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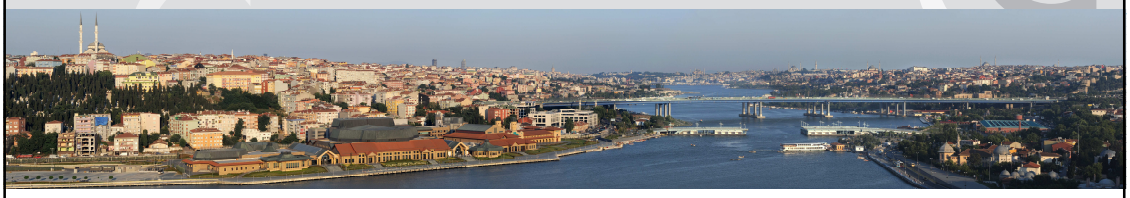

ICNIRP
INTERNATIONAL COMMISSION ON NON-IONIZING RADIATION PROTECTION

THRESHOLDS OF THERMAL DAMAGE

26-28 May 2015, Istanbul, Turkey

World Health Organization

Temperature, sleep and aging

Heidi Danker-Hopfe

Competence Center of Sleep Medicine
Charité University Medicine Berlin, Berlin, Germany

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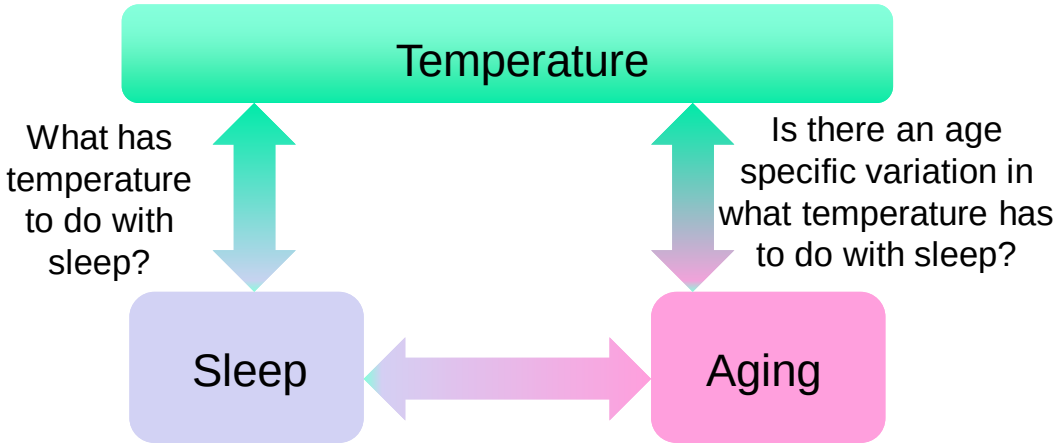
Outline



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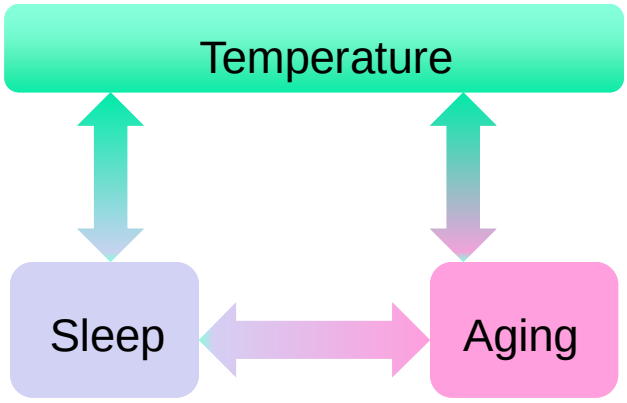

Eus van Someren

Department of Sleep and Cognition, Netherlands Institute for Neuroscience,
Royal Netherlands Academy of Arts and Sciences, 1105 BA, Amsterdam, The Netherlands.

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Sleep - basics

Temperature

Why sleep?

Basics of sleep regulation

Sleep

Aging

One of the most consistent findings is an effect of RF-EMF exposure on brain activity as assessed by powerspectra of the EEG during sleep.

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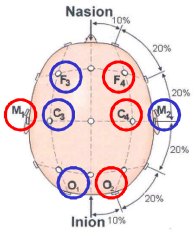
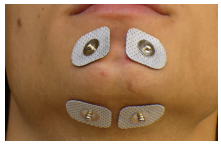
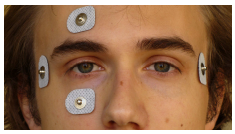
Objective assessment of sleep



Electroence-phalogram
brain activity



Electromyogram
muscle tone



Electrooculogram
eye movements

assingment of (sleep) stages (for every 30 sec)

based on specific combinations of EEG, EMG and EOG

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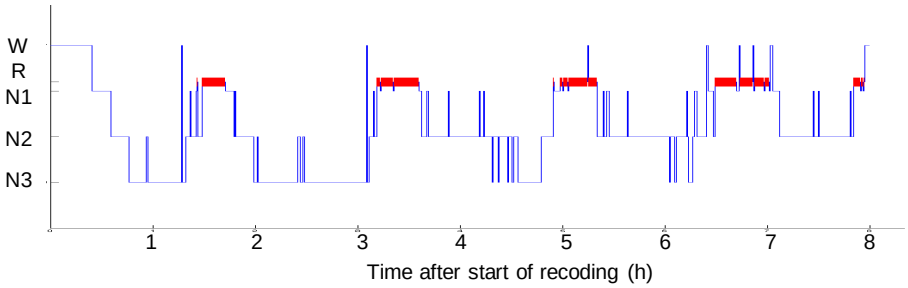
Objective assessment of sleep



graphic representation of scoring results ➔ hypnogram

fundamentally different physiological states

NREM stages (N1, N2, and N3) ◆ **REM sleep (R)**

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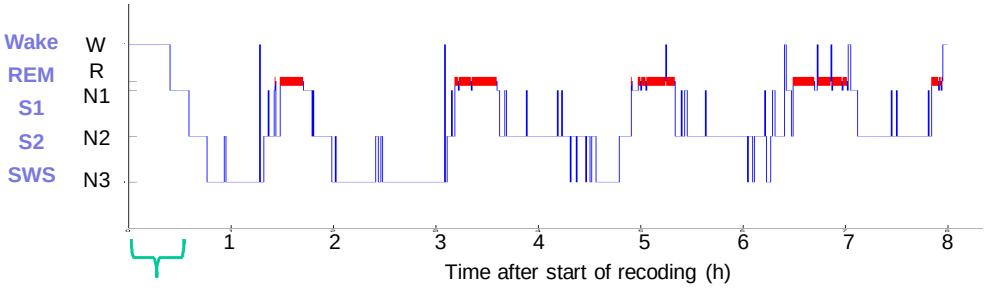
Objective assessment of sleep



