Sleep

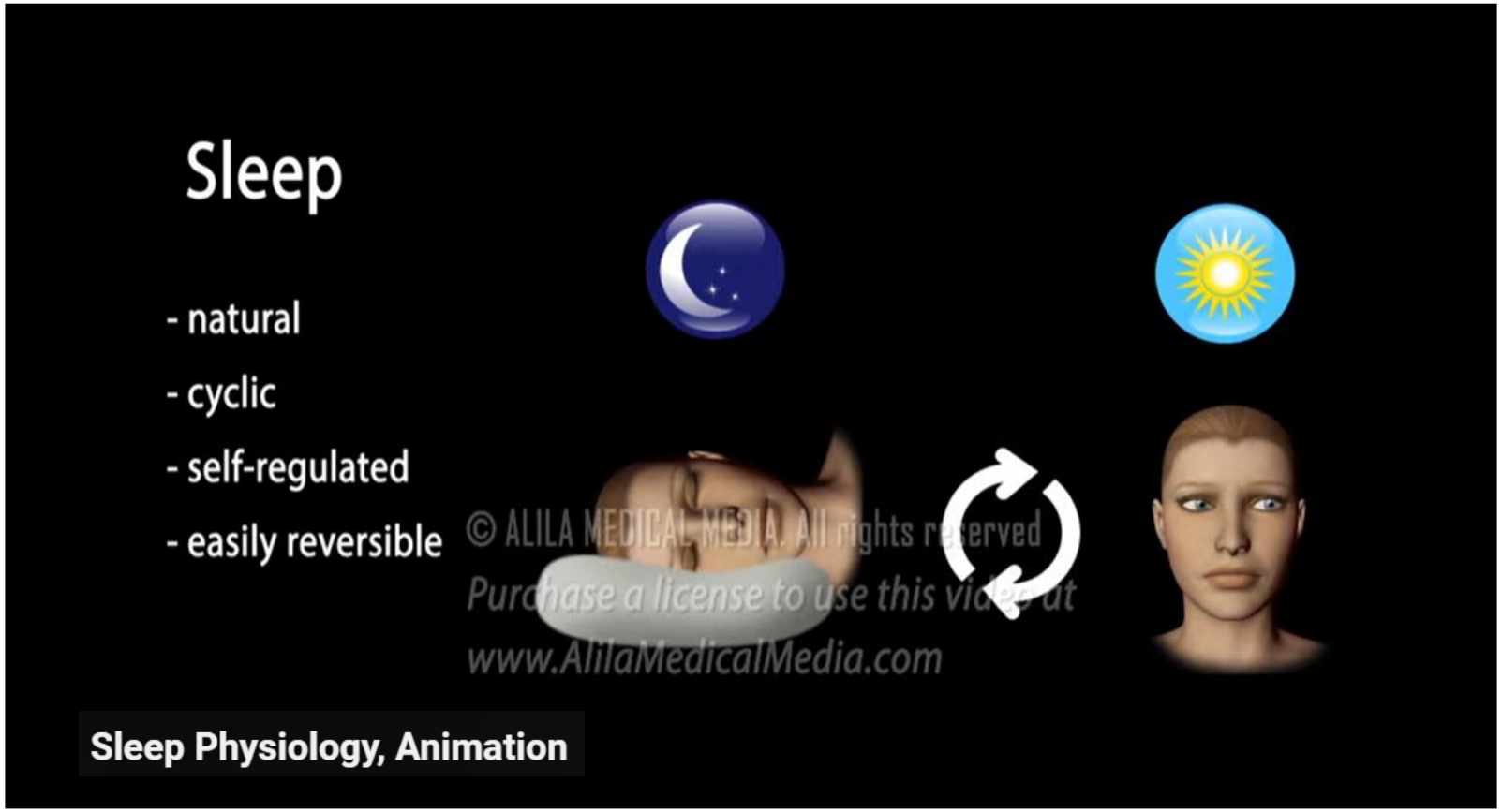
Dr. Lavinia Carmen Uscătescu

January 15th 2024

Outline

1. Polysomnography, the hypnogram and the circadian rhythm
2. Physiology of sleep
3. Sleep disorders

Overview



https://www.youtube.com/watch?v=H25DD0sztSA

Polysomnography, the hypnogram and the circadian rhythm

Richard Caton and **Hans Berger**

Richard Caton
(1842—1926)

1874 => first electrical recordings from the brain surface (monkeys and rabbits)

Hans Berger
(1873—1941)

1929 => first electrical recording from the human scalp

J Med Biogr. 2006 Feb;14(1):30-5. doi: 10.1258/j.jmb.2006.04-22.

Richard Caton (1842–1926): pioneer electrophysiologist and cardiologist

Walter Ormerod [1]

Abstract

Richard Caton is recognized as the discoverer of the waves of electrical potential which today form the basis of electroencephalography. He reported his finding in three communications, two in the British Medical Journal and one to the Ninth International Congress of Medicine at Washington, DC. After defending his priority in having made this discovery, he did no further work on the brain: his family and colleagues were unaware of his discovery for many years after his death. This was possible partly because of many other things that he did in his long life but also because, in his later years, he took deliberate steps to hide the fact that he had worked on the brain. The most important of these other activities was a practical study of the treatment of rheumatic heart disease. The basis of his treatment--complete rest in bed--is still in use today.

https://pubmed.ncbi.nlm.nih.gov/16435031/

J Neurol Neurosurg Psychiatry. 2003 Jan; 74(1): 9.
doi: 10.1136/jnnp.74.1.9

Hans Berger (1873–1941), Richard Caton (1842–1926), and electroencephalography

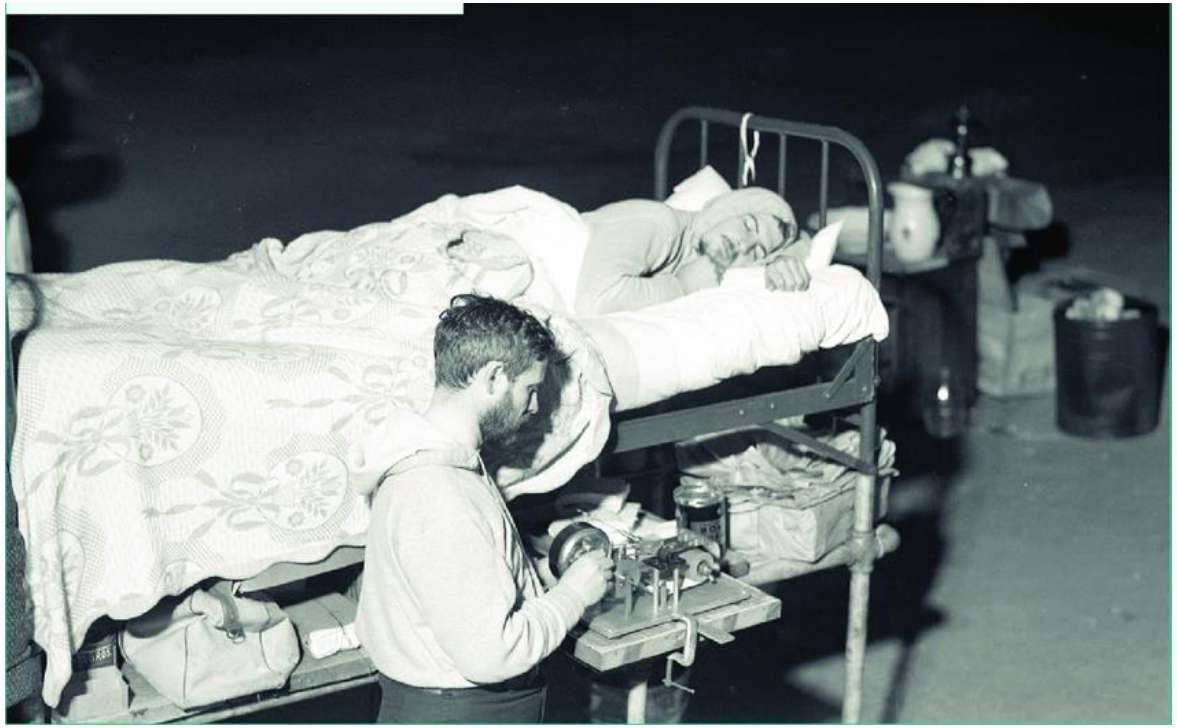
L Haas https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738204/

The beginning of sleep research: **Eugene Aserinsky** and **Nathaniel Kleitman**

Neuroscientist **Eugene Aserinsky** attaches electrodes to his son, Armond

http://tinyurl.com/3bkrd8k8

Physiologist **Nathaniel Kleitman** and his student, Bruce Richardson, camped out in Mammoth Cave (Kentucky)



http://tinyurl.com/mr35bh7m

Rapid eye movements (REM) sleep was discovered in 1953, when **Eugene Aserinsky** and **Nathaniel Kleitman** observed episodes of **jerky conjugate eye movements** in sleeping individuals, some of which also reported **dreams** with visual imagery when awaken at this stage.

Polysomnography: the study of sleep

IEEE Pulse. 2014 Sep-Oct;5(5):26-8. doi: 10.1109/MPUL.2014.2339291.

Polysomnography: understanding this technology's past might guide future developments

Max Hirshkowitz

https://pubmed.ncbi.nlm.nih.gov/25437471/

ELSEVIER

Sleep Medicine Clinics

Volume 4, Issue 3, September 2009, Pages 313-321

The History of Polysomnography

Maryann Deak MD [a], Lawrence J. Epstein MD [a b]

http://tinyurl.com/ym53yevk

Home > Introduction to Modern Sleep Technology > Chapter

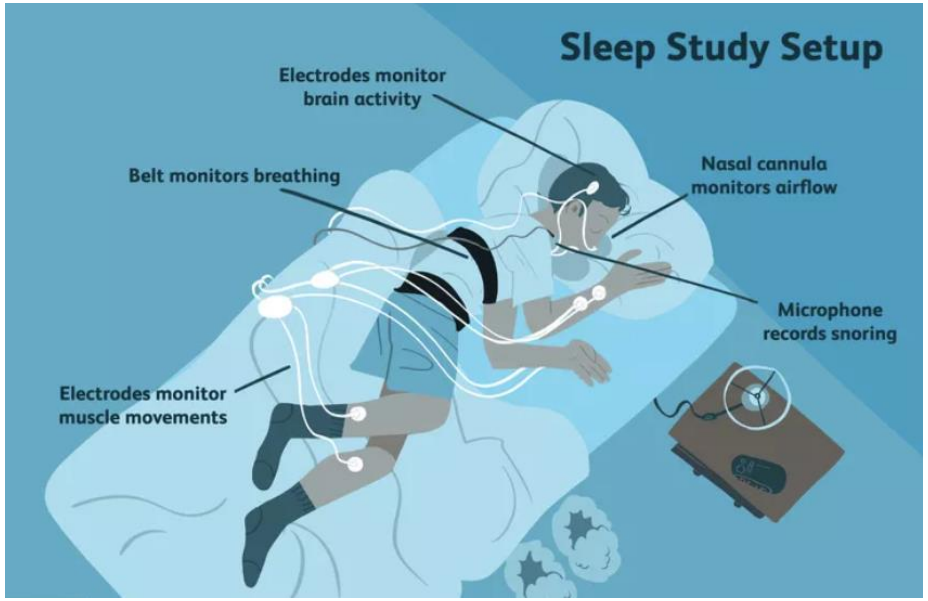
Evaluation Instruments for Sleep Disorders: A Brief History of Polysomnography and Sleep Medicine

José Haba-Rubio M.D. & Jean Krieger M.D., Ph.D.

