Functional Neuroanatomy of the Limbic System

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Introduction and History

Introduction and History

- “Limbic” - Latin word *limbus* - “border”
- 1878 - Paul Broca - group of structures present b/w cerebral cortex & diencephalon - “Le grand lobe limbique"
- 1937 - James Papez - cortical regions linked to hippocampus, mammillary body, and anterior thalamus in a circuit - mediated emotional behaviour - Papez circuit.

Introduction and History contd.

- 1952 - Paul D. MacLean - “limbic system” - Broca's limbic lobe and related subcortical nuclei - collective neural substrate for emotion.
- MacLean - Triune concept of the brain:
  - The Reptilian Brain : Core Brainstem - homeostasis and survival.
  - The Paleomammalian Brain : Limbic system - Social and emotional attachment and motivated behaviours.
  - The Neomammalian Brain : Neocortex and Neocerebellum - skilled movements, logic thinking, languages and higher brain functions.

Anatomy of Limbic system

Constituents

- Constituents of the limbic system vary, but the most common components on which most of the authors agree on include
  - Limbic cortex (cingulate and parahippocampal gyri)
  - Hippocampal formation
  - Amygdala
  - Septal area
  - Hypothalamus
  - Related thalamic and cortical areas.


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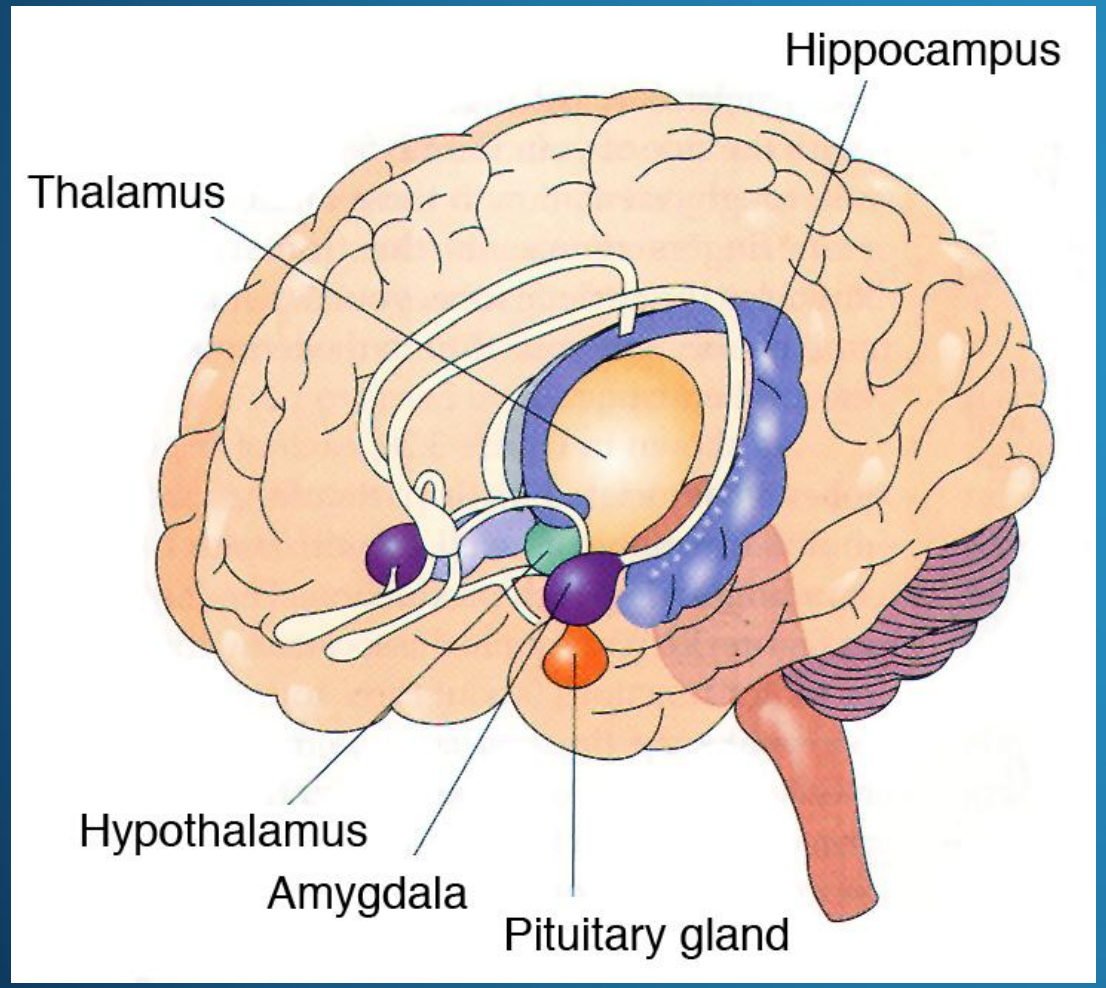
Constituents contd.



- Hippocampus – Learning and memory
- Amygdala – Emotions
- Hypothalamus – Hunger, thirst and temperature control
- Thalamus – Relay centre for sensory information

Constituents contd.

