goto; copenhagen

GOTO Copenhagen 2018
Conference Nov. 19 - 21

The Science of Sleep

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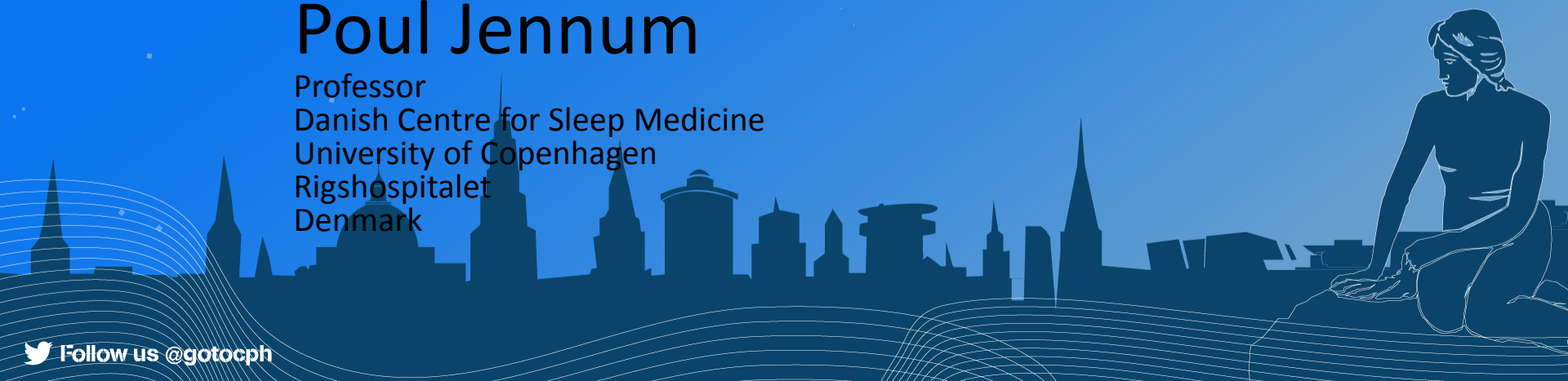
Danish Centre for Sleep Medicine
University of Copenhagen
Rigshospitalet
Denmark



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Function of sleep

Sleep plays an active role in processes such as

- synaptic plasticity and memory functions,
- emotional regulation,
- metabolic functions and energy balance,
- macromolecule biosynthesis,
- removal of toxic substances and metabolic waste, or
- prophylactic cellular maintenance.

Default state of the organism and/or a state of adaptive inactivity.

Vyazovskiy VV. Nat Sle Sci 2015 ; 7:171—184

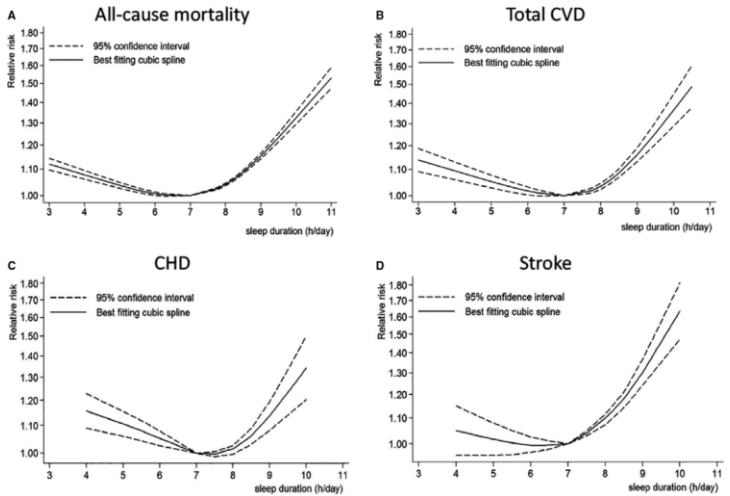
Consequences of poor sleep

- Daytime sleepiness and fatigue
- Cognitive and memory impairment
- Stress and depressive mood
- Emotional and social interaction
- Reduced work efficiency
- Poor health:
  - Sedative behavior
  - Poor lifestyle
  - Morbidity and mortality

Short and long sleep are related to poorer health

Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events

- Total 3 582 016 participants, including 241 107 cases of all-cause mortality
- For all-cause mortality, when sleep duration was <7 hours per day, the pooled relative risk (RR) was 1.06 (95% CI, 1.04–1.07) per 1-hour reduction; when sleep duration was >7 hours per day, the pooled RR was 1.13 (95% CI, 1.11–1.15) per 1-hour increment.
- For total cardiovascular disease, the pooled RR was 1.06 (95% CI, 1.03–1.08) per 1-hour reduction and 1.12 (95% CI, 1.08–1.16) per 1-hour increment of sleep duration.

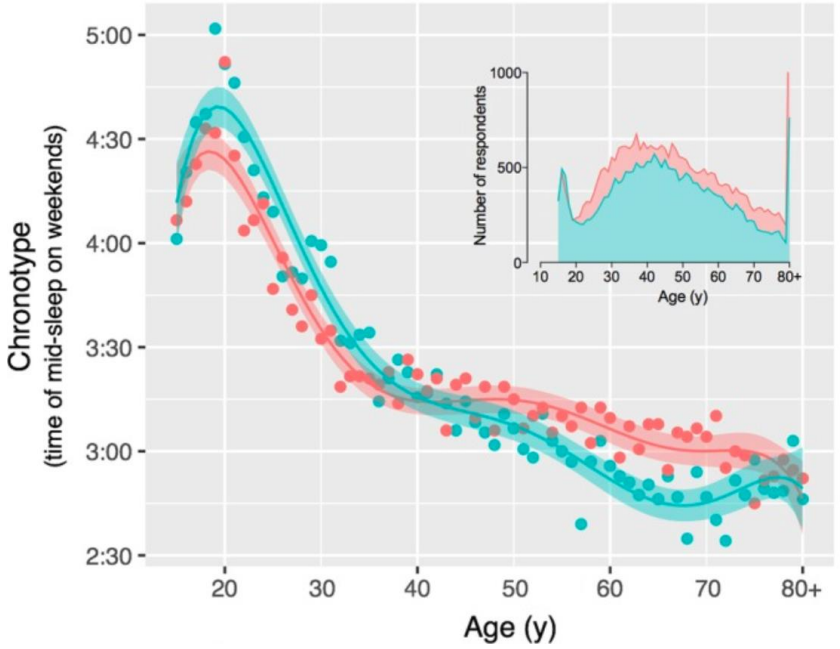


Yin et al. Am Heart Assoc 2017 Sep; 6(9):

Chronotype affect health

Late chronotype is related to:

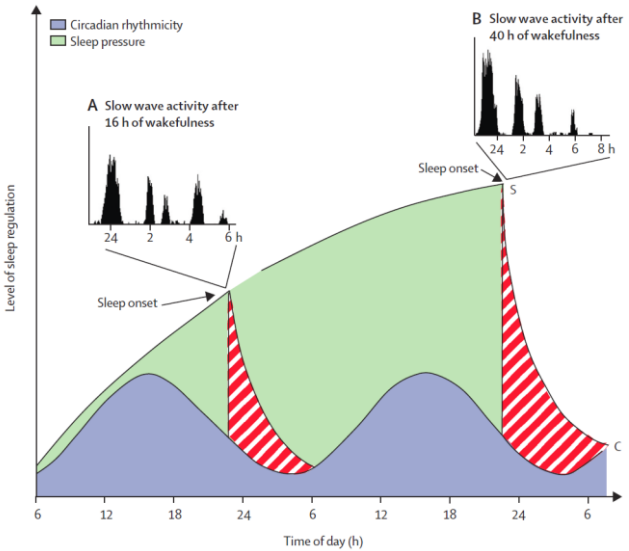
- Sedative behavior
- Smoking
- Obesity
- Mood
- Morbidity and mortality
- Low education and low income
- Societal costs

