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DEPARTMENT: MEDICINE AND SURGERY.

COURSE: NEUROPHYSIOLOGY.

ASSIGNMENT

1. Discuss the physiology of sleeping.
2. Discuss the role of the basal ganglia in coordinating movements.

SLEEP

Introduction

Sleep is the natural, easily reversible periodic state of many living things that is marked by the absence of wakefulness and by the loss of consciousness of one's surroundings, is accompanied by a typical body posture (such as lying down with the eyes closed), the occurrence of dreaming, and changes in brain activity and physiological functioning, is made up of cycles of non-REM sleep and REM sleep, and is usually considered essential to the restoration and recovery of vital bodily and mental functions.

TYPES OF SLEEP

There are two types of sleep, non-rapid eye-movement (NREM) sleep and rapid eye-movement (REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4, representing a continuum of relative depth. Each has unique characteristics including variations in brain wave patterns, eye movements, and muscle tone. Sleep cycles and stages were uncovered with the use of electroencephalographic (EEG) recordings that trace the electrical patterns of brain activity.

A sleep episode begins with a short period of NREM stage 1 progressing through stage 2, followed by stages 3 and 4 and finally to REM. However, individuals do not remain in REM sleep the remainder of the night but, rather, cycle between stages of NREM and REM throughout the night. NREM sleep constitutes about 75 to 80 percent of total time spent in sleep, and REM sleep constitutes the remaining 20 to 25 percent. The average length of the first NREM-REM sleep cycle is 70 to 100 minutes. The second, and later, cycles are longer lasting—approximately 90 to 120 minutes. In normal adults, REM sleep increases as the night progresses and is longest in the last one-third of the sleep episode. As the sleep episode progresses, stage 2 begins to account for the majority of NREM sleep, and stages 3 and 4 may sometimes altogether disappear.

1. **Non Rapid Eye Movement Sleep**

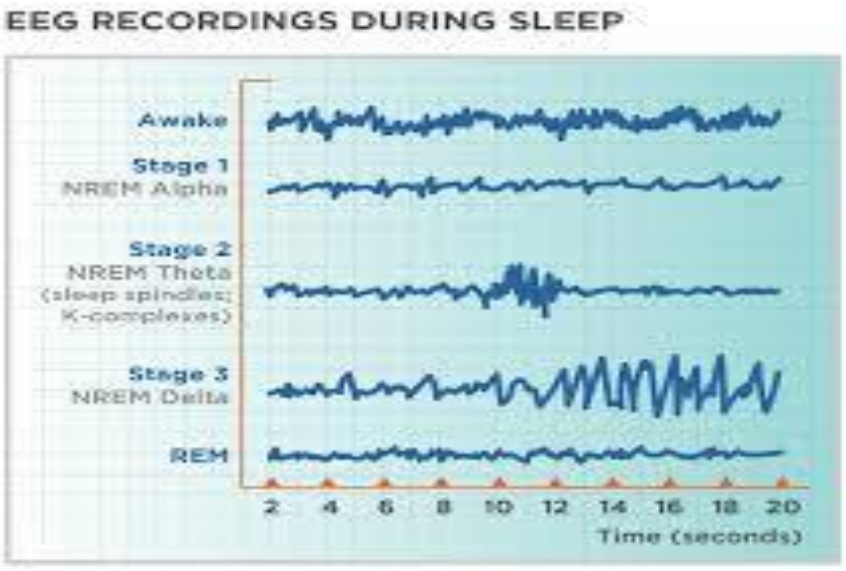
   Non-REM sleep is also referred to as **slow wave sleep** as during this period the brain waves are very strong and of a very low frequency. NREM sleep, or orthodox sleep, is characterized by decreased activation of the EEG; in infants it is called quiet sleep because of the relative lack of motor activity.

Four Stages of NREM sleep

The four stages of NREM sleep are each associated with distinct brain activity and physiology.

Stage 1 Sleep

NREM stage 1 sleep serves a transitional role in sleep-stage cycling. Aside from newborns and those with narcolepsy and other specific neurological disorders, the average individual's sleep episode begins in NREM stage 1. This stage usually lasts 1 to 7 minutes in the initial cycle, constituting 2 to 5 percent of total sleep, and is easily interrupted by a disruptive noise. Brain activity on the EEG in stage 1 transitions from wakefulness (marked by rhythmic alpha waves) to low-voltage, mixed-frequency waves. Alpha waves are associated with a wakeful relaxation state and are characterized by a frequency of 8 to 13 cycles per second.



