Behavioral and Motivational Mechanisms of the Brain (The Limbic System and the Hypothalamus)
Reticular formation:
Reticular formation is a network of neurons. Reticular formation centers pass in the center of medulla, extend upward through Pons, stops in midbrain. Reticular formation is connecting bridge between higher centers and lower one, where ascending pathway passes thorough. Reticular formation can be subdivided functionally into 3 columns: the raphe (midline), the medial and lateral region.

Reticular formation has:

a. Ascending Reticular formation (or Reticular activating system) has sensory component: send ascending fibers to cerebral cortex controls overall degree of cortical alertness. The levels of consciousness are: ① maximum alertness, ② wakefulness, ③ sleep, and ④ coma

b. Descending reticular formation:
   i. it has motor component that project to spinal cord through reticulo-spinal tract that send descending fibers control muscle tone through alpha and gamma motor neurons
   ii. it has autonomic center that regulate visceral motor function (heart rate, respiration)
Ascending Activating-Driving Systems of the Brain
Without continuous transmission of nerve signals from the lower brain into the cerebrum, the cerebrum becomes useless.
Nerve signals in the brain stem activate the cerebral part of the brain in two ways:
(1) Neuronal system (2) Neuro-hormonal systems

1) Neuronal system control of cerebral activity

i. The Brain stem reticular excitatory area continuous excitatory signals

The Brain stem reticular excitatory area is an excitatory area located in the reticular substance of the pons and mesencephalon (Bulboreticular facilitatory area)

Note: This area also do have descending excitatory pathway through extra-pyramidal system
The brain stem reticular excitatory area signals are especially important for controlling longer-term background excitability level of the brain.

ii. The brain stem reticular inhibitory area
The reticular brain stem inhibitory area is in the medulla.

The reticular brain stem inhibitory area

inhibit the reticular facilitory area of the upper brain stem

+ excite serotonergic neurons

decrease activity in the superior portions of the brain
(2) Neurohormonal systems

The Neurohormonal systems mechanism is to secrete excitatory or inhibitory neurotransmitter hormonal agents into the substance of the brain.

The neurohormones often persist for minutes or hours and thereby provide long periods of control, rather than just instantaneous activation or inhibition.

Three neurohormonal systems:

(1) a norepinephrine system,

The locus ceruleus and the norepinephrine system:

The locus ceruleus area for production of norepinephrine.

The locus ceruleus located at the juncture between the pons and mesencephalon.

The axons of noradrenergic neurons are found in many areas of the brain.

The norepinephrine generally excites the brain to increased activity.

Norepinephrine system probably plays an important role in causing dreaming, thus leading to a type of sleep called rapid eye movement (REM) sleep.
2) a dopamine system,

1. **Nigrostriatal pathway**: From substantia nigra to striatum: voluntary movements

2. **Meso-limbic pathway**: From Ventral tagmental area to limbic system (anterior cingulate cortex): Behavior

3. **Meso-cortical pathway**: From Ventral tagmental area to prefrontal area: Behavior

4. **Tuberoinfundibular pathway**: hypothalamus to pituitary gland: prolactin release

Increase of dopamine seen is Schizophrenia and dopamine decrease is seen in Parkinson disease.
(3) a serotonin system.

The **raphe nuclei** and the serotonin system

The raphe nuclei is the main place for production of serotonin

The raphe nuclei little groups of neurons in the midline of the pons and medulla

The raphe nuclei send fibers into

① **many areas** in brain plays an essential inhibitory role to help cause normal sleep

② **spinal cord** has the ability to suppress pain
The gigantocellular neurons of the reticular excitatory area and the acetylcholine system.

The fibers from these giant cells divide immediately into two branches,

1. one passing upward to the higher levels of the brain
2. the other passing downward through the reticulospinal tracts into the spinal cord.

In most places, the acetylcholine functions as an excitatory neurotransmitter.
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
the speed of chemical reactions varies with the temperature and 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 ingestion of food and contraction of skeletal muscle.
Heat production can be varied by endocrine mechanisms as it will be increased by catecholamine, thyroid hormones, and 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
Anterior hypothalamus activated by warmth ▶ inhibit sympathetic system ▶ decrease body temperature
Increase heat loss
Decrease heat production

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 in the skin (peripheral receptors), deep tissue, spinal cord, extra-hypothalamic portion of the brain and anterior hypothalamus-preoptic area for detecting core body temperature

Fever:
Fever (hyperthermia) has a beneficial effect as it
1. possible slow the growth of micro-organisms; tumor cells
2. stimulates 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 act on monocytes, macrophages and Kupffer cells to produce cytokines (interleukin-1B, interleukin-6, beta-interferon, and gamma-interferon) that act 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, the circulation can be stopped for relatively long period because the oxygen need of the tissue is greatly reduced. Blood pressure is low, and bleeding is minimal.

Limbic system:

Main Components of the Limbic System

<table>
<thead>
<tr>
<th>A. Cortical structure (limbic cortex)</th>
<th>B. Subcortical structure</th>
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</thead>
<tbody>
<tr>
<td>① orbitofrontal cortex</td>
<td>① Hippocampus</td>
</tr>
<tr>
<td>② Subcallosal gyrus</td>
<td>② Septum nuclei</td>
</tr>
<tr>
<td>③ Cingulate gyrus</td>
<td>③ Amygdala</td>
</tr>
<tr>
<td>④ Parahippocampal gyrus</td>
<td>④ Hypothalamus</td>
</tr>
<tr>
<td>⑤ uncus</td>
<td>⑤ Anterior thalamic nuclei</td>
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<td></td>
<td>⑥ Basal Ganglia</td>
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<td>⑦ Para-Olfactory area</td>
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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
Sexual behavior, the 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

ان المتعة هو جزء أساسي من غريزة حب البقاء هي اماغريزية موروثة مثل غريزة الطعام و الجنس(التكافث) او مكتسبة مثل غريزة حب التملك او المال

A key brain-reward circuit.
Intracranial self-stimulation follows stimulation along the medial forebrain bundle, which links the nucleus accumbens with the lateral hypothalamus, ventral tegmental area, amygdala, prefrontal cortex, periaqueductal gray (PAG)
The ventral tegmental area (VTA: is found in mid brain) and through the Medial forebrain bundle (MFB) is connected to

1. Nucleus accumbens forms (reward circuit or mesolimbic pathway) is also called ventral striatum
2. Is also part of limbic system
3. Is most associated with pleasure and reward
4. Is a dopaminergic neurons. Dopamine rewards us with a pleasant sensation.
5. 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
   ① 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.

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.

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.

Strong stimulation of the punishment centers of the brain, especially in the periventricular zone of the hypothalamus and in the lateral hypothalamus causes an emotional pattern (the rage)
Fortunately, in the normal animal, the rage phenomenon is held in check mainly by inhibitory signals from the ventromedial nuclei of the hypothalamus. Portions of the hippocampi and anterior limbic cortex, especially in the anterior cingulate gyri and subcallosal gyri, help suppress the rage phenomenon.

Placidity and Tameness

Exactly the opposite emotional behavior patterns occur when the reward centers are stimulated: placidity and tameness.

If no reward and punishment effect, repletion of stimuli will cause habituation and therefore will cause the animal to ignore it.

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

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 pleasure, rage, passivity, or 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 is not function of any specific brain center but 4 basic structure form a circuit is one of the major pathways of the limbic system is chiefly involved in the cortical control of emotion and storing memory.