EEG and Sleep Team Based Learning

Reading Assignment

Objectives:

- Describe the generators of and indications for EEG.
- Describe the EEG appearance of the following: normal, primary generalized epilepsy, focal epilepsy, coma, brain death.
- Describe the physiological changes that occur during normal REM and non-REM sleep.
- Describe the circuitry for photoentrainment, and the consequences of disruption of this pathway.
- Describe the EEG appearance of the following stages of sleep: Wake (Stage W); Stage 1 (N1); Stage 2 (N2); Stages 3 and 4 (N3); and Stage REM.
- Describe the clinical features, diagnostic evaluation, and treatment of the following conditions: Obstructive sleep apnea, narcolepsy, restless legs syndrome/periodic limb movement disorder, sleep terror disorder; and circadian rhythm disorders
- Describe the indications for polysomnograms and multiple sleep latency tests (MSLTs).

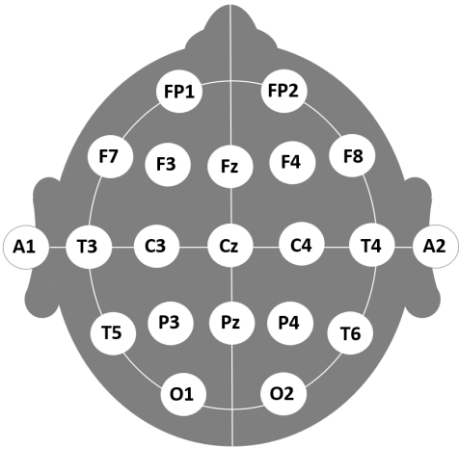
ELECTROENCEPHALOGRAPHY

What is an EEG (electroencephalogram)?

The EEG is a graph of voltage (y axis) versus time (x axis).

How is an EEG recorded?

An EEG is typically recorded by placing leads on the patient's scalp. One lead is referenced to another (the two leads comprising a channel) and voltage is recorded as the difference between 2 leads. The voltage is then plotted over time.



(Image by EC Mader)

Figure 1. EEG lead placement and nomenclature

A=auricular
FP=frontopolar
F=frontal
T=temporal
C=central
P=parietal
O=occipital

Odd numbers are on the left.
Even numbers are on the right.

What is being recorded on EEG?

Rhythmical cortical EEG arises from the interaction between the thalamus and cortex. Postsynaptic potentials (inhibitory and excitatory) are generated mainly by cortical pyramidal cells. The postsynaptic potentials of the cortical pyramidal cells closest to the scalp leads generate the EEG patterns. Scalp electrodes may not be able to detect seizure activity in deeper cortical structures. **Action potentials do NOT contribute significantly to EEG.**

What are the indications for EEG?

The most important indication for EEG is in the diagnosis and localization of epilepsy. Focal-onset seizures (seizures originating in one part of the brain and potentially spreading to involve the entire brain) can be differentiated from primary generalized seizures (seizures originating from abnormal electrical discharges of the entire brain occurring at the same time). EEG is also a vital component of polysomnograms (sleep studies). Staging of sleep is essential in the diagnosis of many sleep disorders. Multiple Sleep Latency Tests (MSLTs), which measure daytime somnolence, require staging of sleep. Commonly, EEG is used in the evaluation of coma. Although it is usually not necessary in the determination of brain death, EEG is sometimes used as a confirmatory study.

EEG frequencies

Frequencies are determined by counting the number of waves (peaks) per second. See Figure 2.

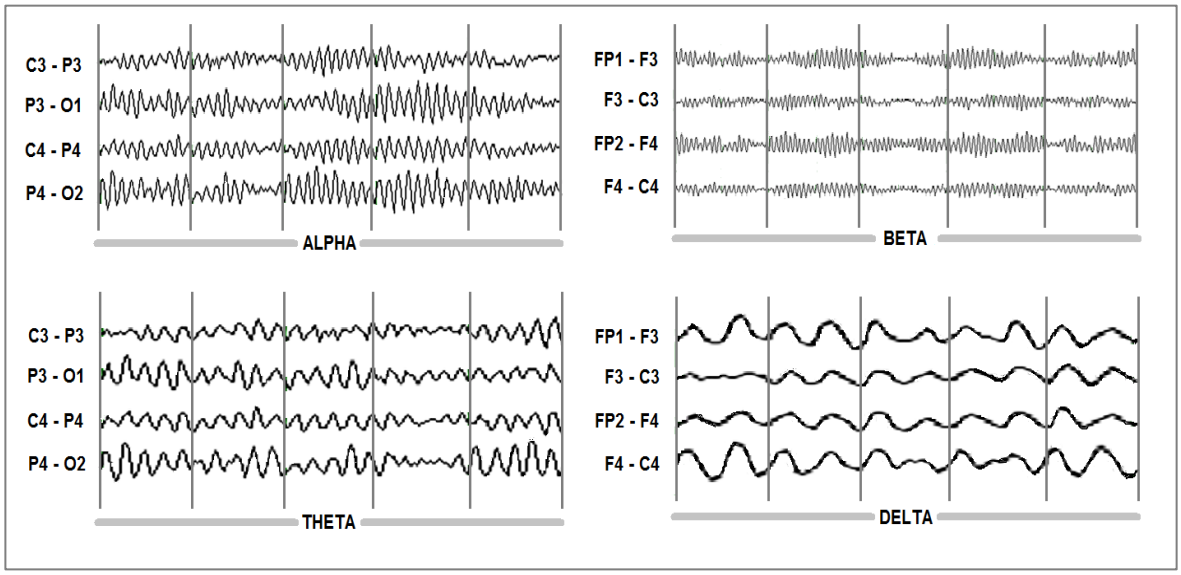


Figure 2. EEG frequencies. a. **Alpha frequency** ranges from 8-13 Hertz (Hz) or cycles per second (/s). b. **Beta frequency** is > 13 Hz. c. **Theta frequency** ranges from 4 to <8 Hz. d. **Delta frequency** is < 4 Hz. (Image by EC Mader)

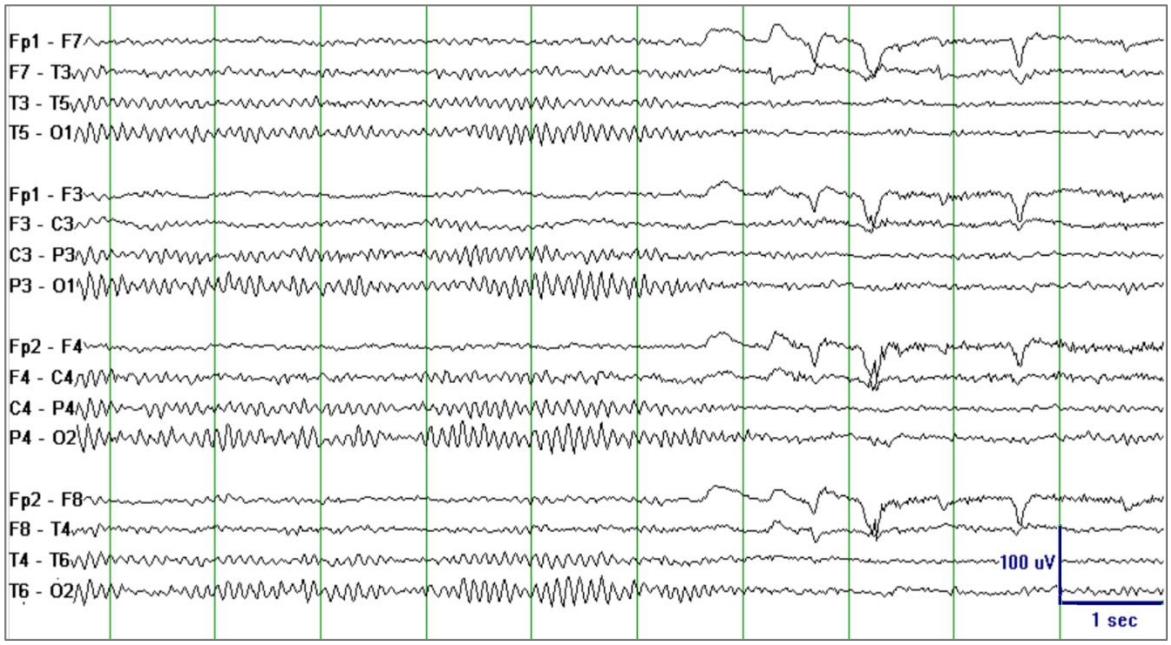


Figure 3. An example of the alpha rhythm. (Image by EC Mader)

During relaxed wakefulness, with eyes closed, a normal adult will have an alpha frequency (8-13 Hz or cycles/second) in the posterior (occipital) leads. This can be seen in the first 6 seconds of the epoch above (see Figure 3). By definition, alpha rhythm is attenuated when the patient opens his or her eyes. Eye movements are seen from the 6th-9th second above. They are the large deflections that occur in the leads closest to the eyes (fronto-polar leads). They appear as in-phase (in the same direction) in the fronto-polar leads. Compare the in-phase eye movements recorded in the fronto-polar leads to the out-of-phase eye movements recorded in the eye channels in a sleep study (Figure 19).

How does one approach an EEG?

Traditionally, 10-second epochs were displayed per page in EEG. However, with large screen computers, longer time periods can be displayed. The vertical lines divide the tracing into one second segments. Start by identifying the background activity. Once the background activity is identified, look for activity that does not fit into background. Examples of activity that does not fit into the background are as follows: spikes; sharp waves; and slow waves (defined below). In addition, note the distribution of the activity. Is it generalized (starting in all leads simultaneously) or focal (occurring only in a few leads)? Does it have a focal onset, then generalize by spreading to contiguous leads? What is the timing of the activity? Does it only occur during drowsiness or sleep, or during provocative maneuvers (hyperventilation, sleep deprivation, photic stimulation)?

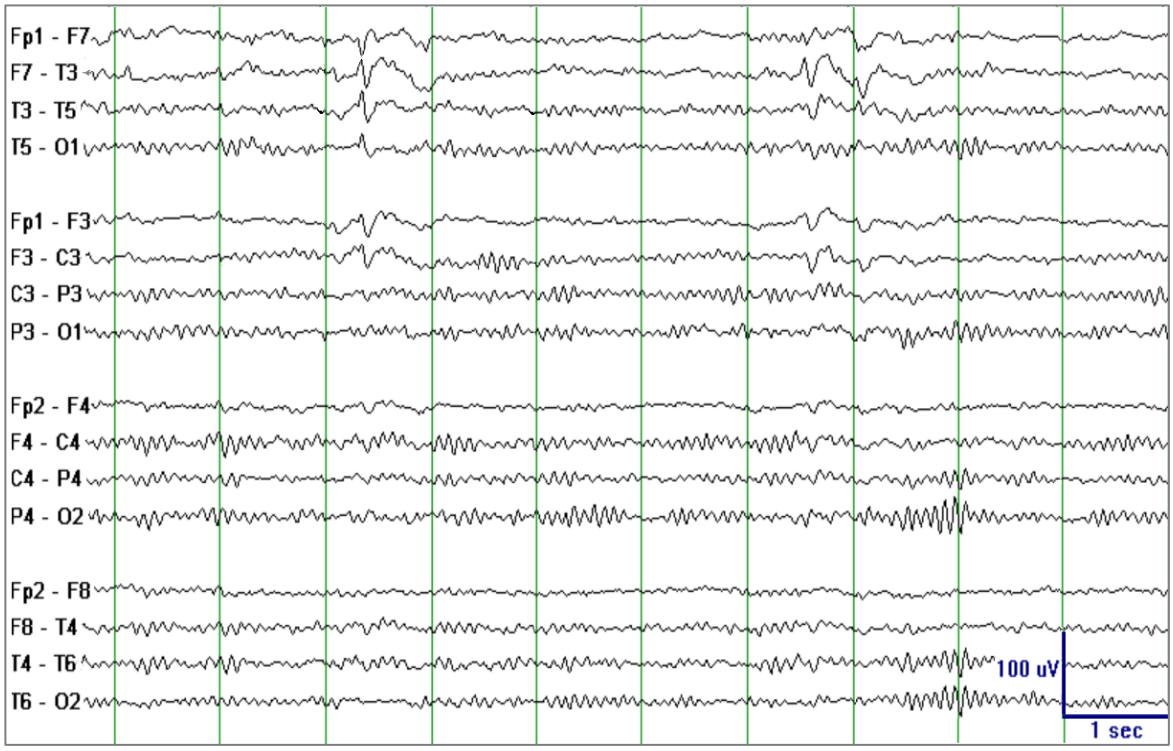


Figure 4. The background activity is alpha frequency. There is inter-ictal spike and slow wave activity in the left anterior temporal region. This patient has partial-onset seizures. (Image by EC Mader)

In Figure 4, the background is alpha frequency in the posterior (occipital) leads. Most likely, the patient is relaxed and awake. There is a sharply contoured wave (spike) that stands out from this background activity. It is followed by a slow wave, and occurs in the left fronto-temporal region. The spike and wave complex can be differentiated from an eye movement, because an eye movement would be seen in all of the fronto-polar leads.

What are the epileptiform EEG patterns?

A **spike** is a sharply contoured wave form (duration from 20-<70 milliseconds) that stands out from the background activity. It can be followed by a slow wave. A **sharp wave** is less sharply contoured than the spike. It also has a pointed peak (duration of 70-200 milliseconds). (Medical students do not need to memorize the precise durations of each of spikes and waves.) Spikes and sharp waves are typically abnormal and indicate

epileptiform activity. Note where they occur on the head (for example, left temporal); see Figure 5.

