Behavioral and Motivational Mechanisms of the Brain (The Limbic System and the Hypothalamus)
Psychiatric illness

Psychosis
- Schizophrenia
  - Mania
  - Depression
  - Bipolar

Neurosis
- OCD
- Phobia
- Anxiety
- PTSD

Psychosis: Pt is not aware of illness and refers to treatment
Neurosis: Less serious and insight present
(Obssessive compulsive disorder, Post traumatic stress disorder)
Schizophrenia
Clinical Presentation of Schizophrenia

General
1. Schizophrenia is a chronic disorder of thought and affects (affect: verb; effect: none) the person in the environment, causing a significant disturbance in the individual’s ability to function vocationally and interpersonally.

A. People with schizophrenia may appear 1. uncooperative 2. suspicious 3. hostile 4. anxious 5. aggressive due to their misinterpretation of reality.

B. They may have 1. poor hygiene and 2. appear 1. dirty 2. unkempt 3. stained crumple clothes as psychosis as well as 3. depressive symptoms ▶ impaired self-care.

C. Sleep and appetite are often disturbed.

D. People with schizophrenia often have 1. difficulty living independently in the community and 2. have difficulty forming close relationships with others.

E. They have problems with initiating or maintaining employment.
Comorbid medical disorders, such as type 2 diabetes and chronic obstructive pulmonary disease, are prevalent in schizophrenia due to sedentary lifestyles, poor dietary habits leading to obesity, and/or heavy cigarette smoking. Approximately 85% of people with schizophrenia smoke, and approximately 50% use drugs and alcohol, rates that are much higher than in the general population.

2. The onset of symptoms in most cases is insidious, usually preceded by a prodromal phase characterized by:
   1. gradual social withdrawal,
   2. diminished interests,
   3. changes in appearance and hygiene,
   4. changes in cognition,
   5. bizarre or odd behaviors.

**Symptoms**

Hallmark symptoms include psychotic symptoms, negative symptoms, and cognitive impairments that last for at least 6 months.

**A. Psychotic symptoms:**

These symptoms are sometimes called positive symptoms, as they are “added on to” or “Behaviors that are present that should not present” a person’s normal experience. They may include:
Hallucinations are false or distorted sensory experiences that appear to be real perceptions. These sensory impressions are generated by the mind rather than by any external stimuli, and may be seen, heard, felt, and even smelled or tasted. They can include:

1. **Auditory hallucinations**: voices are the most common type of hallucination. The voices may
   a. talk to the person about their behavior,
   b. commanding (i.e., commanding the person to perform a particular action),
   c. threatening or warn them of apparent danger.

Patients may feel compelled to perform the commanded task or may experience much anxiety when they do not.

2. **Visual hallucinations** (e.g., recognizable objects or unformed lights or shadows)
3. **Olfactory hallucinations** (e.g., unpleasant odors)
4. **Tactile hallucinations** (e.g., feeling that someone is touching you when no one is nearby)
2. Delusions (الأوهام)

Delusions frequently involve fixed false beliefs despite invalidating evidence, and may be bizarre in nature.

1. delusions of control (e.g., believing one's thoughts and movements are controlled by someone else)

2. delusions of reference (e.g., believing someone on TV is talking specifically to you)

3. erotomantic delusions (e.g., believing Brad Pitt or Angelina Jolie is in love with you)

4. grandiose delusions (e.g., believing one is a billionaire who owns all hotels in the city)

5. persecutory delusions (e.g., believing ones is being followed or try to hurt them or harassed by CIA)

6. somatic delusions (e.g., believing ones nose is infested by worms)
Disorganized (or illogical) speech/thinking, also described as “thought disorder” or “loosening of associations,” is a key aspect of schizophrenia. Disorganized thinking is usually assessed primarily based on the person’s speech. Thought disorders - illogical thought & speech that can include:

- **alogia/poverty of content** - impoverished speech & thinking (very little information conveyed by speech)
- **thought blocking** - a sudden losing train of thought, abrupt interruption in speech
- **word salad** - words strung together nonsensically
- **perseveration** - repeating words or ideas persistently

Thinking and speech may be incomprehensible and illogical, silliness and laughter that is not related to content of speech.

