The Biological Clock and Sleep

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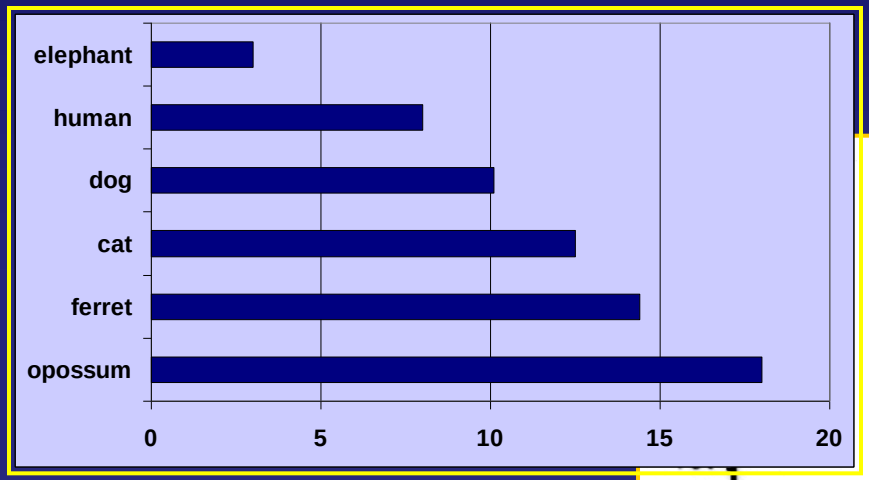
Sleep ….a reversible behavioral state of reduced responsiveness to, and interaction with the environment.

Hypothesized functions of sleep

- **Conservation of energy**
- **Detoxification processes**
- **Generalized restorative processes**
- **Learning/memory consolidation (Francis Crick: sleep allows the brain's short term memory to "*take out the trash*", i.e. to deprogram memory traces not destined for long term memory, and to stabilize and "hardwire" those traces that are destined for long term memory storage)**

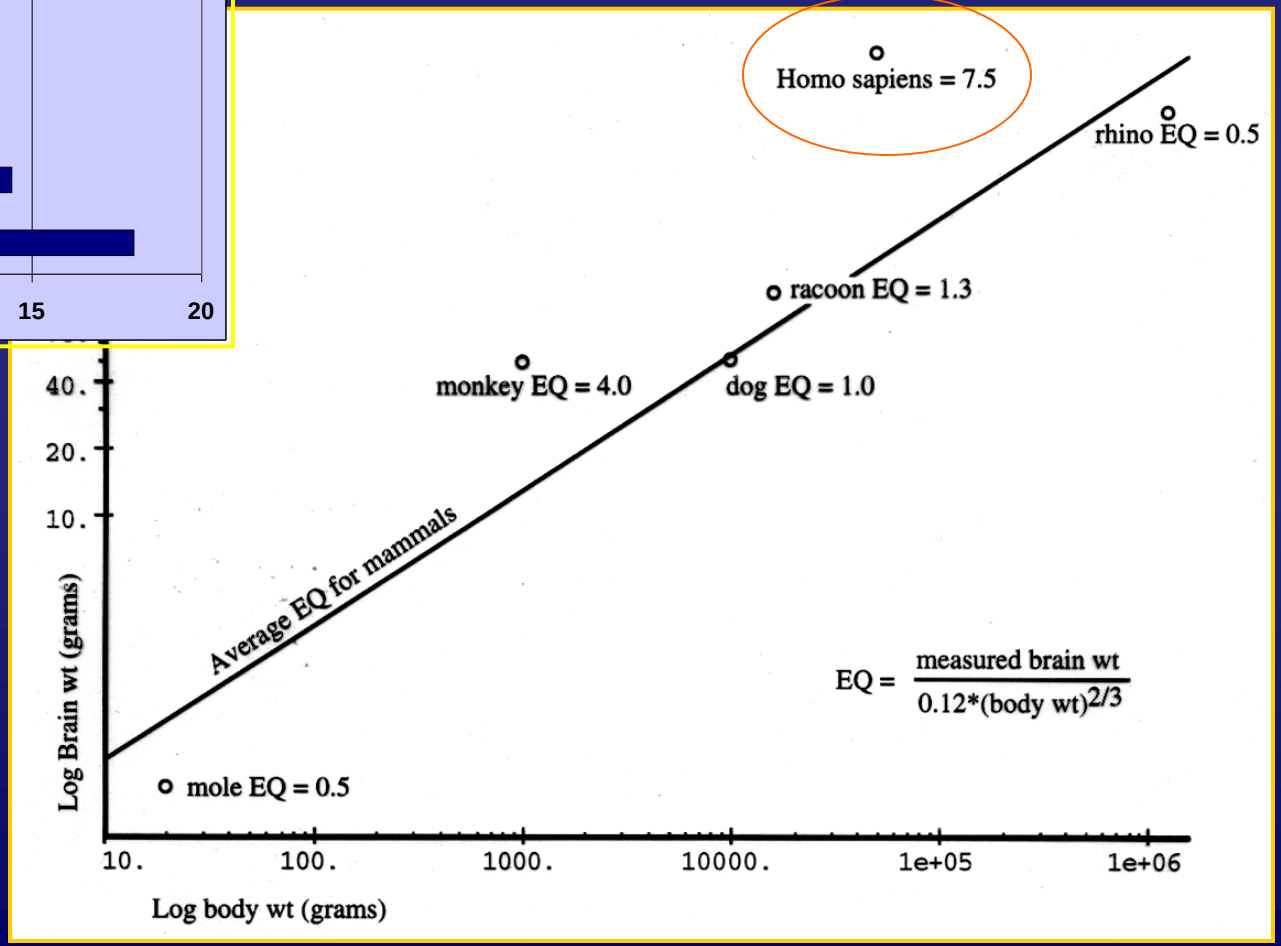
SLEEP: Innate and Universal in Mammals.

However, the hours per day spent in total sleep does NOT correlate to level of encephalization

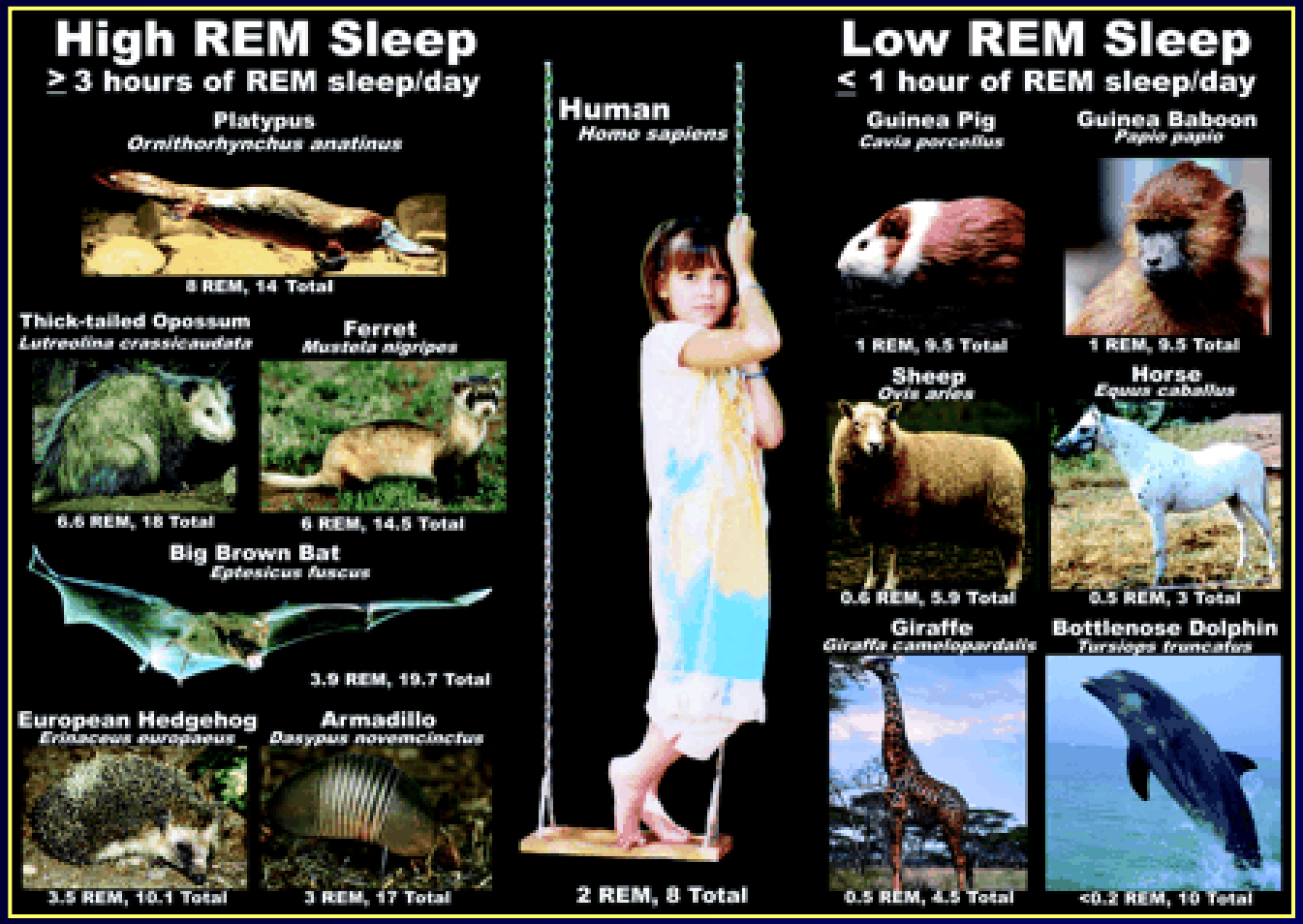


Hours slept per 24h

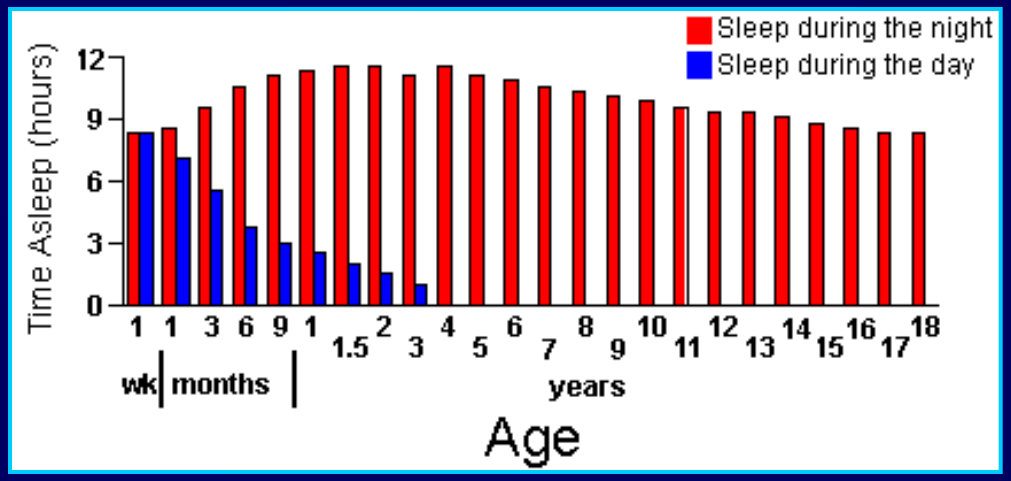
(from Siegel 2001; 2003)

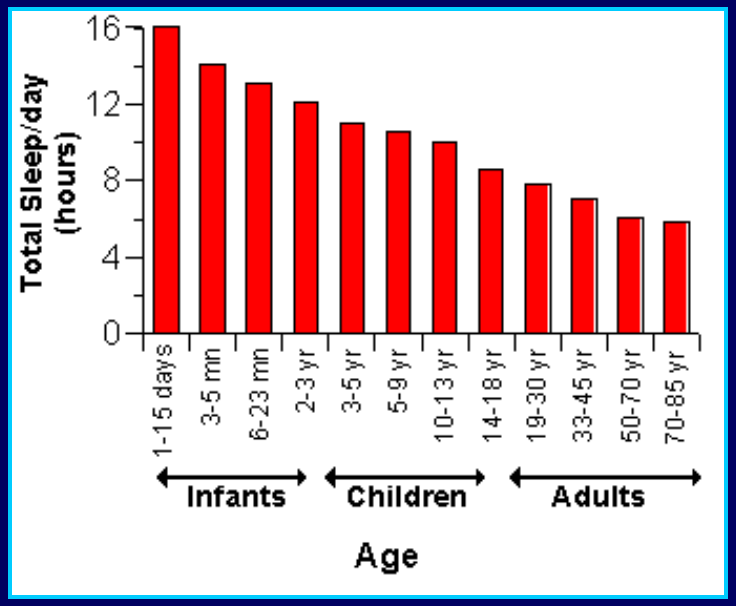


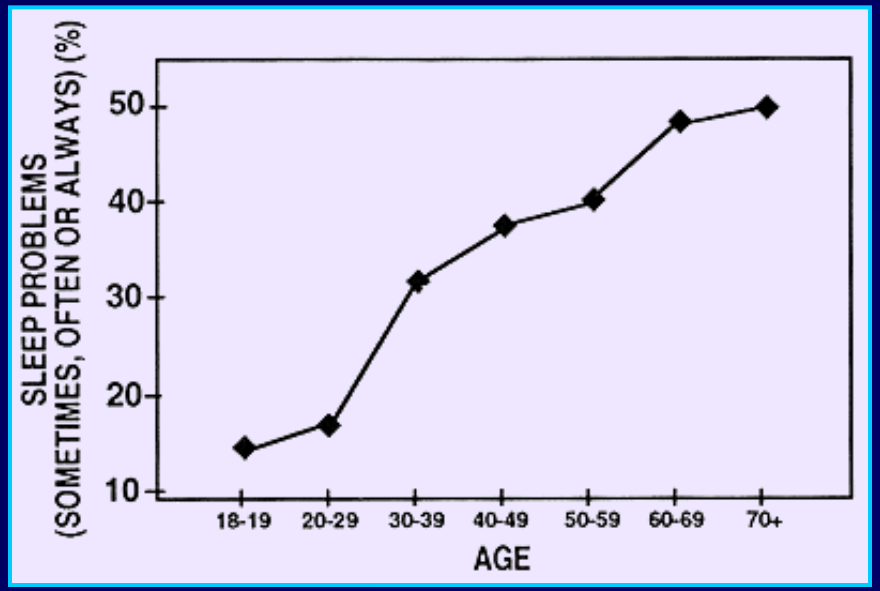
The hours per day spent in REM sleep does NOT correlate to level of encephalization