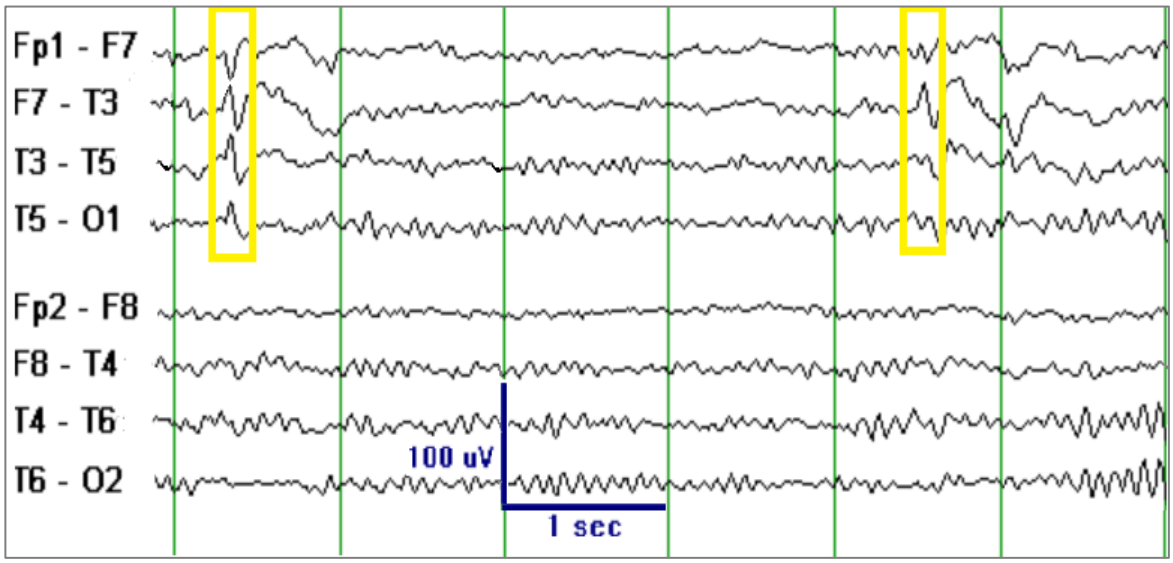


Figure 5. The background activity is alpha frequency, best seen in the occipital leads. Note the sharp waves that stand out from the background activity (yellow rectangles). This patient has an epileptiform focus in the left anterior temporal area. (Image by EC Mader)

Figures 4 and 5 demonstrate inter-ictal (between clinical events) EEG abnormalities, during which the patient appears clinically normal. Because the events were so brief, the patient would not have any symptoms. Figure 6 demonstrates an event lasting between 4-5 seconds. In cases lasting this long, patients would have signs and symptoms.

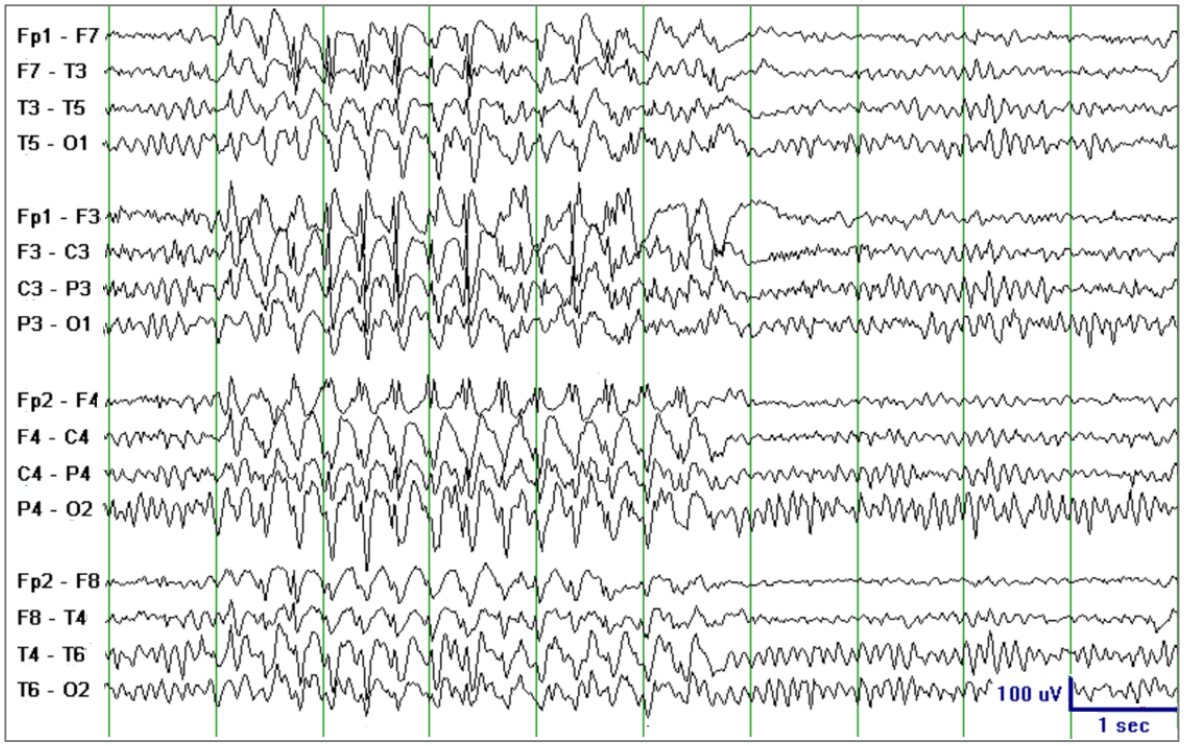


Figure 6. The background is alpha frequency. A generalized (occurring in all leads simultaneously) burst of spike and wave discharges emerges from that background. The frequency of the spike and wave discharges is approximately 3 cycles/second. During the 5-second event, the patient would have some clinical manifestations. After the event, the alpha frequency returns. Although a clinical history would be necessary, a patient with this EEG most likely has primary generalized epilepsy. (Image by EC Mader)

Medical students should be able to recognize a spike and wave pattern.

Although it may be difficult to capture, a patient with epilepsy would likely have **inter-ictal** (between clinical events) epileptiform activity on EEG (See Figures 4 and 5). The spike and slow waves or sharp waves are of such brief duration they don't result in any physical manifestations. It can be difficult to obtain an **ictal** (during the clinical seizure) EEG, because seizures can be unpredictable. However, patients can be admitted into an epilepsy monitoring unit for several consecutive days. The medications are tapered, and patient undergoes continuous EEG monitoring with provocative measures (sleep deprivation, photic stimulation, and hyperventilation). In this manner, the behavioral manifestations can be captured on video and correlated with the EEG findings. After a seizure, there may be **post-ictal** (after the event) slowing in the parts of the brain that were affected by the seizure.

What are other abnormal or potentially abnormal patterns?

Generalized slowing (See Figure 7) can be a normal finding during sleep. Metabolic derangements can also result in generalized slow-wave activity on the EEG. The technician recording the EEG would note the patient's condition at the time of the recording (sleeping, comatose, confused, unresponsive to stimuli). In a patient with encephalopathy, the degree of EEG slowing parallels closely the patient's mental status. Slowing can range from minor slowing of the alpha rhythm frequency (slight inattentiveness and decreased alertness) to continuous delta activity (coma).

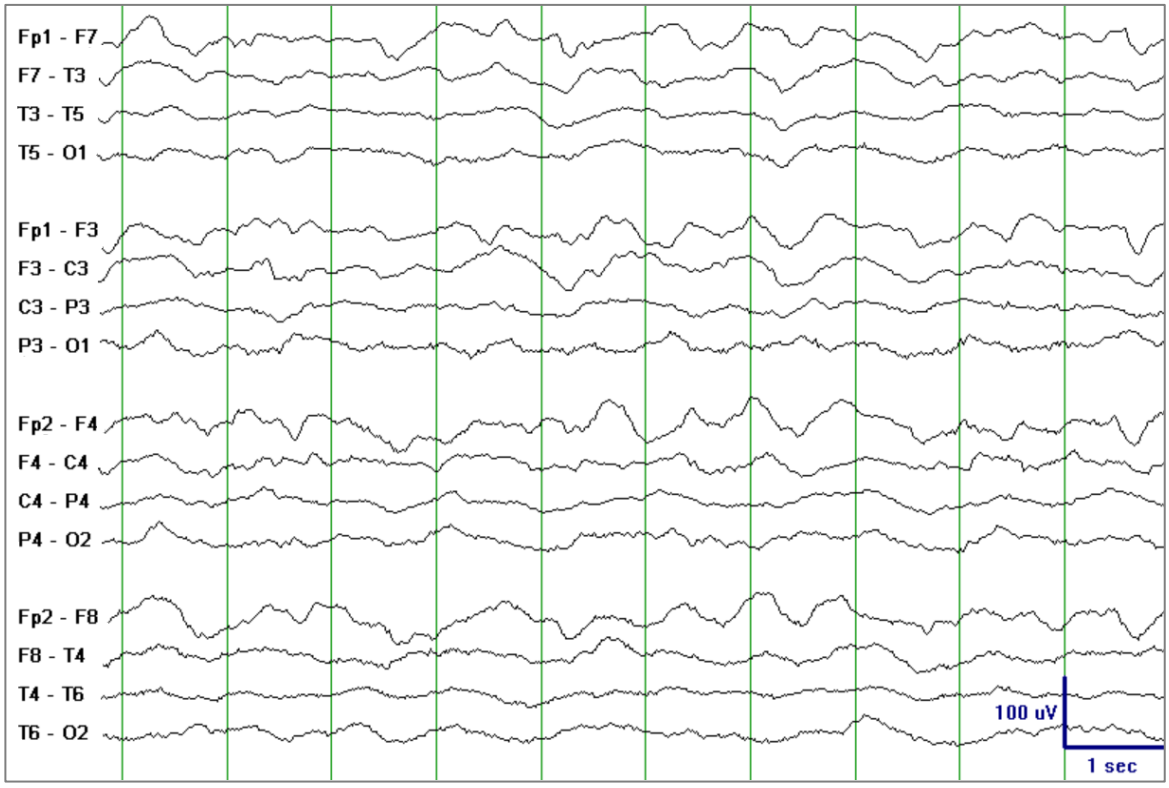


Figure 7. The patient's background activity is delta slowing in all of the EEG channels. Nothing stands out from the background activity. (Image by EC Mader)

Triphasic waves are high-voltage, sharply contoured, and exhibit a triphasic morphology. They occur especially over the frontal head regions in metabolic coma. They are typically associated with hepatic encephalopathy, but occur with equal frequency in uremia, hyponatremia, hyperthyroidism, anoxia, and hyperosmolarity. Medical students are not required to recognize triphasic waves.

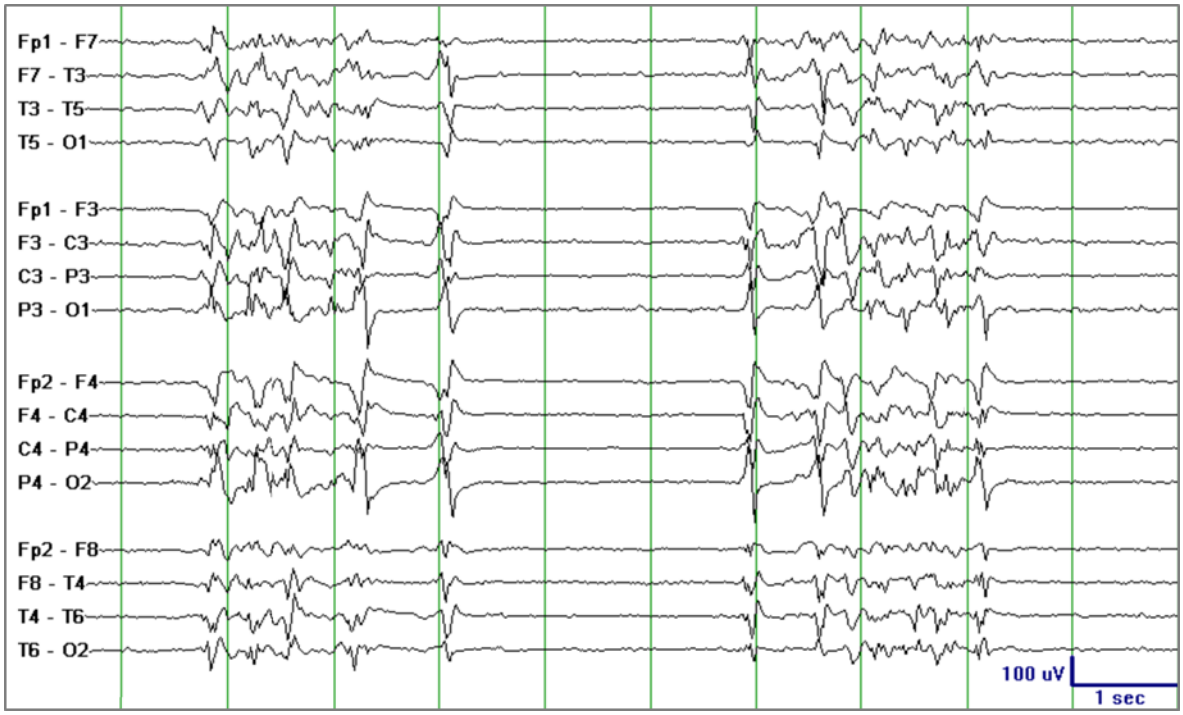


Figure 8. Burst-suppression pattern. (Image by EC Mader)

Burst-suppression (See Figure 8.) is a periodic EEG pattern consisting of bursts of high-voltage slow and sharp waves alternating with severe attenuation or suppression of the EEG. This pattern is seen in patients who are comatose as a result of general anesthesia, hypoxic-ischemic insult to the brain, or other forms of severe encephalopathy. The neural mechanisms underlying EEG burst-suppression are poorly understood. The "hypometabolism" model considers cerebral hypometabolism (suppression) as the fundamental defect and hypersynchronous activity (burst) as a mechanism to prevent membrane potential collapse during low metabolic states. In contrast, the "hyperexcitability" model considers corticothalamic hyperexcitability as the primary defect; enhanced cortical excitability allows subliminal stimuli to trigger cortical bursting activity which then depletes extracellular calcium resulting in suppression of cortical activity. During suppression, the neuronal pumps restore interstitial calcium and the cycle repeats itself.