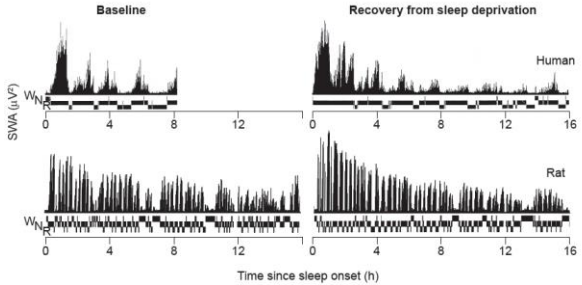


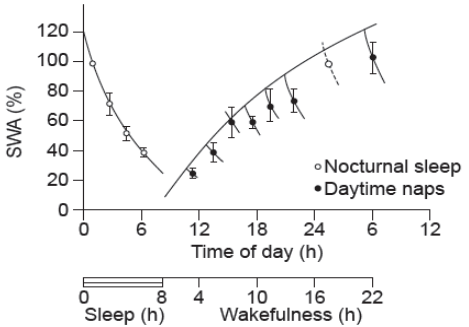
Sivertsen et al. Sleep. 2018 Nov 1;41(11). Knutson et al. Chronobiol Int.2018 Aug;35(8):1045-105, Fischer et al.PLoS One.2017 Jun 21;12(6):e0178782.

The Two Process model

Homeostatic regulation
Circadian regulation

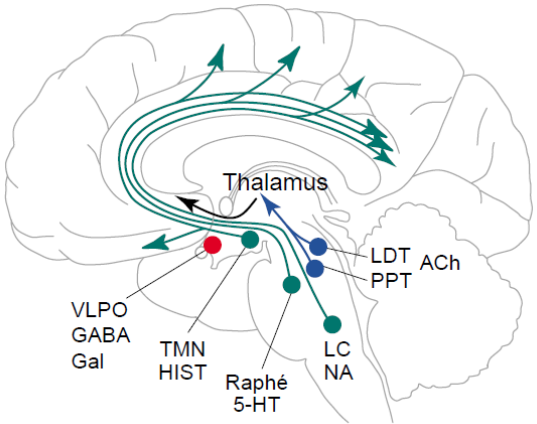


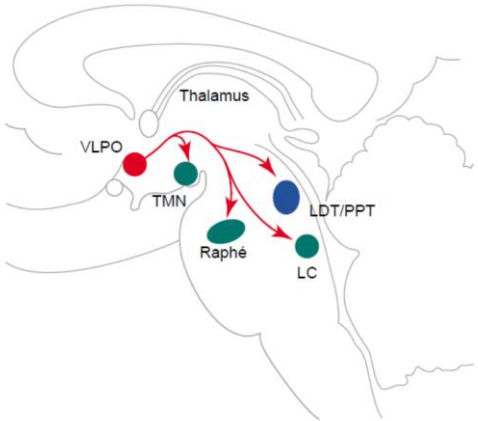




Borbely AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195-204. Dijk DJ. J Clin Sleep Med. 2009 Apr 15;5(2 Suppl):S6-15

Neurobiology of wakefulness - Ascending Reticular Activating System

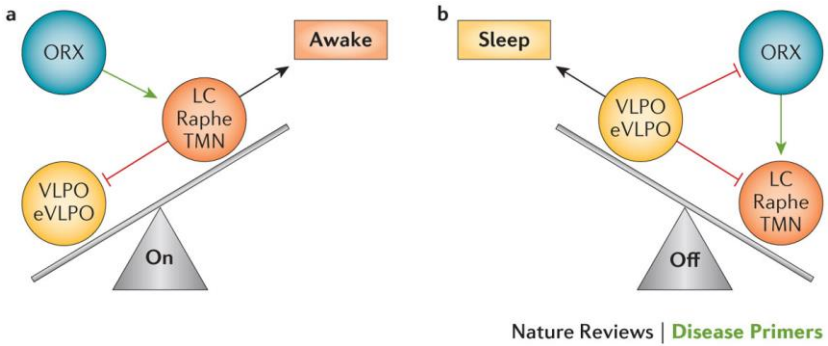




VLPO = Ventrolateral preoptic nucleus; TMN = Tuberomammillary nucleus; LDT = laterodorsal tegmental nucleus; PPT = pedunculopontine tegmental nucleus; LC = locus coeruleus; Ach = acetylcholine; NA = noradrenaline; 5-HT = serotonin; HIST = histamine; Gal = galanine

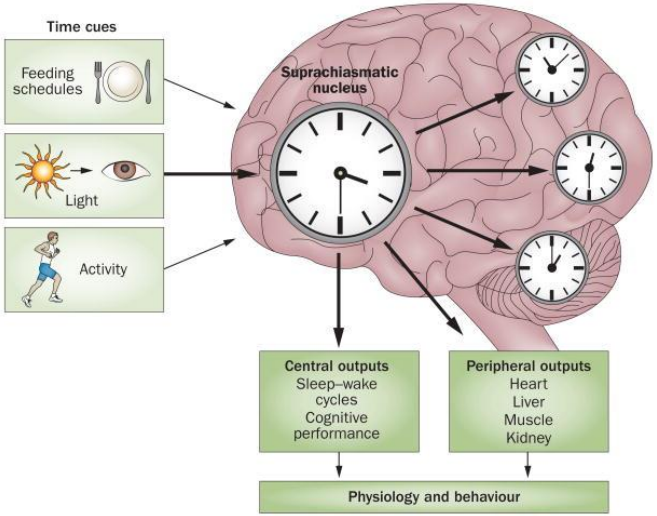
Saper CB, et al. *Trends Neurosci* 2001;24:726-31

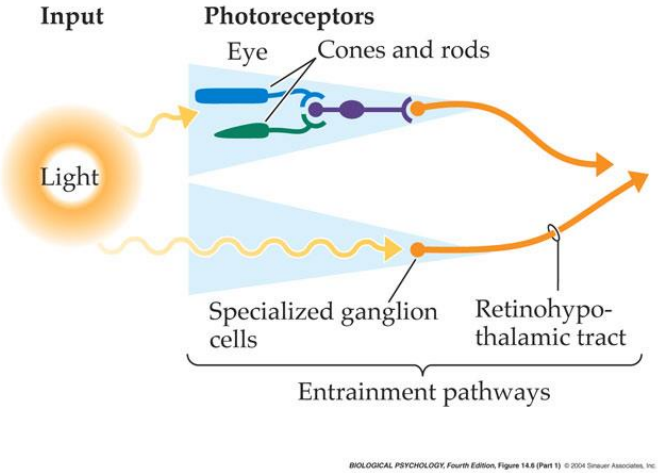
The flip-flop switch model



Saper, C. B., Scammell, T. E. & Lu, J.. *Nature* **437**, 1257–1263 (2005),; Morin, C. M. *et al.* (2015) *Nat. Rev. Dis. Primers*

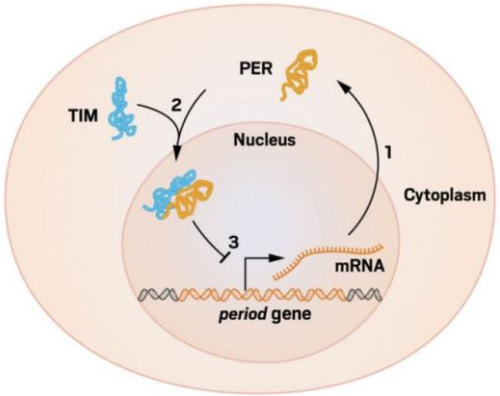
Circadian regulation





Videnovic et al. Nat Rev Neurol. 2014 Dec; 10(12): 683–693

2017 Nobel prize for the discovery of molecular (gene) mechanism regulating the circadian clock



(Jeffrey Hall, Michael Rosbash & Michael Young)