Sleep duration and structure changes with age





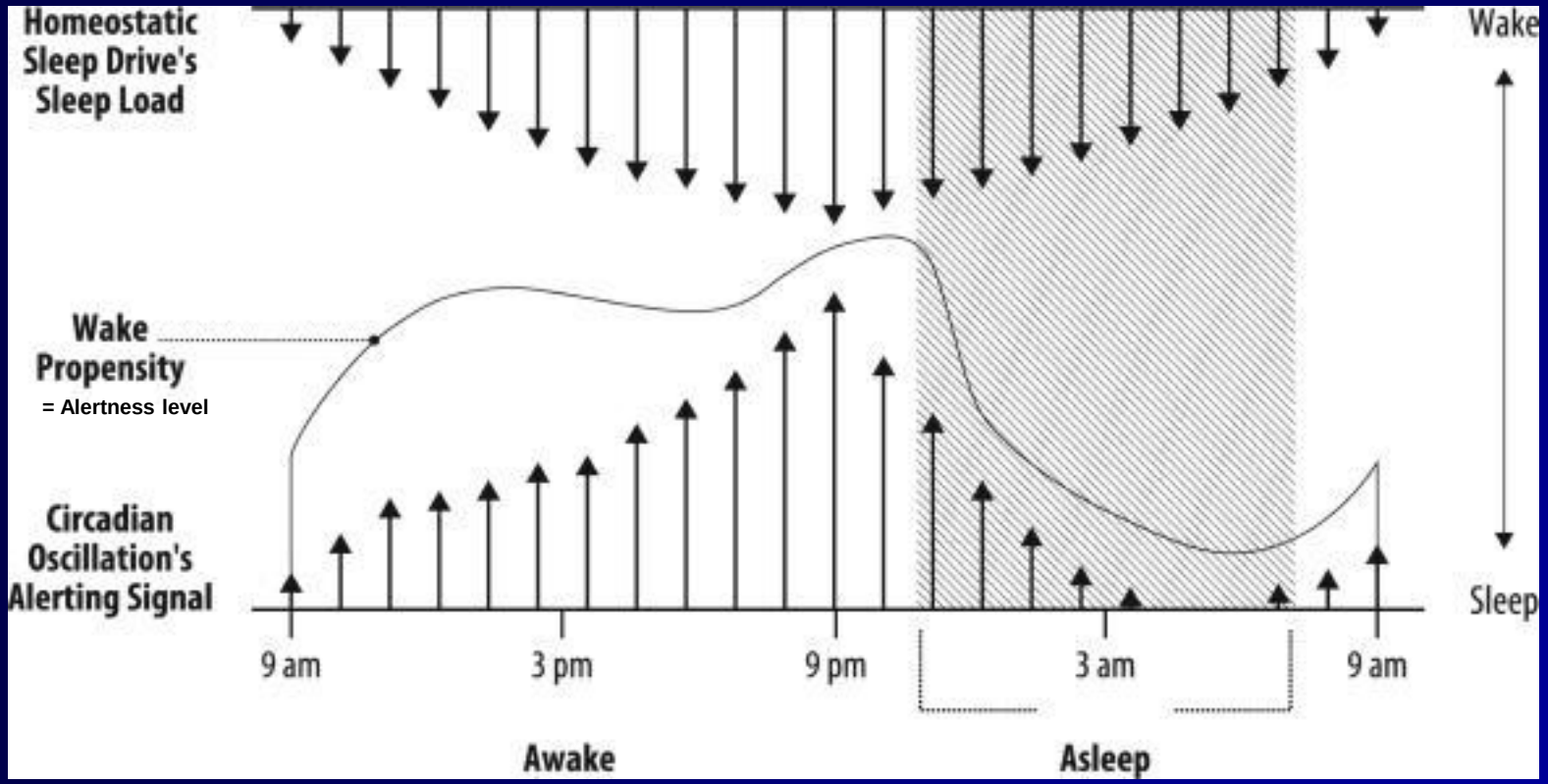


The Current Sleep Model:

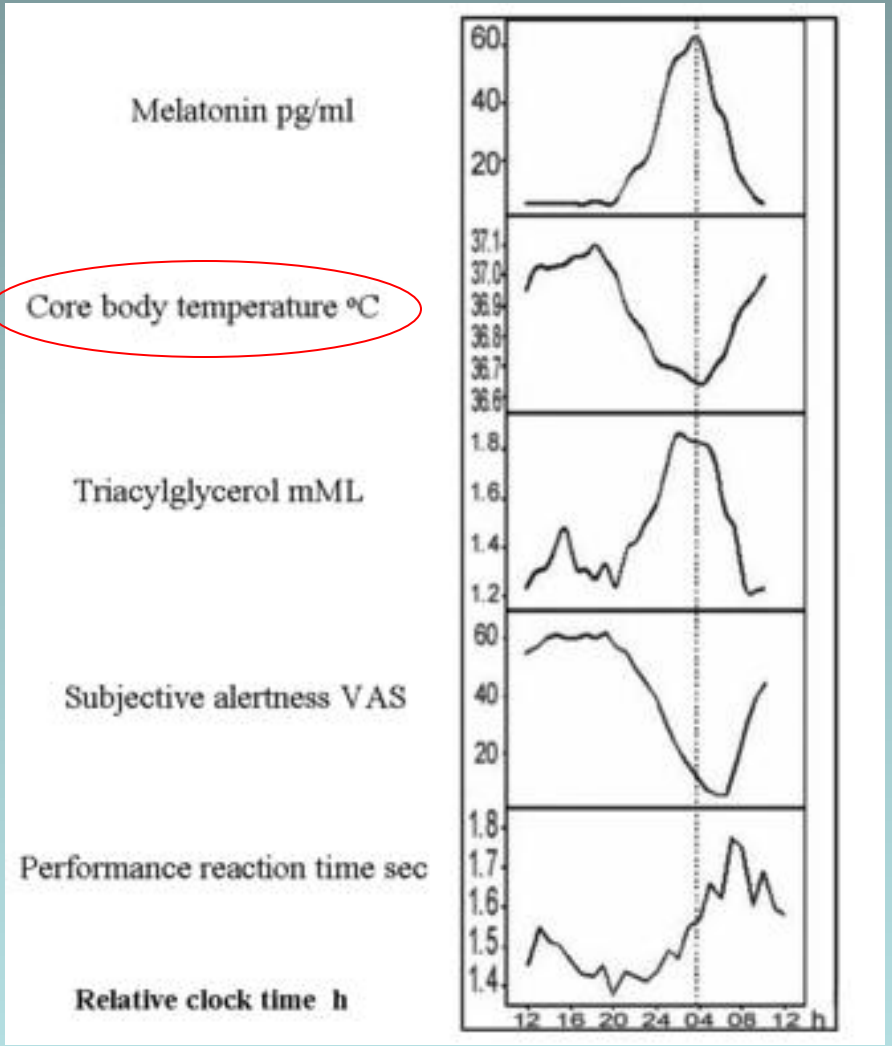
Sleep is regulated by the neurophysiological interaction between homeostatic processes (“sleep load” or “sleep drive”; S) and circadian processes (“alerting signals” or “circadian drive for wakefulness”, C)

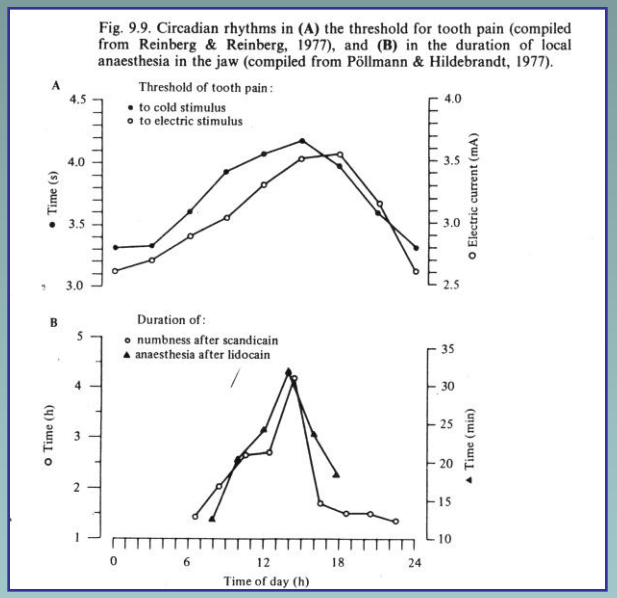
“S”
(“H”)

“C”



Circadian rhythms in human physiology





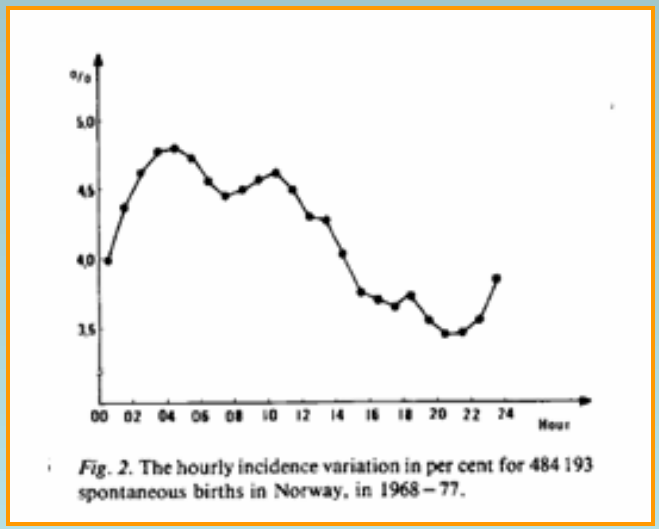
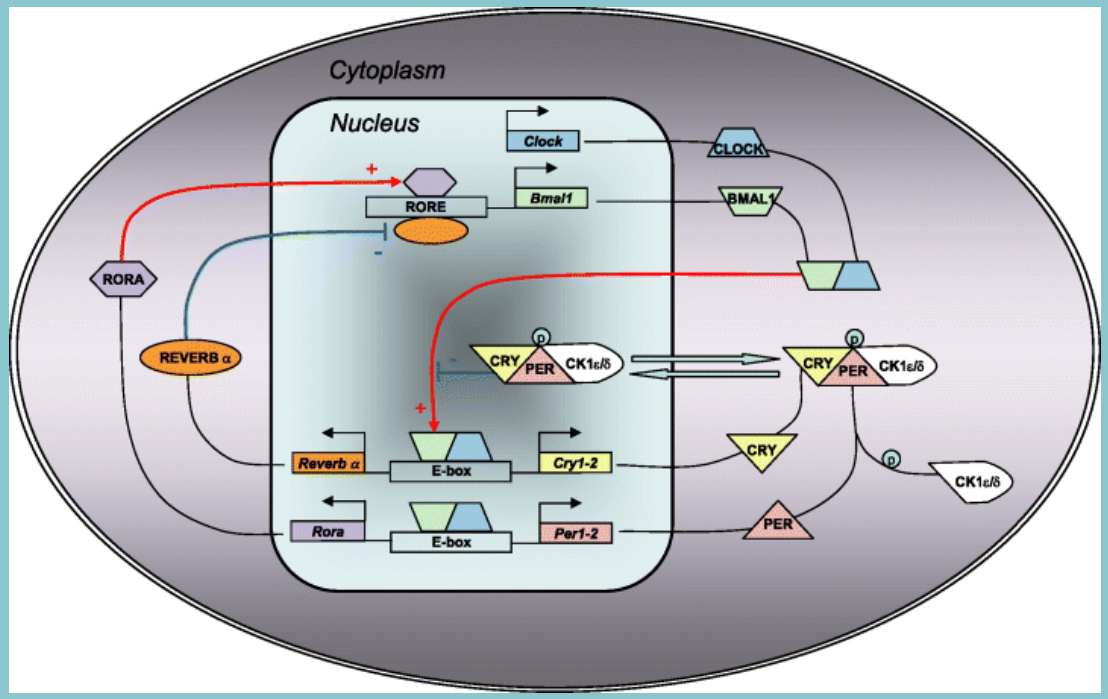
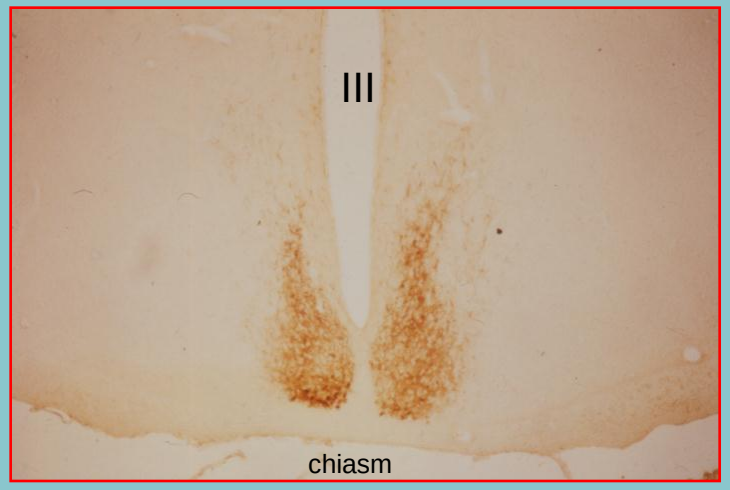


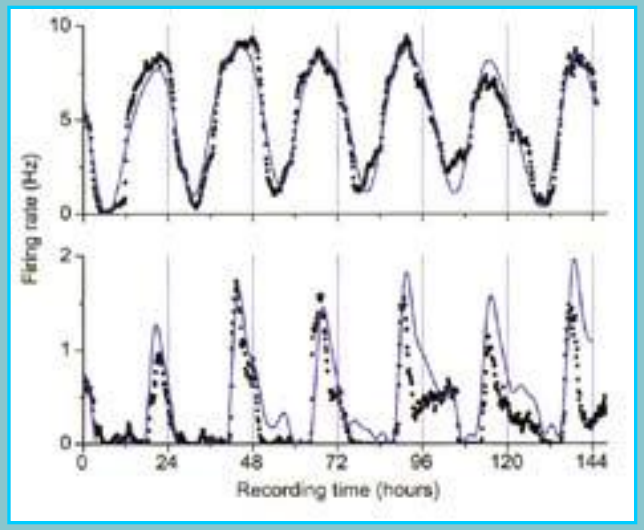
Fig. 2. The hourly incidence variation in per cent for 484 193 spontaneous births in Norway, in 1968–77.