Chapter | First Online: 01 January 2012

https://link.springer.com/chapter/10.1007/978-94-007-5470-6_2

Modern **polysomnography** (sleep study) setup



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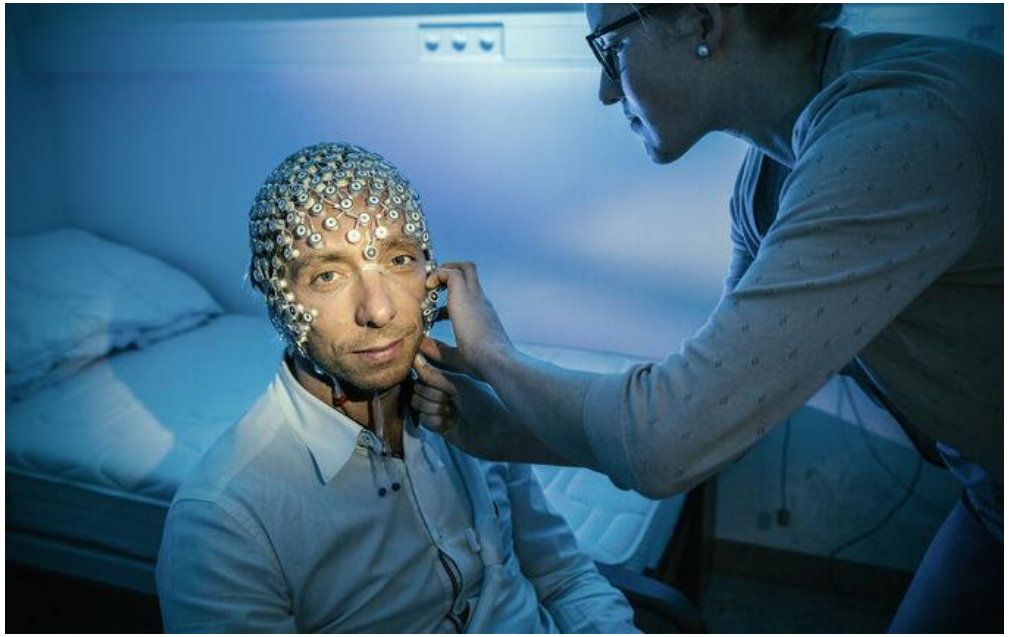


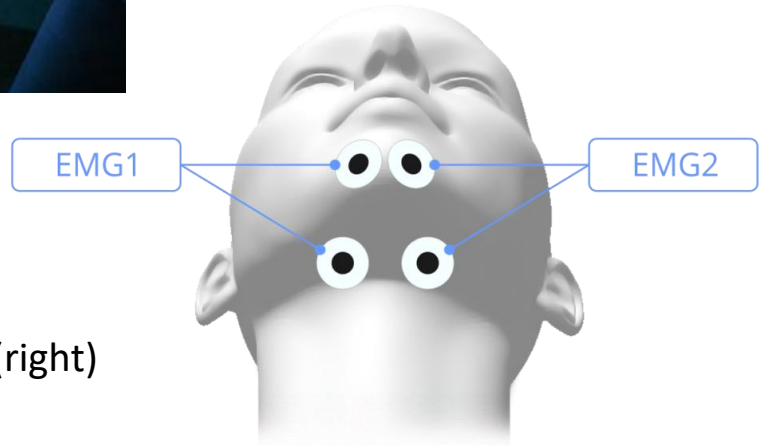
http://tinyurl.com/695jjbv5

High-density Electroencephalography (**EEG**)

(256 channels)

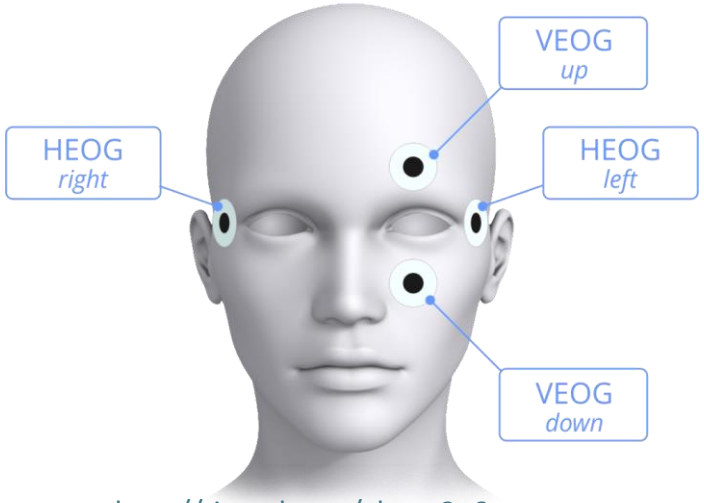
Dr. Manuel Schabus (left) and Dr. Christine Blume (right)

Electromyography (**EMG**)



http://tinyurl.com/4d7a3ptt

Electrooculogram (**EOG**)



http://tinyurl.com/ybxpn2a6

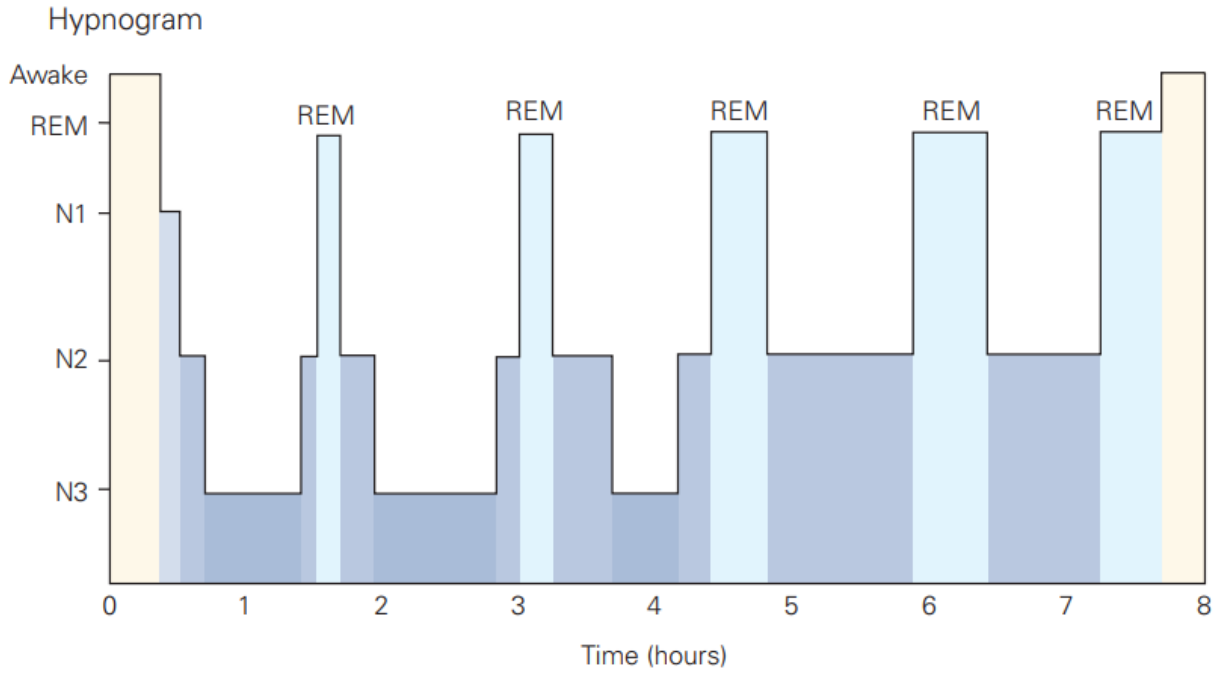
Sleep consists of alternating periods of REM sleep and non-REM sleep.

A **hypnogram** (i.e., graph showing the progression of **sleep stages** over a typical night) in a healthy young person.

Periods of **rapid eye movement (REM)** sleep alternate with **non-REM** sleep about every 90 minutes.

An individual typically progresses from the awake state into **light non-REM sleep (N1)** then progressively **deeper non-REM sleep (N2, N3)**, then back to lighter non-REM sleep before the first period of REM sleep occurs (light blue bars).

As the night progresses, the individual spends **less time in the deepest stage of non-REM sleep**, and the **duration of REM sleep periods increases**.



Kandel et al., (2021), p. 1081

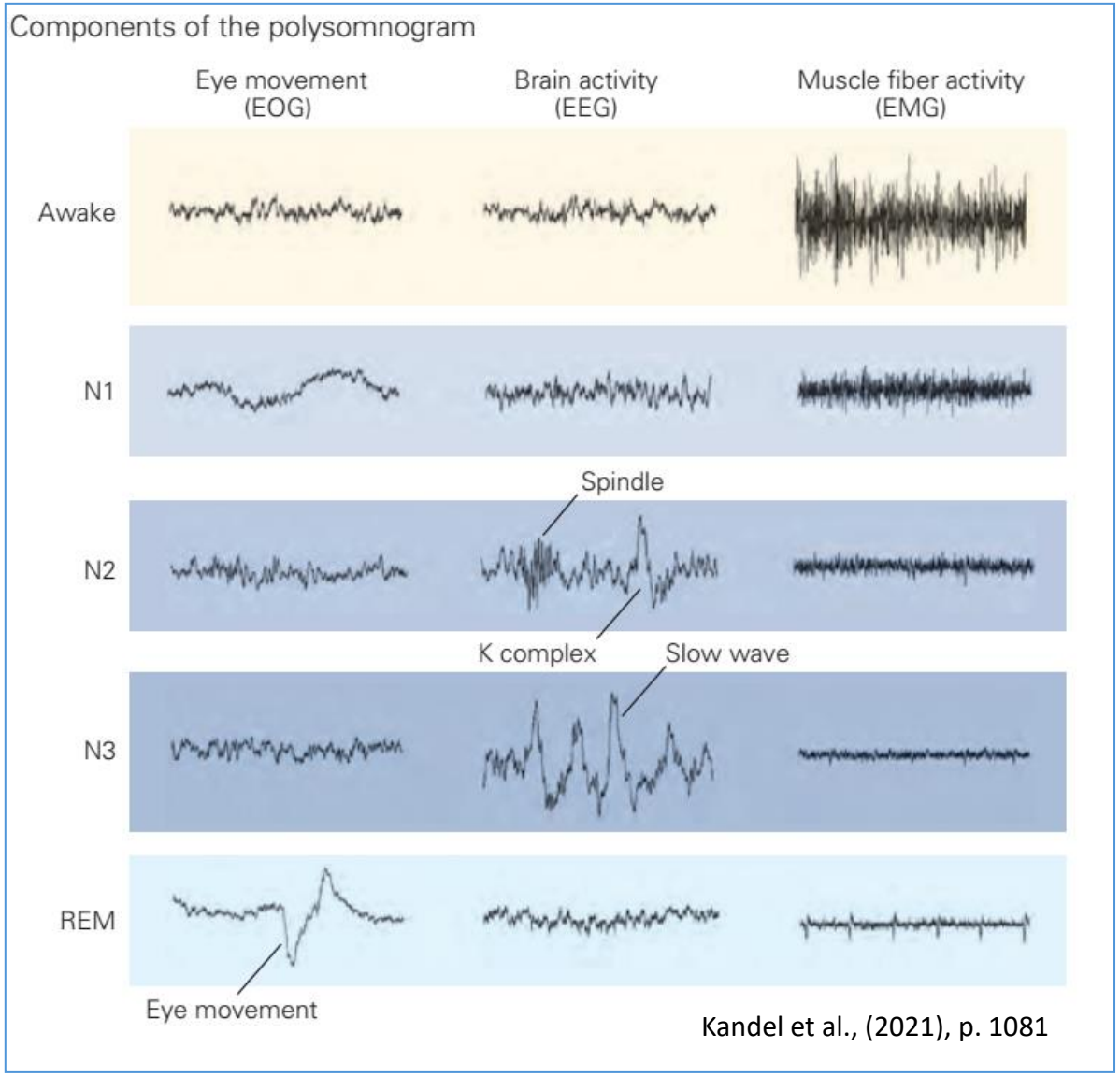
Wakefulness => the EOG shows voluntary eye movements, the EEG shows fast low-amplitude, activity, and the EMG shows variable muscle tone;