Stage 2 Sleep

Stage 2 sleep lasts approximately 10 to 25 minutes in the initial cycle and lengthens with each successive cycle, eventually constituting between 45 to 55 percent of the total sleep episode. An individual in stage 2 sleep requires more intense stimuli than in stage 1 to awaken. Brain activity on an EEG shows relatively low-voltage, mixed-frequency activity characterized by the presence of sleep spindles and K-complexes. It is hypothesized that sleep spindles are important for memory consolidation. Individuals who learn a new task have a significantly higher density of sleep spindles than those in a control group.

Stages 3 and 4, Slow-Wave Sleep

Sleep stages 3 and 4 are collectively referred to as slow-wave sleep (SWS), most of which occurs during the first third of the night. Each has distinguishing characteristics. Stage 3 lasts only a few minutes and constitutes about 3 to 8 percent of sleep. The EEG shows increased high-voltage, slow-wave activity.

The last NREM stage is stage 4, which lasts approximately 20 to 40 minutes in the first cycle and makes up about 10 to 15 percent of sleep. The arousal threshold is highest for all NREM stages in stage 4. This stage is characterized by increased amounts of high-voltage, slow-wave activity on the EEG.

2. Rapid Eye Movement Sleep

REM sleep is defined by the presence of desynchronized (low-voltage, mixed-frequency) brain wave activity, muscle atonia, and bursts of rapid eye movements. “Sawtooth” wave forms, theta activity (3 to 7 counts per second), and slow alpha activity also characterize REM sleep. During the initial cycle, the REM period may last only 1 to 5 minutes; however, it becomes progressively prolonged as the sleep episode progresses. REM sleep is characterised by the presence of **rapid eye movements** during sleep. This type of sleep is less restful than slow-wave sleep and is associated with **dreaming** and **bodily muscle movements**.

AWAKENING

Awakening can mean the end of sleep, or simply a moment to survey the environment and readjust body position before falling back asleep. Sleepers typically awaken soon after the end of a REM phase or sometimes in the middle of REM. Internal circadian indicators, along with successful reduction of homeostatic sleep need, typically bring about awakening and the end of the sleep cycle. Awakening involves heightened electrical activation in the brain, beginning with the thalamus and spreading throughout the cortex.

PHYSIOLOGY DURING SLEEP

Physiological Process	NREM	REM
Brain activity	Decreases from wakefulness	Increases in motor and sensory areas, while other areas are similar to NREM
Heart rate	Slows from wakefulness	Increases and varies compared to NREM
Blood pressure	Decreases from wakefulness	Increases (up to 30 percent) and varies from NREM
Sympathetic nerve activity	Decreases from wakefulness	Increases significantly from wakefulness
Muscle tone	Similar to wakefulness	Absent
Blood flow to brain	Decreases from wakefulness	Increases from NREM, depending on brain region
Respiration	Decreases from wakefulness	Increases and varies from NREM, but may show

Physiological Process	NREM	REM
		brief stoppages; coughing suppressed
Airway resistance	Increases from wakefulness	Increases and varies from wakefulness
Body temperature	Is regulated at lower set point than wakefulness; shivering initiated at lower temperature than during wakefulness	Is not regulated; no shivering or sweating; temperature drifts toward that of the local environment
Sexual arousal	Occurs infrequently	Greater than NREM

Physiological changes also occur in the following systems:

- **Cardiovascular:** Changes in blood pressure and heart rate occur during sleep and are primarily determined by autonomic nervous system activity. For instance, brief increases in blood pressure and heart rate occur with K-complexes, arousals, and large body movements. Further, there is an increased risk of myocardial infarction in the morning due to the sharp increases in heart rate and blood pressure that accompany awakening.
- **Sympathetic-nerve activity:** Sympathetic-nerve activity decreases as NREM sleep deepens; however, there is a burst of sympathetic-nerve activity during NREM sleep due to the brief increase in blood pressure and heart rate that follows K-complexes. Compared to wakefulness, there is a rise in activity during REM sleep..
- **Respiratory:** Ventilation and respiratory flow change during sleep and become increasingly faster and more erratic, specifically during REM sleep. Ventilation data during REM sleep are somewhat unclear, but they suggest that hypoventilation (deficient ventilation of the lungs that results in reduction in the oxygen content or increase in the carbon dioxide content of the blood or both) occurs in a similar