Sleep latency *(Rechtschaffen & Kales 1968 standard)*:
time from lights out to the occurrence of the first three consecutive stages S1 or first occurrence of S2 (or REM sleep) – whatever is shorter.

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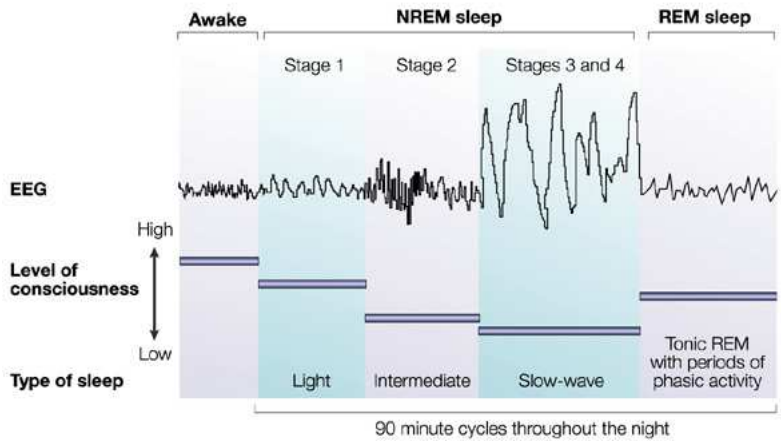
Quantitative description of the sleep EEG



Powerspectrum: quantitative description of the EEG

Bryant et al. *Nature Reviews Immunology* **4**, 457-467 (June 2004)

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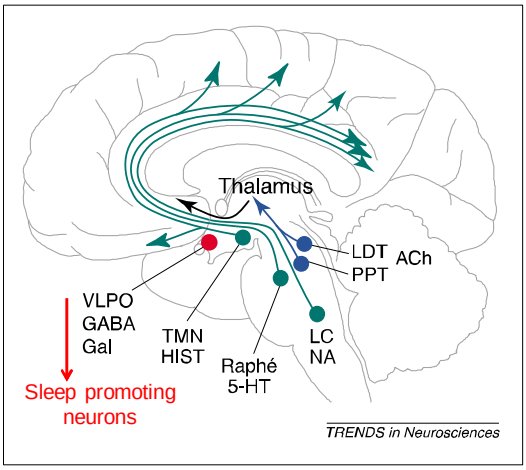
Brain regions and nuclei involved in sleep regulation

Brain regions (cluster of neurons) and neurotransmitter involved in S-W regulation



726 Review TRENDS in Neurosciences Vol.24 No.12 December 2001

The sleep switch: hypothalamic control of sleep and wakefulness

Clifford B. Saper, Thomas C. Chou and Thomas E. Scammell

VLPO: ventrolateral preoptic area

Fig. 1. The ascending arousal system sends projections from the brainstem and posterior hypothalamus throughout the forebrain. Neurons of the laterodorsal tegmental nuclei and pedunculopontine tegmental nuclei (LDT and PPT) (blue circles) send cholinergic fibers (Ach) to many forebrain targets, including the thalamus, which then regulate cortical activity. Aminergic nuclei (green circles) diffusely project throughout much of the forebrain, regulating the activity of cortical and hypothalamic targets directly. Neurons of the tuberomammillary nucleus (TMN) contain histamine (HIST), neurons of the raphé nuclei contain 5-HT and neurons of the locus coeruleus (LC) contain noradrenaline (NA). Sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO, red circle) contain GABA and galanin (Gal).

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Temperature and sleep

Temperature

Sleep

What has temperature to do with sleep?

- Ambient temperature
- Body core temperature
- Brain temperature
- Skin temperature

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Temperature and sleep: anecdotal knowledge

Experiencing difficulty to fall asleep in a very hot or cold environment is a common phenomenon

difficulty falling asleep with cold feet;
easier to fall asleep following a warm bath in the evening

more than anecdotal knowledge?

Thermoregulation

Thermoregulation refers to the process required to maintain the core body temperature within a narrow set range essential for cell functioning

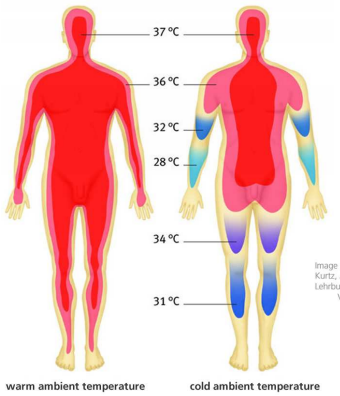


Image source: Klinke, R.; Pape, H-C.; Kurtz, A.; Silbernagel, S.: Physiologie Lehrbuch: 6th edition, 2010, Thieme Verlag, Stuttgart; p. 501

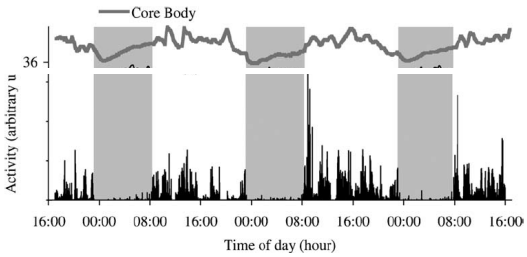
Core temperature: regulated at about 37 °C

Shell temperature: largly depends on ambient temperature and varies with part of the body

Ambient temperature

23 °C: distal parts (hand and feet) 7-8 °C below core temperature
35 °C: distal parts (hand and feet) 3-4 °C below core temperature
Gilbert et al. (2004) Sleep Medicine Reviews 8:81-93

Temperature and sleep-wake rhythms



Humans sleep when their core temperature is low and are awake when core body temperature is high.
Sleep initiation coincides with the decrease in core body temperature.