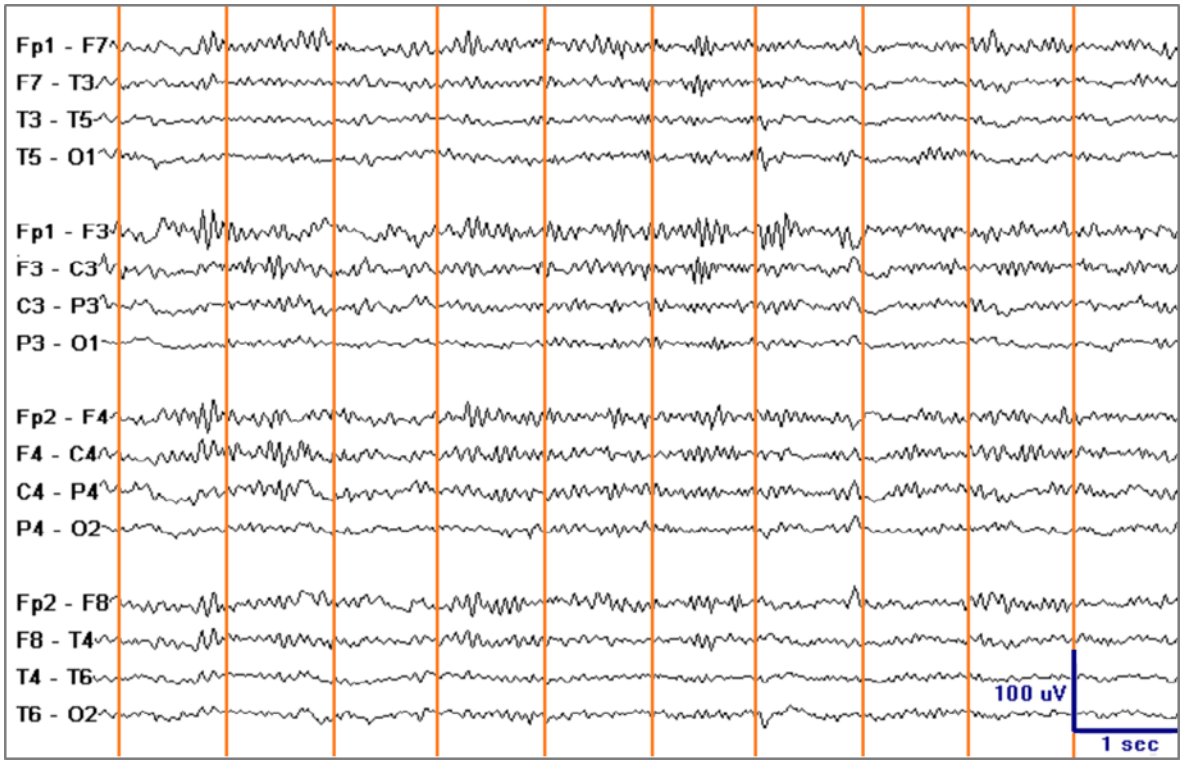


Figure 9. Alpha coma. (Image by EC Mader)

Alpha coma appears as continuous alpha activity in the EEG in a comatose patient. Albeit diffuse, the alpha activity of alpha coma may be more prominent anteriorly (as shown in Figure 9) or posteriorly (mimicking a normal alpha rhythm). In contrast to the normal alpha rhythm, the alpha activity in alpha coma (as well as the patient) does not react to external stimuli. Alpha coma is classically (but not invariably) associated with a pontine lesion and a poor prognosis.

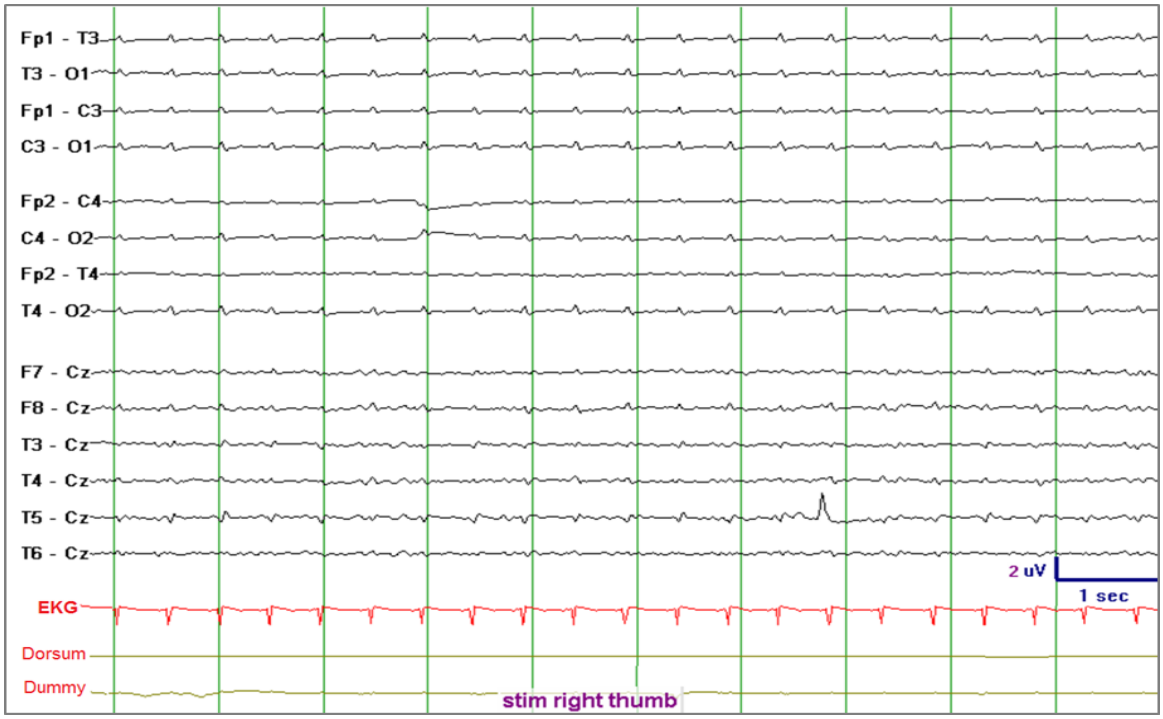


Figure 10. Electrocerebral inactivity (ECI) is present when no EEG waves are greater than 2 microvolts. To demonstrate ECI, the EEG must be displayed using special montage and much higher sensitivity. The high sensitivity "magnifies", not only the EEG, but also the EKG and other artifacts. (Image by EC Mader)

Electrocerebral inactivity (ECI) is an "EEG" diagnosis whereas brain death is a "clinical" diagnosis. To demonstrate ECI, the EEG must be displayed in a special way (see Figure 10). Although EEG recording is not an absolute requirement for brain death determination in adults, there are situations where demonstrating the presence of ECI can help corroborate the diagnosis of brain death.

What constitutes a normal EEG, and what is the significance of a normal EEG?

A normal EEG lacks abnormal patterns known to be associated with clinical disorders. A normal EEG CANNOT guarantee the absence of epilepsy. EEG may appear normal in an epileptic patient because the epileptiform discharges did not occur at the time of the recording. In addition, epileptiform discharges occurring in deeper structures of the brain may be missed by the scalp leads.

What is the significance of an abnormal EEG?

An abnormal EEG is not always clinically significant. Only a few patterns are definitely abnormal.

The Physiology of Sleep

The Reticular Activating System.

The reticular activating system (RAS) is the arousal system of the brain. Definitions of the components of the RAS will vary depending on the author; but as the name implies, the core components are located in the reticular formation of the midbrain and upper pons. The midbrain-pontine RAS neurons are cholinergic and project to the thalamic nuclei (mainly intralaminar nuclei) which in turn project diffusely to the cerebral cortex. Electrical stimulation of these cholinergic neurons leads to desynchronization of thalamic slow-wave EEG activity, thalamocortical activation, and behavioral arousal. On the other hand, low-frequency electrical stimulation of the thalamus immediately induces thalamocortical synchronization and sleep from the awake state.

Neurotransmitter Activity Levels During Wakefulness and Sleep.

Table 1	**Neurotransmitter**
Arousal Promoting	Noradrenalin (NE)
	Acetylcholine (Ach)
	Orexin (hypocretin)
	Histamine
	Glutamate
	Serotonin--controversial
Sleep Promoting	GABA
	Adenosine
	Serotonin--controversial

Increased activity of certain neurotransmitters promote arousal and others promote sleep. Table 1 lists the more well-studied of these. During the wake state, the hormones of arousal (NE, ACh, histamine, glutamate, and Orexin) are at their highest levels. By now, you are familiar with noradrenalin, glutamate, and acetylcholine. Orexin (hypcretin) was discovered in relation to a condition called narcolepsy. Narcolepsy and narcolepsy with cataplexy, which cause hypersomnolence, will be described below. The majority of patients with narcolepsy-cataplexy have virtually undetectable orexin levels in the cerebrospinal fluid (CSF) and an 80-100% reduction in the number of neurons in the lateral hypothalamic area (LHA). Others have mutations in the orexin receptors. Wakefulness is also promoted by histamine, which is why antihistamines make people drowsy. The effects of serotonin on wake and sleep is a little contradictory. References

state it promotes arousal, but it also promotes slow wave sleep. GABA is a major inhibitory neurotransmitter of the brain, promoting sleep. Adenosine also induces sleep. Caffeine is an adenosine antagonist, which is why coffee, tea, and other caffeinated beverages promote wakefulness. **One exception to the table above is Ach.** During non-REM sleep, Ach activity decreases. During REM however, ACh activity increases, while the activity of other arousal neurotransmitters remain low.

Physiological changes during normal sleep.

The body shows distinct physiological and hormonal changes between the awake and sleep states, and between REM and non-REM sleep. Levels of many hormones increase at night, giving rise to the hypothesis that sleep is used for growth and regenerative purposes. Although this is outside of the scope of this activity, thyrotropin, leptins, and prolactin all surge at night. Lack of sleep can lead to stunting of growth, which likely is the consequence of disruption of these nightly hormone surges.

Table 2. Physiological changes that occur during the normal REM and non-REM sleep.

System	Non-REM	REM
Nervous and Musculoskeletal	Progression to synchronized high-amplitude slow-wave EEG activity. Skeletal muscle tone and movement decrease. Eye movements decrease.	EEG changes to low-amplitude, high frequency activity resembling wake state. Ballistic eye movements occur. Pupils constriction. Skeletal muscle paralysis (but not of diaphragm). Inhibition of somatosensory input. Anterior cingulate gyrus becomes highly activated.
Respiratory	Respiration decreases to lowest levels by N3.	Respiration dramatically increases.
Cardiovascular	Heart rate and blood pressure decreases to lowest levels by N3.	Heart rate and blood pressure dramatically increase.
Reproductive	Relaxed.	Penile erections and vaginal engorgement occur.
Metabolism	Temperature and metabolism reach lowest levels by N3.	Temperature and metabolism dramatically increase.

Table 2 list physiological changes that occur during REM and non-REM sleep. For the most part, the body enters into a low level activity state during non-REM sleep, reaching its lowest levels by N3. During REM, the brain becomes reactivated. However, its activity state can be thought of "internalized." The brain is actively disconnected from the spinal cord and outside world through sensory inhibition and skeletal muscle paralysis.

Ballistic eye movements are a defining feature of REM. These movements involve the pontine reticular formation, which projects to the superior colliculi which projects to the PPRF and rostral interstitial nuclei. The atonia that occurs during REM appears to be due to activation of pontine reticular formation GABAergic neurons, which leads to inhibition of lower motor neurons. Finally, the anterior cingulate gyrus becomes activated, which is hypothesized to lead to the emotional content of many dreams.

Dreaming

Dreaming occurs during REM sleep, and dreams tend to be vivid, elaborate, and emotional. You will not be responsible for controversies, but there is debate. Some references state that dreaming occurs during all phases of sleep. Others state that during early non-REM sleep, the so-called dreams are merely thoughts the person is thinking while falling asleep. For the purposes of this activity, you should associate dreams with REM sleep. In addition, understand that during REM, it is easy to awaken a person and the person will have vivid recollection of dreams.

Circadian rhythms:

A circadian rhythm is a daily biological rhythm that is normally synchronized with the Earth's day and night cycle. The process by which circadian rhythms are reset and synchronized with the light-dark cycle is called photoentrainment. Photoentrainment is essential, because humans typically need to be awake during the daytime and asleep at night. Nocturnal animals also have circadian rhythms that result in sleepiness during the day and wakefulness at night.

Circadian rhythms account for the baseline fluctuations in body temperature and the plasma concentration of hormones (See Figure 11). This results in the day-night variations in organ system function (e.g. suppression of urination at night) and, the sleep-wake cycle. The most important graph is the one on melatonin. The others are shown for illustrative purposes.