Biological rhythm

Circadian

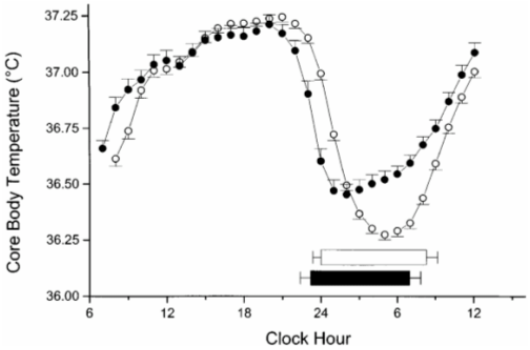
- Temperature, melatonin, cortisol
- Heart frequency, blood pressure

Circannual rhythm

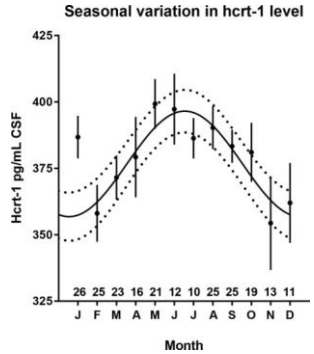
- vitamin D, orexin/hypocretin

Determined by :

- Light-dark
- Day length

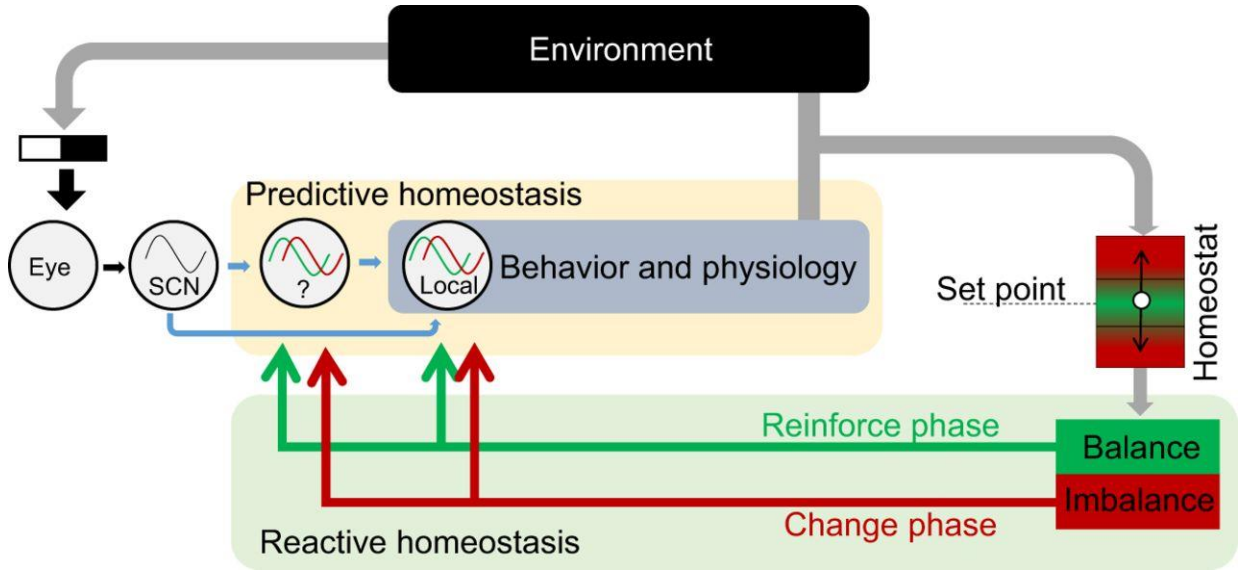


Duffy et al. Am J Physiol 1998; 275: 1478-87



Boddum K et al. PLoS One. 2016 Mar 23;11(3)

Illustration of how circadian clocks allow predictive homeostasis and receive reactive homeostatic feedback

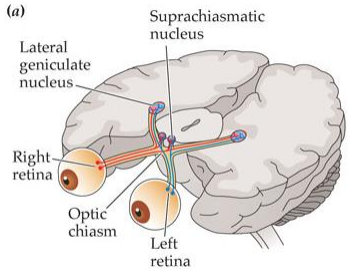


Sjaak J. Riede et al. J Exp Biol 2017;220:738-749

Resetting of the clock

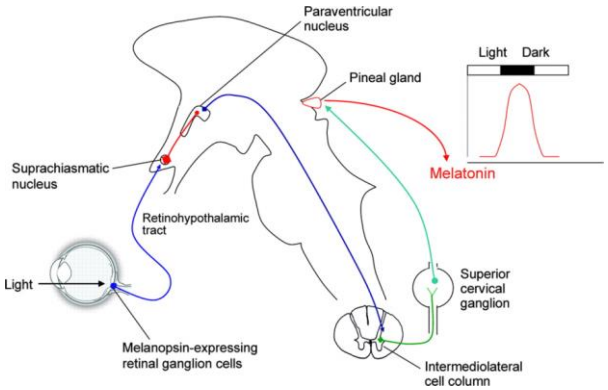
Light (blue 480 nm) effect on SCN

- Presented evening: phase delay
- Presented morning: reset or phase advance.
- Blue light daytime entrain wakefulness



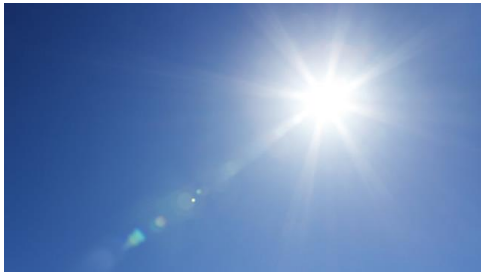
Melatonin

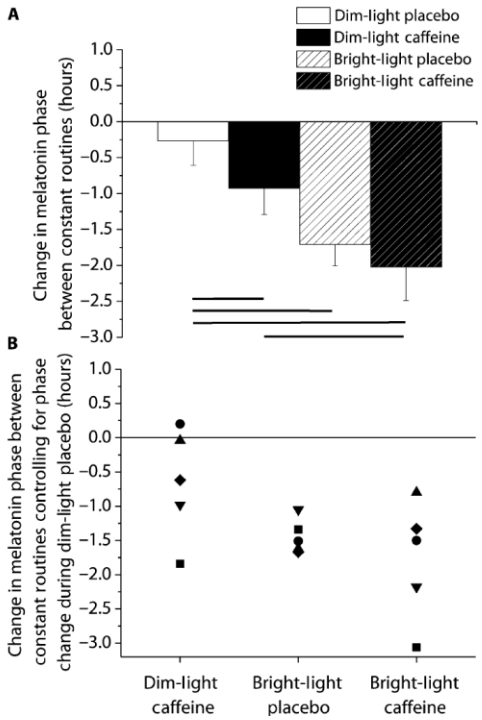
- Secreted from the pineal gland via innervation from the SCN (medullar projection
- Melatonin act on receptors in the SCN to phase-advance the biological clock



Effect of bright light and caffein on phase shift

Phase-shifting responses due to caffeine (2.9 mg/kg body mass) and bright light (3000 lux)





Science Translational Medicine 2015; 305

Resetting of the clock

Light (blue 480 nm) effect on SCN

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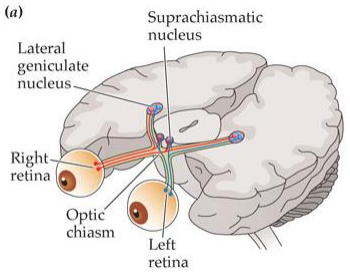
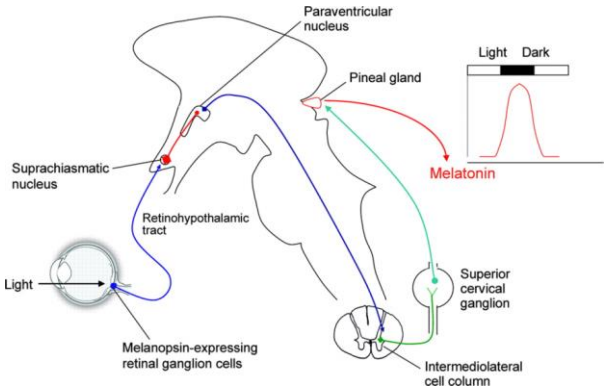