Subtle disturbances in associative thinking may develop years before disorganized thinking (formal thought disorder).
4. Grossly disorganized behavior includes
difficulty in goal-directed behavior (leading to difficulties in activities in daily living)

unpredictable agitation or silliness,
social disinhibition, or
behaviors that are bizarre to onlookers

Their purposelessness distinguishes them from unusual behavior prompted by delusional beliefs.

5. Catatonic behaviors are characterized by a marked decrease in reaction to the immediate surrounding environment, sometimes taking the form of motionless and apparent unawareness, rigid or bizarre postures, or aimless excess motor activity.
B. Negative symptoms or deficit symptoms:
Symptoms “taken away” from a patient’s personality.
People with negative symptoms often neglect basic personal hygiene and need help with everyday tasks.

Specific examples of negative symptoms include:

1. Affective Flattening - decrease in the intensity of emotional expression, apathy

2. Avolition - decrease in initiation of goal-directed behavior

3. Anhedonia - lack of pleasure in activities normally found enjoyable, or social interactions

Approximately 10% to 15% of people with schizophrenia may present primarily with negative symptoms; these people may be referred to as having a deficit syndrome.
C. Cognitive symptoms:
Cognitive symptoms can be subtle and may only be detected when tests are performed. They include:

Decreased working memory: The ability to use information immediately after learning it

Trouble focusing or paying attention: Neuropsychological research shows that patients with schizophrenia show abnormalities in the areas of

1. attention,
2. processing speed,
3. verbal and visual memory,
4. working memory, and
5. problem solving.

There is a loss of, on average, one standard deviation of pre-illness IQ (Intelligence Quotient) with the average IQ of between 80 and 84 (normally 50% of IQ scores fall between 90 and 110).

B. Social/occupational dysfunction:
For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset (or when onset is in childhood or adolescence, failure to achieve the expected level of interpersonal, academic, or occupational achievement).
PATHOPHYSIOLOGY

A. Dopamine hypothesis of schizophrenia:
First-generation antipsychotics are also known as: typical, conventional, dopamine antagonists, neuroleptics and classic antipsychotics.

The oldest theory associated with the patho-physiology of schizophrenia is the dopamine hypothesis, which proposes that psychosis is due to excessive dopamine in the brain.

Evidence with the theory:

Basis of classical dopamine hypothesis of schizophrenia

Dopamine-releasing drugs (amphetamine, mescaline, L-dopa, cocaine) can induce state closely resembling paranoid schizophrenia in normal persons and low dose of them worse schizophrenia symptoms due to increase dopamine.

Typical antipsychotics that are effective in the treatment of schizophrenia have in common the ability to inhibit the dopaminergic system by blocking action of dopamine in the brain.

The four pathways relevant to the pharmacology of antipsychotics in the treatment of schizophrenia are:

1. The mesolimbic pathway over activity: The mesolimbic pathway originates (cell body) in the ventral tegmental area (midbrain) and innervates several structures of the limbic system (axon terminate), including the nucleus accumbens in the ventral striatum.

The mesolimbic pathway is associated with the reward circuit.

The mesolimbic pathway plays a key and complex role in ①motivation, ②emotions, ③reward, and ④positive symptoms of schizophrenia; where there is increase in dopamine release (or increase dopamine receptors (D2) or loss of upper inhibitory neurons).

D2 antagonists reduce positive symptoms of schizophrenia.

All antipsychotic drugs have the ability to reduce dopaminergic neurotransmission.
The mesocortical pathway decrease activity (dysfunction):
Meso-cortical pathway: From Ventral tegmental area to prefrontal cortex which are:

- **a. dorsolateral** responsible for **Cognition and executive function** in normal
- **b. ventromedial** responsible for **Emotions and affect** in normal

Hypofunction (decrease dopamine or due to decrease number of dopamine receptor (D1) of the mesocortical pathway might be related to cognitive and negative symptoms of schizophrenia

The nigrostriatal system

The nigrostriatal system contains about 80% of the brain’s dopamine.