The circadian clockwork involves multimeric protein feedback loops that regulate "*clock genes*" (e.g. Per, Cry) transcription over 24 h





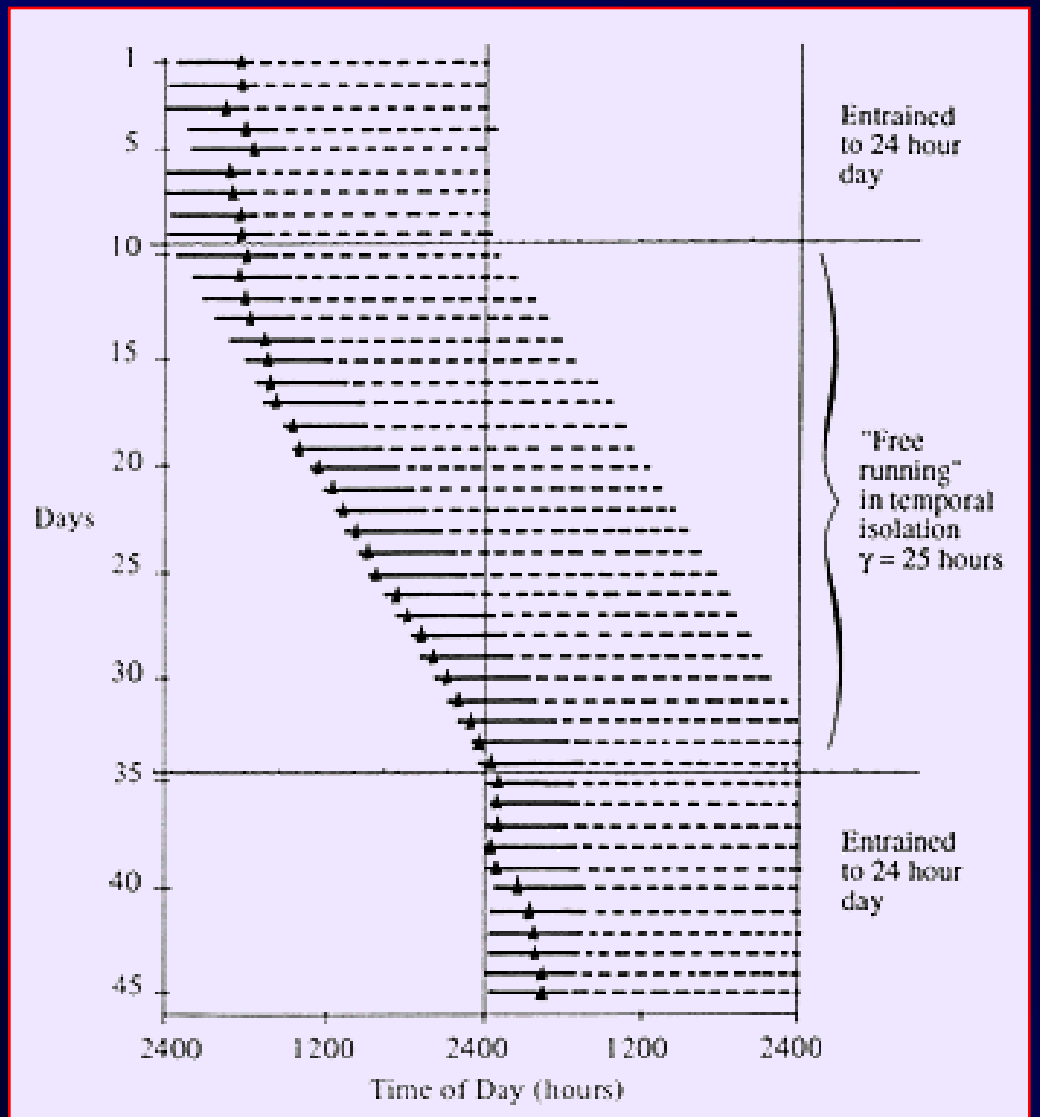
Suprachiasmatic nuclei (SCN)

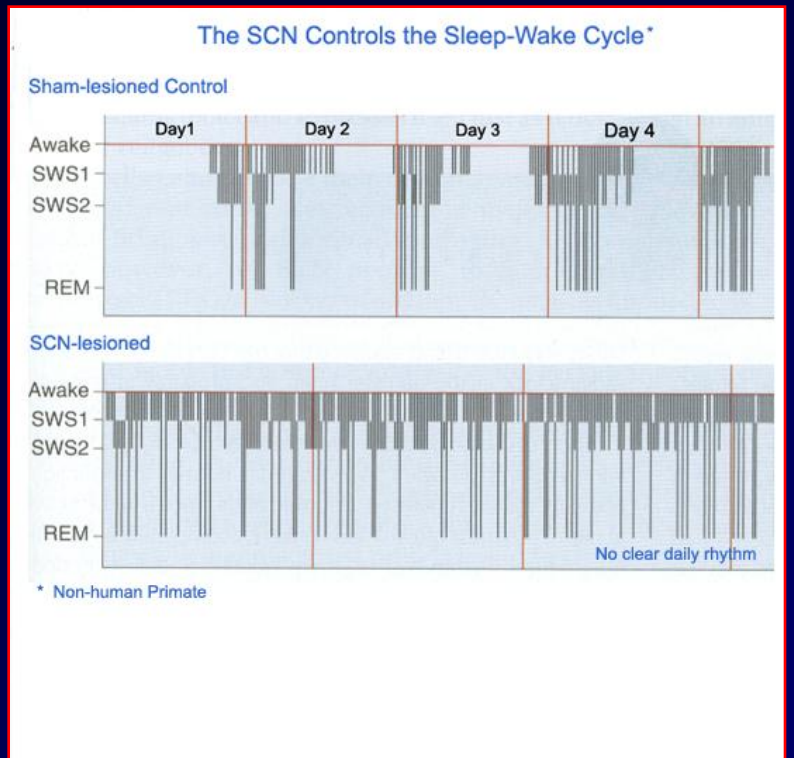


SCN circadian rhythms continue even *in vitro* !

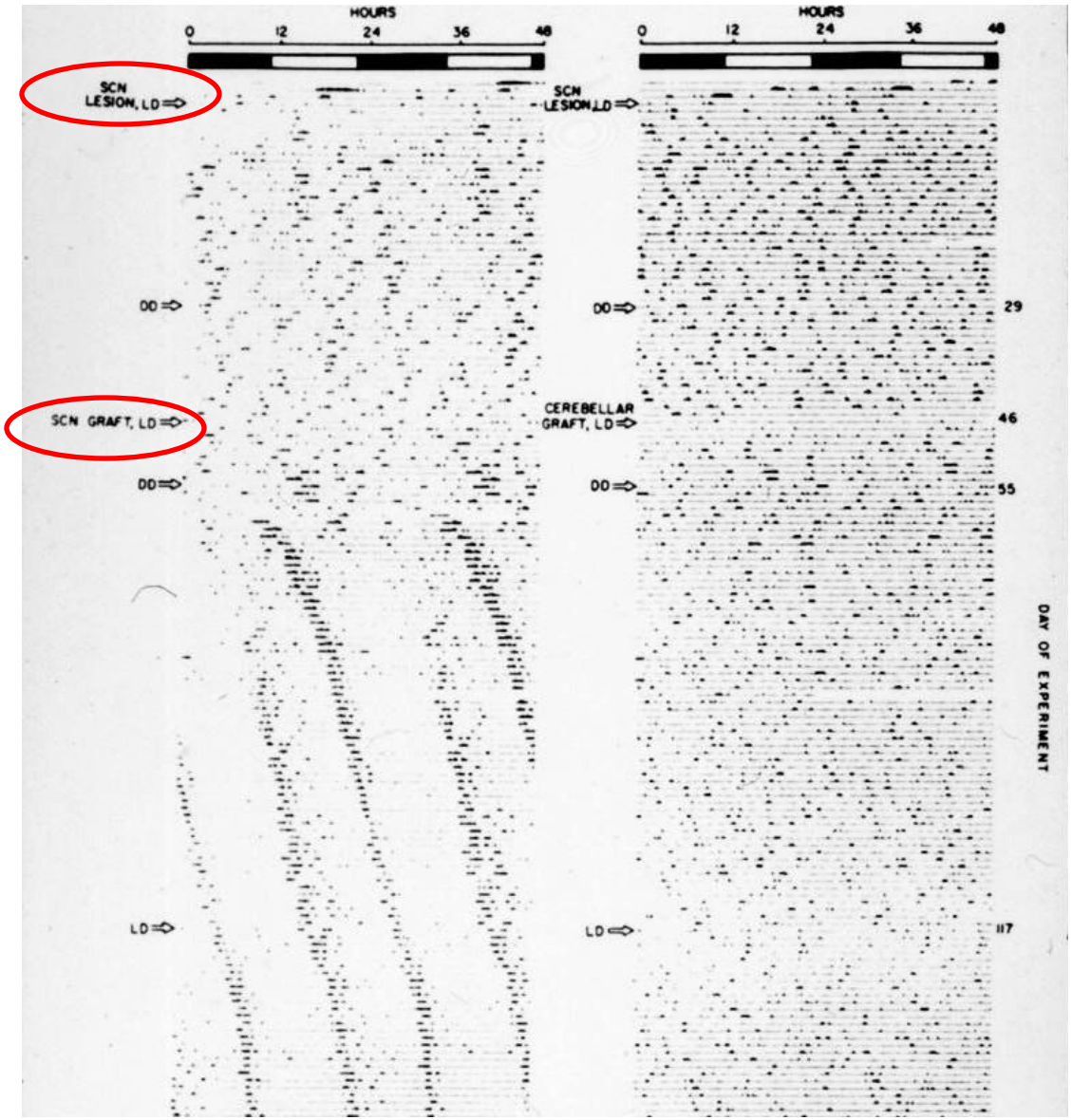
(Herzog 2000)

Sleep-wake cycles are the behavioral expression of the hypothalamic circadian clock



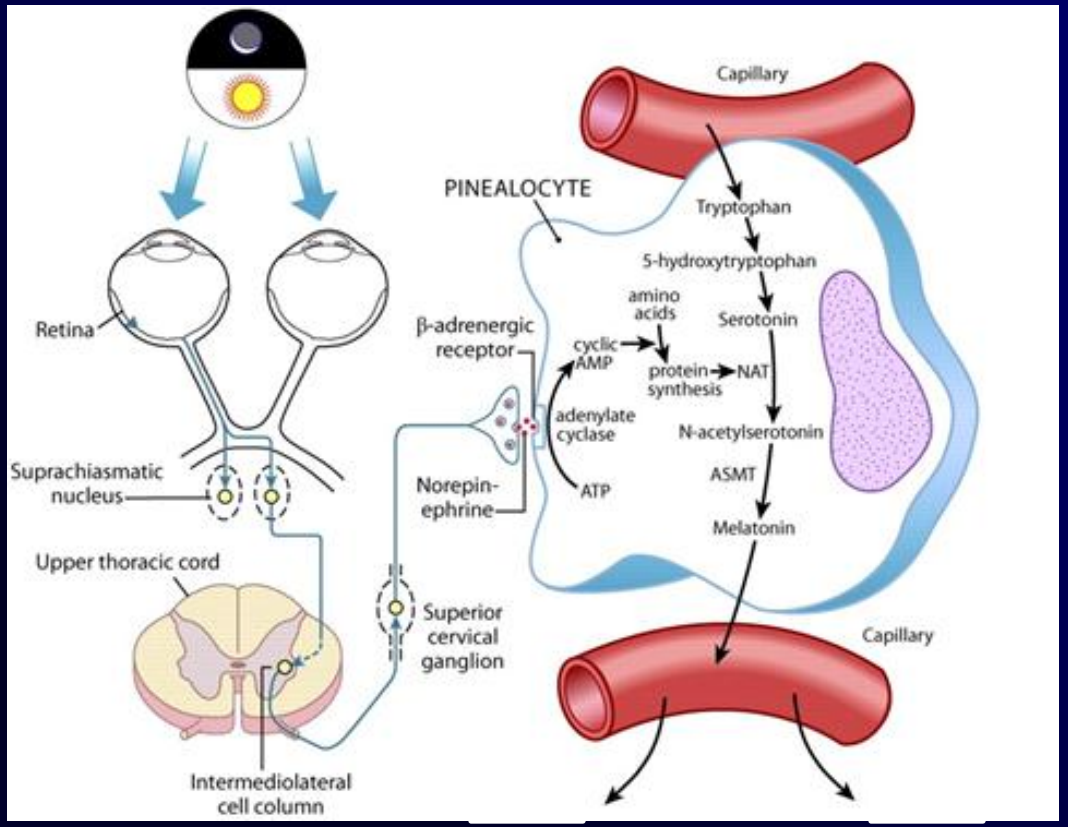


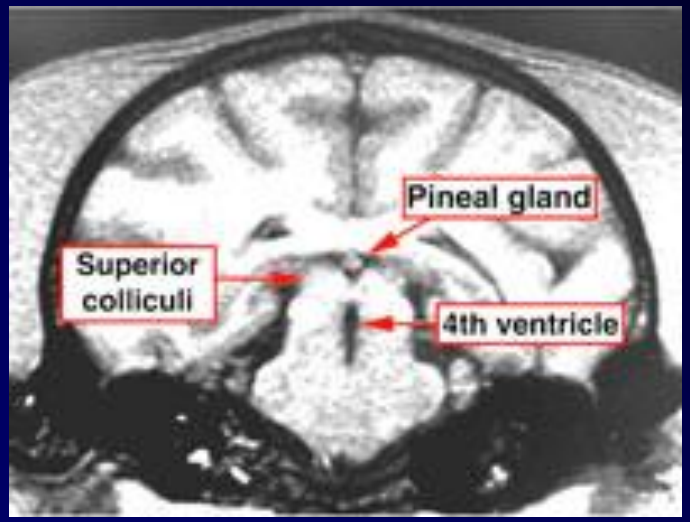
SCN transplants, but not cerebellar grafts, restore rhythmic locomotor activity to SCN −lesioned recipient animals