N1 sleep => slight slowing of EEG frequencies and slow roving eye movements, with less EMG activity;

N2 sleep => bursts of 12- to 14-Hz activity (“sleep spindles”) and high-voltage slow waves (“K-complexes”);

N3 sleep => high-voltage slow waves;

REM sleep => the EEG is similar to that of the awake state. Rapid eye movements can be seen on the EOG, but the EMG is so silent that contamination by tiny electrocardiogram signals can sometimes be seen (as in the illustrated case).



Kandel et al., (2021), p. 1081

Light non-REM sleep (stage N1):

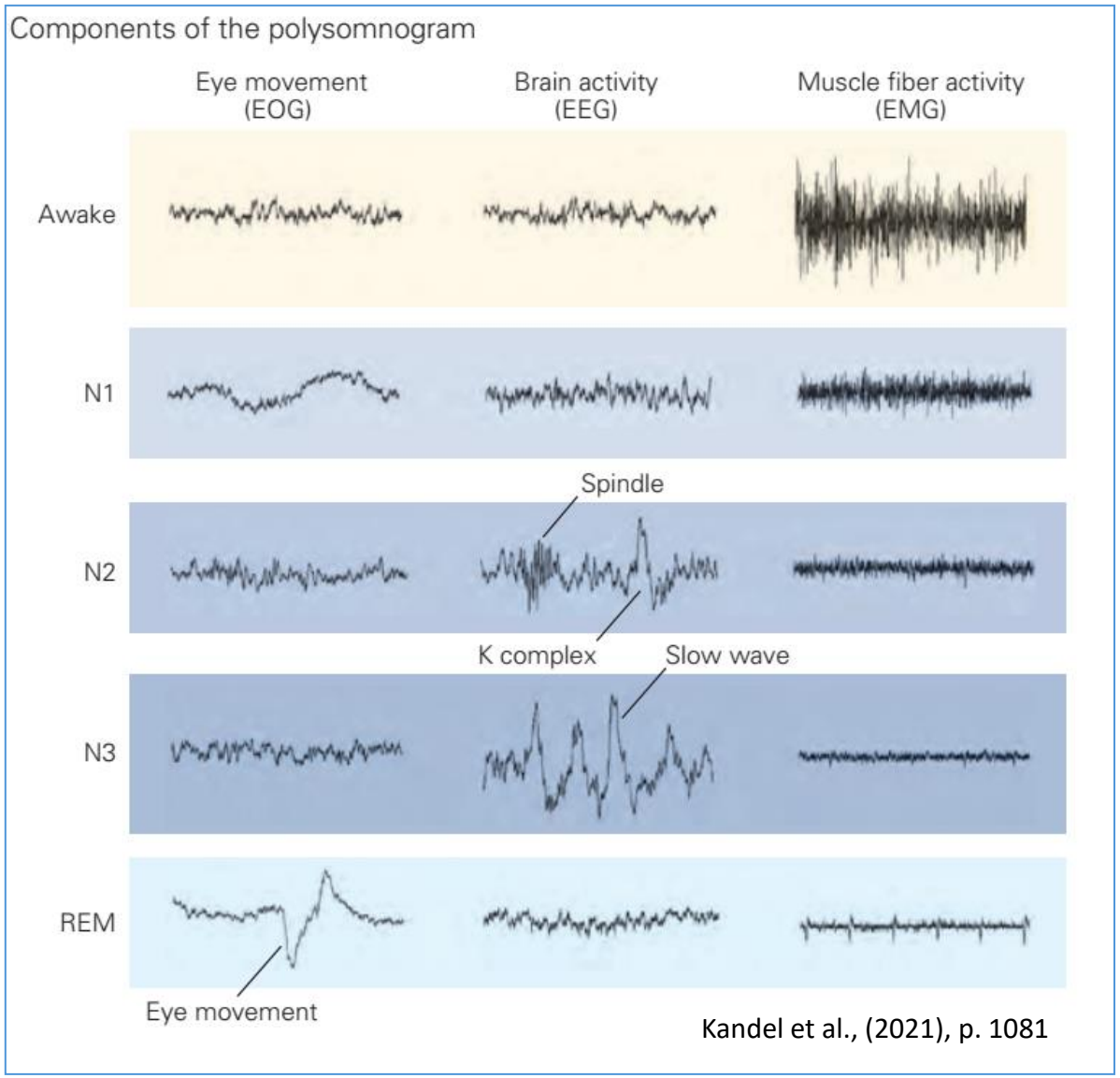
- the EEG slows and shows waves in the **theta** range (4–7 Hz);
- **consciousness** begins to fade, but **minimal stimulation** can trigger wakefulness.

Stage N2:

- slow EEG activity in the **theta** and **delta** range (0.5–4 Hz) as well as **sleep spindles**, 10- to 16-Hz waxing and waning EEG oscillations lasting 1 to 2 seconds, typically with a gradual onset and offset so the EEG waves resemble an old-fashioned spindle tapered at both ends. The EEG also may show large, single slow waves called **K-complexes**.

Stage N3:

- the EEG shows abundant, very slow EEG **delta** activity.

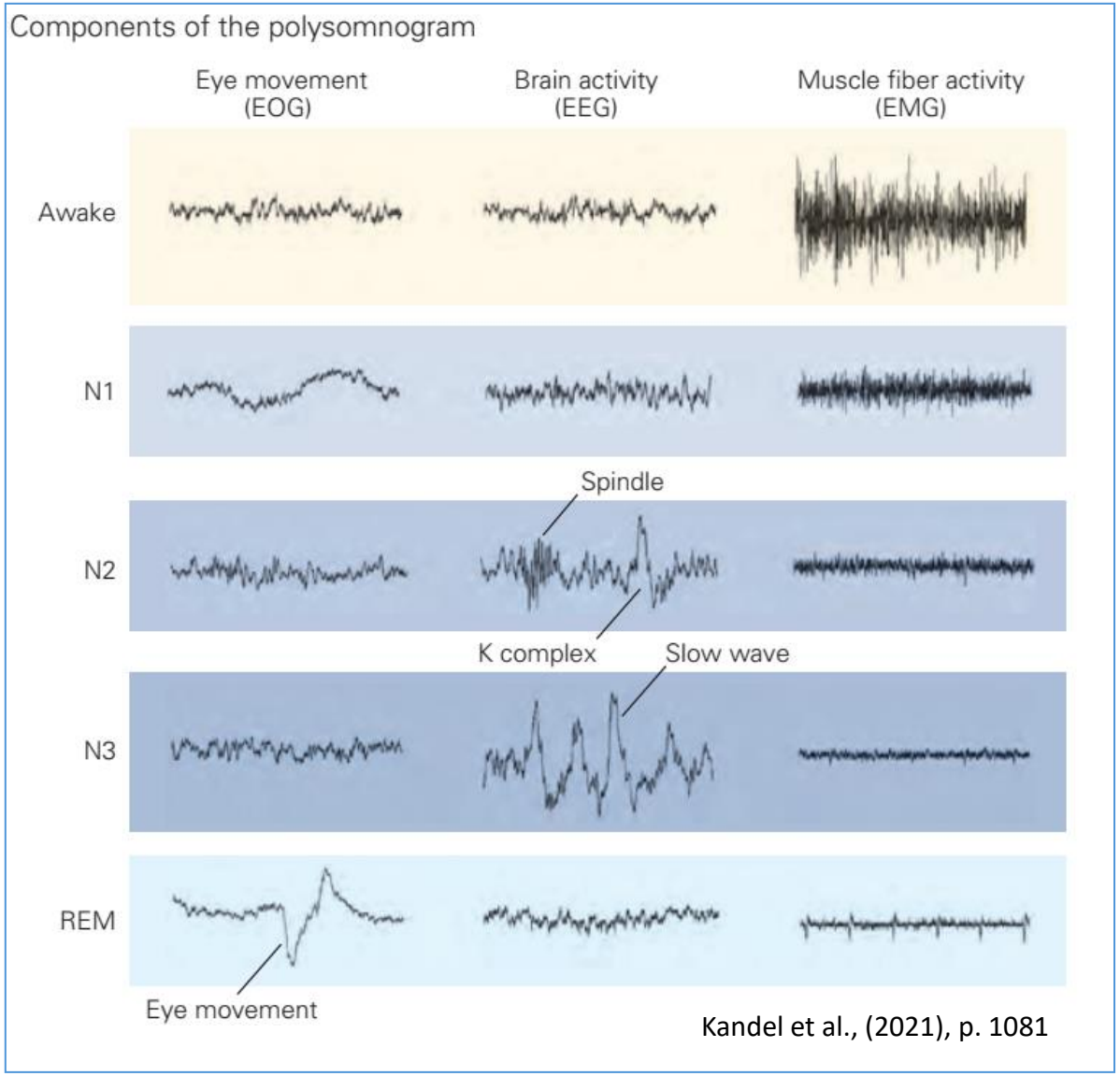


Kandel et al., (2021), p. 1081

During stages **N2 and N3**, people are generally **unconscious** of the world around them as the slow cortical activity disrupts information processing. Across all stages of **non-REM sleep**, **eye movements are absent**, **muscle tone is low**, **breathing is slow and regular**, and **body temperature falls**.

REM:

- **muscle tone is very weak** due to inhibition of motor neurons by descending pathways from the brain stem. This paralysis **does not affect** the neurons that support **respiration**, **eye movements**, and **sphincter control**. This paralysis **prevents** the physical **enactment** of dreams;
- **body temperature falls** further;
- **heart rate** and **blood pressure** can **vary** wildly;
- **vivid** dreams.



Kandel et al., (2021), p. 1081

The circadian rhythm

Mammoth Cave

Nathaniel Kleitman was a faculty member of the Department of Physiology and made significant contributions to modern sleep research. In 1938, Kleitman conducted a sleep research study with graduate student Bruce H. Richardson in Mammoth Cave, Kentucky over the course of 32 days. During the experiment, Richardson and Kleitman adapted to a 28-hour day under "uniform conditions of temperature, illumination, and quiet of the cave." Their experiment demonstrated that the human bodies roughly maintains a 24 hour temperature cycle even with the absence of external cues. Kleitman wrote *Sleep and Wakefulness* in 1939, an account of the Mammoth Cave study findings.