The nigrostriatal system projects from cell bodies in the pars compacta of the substantia nigra to terminals that innervate the striatum (caudate and putamen).

The nigrostriatal system is involved in:

- **motor planning**, **dopaminergic neurons stimulate purposeful movement.**
- D₂ antagonism induces extrapyramidal symptoms. This is the case of first generation antipsychotics, high-potency (high affinity) to D₂ antagonists frequently cause pseudo-parkinsonism (extrapyramidal symptoms because nigrostriatal system is part of extrapyramidal system and tardive dyskinesia).

The tuberoinfundibular pathway

Dopaminergic projections in the tuberoinfundibular pathway influence prolactin release.

**D2** receptors by antipsychotics increases prolactin levels (hyperprolactinemia)
Serotonin hypothesis of schizophrenia:

Second-generation antipsychotics or atypical or dopamine-serotonin antagonists antipsychotics

The serotonin (5-HT) hypothesis of schizophrenia arose from early studies on interactions between the two major classes of psychedelic hallucinogens,

1. the indoleamines (e.g., lysergic acid diethylamide (LSD)
2. phenethylamines (e.g. mescaline),

are mostly 5-HT\(_{2A}\) agonists that result in

1. visual hallucinations and
2. mystical delusions, sometimes with retained insight.

In psychosis there is upregulated 5-HT\(_{2A}\) receptors on glutamate neurons in prefrontal cortex which where serotonin will regulate the release of dopamine at the neurons release dopamine at ventral tegmental area
Serotonin itself inhibits the release of serotonin from the presynaptic neuron; because serotonin will attach to both ① somatodendritic auto-receptors ($5HT_{A1}$ slow neuronal release of serotonin) ② terminal or presynaptic auto-receptors ($5TH_{1B/1D}$ block serotonin release) from the presynaptic neuron as if it is telling that there is enough serotonin and no need for more.

When serotonin is attached to the dopamine neuron postsynaptically (heteroreceptor) ① when serotonin attached to $5HT_3$ dopamine release is increased ② when serotonin attached to $5HT_2$ dopamine release is inhibited.

So release serotonin can be increased (so increase dopamine release), or decreased (so decrease dopamine release).
For atypical antipsychotic drugs it will attached to

1. $5HT_{2A}$ auto-receptors preventing auto-inhibitory effect of serotonin $\Rightarrow$ ↑ serotonin release $\Rightarrow$ ↑ dopamine in the mesocortical pathway that might be related to cognitive and negative symptoms of schizophrenia

2. Dopamine ($D_2$) receptor $\Rightarrow$ ↓ dopamine effect $\Rightarrow$ ↓ positive symptoms of schizophrenia in the mesolimbic pathway.

Note:

Atypical antipsychotic drugs attached to $D_2$ receptor loose and rapidly dissociated this is why it has lower side effect on

1. Nigrostriatal system so has lower extra-pyramidal symptoms (psudo-Parkinsonian and tardive dyskinesia) because:
   a. less affinity to dopamine receptors so cause less severe dopamine deficiency
   b. $5HT_{2A}$ receptors is found in striatum and substantia nigra that will be blocked by the drug

2. Tuberoinfundibular pathway so has lower hyperprolactinemia effect
if D2 receptors in the mesolimbic system are blocked completely as in typical antipsychotic drugs, this may

A. only reduce positive symptoms of schizophrenia,

B. block reward mechanisms "neuroleptic-induced deficit syndrome", leaving patients

① apathetic (لايمبالي)
② Anhedonia (انعدام التلذذ)
③ lacking motivation & interest & joy from social interactions a state very similar to that of negative symptoms of schizophrenia, and this may be a partial explanation for the high incidence of smoking and drug abuse in schizophrenia,

C. it may worsen negative and cognitive symptoms
B. Glutamate (or N-methyl-D-aspartate (NMDA) receptor hypo-function) hypothesis of schizophrenia

Phencyclidine does this by blocking a type of glutamate receptor known as N-methyl-D-aspartate named for the agonist that binds there selectively.

