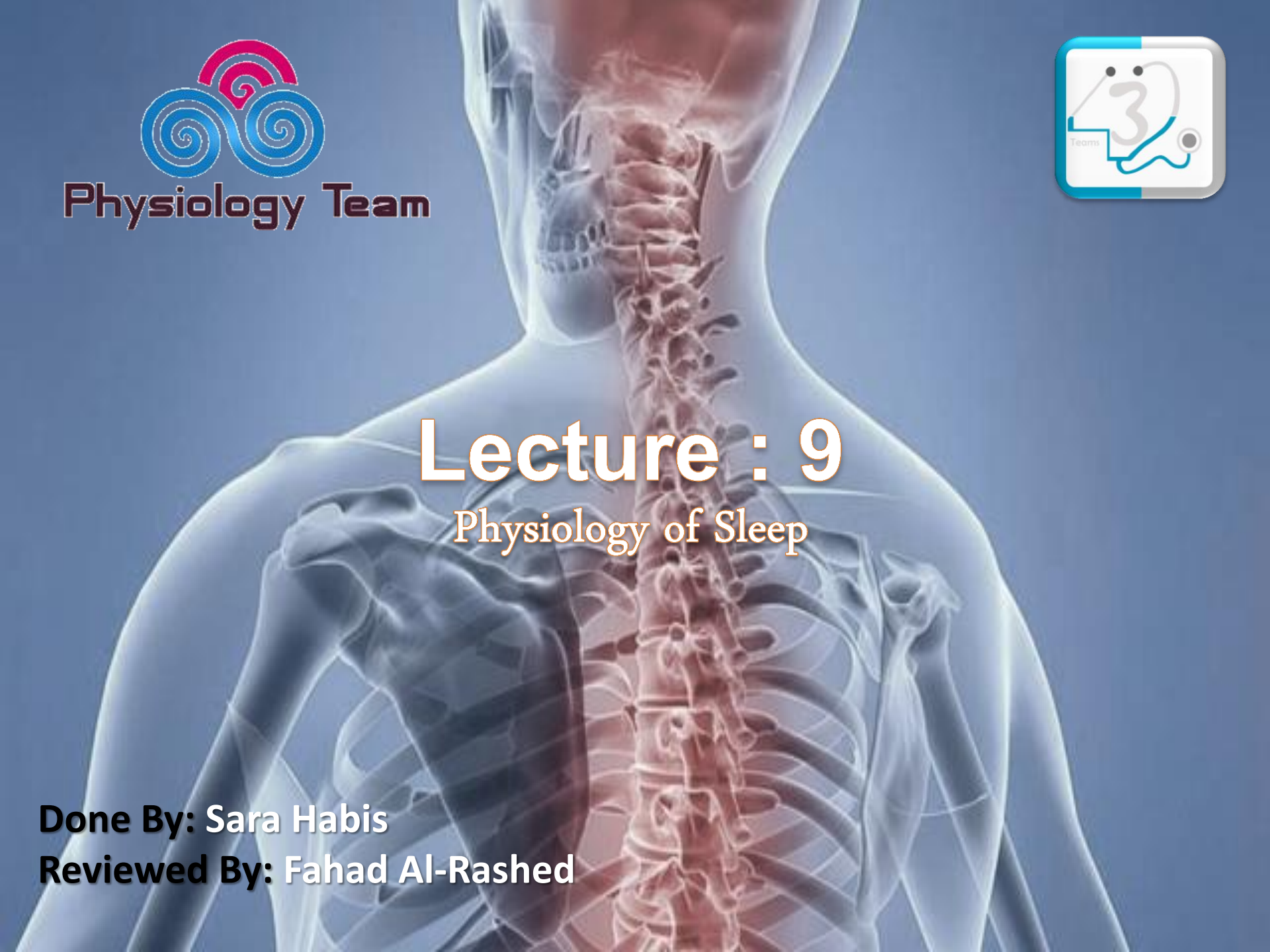

Lecture : 9

Physiology of Sleep

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Physiology Team

OBJECTIVES

At the end of this lecture, student should be able to describe:

1. Difference between sleep & coma.
2. Why do we sleep?
3. Types of sleep: NREM & REM.
4. EEG waves.
5. Stages of NREM sleep.
6. Importance of REM sleep.
7. Sleep cycle and effect of age.
8. Sleep/awake cycle (Role of SCN).
9. Mechanism of sleep (centers/ neurotransmitters).
10. Sleep disorders.