Here is some news footage from that time about the experiment.

Image from the Mammoth Cave Sleep Experiment
From: Box 33 Folder 3, Nathaniel Kleitman Papers. University of Chicago Archives.

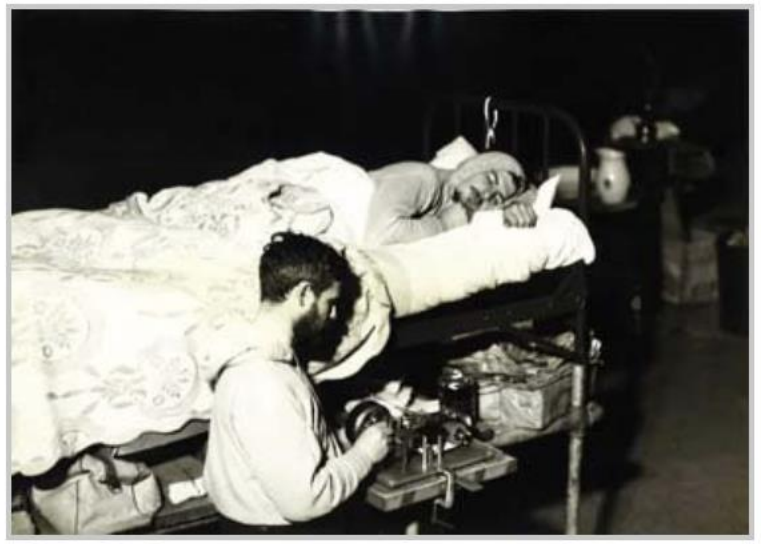
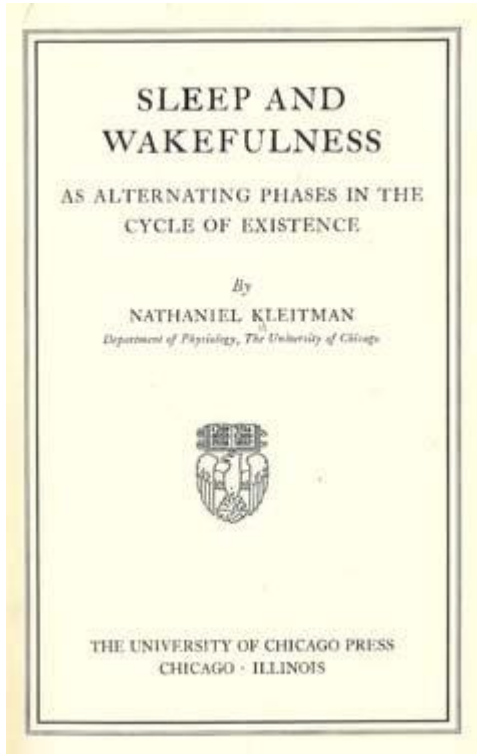


Image from the Mammoth Cave Sleep Experiment
From the Photographic Archive, Special Collections Research Center, University of Chicago Library. Available at: http://photoarchive.lib.uchicago.edu/. Identifer: apf8-03489



http://tinyurl.com/2mzhk9z7

https://www.lib.uchicago.edu/collex/exhibits/discovering-beauty/mammoth-cave/

Old news footage of Kleitman and Richardson in Mammoth Cave

https://storymaps.arcgis.com/stories/643b988969884874ac7a309f9b5c1890

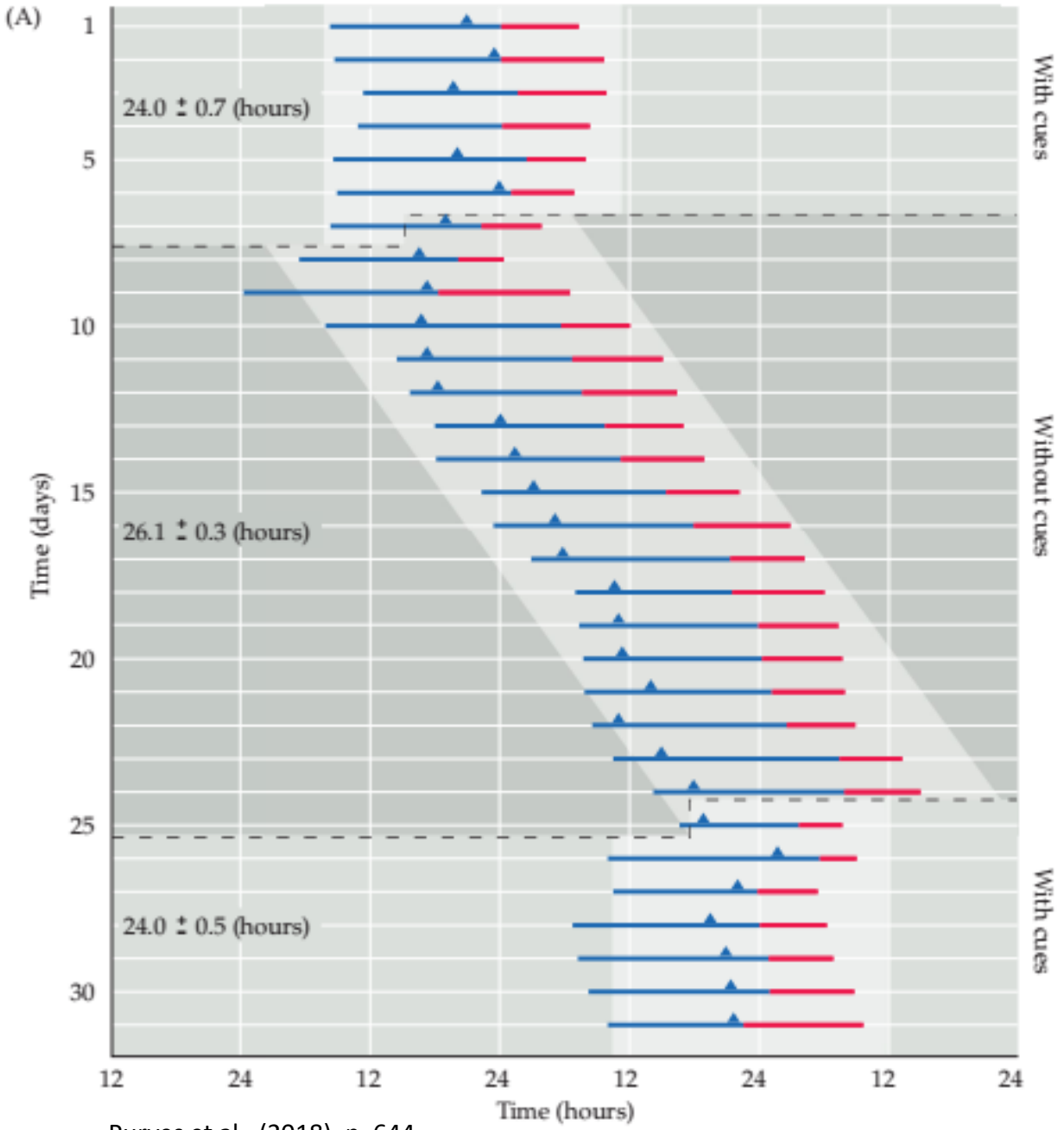
Goal

The goal of their experiment was to determine if humans had an **ingrained 24-hour cycle** or **if we can adjust our circadian rhythm**. Kleitman wanted to adjust himself and graduate student Richardson to a **six-day, 28-hour week**.

Kleitman and Richardson spent **32 days** in the cave with a strict schedule of **sleeping for 9 hours, working for 10, and 9 hours of leisure time**. The **absence of light and noise** and a **constant temperature** made for a great experimental environment.

Results

Because there were only two test subjects, you **can't generalize** this study to the entire human population. That said, **Richardson did adjust** to the study's sleep schedule, while **Kleitman had difficulties and never acclimated**; he was tired during the "days" and had difficulty sleeping through the "nights.“ Richardson was approximately 20 years **younger** than Kleitman; this could be a factor in the ability to adjust to new sleep schedules. Additionally, individual habits, such as Richardson being a **student** and having a less structured sleep schedule to begin with, may impact the ability to adjust your circadian rhythm.



Purves et al., (2018), p. 644

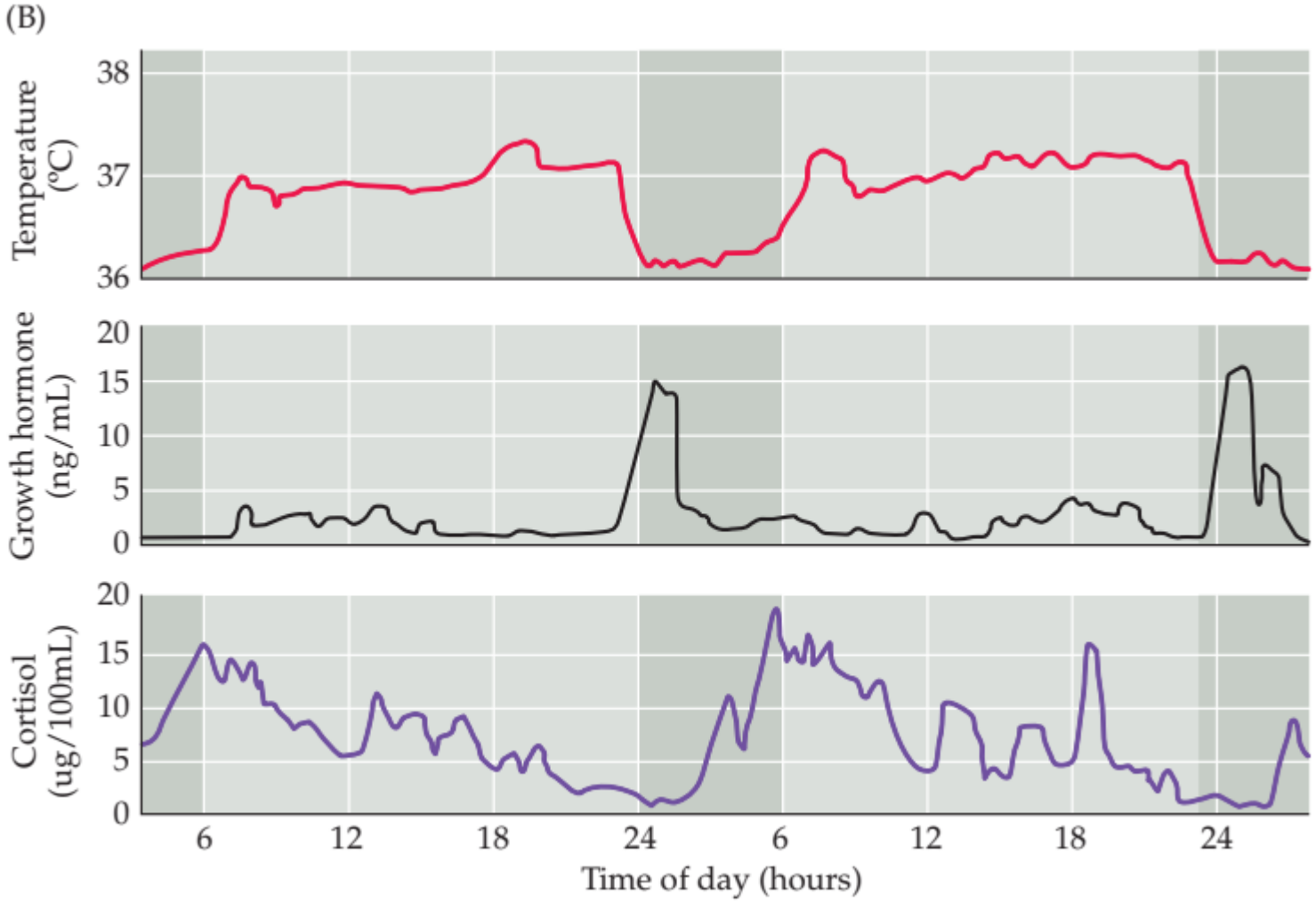
(A) Circadian rhythm in the absence of cues.