This observation has led to the notion that N-methyl-D-aspartate receptors may be pathologically hypo-functional in untreated schizophrenia, much like the condition produced by the ingestion of phencyclidine.

An important descending glutamatergic pathway projects from cortical pyramidal neurons to dopamine neurons in the ventral tegmental area.
A. Positive symptoms of schizophrenia in the mesolimbic pathway:
May be the result of
a. No initial glutamate
b. hypo-functional NMDA receptors on GABA interneurons in the cerebral cortex.

Normally: GLU-GABA-GLU-DA: (+) – (-) – (+) ➤ ↓ dopamine
Schizophrenia: GLU-zero-GABA-DA: (+) – (zero) – (+) ➤ ↑ dopamine

This hypofunction may lead to over activation of downstream glutamate signaling to the ventral tegmental area. Over activation of this pathway may result in excess dopamine in the ventral striatum via the mesolimbic pathway ➤ ↑ positive symptoms of schizophrenia in the mesolimbic pathway

B. Negative symptoms of schizophrenia in the mesocortical pathway:
The circuit has changed from GLU-GABA-GLU-DA to one of GLU-GABA-GLU-GABA-DA and it has an extra step. May be the result of
First: a. No initial glutamate, b. hypo-functional NMDA receptors on GABA interneurons in the cerebral cortex.
Second: Extra GABA interneurons

Normally: GLU-GABA-GLU-DA: (+) – (-) – (+) ➤ ↓ dopamine
Schizophrenia: GLU-zero-GABA-DA: (+) – (zero) – (+) – (-) ➤ ↓ dopamine

Low activation of this pathway may result in turn in low dopamine in the ventral striatum via the mesocortical pathway ➤ ↑ negative symptoms of schizophrenia in the mesocortical pathway
Hypothalamus:

Hypothalamic input:

1. **nucleus of the solitary tract**
   - Visceral sensory information (blood pressure and gut distension.) ➔ vagus ➔ **nucleus of the solitary tract** ➔ hypothalamus

2. **reticular formation**
   - A variety of inputs from the spinal cord. Among them is information about skin temperature ➔ **reticular formation** ➔ hypothalamus

3. **retina**
   - Retina ➔ optic nerve ➔ **suprachiasmatic nucleus** within the hypothalamus
   - This nucleus regulates circadian rhythms, and couples the rhythms to the light/dark cycles.

4. **circumventricular organs**
   - Examples:
     a. The **Organum vasculosum laminae terminalis (OVLT)**, which is sensitive to changes in osmolarity
     b. The **area postrema**, which is sensitive to toxins in the blood and can induce vomiting and angiotensin II.

5. **limbic and olfactory systems**
   - Structures such as the amygdala, the hippocampus, and the olfactory cortex project to the hypothalamus, and probably help to regulate behaviors such as eating and reproduction.
   - The hypothalamus also has some intrinsic receptors, including **thermoreceptors** and **osmoreceptors** to monitor temperature and ionic balance, respectively.
Hypothalamic output:

1. **Neural signals to the autonomic system** - The (lateral) hypothalamus projects to the (lateral) medulla, where the cells that drive the autonomic systems are located (the parasympathetic and the sympathetic system).

   With access to these systems, the hypothalamus can control heart rate, vasoconstriction, digestion, sweating, etc.

2. **Endocrine signals to/through the pituitary**
Hypothalamic functions are:
The internal functions are collectively called *vegetative functions* of the brain, and their control is closely related to behavior.

I. Control of pituitary gland (anterior and posterior lobe).

II. Control of autonomic functions:
The single most important hypothalamic nucleus of the central autonomic network is the paraventricular nucleus (PVN).

The paraventricular nucleus (PVN) has two morphological classes of neurons that fall into three functional categories.

a. The magnacellular (big) neurons cells control posterior pituitary gland secretion.

b. The parvocellular (small) neurons

1. neuroendocrine-related functional control anterior pituitary hormone secretion.
2. central autonomic control.