Sleep is consistently terminated on the ascending portion of the T_C curve

➔ the primary factor driving T_c and sleep onset is the **circadian control**.

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Van Someren (2006) Prog Brain Res 153:309-324

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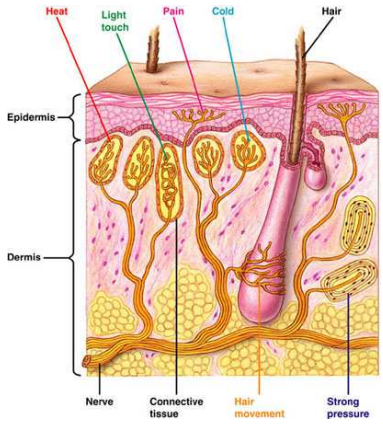
Thermoregulation

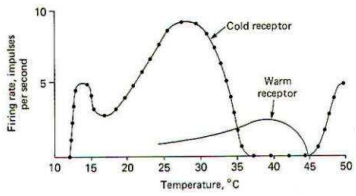
Information about environmental temperature is registered by receptors of the skin



http://www2.nau.edu/lrm22/lessons/human_senses/images/skin_receptors.jpg

Cold receptors:
detect changes in the order of 20 - 30 ºC

Warm receptors:
detect temperature changes above 30 ºC



http://www.humanneurophysiology.com/imagesreceptors/Fig-8.jpg

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Thermoregulation

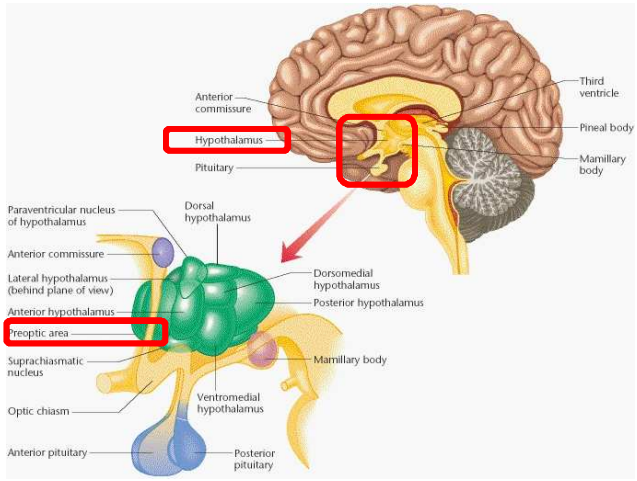
Pre-optoc area / anterior hypothalamus (PoAH)

Information from these receptors is integrated at several levels, the main integrator of thermal information is a region in the **hypothalamus**

Lesions in this region lead to impaired thermoregulatory responses to changes in ambient temperatures

Mechanisms:

Existance of a set point PoAH generates an error signal that is proportional to the difference between the set point and the measured temperature



http://www.hanall.co.kr/upload/HealthNews/2004/preoptics.jpg

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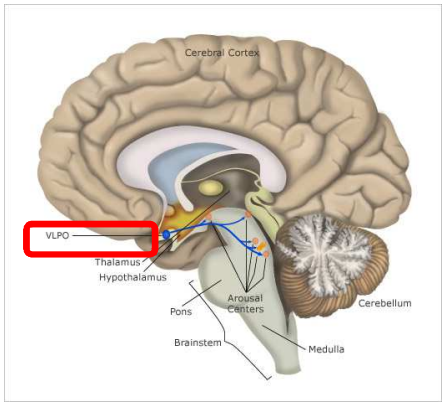
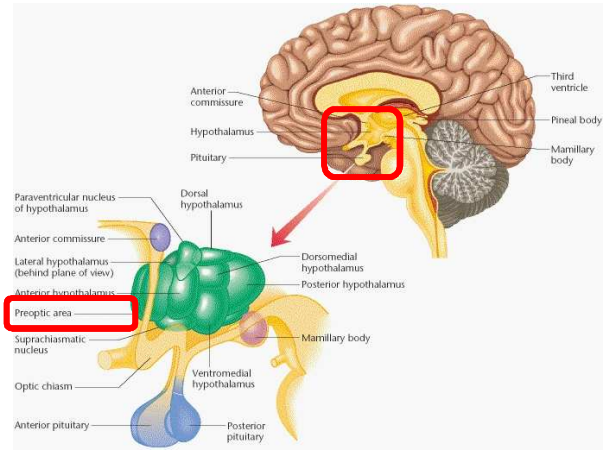
Regions involved in temperature and sleep-wake regulation

Ventro-lateral part of the preoptic area: VLPO known to be involved in sleep-wake regulation



http://healthysleep.med.harvard.edu/_i/193.jpg



http://www.hanall.co.kr/upload/HealthNews/2004/preoptics.jpg

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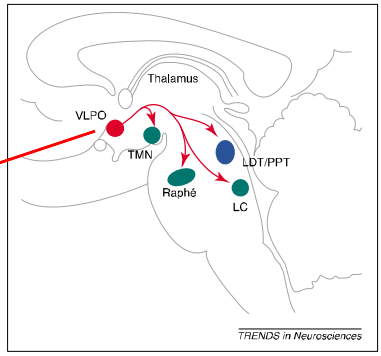
Temperature and sleep regulation: possible mechanism

Saper et al. Trends in neuroscience 2001, 24: 726 - 731

Table 1. Sleep stages and physiological activity[a]

	Wakefulness	NREM sleep	REM sleep
EEG	Fast, low voltage	Slow, high voltage	Fast, low voltage
Eye movement	Vision related	Slow, infrequent	Rapid
Muscle tone	↑↑	↑	0
LDT/PPT	↑	0	↑↑
LC/DR/TMN	↑↑	↑	0
VLPO cluster	0	↑↑	↑?
VLPO extended	0	↑?	↑↑
Orexin/hyprocretin	↑↑	0?	0?