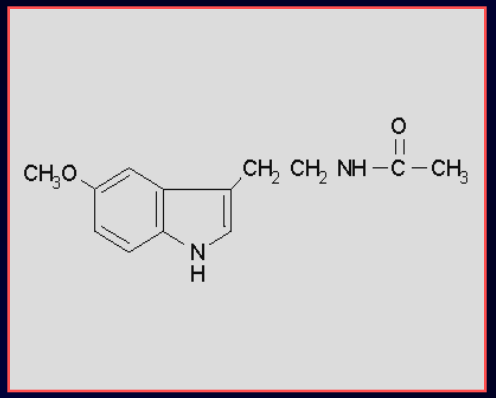


(Davis 1990)

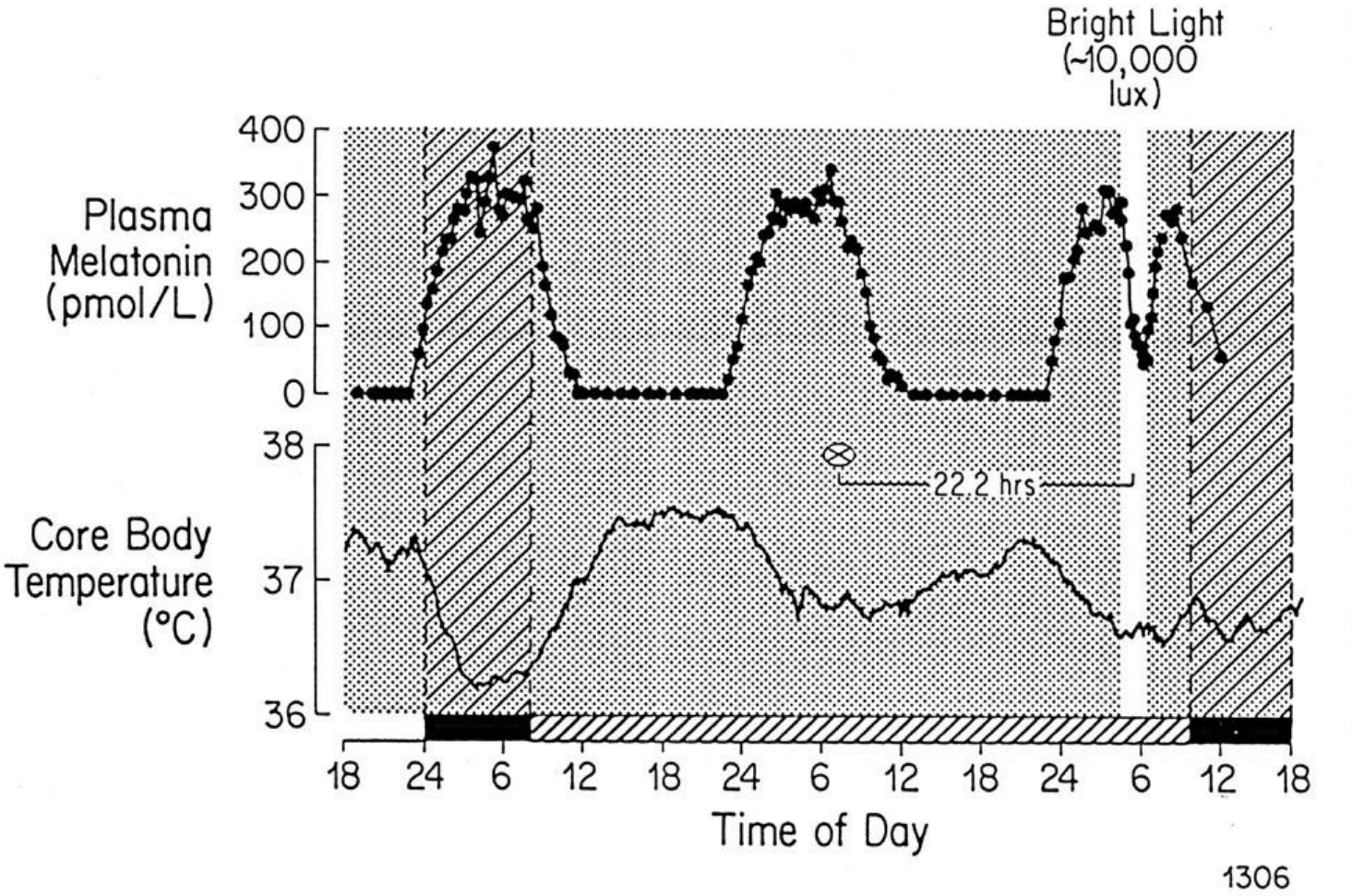
The pineal gland secretes melatonin primarily at night in response to circadian signals under SCN control







Melatonin is secreted at night as an output marker of SCN phase



Melatonin serves as an endocrine *output* signal of the circadian clock as well as a *feedback* signal to the same structure

1) Free-running circadian clock

2) clock entrained to melatonin

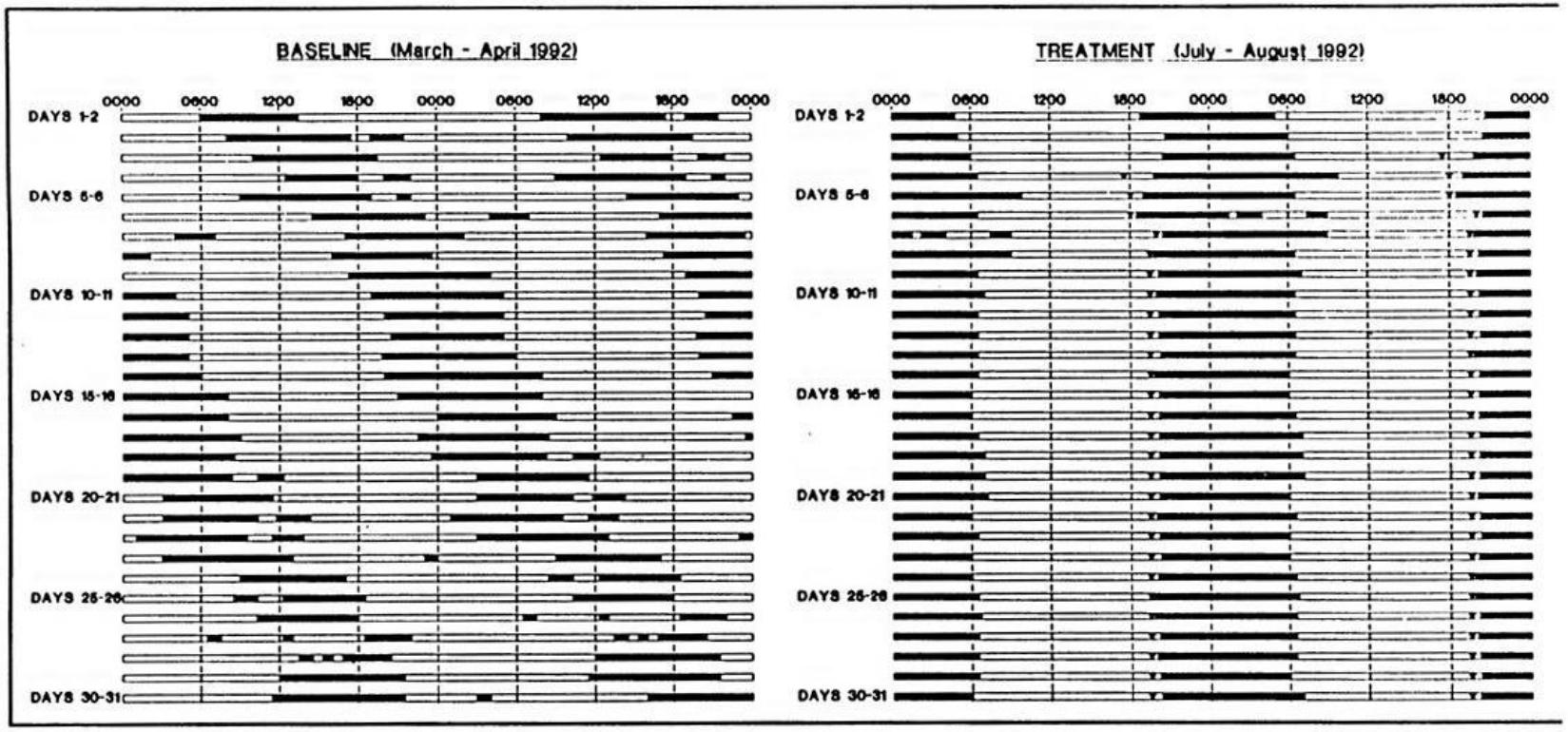
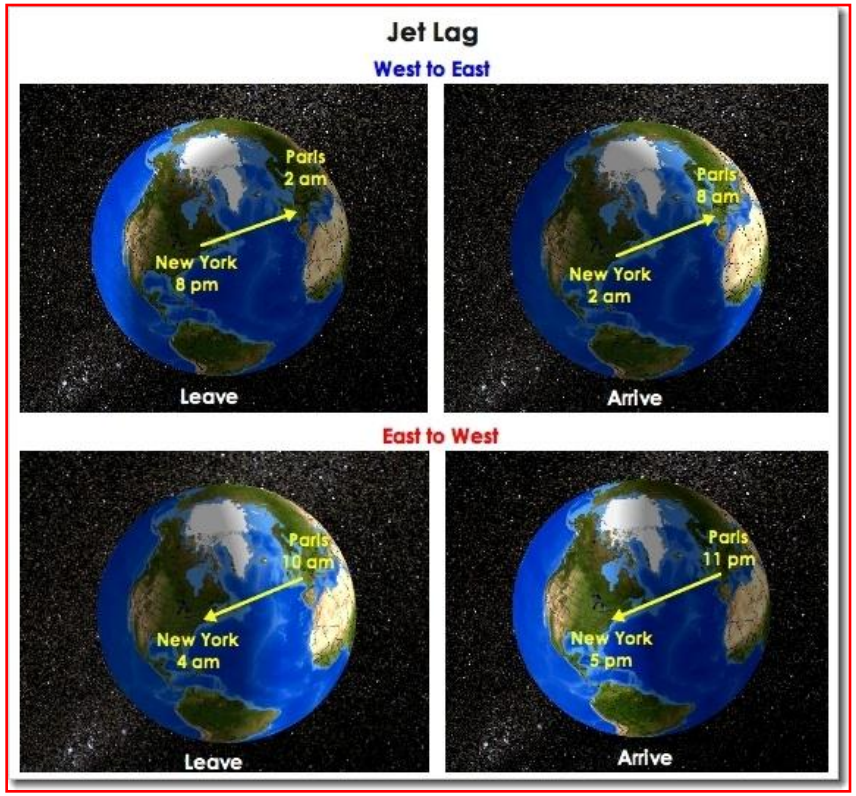


Figure 1. Sleep diary data, double-plotted for 30 days. Black bars represent times when the child was asleep, as reported by the parents. The left panel presents baseline data, collected in March–April, 1992. The right panel presents the first 27 days of melatonin treatment (July–August, 1992). Treatment was initiated on Day 4. Triangles represent the time of melatonin administration.

Lapierre & Dumont 1995 Biol. Psychiatry 38: 119

Jet lag = disruption of the body's circadian phase.

Melatonin ameliorates jet lag if taken at the proper time.



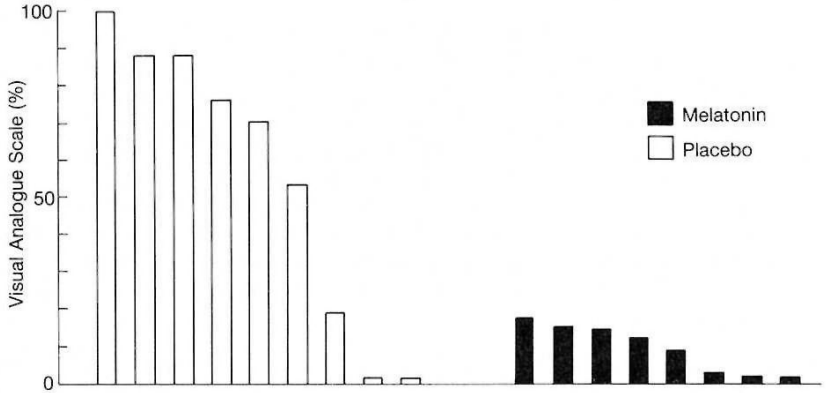


Fig. 2.8. Individual ratings of 'jet-lag' (0=insignificant, 100=very bad) on a 10-cm visual analogue scale in 17 subjects taking either melatonin (■) or placebo (□) in a precisely timed protocol (see text) before and after an 8 time-zone flight from San Francisco to London. The study design was double-blind. Subjects were in San Francisco time zone for 14 days prior to flight. (From Arendt *et al.* 1986, with permission.)