1. the dorsal longitudinal fasciculus (DLF) → the brainstem and lateral to Lamina X of the spinal cord
2. the medial forebrain bundle: joins the limbic system and the hypothalamus
3. the mammillo-tegmental tract: originate in the mammillary nuclei and project to the reticular formation of the pons and medulla

The paraventricular nucleus (PVN) receives direct sympathetic and parasympathetic afferent inputs therefore is the only brain site in a closed efferent-afferent reflex loop with both the sympathetic and parasympathetic nervous systems.
Hypothalamus is the main integration center of autonomic activity.

Subconscious cerebral input via limbic system influence hypothalamic function.

Other control come from the cerebral cortex, the reticular formation, and the spinal cord.

The hypothalamus regulates the functioning of the autonomic nervous system, which in turn means it regulates things like:
1. pulse,
2. blood pressure,
3. breathing
4. GIT motility and
5. arousal in response to emotional circumstances.

Stimulation in the posterior and lateral hypothalamus increases the arterial pressure and heart rate,

Stimulation in the preoptic area often has opposite effects.
III. Relation to cyclic phenomena & Relation to sleep:
Most if not all living organisms have rhythmic fluctuation in bodily function that are about 24 hours in length, i.e. they are (circadian). Normally they become entrained, i.e. synchronized to the day-night light cycle in the environment.
In humans the rhythms that are controlled include the rhythms in
① ACTH secretion,
② melatonin secretion,
③ sleep-awake cycle,
④ the body temperature cycle.
Most of these rhythms are controlled by (Suprachiasmatic nuclei: (Biological clock) in the anterior hypothalamus one nucleus on each side above the optic chiasma.
The optic afferent signal that entrains the circadian rhythms to the day-night comes from the eyes, since removal of the eyes abolishes entrainment and there are (Retinohypothalamic fibers) that pass directly from optic chiasm to the Suprachiasmatic nuclei.
IV. Relation to hunger:
Hypothalamic regulation of the appetite for food depends primarily upon the interaction of two areas:

A. Feeding center associated with hunger is the (lateral hypothalamic nucleus): stimulation of this center evokes eating, and its destruction causes anorexia.

B. Satiety center opposes the desire for food is the (Ventro-medial nucleus of hypothalamus): stimulation of this center causes cessation of eating, whereas lesion of this region causes hyperphagia.

The satiety center functions by inhibiting the feeding center. It appears that then feeding center is chronically active and that it’s activity in the satiety center after the ingestion of food.

There are different hypotheses related to this regulation:

1. Lipostatic hypothesis: This hypothesis holds that adipose tissue produces a leptin that is proportionate to the amount of fat and acts on the hypothalamus to decrease food intake and increase energy output.
Gut peptide hypothesis: The food entering the gastrointestinal tract triggers the release of gastrin-releasing peptide (GRP), glucagon, somatostatin, and cholecystokinin (CCK), which act on the brain to produce satiety. The brain contains both CCK-A and CCK-B receptors.

Glucostatic hypothesis:

Hunger ► Decrease glucose to satiety center ► Decrease activity of satiety center ► Increase activity of feeding center

Thermostatic hypothesis: A decrease in body temperature below a given set-point stimulates appetite, whereas an increase above the set-point inhibits appetite.

V. Relation to Thirst:
Thirst simply means a tendency to seek water and to ingest it

The known stimuli for thirst.

1. ↑ ECF osmolarity, which causes intracellular dehydration in the thirst centers,
2. ↓ ECF volume and arterial pressure
3. Angiotensin II.
4. Dryness of the mouth and mucous membranes of the esophagus
5. Visceral osmoreceptors
6. GIT and pharyngeal stimuli influence thirst (distension of stomach inhibits thirst).
The central controller for water balance is the **hypothalamus**.

There is no single anatomically defined center which is solely responsible for producing an integrated response to changes in water balance.

