Homeostatic and Circadian Regulation of the Sleep-Wake Cycle

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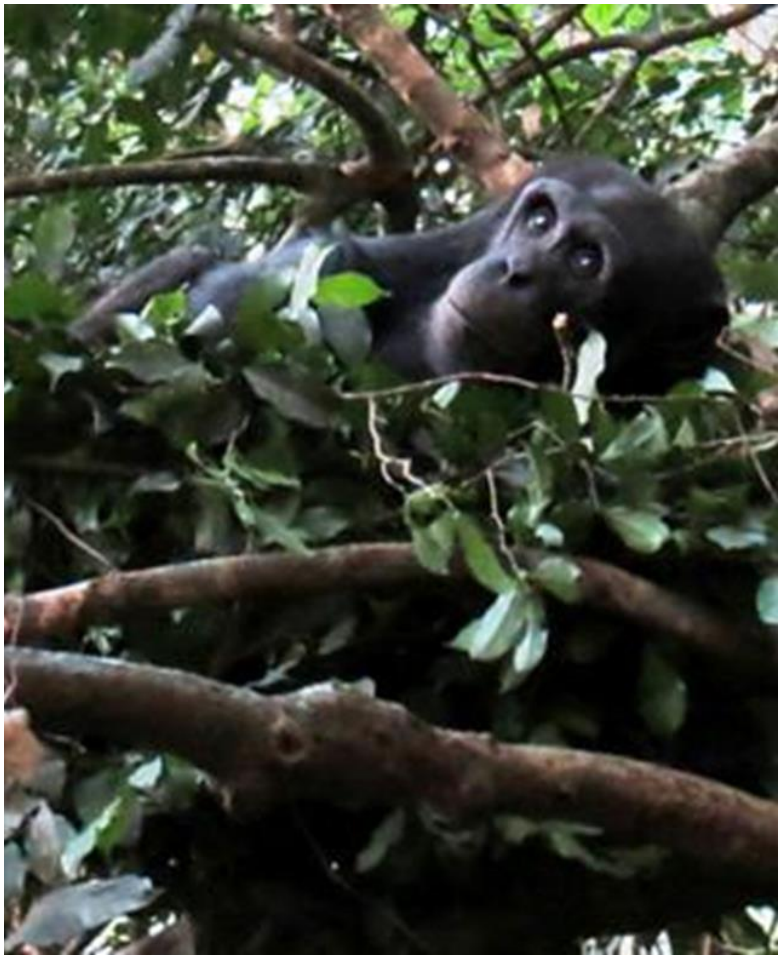
Regulation of sleep/wake cycle

Outline

- Sleep and sleep stages
- Sleep homeostasis
  - Global aspects of sleep regulation
  - Local aspects of sleep regulation
- Circadian aspects of sleep regulation



Many apes sleep in nests in the trees
(Credit: Kathelijne Koops)

Conceptual frame-work for sleep-wake regulation

Waking Performance

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

Sleep-Wake Cycle

Circadian

Homeostat

Biological time

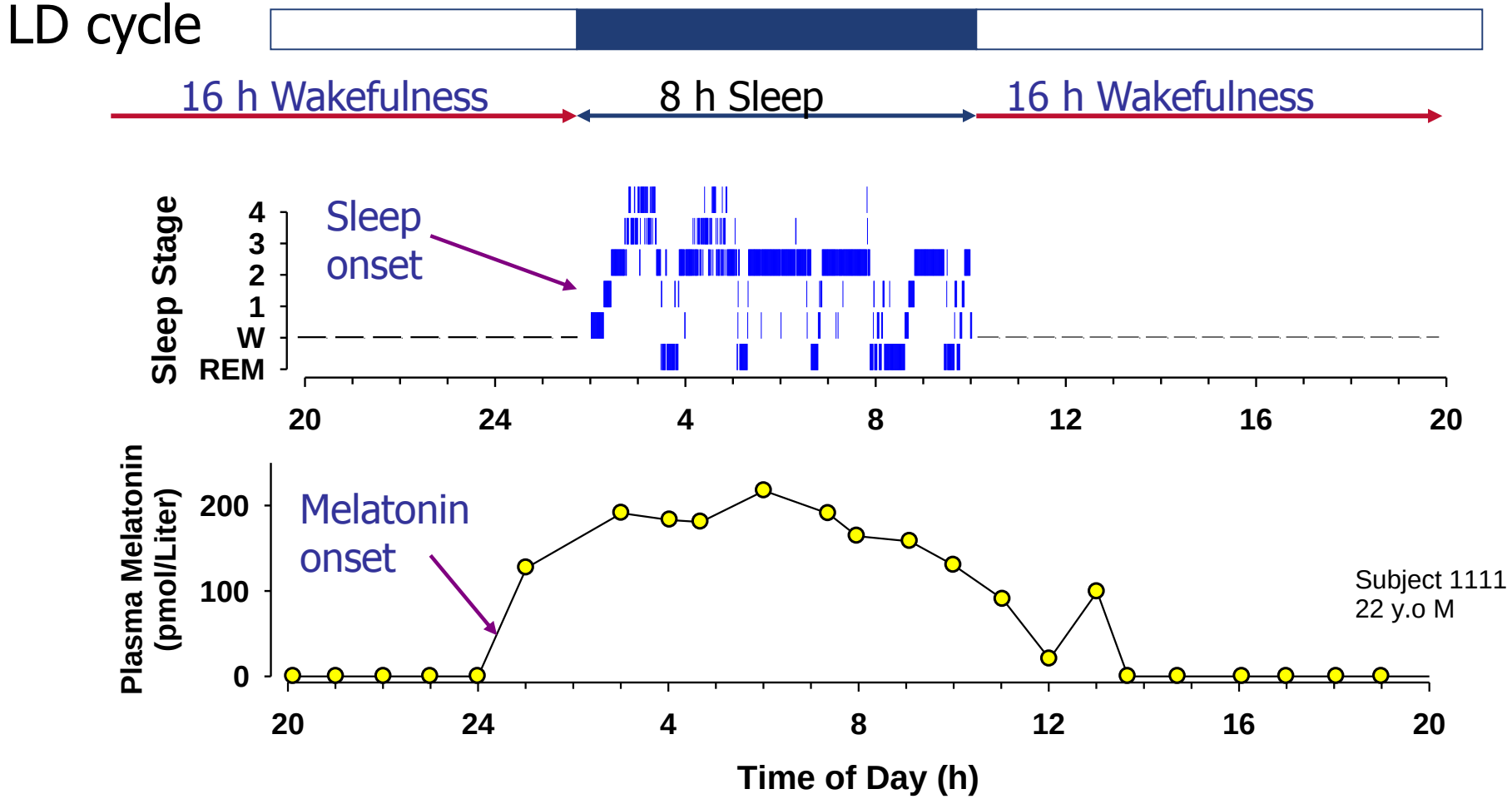
Sleep-wake history

Individual

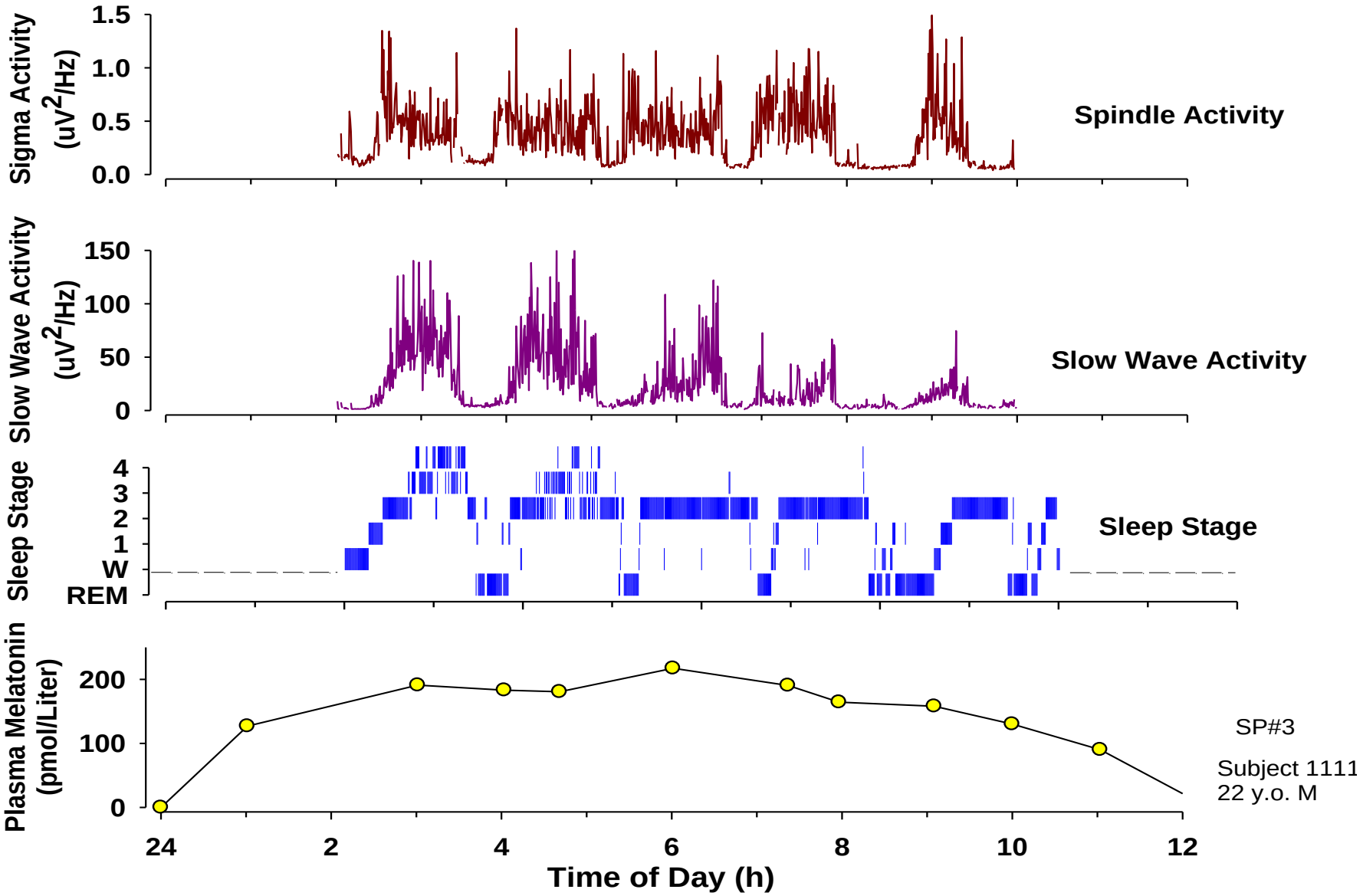
Genetic variation

Dijk and Lockley, 2002; Archer et al. 2013

Timing of sleep and time course of sleep stages



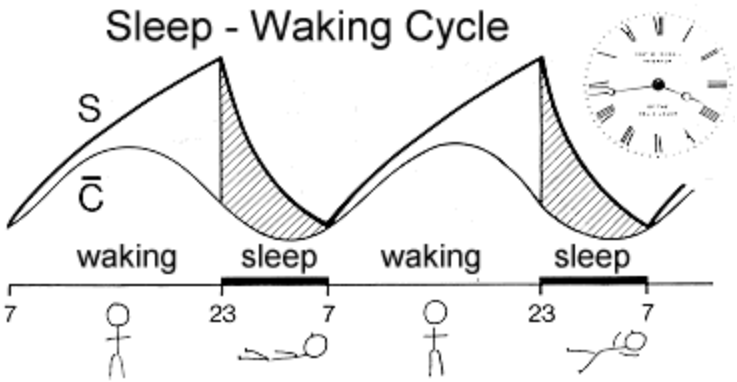
Time course of slow waves and sleep spindles

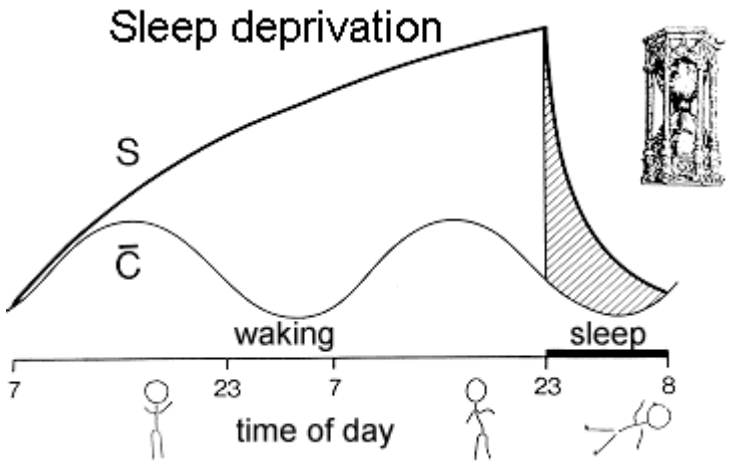


Dijk, Duffy, Czeisler; Unpublished

Sleep Homeostasis

Global regulation of sleep





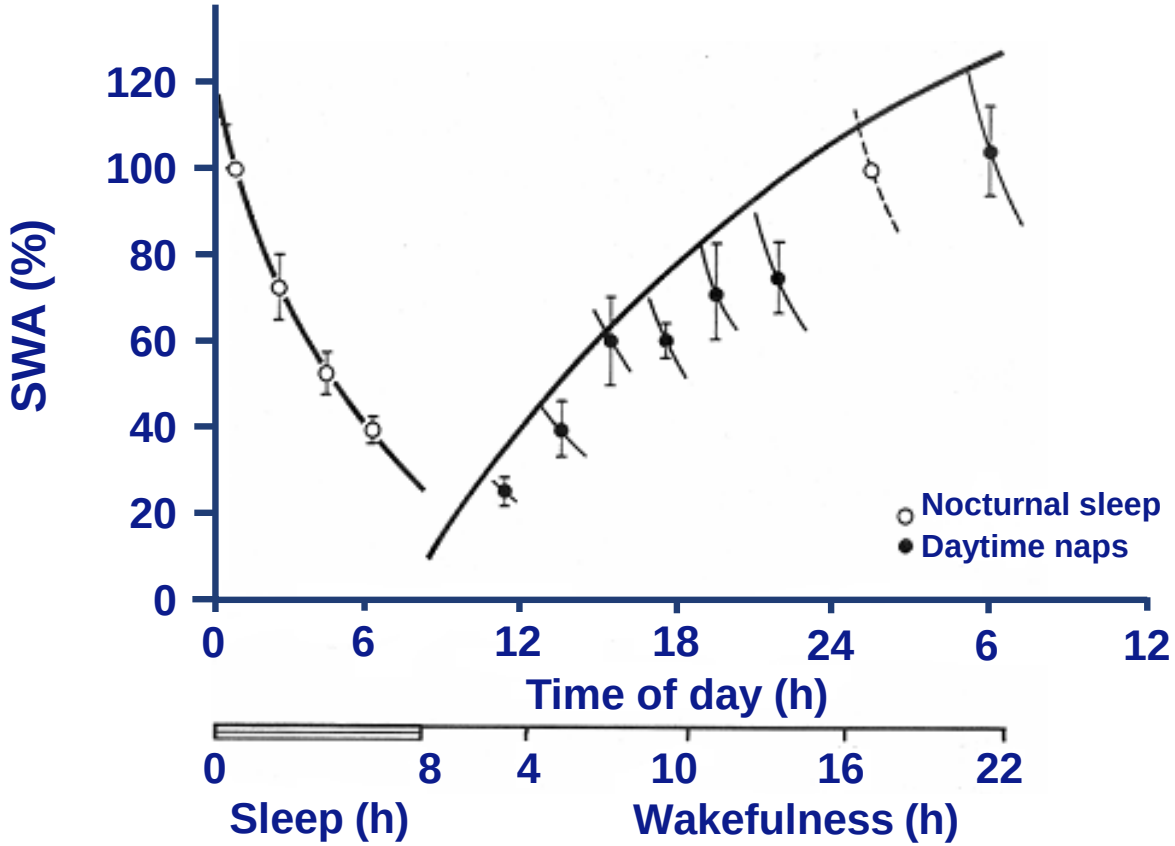
- Build-up of sleep pressure during wakefulness
- Dissipation of sleep pressure during sleep

- Further build-up of sleep pressure during sleep deprivation
- More intense and longer recovery sleep
- Note: Circadian rhythm not affected

Borbely: A two-process model of sleep-regulation; Human Neurobiol 1982

Examples of Sleep Homeostasis (I): Regulation of SWS

Decline and fall of SWA. During nocturnal sleep SWA declines and SWA in daytime naps increases progressively with the duration of wakefulness preceding the nap. Please note that naps were not taken on the same day



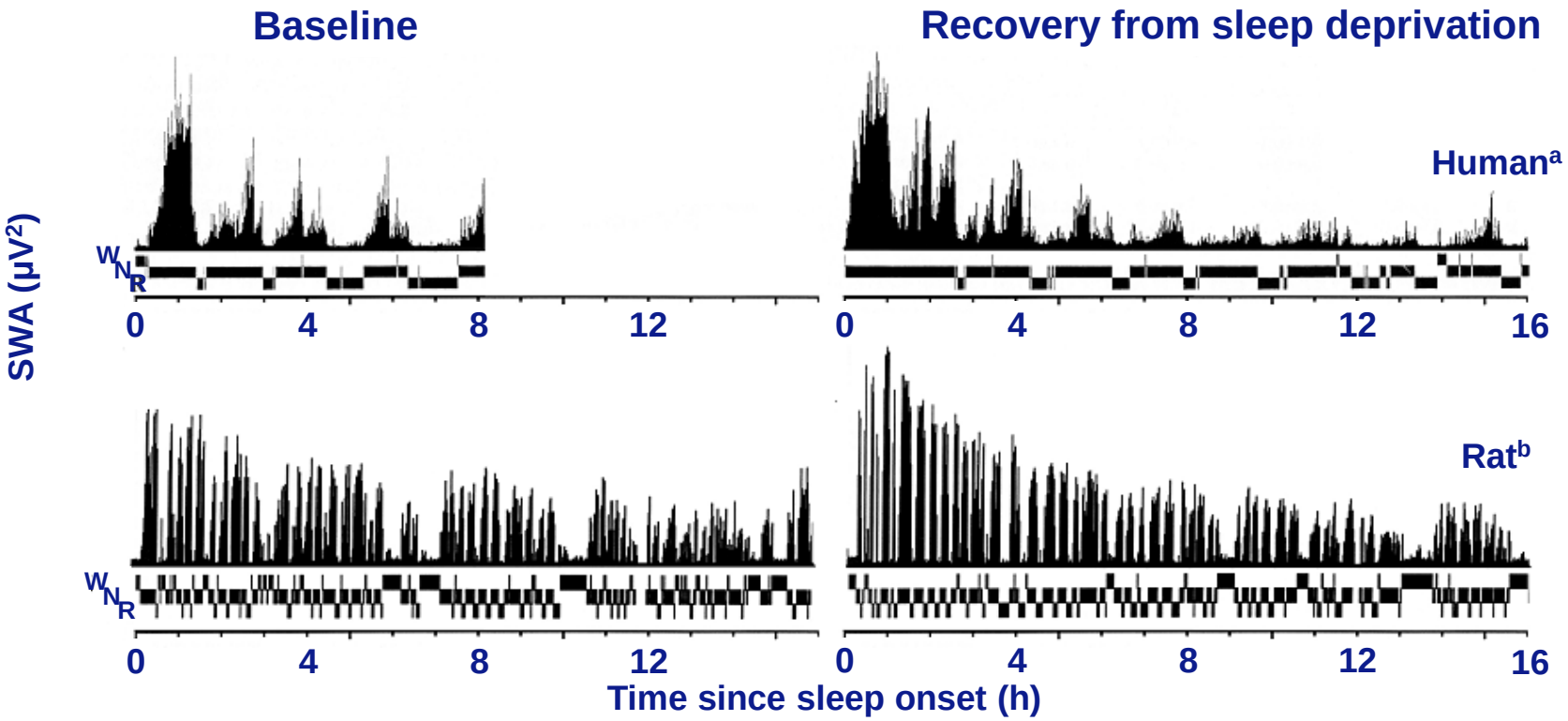
Data from 7 female healthy volunteers

Dijk D-J. Behav Brain Res 1995;69:109–116

Sleep Homeostasis (II): Regulation of SWS

More SWA and longer sleep after total sleep deprivation in humans and rats

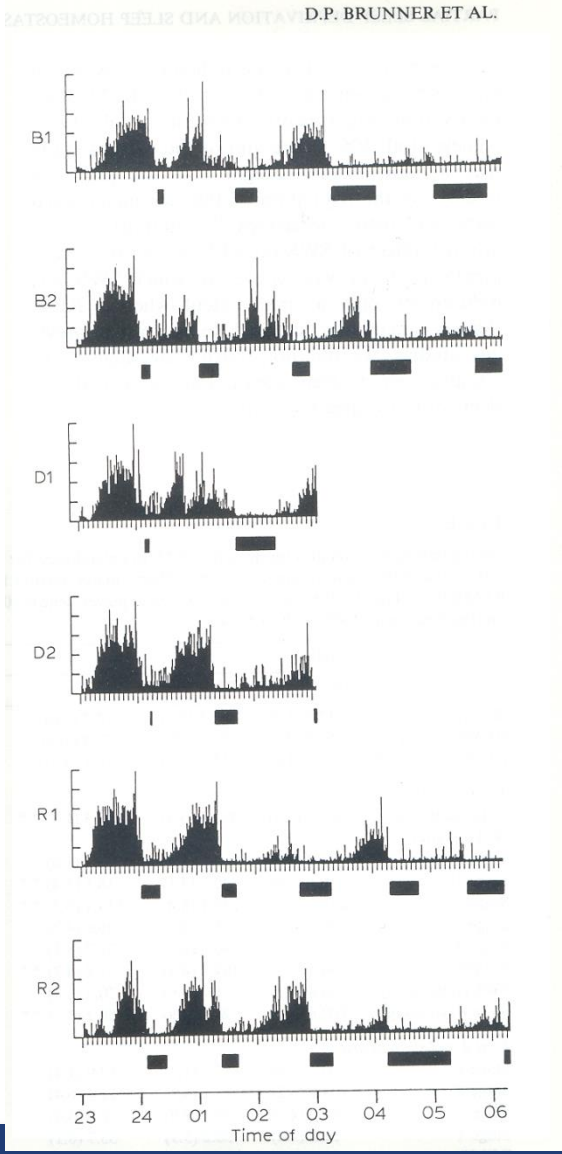
Time course of SWA during baseline sleep and recovery sleep following sleep deprivation in human and rat

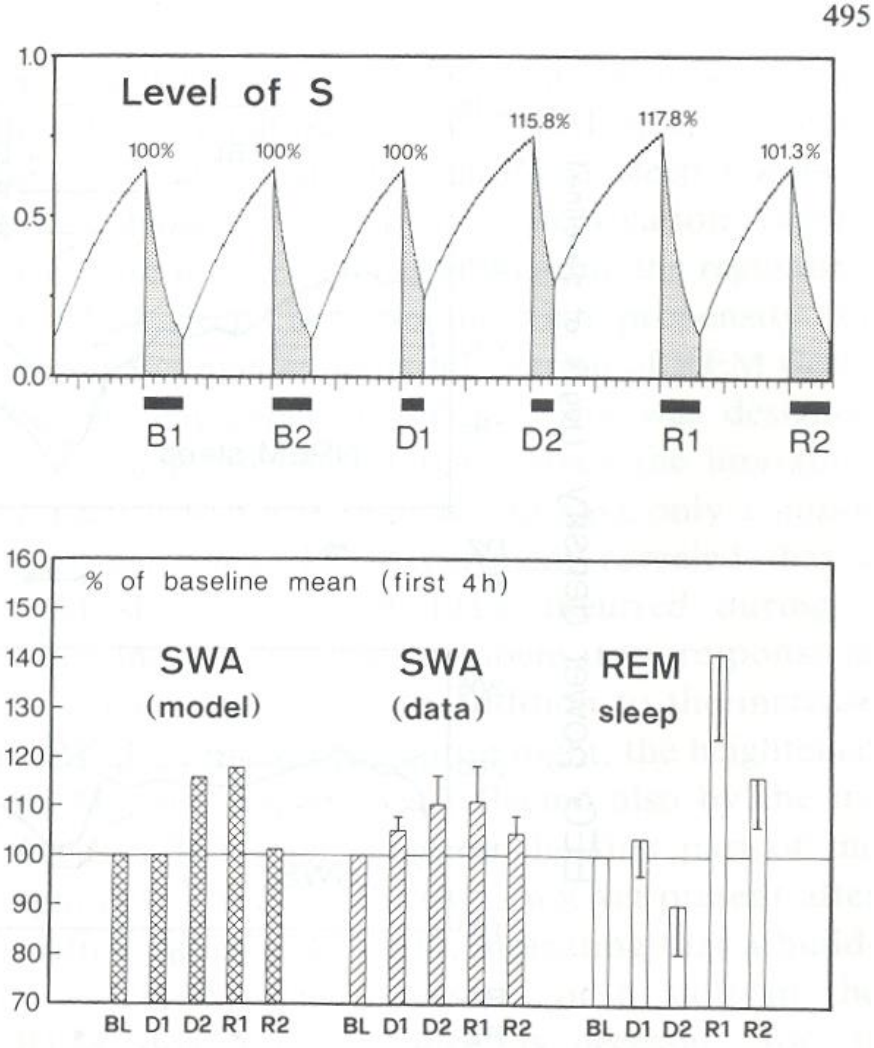


[a]36-h sleep deprivation (data from a single male subject)
[b]24-h sleep deprivation

