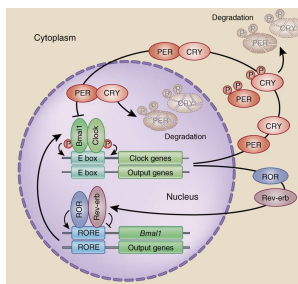
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the mammalian circadian master clock maps in the suprachiasmatic nuclei (SCN)

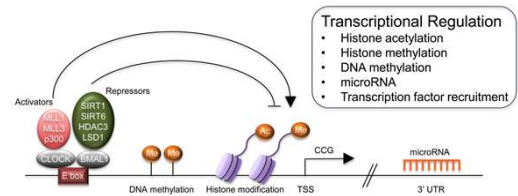


Allada & Bass, NEJM 2021

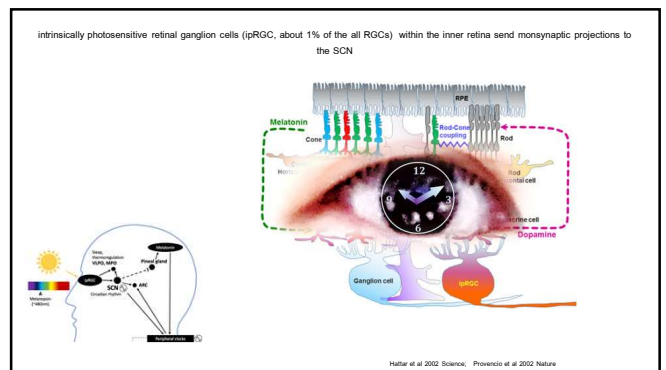
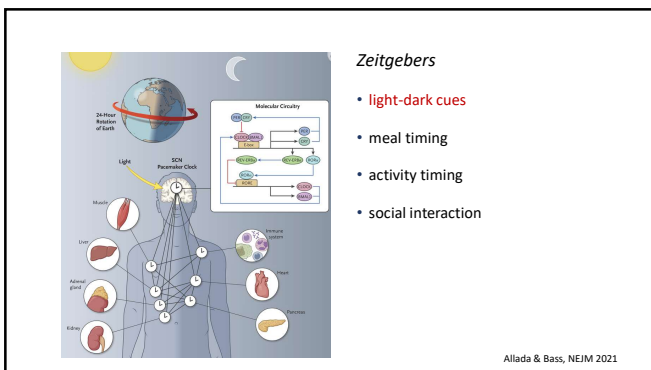
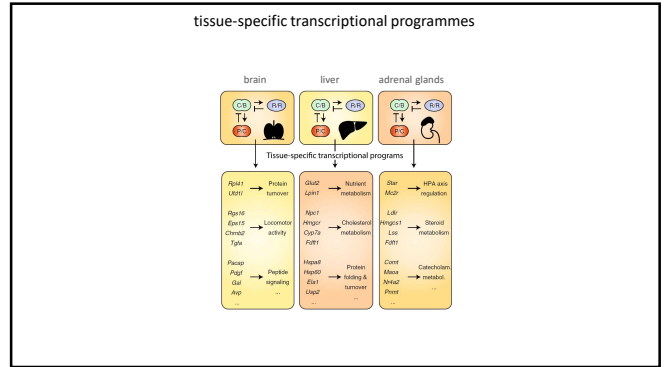
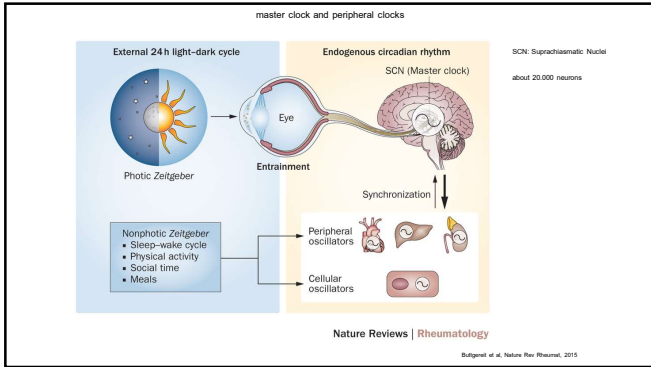
the molecular mechanism of the circadian clock in mammals

