



CNS PHYSIOLOGY

- Text
- **Important**
- Formulas
- Numbers
- **Doctor notes**
- Notes and explanation

Lecture
No.7

“ والله إن المسألة تُغلق في وجهي،
فأستغفر الله ألف مرة فتُفتح لي ”
ابن تيمية

Physiology of sleep

Objectives:

1. Explain the differences between sleep and coma.
2. Define NREM (non-rapid eye movement, SVS) and REM (rapid eye movement) sleep.
3. Describe how NREM and REM sleep are distributed during a normal night sleep in the average adult human.
4. Describe the behavioral and autonomic features associated with NREM and REM sleep.
5. Describe EEG, as a physiological tool, is being used to delineate in which stage of sleep (or wakefulness) a person is.
6. Appreciate how the total sleep duration and different sleep stages vary with different ages in normal humans.
7. Describe the current theories about the neural basis of sleep.

What is sleep?

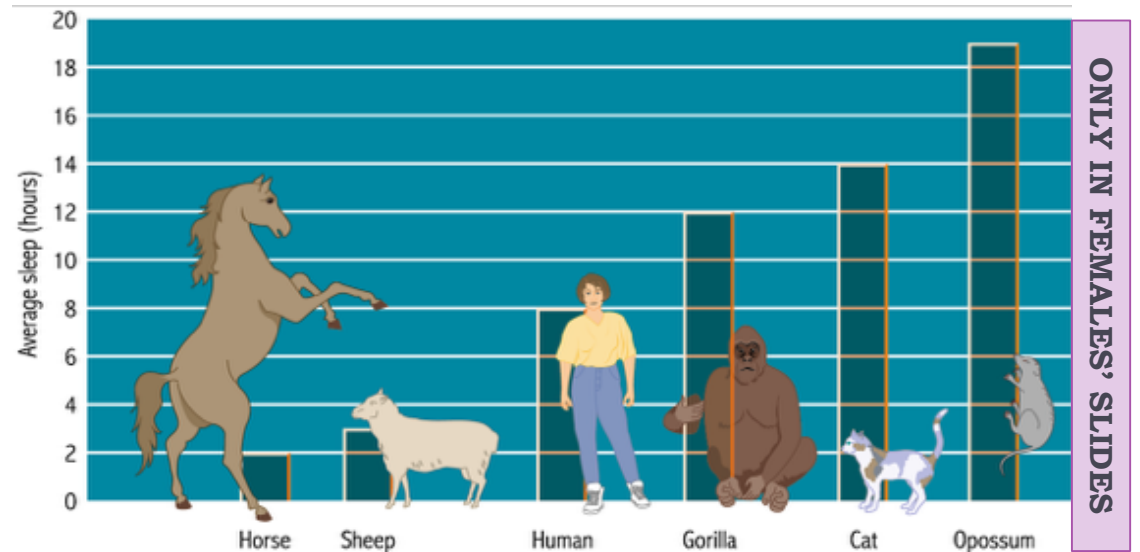
- ▶ **Sleep** (Physiological definition): is a state of unconsciousness from which a subject can be aroused by appropriate sensory or other stimuli.
- ▶ **Sleep may also be defined as** a normal, periodic, inhibition of the reticular activating system. (Anatomical definition)
- ▶ **Awake:** This is the state of readiness / alertness and ability to react consciously to various stimuli.
- ▶ **Coma:** is a state of unconsciousness from which a person cannot be aroused by any external stimuli.
- ▶ Normal sleep requirements:
 - New born = 15 - 20 hours.
 - Children = 10 - 15 hours.
 - Adults = 6 - 9 hours.
 - Old age = 5 - 6 hours.

Theories of sleep

ONLY IN MALES' SLIDES

Restoration theory: Body wears out during the day and sleep is necessary to put it back in shape. This is further supported by findings that many of the major restorative functions in the body like muscle growth, tissue repair, protein synthesis, and growth hormone release occur mostly, or in some cases only, during sleep.

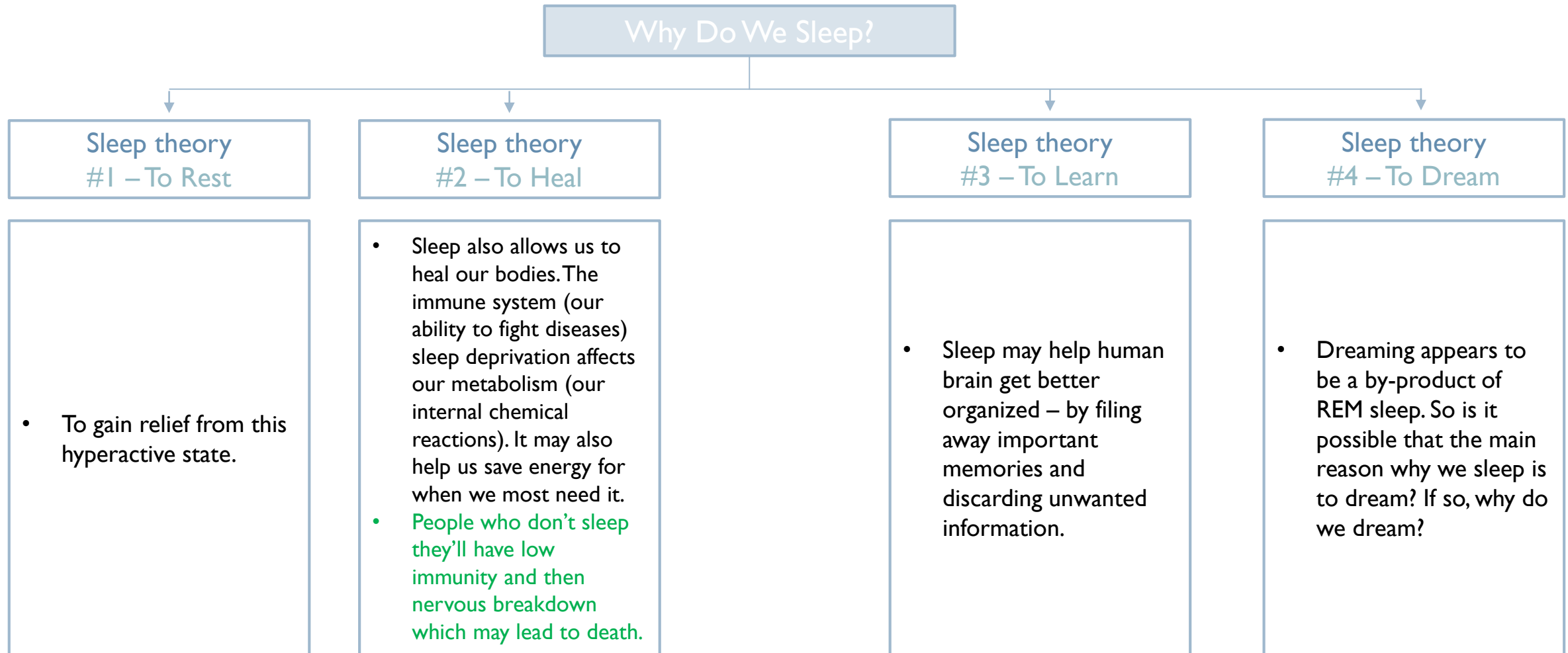
- ▶ **Preservation and protection theory:** Sleep preserve energy and it provides activity. **For example, both body temperature and caloric demand decrease during sleep, as compared to wakefulness.**



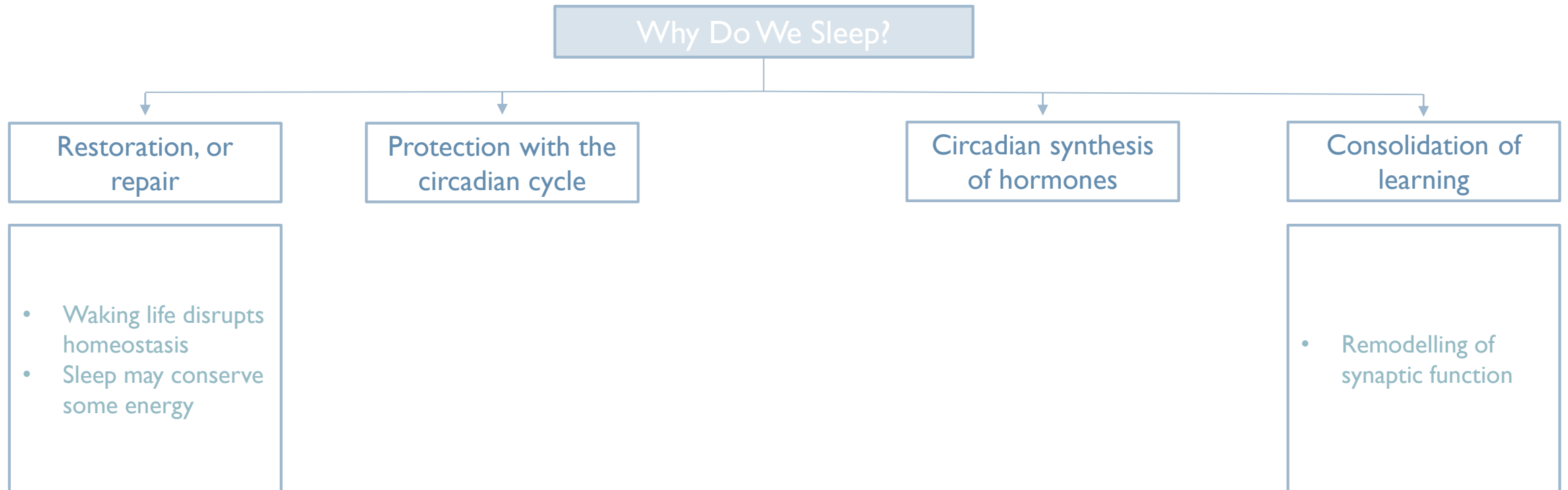
Why do we sleep?