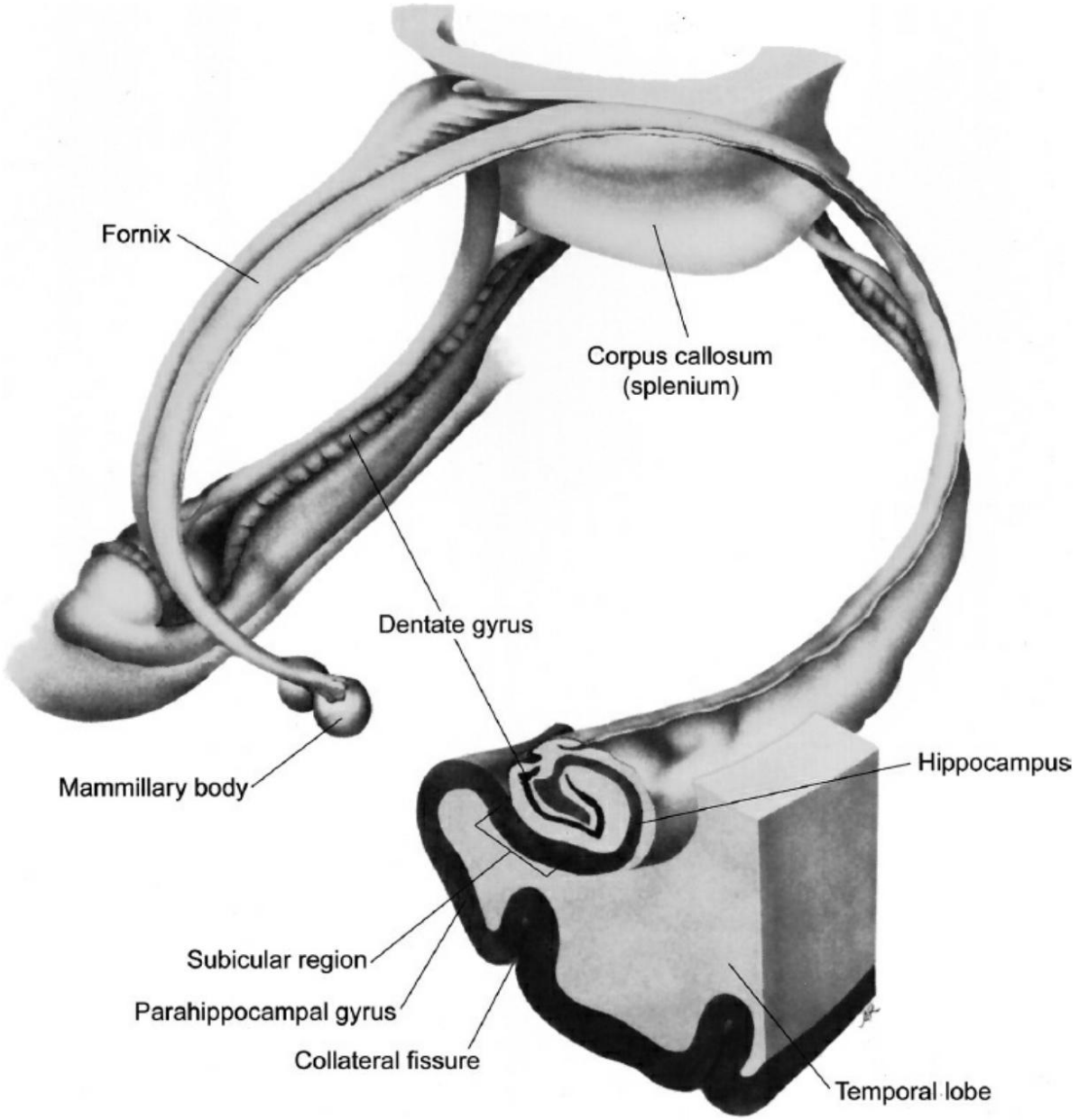


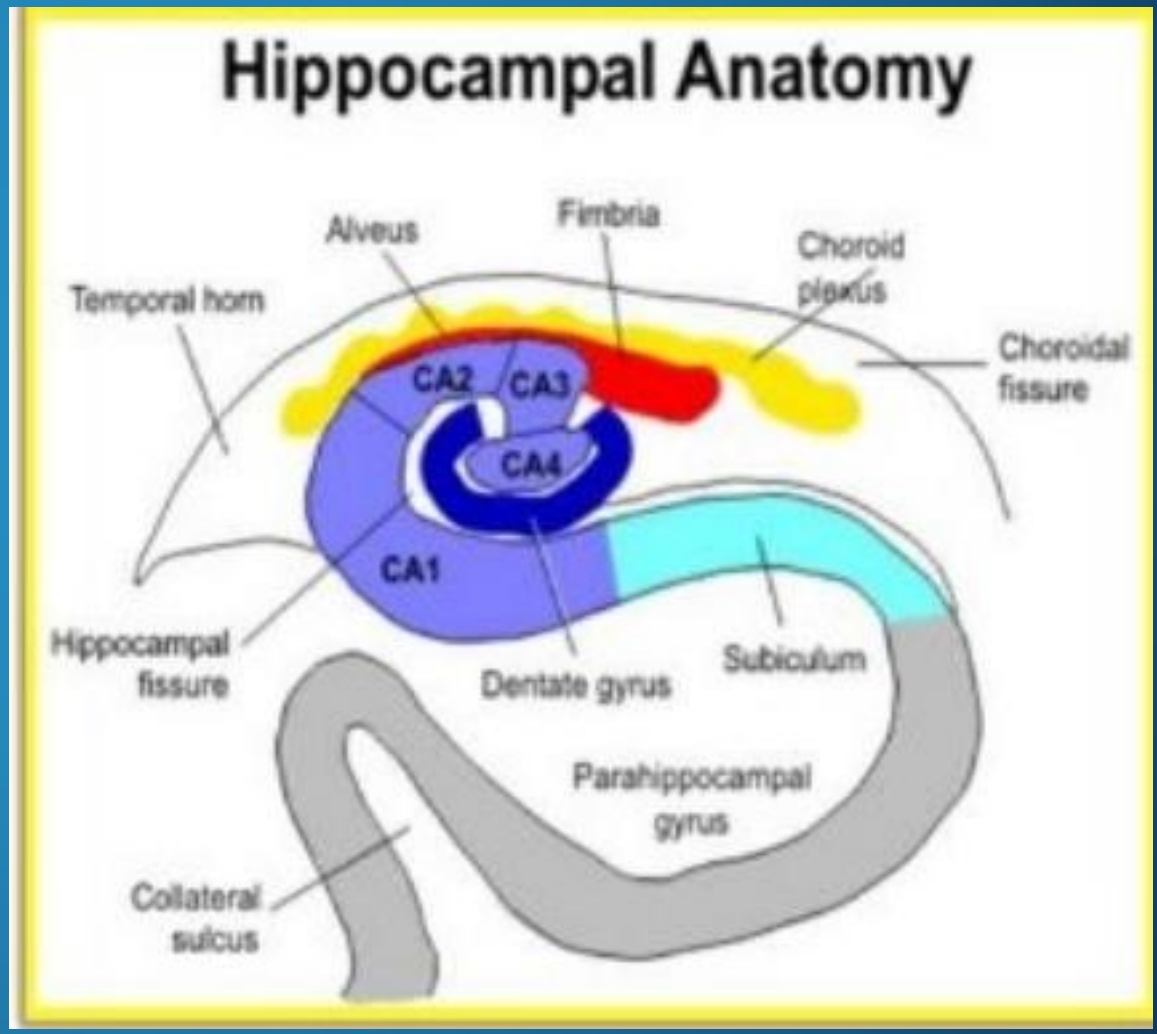
FIGURE 1.2–38. Schematic drawing of a cross-sectional view of the hippocampal formation and the path of the fornix running between that structure and the mammillary bodies. (Adapted from Hendelman WJ. *Student's Atlas of Neuroanatomy*. Philadelphia, PA: WB Saunders; 1994:189.)