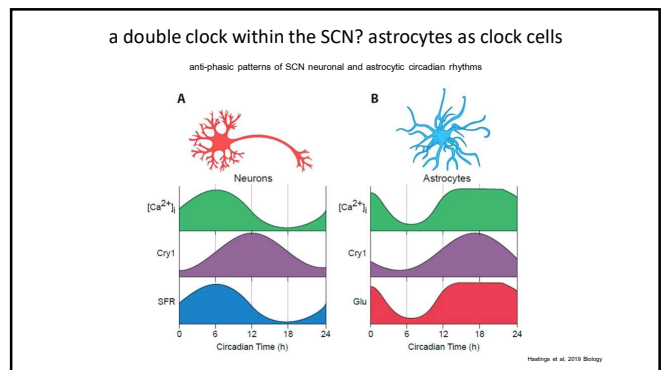
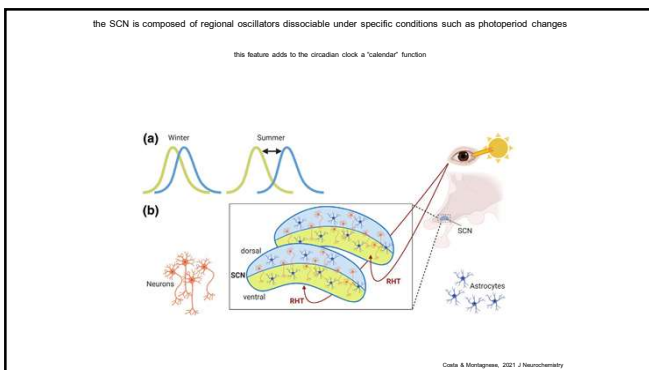
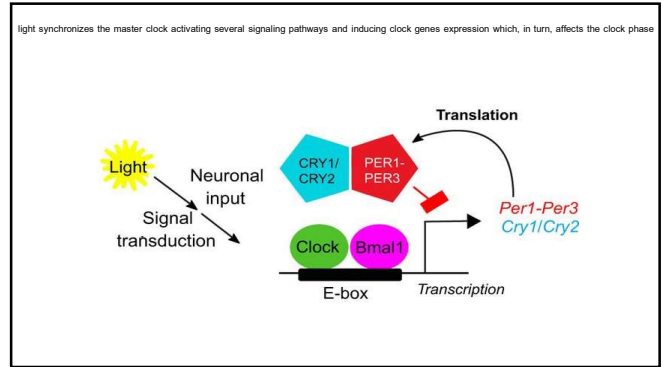
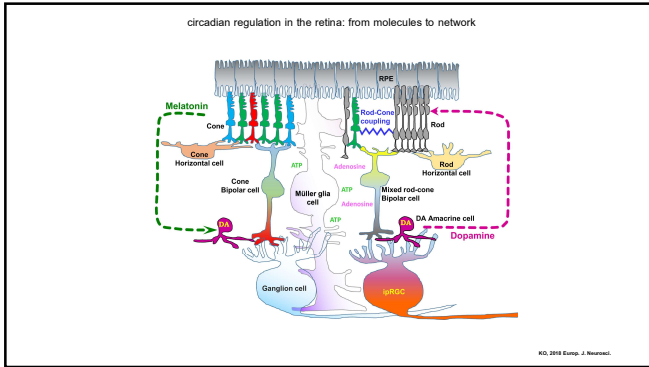


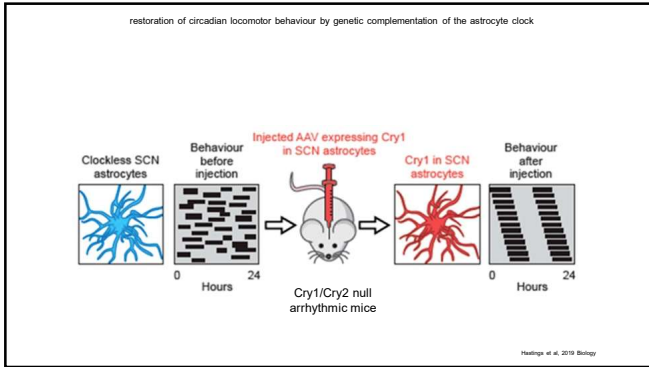
the activating heterodimer CLOCK:BMAL1 binds to the E-box elements on the genome
additional regulators and chromatin remodelers contribute to circadian gene expression