Proximate explanation	Ultimate explanation
Feeling tired (melatonin) ↑	sustains our ability to reproduce successfully, by maintaining good health
Consolidate energy and experiences.	
Restore body cells and promote protein anabolism.	
Maintain hormonal secretions, immune function.	
Maintain hormonal secretions, immune function	

Cont.

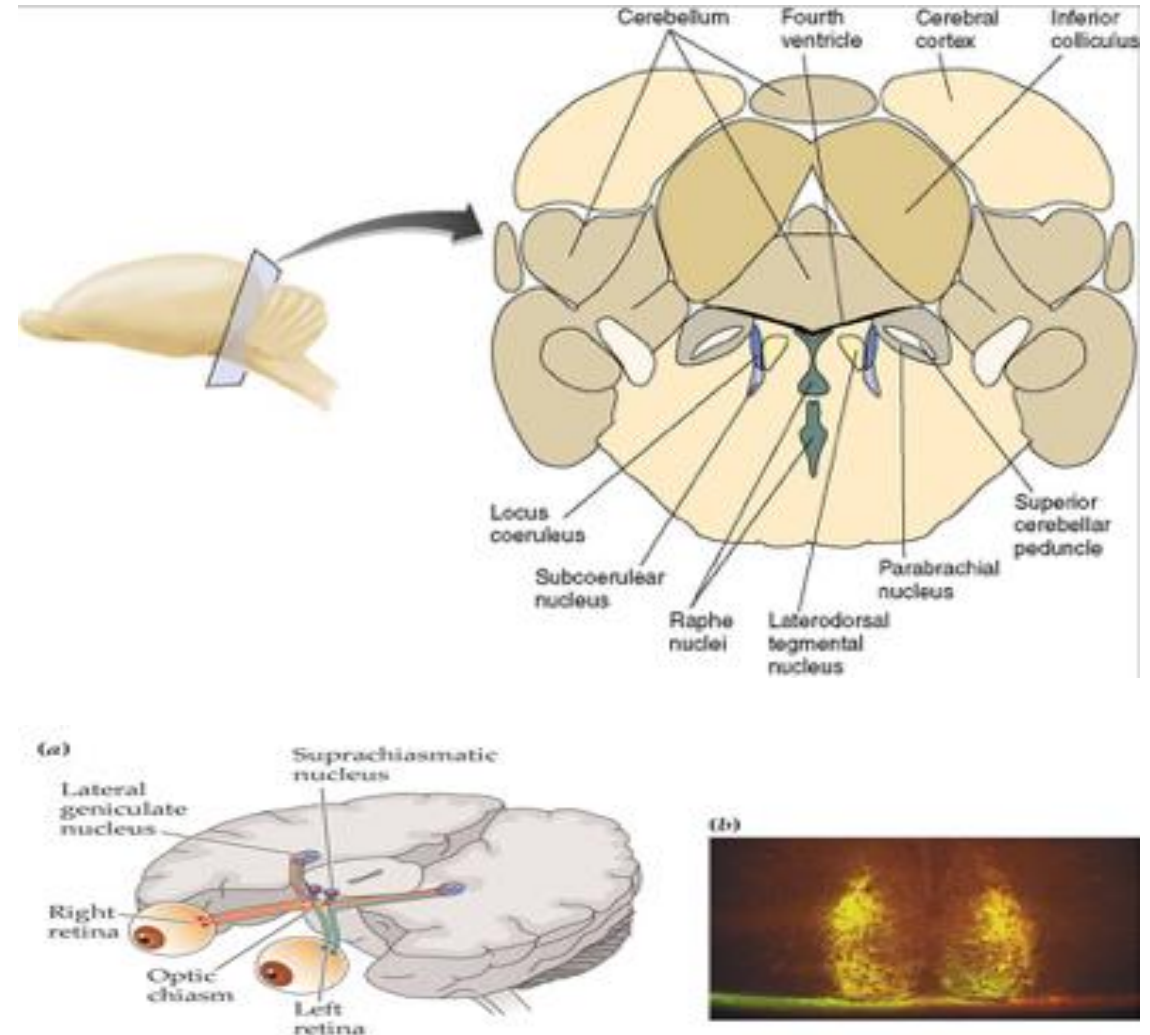
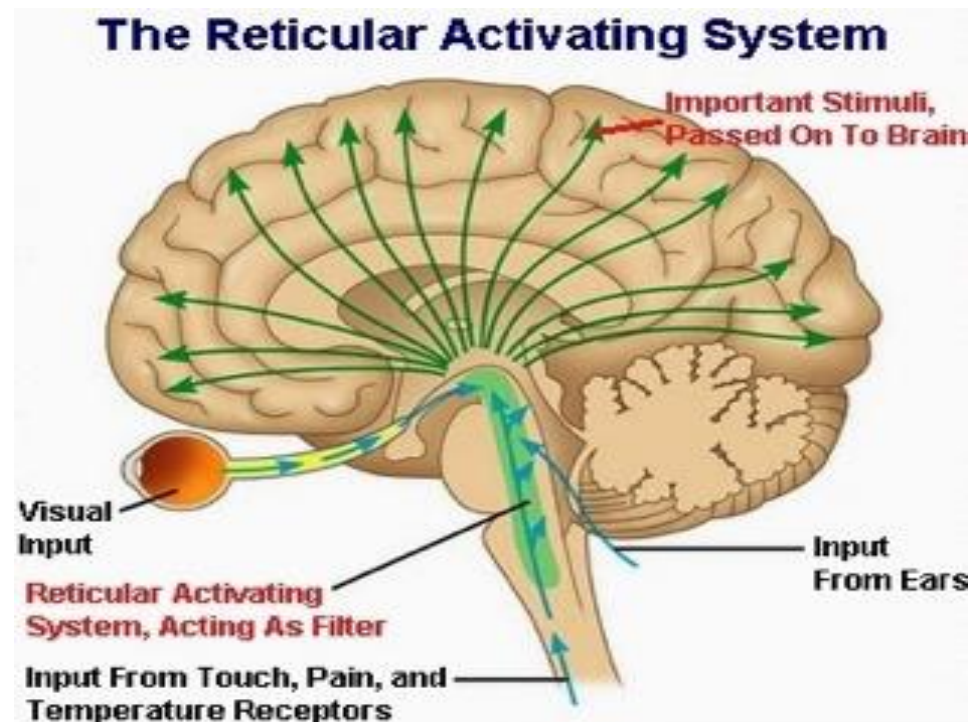


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The reticular activating system

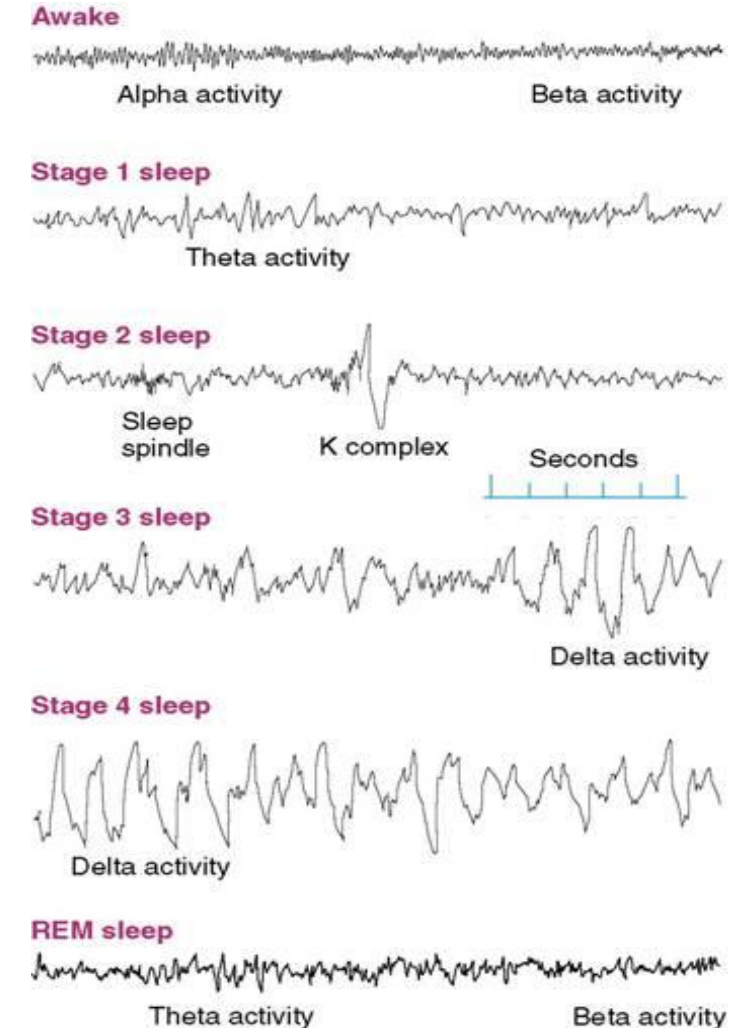
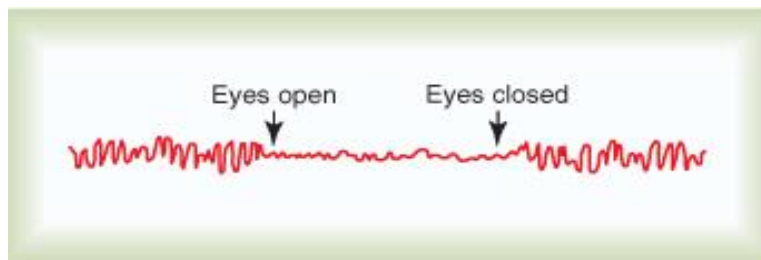
- ▶ A diffuse network of nerve pathways in the brainstem connecting the spinal cord, cerebrum, and cerebellum, and mediating the overall level of consciousness. = 5 - 6 hours.
- ▶ So when we cut it (inhibit it) we will fall asleep.







