



"For the greatest benefit to mankind"
Alfred Nobel



The Nobel Assembly at Karolinska Institutet has today decided to award the

2017 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

to:



**Jeffrey C. Hall
Michael Rosbash
Michael W. Young**

"for their discoveries of molecular mechanisms controlling the circadian rhythm"

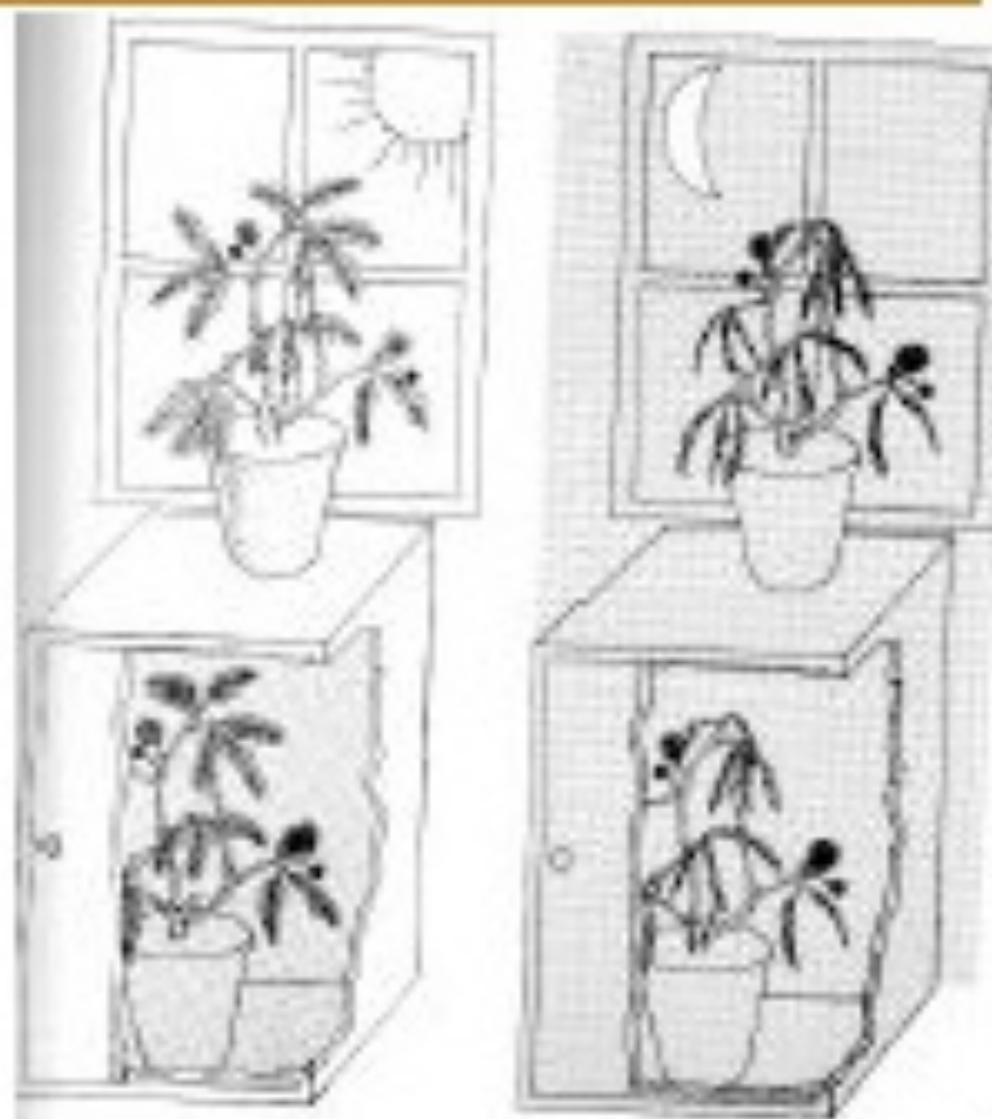
L'esperimento di Jean-Jeaques d'Ortous deMarain

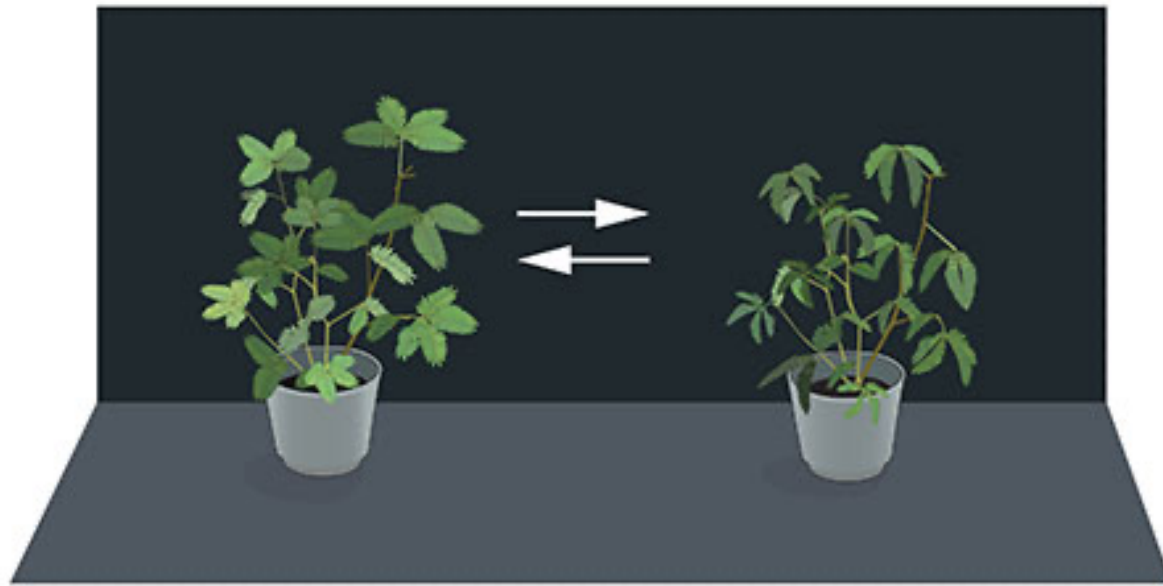
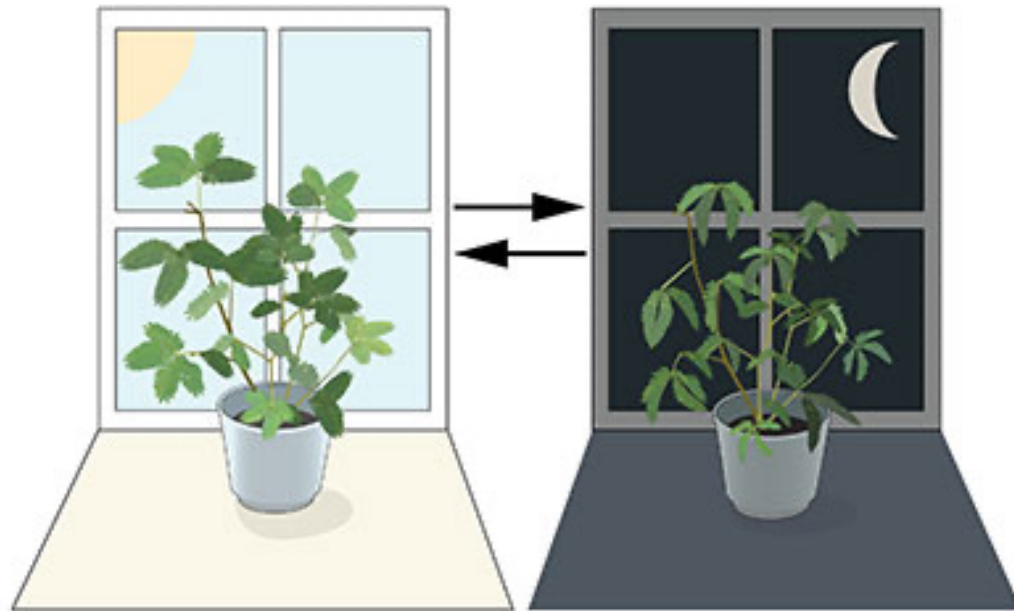




Jean Jeacques d'ortous deMairan - 1729⁴

- 1st experiment of biological rhythms
- Heliotrope plant opened its leaves during the day
- Maintained the rhythm when placed in a light-proof box.
- **No external cues necessary to cause this rhythm**





🕒 Ritmi biologici 🕒

Tipi di ritmi:

1. Ultradiani (NREM-REM, Basic Rest-Activity Cycle, respirazione)
2. Circadiani (ciclo sonno-veglia)
3. Infradiani (ciclo mestruale)
4. Circannuali (ciclo riproduttivo)

Biological Rhythms

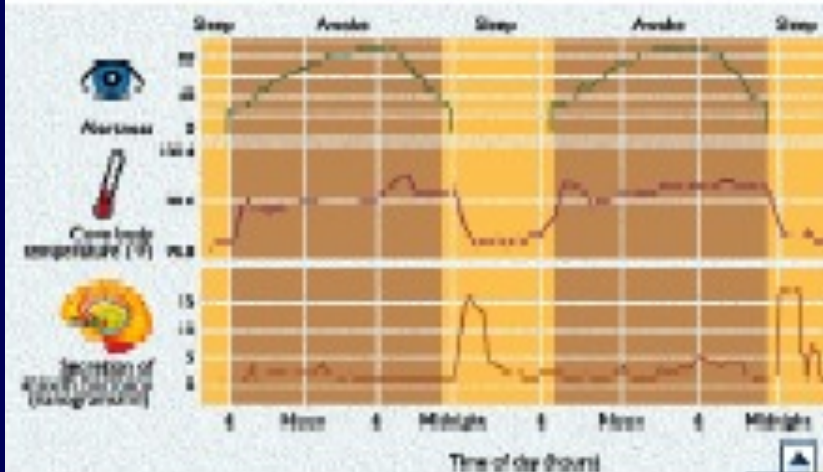
Periodic fluctuations in physiological functions

1 yr.
28 days
24 hrs
90 mins



24 Hour Circadian Rhythm

Affects alertness, body temperature, and hormone secretion



Diurnal variation in temperature

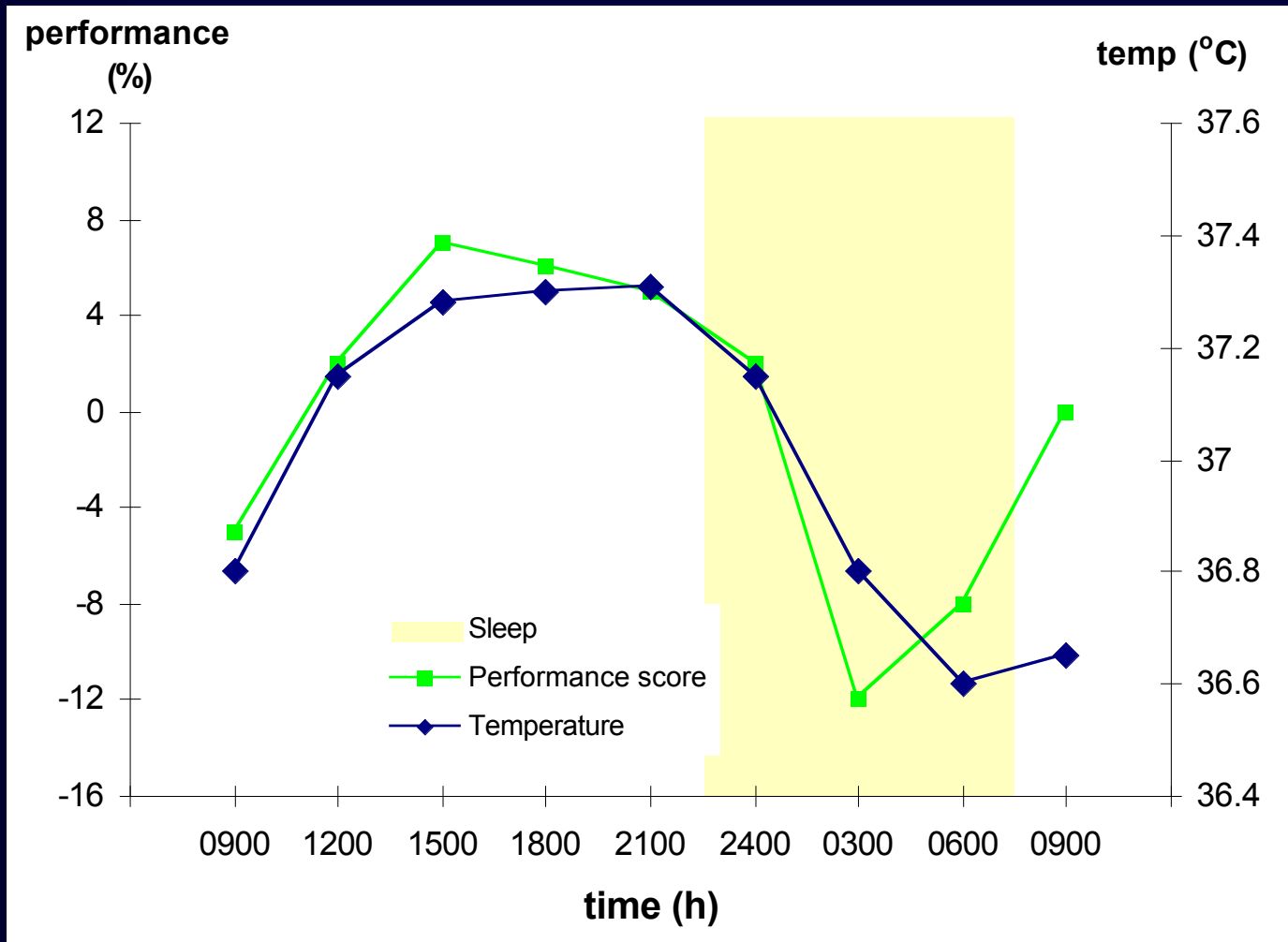
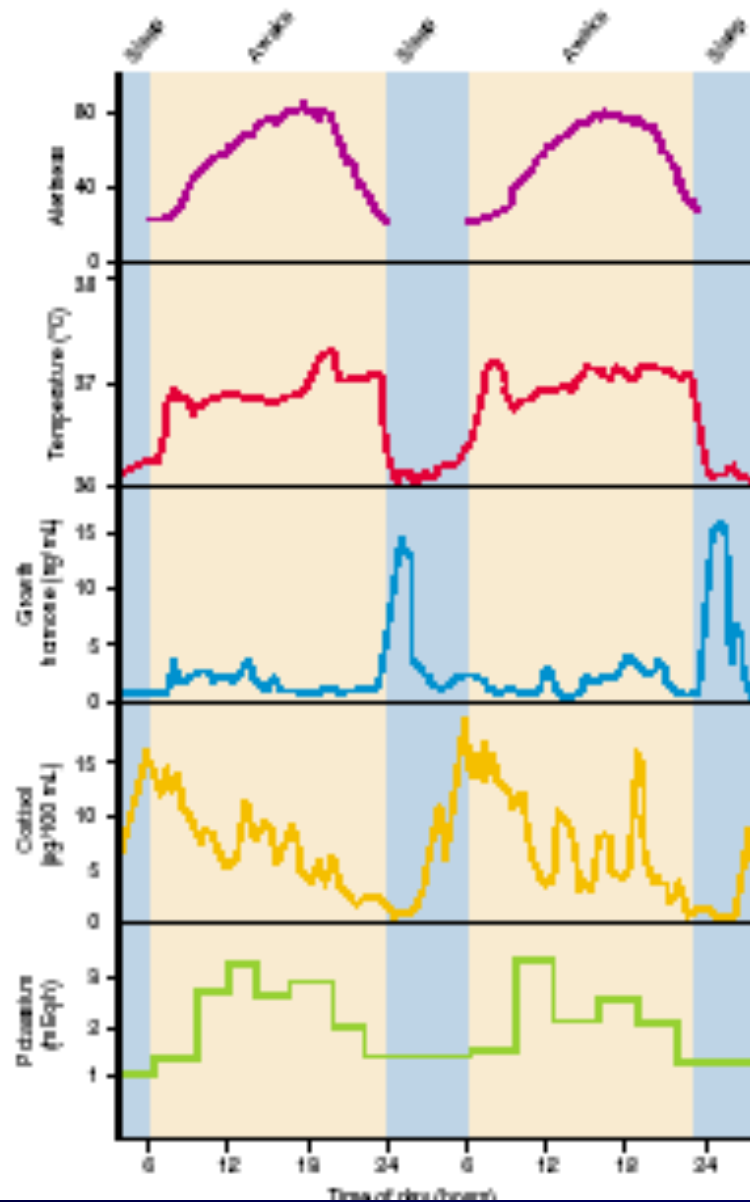
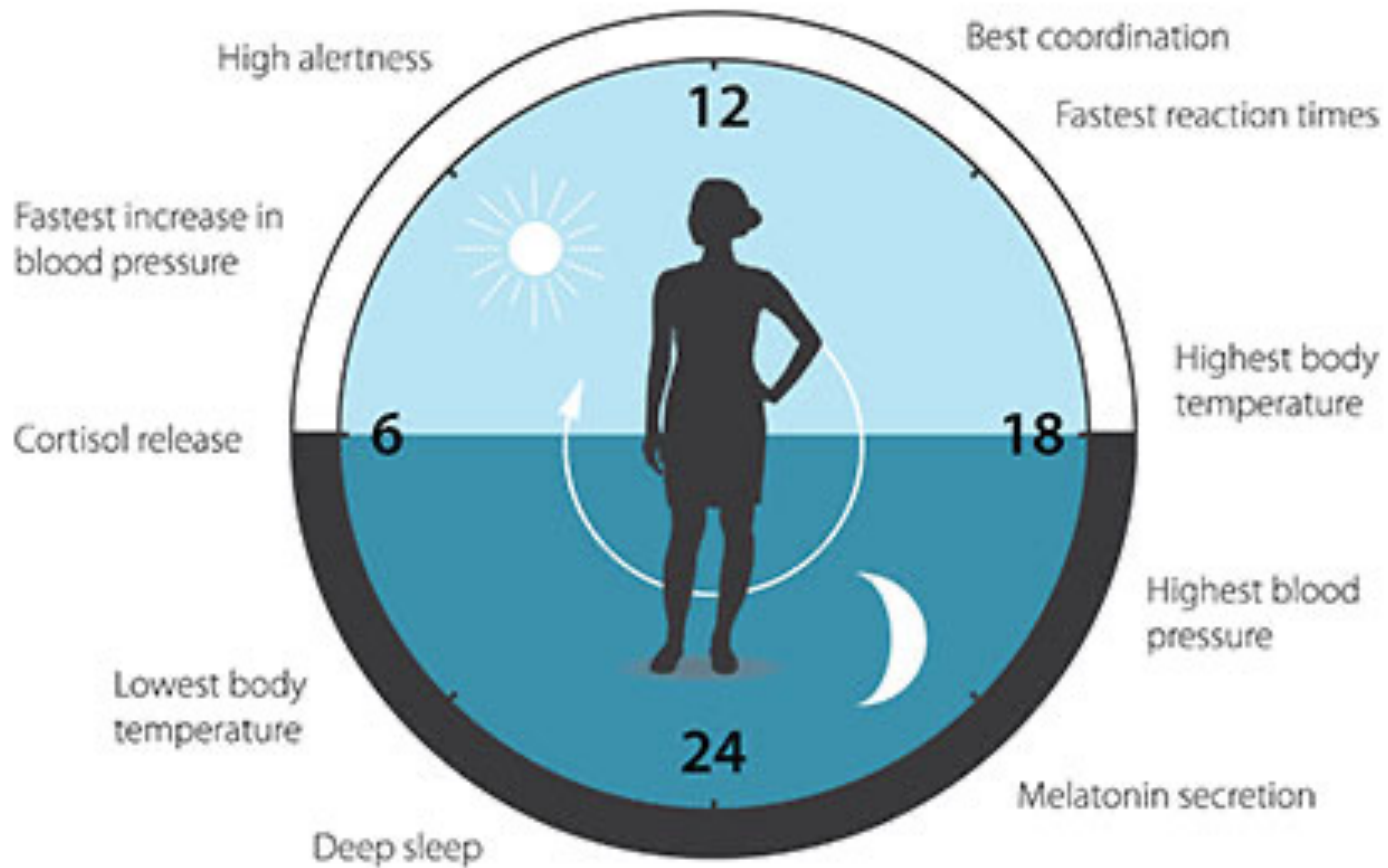


Figure 19.15

Circadian rhythms of physiological functions. Fluctuations over two consecutive days are shown here. Alertness and core body temperature vary similarly. Growth hormone and cortisol levels in the blood, however, are highest during sleep, although at different times. The bottom graph shows the excretion of potassium by the kidneys, which is highest during the day. (Source: Adapted from Coleman, 1996, Fig. 2.1.)