Melatonin

- secreted from the pineal gland via innervation from the SCN (medullar projection
- melatonin can act on receptors in the SCN to phase-advance the biological clock



How can we use this information

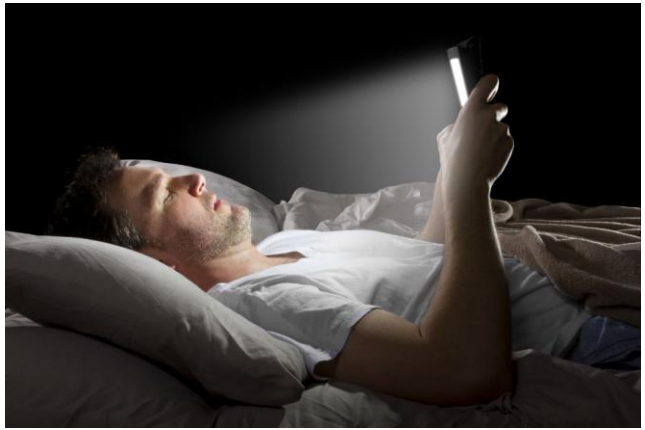
?

Factors that may affect sleep

- Internal
  - Age
  - Circadian
  - Diseases (medical, psychiatric, sleep disorders)
  - Psychological
- External
  - Temperature
  - Noise
  - Light
  - Physical miljeu

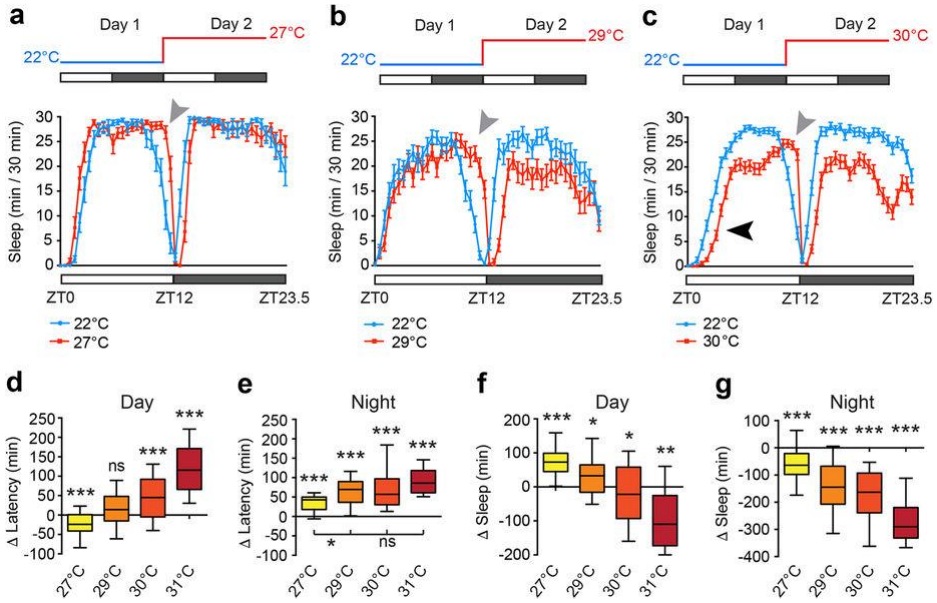
Light and sleep sleep

- Increased circadian sensitivity to evening light is associated with later circadian timing within both control and Delayed Sleep-Wake Phase (DSWPD) groups.
- Light emitted from Mobile and Computer screens can affect sleep quality
- There are currently no evidence that simply filtering blue light or simply removing relevant content improved sleep quality.



Watson et al. J Physiol 2018 oct. Bowler et al. Br J Psychol. 2018 Oct 5

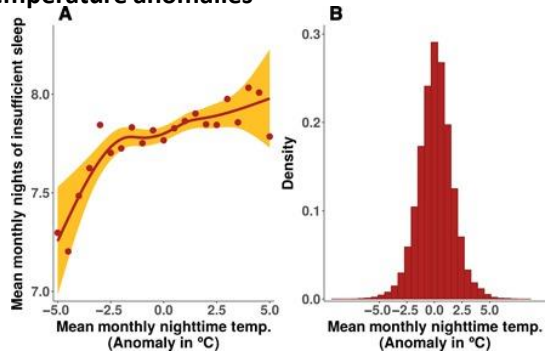
Regulation of sleep by temperature (*Drosophila)*



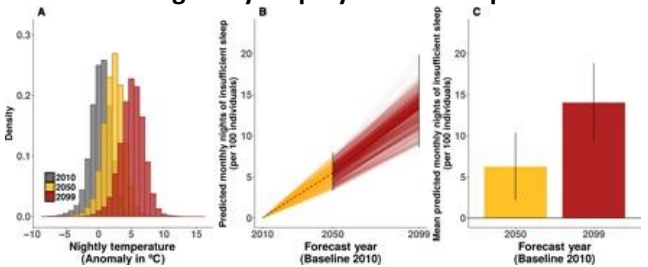
Lamaze et al. Scientific Reports **7**, Article number: 40304 (2017)

Night-time temperature and human sleep loss in a changing climate

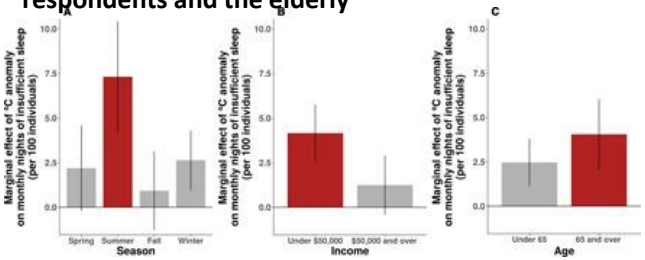
Nights of insufficient sleep increase with night-time temperature anomalies



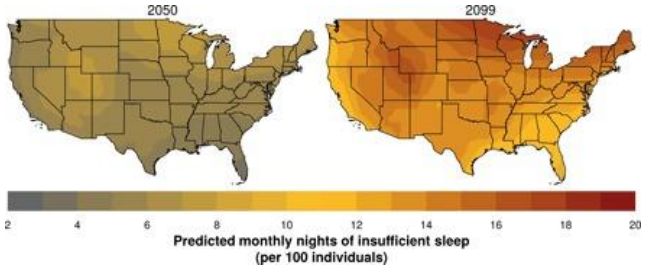
Climate change may amplify human sleep loss



Night-time temperature anomalies is most acute during the summer and among lower-income respondents and the elderly



Geographic dispersion of the predicted effects of climate change–induced night-time warming on human sleep



Obradovich et al. Sci Adv. 2017 May 26;3(5):e1601555

PLOS ONE

RESEARCH ARTICLE

The use of climate information to estimate future mortality from high ambient temperature: A systematic literature review

Michael Sanderson[1]*, Katherine Arbuthnott[2,3], Sari Kovats[2], Shakoor Hajat[2], Pete Falloon[1]

1 Met Office, Exeter, United Kingdom, 2 Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom, 3 Centre for Radiation, Chemical and Environmental Hazards, Public Health England, Didcot, United Kingdom

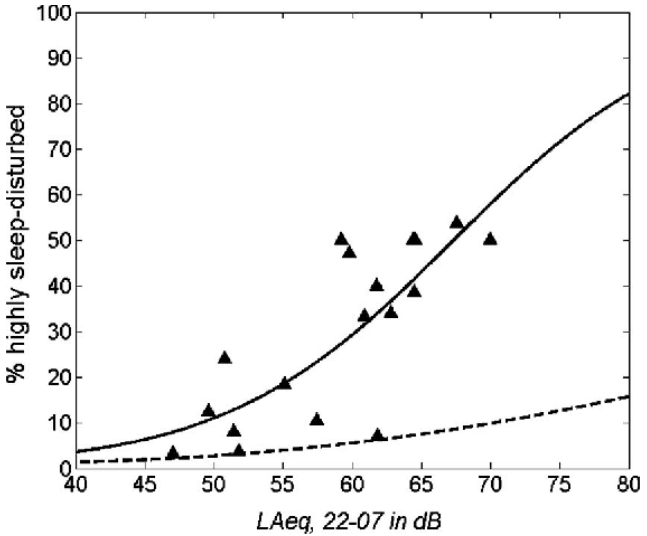
Heat related mortality is of great concern for public health, and estimates of future mortality under a warming climate are important for planning of resources and possible adaptation measures.