Stages of sleep: recorded by EEG

- It can be done while the patient is sleeping or awake depending on his condition

EEG waves				
Waves	Frequency	Type of activity	Recorded from	Associated with / occurs
Alpha	8 – 12 hz	Smooth electrical activity	Brain	Associated with a state of relaxation.
Beta	13 – 30 hz	Irregular electrical activity	Brain	Associated with a state of arousal.
Theta	3.5 – 7.5 hz	-	-	Occurs intermittently during early stages of slow wave sleep and REM sleep.
Delta	Less than 4 hz	Regular, synchronous electrical activity	Brain	Occurs during the deepest stages of slow-wave sleep.



EEG waves						Extra
Waves	Frequency The frequencies of brain waves range from 0.5-500 hz.	Recorded from	Seen in	Occur	Diagram	Other
Alpha	8-13 hz	Most marked in the parieto-occipital	In all age groups but are most common in adults	<ul style="list-style-type: none"> Occur rhythmically on both sides of the head but are often slightly higher in amplitude on the nondominant side, especially in right-handed individuals Occur with closed eyes , relaxation, wondering mind. 		-
Beta	Greater than 13 hz	-	In all age groups.	-		Small in amplitude , usually symmetric and more evident anteriorly.
Theta	3.5-7.5 hz	-	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	3 hz or less	-	Normally seen in deep sleep in adults as well as in infants and children .	-		<ul style="list-style-type: none"> 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 centre

- ▶ Normal sleep is under control of the reticular activating system in the upper brain stem and diencephalon.
- ▶ Sleep is promoted by a complex set of neural and chemical mechanisms:
- ▶ **Daily rhythm of sleep and arousal:** suprachiasmatic nucleus of the hypothalamus which regulate pineal gland's secretion of melatonin (increased melatonin makes us sleepy).

1- SWS (Slow-Wave Sleep)

- because in this type of sleep EEG waves are generally of low frequency .
- It is also called Non-Rapid Eye Movement (NREM) sleep because , unlike the other type of sleep it is not associated with rapid eye movements .
- Raphe nuclei of the medulla and pons and the secretion of serotonin.

2- REM sleep (Rapid Eye Movement)

- Because in this type of sleep the the person makes rapid movements by his eyes, in spite of the fact that he is sleeping.
- **Neurons of the pons**

Reticular activating system

Consists of two parts:

1-Mesencephalic part:

- Composed of area of grey matter of mid brain and pons, when this area is stimulated, nerve impulses going to thalamus and disperse to the cerebral cortex. This greatly effects the cortical activity. Mesencephalic part causes consciousness.

2-Thalamic part:

- Consists of grey matter in the thalamus. When the thalamic part is stimulated, it develops activity in the cerebral cortex. Thalamic part causes arousal that is awakening from deep sleep (sensory input, pain, light).

- The RAS and cerebral cortex continue to activate each other through a feedback system.
- The RAS also has a feedback system with the spinal cord.

Types of sleep

- ▶ Sleep is promoted by a complex set of neural and chemical mechanisms:
 - Daily rhythm of sleep and arousal: suprachiasmatic nucleus of the hypothalamus pineal gland's.
 - Secretion of melatonin.

Types of sleep

1- Slow-wave sleep (non-REM)

- 75% of sleep time.
- restful.
- Decrease in vascular tone.
- Decrease in BP (10-30%)
- Decrease in Resp. rate.
- Decrease in BMR
- **It is not associated with rapid eye movement**
- EEG: Theta + delta waves.
- If dreams occur they are not remembered as they are not consolidated in memory.
- In this type of sleep, EEG waves are generally of low frequency.

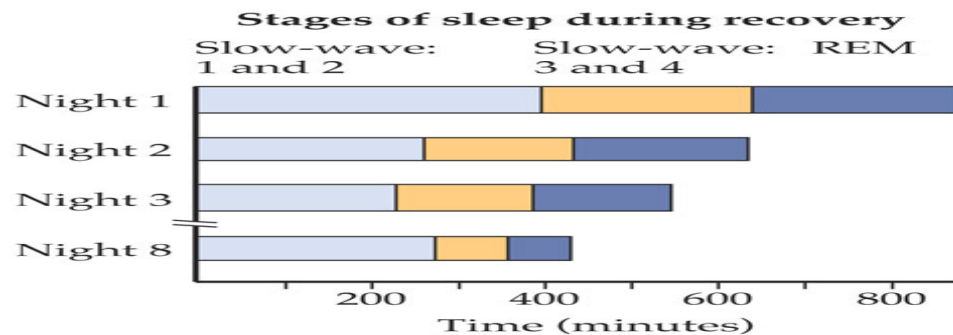
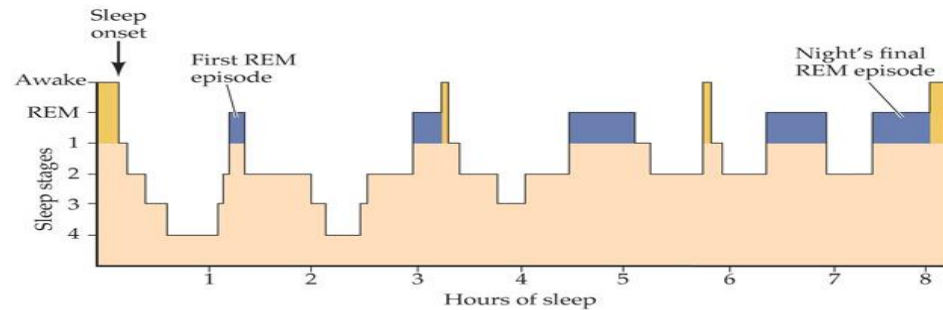
2- Rapid Eye Movement Sleep (REM)

- Is so called because of rapid eye movement.
- Occur in episodes of 5-30 min, recurring every 90 min.
- Tiredness shortens the duration of each episode.
- As you become restful through the night, the duration of each episode increases.
- Active dreaming, remembered later.
- More difficult to awake a person than in slow-wave sleep.
- In this type of sleep, rapid eye movements occur (Neurons of the pons)

Types of sleep

Types of sleep

1- Non rapid eye movement sleep (slow wave sleep – dreamless)



2- Rapid Eye Movement Sleep (dreamful)

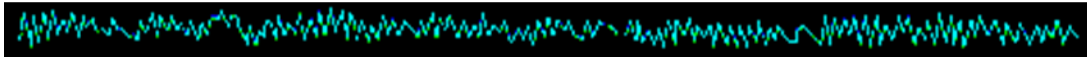
- In normal sleep bouts of REM sleep lasting for 5-20 minutes usually appear on the average after every 90 minutes.
- The first such period occurring 80-100 minutes after the person falls asleep.
- REM duration decreases with each cycle.
- When the person is in extreme sleep, the duration of each bout of REM is very short.
- It may even be absent

Cont.

- ▶ Characteristics of Rapid eye movement sleep:
 - Active dreaming.
 - Difficult to arouse by sensory stimuli.
 - Decreased muscle tone through the body.
 - Heart rate and respiration become irregular which is characteristic of a dream state.
 - Brain is highly active in REM sleep and brain metabolism may be increased by 20%.
 - EEG: Pattern shows brain wave of wakefulness, REM sleep is a type of sleep in which the brain is quite active.

EEG waves in wakefulness

Awake, nonattentive 1 second



Alpha waves

- ▶ Awake, but non-attentive.
- ▶ Large.
- ▶ Regular alpha waves.