[a]Firing rates are as follows: two arrows = rapid firing, one arrow = slower firing, 0 = little or no firing. Question marks represent hypothesized firing patterns for which there is as yet no firm evidence. Abbreviations: DR, dorsal raphé nucleus; EEG, electroencephalogram; LC, locus coeruleus; LDT, laterodorsal tegmental nuclei; NREM, nonrapid eye movement; PPT, pedunculopontine tegmental nuclei; REM, rapid eye movement; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.



The VLPO contains warm- and cold sensitive neurons

(40% of all neurons).

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Temperature and sleep regulation: possible mechanism

CLINICAL IMPLICATIONS OF NEUROSCIENCE RESEARCH

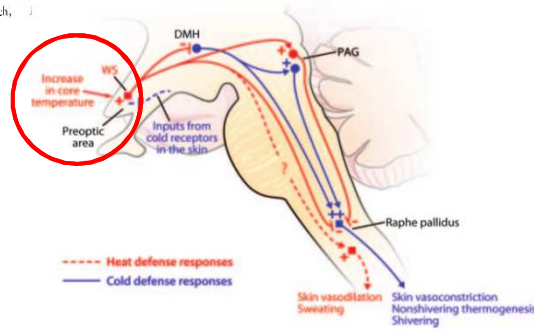
Section Editor
Eduardo E. Benarroch, MD

Thermoregulation

Recent concepts and remaining questions

Figure Central thermoregulatory pathways involved in responses triggered by warm-sensitive (WS) neurons of the medial preoptic/anterior hypothalamic region

Eduardo E. Benarroch,



Neurology®

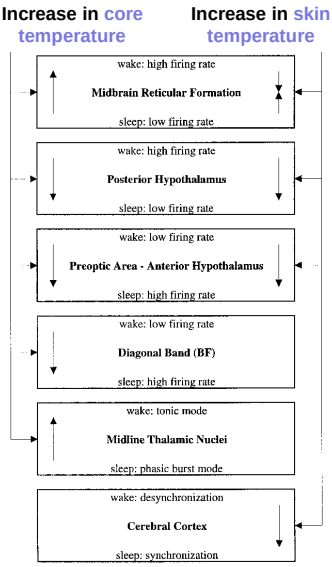
Thermoregulation : Recent concepts and remaining questions
Eduardo E. Benarroch
Neurology 2007;69;1293
DOI 10.1212/01.wnl.0000275537.71623.8e

This information is current as of June 4, 2012

The warm sensitive neurons of the preoptic area are not only involved in sleep but also in thermoregulation.

The WS neurons increase firing following heating of the peripheral skin (Gilbert et al. 2004).

Temperature and sleep regulation: possible mechanism



Summary:

- A mild increase in brain temperature may differentially drive different brain areas towards a more sleep-like or a more wake-like firing pattern. Complex relationships make an unequivocal sleep promoting effect of mild increases in brain temperature unlikely.
- A mild increase in skin temperature seems to drive different brain regions towards a more sleep-like firing rate.

van Someren, Chronobiol Int, 17(3): 313-354 (2000); Romeijn et al., Eur J Physiol. 464:169-176 (2012)

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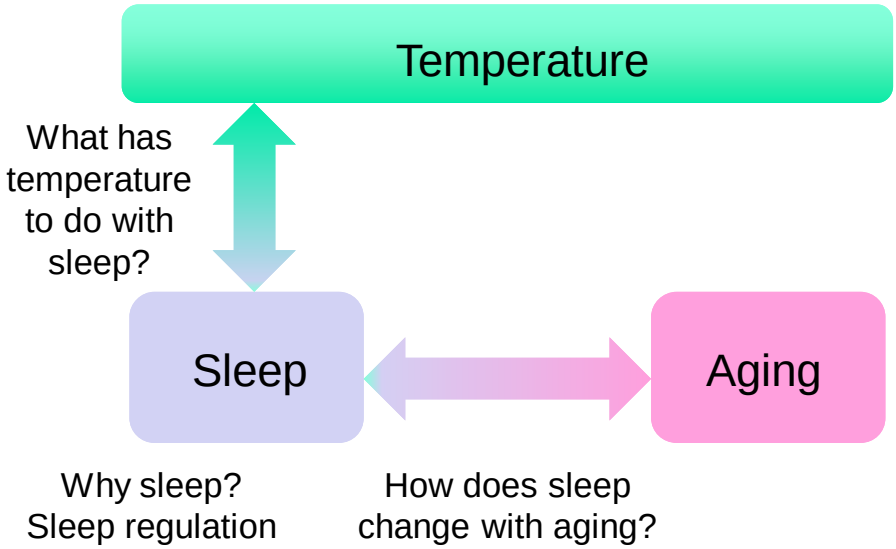