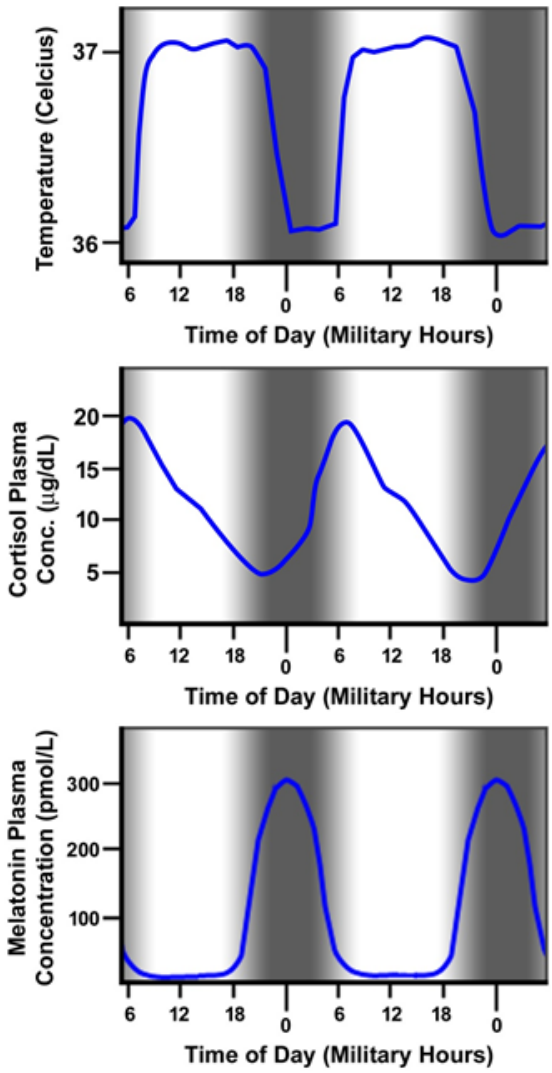


Figure 11. Examples of circadian rhythms in a normal human. At night, melatonin, growth hormone, and thyroid stimulating hormone (TSH) levels rise whereas body temperature and cortisol production fall. (Image by A Oliva)

Neuronal circuitry for photoentrainment:

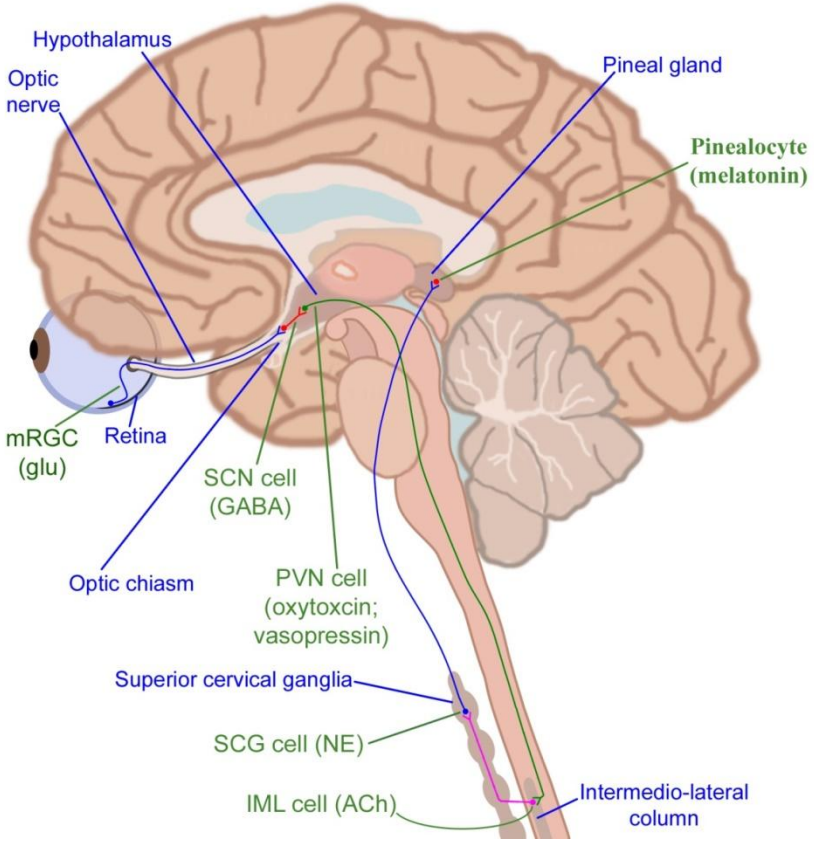


Figure 12. The Retino-hypothalamo-pineal pathway. Photoentrainment begins with the retinohypothalamic tract, which connect the eye to the hypothalamus. First, photons by melanopsin-expressing retinal ganglion cells (mRGCs), which project through the optic nerve to 2nd order neurons in the suprachiasmatic nucleus (SCN). SCN neurons project to 3rd order neurons in the paraventricular nucleus (PVN) of the hypothalamus, which project 4th order preganglionic sympathetic neurons in intermediolateral zone of the thoracic lateral horns (IML) of the spinal cord. IML neurons project to 5th order postganglionic neurons in superior cervical ganglia (SCG), which then project to 6th order cells (pinealocytes) in the pineal gland, which make the neurorhormone melatonin. (Image by A Oliva)

The Retinohypothalamic Tract.

The retinohypothalamic tract (RHT) is the circuitry for photoentrainment (Fig. 12). It begins in the retina, where light stimulates specialized retinal ganglion cells called

melanopsin-expressing retinal ganglion cells (mRGCs). Axons of mRGCs project to the optic chiasm to synapse on 2nd order neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus (expounded upon below).

Further Facts. Axons of the mRGCs also project to the midbrain pretectum, including the olivary pretectal nucleus which participates in the pupillary light reflex.

Further Facts. Note the difference of this "luminosity perception" circuitry with the more familiar "visual perception" circuitry. In vision, photons are absorbed by photoreceptors (rods and cones), not by RGCs. The photoreceptors then synapse on retinal ganglion cells (which are not intrinsically photosensitive) which project to the lateral geniculate nucleus of the thalamus. Rods and cones use the related photosensitive proteins, rhodopsin and iodopsin, respectively, whereas mRGCs use melanopsin, which is more distantly related.

The Hypothalamo-Pineal Pathway.

The exact microcircuitry from the SCN to the pineal gland is still being worked out, and an active area of research. Nonetheless, much of the circuitry is known.

SCN neurons project to 3rd order neurons in the paraventricular nucleus (PVN) of the hypothalamus. PVN neurons project to 4th order preganglionic sympathetic neurons in intermediolateral zone (IML) of the thoracic lateral horns of the spinal cord. IML neurons then project to 5th order postganglionic neurons in superior cervical ganglia (SCG). And finally, SCG neurons then project to 6th order cells (pinealocytes) in the pineal gland, which make the neurorhormone melatonin.

The pineal gland is turned off by the SCN during the day, and turned on at night. The pineal gland is outside of the BBB (it's a circumventricular organ), and releases melatonin directly into the blood. Interruption of the pathway from the hypothalamus to the pineal gland effectively inhibits melatonin secretion.

Further Facts. The microcircuitry within the hypothalamus is largely unknown. However, evidence indicates that in the daytime, the SCN neurons that become activated are GABAergic, and thus inhibitory to the PVN neurons and presumably inhibitory to the ultimate release of melatonin. The neurotransmitters that PVN neurons use are also unclear, but there is good evidence showing that they express oxytocin and vasopressin, and other neurotransmitters.

The Suprachiasmatic Nucleus: the "Master Clock".

The suprachiasmatic nucleus (SCN), as the name implies, is a hypothalamic nucleus that lies above the optic chiasm. It is known as the "master clock", because it controls the synchronization and periodicity of most (if not all) of the biological clocks in the body. In line with its "master" role, the SCN sends projections to many brain areas, including the thalamus, basal forebrain, and other hypothalamic nuclei. And as described above, one of the ultimate targets is the pineal gland.

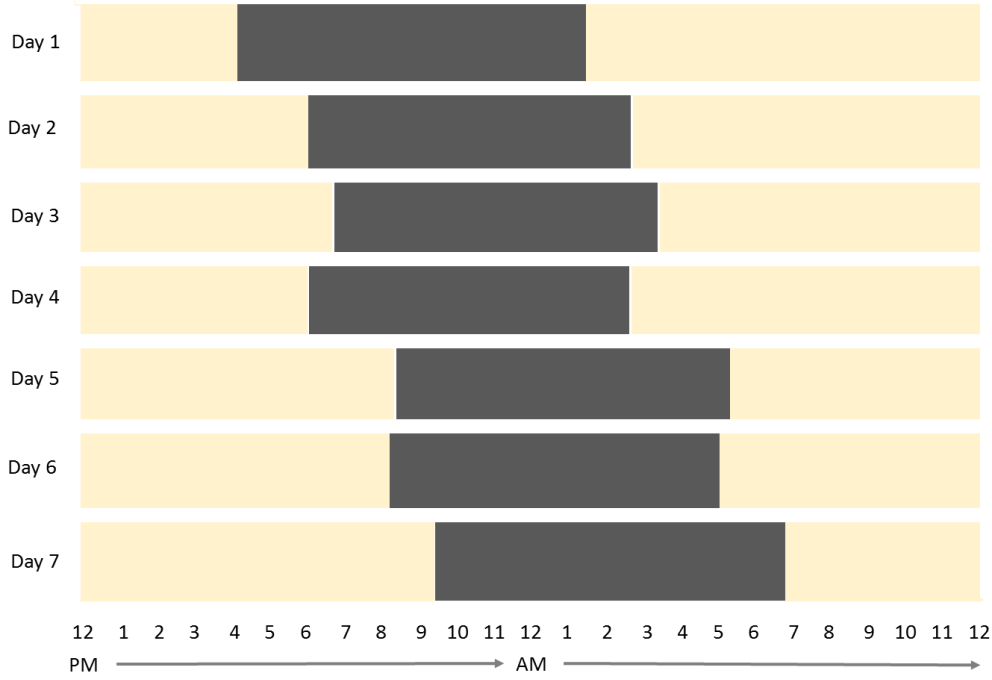


Figure 13. The rest–activity pattern in individual with free-running or nonentrained type circadian rhythm disorder. This disorder typically occurs in blind persons whose biological circadian rhythms are not entrained by the Earth's day/night cycles. (Image by EC Mader)

The SCN has an intrinsic periodicity that is slightly longer than 24 hours (range is 24.2 to 26.0 hours). Normally, ambient light-dark cycles and other external cues will reset, i.e., photoentrain, the SCN to the 24-hour light-dark cycle. However, when deprived of external cues, the SCN goes into a free-running mode defaulting back to its intrinsic periodicity. Persons in the free-running mode will wake up an hour later each day, and go to sleep an hour later each day. This cycle continues and at some point, they may sleep all day and remain awake all night. As the cycle goes on, they eventually get back to a

normal rhythm of being awake all day and asleep all night, and it continues. Blind patients, who have a disruption in the retino-hypothalamic tract exhibit a free-running circadian rhythm. The free-running mode can also be induced experimentally by depriving subjects of light-dark and other cyclical cues (e.g., clocks and temperature changes).

Further Facts. While the SCN is the "master clock", remember that the anterior pituitary is the "master gland", which is highly controlled by specific nuclei of the hypothalamus, making the hypothalamus a "master gland master."

Melatonin: the "hormone of darkness"

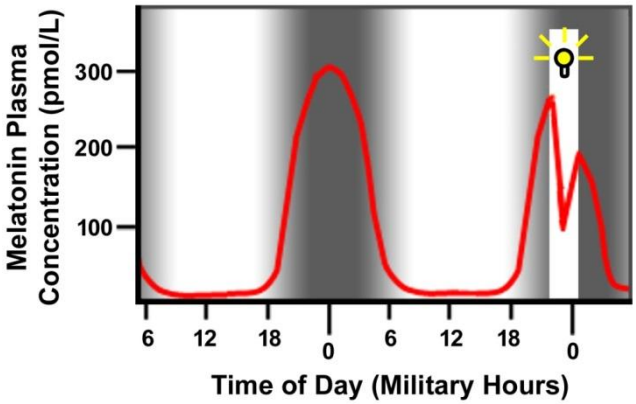


Figure 14. Bright-light exposure during sleep inhibits melatonin release into the blood. (Image by A Oliva)

Melatonin is called the "hormone of darkness," because it only comes out at night. It affects cells throughout the body, including the CNS (e.g., the SCN), because it crosses the BBB. In humans, melatonin induces drowsiness whereas in nocturnal animals, it induces wakefulness. Note however that melatonin in ***not*** a master controller of all daily cycles. This is the domain of the SCN (the master clock).

Melatonin production is inhibited by both natural and artificial light (Fig. 14). Clinically, this is relevant in the case of insomniacs, who tend to turn on the lights in the middle of the night, suppressing melatonin release and further exacerbating their insomnia. Melatonin production also dramatically decreases with aging, likely accounting for some of the sleep pattern changes in the elderly. This change in melatonin production may be due to the calcification of the pineal gland that occurs with aging.

Further Facts. Melatonin is synthesized from tryptophan via 4 enzymatic steps with serotonin (5-HT) as an intermediate. It is cleared from the blood by the liver.

Further Fun Facts. Common belief is that increased tryptophan intake increases melatonin production; but scientific studies so far refute this "Thanksgiving turkey effect", and odds are that the drowsiness is just from eating too much on that day.

Therapeutic Uses of Melatonin:
Melatonin has become an attractive to treat a variety of disorders including those listed in Table 3.

Table 3. Therapeutic Uses of Melatonin Supplementation.

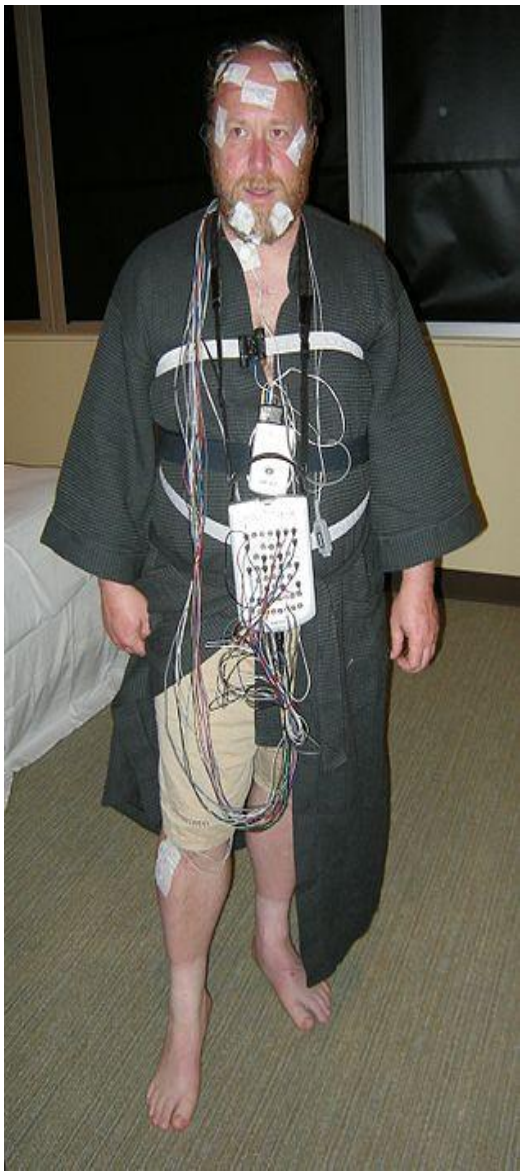
Disorder	Beneficial Function
Insomnia	Induces sleep at appropriate time
Sleep aid for older/elderly adults	Replace the diminishing levels of melatonin produced as a function of aging
Pinealectomy and upper cervical spinal cord injury	As a complete melatonin replacement
Aid for jetlag, night-shift and swing-shift workers	Resets biological clock to new time-zone
Ocular blindness	For entraining biological rhythms daily from free-running mode

Further Facts. "night owls" (phase-delayed) respond best to low-dose melatonin in the afternoon or evening and "morning larks" (phase-advanced) respond best to low-dose melatonin in the morning.