Limbic Cortex

- Cingulate gyrus and the Parahippocampal gyrus.
- Cingulate gyrus - dorsal to the corpus callosum,
- Includes many cortical regions - interconnected with the association areas of the cerebral cortex.
- Posteriorly - continuous with the parahippocampal gyrus in the medial temporal lobe

Hippocampal Formation

- Present in the floor of the temporal horn of the lateral ventricle
- Three distinct zones:-
  - Dentate Gyrus
  - Hippocampus
  - Subicular complex
- Composed of adjacent strips of cortical tissue running in a rostral-caudal direction; fold over each other mediolaterally in a spiral fashion (C-shaped appearance)



Dentate gyrus

- 3 layers:
  - Outer acellular molecular layer - opposite the subarachnoid space of the hippocampal fissure
  - Middle layer of granule cells - extend their dendritic trees into the molecular layer - form mossy fiber projection to hippocampus
  - Inner polymorphic layer

Hippocampus

- Trilaminate structure
- Composed of molecular and polymorphic layers and a middle layer of pyramidal neurons.
- Hippocampus – divided into 3 fields – CA3, CA2 and CA1 – based on differences in cytoarchitecture and connectivity

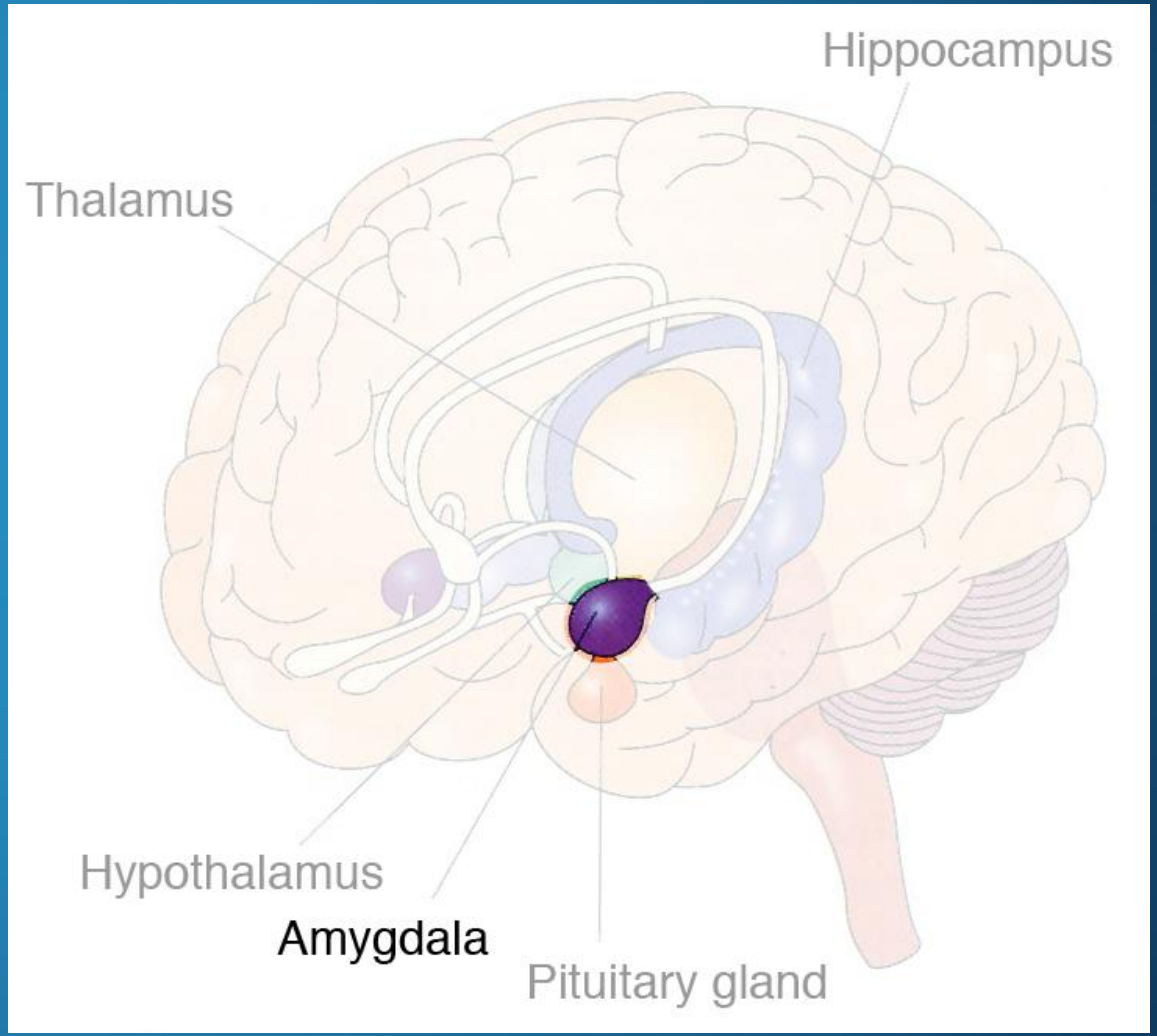
Subicular complex

- 3 components
  - Presubiculum
  - Parasubiculum
  - Subiculum
- Transition regions between the hippocampus and the parahippocampal gyrus.

- Neurons in Layers II and III of entorhinal complex
- Subiculum
- Hippocampus
- Outer 2/3rds of molecular layer of dentate gyrus
- Dendrites of the granule cells
- Pyramidal neurons of CA3
- Axon collaterals within CA3
- Schaffer collaterals