Orologi Biologici e Comportamento



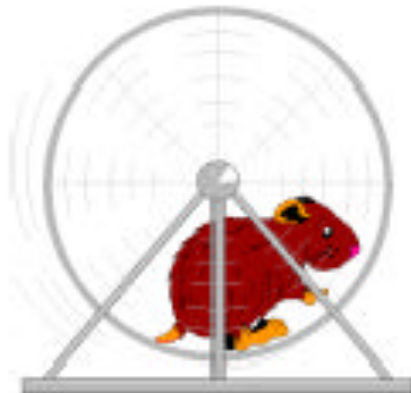
Measuring biological rhythms



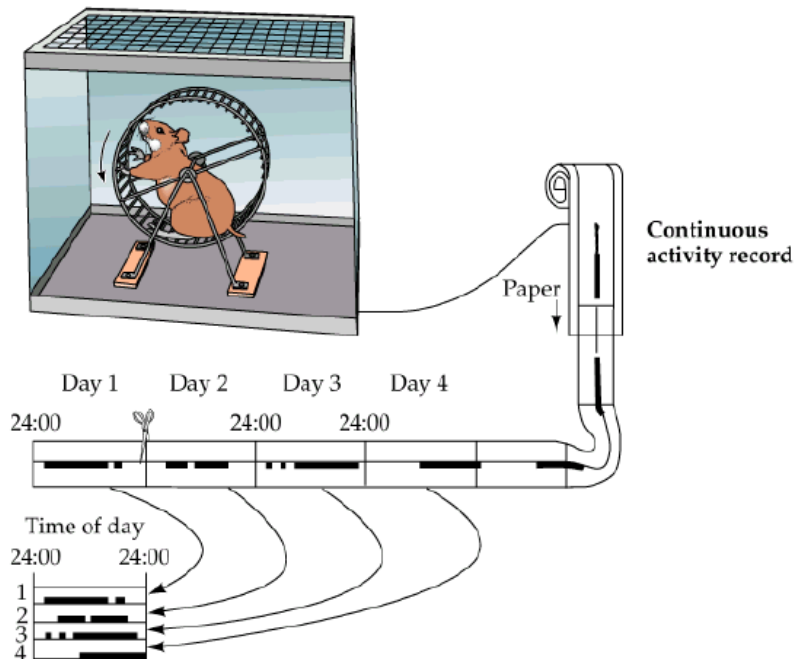
Measuring Circadian Rhythms

8

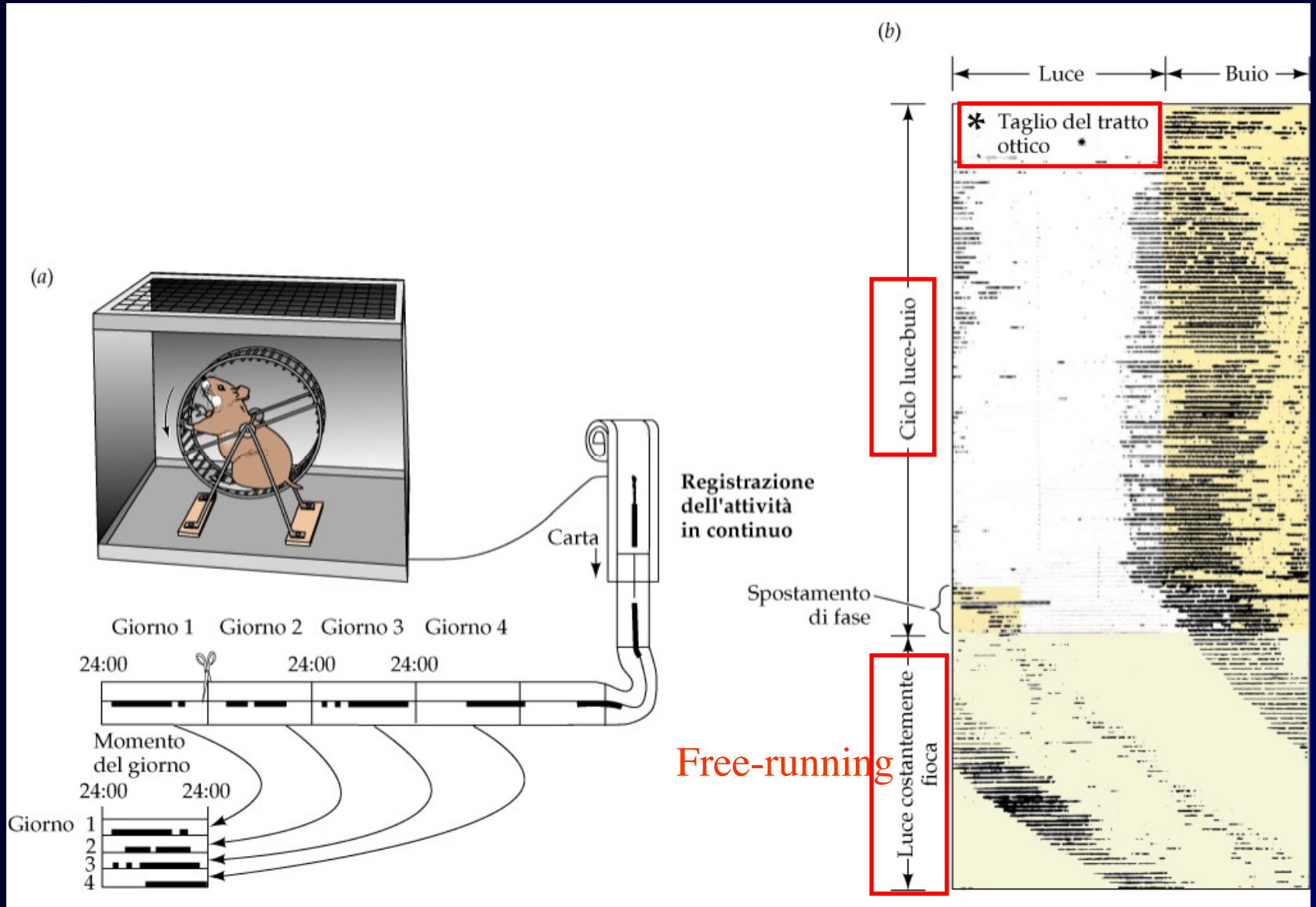
- Event records (*activity records*) are used to depict one measurement over a very long period of time
 - Place an animal in a cage that has a running wheel that they can enter at will.
 - A computer records the number of wheel revolutions during each minute for weeks or months at a time

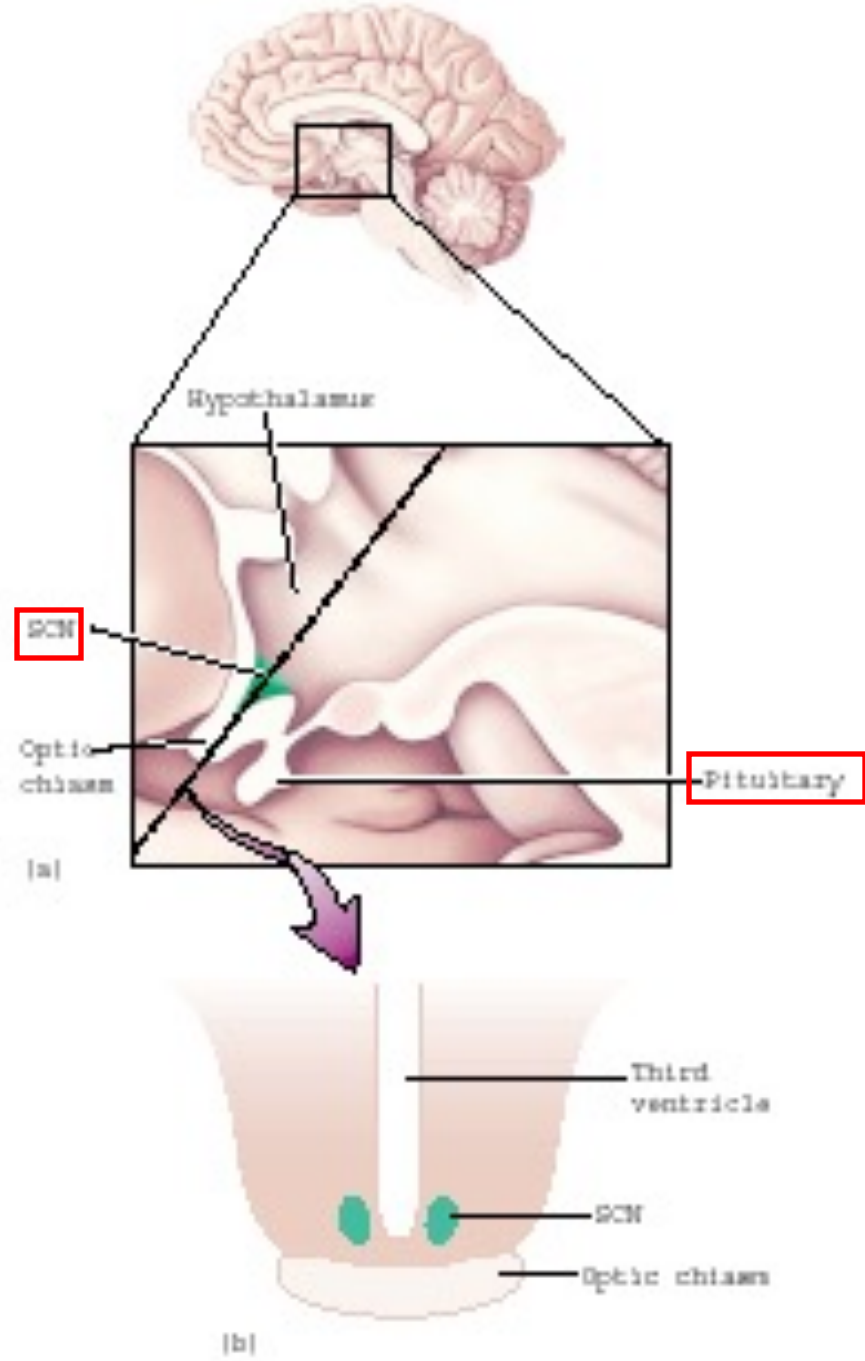


(a)

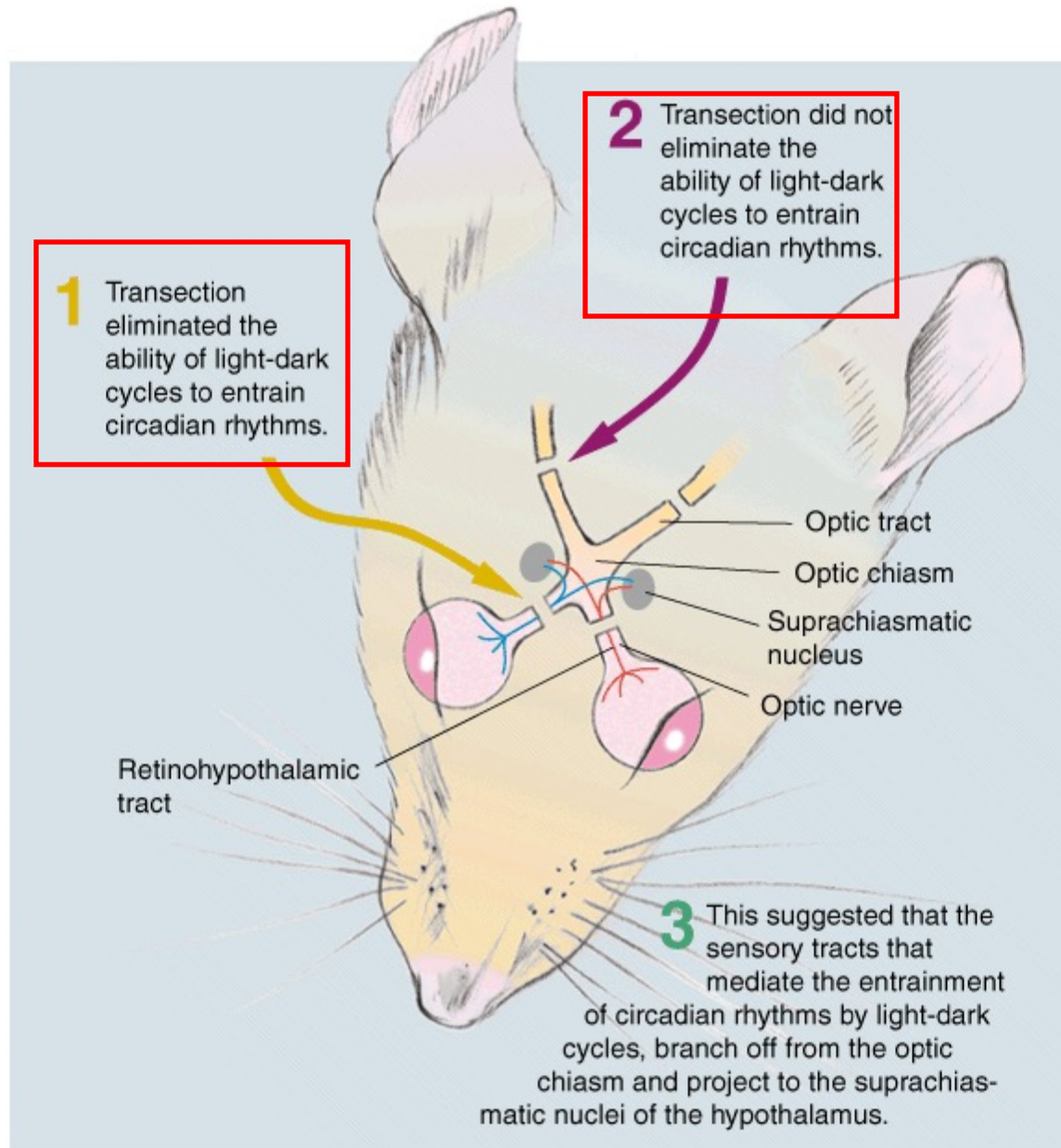


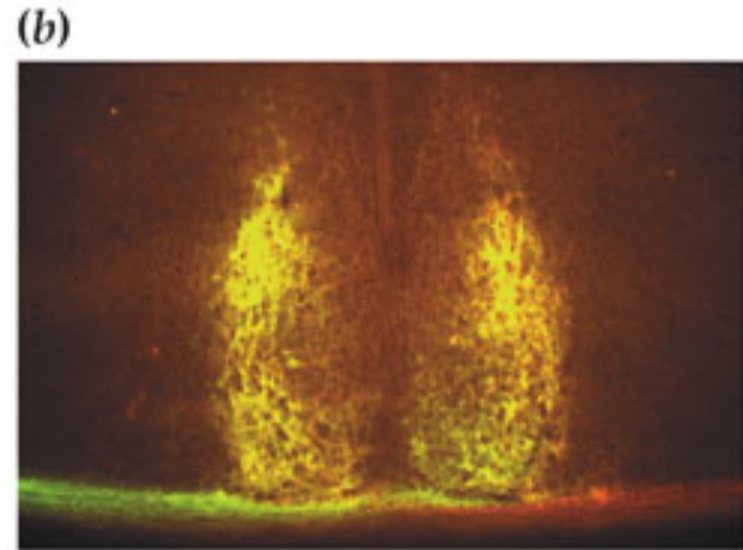
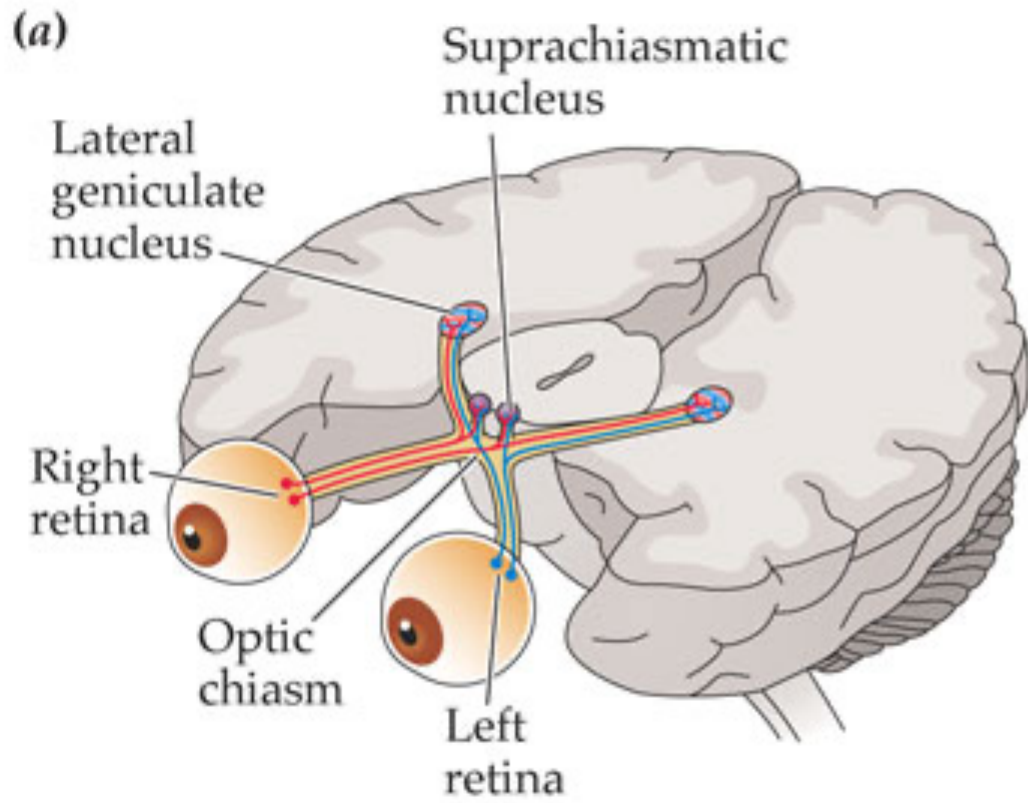
I RITMI BIOLOGICI