The illustration graphs the **waking (blue) and sleeping (red)** status of a volunteer in an **isolation chamber with and without cues** about the **day–night cycle**.

Numbers represent the mean ± standard deviation of a complete wake–sleep cycle in each condition.

Triangles represent times when the rectal **temperature** was maximum.

The individual **maintains daily cycles of about 25.2 hours**, **drifting** an entire day over this period. **Blind people** who cannot relay light signals to the **suprachiasmatic nucleus** often live continuously like this, a condition **called non–24-hour wake–sleep disorder**.



Purves et al., (2018), p. 644

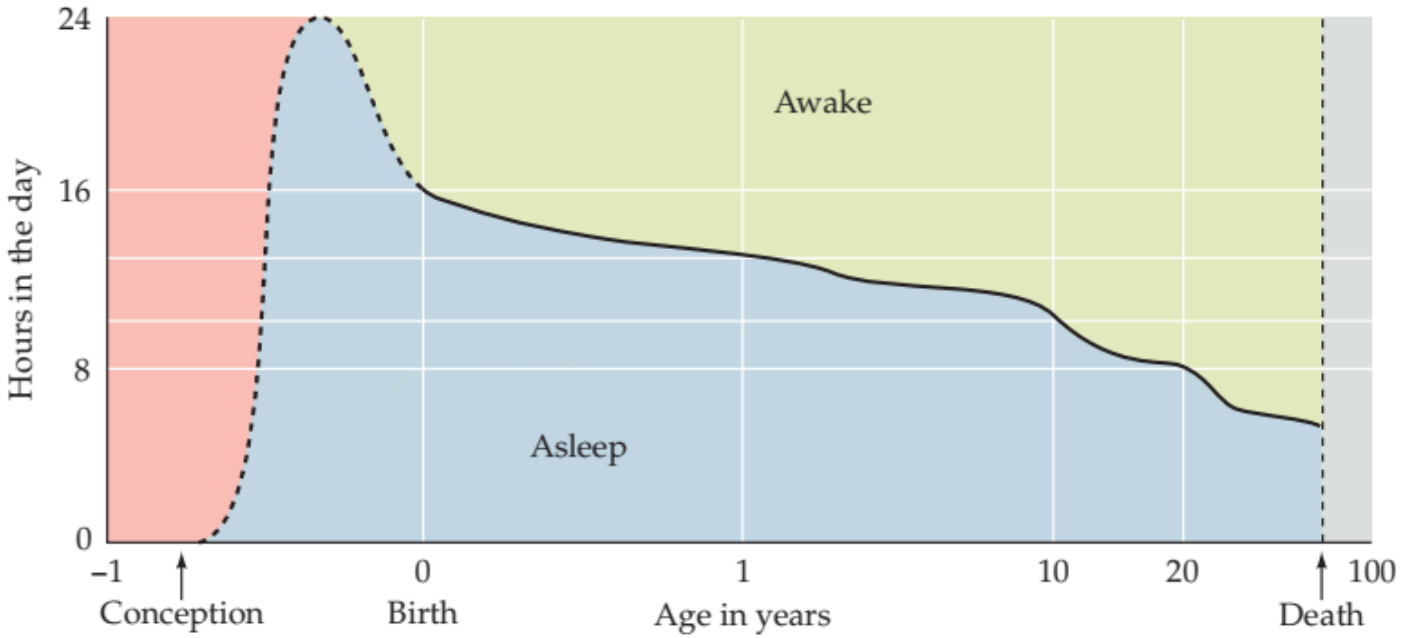
(B) Circadian rhythmicity of homeostatic regulation.

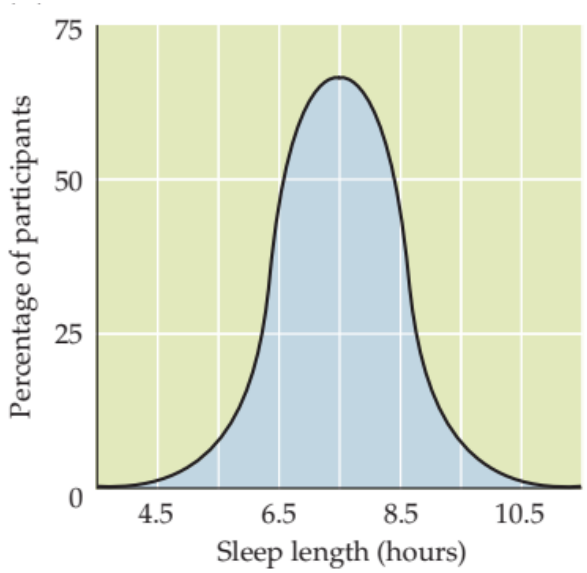
Core body temperature and blood levels of **growth hormone** and **cortisol** all show a rhythmic pattern of roughly 24 hours.

In the early evening, core **temperature** begins to **decrease** whereas **growth hormone** begins to **increase**.

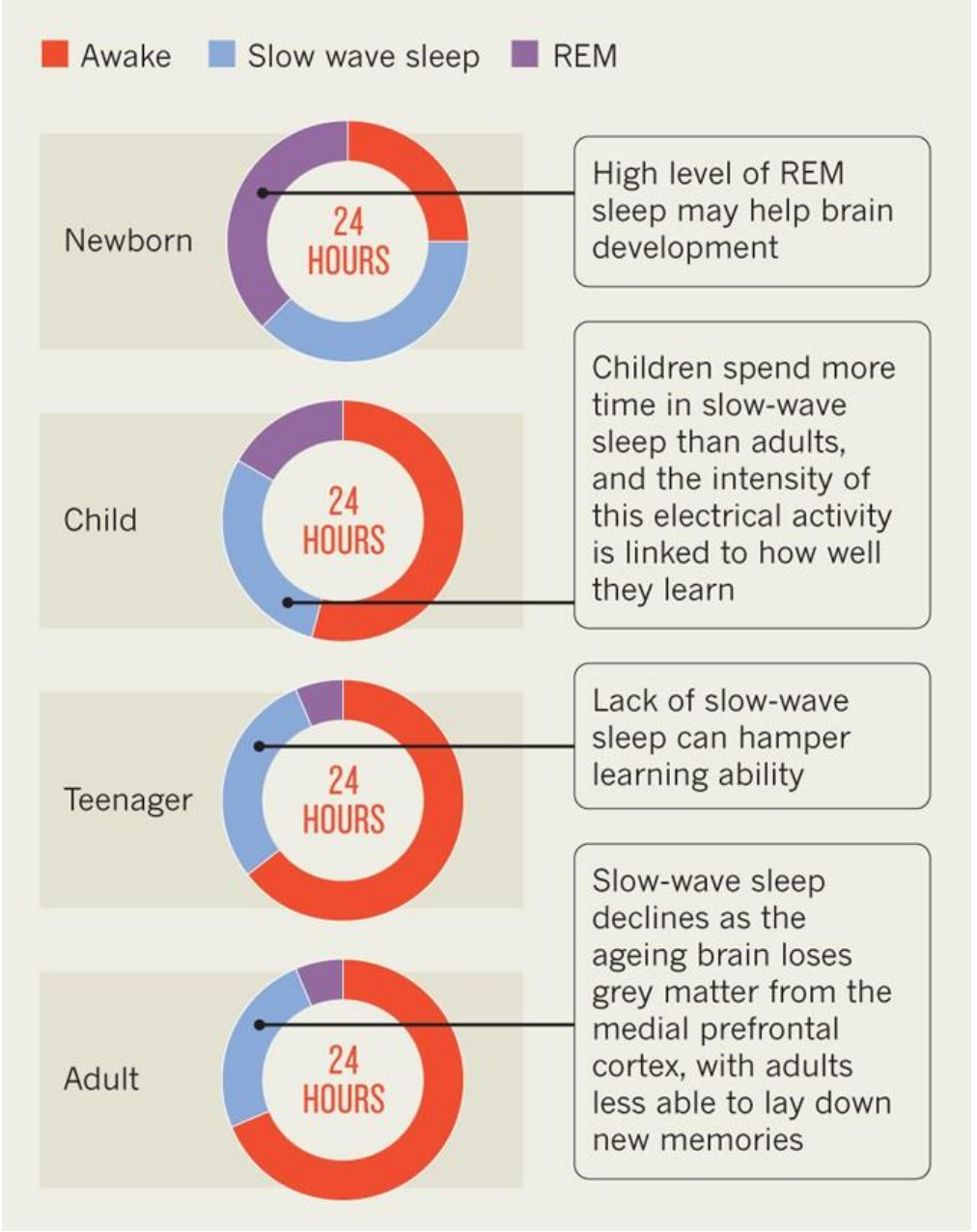
The level of **cortisol**, which reflects stress, begins to **increase toward morning** and stays elevated for several hours.