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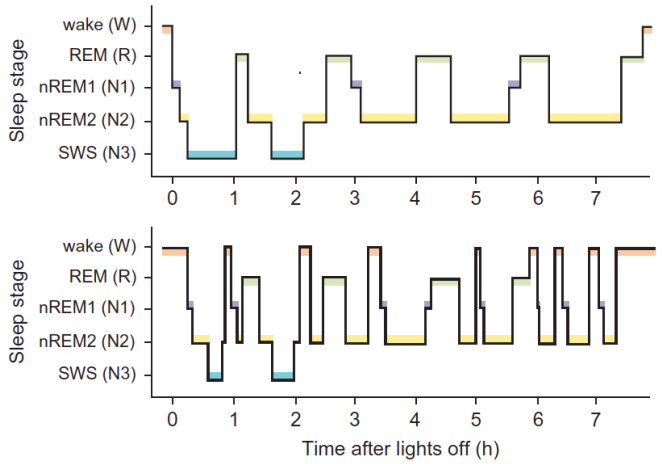
Sleep and aging: changes in the macrostructure of sleep



young subject

older subject

Pace-Schott and Spencer (2011) Prog Brain Res; 191: 75-89

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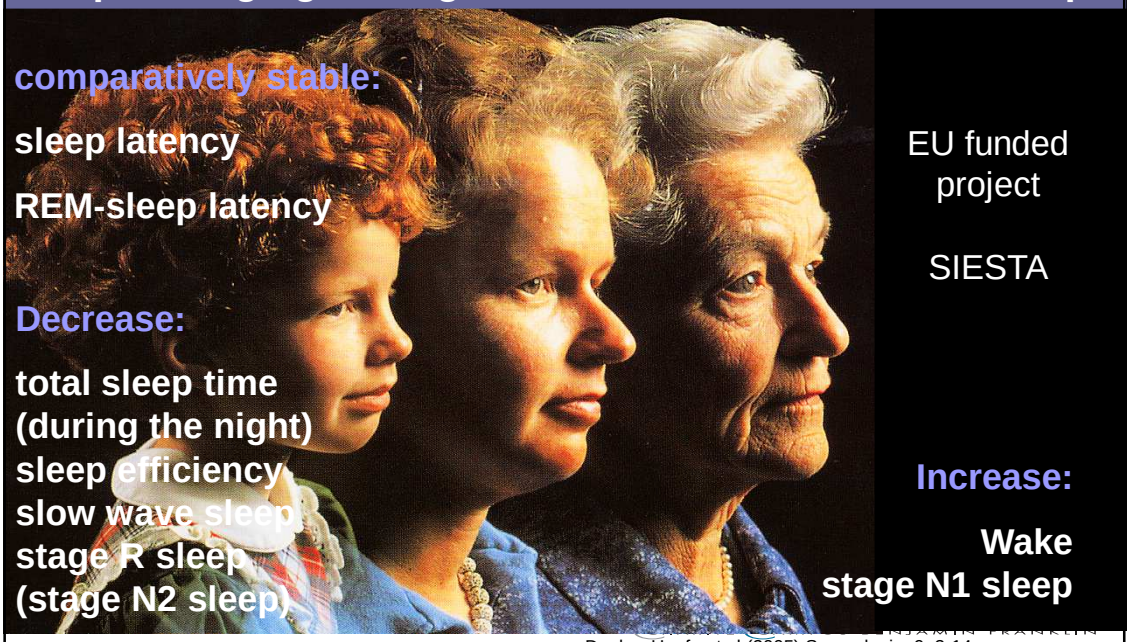
Sleep and aging: changes in the macrostructure of sleep



comparatively stable:

sleep latency

REM-sleep latency

Decrease:

total sleep time (during the night)
sleep efficiency
slow wave sleep
stage R sleep
(stage N2 sleep)

EU funded project

SIESTA

Increase:

Wake
stage N1 sleep

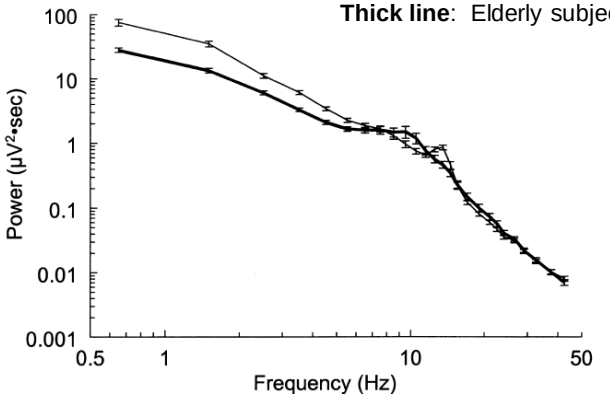
Danker-Hopfe et al (2005) Somnologie; 9: 3-14

Sleep and aging: changes in powerspectra

Power spectra – sleep EEG

Cross-sectional study:

Thin line: Young subjects
Thick line: Elderly subjects



Analysis showed a significant ($p < 0.001$) age group by trend interaction.

Tan et al (2001) Clin Neurophysiol; 112: 1540-1552

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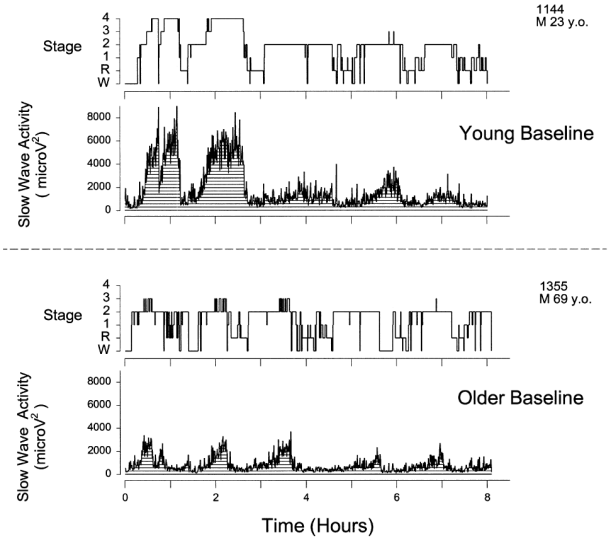
Sleep and aging: slow wave activity



Slow Wave Activity as a correlate of the homoestatic process declines with age

Dijk et al., Chronobiol Internat, 17(3): 285-311 (2000)