Further Facts. Every mammalian cell that has been examined for circadian rhythms has been observed to have some form of innate circadian rhythm. The same is true for plants, fungi, and perhaps all organism that depends on Earth's light-dark cycle. A detailed account of the biochemistry underlying the cellular mechanisms behind circadian rhythms is beyond the scope of this presentation. However, the general concept is this: specific mRNAs and their protein products are constantly being synthesized and degraded in response to light and darkness. These include *Period* and *Clock* mRNAs and their translated proteins.

Polysomnogram (Sleep study)

A polysomnogram (PSG) is a record of the EEG and various other physiological parameters. How those parameters are recorded is described in Figure 15.



Chin EMG: measures muscle tone and can help to determine whether the patient is in REM sleep.

Limb leads: record limb movements (as in period limb movement disorder) or muscle tone

Ocular leads: record eye movements. The leads are placed in such a way that the eye movements are recorded as out-of-phase (in opposite directions) deflections. This helps to differentiate eye movements from slowing that occurs in the deeper stages of sleep.

Snore microphone: placed near the nose and mouth

Nasal airflow: recorded by thermistor. This enables recording of apneas.

Nasal pressure: recorded by pressure transducer. This also enables recording of apneas.

Respiratory effort: recorded using chest and abdominal belts. The effort (or lack thereof) indicates whether the apnea is of central or obstructive origin).

Oxygen saturation: measured by pulse oximetry.

Body position: recorded by the sleep technologist.

Figure 15. A patient about to undergo a polysomnogram. Image credit http://commons.wikimedia.org/wiki/File:Wired_up_for_a_sleep_study_01A.jpg

Continuous positive airway pressure (CPAP), BiPAP and supplemental oxygen levels may also be recorded. EEG was traditionally displayed in 10-second epochs with a page (analog EEG) or screen (digital EEG) showing 10 seconds of EEG at a time. With the increased availability of widescreen monitors, it is now more common to display the EEG using longer epochs (e.g. 12 seconds/screen). Sleep studies are displayed in 30-second epochs. The difference between a more "condensed" 30-second epoch and a 10-second epoch display is demonstrated in Figures 16 and 17.

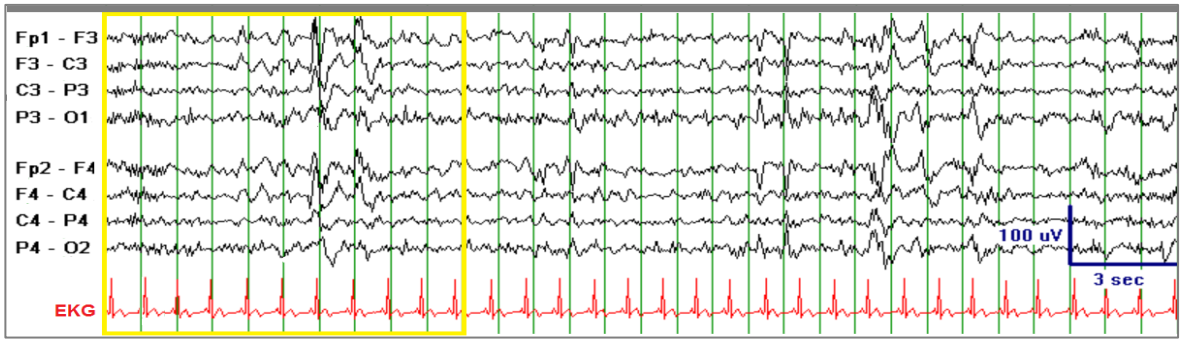


Figure 16. A 30-second epoch showing light sleep (Stage N2). The 10-second interval in yellow box is presented below in Figure 17. (Image by EC Mader)

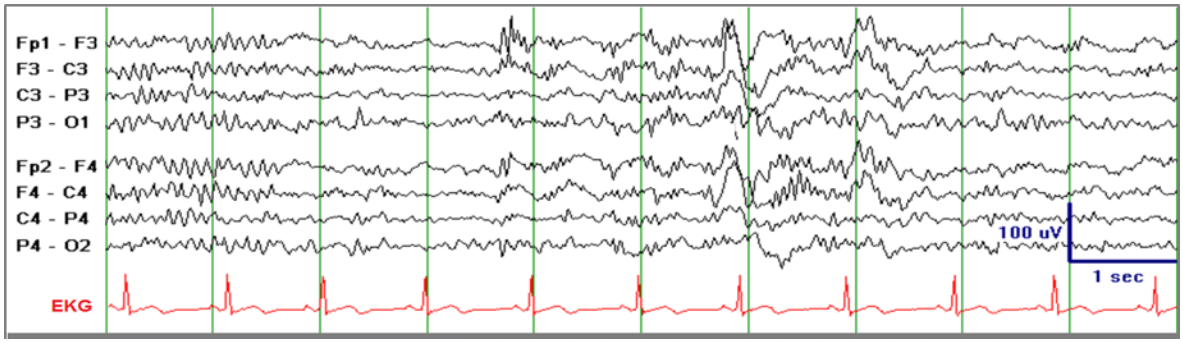


Figure 17. A 10-second epoch showing light sleep (Stage N2). (Image by EC Mader)

Clear-cut indications for polysomnogram are evaluation of the following conditions: obstructive sleep apnea; titration of continuous positive airway pressure (CPAP); narcolepsy with or without cataplexy (followed by a multiple sleep latency test or MSLT); periodic limb movement disorder; REM behavior disorder; and nocturnal seizures. Relative indications for polysomnogram are evaluation of the following conditions: sleep terror disorder; parasomnias with injury; and insomnia of unclear etiology.

Sleep Stages:

Wakefulness is referred to as Stage W. The sleep stages are: Stage N1 (transitional stage), Stage N2 (light NREM sleep), Stage N3 (deep NREM sleep), and Stage R (REM sleep). In the old nomenclature, deep NREM sleep was divided into two stages: Stage 3 when 20-50% of the epoch and Stage 4 when > 50% of the epoch are occupied by slow waves of sleep.

Figures 18-22 show examples of polysomnograms (30-second epoch) that correspond to each of the five stages. The defining features of each stage are described in the captions. **You must be familiar with Stage R, as it is a very important stage of sleep.** It is involved in a number of important sleep disorders and is a frequently tested subject. **It is also very important to be able to differentiate Stage W from Stage R as they are very similar.**

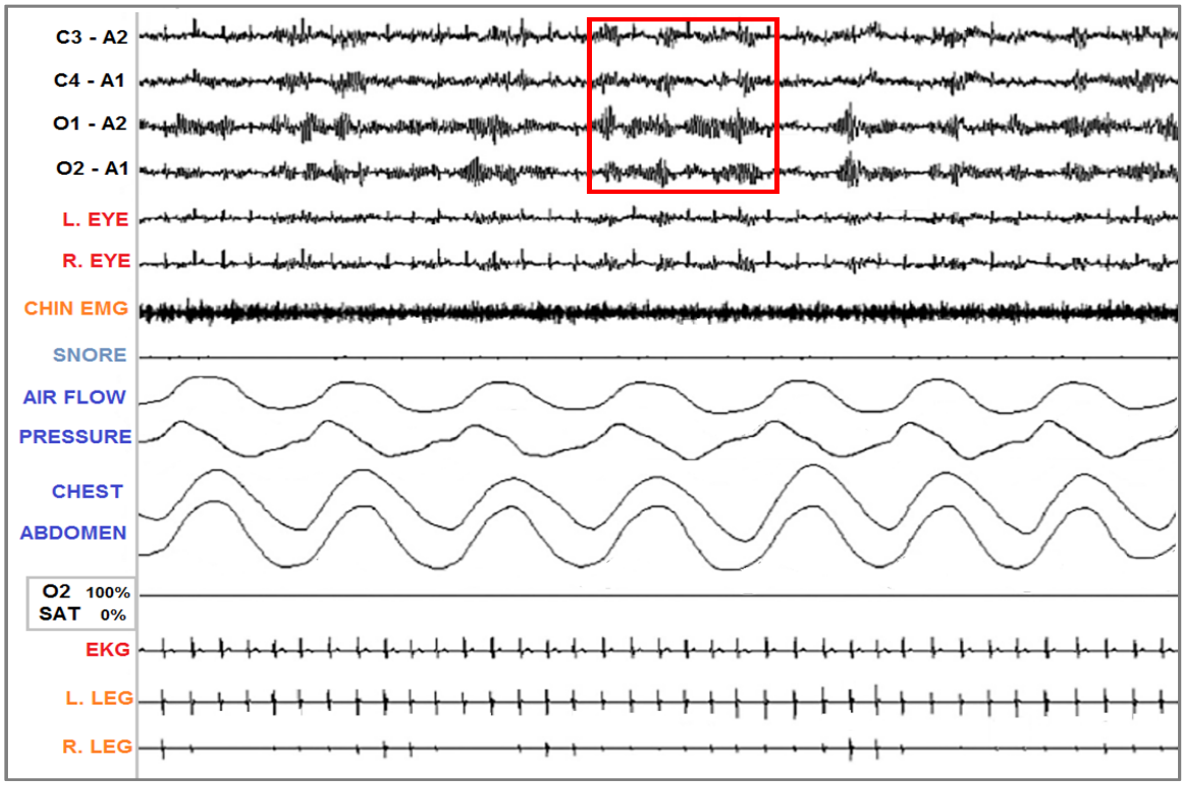


Figure 18. Stage W (30-second epoch). This stage is characterized by the alpha rhythm (box). Wake is characterized by low voltage mixed frequency activity (alpha rhythm in the posterior leads with eyes closed), eye movements, and tonic EMG activity. To consider an epoch as stage W Greater than 50% of the 30 second epoch must show an alpha rhythm**.** (Image by EC Mader)

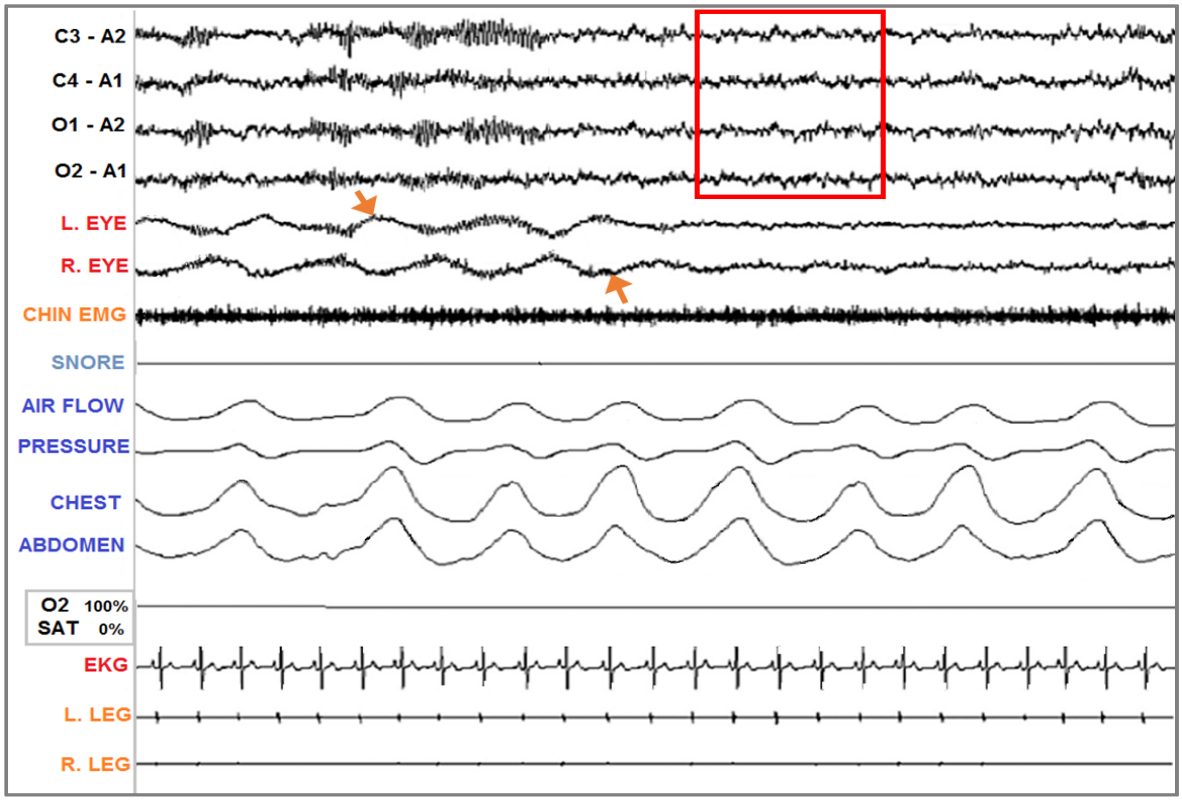


Figure 19. Stage N1 (30-second epoch) is characterized by fragmentation and disappearance of the alpha rhythm. Alpha rhythm decreases to less than 50% of the (30-second) epoch. The dominant EEG activity is low amplitude and mixed frequency, in the 2-7 Hz range (box), and there is tonic activity in the EMG channel. Slow rolling (out of phase) eye movements (arrows) appear in early Stage 1 (N1) sleep. (Image by EC Mader)