- CA1 field of hippocampus
- Subicular complex
- Entorhinal Cortex

Amygdala

- Location: median temporal lobe
- Group of nuclei forming several distinct clusters:
  - Basolateral complex
  - Centromedial amygdaloid group
  - Olfactory group (includes cortical amygdaloid nuclei)



Basolateral complex

- Largest group
- Connectivity and anatomically similar to cortical regions as compared to the other amygdaloid nuclei
  - Basolateral nuclei are directly and reciprocally connected with the temporal, insular, and prefrontal cortices
  - Shares bidirectional connections with the medial dorsal thalamic nucleus and receives projections from the midline and intralaminar thalamic nuclei
  - Neurons with a pyramidal-like morphology send projections to the striatum using neurotransmitters
  - Functions similar to a multimodal cortical region

Centromedial amygdala

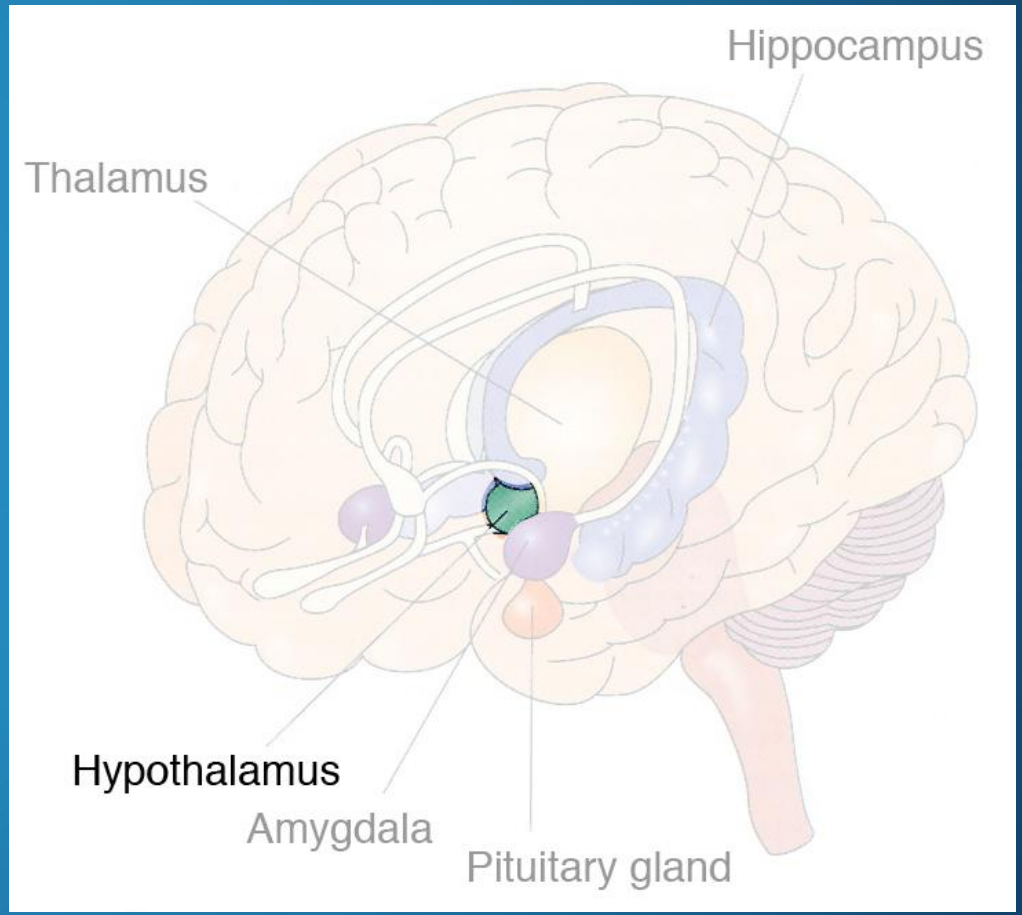
- Central subdivision:
  - Central amygdaloid nucleus and lateral portion of the bed nucleus of the stria terminalis.
  - Reciprocally connected with brainstem viscerosensory and visceromotor regions & lateral hypothalamus.
  - Receives afferents from cortical limbic regions and the basolateral amygdaloid complex.
- Medial Subdivision
  - Medial amygdaloid nucleus and extension into medial part of bed nucleus of stria terminalis.
  - Reciprocally connected with medial endocrine portions of the hypothalamus

Septal Area

- Gray matter structure present above the anterior commissure.
- Reciprocally connected with the hippocampus, the amygdala and the hypothalamus
- Project to a number of structures in the brainstem.