PLoS One.2017 Jul 7;12(7)

External noise and sleep quality

Traffic /external noise is associated with

- Poor sleep quality including impaired mictrosleep pattern
- Insufficient sleep
- Use of psychotropic and sleep medication
- Higher Body Mass Index (children)
- Cardiovascular morbidity
- Brain impairment and cognitive decline (mice)



Evandt et al. Environ Health 2017 Oct 23;16(1):110
Rudzik et al. Sleep. 2018 Jul 1;41(7).
Okokon et al. Environ Int. 2018 Oct;119:287-294
John son et al. Curr Epidemiol Rep. 2018 Jun;5(2):61-69'
Weyde et al. Epidemiology.2018 Sep;29(5):729-738
Héritier et al. Int J Hyg Environ Health. 2018 Apr;221(3):556-563
Jafari et al. Exp Neurol. 2018 Oct;308:1-12

Road traffic noise and human health

Total studies included

Table 1: Studies investigating exposure–effect of road traffic noise in the Indian scenario from 1991 to current

Author	Location (city/province)	Type of study	Data source	Noise measurement/presentation	Measurement of effects
Rao et al.[9]	Vishakapatnam, Andhra Pradesh	Field, Survey	Journal article	Yes	Questionnaire
Rao et al.[10]	Vishakapatnam, Andhra Pradesh	Field, Survey	Journal article	Yes	Questionnaire
Rao et al.[11]	Vishakapatnam, Andhra Pradesh	Field, Survey	Journal article	Yes	Questionnaire
Chakraborty et al.[12]	Kolkata, West Bengal	Field, Survey	Journal article	Yes	Questionnaire, audiometry
Mohan et al.[13]	New Delhi	Field, Survey	Journal article	Yes	Questionnaire
Ingle et al.[14]	Jalgaon, Maharashtra	Field, Survey	Conference proceeding	Measurement done. Not reported	Questionnaire, audiometry
Pachpande et al.[15]	Jalgaon, Maharashtra	Field, Survey	Journal article	Not reported	Questionnaire, audiometry
Tripathi et al.[16]	Ahmedabad, Gujarat	Field, Survey	Journal article	No measurement	Questionnaire
Banerjee et al.[17]	Asansol, West Bengal	Field, Survey	Own library	Yes	Questionnaire
Nandanwar et al.[18]	Nagpur, Maharashtra	Field, Survey	Conference proceeding	No measurement	Questionnaire
Agarwal et al.[19]	Jaipur, Rajasthan	Field, Survey	Journal article	Yes	Questionnaire
Goswami et al.[20]	Balasore, Orissa	Field, Survey	Journal article	Yes	Questionnaire
Mishra et al.[21]	New Delhi	Field, Survey	Journal article	Yes	Questionnaire
Wani et al.[22]	Gwalior, Madhya Pradesh	Field, Survey	Journal article	Yes	Questionnaire
Agarwal et al.[23]	Jaipur, Rajasthan	Field, Survey	Journal article	Yes	Questionnaire
Goswami et al.[24]	Balasore, Orissa	Field, Survey	Journal article	Yes	Questionnaire
Patil et al.[25]	Amravati, Maharashtra	Field, Survey	Journal article	No measurement	Questionnaire

Quality estimates of studies

Table 2: Quality of individual studies considered for evaluation the exposure–effect due to road traffic noise reported in Indian literature from 1991 to current

Author	Study population well defined	Exposure is well defined	Declaration of statistical methods	Sample size*	Random sample selection	Exposure effect studies/ curve
Rao et al.[9]	Yes	Yes	Yes	Large (n=1195)	Yes	Yes
Rao et al.[10]	Yes	Yes	Yes	Large (n=1195)	Yes	Yes
Rao et al.[11]	Yes	Yes	Yes	Large (n=1195)	Yes	Yes
Chakraborty et al.[12]	Yes	Yes	Yes	Large (n=1100)	Yes	Yes
Mohan et al.[13]	Yes	No	No	Medium (n=175)	Yes	No
Ingle et al.[14]	Not reported	No	No	Not reported	Subjects spend atleast 14-16hrs at home	No
Pachpande et al.[15]	Yes	No	No	Not reported	School teachers and Students	Yes including audiometric
Tripathi et al.[16]	Not reported	No	No	Medium (n=86)	Traffic police	No
Banerjee et al.[17]	Yes	Yes	Yes	Large (n=869)	Yes	Yes
Nandanwar et al.[18]	Yes	No	No	Large (n=378)	Yes	No
Agarwal et al.[19]	Not reported	Yes	Yes	Large (n=450)	Yes	Yes
Goswami et al.[20]	Yes	Yes	No	Large (n=212)	Yes	Yes. No curve
Mishra et al.[21]	Not reported	Yes	No	Large (n=350)	Yes	No
Wani et al.[22]	Yes	Yes	No	Medium (n=100)	Yes	Yes. No curve
Agarwal et al.[23]	Yes	Yes	No	Large (n=550)	Yes	Yes
Goswami et al.[24]	Not reported	Yes	No	Medium (n=136)	Yes	No
Patil et al.[25]	Yes	No	No	Large (n=500)	School, shopkeepers	No

*Small (n≤50), medium (n=50≤200) and large (n>200)

1. Road noise may cause sleep disturbances.
2. Road noise is a cause for annoyance to a variety of degree among the respondents.

Banerjee. Noise Health. 2012 May-Jun;14(58):113-8

Sleep changes with age

Decreased sleep consolidation

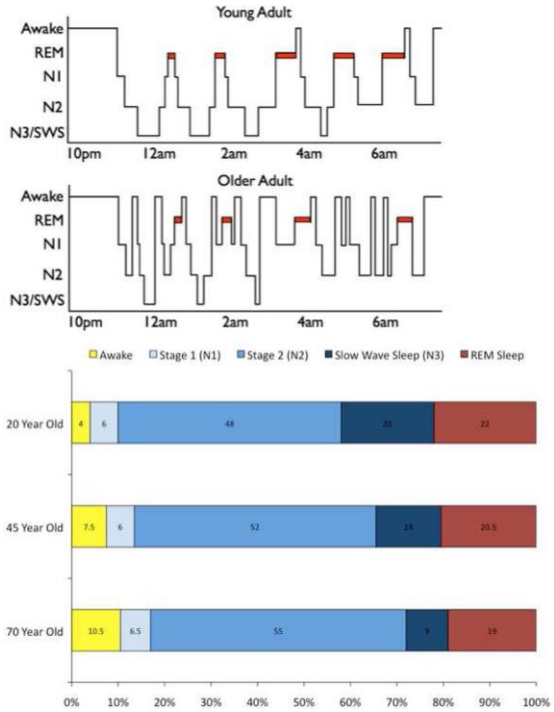
- less sleep efficiency
- less sleep spindles, less N3

Increased sleep disruption

- Sleep fragmentation/arousals
- Sleep-breathing disturbances
- Periodic periodic limb movements and REM sleep Behavior Disorder
- Medical diseases and medication