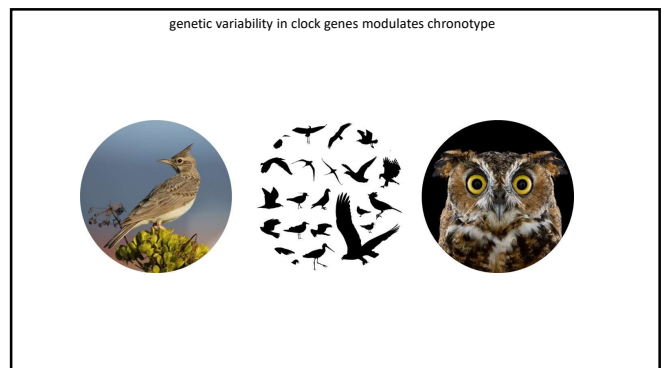
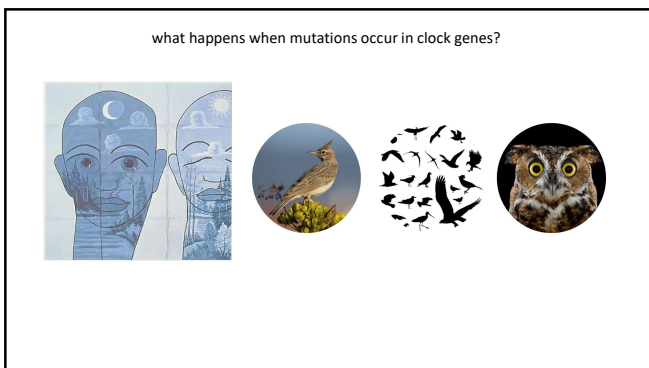
Masi et al. 2015. Curr Opin Oncol

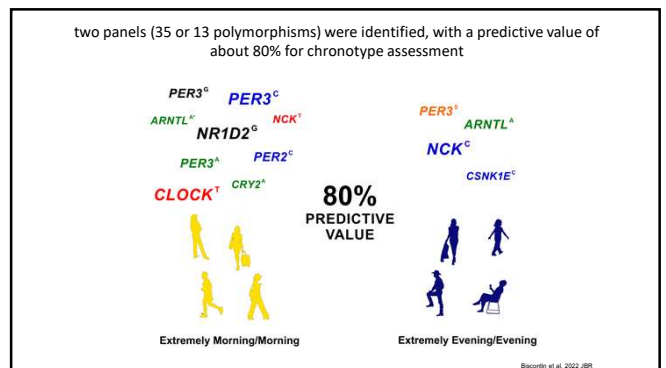
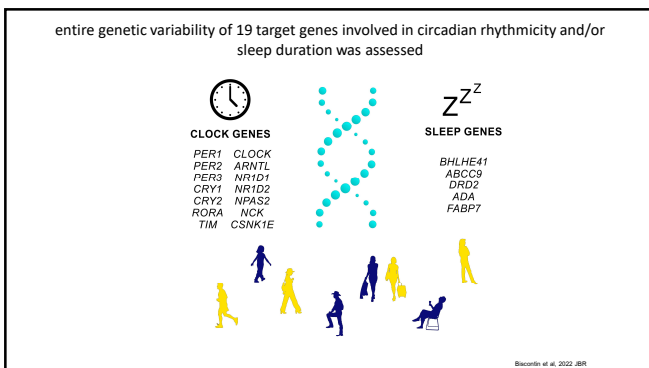
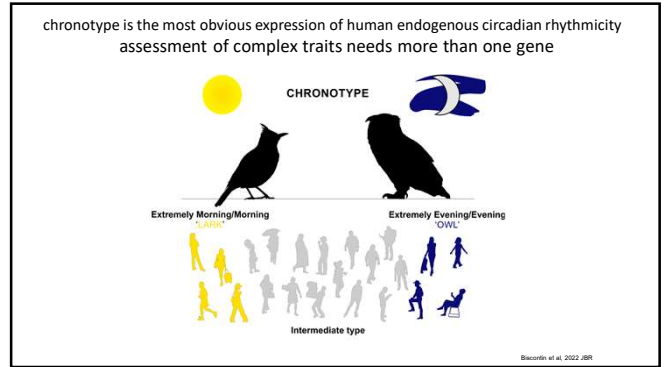
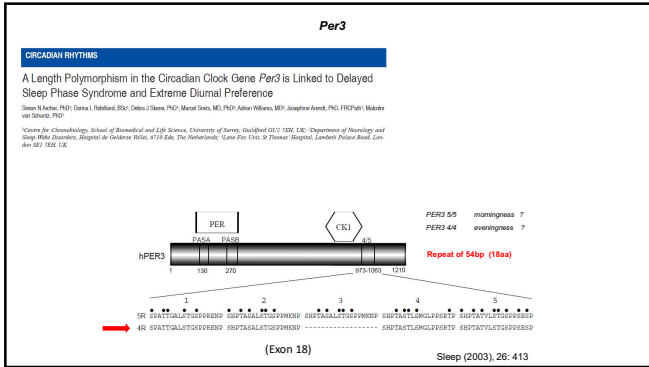