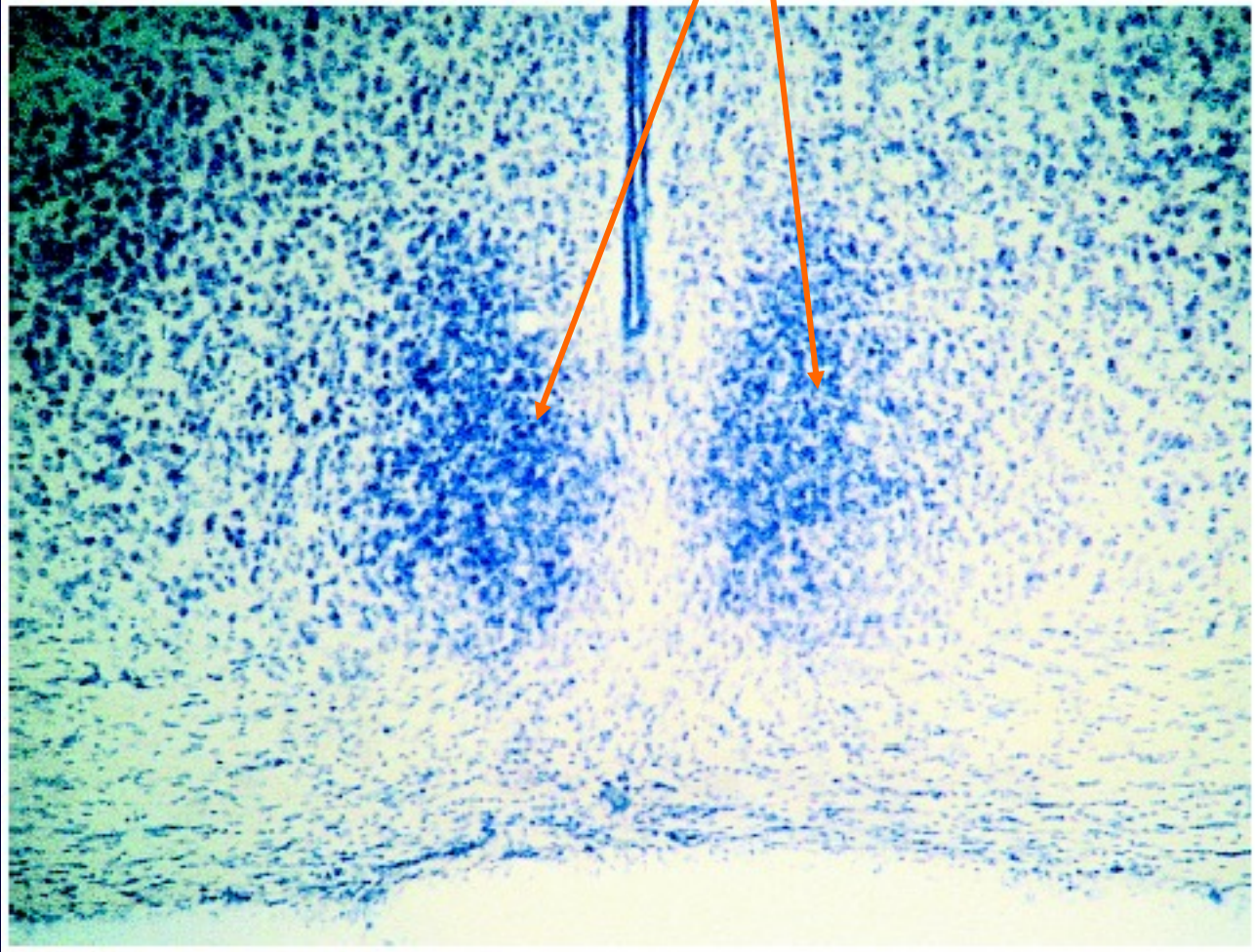


► Discovery of the Retinohypothalamic Tracts



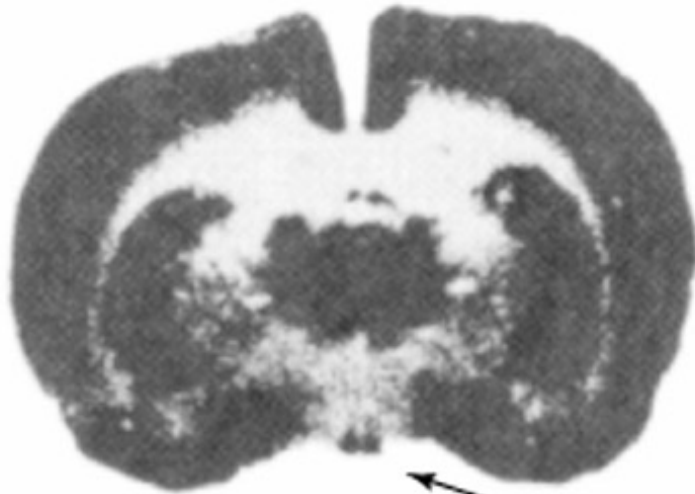


I nuclei soprachiasmatici dell'ipotalamo

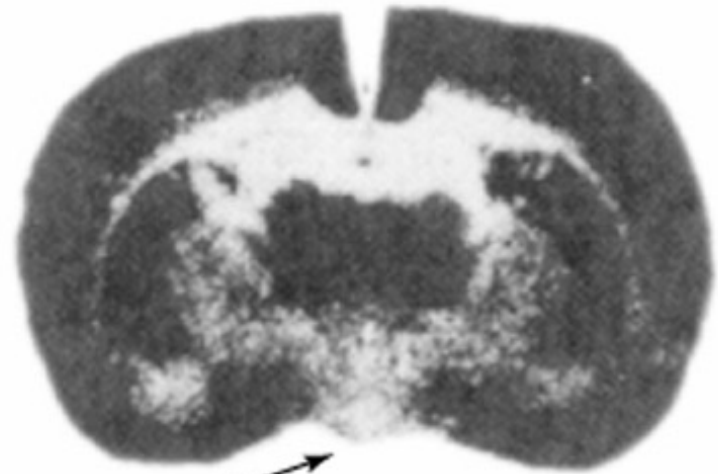


Ritmo circadiano dell'attività metabolica del nucleo soprachiasmatico dell'ipotalamo

(a) Fase alla luce



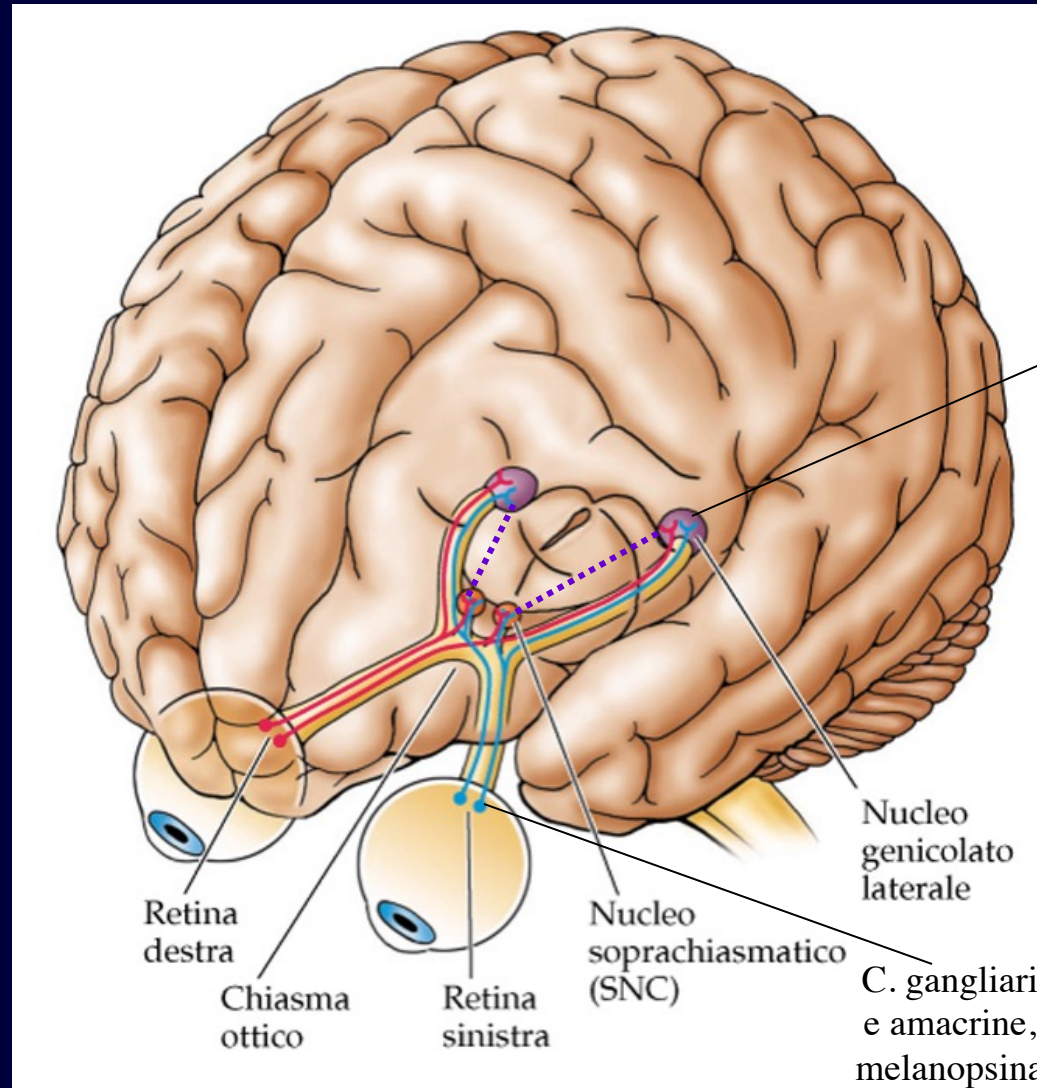
(b) Fase al buio



Il NSC distingue il giorno dalla notte

L'attività metabolica non è legata solo alla presenza di luce, ma è sincronizzata anche a un ritmo endogeno

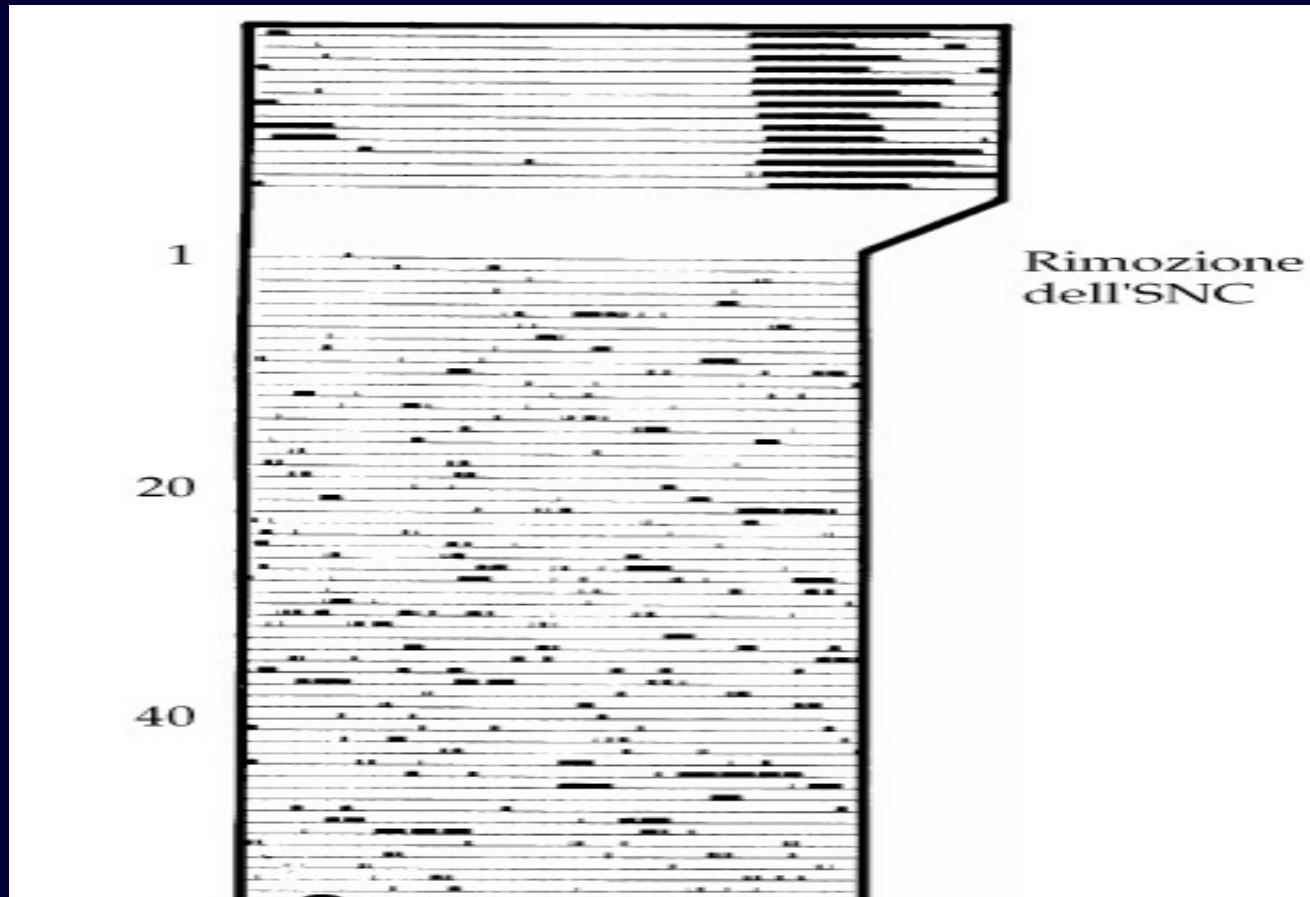
Una via diretta retino-ipotalamica permette la sincronizzazione dei ritmi endogeni scanditi dal pacemaker circadiano con gli *Zeitgebers*



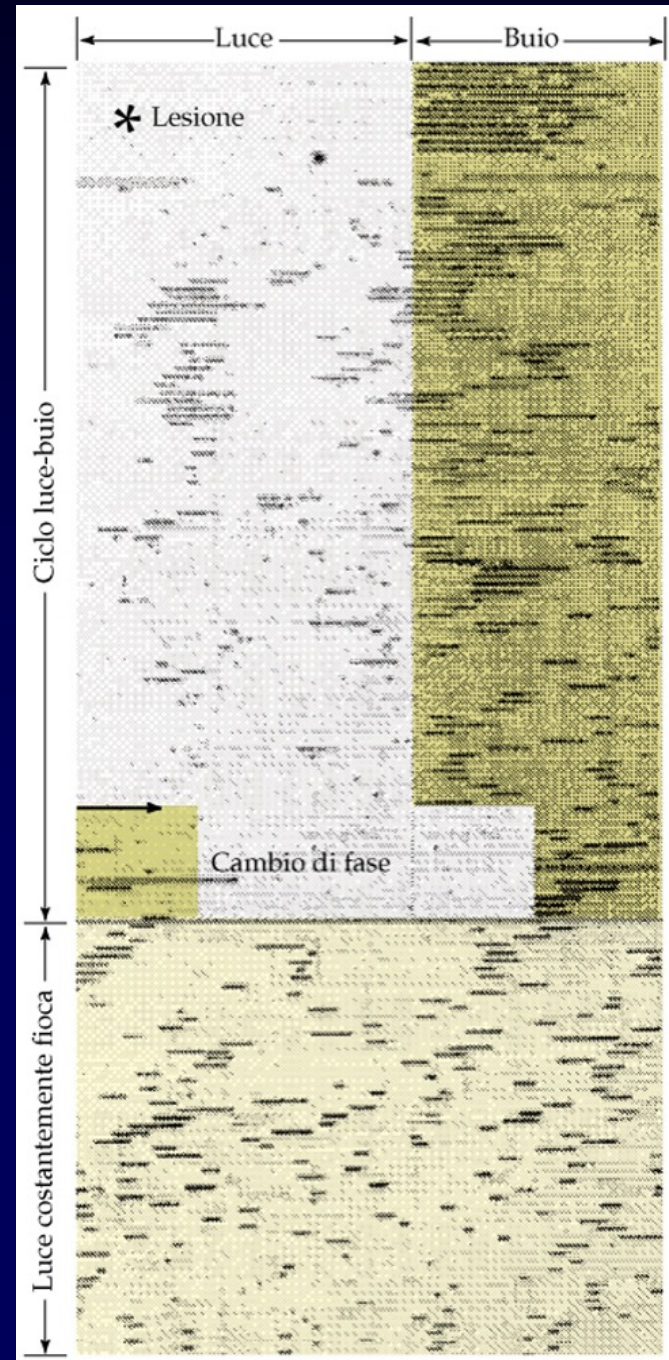
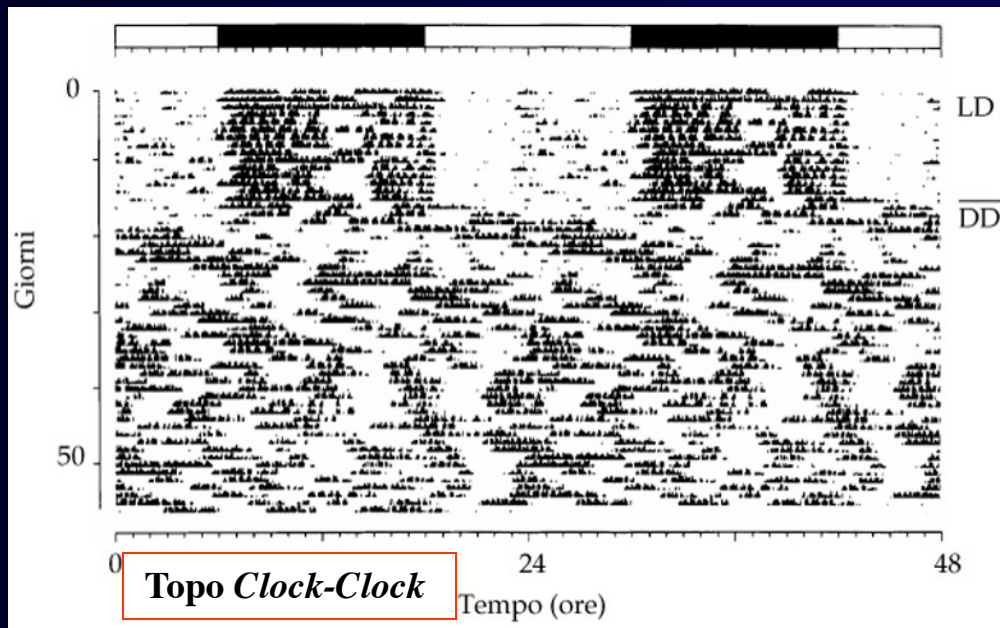
Via indiretta dal foglietto intergenicolato