Hypothalamus

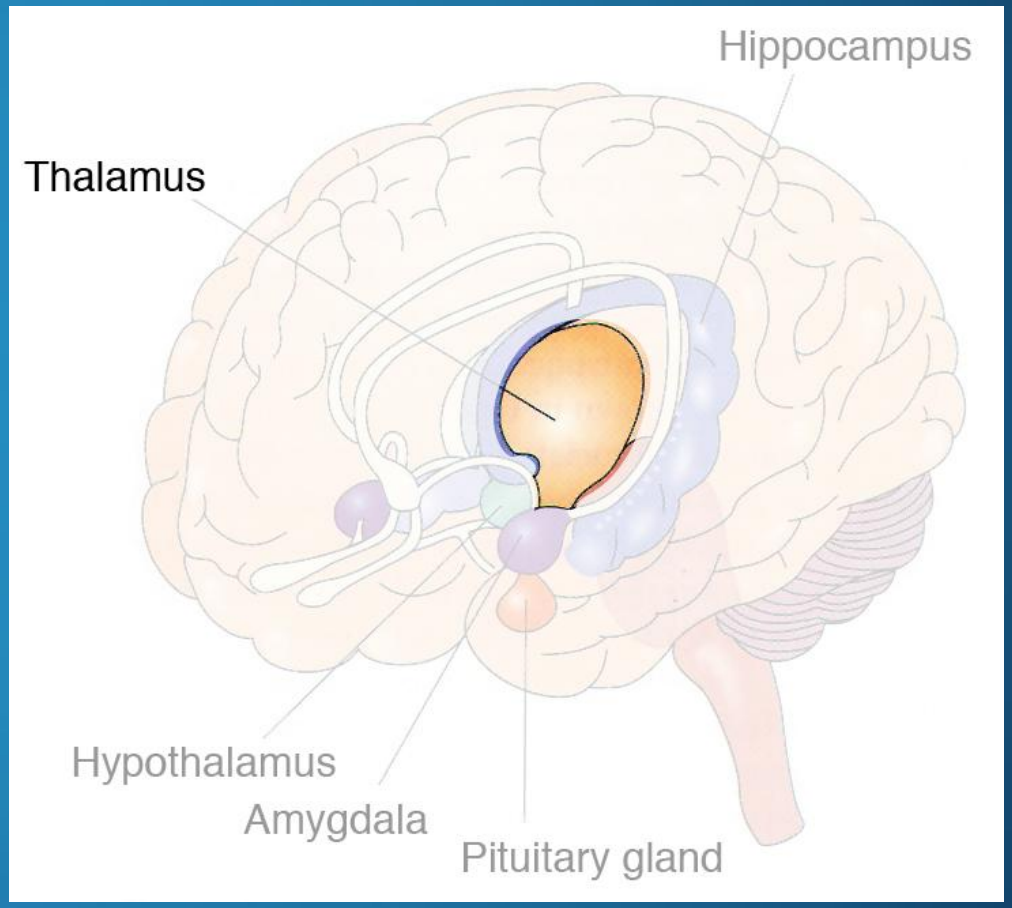
- Location: center of the limbic system
- Subdivided into three zones:
  - Supraoptic region,
  - Tuberal region
  - Mammillary region.
- Divided on each side into medial and lateral areas by the fornix.



Region	Medial area	Lateral area
Supraoptic	Supraoptic nucleus	Lateral nucleus
	Paraventricular nucleus	Part of Supraoptic
	Anterior nucleus	nucleus
	Suprachiasmatic nucleus	
Tuberal	Dorsomedial nucleus	Lateral nucleus
	Ventomedial nucleus	Lateral tuberal nuclei
	Arcuate nucleus	
Mamillary	Mamillary body	Lateral nucleus
	Posterior nucleus	

Thalamus

- Midline symmetrical structure of two halves
- Present between cerebral cortex and midbrain
- Acts as relay centre for sensory information