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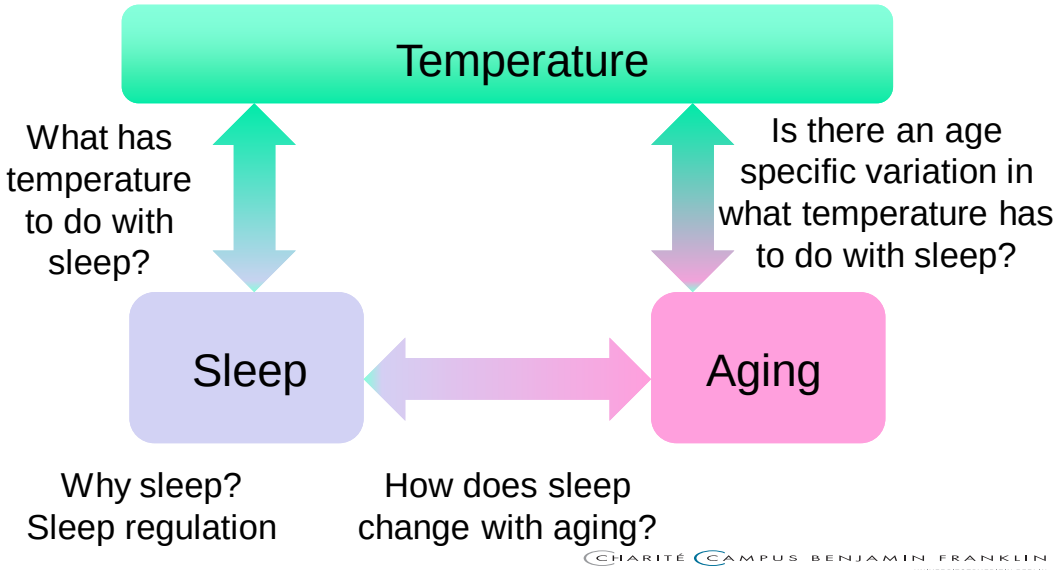

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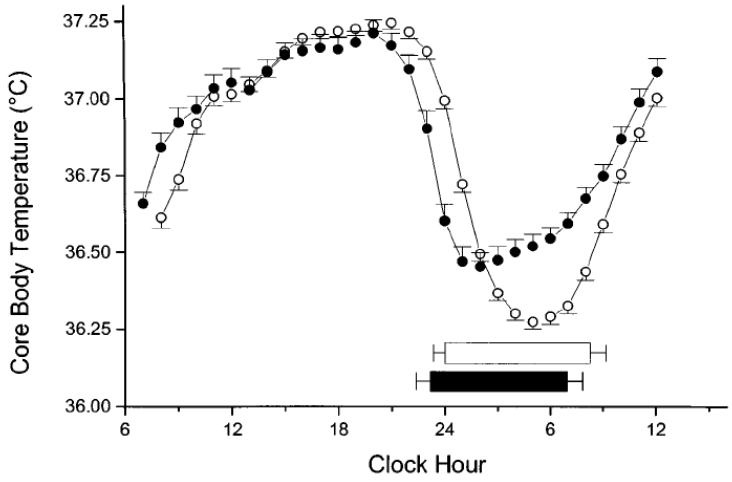
Aging and core body temperature

● older subjects (n=43) ○ younger subjects (n=97)



Aging is associated with a reduced circadian modulation of core temperature as indicator of changes in the circadian rhythms regulation mechanisms

Duffy et al. Am J Physiol, 275:R1478-R1487 (1998)

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sleep and cold feet: more than anecdotal knowledge!

sample size per group = 8 (4 males and 4 females)

Table 3
Sleep-onset latency by treatment condition per group

	Sleep-onset latency (min.)		
	Young adults free from sleep complaints	Elderly free from sleep complaints	Poorly sleeping elderly
Neutral SOCKPRE (baseline)	15.69±3.47	11.19±3.32	10.50±2.87
Warm SOCKPRE	12.94±3.21	9.81±2.71	9.38±3.41
Neutral FBPRE	15.13±3.29	9.50±2.26	11.81±3.02
Warm FBPRE	15.56±3.45	8.13±1.45*	8.06±1.69
Neutral SOCKBED	11.38±3.21*	8.00±1.83*	7.63±1.57
Warm SOCKBED	11.25±3.77*	10.56±2.33	8.31±1.25

Values are means±SE.
*Significantly different from baseline.

SOCKPRE
Socks prior to going to bed

SOCKBED
Socks in bed

FBPRE
Footbath prior to going to bed

Raymann et al., Physiology & Behavior, 90: 257-266 (2007)

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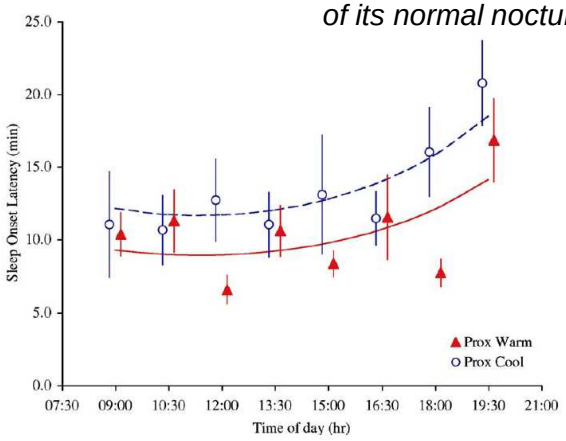
Temperature and sleep regulation: experimental evidence

Skin temperature *causally contributes* ***to sleep onset latency*** *within the range of its normal nocturnal fluctuations.*



Experimental studies (with **thermosuits** and cooled vs. warmed foods and drinks) aiming at manipulating core and skin temperatures within the comfortable range showed that a **proximal skin temperature difference** on (only) 0.8 ± 0.03 ° C (mean ± SEM) around a mean of 35.1 ± 0.1 ° C changed sleep onset latency by 26%.