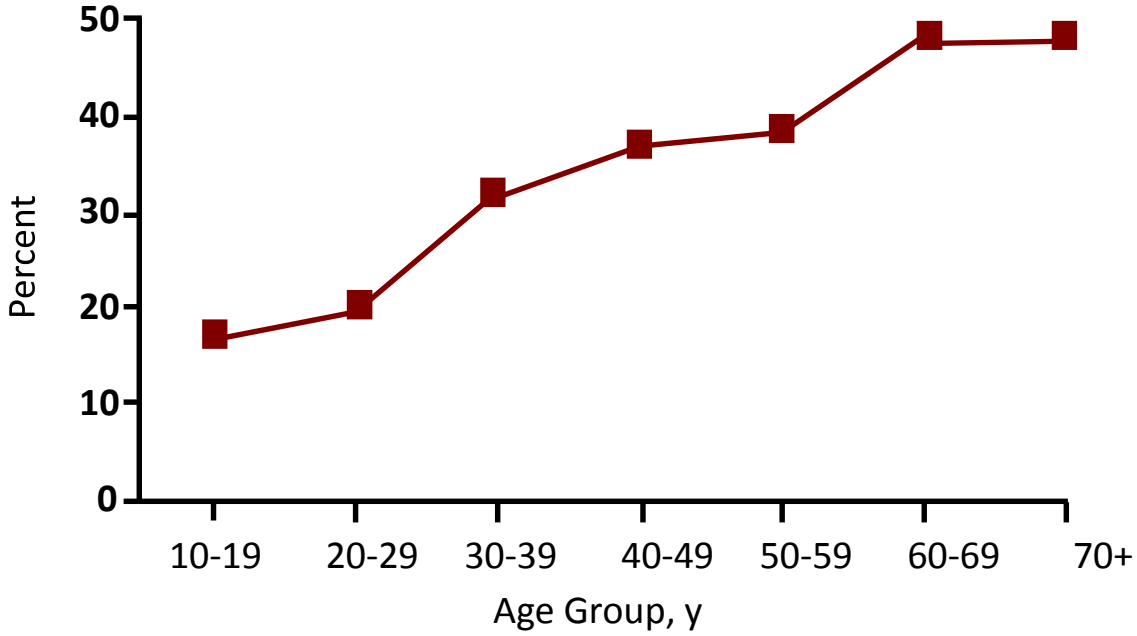
Increased daytime sleep

- Napping
- Polyphasic ultradian rhythm



Scullin & Biwise. Perspect Psychol Sci. 2015 Jan; 10(1): 97–137.

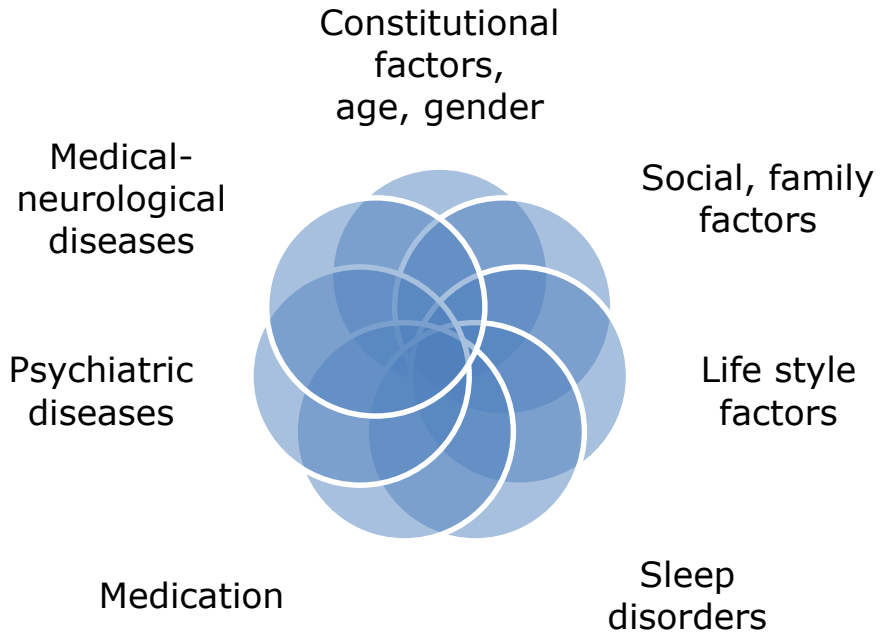
Complaints of sleep problems with age



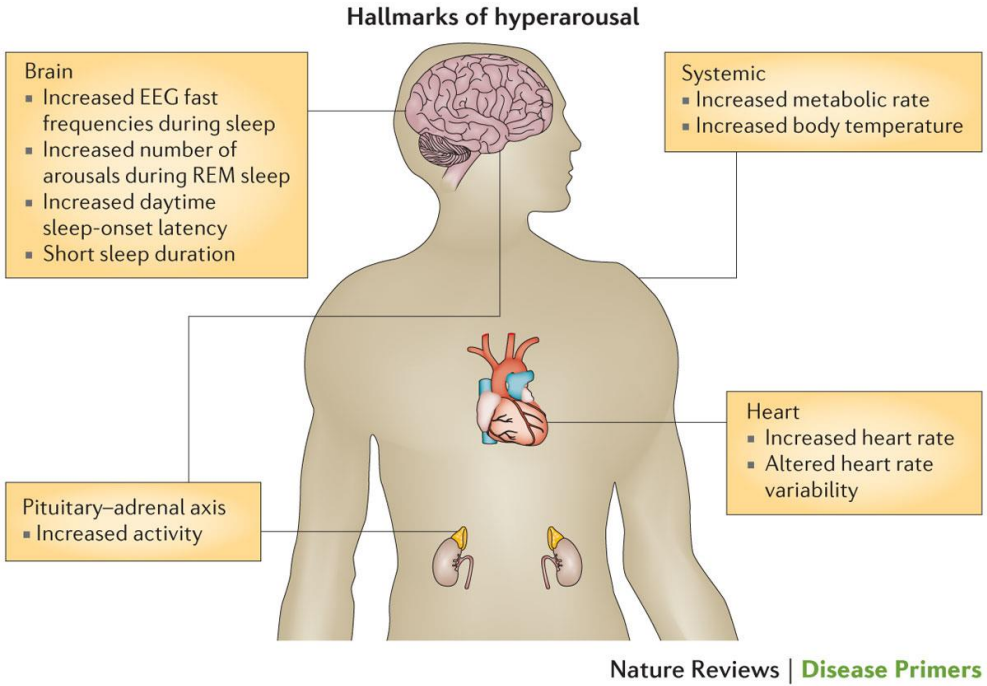
Karacan I et al. *Soc Sci Med*. 1976;10:239-244.

"Trouble With Sleeping" Assessed in a comprehensive survey of 1645 individuals in Alachua County, Florida

Factors involved in sleep disturbances in the elderly



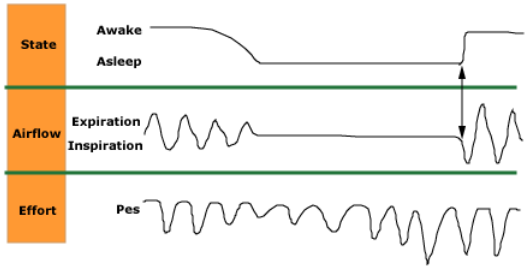
Indicators of hyperarousal in insomnia

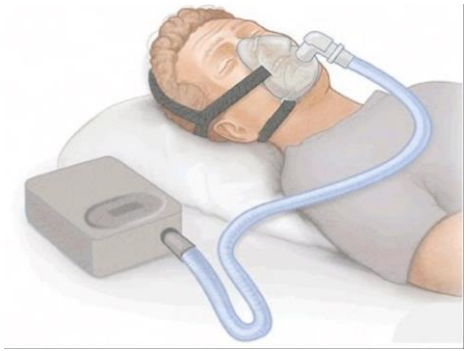


Morin, C. M. *et al.* (2015) Insomnia disorder
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.26