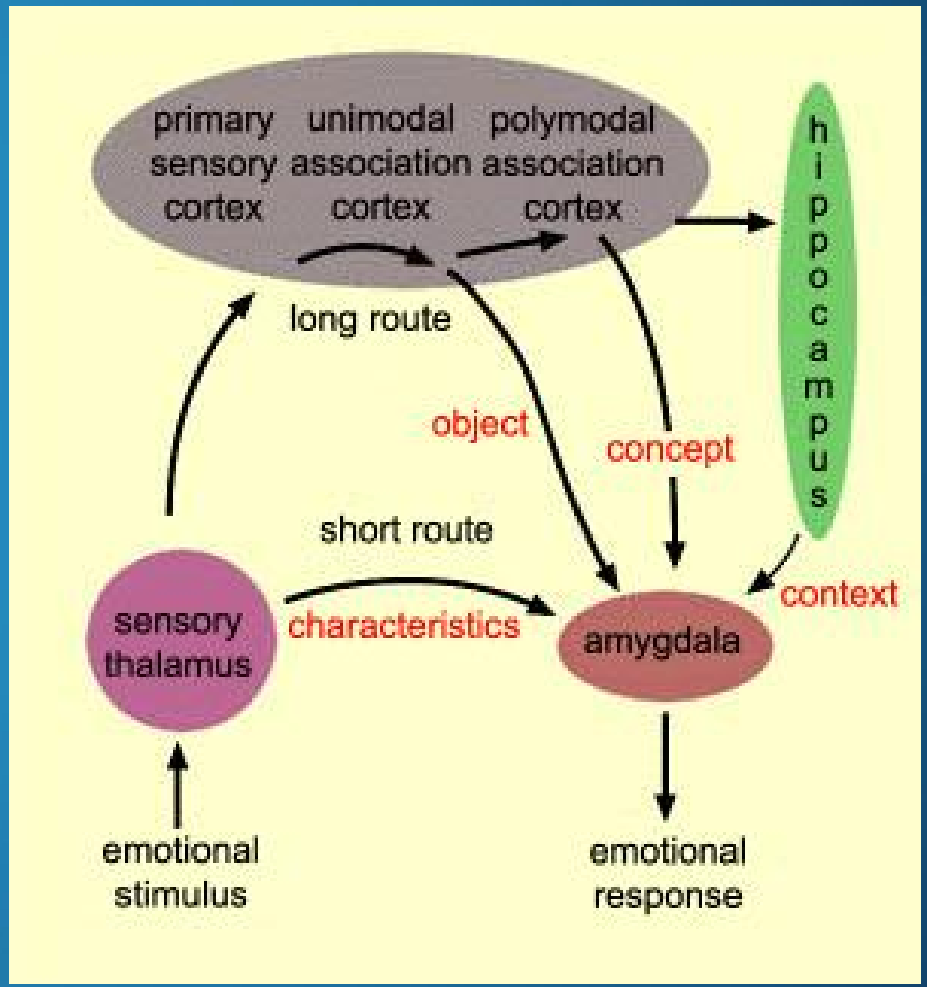


Functions of the Limbic System

Emotional Responses

Fear

- Due to stimulation of the hypothalamus and amygdala.
- Amygdala destruction - abolishes fear & its autonomic and endocrine responses
- Amygdala - fear learning
- Imaging studies - viewing fearful faces - activates left amygdala.



Emotional Responses contd.

Rage and Placidity

- Removal of neocortex – rage responses to minor stimuli
- Destruction of the ventromedial hypothalamic nuclei and septal nuclei with intact cerebral cortices in animals - induce rage.
- Bilateral destruction of the amygdala - placidity
- If ventromedial nucleus is destroyed after the destruction of the amygdala, the placidity generated is converted to rage.

Emotional Responses contd.

Autonomic and endocrine responses to emotion

- Fear and rage responses mediated by cortical & limbic structures (cingulate gyrus)
- Stimulates hypothalamus (lateral areas)
- CRH release from paraventricular nuclei of the hypothalamus
- Diffuse sympathetic discharge
- Autonomic, somatic, immune and endocrine responses - "flight or fright response“

Memory

Emotional memory

- Emotion influences learning and memory
- Amygdala, prefrontal cortex and medial temporal lobe - consolidation and retrieval of emotional memories
- Hippocampus - long-term declarative memory storage

Memory contd.

Medial temporal lobe memory system

- Hippocampus, adjacent cortex, parahippocampal regions, entorhinal and perirhinal regions
- Storage of new memories

Diencephalic memory system

- Hypothalamus, mammillary body, dorsomedial nucleus of thalamus
- Recent memory

Addiction and Motivation

- Addictive behaviour – reward circuitry – includes amygdala and nucleus accumbens
- Relapse associated with cues and stress - release of excitatory neurotransmitters in amygdala and hippocampus
- Motivated behaviour – prefrontal cortex, ventral tegmental area, amygdala (basolateral and extended), nucleus accumbens & ventral pallidum
- Involved in motivation to take drugs of abuse & compulsive nature of drug taking.

Appetite and Eating Behaviour

- Amygdala - food choice and emotional modulation of food intake.
- Lateral nucleus – feeding centre
- Ventromedial nucleus - satiety center.

Sleep and Dreams

- PET & fMRI - limbic system - one of the most active brain areas during dreaming.
- Interweaves unconscious primal emotions with our conscious cognitive thoughts and perceptions
- Ties together emotions and memory during REM sleep to form the content of dreams.
- Suprachiasmatic nucleus- circadian rhythm generator controlling the sleep-wake cycle

Olfaction

- Limbic structures closely related to the olfactory cortex.
- Amygdala - emotional response to smell
- Entorhinal cortex - olfactory memories

Sexual Behavior

- Medial preoptic area of hypothalamus – controls male sexual behavior.
- Chemosensory efferents from olfactory systems project to the medial amygdala (MeA).
- MeA sends innervations (through bed nucleus of stria terminalis, BNST) to the medial preoptic area (MPOA).
- MPOA and MeA receive genitosensory input from the spinal cord through the central tegmental field (CTF).