The osmoreceptors are located in the area known as the AV3V (anteroventral 3rd ventricle) in hypothalamus where the organum vasculosum of the lamina terminalis is part of it.

The thirst center is located in the lateral hypothalamus.

Organum vasculosum of the lamina terminalis are sites for angiotensin II action.

ADH is formed predominantly in the neurons of the supraoptic and paraventricular nuclei.

The supraoptic and paraventricular nuclei receive input from

1. the osmoreceptors
2. The ascending adrenergic pathways from
A. the low pressure baroreceptors
1. Large systemic veins
2. Pulmonary vessels
3. The walls of the right atrium and ventricles of the heart (the atrial volume receptors)

B. the high pressure baroreceptors
1. Transverse aortic arch
2. Carotid sinuses of the left and right internal carotid arteries
3. Juxta-glomerular-apparatus (renal afferent arteriole)

Neural Mechanisms of Thirst
Sensory information from the baroreceptors located in the atria of the heart is sent to a nucleus in the medulla: the **nucleus of the solitary tract**.
This nucleus sends efferent axons to many parts of the brain, including the region around the AV3V.

**Nucleus of the solitary tract.** A nucleus of the medulla that receives information from visceral organs and from the gustatory system.
The second signal for volumetric thirst is provided by angiotensin, located in one of the circumventricular organs. The subfornical organ (SFO), is the site at which blood angiotensin acts to produce thirst.

Subfornical organ (SFO) contains neurons that detect the presence of angiotensin in the blood and excite neural circuits that initiate drinking.

Neuron in the subfornical organ send their axons to the median preoptic nucleus.

The median preoptic nucleus receives information from angiotensin-sensitive neurons in the SFO. In addition, this nucleus receives information from the OVLT (which contains osmoreceptors) and from the nucleus of the solitary tract (which receives information from the atrial baroreceptors).

OVLT will send information to thirst center located at lateral hypothalamus.
IV. Relation to thermal regulation:
The normal body functions depend upon a relatively constant body temperature. Because
① the speed of chemical reactions varies with the temperature
② the enzyme systems of the body have narrow temperature ranges in which their function is optimal
Oral, morning temperature is (36.3 to 37.1 °C)

Heat production and heat loss:
A. Heat production:
Heat production is increased by
① ingestion of food
② contraction of skeletal muscle.
Heat production can be varied by endocrine mechanisms as it will be increased by
① catecholamine
② thyroid hormones
③ sympathetic stimulation

B. Heat loss:
Methods of heat loss:
① radiation and conduction (70%)
② vaporization of sweat (27%)
③ respiration (2%)
④ urination and defecation (1%).
Temperature-regulating mechanisms: The temperature regulating mechanisms includes autonomic, somatic, endocrinal and behavioral changes.

1. Mechanisms activated by cold:
   A. **increase heat production**: Shivering, hunger, increase voluntary activity, increase secretion of nor-epinephrine and epinephrine.
   B. **decrease heat loss**: Cutaneous vasoconstriction, curling up and horripilation.

2. Mechanisms activated by heat:
   a. **Increase heat loss**: Cutaneous vasodilatation, sweating, increase respiration.
   b. **Decrease heat production**: Anorexia, apathy and inertia.

Hypothalamic role in controlling body temperature:
typically 36.7–37.1°C body temperature level is crucial temperature level which is called the “set-point”
Posterior hypothalamus destruction causes hypothermia
Posterior hypothalamus controls the descending pathways to effectors
Posterior hypothalamus receives signals from Anterior hypothalamus (integrated body temperature: this why it is said that set-point is found in posterior hypothalamus)

Anterior hypothalamus activated by warmth ➤ inhibit sympatheticsystem ➤ decrease body temperature
Decrease heat production (indirectly:through Post. Hypo.)
Increase heat loss (Directly through Ant. Hypo.)