Awake, attentive 1 second

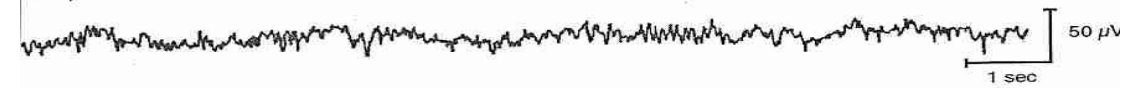


Beta waves

- ▶ Awake and attentive.
- ▶ Low amplitude.
- ▶ Fast.
- ▶ Irregular beta waves

Sleep and EEG

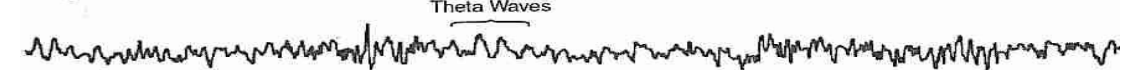
Awake – low voltage – random, fast



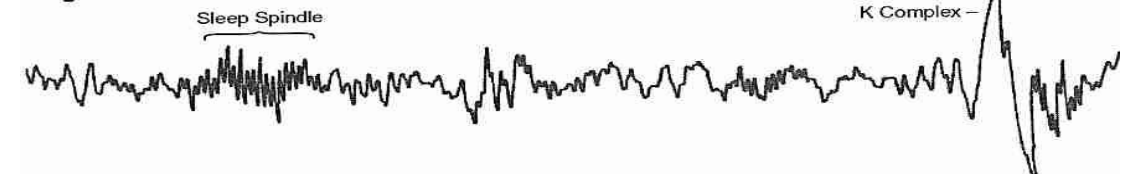
Drowsy – 8 to 12 cps – alpha waves



Stage 1 – 3 to 7 cps – theta waves



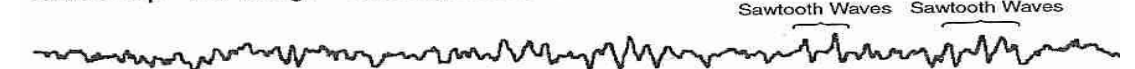
Stage 2 – 12 to 14 cps – sleep spindles and K complexes



Delta Sleep – 1/2 to 2 cps – delta waves >75 microvolts



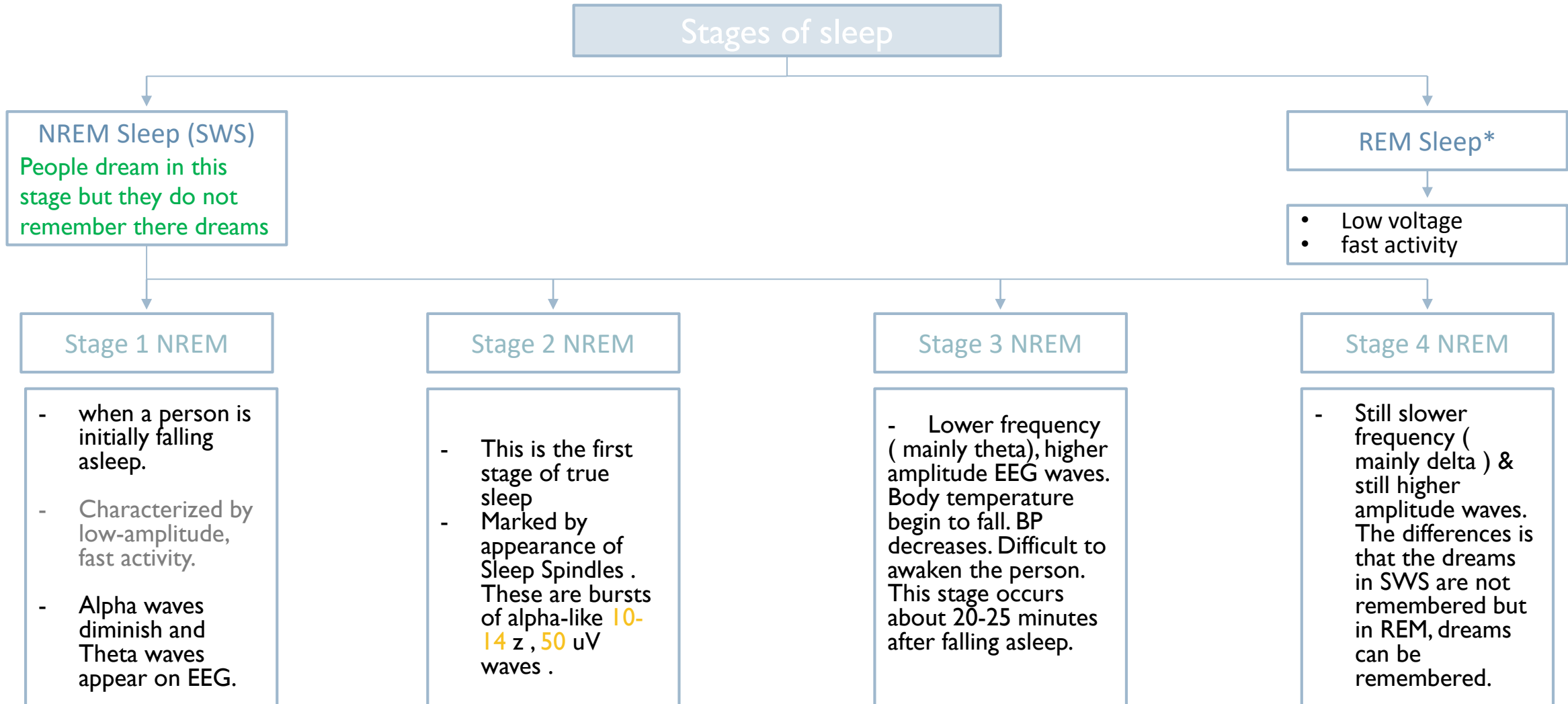
REM Sleep – low voltage – random, fast with sawtooth waves



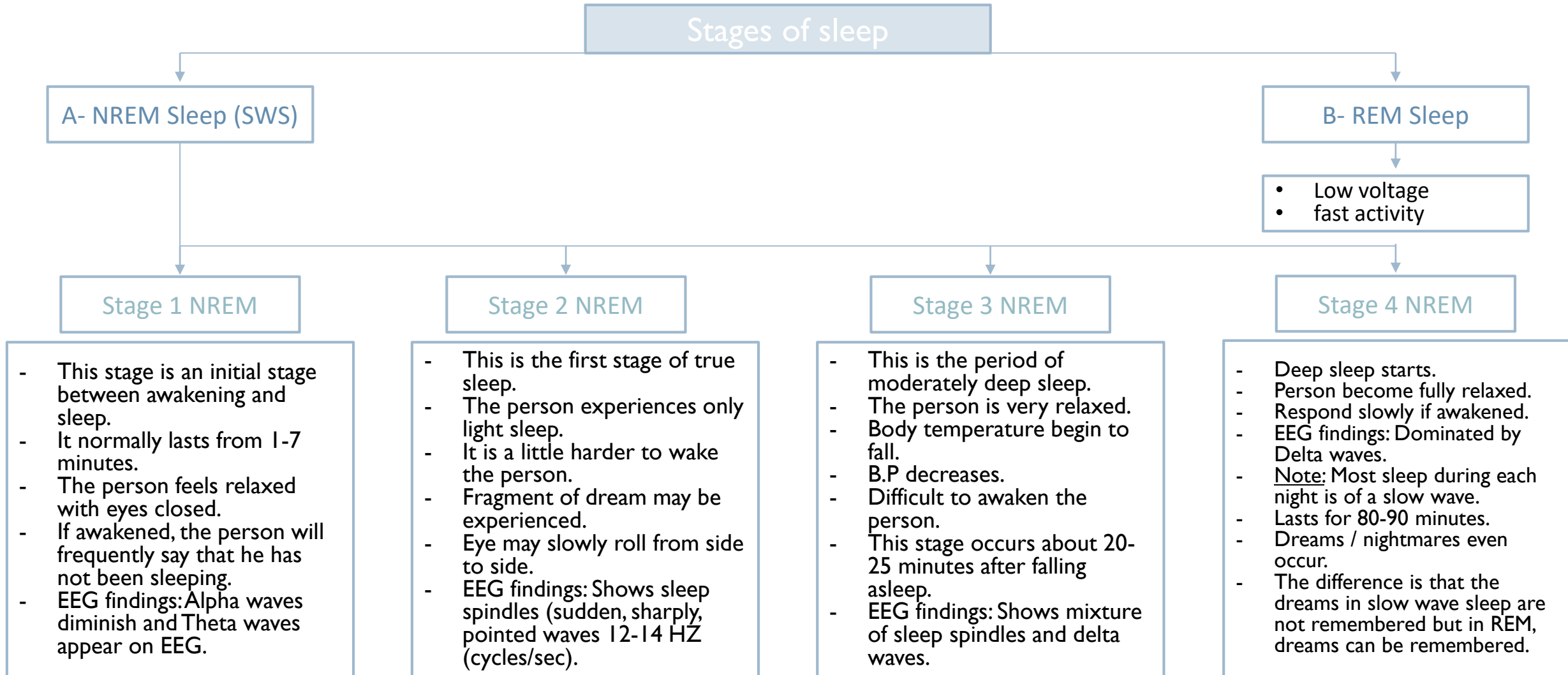
REM sleep (paradoxical sleep)

- ▶ In a normal night of sleep, episodes of REM sleep lasting 5 to 30 minutes usually appear on the average every 90 minutes.
- ▶ REM sleep is not as restful as SWS. It occupies 80% of total sleep time in premature infants & 50% in full term neonates.
- ▶ When the person is extremely sleepy, each episode of REM sleep is short, and it may even be absent.
- ▶ Conversely, as the person becomes more rested through the night, the durations of the REM episodes increase.
- ▶ There are several important characteristics of REM sleep:
 - There are rapid eye movements.
 - Muscle tone throughout the body (except eye muscles) is exceedingly depressed (due to excitation of reticular inhibitory centers).
- ▶ Since during REM there is eye movement ,so the muscles are contracted.
- ▶ Therefore , it is not surprising that REM sleep is also called paradoxical sleep : the paradox being that although the person is asleep , he may seem (because of his eye movements , etc) awake.
- ▶ The portion of REM sleep falls rapidly and plateaus at about 25% until it falls further in old age.
- ▶ Children have more total sleep time and stage 4 sleep than adults.
- ▶ HR & RR are irregular.
- ▶ Erection of penis.
- ▶ Engorgement of clitoris.
- ▶ REM sleep is a type of sleep in which the brain is quite active , but this brain:
 - is not aware cut off the external world.
 - its activity is not channeled into purposeful external motor activity.