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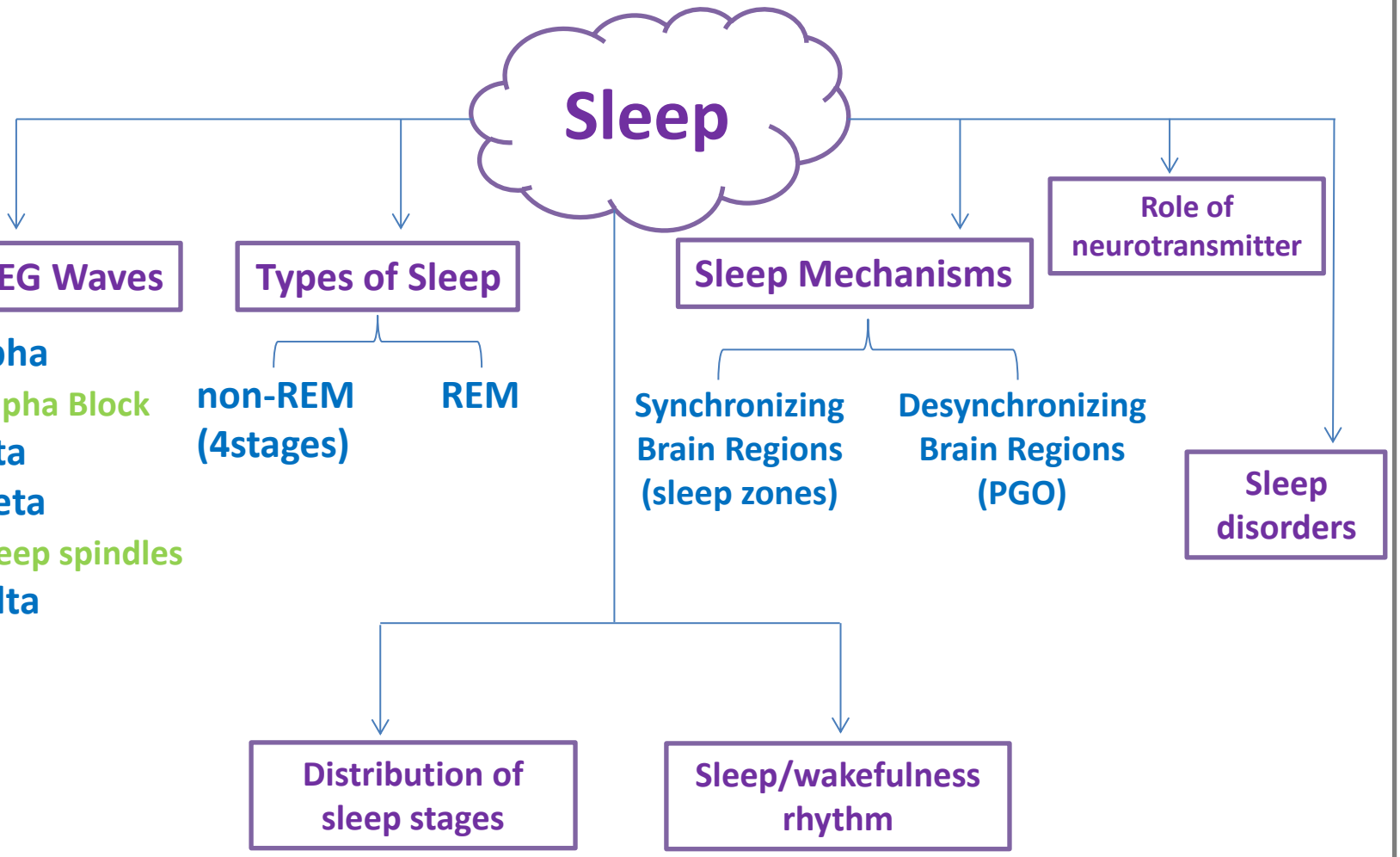
MIND MAP



■ Slides ■ Important ■ Doctor's Notes ■ Explanation ■ Boy's Slides

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Definition

- Sleep is a state of loss of consciousness from which a subject can be aroused by appropriate stimuli.
  If we did an EEG we will see : various waves for various sleep stages (sharp waves).