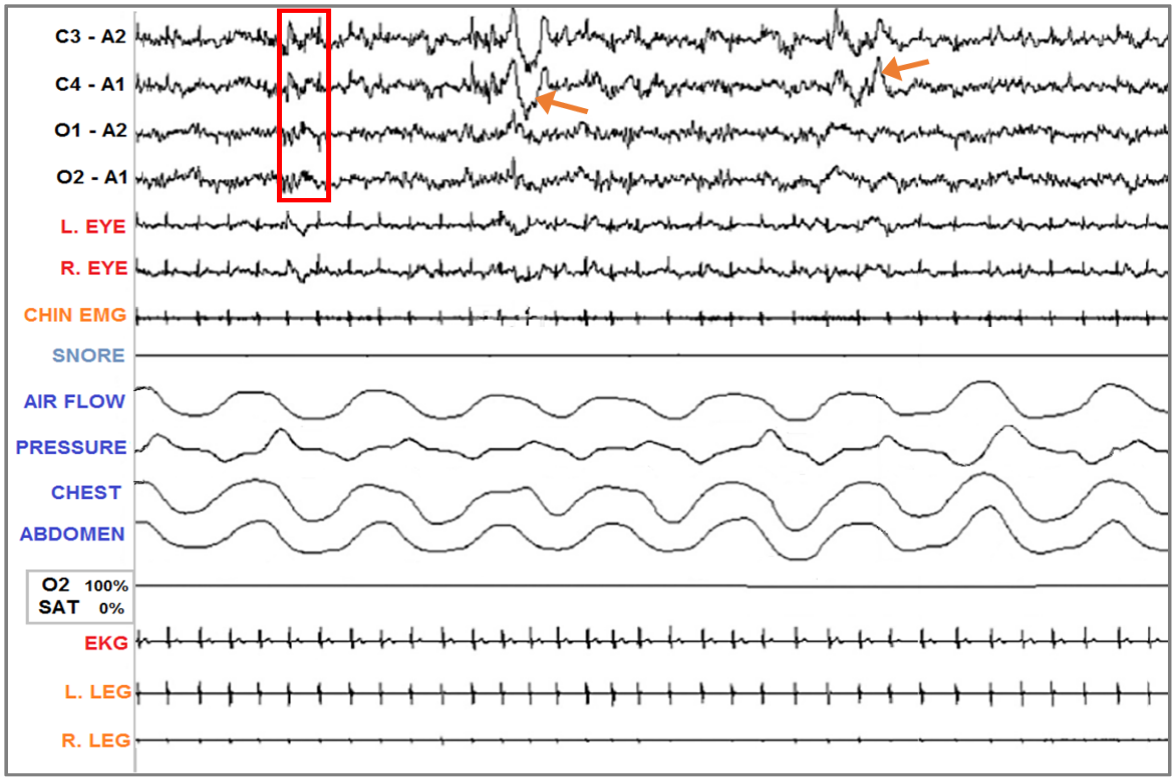


Figure 20. Stage N2 (30-second epoch). This stage is defined by the presence of K complexes or sleep spindles. K complexes (arrows), are high amplitude biphasic deflections seen maximally over the vertex (Cz). Sleep spindles (box) consist of 11- to 14-Hz waves. Medical students will not have to recognize K complexes or sleep spindles on polysomnogram, but be familiar with their description and association with Stage N2 sleep. (Image by EC Mader)

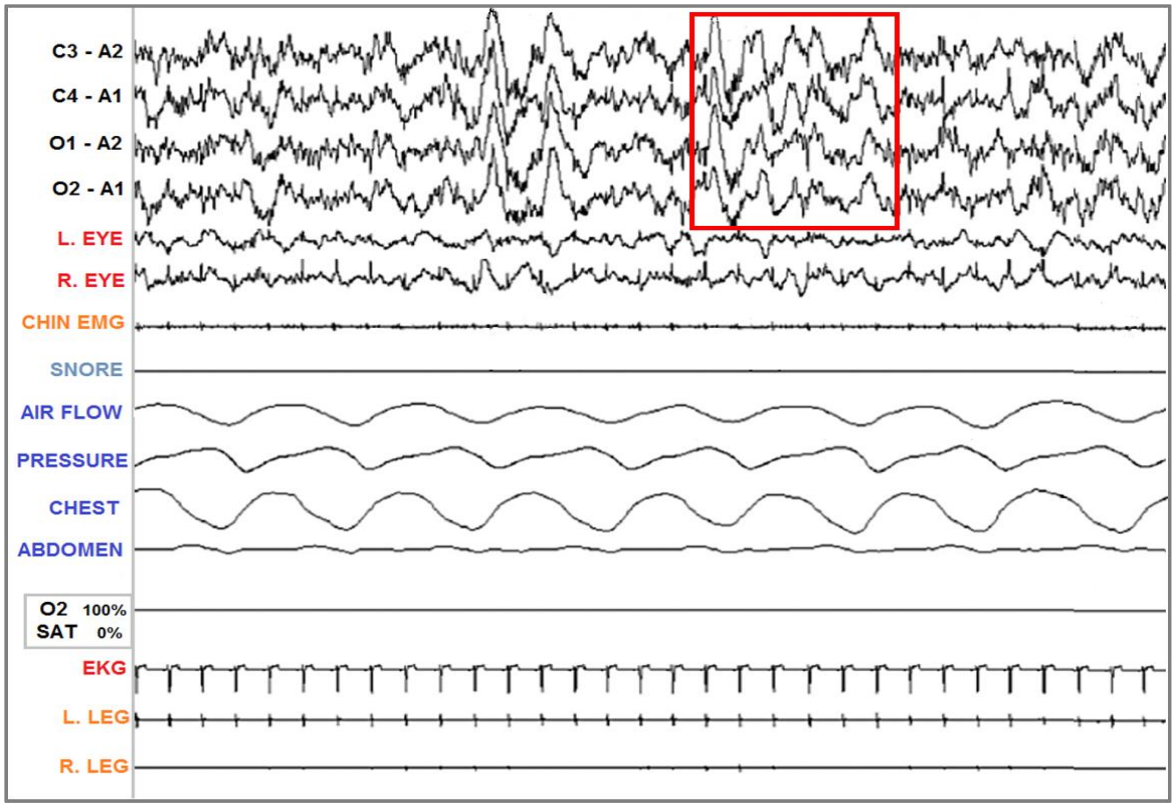


Figure 21. Stage N3 (30-second epoch) requires the presence of slow waves that are slower than 2 Hz and a peak to peak amplitude of > 75 microvolts (box: selected slow waves that satisfy these criteria). The slow waves must occupy >= 20% of the epoch. (Image by EC Mader)

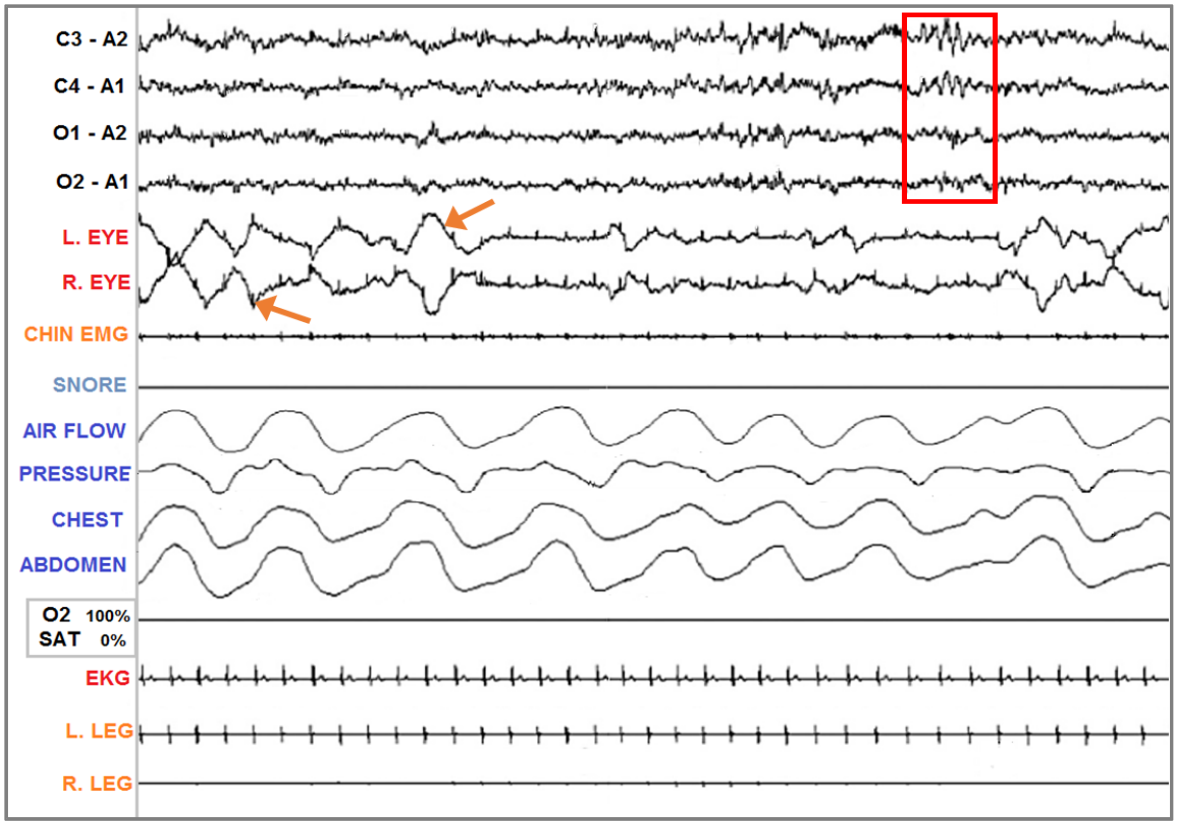


Figure 22. Stage R (30-second epoch). This stage is characterized by rapid eye movements (arrows indicate the out-of-phase deflections in the eye channels). In addition, EEG is low amplitude mixed frequency and may occasionally show saw-tooth waves (box). (Medical students do not need to recognize saw-tooth waves.) EMG tone is flat, or at least the lowest of the entire recording. EKG artifact can be seen in the EMG and eye channels. (Image by EC Mader)

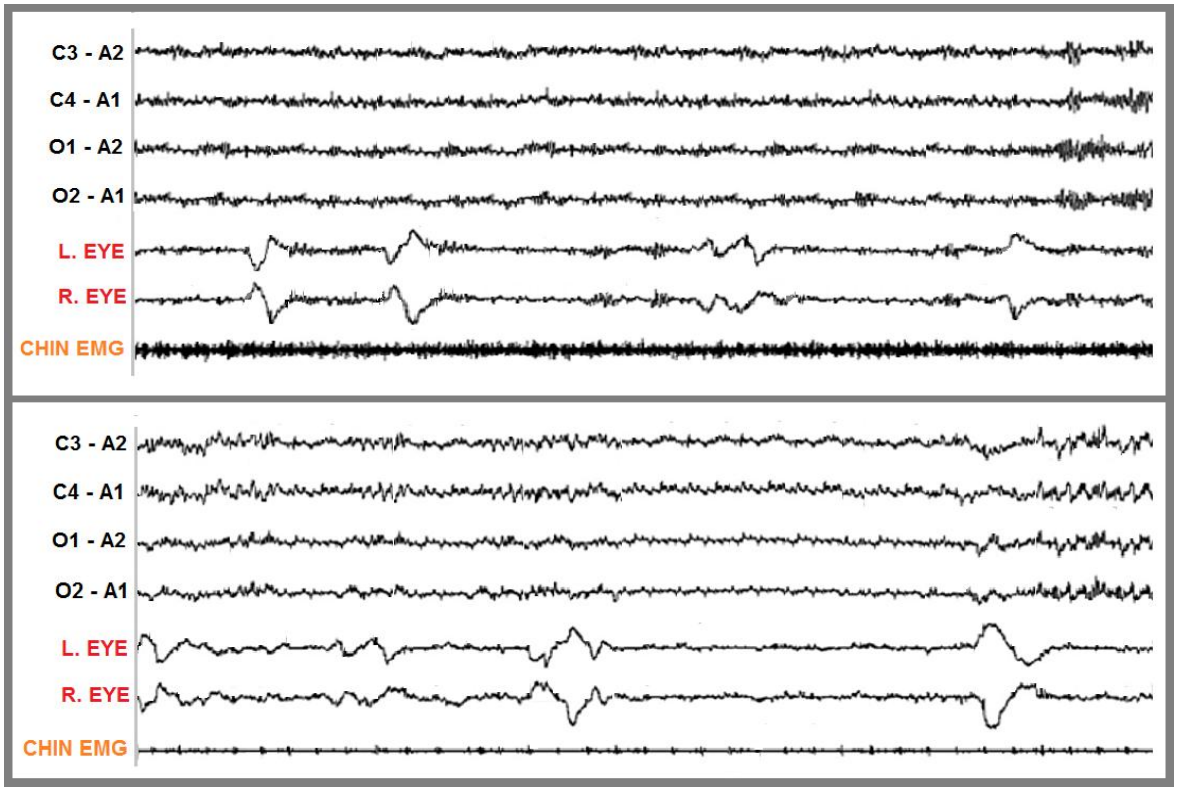


Figure 23. (30-second epoch) This image demonstrates the similarities and differences between wake and REM sleep. Which is which? (Image by EC Mader)

As you are looking at the polysomnograms, note that when an individual moves from Stage W to Stage N3, there is a progression from low amplitude, high frequency EEG to high-amplitude, low frequency (synchronized, slow wave EEG) activity. In addition, the skeletal muscle tone, eye movements, heart rate, and respirations decrease. Although not recorded on the above images, blood pressure, temperature and metabolism reach the lowest levels by Stage N3. As a result, it is difficult to awaken individuals from Stage N3 sleep. When they do awaken from Stage N3 sleep, they are typically confused.

Although Stage R (REM) sleep is associated with skeletal muscle paralysis (EMG channel typically shows atonia), EEG reverts back to low-amplitude, high frequency activity resembling wake state. Ballistic eye movements occur. Respirations, heart rate, blood pressure, temperature, and metabolism dramatically increase. Vivid dreams occur in REM sleep. It is easier to awaken individuals from REM sleep, and they typically remember their dreams.

Normal Sleep Cycles

A hypnogram is a graphical representation of the cyclical nature of sleep. Medical students should be familiar with and be able to interpret hypnograms. After a normal adult falls asleep, slow wave sleep (Stage N3) predominates. REM normally occurs 90 minutes after a person falls asleep, and recurs every 90 minutes. Periods of REM get longer and longer as the sleep cycle progresses. Slow wave sleep becomes less prevalent as the REM periods grow longer. Thus, disorders that occur during slow wave and REM sleep occur early and late in the sleep cycle, respectively. Awakenings occur in normal young adults.