Sleep variations across the lifespan





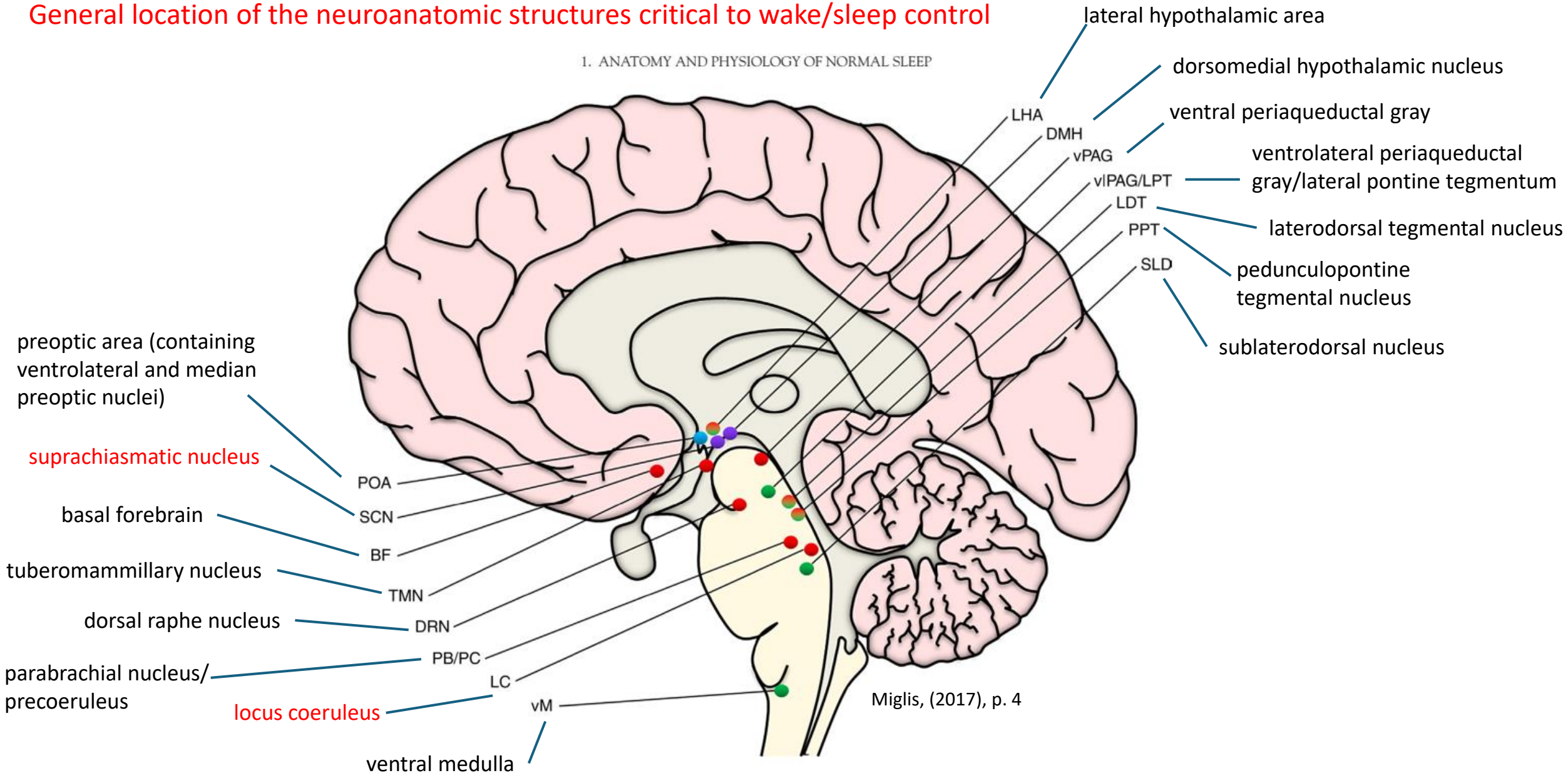
Purves et al., (2018), p. 649



https://pubmed.ncbi.nlm.nih.gov/23698505/

Physiology of sleep

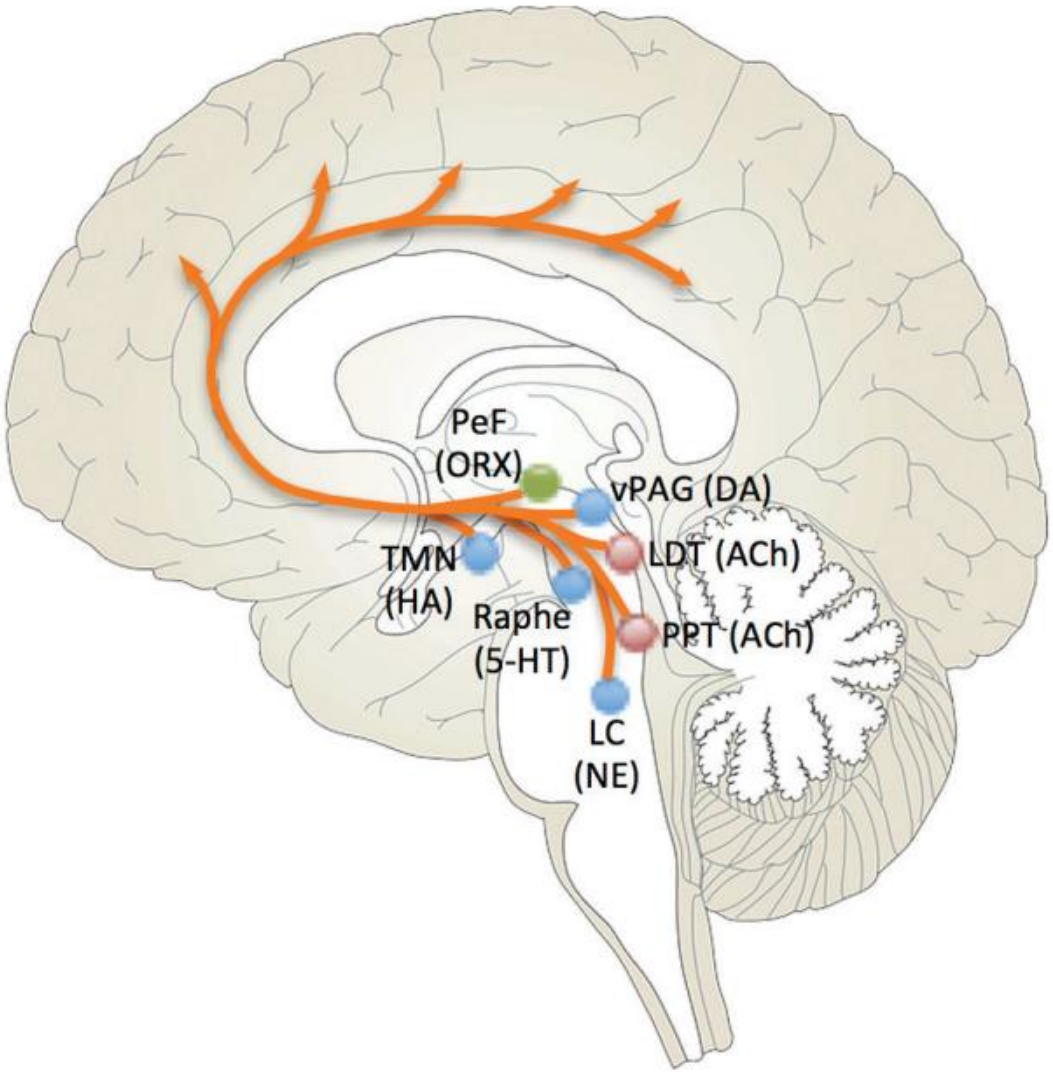
General location of the neuroanatomic structures critical to wake/sleep control



Miglis, (2017), p. 4

The colors of the marker indicate the predominant role played by the structure: red for arousal, blue for sleep, green for REM, purple for circadian regulation, and multicolored markers indicating multistate activity.

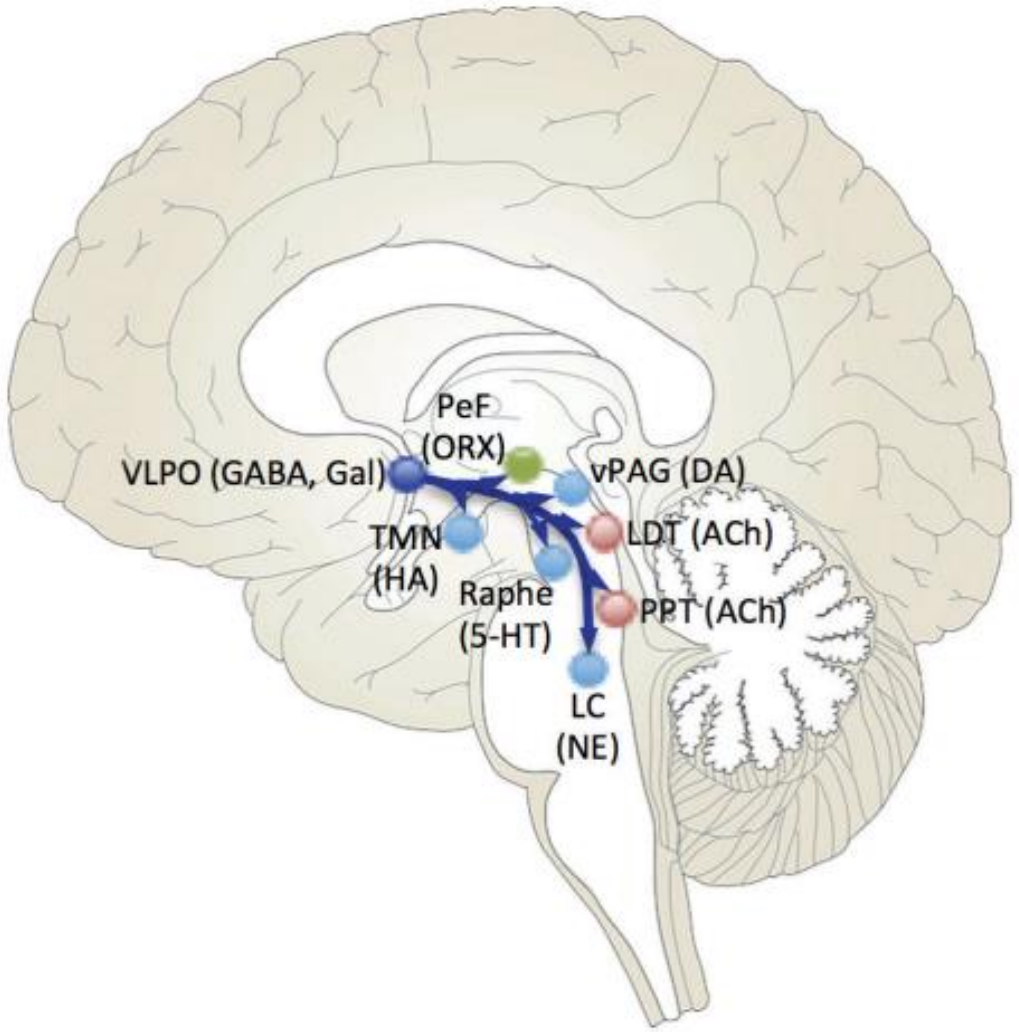
Ascending arousal system => wakefulness



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755451/

Major neurochemicals of this ascending arousal system include excitatory **norepinephrine** arising from the **locus coeruleus (LC)**, **serotonin (5-HT)** from the **midline raphe nuclei**, **histamine** from the **tuberomammillary nucleus**, **dopamine** from the **ventral periaqueductal gray matter**, **acetylcholine** from the **pedunculopontine tegmentum**, and the **laterodorsal tegmentum of the pons** and **orexin** from the **perifornical area**.