- Coma is a state of unconsciousness from which a subject cannot be aroused.
  EEG will be dominated by slow waves.

Why do we sleep?

- Restoration, or repair:
  - Waking life disrupts homeostasis.
  - Sleep may conserve some energy.
- Protection with the circadian cycle.
- Circadian synthesis of hormones, e.g. growth hormone.
- Consolidation of learning.
- **Remodeling of synaptic function**

EEG waves , reflects brain activity

- The frequencies of brain waves range from 0.5-500 Hz.
- The most clinically relevant waves:
  - Alpha waves : 8-13 Hz
  - Beta waves : greater than 13 Hz } awake
  - Theta waves : 3.5-7.5 Hz sleeping
  - Delta waves : 3 Hz or less Deep sleep

Alpha waves

- Seen in all age groups but are most common in adults.
- Most marked in the parieto-occipital area.
- Occur rhythmically on both sides of the head but are often slightly higher in amplitude on the **non-dominant side**, especially in right-handed individuals
- Occur with
  - Closed eyes
  - Relaxation
  - wondering mind.

Alpha block:

(Arousal response)
Alpha activity disappears normally with **attention** (e.g. mental arithmetic, stress, opening eyes, any form of sensory stimulation).
Then become replaced with irregular low voltage activity.

Desynchronization as it represents breakup of synchronized (1) neuronal activity.
(1) making brain in a harmony state which leads to sleep-

An abnormal exception is alpha coma, most often caused by hypoxic-ischemic encephalopathy of destructive processes in the pons(e.g. intracerebral hemorrhage).
In alpha coma, alpha waves are distributed uniformly both anteriorly and posteriorly in patients who are unresponsive to stimuli.

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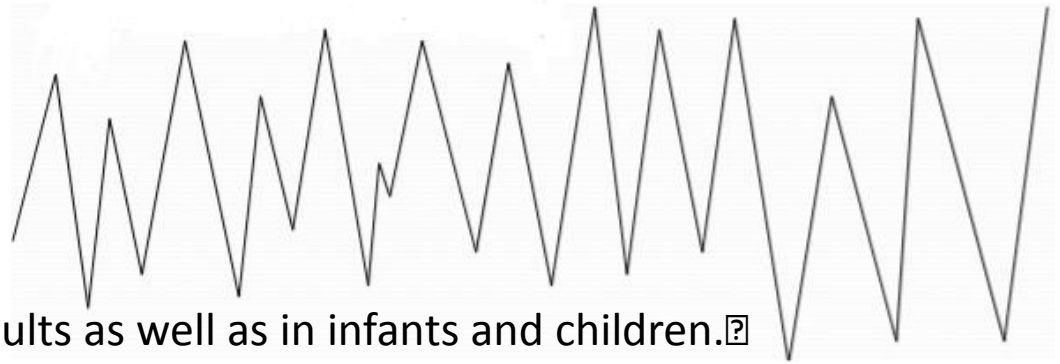
Beta waves

- Seen in all age groups.
- Small in amplitude , usually symmetric and more evident anteriorly.
- Drugs, such as barbiturates and benzodiazepines, augment beta waves.
- >13 Hz / sec.

Theta waves

- Normally seen during sleep at any age.
- In awake adults, these waves are abnormal if they occur in excess.
- Theta and delta waves are known collectively as slow waves.

Delta waves



- Slow waves,
- Normally seen in deep sleep in adults as well as in infants and children.
- Delta waves are abnormal in the awake adult.
- Often, have the largest amplitude of all waves.
- Delta waves can be focal (local pathology) or diffuse (generalized dysfunction).

Sleep spindles

- Spindles are groups of waves that occur during many sleep stages but especially in stage 2.
- They have frequencies in the upper levels of alpha or lower levels of beta.
- Lasting for a second or less, they increase in amplitude initially and then **decrease** slowly. The waveform resembles a spindle.
- They usually are symmetric and are most obvious in the parasagittal regions

Types of Sleep

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Important slide

Depending on EEG criteria:

non-REM (Slow Wave Sleep)

REM (Rapid Eye Movement Sleep)

- not associated with rapid eye movement.
- 75% - 80% of sleep time.
- restful.
- Decrease in vascular tone (peripheral vascular resistance).
- Decrease in Blood pressure (10-30%)
- Decrease in Respiratory rate.
- Decrease in BMR (basal metabolic rate).
- If dreams occur they are not remembered as they are not consolidated in memory.
- There is increased Growth hormone secretion.
- More easy to awake a person than in REM.