Anterior hypothalamus destruction causes hyperthermia
Anterior hypothalamus contains (cold sensitive neurons: heat sensitive neurons 4:1)
Anterior hypothalamus receive the afferent thermal information from thermo-receptors
a. peripheral receptors in the skin
b. detecting core body temperature : ①deep tissue, ②spinal cord, ③extra-hypothalamic portion of the brain
④ anterior hypothalamus-preoptic area

Fever:
Fever (hyperthermia) has a beneficial effect as it
①possible slow the growth of micro-organisms; tumor cells
②stimulates antibody production.
When rectal temperature is over 41 C for prolonged periods, some permanent brain damage results
when it is over 43 C, heat stroke develops and death is common.
Pathogenesis of fever:

Toxins from bacteria acts on monocytes, macrophages and Kupffer cells to produce cytokines (interleukin-1B, interleukin-6, beta-interferon, and gamma-interferon) that acts as (endogenous pyrogens). These cytokines act on organum vasculosum of lamina terminalis (OVLT) this is because these cytokines can not penetrate BBB but OVLT is outside BBB. OVLT in turn activates the anterior preoptic area of the hypothalamus through the release of prostaglandin-E2.

Prostaglandins increase the set-point temperature. The temperature receptors then signal that the actual temperature is below new set point, and the temperature-raising mechanisms are activated. This is usually produces chilly sensations due, to cutaneous vasoconstriction and occasionally enough shivering to produce a shaking chill.

This is why aspirin act as antipyretic through the block of Prostaglandins. Blocking Prostaglandin will decrease set point which is below the actual body temperature; and this will stimulate heat losing mechanism to lower body temperature.
Hypothermia:
Human tolerate body temperature of 21°C to 24°C with permanent ill effect, and induced hypothermia has been extensively used in surgery (as in open heart surgery). In hypothermic patients, ➊ the circulation can be stopped for relatively long period because ➋ the oxygen need of the tissue is greatly reduced ➌ Blood pressure is low, and ➍ bleeding is minimal.

Limbic system:

Main Components of the Limbic System
Functions of limbic system:
Most of limbic system is related to hypothalamus

1. Autonomic function:
   Stimulation of many parts of limbic system, especially that of amygdala, produce autonomic responses (CVS, respiratory, GI through hypothalamus). Such changes are also observed during emotion.

2. Regulation of body feeding behavior:
   It is mainly through hypothalamus

3. Regulation of sexual behavior and reproduction
   ①Sexual behavior, ②the basic sex derive (urge to couple)is the function of limbic system and hypothalamus, which in turn are influenced by gonadal hormones and cerebral cortex

4. Maternal behavior:
   In general maternal behaviors concerned with the nursing and protection of offspring by the mother

5. Emotion behavior: fear, anger, love, hate, joy, grief, contempt, enthusiasm, envy, frustration, embarrassment, disgust, happiness, pride, superior, sadness

6. Motivation behavior:
   (extrinsic: reward and punishment: high grade, money, please someone)
   (intrinsic: enjoy and pleasure: challenge, curiosity, control, cooperation, competition, recognition)
   The last two are one of the most important function.
Reward and punishment function of limbic system

It is already clear that several limbic structures are particularly concerned with:

a. the sensations are pleasant (reward or satisfaction)

b. the sensations are unpleasant (punishment or aversion)

Reward center or pleasure center
The ventral tegmental area (VTA: is found in mid brain) and through the Medial forebrain bundle (MFB) is connected to

1. Nucleus accumbens (المنكئ مناطق forms (reward circuit or mesolimbic pathway)
is also called ventral striatum
is part of limbic system
is most associated with pleasure and reward
is a dopaminergic neurons.
Dopamine rewards us with a pleasant sensation.
is important for memory and for motivating behaviors.

By blocking this pathway, antipsychotic drugs reduce the intense emotions caused by conditions such as schizophrenia.

2. Lateral and ventromedial nuclei of the hypothalamus is the most potent reward centers: hypothalamus
3. Frontal area form mesocortical pathway
4. Others

septum, the amygdala, certain areas of the thalamus and basal ganglia
Punishment Centers

Stimulation in Punishment Centers causes the animal to show all the signs of displeasure, fear, terror, pain, punishment, and even sickness.