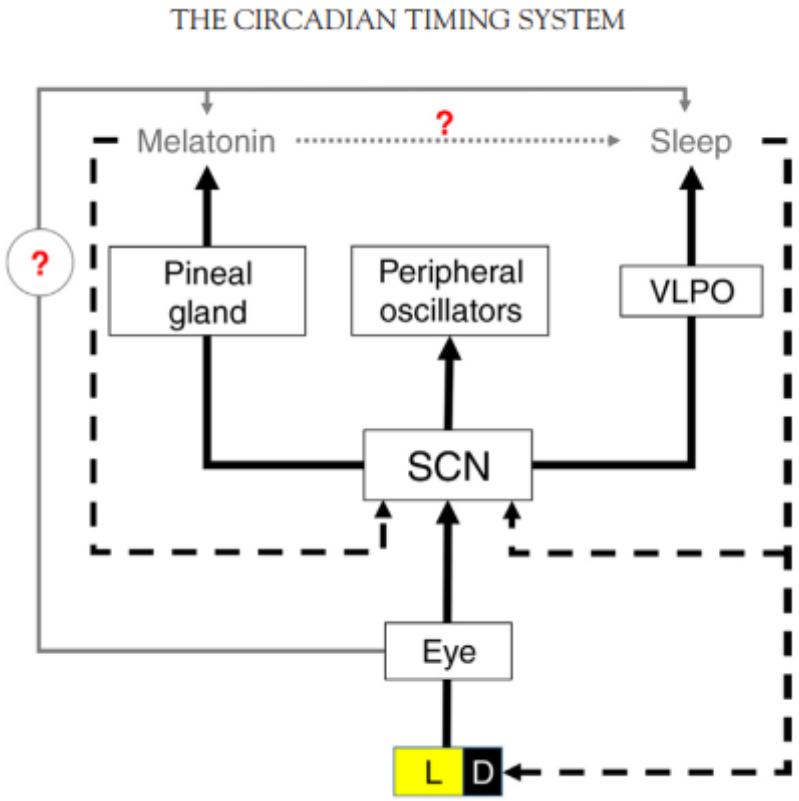
Suppression of activity in the ascending arousal systems => initiation and maintenance of sleep



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755451/

This is accomplished by **inhibitory neurons (GABA and galanin)** of the **ventrolateral preoptic area (VLPO)** which remain active throughout sleep. The molecular triggers that activate the VLPO and initiate sleep onset **have not been fully defined**, but a substantial body of evidence points to **extracellular adenosine** as a candidate. Adenosine accumulates in **basal forebrain** during wakefulness and diminishes with ongoing sleep. Adenosine receptors are expressed in the VLPO and **adenosine activates VLPO** neurons in vivo, making it a reasonable candidate for the “sleep switch.” In addition, the VLPO receives important circadian modulation from the **suprachiasmatic nucleus**—the **central circadian clock**.

The circadian timing system

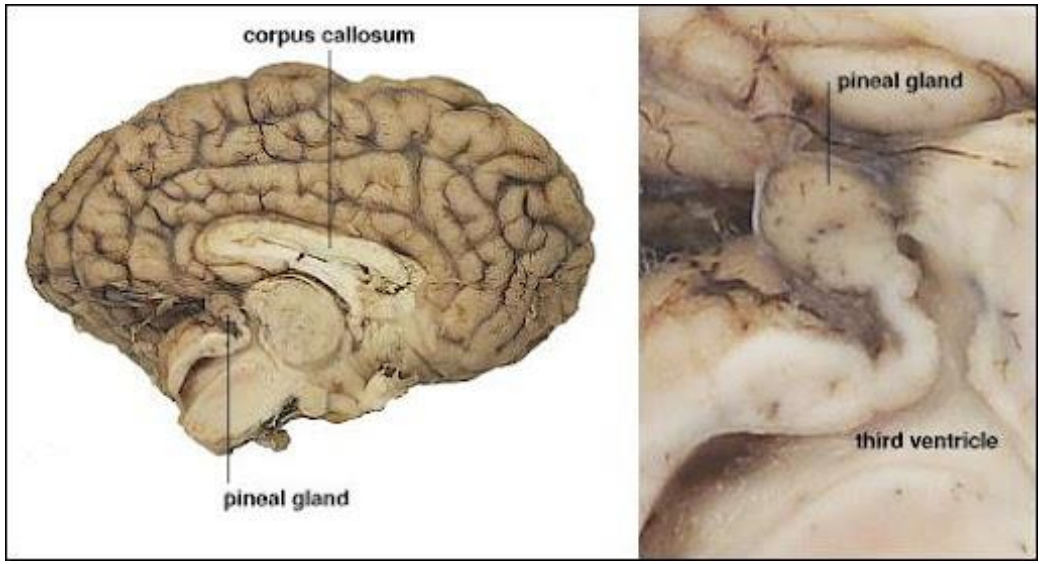


Miglis, (2017), p. 31

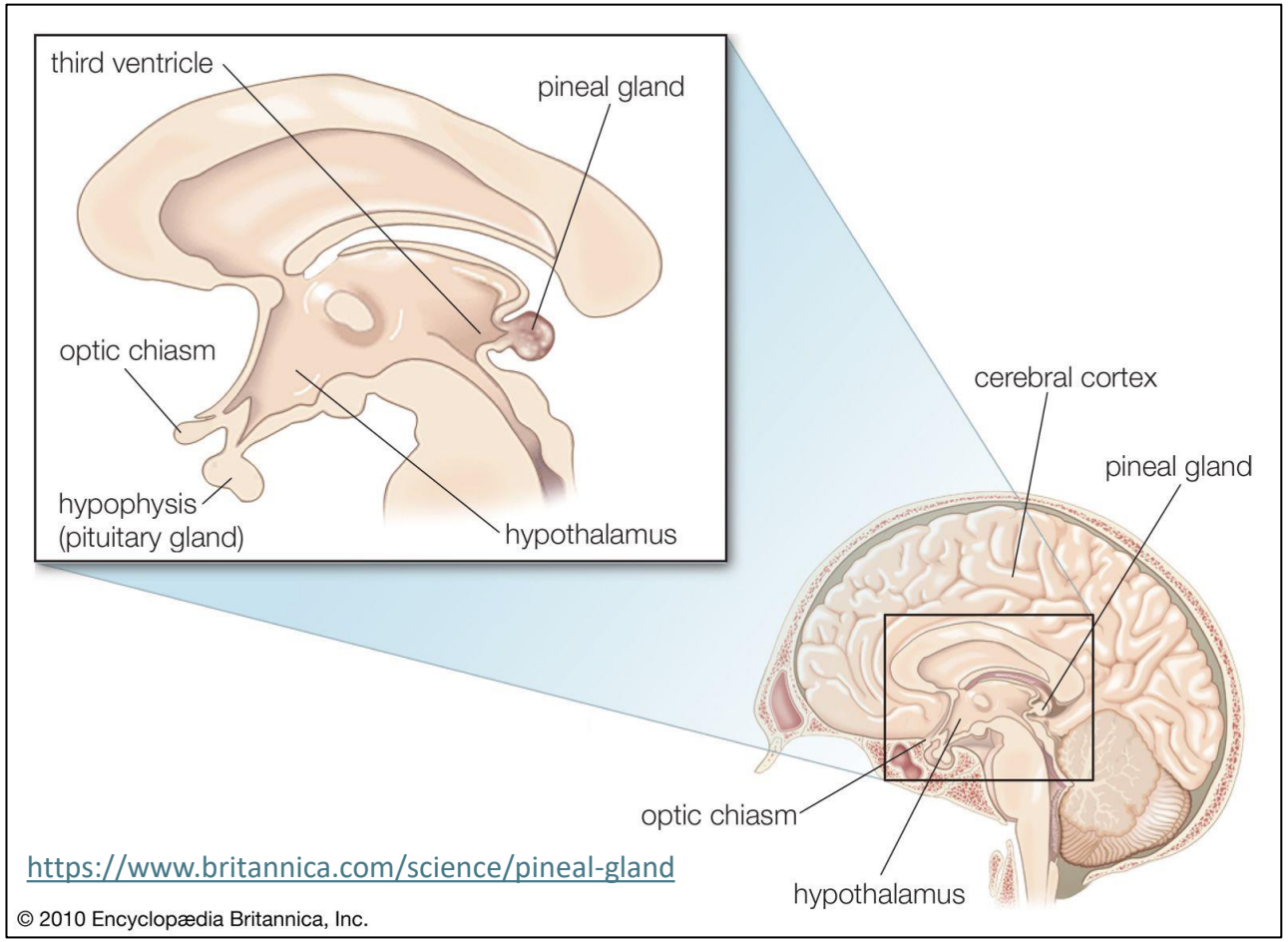
The central pacemaker is located in the **basal hypothalamus**, dorsal to the optic chiasm on both sides of the third ventricle and is called the **suprachiasmatic nucleus**. It is composed of **two nuclei** containing around **10,000 neurons each**, nearly all of which can act as **individual circadian oscillators** with a **high electrical firing rate during the day** and **low activity during the night**.

Melatonin ("hormone of darkness") is the only known hormone synthesized by the **pineal gland** and is **released in response to darkness**. It is produced from **serotonin**.

The pineal gland



http://tinyurl.com/2tdv2452



https://www.britannica.com/science/pineal-gland

"While embryologically part of the brain, the **pineal gland** is located **outside the blood brain barrier** and loses its connections with the central nervous system, having **sympathetic innervation** as its main source.

This perhaps accounts for the ability of the pineal gland to have a **large uptake of tryptophan** (i.e., precursor for serotonin) leading to a **high melatonin production** and secretion in response to darkness." (Masters et al., 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4334454/)

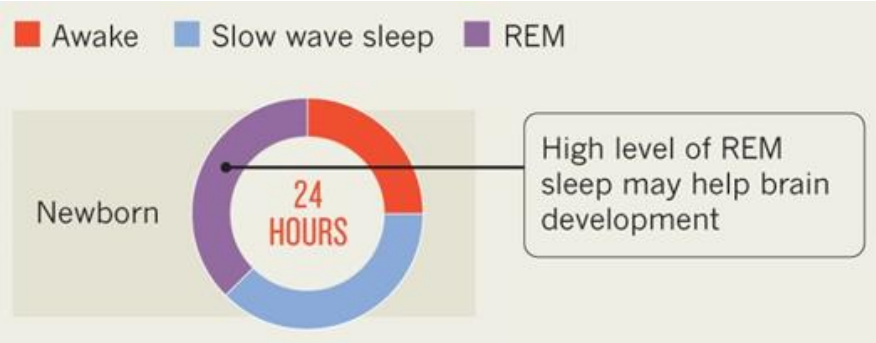
Sleep disorders

Why DO we sleep?

"REM sleep is the proverbial riddle, wrapped in a MYSTERY inside an ENIGMA."

(Siegel, 2003, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9059976/)

"**Restorative**, or **recuperative theories** hypothesize that sleep serves one or more of the following functions: to **rest and repair**; to **consolidate** what we have learned while we were awake; to **dream**; to enhance the **immune response**; to avoid the serious **detrimental effects of deprivation**; to **detoxify**." (Freiberg, 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7120898/)



REM sleep's intense neuronal activity and energy expenditure may have a role early in life in establishing the genetically programmed neuronal connections.

e.g., preventing REM sleep in cats during this early period => abnormalities in the development of the visual system. (Siegel, 2003)

https://www.youtube.com/watch?v=kAG4xQ91WEk

Narcolepsy

https://www.youtube.com/watch?v=d41BfD21b48

Narcolepsy is a **central nervous system hypersomnia disorder**, characterized by:

- cataplexy (sudden loss of muscle tone while a person is awake);
- excessive daytime sleepiness (EDS);
- sleep paralysis (the temporary inability to move or speak while falling asleep or waking up);
- fragmented sleep and insomnia;

(http://tinyurl.com/mr363898)

There are two major types of narcolepsy:

Type 1 narcolepsy (previously known as *narcolepsy with cataplexy*)—This diagnosis is based on the individual either having **low levels** of a brain hormone (**hypocretin**) or reporting **cataplexy** and having **excessive daytime sleepiness** on a special nap test.