Sleep Homeostasis III: Partial sleep deprivation

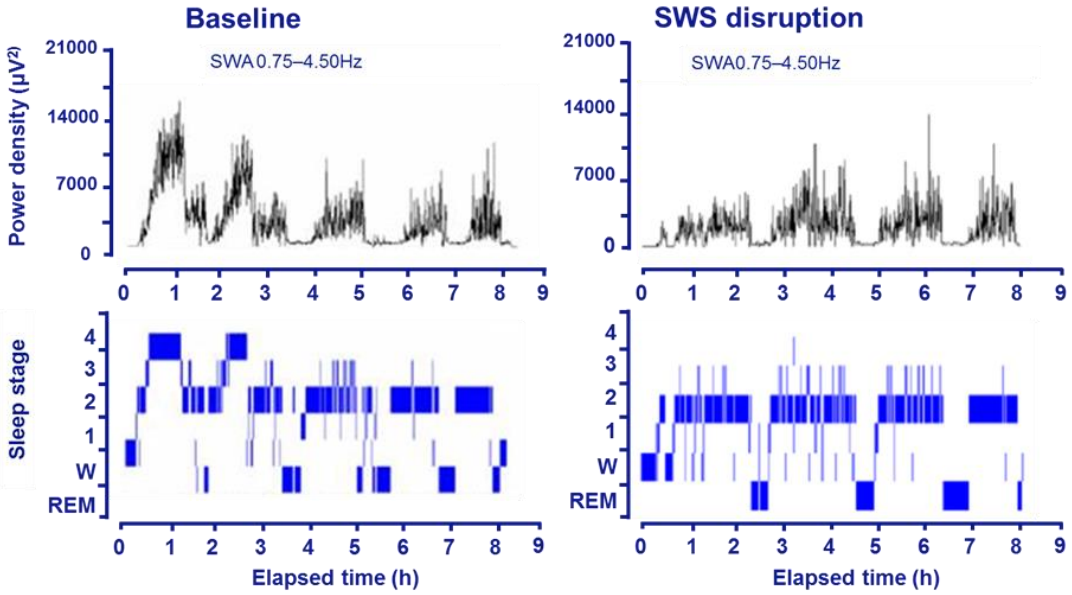
Partial sleep deprivation: primary effect on REM sleep; preservation of SWA; Rebound of REM sleep





Sleep Homeostasis IV: Selective SWS deprivation

Through acoustic stimuli; leads to rebound in subsequent night



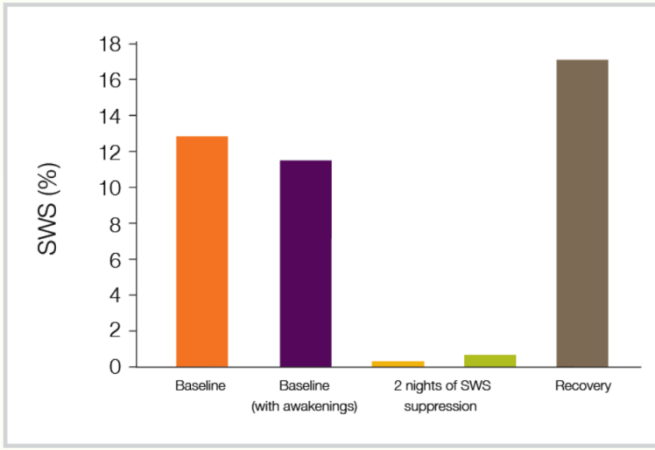


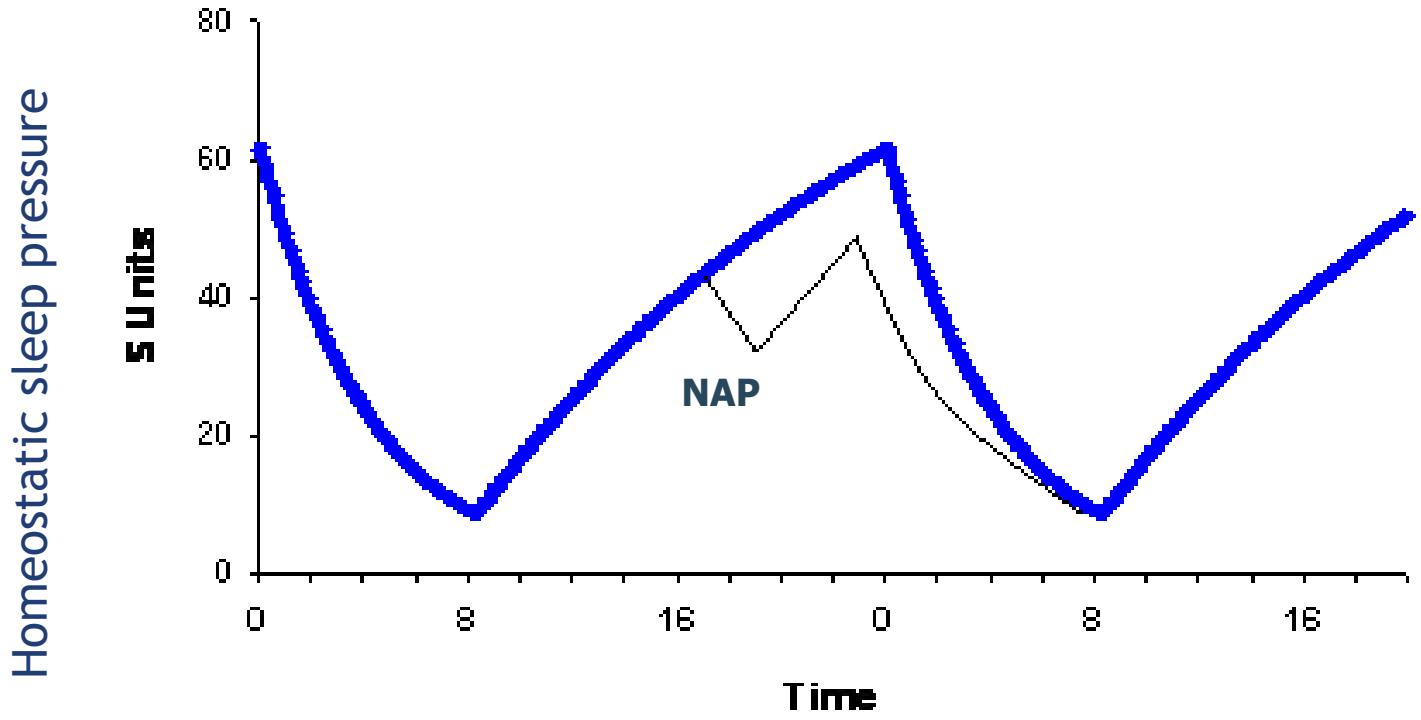
Figure 7. **SWS deprivation and rebound effect.** The proportion of slow-wave sleep (SWS) at baseline, during SWS suppression and on recovery showing rebound effect following selective SWS deprivation. Adapted from Ferrara et al. (1999).

n=1

Dijk D-J et al. J Sleep Res 15 (Suppl. 1):251–252 (Abstr. No. P536)

Sleep Homeostasis V: effects of 'too much' sleep [Nap]

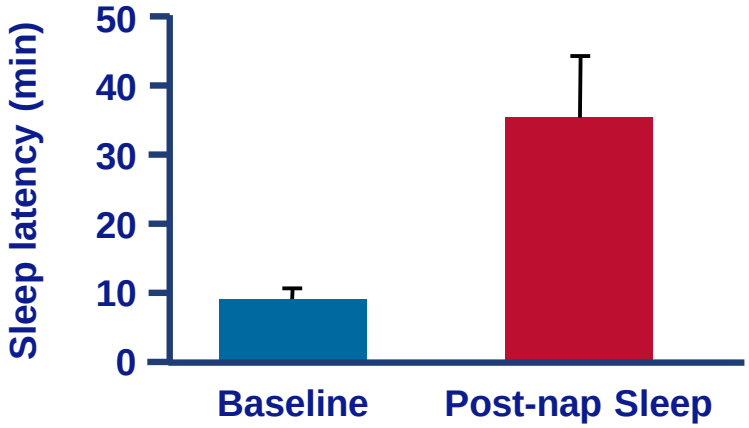
Theoretical influence of nap on subsequent sleep

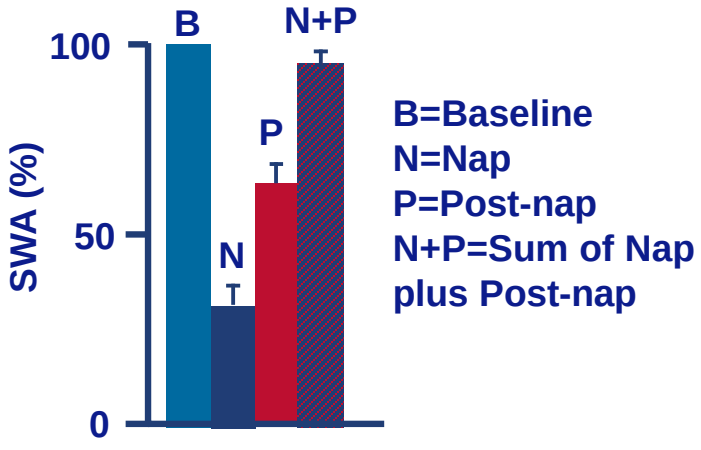


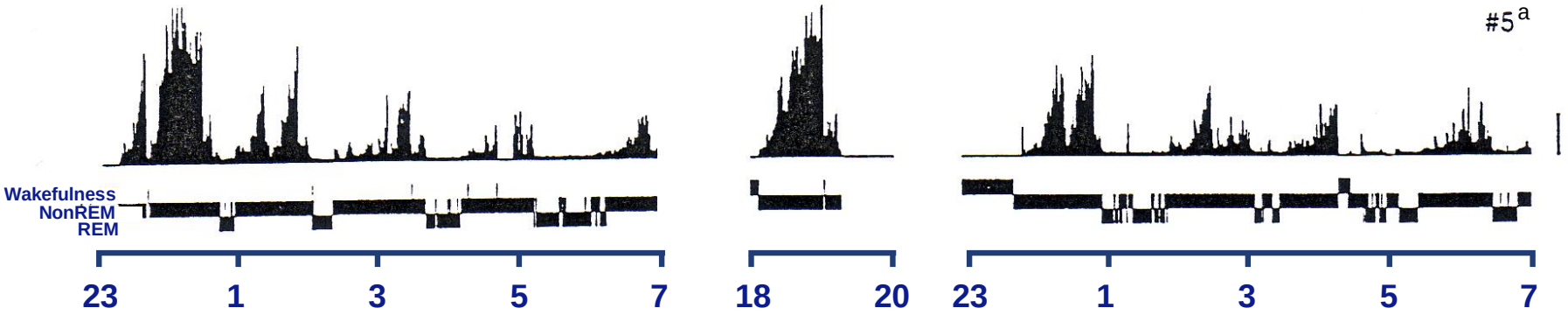
- A nap in the afternoon will lead to a dissipation of sleep pressure
- The increase in sleep pressure during wakefulness after the nap is insufficient to restore sleep pressure at habitual bed time to normal levels

Dijk, Unpublished figure

Reduced sleep propensity and SWA after a nap in the early evening





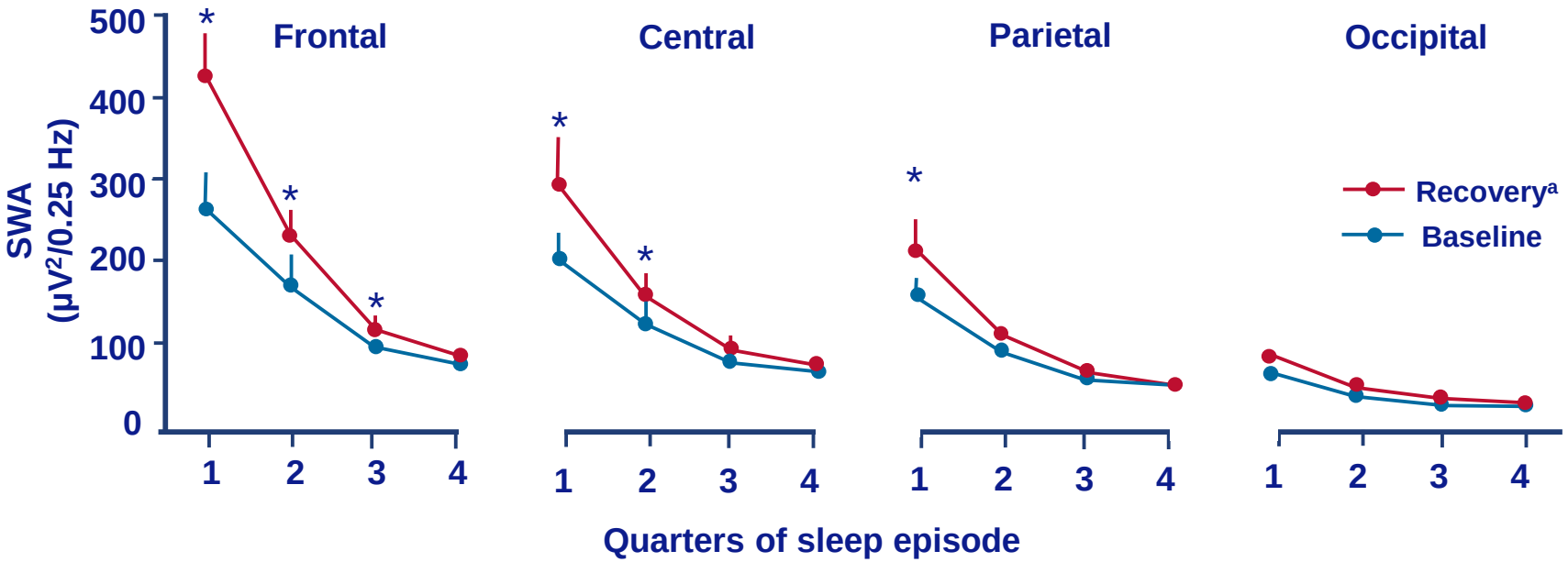


Study in 9 healthy male volunteers

[a]Time course of SWA and vigilance states from a single volunteer

Sleep Homeostasis: Local aspects of sleep regulation

Frontal predominance during baseline and after sleep deprivation

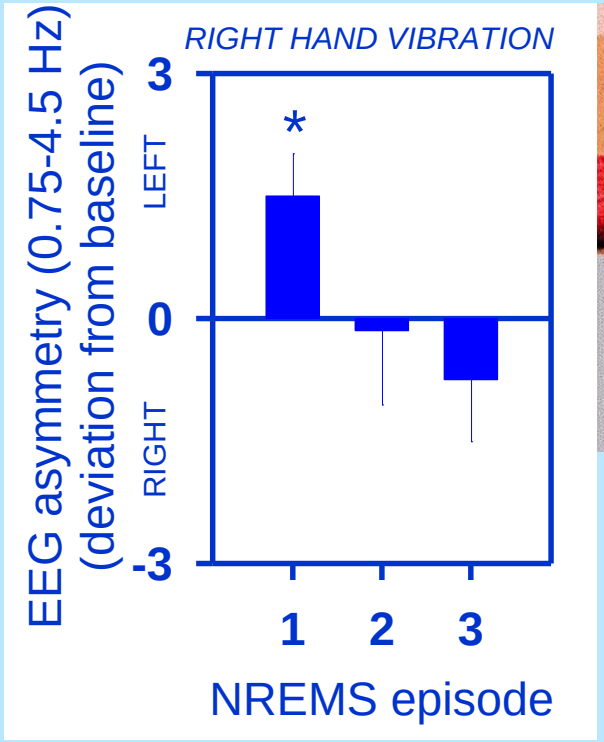


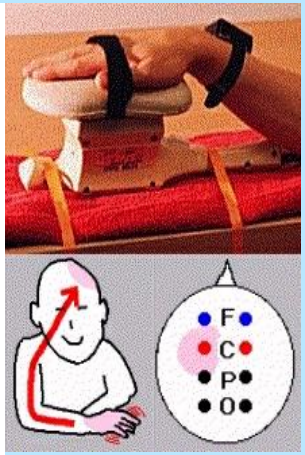
*p<0.05 baseline vs recovery (n=6 healthy volunteers)
[a]First sleep episode following 40-h sleep deprivation

Sleep Homeostasis: Local aspects

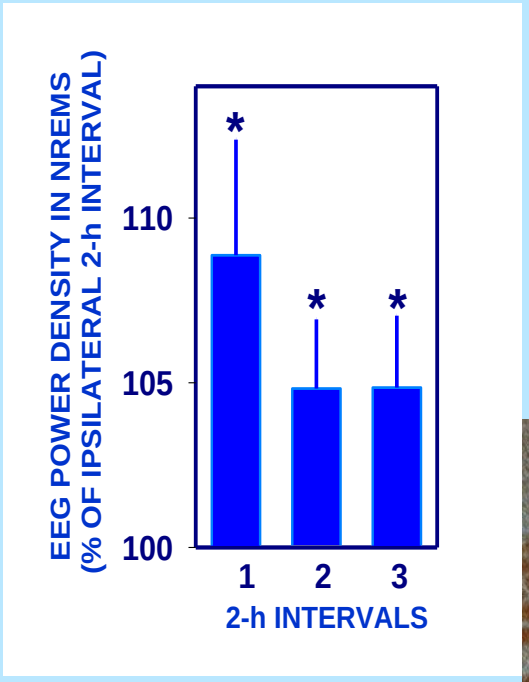
Specific sensory stimulation leads to a use-dependent increase of SWA in non REM sleep

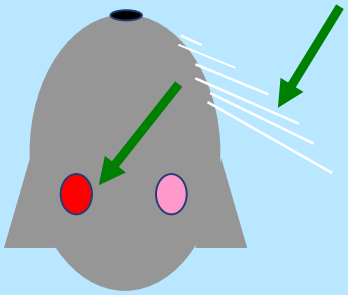
humans





animals





BARREL CORTEX

Kattler et al., J Sleep Res,1994

Vyazovskiy et al., J Sleep Res. 9:367-371, 2000

Consequences of insufficient sleep for waking functioning

Waking Performance

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

Sleep-Wake Cycle

Circadian

Biological time

Homeostat

Sleep-wake history

Individual

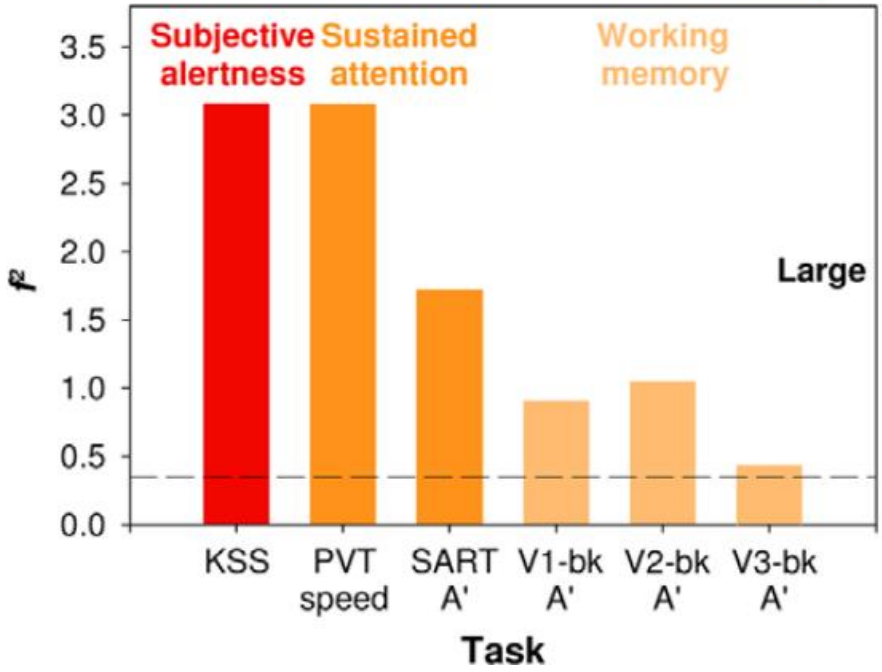
Genetic variation

Dijk and Lockley, 2002; Archer et al. 2013

Effect of **total sleep deprivation** on sleepiness, sustained attention and working memory during the day

N=36; age=27.6 (4.0) years

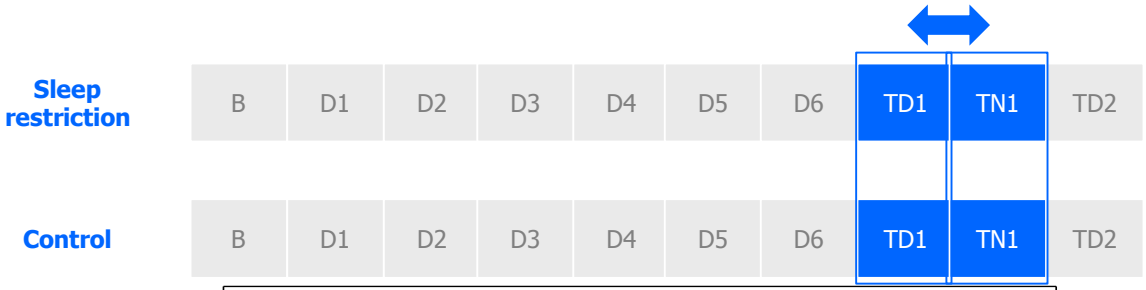
Implied effect size



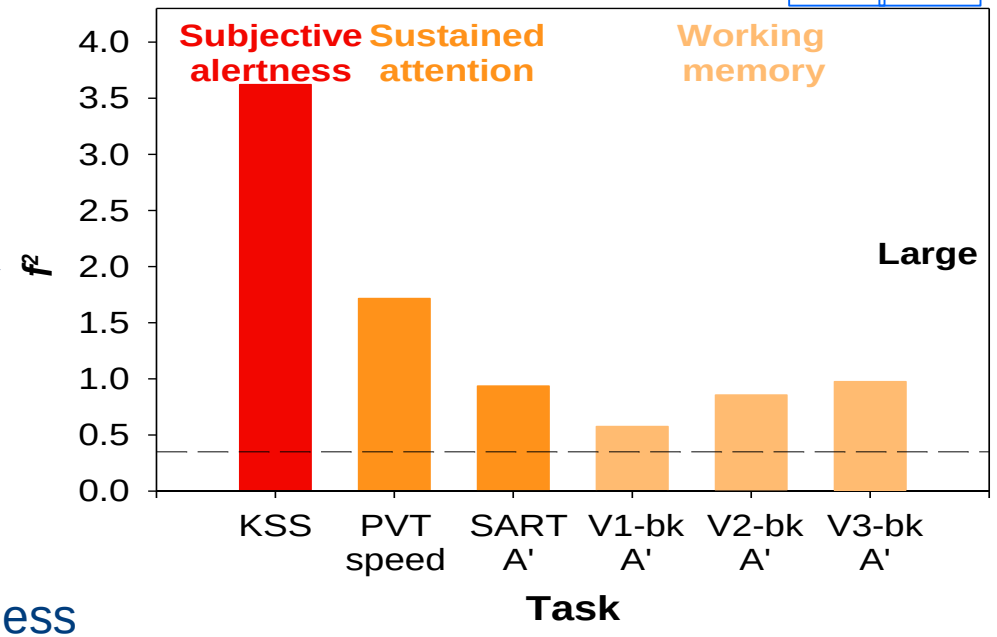
Large effect on sleepiness and sustained attention