1. The most potent areas for punishment and escape tendencies have been found in the central gray area surrounding the aqueduct of Sylvius in the mesencephalon and extending upward into the periventricular zones of the hypothalamus and thalamus.

Strong stimulation of the punishment centers in the periventricular zone of the hypothalamus and in the lateral hypothalamus causes an emotional pattern (the rage)

2. Less potent punishment areas are found in some locations in the amygdala and hippocampus.

It is particularly interesting that stimulation in the punishment centers can frequently inhibit the reward and pleasure centers completely, demonstrating that punishment and fear can take precedence over pleasure and reward.

Fortunately, in the normal animal, the rage phenomenon is held in check mainly by inhibitory signals from

1. The ventromedial nuclei of the hypothalamus.

2. Portions of the hippocampi and anterior limbic cortex, especially in the anterior cingulate gyri and subcallosal gyri, help suppress the rage phenomenon.
If no reward and punishment effect, repletion of stimuli will causes habituation and therefore will cause the animal to ignore it. Exactly the opposite emotional behavior patterns occur when the reward centers and punishment are stimulated to placidity and tameness.

If got reward and punishment effect, stimuli will be reinforced and animal will build up strong memory trace; so this two effects are important in learning and memory

**Effects of Stimulating the Amygdala (اللوز).**

A. Effects of Stimulating the Amygdala similar to hypothalamus stimulation:

1. increases or decreases in arterial pressure; heart rate; gastrointestinal motility and secretion;
2. defecation or micturition;
3. pupillary dilation or, rarely, constriction;
4. pilo-erection
5. secretion of various anterior pituitary hormones, especially the gonadotropins and adreno-corticotropic hormone.
B. amygdala stimulation can cause several types of involuntary movement.
(1) tonic movements, such as raising the head or bending the body;
(2) circling movements;
(3) occasionally clonic, rhythmical movements
(4) different types of movements associated with olfaction and eating, such as licking, chewing, and swallowing.

C. amygdala stimulation can cause several types of emotions (or thread detector):
1. rage, escape, punishment, severe pain, and fear similar to the rage pattern
2. reward and pleasure.
3. sexual activities that include erection, copulatory
Effects of Bilateral Ablation of the Amygdala (The Klüver-Bucy Syndrome). When the anterior parts of both temporal lobes are destroyed in a monkey, this procedure removes not only portions of temporal cortex but also of the amygdalas that lie inside these parts of the temporal lobes. This removal causes changes in behavior called the Klüver-Bucy syndrome, which is demonstrated by an animal that

1. **Tameness (loss of fear)**
2. has extreme **curiosity about everything**, has a tendency to place everything in its mouth
3. **forgets rapidly** (Anterograde amnesia)
4. **Visual agnosia** (cannot recognize objects visually), Psychic blindness (objects in visual field are treated inappropriately as inability to recognize facial expression)
5. **Hypersexuality** (autoerection): often has a sex drive so strong that it attempts to copulate with immature animals, animals of the wrong sex, or even animals of a different species. Although similar lesions in human beings are rare, afflicted people respond in a manner not too different from that of the monkey.
Hippocampus:

Short term memory is lost on removal of bilateral hippocampus

Stimulation of part of hippocampus can elicit

1. pleasure,
2. rage,
3. passivity
4. excessive sex drive

Functions of Hippocampus:

1. memory (dorsal region):
   a. store and processes memories (translation of short into long term memory i.e. store new memory i.e. consolidation of memory)
   b. help to find memories
   c. encode memories, and then helps to find them when you want to remembered something
   d. main relay station that determines whether a new memory should go to long-term memory or be deleted after short-term usefulness is over

2. Comparing sensory information what the brain expect about the world

3. Enable us to form spatial memories for navigation the environment
Papez circuit

Papez (1937) was the first to identify that it is not function of any specific brain center but 4 basic structures form a circuit.

It is one of the major pathways of the limbic system and is chiefly involved in the cortical control of emotion and storing memory.