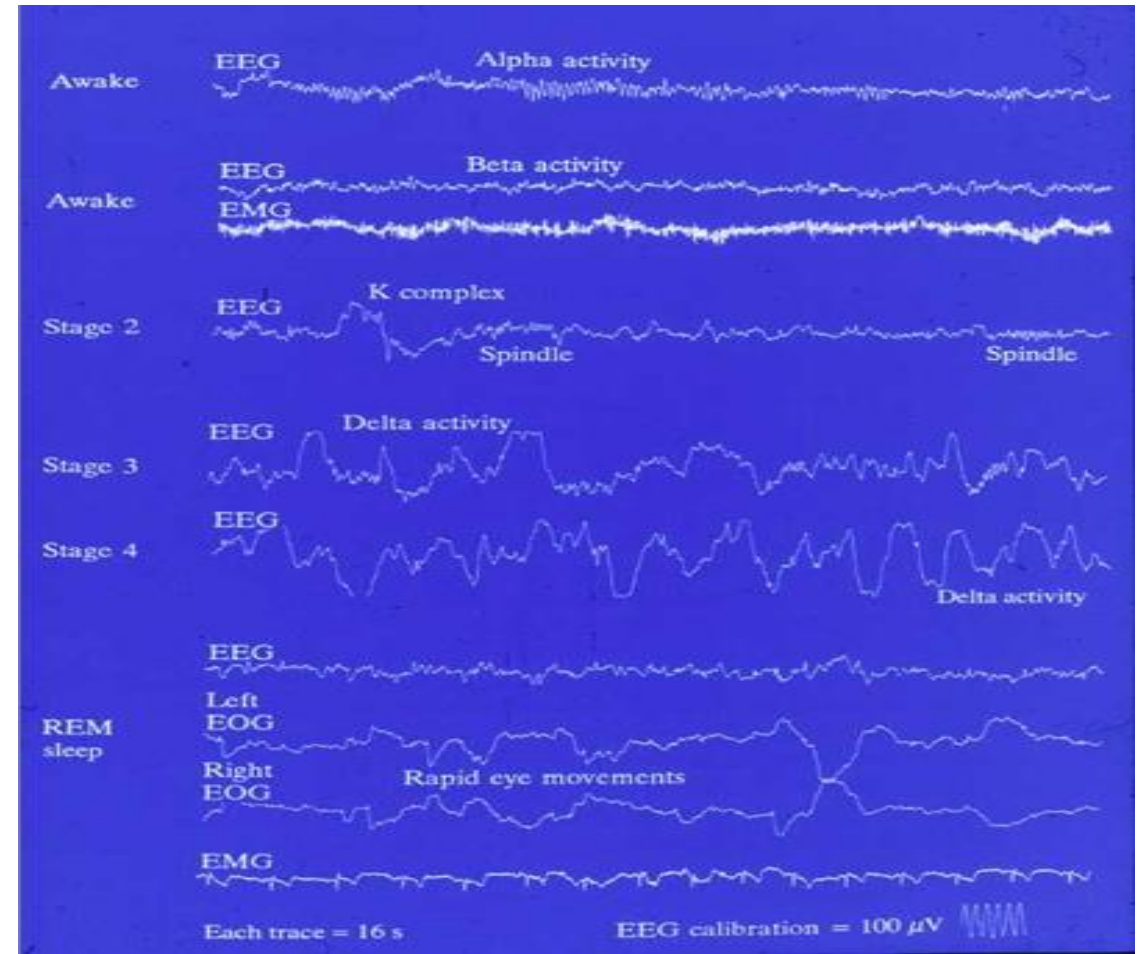
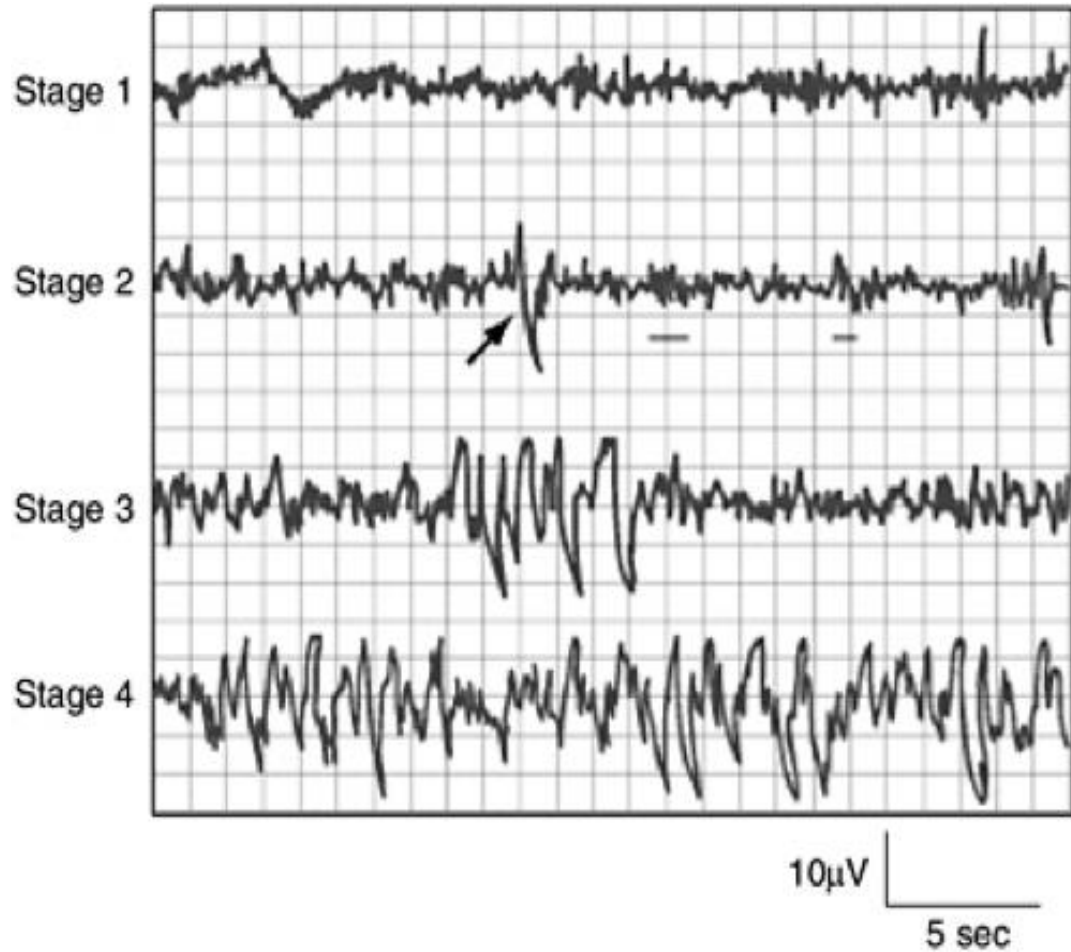
Stages of sleep



Stages of sleep

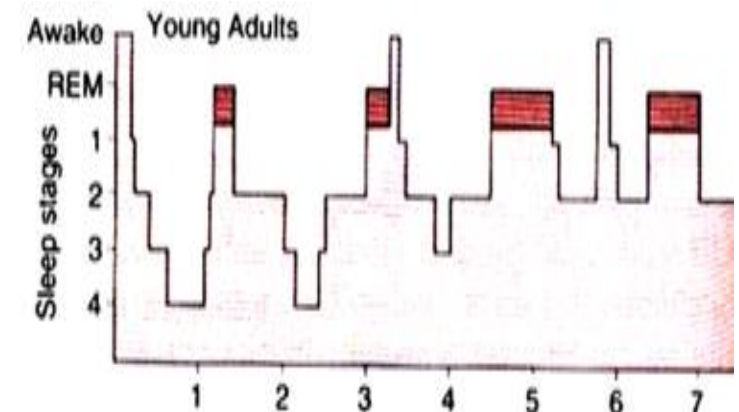


Sleep stages (NREM)



Distribution of Sleep Stages

- ▶ SWS occupies most of the total night sleep time (around 75-80%), it is interrupted by intervening REM sleep periods ,approximately every 90 minutes (In young adults).
- ▶ In a typical night of sleep, a young adult (1) first enters NREM sleep passes through stages 1 , 2 , 3 and 4 SWS , and then, 60-100 minutes from sleep onset , goes into the first REM sleep episode.
- ▶ This cycle is repeated at intervals of about 90 minutes throughout the 8 hours or so of a night sleep.
- ▶ There are 4-6 (8 hours sleep) sleep cycles per night (and 4-6 REM periods per night).
- ▶ As the night goes on there is progressive reduction in stages 3 and 4 sleep and a progressive increase in REM sleep.
- ▶ In a young adult SWS (NREM sleep) occupies 75-80% of a night sleep time , & REM sleep occupies 20-25 % of the sleep time.
- ▶ As long as the people become older their REM period decrease.



REM sleep periods are shown in red*

- ▶ 20 *Notice that you start with stage 1,2,3,4 then go back to stage 1 before you enter REM stage.