Effect of **total sleep deprivation** on sleepiness, sustained attention and working memory during the night

N=36; age=27.6 (4.0) years



Implied effect size

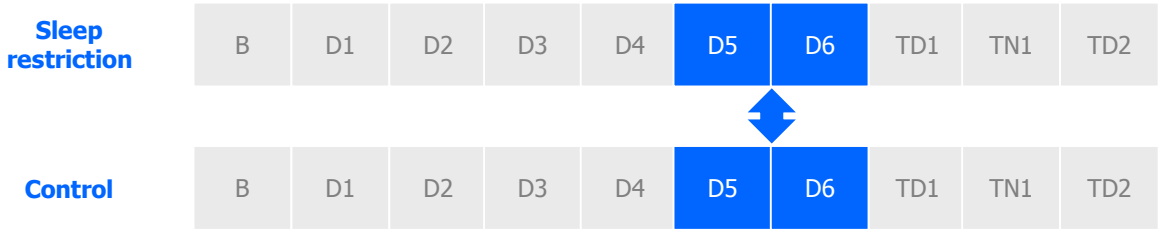


Largest effect on sleepiness and sustained attention

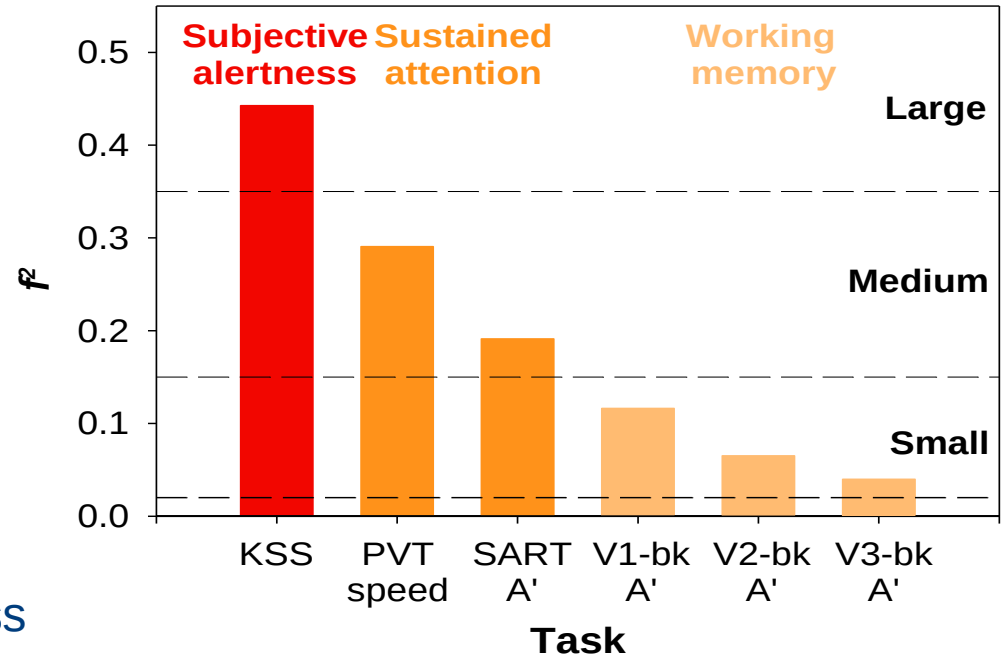
Effect of **repeated partial sleep deprivation** on sleepiness, sustained attention and working memory

N=36; age=27.6 (4.0) years

- 10 h vs. 6 h TIB
- 8.6 vs. 5.8 h TST



Implied effect size



Largest effect on sleepiness and sustained attention

Lo et al. PLoS One, 2012

Conclusion (I)

Sleep homeostasis:

- Total sleep deprivation
- Partial sleep deprivation
- Selective sleep deprivation
- Extra sleep

➔ All these manipulations activate sleep homeostatic mechanisms and lead to changes in subsequent sleep

➔ Slow Wave Activity is one sensitive marker of sleep homeostasis

Sleep homeostasis:

- There are both local and global aspects to sleep and sleep regulation
- There is a use dependent aspect to sleep regulation
  - Neuronal networks that have been activated extensively during wakefulness appear to show more slow waves during subsequent sleep

Insufficient sleep:

- Impaired waking function
  - Increased Sleepiness
  - Reduced Sustained Attention

Circadian aspects of sleep regulation

Waking Performance

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

Sleep-Wake Cycle

Circadian

Biological time

Homeostat

Sleep-wake history

Individual

Genetic variation

Dijk and Lockley, 2002; Archer et al. 2013

Main points of circadian aspect of sleep-regulation

- The master circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus
- Light is the major synchronizer of the SCN
- The SCN drives rhythms in many variables
- Sleep-wake consolidation is achieved by an opponent process organisation
- The duration and structure of sleep are modulated by the phase of the circadian cycle at which sleep occurs
- Clock' genes and individual differences
- Mistimed sleep disrupts circadian rhythmicity in the periphery

New Scientist

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FEATURE 13 April 2016

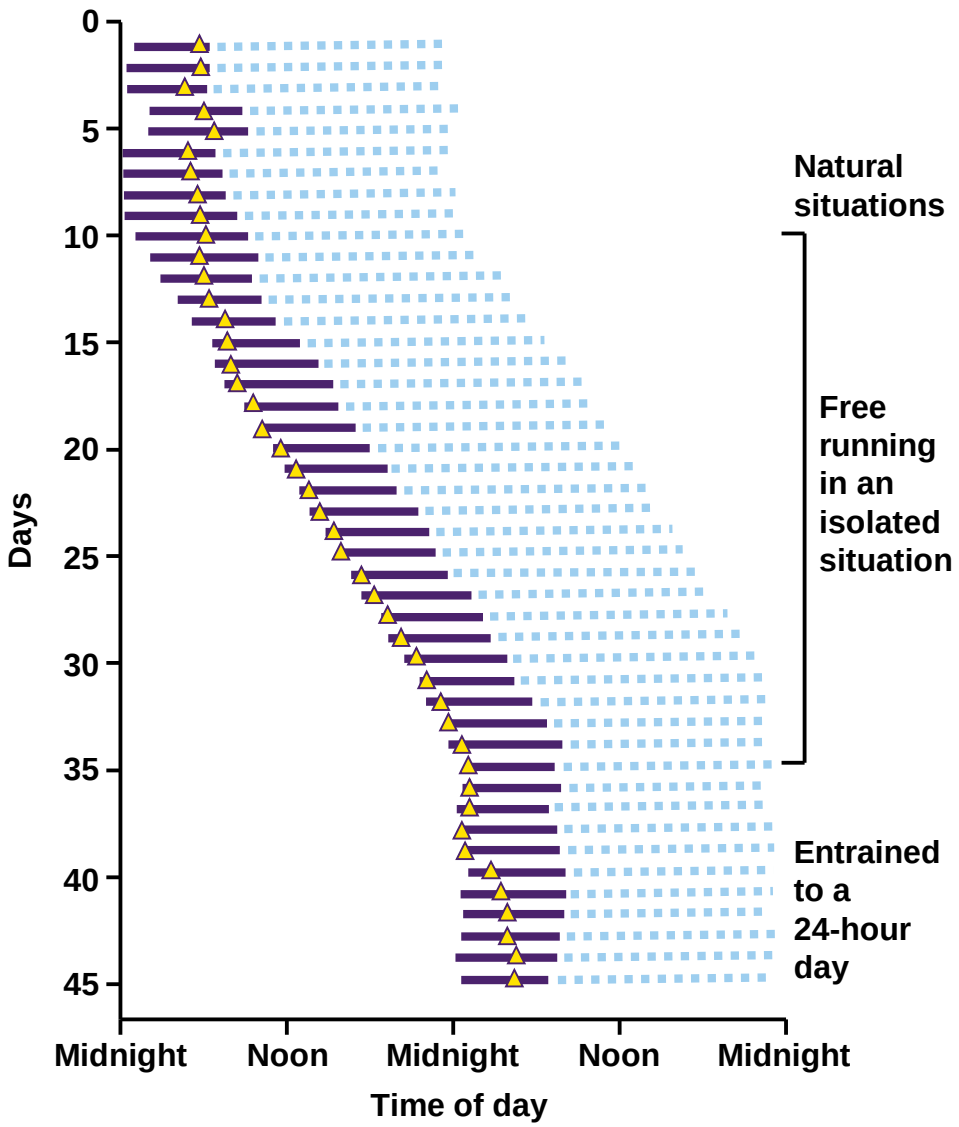
In sync: How to take control of your many body clocks

You have not one, but thousands or even millions of body clocks. Learn to control them, and you can tackle problems from jet lag to weight loss

Clocking in: thousands of body clocks make us tick

Jonny Wan

Circadian sleep–wake rhythms



Sleep–wake cycles:

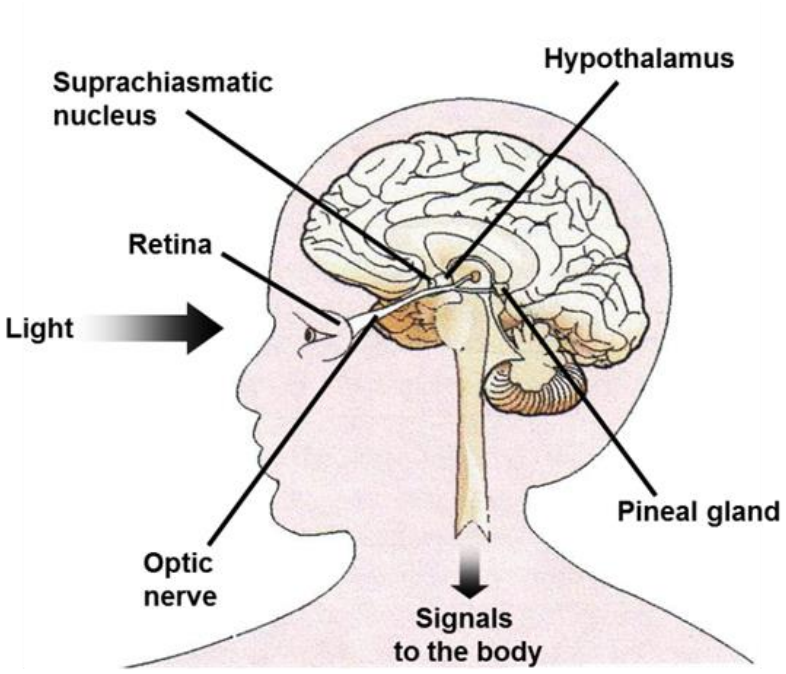
- Persist in the absence of external 24-hour light–dark and social cycles
- Are generated by an internal circadian clock

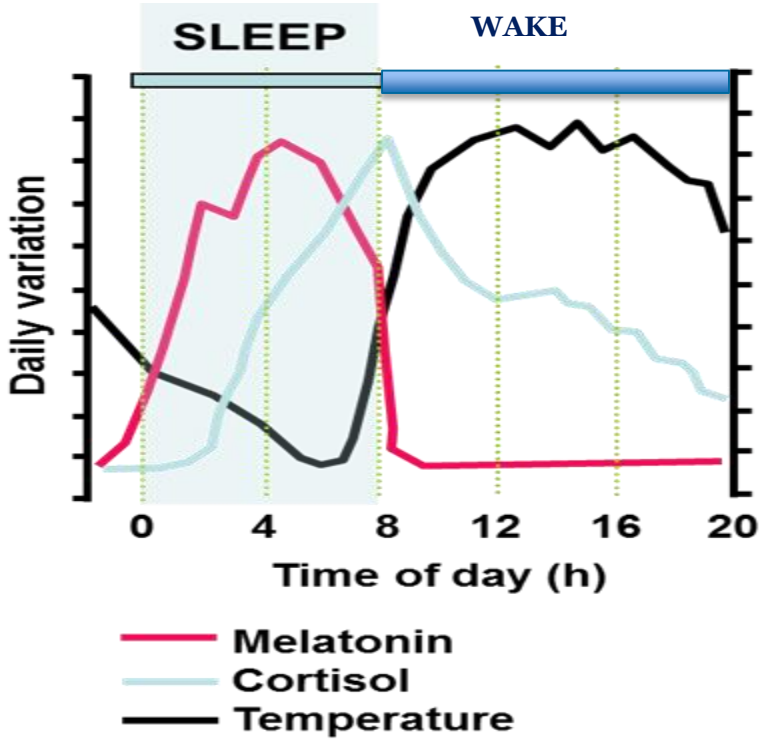
Sleep episode
Wake episode
Core body temperature nadir

Aschoff J. Science 1965; 148: 1427–1432

Physiology of circadian rhythms

- The master circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus
- Light is the major synchronizer of the SCN
- The SCN drives rhythms in many variables





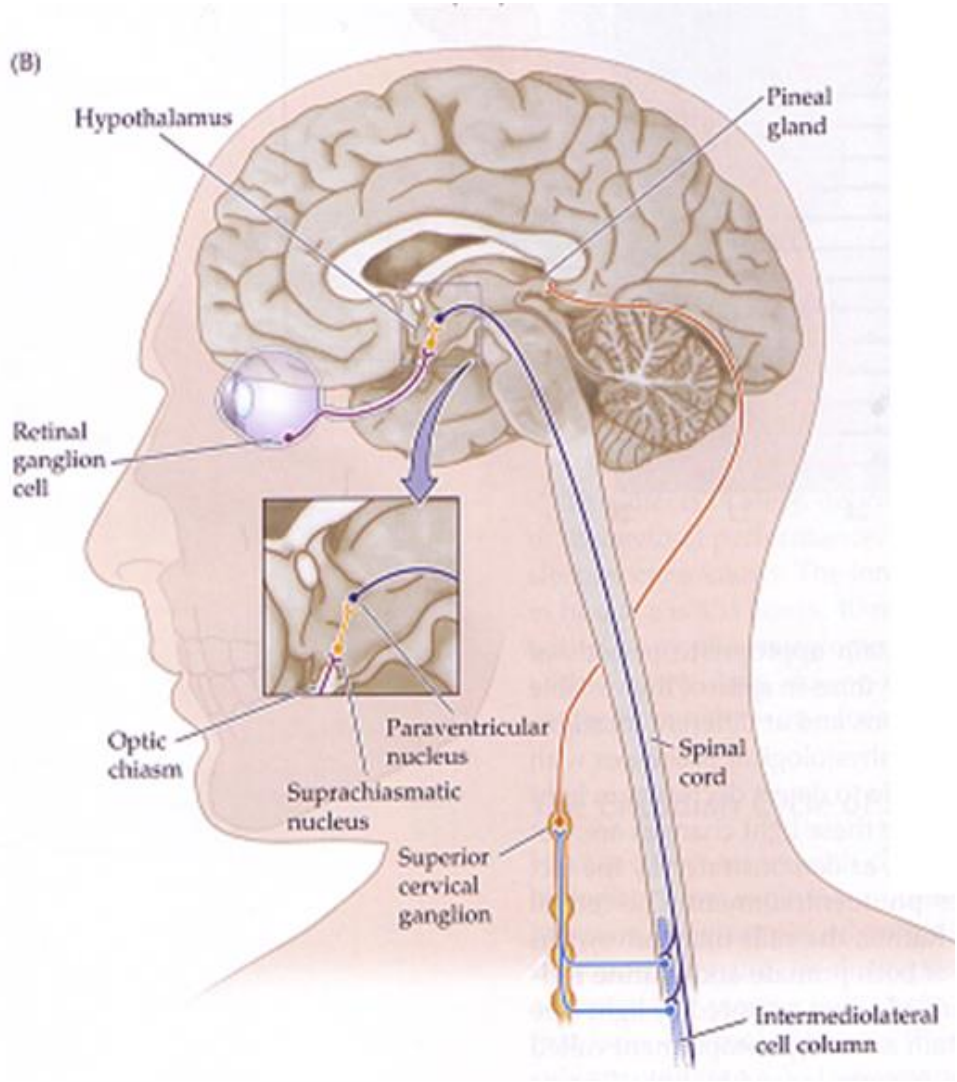
Abbott A. Nature 2003;425:896–898

Suprachiasmatic Nucleus

Melatonin rhythm

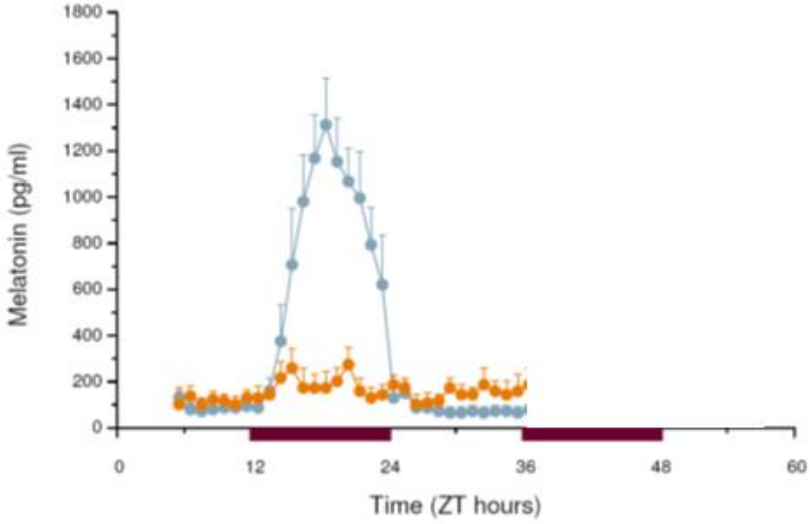
The SCN drives the melatonin rhythm through a:

- A polysynaptic pathway including the
  - paraventricular nucleus of the hypothalamus
    - the intermediolateral cell column
    - the superior cervical ganglion
    - pineal

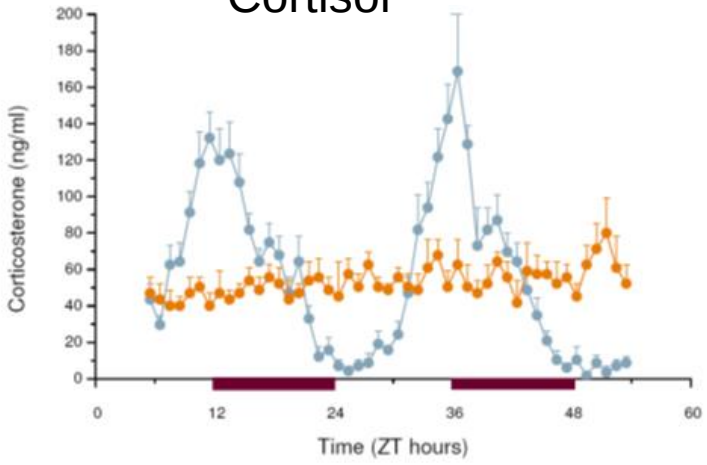


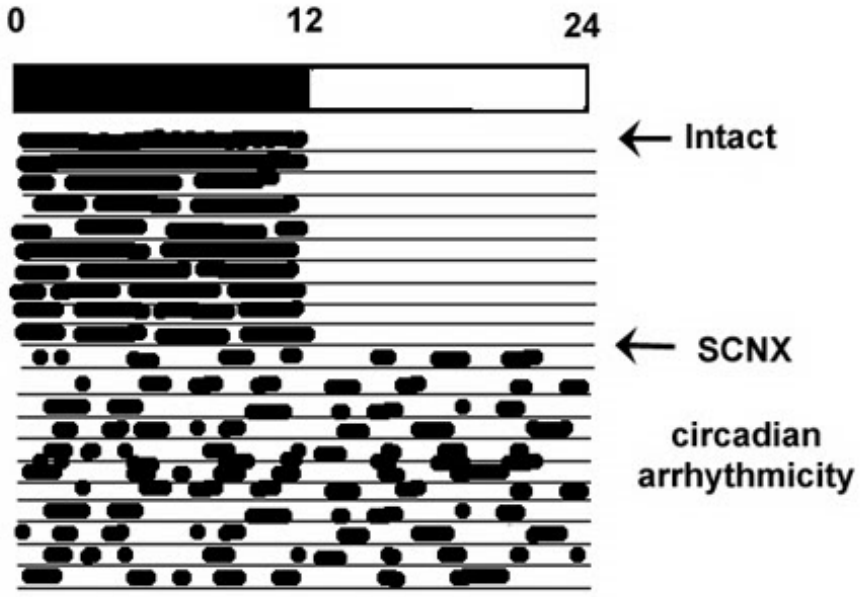
Effects of SCN lesion on melatonin, cortisol, activity

Melatonin



Cortisol

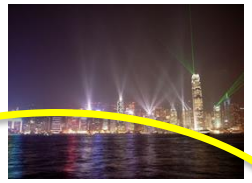




Kalsbeek et al.