The induction of changes in core temperature (δ = 0.2 ± 0.02 ° C) and distal skin temperature (δ = 0.7 ± 0.05 ° C) was not effective.

van Someren, Prog Brain Res, 153: 309-324 (2006)

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Temperature and sleep regulation: experimental evidence

Table 3 Summary of the main effects of temperature manipulations on sleep stages

Stage	Young adults		Elderly without sleep complaints	
	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*
Wake	0.84 (0.77–0.92)***		0.77 (0.73–0.81)***	0.86 (0.81–0.90)***
SI	0.80 (0.73–0.89)***	0.89 (0.81–0.98)*	0.86 (0.81–0.92)***	0.91 (0.85–0.97)**
S2	1.04 (1.01–1.08)*	0.95 (0.92–0.98)**	1.04 (1.01–1.08)*	1.09 (1.06–1.13)***
SWS	1.08 (1.03–1.13)**		1.25 (1.19–1.32)***	
REM		1.20 (1.15–1.26)***		1.12 (1.07–1.17)***
	proximal heating	distal heating	proximal heating	distal heating

Skin temperature differences: ≅ 0.4 ° C
Core body temperature: virtually unchanged

Raymann et al., Brain, 131: 500-5134 (2008)

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Temperature and sleep regulation: experimental evidence

Table 3 Summary of the main effects of temperature manipulations on sleep stages

Stage	Young adults		Elderly without sleep complaints	
	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*	$T_{suit\ prox}$ OR (95% CI) *P*	$T_{suit\ dist}$ OR (95% CI) *P*
Wake	0.84 (0.77–0.92)***		0.77 (0.73–0.81)***	0.86 (0.81–0.90)***
SI	0.80 (0.73–0.89)***	0.89 (0.81–0.98)*	0.86 (0.81–0.92)***	0.91 (0.85–0.97)**
S2	1.04 (1.01–1.08)*	0.95 (0.92–0.98)**	1.04 (1.01–1.08)*	1.09 (1.06–1.13)***
SWS	1.08 (1.03–1.13)**		1.25 (1.19–1.32)***	
REM		1.20 (1.15–1.26)***		1.12 (1.07–1.17)***
	proximal heating	distal heating	proximal heating	distal heating

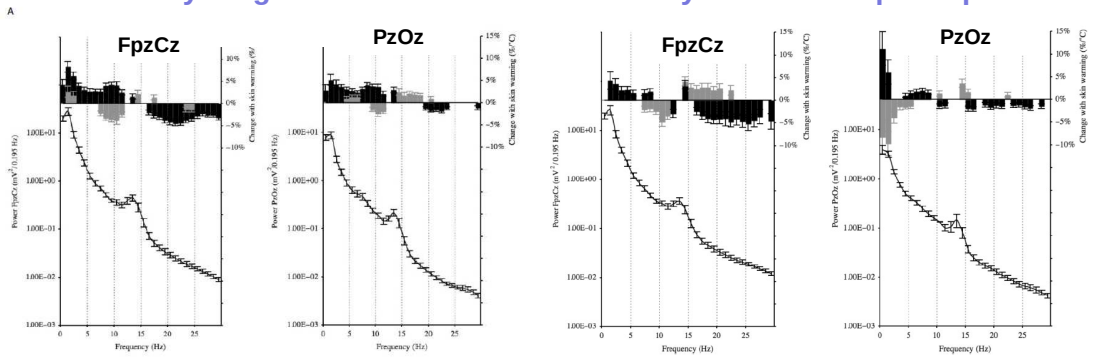
Skin temperature differences: ≅ 0.4 ° C
Core body temperature: virtually unchanged

Raymann et al., Brain, 131: 500-5134 (2008)

Temperature and sleep regulation: experimental evidence

Powerspectra of NREM sleep

young adults **elderly without sleep complaints**



black bars: proximal manipulation, **grey bars** distal manipulations

Raymann et al., Brain, 131: 500-513 (2008)

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Summary

- Evidence from experimental human studies shows that **skin temperature manipulations** (**in the thermoneutral range**, i.e. without changes in core body temperature) have an effect on sleep as reflected by changes in sleep latency and sleep stages and power spectra of the sleep EEG.
- There is a mechanism which can link the observations from the experimental studies. The warm and cold sensitve neurons of the ventrolateral preoptic area respond to changes in skin temperature and are involved in sleep regulation.
- Limitation: small sample sizes

Raymann et al., Brain, 131: 500-513 (2008)

Skin temperature and sleep

Are there implications of these observations for the interpretation of effects on the sleep EEG seen in RF-EMF exposure studies?

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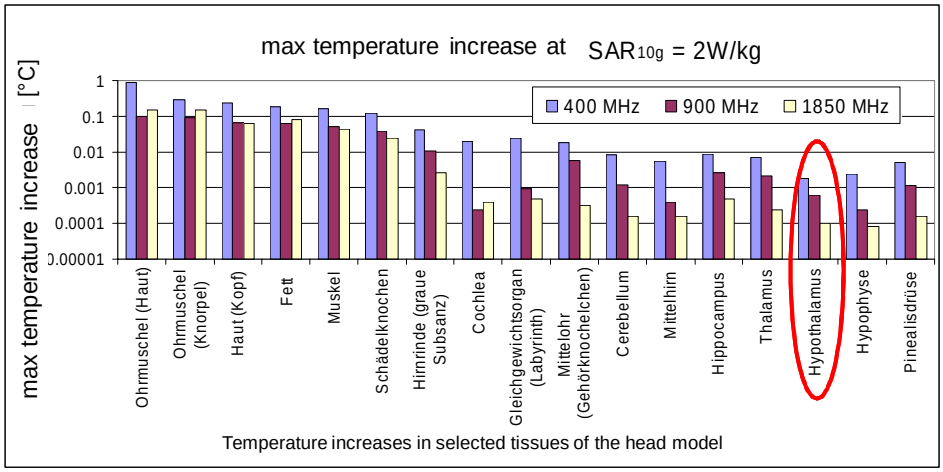
Implications for effects observed under RF-EMF exposure



Temperature increases in selected tissues of the head model

Schmid et al. Determination of exposure distribution from high frequency fields in the human body with regard to small structures and relevant thermo-physiological parameters. Final Report (2008)