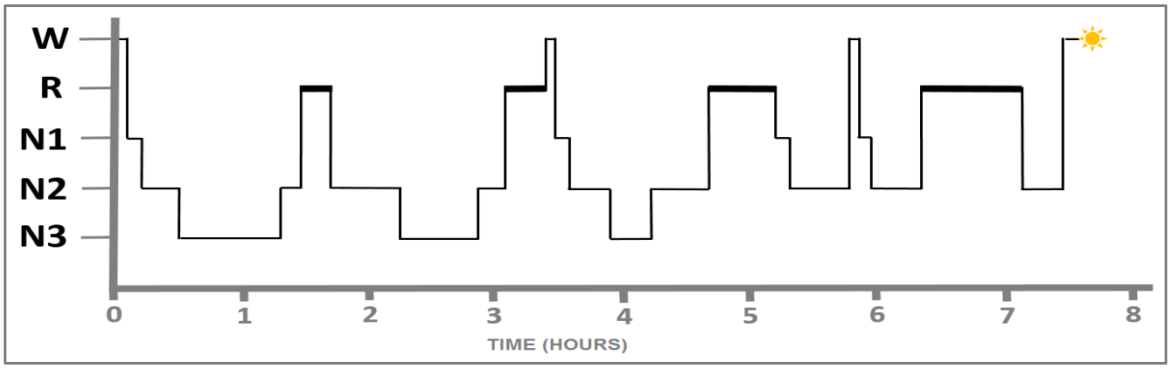


Figure 24. A normal hypnogram. (Image by EC Mader)

Sleep in older adults is characterized by frequent awakenings, fragmented sleep and decreased slow wave sleep (N3). Despite fragmented sleep, the elderly don't necessarily have a shorter REM latency. The need for sleep may decrease with age. The overall percentage of REM sleep declines with age.

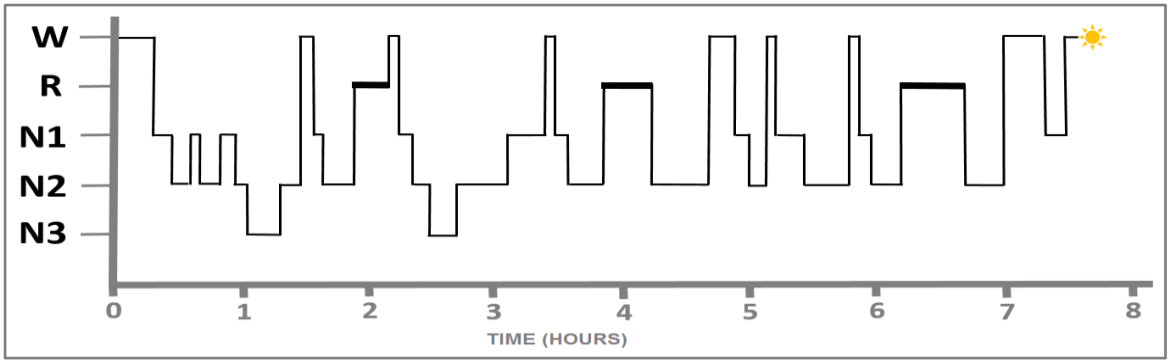


Figure 25. Hypnogram in a normal older adult. (Image by EC Mader)

Multiple Sleep Latency Test (MSLT)

MSLTs are performed after an overnight polysomnogram to evaluate a patient's sleepiness. The patient tries to nap 5 times throughout the day. Mean sleep latency (the time it takes for the person to fall asleep) is measured and averaged. A patient with hypersomnolence may fall asleep quickly and many times during the study, whereas a normal patient may have difficulty falling asleep even once. In addition sleep onset REM periods are noted. A patient with hypersomnolence or narcolepsy may enter REM sleep rather quickly and many times, while a normal patient may not enter REM at all during the MSLT. Overall, a short sleep latency and sleep onset REM can indicate hypersomnolence. Successful treatment of the underlying disorder would result in a longer sleep latency (they are less sleepy and it takes longer for them to fall asleep) and possibly fewer sleep onset REM periods.

SLEEP DISORDERS

Obstructive Sleep Apnea

Obstructive sleep apnea is clinically important and treatable. Although it is hard to quantify, the prevalence is estimated at 4% of men and 2% of women (ages 30-60 years). Prevalence increases with age in general, and after menopause in women. Up to 80% of patients with obstructive sleep apnea are undiagnosed.

The partner will often complain that the patient snores or stops breathing. The patient may awaken gasping or choking. There are daytime symptoms, including hypersomnolence, fatigue, and cognitive deficits. Associated features include obesity, a large neck circumference, and hypertension.

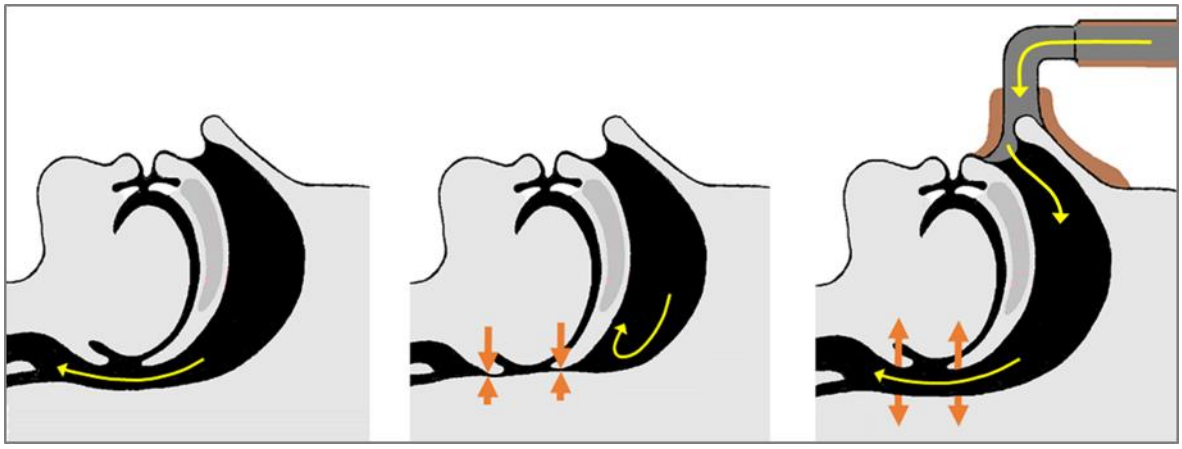


Figure 26. Mechanisms of upper airway occlusion in Obstructive Sleep Apnea. Left: normal muscle tone prevents collapse of the upper airway. Middle: airway obstruction in sleep with the hypopharynx and soft palate sucked against the posterior oropharyngeal wall. Right: CPAP provides a pneumatic splint and keeps the upper airway open. (Image by EC Mader)

The mechanisms of upper airway occlusion are depicted in Figure 26. When the patient is awake, normal muscle tone prevents the airway from collapsing. When the patient falls asleep, there is relaxation of the muscles of the hypopharynx and the soft palate is sucked against the posterior oropharyngeal wall. Obesity and a large neck circumference contribute to the collapse of the airway due to the weight of the excess soft tissue.

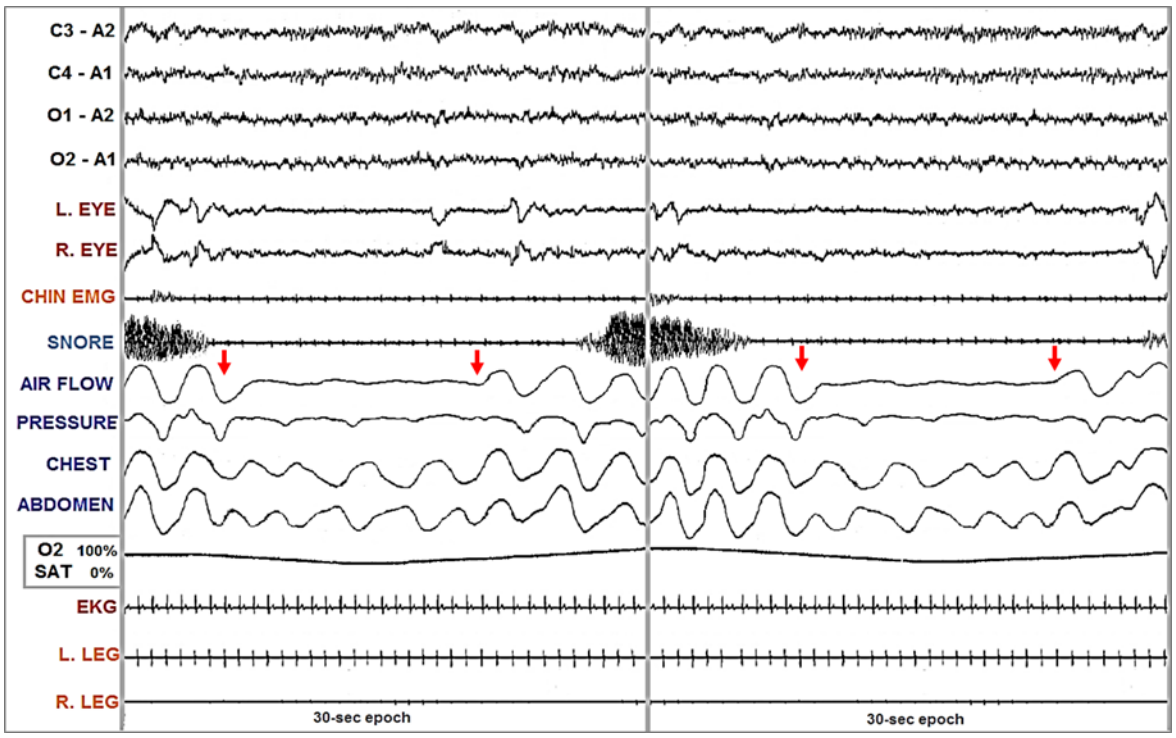


Figure 27. Obstructive Sleep Apnea. Two polysomnogram epochs showing two episodes of obstructive sleep apnea. The arrows mark the onset and termination of the apnea episodes. Also note the presence of oxygen desaturation and snoring. (Image by EC Mader)

Obstructive sleep apnea cannot be diagnosed by history and physical examination alone. Patients must undergo an overnight polysomnogram. The polysomnogram will demonstrate apneas (cessations of airflow) that are obstructive in nature. In Figure 27, snoring is present prior to the onset of the apneas. When airflow ceases, respiratory effort is still seen in the chest and abdominal channels. (In contrast, a central apnea would be accompanied by an absence of respiratory effort in the chest and abdominal leads.) In addition, the 2 epochs above depict REM sleep, as evidenced by the low voltage, mixed frequency EEG, out-of-phase eye movements, and decreased tone in the EMG channel. Obstructive apneas are often more prevalent during REM sleep, when there is paralysis of skeletal muscle, with the exception of the diaphragm. The supine position can also exacerbate obstructive sleep apnea, because the weight of the soft tissue.

Obstructive sleep apnea increases the risk of hypertension and can result in "resistant" hypertension. It can cause bradyarrhythmia and conduction block, and may predispose

patients to development of Type 2 diabetes. It is also a risk factor for stroke and linked to adverse cardiovascular outcomes.

The differential diagnosis of obstructive sleep apnea includes central sleep apnea, narcolepsy, and snoring (upper airway resistance syndrome without apneas).

Treatments for obstructive sleep apnea are as follows. Weight loss, if patients are able to accomplish it, can be an effective treatment for obstructive sleep apnea. If apneas occur mainly when the patient is in the supine position, positional therapy can be therapeutic. Sleep position shirts have a pocket sewn into the back. A pillow or a tennis ball can be inserted into the pocket, and prevents the patient from lying in the supine position. Continuous positive airway pressure (CPAP) is the mainstay of therapy. It acts as a pneumatic splint, keeping the airway open during sleep. Occasionally, a surgical procedure called uvulo-palatal-pharyngeal plasty (UPPP) is employed to remove the extra tissue from the upper airway. A dental appliance, called an oral mandibular repositioning device can also be effective.

Narcolepsy

Narcolepsy is a relatively rare condition, but it is a topic that is frequently tested. It is characterized by the following: hypersomnolence; disturbed nocturnal sleep; and REM intrusion into wakefulness.

Hypersomnolence can manifest as sleep attacks that occur during monotonous or sedentary activity, even occur when the patient is fully engaged in a task. Disturbed nocturnal sleep is not frequently mentioned, but is also a component of narcolepsy.

REM intrusion into wakefulness is manifested by cataplexy, sleep paralysis, hypnopompic and hypnagogic hallucinations. These will be described below. Cataplexy is a sudden episode of weakness, especially after the patient becomes emotional. The patient may lose muscle tone or even collapse. Maintenance of consciousness and memory helps differentiate it from epilepsy. Cataplexy results when the atonia (and areflexia) of REM intrudes into wakefulness. If the episode lasts long enough, the EEG will show REM sleep[i].

Figure 28. Hypnogogic and hypnopompic hallucinations occur when the boundary between REM sleep and wakefulness is not clear. (Image credit http://commons.wikimedia.org/wiki/File:John_Henry_Fuseli_-_The_Nightmare.JPG)

Sleep paralysis occurs when a patient is making the transition between sleep and wakefulness. Upon falling asleep or awakening, the patient is unable to move. Again, this is a manifestation of REM atonia. Awareness and memory are preserved, and patients can be extremely frightened. Sleep paralysis can occur in up to 3-5% of normal population. Hypnogogic (during sleep onset) and hypnopompic (during awakening) hallucinations occur during the transition between sleep and wakefulness. The patient has visual and auditory hallucinations or out-of-body experiences because the boundary between these events and dreams is not clear. It can be mistaken for psychosis. These "hallucinations" can occur in normal individuals, as well.

The prevalence of narcolepsy with cataplexy between 0.025% and 0.05%, but it is likely hugely underdiagnosed. In order to diagnose narcolepsy, an overnight polysomnogram is required to exclude other conditions that could result in hypersomnolence. This is followed by a multiple sleep latency test (MSLT). In narcolepsy, the MSLT will show a decreased sleep latency and an increased number of sleep onset REM periods.