Circadian aspects of sleep regulation

Artificial light and why we sleep so late



Waking Performance

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

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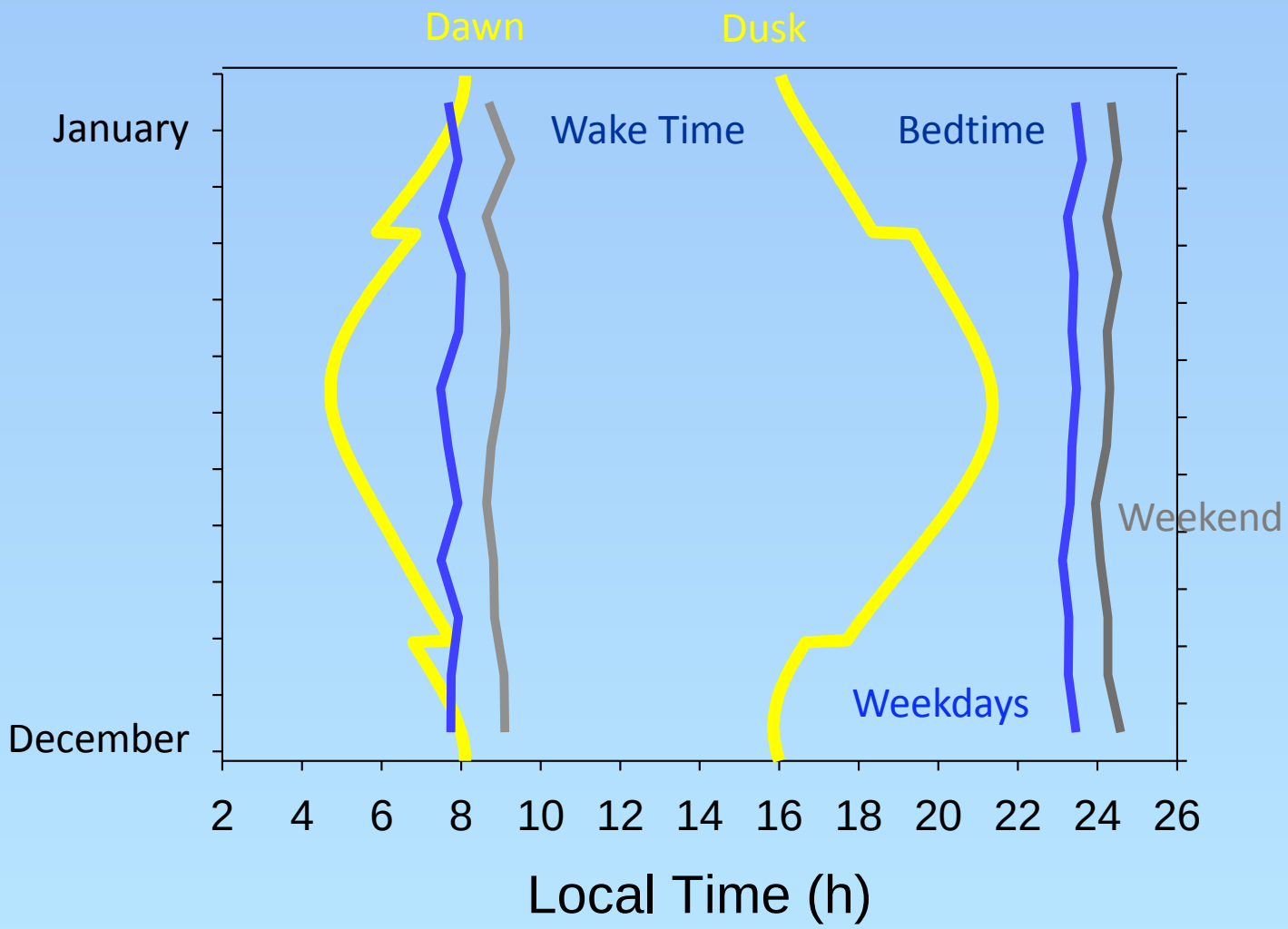
Genetic variation

Dijk and Lockley, 2002; Archer et al. 2013

Why do we sleep so late? [Relative to the natural L-D cycle]

UNIVERSITY OF SURREY

Photoperiod and sleep timing in Surrey

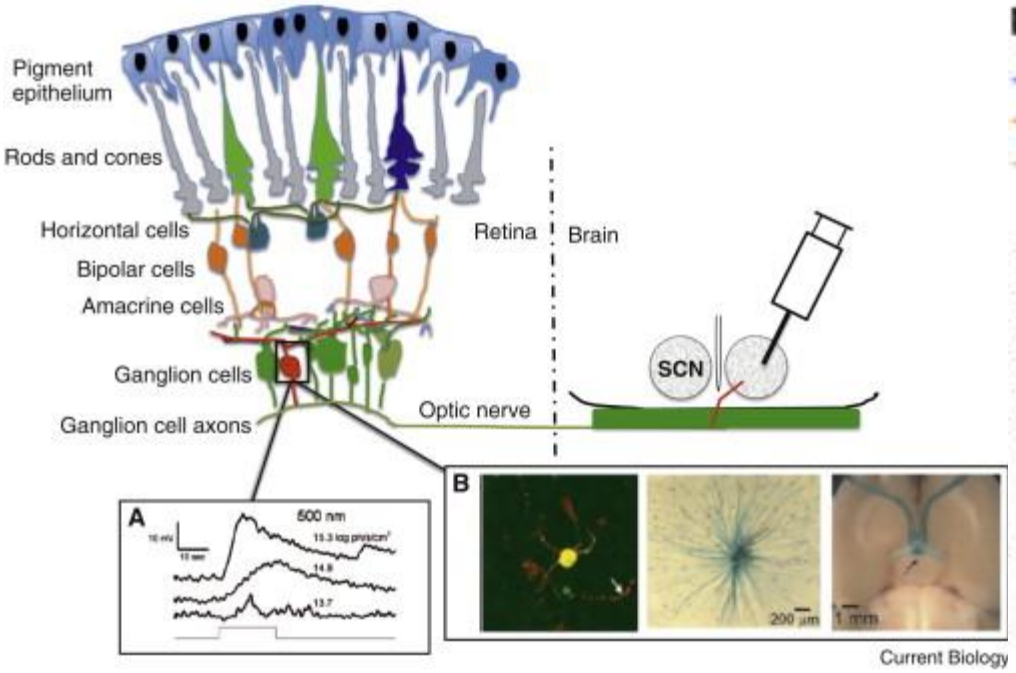


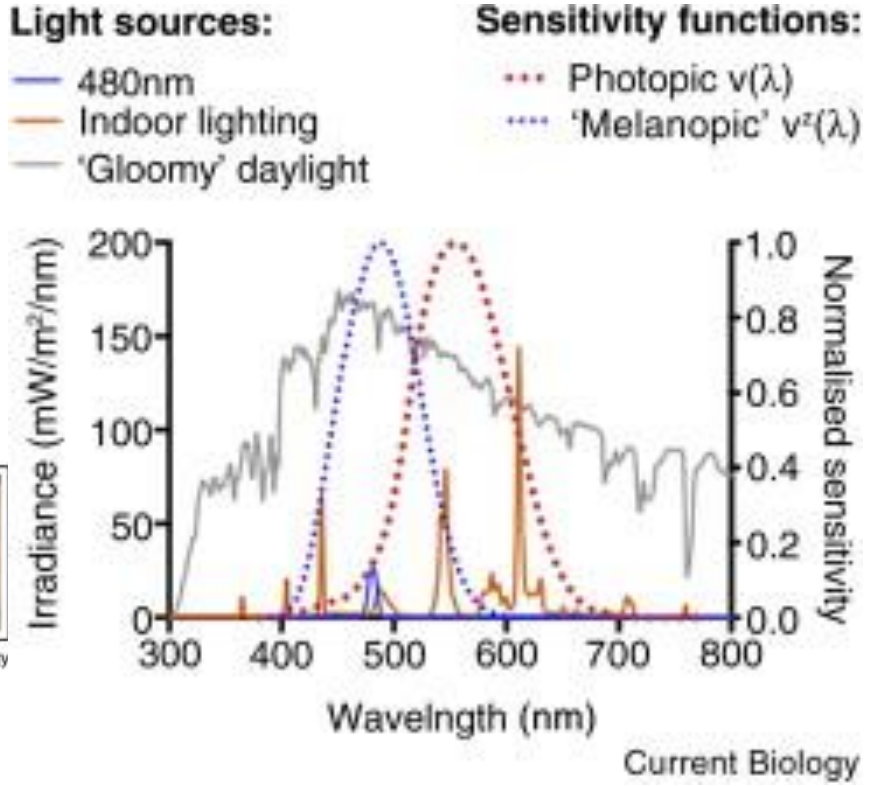
N=837

Based on data published in Lo et al Front Neurol. 5:81:2014

Renewed interest in effects of light on brain function

Melanopsin and intrinsically photosensitive retinal ganglion cells

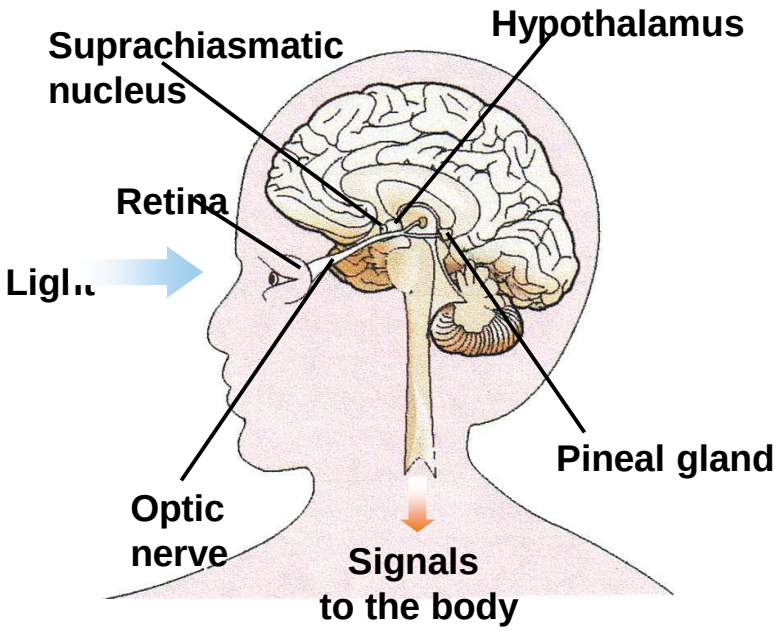




For a review of Mammalian inner retinal photoreception.see Lucas RJ Curr Biol. 2013;23:R125-33.

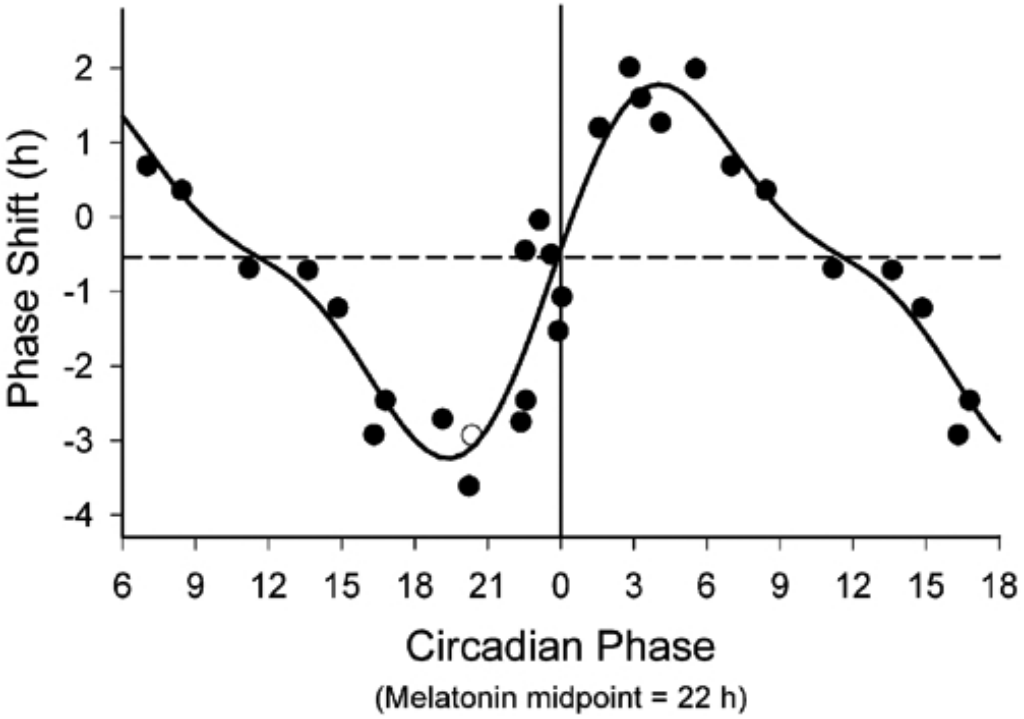
Light: Phase shifting effects

Slowing down and speeding up the clock



Light in the morning:

Advances

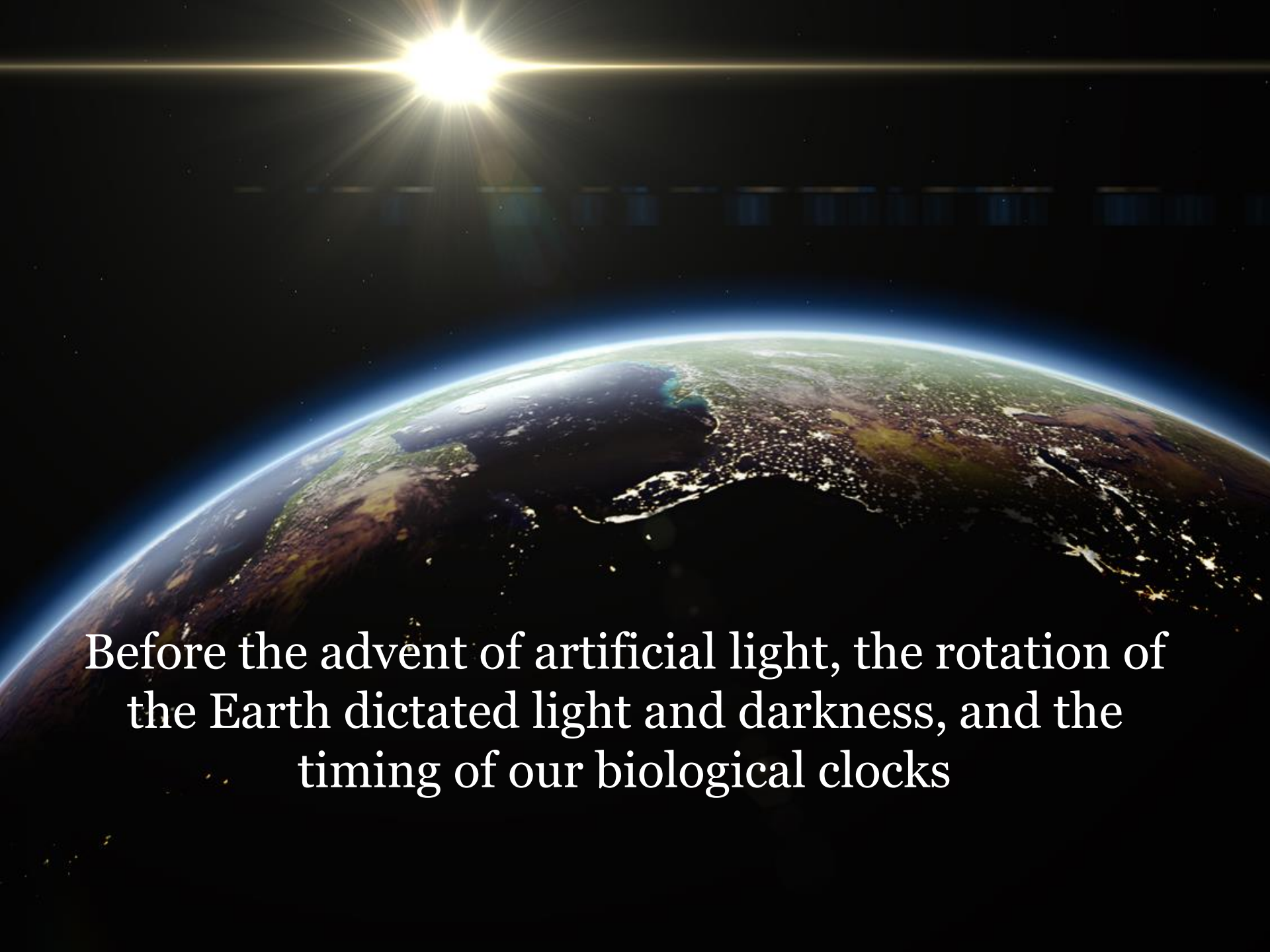


Light in the evening:

Delays

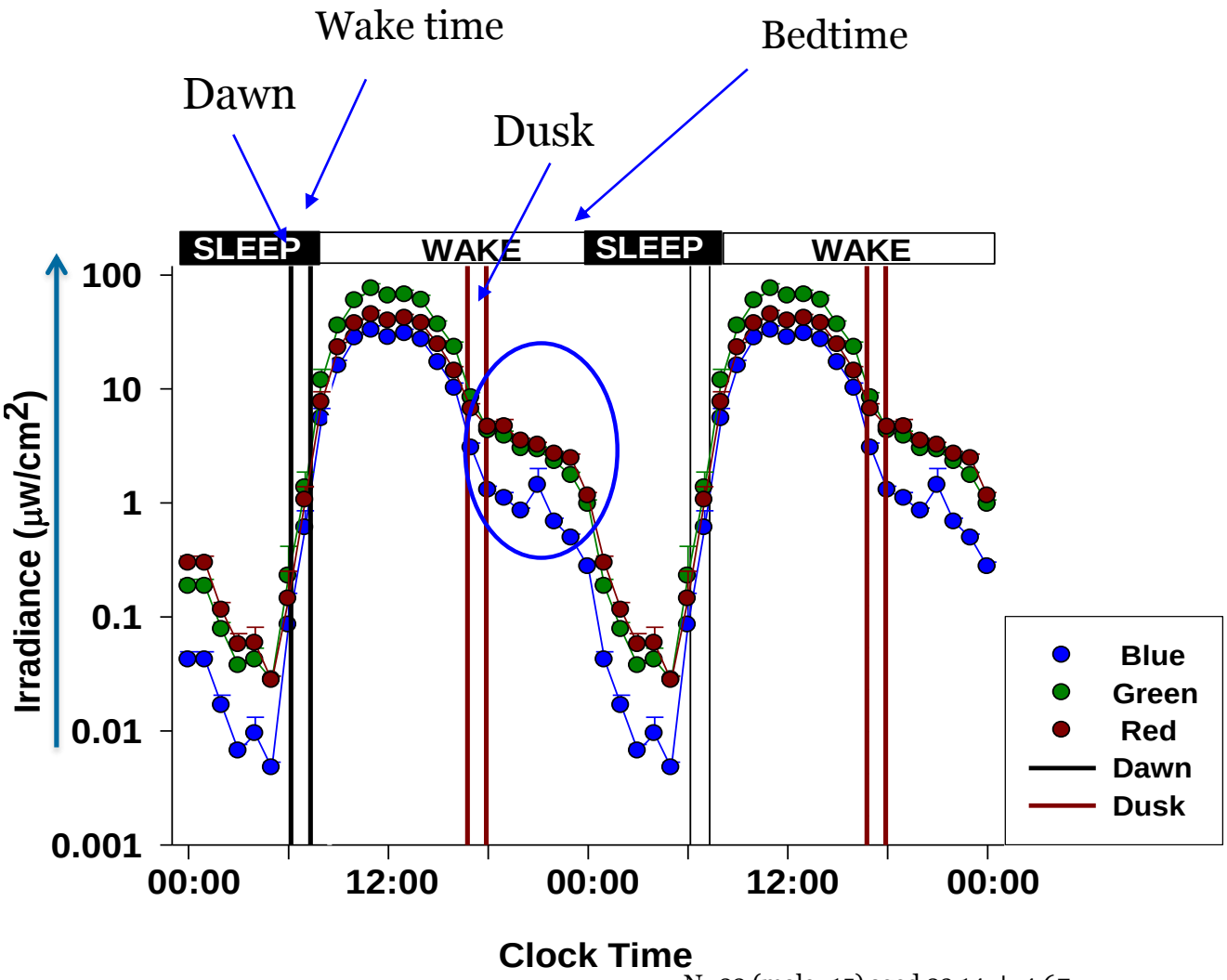
Abbott A. Nature 2003; 425 (6961): 896–898

Zeitzer et al J Physiol 2000 526: 695-702


Before the advent of artificial light, the rotation of the Earth dictated light and darkness, and the timing of our biological clocks

Does this artificial light influence our sleep and biological clocks?

Light exposure at home



N=22 (male=15) aged 23.14 ± 4.67

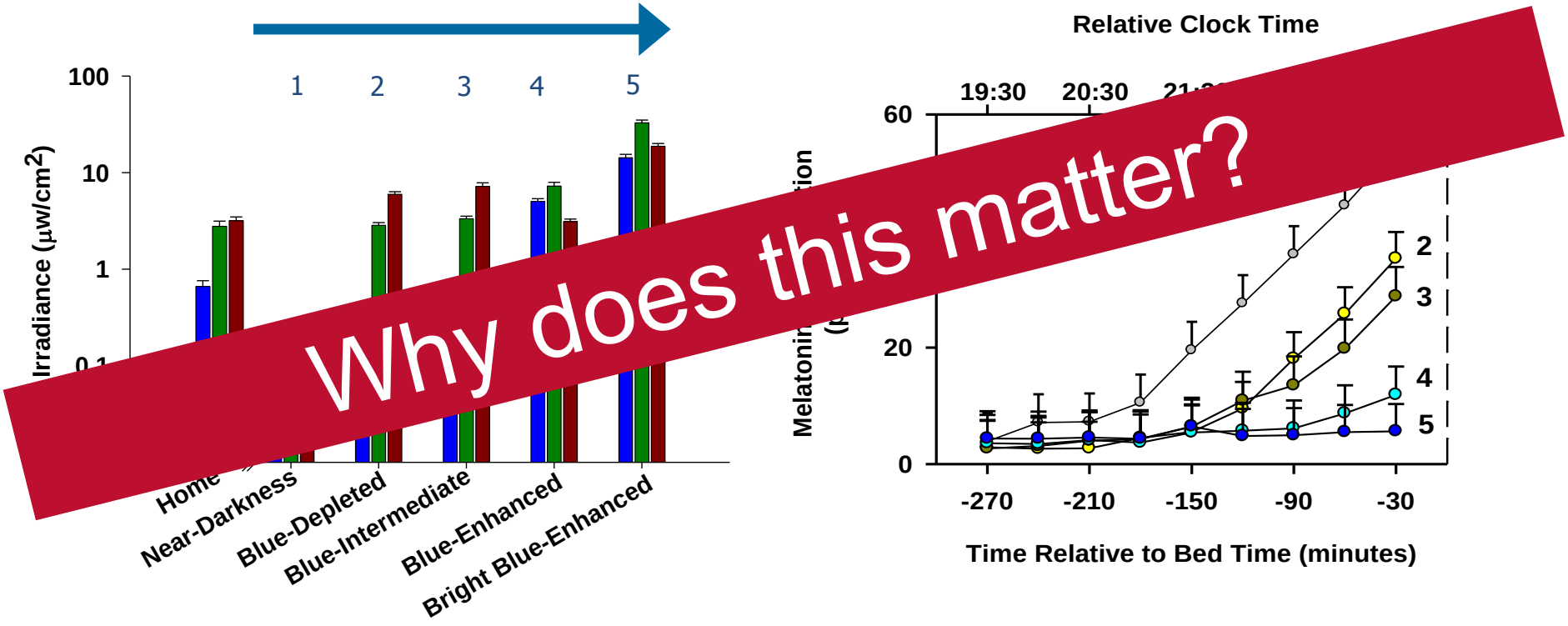
Santhi et al, 2012;J Pineal Research

Investigating the effects of artificial light

Artificial light of an intensity we are exposed to at home suppresses melatonin

More biologically effective light

4 hours of light exposure in the evening



Why does this matter?

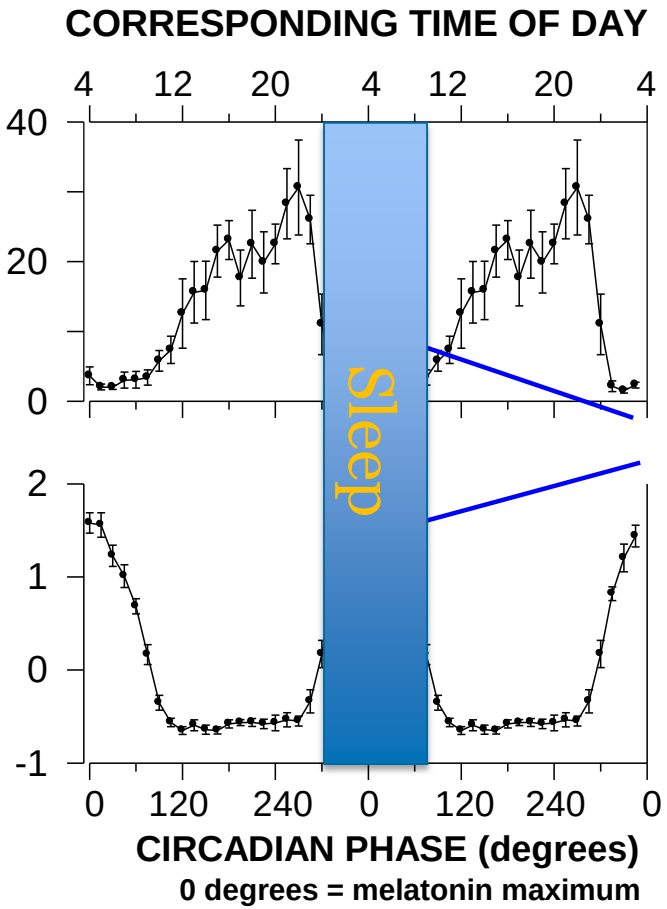
Santhi et al, 2012;J Pineal Research

The rhythm of melatonin and the biological night

Melatonin heralds the biological night and facilitates sleep onset

Drive for wakefulness

Melatonin



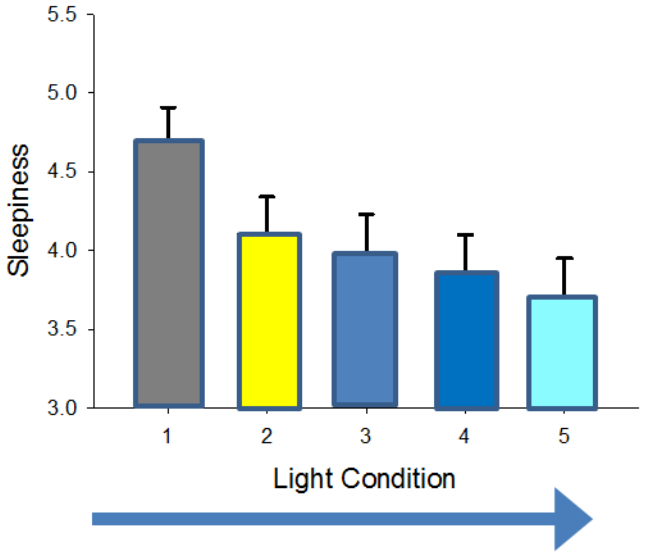
opening of sleep gate

Modified from Dijk et al. J Physiol 1997

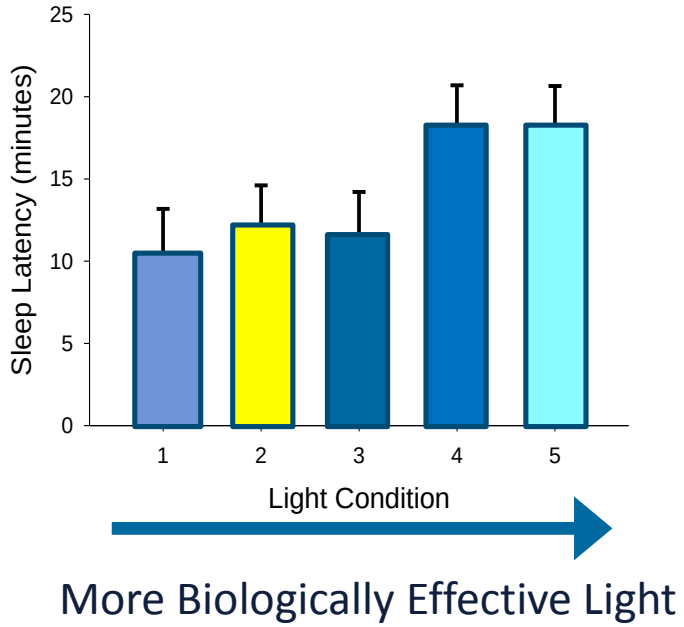
Light in the evening reduces sleepiness & delays sleep onset