C. gangliari e amacrine, melanopsina

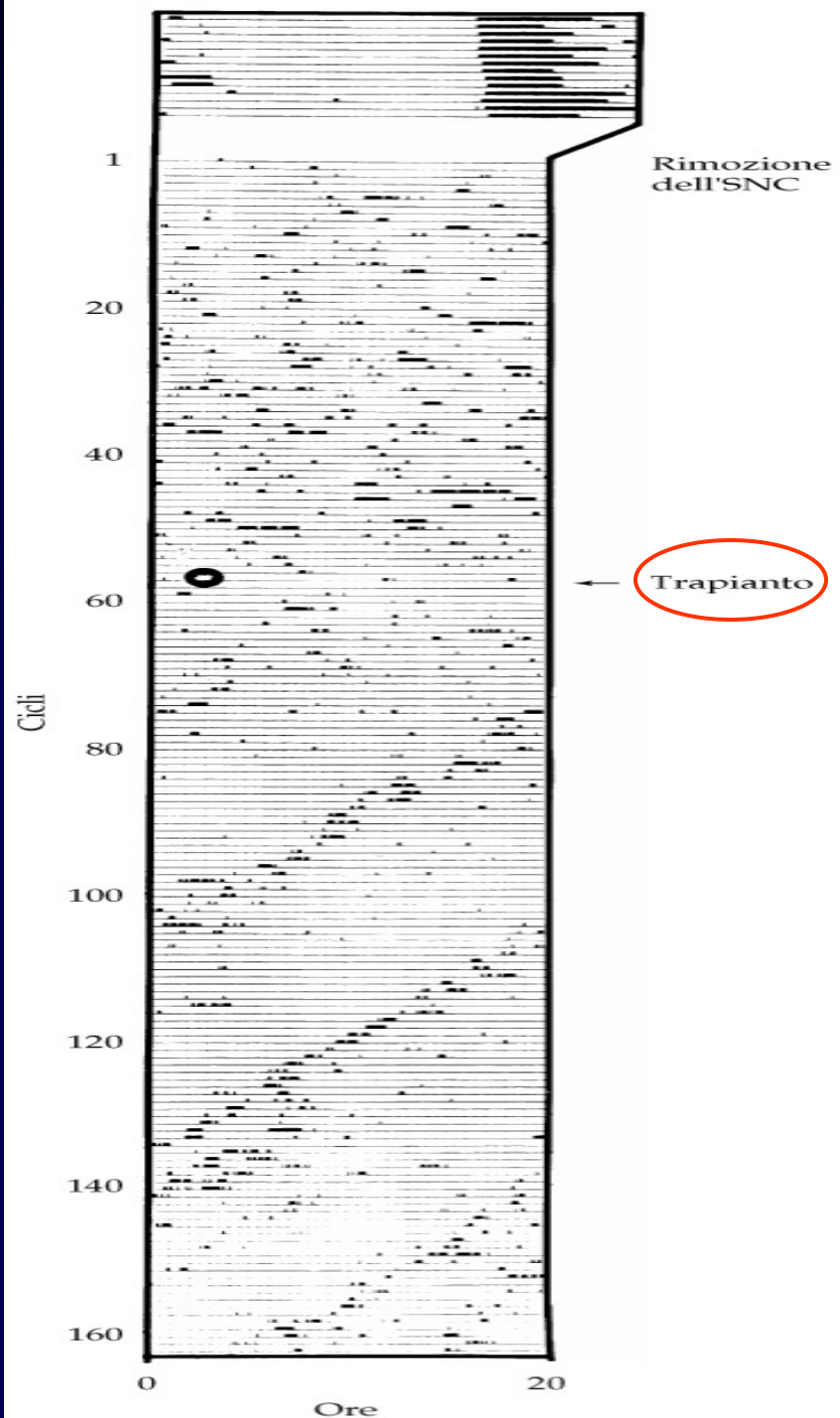
Il NSC contiene un 🕒 “orologio”



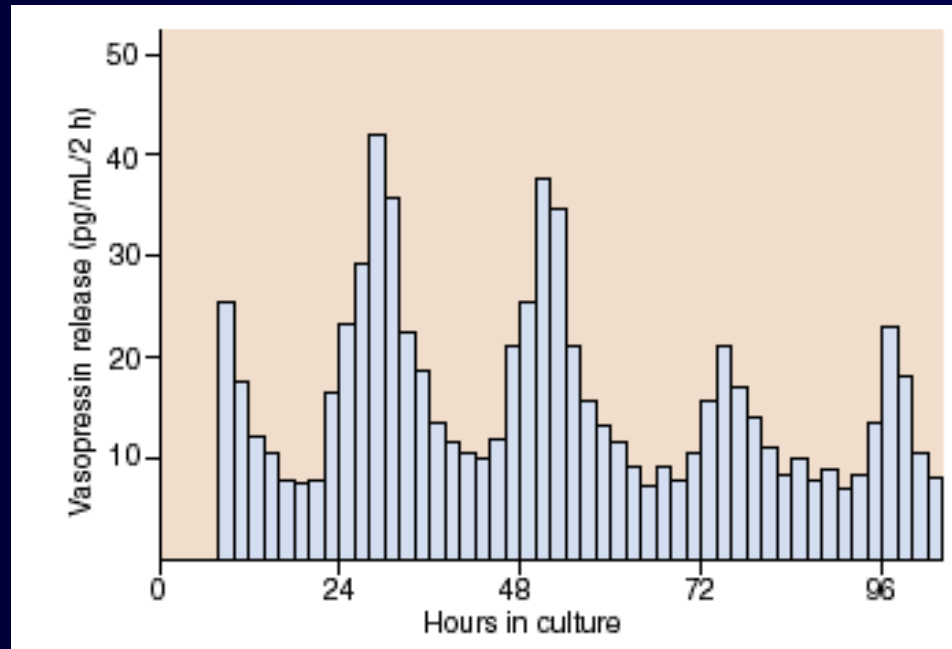
La distruzione del NSC fa perdere la sincronizzazione dei ritmi endogeni con gli *Zeitgebers* e altera vari ritmi comportamentali e ormonali (corticosteroidi)



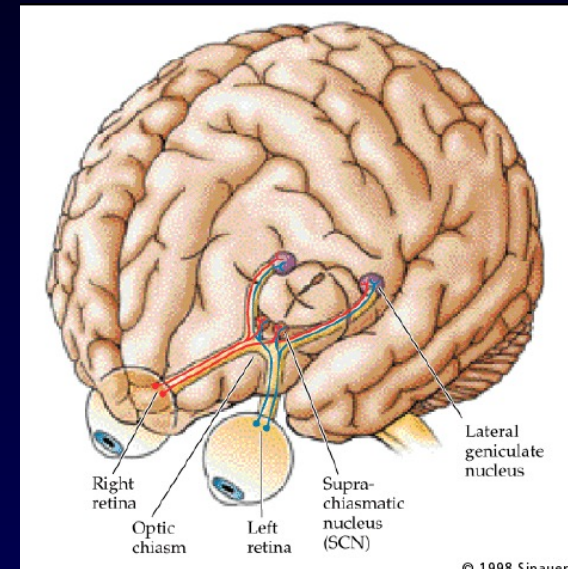
Il trapianto del NSC
ristabilisce la
sincronizzazione dei
ritmi endogeni con gli
Zeitgebers anche se
viene effettuato in
zone diverse del
cervello: **un segnale
chimico controlla i
ritmi circadiani**



Nucleo sovrachiasmatico in coltura mantiene una ritmicità circadiana nella liberazione di vasopressina

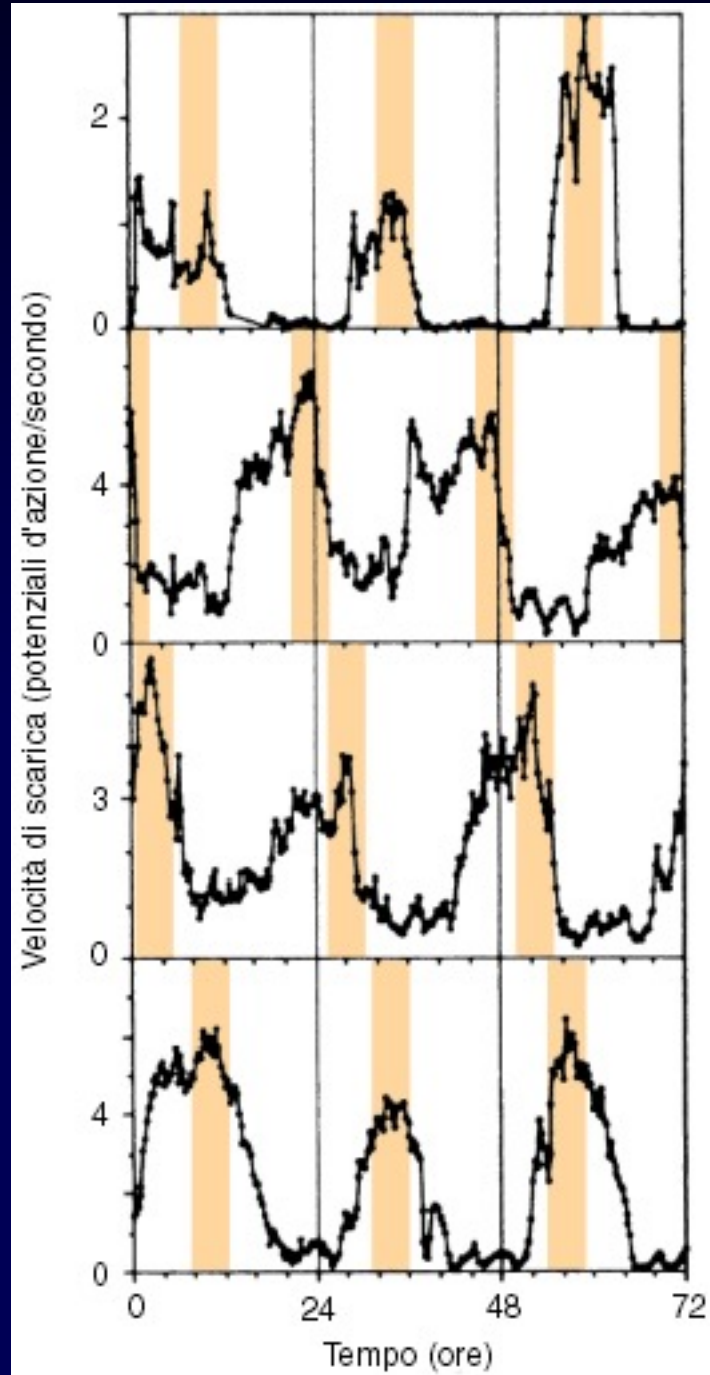


Suprachiasmatic nucleus is master pacemaker



1. Lesions of suprachiasmatic nucleus abolish free-running rhythms
2. Activity in suprachiasmatic nucleus correlates with circadian rhythms
3. Isolated suprachiasmatic nucleus continues to cycle
4. Transplanted suprachiasmatic nucleus imparts rhythm of the donor

Ciascun neurone del NSC
contiene un "orologio"
(un ritmo circadiano
individuale e indipendente
di attività)



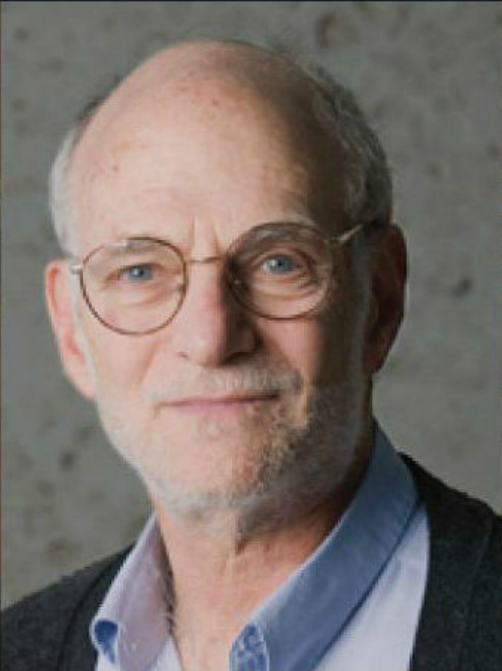
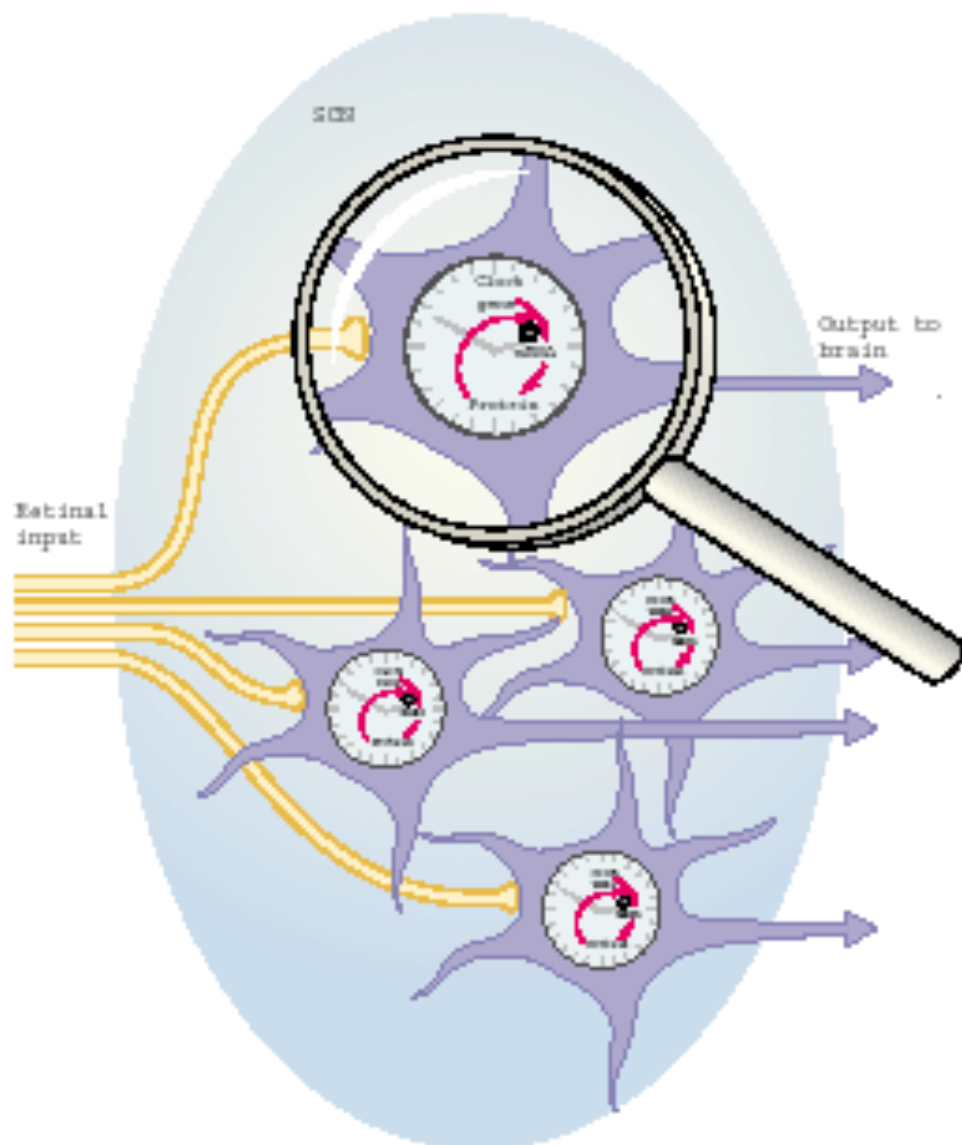


Figure 18.20
 clock genes. in the scn, clock genes produce proteins that inhibit further transcription. genes and the firing rate of individual scn neurons cycle up and down over 24 hours. the cycles of n are synchronized by light exposure (input from the retina).



LA SCANSIONE DEL TEMPO

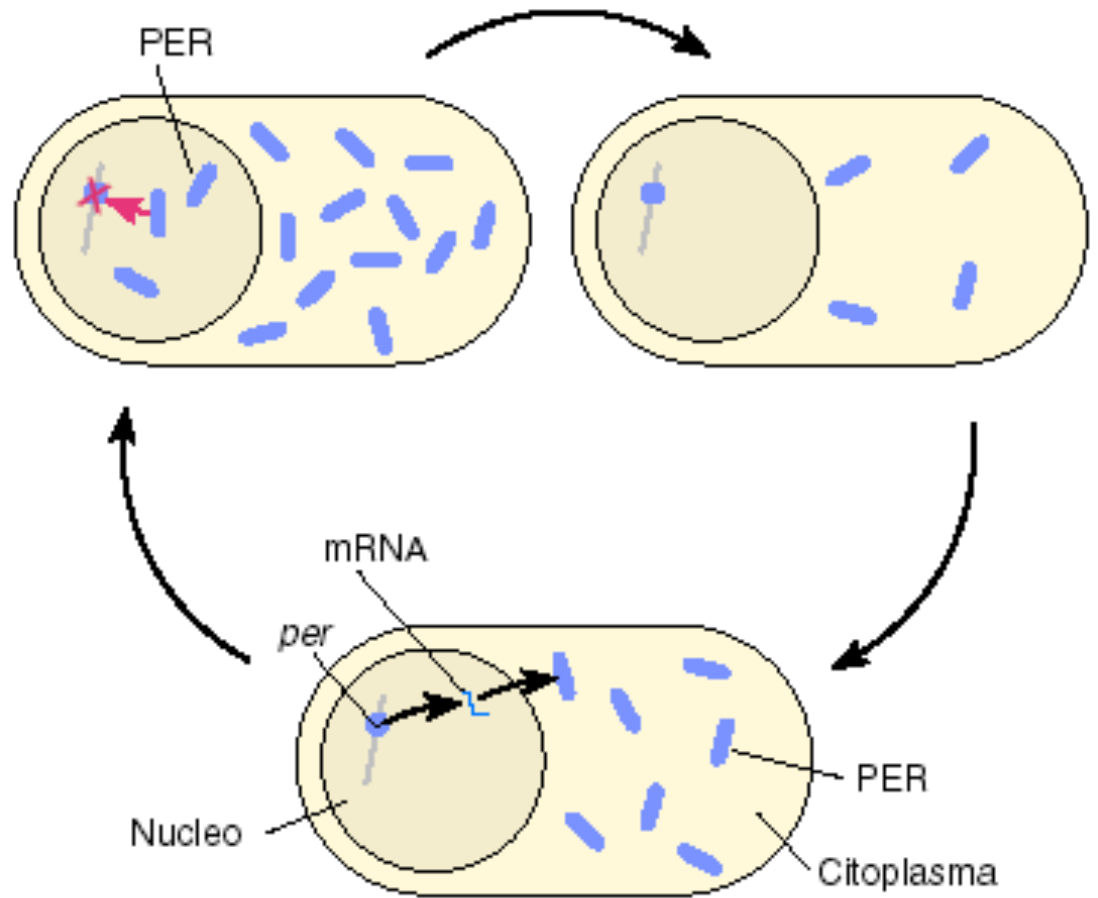
INTRACELLULARE:

ruolo ipotetico di alcune proteine

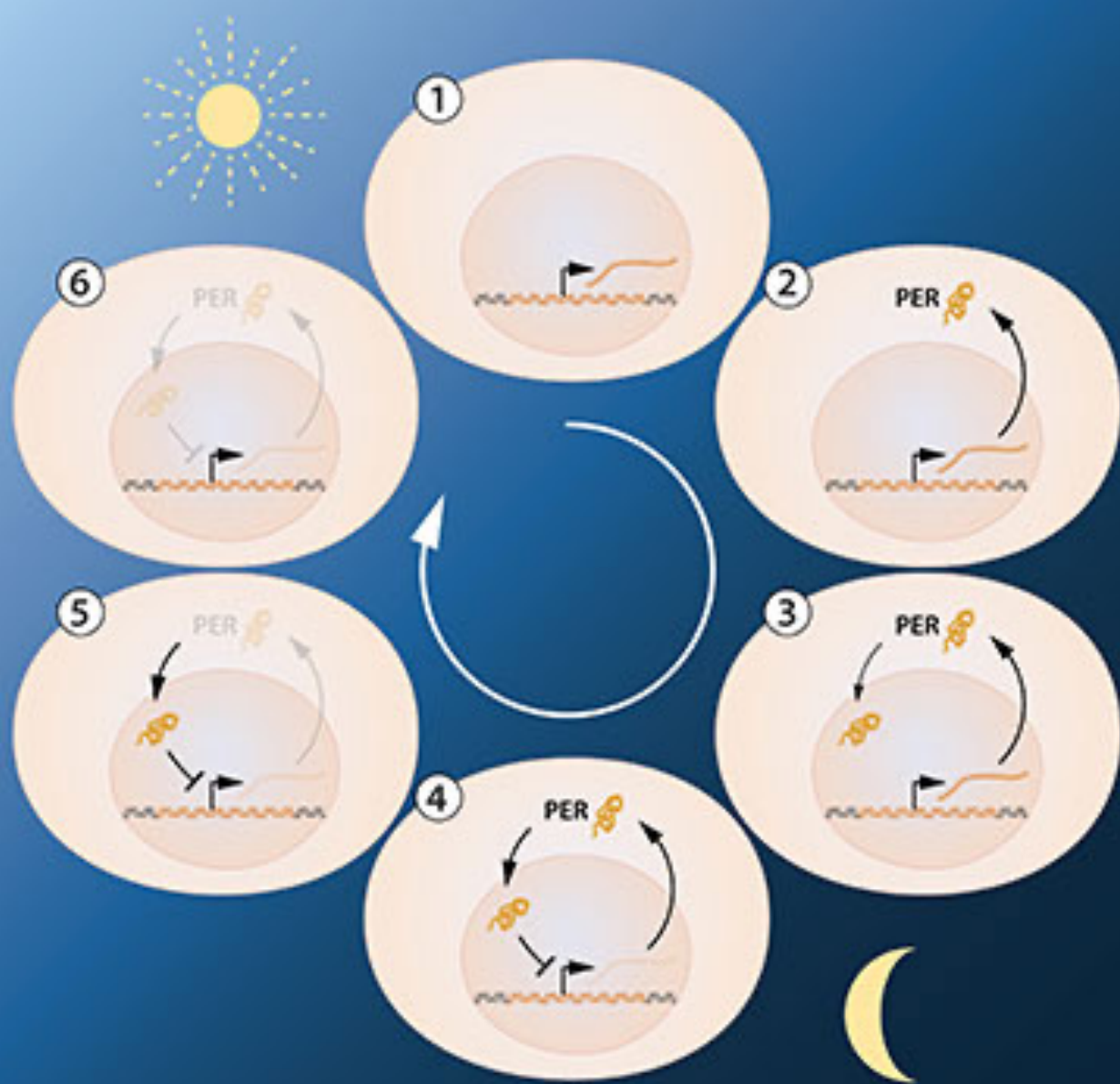
(principalmente la proteina PER -*Period*-) nel controllo dei ritmi circadiani

La proteina PER entra nel nucleo, sopprimendo il gene *per*, responsabile della sua sintesi. La produzione di RNA messaggero si blocca.

Il livello di PER si riduce, al punto che il gene *per* si attiva di nuovo.



Il gene *per* è attivo; l'RNA messaggero lascia il nucleo e induce la sintesi di PER



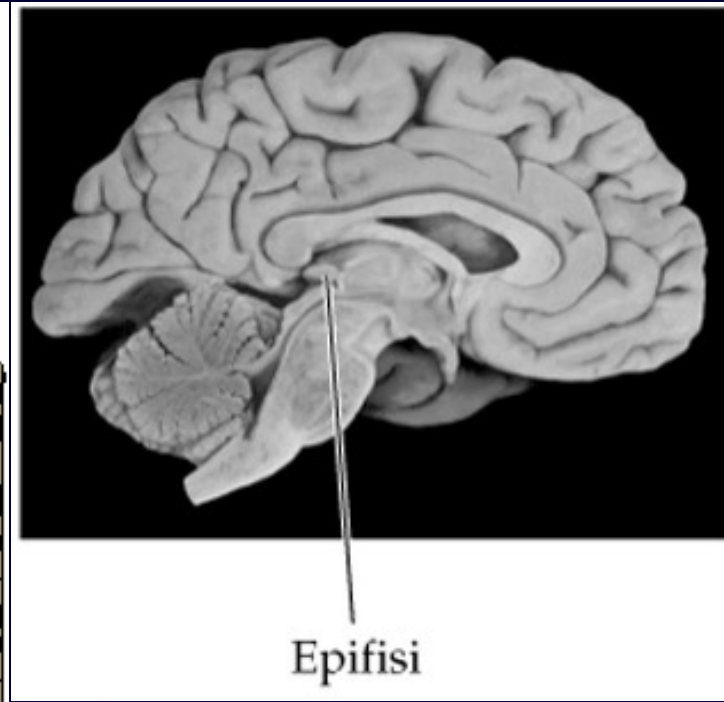
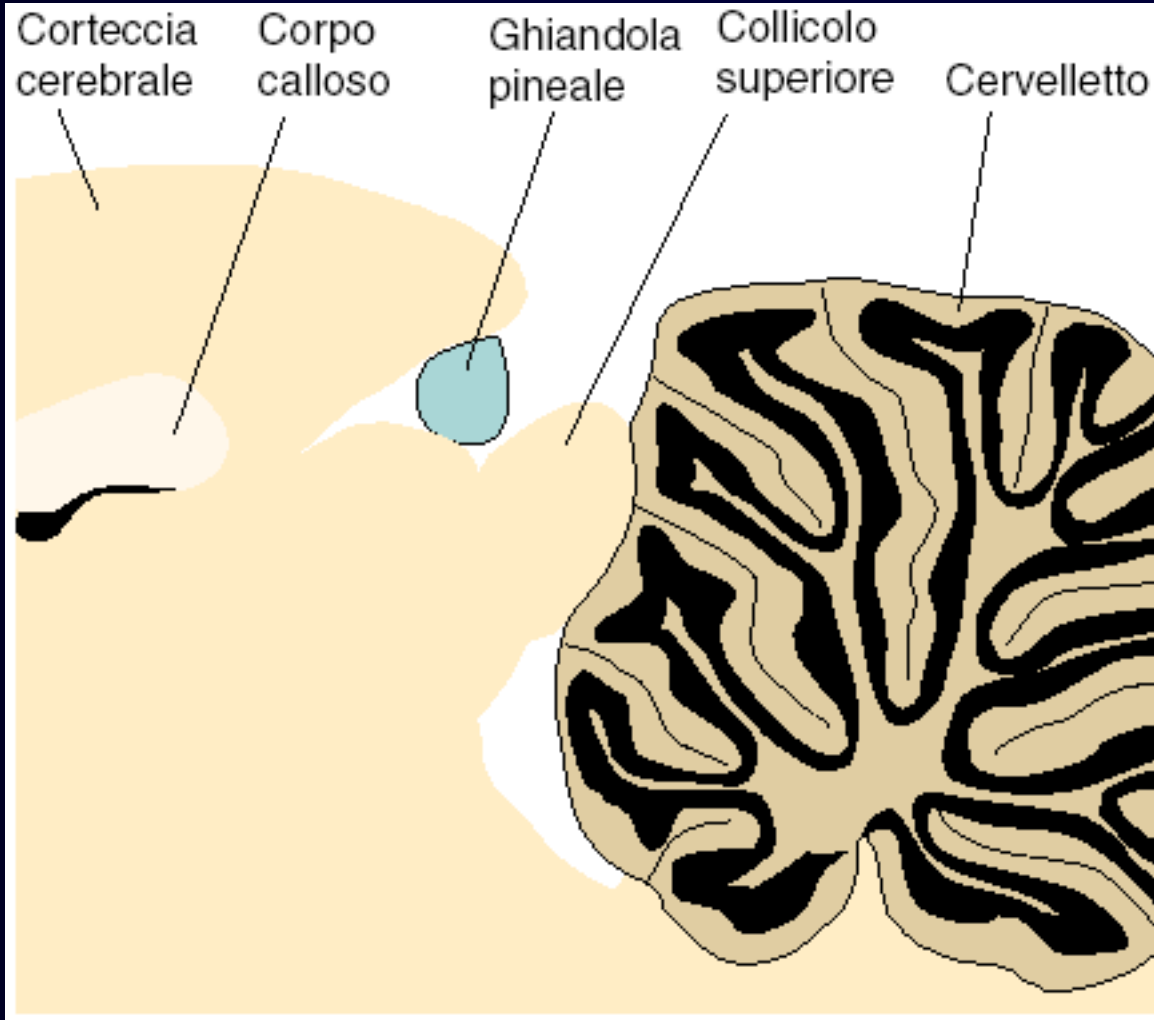
Il nucleo soprachiasmatico dell'ipotalamo (NSC)

- ♣ Via diretta retino-ipotalamica + indiretta genicolo-ipotalamica -> sincronizzazione dei ritmi endogeni scanditi dal pacemaker circadiano con gli *Zeitgebers*
 - ♣ La distruzione del nucleo soprachiasmatico fa perdere tale sincronizzazione e altera vari ritmi comportamentali e ormonali
- ♣ L'attività metabolica di questo nucleo non è legata solo alla presenza di luce, ma è sincronizzata anche a un ritmo endogeno

Il controllo dei ritmi stagionali

- 🕒 Il NSC dell'ipotalamo svolge anche le funzioni di “calendario” biologico
- ♥ Lesioni al NSC del criceto aboliscono il ritmo circannuale di secrezione del testosterone (e di accoppiamento)

Il controllo dei ritmi stagionali: la ghiandola pineale (epifisi)



Biological Rhythms - Mechanisms 15

The **Suprachiasmatic Nucleus (SCN)** & the **Pineal Gland**

Cerebral cortex

Suprachiasmatic nucleus

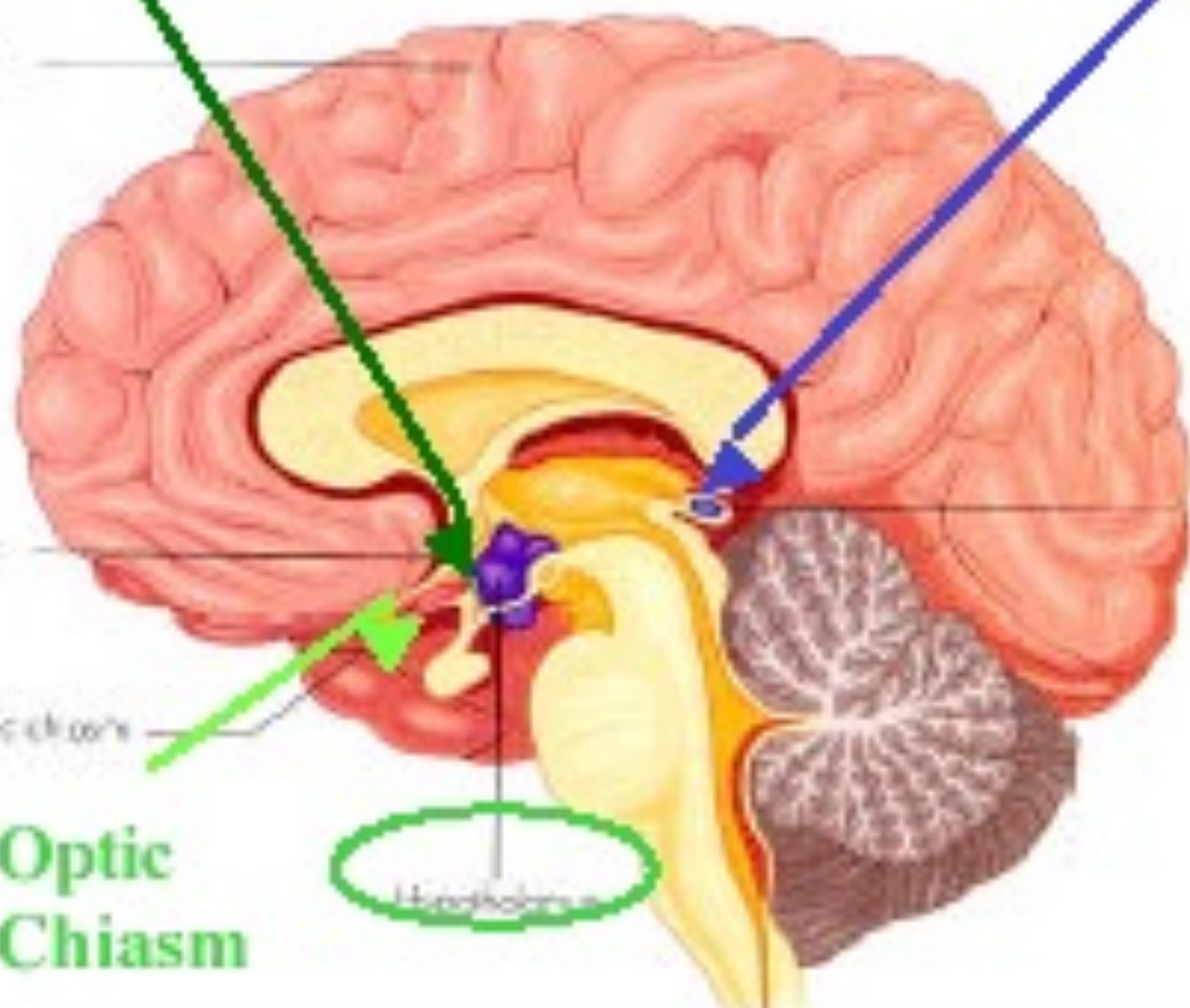
Optic chiasm

Optic Chiasm

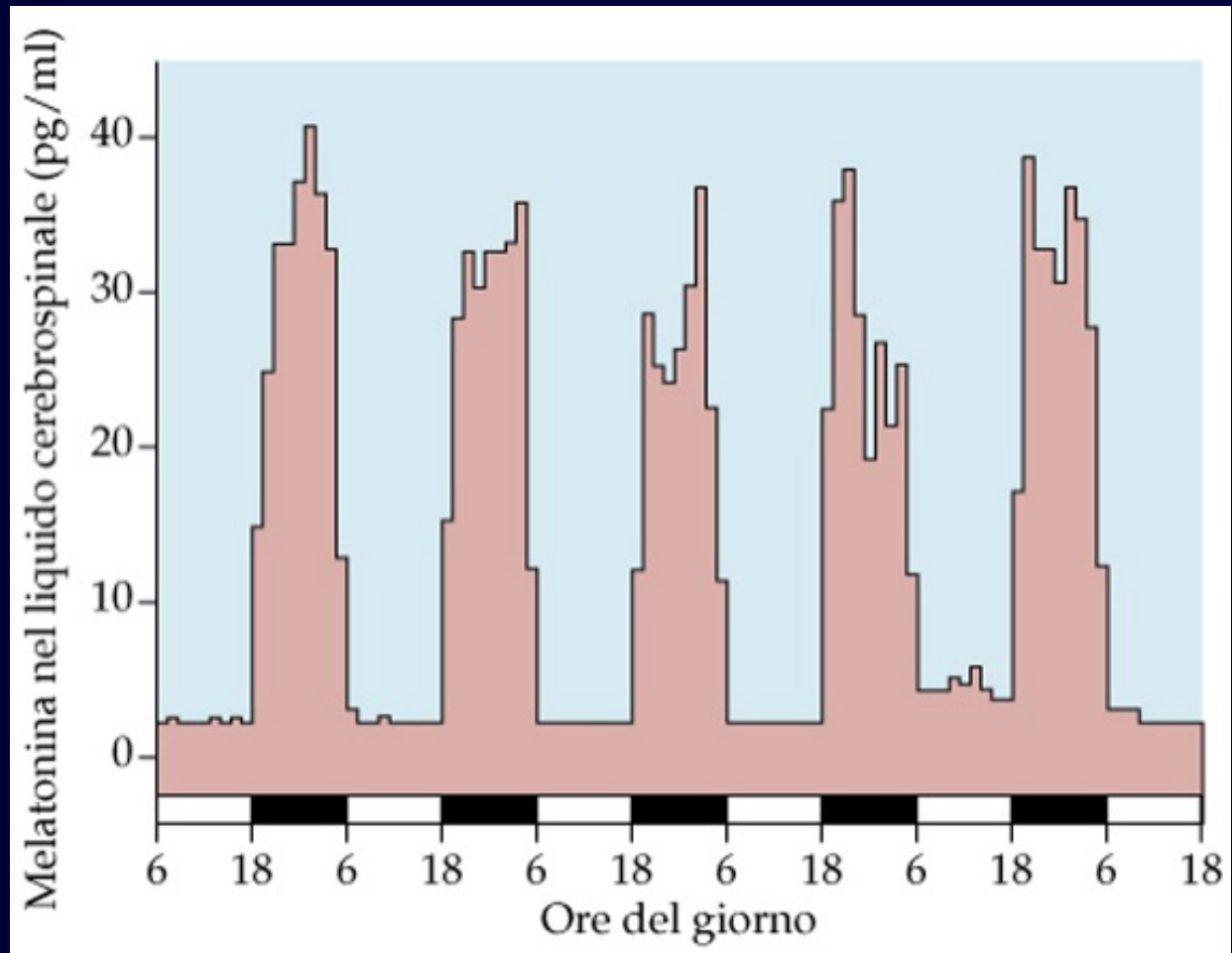
Hypothalamus

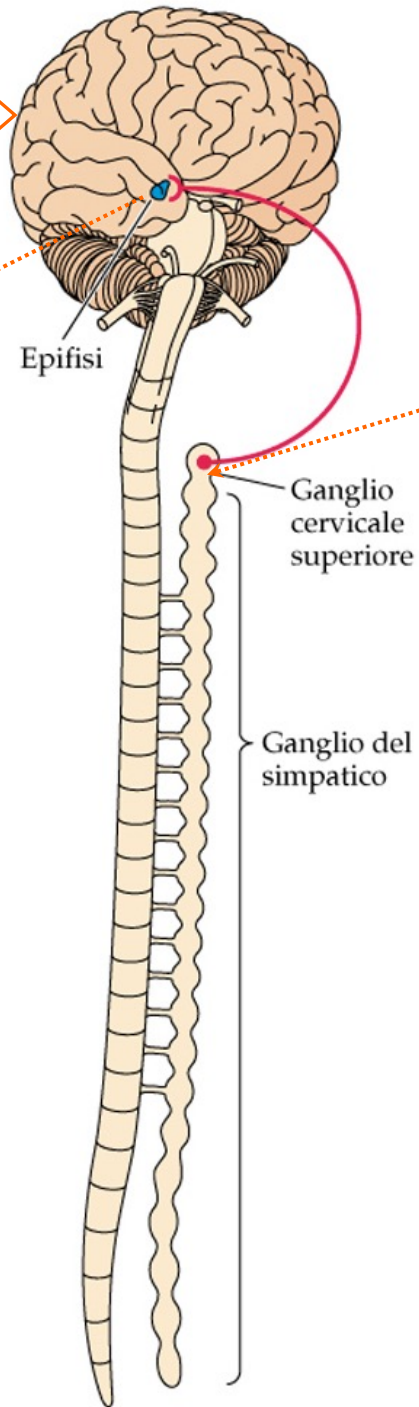
Pineal gland

(e)