way as during NREM sleep. Several factors contribute to hypoventilation during NREM, and possibly REM, sleep such as reduced pharyngeal muscle tone. Further, during REM sleep, there is reduced rib cage movement and increased upper airway resistance due to the loss of tone in the intercostals and upper airway muscles. More generally, ventilation and respiratory flow show less effective adaptive responses dur ing sleep. The cough reflex, which normally reacts to irritants in the airway, is suppressed during REM and NREM sleep. The hypoxic ventilatory response is also lower in NREM sleep than during wakefulness and decreases further during REM sleep. Similarly, the arousal response to respiratory resistance (for example, resistance in breathing in or out) is lowest in stage 3 and stage 4 sleep.

- **Cerebral blood flow:** NREM sleep is associated with significant reductions in blood flow and metabolism, while total blood flow and metabolism in REM sleep is comparable to wakefulness. However, metabolism and blood flow increase in certain brain regions during REM sleep, compared to wakefulness, such as the limbic system (which is involved with emotions), and visual association areas.
- **Renal:** There is a decreased excretion of sodium, potassium, chloride, and calcium during sleep that allows for more concentrated and reduced urine flow. The changes that occur during sleep in renal function are complex and include changes in renal blood flow, glomerular filtration, hormone secretion, and sympathetic neural stimulation.
- **Endocrine:** Endocrine functions such as growth hormone, thyroid hormone, and melatonin secretion are influenced by sleep. Growth hormone secretion typically takes place during the first few hours after sleep onset and generally occurs during SWS, while thyroid hormone secretion takes place in the late evening. Melatonin, which induces sleepiness, likely by reducing an alerting effect from the suprachiasmatic nucleus, is influenced by the light-dark cycle and is suppressed by light.

SLEEP-WAKE REGULATION

The Two-Process Model

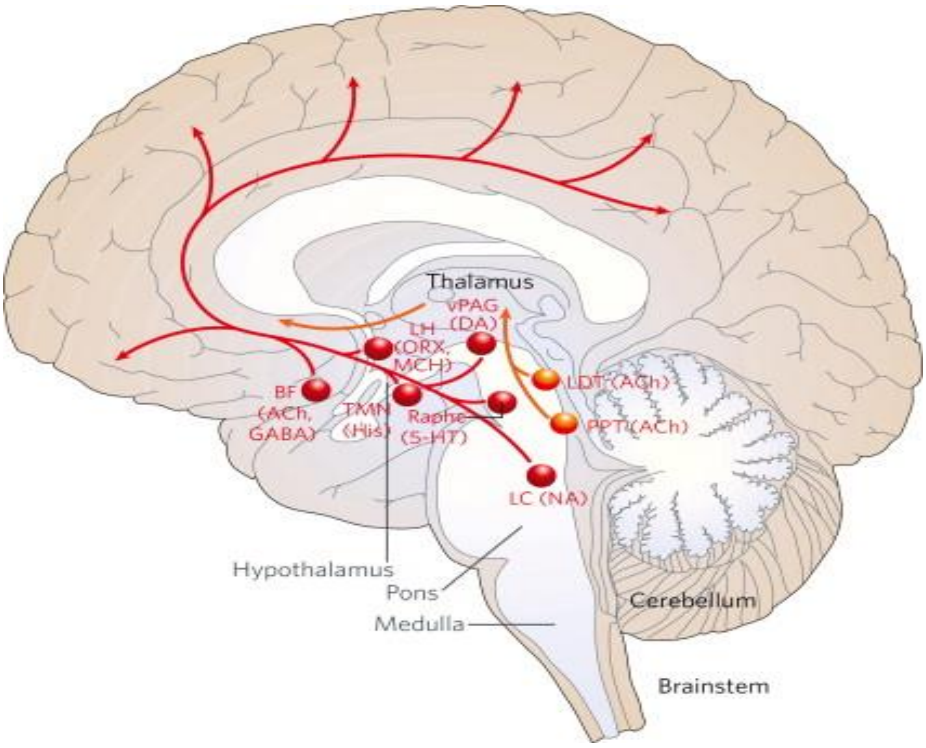
`The sleep-wake system is thought to be regulated by the interplay of two major processes, one that promotes sleep (process S) and one that maintains wakefulness (process C) . Process S is the homeostatic drive for sleep. The need for sleep (process S) accumulates across the day, peaks just before bedtime at night and dissipates throughout the night.