Even light from laptops and other gadgets can have effects

Reduced Evening Sleepiness



Delayed Sleep Onset

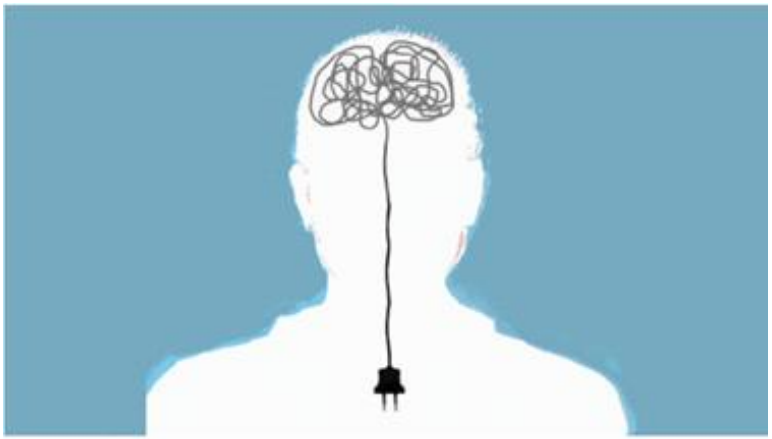


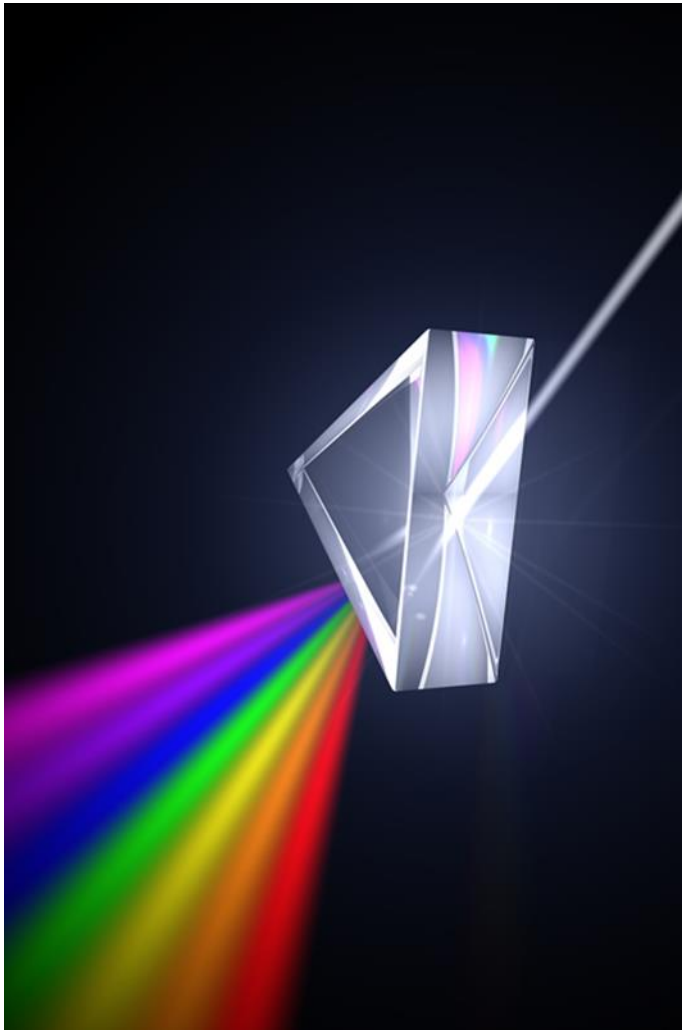
Santhi et al, 2012;J Pineal Research

Light, circadian rhythms and sleep

Summary

- Light of an intensity and spectral composition comparable to the light we are exposed to at home:
- Reduces sleepiness
- Disrupts sleep
- Suppresses melatonin
  - Effects are:
    - Melanopsin mediated (at least in part)





Circadian regulation of sleep

And its interaction with sleep homeostasis

Daytime functioning

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

Sleep-Wake Cycle

Circadian

Homeostat

Biological time

Sleep-wake history

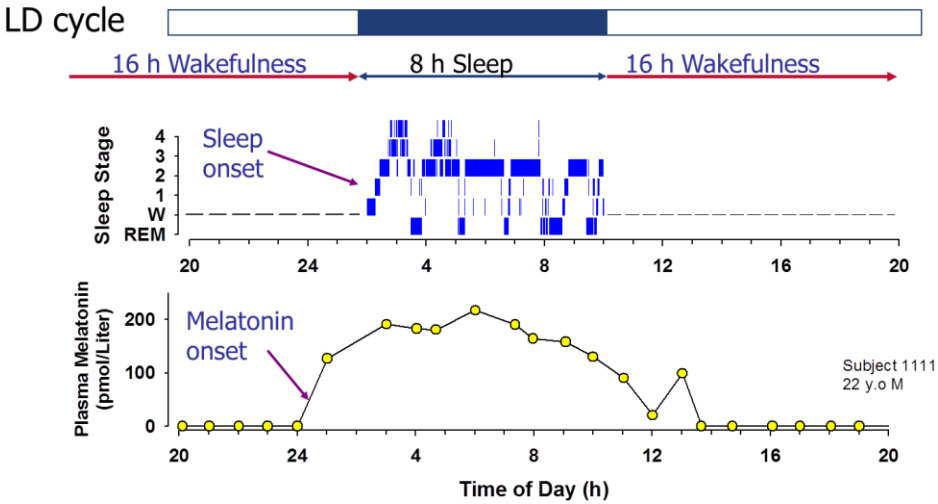
Individual

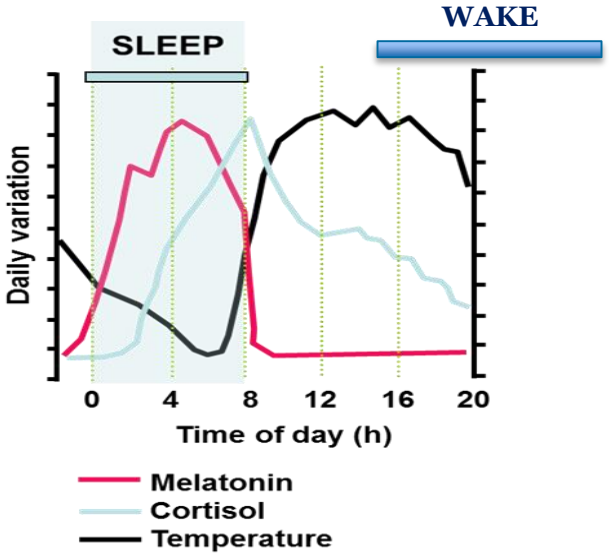
Genetic variation

A closer look at the circadian regulation of human sleep

Estimating the contribution of circadian rhythmicity and time asleep to sleep propensity and sleep structure

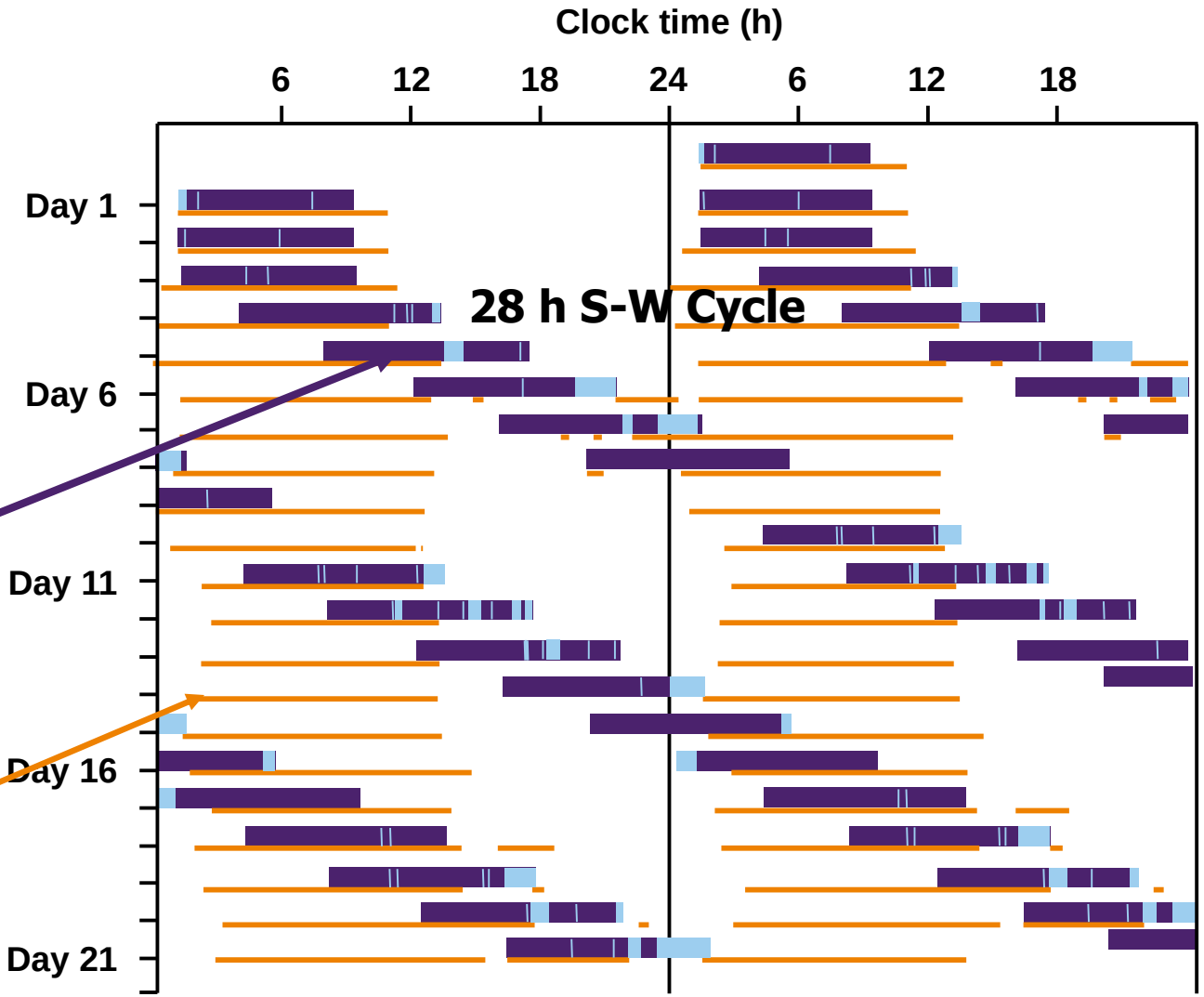
- The problem
  - During a normal nocturnal sleep period we travel through 1/3 of a circadian cycle and at the same time dissipate sleep pressure
- How to estimate the relative contribution of circadian rhythmicity and time asleep to sleep propensity/structure?
  - Desynchronise sleep from circadian rhythms
  - Assess sleep
  - Estimate the main effects of sleep-wake and circadian rhythmicity and their interaction





Separating the circadian and homeostatic component of sleep through forced desynchrony of sleep and SCN driven rhythms

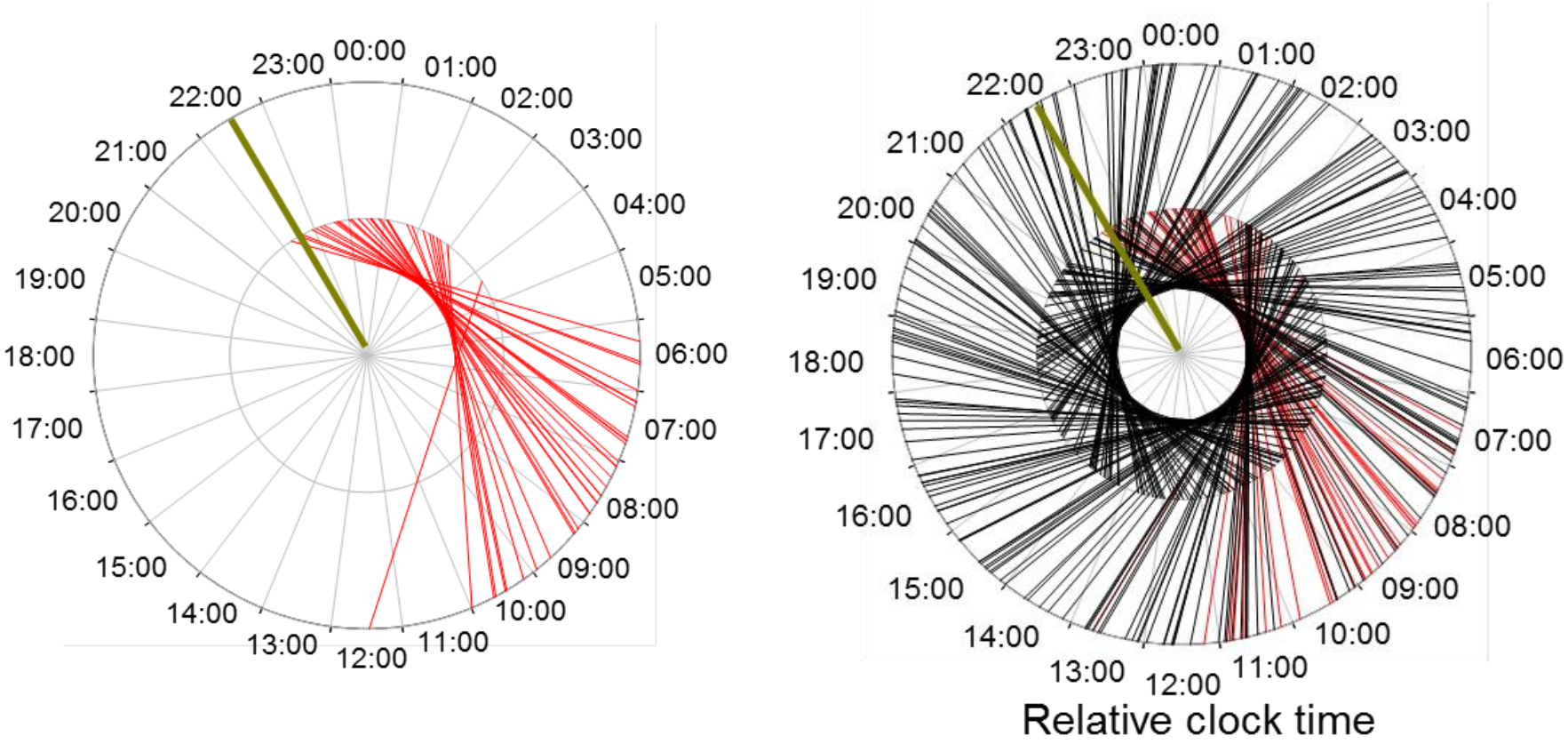
In dim light!



Modified from Dijk DJ, Duffy JF. Ann Med 1999; 31 (2): 130–140

Timing of sleep at baseline and during forced desynchrony

Relative to melatonin time



Maximum circadian drive for wakefulness: Just before the nocturnal increase in melatonin secretion

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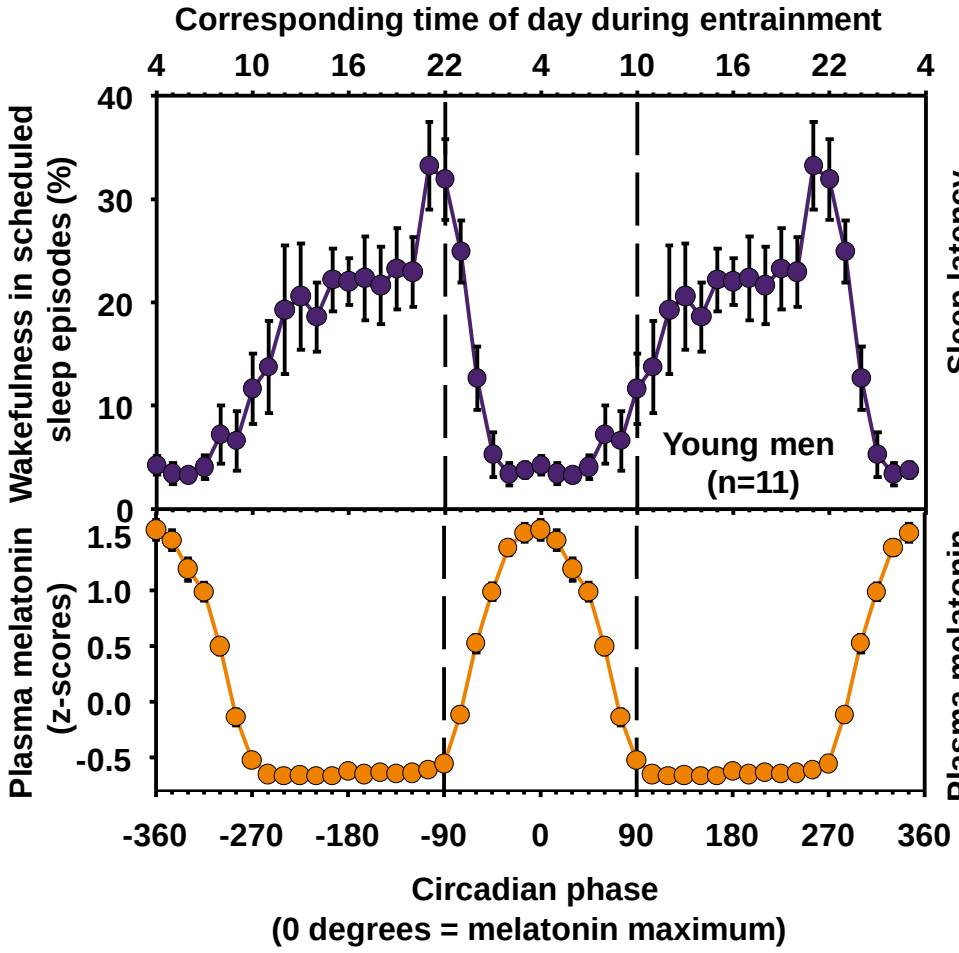
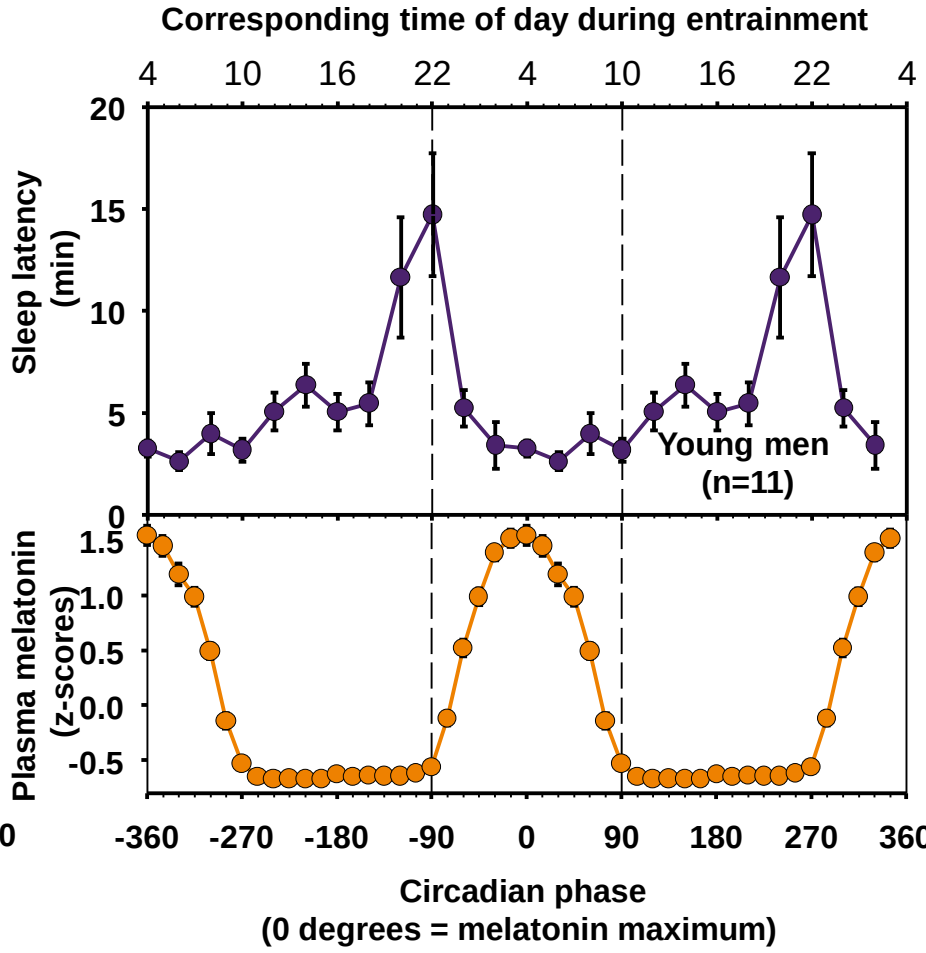
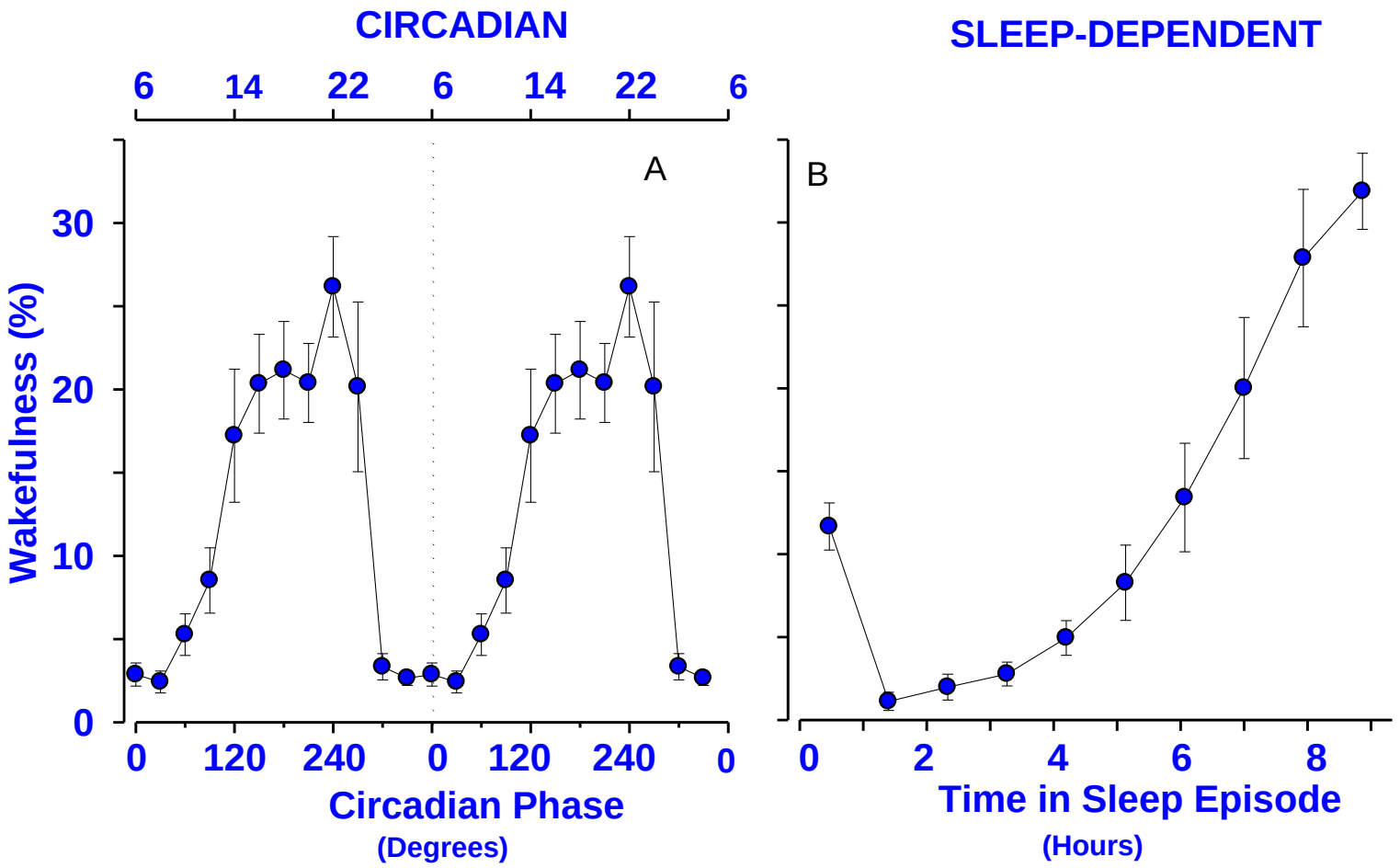
Maximum circadian drive for sleep: in the early morning hours