Hypocretin (or orexin) is produced in the hypothalamus. Absence of hypocretin causes decreased arousal and sleepiness. It's deficiency noted in narcolepsy with cataplexy (and rarely in cases without cataplexy). It can be detected in cerebrospinal fluid, but the test is only recommended in select cases. Laboratory evaluation may also include a serum test for (HLA) DQB1*0602. It will occur in most cases of narcolepsy with cataplexy, but fewer cases of narcolepsy without cataplexy. However, it is present in 12-38% of control subjects.

Treatment of narcolepsy includes stimulants. As you recall from reading about the neurotransmitters involved in the sleep wake cycle, norepinephrine promotes wakefulness. Amphetamines act by promoting release of catecholamines and cocaine blocks reuptake of catecholamines. Older stimulants include methylphenidate, methamphetamine, and dextroamphetamine. Modafinil and armodafinil, newer medications that promote wakefulness, are currently considered standard therapy. Their precise mechanisms of action are unknown. Xyrem (sodium oxybate) is similar to GHB, the date rape drug. It is taken at before bedtime and promotes sleep. The precise mechanism of action of Xyrem in the treatment of narcolepsy is unknown. However, it is a metabolite of the neurotransmitter GABA and hypothesized to work through GABA actions. Although it is FDA approved for use in narcolepsy, it can be difficult to administer because of the potential for abuse. Behavioral modifications can also be helpful. Naps are refreshing. Patients should employ extreme caution while driving.

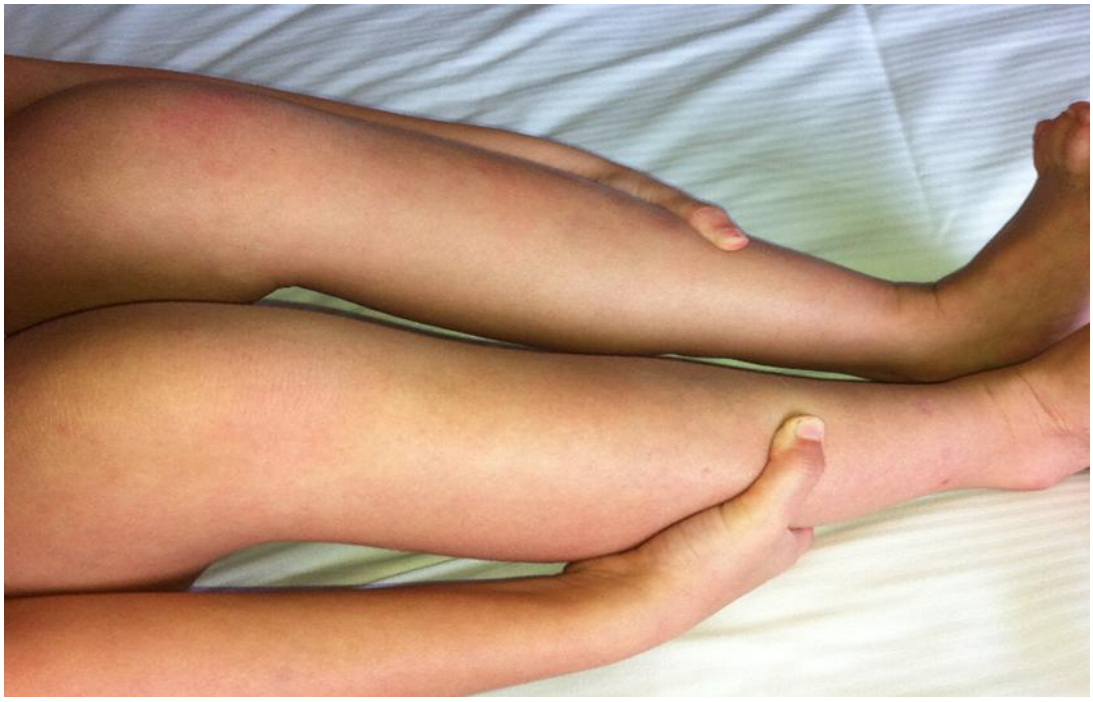


Figure 29. In restless legs syndrome, the symptoms prevent patients from falling asleep. (Image by D Barratt)

Restless Legs Syndrome

The diagnosis of restless legs syndrome is purely clinical. Patients exhibit an urge to move the legs and uncomfortable and unpleasant sensations in the legs. These begin or worsen during periods of rest or inactivity and are partially or totally relieved by movement. The symptoms are worse in the evening or night.

The prevalence of restless legs syndrome is 2-3%, overall. It is higher among the elderly, and occurs in 20% of pregnant women and in 20% of patients in renal failure. Seventy to ninety percent of patients with RLS will also have periodic limb movements.

The etiology and treatment depends upon whether the condition is primary or secondary. Primary restless legs syndrome can be hereditary and involves a deficiency of iron (necessary for the dopaminergic neurons) in the central nervous system. Iron studies can be performed, and supplementation may be helpful. In addition, exercise before bed and dopamine agonists can be helpful. The FDA has approved ropinirole, pramipexole, and rotigotine (available as a patch) to treat moderate to severe RLS. A new FDA approved treatment for RLS is Horizant (gabapentin enacarbil), which becomes gabapentin in the body. The precise mechanism of action is unknown, but it does represent a non-dopaminergic therapy for RLS. Secondary restless legs syndrome can result from iron deficiency, renal failure, neuropathy, pregnancy, and medications such as dopamine

antagonists (haloperidol or phenothiazine derivatives), caffeine, TCAs, and SSRIs. Treatment of the underlying cause would be helpful in secondary restless legs syndrome.

Figure 30. In periodic limb movement disorder, limb movements occur during sleep. The patients may experience frequent awakenings or daytime hypersomnolence. (Image used with patient's permission.)

Periodic Limb Movement Disorder (PLMD)

The diagnosis of PLMD is made by both clinical evaluation and polysomnography. Normal individuals exhibit movements during sleep, and limb movements during sleep normally increase with age. In patients with PLMD, polysomnogram demonstrates increased repetitive movements that are not better explained by another disorder. A disorder is diagnosed only when it causes symptoms, such as disturbed sleep or daytime fatigue. The prevalence of PLMD is not known. There is significant overlap between restless legs syndrome (RLS) and PLMD. However, **RLS is a disorder of sleep onset—the patient cannot fall asleep because of the symptoms. PLMD occurs once the patient is already asleep. The patient may be unaware of the movements, but suffers daytime symptoms**.

Sleep Terror Disorder

Sleep terror disorder is a disorder of **slow wave sleep.** The patient screams, exhibits intense fear and autonomic symptoms (tachycardia and diaphoresis). It is difficult to

arouse the patient, who has amnesia of the event. The patient can become injured during an event. Prevalence is up to 6.5% in children and 2% in adults. If signs and symptoms are typical, no further evaluation is necessary.

If there are atypical features, referral to a sleep lab for an overnight polysomnogram would be indicated to exclude epilepsy or other sleep disorders that could cause arousals.

Sleep walking (somnambulism) occurs during slow wave sleep, and is also in the differential diagnosis. It is characterized by ambulation, impaired consciousness, confusion, and amnesia. Nightmares are also in the differential diagnosis; however, nightmares typically occur during REM sleep. Upon awakening from nightmares, patients are alert and recall is clear. In older adults, REM behavior disorder is in the differential diagnosis.

REM behavior disorder

REM behavior disorder occurs when a patient loses the normal REM atonia. As a result, the patient begins acting out dreams. Violent behavior and injury to the bed partner can occur. Upon awakening, the patient will remember the dream. The condition predominantly affects men over the age of 50. There is also an association with Parkinson's disease and multiple systems atrophy (a Parkinson's plus syndrome). Polysomnogram demonstrates an excessive amount of tonic activity during REM sleep. Treatment should include modification of the sleep environment to prevent injury and consideration of a benzodiazepine called clonazepam.

Acknowledgement: The authors would like to thank Ms. Samantha Syms for her administrative support.

Further reading:

Fish BJ. Fish and Spehlman`s EEG Primer: Basic Principles of Digital and Analog EEG. Third Edition. Amsterdam New York: Elsevier 1999

Tatum WO, Husain AM, Benbadis SR, Kaplan PW. Handbook of EEG Interpretation.

New York: Demos Medical Publishing 2008.

Kryger MH, Roth T., and Dement WC. (Eds.), Principles and practice of sleep medicine, 5th edition, St. Louis: Elsevier Saunders. 2010.

Glossary

Adenosine: a compound that promotes sleepiness

Alpha frequency: an EEG frequency ranging from 8-13 Hertz (Hz) or cycles per second (/s). Alpha frequency is very important because it is one of the criteria for an alpha rhythm.

Alpha rhythm: Alpha rhythm is characterized by an alpha frequency (18-13 Hz or cycles/second) in the posterior (occipital) leads. By definition, alpha rhythm is attenuated with eye opening. The alpha rhythm occurs in normal adults during relaxed wakefulness.

Apnea: the cessation of airflow.

Beta frequency: an EEG frequency > 13 Hertz (Hz) or cycles/second

Cataplexy: sudden and transient episodes of loss of motor tone triggered by emotions

Central apnea: cessation of airflow during which there is no respiratory effort

Circadian rhythms: daily biological rhythms

CPAP (continuous positive airway pressure): a treatment for obstructive sleep apnea that uses air pressure to keep the airway open.

Delta frequency: an EEG frequency of < 4 Hertz (Hz) or cycles/second.

Encephalopathy: global cerebral dysfunction, resulting in altered mental status and possibly other signs and symptoms. Encephalopathy can result from many different etiologies.

Epilepsy: a disorder of the brain that predisposes a patient to having recurrent seizures

Epoch: period of time. In EEG, the recordings were traditionally displayed in 10-second epochs, or 10 seconds per page. On wide screen computers, EEG may be displayed in 12-second epochs. In polysomnograms, the recordings may be displayed in a more

compressed format (30 seconds per page or more). In EEG, one is often looking for activity of short duration, such as a spike or a sharp wave. In polysomnograms, one may be looking at respirations or oxygen saturations over a longer period of time.

Gabapentin: an anti-epileptic medication that is also used in pain management.

Histamine: a compound that promotes wakefulness.

Hypersomnolence: sleepiness.

Hyperventilation: A provocative maneuver performed to induce seizure activity in order to capture it on EEG.

Hypnogram: a graphical representation of the cyclical nature of sleep.

Hypnogogic: occurring during sleep onset.

Hypnopompic: occurring during awakening.

Hypocretin (also known as orexin): a hormone that promotes wakefulness.

Hypopnea: a reduction of breathing during sleep that is often associated with an oxygen desaturation.

Insomnia: inability to fall asleep or stay asleep.

Inter-ictal: occurring between clinical seizures, as in inter-ictal epileptiform activity on the EEG.

Intermediolateral zone of the thoracic lateral horns (IML): among its other functions, it is part of the pathway that links to thalamus to the pineal gland to regulate melatonin production.

K complexes: high amplitude biphasic deflections seen maximally over the vertex (Cz). Part of the definition of N2 sleep.

Melatonin: the "hormone of darkness." Its secretion increases with darkness to induce sleep in humans.

Multiple Sleep Latency Test (MSLT): nap study that measures daytime somnolence.

Obstructive apnea: cessation of airflow during which there is an effort to breathe.

Orexin: (also known as hypocretin) a hormone that promotes wakefulness.

Paraventricular nucleus (PVN): one of the hypothalamic nuclei involved in melatonin production.

Photic stimulation: a provocative maneuver (flashing lights) intended to induce seizure activity while the EEG is being recorded.

Photoentrainment: resetting of circadian rhythms by Earth's day/night cycle or other luminosity cues.

Pineal gland: the epithalamic gland that produces melatonin.

Pinealocytes: cells of the pineal gland that produce melatonin.

Polysomnogram: a study that records information about sleep. It typically includes EEG, eye movements, muscle tone, heart rate, air flow and respiratory effort, oxygenation, and audio and video recordings.

Post-ictal: occurring after a clinical seizure, as in post-ictal confusion or post-ictal EEG slowing.

Postsynaptic potentials: electrical activity (inhibitory and excitatory) generated mainly by cortical pyramidal cells. The postsynaptic potentials of the cortical pyramidal cells closest to the scalp leads generate the EEG patterns.

Raphe nuclei: brainstem nuclei that produce serotonin (5-HT).

REM latency: time that it takes for an individual to enter Stage R or REM sleep after falling asleep. A short REM latency can indicate sleep deprivation or narcolepsy.

Reticular activating system (RAS): the arousal system for consciousness; often, it is defined to encompass nuclei beyond just the reticular formation.

Retinohypothalamic tract: tract from the retina to the hypothalamus consisting primarily of melanopsin-expressing retinal ganglion cells projections to the suprachiasmatic nucleus of the thalamus.

Seizure: results when there is an abnormal electrical discharge in the brain. Clinically, it can have many manifestations-- a convulsion, an impairment of consciousness, or blinking and staring.

Sharp wave: a sharply contoured (although less so than a spike) waveform that stands out from the background activity. It has a pointed peak (duration of 70-200 ms). Sharp waves are typically abnormal and indicate epileptiform activity.

Sleep deprivation: a technique that is used to provoke seizure activity in order to capture it on EEG.

Sleep latency: the time it takes for the person to fall asleep. A short sleep latency could indicate somnolence. A long sleep latency could indicate sleep onset insomnia.

Sleep spindles: an EEG finding that consists of 11- to 14-Hz waves. Part of the definition of N2 sleep.

Spike: a sharply contoured wave form (duration from 20-<70 ms) that stands out from the background activity. It can be followed by a slow wave. Spikes are typically abnormal and indicate epileptiform activity.

Stage N3: This is the new nomenclature, which replaces the former classification of Stages 3 and 4 sleep. It is also known as slow wave sleep or delta sleep.

Superior cervical ganglia (SCG): among its many other functions, it is part of the pathway that links to thalamus to the pineal gland to regulate melatonin production.

Suprachiasmatic nucleus (SCN): hypothalamic nucleus that acts as the "master clock" to reset and synchronize the various circadian rhythm systems of the body

Theta frequency: An EEG frequency ranging from 4 to <8 Hertz (Hz) or cycles/second