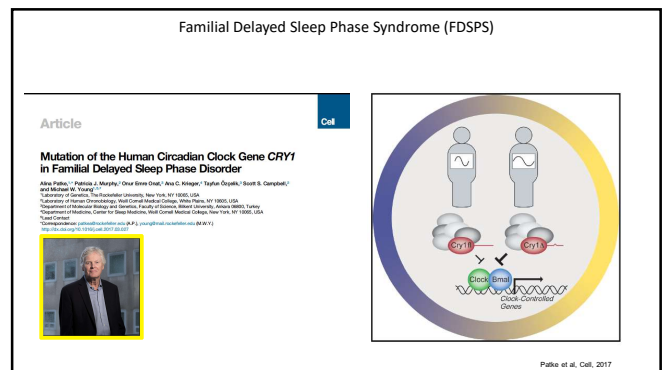
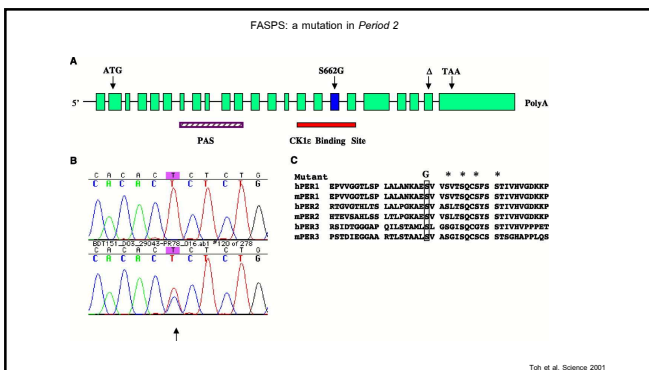
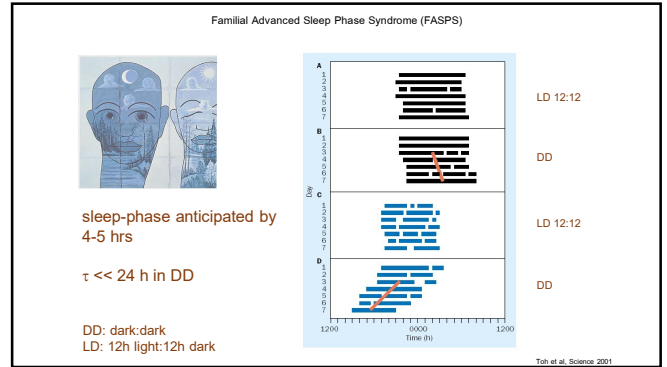
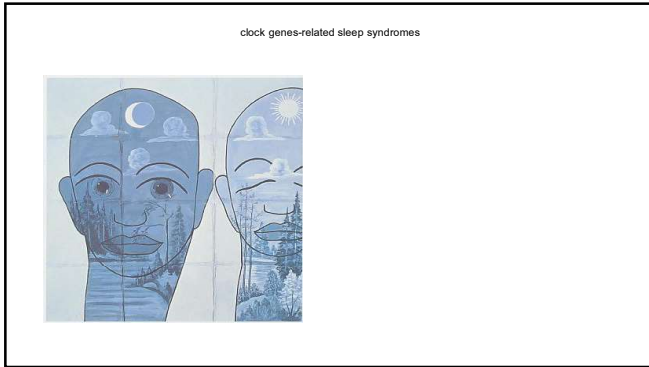