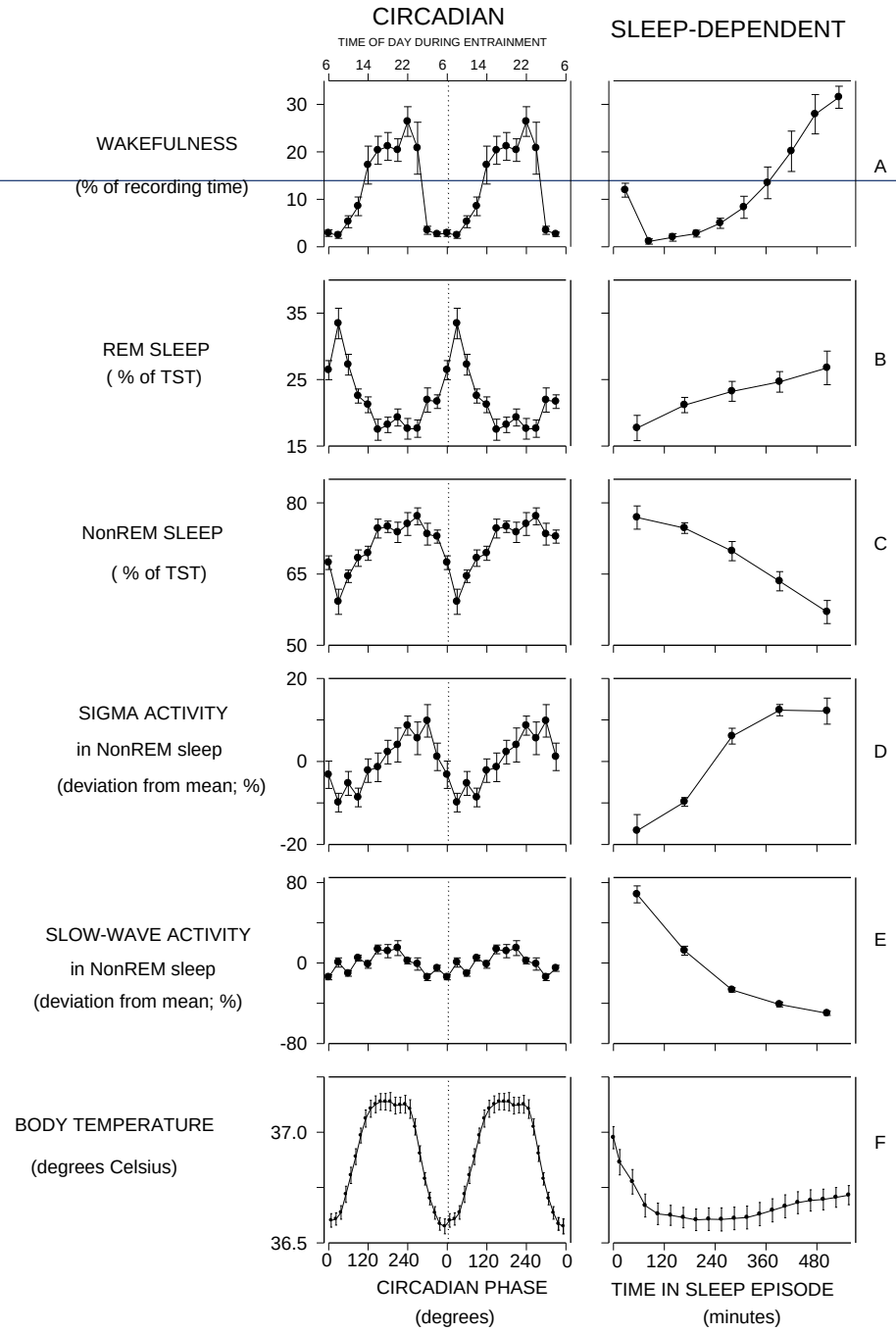


Dijk D-J, et al. J Physiol 1999; 516 (Pt 2): 611–627

The propensity to awaken depends on circadian phase and elapsed time asleep



Dijk and Czeisler; Neurosci Lett 1994



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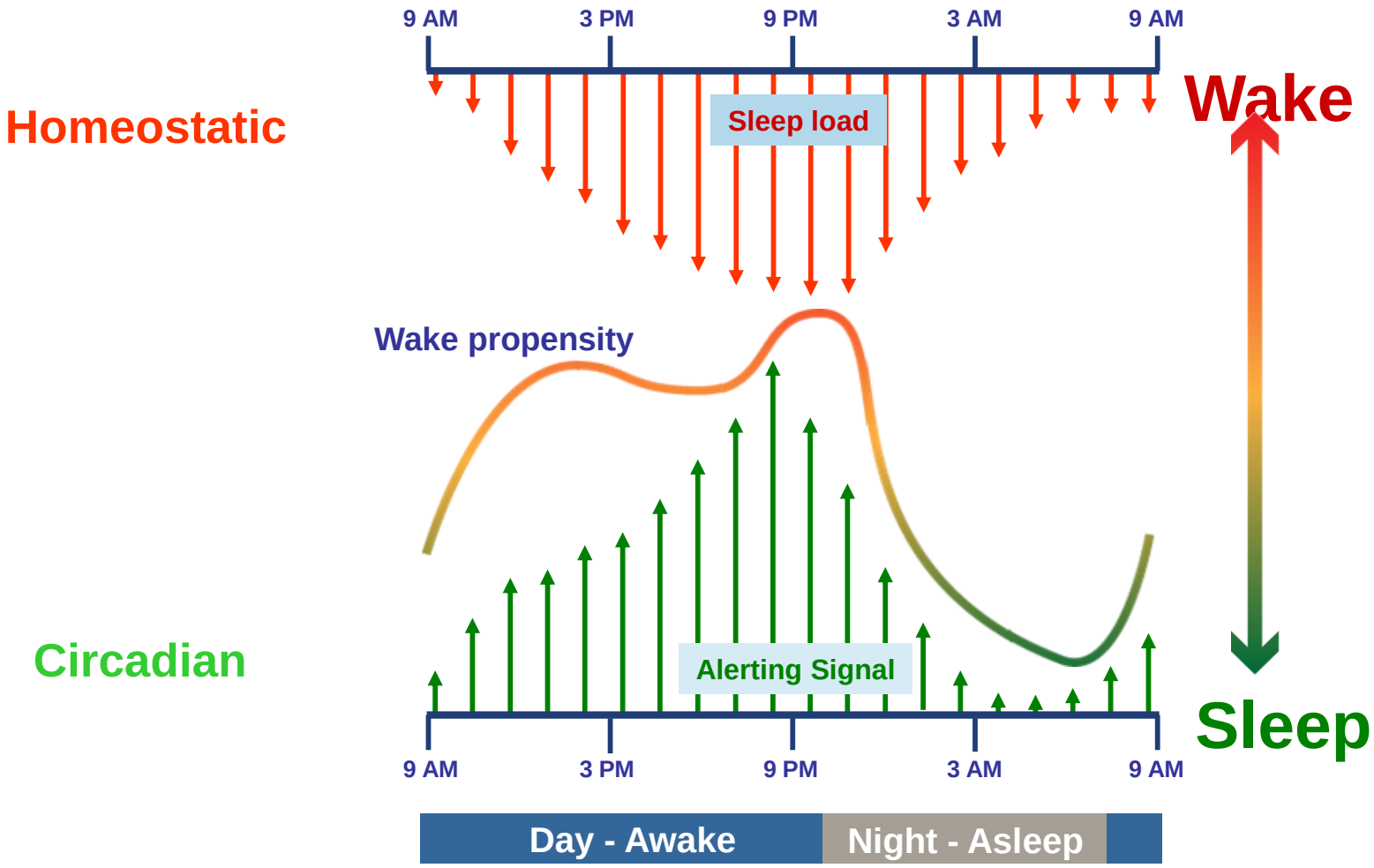
Circadian and sleep-wake dependent regulation of sleep propensity and sleep structure

- Strong circadian regulation of REM sleep
- Strong homeostatic regulation of Slow Wave Sleep and Slow Wave Activity
- Sigma-activity/sleep spindles under both circadian and homeostatic control

Dijk and Czeisler J Neurosci 1995

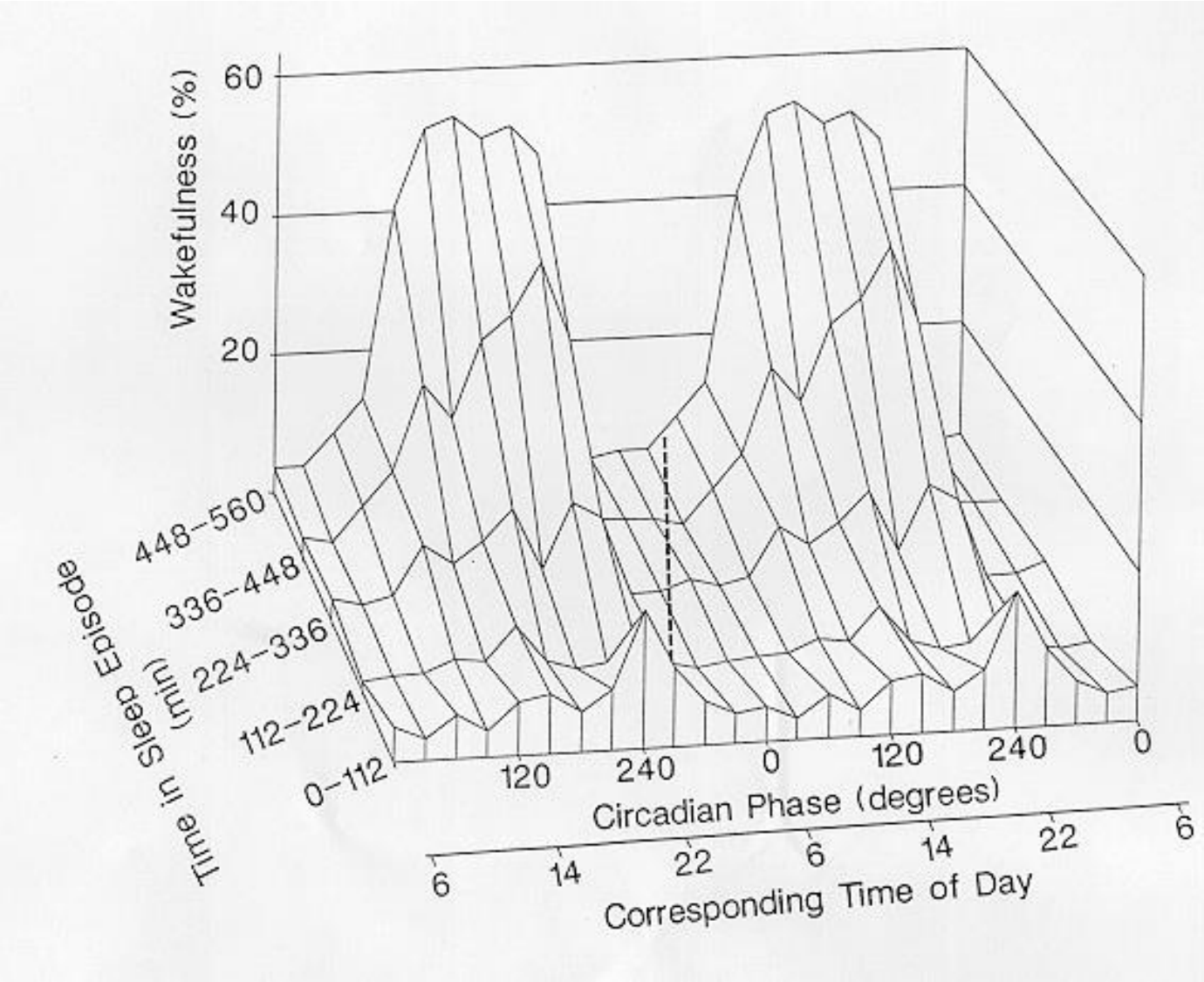
Circadian and Homeostatic Interaction

Opponent processes

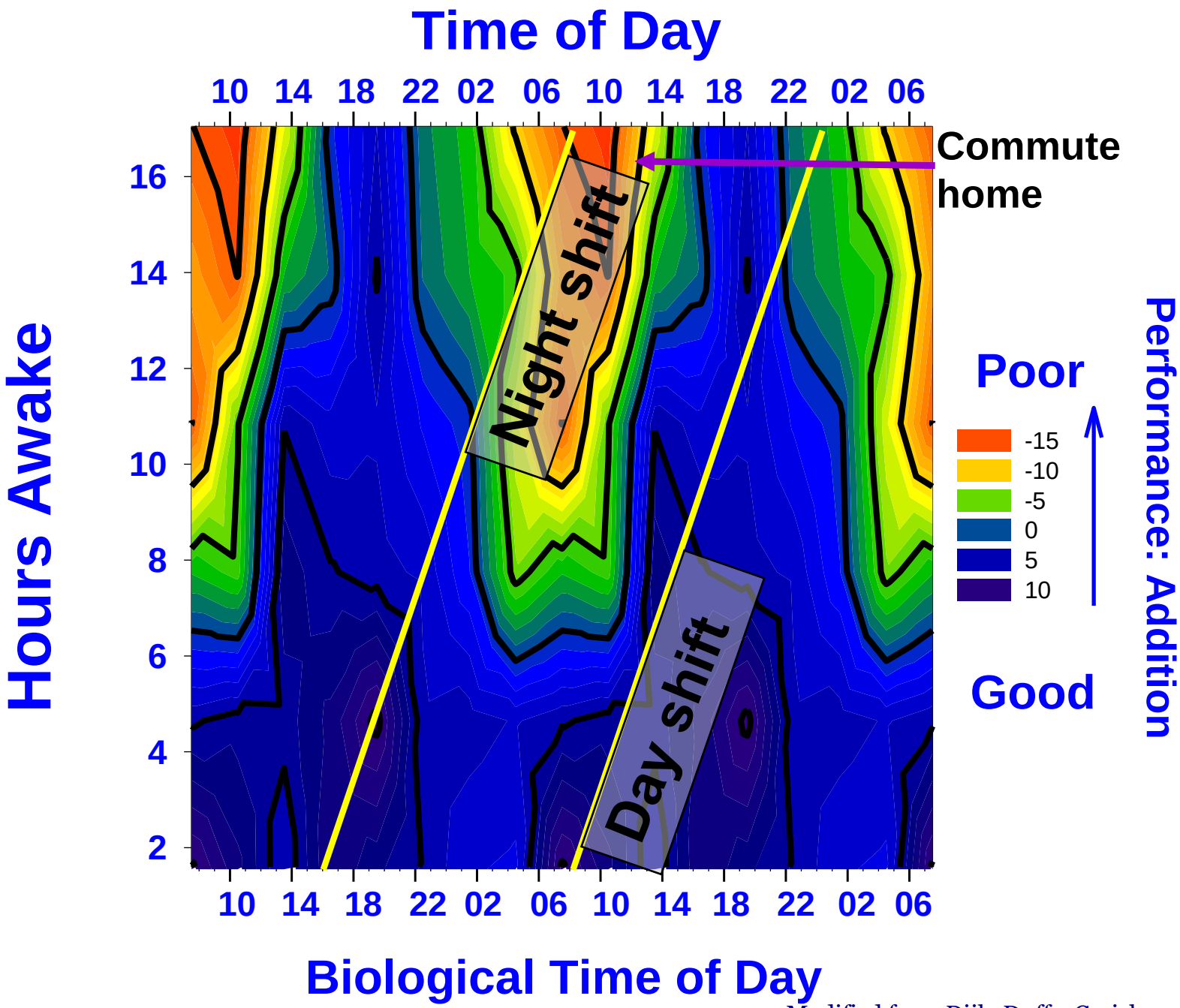


After Edgar et al. J Neurosci. 1993;13:1065

Circadian phase and time asleep interact in the regulation of the propensity to wake-up



Dijk and Czeisler Neurosci Lett 1994



Modified from Dijk, Duffy, Czeisler; 1992

Individual differences in sleep-wake timing

Physiological correlates

Daytime functioning

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

Sleep-Wake Cycle

Circadian

Biological time

Homeostat

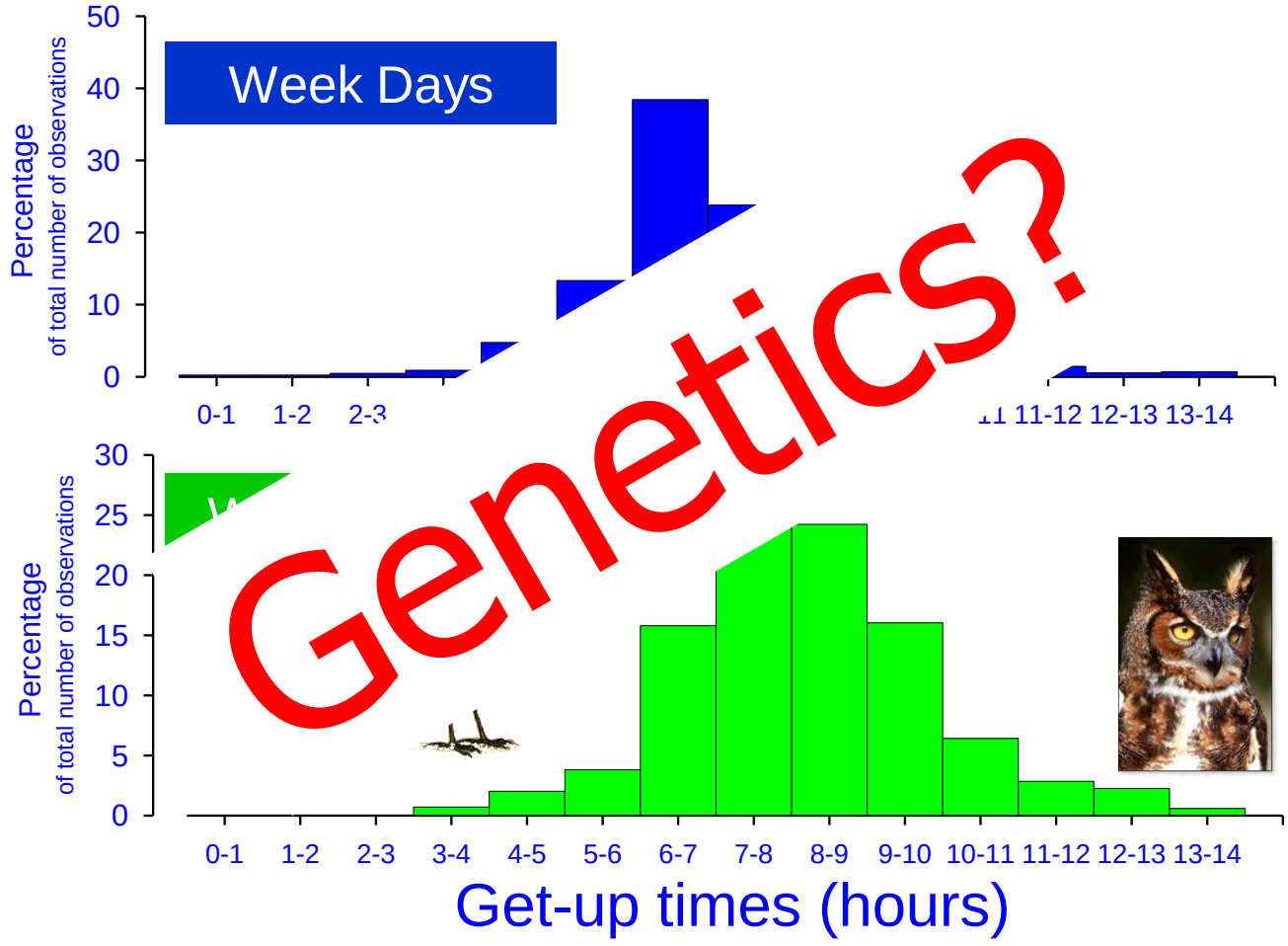
Sleep-wake history

Individual

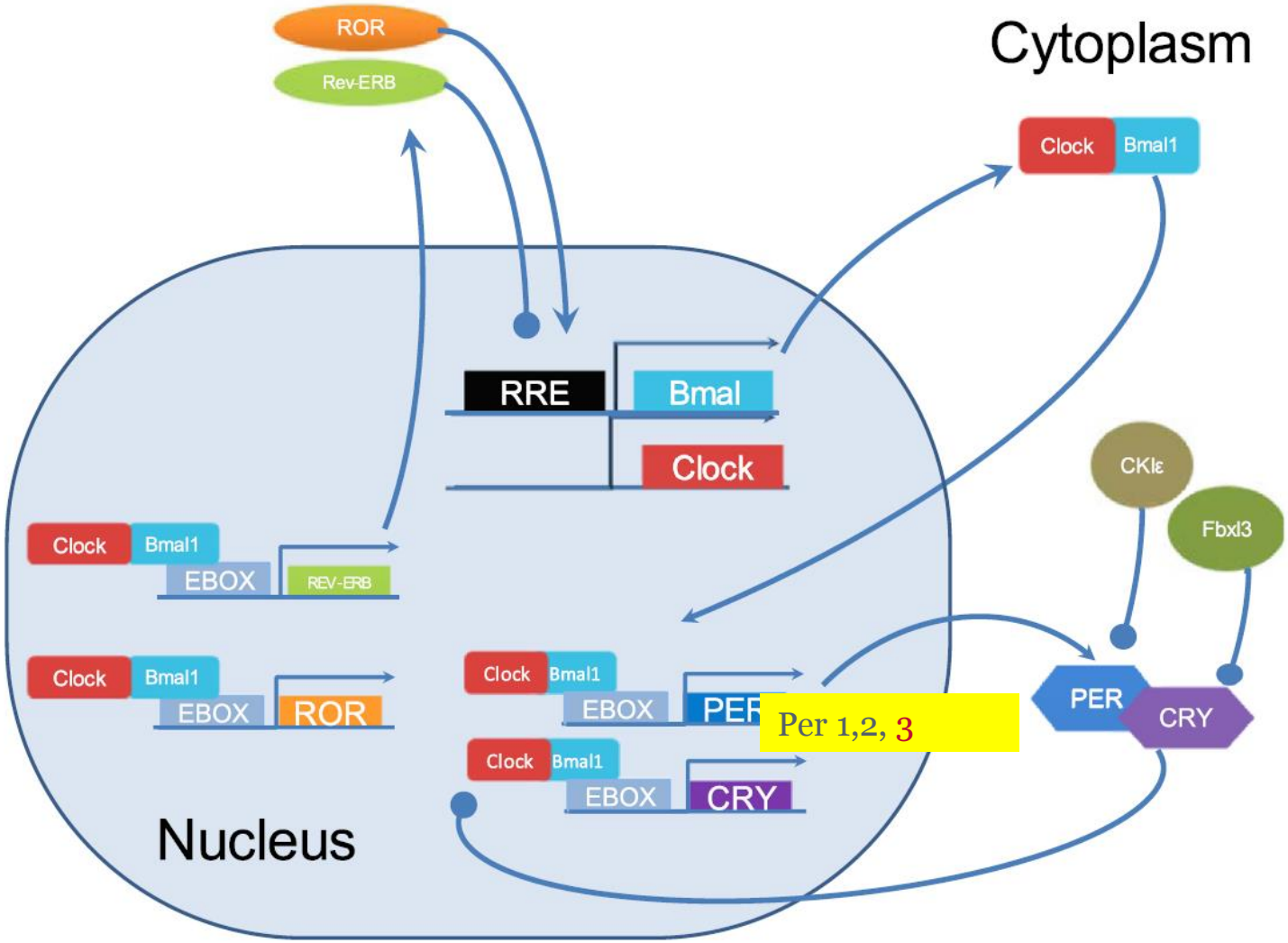
Genetic variation

Individual differences in sleep timing

Morning and evening types?