Andamento circadiano della secrezione di melatonina





melatonina

ormoni
processi fisiologici
comportamenti
stagionali

NSC

NPV

NPV= nucleo paraventricolare dell'ipotalamo

Regolazione dei ritmi stagionali

Kleitman e Richardson nella grotta del Mammuth, nel Kentucky
1938



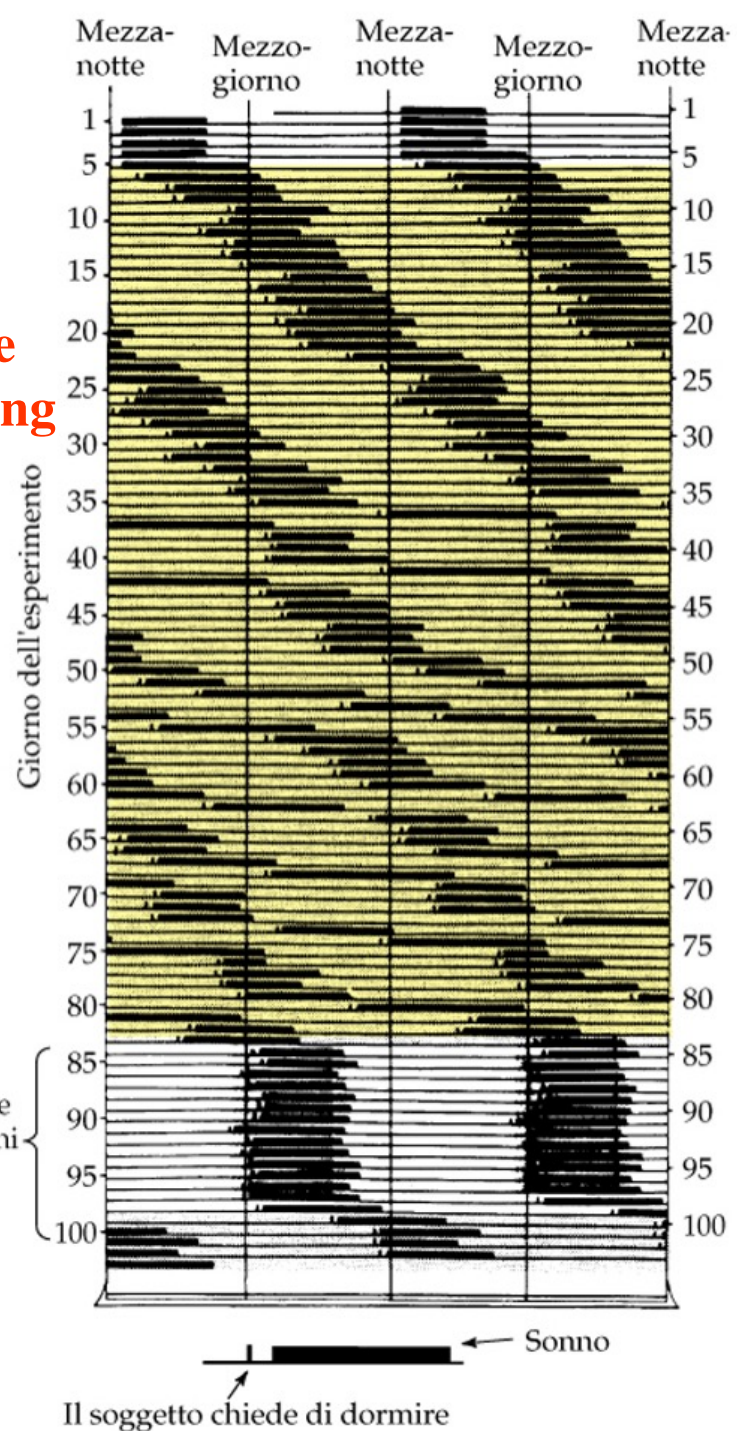


BRITISH
PATHÉ

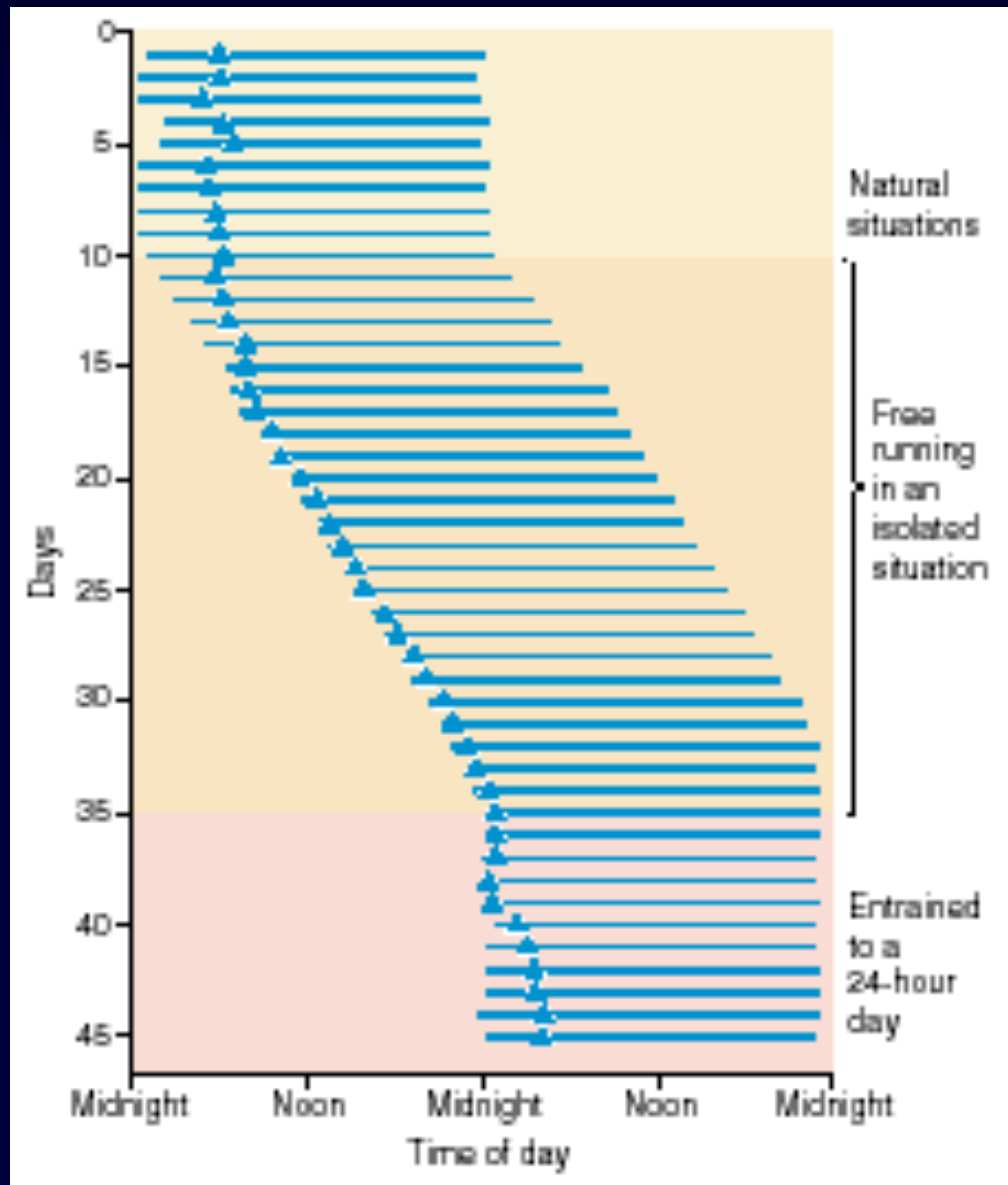
Ritmo sonno-veglia in isolamento

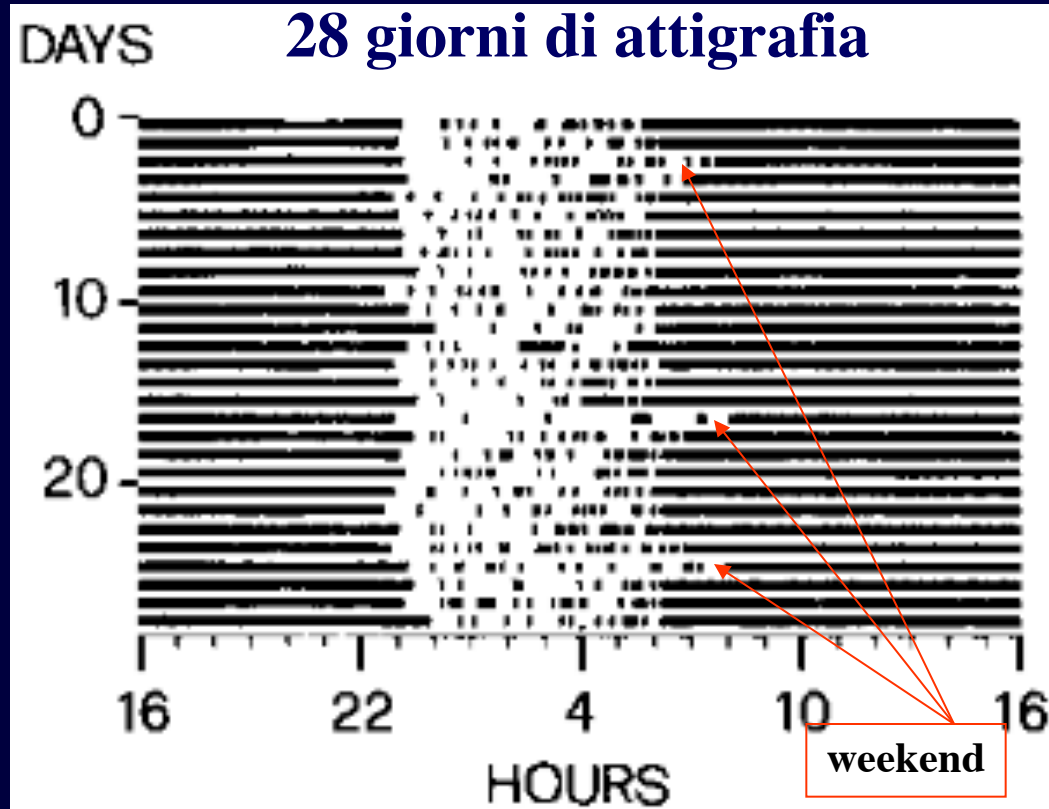
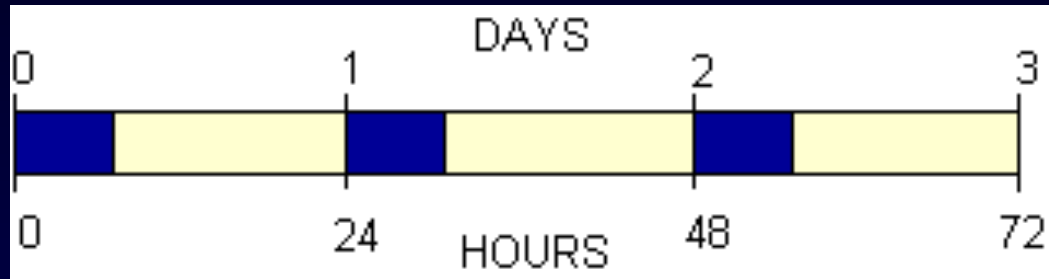
Free
running

Ritornano le
informazioni
sul tempo



Nell'uomo....



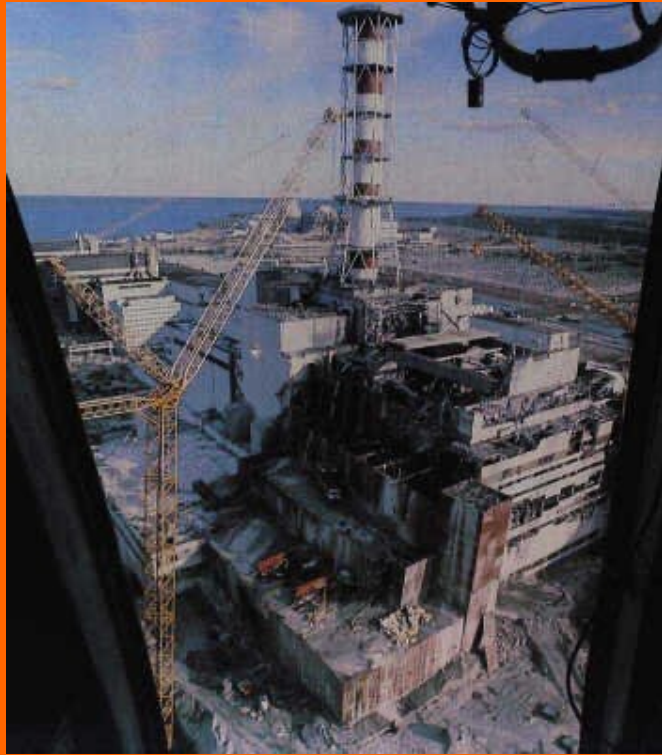


GMN
LIVE



A more typical early morning shiftwork error was also cited by the commission in its reporting of a previous near-catastrophic launch of the shuttle Columbia on January 6, 1986. Console operators at Kennedy Space Center inadvertently drained 18,000 pounds of liquid oxygen from the shuttle external tank within 5 min before scheduled launch. The liquid oxygen loss went undetected until after the mission was cancelled only 31 s before liftoff because of a secondary effect on the engine inlet temperature.

La fatica dell'operatore fu indicata *"come uno dei principali fattori che aveva contribuito a questo incidente"*. Gli operatori erano stati in servizio per 11 ore. Era la loro terza giornata di lavoro su un turno notturno di 12 ore. Come spesso avviene negli incidenti industriali, il contributo dell'errore umano è stato precipitato da un mal funzionamento inusuale del meccanismo o del sistema di controllo. In questo caso, un malfunzionamento si verificò durante la procedura di caricamento finale. La Commissione concluse che *"una valutazione da parte della NASA delle conseguenze degli orari di lavoro dovrebbe essere condotta nell'ambito del suo sforzo per riformare le sue procedure di lancio e di funzionamento"*



Chernobyl



**Piper Alpha disaster in the North Sea in
1988**



Piper Alpha



On 24 March 1989, the Exxon Valdez oil tanker grounded on a reef in Prince William Sound, 40 miles (65 km) off the Alaskan coast



Exxon Valdez



on the night of December 2, 1984, the explosion poured toxic gas from the Union Carbide plant in the Indian city of Bhopal



1988: 35 dead in Clapham rail collision



1979 La fuoriuscita di materiale radioattivo dalla centrale di Three Miles Island in Pennsylvania

1984 L'esplosione della fabbrica chimica dell'Union Carbide a Bophal

1986 Il disastro dello shuttle Challenger della NASA

1988 L'incendio della piattaforma petrolifera Piper Alpha nel Mar del Nord

1988 Il disastro ferroviario di Clapham in Inghilterra

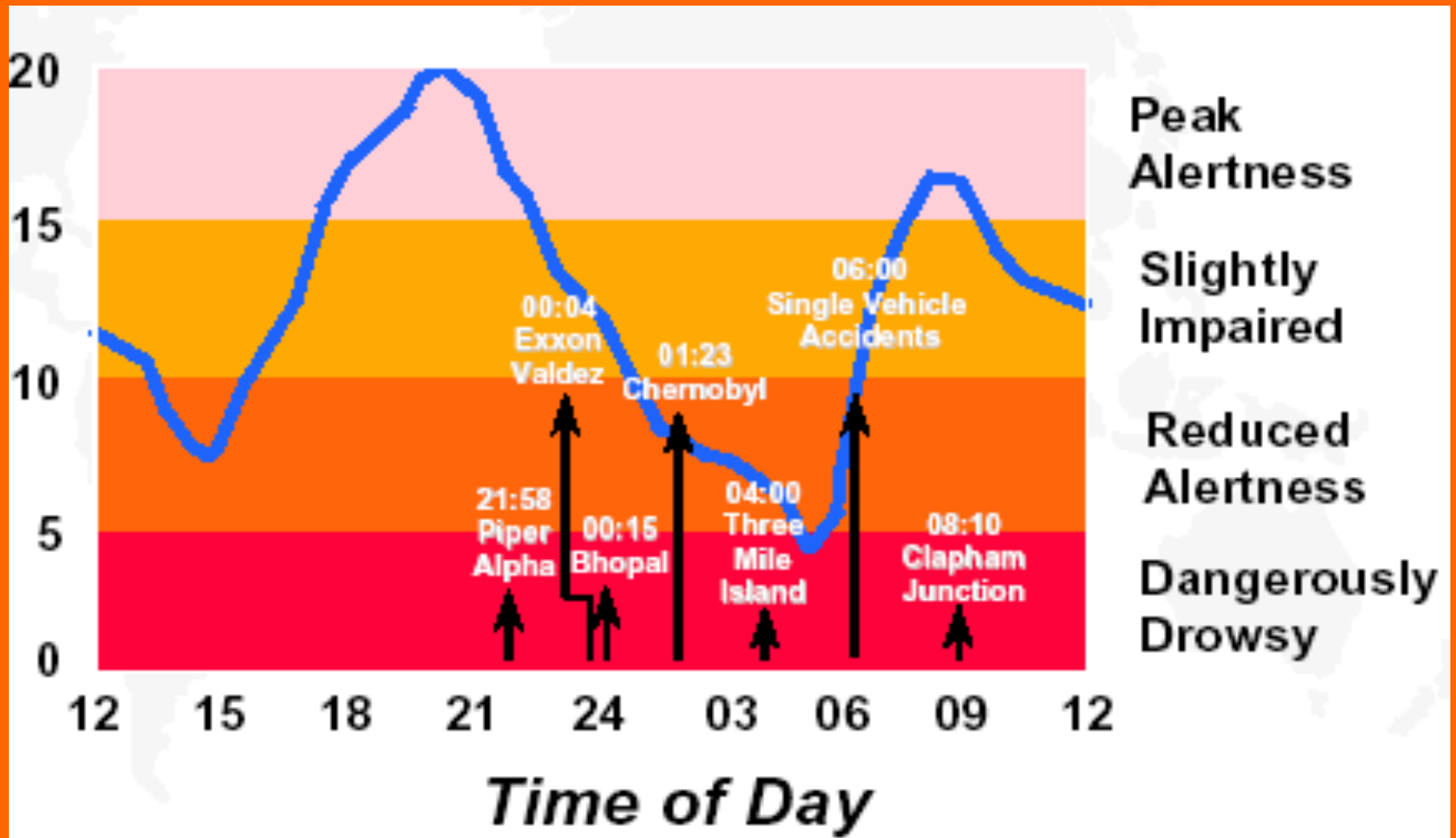
1989 Il disastro della petroliera Exxon Valdez in Alaska

1989 Il disastro nucleare di Chernobyl

1994 L'affondamento del traghetto Estonia nel Mar Baltico.

ERRORE UMANO E FASE CIRCADIANA:

il momento della massima propensione verso il sonno è associato alla massima probabilità di errore umano