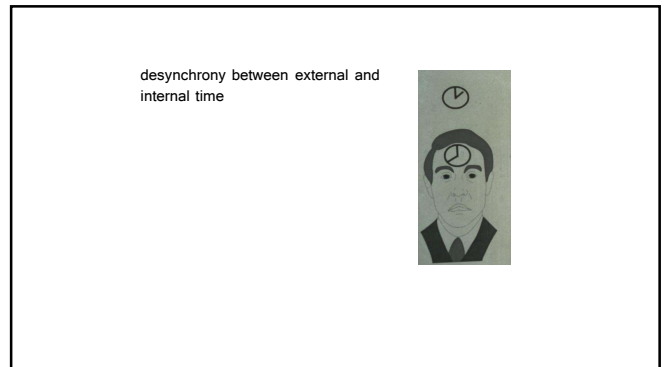
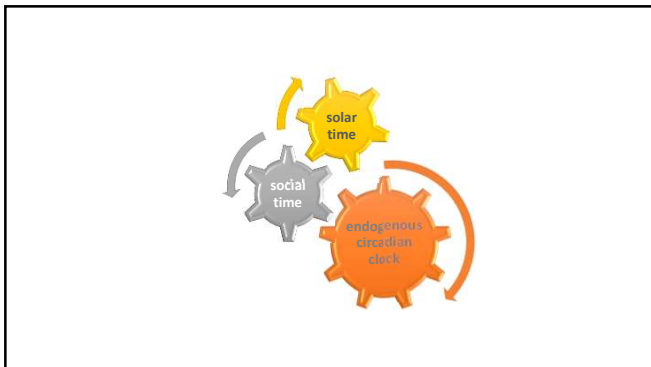
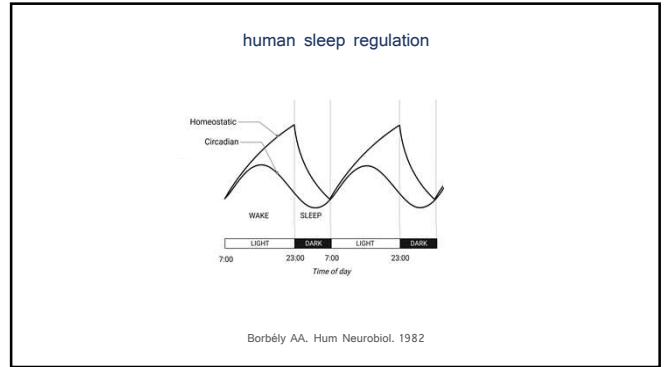
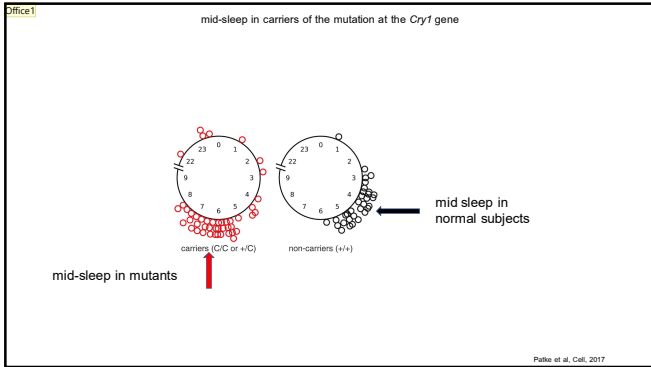


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desynchrony between external and internal time

- poor sleep
- waking hours: napping, fatigue, reduced performance, increased accident/injury risk



desynchrony between external and internal time

- poor sleep
- waking hours: napping, fatigue, reduced performance, increased accident/injury risk
- overweight
- metabolic syndrome
- cardiovascular disease
- some types of cancer