Process C is wake promoting and is regulated by the circadian system. Process C builds across the day, serving to counteract process S and promote wakefulness and alertness. However, this wake-promoting system begins to decline at bedtime, serving to enhance sleep consolidation as the need for sleep dissipates across the night. With an adequate night's rest, the homeostatic drive for sleep is reduced, the circadian waking drive begins to increase, and the cycle starts over. In the absence of process C, total sleep time remains the same, but it is randomly distributed over the day and night; therefore, process C also works to consolidate sleep and wake into fairly distinct episodes. Importantly, through synchronization of the circadian system, process C assists in keeping sleep-wakefulness cycles coordinated with environmental light-dark cycles.

Sleep-Generating Systems in the Brainstem

Sleep process S is regulated by neurons that shut down the arousal systems, thus allowing the brain to fall asleep. Many of these neurons are found in the preoptic area of the hypothalamus. These neurons, containing molecules that inhibit neuronal communication, turn off the arousal systems during sleep. Loss of these nerve cells causes profound insomnia. Inputs from other regions of the brain also greatly influence the sleep system. These include inputs from the lower brainstem that relay information about the state of the body (e.g., a full stomach is conducive to falling asleep), as well as from emotional and cognitive areas of the forebrain. In addition, as described further in the next section, there are inputs from the circadian system that allow the wake-sleep system to

synchronize with the external day-night cycle, but also to override this cycle when it is necessitated by environmental needs.



NOTE: Cholinergic (ACh) cell groups; basal forebrain (BF); dopamine (DA); gamma-aminobutyric acid (GABA); galanin (Gal); histamine (His); serotonin (5-HT); locus coeruleus (LC); laterodorsal tegmental nuclei (LDT); lateral hypothalamus (LH); melanin-concentrating hormone (MCH); noradrenaline (NA); orexin (ORX); perifornical (PeF); the pedunculopontine (PPT); tuberomammillary nucleus (TMN); ventrolateral preoptic nucleus (VLPO); ventral periaqueductal gray (vPAG).

The sleep-generating system also includes neurons in the pons that intermittently switch from NREM to REM sleep over the course of the night. These neurons send outputs to the lower brainstem and spinal cord that cause muscle atonia, REMs, and chaotic autonomic activity that characterize REM sleep. Other outputs are sent to the forebrain, including activation of the cholinergic pathways to the thalamus to activate the EEG.

Wake-Generating Systems in the Brainstem

Wakefulness is generated by an ascending arousal system from the brainstem that activates forebrain structures to maintain wakefulness. This idea, originally put forward by , has more recently been refined. The main