Sleep-related breathing disorders

- Sleep apnea affects >10% of the adult population
- Causes significant personal and societal consequences:
  - Increased morbidity and mortality
  - Mental and social problems
  - Health care costs
- Treatable

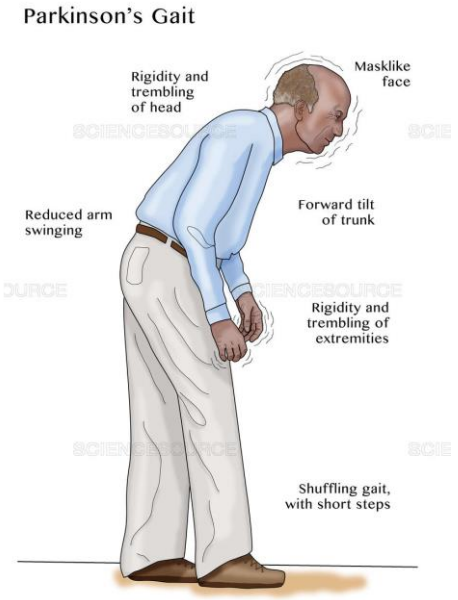




The American Academy of Sleep Medicine (1999), ICSD-2, 3 (2005, 2014)

Neurological disorders associated with sleep problems causing sleep disturbances

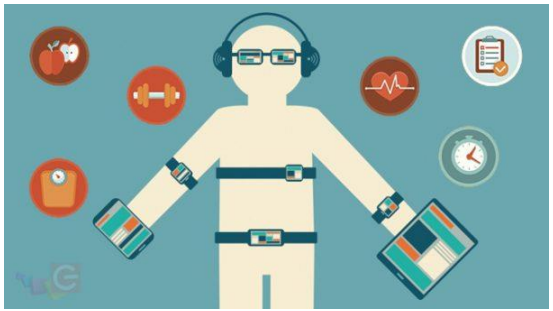
- Neurodegenerative disorders
  - Parkinson's and Alzheimer
- Stroke
- Hereditary diseases
- Epilepsy with nocturnal fits
- Headache
- Pain
- Sleep disorders, e.g.
  - Narcolepsy,
  - sleep related movement disorders,
  - Periodic legs movements,
  - REM and NREM parasomnias



Mayer, Jennum, Sleep Med Rev. 2011;15(6):369-78

Societal and industrial potential for improving sleep

- **Personal** (wearable devices, personal behavior)
- **Architecture** (housing, bedroom, smart homes, light)
- **Work schedules** (long, short, irregular shifts)
- **Technology** (health, personal and wearable devices, micro bed environment)
- **Health** (sleep health, personalized medicine)
- **Industrial** (information technologies, furniture's)
- …



Polygraphic measures during wake and sleep

Macrosleep (sleep pattern)

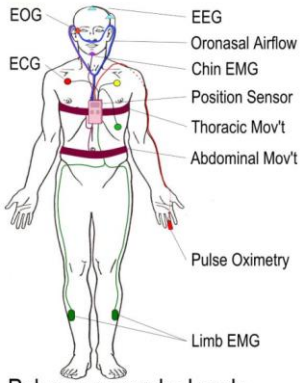
- Total Sleep time
- Sleep distribution
- Arousals and awakenings
- Sleep stability and transitions

Microsleep

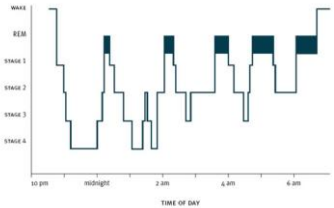
- Electroencephalographic morphology (e.g. sleep spindles etc.)

Physiological variables

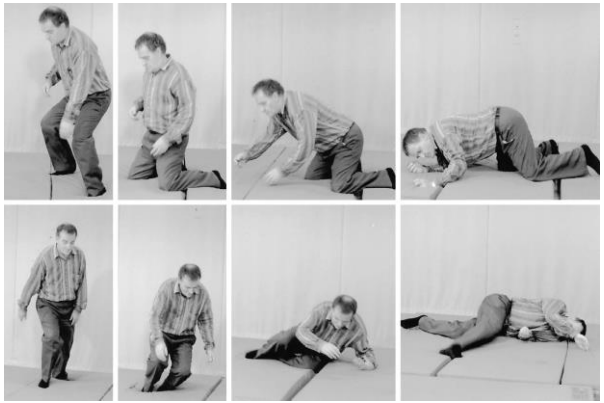
- Respiration
- Activity
- Sound
- Cardiac features (pulse, rhythm, blood pressure)
- Oxygen and CO2
- humidity



Polysomnography Leads



Narcolepsy



Narcolepsy is a disabling brain disease, characterized by sleep-wake dissociation:

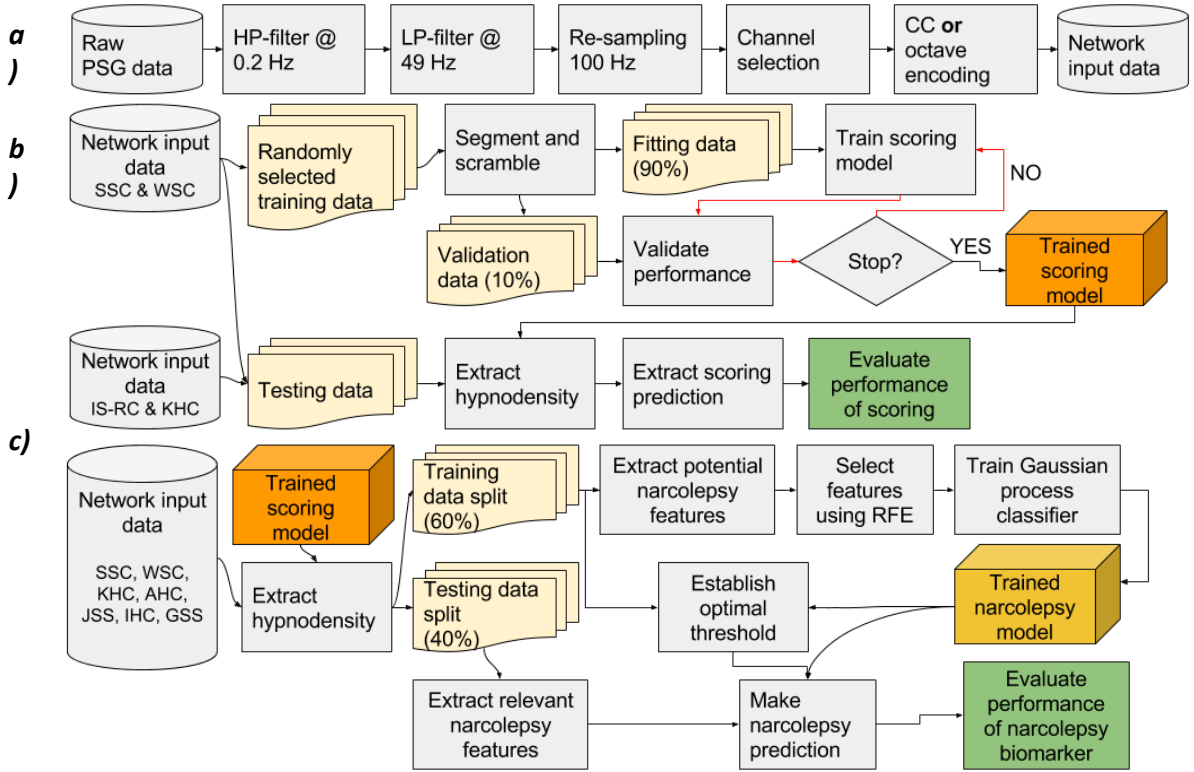
- Excessive daytime sleepiness
- Hypnogogic and hypnopompic hallucinations and vivis dreams
- Cataplexy provoked by emotional stimuli
- Sleep paralysis

- Chronic, debut in childhood, adolescent, chronic
- Causes significant personal, familiar and societal burden.