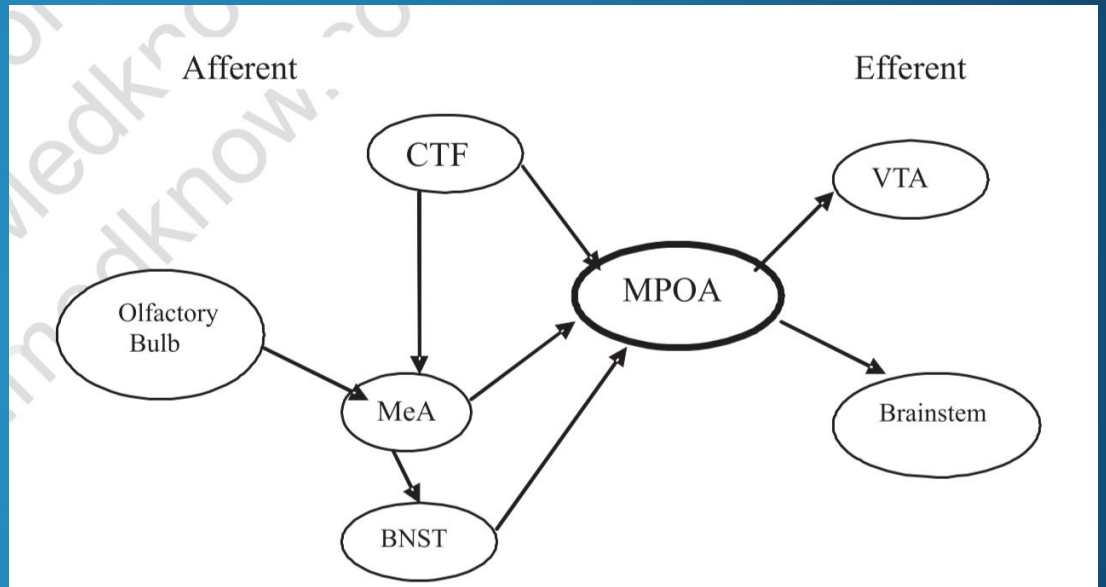
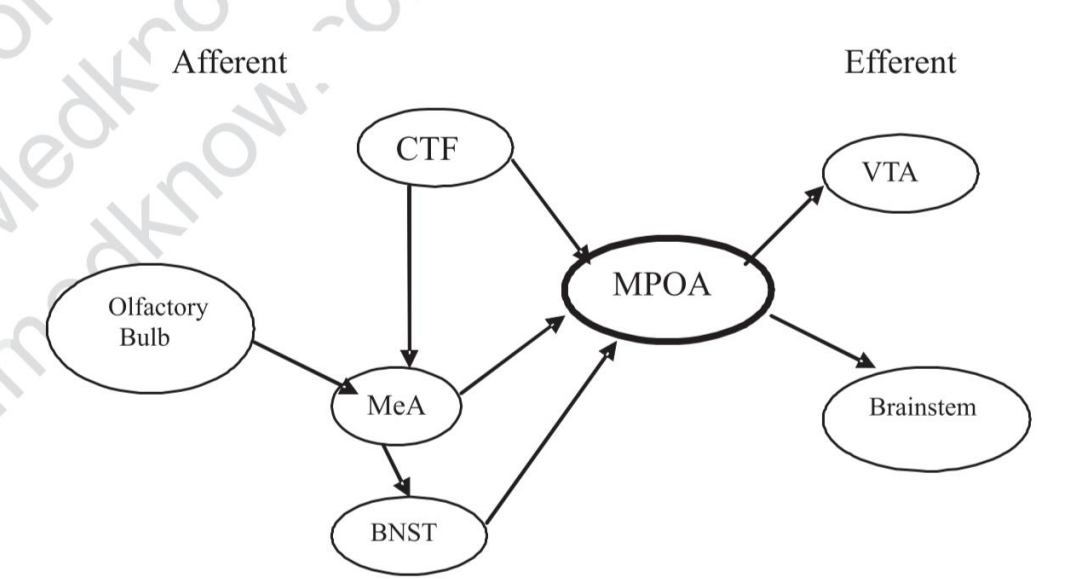


Figure 9: Neural Circuit of Male Sexual Behavior CTF: Central Tegmental Field, MeA: Medial Amygdala, BNST: Bed Nucleus of Stria Terminalis, VTA: Ventral Tegmental Area, MPOA: Medial Preoptic Area

Sexual Behaviour contd.

- MPOA - efferents to PVN, the ventral tegmental area, the nucleus paragigantocellularis and other autonomic and somatomotor areas
- Dopamin - penile erection – acts on oxytocenergic neurons in PVN
- GABA and its agonists, opioid peptides and opioid-like drugs inhibits sexual response
- Glutaminergic inputs from MeA and BNST to MPOA - mediates female stimulated increase in dopamin – enhances copulatory ability
- Extracellular glutamate in MPOA during ejaculation facilitates copulation and genital reflexes



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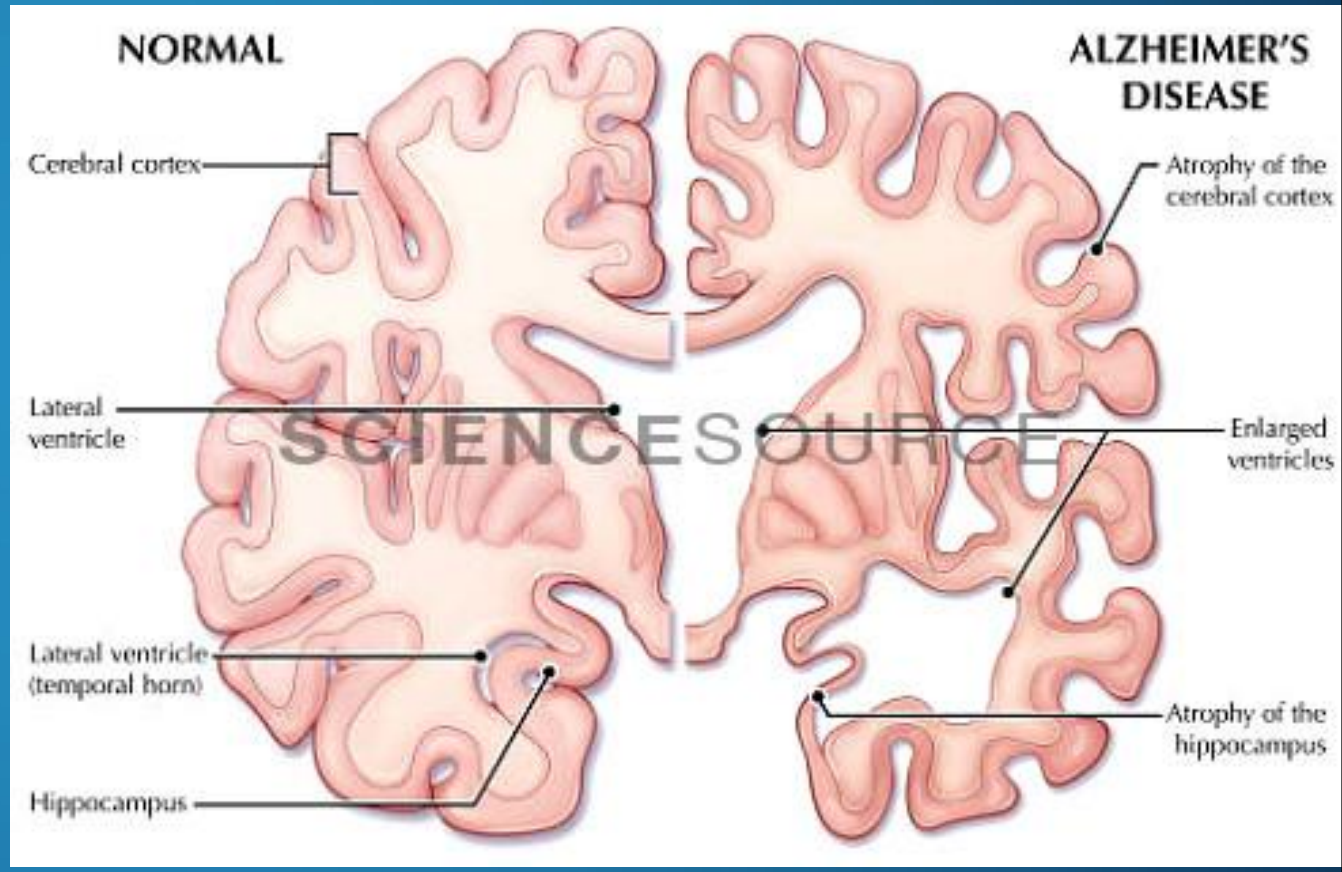
Psychiatric Relevance of the Limbic System