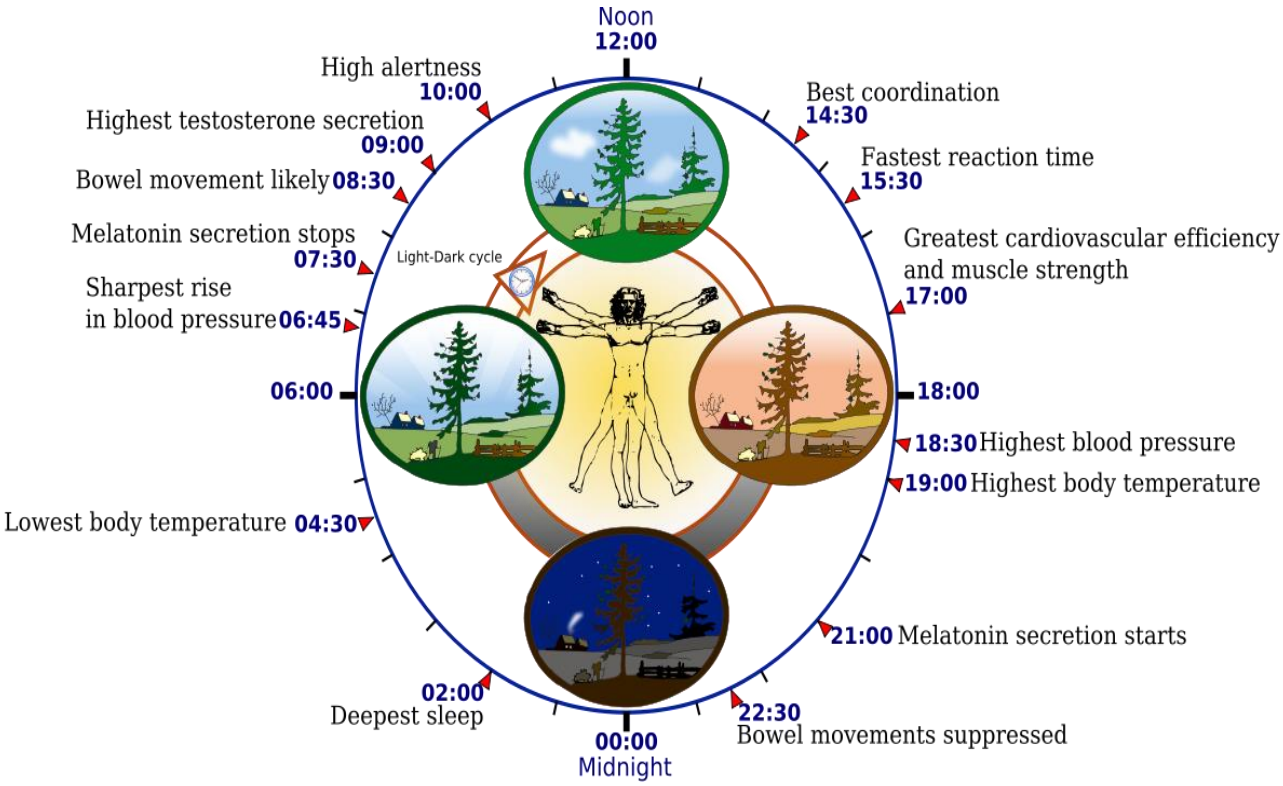
source for the ascending arousal influence includes two major pathways that originate in the upper brainstem. The first pathway, which takes origin from cholinergic neurons in the upper pons, activates parts of the thalamus that are responsible for maintaining transmission of sensory information to the cerebral cortex. The second pathway, which originates in cell groups in the upper brainstem that contain the monoamine neurotransmitters (norepinephrine, serotonin, dopamine, and histamine), enters the hypothalamus, rather than the thalamus, where it picks up inputs from nerve cells that contain peptides (orexin or hypocretin and melanin-concentrating hormone). These inputs then traverse the basal forebrain, where they pick up additional inputs from cells containing acetylcholine and gamma-aminobutyric acid. Ultimately, all of these inputs enter the cerebral cortex, where they diffusely activate the nerve cells and prepare them for the interpretation and analysis of incoming sensory information.

CIRCADIAN RHYTHM

Circadian rhythms refer, collectively, to the daily rhythms in physiology and behavior. They control the sleep-wake cycle, modulate physical activity and food consumption, and over the course of the day regulate body temperature, heart rate, muscle tone, and hormone secretion. The rhythms are generated by neural structures in the hypothalamus that function as a biological clock. Animals and plants possess endogenous clocks to organize daily behavioral and physiological rhythms in accord with the external day-night cycle. The basis for these clocks is believed to be a series of molecular pathways involving “clock” genes that are expressed in a nearly 24-hour rhythm.

In mammals, two proteins, Clock and Bmal1, bind together and move into the nucleus of the cell, where they bind to specific sites in the DNA that activate specific genes. Among the genes that they activate are *Period* and *Cryptochrome*. The products of these genes also move back into the nucleus, where they disrupt the binding of Clock and Bmal1 to the DNA, thus inhibiting their own synthesis. This results in a rising and falling

pattern of expression of the *Period* and *Cryptochrome* gene products with a periodicity that is very close to 24 hours.



The Suprachiasmatic Nucleus

The suprachiasmatic nucleus (SCN) is responsible for regulating circadian rhythms in all organs. It receives direct inputs from a class of nerve cells in the retina that act as brightness detectors, which can reset the clock genes in the SCN on a daily basis. The SCN then transmits to the rest of the brain and body signals that bring all of the daily cycles in synchrony with the external day-night cycle.