Type 2 narcolepsy (previously known as *narcolepsy without cataplexy*)—People with this condition experience **excessive daytime sleepiness** but usually **do not have muscle weakness** triggered by emotions. They usually also have less severe symptoms and have **normal levels** of the brain hormone **hypocretin**. (http://tinyurl.com/mr363898)

FIGURE 8.2 **A cataplectic episode in an adult demonstrating buckling of the knees and falling to the floor.** *Source: Courtesy of Overeem S, Mignot E, van Dijk JB, Lammers GJ. Narcolepsy: clinical features, new pathophysiologic insights, and future perspectives.* J Clin Neurophysiol. *2001;18(2):78–105.*

Miglis, (2017), p. 146

Fatal familial insomnia

https://www.youtube.com/watch?v=nIeTVVAEFn8

Introduction

Go to:

Fatal familial insomnia (FFI) is a remarkably rare and invariably fatal inherited neurodegenerative prion disease. The mode of inheritance of this disease is autosomal dominant and involves a mutation of the prion protein (PRNP) gene. Aggressively progressive insomnia, with subsequent autonomic (tachycardia, hyperhidrosis, hypertension), cognitive (short-term memory and attentional deficits), motor system (balance problems), and endocrine dysfunction are a hallmark of the disease. The disease is currently incurable and has a mean course of 18 months, ultimately leading to death. The earliest description of the disease dates back to 1765 with a report of an Italian man with symptoms suggestive of FFI. The disease was formally identified and clinically described in 1986 by Lugaresi E. et al., followed by subsequent studies, further describing its pathophysiology, etiology, and clinical course.[1][2]

https://www.ncbi.nlm.nih.gov/books/NBK482208/

Genetic prion diseases are **very rare**. Annually, there are **1 to 1.5 new cases** of genetic and non-genetic prion diseases **per one million people**. Genetic forms of prion disease constitute approximately **10% of the total cases** of prion diseases. FFI is exceptionally rare with the disease-causing **mutation** found in around **50 families worldwide**.

It manifests as a **focal neuronal loss in the thalamus, inferior olivary nucleus**, and **cerebellum**.

Remember

**autosomal dominant mutation= a mutation on one of the non-sex chromosomes, with a single copy of the mutated gene (from one parent) being enough to cause the disorder.*

*** prion = a misfolded protein that can induce misfolding of normal variants of the same protein and trigger cellular death.*

Staging

Go to:

FFI has been described to have four stages:[15]

- Stage 1: The first stage of the disease is identified by the subacute onset of insomnia, which worsens over a period of few months and causes psychiatric symptoms such as phobia, paranoia, and panic attacks. During this time, patients may report lucid dreaming.
- Stage 2: In the next 5-month period, psychiatric symptoms worsen along with worsening insomnia, and patients experience hallucinations. Autonomic dysfunction in the form of sympathetic hyperactivity is seen.
- Stage 3: This short stage of around three months is typically dominated by total insomnia and complete disruptions of the sleep-wake cycle.
- Stage 4: The final stage of the disease can last for six months or more and is defined by rapid cognitive decline and dementia. Patients experience an inability to voluntarily move or speak, which is followed by coma and eventual death.

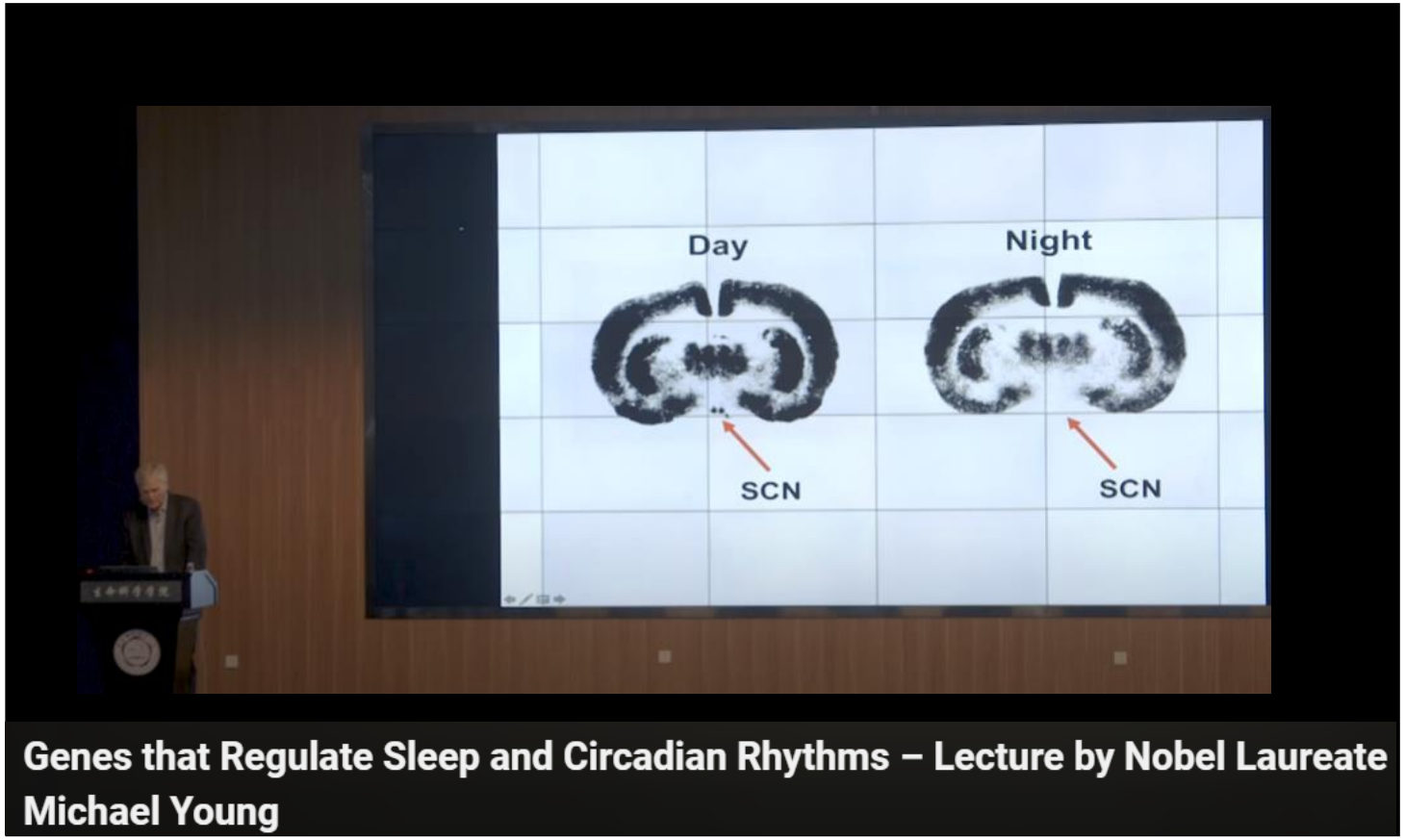
Prognosis

Go to:

The disease course can last from 7 to 36 months, with an average duration of 18 months leading to eventual death. Patients with homozygous (Met-Met) mutation have a shorter mean survival time compared to heterozygous (Met-Val) patients.[16][17]

https://www.ncbi.nlm.nih.gov/books/NBK482208/

Further resources



https://www.youtube.com/watch?v=AIB3E70QzEY

Further resources

https://www.youtube.com/watch?v=pJil_BLs3LM

Further reading

News | Published: 05 October 2017

Medicine Nobel awarded for work on circadian clocks

Ewen Callaway & Heidi Ledford

Nature **550**, 18 (2017) | Cite this article

3553 Accesses | **47** Citations | **512** Altmetric | Metrics

Jeffrey Hall, Michael Rosbash and Michael Young unpicked molecular workings of cells' daily rhythms.

Michael Rosbash (left), Jeffrey Hall (centre) and Michael Young (right) have been recognized for their work on circadian clocks. Credit: Nora Tam/SCMP

https://www.nature.com/articles/nature.2017.22736

Further reading

Journal of the History of the Neurosciences
1996, Vol. 5, No. 3, pp. 213-227

0964-704X/96/0503-213$12.00

MEMORIES OF FAMOUS NEUROPSYCHOLOGISTS

The Discovery of REM Sleep*

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ABSTRACT

The impetus to pursue the study of ocular motility in sleeping adults was derived from a previous study conducted by the author on infants. He noted through visual observation alone that there was an approximate twenty minute interlude of complete ocular quiescence during each hour of sleep. This period of quiescence was termed 'No Eye Movement Period' or 'N.E.M. Period', and it was the intent of the author to ascertain what effect age would have on the distribution of N.E.M. periods during sleep. In the latter part of 1951, the first continuous all-night recording of ocular motility in sleep using a combined EEG and EOG technique was conducted on the author's eight year old son. Instead of N.E.M. Periods, what he found were approximately twenty minute periods of vigorous ocular activity including saccadic-like eye movements. Although he ultimately termed these epochs as 'REM Periods', his initial intent was to name them 'Jerky Eye Movement Periods' or 'JEM Periods'. Ironically, some three decades later he found that a mathematical measure of jerkiness was a better discriminator than velocity in distinguishing REMs from waking saccades. Kleitman, who was the thesis advisor, played the role of skeptic during the REM discovery and demanded unassailable proof of the existence of REM. His feelings had to be ambivalent inasmuch as the REM state, with its concurrent activated cerebral cortex, negated his own theory that sleep was a completely passive phenomenon.

https://www.semel.ucla.edu/sites/default/files/sleep/pdf/96-rem-discovery-aserinsky.pdf

Taylor & Francis Online

Journal of the History of the Neurosciences

Basic and Clinical Perspectives

https://www.tandfonline.com/journals/njhn20

Changing Graphic Representations of the Brain from the Late Middle Ages to the Present
Volume 31, Issue 2-3, 2022 pages 109-393

Gall and Phrenology: New Perspectives
Volume 29, Issue 1, 2020 pages 1-157

Charles Darwin and Neuropsychology
Volume 19, Issue 2, 2010 pages 83-208

Article
Hikikomori (引きこもり): Ancient term, modern concept ›

Régis Olry

Published online: 17 Jul 2023 (Vol.32, No.4, 2023)

Article
The advent of epilepsy directed neurosurgery: The early pioneers and who was first ›

Ian Bone & James L. Stone

Pages: 470-490

Published online: 18 May 2023

Further reading

Review > Sleep. 2005 Feb;28(2):255-73. doi: 10.1093/sleep/28.2.255.

The K-complex: a 7-decade history

Ian M Colrain [1]

Abstract

The K-complex was first described by Loomis et al 67 years ago in a paper that was one of a series of seminal studies of sleep conducted in Loomis' private laboratory. The study of the K-complex was almost immediately taken up by many notable figures in early electroencephalography research, such as Robert Schwab, Mary Brazier, and W. Gray Walter. More than 200 papers have been published in the years since these early studies, including major reviews in 1956 by Roth et al and in 1985 by Peter Halász. More recently, K-complex study has been taken up by event-related potentials researchers such as Ken Campbell and animal neurophysiologists such as Florin Amzica and Mircea Steriade. The present paper provides a historical and thematically based review of the K-complex literature and attempts to integrate the various theoretical positions and neurophysiologic data. Specifically, K-complexes are discussed in terms of their relationship to other electroencephalographic phenomena, their relationship to autonomic activation, their role in the study of information processing during sleep, and what is understood of their underlying neurophysiology.

https://pubmed.ncbi.nlm.nih.gov/16171251/

Further reading