Characteristics of SWS and REMS

TABLE 14.1 *Properties of Slow-Wave and REM Sleep*

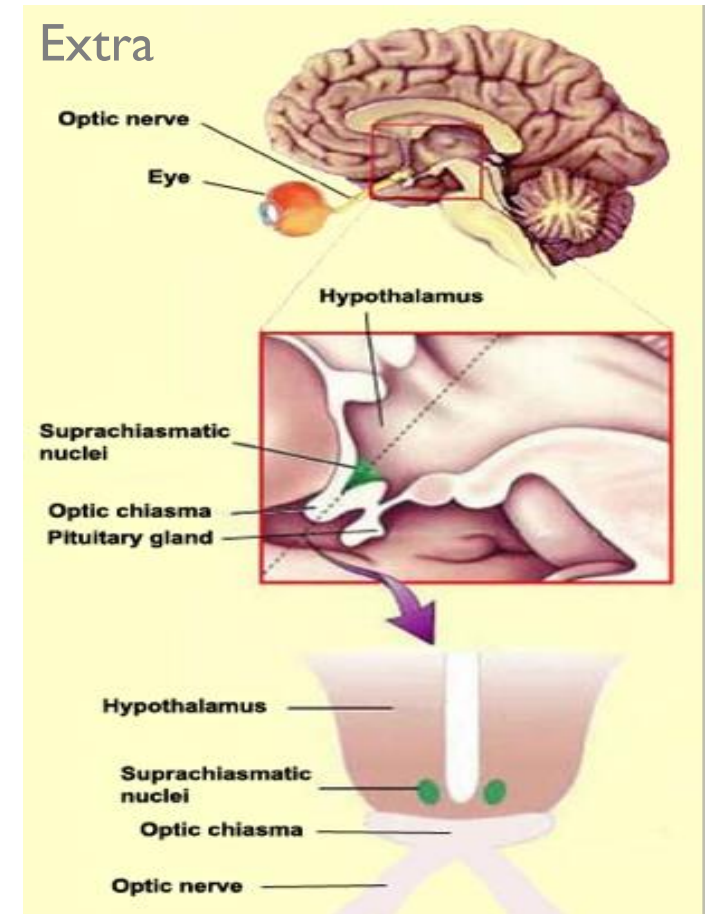
Property	Slow-wave sleep	REM sleep
AUTONOMIC ACTIVITIES		
Heart rate	Slow decline	Variable with high bursts
Respiration	Slow decline	Variable with high bursts
Thermoregulation	Maintained	Impaired
Brain temperature	Decreased	Increased
Cerebral blood flow	Reduced	High
SKELETAL MUSCULAR SYSTEM		
Postural tension	Progressively reduced	Eliminated
Knee jerk reflex	Normal	Suppressed
Phasic twitches	Reduced	Increased
Eye movements	Infrequent, slow, uncoordinated	Rapid, coordinated
COGNITIVE STATE		
	Vague thoughts	Vivid dreams, well organized
HORMONE SECRETION		
Growth hormone secretion	High	Low
NEURAL FIRING RATES		
Cerebral cortex (sustained) activity	Many cells reduced and more phasic	Increased firing rates; tonic
EVENT-RELATED POTENTIALS		
Sensory-evoked	Large	Reduced

TABLE 14.2 *Neural Activity of Neurotransmitter Systems during Sleep and Arousal*

Neurotransmitter	Site of cell bodies	Activity during		
		Wakefulness	SWS	REM
Serotonin	Raphe nuclei	High	Low	Very low
Norepinephrine	Locus coeruleus	High	Low	Very low
Acetylcholine	Brainstem	High	Low	High

Physiological changes during sleep

- ▶ **CVS:** Pulse Rate, cardiac output, blood pressure, and vasomotor tone are decreased but the blood volume is increased. **If the pulse rate is high during sleeping, it is a sign of hyperthyroidism.**
- ▶ **Respiration:**
 - Tidal volume and rate of respiration are decreased.
 - BMR is decreased **10-15%**.
- ▶ **Urine volume:** Urine volume is decreased.
- ▶ **Secretions:** Salivary / lacrimal secretions are reduced, gastric/sweet secretions are increased.
- ▶ **Muscles:** Relaxed.
- ▶ **Superficial reflexes** are unchanged except planter reflex.
- ▶ **Deep reflexes** are reduced.
- ▶ **Effects produced by awakening after 60-100 hours:** Equilibrium disturbed, Meuromuscular junction fatigue, Threshold for pain is lowered, Some cells shrink.



1- neural control of arousal

Neural Control of Arousal

Acetylcholine

- One of the most important neurotransmitters involved in arousal.
- Two groups of acetylcholinergic neurons located in the pons and basal forebrain, produce activation and cortical desynchrony when they are stimulated.

Norepinephrine

Catecholamine agonists produce arousal and sleeplessness; effects appear to be mediated by the locus coeruleus in the dorsal pons.

Locus coeruleus

A dark-colored group of noradrenergic cell bodies located in the pons near the rostral end of the floor of the fourth ventricle; involved in arousal and vigilance

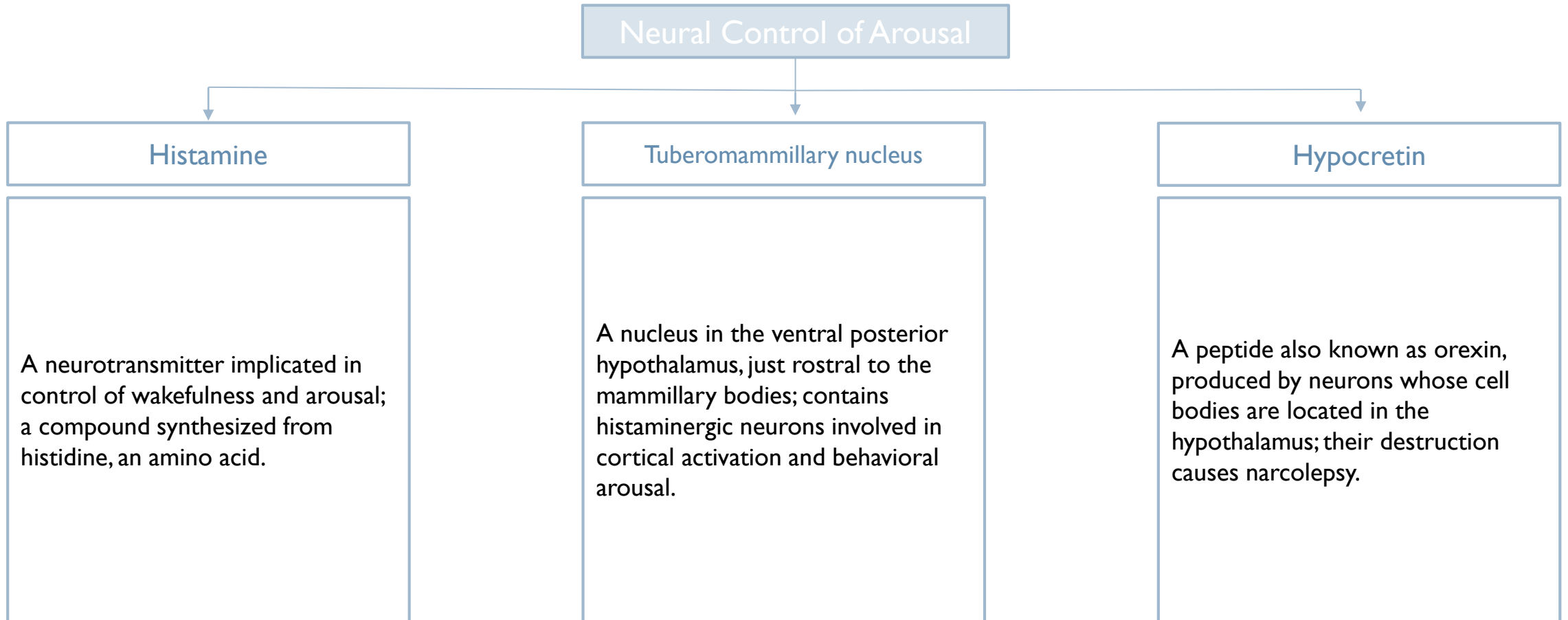
Serotonin (5-HT)

Appears to play a role in activating behavior; almost all of the brain's serotonergic neurons are found in the raphe nucleus, located in the medullary and pontine regions of the brain.

Raphe nucleus

A group of nuclei located in the reticular formation of the medulla, pons, and midbrain, situated along the midline; contain serotonergic neurons.

Cont.



2&3- neural control of REM and SWS

Physiological Mechanisms of Sleep and Waking

Neural Control of REM sleep

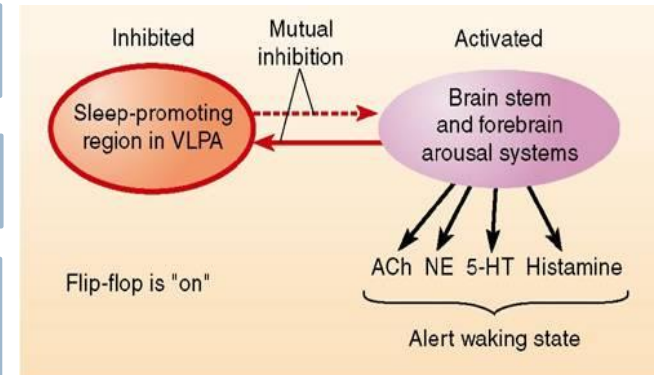
PGO wave (Pontine, Geniculate, Occipital)

Bursts of phasic electrical activity originating in the pons, followed by activity in the lateral geniculate nucleus and visual cortex, a characteristic of REM sleep.