The main influence of the SCN on sleep is due to a series of relays through the dorsomedial nucleus of the hypothalamus, which signals to the wake-sleep systems to coordinate their activity with the day-night cycles. The SCN also coordinates cycles of feeding, locomotor activity, and hormones, such as corticosteroids. Under some conditions (e.g., limited food availability) when there are changes in the external temperature, or even under conditions of behavioral stress (e.g., the need to avoid a predator), animals must shift their daily cycles to survive. In such

circumstances, the dorsomedial nucleus may shift to a new daily cycle, which can be completely out of phase with the SCN and the light-dark cycle, and its signals also shift the daily cycles of sleep, activity, feeding, and corticosteroid hormone secretion.

Another major output of the SCN is to a pathway that controls the secretion of melatonin, a hormone produced by the pineal gland. Melatonin, which is mainly secreted at night, acts to further consolidate the circadian rhythms but has only limited effects directly on sleep.

SLEEP CHANGES ACCORDING TO AGE

Human sleep needs vary by age and amongst individuals; sleep is considered to be adequate when there is no daytime sleepiness or dysfunction. Moreover, self-reported sleep duration is only moderately correlated with actual sleep time as measured by actigraphy, and those affected with sleep state misperception may typically report having slept only four hours despite having slept a full eight hours.

Researchers have found that sleeping 6–7 hours each night correlates with longevity and cardiac health in humans, though many underlying factors may be involved in the causality behind this relationship.

Age and condition	Sleep needs
Newborns (0–3 months)	14 to 17 hours
Infants (4–11 months)	12 to 15 hours
Toddlers (1–2 years)	11 to 14 hours
Preschoolers (3–4 years)	10 to 13 hours
School-age children (5–12 years)	9 to 11 hours

Teenagers (13–17 years)	8 to 10 hours
Adults (18–64 years)	7 to 9 hours
Older Adults (65 years and over)	7 to 8 hours

PHYSIOLOGICAL SIGNIFICANCE OF SLEEP

Sleep is an indispensable phenomenon. Its physiological significance is highlighted.

1) *Sleep may serve as a period of body's rest and metabolic restoration as evidenced* by following physiological changes during non-REM sleep:

- Pulsatile release of growth hormone and gonadotropins from the pituitary and
- Decrease in blood pressure, heart rate and respiration.

2) *Sleep is necessary for certain forms of learning*. In experimental animals, learning sessions do not improve performance until a period of SWS or SWS plus REM sleep has occurred. However, it is not known why sleep is necessary and there is as yet no clinical correlate to this experimental observation.

3) *REM sleep is necessary for mental well-being*. The correlation between dreaming and REM sleep indicates that the brain is highly active at this time. This may allow for the expression, through dreams, of concern in the subconscious and for long-term chemical and structural changes that brain must undergo to make learning and memory possible.

4) *REM sleep plays an important role in homeostatic mechanism*. It is evident from the observation that when the experimental animals are completely deprived of REM sleep for long periods, they lose weight in spite of increased caloric intake and finally die.

SLEEP DISORDERS

1. INSOMNIA

Insomnia is the inability to sleep or abnormal wakefulness. It is the most common sleep disorder. It occurs due to systemic illness or mental conditions such as psychiatric problems, alcoholic addiction and drug addiction.

2. HYPERSOMNIA

Hypersomnia is the excess sleep or excess need to sleep. It occurs because of lesion in the floor of the third ventricle, brain tumors, encephalitis, chronic bronchitis and disease of muscles. Hypersomnia also occurs in endocrine disorders such as myxedema and diabetes insipidus.

3. NARCOLEPSY AND CATAPLEXY

Narcolepsy is the sudden attack of uncontrollable sleep. Cataplexy is sudden outburst of emotion. Both the diseases are due to hypothalamic disorders.

4. SLEEP APNEA SYNDROME

Sleep apnea is the temporary stoppage of breathing repeatedly during sleep. Sleep apnea syndrome is the disorder that involves fluctuations in the rate and force of respiration during REM sleep with short apneic episode. Apnea is due to decreased stimulation of respiratory centers, arrest of diaphragmatic movements, airway obstruction or the combination of all these factors. When breathing stops, the resultant hypercapnia and hypoxia stimulate respiration. Sleep apnea syndrome occurs in **obesity, myxedema, enlargement of tonsil and lesion in brainstem**. Common features of this syndrome are **loud snoring, restless movements, nocturnal insomnia, daytime sleepiness, morning headache and fatigue**. In severe conditions, **hypertension, right heart failure and stroke occur.**

5. NIGHTMARE

Nightmare is a condition during sleep that is characterized by a sense of extreme uneasiness or discomfort or by frightful dreams. Discomfort is felt as of some heavy weight on the stomach or chest or as uncontrolled

movement of the body. After a period of extreme anxiety, the subject wakes with a troubled state of mind. It occurs mostly during REM sleep. Nightmare occurs due to improper food intake, digestive disorders or nervous disorders. It also occurs during drug withdrawal or alcohol withdrawal.