- **EEG:** Theta + delta waves. (which are slow waves)

REM
(Rapid Eye Movement Sleep)
(Paradoxical sleep)

- Called like that because its associated with rapid rolling eye movement.
- occur in episodes of **5-30 min**, recurring every 90 min.
- **20% - 25% of sleep time.**
- tiredness shortens the duration of each episode, while being restful through the night increases the duration.
- Decrease in muscle tone (due to excitation of reticular inhibitory centers).
- Heart Rate & Respiratory Rate are irregular.
- Twitches of facial & limb muscles. - Erection of penis. - Engorgement of clitoris.
- Active dreaming, remembered later.
- Blood pressure fluctuation occur which is characteristic of dreaming.
- The brain is highly active , brain metabolism may increase by 20%.
- More difficult to awake a person than in Non-Rem. But we usually awake in REM in the morning. (hard to wake up because he will be inside his little special world while dreaming XD)

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(Rapid Eye Movement Sleep)
(Paradoxical sleep)

- **EEG:** B-waves,
- indicating a high level of activity in the brain during REM (That is why it is called paradoxical sleep). Similar to that occur during wakefulness.
- PGO* spikes stimulate the Inhibitory Reticular Area leading to Hypotonia**.
- **Exception**: Respiratory + Eye muscles.
  - **Note:** In sleep apnea, respiratory muscles are inhibited.

  * Sleep apnea(a condition when breathing stops for more than ten seconds during sleep) :
    - Obstructive = in infants due to adenoids.
    - non-Obstructive = in adults.

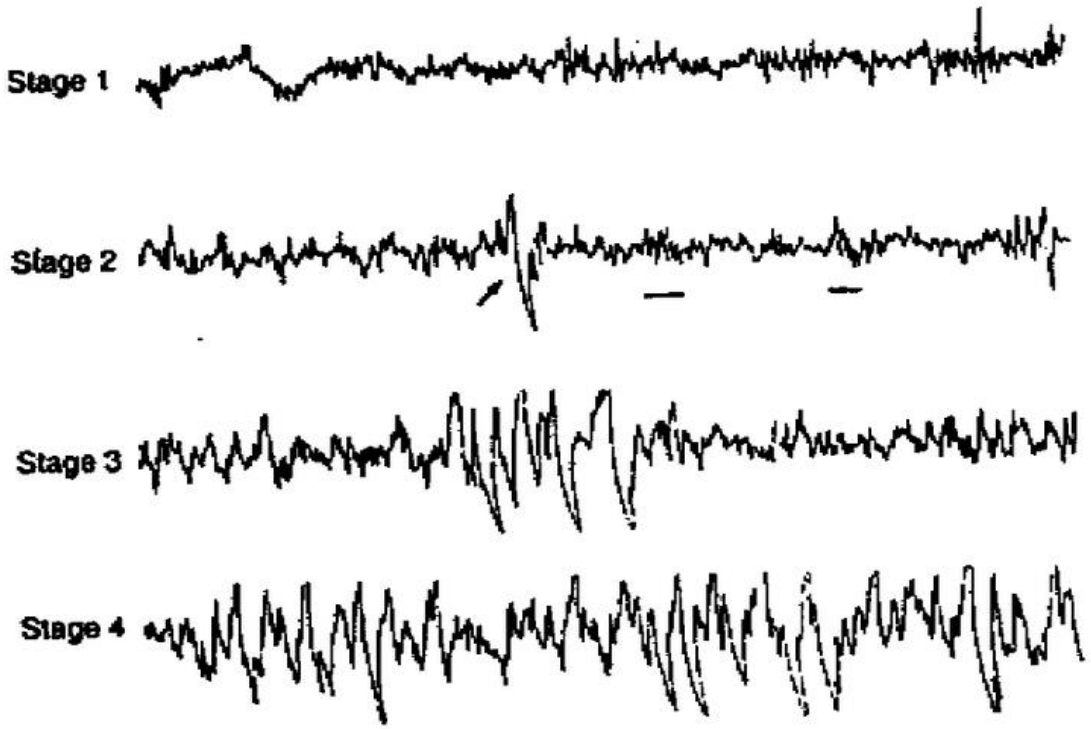
*ponto-geniculo-occipital
** decrease in muscle tone

Importance of REM sleep

1. Expression of concerns in the sub-consciousness(Through dreams).
2. Long-term chemical and structural changes that the brain need to make learning & memory possible.