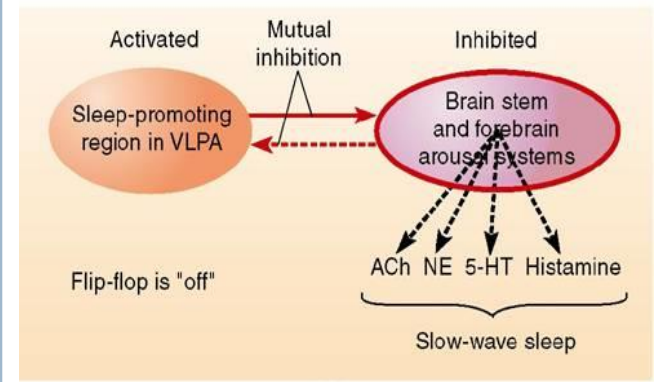
Neural Control of Slow-Wave Sleep

Ventrolateral preoptic area (VLPA)

- A group of GABAergic neurons in the preoptic area whose activity suppresses alertness and behavioral arousal and promotes sleep.
- Destruction of this area has been reported to result in total insomnia, coma, and eventual death in rats.

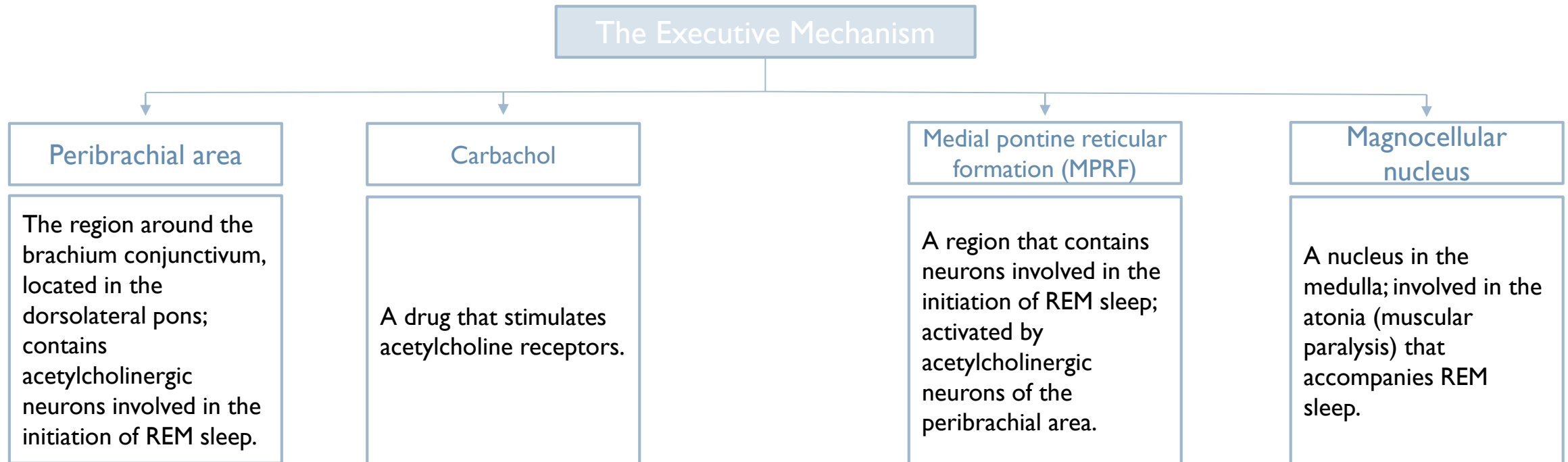


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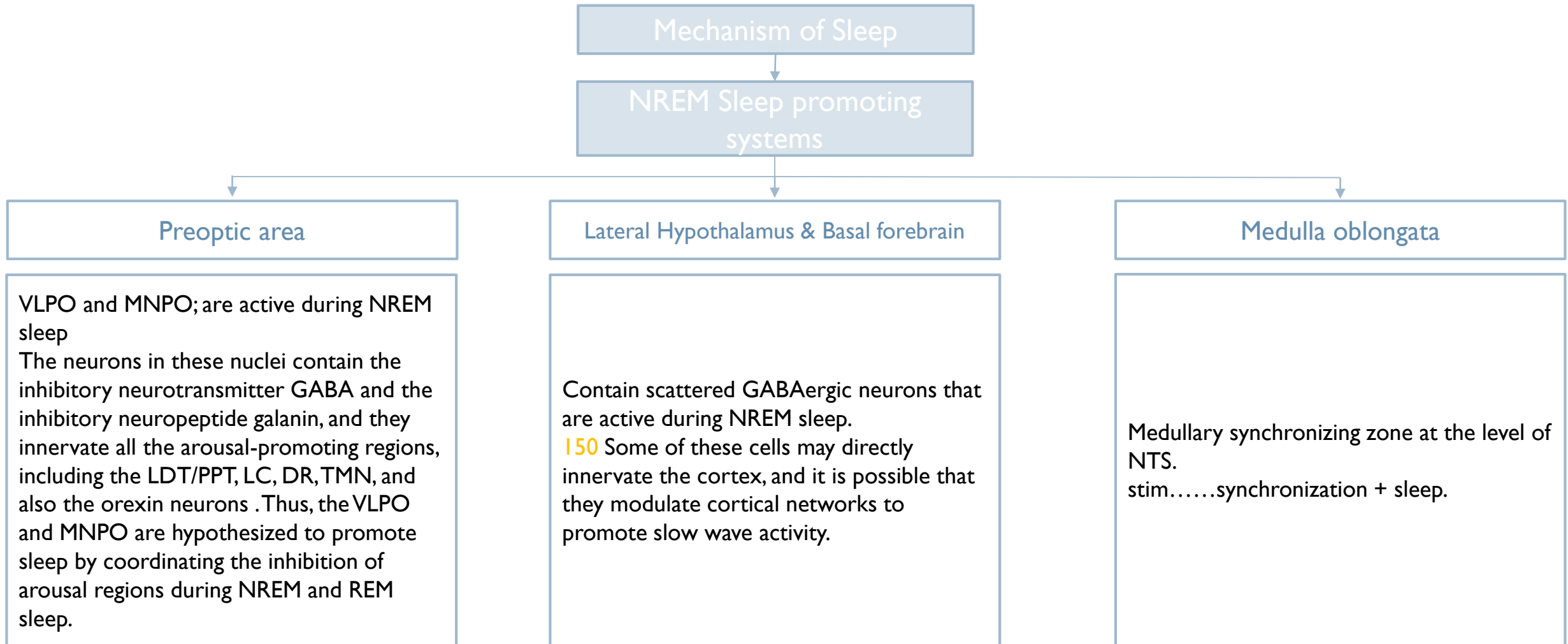


(b)

4- the executive mechanism



Mechanism of sleep

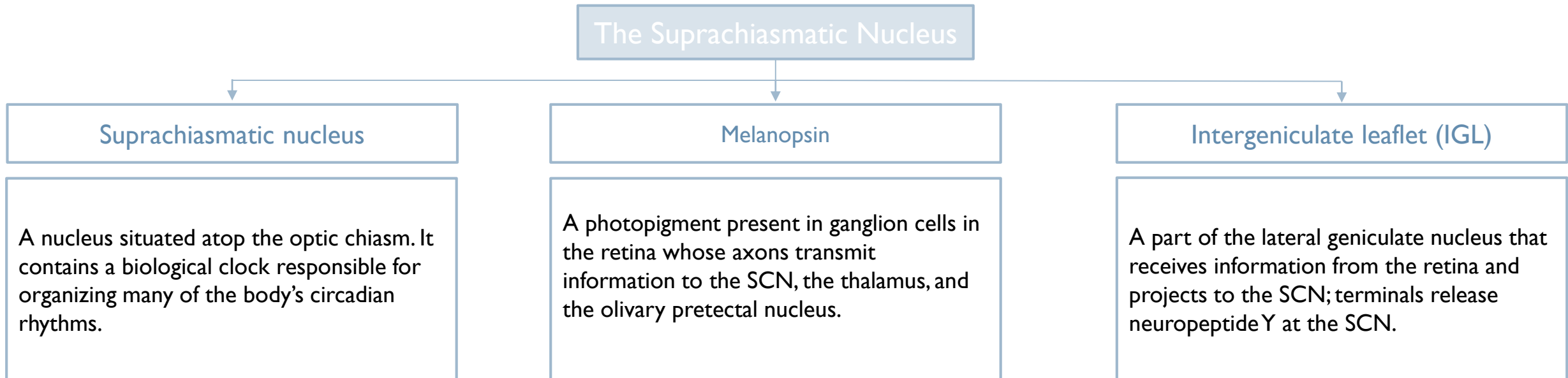


Theories of sleep

▶ Although several theories of sleep have been proposed , most current evidence is in favor of the following :

1. **Serotonin**, produced by the **Raphe Nuclei** , induces SWS sleep.
2. The mechanism that triggers REM sleep is located in the Pontine Reticular Formation & the Ponto-Geniculo-Occipital circuit is instrumental in generation of REM sleep.
3. The hormone **Melatonin** (released from the Pineal Gland) plays an important role in day-night alternation of sleep .

Biological clocks



Role of serotonin & melatonin in SWS

1. Stimulation of **Raphe Nuclei** (which are situated in the lower pons & medulla) induces SW.
2. Destruction of the Raphe Nuclei makes the animal sleepless for several days until it dies.
3. administration of drugs that block serotonin formation make the animal sleepless for several days.
4. 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 of the RAS .
What does this mean? It means that the serotonin-secreting Raphe fibers normally inhibit the Bulboreticular Facilitory Area to produce sleep .
5. injections of melatonin induce sleep.
6. Stimulation of the Suprachiasmatic Nucleus (SCN) of hypothalamus by light falling on the retina →inhibits Melatonin release from Pineal Gland → produces wakefulness.