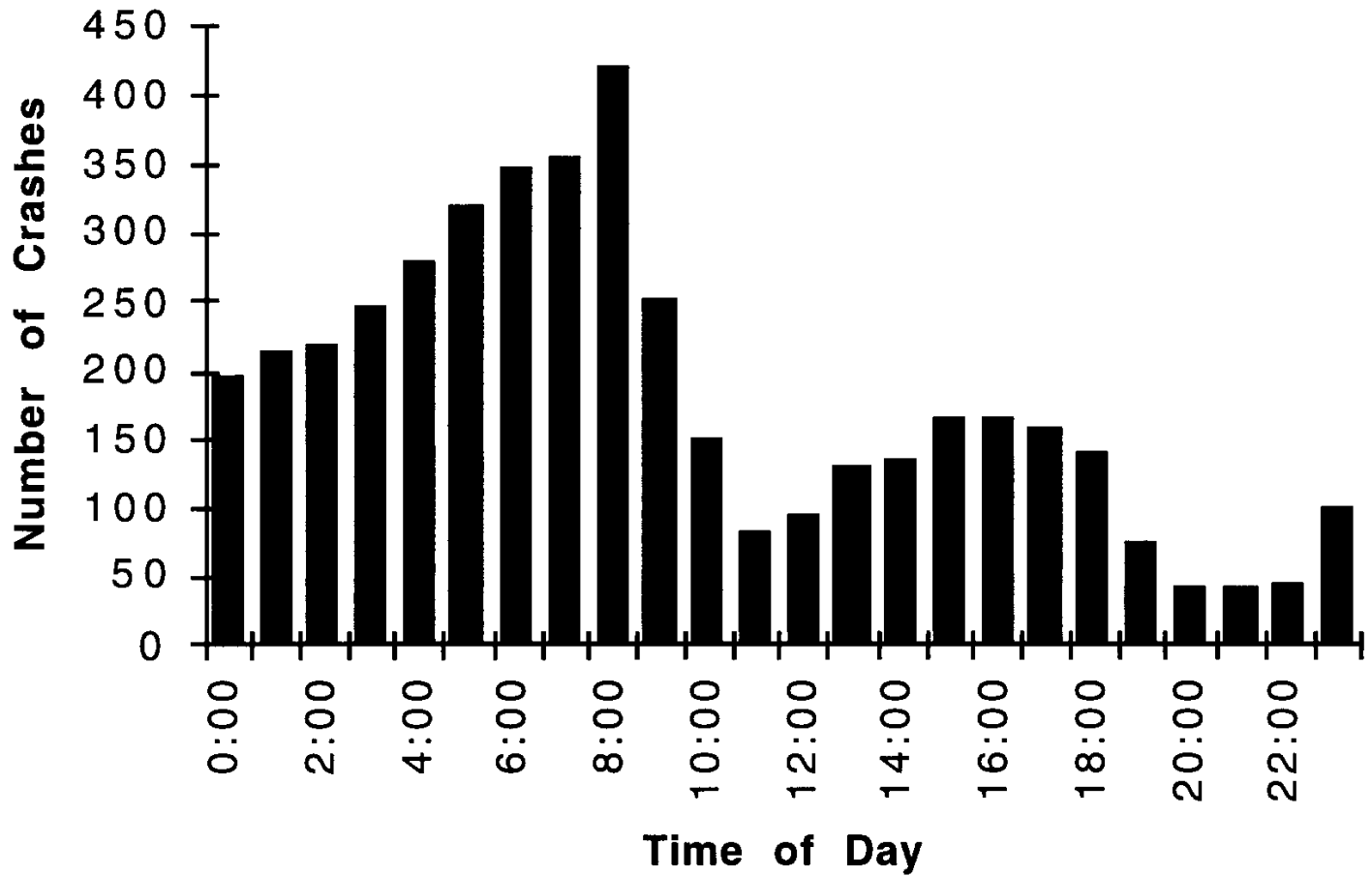


TABLE 5] Circadian Rhythm Sleep-Wake Disorders

Disorder

Delayed sleep-wake phase disorder

Advanced sleep-wake phase disorder

Irregular sleep-wake rhythm disorder

Non-24-h sleep-wake rhythm disorder

Shift work disorder

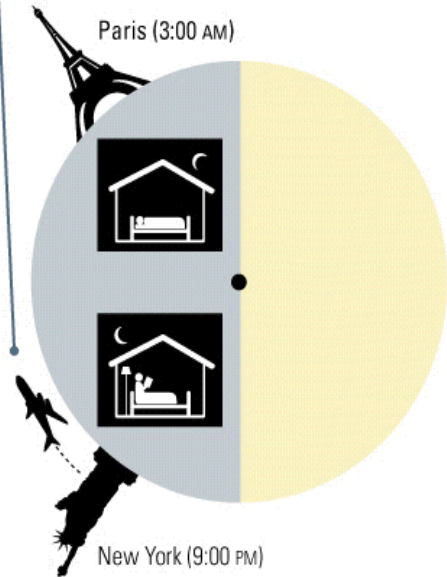
Jet lag disorder

Circadian sleep-wake disorder not otherwise specified

Jet lag

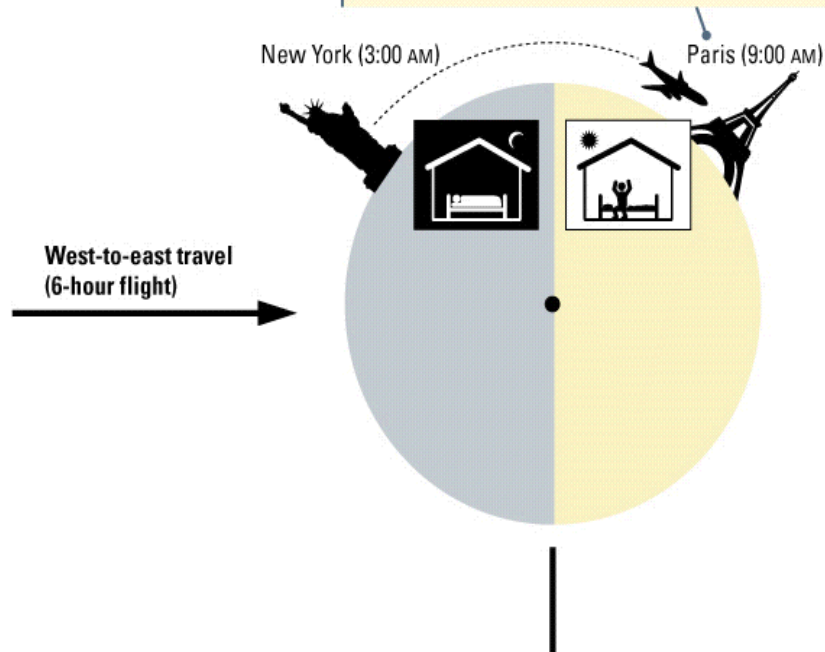
1

Traveler leaves New York at 9:00 PM, when it's 3:00 AM in Paris.

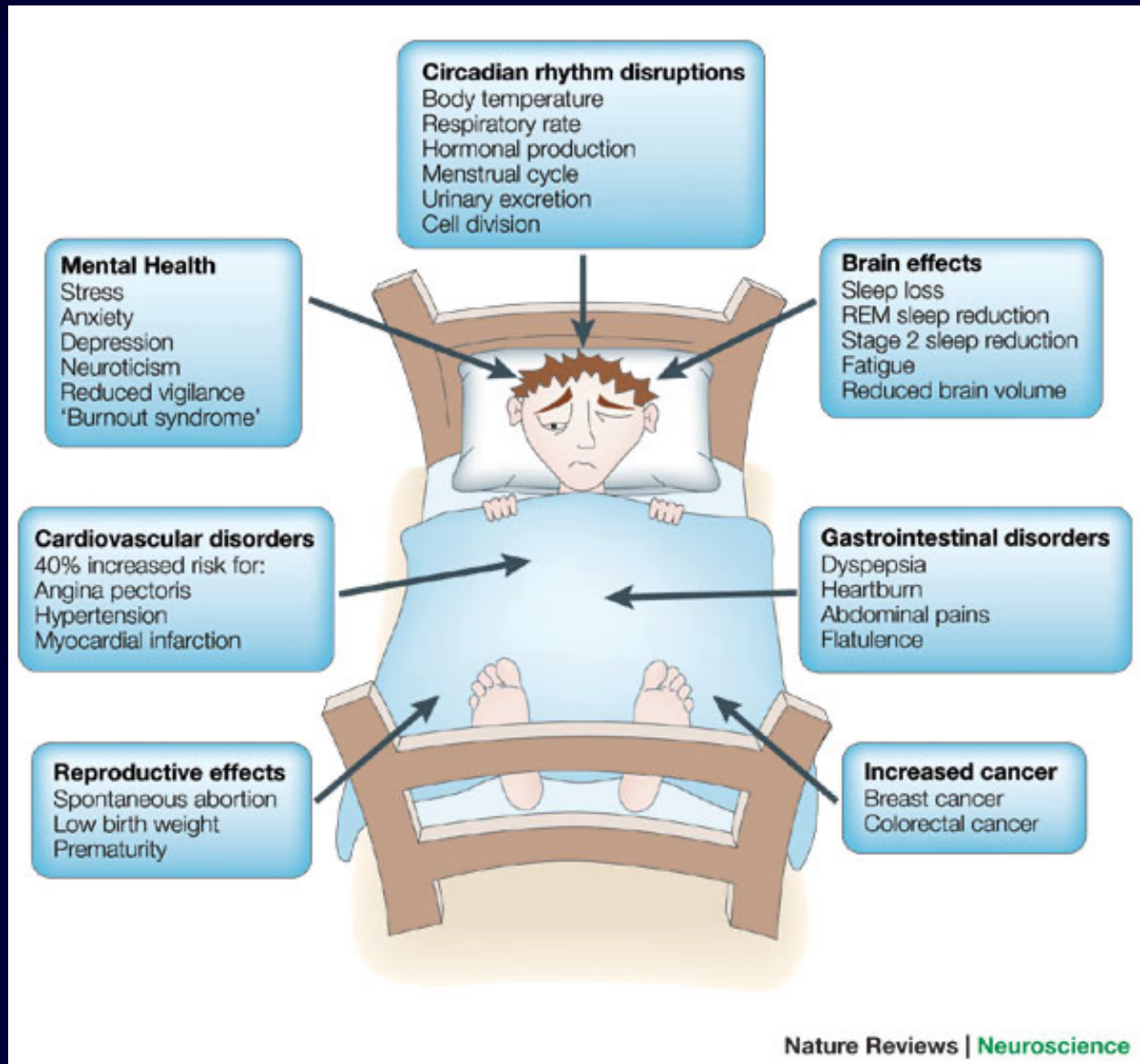


2

Traveler arrives in Paris at 9:00 AM, when it's 3:00 AM in New York. Because his biological clock is set for New York time, he is prepared for sleep, whereas residents of Paris are waking.



Sindrome dei turnisti



RHYTHM WATCH Actogram printout

User identification

Start date 23-May-2001

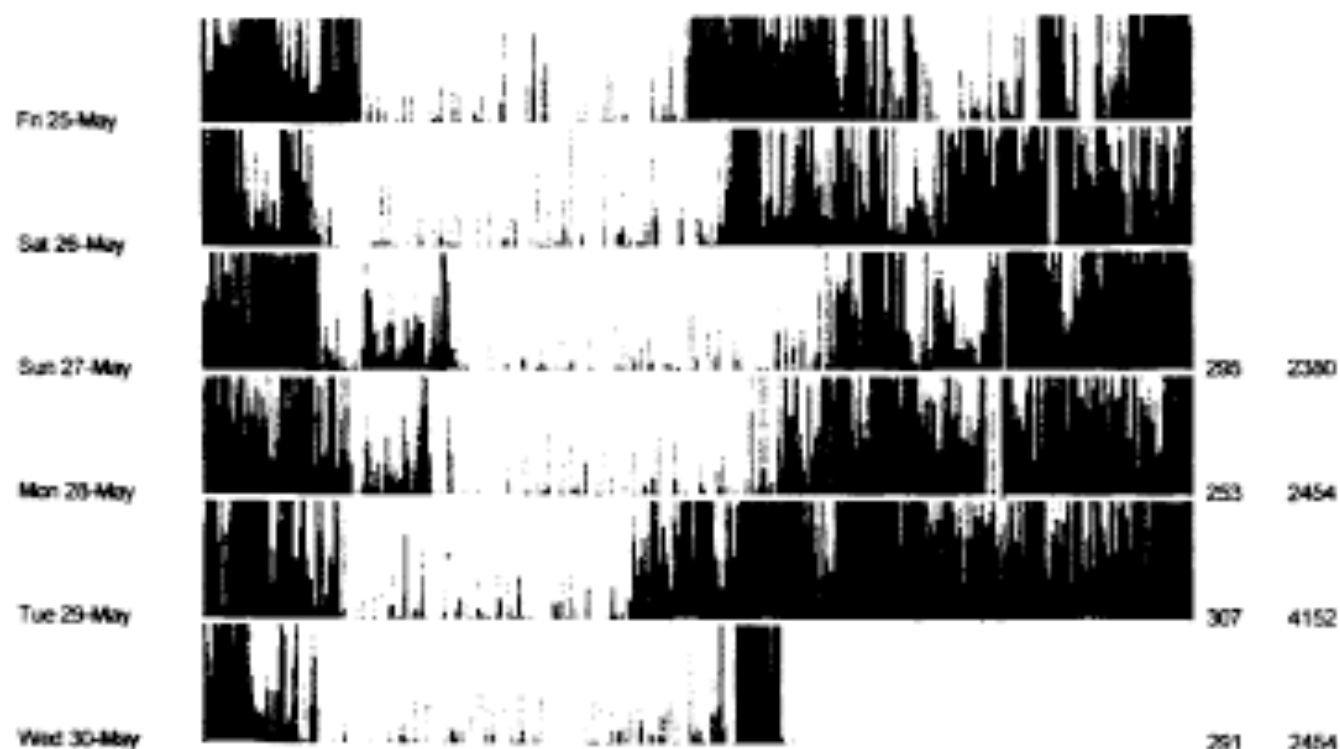
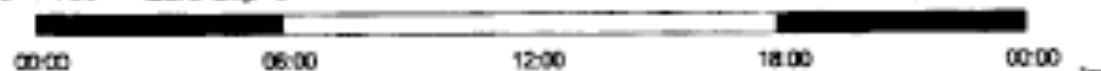
Start time 10:56

Subject age 21

Subject sex M

Epoch length 1.0 (Mins)

Vertical Scale 700 Zero Clip 0



Delayed Sleep Phase Syndrome.

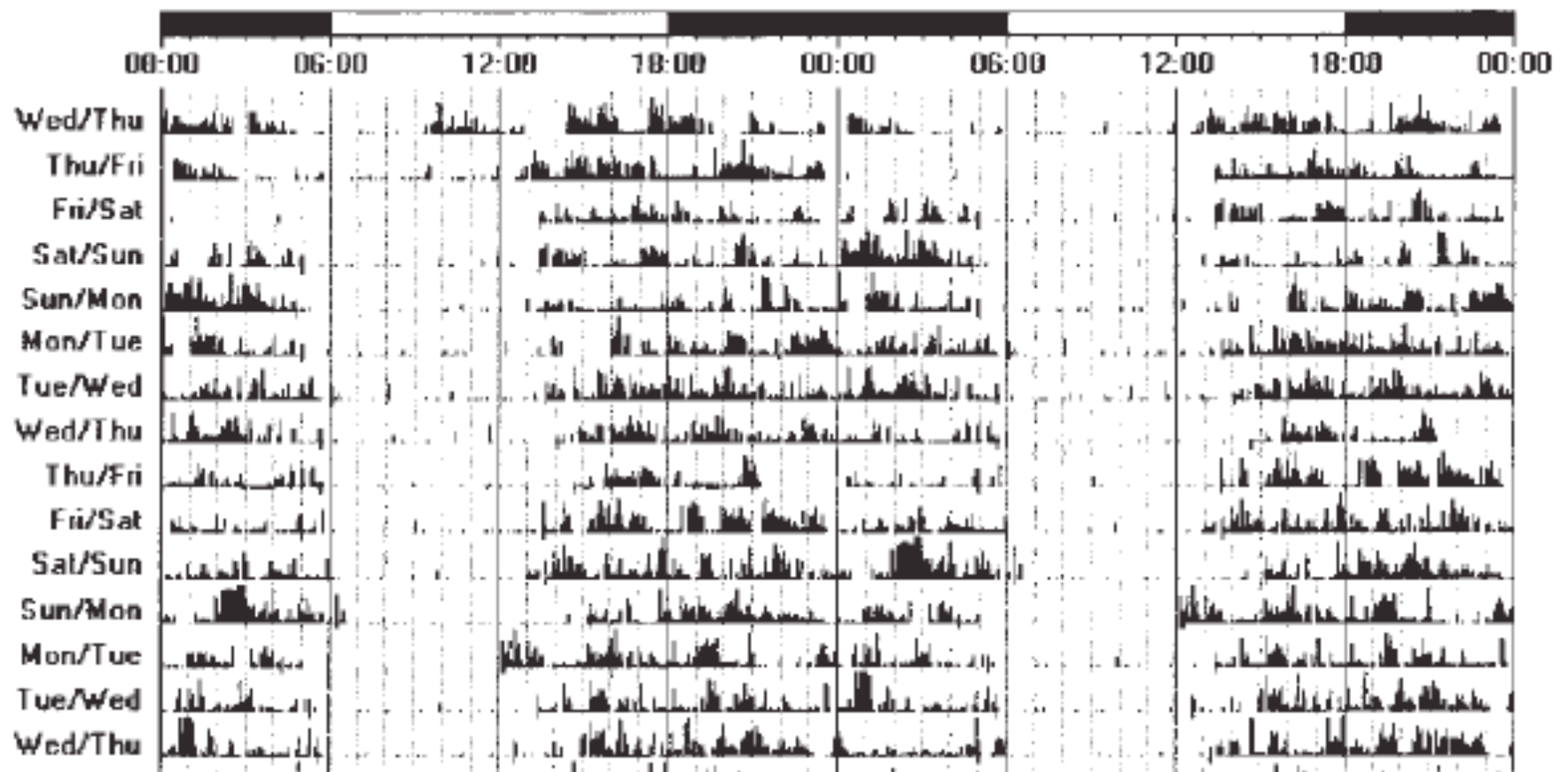


Figure 2. An actogram of sleep-wake activity, recorded using wrist activity monitoring, from an individual with severe **DSPS**. This individual goes to bed between 5:00 and 6:00 AM and wakes at ~ 1:00 to 2:00 PM each day.