6. NIGHT TERROR

Night terror is a disorder similar to nightmare. It is common in children. It is also called pavor nocturnus or sleep terror. The child awakes screaming in a state of fright and semiconsciousness. The child cannot recollect the attack in the morning. Nightmare occurs shortly after falling asleep and during non-REM sleep. There is no psychological disturbance.

7. SOMNAMBULISM

Somnambulism is getting up from bed and walking in the state of sleep. It is also called walking during sleep or sleep walking (somnus = sleep; ambulare = to walk). It varies from just sitting up in the bed to walking around with eyes open and performing some major complex task. The episode lasts for few minutes to half an hour. It occurs during non-REM sleep. In children, it is associated with bedwetting or night terror without any psychological disturbance. However, in adults it is associated with psychoneurosis.

8. NOCTURNAL ENURESIS

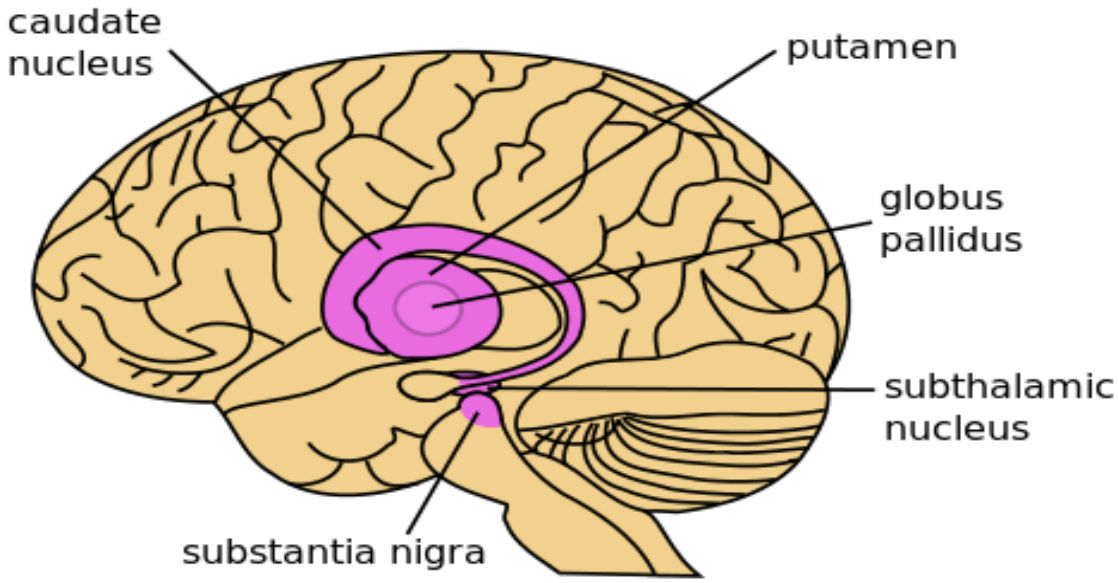
Nocturnal enuresis is the involuntary voiding of urine at bed. It is also called or bedwetting. It is common in children.

9. MOVEMENT DISORDERS DURING SLEEP

Movement disorders occur immediately after falling asleep. Sleep start or hypnic jerk is the common movement disorder during sleep. It is characterized by sudden jerks of arms or legs. Sleep start is a physiological form of clonus. Other movement disorders are teeth grinding (bruxism), banging the head and restless moment of arms or legs.

2) Discuss the role of the basal ganglia in coordinating movements

BASAL GANGLIA



The **basal ganglia** (or **basal nuclei**) are a group of subcortical nuclei, of varied origin, in the brains of vertebrates, including humans, which are situated at the base of the forebrain and top of the midbrain. Basal ganglia are strongly interconnected with the cerebral cortex, thalamus, and brainstem, as well as several other brain areas. The basal ganglia are associated with a variety of functions, including control of voluntary motor movements, procedural learning, habit learning, eye movements, cognition and emotion.