Dementia

- Degenerative changes in Alzheimer’s disease and Pick’s disease
- Marked atrophy in limbic system, esp. the dentate gyrus and hippocampus.
- Alzheimer's disease - senile plaques and neurofibrillary tangles - present throughout the cerebral cortex and basal ganglia - the hippocampus and amygdala often severely involved



Anxiety Disorders

- Anterior cingulate and hippocampus fail to modulate the activity of the amygdala.
- Fear circuitry, involving the amygdala, prefrontal and anterior cingulate has been described.

Schizophrenia

- Limbic system has been hypothesized to be involved in pathophysiology of schizophrenia due to its role in controlling emotions.
- Reduced limbic volumes.
- Papez circuit is probably involved in schizophrenia.
- Decreased size of hippocampus

Schizophrenia contd.

- Reduced number of GABAergic cells in the cingulate and anterior thalamus with glutamatergic excitotoxicity.
- The other circuit involved is the basolateral circuit which mediates the social cognition deficits in schizophrenia

Affective Disorders

- Variation in the volumes of the frontal lobes, basal ganglia, amygdala and hippocampus.
- Functional studies - decreased activity in prefrontal and anterior cingulate
- Anterior cingulate - integration of attentional and emotional output, helps in the effortful control of emotional arousal
- Dysfunction within the anterior limbic network (prefrontal regions and subcortical structures such as the thalamus, striatum and the amygdala)
- Also suggested in bipolar disorder, but its role in depression is unclear.

ADHD

- Hippocampus enlarged - compensatory response to the presence of disturbances in the perception of time, temporal processing and stimulus seeking
- Behavioural disinhibition – disrupted connections between the amygdala and orbitofrontal cortex

Kluver-Bucy Syndrome

- Bilateral destruction of the amygdaloid body and inferior temporal cortex.
- Visual agnosia, placidity, hypermetamorphosis , hyperorality and hypersexuality.
- Causes
  - Cerebral trauma,
  - Infections (herpes and other encephalitides)
  - Alzheimer's disease ,Niemann-Pick disease and other dementias
  - Cerebrovascular disease

Korsakoff's Psychosis

- Amnestic syndrome caused by thiamine deficiency associated with poor nutritional habits of people with chronic alcohol abuse.
- Damage to mammillary bodies, dorsomedial nucleus of thalamus and hypothalamus (diencephalic memory circuit).
- Chronic prominent impairment of recent and remote memory (recent > remote)
- Immediate recall is usually preserved.

Autism

- Disproportionate impairment in specific aspects of social cognition.
- Usually involves the cingulate gyrus and amygdala; responsible for cognitive and affective processing.
- Basolateral circuit, necessary for social cognition is disrupted in autism spectrum disorders.

Epilepsy

- Temporal lobe epilepsy - most common epilepsy in adults
- Caused by hippocampal sclerosis.
- Hippocampal sclerosis with involvement of amygdala and parahippocampal gyrus causes mesial temporal sclerosis (MTS).
  - CA1 – most vulnerable to hypoxia
  - CA2 – most resistant and well preserved sector
  - CA3 – slightly vulnerable
- The frequency and widespread distribution of cerebral abnormalities suggest that MTS is not limited to the medial temporal lobe but instead, represents a limbic system disorder.

Limbic Encephalitis

- Paraneoplastic syndrome
- Associated with Ca lung, breast and some other primaries.
- Manifests as encephalitis - involves hippocampus, amygdala, cingulate gyrus, insula & orbital-frontal cortex.
- Patients have subacute onset of memory loss, dementia, involuntary movements and ataxia.

Conclusion

- Limbic system has an integral role in behaviour
- Intricate functional neuroanatomy of limbic system with its diverse circuits may explain manifestations of neuropsychiatric disorders
- Monitoring role of anterior cingulate, the hippocampal circuitry underlying cognitive functioning and the importance of hypothalamus in many neurovegetative functions suggest the integral role of the limbic system in understanding human behaviour and its abnormalities.

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Thank You