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Implications for effects observed under RF-EMF exposure

TABLE 3. The Mean Value of the Temperature Rise of the Mobile Phone Surface Areas "*Cheek*" and "*Ear*" after 15 and 30 min with the Phone Transmitting at the MIN and MAX Output Power

	Temperature increase (°C)							
	Mobile phone "cheek" area				Mobile phone "ear" area			
	MIN		MAX		power level MIN		MAX	
Time of exposure (min)	LOAD	RFE	LOAD	RFE	LOAD	RFE	LOAD	RFE
15	2.6	2.7	3.5	3.6	2.4	2.5	3.7	3.8
30	3.3	3.3	4.4	4.7	3.1	3.3	4.7	5.0

LOAD: combined effect of insulation and electrical heating; RFE: „normal" use of mobile phone with RF

The insulation and the electrical power dissipation lead to statistically significant rises in the skin temperature, while the RF exposure did not.

Straume et al. Bioelectromagnetics 26:510-510 (2005)

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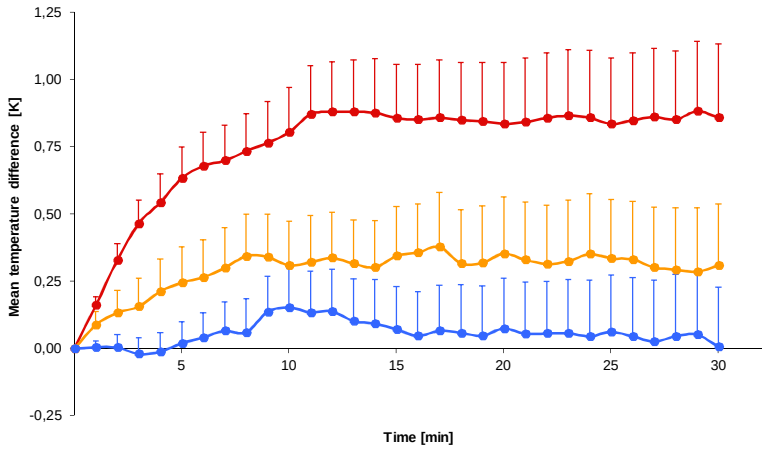
Implications for effects observed under RF-EMF exposure



Mean temperature patterns for sham (●), 1.5 W/kg (●) and 6 W/kg (●) exposure during the 30 min trial measured at sensor 1.
Each measurement point was standardized by subtracting it from the basic value at time point zero.

Dorn et al. Bioelectromagnetics 35:452-458 (2014)

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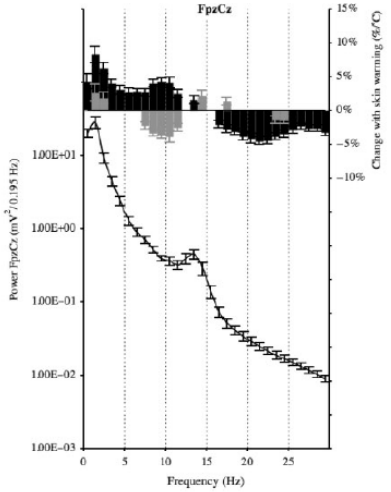
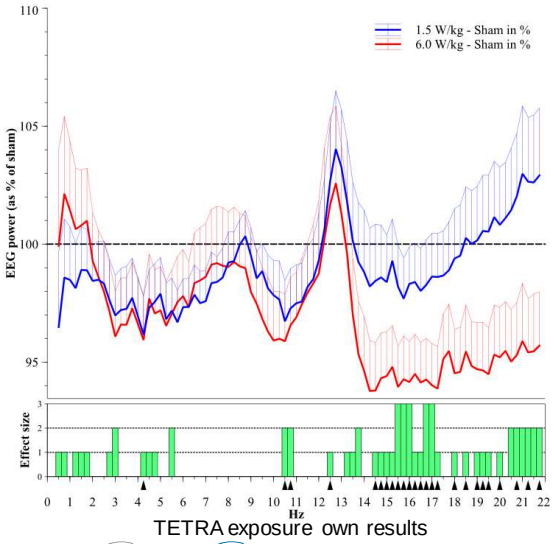
Implications for effects observed under RF-EMF exposure

NREM power



skin temperature manipulation in young adults

Stage N2 power C3



TETRA exposure own results

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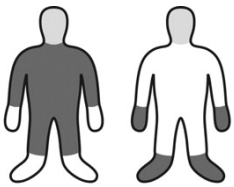
Open questions

Given: Thermosuit studies manipulate distal (hand and feet) and/or proximal (body and limbs) skin temperature over larger body areas.



Fronczek et al. 2008 J Neurol Neurosurg Psychiatry 79:1354-7

Homepage IT'IS foundation

Bortkiewict et al. 2012, Int J Occup Med Environm Health 25:145-50

Schmid et al. 2012, Bioelectromagnetics 33:594-603

- Can a locally focussed, exposure related increase in skin temperature of the head (ear, cheek) explain the observed CNS effects during sleep?

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Open questions

To answer this question we would need a study with a sham, a verum and a heated sham condition.

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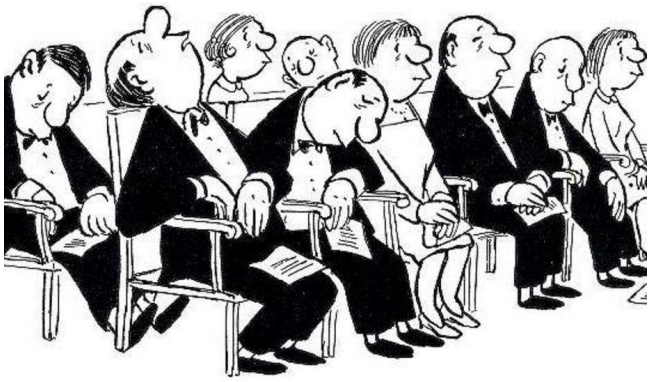
Thank you for your attention



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