Distribution of Sleep Stages

- **Slow wave sleep divided to 4 stages :**



Sleep stages (NREM)

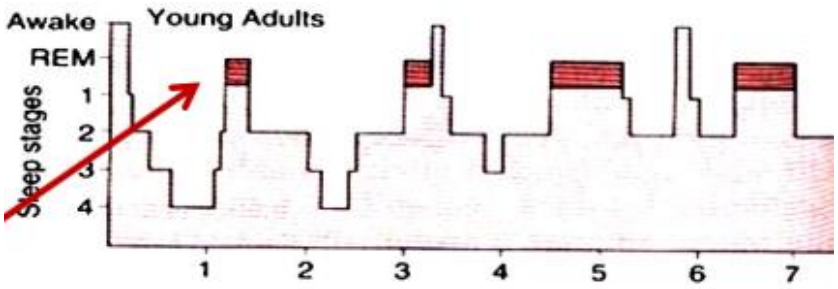
Distribution of Sleep Stages

In typical night of sleep for a young adult :

1- First enters NREM sleep, passes through stages 1,2,3 and 4.

2- Goes into the first REM episode.

- This cycle is repeated at intervals of about 90min (100-80min) throughout 8 hours of a night sleep. therefore, there are **4-6 sleep cycles** per night and **4-6 REM cycles**.
- NREM occupies 75-80% of a night sleep time, while REM occupies 20-25% .
- As the night goes on, there is progressive reduction in stage 3 and 4.
  and a progressive increase in REM sleep.
- REM sleep is lighter than NREM sleep.



REM sleep periods are shown in red

Distribution of Sleep Stages

In typical night of sleep for:

- **Premature infants:**
  REM sleep occupies 80% of total sleep time.

- **Full term neonates:**
  50% of sleep time is occupied by REM.

- **Children:**
  have more sleep time and stage4 than adults.

- **Aged/elderly:**
  in old age , the proportion of REM sleep falls rapidly and plateaus at about 25% (20-69ys) until it falls further in old age.

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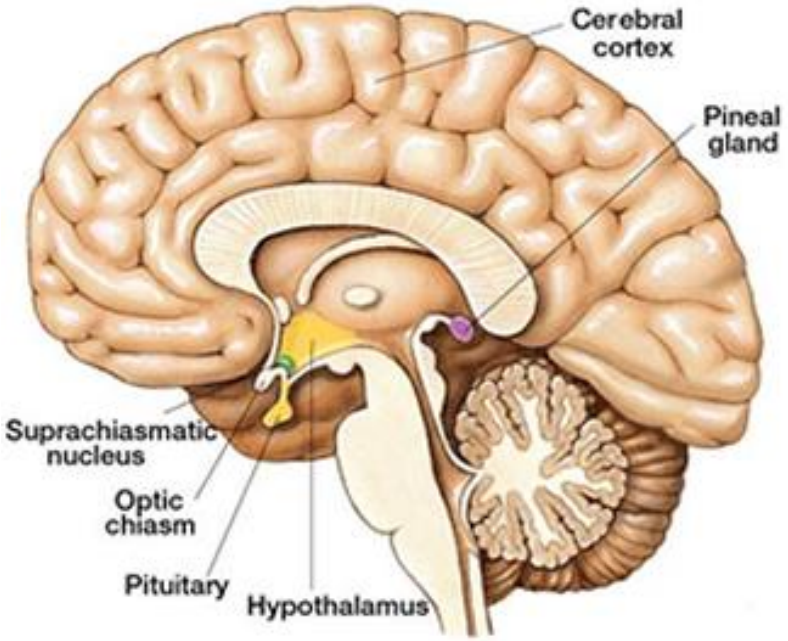
Sleep/wakefulness rhythm



- Periods of sleep and wakefulness alternate about once a day.
- A circadian rhythm consist typically of 8h sleep and 16h awake.
- This rhythm is controlled by the biological clock function of suprachiasmatic (SCN) nucleus in the hypothalamus.
- Within sleep portion of this circadian cycle NREM and REM sleep alternate.