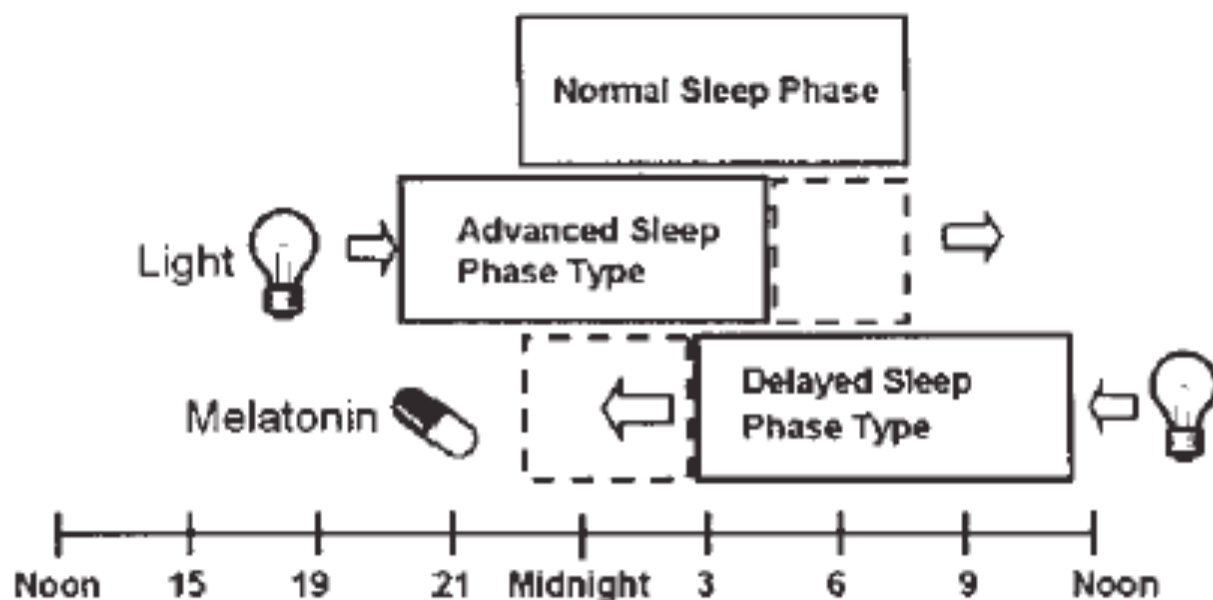


Figure 3 Schematic representation of treatment strategies for ASPS and DSPS. The primary sleep period is indicated by the solid lines, and sleep phase following treatment is indicated by the dashed line. To phase delay the sleep period of an individual with ASPS, bright light should be administered during the first half of the evening between 7:00 and 9:00 PM. To phase advance the sleep period of an individual with DSPS, bright light should be administered in the morning usually between 6:00 and 8:00 AM. Melatonin in the evening, ~5 hours prior to habitual bedtime, has also been used to phase advance circadian rhythms in DSPS.



Circadian typology

Evening type
(owl)



Morning type
(larks)



Tipologia circadiana

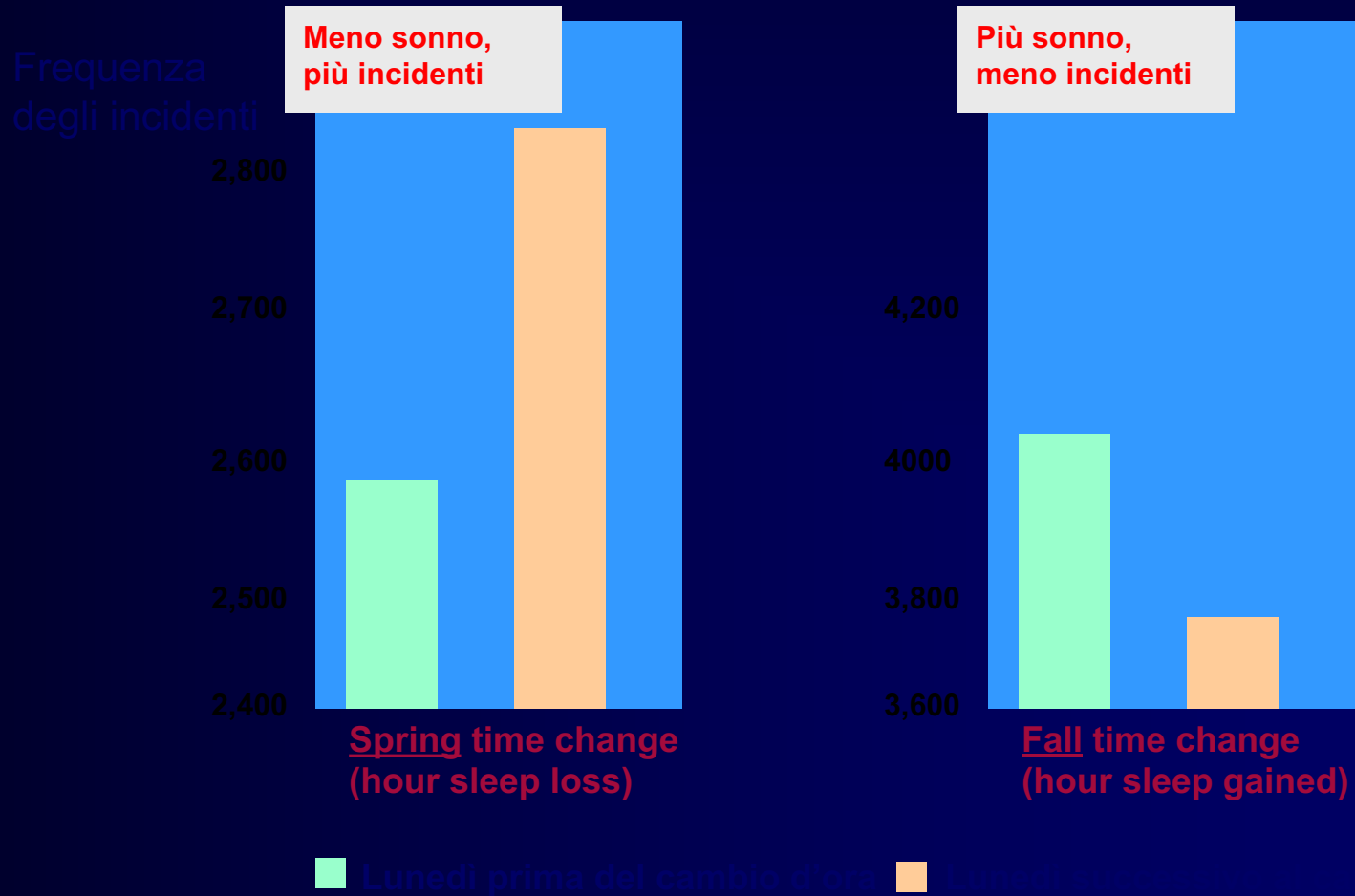
1900-1930 Kleitman 1963

- Le persone vengono classificate in base al loro ciclo veglia sonno in: **mattutini** (allodole) (10-15%), **serotini** (gufi) (15-20%) ed **intermedi** (65-75%).
- **Morningness-Eveningness Questionnaire** (MEQ) (Horne e Östberg, 1976). Traduzione inglese dell'originale versione svedese del 1970 Öqvist. 19 items formato misto.

Ora legale



Cambio dell'ora legale



FATAL ALCOHOL-RELATED TRAFFIC CRASHES INCREASE
SUBSEQUENT TO CHANGES TO AND FROM
DAYLIGHT SAVINGS TIME¹

GREGORY J. HICKS
Mendocino College

JAMES W. DAVIS
University of New Mexico

ROBERT A. HICKS
San Jose State University

TABLE 1

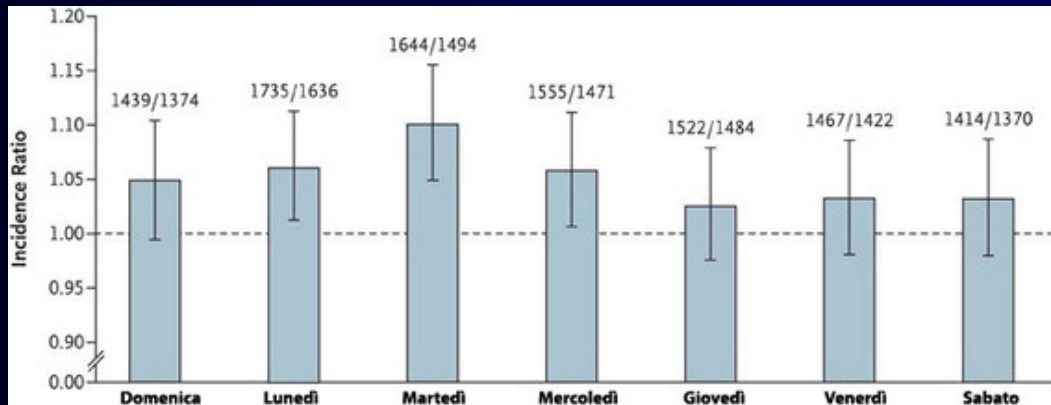
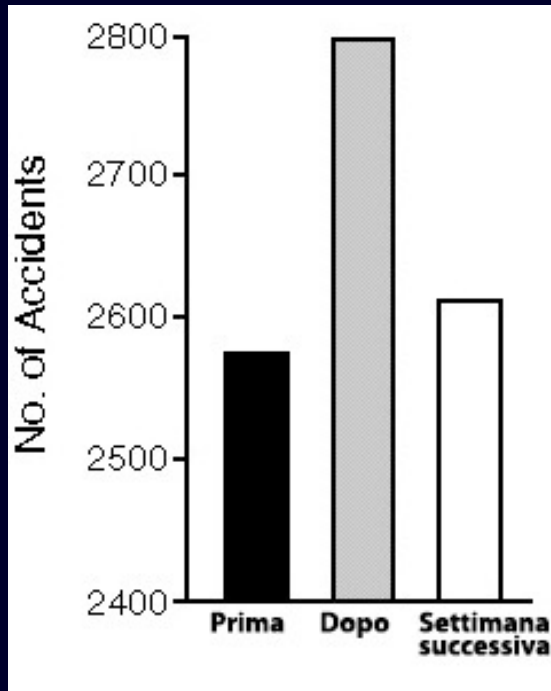
NUMBER AND PERCENTAGE OF ALCOHOL-RELATED AND NONALCOHOL-RELATED FATALITIES FOR
1989-1992 IN STATE OF NEW MEXICO FOR THREE SEVEN-DAY PERIODS WHICH SURROUND
SPRING AND FALL CHANGES TO AND FROM DAYLIGHT SAVINGS TIME

Type of Fatal Crash	Daylight Savings Time Change Related Period					
	Baseline Period*		Post Daylight Savings Time Change Week			
	Fatalities		Week 1 Fatalities		Week 2 Fatalities	
	n	%	n	%	n	%
Alcohol-related	36	53.7	47	71.2	38	53.5
Nonalcohol-related	31	46.3	19	28.7	33	46.5

*The Baseline period was the week which preceded each Daylight Savings Time change.

Influenza del cambio di ora legale sugli
incidenti alcol-relati

Influenza del cambio di ora legale sugli incidenti (Canada - 10 province) e su infarti del miocardio



Luigi De Gennaro Diventa fan
Psicofisiologo, esperto di disturbi del sonno

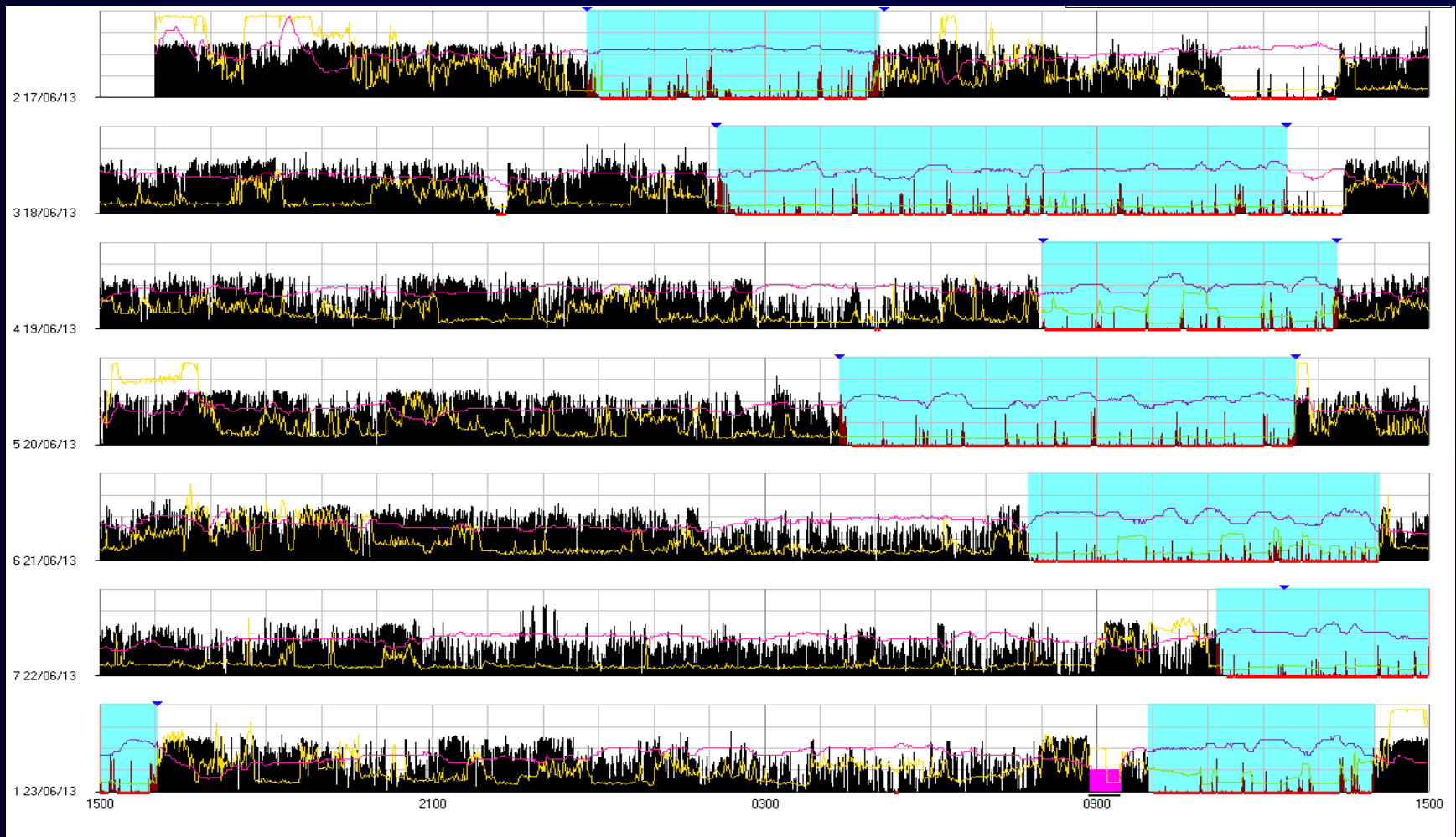
5 ottime ragioni per abolire l'ora legale

Publicato: 25/03/2017 11:05 CET | Aggiornato: 25/03/2017 11:05 CET

A photograph showing a white coffee cup and a black alarm clock on a table. The background is a blurred image of a bed with white linens.

Non entrained type

Maschio, anni 15, ultimo di 5 fratelli, abbandono scolastico, difficoltà risveglio SE%=87%; TST=333min.

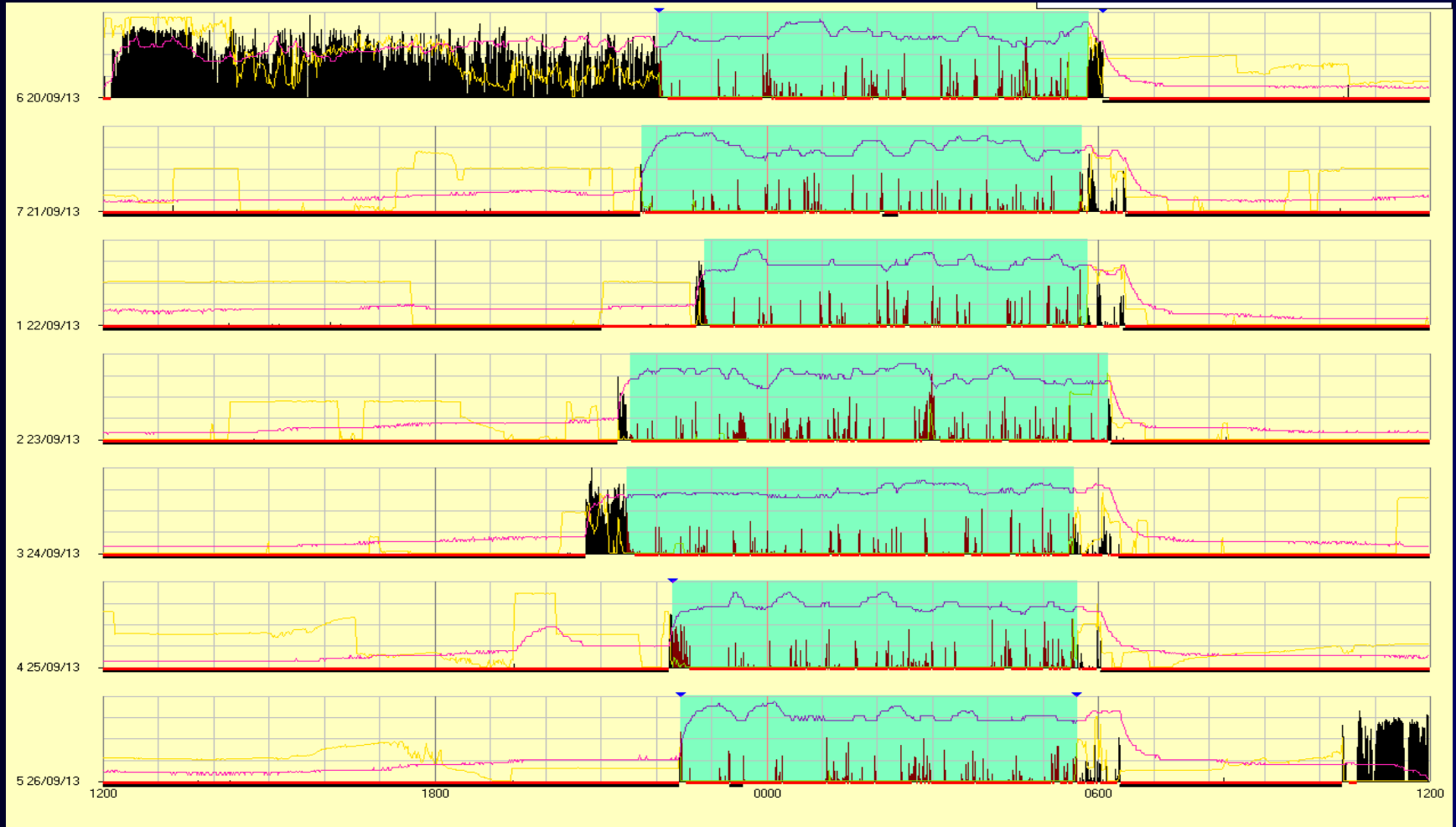


Non entrained type

In questo caso è stata suggerita cronoterapia: spostamento progressivo (in avanti) dell'orario di addormentamento, due o tre ore per volta, al momento di andare a letto, sino a portare a far coincidere il ritmo sonno-veglia con le esigenze di una normale vita di relazione. Tale obiettivo si raggiunge rapidamente, ma deve essere consolidato in un periodo di almeno due settimane, nel quale si esercita uno stretto controllo dell'orario con l'ausilio della luce.

Non entrained type

Dopo una settimana di terapia della luce
SE%=86%; TST=411min.



Are you a lark or an owl?
Are you getting enough sleep?



Circadian typology

Evening type
(owl)



Morning type
(larks)



Tipologia circadiana

1900-1930 Kleitman 1963

- Le persone vengono classificate in base al loro ciclo veglia sonno in: **mattutini** (allodole) (10-15%), **serotini** (gufi) (15-20%) ed **intermedi** (65-75%).
- **Morningness-Eveningness Questionnaire** (MEQ) (Horne e Östberg, 1976). Traduzione inglese dell'originale versione svedese del 1970 Öqvist. 19 items formato misto.