Human sleep behavior shows large individual variations in temporal organization

Chronotypes have been established both qualitatively (questionnaires) and quantitatively (sleep studies) and are based on sleep phase ("morningness" vs "eveningness"), not sleep duration. Chronotypes are attributed (at least in part) to genetic differences in the circadian clock.

Qualitative assessment

Quantitative assessment

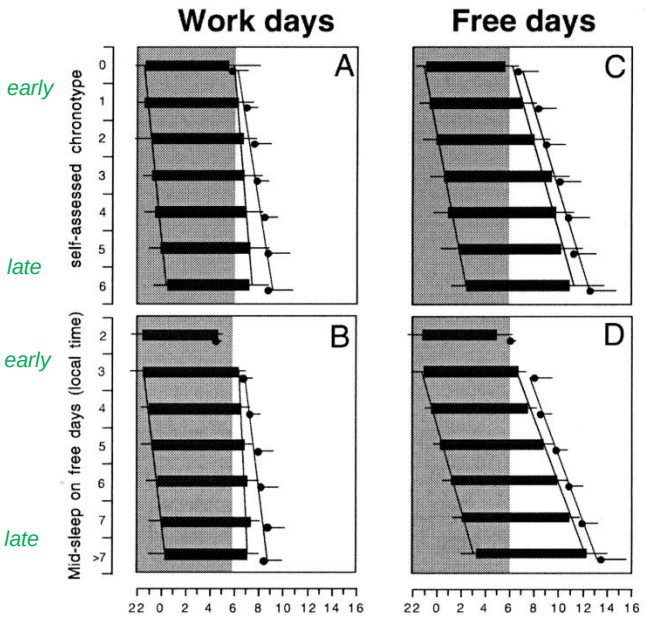
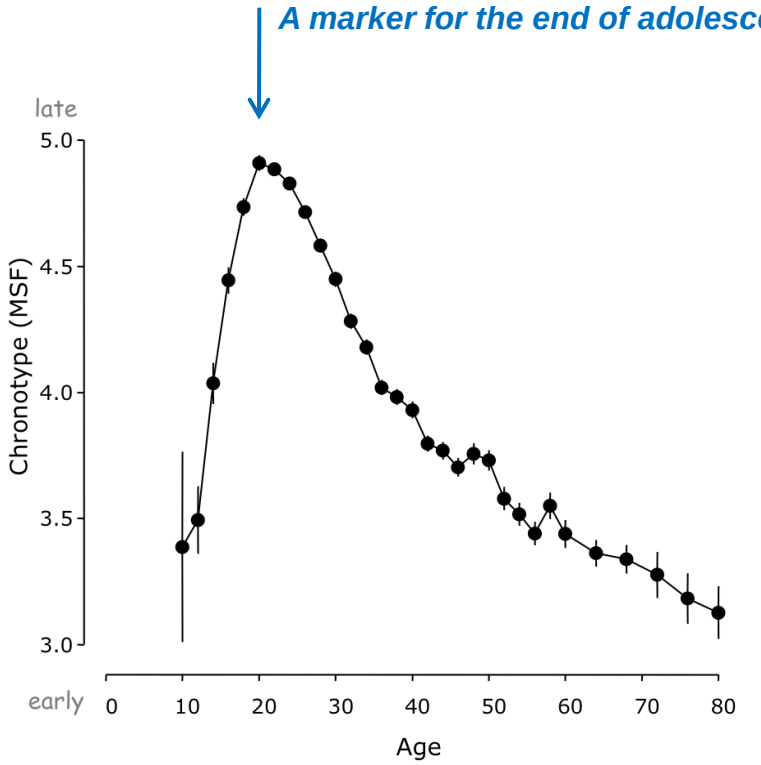


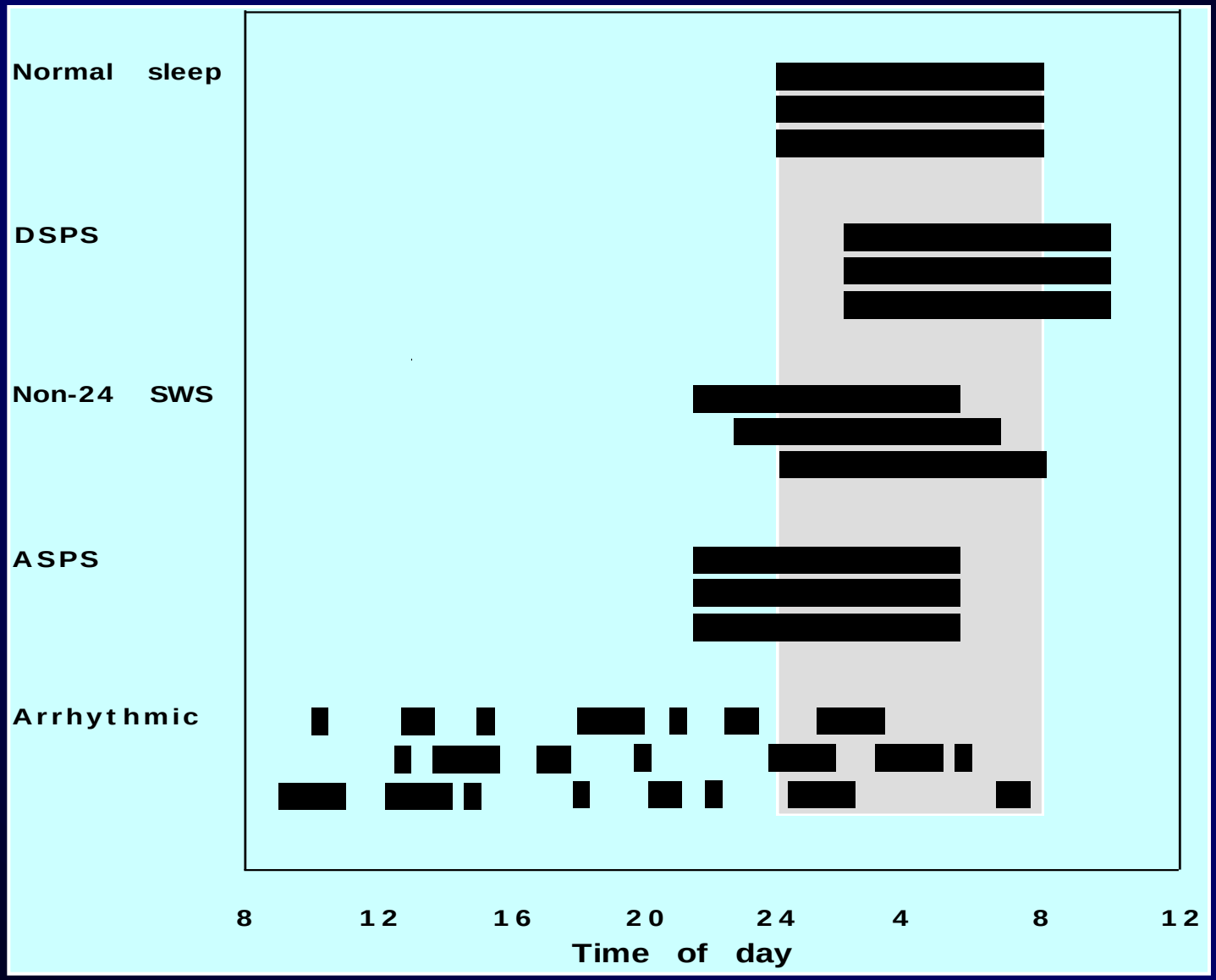
Figure 3. Sleep patterns of different chronotypes grouped by qualitative (A, C) and quantitative (B, D) assessment (see Methods section). Workdays are shown on the left, and free days are shown on the right. Sleep periods (onset to wake up) are drawn as horizontal bars. The bins for grouping quantitative chronotypes by phase of midsleep are the same as in Fig. 1D. Thin horizontal lines represent standard deviation. Dots represent the times when subjects feel fully awake (end of sleep inertia).

Roenneberg et al. 2003
J. Biol. Rhythms 18: 80-90



Roenneberg et al. 2004 Curr. Biol. 14: R1038-R1039

Sleep disorders associated with clock dysfunctions



Overview of SLEEP DISORDERS

I. Dyssomnias (difficulty initiating/maintaining sleep, i.e. insomnia, and associated daytime sleepiness)

A. Intrinsic sleep disorders (sleep apnea, narcolepsy, etc.)

B. Extrinsic sleep disorders (toxins, drugs, etc.)

C. Circadian rhythm disorders

II. Parasomnias (abnormal behaviors during sleep)

A. Arousal disorders (sleepwalking, sleep-related eating disorder, sexsomnia, night terrors, etc.)

B. Sleep-wake transition disorders (sleeptalking, disorientation, sleep paralysis, etc.)

C. Parasomnias usually associated with REM sleep, e.g. REM sleep behavior disorder (intense dreams/nightmares, often associated with agitation)

D. Other

III. Sleep disorders associated with mental, neurological or other medical disorders (e.g. Alzheimer, epilepsy, etc.)

Insomnia in the general population :

- prevalent (1 of 3 adults; 9% chronic)
- reported frequency is increasing
- only 33 % or primary care patients with insomnia actually report it
- 80% of patients in psychiatric care have insomnia associated with their condition, while 40% of insomniacs have had other psychiatric complaints

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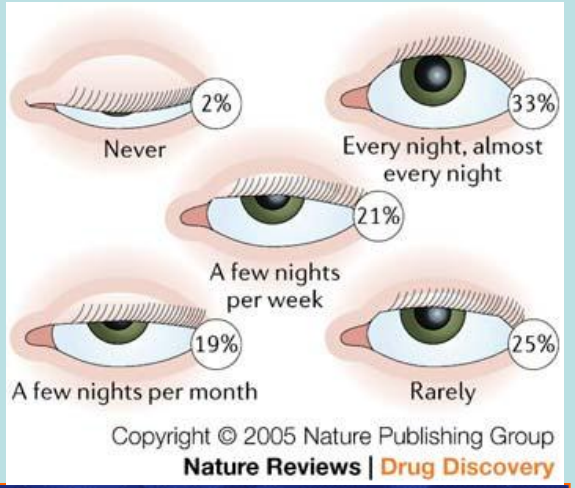
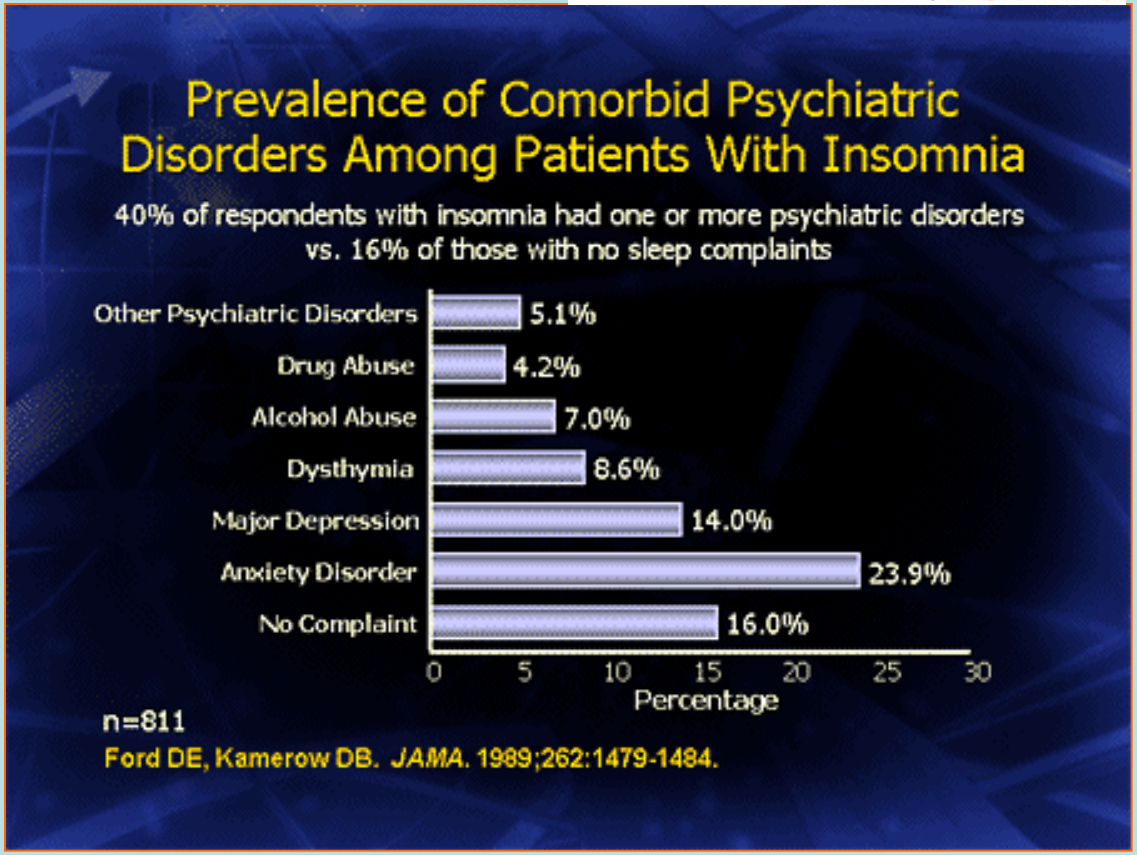


Primary causes of insomnia:

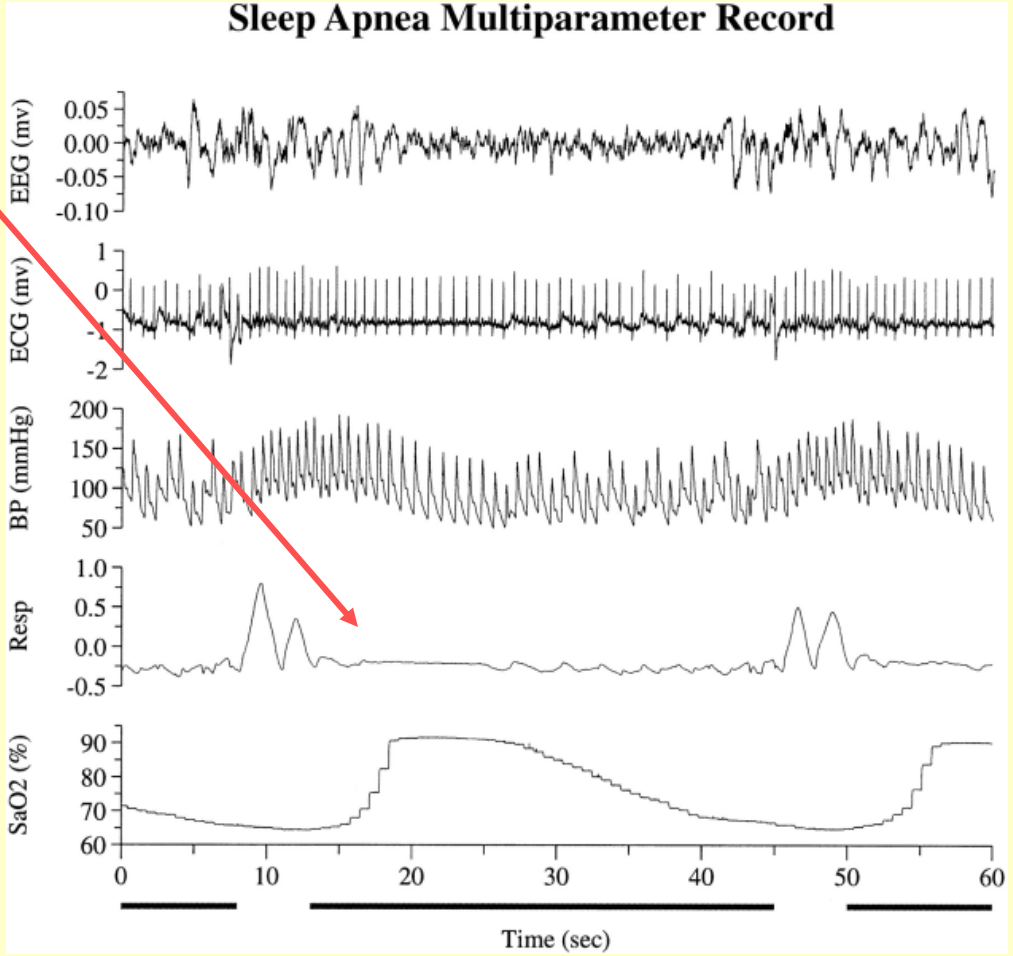
- life style (workaholics, irregular sleep routines, stress, etc.)
- demographics (more older people)
- urbanization (higher population densities) with more environmental disturbances (noise, light, etc.)



Two common examples of dyssomnias

I. Sleep apnea

- Cessation of breathing during sleep
- Most commonly due to physical obstruction in upper airways (95%), e.g. acutely (colds) or chronically (asthma, snoring, etc.)
- Less common is loss of central respiratory drive (5%), possibly as a result of alterations in chemoreceptor feedback to brainstem centers
- Strongly associated with cardio-vascular morbidity (due to repeated activation of oxidative stress and inflammatory responses following hypoxia)
- Usually treated with continuous positive airway pressure (CPAP) mask, or rarely with surgery



II. Narcolepsy

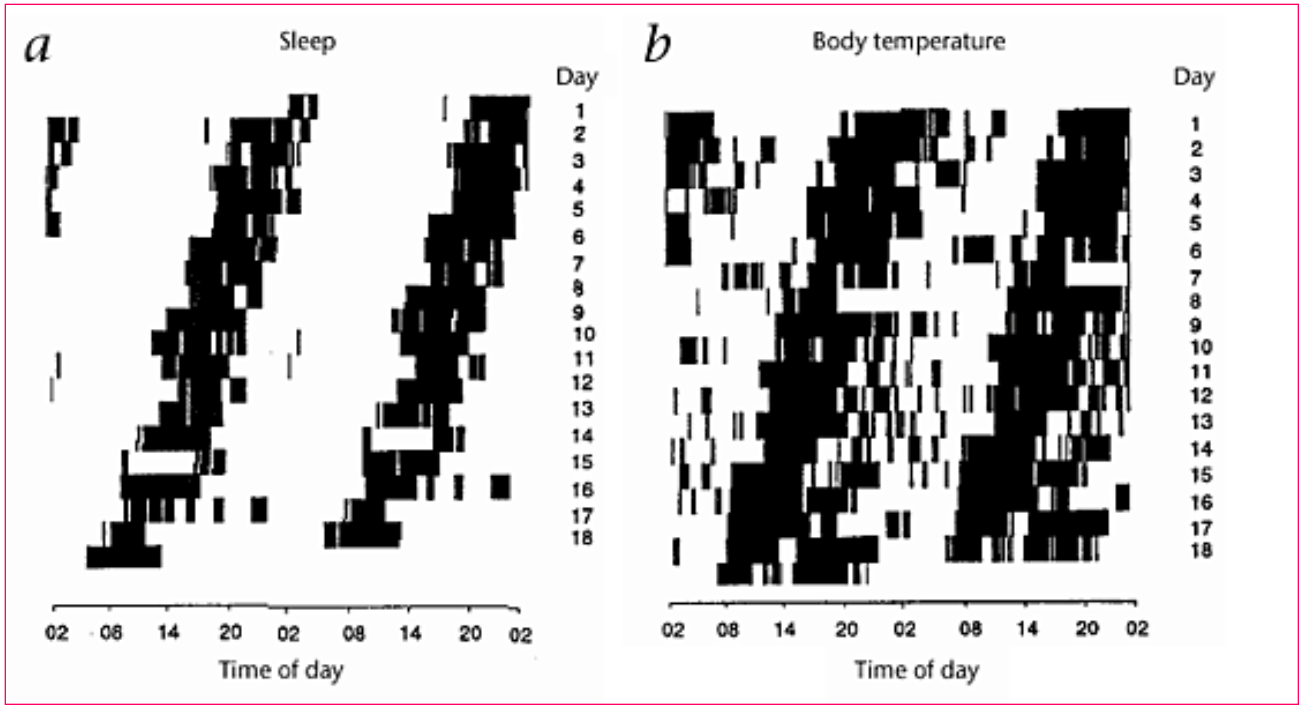
- Frequent recurring irresistible episodes of inappropriate sleep with short duration

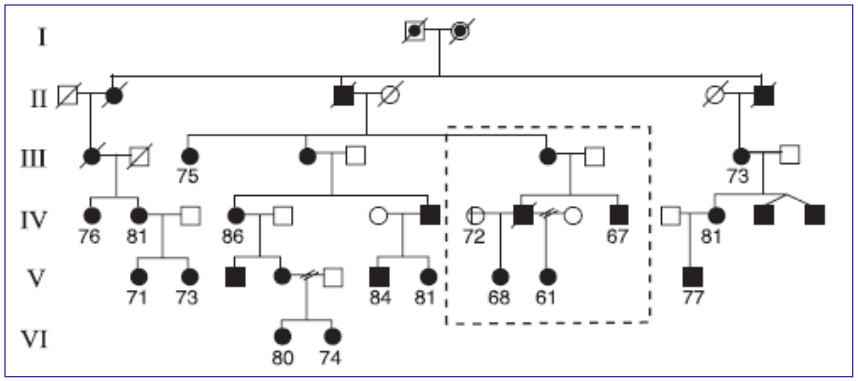
- Associated with REM-like imagery, sleep paralysis and/or loss of motor control (cataplexy; often involves an emotional trigger)

- May have genetic basis in some cases, e.g. mutation in hypocretin (orexin) gene or hypocretin receptor; however other causes for the loss of hypocretin activity are likely, e.g. autoimmune disorders

- Pharmacological treatment with antidepressants (for REM disorders), modafinil (Provigil), methylphenidate (Ritalin), etc.

Circadian Rhythm Disorder (familial advanced sleep phase disorder) due to a mutation of the Per2 protein





Jones et al. 1999 Nature Med. 5:1062

Seasonal affective disorder – a circadian rhythm disorder

Typical symptoms of SAD include depression, lack of energy, increased need for sleep, a craving for sweets and weight gain. Symptoms begin in the fall, peak in winter and usually resolve in the spring. Some individuals experience great bursts of energy and creativity in the spring or early summer

Women comprise 70-80% of SAD cases. Most common age of onset is in 30s, but cases of childhood SAD have been reported and successfully treated. For every individual with full blown SAD, there are many more with milder "winter blues."

Three key elements of phototherapy:

Intensity. The intensity of the light box is recorded in lux (a measure of the amount of light you receive at a specific distance from a light source). Light boxes for phototherapy usually produce between 2,500 - 10,000 lux, with 10,000 lux being typical. In contrast, the lighting in an average living room in the evening is < 400 lux, while a bright sunny day may register 100,000 lux.

Duration. Phototherapy typically involves daily sessions ranging from 30 minutes to two hours. Typically one should begin with shorter blocks of time, such as 15 minutes. One gradually works up to longer periods.

Timing. For most people, phototherapy is most effective if used in morning, after first waking up, rather than during evening. Doing phototherapy at night can disrupt sleep.

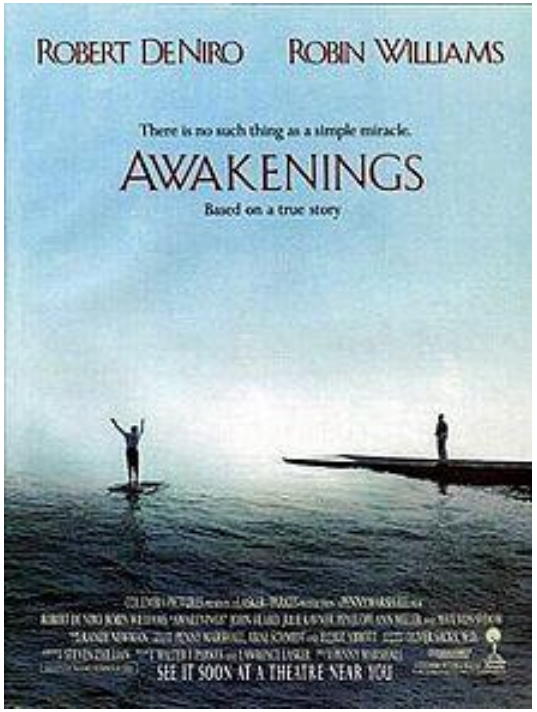
Parasomnias

- Approximately 10% of Americans have some form of parasomnia (esp. children).
- Often runs in families (= genetic component); only occasionally following brain injury.
- Typically resolves itself, or resolved by improving sleeping habits (regular schedule, appropriate environment, dietary changes, etc.)

Encephalitis lethargica

(von Economo's sleeping sickness)

- A disease characterized by high fever, headache, double vision, delayed physical and mental response, and lethargy. In acute cases, patients may enter coma.
- Between 1917 to 1928, an epidemic of encephalitis lethargica (EL) spread throughout the world, but no recurrence of the epidemic has since been reported, although isolated cases continue to occur. Postencephalitic Parkinson's disease may develop after a bout of encephalitis-sometimes as long as a year after the illness.
- The cause of EL is unknown.
- Treatment for EL is symptomatic. Levodopa and other anti-parkinson drugs often produce dramatic responses. Zolpidem (Ambien™) has reported success at treating EL.
- The course of EL varies depending on complications or accompanying disorders. Can be fatal.