- Primarily due to selective destruction of hypocretinergic neurons in hypothalamus

Data selection and pre-processing (N>3000)

Samples from Asia, US, Europe

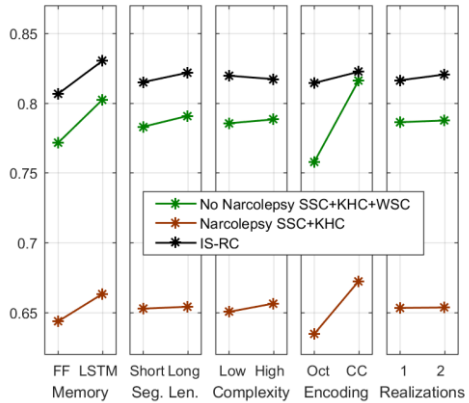


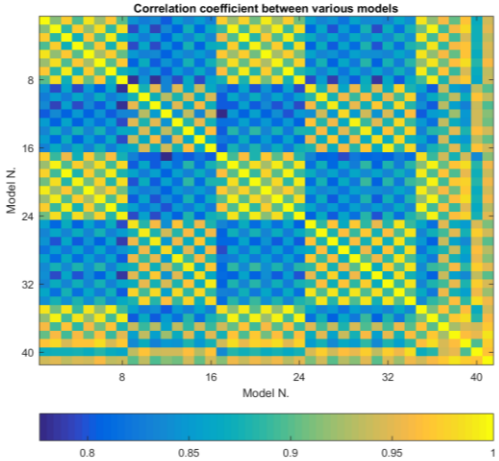
Inter-scorer Reliability Results

Individual and overall scorer performance, expressed as accuracy (upper Table) and Cohen's kappa (lower Table). Both accuracy and Cohen's kappa are presented as both with (biased) and without (unbiased) the assessed scorer included in the consensus standard in a leave-one-out fashion. Accuracy is expressed in percent, and Cohen's kappa is a ratio, and therefore unitless. T-statistics and p-values corresponds to the paired t-test between the unbiased predictions for each scorer against the model predictions on the same consensus.

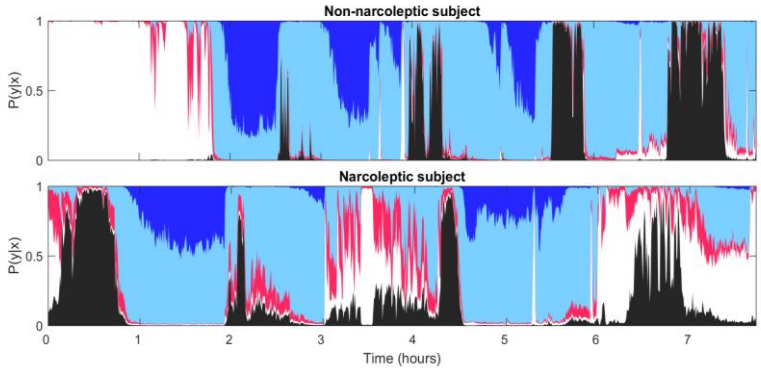
	Overall	**Scorer 1**	**Scorer 2**	**Scorer 3**	**Scorer 4**	**Scorer 5**	**Scorer 6**
Accuracy (%), Biased	81.3±3.0	82.4±6.1	84.6±5.5	74.1±7.9	85.4±5.7	83.1±9.4	78.3±8.9
Accuracy (%), unbiased	**76.0±3.2**	**77.3±6.3**	**79.1±6.3**	**69.0±8.0**	**79.7±6.5**	**77.8±9.6**	**72.9±9.2**
Model accuracy (%) on concensus	-	85.1±4.9	83.8±5.0	86.5±4.3	84.3±4.7	85.6±4.7	87.0±4.5
t-stat (p-value)	-	9.5 (3.8×10^{-14})	6.6 (7.5×10^{-9})	18.3 (6.0×10^{-28})	6.7 (4.7×10^{-9})	6.4 (1.7×10^{-8})	12.2 (7.5×10^{-19})
Cohen's kappa, biased	61.0±6.8	63.6±12.2	68.4±10.5	45.6±19.7	69.6±13.2	64.5±20.9	54.5±19.8
Cohens' kappa, unbiased	57.7±6.1	61.3±11.2	64.6±10.3	43.5±19.2	64.6±13.1	60.9±16.9	51.6±16.7
Model kappa on concensus	-	74.3±12.3	72.4±12.1	76.0±11.8	72.7±12.0	74.7±12.1	76.6±12.2
t-stat (p-value)	-	9.5 (4.6×10^{-14})	7.1 (7.9×10^{-10})	15.4 (7.0×10^{-24})	6.6 (6.4×10^{-9})	7.1 (9.2×10^{-10})	13.2 (2.0×10^{-20})

Optimizing Machine Learning performance for sleep staging:





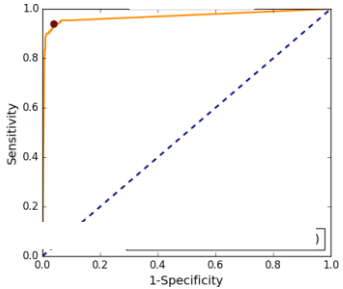
Narcoleptic subject versus normal subject: narcolepsy show higher fragmentation



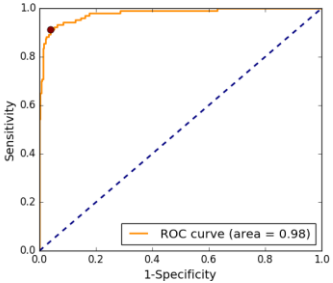
Such sleep staging model outputs could be used as a biomarker for the diagnosis of narcolepsy using a standard nocturnal PSG rather than the MSLT.

Final predictions for creating a separate narcolepsy classifier from each of the sleep scoring models used in the final implementation

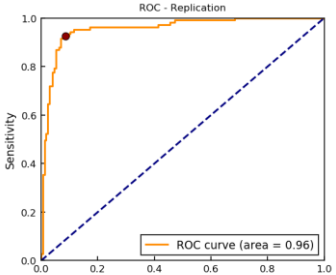
Training data 94%/96%



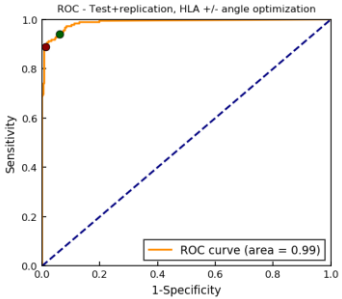
Test data: 91%/96%



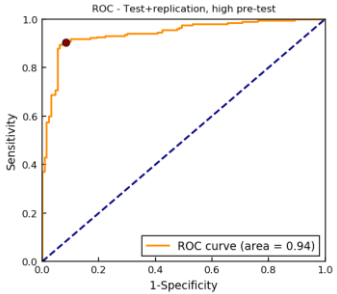
Replication sample:93%/91%



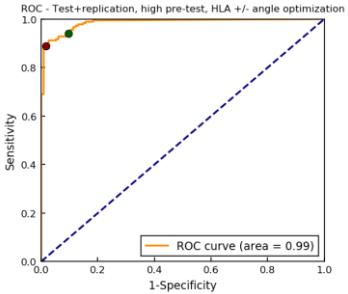
+ HLA:90%/99%



+HLA: 90/92%



+ HLA: 90%/98%



Conclusion

- The brain regulates wake and sleep via to mutual physiological mechanism homeostatic regulation (wake-sleep) and circadian regulation
- Sleep constitute a core physiologic mechanism for regulatory function.
- Sleep and circadian regulation are sensitive to external factors (like temperature, light, noise, physical environment), constitutional, psychological factors and diseases.
- Significant potential for improving sleep and health: personal, micro-bed, architecture and environmental factors
- Significant potential for future application and implementation