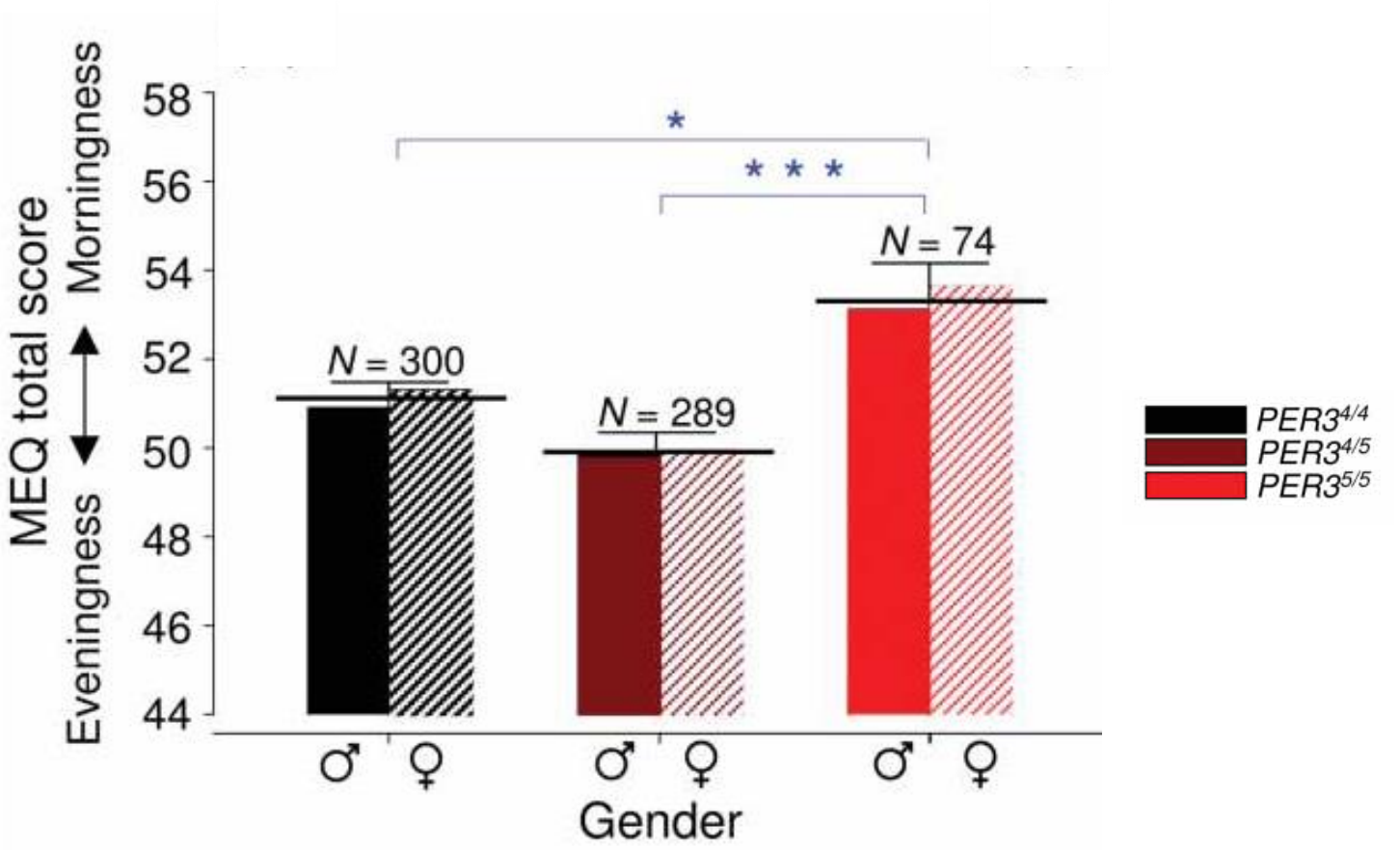
The core molecular circadian clock



I. Robinson , A.B. Reddy; FEBS Letters; 2014

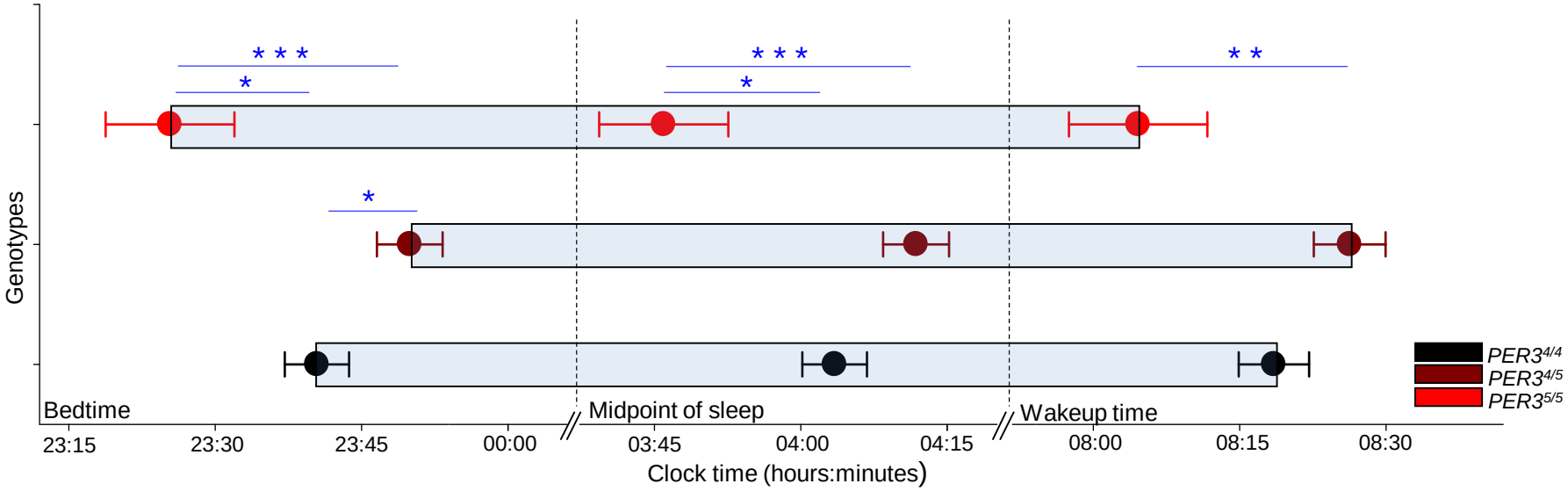
PER3 Variable Number Tandem Repeat predicts diurnal preference

in healthy men and women aged 20-35



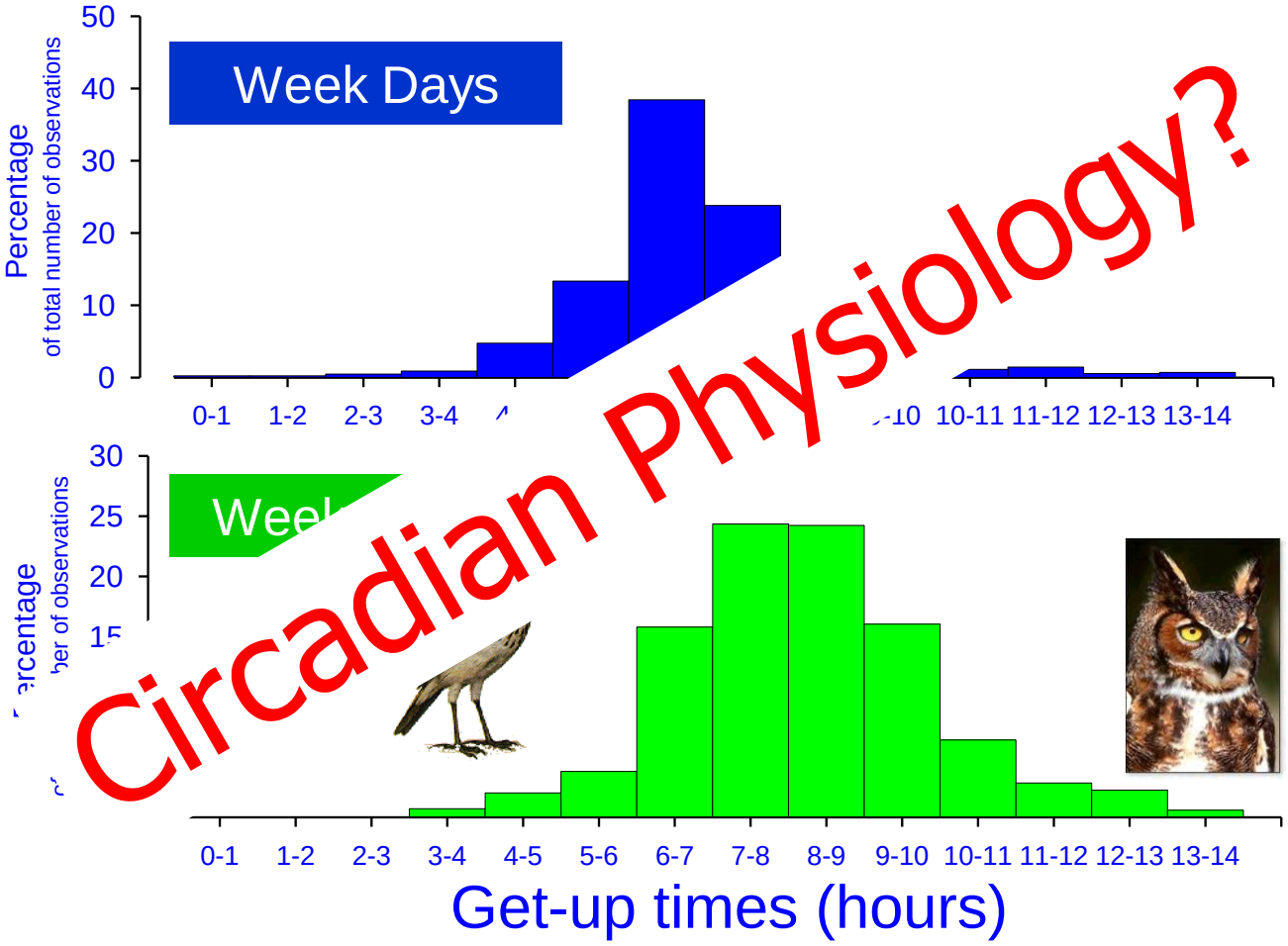
PER3 VNTR predicts self-reported sleep timing

in ~675 healthy men and women aged 20-35



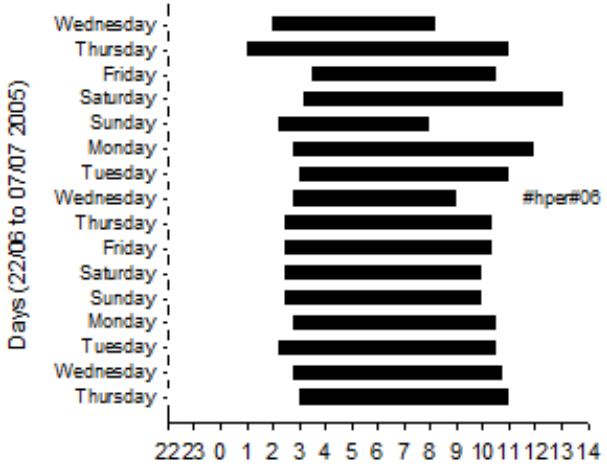
Variation in sleep timing

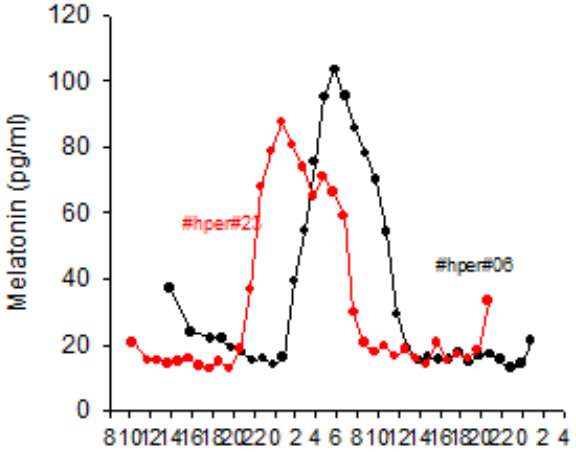
Morning and Evening types

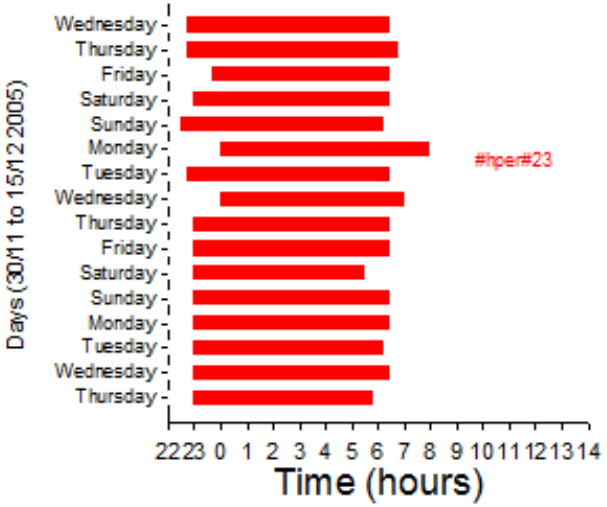


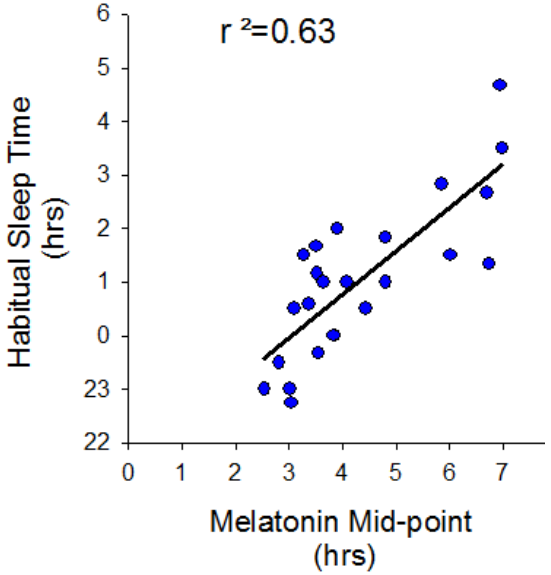
Association: habitual sleep-timing and **phase** of melatonin

Assessed in the absence of sleep-wake cycle



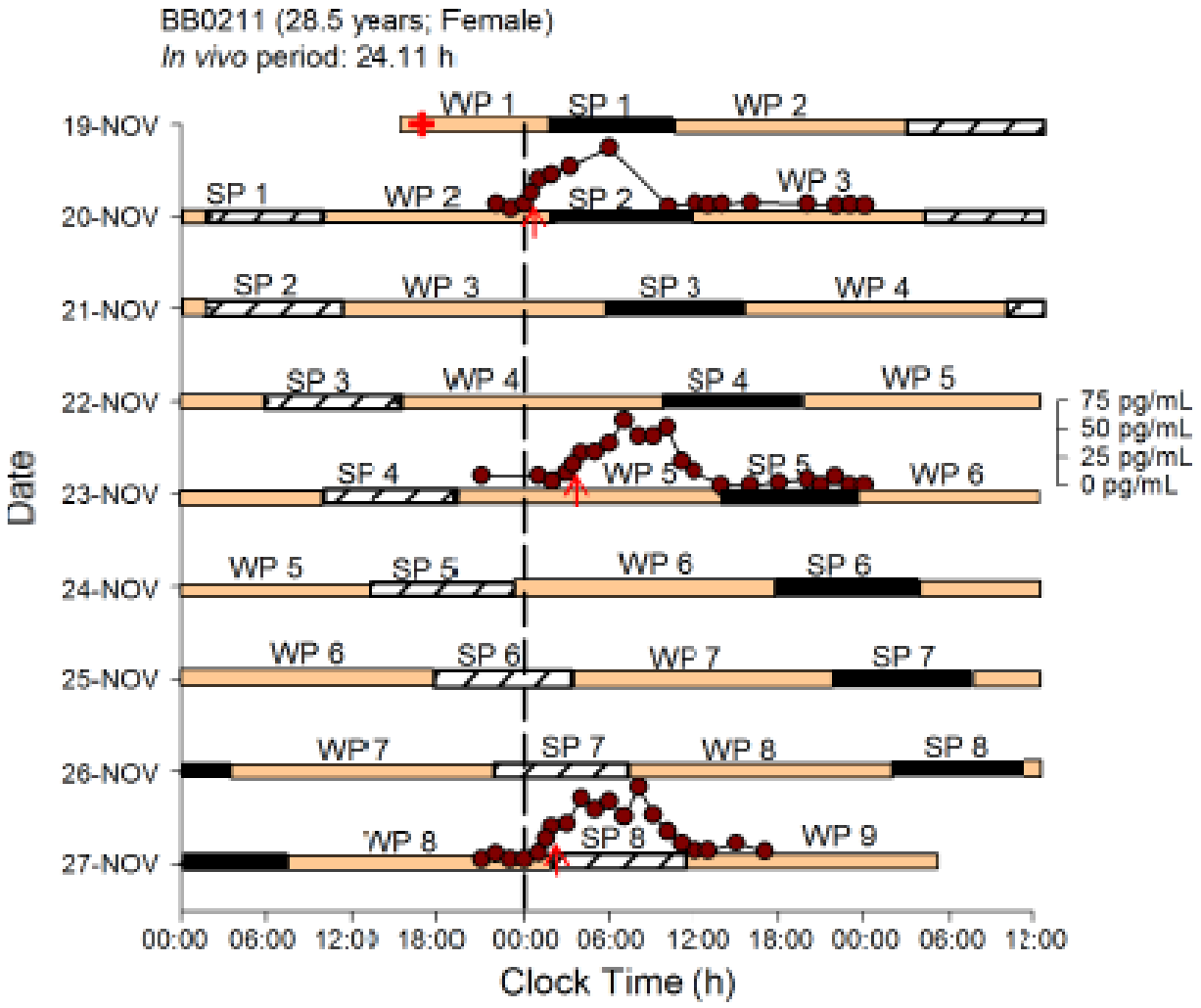






Association between sleep-wake timing and **Period** of melatonin rhythm?

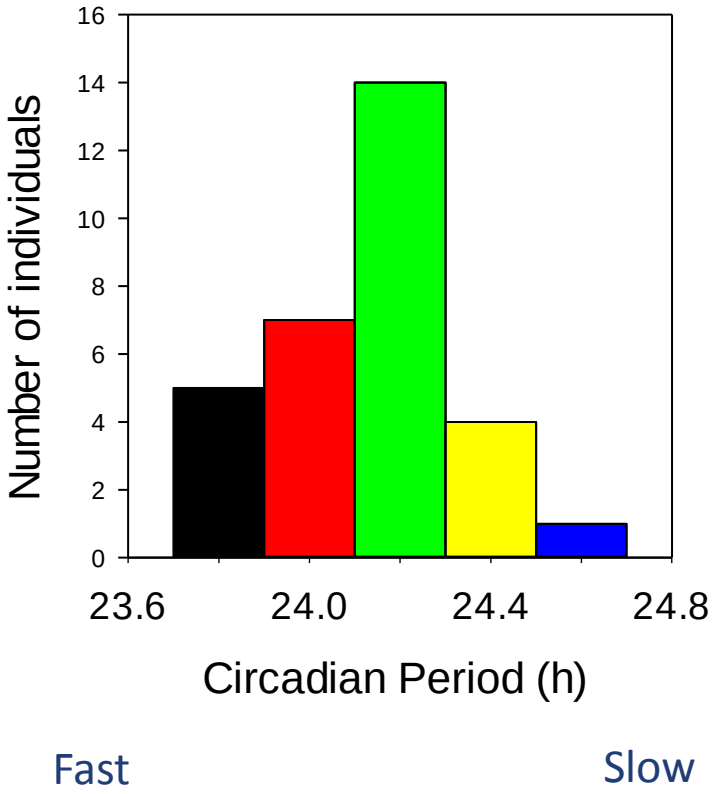
Forced desynchrony protocol to assess intrinsic period of melatonin rhythm