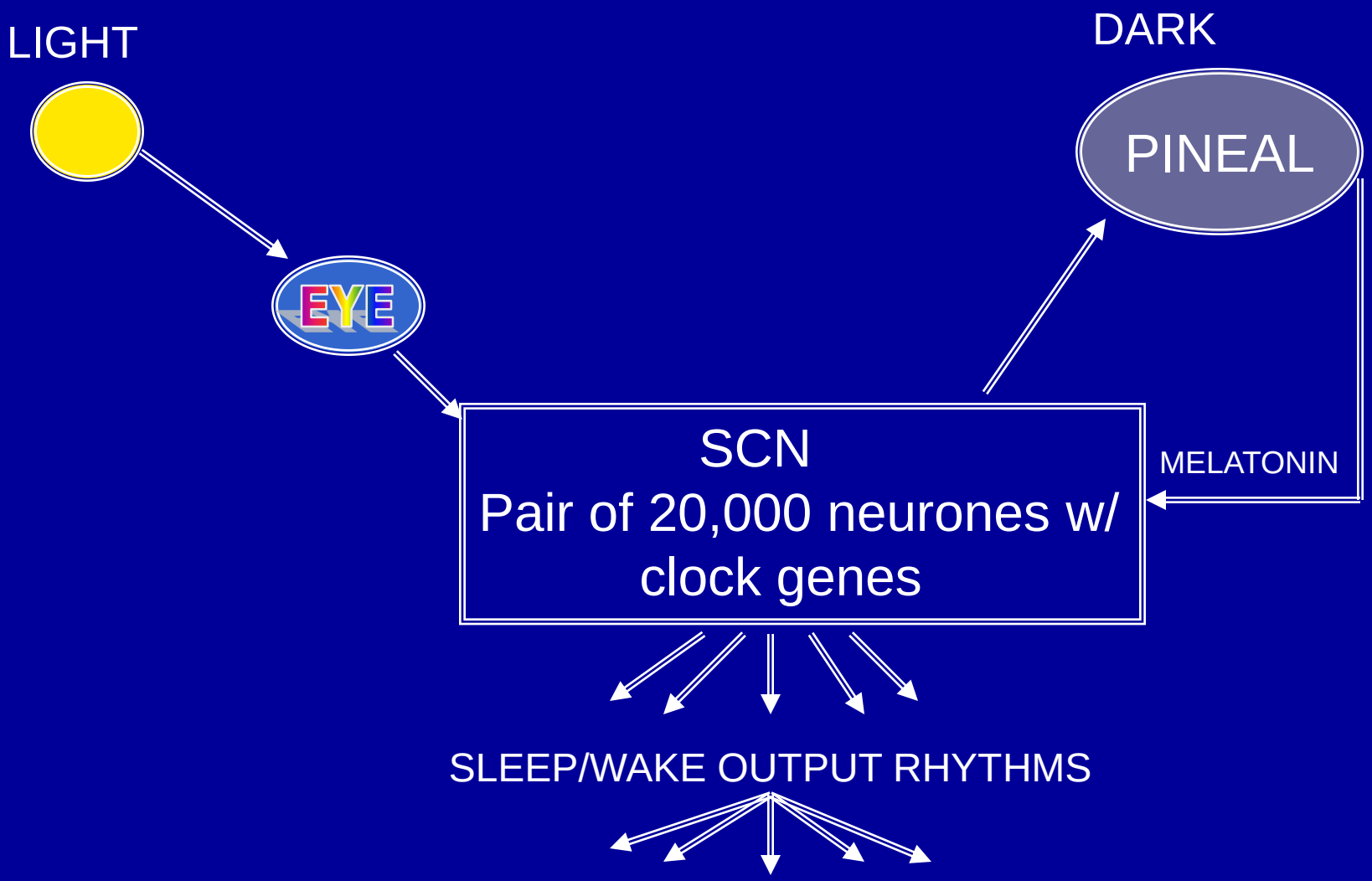
Circadian Rhythm Sleep Disorders

November 9, 2011

G. F. Slade, M.D.

Circadian Rhythms

- Physical, mental & behavioral variations that follow a 24 hr. cycle
- Controlled by biological clocks existing in groups of interacting molecules in individual neuronal & non-neuronal cells throughout the body
- “Master Circadian Clock”: suprachiasmatic nucleus (SCN) in the brain’s hypothalamus
- SCN responds to cues of light/dark & other environmental cues & synchronizes physiologic functions throughout the body



Protein synthesis, hormones, glucose metabolism, body temperature, blood pressure, GI function, heart rate, cognition, urine production, motor activity

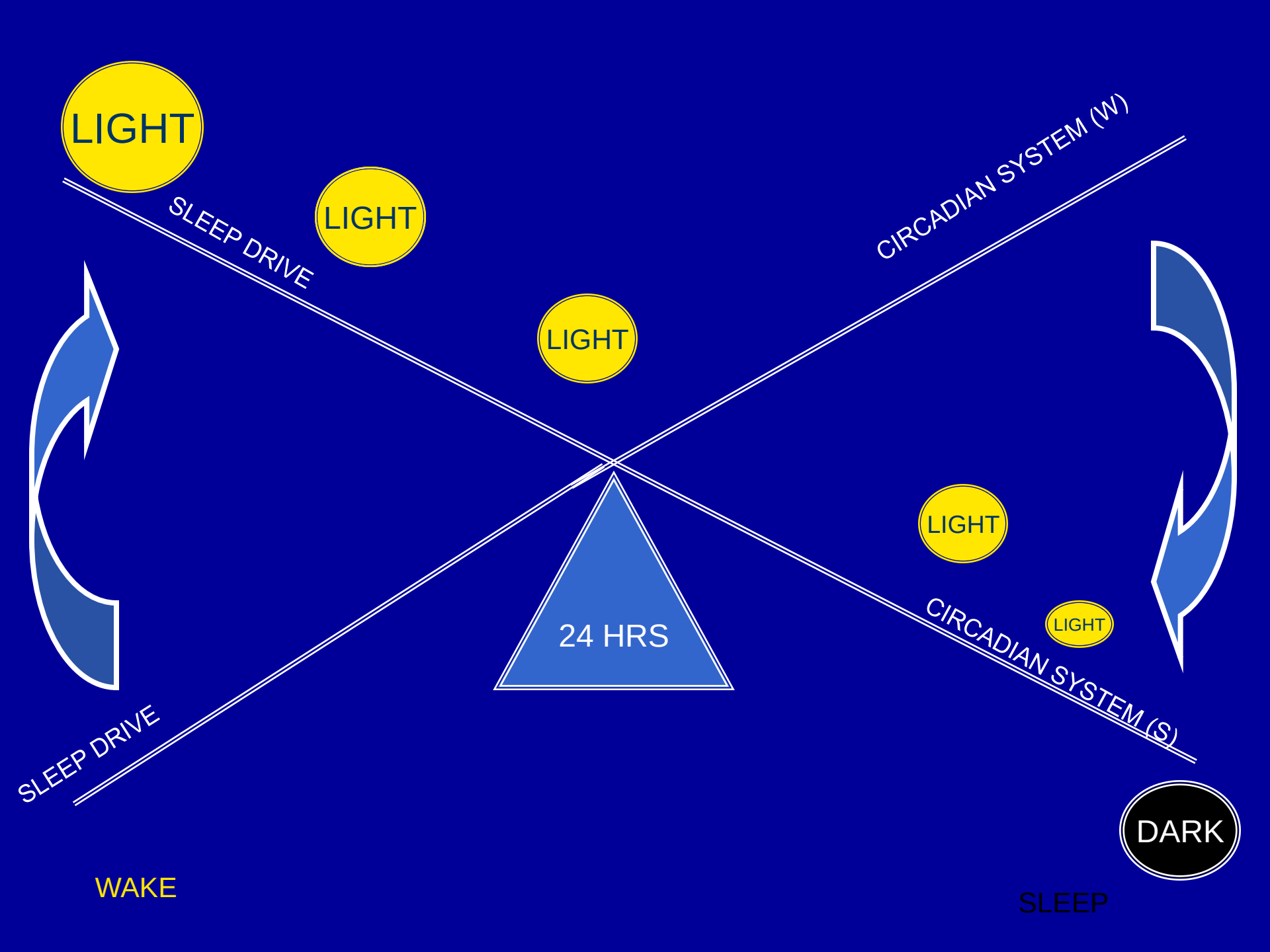
Adapted from Zee P, Herzog ED, Tosini D. *Semin Cell Dev Biol 2001; 12:295-303*

Circadian Pacemaker Physiology

- Retinal photoreceptors entrain SCN via light's effect on the photopigment *melanopsin*
  - most sensitive to blue wavelength light
  - shifts the circadian system & suppress melatonin
- Light exposure in normal, entrained individual:
  - morning (dawn) resets pacemaker to earlier time
  - evening (dusk) resets pacemaker to later time

Sleep Systems

- Homeostatic
  - Dependent upon duration of time w/o sleep
  - As we stay awake, sleep tendency builds
  - Analogy: longer w/o food, hunger increases
- Circadian
  - Wakefulness supported by light exposure
  - Decreasing light exposure: sleep tendency increases


LIGHT
LIGHT
LIGHT
LIGHT
LIGHT
SLEEP DRIVE
CIRCADIAN SYSTEM (W)
24 HRS
SLEEP DRIVE
CIRCADIAN SYSTEM (S)
DARK
WAKE
SLEEP

Circadian Related Sleep Disorders (CRSDs)

- Homeostatic/circadian misalignment: CRSDs symptoms appear

- Circadian system generates a clock-dependent alerting process during the waking hours & attempting sleep at the “wrong circadian phase” undermines sleep quality:
  - shortens duration because of the competing circadian arousal process
  - shortened sleep duration leads to an increase in homeostatic sleep drive

Treatments for CRSDs

- Prescribed sleep scheduling (*chronotherapy*)
- Circadian phase shifting (“resetting the clock”)
- Meds promoting sleep/wakefulness to counteract symptoms generated by the circadian misalignment & sleep deprivation

Prescribed Sleep Scheduling

Chronotherapy:

- first coined to describe a treatment for DSPD that involved prescribed scheduling of sleep times
- establishing an optimal schedule for shift workers based on circadian principles
- planned napping to counteract nighttime sleepiness in night shift workers

Circadian Phase Shifting with Timed Light Exposure

Goal: synchronize the circadian rhythm to the desired sleep schedule

Properly timed light exposure: useful for most of the CRSDs.

Circadian Phase Shifting with Timed Melatonin Administration

- Melatonin administration to animals can entrain free-running rhythms
- Melatonin can shift circadian rhythms in humans in a phase dependent manner.
- Human phase response curve (PRC):
  - Morning melatonin shifts rhythms later
  - Evening melatonin shifts rhythms earlier
  - melatonin PRC is about 180 degrees out of phase with the light PRC & in a sense, a **“darkness signal”**

Melatonin

- Not approved (FDA) as a drug, but widely available in the United States as a nutritional supplement
- Concerns raised about the purity/reliability of available preparations
- No serious adverse reactions have been documented
- Available formulations (3 mg) produce “pharmacologic” blood levels: typically peaking @10-fold higher concentration than physiological blood levels. Formulations that have a GLP (good laboratory practice) stamp are considered to be the most reliable
- A specific melatonin receptor agonist, ramelteon, licensed as a hypnotic in the U.S. in 2005
- Animal/human studies: phase shifting effects analogous to melatonin

Circadian Rhythm Sleep Disorders

(CRSDs)

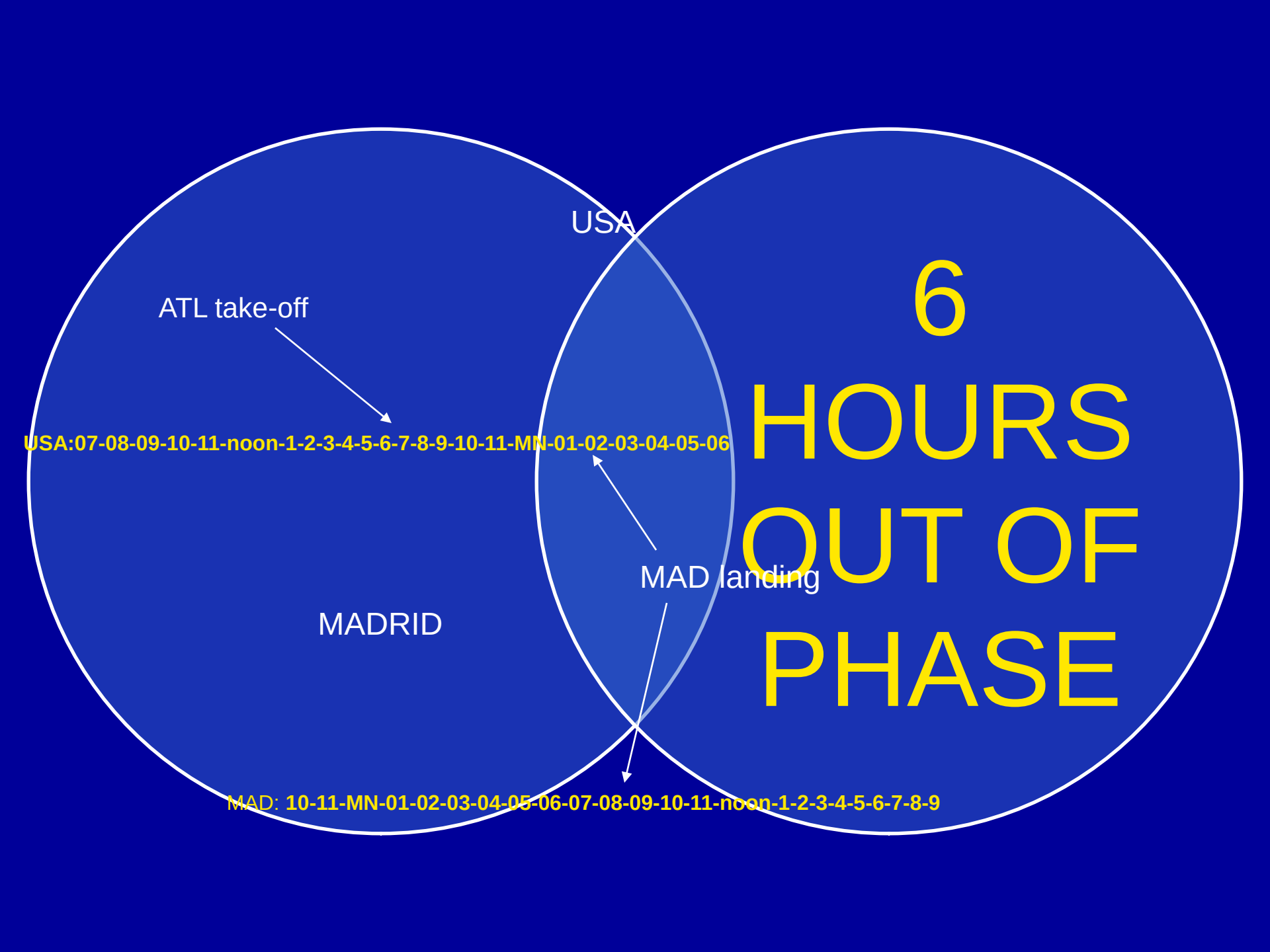
JET LAG DISORDER

- Circadian misalignment: crossing time zones too rapidly for the circadian system to keep pace

- The intensity & duration of the disorder are related to:
  1) the number of time zones crossed
  2) the direction of travel
  3) the ability to sleep while traveling
  4) the availability and intensity of local circadian time cues,
  5) individual differences in phase tolerance

- May take days to recover/resynchronize

- Usually benign/self-limited, but may be serious (pilot error, misjudged business negotiation)