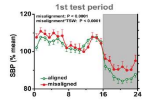

NHS female nurses

	Baseline History of Rotating Night Shift Work				P Value for Trend
	None	<5 y	5-9 y	≥10 y	
NHS cohort					
CHD incidence rate ^a	425.5	435.1	525.7	596.9	
HR (95% CI) ^b	1 [Reference]	1.02 (0.97-1.08)	1.12 (1.02-1.22)	1.18 (1.10-1.26)	<.001
First half of follow-up					
CHD incidence rate ^a	367.3	382.4	483.1	494.4	
HR (95% CI) ^b	1 [Reference]	1.10 (1.01-1.21)	1.19 (1.03-1.39)	1.27 (1.13-1.42)	<.001
Second half of follow-up					
CHD incidence rate ^a	436.6	424.8	520.7	556.2	
HR (95% CI) ^b	1 [Reference]	0.98 (0.92-1.05)	1.08 (0.96-1.21)	1.13 (1.04-1.24)	.004
NHS cohort					
CHD incidence rate ^a	122.6	130.6	151.6	178.0	
HR (95% CI) ^b	1 [Reference]	1.05 (0.97-1.13)	1.12 (0.99-1.26)	1.15 (1.01-1.32)	.01

^aAge-adjusted rates per 100 000 person-years.
^bMultivariable-adjusted hazard ratio (HR).

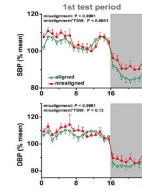
Vetter et al., JAMA 2016

misalignment,
BP and HR



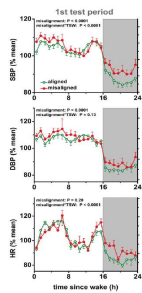
Morris et al., PNAS 2016

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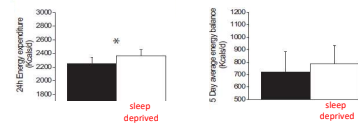
Morris et al., PNAS 2016

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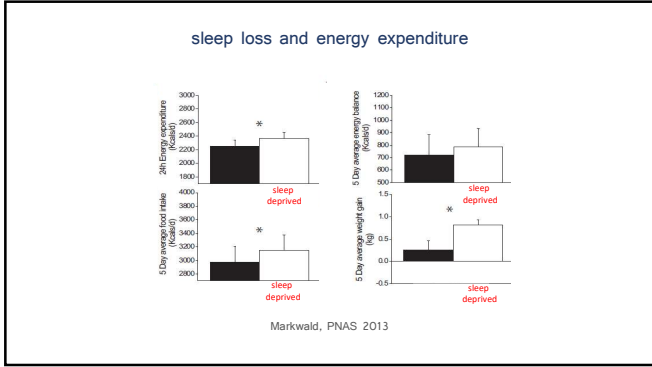


Morris et al., PNAS 2016

sleep loss and energy expenditure



Markwald, PNAS 2013



disturbance of daily rhythms in chronic illness

- epidemiological data on chronic illnesses that have been associated with misalignment
- pertinent pilot treatment data /mechanistic data in healthy volunteers

disturbance of daily rhythms in chronic illness

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- pertinent pilot treatment data /mechanistic data in healthy volunteers
- sporadic examples of the relevance of daily rhythms to disease outcome/management

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

David Montagna, Xavier Morellet, Thomas Muller, Augustin Colone, Séphora Mouton, Georges Fayat, Sandra Nivet, Céline Metz, David Séverin, Clève Sarrès, Charlotte Pirelli, Alexandre Berthelot, Céline Chénouart, Catherine Piretton, Fabrice Dupont, Jérôme Escalhout, William Chau, Dominique Lantier, Benoît Dupont, Bruno Jégou, Mathieu Bouvier, Jean Louis Gillet, Philippe Lefebvre, Axel Souch

Lancet 2018

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- circadian profiles in a few illnesses of interest
- circadian sleep-wake disturbance within such profiles
- pertinent pilot treatment data

organ clock disruption


organ disease/complications

organ clock disruption



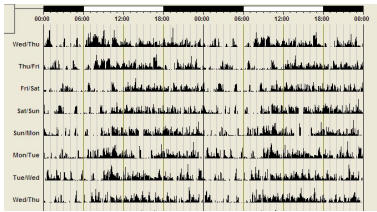
organ disease/complications



organ clock disruption 

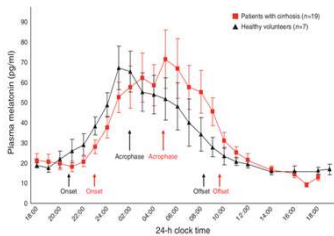
organ disease/complications

disturbed sleep and cirrhosis



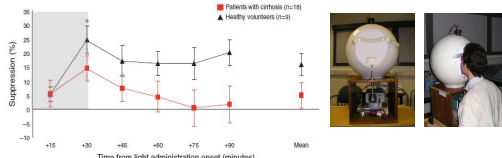
Cordoba et al., 1998; Montagnese et al., 2009; Kim et al., 2021