That means:

The role of suprachiasmatic nucles (SNC) is to control the circadian rhythm.

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Big Note

Before studying theories\mechanism of sleep. Dr.Taha said that this objective is still under experiments so we will find a lot of information and it may oppose each other. Like in the boys & girls slides! So we will put this small paragraph from Guyton pocket book.

Mechanisms that cause sleep :

- **Non-Rem:**

Sleep can occur by stimulating anyone of three brain location. The most potent site is **Raphe** of the caudal pons and medulla. Many of the neurons in the Raphe nuclei utilize Serotonin as transmitter, and it's known that drugs that block the formation of Serotonin prevent sleep. In addition, stimulation in the **nucleus of Solitary tract** promotes sleep, but this occurs only if the **raphe nuclei are also functional**. Activation of the **Suprachiasmatic level** of the **Hypothalamus** or the **Midline nuclei** of the **Thalamus** produce sleep. Some studies however shown that blood levels of Serotonin are lower during sleep that wakefulness, suggesting that some other substance is responsible for sleep production. One possibility is Muramyl Peptide, which accumulate in CSF and urine. When microgram amounts of this substance are injected into the third ventricle, sleep is induced within munities.

- **Rem:**

REM sleep is enhanced by **cholinergic agonists**. It's postulated that certain of the projection cholinergic neurons of the midbrain reticular formation are responsible for the initiation of REM sleep. These projection would activate only neurons that lead to REM sleep activation and avoid other systems that contribute to waking state production and the reticular activating system.

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Mechanisms of Sleep

Genesis of slow wave sleep:

- Active process produced by inhibition of areas in RAS (*Reticular activating system*) responsible for alert conscious state of wakefulness.
- Stimulation of the following sites "**Sleep Zones**" will lead to sleep and synchronization of slow–wave sleep EEG:

1. Diencephalon :

- suprachiasmatic region of post hypothalamus.
- diffuse thalamic nuclei: intra-laminal & ant.thalamic
- Slow frequency stimulation of diencephalon → sleep.
- High frequency stimulation of diencephalon → arousal.

2. Medulla oblongata:

- Medullary synchronizing zone at the level of NTS (*nucleus tractus solitarius*).

3. Basal forebrain: pre-optic area:

- High or slow frequency stimulation → synchronization + sleep.
- 1,2&3 are connected together and with **reticular area of the brain stem**

Genesis REM sleep

Mechanisms of Sleep

Genesis of slow wave sleep

Genesis REM sleep:

- The mechanism producing REM sleep is located in pontine (pons) reticular formation.
- Large cholinergic ponto-geniculo-occipital (PGO) spikes arise in this area and are thought to initiate sleep.
- Discharge of noradrenergic neurons of locus ceruleus + discharge of serotonergic neurons of midbrain raphe causes wakefulness. They become silent when PGO active during REM.

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Dr.Taha notes

Mechanisms of Sleep

- Non-REM\Slow wave sleep is induced by Serotonin + Melatonin.
- REM sleep is induced by Cholinergic Neurons located in the Pons (PGO).
- Bulboreticular Facilitory Area is responsible for wakefulness.

Note: it's better to take a look on the next four slides. They are taken from boy's slides No.(12-18) it may look long but it's very easy :>

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What Makes Us Fall Asleep Sleep ?

Boy's slide

- Theories of sleep : old and modern :
- SWS is induced by Serotonin and Melatonin
- REM is initiated by the Pontine RF

Theories of sleep : old and modern :

The old theory of sleep states that sleep is caused only by a passive process due to fatigue of RAS neurons after discharging for many hours of wakefulness .
This theory was abandoned after experiments in laboratory animals led to development of a new theory stating that in addition , a strong active sleep-inducing inhibitory process that inhibits the RAS to produce sleep .
Sleep is an active field of ongoing research , and many chemicals (e.g., adenosine , orexin etc) are claimed by different sleep researchers to play a role , but what all Researcher Scientists and Medical doctors agree upon are 3 things :
(1) that the neurotransmitter serotonin (produced by the Raphe Nuclei) plays an important role in SWS sleep ,
(2) that Ponto-Geniculo-Occipital circuit plays an important role in generation of REM sleep.
(3) that the hormone Melatonin (released from the Pineal Gland) plays an important role in day-night entrainment of sleep .