The main components of the basal ganglia – as defined functionally – are the **striatum**, consisting of both **the dorsal striatum (caudate nucleus and putamen) and the ventral striatum (nucleus accumbens and olfactory tubercle), the globus pallidus, the ventral pallidum, the substantia nigra, and the subthalamic nucleus**. Each of these components has a complex internal anatomical and neurochemical organization. The largest component, **the striatum (dorsal and ventral), receives input from many brain areas beyond the basal ganglia, but only sends output to other**

components of the basal ganglia. **The pallidum receives input from the striatum, and sends inhibitory output to a number of motor-related areas. The substantia nigra is the source of the striatal input of the neurotransmitter dopamine, which plays an important role in basal ganglia function. The subthalamic nucleus receives input mainly from the striatum and cerebral cortex and projects to the globus pallidus.**

The original functional organization of the basal ganglia was conceived as a loop, in which cortical afferent activity is dispatched to and modulated by the basal ganglia, which subsequently sends back a signal to the cortex to facilitate (or inhibit) motor activity. The basal ganglia were featured as a "go through" station within the motor loop. Current thinking now is that the basal ganglia has several loops, where cortical and subcortical projections interact with internal reentry loops forming a complex network, ideally designed for selecting and inhibiting simultaneously occurring events and signals.

PATHOPHYSIOLOGY

The basal ganglia are particularly associated with movement disorders. Associated with damage to the BG are: tremors; involuntary muscle movements; abnormal increase in tone; difficulty initiating movements; abnormal posture.

Movement disorders comprise a variety of motor problems, not all of which are associated with dysfunction of the basal ganglia.

Parkinson's

Parkinson's is the most notorious disease of the basal ganglia. Classic clinical symptoms include bradykinesia, resting tremor, postural instability, and shuffling gait. This disease is a result of neurodegeneration of the SNpc dopaminergic neurons. Often found in the Parkinsonian striatum, alpha-synuclein protein aggregates form toxic "Lewy bodies," which are inclusions within neurons. The substantia nigra, due to degeneration, loses its grossly visible dark pigmentation, a concomitant sign of dopamine biosynthesis dysfunction. This loss of dopamine depresses the nigrostriatal pathway.

With decreased dopaminergic input the striatum exerts less positive motor activity and more negative motor inhibition. This gives the characteristic hypokinetic dysfunction found in these patients.

Huntington Disease

Huntington disease is a hyperkinetic movement disorder. Its cause is a genetic defect manifesting as a CAG repeat on chromosome 4p on the HTT gene. This creates an abnormally long Huntington gene which leads to neuronal death in the caudate and the putamen. The indirect pathway is interrupted and leads to a hyperkinetic presentation. Symptoms include involuntary movements such as chorea, cognitive degeneration, and psychiatric dysfunction.

Hemiballism

Hemiballism (from the Greek “to throw”) is used to describe hyperkinetic, involuntary, forceful movements of the ipsilateral arm and leg. Commonly, a lesion in the contralateral subthalamic nuclei causes hemiballism. Given that the subthalamus is part of the indirect pathway this lesion reduces or eliminates indirect pathway signalling, leading to a relative overabundance of activity in the direct pathway. Such causes include stroke, traumatic brain injury, amyotrophic lateral sclerosis, nonketotic hyperglycemia, neoplasm, vascular malformation, and other causes.]

Tourette Syndrome

Tourette syndrome has been shown to have a significant neurological basal ganglia component which manifests as sudden, repetitive uncontrolled movements and vocalizations, called “tics.” These tics have been associated with dysfunction of the GABAergic projections from the striatum, leading to a relative increase in dopaminergic activity much like in hemiballism and Huntington’s disease

Additionally, parts of the basal ganglia play a key role in reward and reinforcement, addictive behaviours and habit formation. Pathophysiological processes underlying psychiatric disorders such

as depression and obsessive-compulsive disorder involve the basal ganglia and their connections with many other structures (particularly to the prefrontal cortex and the limbic system). In terms of cognitive disorders, basal ganglia abnormalities have been found in individuals with schizophrenia and may explain have learning deficits associated with the disorder.