Melatonin as Circadian Controller of Sleep-Wake Cycles

- ▶ Alternating “ Sleep-Wake Cycles ” are under marked Circadian Control.
- ▶ “ Circadian Control/Rhythm ” : means regulation of a biological rhythm (e.g. sleep-wakefulness , hormone secretion , etc) by day-night cycles.
- ▶ Darkness (e.g., at night) stimulates the Pineal Gland to secrete the hormone melatonin.
- ▶ Melatonin inhibits the RAS & thereby induces SWS.
- ▶ Daylight falling on the retina stimulates the Suprachiasmatic Nucleus (SCN) of hypothalamus.
- ▶ SCN inhibits melatonin secretion by the Pineal Gland , & thereby it inhibits sleep and promotes wakefulness.

Genesis of REM sleep

- ▶ **Pons:**
 - The mechanism producing REM sleep is located in pontine reticular formation.
 - Large cholinergic ponto-geniculo-occipital (PGO) spikes arise in this area and are thought to initiate REM 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.

Physiological mechanisms of sleep & waking

- ▶ Acetylcholine:
 - Neurons in the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) may help generate the cortical activation and atonia of REM sleep.
 - The LDT/PPT is the main source of ACh to the thalamus, and ACh depolarizes thalamic neurons to promote the transmission of information through the thalamus, driving the cortical activation that is probably required for the complex dreams of REM sleep.
 - The LDT/PPT neurons may also activate atonia-promoting neurons in the ventromedial medulla.
 - These medullary cells release GABA and another inhibitory neurotransmitter glycine onto spinal and brainstem motor neurons during REM sleep, producing hyperpolarization and inhibition.
 - This descending inhibition is clearly important for atonia as drugs that block glycine signaling such as strychnine can markedly increase muscle tone in REM sleep and wakefulness.

Sleep disorders /burden

- ▶ 70 million people in the US suffer from sleep problems [50% have chronic sleep disorder].
- ▶ Insomnia = 30 million.
- ▶ sleep apnea= 18 million.
- ▶ Narcolepsy= 250,000 Americans have.
- ▶ Motor Car Accidents= 100,000.
- ▶ traffic fatalities= 1500 drowsy driving / annum.
- ▶ Approximately 16 billion\$ annually to the cost of health care in the US and result in 50 billion\$ annually in lost productivity.

Disorders of sleep

▶ Disorders of sleep:

1. Insomnia: Inability to sleep.
2. Somnolence: Extreme sleepiness.

▶ Disorders of slow wave sleep:

1. Sleep talking / sleep walking (common in children).
2. Night tremors: Are seen in III, IV stage of slow wave sleep (common in children).

▶ Disorders of REM sleep:

1. Nightmare = Frightening dreams, awake from REM.
2. Sleep paralysis = Subject is awake but unable to speak or move. Sleeping Sickness.

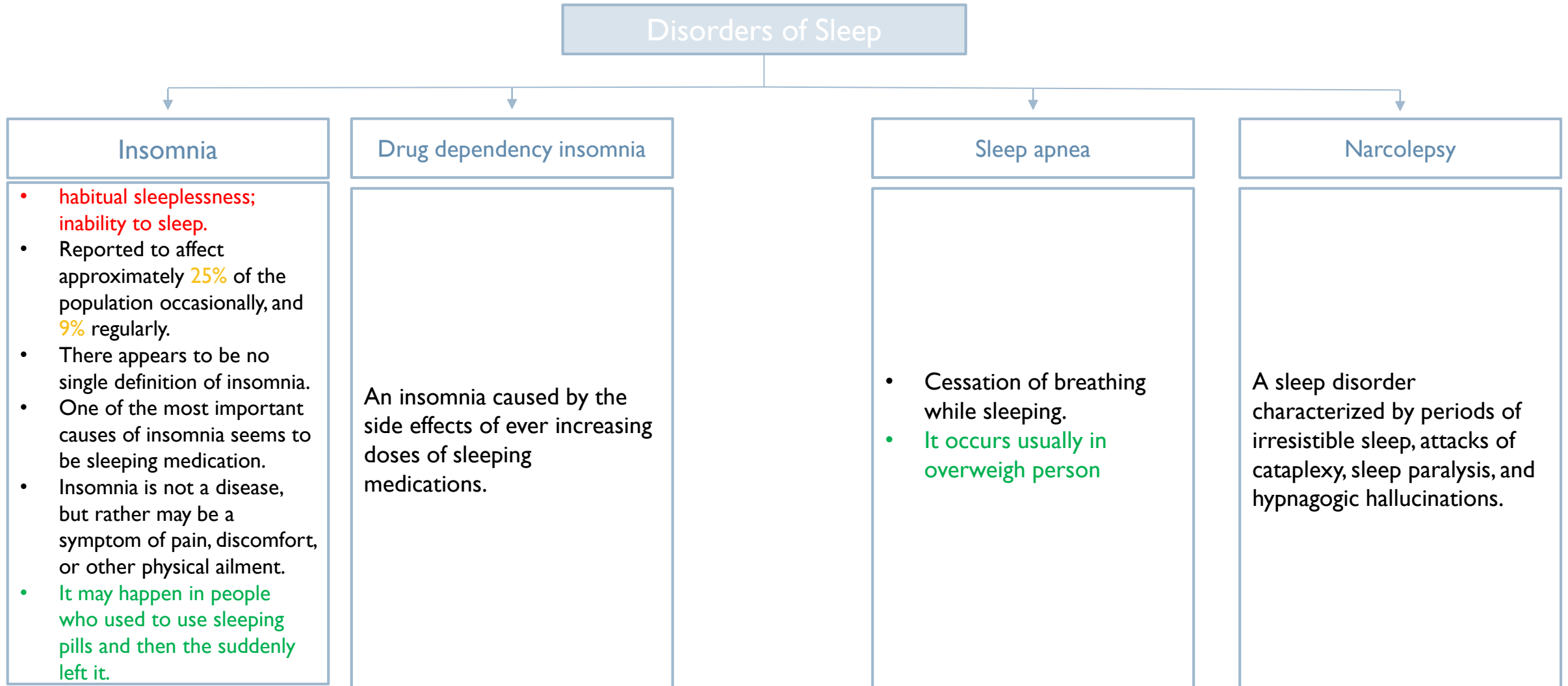
▶ Somnambulism: Walking during sleep.

▶ Night terrors: Sudden arousal from sleep and intense fear accompanied by physiological reactions (e.g. rapid heart rate, perspiration) that occur during slow-wave sleep.

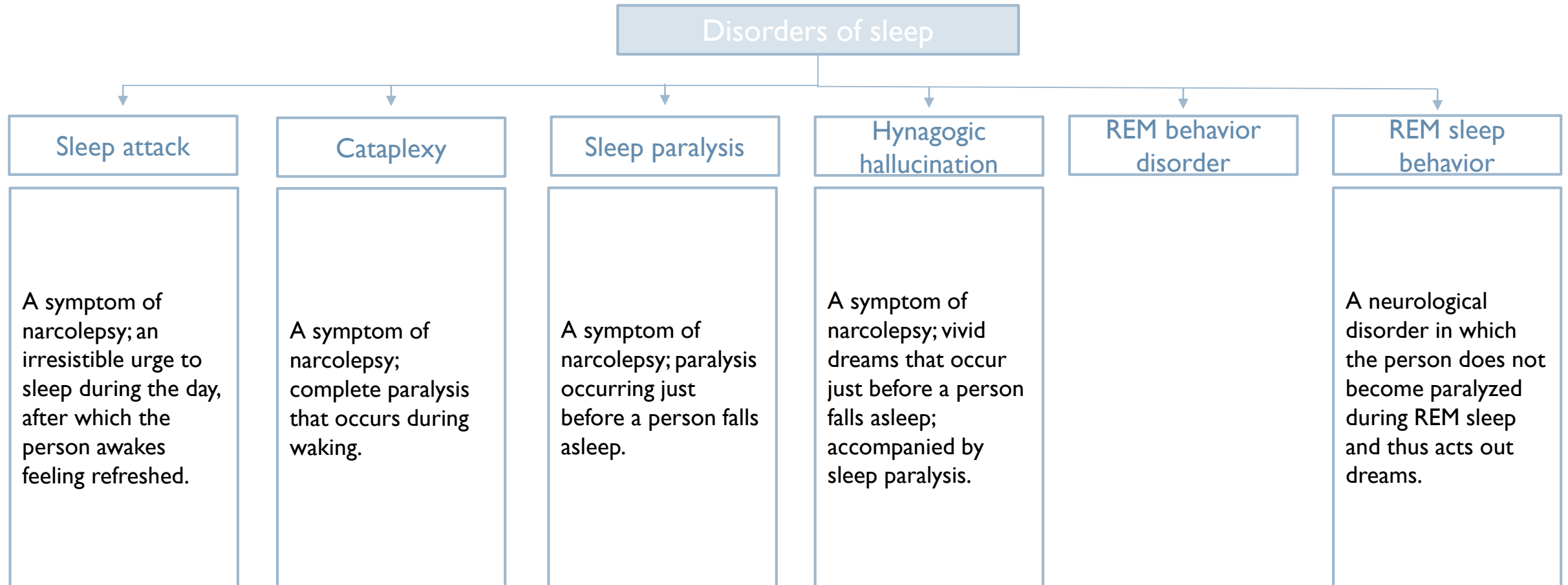
▶ Narcolepsy: Excessive sleepiness may occur while talking, sitting, decreased ability to regulate sleep.

▶ Sleep apnea: Failure of breathing when asleep.

Disorders of Sleep



Cont.



Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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QUIZ



اقتراحات وشكاوي

References:

- Females and Males slides.
- Guyton and Hall Textbook of Medical Physiology (Thirteenth Edition.)