Experimental findings supporting the modern theory are :

✓(1) Transecting the brainstem at the level of the midpons , leaves the animal in a state of intense wakefulness for a period of days

The above-mentioned transection cuts the nerves going from the inhibitory serotonin-secreting Raphe Nuclei to the Bulboreticular Facilitory Area

(N.B .: the Bulboreticular Facilitory Area + intralaminar thalamic nuclei constitute the reticular activating system , RAS) .

What does this mean ? It means that the serotonin-secreting Raphe fibers normally inhibit the Bulboreticular Facilitory Area to produce sleep .

✓(2) lesions that destroy the Raphe Nuclei themselves make the animal sleepless for days .

✓(3) Serotonin agonists and antagonists greatly influence SWS in humans.

✓(4) Stimulation of the Suprachiasmal Nucleus (SCN) of hypothalamus (which inhibits Melatonin release) produces wakefulness .

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Boy's slide

Melatonin as Circadian Controller of Sleep-Wake Cycles

- Alternating " Sleep-Wake Cycles " are **under marked Circadian Control .**
- **" Circadian Control " : means regulation of a biological rhythm**

  (e.g. sleep-wakefulness , hormone secretion , etc) by day-night cycles .
- **Melatonin is a hormone secreted by the Pineal Gland during darkness . It inhibits RAS & thereby induces sleep .**
- **The Suprachiasmatic Nucleus (SCN) inhibits melatonin secretion → thereby inhibits sleep & promotes wakefulness .**

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Why do we have sleep-waking cycles ?

Boy's slide

- During the morning , and after a restful night sleep , the Bulboreticular Facilitory Area becomes maximally active , and overcomes any inhibition by the Raphe Nuclei . Moreover , Melatonin falls to very low levels in the morning .
- This release of the Bulboreticular Facilitory Area from inhibition (1) activates (through the thalamic nuclei) the cerebral cortex to increased vigilance , and also

  (2) excites the Peripheral Nervous System (PNS) to become more receptive to incoming sensory stimuli + be more ready to respond by increasing muscle tone .

, Both (1) and (2) above send numerous positive feedback signals back to the Bulboreticular Facilitory Area to activate it still further.

- Therefore, once wakefulness begins, it has a natural tendency to sustain itself because of all this positive feedback activity.
- Then, after the brain remains activated for many hours, the activating neurons in the Bulboreticular Facilitory Area gradually become fatigued.
- Consequently, the positive feedback cycle between the mesencephalic reticular nuclei and the cerebral cortex fades,
- and then the effects of →
- (1) the sleep-promoting centers (Raphe Nuclei) , and
- (2) the rising melatonin levels ,
- Take over → leading to rapid transition from wakefulness back to sleep.

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Boy's slide

Possible Mechanisms for Genesis (Generation) of REM Sleep

- The mechanism that triggers REM sleep is believed to be Cholinergic Neurons located in the Pons .
- This is because animal experiments have shown that → at the onset of REM sleep , large groups of spikes originate in the Pontine RF (Lateral Pontine Tegmentum)
- These spikes discharges rapidly spread from the Pons to the Lateral Geniculate Nucleus (LGN) (i.e., thalamus) & from there the Occipital cortex . Hence they are called Ponto-Geniculo-Occipital (PGO) spikes .
- These PGO discharges initiate REM sleep .

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Role of neurotransmitters

- **Serotonin:**
  - Agonist: (-) sleep.
  - antagonist: (+) slow-wave sleep.
  - Serotonin appears to modulate sleep through its effect on other hypnogenic factors in the anterior hypothalamus and suprachiasmatic nucleus
  - Serotonin is a melatonin precursor.

- **Melatonin**
  - is synthesized and released by the pineal gland through sympathetic activation from the retino-hypothalamic tract.
  - Melatonin enhances sleep.
  - prolonged **bright light** stimulation **suppresses** melatonin and sleep while subsequent melatonin injections can restore normal sleep patterns.
  - Melatonin as Circadian Controller of Sleep-Wake Cycles. And its increase in sleep.