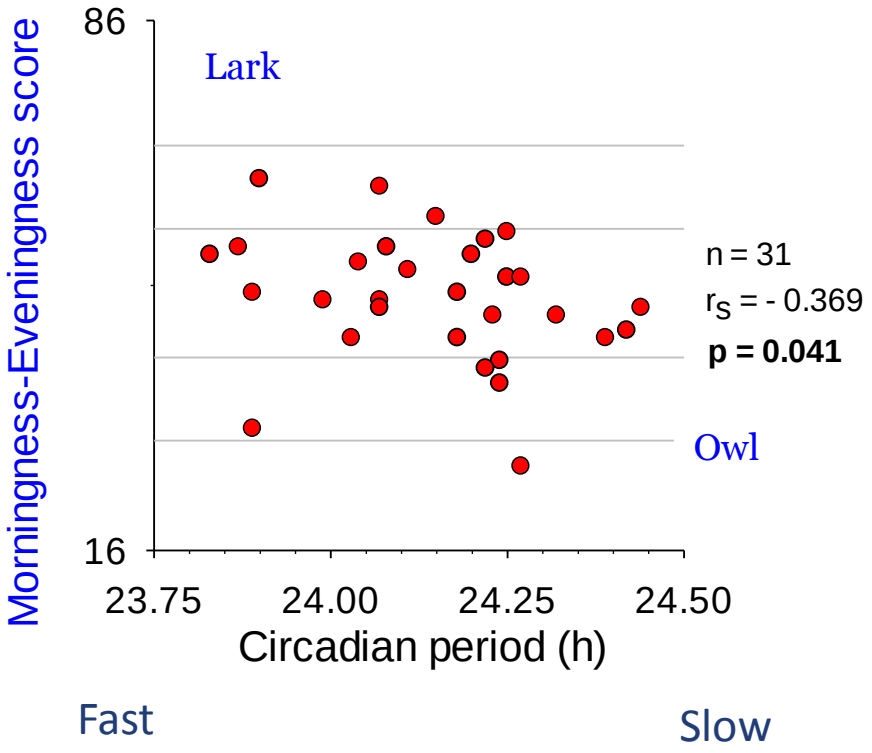


Hasan et al. FASEB, 2012

Period of melatonin rhythm correlates with diurnal preference

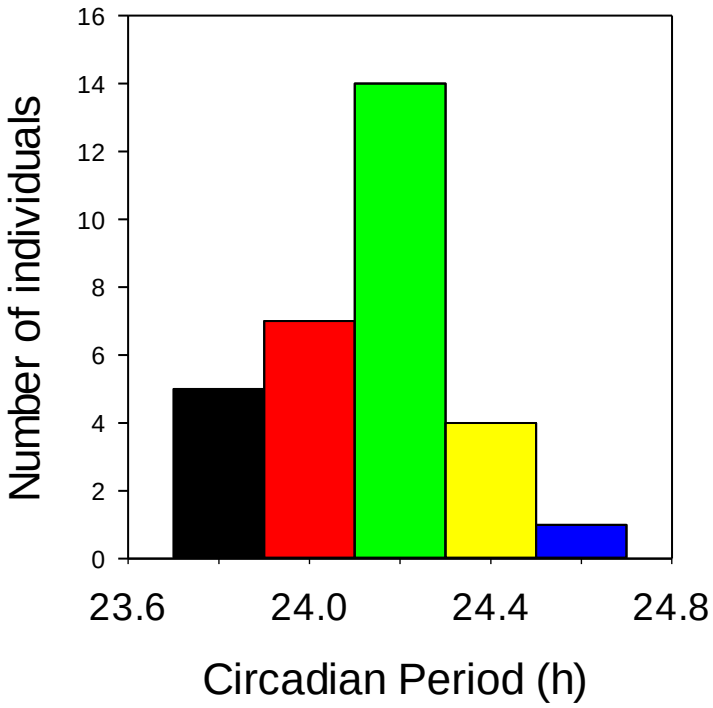
Owls: Slow clock; Larks: Fast clock



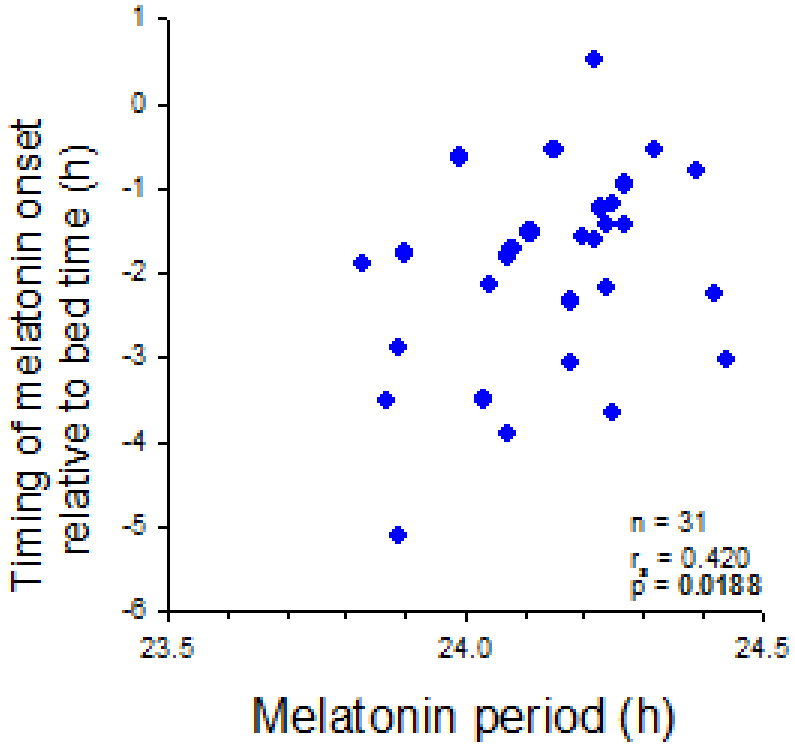


Period of melatonin rhythm correlates with melatonin phase

Fast clock-> melatonin rises well before bedtime

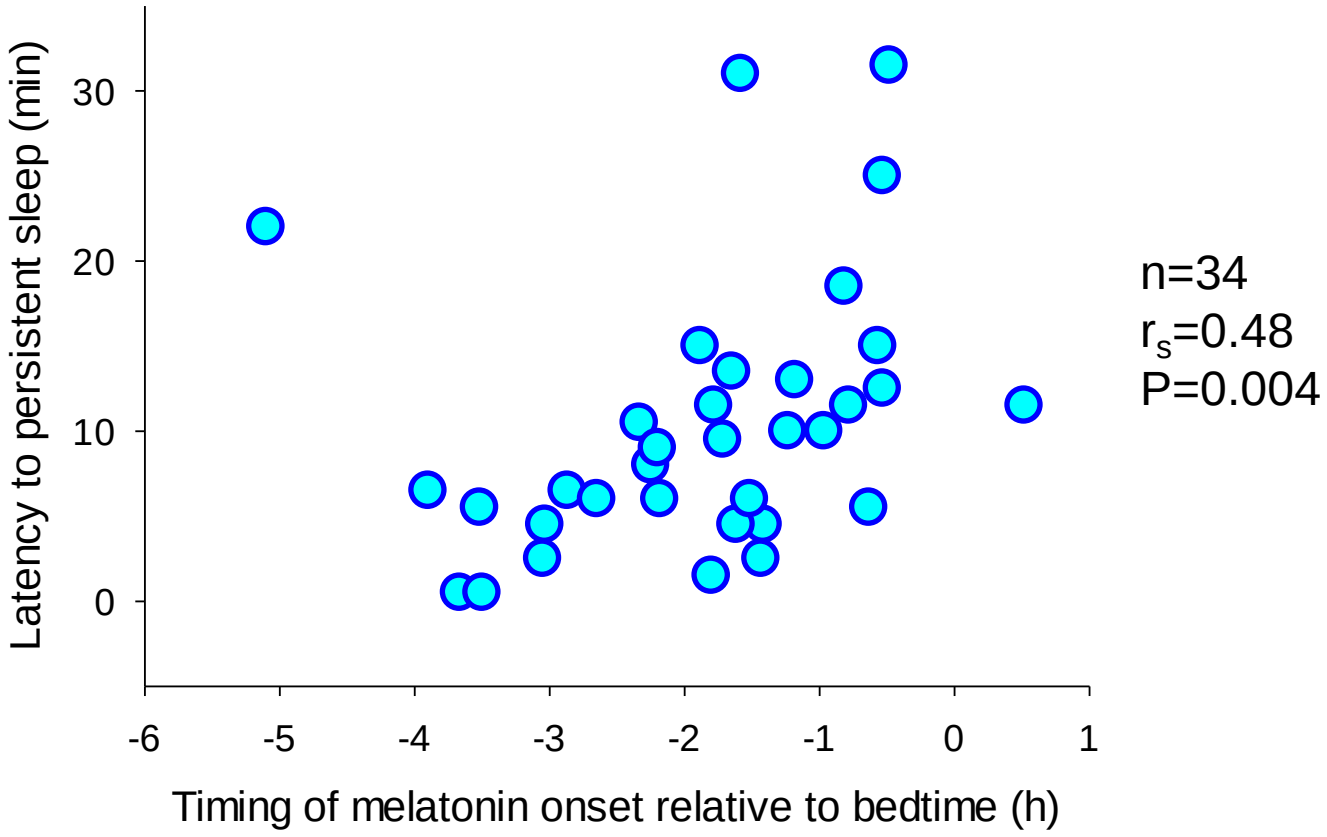


Fast Slow



Melatonin phase predicts latency to sleep onset when sleeping at habitual time

Early melatonin phase→ easy to fall asleep

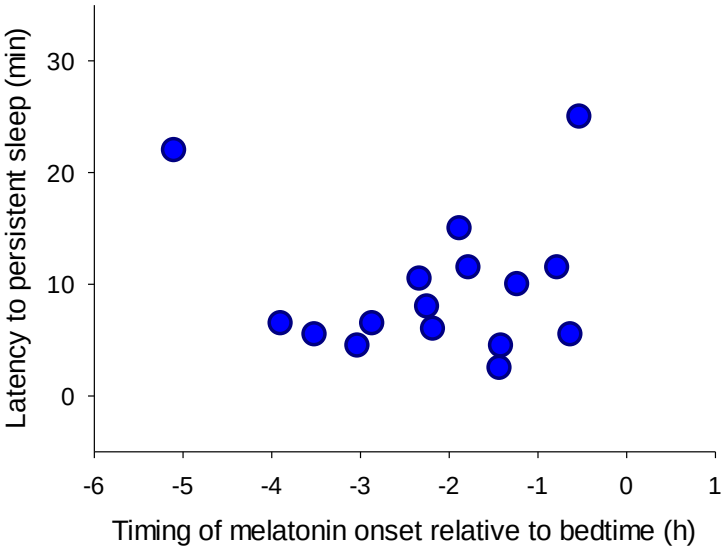


Lazar et al. J Sleep Res, 2013

… and especially so in women

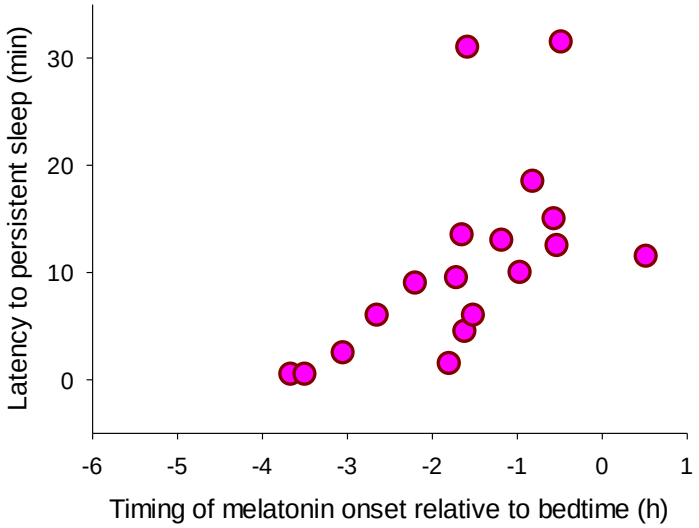
Men

n = 16, r_s=0.1, p =0.723



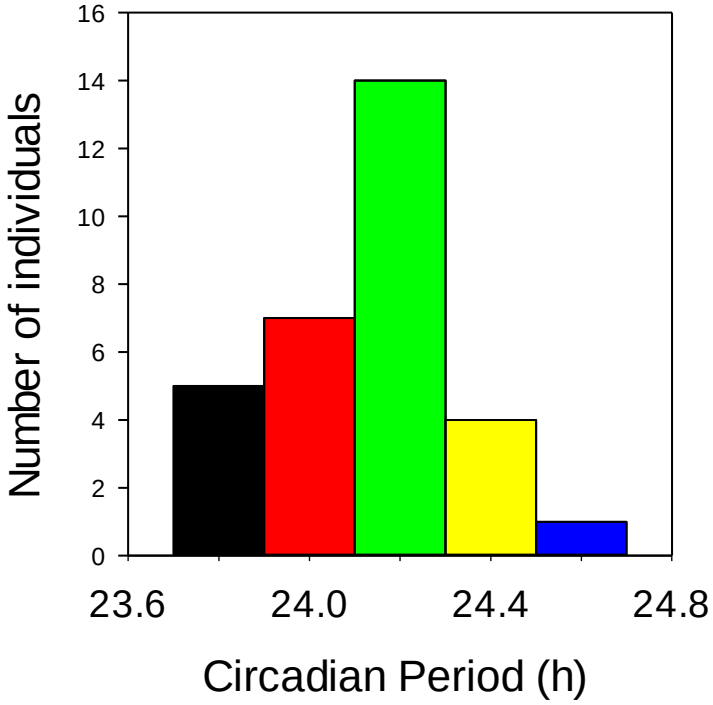
Women

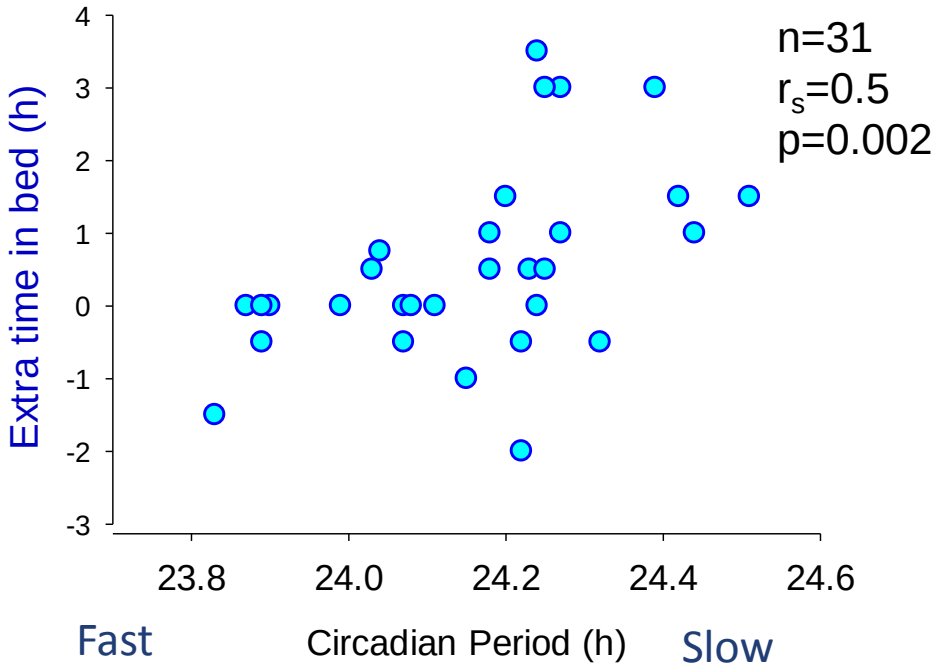
n=18, r_s=0.76, *P*<0.001)



Period of melatonin rhythm and extra sleep during the weekend

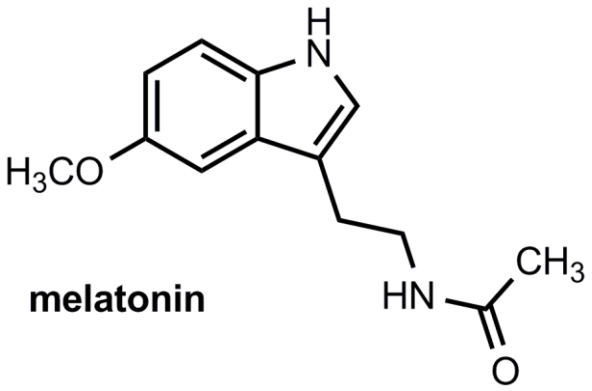
Those with a slow clock sleep longer during the weekend (and less during the week)





Phase and Period of melatonin rhythm and sleep-wake timing

- Phase of melatonin rhythm correlates with
  - Sleep timing
  - Sleep latency
- Period of melatonin rhythm correlates with
  - Diurnal preference
  - Melatonin phase
  - Extra time in bed during the weekend



melatonin

Feedback of sleep-wake cycle on circadian rhythmcity in periphery

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Physiological correlates

Daytime functioning

Social/Behavioural Factors

Light-Dark Cycle

Circadian Photoreception

Sleep-Wake Cycle

Circadian

Homeostat

Biological time

Sleep-wake history

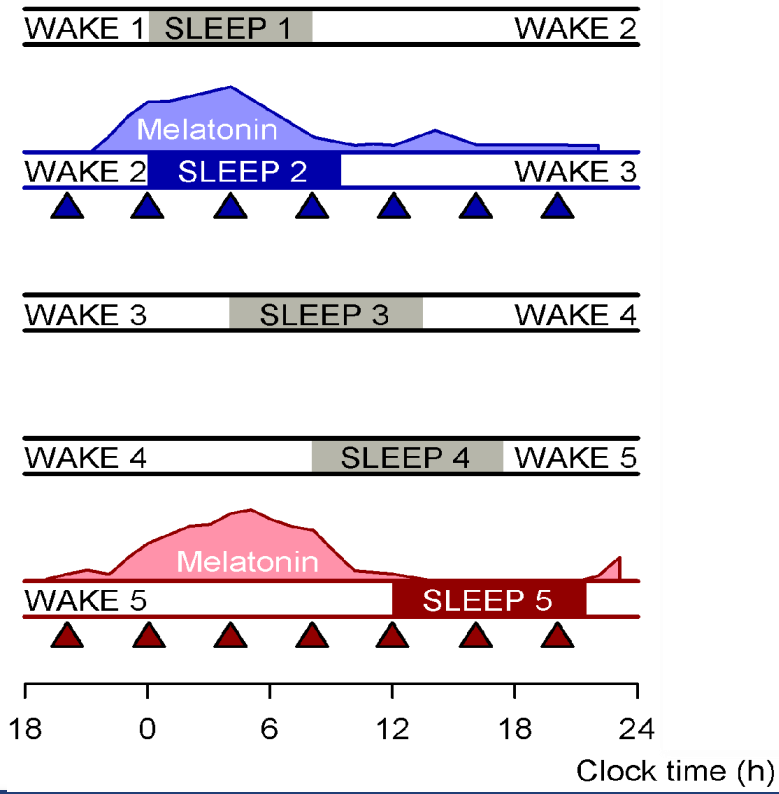
Individual

Genetic variation

Effects of mistimed sleep on the blood transcriptome

A model for circadian disruption?

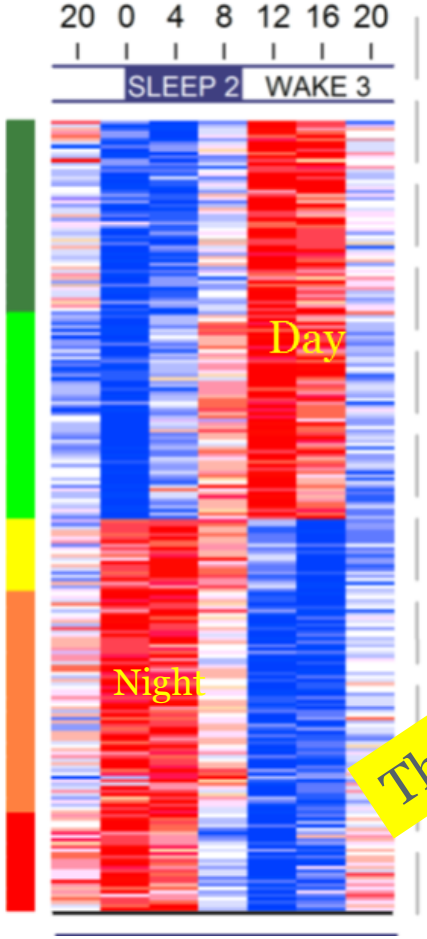
- 22 participants (11 male) 2 Conditions (sequential design)
  - Control (sleeping in phase with melatonin)
  - Mistimed sleep (sleep out of phase with melatonin)
  - RNA Sampling during 28-h sleep-wake cycle (7 samples per condition)



Archer et al. PNAS 2014;111(6):E682-91

Circadian rhythmicity in the periphery [The blood transcriptome]

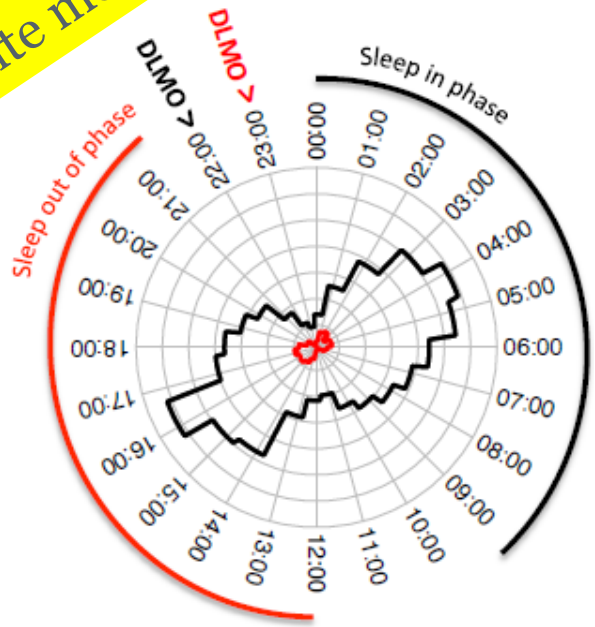
6 Fold reduction in 'rhythmic genes' when sleep is mistimed



These changes were observed despite melatonin not being affected

In phase: **1,396** rhy genes'; 6.4%

Out of phas rhythmic 'genes'; 1.0%



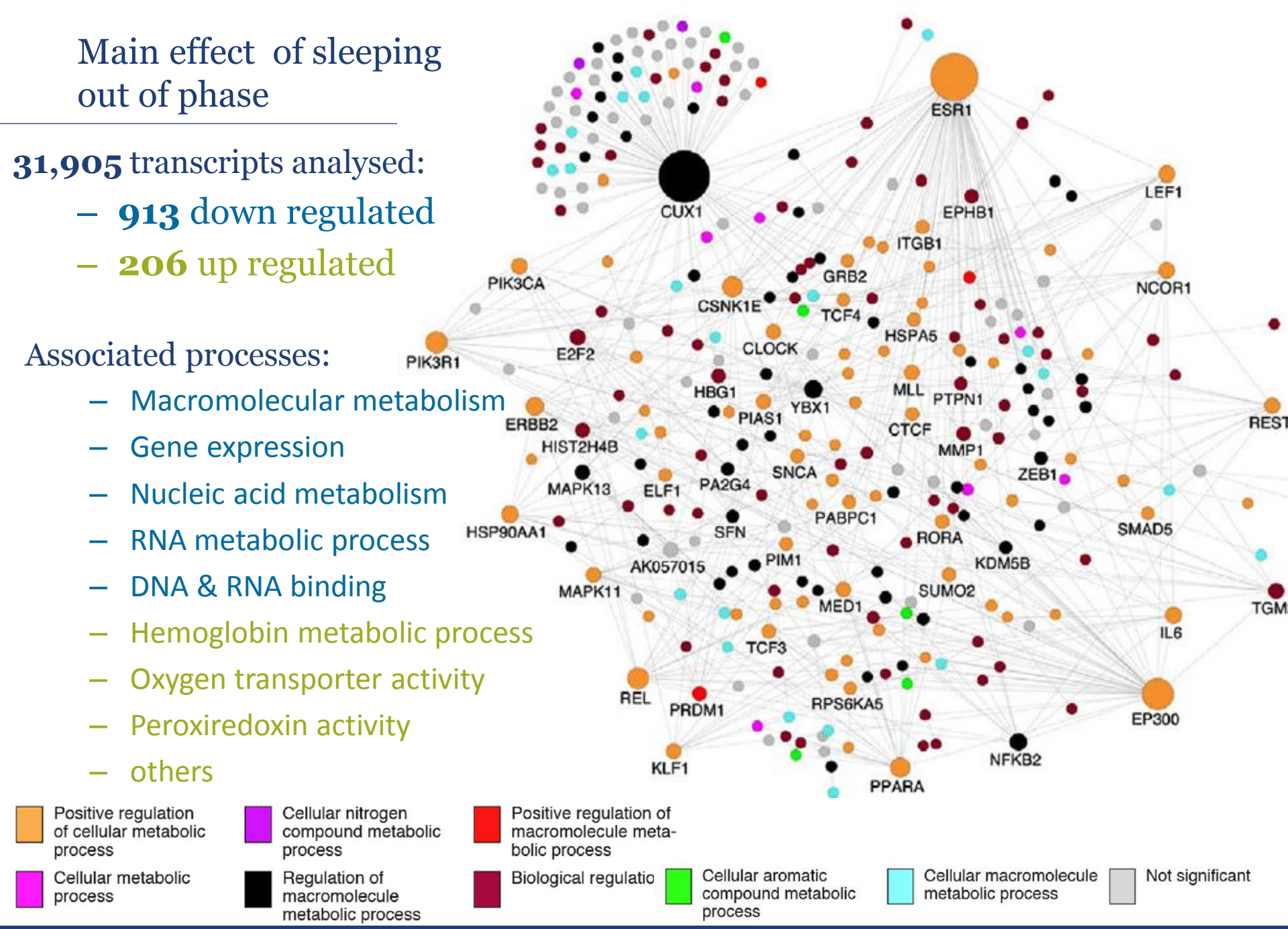
Main effect of sleeping out of phase

31,905 transcripts analysed:

- **913** down regulated
- **206** up regulated

Associated processes:

- Macromolecular metabolism
- Gene expression
- Nucleic acid metabolism
- RNA metabolic process
- DNA & RNA binding
- Hemoglobin metabolic process
- Oxygen transporter activity
- Peroxiredoxin activity
- others



Archer et al. PNAS 2014;111(6):E682-91

Laing *et al.* BioEssays 2015; 37:544-56.

Effects of Desynchrony/Mistimed sleep

Relation to health effects?

- Mistiming of sleep-wake cycles affects molecular processes that are at the core of the regulation of the temporal organisation of the transcriptome and circadian rhythmicity
  - This is observed while melatonin is not supressed
- Genes and processes affected are involved in many of the negative health outcomes associated with shift work
- Transcriptomics of whole blood holds promise for biomarker ‘discovery’

Circadian regulation of sleep-wake cycle

Summary

- SCN is a master circadian pacemaker
- Light as a very relevant environmental factor for sleep timing
- Circadian rhythmicity and sleep homeostasis: opponent processes
- Melatonin phase and period as a correlates of individual differences in sleep timing
- Polymorphisms in clock genes as correlates of individual differences in sleep timing and diurnal preference
- Mistimed sleep affect the temporal organisation of the blood transcriptome
- A better understanding of these effects and the underlying mechanisms may help to prevent the adverse health consequences of insufficient and mistimed sleep

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  - Lynette James
  - Ana Slak
  - Ciro Della Monica
  - Emma Arbon
  - Mathieu Nolllet
  - Giuseppe Atzori
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  - Dr Julia Boyle
  - Statisticians: Dr Sigurd Johnsen & Mr Patrick McCabe
  - Clinical, research, and recruitment teams
- Participants
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