USA
ATL take-off
USA:07-08-09-10-11-noon-1-2-3-4-5-6-7-8-9-10-11-MN-01-02-03-04-05-06
MAD landing
MADRID
MAD: 10-11-MN-01-02-03-04-05-06-07-08-09-10-11-noon-1-2-3-4-5-6-7-8-9
6
HOURS
OUT OF
PHASE

Jet Lag: Therapy

- Remain on home-based sleep schedule (if <2 days)
- Adjust sleep hours (eastward) to match destination sleep
- Adopt the sleep schedule of destination upon arrival
- Prior bright light to shift rhythms in desired direction
- Melatonin reduces jet lag symptoms/improves sleep
- Hypnotic use rational/consistent as in short-term insomnia

Shift Work Sleep Disorder

- Short/long term problems (insomnia & EDS):
  - Prevalence: 32% night & 26% rotating nights
  - Accidents @ work: double
  - pooled data: 18% ↑ w/ afternoon shift; 30% ↑ w/ night
- Medical conditions
  - GI: ulcers 4x; IBS 48%; pain 61-81%
  - CHD: esp. rotating shift workers; lipid abnormalities
  - Ischemic stroke risk factor
  - WHO: shift work w/ circadian disruption: probably a carcinogen in humans
  - Obesity risk increased

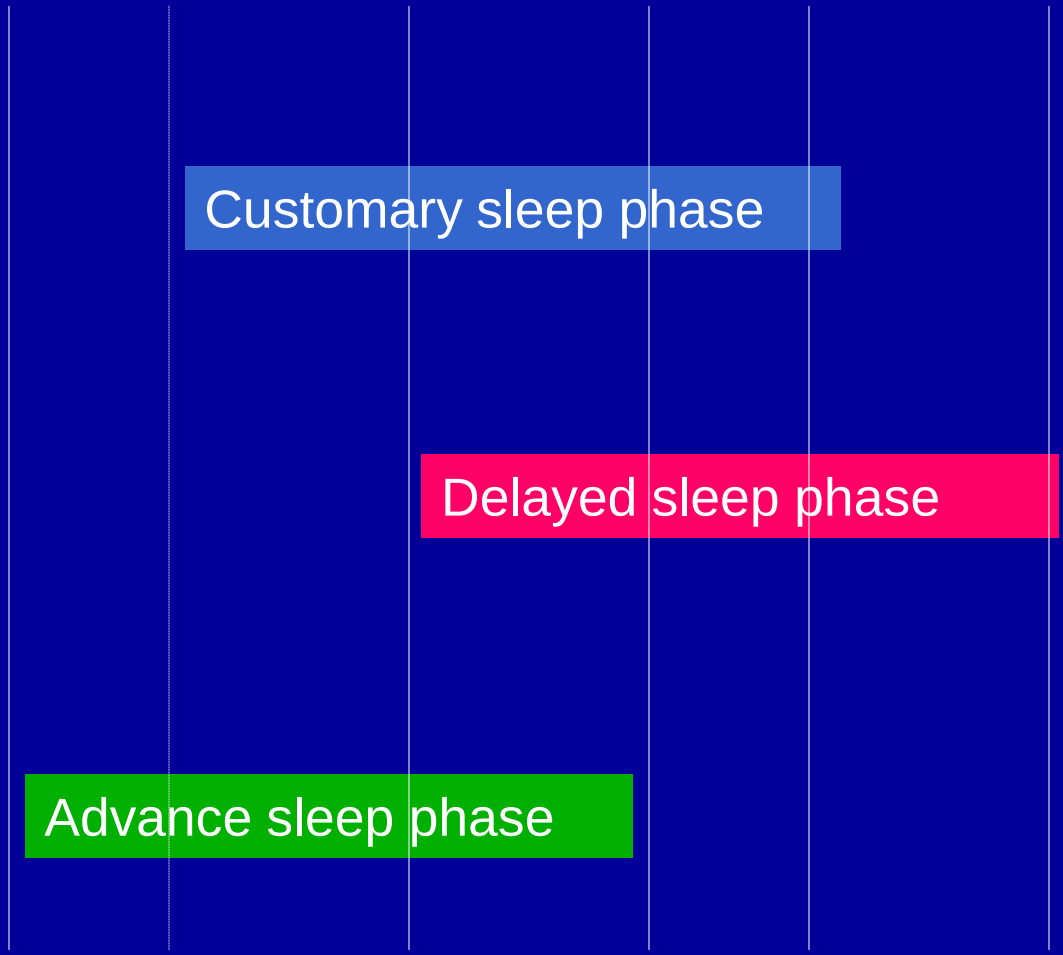
Shift Work Disorder: Treatment

- Bright light
- Planned napping
- Caffeine
- Pharmacologic agents
  - *Armodafinil*
  - *Modafinil*

CRSDs: Intrinsic + External Factors

- Advanced sleep phase disorder (ASPD)
- Delayed sleep phase disorder (DSPD)
- Free-running disorder (FRD)
- Irregular sleep-wake rhythm (ISWD)

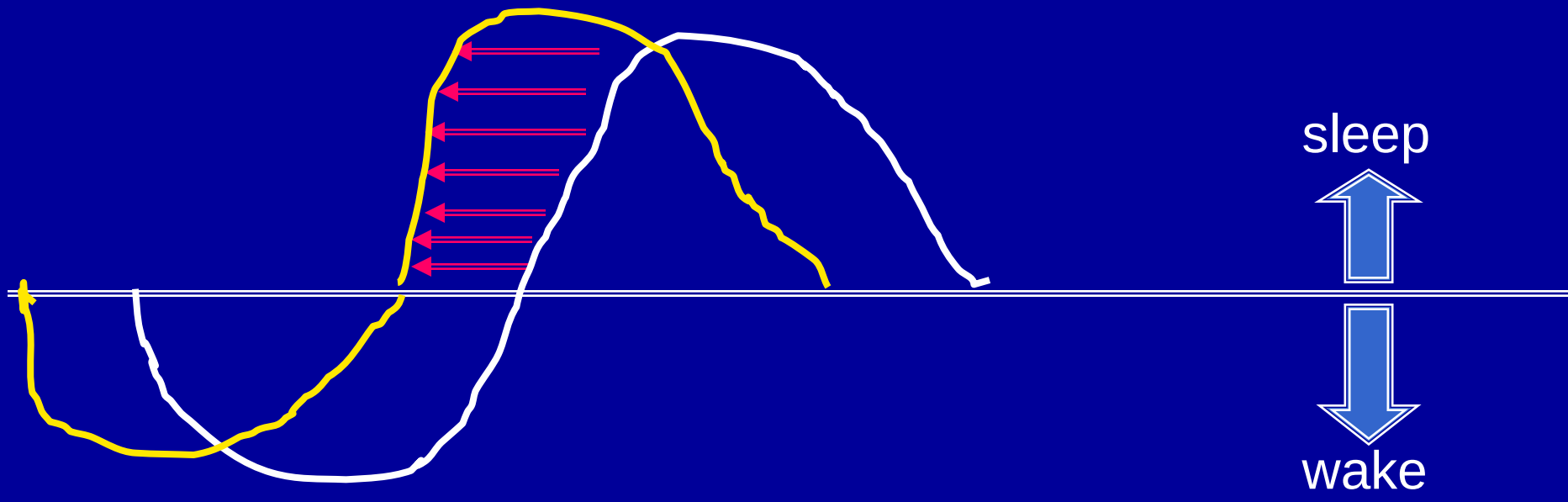
noon-1-2-3-4-5-6-7-8-9-10-11-MN-01-02-03-04-05-06-07-08-09-10-11



ADVANCED SLEEP PHASE DISORDER (ASPD)

- Stable schedule several hours earlier than conventional/desired time
- ASPD is thought to be much less common than DSPD
- Mechanism unknown: shorter circadian period in familial ASPD
- Characteristic associations:
  - advanced sleep phase
  - less total sleep time
  - increased wake time during the last 2 hours of sleep
- Pathologic qualification:
  - degree of difficulty experienced with conforming to desired sleep schedule
  - other causes of sleep maintenance insomnia must be ruled out: OSA, depression

Advanced Sleep Phase Disorder



Early evening

Late evening

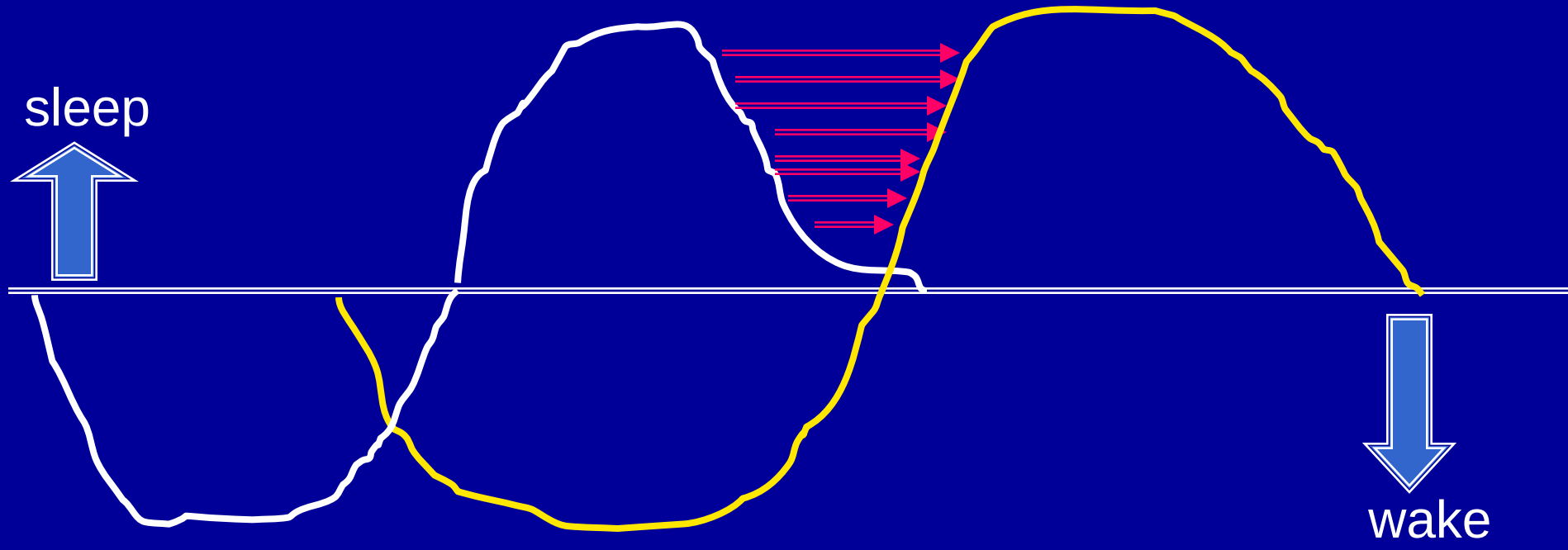
ASPD: Treatment

- Phase-advance chronotherapy: research required
- Timed bright evening light exposure:
  - Objective results conflicting
  - Subjective improvements consistently demonstrated
  - Lackluster: patients with early-morning awakenings
- Melatonin administration: insufficient data to assess

DELAYED SLEEP PHASE DISORDER (DSPD)

- Stable sleep schedule w/ onset later than standard/desired time
- DSPD patients: sleep onset insomnia & extreme difficulty arising
- Etiology: unknown - diminished ability to compensate for lost sleep & difficulty falling asleep even when previously awakened early
- Rare in older people (3.1%); common in teens (psychopathology?)
- Psychophysiological insomnia: the major differential to consider

Delayed Sleep Phase Disorder



Normal bedtime

Very late evening/early morning

DSPD: treatment

- Prescribed Sleep Scheduling or *chronotherapy*
- Timed AM light exposure to advance rhythms
- Timed melatonin administration: evidence strong that melatonin timed to promote a corrective phase advance is an effective treatment for DSPD
- Chronic nightly melatonin agonist (ramelteon) x 90 days

FREE-RUNNING DISORDER (FRD): NON–24 HOUR SLEEP-WAKE SYNDROME.

- Circadian cycles mimic those in time-free environments & reflect a failure of entrainment
- Very rare in normally sighted people, but common in the totally blind with absent entrainment from light/dark cycle
- In sighted people: ~25% w/ psychiatric disorders
- Prodromal DSPD seen in ~25%
- Onset: teens & rarely after age 30 (males>females)

FRD: Treatment (sighted)

- Timed (morning) bright light exposure
- Melatonin administered around the hour of the desired bedtime
- Melatonin agonist (ramelteon) presumably

FRD: Treatment (Blind)

- Prescribed sleep/wake scheduling
- Timed melatonin administration: 0.5-10 mg
- Treatment must be sustained (relapse) as entrainment may not occur for weeks or months after initiating treatment

IRREGULAR SLEEP-WAKE RHYTHM (ISWR)

- Relative absence of a circadian pattern to s-w cycle
  - Sleep volume may be normal, but fractured into distinct bouts
  - Bouts shortened & in the extreme almost randomly distributed
  - Can result from extremely poor sleep hygiene in healthy people
  - Commonly associated with neurological impairment

- Causes: likely damage to SCN or its central connections (ablation studies in exp. animals) w/ loss of rhythmicity

- Prevalence increases with age secondary to increased prevalence of associated medical disorders; age itself is not an independent risk factor

IRREGULAR SLEEP-WAKE RHYTHM (ISWR): Treatment

- Bright light exposure
  - daytime: may improve sleep & wake consolidation in NH patients w/ AD & ISWR
  - effect modest
  - more data needed
- Melatonin:
  - available data: no support at least in association with AD
  - impact of melatonin & melatonin receptor agonists has yet to be determined
- Combinations of the above: more research needed
- Hypnotic medication: no published reports of controlled trials; the absence of rigorous, well-controlled clinical trials of pharmacological treatments for sleep disturbance in demented patients represents a serious & continuing gap in our knowledge