- **Adenosine:**
  - sleep inducing factor. It accumulates in brain with prolonged wakefulness. Adenosine antagonists e.g. caffiene →(+) alertness.

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Working Together in Sleep

Brainstem Nucleus	Neurotransmitter	Activity State of Nucleus
Wakefulness		
Pedunculopontine	ACh	Active
Locus coeruleus	NE	Active
Raphe	5-HT	Active
Non-REM Sleep		
Pedunculopontine	ACh	Silent
Locus coeruleus	NE	Decreased Activity
Raphe	5-HT	Decreased Activity
REM Sleep On		
Pedunculopontine	ACh	Active as REM Approaches
Locus coeruleus	NE	Become Silent
Raphe	5-HT	Inactive
REM Sleep Off		
Locus coeruleus	NE	Become Active
Raphe	5-HT	Become Active

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Boy's slide

Sleep Deprivation

- Sleep deprivation (forced lack of sleep) experiments in humans have shown that the subject :
  1. Experiences at first progressively increasing sluggishness of thought.
  2. Then becomes markedly irritable.
  3. Then may become psychotic .

- It seems that sleep restores both normal levels of brain activity and normal "balance" among the different functions of the CNS .

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Sleep Disorders

- **Insomnia**.
  -Fatal familial insomnia: impaired autonomic & motor functions, dementia, death.

- **Disorders during NREM;**
  -Sleep walking.
  -Bed wetting.
  -Night terrors.

- **Narcolepsy:**
  -episodic sudden loss of muscle tone... irresistible urge to sleep during day time (Bursts of REM).

- **Sleep apnea:** airway obstruction.

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SUMMARY

EEG	Hz	awake	Sleep	Age	amplitude	Extra
Alpha (α)	8-13	√ Relaxed	X	All (adult)	___	____
Beta (β)	> 13	√	REM	All	Smallest	↑ drug
Theta (θ)	3.5 – 7.5	X	√	All	___	Slow
Delta (δ)	< 3	X	√ deep	All	Greatest	Slow
Spindle Waves	α <> β	X	√ stage2	___	____	Spindle like

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SUMMARY

	NON-REM\SWS	REM
Time	75 – 80%	20 – 25%
HR\RR	↓	irregular
Muscle tone	_____	↓ (expect eyes + respiratory muscles)
Metabolic Rate	↓	↑ (Maybe to 20%)
Dreams	Not Remembered	Remembered
wakefulness	Easy	Hard
EEG	Θ – δ	β

Typical night	infants	neonates	Old people	children
REM	80%	50%	decrease	More sleep time

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SUMMARY

- Sleep can be aroused by appropriate stimuli but Coma cannot.
- In typical night of sleep for a young adult First enters NREM then goes into the first REM episode.
- The role of suprachiasmatic nucles (SNC) is to control the circadian rhythm.
- Non-REM\Slow wave sleep is induced by Serotonin + Melatonin.
- REM sleep is induced by Cholinergic Neurons located in the Pons (PGO).
- Bulboreticular Facilitory Area is responsible for wakefulness.
- Sleep Disorders are Insomnia – Narcolepsy - Sleep apnea.

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QUESTIONS

Q1: All of the following are the characteristics of Slow Wave Sleep Except:

A- Decrease heart rate
B-Decrease Respiratory rate
C-Increase growth hormone secretion
D-Increased cerebral blood flow

Q2: Characteristics of the Rapid Eye Movement Sleep (REM) sleep:

A. The first bout occurs 80-100 minutes after the person falls asleep
B. Subject doesn't remember his dream.
C. Subject is easy to arouse by sensory stimuli
D. Heart rate and respiration usually become regular

regulate sleep process : Q3: Which Hormone

A. Dopamine
B. Melatonin
C. ACH
D. Estrogen

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QUESTIONS

Q4: Which of the following is not one of the function of sleep ?

A- Remodeling of synaptic function
B-conserve some energy
C- Decrease growth hormone secretion
D-Circadian synthesis of hormones

Q5: The mechanisms that triggers REM sleep is located in :

A. Pituitary gland
B. Auditory cortex
C. Motor area
D. Pontine reticular formation

Q1	Q2	Q3	Q4	Q5
D	A	B	C	D

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THE END

If there are any Problems or Suggestions,
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THANK YOU