24-hour melatonin rhythm in cirrhosis



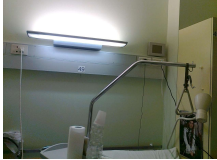
Steindl et al., 1995; Veilssaris et al., 2008; Montagnese et al., 2010

melatonin response to light in cirrhosis



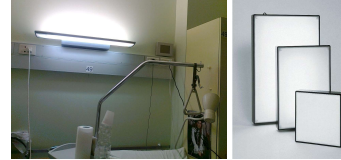
Montagnese et al., Am J Gastro 2010

treatment with light in cirrhosis



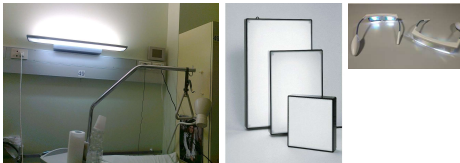
De Rui et al., Neurochemical Research 2015

treatment with light in cirrhosis



De Rui et al., Neurochemical Research 2015

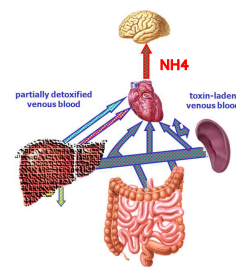
treatment with light in cirrhosis



De Rui et al., Neurochemical Research 2015

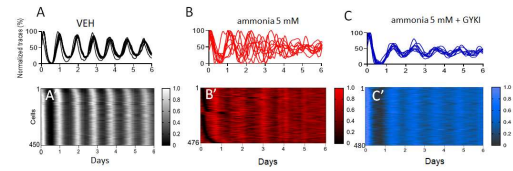
hepato-cellular failure

portal-systemic shunt



....with a little help from my friends

....with a little help from my friends



Granados-Fuentes et al., Liver International 2023

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- pertinent pilot treatment data
- circadian/daily profiles in clinical environments of interest

intensive care units



pediatric intensive care units

Effect of night and day on preterm infants in a newborn nursery:
randomised trial

N F MANN, R HADDOW, L STOKES, S GOODLEY, N RUTTER

BMJ, 1986



pediatric intensive care units

Effect of night and day on preterm infants in a newborn nursery:
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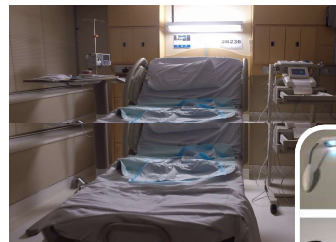
N F MANN, R HADDOW, L STOKES, S GOODLEY, N RUTTER

BMJ, 1986



medical wards

medical wards



Formentin et al., Front Physiol - Chronobiol. 2020

medical wards



	Morning	Evening	Breakfast	Lunch	Dinner	Morning	Evening
Morning type	06:45	20:00	07:00	12:30	18:30	08:00-08:30	18:00-18:30
Intermediate type	07:45	21:00	08:00	13:30	19:30	09:00-09:30	18:30-19:00
Evening type	08:45	22:00	09:00	14:30	20:30	10:00-10:30	19:00-19:30

disturbance of daily rhythms in chronic illness



disturbance of daily rhythms in chronic illness

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- reasonable pathophysiological implications vs. RCTs

disturbance of daily rhythms in chronic illness

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- lack of normative data

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disturbance of daily rhythms in chronic illness

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- no normative data → no abnormality thresholds
- prescription and reimbursement

disturbance of daily rhythms in chronic illness

- reasonable pathophysiological implications vs. RCTs
- lack of normative data
- no normative data → no abnormality thresholds
- prescription and reimbursement
- access to in- and outpatient circadian services

suggested readings

<https://www.sleephythm.org/>

